11-8-2013

The Influence of Neurocognitive Impairment, Alcohol and other Drug (AOD) Use, and Psychosocial Factors on Antiretroviral Treatment Adherence, Service Utilization and Viral Load Among HIV-Seropositive Adults

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DOI: 10.25148/etd.FI13120404

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THE INFLUENCE OF NEUROCOGNITIVE IMPAIRMENT, ALCOHOL AND OTHER DRUG (AOD) USE, AND PSYCHOSOCIAL FACTORS ON ANTIRETROVIRAL TREATMENT ADHERENCE, SERVICE UTILIZATION AND VIRAL LOAD AMONG HIV-SEROPOSITIVE ADULTS

A dissertation submitted in partial fulfillment of

the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

PUBLIC HEALTH

by

Jennifer Attonito

2013

To: Dean Michele Ciccazzo
Robert Stempel College of Public Health and Social Work

This dissertation, written by Jennifer Attonito, titled The Influence of Neurocognitive Impairment, Alcohol and other Drug (AOD) Use, and Psychosocial Factors on Antiretroviral Treatment Adherence, Service Utilization and Viral Load Among HIV-Seropositive Adults, having been approved in respect to style and intellectual content, is referred to you for judgment.

We have read this dissertation and recommend that it be approved.

_____
William Darrow

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Consuelo Beck Sague

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Robert Dollinger

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Jessy G. Dévieux, Major Professor

Date of Defense: November 8, 2013

The dissertation of Jennifer Attonito is approved.

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Florida International University, 2013

DEDICATION

I dedicate this dissertation to those who lost the battle against HIV/AIDS and those still living with the disease. This work is also dedicated to Dr. Robert Malow who left this world in February, 2013. Dr. Malow was an impressive, prolific researcher and I am eternally grateful for his mentorship, support, and good humor.

ACKNOWLEDGMENTS

First, I would like to recognize the FIU Graduate School for financial support through the Dissertation Year Fellowship.

I wish to acknowledge the support and wisdom of my committee members, each of whom shared with me distinct areas of rich knowledge and experience along this path. My major professor, Dr. Jessy G. Dévieux has been a source of calm and professionalism throughout my doctoral work. I am honored to have absorbed some of her expansive knowledge of community-based research in HIV. I thank Dr. Consuelo Beck-Sague for teaching me HELP (humility, enthusiasm, listening, and practice) and for reminding me that public health is primarily about love and rock and roll. Additional thanks to Dr. William Darrow for sharing his impressive experience fighting against the social disease of HIV/AIDS. He was a primary motivator for my applying to the RSCPHSW. Extra appreciation is extended to Dr. Robert Dollinger for many, many years of friendship and mentorship. Thank you for giving me my first job in HIV/AIDS at FIU.

Additional thanks to faculty outside of the department of Health Promotion & Disease Prevention who kindly contributed their time to my dissertation. Dr. Michelle Hospital at the FIU Department of Social Work served as my statistics advisor and shared her immense expertise in structural equation modeling. Dr. Drenna Waldrop-Valverde at Emory University educated me in neurocognitive measurement instruments and research. Finally, thanks to Brenda Learner in the AIDS Prevention Program who taught me every detail about the HHRP-A intervention and guided me through the amazing process of IRB application.

Several grand old colleagues and still dear friends encouraged me to pursue this degree and have made the field of public health interesting (to say the least) for many years. The “D-7 Ladies” kept me laughing, eating, and on-track throughout this entire dissertation process. And to all of my other brilliant doctoral classmates in HPDP: I wish us all great success in promoting good health throughout the world.

I wouldn’t have made it to this point in life without extraordinary parents. My father’s passion for higher education is in my blood and I know how excited he is for me. I wish my mother were here with me today. I’m grateful she taught me how to dream and be playful.

Finally, the lion’s share of gratitude goes to my wife, Kristin Fries who encouraged me to take on this challenge when she could clearly see it was what I wanted. My “rock” (and an excellent writer), Kristin read and reviewed papers, chapters, articles and Power Point slides until she was cross-eyed and heard story after boring story about my research until she was cross-eared. She never doubted I could do this, and I love her with all my heart.

ABSTRACT OF THE DISSERTATION

THE INFLUENCE OF NEUROCOGNITIVE IMPAIRMENT, ALCOHOL AND OTHER DRUG (AOD) USE, AND PSYCHOSOCIAL FACTORS ON ANTIRETROVIRAL TREATMENT ADHERENCE, SERVICE UTILIZATION AND VIRAL LOAD AMONG HIV-SEROPOSITIVE ADULTS

by

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Among people living with HIV (PLWH), adherence to antiretroviral therapy (ART) can be affected by problems of neurocognitive (NC) impairment, stress, alcohol and other drug (AOD) abuse, and other barriers. The aims of this research were to: (1) examine factors associated with NC impairment, (2) explore relationships between psychosocial variables with ART adherence and viral load (VL), and (3) evaluate the efficacy of an evidence-based intervention in improving ART adherence, increasing service utilization, and decreasing VL.

The first study (n=370) was cross sectional and used structural equation modeling to test whether AOD use, years living with HIV, and time from HIV diagnosis to seeking care were associated with poorer NC functioning. The second study (n=246) used similar methods to test the hypothesis that stress, barriers to adherence, NC impairment, poor social support, and AOD use were related to lower VL mediated by ART adherence. The third study (n=243) evaluated an evidence-based, eight-session program to improve ART

adherence, reduce VL, and increase service utilization in a randomized controlled trial. Study participants were PLWH living in South Florida, 18 to 60 years old, with a history of alcohol abuse enrolled from January 2009 through November 2012.

Secondary analysis of available data showed: (1) scores on interference with executive functioning increased by 0.32 for each day of marijuana use and 1.18 for each year living with HIV, but no association was found between alcohol use and NC functioning; (2) each barrier to adherence was associated with a 10% decrease in adherence to ART and a 0.42 unit increase in VL (log10) and the relationship between barriers and VL was partially mediated by ART adherence; (3) participants in the evidence-based program were more likely than the comparison group to report an undetectable VL (OR=2.25, $p<0.01$) at 6 months, but not 3 months, post-intervention.

Psychosocial factors affect VL, but ART adherence is essential in achieving an undetectable VL in PLWH.

TABLE OF CONTENTS

LIST OF TABLES

TABLE PAGE

ACRONYMS AND ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
AOD	Alcohol and Other Drug(s)
ART	Antiretroviral Therapy
AVLT	Auditory Verbal Learning Test
CBO	Community-Based Organization
CTT2	Color Trails Test 2
EBI	Evidence-Based Intervention(s)
HAART	Highly Active Antiretroviral Therapy
HAND	HIV-Associated Neurocognitive Disorders
HHRP-A	Holistic Health Recovery Program - Adapted
HIV	Human Immunodeficiency Virus
HPC	Health Promotion Comparison
IMB	Information Motivation Behavior Skills
NC	Neurocognitive
PLWH	People Living with HIV/AIDS
RCT	Randomized Controlled Trial
SCT	Short Category Test
TLFB	Time Line Follow-back

CHAPTER I

BACKGROUND

Treatment for Human Immunodeficiency Virus (HIV)

Although over 600,000 people in the United States have died from complications related to acquired immune deficiency syndrome (AIDS) since the beginning of the epidemic, AIDS death rates have decreased dramatically since the mid-1990s. This decline is due in great part to the advent of highly active antiretroviral therapy (HAART; Centers for Disease Control and Prevention Division of HIV/AIDS, 2012a, 2012b). Chemotherapy for human immunodeficiency virus (HIV) has evolved over the years from no treatment to treatment with a single drug (AZT or Zidovudine) to dual-drug therapy and, since 1996, to HAART (also referred to as ART). ART is defined as treatment with at least three active anti-retroviral medications—typically two nucleoside or nucleotide reverse transcriptase inhibitors (NRTI's) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) or another NRTI—and is often called the drug "cocktail" or triple-therapy (Thompson, Aberg, & Hoy, 2012). Because each class of antiretroviral medications intercepts viral replication and proliferation at different stages in the HIV life cycle, a combination of antiretrovirals is considered to be most effective for achieving undetectable blood levels of the virus and preventing the emergence of resistance.

HIV Treatment Adherence

HAART has essentially transformed HIV from a fatal to a chronic illness. Thus, the goal of HIV care has shifted toward achieving long-term optimal health outcomes through consistent adherence to ART. Proper ART adherence can stop viral replication,

rendering virus levels undetectable in both blood and sexual fluids and reducing risk of HIV transmission (Cohen & Chen, 2011; Volkow & Montaner, 2010). Optimal adherence to ART—defined as following prescribed treatment at least 80% of the time (Parienti et al., 2008)—directly improves health outcomes and is critical for successful treatment (Bangsberg et al., 2000; Carpenter et al., 1997; Deeks, Smith, Holodniy, & Kahn, 1997; Descamps & Flandre, 2000; Katzenstein, 1997; Paterson, Swindells, Mohr, Brester, & Vergis, 2000).

Conversely, treatment interruption and inconsistent ART adherence is known to result in poorer health outcomes and the emergence of treatment resistant strains of HIV, reducing treatment options for an infected individual over time (Parienti et al., 2008; Bangsberg et al., 2001). Additionally, these resistant strains may be transmitted to others through infected body fluids, resulting in treatment failure and reduced treatment options on a community level. Even in a time of heightened awareness of HIV in the U.S., about 50,000 people continue to be infected annually (Centers for Disease Control and Prevention Division of HIV/AIDS, 2012). Because of the convincing body of knowledge suggesting that consistent ART adherence can not only improve health outcomes for individuals but also reduce HIV transmission at population levels, the Centers for Disease Control and Prevention (CDC), National Institutes for Health (NIH), and Health Resources and Services Administration (HRSA) have placed increasing priority on improving treatment adherence and access to care for people living with HIV (PLWH; *White House Office of National AIDS Policy*, 2010).

Adherence to ART is possibly the most important determinant of survival among PLWH (Hogg et al. 2002) with earlier studies suggesting that as much as 95% adherence

was necessary to achieve positive clinical outcomes with regimens used in the 1990s and early 2000s (Bangsberg, Moss, & Deeks, 2004; Lucas, 2005; Paterson et al., 2000). Even with the newest regimens, uninterrupted adherence of >80% is typically considered essential to guarantee optimal virologic response (Parienti 2008). Furthermore, inadequate treatment adherence is associated with increased mortality, drug resistance and limited future treatment options for the patient, and increased risk of HIV transmission to others (Bangsberg et al., 2001).

More recently, ART has been shown to be an effective means of HIV prevention. Results from the nine-country HIV Prevention Trials Network (HPTN 052) revealed that HIV-seropositive partners were significantly less likely to transmit the virus sexually to uninfected partners if ART was initiated when CD4 counts were higher (350-499) than levels considered absolute indications for ART initiation for patient's health (CD4 count<350), indicating potential effectiveness of use of treatment as prevention of sexual HIV transmission (Cohen et al. 2011). Other research has reported similar outcomes in the use of treatment-as-prevention for HIV transmission related to injection drug use (Choopanya et al., 2013; Wood, Kerr, & Marshall, 2009). While ART adherence is strongly associated with viral suppression and reduction of HIV transmission to others, this relationship may be related to the classes of antiretrovirals used (Bangsberg et al., 2004; Katzenstein, 1997) and strain resistance to antiretrovirals used (Liao et al., 2013).

The reduction of VL has been shown to result in lower rates of new infection on a community level (Das et al. 2010). However adequate viral suppression is achieved only through treatment adherence by each individual. While efforts to simplify treatment particularly to once-a-day one-pill ART, have been successful, ART regimens can still be

complicated, requiring patients to take multiple doses daily of each medication in the combination (Abgrall & The Antiretroviral Therapy Cohort Collaboration (ART-CC), 2012). Each medication may also carry specific dose-timing and storage requirements. Different medications may need to be taken with food, without food, with water, or in an order relative to other drugs in the combination (Catz, Kelly, Bogart, Benotsch, & Mcauliffe, 2000).

Achieving the nearly perfect adherence recommended to suppress viral replication, experience optimal health outcomes, and prevent HIV transmission can be challenging. U.S. studies have reported that as few as 18% to 73% of participants were non-adherent to antiretroviral therapy (Catz et al., 2000; Paterson et al., 2000; Tesoriero et al., 2003). These percentages may be even lower for PLWHs dealing with neurocognitive impairment, substance abuse problems, and added environmental and psychosocial constraints. Additional predictors of poor ART adherence include poor social support (Safren et al., 2001), mental health problems (Bottonari et al., 2012; Nel & Kagee, 2011; Sherr, Clucas, Harding, Sibley, & Catalan, 2011), and alcohol abuse (Baum et al., 2010; Bryant, 2006; Samet, Phillips, Horton, Traphagen, & Freedberg, 2004), which will be discussed in greater detail below.

In addition to helping individual patients adhere to treatment regimens, the full implementation of community-level treatment as prevention (i.e., "seek, test, treat, retain") requires stabilization of many policy and institutional factors, including improving access to and utilization of available care (Mayer & Krakower, 2012). Increasing access to care and optimizing health outcomes for PLWH is one of the three primary goals of the National HIV/AIDS Strategy (White House Office of National AIDS

Policy, 2010). It is estimated that as many as 30 percent of people diagnosed with HIV in the U.S. are not accessing care (White House Office of National AIDS Policy, 2010). Through adequate and consistent care, patients are better able to receive the support necessary to achieve complete treatment adherence, sustain optimal health outcomes and, ultimately, help to reduce the incidence of HIV.

HIV-Associated Neurocognitive Impairment

Over the next 20 years, neuropsychiatric disorders are estimated to exact a global cost of $16.1 trillion with ‘‘dramatic impacts on productivity and quality of life’’ (Bloom et al., 2012, p. 5). Mental, neurological, and substance use disorders are associated with low rates of care utilization, poor treatment adherence and response, and increases in high risk behaviors (Bass et al., 2012).

With HIV-positive individuals living longer because of increased availability and use of HIV treatments, new neurologic syndromes often associated with HIV status are emerging with greater frequency over the life span (Antinori et al., 2007; Durvasula, Norman, & Malow, 2009; Norman, Basso, Kumar, & Malow, 2009; Palacio, Alvarez, & Munoz-Fernandez, 2012). Thus, it is important to study the effects of neurocognitive (NC) impairment on risk behaviors among PLWH. Since the advent of combination ART, the incidence of HIV-associated dementia (HAD) has declined from 10-15% (Janssen, Nwanyanwu, Selik, & Stehr-Green, 1992; J. McArthur & Grant, 1998) to 2-5% (Heaton et al., 2010; Robertson et al., 2007; Sacktor, 2002). However, milder forms of HIV-associated neurocognitive disorders (HAND) have been reported in up to 40% of this population, especially as HIV-positive individuals are living longer with the disease

(Antinori et al., 2007; Durvasula et al., 2009; McArthur, 2004; Sacktor, 2002; Sacktor et al., 2007).

HAND is divided into minor cognitive motor disorder (MCMD) and HAD (Antinori et al., 2007). MCMD in turn is subdivided into asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND). MND is accompanied by mild interference in daily functioning, whereas ANI is not (Foley et al., 2010; Gandhi et al., 2011). ANI and MND are both identified by performance scores at least one standard deviation (SD) below the mean of normative scores in at least two cognitive domains: attention-information, processing, language, abstraction-executive, complex perceptual motor skills, memory, including learning and recall, simple motor skills or sensory perceptual abilities. In contrast, HAD is characterized by marked neurocognitive dysfunction ($\geq$ 2 standard deviations below the mean normative scores) in at least two cognitive domains. This level of cognitive impairment produces marked interference with activities of daily living (Antinori et al., 2007; Foley et al., 2010; Gandhi et al., 2011; Gisslén, Price, & Nilsson, 2011; Palacio et al., 2012).

The types of impairments exhibited by persons with these neurologic syndromes can affect functioning at work or in everyday activities (Gandhi et al., 2011). Even though HAD has become less frequent, HIV-positive individuals are still at risk for HIV-associated neurological complications. Two to five percent of HIV-positive individuals are estimated to develop HAD and up to 37% will suffer a less severe ANI or MND (Sacktor et al., 2002). Several of the neurocognitive deficits seen in patients with HAND are believed to contribute to HIV risk behavior, affecting impulse control (Lopez, Smith,

Meltzer, & Becker, 1999) and episodic memory functions that may impair the ability to plan and execute intentions (Woods, Moore, Weber, & Grant, 2009).

HAND is mostly seen in advanced stages of HIV disease but can occur even in PLWH with medically asymptomatic HIV infection (Grant et al., 1987; Heaton, Grant, Butters, White, Kirkson, et al., 1995; White, Heaton, & Monsch, 1995). Increased duration living with the virus, particularly during the acute phase of infection, has been identified as partially responsible for NC impairment. Yet HAND has still been observed to varying degrees among PLWH who have been consistently maintained at low-to-undetectable VLs on ART (Simioni et al., 2010; Tozzi et al., 2007).

Multiple possible causes of HAND have been suggested: the inability of commonly-used ART to penetrate the blood-brain barrier, with reduced levels in the central nervous system (CNS) leading to incomplete viral suppression; brain damage during acute HIV infection and prior to ART initiation; prolonged inflammatory response and CNS immune reconstitution inflammatory syndrome (IRIS); possible neurotoxicity of specific antiretrovirals; and exposure to other conditions associated with long-term survival with HIV such as vascular dementia, Parkinson's-related dementia, Alzheimer's disease and depression (Heaton et al., 2011; Johnson & Nath, 2011; Mateen & Mills, 2012). In addition, it has been suggested that HIV in the brain could develop increased adaptation and neurovirulence in the presence of ART over time, potentially spreading to other body tissues (Churchill & Nath, 2013).

Even the mildest form of HAND may be a precursor to more severe NC disorders (McArthur, Steiner, Sacktor, & Nath, 2010). HAND in general can present clinically as impairment in episodic memory, information processing, attention and executive

functions (Woods et al., 2009). Heaton (2011) found that patients in the pre-ART era and those with later stage disease had poorer degrees of functioning in multiple NC domains. Those in the ART era showed poorer functioning in cognitive domains of memory and executive functioning. Visual working memory has been shown to improve with greater viral suppression and improved immune function (Gupta et al., 2007). In patients presenting with even milder forms of HAND, quality of life can be affected, with struggles to perform activities of daily living, personal health care management and control of risk behaviors (Malow et al., 2012; McArthur, 2004). In addition to impacting risk behaviors and impulsivity, overall NC impairment has been linked with poorer ART adherence among PLWH (Hinkin, Castellon, & Durvasula, 2002). Additionally, studies have identified impairment in specific domains of functioning — such as verbal memory (Applebaum, Reilly, et al., 2009; Wright et al., 2011) and executive functioning (Hinkin & Hardy, 2004; Waldrop-Valverde, Jones, Gould, Kumar, & Ownby, 2010) — associated with deficiencies in ART adherence. Whereas memory and information processing may affect patients' ability to understand complex medication information, executive functioning may impact patients' ability to make personal medication decisions and manage the myriad life complexities that interfere with a treatment regimen.

Alcohol and other Drug Use

Studies have reported that more than 50% of HIV-infected clinic-based samples reported illicit drug and heavy alcohol use (Bing et al., 2001; Martin et al., 2004; Samet et al., 2004). Each additional substance use disorder contributes to poorer health outcomes and is associated with decreased access to and use of health care and reduced likelihood of being prescribed and/or adhering to ART (Bruce & Altice, 2007).

HIV and alcohol abuse are considered to be converging epidemics and, as a result, a greater number of individuals are at risk for alcohol use disorders, HIV infection and rapid progression to AIDS (Bryant, 2006). Shared high-risk environments and behaviors, as well as shared individual characteristics, have contributed to the HIV and alcohol abuse epidemics, creating a synergistic phenomenon (Bryant, Nelson, Braithwaite, & Roach, 2010; Bryant, 2006). In non-HIV clinic samples, 20-30% of patients are reported to have met criteria for past or present alcohol problems (Buchsbaum, Buchanan, Centor, Schnoll, & Lawton, 1991; Cleary, Miller, Bush, Warburg, & Delbanco, Aronson, 1988; Fleming, Manwell, Barry, & Johnson, 1998). Furthermore, studies of HIV-infected clinic patients have reported that more than 50% reported heavy alcohol use (Martin et al., 2004; Samet et al., 2004). In a longitudinal cohort study of HIV-positive veterans, 33% reported binge drinking and 32% had a clinical diagnosis of alcohol addiction or dependence (Justice, Dombrowski, & Conigliaro, 2006).

Alcohol influences the complex decision-making process to engage in acts that place one at risk for acquiring and transmitting HIV and other STIs (Bryant, 2006). Both the degree of alcohol intoxication and history of alcohol abuse tend to be associated with involvement in more risk behaviors (Bryant, 2006). Alcohol misuse and abuse have other deleterious physical and mental health outcomes (Conigliaro, Gordon, McGinnis, Rabeneck, & Justice, 2003; Justice et al., 2004) as well as hindering adherence to healthcare recommendations, particularly medication regimens (Baum et al., 2010; Bryant, 2006; Samet, Horton, Meli, Freedberg, & Palepu, 2004). Research shows that severity of alcohol use is correlated with levels of ART non-adherence (Cook et al., 2001).

Several reasons have been cited for the negative impact of active alcohol use on ART adherence (Lucas, Gebo, Chaisson, & Moore, 2002), including: (a) lifestyle instability not conducive to ART (Sherer, 1998); (b) poor social support and mistrust of the medical establishment (O'Connor, Selwyn, & Schottenfeld, 1994); (c) non-adherence to scheduled clinic visits (Lucas et al., 2002); and (d) coexisting mental health disorders that act as further barriers to adherence (Batki, Ferrando, Sorensen, & Wall, 1996). HIV-infected patients have also reported stopping treatment when drinking because of beliefs about the toxicity of drinking while on ART (Kalichman et al., 2012; Sankar, Wunderlich, Neufeld, & Luborsky, 2007). While there is evidence of combined or enhanced toxicity effects, optimal ART adherence remains advised for HIV-positive alcohol users (Braithwaite & Bryant, 2000). Although no consistent associations between gender and ART adherence have been found, it should be noted that women may be more adversely affected by alcohol abuse in terms of ART adherence (Applebaum, Richardson, Brady, Brief, & Keane, 2009; Berg & Demas, 2004).

Alcohol abuse frequently co-occurs with HIV and may further impair NC functioning among PLWH, however evidence of interactions between AOD use and HIV upon NC performance has varied. Studies have reported that more than 50% of HIV-infected clinic patients reported heavy alcohol use (Martin et al., 2004; Samet et al., 2004) and that up to 80% of people with alcohol use disorders may suffer from some degree of NC impairment (Bates, Bowden, & Barry, 2002). Among individuals with HIV infection and drug and alcohol use disorders, impaired verbal working memory (Farinpour et al., 2000), impaired auditory working memory, and enhanced cognitive impulsivity have been observed (Martin et al., 2004). Additionally, synergistic negative

effects of HIV and heavy alcohol use together have been observed in motor and visual spatial tasks (Rothlind et al., 2005). Alcohol use and HIV progression compromise information processing, executive functioning, and emotion regulatory functions that may be important in adhering to safe sex practices and other preventive behavior (Bryant, 2006). Alternately, several studies have been unable to identify interactions between drug use and HIV upon NC performance (Bornstein et al., 1993; Concha et al., 1992; Durvasula, Miller, Myers, & Wyatt, 2001; Selnes, Galai, McArthur, & Cohn, 1997). Compounding the direct effects of NC impairment on ART adherence, substance use may contribute further to substandard ART adherence (Hinkin et al., 2002; Rothlind et al., 2005).

Alcohol use has been shown to play a possible confounding role in the assessment of NC impairment among PLWH (Justice et al., 2004). In order to deliver targeted and effective clinical care as well as HIV risk reduction and treatment adherence interventions, it is important to understand not only specific domains of impairment associated with HIV infection and alcohol abuse but also the effects of any potential interactions between these two commonly coexisting conditions.

Although most research on the use of illicit substances and HIV infection center upon injection drug use, marijuana and cocaine are reported to be the most commonly-used illicit substances among PLWH (Cook et al., 2001; Korthuis et al., 2008; Kuo et al., 2004). Substantive evidence has linked general illicit drug use and ART non-adherence (Lucas et al., 2006); however, research regarding adherence and marijuana use in particular is mixed. Research on medical cannabis use has shown that participants report considerable symptom relief (Prentiss, Power, Balmas, Tzuang, & Israelski, 2004), but

several studies indicate that adherence rates are nonetheless lower for marijuana users (Corless et al., 2009; Tucker, Burnam, Sherbourne, Kung, & Gifford, 2003). Conversely, De Jong et al. (2005) observed greater ART adherence among participants who used marijuana medicinally as opposed to recreationally. Research concerning marijuana use's impact on virologic, immunologic and other health markers among PLWH remains limited. Research examining psychostimulants such as cocaine and methamphetamines, however, has consistently shown an association with decreased adherence (Arnsten et al., 2002; Hinkin et al., 2007; Tucker et al., 2003). Cocaine use may also be directly associated with higher VLs (Arnsten et al., 2002).

Stressful Life Events

Life stress is a contextual variable commonly associated with risk and protective health behaviors such as ART adherence (Chesney, Morin, & Sherr, 2000). According to a 2010 CDC white paper on social determinants of HIV/AIDS in the U.S., distribution of power and resources affect environmental conditions such as housing and social support; social and physical environments, and availability, cost of, and access to healthcare services and contribute as pathways to HIV infection or barriers to overall health (Koopman et al., 2000). High levels of perceived stress among PLWH have been associated with lower income, and financial difficulty is one of the most frequently reported stressful events among PLWH (Mugavero et al., 2009; Reif et al., 2011). Other stressful life events are exceedingly common in the lives of PLWH and are negatively associated with antiretroviral medication adherence and treatment outcomes.

Associations between stress and substance abuse also have been identified, but the exact relationship remains somewhat elusive. A review of animal studies identified

several neurobiological connections between the changes in the brain produced by both acute and chronic alcohol and other drug (AOD) use resulting from the introduction of stressors (Piazza & Moal, 1998). Identifying relationships between stress and alcohol use in clinical settings has been more challenging, in part because of inherent limitations in attempting to conduct research with alcoholic participants (Brady & Sonne, 1999; Russell, Cooper, Frone, & Peirce, 1999). Patients may vary in their likelihood of drinking in response to stress, suggesting that individual factors moderate the relationship between stress and alcohol use. However, in some studies, exposure to stressors has been consistently associated with increased alcohol use, particularly as an avoidance coping mechanism (Brady & Sonne, 1999; Russell et al., 1999). This relationship may indicate that, in addition to directly affecting ART adherence, stress may also act through alcohol to affect ART adherence.

Social Support

Stronger social support is known to reduce one's reliance on avoidance coping strategies and dampen the effects of stress in some situations (Heaney & Israel, 1997). The term "social support" is typically used to describe mechanisms by which interpersonal relationships may buffer a person against a stressful environment (Cohen & McKay, 1985). Social support is a multidimensional construct and can involve networks of individuals providing different modes of support: "(1) emotional support (the expression of positive affect, empathetic understanding, and the encouragement of expressions of feelings), (2) informational support (the offering of advice, information, guidance or feedback), (3) tangible support (the provision of material aid or behavioral assistance), (4) positive social interaction (the availability of other persons to do fun

things with you), and (5) affectionate support (involving expressions of love and affection)"(Sherbourne & Stewart, 1991, p. 707). Researchers have identified these modes of support as influential in understanding health behaviors, and have suggested that they be matched to the other factors examined in a given study in order to detect a relationship (House & Kahn, 1985). For example, if the primary area of social support perceived by the participant is "emotional," its buffering effect may not be observable if the actual form of social support needed to achieve an outcome is "tangible" (Cohen & McKay, 1985).

The positive association between social support and adherence to ART regimens among PLWH is well documented (Catz et al., 2000; Diiorio et al., 2009; Gordillo, del Amo, Soriano, & González-Lahoz, 1999; Holzemer, 1999; Safren et al., 2001; Samet et al., 2004; Simoni, Frick, & Huang, 2006; Singh et al., 1999), although few studies have focused on specific roles and mechanisms of social support. A meta-analysis found that, among people with different diseases, practical support was a much stronger predictor of treatment adherence than emotional support (DiMatteo, 2004), but this analysis excluded studies that involved substance abusing populations. Further, it has been found that emotional support was a stronger predictor of medical care utilization (Broadhead, Gehlbach, & Kaplan, 1989) and functional (e.g. financial) support was more closely associated with treatment access (Knowlton et al., 2001). One study found that social support did not directly influence ART adherence among PLWH, but instead acted through the mediators, depression and self-efficacy (Diiorio et al., 2009). Similarly Simoni, Frick, and Huang (2006) found that social support operated through affect and spirituality in its relationship with efficacy to adhere to ART. Less present in the

literature are studies examining the role of social support as a moderator, buffering the effects of factors such as substance abuse, NC impairment, and stress on the outcomes of ART adherence and response.

Statement of the Problem

While there is a greater understanding of HAND and the domains affected by HIV, there is also an increasing frequency with which NC impairment is experienced by PLWH today. Hence it becomes increasingly important to explore areas of daily functioning that are potentially influenced by HAND. The increasing value being placed upon ART as treatment and prevention on individual and community levels, both nationally and internationally, underscores the importance of exploring the relationship between NC impairment and ART adherence in the lives of PLWH. However, health behaviors like ART adherence are not enacted in isolation; they are impacted by many psychological, biological, and social factors. Complex contributions of common factors such as alcohol use, life stress, and social support upon ART adherence must also be taken into account. Only from a biopsychosocial perspective can we assess a "real world" environment, achieving a broad perspective of the myriad influences on ART adherence and service utilization in the lives of PLWH. According to Applebaum (2009, p.455), "Given the extent of neuropsychological impairment [among HIV-positive substance abusers], future studies should examine the degree to which the impact of neuropsychological impairment may moderate interventions for this population, and the extent to which skills to cope with neuropsychological problems may boost the potential efficacy of such interventions."

Study Aims and Hypotheses

The overarching question to be answered in this research was: To what extent do psychosocial factors — including neurocognitive impairment, drug use, and alcohol use — influence ART adherence, service utilization and VL at baseline and following an evidence-based intervention among HIV-positive alcohol abusers? Three study aims and accompanying hypotheses were proposed to facilitate answering this question:

Aim 1

To determine the degree to which alcohol use, drug use, time from HIV diagnosis to treatment, and years living with HIV affect three measures of neurocognitive functioning among HIV-seropositive adult alcohol abusers at a single time point.

- Hypothesis 1a: Greater alcohol, marijuana, and cocaine use will be associated with increased neurocognitive impairment.
- Hypothesis 1b: Living longer with HIV and waiting longer after HIV diagnosis to seek treatment will be associated with increased neurocognitive impairment.

Aim 2

To explore the degree to which stress, social support and barriers impact ART adherence and VL among HIV-seropositive adult alcohol users at baseline.

- Hypothesis 2a: Greater perceived stress will be associated with higher VL.
- Hypothesis 2b: Greater social support will be associated with lower VL.
- Hypothesis 2c: More barriers to adherence will be associated with higher VL.
- Hypothesis 2d: The above relationships with VL will be partially mediated by ART adherence.

- Hypothesis 2e: Relationships between psychosocial factors and outcomes of ART adherence and VL will be moderated by behavioral and cognitive variables: alcohol use, marijuana use and neurocognitive impairment.

Aim 3

To evaluate the effectiveness of the adapted Holistic Health Recovery Program (HHRP-A) on improving treatment adherence, service utilization and health outcomes (VL) among HIV-seropositive adult alcohol users.

- Hypothesis 3a: Greater improvement in ART adherence, VL, and service utilization will be observed in the experimental condition than in the comparison condition.
- Hypothesis 3b: Greater reduction in perceived stress and increase in social support will be observed in the experimental condition than in the comparison condition.

REFERENCES

Abgrall, S., & The Antiretroviral Therapy Cohort Collaboration (ART-CC). (2012). Durability of first ART regimen and risk factors for modification, interruption or death in HIV-positive patients starting ART in Europe and N. America 2002-2009. *AIDS*, *27*(5), 803–813.

Antinori, A., Arendt, G., Becker, J. T., Brew, B. J., Byrd, D. A., Cherner, M., … Wojna, V. E. (2007). Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*, *69*(18), 1789–99. doi:10.1212/01.WNL.0000287431.88658.8b

Applebaum, A. J., Reilly, L. C., Gonzalez, J. S., Richardson, M. A., Leveroni, C. L., & Safren, S. A. (2009). The impact of neuropsychological functioning on adherence to HAART in HIV-infected substance abuse patients. *AIDS Patient Care and STDs*, *23*(6), 455–62. doi:10.1089/apc.2008.0181

Applebaum, A. J., Richardson, M. A., Brady, S. M., Brief, D. J., & Keane, T. M. (2009). Gender and other psychosocial factors as predictors of adherence to highly active antiretroviral therapy (HAART) in adults with comorbid HIV/AIDS, psychiatric and substance-related disorder. *AIDS and Behavior*, *13*(1), 60–5. doi:10.1007/s10461-008-9441-x

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

Bangsberg, D., Hecht, F., Charlebois, E., Zolopa, A., Holodniy, M., Sheiner, L., … Moss, A. (2000). Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS*, *14*(4), 357–66.

Bangsberg, D., Perry, S., Charlebois, E., Clark, R., Roberston, M., Zolopa, A., & Moss, A. (2001). Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS*, *15*(9), 1181–1183.

Bangsberg, D. R., Moss, A. R., & Deeks, S. G. (2004). Paradoxes of adherence and drug resistance to HIV antiretroviral therapy. *The Journal of Antimicrobial Chemotherapy*, *53*(5), 696–9. doi:10.1093/jac/dkh162

Bass, J. K., Bornemann, T. H., Burkey, M., Chehil, S., Chen, L., Copeland, J. R. M., … Patel, V. (2012). A United Nations General Assembly Special Session for mental, neurological, and substance use disorders: the time has come. *PLoS medicine*, *9*(1), e1001159.

Bates, M. E., Bowden, S. C., & Barry, D. (2002). Neurocognitive impairment associated with alcohol use disorders: Implications for treatment. *Experimental and Clinical Psychopharmacology*, *10*(3), 193–212. doi:10.1037//1064-1297.10.3.193

Batki, S., Ferrando, S., Sorensen, J., & Wall, T. (1996). Psychiatric morbidity, illicit drug use and adherence to zidovudine (AZT) among injection drug users with HIV disease. *American Journal of Drug and Alcohol Abuse*, *22*(4), 475.

Baum, M. K., Rafie, C., Lai, S., Sales, S., Page, J. B., & Campa, A. (2010). Alcohol use accelerates HIV disease progression. *AIDS Research and Human Retroviruses*, *26*(5), 511–518.

Berg, K., & Demas, P. (2004). Gender differences in factors associated with adherence to antiretroviral therapy. *Journal of General Internal Medicine*, *19*, 1111–1117. Retrieved from http://onlinelibrary.wiley.com/doi/10.1111/j.1525-1497.2004.30445.x/full

Bing, E. G., Burnam, M. A., Longshore, D., Fleishman, J. A., Sherbourne, C. D., London, A. S., … Shapiro, M. (2001). Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. *Archives of General Psychiatry*, *58*(8), 721–8.

Bloom, D., Cafiero, E., Jane-Llopis, E., Abrahams-Gessel, S., Bloom, L., Fathima, S., … Weinstein, C. (2012). *The global economic burden of noncommunicable diseases*. Retrieved from http://ideas.repec.org/p/gdm/wpaper/8712.html

Bornstein, R. A, Fama, R., Rosenberger, P., Whitacre, C. C., Para, M. F., Nasrallah, H. a, & Fass, R. J. (1993). Drug and alcohol use and neuropsychological performance in asymptomatic HIV infection. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *5*(3), 254–9.

Bottonari, K. A, Tripathi, S. P., Fortney, J. C., Curran, G., Rimland, D., Rodriguez-Barradas, M., … Pyne, J. M. (2012). Correlates of antiretroviral and antidepressant adherence among depressed HIV-infected patients. *AIDS Patient Care and STDs*, *26*(5), 265–73. doi:10.1089/apc.2011.0218

Brady, K., & Sonne, S. (1999). The role of stress in alcohol use, alcoholism treatment, and relapse. *Alcohol Research & Health*, *24*(3), 263–271.

Braithwaite, R. S., & Bryant, K. J. (2000). Influence of Alcohol Consumption on Adherence to and Toxicity of Antiretroviral Therapy and Survival. *Alcohol Research & Health*, *33*(3), 280–287.

Broadhead, W., Gehlbach, S., & Kaplan, B. (1989). Functional versus structural social support and health care utilization in a family medicine outpatient practice. *Medical Care*, *27*(3), 221–233.

Bruce, R., & Altice, F. (2007). Clinical care of the HIV-infected drug user. *Infectious Disease*, *21*(1), 149–179.

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), 1465–507. doi:10.1080/10826080600846250

Bryant, K. J., Nelson, S., Braithwaite, R. S., & Roach, D. (2010). Integrating HIV/AIDS and alcohol research. *Alcohol Research & Health*, *33*(3), 167–178.

Buchsbaum, D., Buchanan, R. G., Centor, R. M., Schnoll, S. H., & Lawton, M. J. (1991). Screening for alcohol abuse using CAGE scores and likelihood ratios. *Annals of Internal Medicine*, *115*(10), 774–777.

Carpenter, C. C. J., Fischl, M. A., Hammer, S. M., Hirsch, M. S., Jacobsen, D. M., Katzenstein, D. A., … Volberding, P. A. (1997). Antiretroviral therapy for HIV infection in 1997: Updated recommendations of the International AIDS Society - USA Panel. *Journal of the American Medical Association*, *277*(24), 1962–1969.

Catz, S. L., Kelly, J. A., Bogart, L. M., Benotsch, E. G., & Mcauliffe, T. L. (2000). Patterns , Correlates , and Barriers to Medication Adherence Among Persons Prescribed New Treatments for HIV Disease. *Health Psychology*, *19*(2), 124–133. doi:10.1037//0278-

Centers for Disease Control and Prevention Division of HIV/AIDS. (2012a). Estimated HIV incidence in the United States, 2007–2010. *HIV Surveillance Supplemental Report 2012*, *17*(4). Retrieved from http://www.cdc.gov/hiv/surveillance/resources/reports/2010supp_vol17no4/

Centers for Disease Control and Prevention Division of HIV/AIDS. (2012b). *HIV Surveillance Report, 2010* (Vol. 22). Retrieved from http://www.cdc.gov/hiv/library/reports/surveillance/2011/surveillance_Report_vol_23.html

Chesney, M., Morin, M., & Sherr, L. (2000). Adherence to HIV combination therapy. *Social Science & Medicinee*, *50*(11), 1599–605.

Choopanya, K., Martin, M., Suntharasamai, P., Sangkum, U., Mock, P. A., Leethochawalit, M., ... & Vanichseni, S. (2013). Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir

Study): a randomised, double-blind, placebo-controlled phase 3 trial.*The Lancet*, *381*(9883), 2083-2090.

Churchill, M., & Nath, A. (2013). Where does HIV hide? A focus on the central nervous system. *Current opinion in HIV and AIDS*. doi:10.1097/COH.0b013e32835fc601

Cleary, P. D., Miller, M., Bush, T., Warburg, M. M., & Delbanco, Thomas L Aronson, M. D. (1988). Prevalence and recognition of alcohol abuse in a primary care population. *American Journal of Medicine, 85*(4), 466–471.

Cohen, M., Chen, Y., McCauley, M., Gamble, T., Hosseinipour, M., Kumarasamy, M., … Fleming, T. R. (2011). Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *New England Journal of Medicine*, *365*(6), 493–505.

Cohen, S., & McKay, G. (1985). Social support, stress and the buffering hypothesis: A theoretical analysis. In A. Baum, S. Talor, & J. Singer (Eds.), *Handbook of Psychology and Health* (pp. 253–266). Hillsdale, NJ.

Concha, M., Graham, N., Muñoz, A., Vlahov, D., Royal, W., Updike, M., & McArthur, J. (1992). Effect of chronic substance abuse on the neuropsychological performance of intravenous drug users with a high prevalence of HIV-1 seropositivity. *American Journal of Epidemiology*, *136*(11), 1338–1348.

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*, *33*(4), 521–5.

Cook, R., Sereika, S., Hunt, S., Woodward, W., Erlen, J., & Conigliaro, J. (2001). Problem drinking and medication adherence among persons with HIV infection. *Journal of General Internal Medicine*, *16*(2), 83–8.

Corless, I. B., Lindgren, T., Holzemer, W., Robinson, L., Moezzi, S., Kirksey, K., … Reynolds, N. (2009). Marijuana effectiveness as an HIV self-care strategy. *Clinical Nursing Research*, *18*(2), 172–93. doi:10.1177/1054773809334958

Das, M., Chu, P. L., Santos, G. M., Scheer, S., Vittinghoff, E., McFarland, W., & Colfax, G. N. (2010). Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. *PloS one*, *5*(6), e11068.

De Jong, B. C., Prentiss, D., McFarland, W., Machekano, R., & Israelski, D. M. (2005). Marijuana use and its association with adherence to antiretroviral therapy among HIV-infected persons with moderate to severe nausea. *Journal of Acquired Immune Deficiency Syndromes*, *38*(1), 43–6.

Deeks, S. G., Smith, M., Holodniy, M., & Kahn, J. O. (1997). HIV-1 protease inhibitors. A review for clinicians. *Journal of the American Medical Association*, *277*(2), 145–53.

Descamps, D., & Flandre, P. (2000). Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy. *Journal of the American Medical Association*, *283*(2), 205–212.

Diiorio, C., McCarty, F., Depadilla, L., Resnicow, K., Holstad, M. M., Yeager, K., … Lundberg, B. (2009). Adherence to antiretroviral medication regimens: a test of a psychosocial model. *AIDS and Behavior*, *13*(1), 10–22. doi:10.1007/s10461-007-9318-4

DiMatteo, M. R. (2004). Social support and patient adherence to medical treatment: a meta-analysis. *Health Psychology*, *23*(2), 207–18. doi:10.1037/0278-6133.23.2.207

Durvasula, R, Norman, L., & Malow, R. (2009). Current perspectives on the neuropsychology of HIV. In M. R. Pope C, White R (Ed.), *HIV/AIDS: Global Frontiers in Prevention/Intervention* (pp. 177–190). New York: Routledge.

Durvasula, RS, Miller, E., Myers, H., & Wyatt, G. (2001). Predictors of Neuropsychological Performance in HIV Positive Women. *Journal of Clinical and Expermental Neuropsychology*, *23*(2), 149–164.

Engel, G. L. (1977). The need for a new medical model: a challenge for biomedicine. Science, 196(4286), 129-136.

Farinpour, R., Martin, E. M., Seidenberg, M., Pitrak, D. L., Pursell, K. J., Mullane, K. M., … Harrow, M. (2000). Verbal working memory in HIV-seropositive drug users. *Journal of the International Neuropsychological Society*, *6*(5), 548–55.

Fleming, M. F., Manwell, L. B., Barry, K. L., & Johnson, K. (1998). At-risk drinking in an HMO primary care sample: prevalence and health policy implications. *American journal of public health*, *88*(1), 90–3.

Foley, J. M., Wright, M. J., Gooding, a L., Ettenhofer, M., Kim, M., Choi, M., … Hinkin, C. H. (2010). Operationalization of the updated diagnostic algorithm for classifying HIV-related cognitive impairment and dementia. *International psychogeriatrics / IPA*, *1991*, 1–9. doi:10.1017/S1041610210002085

Gandhi, N. S., Skolasky, R. L., Peters, K. B., Moxley, R. T., Creighton, J., Roosa, H. V., … Sacktor, N. (2011). A comparison of performance-based measures of function in HIV-associated neurocognitive disorders. *Journal of Neurovirology*, *17*(2), 159–65. doi:10.1007/s13365-011-0023-8

Gisslén, M., Price, R. W., & Nilsson, S. (2011). The definition of HIV-associated neurocognitive disorders: are we overestimating the real prevalence? *BMC Infectious Diseases*, *11*(1), 356. doi:10.1186/1471-2334-11-356

Gordillo, V., del Amo, J., Soriano, V., & González-Lahoz, J. (1999). Sociodemographic and psychological variables influencing adherence to antiretroviral therapy. *AIDS*, *13*(13), 1763–9.

Grant, I., Atkinson, J., Hesselink, J., Kennedy, C., Richman, D., Spector, S., & McCutchan, J. (1987). Evidence for early central nervous system involvement in the acquired immunodeficiency syndrome (AIDS) and other human immunodeficiency virus (HIV) infections. *Annals of Internal Medicine*, *107*, 828–836.

Gupta, J. Das, Satishchandra, P., Gopukumar, K., Wilkie, F., Waldrop-Valverde, D., Ellis, R., … Kumar, M. (2007). Neuropsychological deficits in human immunodeficiency virus type 1 clade C-seropositive adults from South India. *Journal of Neurovirology*, *13*(3), 195–202. doi:10.1080/13550280701258407

Heaney, C., & Israel, B. (1997). Social networks and social support. In K. Glanz, F. Marcus-Lewis, & B. Rimer (Eds.), *Health Behavior and Health Education: Theory, Research, and Practice* (2nd ed., pp. 179–205). San Francisco, CA: Jossey-Bass.

Heaton, R., Clifford, D., Franklin, D., Woods, S., Ake, C., Vaida, F., … Grant, I. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology*, *75*(23), 2087–96. doi:10.1212/WNL.0b013e318200d727

Heaton, R., Grant, I., Butters, N., White, D., Kirkson, D., Atkinson, J., … Kelly, M. (1995). The HNRC 500-neuropsychology of HIV infection at different disease stages. *Journal of the International Neuropsychological Society*, *1*(3), 231–251.

Heaton, R. K., Franklin, D. R., Ellis, R. J., McCutchan, J. A., Letendre, S. L., Leblanc, S., … Grant, I. (2011). HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *Journal of Neurovirology*, *17*(1), 3–16. doi:10.1007/s13365-010-0006-1

Hinkin, C., Castellon, S., & Durvasula, R. (2002). Medication adherence among HIV+ adults Effects of cognitive dysfunction and regimen complexity. *Neurology*, *59*(12), 1944–1950.

Hinkin, C. H., Barclay, T. R., Castellon, S. A, Levine, A. J., Durvasula, R. S., Marion, S. D., … Longshore, D. (2007). Drug use and medication adherence among HIV-1 infected individuals. *AIDS and Behavior*, *11*(2), 185–94. doi:10.1007/s10461-006-9152-0

Hinkin, C., & Hardy, D. (2004). Medication adherence in HIV-infected adults: effect of patient age, cognitive status, and substance abuse. *AIDS (London)*, *18*(Suppl 1), 1–13.

Holzemer, W. (1999). Predictors of self-reported adherence in persons living with HIV disease. *AIDS Patient Care and STDs*, *13*(3), 185–197.

House, J., & Kahn, R. (1985). Measures and concepts of social support. In S Cohen & S. Syme (Eds.), *Social Support and Health* (pp. 83–108). San Diego, CA: Academic Press.

Janssen, R., Nwanyanwu, O., Selik, R., & Stehr-Green, J. (1992). Epidemiology of human immunodeficiency virus encephalopathy in the United States. *Neurology*, *42*(8), 1472–1472.

Johnson, T., & Nath, A. (2011). Immune reconstitution inflammatory syndrome and the central nervous system. *Current Opinion in Neurology*, *24*(3), 284–90. doi:10.1097/WCO.0b013e328346be57

Justice, A. C., McGinnis, K. A., Atkinson, J. H., Heaton, R. K., Young, C., Sadek, J., … Simberkoff, M. (2004). Psychiatric and neurocognitive disorders among HIV-positive and negative veterans in care: Veterans Aging Cohort Five-Site Study. *AIDS*, *18 Suppl 1*(ext 5309), S49–59.

Justice, A., Dombrowski, E., & Conigliaro, J. (2006). Veterans aging cohort study (VACS): overview and description. *Medical Care*, *44*, 1–24. doi:10.1097/01.mlr.0000223741.02074.66.

Kalichman, S. C., Amaral, C. M., White, D., Swetsze, C., Kalichman, M. O., Cherry, C., & Eaton, L. (2012). Alcohol and adherence to antiretroviral medications: Interactive toxicity beliefs among people living with HIV. *The Journal of the Association of Nurses in AIDS Care*, *23*(6), 1–10. doi:10.1016/j.jana.2011.11.005

Katzenstein, D. A. (1997). Adherence as a particular issue with protease inhibitors. *The Journal of the Association of Nurses in AIDS Care*, *8 Suppl*, 10–7.

Knowlton, A. R., Hoover, D. R., Chung, S. E., Celentano, D. D., Vlahov, D., & Latkin, C. A. (2001). Access to medical care and service utilization among injection drug users with HIV/AIDS. *Drug and Alcohol Dependence*, *64*(1), 55–62.

Koopman, C., Gore-Felton, C., Marouf, F., Butler, L., Field, N., Gill, M., … Spiegel, D. (2000). Relationships of perceived stress to coping, attachment and social support among HIV-positive persons. *AIDS Care*, *12*(5), 663–672.

Korthuis, P. T., Zephyrin, L. C., Fleishman, J. A, Saha, S., Josephs, J. S., McGrath, M. M., … Gebo, K. a. (2008). Health-related quality of life in HIV-infected patients: the role of substance use. *AIDS Patient Care and STDsare and STDs*, *22*(11), 859–67. doi:10.1089/apc.2008.0005

Kuo, W.-H., Wilson, T. E., Weber, K. M., Madhava, V., Richardson, J., Delapenha, R., & Des Jarlais, D. (2004). Initiation of regular marijuana use among a cohort of women infected with or at risk for HIV in the Women's Interagency HIV Study (WIHS). *AIDS Patient Care and STDs*, *18*(12), 702–13. doi:10.1089/apc.2004.18.702

Liao, L., Xing, H., Su, B., Wang, Z., Ruan, Y., Wang, X., … Shao, Y. (2013). Impact of HIV drug resistance on virologic and immunologic failure and mortality in a cohort of patients on antiretroviral therapy in China. *AIDS*, *27*(11), 1815–24. doi:10.1097/QAD.0b013e3283611931

Lopez, O., Smith, G., Meltzer, C. C., & Becker, J. T. (1999). Dopamine systems in Human Immunodeficiency Virus-associated dementia. *Cognitive and Behavioral Neurology*, *12*(3), 184–192.

Lucas, G. M. (2005). Antiretroviral adherence, drug resistance, viral fitness and HIV disease progression: a tangled web is woven. *The Journal of Antimicrobial Chemotherapy*, *55*(4), 413–6. doi:10.1093/jac/dki042

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), 767–74.

Lucas, G. M., Griswold, M., Gebo, K.A, Keruly, J., Chaisson, R. E., & Moore, R. D. (2006). Illicit drug use and HIV-1 disease progression: a longitudinal study in the era of highly active antiretroviral therapy. *American Journal of Epidemiology*, *163*(5), 412–20. doi:10.1093/aje/kwj059

Malow, R., Devieux, J., Stein, J., Rosenberg, R., Lerner, B., Attonito, J., & Villalba, K. (2012). Neurological function, information-motivation-behavioral skills factors, and risk behaviors among HIV-positive alcohol users. *AIDS and Behavior*, *16*(8), 2297–308. doi:10.1007/s10461-012-0246-6

Martin, E. M., Pitrak, D. L., Weddington, W., Rains, N. A., Nunnally, G., Nixon, H., … Bechara, A. (2004). Cognitive impulsivity and HIV serostatus in substance dependent males. *Journal of the International Neuropsychological Society*, *10*(7), 931–8.

Mateen, F. J., & Mills, E. J. (2012). Aging and HIV-related cognitive loss. *Journal of the American Medical Association*, *308*(4), 349–50. doi:10.1001/jama.2012.8538

Mayer, K. H., & Krakower, D. (2012). Ideas and opinions Annals of Internal Medicine antiretroviral medication and HIV prevention : New Steps Forward and New Questions. *Annals of Internal Medicine*, *156*(9), 10–13.

McArthur, J. C. (2004). HIV dementia: an evolving disease. *Journal of Neuroimmunology*, *157*(1-2), 3–10. doi:10.1016/j.jneuroim.2004.08.042

McArthur, J. C., Steiner, J., Sacktor, N., & Nath, A. (2010). Human immunodeficiency virus-associated neurocognitive disorders: Mind the gap. *Annals of Neurology*, *67*(6), 699–714. doi:10.1002/ana.22053

McArthur, J., & Grant, I. (1998). HIV Neurocognitive. In H. Gendelman, S. Lipton, L. Epstein, & S. Swindells (Eds.), *The Neurology of AIDS* (pp. 499–523). New York: International Thompson Publishing.

Miller, L. (1993). Psychotherapy of the brain-injured patient: Reclaiming the shattered self. WW Norton & Co. Chicago

Mugavero, M. J., Raper, J. L., Reif, S., Whetten, K., Leserman, J., Thielman, N. M., & Pence, B. W. (2009). Overload: impact of incident stressful events on antiretroviral medication adherence and virologic failure in a longitudinal, multisite human immunodeficiency virus cohort study. *Psychosomatic Medicine*, *71*(9), 920–6. doi:10.1097/PSY.0b013e3181bfe8d2

Muthén, L.K. and Muthén, B.O. (1998-2012). Mplus User's Guide. Seventh Edition. Los Angeles, CA: Muthén & Muthén

Nel, A., & Kagee, A. (2011). Common mental health problems and antiretroviral therapy adherence. *AIDS Care*, *23*(11), 1360–5. doi:10.1080/09540121.2011.565025

Norman, L., Basso, M., Kumar, A., & Malow, R. (2009). Neuropsychological consequences of HIV and substance abuse: A literature review and implications for treatment and future research. *Current Drug Abuse Reviews*, *2*(2), 143–156.

O'Connor, P., Selwyn, P., & Schottenfeld, R. (1994). Medical care for injection-drug users with human immunodeficiency virus infection. *New England Journal of Medicine*, *331*(7), 450–459.

Palacio, M., Alvarez, S., & Munoz-Fernandez, M. (2012). HIV1 infection and neurocognitive impairment in the current era. *Reviews in Medical Virology*, *22*, 33–45. doi:10.1002/rmv

Parienti, J.-J., Das-Douglas, M., Massari, V., Guzman, D., Deeks, S. G., Verdon, R., & Bangsberg, D. R. (2008). Not all missed doses are the same: sustained NNRTI

treatment interruptions predict HIV rebound at low-to-moderate adherence levels. *PLoS ONE*, *3*(7), e2783. doi:10.1371/journal.pone.0002783

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

Piazza, P., & Moal, M. (1998). The role of stress in drug self-administration. *Trends in Pharmacological Sciences*, *19*(February), 67–74.

Prentiss, D., Power, R., Balmas, G., Tzuang, G., & Israelski, D. M. (2004). Patterns of marijuana use among patients with HIV/AIDS followed in a public health care setting. *Journal of Acquired Immune Deficiency Syndromes*, *35*(1), 38–45.

Reif, S., Mugavero, M., Raper, J., Thielman, N., Leserman, J., Whetten, K., & Pence, B. W. (2011). Highly stressed: stressful and traumatic experiences among individuals with HIV/AIDS in the Deep South. *AIDS Care*, *23*(2), 152–162.

Robertson, K. R., Smurzynski, M., Parsons, T. D., Wu, K., Bosch, R. J., Wu, J., … Ellis, R. J. (2007). The prevalence and incidence of neurocognitive impairment in the HAART era. *AIDS*, *21*(14), 1915–21. doi:10.1097/QAD.0b013e32828e4e27

Rothlind, J. C., Greenfield, T. M., Bruce, A. V, Dieter, J., Flenniken, D. L., Lindgren, J. A., & Michael, W. (2005). Heavy alcohol consumption in individuals with HIV infection: Effects on neuropsychological performance. *Journal of the International Neuropsychological Society*, *11*(1), 70–83.

Russell, M., Cooper, M., Frone, M., & Peirce, R. (1999). A longitudinal study of stress, alcohol, and blood pressure in community-based samples of blacks and non-blacks. *Alcohol Research and Health*, *23*(4), 299–307.

Sacktor, N. (2002). The epidemiology of human immunodeficiency virus-associated neurological disease in the era of highly active antiretroviral therapy. *Journal of neurovirology*, *8 Suppl 2*, 115–21. doi:10.1080/13550280290101094

Sacktor, N., McDermott, M. P., Marder, K., Schifitto, G., Selnes, O. A, McArthur, J. C., … Epstein, L. (2002). HIV-associated cognitive impairment before and after the advent of combination therapy. *Journal of Neurovirology*, *8*(2), 136–42. doi:10.1080/13550280290049615

Sacktor, N., Skolasky, R., Selnes, O. A, Watters, M., Poff, P., Shiramizu, B., … Valcour, V. (2007). Neuropsychological test profile differences between young and old human immunodeficiency virus-positive individuals. *Journal of Neurovirology*, *13*(3), 203–9. doi:10.1080/13550280701258423

Safren, S. A., Otto, M. W., Worth, J. L., Salomon, E., Johnson, W., Mayer, K., & Boswell, S. (2001). Two strategies to increase adherence to HIV antiretroviral medication: life-steps and medication monitoring. *Behaviour Research and Therapy*, *39*(10), 1151–62.

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. doi:10.1097/01.ALC.0000122103.74491.78

Samet, J., Phillips, S., Horton, N., Traphagen, E., & Freedberg, K. (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 and Behavior*, *11*(2), 195–203. doi:10.1007/s10461-006-9144-0

Selnes, O., Galai, N., McArthur, J., & Cohn, S. (1997). HIV Infection and Cognition in Intravenous Drug Users: Long-term Follow-up. *Neurology*, *48*, 227–229.

Sherer, R. (1998). Adherence and antiretroviral therapy in injection drug users. *Journal of the American Medical Association*, *280*(6), 567–8.

Sherbourne, C., & Stewart, A. (1991). The MOS Social Support Survey. *Social Science & Medicine*, *32*(6), 705–714.

Sherr, L., Clucas, C., Harding, R., Sibley, E., & Catalan, J. (2011). HIV and depression--a systematic review of interventions. *Psychology, Health & Medicine*, *16*(5), 493–527. doi:10.1080/13548506.2011.579990

Simioni, S., Cavassini, M., Annoni, J.-M., Rimbault Abraham, A., Bourquin, I., Schiffer, V., … Du Pasquier, R. A. (2010). Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS*, *24*(9), 1243–50. doi:10.1097/QAD.0b013e3283354a7b

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. doi:10.1037/0278-6133.25.1.74

Singh, N., Berman, S. M., Swindells, S., Justis, J. C., Mohr, J. A., Squier, C., & Wagener, M. M. (1999). Adherence of human immunodeficiency virus-infected patients to antiretroviral therapy. *Clinical infectious Diseases*, *29*(4), 824–30. doi:10.1086/520443

Tesoriero, J., French, T., Weiss, L., Waters, M., Finkelstein, R., & Agins, B. (2003). Stability of adherence to highly active antiretroviral therapy over time among clients enrolled in the treatment adherence demonstration project. *Journal of Acquired Immune Deficiency Syndromes*, *33*(4), 484–93.

Thompson, M., Aberg, J., & Hoy, J. (2012). Antiretroviral treatment of adult HIV infection 2012 recommendations of the International Antiviral Society–USA Panel. *Journal of the American Medical Association*, *308*(4).

Tozzi, V., Balestra, P., Bellagamba, R., Corpolongo, A., Salvatori, M. F., Visco-comandini, U., … Narciso, P. (2007). Persistence of neuropsychologic deficits despite long-term highly active antiretroviral therapy in patients prevalence and risk Factors. *Journal of Acquired Immune Deficiency Syndromes*, *45*(2), 174–182.

Tucker, J. S., Burnam, M. A., Sherbourne, C. D., Kung, F., & 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*, 573–580. doi:10.1016/S0002-9343(03)00093-7

Volkow, N., & Montaner, J. (2010). Enhanced HIV testing, treatment, and support for HIV-infected substance users. *Journal of the American Medical Association*, *303*(14), 1423–1424.

Waldrop-Valverde, D., Jones, D. L., Gould, F., Kumar, M., & Ownby, R. L. (2010). Neurocognition, health-related reading literacy, and numeracy in medication management for HIV infection. *AIDS Patient Care and STDs*, *24*(8), 477–84. doi:10.1089/apc.2009.0300

White, D., Heaton, R., & Monsch, A. (1995). Neuropsychological studies of asymptomatic Human Immunodeficiency Virus-Type-1 infected individuals. *Journal of the International Neuropsychological Society*, *1*(3), 304–315.

White House Office of AIDS Policy. *National HIV/AIDS Strategy Implementation Plan*. (2010). Washington, DC. Retrieved from http://www.whitehouse.gov/sites/default/files/uploads/NHAS.pdf

Wood, E., Kerr, T., & Marshall, B. (2009). Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: prospective cohort study. *British Medical Journal*, *338*. doi:10.1136/bmj.b1649

Woods, S. P., Moore, D. J., Weber, E., & Grant, I. (2009). Cognitive neuropsychology of HIV-associated neurocognitive disorders. *Neuropsychology Review*, *19*(2), 152–68. doi:10.1007/s11065-009-9102-5

Wright, M. J., Woo, E., Foley, J., Ettenhofer, M. L., Cottingham, M. E., Gooding, A. L., … Hinkin, C. H. (2011). Antiretroviral adherence and the nature of HIV- memory impairment. *Journal of Neurpsychiatry and Clinical Neurosciences*, *23*(3), 324–331.

CHAPTER II

METHODOLOGY

Using data from a parent study described below, the three following manuscripts mirror the three aims already described. Each paper draws from the same parent study, but each has a different sample size, utilizes a different set of measures and employs different analytic techniques. This dissertation study was approved by the Florida International University Institutional Review Board (IRB-13-0072) most recently on September 28, 2013.

Data Source

To address the research aims proposed in this dissertation, data were analyzed from an NIH-funded parent study conducted by Dr. Jessy G. Dévieux (and the late Dr. Robert Malow) titled "Intervening with HIV+ Alcohol Abusers: Influence of Neuro-Behavioral Factors" (1 R01 AA017405). Their longitudinal (12-month follow-up) randomized controlled trial attempted to reduce HIV sexual transmission risk and substance use in 370 alcohol-using, HIV+ individuals. The experimental condition included an adaptation of the Holistic Health Recovery Program (HHRP), an information-motivation-behavioral skills (IMB)-guided, evidence-based intervention for improving sexual risk and adherence outcomes for an HIV-positive addicted population (Margolin, Avants, Warburton, Hawkins, & Shi, 2003). In this dissertation's parent study, the intervention was adapted for use in a culturally diverse, alcohol-abusing sample. The adapted intervention (HHRP-A) is compared to a Health Promotion Comparison (HPC) condition, which addresses common health problems, including personal hygiene and healthy living.

HHRP was developed in recognition of the need to provide an intervention sensitive to neurobehavioral problems experienced in this population and was adapted for this AOD-abusing population because it is the only CDC-identified intervention for an HIV-positive, substance-abusing population that has been shown to reduce HIV transmission risk behaviors among PLWH (Margolin et al., 2003). Whereas the original HHRP addressed a methadone-maintained, drug abusing population, this adapted version was specifically geared toward alcohol users, within an AOD prevention approach. In developing HHRP-A, the research team attempted to achieve a reasonable balance between maintaining fidelity to the original HHRP and enhancing key characteristics to respond to the local context (e.g., community setting, clientele and cultural composition or history, resources, priorities). The HHRP intervention had been adapted and evaluated in multiple studies among diverse samples of HIV-positive drug users (Anand, Springer, Copenhaver, & Altice, 2010; Copenhaver, Bruce, & Altice, 2008; Copenhaver, Lee, Margolin, Bruce, & Altice, 2012; Copenhaver & Lee, 2006).

The primary aims of the parent study were to reduce sex and alcohol-related risk behaviors associated with HIV transmission. This dissertation research sought to explore secondary aims of the parent study — improving ART adherence and service utilization — which were also addressed in the intervention modules.

Participants

Recruitment sites were located in densely populated, multicultural, low-income, urban areas of South Florida, primarily Miami-Dade County, with high rates of AOD abuse, HIV, violence and poverty. The vast majority of the participants were uninsured with a disproportionate burden of chronic conditions associated with racial and ethnic

health disparities. Thirteen Community-Based Organizations (CBOs) serving the target population agreed to act as recruitment sites (see Appendix for list of sites). These CBOs were among the largest in the local area providing outpatient AOD abuse treatment programs and mental health services to HIV-positive men and women. Recruitment settings were selected from a wide range of nonacademic institutions, specialty and primary care, public and private facilities as per the National Institutes on Mental Health (NIMH) Therapeutic Effectiveness Protocol Development Program. The agencies providing outpatient mental health and alcohol and drug abuse treatment shared certain attributes: Each program was designed to promote progression from preliminary screening and biopsychosocial assessment to individually tailored addiction treatment; each program focused on helping patients achieve and maintain abstinence from alcohol, drugs, and sexual behaviors through case management and therapeutic activities; and the majority of clients at these sites represented families in the lowest socioeconomic class and received Medicaid benefits.

Intervention studies with a public health focus are designed to maximize generalizability of findings to broad populations, providers, and settings. They have broad sample inclusion and relatively few exclusion criteria. A total of 370 participants meeting inclusion/exclusion criteria were recruited from the study sites between January 2009 and November 2012. The parent study was designed to maximize generalizability of findings to broad populations, providers, and settings by including diverse subgroups representative of "real world" settings, and minimizing exclusion criteria. The inclusion criteria were: 1) living in Miami-Dade County; 2) being ≥18 and ≤60 years old; 3) being HIV-positive and willing to present documentation to confirm serostatus; having

consumed any alcohol in the past 3 months; and 4) having a history of alcohol abuse or dependence within the past 2 years. Further criteria included: 1) facility in English; 2) understanding of the informed consent process; 3) ability to provide contact information to be located for more interviews; 4) willingness to be randomized to a treatment or control group and to be contacted for follow-up assessments; 5) planning to be in the area for the next 12 months; 6) not facing immediate incarceration or residence in a restricted environment; and 7) currently not showing overt signs of major psychiatric disorder including psychosis or suicidality. In addition to the parent study's inclusion/exclusion criteria, Aims 2 and 3 of this dissertation research also required exclusion of participants who had not been prescribed ART. Information regarding ART prescription was collected at baseline of the parent study.

Compensation

Participants were offered decreasing compensation: $50 gift card for a local store upon completing the first assessment; $25 gift card for a local store upon completing post-assessment; $15 cash or gift card for attendance at each group session; and $5 cash for transportation.

Group Randomization

After participants completed the baseline assessment, they were entered into the study in cohorts of eight participants of the same gender from across the recruitment sites. Using randomized block design, cohorts were assigned to receive either the experimental or control condition according to a computer-generated random sequence. The random sequencing was expected to control for bias in subject assignments across

conditions. Treatment and comparison intervention sessions were scheduled to begin when baseline data collection was completed on a group.

To prevent cross-group contamination, each cohort group was staggered in time and space (sessions were scheduled to take place at alternating locations). Since participants came from different locations, there was a reduced possibility of cohorts interacting and thus discussing their respective experiences on site.

Treatment Condition: HHRP-A

HHRP is an interactive, cognitive-behavioral group intervention that includes components the CDC has specified as important for HIV-positive transmission risk reduction: 1) guided by behavioral theory; 2) focused on HIV transmission risk; 3) provided skill building and practice in coping or problem-solving skills; 4) included role-playing safer sex communication with partners; 5) delivered in settings in which PLWH receive services; 6) delivered in an intensive manner; and 7) including issues related to coping with HIV status and medication adherence. HHRP-A was guided by IMB Theory (Amico, Toro-Alfonso, & Fisher, 2005; Fisher, Fisher, Amico, & Harman, 2006; Starace, Massa, Amico, & Fisher, 2006) and contains intervention principles similar to those of Cognitive Behavioral Stress Management (CBSM), such as relaxation and coping skills training designed to reduce negative mood and slow disease progression. In addition, the group-based intervention is designed to promote interaction between participants so that they build positive social support networks with peers. Diffusing risk-reduction messages in peer-based social support networks may help to sustain benefits of HIV interventions (Latkin and Knowlton, 2006).

Group facilitators were staff similar in profile to staff at the CBO recruitment sites, per the design of the evidence-based HHRP. Facilitators had a bachelor or high school level education and were familiar with the study population. Participants attended eight 2-hour sessions scheduled twice a week over four consecutive weeks. The HHRP-A therapy manual was highly structured, and involves both didactic presentation of material and experiential exercise. Content matter was comprehensive in order to address the medical, emotional, and spiritual needs of PLWH. Topics addressed by HHRP-A included: 1) harm reduction skills training; 2) relapse prevention; 3) training to improve emotional, social, and spiritual health, including coping with stigma and grief; 4) techniques to increase medication adherence and improve participation in medical care; and 5) strategies for making healthy lifestyle choices including reducing HIV sexual transmission risk behavior (the original version of the intervention manual can be accessed at http://info.med.yale.edu/psych/3s/HHRP_manual.html; fact sheet in Appendix). Each session was co-facilitated by two trained counselors using a nonjudgmental, motivational enhancing therapeutic style (Miller & Rollnick, 1991).

Cognitive remediation strategies were incorporated because of the potential for cognitive impairment in this population. These strategies included: varied presentation modalities; repetition and review; behavioral games; memory books; reduction of distraction and fatigue; emphasis on structure and consistency; ongoing assessment of new learning and retention, with immediate provision of feedback; and stress management (Miller, 1993).

Treatment Condition: Health Promotion Comparison

The proposed randomized design compared the intervention approach of HHRP-A to a Health Promotion Comparison (HPC) condition. The HPC was not designed to provide the IMB-driven techniques of HHRP-A. This condition was meant to be educational and didactic, addressing common health problems, personal hygiene, nutrition, physical fitness, smoking avoidance/cessation, and healthy living. HPC did not incorporate behavioral skills training or motivational enhancement techniques and did not promote interaction or social support network development. HPC matched HHRP- A in total administration time and format (eight 2-hour sessions); however this modality was condensed and delivered over a period of only two days in order to reduce the risk of possible inflated effects in comparison group outcomes as a result of longer-term group involvement and attention. As in HHRP-A, HPC was guided by a written manual and implemented and held under the same conditions so as to produce equivalent expectancy of benefit and to control for effects that could be attributed to nonspecific features of HHRP-A.

A standard care HIV education component was included in the HPC, because it was deemed ethically irresponsible not to include some level of HIV education in a comparison condition, given the high-risk nature of this population. Thus, the first session of the HPC condition included a standard care level of HIV risk reduction, approaching what may be considered a "usual" care level that participants might expect to receive in a typical CBO program.

Data Collection

Several data-gathering techniques were utilized depending on the nature/content of the instrument, and a wide range of information was covered. Assessment methods included: 1) computer-assisted personal interview (CAPI); 2) audio computer-assisted self-interview for subjective sensitive topics (ACASI); 3) paper and pen as specified for neurological measures.

Measurement Instruments

The following instruments were used to measure constructs listed in the three aims. Below is a brief description of the measurement instruments. Additional information such as reliability and scoring is described in greater detail in the manuscripts that follow.

Years Living with HIV(Aim 1)

Years living with HIV is a single intake questionnaire item asking the year of HIV diagnosis. This value was subtracted from the year of intake to estimate number of years living with HIV.

Time from HIV Diagnosis to Seeking Care (Aim 1)

Time from HIV diagnosis to seeking care is an ordinal item from the Community Programs for Clinical Research on AIDS (CPCRA) asking "How soon after your positive test for HIV did you first go for medical care for your HIV?" (Mannheimer, Matts, Telzak, & Chesney, 2010). Response options included: (1) within 6 weeks; (2) 6-12 weeks; (3) 3-6 months; (4) 6-12 months; (5) more than a year; and (6) I have not gone for medical care for my HIV.

Alcohol and Drug Use (Aims 1 and 2)

Alcohol use, marijuana use and cocaine use were assessed using a calendar format called time line follow-back (TLFB; Carey, Carey, Maisto, Gordon, & Weinhardt, 2001; Weinhardt et al., 1998) to enhance accurate recall and to provide a continuous three month history for intensity of drug and alcohol consumption. In Aim 1, these variables were measured using three items from the TLFB: total number of "heavy drinking days" (defined as ≥ 5 drinks), total number of marijuana use days, and total number of cocaine use days. Aim 2 variables were measured by asking the total number of standard drinks consumed and total number of times using marijuana in the past 3 months.

Neurocognitive Instruments (Aims 1 and 2)

The Auditory Verbal Learning Test, University of California Los Angeles/World Health Organization Version (AVLT; Maj et al., 1994; Rey, 1964) is a test of immediate verbal memory capacity, retrieval efficiency, and learning. Fifteen words are read to the participant, requesting both immediate and longer-term recall. Scores for immediate recall, delayed recall, and percent of words retained can be derived. This study utilized the total of immediate recall scores for trials 1-5, with higher scores indicating greater functioning.

The Color Trails Test 2, Form A (CTT2; D'Elia, 1989; D'Elia, Satz, Uchiyama, & White, 1996; Lezak, 2004) is primarily a measure of executive functioning, but also assesses attention, information processing, psychomotor coordination and speed. CTT-2 requires the participant to connect encircled numbers 1 through 25, randomly arranged on a page, in proper order. CTT-2 shows all numbers twice and the participant must connect the numbers from 1 to 25, alternating between pink and yellow circles, disregarding the

numbers in circles of the alternate color. This analysis uses the raw time in seconds the participant needs to complete the test, with higher scores indicating poorer functioning.

The Category Test Short Form-Booklet Format (SCT; Halstead, 1947; Wetzel, 1987) measures executive function, assessing problem-solving ability by requiring the examinee to determine the organizing principle behind a series of visually presented stimuli, based on the correct or incorrect external feedback from the test administrator. This study uses the total raw error score derived, with higher scores indicating poorer functioning.

Barriers to ART Adherence (Aim 2)

Barriers to adherence is a self-report portion of the CPCRA that includes in its ART adherence assessment a section proposing reasons for participants' missing any doses of ART medication with 10 options provided; responses are dichotomous (Mannheimer et al., 2002). Options include: "I forget to take my pills;" "I was away from home;" and "I am too busy."

Social Support (Aims 2 and 3)

Social support was measured using 19 items from the Medical Outcomes Study (MOS; Sherbourne & Stewart, 1991). Questions concerned medical-related quality of life and included four functional support scales: emotional/informational, tangible, affectionate, and positive social interaction. Each item was rated from (1) "All of the time" to (5) "None of the time." For Aim 2 only four "tangible social support" subscale items were used. This functional subscale of the MOS asks the degree to which the participant believes s/he have available instrumental help with medical or daily living needs. The use of subscales increases sensitivity of the instrument (Sherbourne &

Stewart, 1991). The tangible support subscale was selected because of its strength of association with medication adherence (Gallant & Block, 1998; Gallant, 2003; Woloshin et al., 1993). For Aim 3, the overall social support index (total score) was used, with a higher score indicating more support.

Stress (Aims 2 and 3)

Stress was measured with 40 items modified from the Life Experiences Survey (LES; Sarason, Johnson, & Siegel, 1978) and the Life Events Questionnaire (Cohen et al., 1983). The first section lists 32 events common to people in a wide variety of situations and eight additional items address issues more specific to this population, such as their illness and alcohol use. Items were scored on an ordinal scale based upon the degree to which participants perceived impact of each event over the past three months. The first 32 items were two points each and the additional eight items offered three points each. Responses to all items were summed for a total stress score (continuous measure) with higher scores representing greater stress.

ART Adherence (Aims 2 and 3)

ART adherence was measured by the self-reported percentage of time ART medications were taken as prescribed over the course of a week, using a portion of the Community Programs for Clinical Research on AIDS (CPCRA; Mannheimer, Matts, Telzak, & Chesney, 2010). The adherence score was calculated as the mean of the combined total amount of each medication taken during the previous week, according to the scale: “all” (100%), “most” (75%), “about half” (50%), “few” (25%), or “none” (0%) (Mannheimer, Morse, John, & Andrews, 2006). In Aim 3, this measure was dichotomized as $< 95\%$ and $\geq 95\%$ average reported adherence.

Viral Load (Aims 2 and 3)

For Aim 2, documentation of recent RNA VL (collected by participant's own health care provider within one month from study intake) was supplied by the participant upon entry into the study. VL was log 10 transformed to accommodate the wide range of values for this variable. For Aim 3, VL was a self-report measure using a single question from the CPCRA (Mannheimer, Friedland, Matts, Child, & Chesney, 2002; McLellan et al., 1992). Participants were asked to "Indicate your viral load the last time it was measured" with available responses: (1) undetectable, (2) 50-500, (3) 501-5,000, (4) 5,001-10,000, (5) 10,001-30,000, (6) 30,001 or more, and (7) don't know. Self-reported measures of VL were significantly correlated with blood measures at baseline. This ordinal measure was dichotomized; percent reporting an undetectable VL was reported.

Service Utilization (Aim 3)

Service utilization was assessed using a section of the Treatment Services Review (TSR) portion of the CSAT-GPRA Client Outcome Measures for Discretionary Programs (McLellan et al., 1992; Mclellan et al., 1989). The TSR is an intake instrument designed for addictions treatment facilities. The section of the assessment used in this study consists of 52 items asking whether the participant is currently or has ever received services relevant to HIV-positive substance abusers: screening, recovery services, case management services, medical services, after care services, education services, and peer-based recovery support services. Three additional items from the CPCRA were included: 1) "Do you receive any financial assistance to buy medications (such as ADAP, Ryan White or other government or charitable agency)?"; 2) "Is there a clinic, health center,

doctor's office, or some other place that you usually go if you are sick or need medical care?"; and 3) "Do you have health insurance?"

Analysis

Basic descriptive statistics were calculated and reported for all variables in the three studies. In order to gain an understanding of the overall degree of NC impairment in this sample, single sample t-tests were conducted to compare mean raw NC scores with normative scores on each instrument. Norms for NC measures were obtained from professional manuals provided for the instruments (D'Elia et al., 1996; Mitrushino, Boone, Razan, & D'Elia, 2005; Van der Elst, van Boxtel, van Breukelen, & Jolles, 2005; Wetzel, 1987). Proportions of participants whose scores were 1 or more standard deviations below the norm and characteristics associated with this level of impairment were reported.

Aims 1 and 2 were cross-sectional studies, using multivariate linear regression to test hypothesized relationships between independent and dependent variables at a single time point. When using linear regression for testing baseline, non-recursive models the primary assumption is normal distribution of the data; however non-normal data can be analyzed with the use maximum likelihood estimation (Kline, 2012). MPlus version 5.1 was used (Muthen & Muthen, 1998-2012). This software includes functions such as robust maximum likelihood framework (MLR) and full information maximum likelihood (FIML) to accommodate non-normality, missing data, and distributional issues of the data (Yuan & Bentler, 2000). A limited information approach was used to obtain a rough approximation of sample size and statistical power, accounting for at least 5% variance in the outcome. This technique uses traditional power analysis software to gain a sense of

sample size demands (Jaccard & Wan, 1996). Sample sizes in this study were determined to yield a satisfactory power coefficient of > 0.95 for linear models with 10 predictors. After addressing all diagnostic statistics, the final hypothesized structural equation model was analyzed for its overall fit.

Aim 3 was a randomized controlled trial and analyses were conducted with SPSS version 20. Data were assessed for random missingness (MCAR) using Little's Missing Completely At Random Test (Allison, 2001; Little, 1988), and continuous quantitative missing values were imputed using the expectation maximization algorithm (Dempster, Laird, & Rubin, 1977). Change over time on continuous measures was analyzed using 2 X 3 or 4 repeated measures analyses of variance (ANOVAs) to account for treatment condition and time variables. Data not normally distributed were square root transformed. Where change over time in any continuous variable was detected, effect sizes (partial η^2) were reported if significant (Richardson, 2011). For the dichotomous variables, changes between each time point were analyzed using McNemar-Bowker tests (Bowker, 1948). Dichotomous variables were also cross-tabulated by treatment group at each time point using chi-square analyses. Rate ratios (RRs) and 95% confidence intervals (CIs) were presented. Significance criteria were Bonferroni-adjusted for number of analyses. Missing categorical data were not imputed. Finally, Spearman's rank correlation between baseline adherence and VL at T4 was calculated as a test of veracity and accuracy of the self-reported adherence measure (Margolin et al., 2003). Additional Spearman's rho and Pearson correlations between process and outcome variables, as appropriate, were calculated.

Theoretical Underpinnings

This three-manuscript style dissertation incorporates elements of different theoretical health promotion models. The first manuscript tests a biomedical model. NC outcomes are measured in context of their association with non-behavioral factors: exposure to factors known to promote NC impairment such as living with HIV, extended time off ART, drug use and alcohol use. The second manuscript is a baseline study utilizing a biopsychosocial model. This study examines the direct impact of psychosocial factors such as stress and social support on a biomedical outcome (VL) and also analyzes this relationship through the behavioral mediator of ART adherence. The third manuscript evaluates the effects of an intervention guided by the IMB model upon three outcomes: ART adherence, service utilization, and VL. Variables thought to act as processes toward the development of these outcomes are adopted from the social support stress buffering hypothesis.

Biopsychosocial Model

George Engel posited in 1977 that humans are biological, psychological, and social creatures who may consciously or unconsciously choose behaviors that can promote or harm their health (Borrell-Carrio, Suchman, & Epstein, 2004; Engel, 1977). The biopsychosocial model was adapted from the General Systems Theory (Bertalanffy, 1969), which states that all levels of an organization have linked relationships so that a change in one level affects changes in others (Mkanta & Uphold, 2006). In a comprehensive review of psychosomatic literature, researchers discussed key values within the psychosomatic model, proposing that multiple psychosocial factors may interact to promote or maintain illness and suggesting to the medical field that

interventions utilize not only biomedical but also cognitive, behavioral, and emotional strategies in dealing with disease (Novack et al., 2012). This holistic perspective is important when considering the recent interest in putting ART treatment to higher use in the prevention of HIV transmission. Not only is HIV transmission a function of behavioral, psychological, and cognitive influences, but adherence to treatments that aim to reduce VL are equally functions of these interacting factors.

The biopsychosocial model has been applied to many chronic diseases and several areas of HIV research (Mkanta & Uphold, 2006). For example, Hermann et al., (2008) suggested that the concept of ART adherence is dynamic and influenced by multiple biopsychosocial factors in order to survey the scope and determinants of non-adherence. Influential in social work, the biopsychosocial model is most often applied to suggest multimodal approaches to care. For example, in linking PLWH with NC impairment to care and services, multiple approaches — cognitive, biomedical, and psychosocial — have been recommended (Vance & Struzick, 2007). One such approach, a therapeutic technique called "cognitive remediation," is an important feature of the intervention examined in Aim 3 of this dissertation study (Miller, 1993). While the model has been used to offer a view of service/care utilization as a combination of biologic characteristics (e.g., genetic predisposition), psychological factors (e.g., lifestyle, stress), and social conditions (e.g., social support) in general medicine (Jones, Edwards, & Gifford, 2002; Rock et al., 1996), research using the model in HIV-specific care is lacking.

Information Motivation Behavioral (IMB) Model

Several models of health behavior change have been developed to better understand the interaction of biopsychosocial factors that influence HIV transmission,

prevention, and treatment. One theoretical framework that has effectively predicted HIV risk and preventive behavior in diverse samples and conditions is the IMB model (Fisher & Fisher, 1992). According to the IMB model, there are three fundamental determinants of ART adherence: knowledge of the ART regimen and associated recommendations; motivation to maintain ART adherence and low VL; and behavioral skills for performing the specific adherence behaviors. This model proposes that ART adherence information (e.g., ART regimen and side effects) and motivation (e.g., attitudes and beliefs about adherent and non-adherent behavior), through necessary behavioral skills (e.g., medication self-administration and side-effects minimization), will influence adherence-related health behaviors (Fisher, Amico, Fisher, & Harman, 2008).

Several empirical tests of the IMB model have been conducted and have established the strength of its three major constructs in predicting ART adherence (Amico, Toro-Alfonso, & Fisher, 2005; Starace, Massa, Amico, & Fisher, 2006). Alternately, the model has not consistently performed in predicting adherence, with particular weakness in defining and measuring the "motivation" construct (Amico et al., 2009; Rongkavilit et al., 2010). Like most models designed to explain health and risk behaviors, the IMB model requires precision in the definition of variables to be measured (Peltzer, Friend-du Preez, Ramlagan, & Anderson, 2010).

The IMB model has been tested in a broad range of populations, including college students (Fisher, Fisher, Williams, & Malloy, 1994), heroin injectors (Bryan, Fisher, Fisher, & Murray, 2000), severely mentally ill adults (Kalichman, Malow, Devieux, Stein, & Piedman, 2005), and adolescents (Kalichman et al., 2002). However, the

constructs are likely to be most generalizable when applied to a well-defined population (Kalichman et al., 2002).

In applying IMB to ART adherence, Fisher, Fisher, Amico & Harman (2006) proposed a model designed to explain adherence behaviors as a function of information and motivation operating through adherence behaviors. In their model, the outcome behavior of adherence was actually a mediator on the path to health outcomes such as CD4 + T-lymphocyte count and VL. This model also suggests that several moderating factors, such as mental health and substance use, may impact health outcomes.

Buffering Hypothesis of Social Support

Although adherence and VL outcomes have been examined via the Fisher et al., (2008) IMB model, additional processes through which these outcomes are hypothesized to evolve have been derived from the buffering hypothesis of social support (Cohen & McKay, 1985). The buffering model proposes that support protects persons from the potentially deleterious impact of stressful events. According to Cohen & McKay (1985), an alternative model suggests that social support has a positive effect regardless of whether a person is under stress. Evidence for this main effects model can be tested via a statistical analysis of support with no stress × support interaction. However, this study simply examines each variable's independent contributions to the outcomes of a longitudinal randomized controlled trial. Prior research examining direct impacts of social support and the buffering hypothesis has found that both reduction of stress and increasing social support are strongly predictive of ART adherence and service utilization outcomes (Catz et al., 2000; DiMatteo, 2004; Gonzalez et al., 2004; Mugavero et al.,

2009; Simoni, Frick, Lockhart, & Liebovitz, 2002; Simoni, Frick, et al., 2006; Wong, Sarkisian, Davis, Kinsler, & Cunningham, 2007).

REFERENCES

Allison, P. (2001). *Missing Data*. (pp. 3-5). Thousand Oaks: SAGE Publications.

Amico, K R, Toro-Alfonso, J., & Fisher, J. (2005). An empirical test of the information, motivation and behavioral skills model of antiretroviral therapy adherence. *AIDS Care*, *17*(6), 661–73. doi:10.1080/09540120500038058

Amico, K Rivet, Barta, W., Konkle-Parker, D. J., Fisher, J. D., Cornman, D. H., Shuper, P. A, & Fisher, W. A. (2009). The information-motivation-behavioral skills model of ART adherence in a Deep South HIV+ clinic sample. *AIDS and Behavior*, *13*(1), 66–75. doi:10.1007/s10461-007-9311-y

Anand, P., Springer, S., Copenhaver, M., & Altice, F. (2010). Neurocognitive impairment and HIV risk facotrs: A reciprocal relationship. *AIDS and Behavior*, *14*(6), 1213–1226. doi:10.1007/s10461-010-9684-1.Neurocognitive

Bertalanffy, L. Von. (1969). *General Systems Theory: Foundations, Development, Applications*. New York: G. Braziller.

Borrell-Carrio, F., Suchman, A. L., & Epstein, R. M. (2004). The Biopsychosocial Model 25 years later: principles, practice, and scientific inquiry. *Annals of Family Medicine*, *2*(6), 576–582. doi:10.1370/afm.245.

Bowker, A. H. (1948). A Test for Symmetry in Contingency Tables. *Journal of the American Statistical Association*, *43*(244).

Bryan, A. D., Fisher, J. D., Fisher, W. A., & Murray, D. M. (2000). Understanding condom use among heroin addicts in methadone maintenance using the information-motivation-behavioral skills model. *Substance Use & Misuse*, *35*(4), 451–71.

Carey, M. P., Carey, K. B., Maisto, S. A., Gordon, C. M., & Weinhardt, L. S. (2001). Assessing sexual risk behaviour with the Timeline Followback (TLFB) approach: continued development and psychometric evaluation with psychiatric outpatients. *International Journal of STD & AIDS*, *12*(6), 365–375. doi:10.1258/0956462011923309

Catz, S. L., Kelly, J. A., Bogart, L. M., Benotsch, E. G., & Mcauliffe, T. L. (2000). Patterns , Correlates , and Barriers to Medication Adherence Among Persons Prescribed New Treatments for HIV Disease. *Health Psychology*, *19*(2), 124–133. doi:10.1037//0278-

Cohen, S., & McKay, G. (1985). Social support, stress and the buffering hypothesis: A theoretical analysis. In A. Baum, S. Talor, & J. Singer (Eds.), *Handbook of Psychology and Health* (pp. 253–266). Hillsdale, NJ.

Copenhaver, M., Bruce, R., & Altice, F. (2008). Behavioral cousneling content for optimizing the use of buprenorphine for treatment of opioid dependence in community-based settings: A review of the empirical evidence. *American Journal of Drug and Alcohol Abuse*, *33*(5).

Copenhaver, M., Lee, I.-C., Margolin, A., Bruce, R., & Altice, F. (2012). Testing an optimized community-based HIV risk reduction and antiretroviral adherence intervention for HIV-infected injection drug users. *Substance Abuse*, *32*(1), 16–26. doi:10.1080/08897077.2011.540466.Testing

Copenhaver, M. M., & Lee, I.-C. (2006). Optimizing a community-friendly HIV risk reduction intervention for injection drug users in treatment: a structural equation modeling approach. *Journal of Urban Health*, *83*(6), 1132–42. doi:10.1007/s11524-006-9090-1

D'Elia L, S. P. (1989). *Color Trails 1 and 2*. Odessa, FL: Psychological Assessment Resources.

D'Elia, L., Satz, P., Uchiyama, C., & White, T. (1996). *Color Trails Test professional manual*. Odessa, FL: Psychological Assessment Resources.

Dempster, A. P., Laird, N. M., & Rubin, D. B. (1977). Maximum likelihood from incomplete data via the EM algorithm. *Journal of the Royal Statistical Society*, *Series B (*, 1–38.

DiMatteo, M. R. (2004). Social support and patient adherence to medical treatment: a meta-analysis. *Health Psychology*, *23*(2), 207–18. doi:10.1037/0278-6133.23.2.207

Fisher, J D, & Fisher, W. A. (1992). Changing AIDS-risk behavior. *Psychological Bulletin*, *111*(3), 455–74.

Fisher, J., Fisher, W., Williams, S., & Malloy, T. (1994). Empirical tests of an information-motivation-behavioral skills model of AIDS-preventive behavior with gay men and heterosexual university students. *Health Psychology*, *13*(3), 238–50.

Fisher, Jeffrey D, Amico, K. R., Fisher, W. A., & Harman, J. J. (2008). The information-motivation-behavioral skills model of antiretroviral adherence and its applications. *Current HIV/AIDS Reports*, *5*(4), 193–203.

Fisher, Jeffrey D, Fisher, W. A., Amico, K. R., & Harman, J. J. (2006). An information-motivation-behavioral skills model of adherence to antiretroviral therapy. *Health Psychology*, *25*(4), 462–73. doi:10.1037/0278-6133.25.4.462

Gonzalez, J. S., Penedo, F. J., Antoni, M. H., Durán, R. E., McPherson-Baker, S., Ironson, G., … Schneiderman, N. (2004). Social support, positive states of mind, and HIV treatment adherence in men and women living with HIV/AIDS. *Health Psychology*, *23*(4), 413–8. doi:10.1037/0278-6133.23.4.413

Halstead, W. (1947). *Brain and Intelligence*. Chicago: University of Chicago Press.

Herrmann, S., McKinnon, E., John, M., Hyland, N., Martinez, O. P., Cain, A., … Mallal, S. (2008). Evidence-based, multifactorial approach to addressing non-adherence to antiretroviral therapy and improving standards of care. *Internal Medicine Journal*, *38*(1), 8–15. doi:10.1111/j.1445-5994.2007.01477.x

Jaccard, J., & Wan, C. (1996). *LISREL approaches to interaction effects in multiple regression*. Thousand Oaks, CA: Sage Publicaations.

Jones, M., Edwards, I., & Gifford, L. (2002). Conceptual models for implementing biopsychosocial theory in clinical practice. *Manual Therapy*, *7*(1), 2–9. doi:10.1054/math.2001.0426

Kalichman, S, Stein, J., Malow, R., Averhart, J., Devieux, J., Jennings, T., … Feaster, D. (2002). Predicting protected sexual behaviour using the information-motivation-behaviour skills model among adolescent substance abusers in court-ordered treatment. *Psychology, Health & Medicine*, *7*(3), 327–338.

Kalichman, Seth, Malow, R., Devieux, J., Stein, J. A., & Piedman, F. (2005). HIV risk reduction for substance using seriously mentally ill adults: test of the information-motivation-behavior skills (IMB) model. *Community Mental Health Journal*, *41*(16131007), 277–290.

Latkin, C. A., & Knowlton, A. R. (2005). Micro-social structural approaches to HIV prevention: a social ecological perspective. *AIDS Care, 17*(S1), 102-113.

Lezak, M. (2004). *Neuropsychological Assessment* (4th ed.). New York: Oxford University Press.

Little, R. J. (1988). A Test of Missing Completely at Random for Multivariate Data with Missing Values. *Journal of the American Statistical Association*, *83*(404), 1198–1202.

Maj, M., Satz, P., Janssen, R., Zaudig, M., Starace, F., Schulte, G., & Sartorius, N. (1994). WHO Neuropsychiatric AIDS Study, Cross-sectional Phase II. *Archives of General Psychiatry*, *51*, 51–61.

Mannheimer, S. B., Morse, E., John, P., & Andrews, L. (2006). Sustained benefit from a long-term antiretroviral adherence intervention. *Journal of Acquired Immune Deficiency Syndromes*, *43*, 41–47.

Mannheimer, SB, Matts, J., Telzak, E., & Chesney, M. (2010). Psychological and Socio-medical Aspects of AIDS / HIV Quality of life in HIV-infected individuals receiving antiretroviral therapy is related to adherence. *AIDS Care*, *17*(1), 10–22.

Mannheimer, Sharon, Friedland, G., Matts, J., Child, C., & Chesney, M. (2002). The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. *Clinical Infectious Diseases*, *34*(8), 1115–21. doi:10.1086/339074

Margolin, A., Avants, S., Warburton, L., Hawkins, K., & Shi, J. (2003). A randomized clinical trial of a manual-guided risk reduction intervention for HIV-positive injection drug users. *Health Psychology*, *22*(2), 223–228. doi:10.1037/0278-6133.22.2.223

McLellan, A., Alterman, A., Cacciola, J., Metzger, D., & O'Brien, C. (1992). A new measure of substance abuse treatment initial studies of the treatment services review. *The Journal of Nervous and Mental Disease*, *180*(2), 101–110.

Mclellan, A. T., Zanis, D., Incmikoski, R., Parikh, G., Stevens, G., & Brock, M. (1989). *Administration Manual for the Treatment Services Review "TSR."* Washington, DC.

Miller, L. (1993). *Psychotherapy of the Brain-Injured Patient: Reclaiming the Shattered Self*. WW Norton & Co. Inc.

Miller, W., & Rollnick, S. (1991). *Motivational Interviewing: Preparing People to Change Addictive Behavior*. New York: Guilford Press.

Mitrushino, M., Boone, K., Razan, J., & D'Elia, L. (2005). *Handbook of Normative Data for Neuropsychological Assessment* (2nd ed., pp. 359–882). New York: Oxford University Press.

Mkanta, W. N., & Uphold, C. R. (2006). Theoretical and methodological issues in conducting research related to health care utilization among individuals with HIV infection. *AIDS Patient Care and STDs*, *20*(4), 293–303. doi:10.1089/apc.2006.20.293

Mugavero, M. J., Raper, J. L., Reif, S., Whetten, K., Leserman, J., Thielman, N. M., & Pence, B. W. (2009). Overload: impact of incident stressful events on antiretroviral medication adherence and virologic failure in a longitudinal, multisite human immunodeficiency virus cohort study. *Psychosomatic Medicine*, *71*(9), 920–6. doi:10.1097/PSY.0b013e3181bfe8d2

Novack, D. H., Cameron, O., Epel, E., Ader, R., Waldstein, S. R., Levenstein, S., … Wainer, A. R. (2012). Psychosomatic medicine: the scientific foundation of the biopsychosocial model. *Academic Psychiatry*, *31*(5), 388–401. doi:10.1176/appi.ap.31.5.388

Peltzer, K., Friend-du Preez, N., Ramlagan, S., & Anderson, J. (2010). Antiretroviral treatment adherence among HIV patients in KwaZulu-Natal, South Africa. *BMC Public Health*, *10*(1), 111. doi:10.1186/1471-2458-10-111

Rey, A. (1964). *L'examen Clinique en Psychologie*. Paris: Universitaires de France.

Richardson, J. T. E. (2011). Eta squared and partial eta squared as measures of effect size in educational research. *Educational Research Review*, *6*(2), 135–147. doi:10.1016/j.edurev.2010.12.001

Rock, B., Goldstein, M., Harris M, Kaminsky, P., Quitkin, E., Auerbach, C., & Beckerman, N. (1996). A biopsychosocial approach to predicting resource utilization in hospital care of the frail elderly. *Social Work in Health Care*, *22*(3), 21–37.

Rongkavilit, C., Naar-King, S., Kaljee, L. M., Panthong, A., Koken, J. A, Bunupuradah, T., & Parsons, J. T. (2010). Applying the information-motivation-behavioral skills model in medication adherence among Thai youth living with HIV: a qualitative study. *AIDS Patient Care and STDs*, *24*(12), 787–94. doi:10.1089/apc.2010.0069

Sarason, I., Johnson, J., & Siegel, J. (1978). Assessing the impact of life changes: Development of the Life Experiences Survey. *Journal of Consulting and Clinical Psychology*, *46*(5), 392–46.

Sherbourne, C., & Stewart, A. (1991). The MOS Social Support Survey. *Social Science & Medicine*, *32*(6), 705–714.

Simoni, J. M., Frick, P. A, Lockhart, D., & Liebovitz, D. (2002). Mediators of social support and antiretroviral adherence among an indigent population in New York City. *AIDS Patient Care and STDs*, *16*(9), 431–9. doi:10.1089/108729102760330272

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. doi:10.1037/0278-6133.25.1.74

Starace, F., Massa, A., Amico, K. R., & Fisher, J. D. (2006). Adherence to antiretroviral therapy: an empirical test of the information-motivation-behavioral skills model. *Health Psychology*, *25*(2), 153–62. doi:10.1037/0278-6133.25.2.153

Van der Elst, W., van Boxtel, M. P. J., van Breukelen, G. J. P., & Jolles, J. (2005). Rey's verbal learning test: normative data for 1855 healthy participants aged 24-81 years and the influence of age, sex, education, and mode of presentation. *Journal of the International Neuropsychological Society*, *11*(3), 290–302. doi:10.1017/S1355617705050344

Vance, D., & Struzick, T. (2007). Addressing risk factors of cognitive impairment in adults aging with HIV. *Journal of Gerontological Social Work*, *49*(4), 51–77.

Weinhardt, L. S., Carey, M. P., Maisto, S. A., Carey, K. B., Cohen, M. M., & Wickramasinghe, S. M. (1998). Reliability of the timeline follow-back sexual behavior interview. *Annals of Behavioral Medicine*, *20*(1), 25–30.

Wetzel L, B. T. (1987). *Short Category Test, Booklet Format*. Los Angeles: Western Psychological Services.

Wong, M. D., Sarkisian, C. A, Davis, C., Kinsler, J., & Cunningham, W. E. (2007). The association between life chaos, health care use, and health status among HIV-infected persons. *Journal of General Internal Medicine*, *22*(9), 1286–91. doi:10.1007/s11606-007-0265-6

Yuan, K., & Bentler, P. (2000). Three likelihood-based methods for mean and covariance structure analysis with nonnormal missing data. *Sociological Methodology*, *30*(1), 165–200.

CHAPTER III

TRANSITION TO MANUSCRIPT 1

This dissertation is written in manuscript style with three publishable articles. To adhere to word limits typically expected by journal editors, the manuscripts report only the most essential outcomes. It is important to note additional exploration conducted in the process of reaching the final model presented in Manuscript 1. These explorations did not yield significant outcomes and so, while informative, were not included in the final manuscript.

Latent variable analysis: A strategy of using the three neurocognitive (NC) functioning variables (memory, attention and executive functioning) as indicators of one latent variable was considered. However, limited information analyses revealed that these variables were differentially related to other constructs in the model and this strategy was abandoned. It was instead decided to leave the three NC factors as conceptually distinct variables. Residual terms for these three factors were instead correlated, based upon modifications recommended by the statistical software.

Testing for moderation: Interaction analyses were pursued to identify and examine significant differences in the model path coefficients as a function of duration of HIV infection (i.e., duration of HIV was considered the moderator). Product terms were introduced into the model for all relevant paths (Jaccard & Turrisi, 2003) and included: alcohol use x HIV exposure, marijuana use x HIV exposure, and cocaine use x HIV exposure. Single degree of freedom interaction contrasts were performed to compare the effects of each drug/alcohol use variable on each of the three NC variables as a function of HIV exposure. Although statistically significant interaction contrasts were identified,

the decision was made to not interpret these findings because there seemed to be evidence of a suppressor effect. Specifically, the path coefficient between reported alcohol use and memory variables was positive (greater alcohol use was associated with better memory) among those not receiving ART. Conversely, the correlation matrix revealed that these same variables were marginally correlated in the expected direction (greater alcohol use was associated with poorer memory). This reversal provided evidence of a possible suppressor effect—i.e. when a moderating variable that has a zero correlation with the dependent variable still, paradoxically, contributes to the predictive validity of the independent variable. All product terms were excluded from the final model.

Reference

Jaccard, J., & Turrisi, R. (2003). *Interaction Effects in Multiple Regression* (2nd ed.). Thousand Oaks, CA: Sage Publications.

MANUSCRIPT 1: EXPLORING FACTORS ASSOCIATED WITH NEUROCOGNITIVE IMPAIRMENT AMONG PEOPLE LIVING WITH HIV/AIDS

ABSTRACT

Purpose/Aims: Neurocognitive (NC) impairment continues to occur among people living with HIV (PLWH). Alcohol and other drug (AOD) abuse may further affect NC functioning. This study assesses the degree to which AOD use, time from HIV diagnosis to treatment, and years living with HIV affect three areas of neurocognitive functioning among HIV-seropositive adult alcohol abusers at a single time point.

Methods: The outcome of NC functioning in 370 PLWH living in Miami-Dade County was assessed using: the Auditory Verbal Learning Test (AVLT; UCLA/WHO version), the Category Test Short Format (SCT), and the Color Trails Test 2 (CTT2) which measures several executive functions including information processing. Participants reported the number of days using alcohol, marijuana and cocaine over the previous three months using a calendar format. Years living with HIV infection was a single item continuous measure and time from HIV diagnosis to seeking care was a categorical single item measure. A Bivariate linear regression and multivariate linear regression were used to test associations between independent and dependent variables.

Results: Mean scores on NC measures for this population were significantly lower than mean normative scores; 39% of participants displayed NC impairment $\geq$1 standard deviation below normative sample means on >2 NC tests. No significant associations were found between alcohol or cocaine use and any NC measure. Marijuana use was associated with CTT2 in the bivariate analysis (β=1.031; p=0.007). In multivariate

analysis, each day of marijuana use and year living with HIV were associated with a .32 (p=0.05) point and 1.18 (p=0.03) point poorer performance score on the CTT2, respectively.

Conclusion: Outcomes from this study suggest that both marijuana use and duration of HIV infection may impair cognitive functioning among PLWH in ways that may impair their ability to follow important treatment recommendations.

Key Words: HIV, neurocognitive, alcohol, marijuana, cocaine

INTRODUCTION

Since the introduction of highly active antiretroviral therapy (ART), the incidence of HIV-associated dementia has declined from 10%-15% to rates of 2%-5% of people living with HIV (PLWH; Heaton et al., 2010; Robertson et al., 2007; Sacktor, 2002). However, milder forms of HIV-associated neurocognitive disorders (HAND) have been reported in up to 40% of this population, in part because HIV-positive individuals are living longer with the disease (Antinori et al., 2007; Durvasula, Norman, & Malow, 2009; McArthur, 2004; Sacktor, 2002; Sacktor et al., 2007).

HAND, ranging from asymptomatic neurocognitive impairment to profoundly disabling HIV-associated dementia (Antinori et al., 2007), are mostly seen in advanced stages of HIV disease but can occur even in PLWH who have medically asymptomatic HIV infection (Grant et al., 1987; Heaton et al., 1995; White, Heaton, & Monsch, 1995). While increased exposure to the virus, particularly during the acute phase of HIV infection, is associated with neurocognitive (NC) impairment, HAND has been observed to varying degrees even among PLWH who have consistently maintained low-to-undetectable viral loads on ART (Simioni et al., 2010; Tozzi et al., 2007).

HAND can express clinically as impairment in episodic memory, information processing, attention, and executive functions (Woods et al., 2009). In patients presenting with even milder forms of HAND, quality of life can be greatly affected, with individuals suffering from difficulties in ability to perform activities of daily living, personal health care management, medication management and controlling risk behaviors (Hinkin et al., 2002; Malow et al., 2012; McArthur, 2004).

Abuse of alcohol and other drugs frequently co-occurs with HIV and may further impair NC functioning (Substance Abuse and Mental Health Services Administration, 2011; Volkow, 2012). More than 50% of HIV-infected patients in clinic-based samples have reported illicit drug and heavy alcohol use (Bing et al., 2001; Martin et al., 2004; Samet et al., 2004) with marijuana and cocaine reported as the most commonly used illicit substances among PLWH (Cook et al., 2001; Korthuis et al., 2008; Kuo et al., 2004). Negative effects of HIV and heavy drug or alcohol use together have been observed to affect synergistically NC functioning and the progression of HAND (Anthony, Arango, Stephens, Simmonds, & Bell, 2007; Nath, Maragos, Avison, Schmitt, & Berger, 2001; Rothlind et al., 2005). Among individuals with HIV infection and drug and alcohol use disorders, impaired verbal working memory, impaired auditory working memory, and enhanced cognitive impulsivity have been observed (Farinpour et al., 2000; Martin et al., 2004). These cognitive functions are associated with the higher-order thinking required to conduct safer sex practices and health management behaviors such as ART adherence (Bryant, 2006; Hinkin et al., 2002; Meade, Conn, Skalski, & Safren, 2011; Rothlind et al., 2005).

Abuse of alcohol and other drugs has been shown to play a possible confounding role in the assessment of NC impairment among PLWH (Justice et al., 2004). In order to deliver targeted and effective clinical care, as well as HIV risk reduction and treatment adherence interventions, it is important to understand specific domains of impairment associated with exposure to HIV and the use of commonly abused substances such as alcohol, marijuana and cocaine. By testing a biomedical model with structural equation modeling, this study seeks to explore direct relationships between exposure to HIV and

degree of alcohol and drug use upon several major domains of NC functioning including memory, information processing, attention, and executive function.

METHODS

Study Design

This study employed a cross-sectional design, utilizing baseline data gathered between 2009 and 2012 as part of a prospective randomized controlled trial for HIV-positive, adult alcohol users (R01 AA017405). Participants (N=370) were recruited from 13 community-based organizations in densely populated, multicultural, low-income areas of Miami-Dade County, Florida with high rates of alcohol use and HIV. The inclusion criteria were: being 18 to 60 years old; being HIV-positive; having consumed any alcohol in the past 3 months; and having a history of alcohol abuse or dependence within the past 2 years. Further criteria included facility in English, ability to understand the informed consent, planning to be in the area for the next 12 months, and currently not showing overt signs of any major psychiatric disorder, including psychosis or suicidality.

Several data-gathering techniques were utilized depending on the nature and content of the instrument being administered. Assessment methods consisted of: 1) computer-assisted personal interview (CAPI); 2) audio computer-assisted self-interview for subjective sensitive topics (ACASI); 3) paper and pen as specified for neurological measures and time line follow back (TLFB).

Measures: Independent Variables

"Years living with HIV" was measured as a single intake questionnaire item asking the year they received their first HIV-positive test. This value was subtracted from the year of intake to calculate number of years living with HIV.

Time from HIV diagnosis to seeking care was an ordinal item from the Community Programs for Clinical Research on AIDS (CPCRA; Mannheimer, Matts, Telzak, & Chesney, 2010) asking "How soon after your positive test for HIV did you first go for medical care for your HIV?" Response options were: (1) within 6 weeks; (2) 6-12 weeks; (3) 3-6 months; (4) 6-12 months; (5) more than a year; and (6) I have not gone for medical care for my HIV. This final response option did not provide an interval time measurement. Two participants selecting option (6) had been diagnosed at least one year before interview and were classified as option (5) and one participant had been diagnosed recently so this response was coded as "missing."

Alcohol use, marijuana use and cocaine use were assessed by TLFB using a calendar format to enhance accurate recall and to provide a continuous three-month history for intensity of drug and alcohol consumption. These variables were measured using three items from the TLFB: total number of "heavy drinking days" (defined as ≥ 5 drinks), total number of marijuana use days, and total number of cocaine use days. Up to three months' recall of alcohol and other drug use has proved to provide reliable data (Schroder, Carey, & Vanable, 2003). TLFB has strong agreement with other measures of AOD use and has reliability measures ranging from 0.75 to 0.90 (Fals-Stewart, O'Farrell, Freitas, McFarlin, & Rutigliano, 2000).

Measures: Dependent (Outcome) Variables

A battery of three neuropsychological tests was administered to derive scores in various cognitive domains, including memory and executive functions. These domains were selected for importance to the parent study intervention and outcomes in this study. For example, executive functions assess problem-solving skills and the ability to change behavior based on external feedback, whereas information processing and memory are related to comprehending, retaining, and applying instructions such as medical advice and medication dosing (Lezak, 2004). The tests selected have been used in previous studies with HIV-positive users of alcohol, marijuana and cocaine (Di Sclafani, Tolou-Shams, Price, & Fein, 2002; Durvasula et al., 2001; Maj et al., 1994; Mason et al., 1998; Messinis, Kyprianidou, Malefaki, & Papathanasopoulos, 2006; Rothlind et al., 2005) and have well-developed norms, high reliability and high validity (Basso & Bornstein, 2000; Bono et al., 1996; Selnes et al., 1997; Stern, Silva, Chaisson, & Evans, 1996). Raw NC scores were analyzed; unadjusted NC measures provide better ecological validity when scores are not intended to diagnose "impairment" in the sample (Silverberg & Millis, 2009).

The Auditory Verbal Learning Test, University of California Los Angeles/World Health Organization Version (AVLT; Maj et al., 1994; Rey, 1964) measures immediate verbal memory capacity, retrieval efficiency, and learning. Fifteen words were read to the participant, requesting both immediate and longer-term recall. Scores for immediate recall, delayed recall, and percent of words retained can be derived. This study utilized the total of immediate recall scores for trials 1-5, with higher scores indicating greater

functioning. This instrument demonstrated high test-retest reliability, with alpha scores ranging from 0.51 to 0.72 (Lezak, 2004).

The Color Trails Test 2, Form A (CTT2; D'Elia, 1989; D'Elia, Satz, Uchiyama, & White, 1996; Lezak, 2004) is primarily a measure of attention, cognitive flexibility, information processing, and psychomotor speed. CTT-2 requires the participant to connect encircled numbers 1 through 25, randomly arranged on a page, in proper order. In addition to measuring functions of attention and information processing, this instrument adds elements of mental flexibility and response inhibition. CTT-2 shows all numbers twice, and the participant must connect the numbers from 1 to 25, alternating between pink and yellow circles, disregarding the numbers in circles of the alternate color. This analysis uses the raw time in seconds the participant needs to complete the test, with higher scores indicating poorer functioning. The CTT-2 was developed for the World Health Organization multicenter study of HIV infection (D'Elia, Satz, Uchiyama & White, 1996). The test is sensitive to a variety of neurological impairments and processes (Tombaugh, 2004) and, because it is entirely numeric and requires no language skills, it is considered culturally unbiased (Maj et al.,1994). Additionally, the instrument has shown strong agreement with other cognitive assessments among PLWH (Maj et al., 1993; Maj et al.,1994) and has displayed good temporal stability with test-retest reliability between 0.85-1.00 (D'Elia et al., 1996).

The Category Test Short Form-Booklet Format (SCT; Halstead, 1947; Wetzel, 1987) measures executive function, assessing problem-solving ability by requiring the examinee to determine the organizing principle behind a series of visually presented stimuli, based on the correct or incorrect external feedback from the test administrator.

This study uses the total raw error score derived, with higher scores indicating poorer functioning. Test-retest coefficients have varied from 0.60 to 0.96 depending upon the severity of impairment in the sample (Wetzel L, 1987).

A hypothesized directional model was constructed to assess the degree to which independent relationships exist between HIV exposure, alcohol use, marijuana use and cocaine use on the outcome of NC functioning as indicated by three different cognitive performance measures. Because advanced age is the most common predictor of deterioration in NC functioning, analyses of duration of HIV infection were controlled for age in the model (see below).

Analytic Strategy

Descriptive statistics were calculated for all of the variables in the model. Means, standard deviations, skewness and kurtosis levels were calculated for all continuous variables; frequencies were generated for dichotomous and categorical variables. In order to gain an understanding of the overall degree of NC impairment in this sample, one-sample t-tests were used to compare mean raw NC scores with normative scores on each instrument. Raw scores were square root transformed and confidence intervals represent the difference between the raw, transformed scores and square roots of the normative scores. Norms for NC measures were obtained from professional manuals provided for the instruments (D'Elia et al., 1996; Mitrushino, Boone, Razan, & D'Elia, 2005; Van der Elst, van Boxtel, van Breukelen, & Jolles, 2005; Wetzel, 1987). Raw NC scores were used in bivariate and multivariate regression analyses; age, gender and educational level were entered as covariates. Bivariate regression analyses assessed relationships between each independent and dependent variable using SPSS version 21. NC scores were square

root transformed to adjust for non-normality for t tests and robust Maximum Likelihood framework was invoked in MPlus version 5.1 to accommodate non-normality in the multivariate analysis (Yuan & Bentler, 2000). Missing data bias was assessed by computing a dummy variable reflecting the presence or absence of missing data for each variable, which was correlated with all other variables in the model, as well as demographic variables. No correlations between dummy variables for missing data and all other variables in the model were statistically significant, suggesting that data were most likely missing at random. With no systematic patterns observed in the missing data, a full information maximum likelihood (FIML) method was used to accommodate the missing data. A limited information approach was used to approximate sample size and statistical power, accounting for at least 5% variance in the outcome (Jaccard & Wan, 1996). To assess non-model-based outliers, leverage indices were examined for each participant based on their multivariate profile for the variables included in the model analyses. An outlier was defined as an observation with a leverage score four times greater than the mean leverage. The mean leverage score across participants was 0.09. Based on the criteria described above, no outliers were evident in the sample data. After addressing all diagnostic statistics, the final hypothesized model was analyzed using Mplus software version 5.1 (Muthen & Muthen, 2008); strengths of association were reported.

RESULTS

The mean age of participants was 44.79 years; most (63.5%) were men and identified as black (76.2%). Most (55.7%) of participants reported at least high school

completion; however few (8.2%) were employed. The mean number of years living with HIV was 12.2. While most (58.4%) sought treatment within 6 weeks of receiving a positive HIV test, 24.6% of participants waited over a year before seeking care (Table 1.1). Although not included in the tested model, the majority (76.7%) reported that they were currently taking ART; 80% reported perfect (100%) treatment adherence; and 45% had an undetectable viral load when last tested.

Single sample t-tests comparing the mean raw NC scores with normative scores on each instrument showed that measures of memory, executive functioning, and information processing for the study group were significantly poorer (all $p<0.001$) than those observed in healthy samples as follows: AVLT, t=-16.25 [95% CI = -0.67, -0.52]; CTT2, t=6.65 [95% CI = 0.53, 0.97]; and SCT, t=11.52[95% CI = 0.66, 0.93]. Over a third (39%) of the study population scored at least one standard deviation below the mean for normative samples on at least two NC tests, consistent with clinically significant NC impairment (Antinori et al., 2007).

Table 1.1 (1). Sociodemographic characteristics of participants at baseline (N=370)

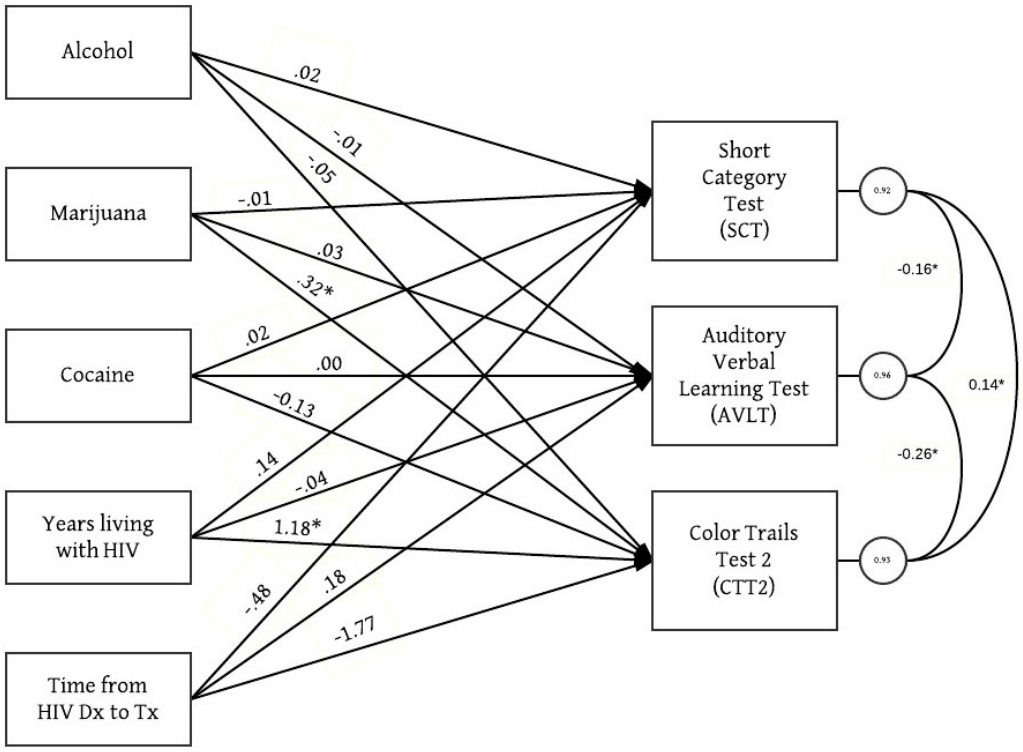
	Mean (SD) N (%)	Skewness / Kurtosis
Age	44.79 (7.3)	-0.56 / -0.13
Gender (Male)	233 (63.5%)	-0.56 / -0.69
Hispanic Ethnicity (Yes)	53 (15%)	1.97 / 1.90
Race		
Black	266 (76.2%)	-1.24 / -0.47
White	50 (14.3%)	2.05 / 2.20
Years education		0.41 / -0.17
<8th grade	29 (8.2%)	-
Some high school	128 (36.1%)	-
HS diploma	109 (30.7%)	-
Some college/tech	71 (20%)	-
College degree	15 (4.2%)	-
Graduate training	3 (0.8%)	-
Employed (Yes)	29 (8.2%)	3.07 / 7.45
Years since HIV diagnosis	12.15 (7.5)	0.20 / -1.01
Time from HIV Diagnosis to Treatment		0.65 / -1.41
Within 6 weeks	206 (58.4%)	-
6 – 12 weeks	13 (3.7%)	-
3 – 6 months	22 (6.2%)	-
6 months – 1 year	25 (7.1%)	-
1 year +	87 (24.6%)	-
Taking ART (Yes)	273 (76.7)	-1.27 / -0.40
Days using in last 3 mos.		
Alcohol	15.77 (23.33)	1.86 / 2.83
Marijuana	9.29 (20.68)	2.84 / 7.59
Cocaine	15.68 (23.89)	1.89 / 2.80
Neurocognitive Functioning		
CTT2	116.31 (49.82)*	1.71 / 4.97
SCT	38.09 (15.58)*	-0.38 / -0.86
AVLT	43.44 (9.63)*	-0.03 / -0.22

* Raw scores reported. All sample means are significantly different from normative sample at $p<0.01$. Normative scores used for comparison testing represented mean age and education for this sample. Skewness and kurtosis values for neurocognitive instruments reflect distribution of scores prior to square root transformation.

Bivariate analyses (Table 1.3) identified one significant relationship. Marijuana use was associated with a poorer scores on the CTT2 (β=1.031; 95% CI: 0.285, 1.777; p=0.007). After examining diagnostics for normality, outliers and patterns of missing

data, the final model was tested. Figure 1.1 presents both significant and non-significant path coefficients of the final model. The straight lines with arrows from observed variables represent presumed pathways of association, and the values along the pathways are unstandardized path coefficients. All exogenous variables were assumed to be correlated. Unstandardized path coefficients, standard errors and 95% confidence intervals are listed in Table 1.4. Following modification indices, it was decided to correlate residual terms (i.e. error variance) between three measures of NC functioning. Focused fit indices did not show evidence of Heywood cases. Standardized residual values were <2. Focused fit indices suggested satisfactory model fit after correlating error terms. The final model explained 8% of variance in memory, 7% of variance in information processing, and 4% of variance in executive functions. When examining the model, two associations approached or achieved statistical significance. On average, for each day of marijuana use, the CTT2 score increased by 0.32, indicating poorer performance on this NC measure. Similarly, on average, each year living with HIV increased the CTT2 score by 1.18.

Figure 1.1 (1). Significant regression paths among measured variables in the structural equation model among HIV-positive alcohol abusers (N=370)



*Significant at $p<0.05$
Regression coefficients (represented as one-way arrows) are unstandardized.

Table 1.2 (2). Bivariate regression statistics, 95% confidence intervals, and p-values (N=370)

		β	95% CI	P
Alcohol Days[1]	AVLT[6]	-0.005	-0.049, .039	0.82
	CTT2[7]	-0.137	-0.386, 0.111	0.28
	SCT[8]	-0.017	-0.089, 0.056	0.65
Marijuana Days[2]	AVLT	0.009	-0.044, 0.063	0.73
	CTT2	0.275	-0.024, 0.573	0.07
	SCT	-0.049	-0.137, 0.038	0.27
Cocaine Days[3]	AVLT	0.011	-0.032, 0.053	0.63
	CTT2	-0.172	-0.413, 0.069	0.16
	SCT	0.027	-0.033, 0.097	0.46
Years of HIV Infection[4]	AVLT	-0.075	-0.208, 0.059	0.27
	CTT2	1.031	0.285, 1.777	0.007
	SCT	0.096	-0.124, 0.316	0.39
Time from HIV Diagnosis to Seeking Medical Care[5]	AVLT	-0.045	-0.570, 0.480	0.87
	CTT2	0.384	-2.509, 3.277	0.79
	SCT	-0.333	-1.192, 0.526	0.447

[1]Number of days using alcohol in past 3 months
[2]Number of days using marijuana in past 3 months
[3]Number of days using cocaine in past 3 months
[4]Duration of known HIV infection in years
[5]Time interval from diagnosis of HIV infection to seeking medical care.
[6]Auditory Verbal Learning Test
[7]Color Trails Test 2
[8]Short Category Test

Table 1.3 (3). Unstandardized path coefficients, standard errors, 95% confidence intervals, and p-values (N=370)

		Coefficient	SE	95% CI	P
Alcohol Days[1]	AVLT[6]	-0.01	0.03	-0.07, 0.51	0.79
	CTT2[7]	-0.05	0.16	-0.36, 0.26	0.75
	SCT[8]	0.02	0.04	-0.06, 0.11	0.59
Marijuana Days[2]	AVLT	0.03	0.04	-0.05, 0.11	0.45
	CTT2	0.32**	0.17	-0.001, 0.65	0.05
	SCT	-0.01	0.06	-0.13, 0.10	0.82
Cocaine Days[3]	AVLT	0.00	0.03	-0.05, 0.06	0.94
	CTT2	-0.13	0.14	-0.40, 0.15	0.37
	SCT	0.02	0.05	-0.07, 0.11	0.65
Years of HIV Infection[4]	AVLT	-0.04	0.10	-0.23, 0.15	0.66
	CTT2	1.18*	0.54	0.12, 2.25	0.03
	SCT	0.14	0.15	-0.17, 0.44	0.37
Time from HIV Diagnosis to Seeking Medical Care[5]	AVLT	0.18	0.38	-0.56, 0.92	0.63
	CTT2	-1.77	2.33	-6.34, 2.79	0.45
	SCT	-0.48	0.61	-1.68, 0.44	0.43

[1] Number of days using alcohol in past 3 months
[2] Number of days using marijuana in past 3 months
[3] Number of days using cocaine in past 3 months
[4] Duration of known HIV infection in years
[5] Time interval from diagnosis of HIV infection to seeking medical treatment.
[6] Auditory Verbal Learning Test
[7] Color Trails Test 2
[8] Short Category Test
*Significant at $p<0.05$
**Approaching significance

DISCUSSION

This study found that NC impairment was common (39%) in this group. Other U.S. studies of HIV-seropositive adults using similar NC measures have yielded different results. A U.S. study of adult PLWH found their participants scored lower on CTT2 ($\bar{x}$ =100.1) than participants in this study (Ammassari et al., 2004). Another study of HIV-seropositive African American men also reported significantly lower CTT2 scores with

mean score of 93.09 for their HIV+ symptomatic group (Richardson et al., 1999). These higher functioning levels could be explained by their samples' lower mean age and AOD use characteristics.

Two variables—more frequent marijuana use and prolonged duration of HIV infection—were associated with poorer performance on one NC measure. Higher number of days of marijuana use predicted poorer performance on the CTT2, which measured frontal systems functioning such as attention, executive functions and information processing (D'Elia et al., 1996; Horton Jr, 1979). Although significant differences in CTT2 scores have been identified between HIV-positive intravenous drug users and non-users (Starace et al., 1998), previous research on the NC effects of marijuana use has yielded mixed results. Most studies examining marijuana-associated NC functioning found long-term use to impede performance in domains of executive functions, verbal memory and psychomotor speed (Bolla, Cadet, & London, 1998; Gonzalez, Carey, & Grant, 2002; Messinis et al., 2006). While it is believed that chronic illicit drug use can exacerbate NC sequelae of HIV infection (Anthony, Arango, Stephens, Simmonds, & Bell, 2008; Basso & Bornstein, 2000; Norman, Basso, Kumar, & Malow, 2009), little actual exploration of long-term cognitive impact of marijuana use has been conducted among PLWH. One study by Cristiani, Pukay-Martin, & Bornstein (2004) reported a significant association between marijuana use and poorer NC functioning among PLWH with more advanced disease. These effects were most profound in the area of memory performance.

Methodological issues associated with NC assessments and the classification of acute versus non-acute effects of marijuana use should be considered when interpreting

these and similar study outcomes (Gonzalez et al., 2002). In this study, a three-month drug use history was collected with no control for any recent period of drug abstinence; thus, marijuana use was believed to be continuous and NC performance measures may have actually measured acute or intoxication effects of marijuana. Additionally, only associations with performance on the CTT2 measure were significant; however, this instrument may measure several domains of functioning, including psychomotor speed attention (D'Elia et al., 1996). Without the corroboration of results of testing using instruments measuring similar NC domains, the exact areas of neuropsychological impact associated with marijuana use cannot be determined with certainty.

An additional finding of this research was that the number of years living with HIV predicted poorer performance on the CTT2 instrument. Although the introduction of ART has significantly reduced incidence of severe NC disorders, particularly dementia, among PLWH, evidence of milder HAND is common even among virally suppressed patients (McArthur et al., 2010). In this sample, no significant association was found between NC functioning and the length of time from HIV diagnosis to seeking care. It should also be noted that the patients evaluated in this study were heterogeneous in ART treatment and viral suppression.

Moreover, there was a high prevalence (39%) of clinically significant NC impairment. There are several possible explanations for the poorer NC functioning observed to be a function of time living with HIV in this study and not necessarily as a function of delayed ART initiation. An inflammatory response can occur when immune functioning rebounds after treatment with ART immune reconstitution inflammatory syndrome (IRIS). However, regardless of possible IRIS, greater immunosuppression

remains a strong predictor of NC impairment among PLWH (Gupta et al., 2007; Heaton et al., 2010); thus early initiation of ART is reported to be one of the most important preventive measures against developing HAND (Müller et al., 2010; Tozzi et al., 2007). Continuous ART adherence is also a protective factor against NC impairment (Hinkin et al., 2002). While some participants in this study may have initiated treatment early, only 77% of participants in this group report currently taking ART. It is also possible that the association found between years living with HIV and poorer CTT2 performance may be a function of age-related cognitive decline (Mateen & Mills, 2012); although the analyses were controlled for age, older age remains a strong predictor of NC impairment, and is highly correlated with duration of HIV infection.

Certain limitations of this study are important to note. These participants were drawn from clinical sites and may not be representative of PLWH not receiving drug/alcohol addiction or HIV treatment. Reporting bias should also be considered in interpreting outcomes. Nearly a quarter of the study population was in abstinence-based, residential addiction treatment at the time of this study, and it is possible that recent substance use was underreported, and/or that answers reflected months of abstinence in the treatment center. Moreover, underreporting may have varied by substance; marijuana use is likely to be less stigmatized than cocaine use (Flom et al., 2001) and possibly less than alcohol use. Additionally, this is a cross-sectional analysis; not only is it impossible to infer causality, but participants were heterogeneous and at different stages of care for HIV and drug and/or alcohol treatment. Measurement issues should be considered when interpreting this study's results. Only three NC instruments were used; however, HIV or drug/alcohol use can affect many other cognitive functions not evaluated here, such as

psychomotor speed and coordination, prospective memory, and cognitive impulsivity (Reger, Welsh, Razani, Martin, & Boone, 2002; Schuster & Gonzalez, 2012; Woods et al., 2009). The NC instruments used were, however, commonly utilized in similar research and considered to be reliable. Of greater concern is that poor mean NC scores for this group may also suggest poorer recall on self-report measures.

Finally, the construct validity of some study measures should be taken into account. As mentioned, the CTT2 may be evaluating several domains of cognitive functioning, reducing the ability to pinpoint exact areas of impairment. In addition, the item assessing amount of time from HIV diagnosis to seeking care did not provide information on actual time to ART initiation. This item was intended as a measure of care utilization; however, for the purpose of this study, the measure was used as a proxy for ART initiation—i.e. one who sought care sooner might also be treated with ART sooner.

Counter to reports that cocaine and alcohol use exacerbate NC impairment among PLWH (Nath, 2010), this particular study did not find such associations. Because abuse of alcohol and illicit substances is inextricably linked to HIV (Volkow, 2012), further investigation into interaction effects between long-term drug/alcohol use and HIV is recommended. Further, future research should consider the contributions of substance use to overall NC functioning for the delivery of clinical care and health behavior interventions. Early HIV care can help decrease potential NC impairment and yield better health outcomes for HIV-infected populations; however people suffering from substance use disorders or cognitive impairment may find it difficult to follow important medical recommendations (Baum et al., 2010; Braithwaite & Bryant, 2010; Bryant, 2006; Cook et al., 2001; Hinkin, Castellon, & Durvasula, 2002; Rothlind et al., 2008). Outcomes from

this study provide further evidence of the prevalence of NC impairment that can help to guide and enhance interventions for PLWH who use alcohol and drugs. The delivery of health interventions and clinical care should consider taking a harm-reduction approach: working with the patient's current substance use status to improve HIV treatment adherence and service utilization and delivering interventions and services that are sensitive to cognitive difficulties (Margolin, Avants, Warburton, & Hawkins, 2002; Margolin et al., 2003; Miller, 1993).

REFERENCES

Ammassari, A., Antinori, A., Aloisi, M. S., Trotta, M. P., Murri, R., Bartoli, L., ... & Starace, F. (2004). Depressive symptoms, neurocognitive impairment, and adherence to highly active antiretroviral therapy among HIV-infected persons. *Psychosomatics, 45(5),* 394-402.

Anthony, I., Arango, J., Stephens, B., Simmonds, P., & Bell, J. (2008). The effects of illicit drugs on the HIV-infected brain. *Frontiers in Bioscience*, *13*, 1294–1307.

Antinori, A., Arendt, G., Becker, J. T., Brew, B. J., Byrd, D. A., Cherner, M., … Wojna, V. E. (2007). Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*, *69*(18), 1789–99. doi:10.1212/01.WNL.0000287431.88658.8b

Basso, M. R., & Bornstein, R. a. (2000). Neurobehavioural consequences of substance abuse and HIV infection. *Journal of Psychopharmacology*, *14*(3), 228–237. doi:10.1177/026988110001400306

Baum, M. K., Rafie, C., Lai, S., Sales, S., Page, J. B., & Campa, A. (2010). Alcohol use accelerates HIV disease progression. *AIDS Research and Human Retroviruses*, *26*(5), 511–518.

Bing, E. G., Burnam, M. A., Longshore, D., Fleishman, J. A., Sherbourne, C. D., London, A. S., … Shapiro, M. (2001). Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. *Archives of General Psychiatry*, *58*(8), 721–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11483137

Bolla, K., Cadet, J., & London, E. (1998). The neuropsychiatry of chronic cocaine abuse. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *10*(3), 280–289.

Bono, G., Mauri, M., Sinforiani, E., Barbarini, G., Minoli, L., & Fea, M. (1996). Longitudinal neuropsychological evaluation of HIV-infected intravenous drug users. *Addiction*, *91*, 263–268.

Braithwaite, S. R., & Bryant, K. J. (2010). Influence of alcohol consumption on adherence to and toxicity of antiretroviral therapy and survival. *Alcohol Research & Health*, *33*(3), 280–287.

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), 1465–507. doi:10.1080/10826080600846250

Cook, R., Sereika, S., Hunt, S., Woodward, W., Erlen, J., & Conigliaro, J. (2001). Problem drinking and medication adherence among persons with HIV infection. *Journal of General Internal Medicine*, *16*(2), 83–8.

Cristiani, S. A., Pukay-Martin, N. D., & Bornstein, R. A. (2004). Marijuana use and cognitive function in HIV-infected people. *Journal of Neuropsychiatry and Clinical Neuroscience*, *16*(3), 330–335.

D'Elia L, S. P. (1989). *Color Trails 1 and 2*. Odessa, FL: Psychological Assessment Resources.

D'Elia, L., Satz, P., Uchiyama, C., & White, T. (1996). *Color Trails Test professional manual*. Odessa, FL: Psychological Assessment Resources.

Di Sclafani, V., Tolou-Shams, M., Price, L. J., & Fein, G. (2002). Neuropsychological performance of individuals dependent on crack-cocaine, or crack-cocaine and alcohol, at 6 weeks and 6 months of abstinence. *Drug and alcohol dependence*, *66*(2), 161–71.

Durvasula, R, Norman, L., & Malow, R. (2009). Current perspectives on the neuropsychology of HIV. In M. R. Pope C, White R (Ed.), *HIV/AIDS: Global Frontiers in Prevention/Intervention* (pp. 177–190). New York: Routledge.

Durvasula, RS, Miller, E., Myers, H., & Wyatt, G. (2001). Predictors of Neuropsychological Performance in HIV Positive Women. *Journal of Clinical and Expermental Neuropsychology*, *23*(2), 149–164.

Fals-Stewart, W., O'Farrell, T. J., Freitas, T. T., McFarlin, S. K., & Rutigliano, P. (2000). The timeline followback reports of psychoactive substance use by drug-abusing patients: psychometric properties. *Journal of Consulting and Clinical Psychology, 68(1)*, 134.

Farinpour, R., Martin, E. M., Seidenberg, M., Pitrak, D. L., Pursell, K. J., Mullane, K. M., … Harrow, M. (2000). Verbal working memory in HIV-seropositive drug users. *Journal of the International Neuropsychological Society*, *6*(5), 548–55.

Flom, P. L., Friedman, S. R., Kottiri, B. J., Neaigus, A., Curtis, R., DesJarlais, D., … Zenilman, J. M. (2001). Stigmatized drug use, sexual partner concurrency, and other sex risk network and behavior characteristics of 18-24 year-old youth in a high-risk neighborhood. *Sexually Transmitted Diseases*, *28*(10), 598–607.

Gonzalez, R., Carey, C., & Grant, I. (2002). Nonacute (residual) neuropsychological effects of cannabis use: A qualitative analysis and systematic review. *Journal of Clinical Pharmacology*, *42*, 48S–57S.

Grant, I., Atkinson, J., Hesselink, J., Kennedy, C., Richman, D., Spector, S., & McCutchan, J. (1987). Evidence for early central nervous system involvement in the acquired immunodeficiency syndrome (AIDS) and other human immunodeficiency virus (HIV) infections. *Annals of Internal Medicine*, *107*, 828–836.

Gupta, J. Das, Satishchandra, P., Gopukumar, K., Wilkie, F., Waldrop-Valverde, D., Ellis, R., … Kumar, M. (2007). Neuropsychological deficits in human immunodeficiency virus type 1 clade C-seropositive adults from South India. *Journal of Neurovirology*, *13*(3), 195–202. doi:10.1080/13550280701258407

Halstead, W. (1947). *Brain and Intelligence*. Chicago: University of Chicago Press.

Heaton, R., Clifford, D., Franklin, D., Woods, S., Ake, C., Vaida, F., … Grant, I. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology*, *75*(23), 2087–96. doi:10.1212/WNL.0b013e318200d727

Heaton, R., Grant, I., Butters, N., White, D., Kirson, D., Atkinso, n J., … Ellis, R. (1995). The HNRC 500-Neuropsychology of Hiv infection at different disease stages. *Journal of the International Neuropsychological Society*, *1*(3), 231–251.

Hinkin, C., Castellon, S., & Durvasula, R. (2002). Medication adherence among HIV+ adults Effects of cognitive dysfunction and regimen complexity. *Neurology*, *59*(12), 1944–1950.

Horton Jr, A. (1979). Some suggestions regarding the clinical interpretation of the Trail Making Test. *Clinical Neuropsychology*, *1*(1), 20–23.

Jaccard, J., & Wan, C. (1996). *LISREL approaches to interaction effects in multiple regression*. Thousand Oaks, CA: Sage Publications.

Justice, A. C., McGinnis, K. A., Atkinson, J. H., Heaton, R. K., Young, C., Sadek, J., … Simberkoff, M. (2004). Psychiatric and neurocognitive disorders among HIV-positive and negative veterans in care: Veterans Aging Cohort Five-Site Study. *AIDS*, *18 Suppl 1*(ext 5309), S49–59.

Korthuis, P. T., Zephyrin, L. C., Fleishman, J. A, Saha, S., Josephs, J. S., McGrath, M. M., … Gebo, K.A. (2008). Health-related quality of life in HIV-infected patients: the role of substance use. *AIDS Patient Care and STDsare and STDs*, *22*(11), 859–67. doi:10.1089/apc.2008.0005

Kuo, W.-H., Wilson, T. E., Weber, K. M., Madhava, V., Richardson, J., Delapenha, R., & Des Jarlais, D. (2004). Initiation of regular marijuana use among a cohort of women infected with or at risk for HIV in the Women's Interagency HIV Study (WIHS). *AIDS Patient Care and STDs*, *18*(12), 702–13. doi:10.1089/apc.2004.18.702

Lezak, M. (2004). *Neuropsychological Assessment* (4th ed.). New York: Oxford University Press.

Maj, M, D'Elia, L., Satz, P., Janssen, R., Zaudig, M., Uchiyama, C., & Chervinsky, A. (1993). Evaluation of two new neuropsychological tests designed to minimize cultural bias in the assessment of HIV-1 seropositive persons: a WHO study. *Archives of Clinical Neuropsychology*, *8*(2), 123–135.

Maj, Mario, Satz, P., Janssen, R., Zaudig, M., Starace, F., Schulte, G., & Sartorius, N. (1994). WHO Neuropsychiatric AIDS Study, Cross-sectional Phase II. *Archives of General Psychiatry*, *51*, 51–61.

Malow, R., Devieux, J., Stein, J., Rosenberg, R., Lerner, B., Attonito, J., & Villalba, K. (2012). Neurological function, information-motivation-behavioral skills factors, and risk behaviors among HIV-positive alcohol users. *AIDS and Behavior*, *16*(8), 2297–308. doi:10.1007/s10461-012-0246-6

Mannheimer, S., Matts, J., Telzak, E., & Chesney, M. (2010). Psychological and Socio-medical Aspects of AIDS / HIV Quality of life in HIV-infected individuals receiving antiretroviral therapy is related to adherence. *AIDS Care*, *17*(1), 10–22.

Margolin, A., Avants, S., Warburton, L., & Hawkins, K. (2002). Factors Affecting Cognitive Functioning in a Sample of Human Immunodeficiency Virus-Positive Injection Drug Users. *AIDS Patient Care and STDs*, *16*(6).

Margolin, A., Avants, S., Warburton, L., Hawkins, K., & Shi, J. (2003). A randomized clinical trial of a manual-guided risk reduction intervention for HIV-positive injection drug users. *Health Psychology*, *22*(2), 223–228. doi:10.1037/0278-6133.22.2.223

Maj, M., Satz, P., Janssen, R., Zaudig, M., Starace, F., D'Elia, L., ... & Sartorius, N. (1994). WHO Neuropsychiatric AIDS Study, cross-sectional phase II: neuropsychological and neurological findings. *Archives of General Psychiatry*, *51*(1), 51.

Martin, E. M., Pitrak, D. L., Weddington, W., Rains, N. A., Nunnally, G., Nixon, H., … Bechara, A. (2004). Cognitive impulsivity and HIV serostatus in substance dependent males. *Journal of the International Neuropsychological Society*, *10*(7), 931–8.

Mason, K. I., Campbell, A, Hawkins, P., Madhere, S., Johnson, K., & Takushi-Chinen, R. (1998). Neuropsychological functioning in HIV-positive African-American women with a history of drug use. *Journal of the National Medical Association*, *90*(11), 665–74.

Mateen, F. J., & Mills, E. J. (2012). Aging and HIV-related cognitive loss. *Journal of the American Medical Association*, *308*(4), 349–50. doi:10.1001/jama.2012.8538

McArthur, J. C. (2004). HIV dementia: an evolving disease. *Journal of Neuroimmunology*, *157*(1-2), 3–10. doi:10.1016/j.jneuroim.2004.08.042

McArthur, J. C., Steiner, J., Sacktor, N., & Nath, A. (2010). Human immunodeficiency virus-associated neurocognitive disorders: Mind the gap. *Annals of Neurology*, *67*(6), 699–714. doi:10.1002/ana.22053

Meade, C. S., Conn, N. A., Skalski, L. M., & Safren, S. A. (2011). Neurocognitive impairment and medication adherence in HIV patients with and without cocaine dependence. *Journal of Behavioral Medicine*, *34*(2), 128–38. doi:10.1007/s10865-010-9293-5

Messinis, L., Kyprianidou, A., Malefaki, S., & Papathanasopoulos, P. (2006). Neuropsychological deficits in long- term frequent cannabis users. *Neurology*, *66*, 737–739.

Miller, L. (1993). *Psychotherapy of the Brain-Injured Patient: Reclaiming the Shattered Self*. WW Norton & Co. Inc.

Mitrushino, M., Boone, K., Razan, J., & D'Elia, L. (2005). *Handbook of Normative Data for Neuropsychological Assessment* (2nd ed., pp. 359–882). New York: Oxford University Press.

Müller, M., Wandel, S., Colebunders, R., Attia, S., Furrer, H., & Egger, M. (2010). Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *The Lancet Infectious Diseases*, *10*(4), 251–61. doi:10.1016/S1473-3099(10)70026-8

Muthen, B., & Muthen, L. (2008). *Mplus Version 5.1*. Los Angeles: Muthen & Muthen.

Nath, A. (2010). Human immunodeficiency virus-associated neurocognitive disorder: pathophysiology in relation to drug addiction. *Annals of the New York Academy of Sciences*, *1187*, 122–8. doi:10.1111/j.1749-6632.2009.05277.x

Nath, A., Maragos, W., Avison, M., Schmitt, F., & Berger, J. (2001). Acceleration of HIV dementia with methamphetamine and cocaine. *Journal of neurovirology*, *7*(1), 66–71. doi:10.1080/135502801300069737

Norman, L., Basso, M., Kumar, A., & Malow, R. (2009). Neuropsychological consequences of HIV and substance abuse: A literature review and implications for treatment and future research. *Current Drug Abuse Reviews*, *2*(2), 143–156.

Reger, M., Welsh, R., Razani, J., Martin, D., & Boone, K. (2002). A meta-analysis of the neuropsychological sequelae of HIV infection. *Journal of the International Neuropsychological Society*, *8*(3), 410–424.

Rey, A. (1964). *L'examen Clinique en Psychologie*. Paris: Universitaires de France.

Richardson, M. A., Satz, P., Myers, H. F., Miller, E. N., Bing, E. G., Fawzy, F. I., & Maj, M. (1999). Effects of depressed mood versus clinical depression on neuropsychological test performance among African American men impacted by HIV/AIDS. *Journal of Clinical and Experimental Neuropsychology, 21(6),* 769-783.

Robertson, K. R., Smurzynski, M., Parsons, T. D., Wu, K., Bosch, R. J., Wu, J., … Ellis, R. J. (2007). The prevalence and incidence of neurocognitive impairment in the HAART era. *AIDS*, *21*(14), 1915–21. doi:10.1097/QAD.0b013e32828e4e27

Rothlind, J. C., Greenfield, T. M., Bruce, A. V, Dieter, J., Flenniken, D. L., Lindgren, J. A., & Michael, W. (2005). Heavy alcohol consumption in individuals with HIV infection: Effects on neuropsychological performance. *Journal of the International Neuropsychological Society*, *11*(1), 70–83.

Sacktor, N. (2002). The epidemiology of human immunodeficiency virus-associated neurological disease in the era of highly active antiretroviral therapy. *Journal of Neurovirology*, *8 Suppl 2*, 115–21. doi:10.1080/13550280290101094

Sacktor, N., Skolasky, R., Selnes, O. a, Watters, M., Poff, P., Shiramizu, B., … Valcour, V. (2007). Neuropsychological test profile differences between young and old human immunodeficiency virus-positive individuals. *Journal of Neurovirology*, *13*(3), 203–9. doi:10.1080/13550280701258423

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

Schroder, K., Carey, M., & Vanable, P. (2003). Methodological challenges in research on sexual risk behavior: II. Accuracy of self-reports. *Annals of Behavioral Medicine*, *26*(2), 104–123.

Schuster, R. M., & Gonzalez, R. (2012). Substance abuse , hepatitis C , and aging in HIV : common cofactors that contribute to neurobehavioral disturbances. *Neurobehavioral HIV Medicine*, *4*, 15–34.

Selnes, O., Galai, N., McArthur, J., & Cohn, S. (1997). HIV Infection and Cognition in Intravenous Drug Users: Long-term Follow-up. *Neurology*, *48*, 227–229.

Silverberg, N. D., & Millis, S. R. (2009). Impairment versus deficiency in neuropsychological assessment: Implications for ecological validity. *Journal of the International Neuropsychological Society : JINS*, *15*(1), 94–102. doi:10.1017/S1355617708090139

Simioni, S., Cavassini, M., Annoni, J.-M., Rimbault Abraham, A., Bourquin, I., Schiffer, V., … Du Pasquier, R. a. (2010). Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS*, *24*(9), 1243–50. doi:10.1097/QAD.0b013e3283354a7b

Starace, F., Baldassarre, C., Biancolilli, V., Fea, M., Serpelloni, G., Bartoli, L., & Maj, M. (1998). Early neuropsychological impairment in HIV-seropositive intravenous drug users: evidence from the Italian Multicentre Neuropsychological HIV Study. *Acta Psychiatrica Scandinavica, 97(2)*, 132-138.

Stern, R., Silva, S., Chaisson, N., & Evans, D. (1996). Influence of cognitive reserve on neuropsychological functioning in asymptomatic human immunodeficiency virus-1 infection. *Archives of Neurology*, *53*, 148–153.

Substance Abuse and Mental Health Services Administration. (2011). *Results from the 2010 National Survey on Drug Use and Health : Summary of National Findings, NSDUH Series H-41, HHS Publication No. (SMA) 11-4658*. Rockville, MD.

Tombaugh, T. N. (2004). Trail Making Test A and B: normative data stratified by age and education. *Archives of Clinical Neuropsychology*, *19*(2), 203–14. doi:10.1016/S0887-6177(03)00039-8

Tozzi, V., Balestra, P., Bellagamba, R., Corpolongo, A., Salvatori, M. F., Visco-comandini, U., … Narciso, P. (2007). Persistence of neuropsychologic deficits despite long-term highly active antiretroviral therapy in patients prevalence and risk Factors. *Journal of Acquired Immune Deficiency Syndromes*, *45*(2), 174–182.

Van der Elst, W., van Boxtel, M. P. J., van Breukelen, G. J. P., & Jolles, J. (2005). Rey's verbal learning test: normative data for 1855 healthy participants aged 24-81 years and the influence of age, sex, education, and mode of presentation. *Journal of the International Neuropsychological Society*, *11*(3), 290–302. doi:10.1017/S1355617705050344

Volkow, N. D. (2012). *Drug Abuse and HIV*. Washington, D.C. Retrieved from http://www.drugabuse.gov/sites/default/files/rrhiv.pdf

Wetzel L, B. T. (1987). *Short Category Test, Booklet Format*. Los Angeles: Western Psychological Services.

Wetzel, L., & Boll, T. (1987). *Short Category Test, Booklet Format*. Los Angeles: Western Psychological Services.

White, D., Heaton, R., & Monsch, A. (1995). Neuropsychological studies of asymptomatic Human Immunodeficiency Virus-Type-1 infected individuals. *Journal of the International Neuropsychological Society*, *1*(3), 304–315.

Woods, S. P., Moore, D. J., Weber, E., & Grant, I. (2009). Cognitive neuropsychology of HIV-associated neurocognitive disorders. *Neuropsychology Review*, *19*(2), 152–68. doi:10.1007/s11065-009-9102-5

Yuan, K., & Bentler, P. (2000). Three likelihood-based methods for mean and covariance structure analysis with nonnormal missing data. *Sociological Methodology*, *30*(1), 165–200.

CHAPTER IV

TRANSITION TO MANUSCRIPT 2

Manuscript 2 tested a model proposing associations between psychosocial factors on the outcome VL, mediated by ART adherence. Features of this study drew from results found in Manuscript 1. Latent variables were not considered in the structural equation model, so all variables were single-measure items. Cocaine was removed from the analysis, because fewer participants reported using this drug and because no significant associations were identified with cocaine in the first study. Although the three NC measures did not load sufficiently to create a latent variable, they were all retained in the analysis because each one measures unique domains of functioning.

This study used structural equation modeling to test the biopsychosocial model, evaluating direct effects of independent and interaction variables on two dependent variables, VL and ART adherence. A biomedical model such as that tested in manuscript 1, addresses only associations of factors known to have direct biological impact upon health (e.g. the association of taking insulin upon blood sugar levels); whereas a biopsychosocial model tests associations between psychological and social factors—such as stress and social support—upon a biomarker or measurable health outcome.

Upon originally testing these relationships, interaction effects were identified between social support and marijuana on VL and between barriers and marijuana on ART adherence. However, after eliminating 27 non model-based outliers (9.9% of participants) from the analysis, these interaction effects became non-significant. To assess non-model-based outliers, leverage indices were calculated for each participant based on their multivariate profile for the variables included in the model analyses. The leverage score

is based on how much the observation's value on the predictor variable differs from the mean of the predictor variable. The greater an observation's leverage, the more potential it has to be an influential observation. A leverage score four times greater than the mean leverage indicated presence of outliers (Jaccard & Wan, 1996). Only cases with outliers that were statistically impossible—either due to misreporting or data entry error—were removed. Model was analyzed with and without outliers – results were substantively the same. However, given that outliers can bias parameter estimates the decision was made to trim the outliers for the final model (Aguinis, Gottfredson, & Joo, 2013). The identification of marijuana as a potential moderator should be noted for future study.

Model-based outliers were examined using limited information regression analyses for each of the linear equations generated by the various paths included in the model tested. Each endogenous variable was regressed onto the indicators of the exogenous predictor variables. DfBeta is the change in the regression coefficient that emerges after that case is deleted. An outlier was defined as an individual who had a dfBeta three times larger than the standard error of a coefficient (> 1.0). No model-based outliers were evident in these analyses.

In the biopsychosocial model, psychosocial factors are hypothesized to directly affect a biomedical health outcome. Taking medication would not necessarily be included as a mediator in this model; however, possible partial mediation by ART adherence seemed to be an essential role to consider in a model attempting to explain VL. This exploration was conducted because of the abundance of research supporting the importance of ART adherence for positive health outcomes among PLWH.

References

Jaccard, J., & Wan, C. (1996). *LISREL approaches to interaction effects in multiple regression*. Thousand Oaks, CA: Sage Publications.

Aguinis, H., Gottfredson, R. K., & Joo, H. (2013). Best-Practice Recommendations for Defining, Identifying, and Handling Outliers. *Organizational Research Methods, 16(2),* 270-301.

MANUSCRIPT 2: TESTING A MEDIATED BIOPSYCHOSOCIAL MODEL TO PREDICT VIRAL LOAD AMONG PEOPLE LIVING WITH HIV

ABSTRACT

Purpose/Aims: Antiretroviral therapy (ART) adherence is associated with improved HIV-related health outcomes, whereas inadequate treatment adherence predicts increased mortality, viral replication, and increased risk of transmitting the virus to others. Neurocognitive (NC) impairment, drug and alcohol abuse, and psychosocial factors such as stress all have been associated with poorer adherence, while social support has predicted better adherence rates. This study sought to explore the degree to which stress, social support and ART adherence barriers impact viral load (VL) via ART adherence among HIV-seropositive adults.

Methods: This study used multivariate linear regression modeling using Mplus to test a mediated biopsychosocial model predicting VL among a cross-sectional sample of 246 HIV-positive adults who were on ART. Exogenous variables were tangible social support, barriers to ART adherence, and stress. Moderators were alcohol use, marijuana use and NC impairment. The mediator was ART adherence. Baron and Kenny's four-step approach was used to test mediation.

Results: A small positive association between marijuana use and adherence approached significance (β=0.15, p=0.057). Each additional barrier predicted a 10% decrease in adherence rates and a 0.42-unit increase in log10 VL. No interaction effects were identified. The relationship between barriers to adherence and log10VL was partially mediated by ART adherence.

Discussion: These findings provide modest support for the biopsychosocial model in predicting virologic response to ART. Outcomes may provide a more complete picture of the complex factors affecting the lives of HIV-positive adults. A holistic perspective should be considered when providing health care or delivering interventions aimed at improving ART adherence and health outcomes.

Key Words: HIV, biopsychosocial, viral load, adherence

INTRODUCTION

Over 600,000 people in the United States have died from complications related to infection with HIV since the beginning of the epidemic (Centers for Disease Control and Prevention, 2013). Dramatic decreases in HIV-related death rates since the mid-1990s are due to the introduction of highly active antiretroviral therapy (ART; Centers for Disease Control and Prevention Division of HIV/AIDS, 2012). Optimal adherence to ART can stop viral replication, rendering viral levels undetectable in both blood and sexual fluids and reducing risk of HIV transmission (Lima et al., 2011; Volkow, 2012). ART adherence improves health outcomes by promoting ART's effectiveness in suppressing viral replication and restoring immune function and is believed to be central to successful treatment (Bangsberg et al., 2000; Carpenter et al., 1997; Deeks et al., 1997; Descamps & Flandre, 2000; Katzenstein, 1997; Paterson et al., 2000). Inadequate treatment adherence is associated with increased mortality, viral replication, and increased risk of transmitting HIV to others (Bangsberg, Perry, Charlebois, et al., 2001; Quinn et al., 2000).

Several psychosocial factors, including social support, are known to have a direct impact on ART adherence (Amico & Orrell, 2013; Diiorio et al., 2009; DiMatteo, 2004; Safren et al., 2001; Simoni, Frick, et al., 2006). Studies have shown that psychosocial factors may also directly improve virologic response and slow HIV disease progression (Ironson & Hayward, 2008); however, results are mixed. Social support may be the most frequently tested predictor of HIV-related health outcomes. Several studies have found significant positive associations between support and immunologic response or HIV symptoms (Ashton et al., 2005; Solano et al., 1993; Theorell et al., 1995). Other research

has not found a direct relationship between social support and either biomarkers (Ironson, O'Cleirigh, et al., 2005) or clinical evidence of HIV disease progression (Luigi Solano et al., 2002; Thornton et al., 2000), although these studies show more evidence of effects of various psychosocial factors on clinical and immunologic disease progression than directly on VL. In addition, other psychosocial factors associated with HIV medication management such as conscientiousness and proactive coping have been found to positively impact ART adherence (Ironson, Balbin, et al., 2005; O'Cleirigh, Ironson, Weiss, & Costa, 2007). However, no prior studies have explored links between these psychosocial constructs and virologic response to ART, controlled for ART adherence.

People living with HIV/AIDS (PLWH), particularly from low-income or disadvantaged populations, may be exposed to a range of life stressors that could inhibit treatment adherence (Mugavero et al., 2009; Wong et al., 2007). Stressful life events and trauma have not only been linked with poorer health behaviors but may also be associated with lower CD4 count, higher viral load (VL), and more rapid disease progression (Ironson, O'Cleirigh, et al., 2005; Leserman, 2008; Leserman et al., 2007; Mugavero et al., 2013). Psychosocial factors such as stressful life events have also been found to affect health biomarkers such as CD4 count and VL via neural/endocrine mediation of stress-related hormones such as cortisol and norepinephrine (Cole, 2008).

Supporting Engel's (Engel, 1977) biopsychosocial model, the field of psychosomatic medicine has proposed that multiple psychological and social factors may promote or maintain illness, suggesting that interventions should consider not only biological intervention (i.e. surgery and medicine) but also cognitive, behavioral, and emotional strategies in dealing with disease (Novack et al., 2012). The medical model,

accounting only for factors with a direct biological association to health outcomes, has reigned as the predominant paradigm of health and disease, however it is becoming more commonly accepted that illness and wellness are the result of an interaction between biological, psychological and social factors (Leigh & Reiser, 1985; Matarazzo, Weiss, Herd, & Miller, 1984; Sarafino, 1994).

This holistic perspective of health and disease is important to consider, especially with recent efforts to increase the role of ART in the prevention of HIV transmission. For example, Hermann et al. (2008) suggested in their research that the concept of ART adherence is dynamic, influenced by multiple biopsychosocial factors. While correlates of ART adherence have been studied extensively, there remains a gap in research examining relationships of common biopsychosocial factors and their influence on biomarkers such as VL. ART adherence is certainly of great importance in HIV disease management and prevention, but adherence alone is useless without related improvement in the biomarkers that measure immune function and viremia.

When examining the effects of psychosocial predictors on health behaviors and outcomes, cognitive and behavioral factors believed to moderate these relationships are important to consider. Many PLWH are affected by neurocognitive (NC) impairment and drug or alcohol abuse. Mild forms of HIV-associated NC disorders (HAND) continue to be observed in up to 40% of PLWH (Durvasula et al., 2009; Sacktor et al., 2002, 2007; Tozzi et al., 2007) and such impairment can hinder ART adherence (Hinkin et al., 2002).

Studies have identified specific domains of functioning — such as verbal memory and executive functioning — associated with deficiencies in optimal ART adherence (Applebaum, Reilly, et al., 2009; Hinkin & Hardy, 2004; Waldrop-Valverde et al., 2006;

Wright et al., 2011). There is substantive evidence of the link between alcohol and general illicit drug use and ART non-adherence (Bryant et al., 2010; Lucas et al., 2006; Samet et al., 2004), but research regarding adherence and marijuana use in particular is mixed (Corless et al., 2009; de Jong et al., 2005; Prentiss et al., 2004; Tucker et al., 2003). Further, research concerning marijuana use, and its potential effects upon virologic, immunologic and other health markers among PLWH, is limited.

METHODS

Sample

This study sought to test a biopsychosocial model as described above, predicting VL, mediated by ART adherence. Internal (constant) independent variables were age, education and gender. External independent variables were social support, stress and barriers to treatment adherence, moderated by cognitive and behavioral factors (NC impairment, alcohol use and marijuana use). Cross-sectional data was gathered between 2009 and 2012 at baseline of a prospective randomized controlled trial for HIV-positive, adult alcohol-users. Participants were recruited from 13 community-based organizations in urban, low income areas of Miami, Florida. The inclusion criteria were: being ≥18 and ≤60 years old; being HIV-positive; having consumed any alcohol in the past 3 months; and having a history of alcohol abuse or dependence within the past 2 years. Further criteria included facility in English, planning to be in the area for the next 12 months, understanding the informed consent, and currently not displaying overt signs of major psychiatric disorder including psychosis or suicidality. An additional inclusion criterion for this study was self-report of current prescription of ART. Of the 370 participants

recruited, 77% (N=273) had been prescribed ART and were eligible for this study. After removing 27 model-based outliers, 246 participants were evaluated.

Measures

Several data-gathering techniques were utilized depending on the nature and content of the instrument being administered. Assessment methods included: 1) computer-assisted personal interview (CAPI); 2) Audio computer-assisted self-interview (ACASI) for subjective sensitive topics; 3) paper and pen as specified for neurological measures and a calendar format; and 4) timeline follow-back (TLFB; Carey, Carey, Maisto, Gordon, & Weinhardt, 2001; Weinhardt et al., 1998) which enhances recall and provides a continuous three month history to assess intensity of drug and alcohol consumption.

ART adherence data consisted of self-reported percentage of time ART medications were taken as prescribed over the course of a week, per the Community Programs for Clinical Research on AIDS (CPCRA; Mannheimer, Matts, Telzak, & Chesney, 2010). The adherence score was calculated as the mean of the combined total amount of each medication taken during the previous week, according to the scale: “all” (100%), “most” (75%), “about half” (50%), “few” (25%), or “none” (0%) (Mannheimer, Morse, John, & Andrews, 2006). The CPCRA has shown significant correlation with other self-report instruments (Wang et al., 2008) and has effectively predicted biologic outcomes (Mannheimer, Friedland, Matts, Child, & Chesney, 2002). Documentation of recent RNA viral load (collected by the participant’s own health care provider) was supplied by the participant upon entry into the study. Lab measures must have been

collected one month before or after the date of baseline assessment. VL was log10-transformed for analysis.

Tangible social support was measured using four items from the Medical Outcomes Study (MOS; Sherbourne & Stewart, 1991). This functional subscale of the 19-item social support measure measures the degree to which the participant has instrumental help with medical or daily living needs. Each item is rated from (1) "none of the time" to (5) "all of the time." A higher score indicates greater tangible support. The use of subscales increases sensitivity of the instrument (Sherbourne & Stewart, 1991). The tangible support subscale was selected because of its strength in predicting health outcomes and medication adherence (Gallant & Block, 1998; Gallant, 2003; Woloshin et al., 1993). The MOS had strong internal consistency with a Cronbach's alpha of 0.96 for the full instrument and 0.89 for the tangible support subscale. All subscales have shown strong reliability over time (alphas > 0.91) and the four tangible support subscale items have high convergent validity with scale items correlating from 0.72 to 0.87 (Sherbourne & Stewart, 1991).

Stress was measured with 40 items modified from the Life Experiences Survey (LES; Sarason, Johnson, & Siegel, 1978). The first section lists 32 potentially stressful events common to people in a wide variety of situations and eight additional items address issues more specific to this population, such as their illness and alcohol use. Items were scored on a Likert scale based upon the degree to which participants' perceived impact of each event over the previous three months. The first 32 items were scored with two possible points each and the additional 8 items were scored with three possible points each. Higher scores indicated higher potentially stressful impact.

Responses to all items were summed for a total stress score. Reliability for this measure was strong for this sample with a Cronbach's alpha calculated at 0.95.

Barriers to adherence is a self-report portion of the CPCRA that offers ten possible reasons for missing any doses of antiretroviral medication with dichotomous (yes/no) responses (Mannheimer et al., 2002). Options include: "I forget to take my pills"; "I was away from home"; and "I am too busy." Internal consistency of items was 0.81.

A battery of three neuropsychological tests was administered to derive scores in a range of cognitive domains including memory, information processing, and executive functions. The tests selected have been used in previous studies with PLWH who use alcohol and other drugs, and these tests have well-developed norms and high reliability and validity (Basso & Bornstein, 2000; Bono et al., 1996; Selnes et al., 1997; Stern et al., 1996). The Auditory Verbal Learning Test, University of California Los Angeles/World Health Organization Version (AVLT; Maj et al., 1994; Rey, 1964) measures immediate verbal memory capacity, retrieval efficiency, and learning. Fifteen words were read to the participant, requesting both immediate and longer-term recall. Scores for immediate recall, delayed recall, and percent of words retained can be derived. This study utilized the total of immediate recall scores for trials 1-5, with higher scores indicating greater functioning. This instrument demonstrated high test-retest reliability, with alpha scores ranging from 0.51 to 0.72 (Lezak, 2004). The Color Trails Test 2, Form A (CTT2; D'Elia, 1989; D'Elia, Satz, Uchiyama, & White, 1996; Lezak, 2004) is primarily a measure of executive functioning but also assesses attention, information processing, psychomotor coordination and speed. CTT-2 requires the participant to connect encircled

numbers 1 through 25, randomly arranged on a page, in proper order. In addition to measuring functions of attention and information processing, this instrument adds elements of mental flexibility and response inhibition. CTT-2 shows all numbers twice, and the participant must connect the numbers from 1 to 25, alternating between pink and yellow circles, disregarding the numbers in circles of the alternate color. This analysis uses the raw time in seconds the participant needs to complete the test, with higher scores indicating poorer functioning. The CTT-2 was developed for the World Health Organization multicenter study of HIV infection (D'Elia, Satz, Uchiyama & White, 1996). The test is sensitive to a variety of neurological impairments and processes (Tombaugh, 2004) and, because it is entirely numeric and requires no language skills, it is considered culturally unbiased (Maj et al.,1994). Additionally, the instrument has shown strong agreement with other cognitive assessments among PLWH (Maj et al., 1993; Maj et al.,1994) and has displayed good temporal stability with test-retest reliability between 0.85-1.00 (D'Elia et al., 1996). The Category Test Short Form-Booklet Format (SCT; Halstead, 1947; Wetzel, 1987) measures executive function, assessing problem-solving ability by requiring the examinee to determine the organizing principle behind a series of visually presented stimuli, based on the correct or incorrect external feedback from the test administrator. This study uses the total raw error score derived, with higher scores indicating poorer functioning. Test-retest coefficients have varied from 0.60 to 0.96 depending upon the severity of impairment in the sample (Wetzel L, 1987).

Raw NC scores were analyzed; unadjusted NC measures are known to provide better ecological validity when scores are not intended to diagnose impairment in the sample (Silverberg & Millis, 2009b). Scores on this battery were dichotomized. Participants who scored at least one standard deviation below normative means on at least two instruments were identified as displaying greater NC impairment (Antinori et al., 2007). Normative data for CTT2 and AVLT were obtained from professional manuals provided for the instruments (D'Elia et al., 1996; Van der Elst et al., 2005; Wetzel & Boll, 1987). Norms for AVLT were retrieved from *The Handbook of Normative Data for Neuropsychological Assessment* (Mitrushina et al., 2005). Comparison groups were assumed to be healthy, uninfected populations.

Recent alcohol and marijuana use were assessed by TLFB (Carey et al., 2001; Weinhardt et al., 1998; Weinhardt, Otto-Salaj, Brondino, Norberg, & Kalichman, 2002), using a calendar format to enhance accurate recall and to provide a continuous history of drug and alcohol consumption. These two variables were measured by asking the total number of drinks consumed and total number of times using marijuana in the past three months. Up to three months recall of alcohol and other drug use has proven to provide reliable data (Schroder et al., 2003). An analysis of test-retest reliability yielded intraclass correlations ranging from 0.70 to 0.94 in a drug-using sample (Fals-Stewart et al., 2000).

Analytic Strategy

Descriptive statistics and skewness/kurtosis values were calculated for all of the variables in the model. Means and standard distributions were calculated for all continuous variables; percentages were provided for categorical and ordinal variables.

Missing data bias was evaluated by computing a dummy variable that reflected the presence or absence of missing data for each variable. A full information maximum likelihood (FIML) method was used to accommodate the missing data. Robust Maximum Likelihood framework accommodated issues of data distribution (Yuan & Bentler, 2000). A limited information approach provided approximate sample size and statistical power, accounting for at least 5% of variance in the outcome (Jaccard & Wan, 1996). To assess non-model-based outliers, leverage indices were examined for each participant based on his/her multivariate profile for the variables included in the model analyses. A leverage score four times greater than the mean leverage indicated presence of outliers. Only outlier cases that were uninterpretable and significantly impossible were eliminated from final model analysis (N=27). Model-based were defined as a participant with an absolute standardized DfBeta coefficient > 1.0 and none were detected based upon this criterion.

Moderation analysis first requires the creation of product terms between each independent variable and each moderator, which represented the interaction effect (Aiken & West, 1991; Jaccard, Turrisi, & Wan, 1990). All predictor variables were centered to protect against multicollinearity.

After addressing all diagnostic statistics, the final hypothesized multivariate linear regression model was analyzed using the Mplus software version 5.1 (Muthen & Muthen, 2008). Non-significant product terms were sequentially dropped from the model until only significant ones remained. The SEM approach tested a linear moderated model such that $Y = b_0 + b_1X_1 + b_2X_2 + b_3X_1X_2 + e$. Fit indices, path values and confidence intervals were reported.

Interaction effects and mediation were analyzed separately (Fairchild & Mackinnon, 2009; Ryu, West, & Sousa, 2009). After confirming that all variables considered for a mediation model were correlated, mediation was tested in four traditional steps (Baron & Kenny, 1986; James & Brett, 1984; Judd & Kenny, 1981): Step 1 was to test associations between independent variables and the mediator. Step 2 was to test associations between independent and dependent variables. Step 3 was to test the relationship between the mediator and dependent variables. Step 4 was to regress the independent variables on the dependent variables, controlling for the mediator to assess whether the association between independent and dependent variables persisted. Linear regression for testing mediation was conducted using SPSS version 20 (IBM, 2011). In addition, a Sobel Test was conducted to confirm mediation using the Sobel online calculator (Sobel, 1982).

RESULTS

The mean age of participants was 45 years; 66% were male, 77.3% reported their race as black and 13.5% reported their ethnicity as Hispanic (Table 2.1). Most (55.9%) participants reported at least high school graduation, but few (9%) were employed. Mean self-reported ART adherence over a one-week period was 93.5%, with 81.5% of participants reporting adherence of ≥ 95%. VL ranged from undetectable to over 900,000 copies per mL with a mean VL of 16,246 (64,685); 28% had <50 copies/mL. NC impairment was observed in 34 of participants. Mean scores on all three NC measures were significantly lower than mean scores healthy, uninfected norms (Table 2.2).

Table 2.1 (1). Sociodemographic characteristics of participants and descriptive statistics of variables in the model (N=246)

	Mean (SD) / N (%)	Skewness/ Kurtosis
Age	45.24 (7.04)	-0.58 / -0.05
Gender (Male)	161 (66%)	-0.68 / -1.55
Hispanic ethnicity (Yes)	33 (13.5%)	-
Race		-
Black	187 (77.3%)	-
White	36 (14.9%)	-
Years education		0.44/ -0.18
<8th grade	19 (7.8%)	-
Some high school	89 (36.3%)	-
High school graduate	70 (28.6%)	-
Some college/tech	53 (21.6%)	-
College degree	11 (4.5%)	-
Graduate training	3 (1.2%)	-
Employed (Yes)	22 (8.9%)	-
ART adherence (percent)[1]	93.5 (19.96)	-3.59/ 12.83
VL	16,948 (64,685)	7.06 / 58.27
VL (undetectable)	69 (28%)	-
Social Support (MOS)	13.30 (4.85)	-0.23 / -0.74
Stress (LES)	47.85 (34.46)	-0.33 / -0.88
Barriers to adherence (zero)	165 (89.2%)	3.37 / 11.30
Alcohol (# drinks/90 days)	173 (261.18)	3.18/ 12.02
Marijuana (# times using/90 days)	19.17 (34.77)	1.62 / 1.11
NC impairment (Yes)	84 (34.1%)	0.54 -1.71

[1] Median adherence = 100%

Table 2.2 (2). Neurocognitive scores for participants and healthy norms (N=246)

NC Instrument	Raw Score (SD)	Norms
CTT2	129.14 (53.72)*	96.35 (29.57)
SCT	36.65 (15.58)*	27.35 (12.1)
AVLT	43.13 (9.44)*	51.1 (8.6)

*significant at $p<0.001$

The sample size (246) accounted for at least 5% of unique variance in the outcome, modeling for multiple regression analysis with 11 predictors, squared multiple correlation of 0.10 (the lowest observed in the modeling) and a 0.05 alpha level, yielding a satisfactory power coefficient of 0.98. The mean leverage score across participants was 0.139, and 27 outliers were identified based upon the leverage score criterion described above. None of the correlations to assess missing data bias were statistically significant, indicating that data were missing at random. After examining data for distribution issues, outliers and patterns of missing data, the final moderated model was tested (Figure 2.1), presenting both significant and non-significant path coefficients of the final model with non-significant product terms removed. The straight lines with arrows from observed variables represent presumed pathways of association and the values along the pathways are unstandardized path coefficients—expressed in terms of actual scores. All exogenous variables were assumed to be correlated. Unstandardized path coefficients, standard errors and 95% confidence intervals are listed in Table 2.3. The final model was just identified and no fit indices are reported.

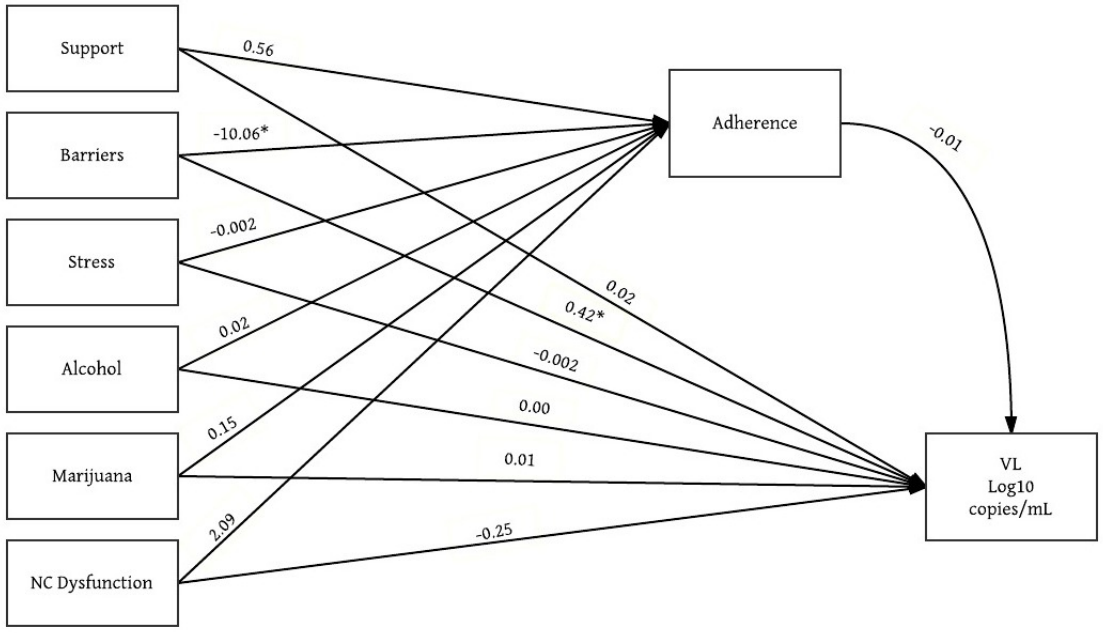
The final model explained 31% of variance in ART adherence and 18% of variance in log10 VL. When examining associations between predictors and outcomes, two significant paths were identified. Each increase in number of barriers to adherence predicted a 10.06% decrease in adherence to ART and also predicted a 0.42 unit increase in log10 VL. No interaction effects were identified.

A modest association between marijuana use and ART adherence was observed and approached significance (β=0.15, p=0.057); however the variable "barriers to medication adherence" was the only independent variable significantly associated with

both ART adherence and VL in the SEM, so this was the only variable considered for further testing in a mediated relationship. Barriers, ART adherence and VL were significantly correlated (Table 2.4).

Linear regression results for mediation testing are reported in Table 2.5. Step 1: "Barriers" was significantly negatively associated with adherence (β=-9.47; $p < 0.001$). Step 2: "Barriers" was significantly associated with higher VL (β= 0.30; p=0.002). Step 3: Adherence was associated with lower VL (β=-0.02; p=0.05). Step 4: "Barriers" ceased to be associated with VL when controlling for adherence (β=0.20; p=0.09). This suggests that mediation was not full, as confirmed by the Sobel Test (β=0.99, p=0.32) but much of the effect of "barriers to adherence" on VL was apparently due to their effect on ART adherence.

Figure 2.2 (2). Regression paths among measured variables in the structural equation model among HIV-positive alcohol abusers (N=246)



*P<0.05
Regression coefficients (represented as one-way arrows) are unstandardized.

Table 2.3 (3). Unstandardized path coefficients, standard errors, 95% confidence intervals and p-values (N=246)

		Coefficient	SE	95% CI	P
Support	Adherence	0.56	0.41	-0.49, 1.60	0.17
	VL	0.02	0.13	-0.05, 0.08	0.54
Stress	Adherence	-0.002	0.05	-0.13, 0.13	0.97
	VL	-0.002	0.004	-0.01, 0.01	0.57
Barriers to Adherence	Adherence	-10.06	1.72	-14.49, -5.63	<0.001
	VL	0.42	0.13	0.08, 0.75	0.001
NC[1]Impairment	Adherence	2.09	2.29	-3.81, 7.99	0.36
	VL	-0.25	0.26	-0.91, 0.41	0.33
Marijuana	Adherence	0.15	0.08	-0.05, 0.34	0.06
	VL	0.01	0.01	-0.01, 0.02	0.14
Alcohol	Adherence	0.02	0.07	-0.18, 0.21	0.84
	VL	0.00	0.01	-0.02, 0.02	0.95
Age	Adherence	0.19	0.19	-0.30, 0.69	0.31
	VL	0.02	0.02	-0.04, 0.07	0.44
Education	Adherence	1.51	1.52	-2.40, 5.42	0.32
	VL	-0.15	0.11	-0.44, 0.13	0.16
Gender	Adherence	3.63	2.91	-3.86, 11.11	0.21
	VL	0.20	0.29	-0.45, 0.85	0.49

[1] NC Neurocognitive

Table 2.4 (4). Correlation matrix for all variables in the model (N=246)

	1	2	3	4	5	6	7	8	9	10
1.Adhere	1.00									
2. VL	-0.26*	1.00								
3.Support	0.15	-0.01	1.00							
4. Stress	0.04	-0.06	0.02	1.00						
5. Barriers	-0.50*	0.36*	-0.07	0.02	1.00					
6. NC.Impairment	0.06	-0.08	0.00	0.14	-0.01	1.00				
7. Alcohol	0.01	0.01	-0.07	-0.06	0.00	0.08	1.00			
8. Marijuana	0.11	0.10	-0.04	-0.04	0.04	0.00	-0.04	1.00		
9. Age	0.08	0.01	-0.16	-0.07	0.06	0.14	0.02	0.18	1.00	
10. Gender	0.06	0.08	-0.13	-0.13	0.15	0.03	0.08	0.10	-0.04	1.00
11. Education	0.01	-0.06	-0.03	-0.17	-0.01	-0.11	-0.04	-0.02	0.00	0.06

*Significant at $p<0.01$

Table 2.5 (5). Linear regressions, test for mediation (N=246)

	Unstd. β	SE	95% CI	P	R^2
Barriers[1] =>Adherence	-9.47	1.03	-11.50, -7.43	0.00	0.35
Barriers =>VL	0.30	0.10	0.11, 0.49	0.002	0.08
ART Adherence=>VL	-0.02	0.01	-0.03, -0.003	0.02	0.05
Barriers (control for Adherence) =>VL	0.21	0.01	-0.03, 0.01	0.09	0.1
Adherence (control for Barriers) =>VL	-0.01	0.01	-0.03, 0.009	0.29	0.1

[1] Barriers to ART Adherence
Sobel p=0.32

DISCUSSION

Results from this study provide modest support for a biopsychosocial approach to understanding the HIV-related health outcome studied, specifically, virologic suppression. The biopsychosocial model suggests that psychosocial, cognitive and behavioral factors may directly influence a biomedical outcome (Engel, 1977). This model has been successfully applied to disease processes and causes (Alonso, 2004; Matarazzo & Leckliter, 1988) but less successfully applied to health outcomes. When used to examine health outcomes, the biopsychoscial model is most often applied to

disease symptoms such as pain (Jones et al., 2002; McLean, Clauw, Abelson, & Liberzon, 2005), and biomarkers of chronic disease (blood pressure, blood sugar) or gastrointestinal illnesses (Drossman, 1998). In HIV infection, a considerable body of evidence suggests that stressors may adversely affect biomarkers of disease progression, particularly CD4 count and mortality (Ironson & Hayward, 2008). Unlike VL, these health outcomes have been clearly linked to the stress-response system, also termed the hypothalamo-pituitary-adrenal (HPA) axis. In a comprehensive review of empirical studies, Cole (2008) suggested that sympathetic nervous system and HPA axis mediation may exist between psychosocial factors and HIV pathogenesis, that is, how HIV causes illness, particularly immunosuppression. Less support exists for a direct link between HPA axis function and VL.

In this study, the only psychosocial variable found to be significantly associated with VL was barriers to adherence to ART. Although it is a measure of perceived barriers, this construct may be a proxy for ART adherence itself. Hence, this study provides only modest support for the application of a biopsychosocial model predicting VL among PLWH. The relationship between number of barriers and actual adherence rates has been observed in other studies (Catz et al., 2000). However, no such studies were identified that include VL as a health outcome. The present study suggests, however, that ART adherence does not mediate fully the relationship between perceived barriers and VL. Were adherence to mediate fully the relationship between barriers and VL, no direct influence of the psychosocial predictor on the biomedical outcome could be supported.

Identifying direct links between psychosocial factors and HIV biomarkers has proved challenging. Thornton et al., (2000) conducted a longitudinal analysis of CD4 count and time to AIDS diagnosis, predicted by stressful life events and social support. Neither was found to be significantly associated with these outcomes. In addition, a meta-analysis conducted by Zorilla, et al. similarly found no psychosocial predictors of HIV progression (Zorrilla, McKay, Luborsky, & Schmidt, 1996). Finally, Solano et al., (1993) reported several psychosocial variables associated with disease progression in PLWH with poorer immune functioning, although these were not strong predictors for those with higher CD4 counts.

Multiple studies have revealed effects of stress or social support on HIV biomarkers or other indicators of disease progression (Ashton et al., 2005; Ironson & Hayward, 2008; Ironson, O'Cleirigh, et al., 2005; Leserman, 2008; Mugavero et al., 2013; Theorell et al., 1995). None of the studies describing such effects after the introduction of ART investigated the possibility of ART adherence acting as a mediating variable. As reported for a biopsychosocial model exploring the effects of stress, stability and treatment adherence on insulin-dependent diabetes (Peyrot, Mcmurry, & Kruger, 2013), medication adherence (ART adherence in the case of this study) is essential in chronic disease management to achieve optimal health outcomes.

Alcohol abuse has been shown to result in deleterious physical outcomes including poor adherence to health care recommendations, particularly for following a medication regimen (Bryant, 2006; Cook et al., 2001; Samet et al., 2004), however this study did not identify such associations. On the contrary, a modest positive association between marijuana use and ART adherence approached statistical significance in this

study. Although research has found marijuana use to decrease ART adherence (Tucker et al., 2003), some studies suggest that marijuana use may serve to reduce symptoms and improve ART adherence among PLWH (de Jong et al., 2005). It is possible that different degrees of use or dependence may play a role in whether this drug serves to improve or hinder ART adherence (Bonn-Miller, Oser, Bucossi, & Trafton, 2012).

Certain limitations of this study should be noted when interpreting results. First, participants were recruited from clinical sites, reducing generalizability to non-clinical samples. Also, about one-third of the sample was in residential drug or alcohol treatment at the time data were collected, and reporting bias may exist particularly for responses to questions about drug and alcohol use. The fact that many participants were engaged in care may also account for the unusually high adherence rates reported in this sample. High adherence rates may also be explained by the use of self-report measurement which has been found to provide inflated values (Cramer, Mattson, Prevey, Scheyer, & Ouellette, 2013; Waterhouse, 1993). Finally, findings reported are based on a cross-sectional analysis. In examining mediation, Maxwell and Cole (2007) note that estimates using cross-sectional data may be biased (as compared with longitudinal data) because of the failure to allow for autoregressive effects of the mediator and outcome variables. Baron and Kenny (1986), Holland (2013), and MacKinnon (2007) caution that without a randomized experiment one cannot rule out possible alternative explanations accounting for significant associations identified.

Findings from this study suggest that viral suppression among PLWH is largely a product of ART adherence, with a modest direct effect of psychosocial factors. Since ART adherence remains the primary predictor of virologic suppression and improved

health outcomes among PLWH, fostering adequate medication management must remain a priority for the HIV care community. However, ART adherence rates are subject to fluctuations based upon stress, social support, NC impairment and drug and alcohol use. Thus, maintaining a holistic perspective of health care and regard for the myriad psychosocial factors in the lives of PLWH can improve health outcomes. It is important to assess broader, more ecological models for determining health outcomes such as viral load when a biomedical approach alone has failed to eradicate HIV progression and transmission. Findings from this study may help shed light on psychosocial factors associated with HIV-related health and illness that are responsive to intervention.

REFERENCES

Aiken, L., & West, S. (1991). *Multiple Regression: Testing and Interpreting Interactions*. Newbury Park, CA: Sage Publications.

Alonso, Y. (2004). The biopsychosocial model in medical research: the evolution of the health concept over the last two decades. *Patient Education and Counseling*, *53*(2), 239–44. doi:10.1016/S0738-3991(03)00146-0

Amico, K. R., & Orrell, C. (2013). Antiretroviral therapy adherence support: recommendations and future directions. *Journal of the International Association of Providers of AIDS Care*, *12*(2), 128–37. doi:10.1177/1545109712459041

Antinori, A., Arendt, G., Becker, J. T., Brew, B. J., Byrd, D. A., Cherner, M., … Wojna, V. E. (2007). Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*, *69*(18), 1789–99. doi:10.1212/01.WNL.0000287431.88658.8b

Applebaum, A. J., Reilly, L. C., Gonzalez, J. S., Richardson, M. A., Leveroni, C. L., & Safren, S. A. (2009). The impact of neuropsychological functioning on adherence to HAART in HIV-infected substance abuse patients. *AIDS Patient Care and STDs*, *23*(6), 455–62. doi:10.1089/apc.2008.0181

Ashton, E., Vosvick, M., Chesney, M., Gore-Felton, C., Koopman, C., O'Shea, K., … Spiegel, D. (2005). Social support and maladaptive coping as predictors of the change in physical health symptoms among persons living with HIV/AIDS. *AIDS patient care and STDs*, *19*(9), 587–98. doi:10.1089/apc.2005.19.587

Bangsberg, D., Hecht, F., Charlebois, E., Zolopa, A., Holodniy, M., Sheiner, L., … Moss, A. (2000). Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS*, *14*(4), 357–66.

Bangsberg, D., Perry, S., Charlebois, E., Clark, R., Roberston, M., Zolopa, A., & Moss, A. (2001). Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS*, *15*(9), 1181–1183.

Baron, R. M., & 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*(3806354), 1173–1182.

Basso, M. R., & Bornstein, R. a. (2000). Neurobehavioural consequences of substance abuse and HIV infection. *Journal of Psychopharmacology*, *14*(3), 228–237. doi:10.1177/026988110001400306

Bonn-Miller, M. O., Oser, M. L., Bucossi, M. M., & Trafton, J. a. (2012). Cannabis use and HIV antiretroviral therapy adherence and HIV-related symptoms. *Journal of behavioral medicine*. doi:10.1007/s10865-012-9458-5

Bono, G., Mauri, M., Sinforiani, E., Barbarini, G., Minoli, L., & Fea, M. (1996). Longitudinal neuropsychological evaluation of HIV-infected intravenous drug users. *Addiction*, *91*, 263–268.

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), 1465–507. doi:10.1080/10826080600846250

Bryant, K. J., Nelson, S., Braithwaite, R. S., & Roach, D. (2010). Integrating HIV/AIDS and alcohol research. *Alcohol Research & Health*, *33*(3), 167–178.

Carey, M. P., Carey, K. B., Maisto, S. A., Gordon, C. M., & Weinhardt, L. S. (2001). Assessing sexual risk behaviour with the Timeline Followback (TLFB) approach: continued development and psychometric evaluation with psychiatric outpatients. *International Journal of STD & AIDS*, *12*(6), 365–375. doi:10.1258/0956462011923309

Carpenter, C. C. J., Fischl, M. A., Hammer, S. M., Hirsch, M. S., Jacobsen, D. M., Katzenstein, D. A., … Volberding, P. A. (1997). Antiretroviral therapy for HIV infection in 1997: Updated recommendations of the International AIDS Society - USA Panel. *Journal of the American Medical Association*, *277*(24), 1962–1969.

Catz, S. L., Kelly, J. A., Bogart, L. M., Benotsch, E. G., & Mcauliffe, T. L. (2000). Patterns , Correlates , and Barriers to Medication Adherence Among Persons Prescribed New Treatments for HIV Disease. *Health Psychology*, *19*(2), 124–133. doi:10.1037//0278-

Centers for Disease Control and Prevention Division of HIV/AIDS. (2012). *HIV Surveillance Report, 2010* (Vol. 22). Retrieved from http://www.cdc.gov/hiv/library/reports/surveillance/2011/surveillance_Report_vol_23.html

Cole, S. W. (2008). Psychosocial influences on HIV-1 disease progression: neural, endocrine, and virologic mechanisms. *Psychosomatic Medicine*, *70*(5), 562–8. doi:10.1097/PSY.0b013e3181773bbd

Cook, R., Sereika, S., Hunt, S., Woodward, W., Erlen, J., & Conigliaro, J. (2001). Problem drinking and medication adherence among persons with HIV infection. *Journal of General Internal Medicine*, *16*(2), 83–8.

Corless, I. B., Lindgren, T., Holzemer, W., Robinson, L., Moezzi, S., Kirksey, K., … Reynolds, N. (2009). Marijuana effectiveness as an HIV self-care strategy. *Clinical Nursing Research*, *18*(2), 172–93. doi:10.1177/1054773809334958

Cramer, J. A., Mattson, R. H., Prevey, M. L., Scheyer, R. D., & Ouellette, V. L. (1989). How often is medication taken as prescribed?. JAMA: *the Journal of the American Medical Association, 261(22),* 3273-3277.

D'Elia L, S. P. (1989). *Color Trails 1 and 2*. Odessa, FL: Psychological Assessment Resources.

D'Elia, L., Satz, P., Uchiyama, C., & White, T. (1996). *Color Trails Test professional manual*. Odessa, FL: Psychological Assessment Resources.

De Jong, B. C., Prentiss, D., McFarland, W., Machekano, R., & Israelski, D. M. (2005). Marijuana use and its association with adherence to antiretroviral therapy among HIV-infected persons with moderate to severe nausea. *Journal of Acquired Immune Deficiency Syndromes*, *38*(1), 43–6.

Deeks, S. G., Smith, M., Holodniy, M., & Kahn, J. O. (1997). HIV-1 protease inhibitors. A review for clinicians. *Journal of the American Medical Association*, *277*(2), 145–53.

Descamps, D., & Flandre, P. (2000). Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy. *Journal of the American Medical Association*, *283*(2), 205–212.

Diiorio, C., McCarty, F., Depadilla, L., Resnicow, K., Holstad, M. M., Yeager, K., … Lundberg, B. (2009). Adherence to antiretroviral medication regimens: a test of a psychosocial model. *AIDS and Behavior*, *13*(1), 10–22. doi:10.1007/s10461-007-9318-4

DiMatteo, M. R. (2004). Social support and patient adherence to medical treatment: a meta-analysis. *Health Psychology*, *23*(2), 207–18. doi:10.1037/0278-6133.23.2.207

Drossman, D. A. (1998). Presidential address: Gastrointestinal illness and the biopsychosocial model. *Psychosomatic medicine*, *60*(3), 258–67.

Durvasula, R., Norman, L., & Malow, R. (2009). Current perspectives on the neuropsychology of HIV. In M. R. Pope C, White R (Ed.), *HIV/AIDS: Global Frontiers in Prevention/Intervention* (pp. 177–190). New York: Routledge.

Engel, G. L. (1977). The need for a new medical model: A challenge for biomedicine. *Science*, *196*(4286), 129–196.

Fairchild, A. J., & Mackinnon, D. P. (2009). A geneeral model for testing mediation and moderation effects. *Prevention Science*, *10*(2), 87–99. doi:10.1007/s11121-008-0109-6.A

Fals-Stewart, W., O'Farrell, T. J., Freitas, T. T., McFarlin, S. K., & Rutigliano, P. (2000). The timeline followback reports of psychoactive substance use by drug-abusing patients: psychometric properties. *Journal of Consulting and Clinical Psychology, 68(1),* 134.

Gallant, J., & Block, D. (1998). Adherence to antiretroviral regimens in HIV-infected patients: results of a survey among physicians and patients. *Journal of the International Association of Physicians in AIDS Care*, *4*(5), 32–5.

Gallant, M. (2003). The Influence of Social Support on Chronic Illness Self-Management: A Review and Directions for Research. *Health Education & Behavior*, *30*(2), 170–195. doi:10.1177/1090198102251030

Halstead, W. (1947). *Brain and Intelligence*. Chicago: University of Chicago Press.

Herrmann, S., McKinnon, E., John, M., Hyland, N., Martinez, O. P., Cain, A., … Mallal, S. (2008). Evidence-based, multifactorial approach to addressing non-adherence to antiretroviral therapy and improving standards of care. *Internal Medicine Journal*, *38*(1), 8–15. doi:10.1111/j.1445-5994.2007.01477.x

Hinkin, C., Castellon, S., & Durvasula, R. (2002). Medication adherence among HIV+ adults Effects of cognitive dysfunction and regimen complexity. *Neurology*, *59*(12), 1944–1950.

Hinkin, C., & Hardy, D. (2004). Medication adherence in HIV-infected adults: effect of patient age, cognitive status, and substance abuse. *AIDS*, *18*(Suppl 1), 1–13.

Holland, P. W. (2013). Causal Inference , Path Analysis, and Recursive Structural Equations Models. *American Sociological Association, 18*(1988), 449–484.

IBM Corporation. (2010). IBM SPSS Base 19.0 for Windows User's Guide. IBM Corporation, New York.

Ironson, G., Balbin, E., Stuetzle, R., Fletcher, M. A., O'Cleirigh, C., Laurenceau, J. P., … Solomon, G. (2005). Dispositional optimism and the mechanisms by which it predicts slower disease progression in HIV: proactive behavior, avoidant coping, and depression. *International Journal of Behavioral Medicine*, *12*(2), 86–97. doi:10.1207/s15327558ijbm1202_6

Ironson, G., & Hayward, H. (2008). Do positive psychosocial factors predict disease progression in HIV-1? A review of the evidence. *Psychosomatic Medicine*, *70*(5), 546–54. doi:10.1097/PSY.0b013e318177216c

Ironson, G., O'Cleirigh, C., Fletcher, M. A., Laurenceau, J. P., Balbin, E., Klimas, N., … Solomon, G. (2005). Psychosocial factors predict CD4 and viral load change in men and women with human immunodeficiency virus in the era of highly active antiretroviral treatment. *Psychosomatic Medicine*, *67*(6), 1013–21. doi:10.1097/01.psy.0000188569.58998.c8

Jaccard, J., Turrisi, R., & Wan, C. (1990). *Interaction Effects in Multiple Regression*. Newbury Park, CA: Sage Publications.

Jaccard, J., & Wan, C. (1996). *LISREL approaches to interaction effects in multiple regression*. Thousand Oaks, CA: Sage Publications.

James, L. R., & Brett, J. M. (1984). Mediators, moderators, and tests for mediation. *Journal of Applied Psychology*, *69*(2), 307–321. doi:10.1037//0021-9010.69.2.307

Jones, M., Edwards, I., & Gifford, L. (2002). Conceptual models for implementing biopsychosocial theory in clinical practice. *Manual Therapy*, *7*(1), 2–9. doi:10.1054/math.2001.0426

Judd, C. M., & Kenny, D. a. (1981). Process analysis: Estimating mediation in treatment evaluations. *Evaluation Review*, *5*(5), 602–619. doi:10.1177/0193841X8100500502

Katzenstein, D. A. (1997). Adherence as a particular issue with protease inhibitors. *The Journal of the Association of Nurses in AIDS Care*, *8 Suppl*, 10–7.

Leigh, H., & Reiser, M. (1985). *The patient: Biological, psychological, and social dimensions of medical practice.* Plenum Medical Book Company.

Leserman, J. (2008). Role of depression, stress, and trauma in HIV disease progression. *Psychosomatic Medicine*, *70*(5), 539–45. doi:10.1097/PSY.0b013e3181777a5f

Leserman, J., Pence, B. W., Whetten, K., Mugavero, M. J., Thielman, N. M., Swartz, M. S., & Stangl, D. (2007). Relation of lifetime trauma and depressive symptoms to mortality in HIV. *The American Journal of Psychiatry*, *164*(11), 1707–13. doi:10.1176/appi.ajp.2007.06111775

Lezak, M. (2004). *Neuropsychological Assessment* (4th ed.). New York: Oxford University Press.

Lima, V. D., Bangsberg, D. R., Harrigan, P. R., Deeks, S. G., Hogg, R. S., & Montaner, J. S. G. (2011). Risk of Viral Failure Declines with Duration of Suppression on.

Journal of Acquired Immune Deficiency Syndromes, *55*(4), 460–465. doi:10.1097/QAI.0b013e3181f2ac87.Risk

Lucas, G. M., Griswold, M., Gebo, K. a, Keruly, J., Chaisson, R. E., & Moore, R. D. (2006). Illicit drug use and HIV-1 disease progression: a longitudinal study in the era of highly active antiretroviral therapy. *American Journal of Epidemiology*, *163*(5), 412–20. doi:10.1093/aje/kwj059

MacKinnon, D. (2007). *Introduction to statistical mediation analysis*. CRC Press.

Maj, M., Satz, P., Janssen, R., Zaudig, M., Starace, F., D'Elia, L., ... & Sartorius, N. (1994). WHO Neuropsychiatric AIDS Study, cross-sectional phase II: neuropsychological and neurological findings. *Archives of General Psychiatry*, *51*(1), 51.

Mannheimer, S. B., Morse, E., John, P., & Andrews, L. (2006). Sustained benefit from a long-term antiretroviral adherence intervention. *Journal of Acquired Immune Deficiency Syndromes*, *43*, 41–47.

Mannheimer, SB, Matts, J., Telzak, E., & Chesney, M. (2010). Psychological and socio-medical aspects of AIDS / HIV quality of life in HIV-infected individuals receiving antiretroviral therapy is related to adherence. *AIDS Care*, *17*(1), 10–22.

Mannheimer, Sharon, Friedland, G., Matts, J., Child, C., & Chesney, M. (2002). The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. *Clinical Infectious Diseases*, *34*(8), 1115–21. doi:10.1086/339074

Matarazzo, J., & Leckliter, I. (1988). Behavioral health: the role of good and bad habits in health and illness. In S. Maes, C. Spielberger, P. Defares, & I. Sarason (Eds.), *Topics in health psychology* (pp. 3–18). Chichester: Wiley.

Matarazzo, J., Weiss, S., Herd, J., & Miller, N. (Eds.). (1984). *Behavioral health. A handbook of health enhancement and disease prevention*. New York: Wiley.

Maxwell, S. E., & Cole, D. A. (2007). Bias in cross-sectional analyses of longitudinal mediation. *Psychological Methods*, *12*(1), 23–44. doi:10.1037/1082-989X.12.1.23

McLean, S.A, Clauw, D. J., Abelson, J. L., & Liberzon, I. (2005). The development of persistent pain and psychological morbidity after motor vehicle collision: integrating the potential role of stress response systems into a biopsychosocial model. *Psychosomatic Medicine*, *67*(5), 783–90. doi:10.1097/01.psy.0000181276.49204.bb

Mugavero, M. J., Amico, K. R., Westfall, A. O., Crane, H. M., Kitahata, M., & Saag, M. S. (2013). Early retention in HIV care and viral load supression: Implications for a

test and treat approach to HIV prevention. *Journal of Acquired Immune Deficiency Syndromes*, *59*(1), 86–93. doi:10.1097/QAI.0b013e318236f7d2.

Mugavero, M. J., Raper, J. L., Reif, S., Whetten, K., Leserman, J., Thielman, N. M., & Pence, B. W. (2009). Overload: impact of incident stressful events on antiretroviral medication adherence and virologic failure in a longitudinal, multisite human immunodeficiency virus cohort study. *Psychosomatic Medicine*, *71*(9), 920–6. doi:10.1097/PSY.0b013e3181bfe8d2

Muthen, B., & Muthen, L. (2008). *Mplus Version 5.1*. Los Angeles: Muthen & Muthen.

Novack, D. H., Cameron, O., Epel, E., Ader, R., Waldstein, S. R., Levenstein, S., … Wainer, A. R. (2012). Psychosomatic medicine: the scientific foundation of the biopsychosocial model. *Academic Psychiatry*, *31*(5), 388–401. doi:10.1176/appi.ap.31.5.388

O'Cleirigh, C., Ironson, G., Weiss, A., & Costa, P. T. (2007). Conscientiousness predicts disease progression (CD4 number and viral load) in people living with HIV. *Health Psychology*, *26*(4), 473–80. doi:10.1037/0278-6133.26.4.473

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

Peyrot, M., Mcmurry, J. F., & Kruger, D. F. (2013). A Biopsychosocial Model of Glycemic Control in Diabetes : Stress, Coping and Regimen Adherence. *Journal of Health and Social Behavior*, *40*(2), 141–158.

Prentiss, D., Power, R., Balmas, G., Tzuang, G., & Israelski, D. M. (2004). Patterns of marijuana use among patients with HIV/AIDS followed in a public health care setting. *Journal of Acquired Immune Deficiency Syndromes*, *35*(1), 38–45.

Quinn, T. C., Wawer, M. J., Sewankambo, M., Serwadda, D., Li, C., Wabwire-Mangen, F., … Gray, R. H. (2000). Viral load and heterosexual transmission of human immunodeficiency virus type 1. *New England Journal of Medicine*, *342*(13), 921–929.

Rey, A. (1964). *L'examen Clinique en Psychologie*. Paris: Universitaires de France.

Ryu, E., West, S. G., & Sousa, K. H. (2009). Mediation and Moderation: Testing Relationships Between Symptom Status, Functional Health, and Quality of Life in HIV Patients. *Multivariate Behavioral Research*, *44*(2), 213–232. doi:10.1080/00273170902794222

Sacktor, N., McDermott, M. P., Marder, K., Schifitto, G., Selnes, O. A, McArthur, J. C., … Epstein, L. (2002). HIV-associated cognitive impairment before and after the advent of combination therapy. *Journal of Neurovirology*, *8*(2), 136–42. doi:10.1080/13550280290049615

Sacktor, N., Skolasky, R., Selnes, O. A, Watters, M., Poff, P., Shiramizu, B., … Valcour, V. (2007). Neuropsychological test profile differences between young and old human immunodeficiency virus-positive individuals. *Journal of Neurovirology*, *13*(3), 203–9. doi:10.1080/13550280701258423

Safren, S. A., Otto, M. W., Worth, J. L., Salomon, E., Johnson, W., Mayer, K., & Boswell, S. (2001). Two strategies to increase adherence to HIV antiretroviral medication: life-steps and medication monitoring. *Behaviour Research and Therapy*, *39*(10), 1151–62.

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. doi:10.1097/01.ALC.0000122103.74491.78

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

Sarafino, E. (Ed.). (1994). *Health psychology. Biopsychosocial interactions.* . New York: Wiley.

Sarason, I., Johnson, J., & Siegel, J. (1978). Assessing the impact of life changes: Development of the Life Experiences Survey. *Journal of Consulting and Clinical Psychology*, *46*(5), 392–46.

Schroder, K., Carey, M., & Vanable, P. (2003). Methodological challenges in research on sexual risk behavior: II. Accuracy of self-reports. *Annals of Behavioral Medicine*, *26*(2), 104–123.

Selnes, O., Galai, N., McArthur, J., & Cohn, S. (1997). HIV infection and cognition in intravenous crug users: Long-term follow-up. *Neurology*, *48*, 227–229.

Sherbourne, C., & Stewart, A. (1991). The MOS Social Support Survey. *Social Science & Medicine*, *32*(6), 705–714.

Silverberg, N. D., & Millis, S. R. (2009). Impairment versus deficiency in neuropsychological assessment: Implications for ecological validity. *Journal of the*

International Neuropsychological Society, *15*(1), 94–102. doi:10.1017/S1355617708090139

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. doi:10.1037/0278-6133.25.1.74

Sobel, M. (1982). Asymptotic confidence intervals for indirect effects in structural equation models. In S. Leinhardt (Ed.), *Sociological Methodology* (pp. 290–312). Washington DC: American Sociological Association.

Solano, L, Costa, M., Salvati, S., Coda, R., Aiuti, F., Mezzaroma, I., & Bertini, M. (1993). Psychosocial factors and clinical evolution in HIV-1 infection: a longitudinal study. *Journal of Psychosomatic Research*, *37*(1), 39–51.

Solano, Luigi, Costa, M., Temoshok, L., Coda, R., Aiuti, F., Sora, F. Di, … Bertini, M. (2002). Social support and the development of immune function in human immunodeficiency virus infection. *Psychology and Health*, *17*(5), 641–655.

Stern, R., Silva, S., Chaisson, N., & Evans, D. (1996). Influence of cognitive reserve on neuropsychological functioning in asymptomatic human immunodeficiency virus-1 infection. *Archives of Neurology*, *53*, 148–153.

Theorell, T., Blomkvist, V., Jonsson, H., Schulman, S., Berntorp, E., & Stigendal, L. (1995). Social support and the development of immune function in human immunodeficiency virus infection. *Psychosomatic Medicine*, *57*(1), 32–6.

Thornton, S., Troop, M., Burgess, A. P., Button, J., Goodall, R., Flynn, R., … Easterbrook, P. J. (2000). The relationship of psychological variables and disease progression among long-term HIV-infected men. *International Journal of STD & AIDS*, *11*(11), 734–742. doi:10.1258/0956462001915165

Tozzi, V., Balestra, P., Bellagamba, R., Corpolongo, A., Salvatori, M. F., Visco-comandini, U., … Narciso, P. (2007). Persistence of neuropsychologic deficits despite long-term highly active antiretroviral therapy in patients prevalence and risk Factors. *Journal of Acquired Immune Deficiency Syndromes*, *45*(2), 174–182.

Tucker, J. S., Burnam, M. A., Sherbourne, C. D., Kung, F., & 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*, 573–580. doi:10.1016/S0002-9343(03)00093-7

Van der Elst, W., van Boxtel, M. P. J., van Breukelen, G. J. P., & Jolles, J. (2005). Rey's verbal learning test: normative data for 1855 healthy participants aged 24-81 years

and the influence of age, sex, education, and mode of presentation. *Journal of the International Neuropsychological Society*, *11*(3), 290–302. doi:10.1017/S1355617705050344

Volkow, N. D. (2012). Support for HIV-infected substance users. *Journal of the American Medical Association*, *303*(14), 1423–24.

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 and Behavior*, *10*(3), 287–97. doi:10.1007/s10461-005-9062-6

Waterhouse, D. M., Calzone, K. A., Mele, C., & Brenner, D. E. (1993). Adherence to oral tamoxifen: a comparison of patient self-report, pill counts, and microelectronic monitoring. *Journal of Clinical Oncology, 11(6),* 1189-1197.

Weinhardt, L S, Carey, M. P., Maisto, S. A., Carey, K. B., Cohen, M. M., & Wickramasinghe, S. M. (1998). Reliability of the timeline follow-back sexual behavior interview. *Annals of Behavioral Medicine*, *20*(1), 25–30.

Weinhardt, Lance S, Otto-Salaj, L. L., Brondino, M. J., Norberg, M. M., & Kalichman, S. C. (2002). Sex-related alcohol expectancies predict sexual risk behavior among severely and persistently mentally ill adults. *Psychology of Addictive Behaviors*, *16*(1), 64–67. doi:10.1037//0893-164X.16.1.64

Wetzel, L., & Boll, T. (1987). *Short Category Test, Booklet Format*. Los Angeles: Western Psychological Services.

Woloshin, S., Schwartz, L. M., Tosteson, A. N. A., Chang, C., Wright, B., Plohman, J., & Fisher, E. S. (1993). Perceived Adequacy of Tangible Social Support and Artery Disease. *Journal of General Internal Medicine*, *12*, 613–618.

Wang, H., He, G., Li, X., Yang, A., Chen, X., Fennie, K. P., & Williams, A. B. (2008). Self-reported adherence to antiretroviral treatment among HIV-infected people in Central China. *AIDS patient care and STDs, 22(1),* 71-80.

Wong, M. D., Sarkisian, C. a, Davis, C., Kinsler, J., & Cunningham, W. E. (2007). The association between life chaos, health care use, and health status among HIV-infected persons. *Journal of General Internal Medicine*, *22*(9), 1286–91. doi:10.1007/s11606-007-0265-6

Wright, M. J., Woo, E., Foley, J., Ettenhofer, M. L., Cottingham, M. E., Gooding, A. L., … Hinkin, C. H. (2011). Antiretroviral adherence and the nature of HIV- memory impairment. *Journal of Neurpsychiatry and Clinical Neurosciences*, *23*(3), 324–331.

Yuan, K., & Bentler, P. (2000). Three likelihood-based methods for mean and covariance structure analysis with nonnormal missing data. *Sociological Methodology*, *30*(1), 165–200.

Zorrilla, E., McKay, J., Luborsky, L., & Schmidt, K. (1996). Relation of stressors and depressive symptoms to clinical progression of viral illness. *The American Journal of Psychiatry*, *153*(5), 626–635.

CHAPTER V

TRANSITION TO MANUSCRIPT 3

Following is the final manuscript of this dissertation. This study evaluates the effectiveness of an evidence-based intervention on improving antiretroviral treatment adherence, increasing service utilization and reducing viral load among people living with HIV. Although Manuscripts 1 and 2 also examined data gathered in the same parent study, this study is prospective, utilizing data before and up to six months after the delivery of the intervention. Hence, the study population size is smaller than those of the former studies because of attrition: of the 337 participants assigned to cohorts at baseline, 211 were available to complete assessments at 6 months post-intervention.

Outcomes from the prior two cross-sectional manuscripts helped contribute to the conceptualization of this set of analyses. For example, Manuscript 1 provided information about the overall neurocognitive functioning for this sample, which helped explain how this intervention's cognitive remediation strategies may have aided in positive health behavior outcomes. In Manuscript 2 no association was found between tangible social support and ART adherence, so in this study the general social support scale was utilized. Although "barriers to adherence" was a significant predictor of adherence in Aim 2 of this dissertation, it was not central to the theoretical model for the following study and was therefore dropped.

MANUSCRIPT 3: EFFECTIVENESS OF AN EVIDENCE-BASED INTERVENTION IN IMPROVING TREATMENT ADHERENCE, SERVICE UTILIZATION AND VIRAL LOAD AMONG HIV-SEROPOSITIVE ADULT ALCOHOL USERS

ABSTRACT

Background: Up to 95% adherence to antiretroviral therapy (ART) may be necessary to sustain viral suppression and reduce risk of HIV transmission; however, achieving high levels of adherence may be challenging for people who abuse alcohol or suffer from neurocognitive impairment. This study evaluated whether a manual-guided intervention significantly improved ART adherence, service utilization and VL among HIV-positive adults with a history of alcohol abuse.

Methods: A total of 243 HIV-seropositive adults, recruited from community based organizations in South Florida were randomized to the Holistic Health Recovery Program (HHRP-A) or a comparison condition. Both groups attended eight sessions and provided self-reported data on outcomes, including adherence, service utilization, and viral load (VL), and on processes, including social support and stress. Data were collected at baseline, immediately post-intervention, 3-month, and 6-month follow-up time points.

Results: Participants were ≥18 and ≤60 ($\bar{x}$=45.7 years old), 74% male, and 78% black. Participants randomized to the HHRP-A condition were significantly more likely to report adequate ART adherence and to report an undetectable VL at 6 months post-intervention. An effect was also observed on social support, with participants in the HHRP-A condition showing significantly greater improvement than the comparison group.

Discussion: Findings suggest that providing comprehensive health promotion interventions, particularly those incorporating cognitive remediation strategies, could greatly improve self-reported health outcomes for HIV-seropositive substance users.
Key Words: HIV, alcohol, adherence, intervention, addiction

INTRODUCTION

Since the mid-1990s, antiretroviral therapy (ART) has successfully extended the lives of people living with HIV/AIDS (PLWH; Centers for Disease Control and Prevention Division of HIV/AIDS, 2012a, 2012b; Palella et al., 1998). Thus, the goal of HIV care has shifted toward achieving long-term optimal health outcomes through consistent treatment. Adequate adherence to ART improves health outcomes and is critical for successful disease management; conversely, inadequate treatment adherence is associated with increased morbidity and mortality, viral resistance, limited future treatment options and increased risk of HIV transmission to others (Bangsberg, Perry, & Charlebois, 2001; Bangsberg et al., 2000; Carpenter et al., 1997; Deeks, Smith, Holodniy, & Kahn, 1997; Paterson et al., 2000; Volkow & Montaner, 2010). As much as 95% adherence may be necessary to achieve positive clinical outcomes. However, achieving the level of adherence necessary to suppress viral replication can be challenging, with recent studies reporting that anywhere between 18% and 73% of PLWH are non-adherent to antiretroviral therapy (Bangsberg, Moss, & Deeks, 2004; Catz, Kelly, Bogart, Benotsch, & Mcauliffe, 2000; Lucas, 2005; Paterson et al., 2000; Tesoriero et al., 2003).

These adherence levels may be even lower for PLWH experiencing alcohol abuse or neurocognitive impairment [NCI] (Baum et al., 2010; Braithwaite & Bryant, 2010; Bryant, 2006; Cook et al., 2001; Hinkin, Castellon, & Durvasula, 2002; Rothlind et al., 2008), both of which are commonly comorbid with HIV. Alcohol abuse has been reported by up to 53% of adults with HIV (Galvan et al., 2002; Heaton et al., 2010) and NCI ranging from asymptomatic neurocognitive impairment (ANI) to HIV-associated dementia (HAD) has been observed in about 37% of adult PLWH (Sacktor, 2002). Heavy

alcohol use and NCI may have a negative synergistic effect on self-reported medication adherence and service utilization rates (Bass et al., 2012; Marx, Malka, Ravishankar, & Schwartz, 2011; Rothlind et al., 2005). Improving utilization of both HIV and substance abuse services is central to increasing treatment adherence and optimizing health outcomes for PLWH (Mugavero et al., 2009, 2013; White House Office of National AIDS Policy, 2010). Through adequate and consistent care, patients are better able to receive the support necessary to achieve adequate treatment adherence, sustain optimal health outcomes, and, ultimately, help to reduce the incidence of HIV. Hence, there remains a pressing need to continue developing, adapting, and testing evidence-based interventions aimed at improving service and care utilization and improving health behaviors such as ART adherence.

One theoretical framework that has effectively predicted HIV-related health behaviors in diverse samples is the Information-Motivation-Behavioral Skills (IMB) model (Fisher & Fisher, 1992). Several empirical tests of this model have established the strength of its three major constructs in predicting ART adherence and service utilization (Amico et al., 2005; Margolin et al., 2003; Smith, Fisher, Cunningham, & Amico, 2012; Starace et al., 2006). An adaptation of the IMB model proposed by Fisher et al. (2008) posits that ART treatment-related information and motivation to be adherent will operate through necessary behavioral skills to influence adherence-related health behaviors (Fisher, Amico, Fisher, & Harman, 2008). To benefit from an IMB-guided intervention, participants are expected to possess the cognitive capacity to process and translate intentions into health behaviors. These capacities may be diminished among HIV-

seropositive adults with a history of alcohol abuse (e.g., Farinpour et al., 2000), thus impeding their abilities to benefit from a therapeutic intervention.

This study evaluated the effectiveness of an IMB-based, manual-guided intervention on improving outcomes of viral load (VL), ART adherence and service utilization among PLWH with a history of alcohol abuse. While this intervention was geared primarily toward reducing sex and drug/alcohol risk behaviors, service utilization, ART adherence and virologic response were secondary aims of the intervention. Process variables associated with the development of these outcomes were derived from the Fisher et al. (2008) IMB adherence model and the buffering model of social support (Cohen & McKay, 1985). Prior research applying these models have found that both stress reduction and increasing social support are strongly predictive of ART adherence and service utilization outcomes (Catz et al., 2000; DiMatteo, 2004; Gonzalez et al., 2004; Mugavero et al., 2009; Simoni et al., 2002; Simoni, Frick, et al., 2006; Wong et al., 2007).

Using recommended methodologies for testing manual-guided interventions (Hirokazu, Wilson, Peterson, & Shinn, 2005), a randomized clinical trial was conducted to determine whether a manual-guided risk reduction intervention produced lower VL and greater antiretroviral treatment adherence and service utilization outcomes over and above a standard-of-care, health promotion comparison group. The delivery of a group intervention that included cognitive remediation strategies and addressed this population's unique needs was expected to facilitate learning and retention of risk reduction behavioral skills central to achieving these outcomes. In addition, the study sought to assess whether a reduction of stress and an increase in social support was

achieved and if these factors provided any additional contribution to achieving the intended outcomes.

METHODS

Participants

A total of 370 HIV-seropositive, alcohol-using adults were recruited from community-based organizations (CBOs) in Miami, Florida between January 2009 and November 2012. A slower recruitment period was planned to help prevent against treatment group contamination and group assignment bias. The inclusion criteria were: being 18-60 years old; documented HIV infection; having consumed any alcohol in the past 3 months; having a history of alcohol abuse or dependence within the past 2 years; displaying facility in English; ability to understand the informed consent; ability to be located for follow-up over the course of a year; willingness to be randomized to a treatment or control group; and currently not showing overt signs of major psychiatric disorder including psychosis or suicidality. An additional inclusion criterion for this study was self-report of current prescription of ART.

After participants completed the baseline assessment, they were entered into the study in cohorts of eight participants of the same gender. Cohorts were assigned to receive either the experimental or control condition according to a computer-generated random sequence. The random sequencing was expected to control for bias in subject assignments across conditions. Assessment methods included: CAPI (computer assisted personal interview); ACASI (audio computer assisted self-interview) for subjective sensitive topics; and paper and pen as specified for neurological measures. Data were

collected at baseline (T1), immediately post-intervention (T2), 3 month follow-up (T3), and 6 month follow-up (T4) for all measures; however, no adherence or stress data were collected at T2.

The research protocol was approved by the Institutional Review Board of Florida International University, and all participants provided signed informed consent prior to participating in the study. Participants were offered decremental monetary compensation: $50 gift cards to local stores upon completing the first assessment; $25 gift card upon completing post-assessments; $15 cash or gift card for attendance at each group session; and $5 cash for transportation.

Outcome measures

ART adherence was defined as the self-reported percentage of time ART medications were taken as prescribed over the course of a week. The Community Programs for Clinical Research on AIDS (Mannheimer, Matts, Telzak, & Chesney, 2010) assesses whether the individual has accurately taken all doses of the medications. For each antiretroviral medication taken, participants rated their adherence according to the scale: “all” (100%), “most” (75%), “about half” (50%), “few” (25%), or “none” (0%); the mean adherence for all medications was calculated (Mannheimer, Morse, John, & Andrews, 2006). Perfect adherence was defined as greater than 95%. While definitions of adherence have varied greatly in the literature, this cutoff was set to compare with the level established by Margolin (2003). Self-reported adherence was significantly correlated with serum VL at baseline (r_s=-0.33, p=0.02).

Service utilization was assessed using a section of the Treatment Services Review (TSR) portion of the CSAT-GPRA Client Outcome Measures for Discretionary Programs

(McLellan et al., 1992; Mclellan et al., 1989). The TSR is an instrument designed to collect intake data at addictions treatment facilities. The section of the assessment used in this study asked the participant "Are you currently or ever received any of the following Treatment Service?" The 52 services listed are relevant to HIV-positive substance abusers, including screening, recovery, case management, medical, after care, education, and peer-based recovery support services. Three additional items from the CPCRA were included: 1) "Do you receive any financial assistance to buy medications (such as ADAP, Ryan White or other government or charitable agency?"); 2) "Is there a clinic, health center, doctor's office, or some other place that you usually go if you are sick or need medical care?"; and 3) "Do you have health insurance?" The TSR has high test-retest reliability, concurrent validity in differentiating between levels of care (McLellan et al., 1992), and a Cronbach's alpha of 0.93 at baseline of this study.

Viral load (VL) was a self-report measure using a single question from the CPCRA (Mannheimer, Friedland, Matts, Child, & Chesney, 2002; McLellan et al., 1992). Participants were asked to "Indicate your viral load the last time it was measured" with available responses: 1) undetectable, 2) 50-500, 3) 501-5,000, 4) 5,001-10,000, 5) 10,001-30,000, 6) 30,001 or more, 7) don't know. Self-reported VL measures were significantly correlated with blood measures at baseline (r_s=-0.21, p=0.03). Percent reporting an undetectable VL was reported.

Process measures

Social support was measured using all 19 items from the Medical Outcomes Study (MOS; Sherbourne & Stewart, 1991). Questions concerned medical condition-related quality of life and comprised of four functional support scales:

emotional/informational, tangible, affectionate, and positive social interaction. Each item is rated from (1) "all of the time" to (5) "none of the time." The overall social support index (total score) was used, with a higher score indicating more support. The MOS was developed for patients involved in a 2-year study investigating chronic conditions. All subscales have shown strong reliability over time (alphas > 0.91). For this study sample the Cronbach's alpha was 0.96.

Stress was measured with 40 items modified from the Life Experiences Survey (Sarason, Johnson, & Siegel, 1978) and the Perceived Stress Scale (Cohen et al., 1983) developed by the Semel Institute-Neuropsychiatric Institute (NPI) of the University of California, Los Angeles (available at http://chipts.ucla.edu/wp-content/uploads/downloads/2012/02/Life-Events.pdf). The first section is a list of 32 events common to people in a wide variety of situations such as divorce, moving, and loss. If a participant indicated that an event occurred in the past three months, s/he rated it: (1) "very bad," (2) "somewhat bad," (3) "somewhat good," and (4) "very good." Items rated (1) or (2) were reverse scored and summed for a negative impact score. Items rated 3 or 4 were not counted (Sarason, et al., 1978). Eight additional items listed issues more specific to PLWH, such as their illness and alcohol use and rated on the degree to which each issue bothered them from (1) "not at all" to (5) "extremely." Items scored (3), (4), or (5) were recoded from 1-3 respectively and added to the negative impact score for a total of 88 possible points. Reliability for this measure was strong for this group with a Cronbach's alpha calculated at 0.95.

Treatment conditions

Experimental Condition (n=127, 52.3%)

The evidence-based intervention evaluated was an adapted version of the Holistic Health Recovery Program (HHRP-A) which has been translated to manual format for in detail uniform implementation (Margolin et al., 2003), and disseminated by the CDC's Diffusion of Effective Behavioral Intervention (DEBI) program (www.effectiveinterventions.org) program. Some HHRP-A core elements include teaching: decision-making and problem solving skills using cognitive remediation strategies; goal-setting skills, including developing action plans; skills to manage stress, including relaxation exercises and understanding what aspects of the stressful situation can, and cannot, be controlled; skills to improve health, healthcare participation, and adherence to medical treatments; skills to increase clients' access to their own self-defined spiritual beliefs, in order to increase motivation to engage in harm reduction behaviors; and skills to increase awareness of how different senses of self can affect self-efficacy and hopelessness. In addition, the group-based intervention is designed to promote interaction between participants so that they build positive social support networks with peers. Diffusing risk-reduction messages in peer-based social support networks may help to sustain benefits of HIV interventions (Latkin and Knowlton, 2006).

Per the design of the evidence-based HHRP, group facilitators were staff similar in profile to those of the CBO recruitment sites in that they had a high school-to-bachelor level education and were familiar with urban Miami-Dade County. Participants attended eight 2-hour sessions scheduled 1 to 2 times per week over consecutive weeks conducted from February 2009 through December, 2012. The HHRP therapy manual

(http://info.med.yale.edu/psych/3s/HHRP_manual.html) was highly structured, and involves both didactic presentation of material as well as experiential exercises. Content matter was comprehensive in order to address the medical, emotional, and spiritual needs of individuals living with HIV. Topics addressed by HHRP-A included: stress reduction, harm reduction skills training; relapse prevention; improving emotional, social, and spiritual health, including coping with stigma and grief; increasing medication adherence; improving participation in medical care; and making healthy lifestyle choices, including reducing HIV sexual transmission risk behavior. Each session was co-facilitated by two counselors using a nonjudgmental, motivational enhancing therapeutic style (Miller & Rollnick, 1991).

Cognitive remediation strategies (Miller, 1993) were incorporated because of the potential for NCI in this population. These strategies included: varied presentation modalities; repetition and review; behavioral games; memory books; reduction of distraction and fatigue; emphasis on structure and consistency; ongoing assessment of new learning and retention, with immediate provision of feedback, and stress management.

Comparison Condition (n=116, 47.7%)

The randomized design compared the experimental treatment to a Health Promotion Comparison (HPC) condition. The HPC was not designed to provide the IMB-driven techniques of HHRP-A. This condition was meant to be educational and didactic, addressing common health problems, personal hygiene, nutrition, physical fitness, smoking avoidance/cessation, and healthy living. HPC did not incorporate behavioral skills training or motivational enhancement techniques and did not promote interaction or

social support network development. HPC matched HHRP-A in total administration time and format (eight 2-hour sessions); however this modality was condensed and delivered over a period of only two days in order to reduce the risk of possible inflated effects in comparison group outcomes as a result of longer-term group involvement and attention.

As in HHRP-A, HPC was guided by a written manual, implemented, and held under the same conditions so as to produce equivalent facilitator attention and expectancy of benefit and to control for effects that could be attributed to nonspecific features of HHRP-A.

A standard care HIV education component was included in the HPC as it was deemed ethically responsible to include some HIV education in a comparison condition, given the high-risk nature of this population. Thus, one session of the HPC condition delivered a standard care level of HIV risk reduction, simulating what may be considered a "usual" care level that participants might expect to receive in a typical CBO program.

To prevent cross-group contamination, each cohort group was staggered in time and space (sessions were scheduled to take place at alternating locations). Since participants came from different locations, there was a reduced possibility of cohorts interacting and thus discussing their respective experiences on site. Finally, study coordinators estimated that any inadvertent exchange of information between HHRP-A and HPC members would be more likely to reduce the differences between the two groups than bias the results to inflate Type 1 errors.

Analysis

Analyses were conducted with SPSS version 20 (IBM, 2011). Continuous measures were service utilization, stress and social support. Data were assessed for

random missingness (MCAR) using Little's Missing Completely At Random Test (Allison, 2001; Little, 1988) and continuous quantitative missing values were imputed using the expectation maximization algorithm (Dempster et al., 1977). The three continuous variables were square root transformed for analysis due to moderate non-normal distribution (Tabachnick and Fidell, 2007; Howell, 2007). Change over time on continuous measures was analyzed using 2 X 3 or 4 repeated measures analyses of variance (ANOVAs) to account for treatment condition and time variables. Where change over time in any continuous variable was detected, effect sizes (partial η^2) were reported if statistically significant (Richardson, 2011).

For the dichotomous variables, VL (detectable or undetectable) and adherence ($\geq$95% versus lower), changes between each time point were analyzed using McNemar-Bowker tests (Bowker, 1948). Dichotomous variables were also cross-tabulated by treatment group at each time point using chi-square analyses. Rate (prevalence) ratios (RRs) and 95% confidence intervals (CIs) are presented. Significance criteria were Bonferroni-adjusted for number of analyses. Missing categorical data were not imputed.

Controlling for VL at baseline, Spearman's rank correlation between baseline adherence and VL at T4 was calculated as a partial test of veracity and accuracy of the self-reported adherence measure (Margolin et al., 2003), implicitly assuming absence of significant resistance to the antiretrovirals prescribed. Additional Spearman's rho and Pearson correlations (as appropriate) were calculated between process and outcome variables.

RESULTS

Socio-demographics

All consecutively recruited PLWH were screened for eligibility; 337 of the eligible participants met all requirements for randomization and the 243 who reported receiving ART at all time points were included in this study. Table 1 presents sociodemographic, HIV, and NC descriptive characteristics of the participants at baseline prior to randomization. The final sample for the intervention was 70.8% male and had a mean age of 45 (SD=6.9) years. Nearly 80% identified as African American and 12.2% as White. Fourteen percent considered themselves to be of Hispanic ethnicity. A total of 55% had at least a high school diploma and 9% were employed. At entry into the study, participants provided recent (within one month from intake) lab tests of CD4 count and VL; means were 440 and 11,588 copies/ml, respectively with 26% showing an undetectable viral load. A large proportion of participants displayed a degree of NCI; 38.7% scored at least one standard deviation below the mean for normative samples on at least two neuropsychological tests sensitive to a range of cognitive capacities (Antinori et al., 2007).

Table 3.1 (1). Descriptive characteristics of all randomized sample at baseline

	HHRP-A N=127 Mean (SD) N (%)	**HPC N=116 Mean (SD) N (%)**	**TOTAL N=243 Mean (SD) N(%)**
Age	45.71 (6.3)	44.68 (7.5)	45.22 (6.90)
Gender			
Male	93 (74%)	77 (67%)	170 (71%)
Female	32 (26%)	38 (33%)	70 (29%)
Education			
<8th Grade	9 (7%)	10 (9%)	19 (8%)
Some HS, not graduate a	45 (37%)	40 (36%)	85 (37%)
HS graduate or GED	32 (26%)	34 (31%)	66 (29%)

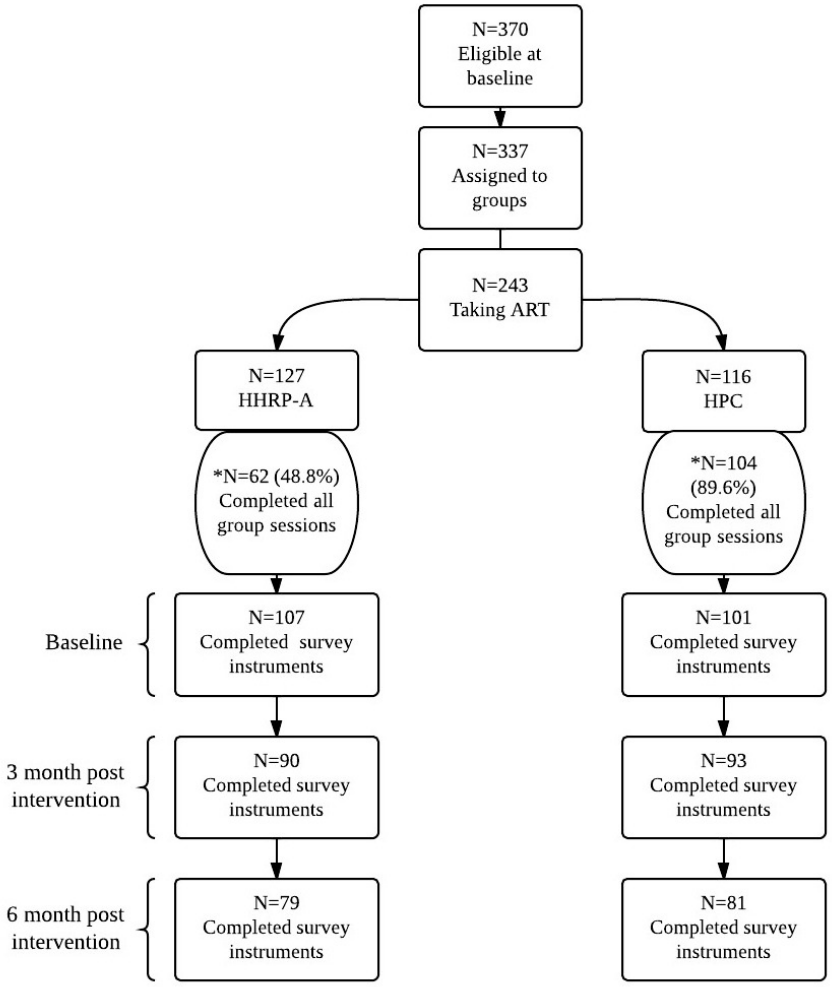
Some college	26 (22%)	19 (17%)	45 (19%)
College degree	7 (5.8%)	6 (6%)	13 (6%)
Any graduate training	2 (2%)	1 (1%)	3 (1%)
Hispanic Ethnicity	16 (13%)	17 (16%)	33 (14%)
Race			
Black	92 (78%)	87 (80%)	179 (79.6%)
White	17 (15%)	11 (10%)	28 (12.4%)
Employed (Yes)	9 (7%)	12 (11%)	21 (9%)
Years living with HIV	12.89 (6.92)	13.55 (7.53)	13.20 (7.23)
CD4 count (copies/ml)	449 (218)	430 (240)	440 (228)
Plasma Viral Load (copies/ml)[1]	10,870 (22,159)	13,411 (73,158)	12,083 (52,921)
Viral Load (<50 copies/mL)	25 (20%)	38 (33%)	63 (26%)
Neurocognitive functioning (raw scores)			
Auditory Verbal Learning Test	43.78 (9.04)	43.46 (9.75)	43.62 (9.35)
Short Category Test (trials 1-5)	37.23 (15.92)	39.95 (12.93)	38.53 (14.60)
Color Trails Test 2	119.63 (50.40)	114.25 (55.04)	117.06 (52.62)

[1]Median VL=2,460 for all participants

Receipt of intended level of treatment and retention

Group participants agreed to be videotaped and rated for counselor competence and observance of the implementation manual (Carroll, Kadden, Donovan, Zweben, & Rounsaville, 1994). There were no significant differences in adherence, service utilization, or VL measures by treatment group assignment at baseline. Of the 243 randomized participants, 87% completed at least 6 out of 8 intervention sessions; 63% were available at the 6-month follow up to complete the survey instruments (Figure 3.1) and those completing 6 month assessments did not differ significantly by group assignment However, session completion varied significantly by study assignment, with 84/127 (66.1%) of eligible participants assigned to the treatment condition completing >6 sessions, versus 104/116 (89.7%) of comparison group participants ($t=4.95$; $p<0.001$).

Figure 3.1 (1). Number of participants enrolled at each time point (N=243)



*Number of sessions attended was significantly different between groups (t=4.95, p<0.001)
Proportion who completed all sessions was significantly different between groups (χ^2=46.70, p<0.001)

Outcomes

Of all participants who reported being on ART throughout the study (N=243), the following proportions reported better than 95% adherence: 83% at baseline, 89.3% at T3 and 86.6% at T4 (Table 3.2). Changes in reported adherence across time points were not statistically significant. Chi square analyses (Table 3.3) showed a significant difference (RR=1.55; 95% CI: 1.09, 2.18; p=0.049) between treatment groups in the proportions of

participants reporting >95% adherence at T4 (HPC=80.6% versus HHRP-A=90.3%). No differences in adherence or VL between conditions observed at other time points approached statistical significance. Self-reported adherence at baseline was significantly correlated with VL at 6 months when controlling for VL at baseline (r_s=-0.310, p<0.01).

The mean number of services utilized (out of possible 52) by all participants at baseline was 17.62 (SD=10.11) which decreased at T2 to 11.89 (SD=8.53), increased at T3 to 16.08 (SD=9.76), and decreased again at T4 to 14.38 (SD=8.60). A significant change in utilization was observed over time regardless of treatment condition [F (3, 645)=19.07, p<0.001; partial η^2 =0.073]. No time x condition interaction or between-group difference in utilization were observed (Table 3.4).

Upon entry into the study, 103 (55.1%) participants reported their VL to be undetectable with no significant difference in VL between treatment conditions. Change in percentages of those reporting an undetectable VL between baseline (T1) and T2, T3 or T4 was not significant: 56.8% at T2, 66.0% at T3, and 66.1% at T4. As shown in Table 3.3, at the 6-month follow-up, participants assigned to the HHRP-A group were more likely (74.6%; RR=1.49; 95% CI: 1.05, 2.13) to report an undetectable VL than those assigned to the HPC condition (56.7%, p<0.01).

Processes

Participants at baseline, regardless of group assignment, reported a mean support score of 67.98 (SD=17.61) out of a possible score of 95. A significant change in scores over time for both HPC and HHRP-A groups was observed, with mean scores increasing at T2 to 70.36 (+14.98), at T3 to 70.90 (+15.25) and at T4 to 70.46 (+14.04) [F=4.19, p<0.01, partial η^2 =0.02]. The interaction between time point and condition approached

significance [F=2.37, p<0.06, partial η^2 =0.01] whereby the experimental condition performed significantly better over time than the comparison group. No between-groups effect was observed when time points were collapsed.

Stress measures were collected at baseline, T3 and T4. Participants regardless of condition assignment had a mean stress score of 26.87(SD=17.10) at baseline. The scores decreased to 25.99 (SD=15.55) at T3 and increased to 26.37 (SD=14.45) at T4. Differences in overall scores over time were not significant. No time x condition or between-groups effects were observed (Table 3.4).

One significant correlation was identified between process and outcome variables: at 6 month follow-up for participants in the HHRP-A condition, adherence was positively associated with support (r=0.28, p<0.05; Table 3.5).

Table 3.2 (2). Outcome and process values (N/% and Mean/SD) at all available time points (N=243)

		T1	T2	T3	T4
		Mean (SD) N (%)	Mean (SD) N (%)	Mean (SD) N (%)	Mean (SD) N (%)
Adherence >95%	HPC	64/79 (81.0%)	-	67/74 (90.5%)	50/62 (80.6%)
	HHRP-A	63/74(85.1%)	-	58/66 (87.9%)	53/57 (93%)
	All	127/153 (83.0%)	-	125/140 (89.3%)	103/119 (86.6%)
Utilization	HPC	17.62 (10.11)	12.55 (8.88)	15.79 (9.61)	14.74 (9.48)
	HHRP-A	16.20 (9.58)	11.28 (8.19)	16.35 (9.93)	14.05 (7.74)
	All	16.88 (9.85)	11.89 (8.53)	16.08 (9.76)	14.38 (8.60)
Undetectable VL	HPC	51/91 (56.0%)	50/82 (61.0%)	44/71 (62.0%)	34/60 (56.7%)
	HHRP-A	52/96 (54.2%)	42/80 (52.5%)	55/79 (69.6%)	50/67 (74.6%)
	All	103/187 (55.1%)	92/162 (56.8%)	99/150 (66.0%)	84/127 (66.1%)
Stress	HPC	27.36 (17.86)	-	26.61 (16.54)	25.99 (15.55)
	HHRP-A	26.41 (16.44)	-	28.31 (16.19)	26.72 (13.42)
	All	26.87 (17.10)	-	27.49 (16.34)	26.37 (14.45)
Support	HPC	68.89 (17.80)	71.37 (13.90)	70.40 (15.77)	69.20 (14.52)
	HHRP-A	67.14 (17.47)	69.44 (15.90)	71.37(14.81)	71.61(13.53)
	All	67.98 (17.61)	70.36 (14.98)	70.90 (15.25)	70.46 (14.04)

Table 3.3 (3). Rate ratios for 95% ART adherence and undetectable viral load, by study assignment (N=243)

	T1 x Condition	T1-T2	T2 x Condition	T1-T3	T3 x Condition	T1-T4	T4 x Condition
Self-Reported Adherence	1.15	-	-	1.69	0.87	0.97	1.55*
Self-Reported Undetectable VL	0.96	5.52	0.84	6.08	1.19	2.49	1.49**

* p=0.049
** p=0.033

Table 3.4 (4). Effects (F statistics) for continuous variables by time and study assignment (N=243)

	Time (p)	Time x Condition (p)	Between Groups (p)
Utilization (*df:* 3, 645)	19.07 (p<.001)	0.37 (p=0.75)	0.30 (p=0.58)
Stress (*df:* 2, 440)	0.46 (p=0.61)	0.98 (p=0.37)	0.45 (p=0.50)
Support (*df:* 3, 687)	4.19 (p=0.01)	2.36 (p=0.06)	0.01 (p=0.92)

*Derived from Greenhouse-Geisser statistics

Table 3.5 (5). Pearson and Spearman Rank correlations between outcome and process variables at baseline, post-intervention, 3 months, and 6 months (N=243)

		Stress		Support	
		HPC	HHRP-A	HPC	HHRP-A
Self-Reported Adherence	T1	-.07	.09	-0.22	0.06
	T3	.06	.19	-0.05	-0.05
	T4	.19	-.09	0.09	0.28*
Service Utilization	T1	0.04	0.05	0.06	0.00
	T2	-	-	0.16	0.16
	T3	0.03	0.04	0.10	-0.14
	T4	0.02	-0.13	0.08	0.07
Self-Reported VL	T1	0.002	0.10	0.04	0.14
	T2	-	-	0.20	0.13
	T3	0.11	0.11	0.15	-0.05
	T4	0.06	0.00	-0.08	-0.11

*significant at $p<0.05$

DISCUSSION

Participants enrolled in this study were at high risk of disease progression and reported risk behaviors associated with HIV transmission (Malow et al., 2012). Many reported less-than-optimal ART adherence, and most reported a detectable viral load and clinically significant NCI. The study group showed significantly lower NC functioning when compared to published norms. This study found that the HHRP-A group showed improved VL and adherence at 6 months post intervention. In addition, social support improved throughout follow up and was significantly associated with adherence at 6 months post intervention.

The evidence-based intervention evaluated in this study improved self-reported ART adherence in HIV-positive adults who used alcohol, more than the HPC at the six-month follow-up time point, but not at other time points post-intervention. Other IMB model-based interventions, particularly those that employ strategies to facilitate learning

and retention, have yielded similar outcomes. Margolin et al. (2003) found success in improving self-reported adherence rates among methadone-maintained injection drug users after delivery of an adapted HHRP intervention. Another study developed an IMB-based health literacy training which showed some effectiveness in improving adherence among a heterogeneous sample of HIV-positive adults (Ownby, Waldrop-Valverde, Caballero, & Jacobs, 2013). Similar to the research presented here, both of those intervention studies involved PLWH who were engaged in clinical care, adherence rates were high at the outset and "adequate adherence" was set at 95%. Ownby found the greatest improvement among participants who began at the lowest levels of adherence; however that study did not include a comparison condition. Additionally, neither of the previous interventions studies examined prospective outcomes. Finally, although the accuracy and veracity of self-report adherence measures vary greatly in the literature (Simoni, Kurth, et al., 2006), the fact that adherence values at baseline in this study were significantly correlated with VL at 6 months suggest high accuracy in adherence reporting.

While improvement in ART adherence is a promising outcome, undetectable VL should be the ultimate marker of health improvement. Uncontrolled viral replication and associated immune activity can result in a chronic inflammatory state, organ damage and other conditions, including NC impairment (Thompson et al., 2012). In this study, significantly more participants in the HHRP-A condition reported an undetectable VL six months, but not at other time points after the intervention. A recent meta analysis examining associations between both self-reported and directly observed ART adherence and VL suggested that longer term analysis, such as the 6-month time frame used in this

study, yields stronger associations (Kahana, Rohan, Allison, Frazier, & Drotar, 2013). Also, an incrementally larger proportion of the sample in the experimental condition reported an undetectable VL at each follow-up time point, but this improvement was not statistically significant. The magnitude of association between these variables is often due to methodological factors, particularly using a dichotomous measure of VL (Kahana et al., 2013). Hence, a continuous measure of VL could have provided different outcomes in this study.

Although this study did not employ a mediated model, an attempt was made, nonetheless, to explore possible mechanisms through which improvements in outcomes may have operated. Effectiveness of the intervention in improving social support and reducing stress were mixed. The intervention included numerous stress-reduction and relaxation activities; however perceptions of life stress appeared to be unaffected by the intervention, in contrast to trials delivering similar cognitive-behavioral techniques, which have resulted in better stress outcomes (Antoni et al., 1991; Lopez et al., 2011). Social support, on the other hand, improved significantly as a function of both time and treatment condition. Between baseline and post-intervention, participants' participation in either group may have provided a greater perception of support (Lutgendorf et al., 1998). However, support scores for the HPC condition declined after T2, while participants in the HHRP-A group continued to report increased social support throughout the study period. This longitudinal difference in social support between the two conditions could have been due to the difference in format of the two intervention groups; HHRP-A met over a longer period of time.

The study did not completely support the buffering model of social support. Although at 6-month follow-up, report of ≥95% adherence among participants randomized to the HHRP-A condition was positively correlated with social support, adherence was not correlated with stress at this time point. The relationship between social support, stress and adherence has been repeatedly supported in the literature (Catz et al., 2000; Gonzalez et al., 2004; Paterson et al., 2000; Singh et al., 1999), however the use of more focused indicators of support, particularly instrumental or adherence-specific support scales, could yield stronger associations with health behavior outcomes (DiMatteo, 2004; Lehavot et al., 2011; Simoni, Frick, et al., 2006).

Contrary to one of this study's hypotheses, a significant reduction in reported service utilization was observed for all participants in the months following the intervention. This finding may be explained by changes in residential status during this study: nearly a quarter of the sample was in residential drug or alcohol treatment at baseline, dropping to under 5% in residential treatment at follow up time points. As reported in prior studies, a change in structured inpatient support is likely to have disrupted participants' access to services (Arno et al., 1996; Kim, Kertesz, Horton, Tibbetts, & Samet, 2006; Smith et al., 2000). Additionally, a comprehensive literature review by Azar (2010) suggests that service utilization may be less consistent among persons abusing alcohol than those abusing other drugs. The supportive inpatient status of many participants at baseline may also help explain the higher-than-expected adherence rates in this sample (Azar et al., 2010; Sylla, Bruce, Kamarulzaman, & Altice, 2007). Eighty-three percent of participants in this study reported adequate adherence at baseline, whereas in the intervention evaluation study by Margolin et al. (2003) baseline self-report

measures of adherence were collected prior to entering a structured substance abuse treatment program and only 51% reported adequate adherence.

Several strengths of this study are important to note. While all participants were HIV-seropositive and had a history of alcohol abuse, the sample was still heterogeneous, representing a diverse cross-section of hard-to-access, high-risk adults living in urban Miami-Dade County. In addition, the intervention was highly comprehensive, offering multiple topics relevant to HIV-positive alcohol abusers using cognitive remediation strategies to improve efficacy for those with NCI. Both arms of the study were manual-guided, ensuring treatment fidelity. Finally, process variables were integrated into this study and the intervention design (National Institute of Mental Health Multisite HIV Prevention Trial Group, 2001).

Unique features and limitations of this study should also be considered when interpreting results. For ethical reasons, to ensure that participants in both arms received equitable treatment benefit, the study required that the comparison condition offered a healthy alternative to HHRP-A. A dose-effect analysis between groups could not be conducted nor was it possible to determine which treatment components were most effective. Similarly, participants in the HPC arm attended a significantly greater number of sessions than the HHRP-A group. Although the two programs were designed to be equivalent on both time and administration, the HPC group was condensed into two days where the HHRP-A group was conducted over the course of several weeks, likely contributing to greater absenteeism. Also, interpretation of findings may be limited by the loss of over 30% of the sample by the 6-month follow-up time point. Finally, all measures in this study were self-report. While both VL and adherence self-report

measures were checked for veracity by correlating measures with serum VL at baseline in this study, it should nonetheless be noted that self-reported treatment adherence, in particular, has been found to be inflated in some samples (Duran et al., 2001) and adequately correlated with observational adherence measures in other studies (Shi et al., 2010).

In conclusion, the results of this study suggest that treatment adherence and viral load could be improved greatly by incorporating comprehensive, cognitive-behavioral risk reduction interventions into HIV and substance abuse care. It is equally important that interventions employ essential cognitive remediation strategies to further enhance skills development and information retention among persons with HIV-related NC impairment. The implementation and further translation of evidence-based interventions require considerable time, effort and funding. Thus, the goal after finding an intervention effective in community settings is to synthesize results for rapid dissemination to clinicians and care providers in order to reduce the risk of HIV transmission and disease progression on a public level (Copenhaver et al., 2012; Lyles, Crepaz, Herbst, & Kay, 2006).

REFERENCES

Allison, P. (2001). *Missing Data*. (pp. 3-5). Thousand Oaks: SAGE Publications.

Amico, K. R., Toro-Alfonso, J., & Fisher, J. (2005). An empirical test of the information, motivation and behavioral skills model of antiretroviral therapy adherence. *AIDS Care*, *17*(6), 661–73. doi:10.1080/09540120500038058

Antinori, A., Arendt, G., Becker, J. T., Brew, B. J., Byrd, D. A., Cherner, M., … Wojna, V. E. (2007). Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*, *69*(18), 1789–99. doi:10.1212/01.WNL.0000287431.88658.8b

Antoni, M. H., Baggett, L., Ironson, G., LaPerriere, A., August, S., Klimas, N., … Fletcher, M. a. (1991). Cognitive-behavioral stress management intervention buffers distress responses and immunologic changes following notification of HIV-1 seropositivity. *Journal of Consulting and Clinical Psychology*, *59*(6), 906–15.

Arno, P. S., Bonuck, K. A., Green, J., Fleishman, J., Bennett, C. L., Fahs, M. C., … Drucker, E. (1996). The impact of housing status on health care utilization among persons with HIV disease. *Journal of Health Care for the Poor and Underserved*, *7*(1), 36–49. doi:10.1353/hpu.2010.0013

Azar, M. M., Springer, S. A., Meyer, J. P., & Altice, F. L. (2010). A systematic review of the impact of alcohol use disorders on HIV treatment outcomes, adherence to antiretroviral therapy and health care utilization. *Drug and Alcohol Dependence*, *112*(3), 178–93. doi:10.1016/j.drugalcdep.2010.06.014

Bangsberg, D., Hecht, F., Charlebois, E., Zolopa, A., Holodniy, M., Sheiner, L., … Moss, A. (2000). Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS*, *14*(4), 357–66.

Bangsberg, D., Perry, S., & Charlebois, E. (2001). Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS*, *15*(9), 1181–1183.

Bangsberg, D. R., Moss, A. R., & Deeks, S. G. (2004). Paradoxes of adherence and drug resistance to HIV antiretroviral therapy. *The Journal of Antimicrobial Chemotherapy*, *53*(5), 696–9. doi:10.1093/jac/dkh162

Bass, J. K., Bornemann, T. H., Burkey, M., Chehil, S., Chen, L., Copeland, J. R. M., … Patel, V. (2012). A United Nations General Assembly Special Session for mental, neurological, and substance use disorders: the time has come. *PLoS medicine*, *9*(1), e1001159.

Baum, M. K., Rafie, C., Lai, S., Sales, S., Page, J. B., & Campa, A. (2010). Alcohol use accelerates HIV disease progression. *AIDS Research and Human Retroviruses*, *26*(5), 511–518.

Bowker, A. H. (1948). A test for symmetry in contingency tables. *Journal of the American Statistical Association*, *43*(244).

Braithwaite, S. R., & Bryant, K. J. (2010). Influence of alcohol consumption on adherence to and toxicity of antiretroviral therapy and survival. *Alcohol Research & Health*, *33*(3), 280–287.

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), 1465–507. doi:10.1080/10826080600846250

Carpenter, C. C. J., Fischl, M. A., Hammer, S. M., Hirsch, M. S., Jacobsen, D. M., Katzenstein, D. A., … Volberding, P. A. (1997). Antiretroviral therapy for HIV infection in 1997: Updated recommendations of the International AIDS Society - USA Panel. *Journal of the American Medical Association*, *277*(24), 1962–1969.

Carroll, K., Kadden, R., Donovan, D., Zweben, A., & Rounsaville, B. (1994). Implementing treatment and protecting the validity of the independent variable in treatment matching studies. *Journal of Studies on Alcohol and Drugs*, *12*, 149.

Catz, S. L., Kelly, J. A., Bogart, L. M., Benotsch, E. G., & Mcauliffe, T. L. (2000). Patterns , correlates , and barriers to medication adherence among persons prescribed new treatments for HIV disease. *Health Psychology*, *19*(2), 124–133. doi:10.1037//0278-

Centers for Disease Control and Prevention Division of HIV/AIDS. (2012a). Estimated HIV incidence in the United States, 2007–2010. *HIV Surveillance Supplemental Report 2012*, *17*(4). Retrieved from http://www.cdc.gov/hiv/surveillance/resources/reports/2010supp_vol17no4/

Centers for Disease Control and Prevention Division of HIV/AIDS. (2012b). *HIV Surveillance Report, 2010* (Vol. 22). Retrieved from http://www.cdc.gov/hiv/library/reports/surveillance/2011/surveillance_Report_vol_23.html

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior, 24(4)*, 385-396.

Cohen, S., & McKay, G. (1985). Social support, stress and the buffering hypothesis: A theoretical analysis. In A. Baum, S. Talor, & J. Singer (Eds.), *Handbook of Psychology and Health* (pp. 253–266). Hillsdale, NJ.

Cook, R., Sereika, S., Hunt, S., Woodward, W., Erlen, J., & Conigliaro, J. (2001). Problem drinking and medication adherence among persons with HIV infection. *Journal of General Internal Medicine*, *16*(2), 83–8.

Deeks, S. G., Smith, M., Holodniy, M., & Kahn, J. O. (1997). HIV-1 protease inhibitors. A review for clinicians. *Journal of the American Medical Association*, *277*(2), 145–53.

Dempster, A. P., Laird, N. M., & Rubin, D. B. (1977). Maximum likelihood from incomplete data via the EM algorithm. *Journal of the Royal Statistical Society*, *Series B (*, 1–38.

DiMatteo, M. R. (2004). Social support and patient adherence to medical treatment: a meta-analysis. *Health Psychology*, *23*(2), 207–18. doi:10.1037/0278-6133.23.2.207

Duran, S., Solas, C., Spire, B., Carrieri, M., Fuzibet, J., Costagliola, D., & Moatti, J. (2001). Do HIV-infected injecting drug users over-report adherence to highly active antiretroviral therapy? A comparison between patients' self-reports and serum protease inhibitor concentrations in the French Manif 2000 cohort study. *AIDS*, *15*(8), 1075–81.

Farinpour, R., Martin, E. M., Seidenberg, M., Pitrak, D. L., Pursell, K. J., Mullane, K. M., … Harrow, M. (2000). Verbal working memory in HIV-seropositive drug users. *Journal of the International Neuropsychological Society*, *6*(5), 548–55.

Fisher, J D, & Fisher, W. A. (1992). Changing AIDS-risk behavior. *Psychological Bulletin*, *111*(3), 455–74.

Fisher, Jeffrey D, Amico, K. R., Fisher, W. A., & Harman, J. J. (2008). The information-motivation-behavioral skills model of antiretroviral adherence and its applications. *Current HIV/AIDS Reports*, *5*(4), 193–203.

Galvan, F., Bing, E., Fleishman, J., London, A., Caetano, R., Burnam, M., & Shapiro, M. (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 and Drugs*, *63*(2), 179.

Gonzalez, J. S., Penedo, F. J., Antoni, M. H., Durán, R. E., McPherson-Baker, S., Ironson, G., … Schneiderman, N. (2004). Social support, positive states of mind, and HIV treatment adherence in men and women living with HIV/AIDS. *Health Psychology*, *23*(4), 413–8. doi:10.1037/0278-6133.23.4.413

Heaton, R., Clifford, D., Franklin, D., Woods, S., Ake, C., Vaida, F., … Grant, I. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral

therapy: CHARTER Study. *Neurology*, *75*(23), 2087–96. doi:10.1212/WNL.0b013e318200d727

Hinkin, C., Castellon, S., & Durvasula, R. (2002). Medication adherence among HIV+ adults Effects of cognitive dysfunction and regimen complexity. *Neurology*, *59*(12), 1944–1950.

Howell, D. C. (2007). *Statistical methods for psychology (6th ed.)*. Belmont, CA: Thomson Wadsworth.

Hirokazu, Y., Wilson, P. A., Peterson, J. L., & Shinn, M. (2005). Multiple Pathways to Community-Level Impacts in HIV Prevention: Implications for Conceptualization, Implementation, and Evaluation of Interventions. In W. Trickett, E. J., & Pequegnat (Ed.), *Community Interventions and AIDS*. New York: Oxford University Press.

IBM Corporation. (2010). IBM SPSS Base 19.0 for Windows User's Guide. IBM Corporation, New York.

Kahana, S. Y., Rohan, J., Allison, S., Frazier, T. W., & Drotar, D. (2013). A meta-analysis of adherence to antiretroviral therapy and virologic responses in HIV-infected children, adolescents, and young adults. *AIDS and Behavior*, *17*(1), 41–60. doi:10.1007/s10461-012-0159-4

Kim, T. W., Kertesz, S. G., Horton, N. J., Tibbetts, N., & Samet, J. H. (2006). Episodic homelessness and health care utilization in a prospective cohort of HIV-infected persons with alcohol problems. *BMC Health Services Research*, *6*, 19. doi:10.1186/1472-6963-6-19

Lehavot, K., Huh, D., Walters, K. L., King, K. M., Andrasik, M. P., & Simoni, J. M. (2011). Buffering effects of general and medication-specific social support on the association between substance use and HIV medication adherence. *AIDS Patient Care and STDs*, *25*(3), 181–9. doi:10.1089/apc.2010.0314

Little, R. J. (1988). A test of missing completely at random for multivariate data with missing values. *Journal of the American Statistical Association*, *83*(404), 1198–1202.

Lopez, C., Antoni, M., Penedo, F., Weiss, D., Cruess, S., Segotas, M.-C., … Fletcher, M. A. (2011). A pilot study of cognitive behavioral stress management effects on stress, quality of life, and symptoms in persons with chronic fatigue syndrome. *Journal of Psychosomatic Research*, *70*(4), 328–34. doi:10.1016/j.jpsychores.2010.11.010

Lucas, G. M. (2005). Antiretroviral adherence, drug resistance, viral fitness and HIV disease progression: a tangled web is woven. *The Journal of Antimicrobial Chemotherapy*, *55*(4), 413–6. doi:10.1093/jac/dki042

Lutgendorf, S. K., Antoni, M. H., Ironson, G., Starr, K., Costello, N., Zuckerman, M., … Schneiderman, N. (1998). Changes in cognitive coping skills and social support during cognitive behavioral stress management intervention and distress outcomes in symptomatic human immunodeficiency virus (HIV)-seropositive gay men. *Psychosomatic medicine*, *60*(2), 204–14.

Malow, R., Devieux, J., Stein, J., Rosenberg, R., Lerner, B., Attonito, J., & Villalba, K. (2012). Neurological function, information-motivation-behavioral skills factors, and risk behaviors among HIV-positive alcohol users. *AIDS and Behavior*, *16*(8), 2297–308. doi:10.1007/s10461-012-0246-6

Mannheimer, S. B., Morse, E., John, P., & Andrews, L. (2006). Sustained Benefit From a Long-Term Antiretroviral Adherence Intervention. *Journal of Acquired Immune Deficiency Syndromes*, *43*, 41–47.

Mannheimer, SB, Matts, J., Telzak, E., & Chesney, M. (2010). Psychological and Socio-medical Aspects of AIDS / HIV Quality of life in HIV-infected individuals receiving antiretroviral therapy is related to adherence. *AIDS Care*, *17*(1), 10–22.

Mannheimer, Sharon, Friedland, G., Matts, J., Child, C., & Chesney, M. (2002). The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. *Clinical Infectious Diseases*, *34*(8), 1115–21. doi:10.1086/339074

Margolin, A., Avants, S., Warburton, L., Hawkins, K., & Shi, J. (2003). A randomized clinical trial of a manual-guided risk reduction intervention for HIV-positive injection drug users. *Health Psychology*, *22*(2), 223–228. doi:10.1037/0278-6133.22.2.223

Marx, K. A., Malka, E. S., Ravishankar, J., & Schwartz, R. M. (2011). Measurement of retention in care among adults infected with HIV in an urban clinic. *AIDS care*, *23*(10), 1298–304. doi:10.1080/09540121.2011.555942

McLellan, A., Alterman, A., Cacciola, J., Metzger, D., & O'Brien, C. (1992). A new measure of substance abuse treatment initial studies of the treatment services review. *The Journal of Nervous and Mental Disease*, *180*(2), 101–110.

Mclellan, A. T., Zanis, D., Incmikoski, R., Parikh, G., Stevens, G., & Brock, M. (1989). *Administration Manual for the Treatment Services Review "TSR."* Washington, DC.

Miller, L. (1993). *Psychotherapy of the Brain-Injured Patient: Reclaiming the Shattered Self*. WW Norton & Co. Inc.

Miller, W., & Rollnick, S. (1991). *Motivational Interviewing: Preparing People to Change Addictive Behavior*. New York: Guilford Press.

Mugavero, M. J., Amico, K. R., Westfall, A. O., Crane, H. M., Kitahata, M., & Saag, M. S. (2013). Early retention in HIV care and viral load supression: Implications for a test and treat approach to HIV prevention. *Journal of Acquired Immune Deficiency Syndromes*, *59*(1), 86–93. doi:10.1097/QAI.0b013e318236f7d2.Early

Mugavero, M. J., Raper, J. L., Reif, S., Whetten, K., Leserman, J., Thielman, N. M., & Pence, B. W. (2009). Overload: impact of incident stressful events on antiretroviral medication adherence and virologic failure in a longitudinal, multisite human immunodeficiency virus cohort study. *Psychosomatic Medicine*, *71*(9), 920–6. doi:10.1097/PSY.0b013e3181bfe8d2

National HIV/AIDS Strategy Implementation Plan. (2010). Washington, DC. Retrieved from http://www.whitehouse.gov/sites/default/files/uploads/NHAS.pdf

National Institute of Mental Health Multisite HIV Prevention Trial Group. (2001). Social-cognitive theory mediators of behavior change in the National Institute of Mental Health Multisite HIV Prevention Trial. *Health Psychology*, *20*(5), 369–376. doi:10.1037//0278-6133.20.5.369

Ownby, R., Waldrop-Valverde, D., Caballero, J., & Jacobs, R. (2013). Baseline medication adherence and response to an electronically delivered health literacy intervention targeting adherence. *Neurobehavioral HIV Medicine*, *4*, 113–121. doi:10.2147/NBHIV.S36549.Baseline

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

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

Richardson, J. T. E. (2011). Eta squared and partial eta squared as measures of effect size in educational research. *Educational Research Review*, *6*(2), 135–147. doi:10.1016/j.edurev.2010.12.001

Rothlind, J. C., Greenfield, T. M., Bruce, A. V, Dieter, J., Flenniken, D. L., Lindgren, J. A., & Michael, W. (2005). Heavy alcohol consumption in individuals with HIV

infection: Effects on neuropsychological performance. *Journal of the International Neuropsychological Society*, *11*(1), 70–83.

Sacktor, N. (2002). The epidemiology of human immunodeficiency virus-associated neurological disease in the era of highly active antiretroviral therapy. *Journal of Neurovirology*, *8 Suppl 2*, 115–21. doi:10.1080/13550280290101094

Sarason, I., Johnson, J., & Siegel, J. (1978). Assessing the impact of life changes: Development of the Life Experiences Survey. *Journal of Consulting and Clinical Psychology*, *46*(5), 392–46.

Sherbourne, C., & Stewart, A. (1991). The MOS Social Support Survey. *Social Science & Medicine*, *32*(6), 705–714.

Shi, L., Liu, J., Koleva, Y., Fonseca, V., Kalsekar, A., & Pawaskar, M. (2010). Concordance of adherence measurement using self-reported adherence questionnaires and medication monitoring devices. *PharmacoEconomics*, *28*(12), 1097–107. doi:10.2165/11537400-000000000-00000

Simoni, J. M., Frick, P. A, Lockhart, D., & Liebovitz, D. (2002). Mediators of social support and antiretroviral adherence among an indigent population in New York City. *AIDS Patient Care and STDs*, *16*(9), 431–9. doi:10.1089/108729102760330272

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. doi:10.1037/0278-6133.25.1.74

Simoni, J. M., Kurth, A. E., Pearson, C. R., Pantalone, D. W., Merrill, J. O., & Frick, P. A. (2006). Self-report measures of antiretroviral therapy adherence: A review with recommendations for HIV research and clinical management. *AIDS and Behavior*, *10*(3), 227–45. doi:10.1007/s10461-006-9078-6

Singh, N., Berman, S. M., Swindells, S., Justis, J. C., Mohr, J. A., Squier, C., & Wagener, M. M. (1999). Adherence of human immunodeficiency virus-infected patients to antiretroviral therapy. *Clinical infectious Diseases*, *29*(4), 824–30. doi:10.1086/520443

Smith, L. R., Fisher, J. D., Cunningham, C. O., & Amico, K. R. (2012). Understanding the behavioral determinants of retention in HIV care: a qualitative evaluation of a situated information, motivation, behavioral skills model of care initiation and maintenance. *AIDS Patient Care and STDs*, *26*(6), 344–55. doi:10.1089/apc.2011.0388

Smith, M. Y., Rapkin, B. D., Winkel, G., Springer, C., Chhabra, R., & Feldman, I. S. (2000). Housing status and health care service utilization among low-income persons with HIV/AIDS. *Journal of General Internal Medicine*, *15*(10), 731–8.

Starace, F., Massa, A., Amico, K. R., & Fisher, J. D. (2006). Adherence to antiretroviral therapy: an empirical test of the information-motivation-behavioral skills model. *Health Psychology*, *25*(2), 153–62. doi:10.1037/0278-6133.25.2.153

Sylla, L., Bruce, R. D., Kamarulzaman, A., & Altice, F. L. (2007). Integration and co-location of HIV/AIDS, tuberculosis and drug treatment services. *The International Journal on Drug Policy*, *18*(4), 306–12. doi:10.1016/j.drugpo.2007.03.001

Tabachnick, B. G., & Fidell, L. S. (2007). *Using multivariate statistics (5th ed.)*. Boston: Allyn and Bacon.

Tesoriero, J., French, T., Weiss, L., Waters, M., Finkelstein, R., & Agins, B. (2003). Stability of adherence to highly active antiretroviral therapy over time among clients enrolled in the treatment adherence demonstration project. *Journal of Acquired Immune Deficiency Syndromes*, *33*(4), 484–93.

Thompson, M., Aberg, J., & Hoy, J. (2012). Antiretroviral treatment of adult HIV infection 2012 recommendations of the International Antiviral Society–USA Panel. *Journal of the American Medical Association*, *308*(4).

Volkow, N., & Montaner, J. (2010). Enhanced HIV testing, treatment, and support for HIV-infected substance users. *Journal of the American Medical Association*, *303*(14), 1423–1424.

Wong, M. D., Sarkisian, C. a, Davis, C., Kinsler, J., & Cunningham, W. E. (2007). The association between life chaos, health care use, and health status among HIV-infected persons. *Journal of General Internal Medicine*, *22*(9), 1286–91. doi:10.1007/s11606-007-0265-6

CHAPTER VI

SUMMARY OF CONCLUSIONS

The overarching purpose of the three studies comprising this dissertation was to investigate the extent to which biopsychosocial factors—including NC impairment — influence ART adherence, service utilization and VL before and after the delivery of an evidence-based intervention among HIV-positive alcohol abusers. Each study built upon information gained in the preceding study, concluding with the final analysis which evaluated the effectiveness of the HHRP-A intervention. The HHRP-A intervention is unique in two ways: first, it is delivered using a holistic, harm-reduction approach, addressing multiple, complex psychosocial factors prevalent in the lives of people who abuse drugs or alcohol; second, the intervention includes cognitive remediation strategies to maximize information retention and synthesis for PLWH who may also suffer from a degree of neurocognitive impairment.

The first study examined factors hypothesized to contribute to NCI: drug and alcohol use and time living with HIV. This baseline analysis, using structural equation modeling, positioned five exogenous variables—years living with HIV; time from HIV diagnosis to seeking care; and days using alcohol, marijuana and cocaine in the prior three months—as predictors of three NC measures selected to address a range of cognitive domains. Mean scores on NC measures for this sample were significantly lower than mean normative scores suggesting a degree of impairment. In addition, both marijuana use and years living with HIV were associated with poorer scores on the CTT2 which measures several executive functions including information processing.

The second study also used structural equation modeling at baseline to test a biopsychosocial model predicting VL with ART adherence as a mediator. Independent variables included tangible social support, barriers to ART adherence, and stress. Moderators included alcohol use, marijuana use and NC impairment. Employing Baron and Kenny's 4-step approach to testing mediation (Baron & Kenny, 1986; James & Brett, 1984; Judd & Kenny, 1981), the relationship between barriers to adherence and VL was found to be to a considerable degree mediated by ART adherence.

The final study was a randomized controlled trial, modeled after the research conducted by Margolin et al. (2003) who conducted a previous assessment of the HHRP intervention adapted for PLWH who were intravenous drug users enrolled in a methadone maintenance program. Participants were randomized to the HHRP-A or a comparison group and data were collected at baseline, post-intervention, 3-month, and 6-month follow-up time points. Participants in the HHRP-A condition were significantly more likely to report optimal ART adherence and undetectable VL at 6 months post-intervention. A significant time-by-condition effect was also observed in social support, with the experimental condition showing greater improvement than the comparison group.

Some limitations and strengths of this research are important to note. These participants were drawn from clinical sites and may not be representative of PLWH who are not engaged in care for HIV. Reporting bias should be considered in interpreting outcomes; this proportion of participants who were engaged in care may also account for the relatively high adherence rates reported in this sample. Nearly a quarter of the sample was in residential addictions treatment at baseline and it is possible that recent substance

use was underreported or atypically low for the group. Measurement issues should be considered when interpreting this study's results. A battery of only three NC assessment instruments were used which may limit the sensitivity for finding NC impairment. Also, ART adherence was a self-reported measure which could provide an underestimate of actual adherence rates. This research also had several strengths. The sample was highly heterogeneous, contributing to the external validity of the outcomes. In addition, the HHRP-A intervention assessed in Aim 3 was manual-guided contributing to the internal validity of outcomes.

Overall findings from the three studies suggest that: (a) marijuana and time living with HIV may be important contributors to NC impairment among PLWH; (b) a biopsychosocial model can be an effective tool for understanding factors that contribute to changes in ART adherence and VL; and (c) providing comprehensive health promotion interventions such as HHRP-A particularly those incorporating cognitive remediation strategies, could improve health outcomes for HIV-seropositive substance users. Future research should further investigate possible substance use and HIV-related factors (as well as interactions between these variables) contributing to NC impairment. Greater understanding of psychosocial variables and their direct effect upon viral suppression and disease progression among PLWH is also needed. Finally, health outcomes for PLWH could be improved by the ongoing delivery, evaluation and adaptation of holistic, evidence-based interventions that address the complex medical, psychological, cognitive, and social needs of PLWH who use alcohol and other drugs.

References

Baron, R. M., & 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*(3806354), 1173–1182.

James, L. R., & Brett, J. M. (1984). Mediators, moderators, and tests for mediation. *Journal of Applied Psychology*, *69*(2), 307–321. doi:10.1037//0021-9010.69.2.307

Judd, C. M., & Kenny, D. a. (1981). Process analysis: Estimating mediation in treatment evaluations. *Evaluation Review*, *5*(5), 602–619. doi:10.1177/0193841X8100500502

Margolin, A., Avants, S., Warburton, L., Hawkins, K., & Shi, J. (2003). A randomized clinical trial of a manual-guided risk reduction intervention for HIV-positive injection drug users. *Health Psychology*, *22*(2), 223–228. doi:10.1037/0278-6133.22.2.223

APPENDICES

Appendix 1: HHRP Fact sheet

HOLISTIC HEALTH RECOVERY PROGRAM

A Group-level Intervention for HIV-positive and HIV-negative Injection Drug Users
FACT SHEET

Program Overview
The Holistic Health Recovery Program (HHRP) is a 12-session, manual-guided, group level program to promote health and improve quality of life.

The primary goals of HHRP are health promotion and improved quality of life. More specific goals are abstinence from illicit drug use or from sexual risk behaviors; reduced drug use; reduced risk for HIV transmission; and improved medical, psychological, and social functioning. HHRP is based on the Information-Motivation-Behavioral Skills (IMB) model of HIV prevention behavioral change. According to this model, there are three steps to changing behavior: Providing HIV prevention information, motivation to engage in HIV prevention and opportunities to practice behavior skills for HIV prevention.

Core Elements
The core elements of HHRP are:
- Teaches skills to reduce harm of injection drug use and unprotected sexual activities.
- Teaches negotiation skills to reduce unsafe sexual behaviors with sexual partners and teaches skills to heal social relationships.
- Teaches decision making and problem solving skills using cognitive remediation strategies.
- Teaches goal setting skills including developing action plans to achieve goals.
- Teaches skills to manage stress, including relaxation exercises and understanding what aspects of the stressful situation can, and cannot, be controlled.
- Teaches skills to improve health, health care participation, and adherence to medical treatments.
- Teaches skills to increase clients' access to their own self-defined spiritual beliefs, in order to increase motivation to engage in harm reduction behaviors.
- Teaches skills to increase awareness of how different senses of self can affect self-efficacy and hopelessness.

Target Population
HHRP targets HIV-positive and HIV-negative injection drug users.

Program Materials
- Program manuals for both HIV-positive and HIV-negative injection drug users are available, which include all the materials required to implement the intervention.

Research Results
Implementation of HHRP produced the following results:
- Decrease in addiction severity.
- Decrease in risk behavior.
- Significant improvement in behavioral skills, motivation, and quality of life.

For More Information on the Holistic Health Recovery Program
Currently, CDC does not offer trainings for Holistic Health Recovery Program (HHRP). However, the intervention implementation materials are available for download from Yale University School of Medicine, Department of Psychiatry - http://info.med.yale.edu/psych/3s/training.html

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Margolin, A., Avants, S.K., Warburton, L.A., Hawkins, K.A., Shi, J. (2003). A randomized clinical trial of a manual-guided risk reduction intervention for HIV-positive injection drug users. *Health Psychology*, 22(2), 223-228.

Revised 10/04/11

APPENDIX 2: recruitment sites accessed by parent study

1. Borinquen Health Care Center*
2. Florida Department of Health: Broward County Department Sexually Transmitted Disease Program
3. Center for Haitian Studies
4. South Florida Provider Coalition
5. The Salvation Army
6. Care Resource
7. Empower U, Inc.*
8. The Village*
9. South Florida AIDS Network
10. The Center for Positive Connections Support & Resource Center
11. South Beach AIDS Project, Inc.
12. Miami Beach Community Health Center, Inc.
13. Helen B. Bentley Family Health Center, Inc.

*Indicates sites from where the majority of participants were recruited.

APPENDIX 3: additional Tables and Figures for Manuscript 1

Figure Appendix 3.1. Hypothesized directional model with one proposed latent variable

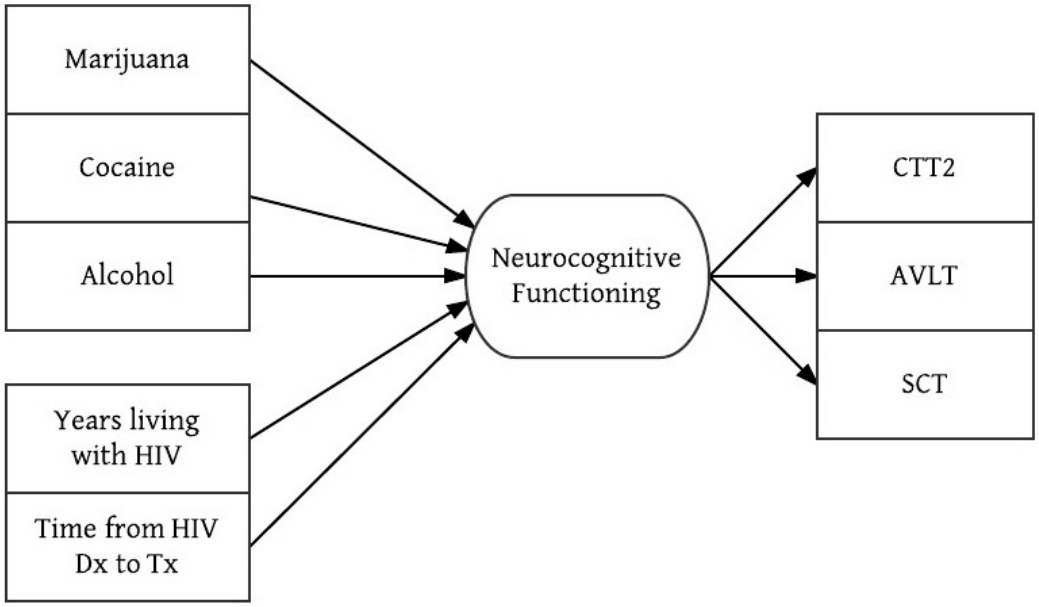


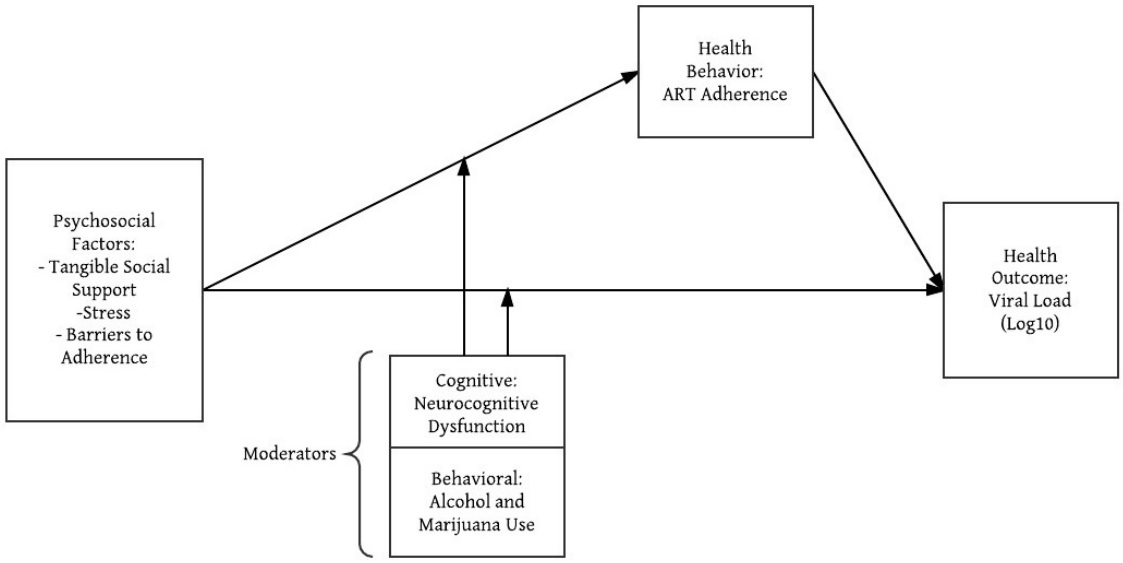
Table Appendix 3.1. Correlation matrix for all variables in the model (N=370)

	AVLT	CTT2	SCT	Alcohol	Marijuana	Cocaine	Yrs HIV[1]	Dx to Tx[2]
AVLT[1]	1.000							
CTT2[2]	-0.293	1.000						
SCT[3]	-0.206	0.174	1.000					
Alcohol	-0.040	0.002	0.070	1.000				
Marijuana	0.061	0.070	-0.016	0.171	1.000			
Cocaine	0.003	-0.038	0.051	0.386	0.195	1.000		
Yrs HIV[4]	-0.087	0.176	0.095	0.081	-0.056	0.046	1.000	
Dx to Tx[5]	0.030	0.002	-0.038	0.021	0.139	0.012	0.246	1.000

[1]AVLT Auditory Verbal Learning Test
[2]CTT2 Color Trails Test 2
[3]SCT Short Category Test
[4]Yrs. HIV Duration of known HIV infection in years
[5]Dx. to Tx Years between diagnosis of HIV infection and initiation of ART

APPENDIX 4: ADDITIONAL FIGURE FOR MANUSCRIPT 2

Figure Appendix 4.1. Hypothesized partially mediated model predicting viral load, moderated by cognitive and behavioral factors (N=246)



APPENDIX 5: ADDITIONAL FIGURES FOR MANUSCRIPT 3

Figure Appendix 5.1. Mean number of services utilized at each time point (N=243)

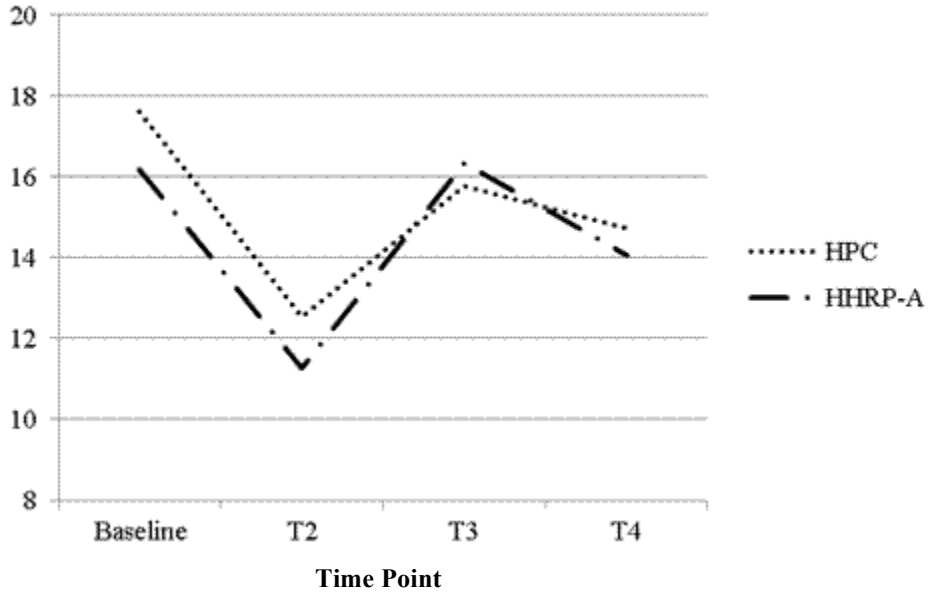


Figure Appendix 5.2. Mean support scores, all time points (N=243)

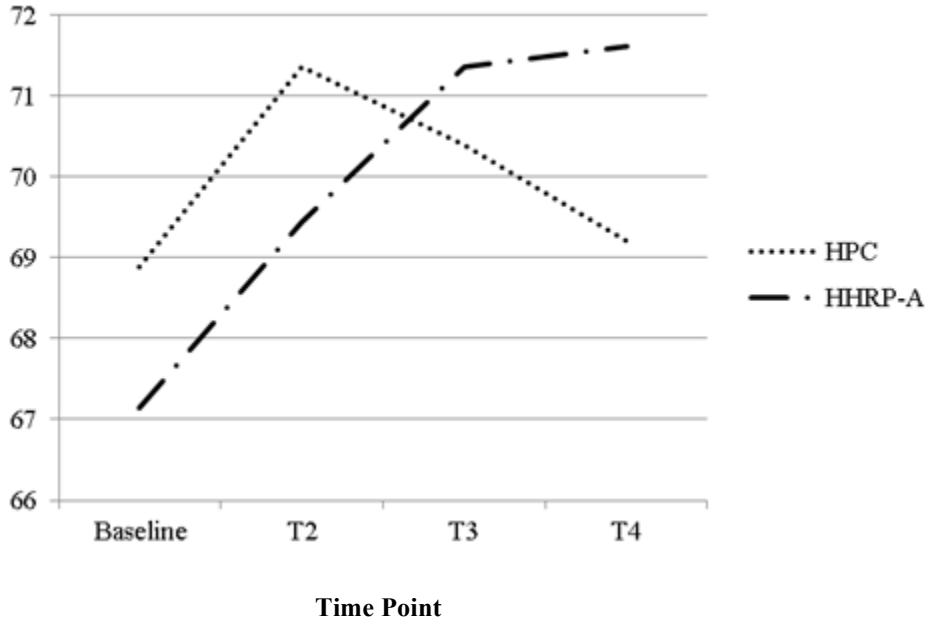


Figure Appendix 5.3. Mean stress scores at T1, T3 and T4 (N=243)

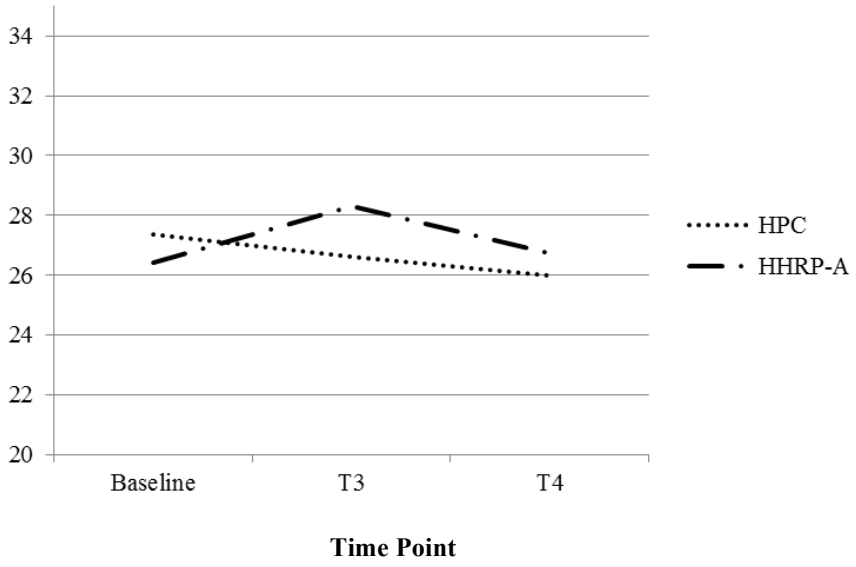


Figure Appendix 5.4. Percent participants reporting >95% adherence to ART at each time point. N=243

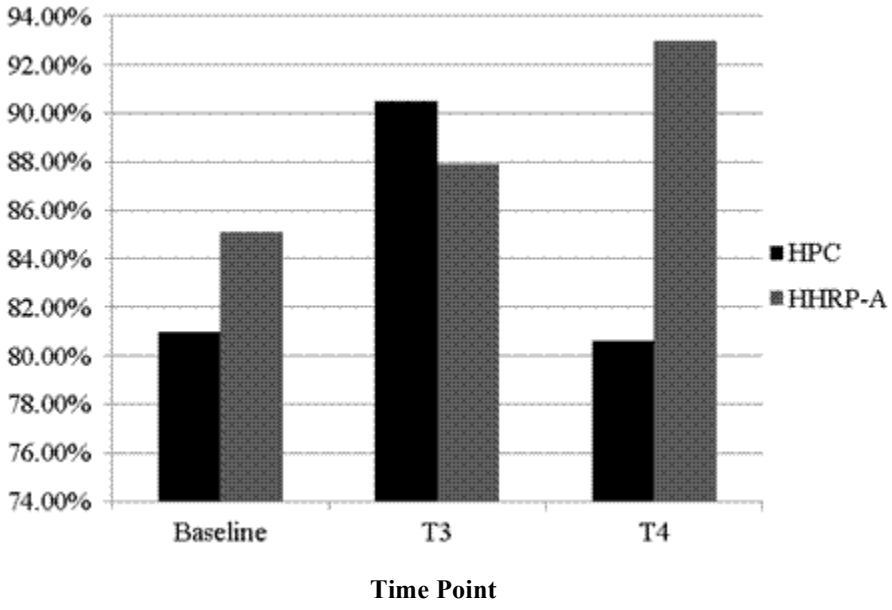
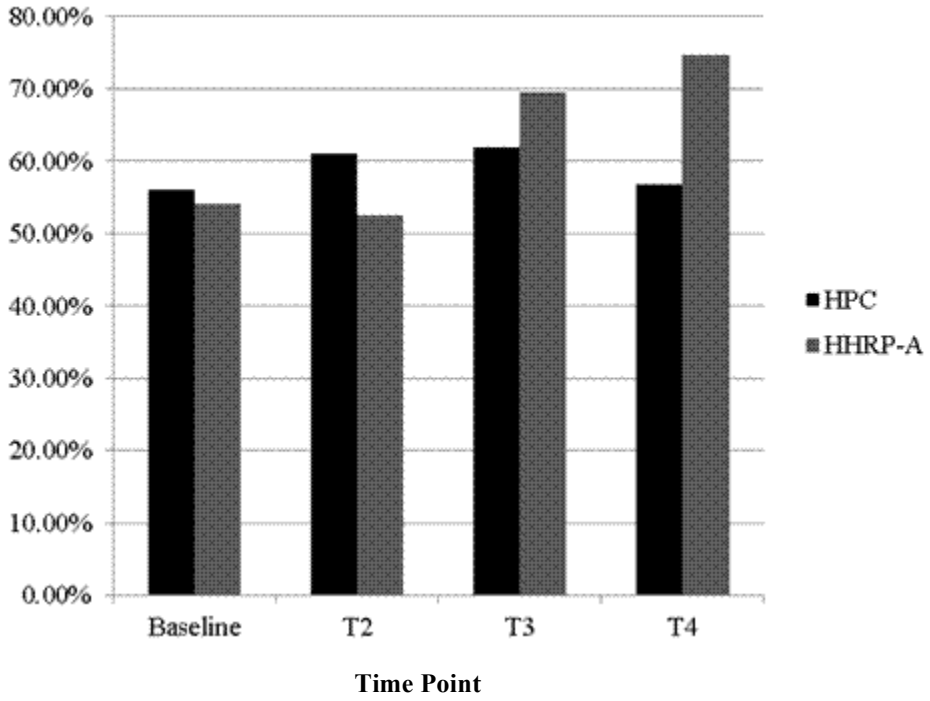


Figure Appendix 5.5. Proportion of participants reporting undetectable VL at each time point (N=243)



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Malow, R., Dévieux, J. G., Stein, J. A., Rosenberg, R., Jean-Gilles, M., **Attonito**, J., ... & Pape, J. W. (2013). Depression, Substance Abuse and Other Contextual Predictors of Adherence to Antiretroviral Therapy (ART) Among Haitians. *AIDS and Behavior*, 1-10.

Malow, R. M., Dévieux, J. G., Stein, J. A., Rosenberg, R., Lerner, B. G., **Attonito**, J., & Villalba, K. (2012). Neurological Function, Information–Motivation–Behavioral Skills Factors, and Risk Behaviors Among HIV-Positive Alcohol Users. *AIDS and Behavior*, *16*(8), 2297-2308.

Malow R, **Attonito** J, Sussman S, McMahon R. Adolescent substance use associated with exposure to trauma and natural disasters. *Textbook of Addiction Treatment: International Perspectives.* The International Society of Addiction Medicine (ISAM) eds. New York: Springer (invitation. submitted to editor)