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The Influence of Neurocognitive Impairment on Treatment Outcomes among Drug-involved People Living with HIV/AIDS

Ifeoma O. Ezeabogu

University of Connecticut, ifeoma.ezeabogu@uconn.edu

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The Influence of Neurocognitive Impairment on Treatment Outcomes among Drug-
involved People Living with HIV/AIDS

Ifeoma Obianuju Ezeabogu

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The Influence of Neurocognitive Impairment on Treatment Outcomes among Drug-
involved People Living with HIV/AIDS

Presented by

Ifeoma Obianuju Ezeabogu

Major Advisor _____
Michael Copenhaver

Associate Advisor _____
Pouran Faghri

Associate Advisor _____
Declan Barry

University of Connecticut

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ABSTRACT

Drug- and sex-related HIV risk behaviors and sub-optimal adherence to HIV medication regimens can jeopardize the health of HIV–infected injection drug users (IDUs) and threaten community health. Findings to date indicate that it is feasible to deliver a brief behavioral risk reduction/medication adherence group intervention to HIV-infected IDUs in a community-based setting. Being adherent to HAART or being able to successfully participate in behavioral interventions targeting adherence and harm reduction often requires a relatively high level of cognitive abilities. HIV infection and substance abuse are known to independently affect the central nervous system and this can result in neuro-cognitive impairment. In combination, their effects can be even more profound and this is directly relevant to intervention development because a significant number of people living with HIV/AIDS have a positive history of substance abuse. **AIM:** To evaluate if changes in information, motivation and behavior skills (IMB) with respect to medication adherence, sex- and drug-risk behavior outcomes is predicted by cognitive impairment following the brief 4-session Community-Friendly Health Recovery Program for HIV-infected Drug Users (CHRP+). Findings suggest that it may be helpful to specifically tailor such behavioral interventions to accommodate cognitive impairment.

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INTRODUCTION

HIV/AIDS and substance abuse are major public health concerns in the United States and most countries of the world today. HIV (Human Immunodeficiency Virus) is transmitted via body fluids including blood, semen, vaginal fluid, and breast milk. There are over 33 million people living with HIV/AIDS (PLWHA) worldwide, with over 60% of these in Sub-Saharan Africa (UNAIDS, 2009). In the US, it is estimated that there are currently over 1 million PLWHA (CDC, 2008). HIV/AIDS has no cure and was considered a terminal disease since its discovery in 1981 through the 1990's, when Highly Active Antiretroviral Therapy (HAART) was discovered. This combination therapy, which has been improved over the years, has the potential to reduce viral RNA levels to undetectable amounts (CDC, 2010). This leads to a boost in CD4 cell counts, thereby providing adequate immunity from opportunistic infections that used to claim the lives of HIV patients. PLWHA still cannot be cured from the infection and therefore can still transmit HIV to others, but with the proper medical management, they can live much longer and healthier lives.

Unprotected sex and sharing of unsterilized injection equipment are currently the main modes of HIV transmission. Transmissions via birth, breastfeeding, and blood transfusion have been reduced to almost negligible levels in the US but remain a concern in many developing countries. In the US, men who have sex with men (MSM), heterosexual intercourse, and injection drug use (IDU) are the major modes of HIV transmission. Acquired Immunodeficiency Syndrome (AIDS) is the terminal stage of HIV infection and can develop up to 10 years following the initial infection depending on an individual's health status and health-related behavior (CDC, 2006).

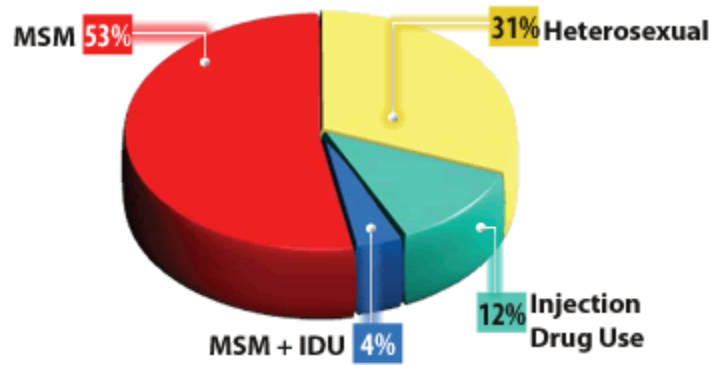


Fig. 1: HIV incidence by transmission category (<http://www.cdc.gov/>)

HIV infection and substance abuse can each independently result in Neurocognitive impairment (NCI; Al-Zahrani & Elsayed, 2009; Aydin, Kircan, Sarwar, Okur, & Balaban, 2009; Foley, Ettenhofer, Wright, & Hinkin, 2008; I. Grant, Heaton, & Atkinson, 1995). In combination, they have an even more profound effect on the central nervous system (Margolin, Avants, Warburton, & Hawkins, 2002; Norman, Basso, Kumar, & Malow, 2009; Rippeth et al., 2004). Domains commonly affected include executive functioning, information processing, motor functioning, attention, learning, and memory (Al-Zahrani & Elsayed, 2009; I. Grant & Heaton, 1990; Heaton et al., 1995). NCI symptoms can range from very mild to very severe, and studies suggest that symptoms tend to worsen with advancing HIV disease and prolonged drug use (Heaton et al., 1995). Most drugs of abuse have the ability to cross the blood-brain-barrier and directly affect the CNS, resulting in NCI symptoms. Studies suggest a more indirect mechanism of action by HIV infection. Antiretroviral therapy (ART) can significantly reduce NCI symptoms but mild forms persist in a large proportion of PLWHA who are also on ART (Foley et al., 2008; Joska, Gouse, Paul, Stein, & Flisher, 2010a).

NCI has been shown to demonstrate a significant association with sex- and drug related risk behaviors (Chander et al., 2009), and a negative association with HAART adherence (Hinkin, Castellon, Durvasula, Hardy et al., 2002; Lovejoy & Suhr, 2009). The mechanism of these relationships is not yet known but hypothesized to be due to deficits in memory, executive functioning, and possibly psychomotor skills.

Since HIV infection is spread primarily by risk behaviors, and successful HIV treatment depends on optimal adherence, improving antiretroviral adherence and reducing HIV transmission risk behaviors is the main focus of most interventions targeting drug-involved PLWHA. Evidence-based behavioral intervention approaches targeting injection drug users include: the Holistic Health Recovery Program (HHRP+), a cognitive behavioral therapy based intervention, aimed at improving medication adherence and reducing HIV risk behaviors (Margolin, Avants, Warburton, Hawkins, & Shi, 2003), and the Informational and Enhanced AIDS education aimed at reducing drug- and sex-related risk behaviors (McCusker, Stoddard, Zapka, & Lewis, 1993). Other effective interventions that target IDUs are the Modelo de Intervencion (MIP; Robles et al., 2004) and Safety Counts (Hershberger, Wood, & Fisher, 2003) interventions. These interventions typically consist of a series of group ‘treatment’ sessions, where participants are provided information on adherence, risk behaviors, and how to maximize their outcomes. Participants are also taught harm reduction skills, such as how to properly use condoms and how to sterilize needles. Such intervention sessions typically place a high demand on various cognitive domains including memory, learning, and attention. Some interventions take into account the possibility of NCI in the target populations and

try to tailor intervention content delivery accordingly (e.g. the use of cognitive remediation strategies; Copenhaver, Avants, Warburton, & Margolin, 2003).

NCI may be a potential confounding variable in assessing treatment outcomes because NCI symptom severity can differ across patients, and different cognitive domains may be affected to a different degree across patients. Also, most patients on ART have very mild symptoms of NCI which can very easily go unnoticed, but may be evident when patients are screened with an appropriately sensitive instrument. Although associations have been established between cognitive impairment and adherence and between cognitive impairment and HIV risk behavior, it is not known how cognitive impairment may influence the treatment outcomes of these two very important variables in PLWHA.

The purpose of the current study was to assess the relationship between NCI and treatment outcomes in a sample of drug-involved PLWHA who participated in the Community-Friendly Health Recovery Program for HIV-infected drug users (CHRP+; (Copenhaver et al., 2010) in New Haven, Connecticut. The primary outcome variables of interest were constructs representing changes in antiretroviral adherence and HIV risk behavior as associated with constructs representing NCI.

LITERATURE REVIEW

Drug abuse has had a strong and lasting influence on the HIV/AIDS pandemic. The National Institute on Drug Abuse (NIDA) recognizes 13 categories of drugs of abuse. These include legal recreational substances (e.g. alcohol), prescription medications (e.g. opioids), and illegal substances (e.g. cocaine; NIDA, 2010). IDU is a direct means of transmitting HIV. It is also common for HIV transmission to result from behavior that occurs while under the influences of drugs (e.g., practicing unprotected sex, having multiple sexual partners, exchanging sex for money or drugs, sharing needles or other equipment). It is estimated that 425,000 people in the United States (aged 12 and older) injected heroine, cocaine, methamphetamines, or other stimulants within the past year (SAMHSA, 2009). IDU and IDU/MSM accounted for approximately 12% and 4% respectively of the 54,230 new HIV infections in 2006 (CDC, 2009). In the same year, MSM accounted for 53% and heterosexual intercourse accounted for 31% (CDC, 2009).

It is also important to note that the heterosexual classification, according to the CDC, includes heterosexual contact with seropositive persons or persons at high risk for HIV (CDC, 2009). Thus, IDU's are likely to be contributing to this classification through contact with their sexual partners. Almost 40% of IDU related HIV transmission is classified as either MSM and IDU or heterosexual contact with IDU (CDC, 2009). In Connecticut, direct IDU related HIV incidence has been on the steady decrease from 45.4% in 2002 to 12.5% in 2009 (DPH, 2010). IDU is also a concern in South, East, and Southeast Asia for growing proportions of new HIV infections (Avert, 2010).

HIV is one of the focus areas of Healthy People 2020. Recognition of co occurring HIV and substance abuse is reflected in one of the proposed objectives:

‘increase the proportion of substance abuse facilities that offer HIV/AIDS education, counseling, and support’ (US Department of Health and Human Services, 2009). In the United States and around the world, HIV risk and substance abuse have been associated with low socio-economic status (SES). These associations between low educational level, poverty and HIV risk have been shown in across the globe (Hargreaves & Glynn, 2002; Hargreaves et al., 2008; Hargreaves & Howe, 2010; Nyindo, 2005). In the US, being a member of the black race is a high risk factor for HIV, with 45% of new infections occurring in blacks, even though African Americans make up only 12% of the total population (CDC, 2010). Studies have also showed that in the post HAART era, black ethnicity has been associated with fewer declines in HIV mortality (Rubin, Colen, & Link, 2010), more advanced disease related death not explained by SES (Lopez, Simone, Madariaga, Anderson, & Swindells, 2009), and more hospitalizations (Oramasionwu et al., 2009) compared to whites. In PLWHA, substance abuse was also found to be higher in blacks (Oramasionwu et al., 2009). According to the CDC, 57.5% of IDUs with a new diagnosis of HIV between 2004 and 2007 were black or African American (Centers for Disease Control and Prevention (CDC), 2009).

HIV and substance abuse are also highly associated with poor mental health (Schulden, Thomas, & Compton, 2009; Zahari et al., 2010). Conover et al. (2009) estimated the cost of care for triply diagnosed patients (PLWHA with co occurring substance and psychiatric disorders) to be \$3880 per month which is almost twice as much as the cost of care for PLWHA in general. For 2010, the federal government has estimated \$12.1 billion, and \$13.8 billion in mandatory and discretionary spending, respectively, for HIV. Care and treatment for PLWHA accounts for about 50% of total

expenditure (Kaiser Family Foundation 2010). Co-occurring HIV and substance abuse is therefore not simply a medical issue, but a social and economic one.

HIV Treatment: Antiretroviral therapy (ART) has shown efficacy and effectiveness in treating HIV infection and the discovery of ART changed HIV/AIDS from a ‘death sentence’ to another chronic illness that can be managed. ART acts by preventing viral replication in the body. The aim of treatment is to lower viral RNA levels to below detectable levels. This can boost CD4 counts to close to normal values. ART has also been shown to improve HIV-associated neurocognitive symptoms, although mild symptoms persist in the post-ART era and these symptoms tend to worsen with advancing HIV disease (Joska, Gouse, Paul, Stein, & Flisher, 2010a). Another key benefit of successful ART treatment is that PLWHA become less infectious when they have viral loads below detectable levels and, as a result, ART is now being investigated as a potential means of primary prevention (pre-exposure prophylaxis [PREP]) (Reuter et al., 2009; Rosengarten & Michael, 2009). Like most chronic diseases, HIV treatment outcomes depend on medication adherence, and adherence has become the greatest challenge of HIV management in the post-ART era.

Medication adherence is a measure of how compliant a patient has been to his/her prescribed medication. It takes into account taking the right quantity of medication at the right time and under the right conditions (e.g. with or without food). Adherence can be measured at various time intervals (e.g., the past day, two days, three days, one week, or more). Studies have demonstrated that most patients on an ART regimen require near perfect (90-95%) adherence to achieve desired treatment outcomes. Suboptimal adherence can lead to development of drug resistant strains of HIV which may require

different treatment combinations and can generally complicate management. Substance abuse is a major barrier to adherence in PLWHA (Battaglioli-DeNero, 2007; Friedman et al., 2009) and IDU specifically has been associated with non-adherence (Carrieri et al., 2003). Among other factors, regimen complexity has been shown to negatively affect adherence to HAART in PLWHA in general (Battaglioli-DeNero, 2007; Beusterien, Davis, Flood, Howard, & Jordan, 2008; Chesney, 2003), and specifically in IDUs (AIDS Alert, 1998). Currently there is a wide variation in regimen complexity from as simple as a single dose daily, to much more complex regimen which require different drugs to be taken at different times of the day, some before, after or without meals. .

Many measures of antiretroviral adherence utilize a self-report approach which has been criticized. First, people may be unwilling to accurately report their adherence, especially if they have not been optimally adherent. Second, there is the possibility that people may forget exactly when and how they missed drug doses. Generally, most studies use treatment outcome (i.e., CD4 count and viral load) as a secondary measure of adherence. This is based on strong correlations that have been shown between adherence and treatment outcome (Glass et al., 2006). The validity of self-reported adherence in IDUs has been questioned by some (Kerr et al., 2008) although other investigators have found undetectable viral load to be strongly associated with self-reported good adherence among IDUs (> or = 90%) (Arnsten et al., 2007). Substance abuse - and specifically injection drug use - has been associated with suboptimal adherence (Carrieri et al., 2003; Friedman et al., 2009) and, not surprisingly, studies have shown that injection drug using PLWHA tend to demonstrate poor adherence levels (Battaglioli-DeNero, 2007).

Risk behavior is another major challenge in drug-involved PLWHA. Recent reports from the CDC show that a significant proportion of PLWHA are involved in sex- and drug- related risk behaviors such as unprotected sex with seropositive and seronegative individuals, having multiple sexual partners, sharing needles and other injecting paraphernalia with seronegative, seropositive, and unknown status individuals (MMWR, 2009). This can not only lead to infection of seronegative persons, but can also result in superinfection of seropositive persons. Superinfection is the reinfection of an individual who already has an established infection with a heterologous HIV strain (Smith, Richman, & Little, 2005). This can result in variant strains of HIV that are resistant to a range of antiretroviral medications, thus leading to increased morbidity and mortality in the recipient.

Measurement of HIV risk behavior is usually based on self-report which is subject to question as it is known that people may not be willing to accurately report socially undesirable behaviors. Secondary tests for risk behavior include screening for newly acquired STDs (for sexual risk) and urinalysis (for drug use). The use of computer programs such as Audio Computer-Assisted Self Interview (ACASI), however, brings some reasonable expectations that self-reported behavior will be more accurate since responses are entered privately into a computer. HIV-related risk behaviors have been associated with substance use (Chan, Passetti, Garner, Lloyd, & Dennis, 2010; Friedman et al., 2009), and poor medication adherence (Arnsten et al., 2007; Kalichman, 2008).

Due to the high prevalence of co-occurring HIV and substance abuse, a number of behavioral interventions have been designed to address medication non-adherence, risk behaviors, and substance abuse (Bruce, Kresina, & McCance-Katz, 2010; J. T. Parsons,

Rosof, Punzalan, & Di Maria, 2005). There are also interventions that are specifically designed to address medication non-adherence in substance abuse treatment settings (Avants, Margolin, Warburton, Hawkins, & Shi, 2001). Better adherence outcomes have been observed in drug users who are also receiving substance abuse treatment (Malta, Magnanini, Strathdee, & Bastos, 2008) and use of methadone maintenance therapy (MMT) has been associated with more rapid uptake of antiretroviral therapy (Uhlmann et al., 2010).

Recently, studies have been investigating associations between HIV medication adherence and HIV related risk behavior with neurocognitive impairment (NCI) and this has become a major emerging area of study in HIV research. Drug-involved people living with HIV are at a very risk of NCI. It is important to study the associations between NCI and treatment outcomes in this population in order to adequately tailor interventions and more accurately measure the effectiveness of behavioral treatments targeting this group.,

Medication adherence, HIV-related risk behavior, and neurocognitive impairment all appear to be inter-related. The following sections will discuss these variables, their relationships, and introduce a potential relationship between neurocognitive impairment and behavioral treatment outcomes (adherence and risk behavior).

MEDICATION ADHERENCE

Antiretroviral medication has been shown to significantly improve the prognosis of PLWHA. Studies have shown that treatment with ART results in a reduction of relative risk of death and crude mortality rate in PLWHA (Antiretroviral Therapy Cohort Collaboration, 2008; Kitahata et al., 2009). It has also been shown that PLWHA with

positive histories of IDU have lower life expectancies despite being on ARTs (Antiretroviral Therapy Cohort Collaboration, 2008; Kitahata et al., 2009). Other factors that affect successful treatment include how early treatment is initiated, the age of the patient and the CD4 cell count at treatment initiation (Kitahata et al., 2009).

Medication adherence has become the most important issue in HIV management. This is because very high levels of adherence are required for successful treatment and, suboptimal adherence can result in adverse outcomes such as the development of drug resistance which can lead to increased morbidity and mortality.

In a study carried out in Uganda involving 897 HIV-infected patients who initiated ARV between May, 2004 and December 2005, adherence to ART was associated with survival after adjusting for age, sex, and educational level. It was also observed that patients who initiated ART with a CD4 cell count of <50 cells had a four-fold reduction in survival compared to those who initiated ART with a cell count of >50 who had a two-fold reduction in survival (Abaasa et al., 2008). In another study involving 80 subjects who had just initiated ART, those reporting high adherence at one month had undetectable viral loads compared to those reporting low adherence at one month (Cooper, Gellaitry, Hankins, Fisher, & Horne, 2009). The importance of adherence in HIV management was also demonstrated in a different study where improving adherence with the use of pillboxes was also associated with a significant increase in viral suppression in a sample of PLWHA (Petersen et al., 2007).

A number of potential barriers to adherence have been identified. There are some factors that have to do with the medication itself. Having to take more doses per day, drug toxicity, and lack of an adherence aid have all been associated with poor adherence

(Golin et al., 2002). Lack of improvement in symptoms attributed to ART and regimen complexity have been associated with low adherence (Cooper et al., 2009; Hinkin, Castellon, Durvasula, Lam et al., 2002). There are also factors that have to do with the patient such as substance use and neurocognitive impairment.

Substance abuse generally, and injection drug use specifically, are negatively associated with ARV receipt, viral suppression, and medication adherence. Suboptimal adherence has been associated with current drug use/dependence (Hinkin et al., 2004) and acquiring HIV through IDU has been linked to non adherence to HAART (Ammassari et al., 2004). Global severity of substance use significantly predicted ARV adherence in a sample of IDUs (Applebaum 2009) and HAART failure has also been associated with substance abuse (Parsons, Braaten, Hall, & Robertson, 2006). In a multisite cross sectional study, the odds of HAART receipt and viral suppression was significantly lower in drug users compared to non drug users and worse in those who were drug users and had a mental illness (Chander et al., 2009). Co-occurring substance abuse and mental illness is very common and this is important because significant associations have been shown between mental illness and ART adherence. Among IDUs with depression, improving depression was associated with better adherence and increased CD4 counts while worsening depression was associated with increased viral levels and active drug use (Springer, Chen, & Altice, 2009). In a sample of PLWHA who were infected through IDU and were adherent at the beginning of the study, adherence failure at follow up was significantly associated with active IDU and depression (Carrieri et al., 2003). Depressive symptoms have also been associated with medication errors in HIV positive injection drug users (Arnsten et al., 2007).

A meta-analysis conducted by Malta et al. (2008) suggests that drug users may be able to attain similar adherence levels as observed in non-drug using populations but some of the independent studies showed lower levels of adherence in past and active drug users. For example, in a study by Golin et al. (2002), active drug users and non-drug users took 59% and 72% of their prescribed drug doses, respectively. Friedman et al. (2009) found substance use to be negatively correlated with medication adherence in a sample of homeless PLWHA, Hinkin et al. (2004) found drug use/drug dependence to be associated with poor adherence, and past drug use was significantly associated with non-adherence in a study by Silva et al. (2009).

Neurocognitive impairment puts PLWHA at risk for poor adherence. Global neuropsychological performance has been shown to be significantly associated with medication adherence and PLWHA who were neuropsychologically compromised were up to 2.5 times more likely to be poor adherers (Hinkin, Castellon, Durvasula, Lam et al., 2002; Hinkin et al., 2004). In performing medication management tasks, cognitively impaired patients were more likely to fail than their unimpaired counterparts (Benedict et al, 2000). Specific cognitive functions including executive functioning, psychomotor skills, and memory also positively correlated with medication adherence in PLWHA (Contardo, Black, Beauvais, Dieckhaus, & Rosen, 2009; Hinkin, Castellon, Durvasula, Lam et al., 2002; Hinkin et al., 2004; Woods et al., 2009). One study suggests that older patients who are cognitively impaired are at greater risk of sub-optimal adherence than younger patients (Ettenhofer et al., 2009) and this may be due to deteriorating cognition that normally comes with aging. NCI may also explain the relationship between regimen complexity and adherence. In a study by Hinkin et al (2002), the cognitively impaired

who were on more complex medication regimen had the lowest adherence. Also, among those with low levels of executive functioning and compromised attention, adherence was worsened by more complex medication regimen (Hinkin, Castellon, Durvasula, Lam et al., 2002). This interaction effect with regimen complexity was not observed in cognitively intact participants. Specifically in HIV positive IDUs low literacy and cognitive impairment predicted poor medication adherence after adjusting for recent drug use (Waldrop et al 2008) while delayed word list recall predicted poor self reported adherence (Applebaum, 2009).

HIV-RELATED RISK BEHAVIOR

Because HIV is transmitted primarily by unprotected sex and unsafe injecting practices, drug- and sex- related risk behaviors have always been important aspects of HIV research. Recent statistics show that significant proportions of PLWHA still practice behaviors that can put themselves and others at risk.

Studies have shown that drug-involved PLWHA tend to practice HIV-related risky behaviors more than other PLWHA. This may be due to direct drug using practices such as sharing needles and other injecting equipment, or having unprotected sex especially while under the influence of drugs. Trading sex for money or for drugs are also activities that put drug-involved individuals at risk for contracting or transmitting HIV. Studies involving IDUs specifically suggest high levels of sex- and drug- related HIV risk behaviors. A study in Vietnam on risk behaviors among PLWHA showed high levels of sex- and drug-related HIV risk behaviors. 20% of the sample reported sex with multiple partners in the past year and consistent condom use with non-regular partners

was reported by 30.1% and 23.1% of males and females respectively. 86% of the males and 21% of the females reported injection drug use and 35% of those who injected drugs in the past month reported sharing needles and syringes (Thanh et al., 2009). Among IDUs who participated in a CDC study involving data from the National HIV Behavioral Surveillance System (NHBS) collected between May 2005 – February 2006, in the past 12 months, 31.8% and 33.4% had shared syringes and injections respectively, and 62.6% and 47.2% had had unprotected vaginal sex and had more than one sex partner (MMWR, 2009). Sex-related risk behavior was more prevalent compared to needle risk behavior in a sample of youths (aged 12-18) in substance treatment, but substance abuse was still associated with greater involvement in HIV risk behavior (Chan et al., 2010). Among homeless or unstably housed PLWHA, high levels of using various substances including cocaine and heroine were observed and those who engaged in high risk sex were more likely to have injected drugs or used two or more drugs (Friedman et al., 2009).

Mental health has been associated with risk behavior and studies suggest that poor mental health may also play a role in risk behaviors in drug users. Severity of psychiatric history predicted level of HIV risk in Puerto Rican women diagnosed with mental illness (Heaphy, Loue, Sajatovic, & Tisch, 2009) and Gu et al. (2009) observed that among female sex workers who were also IDUs in China, inconsistent condom use was associated with worse depression scores. Depression and anxiety remained significant predictors of sexual- and needle use- risk, after adjusting for substance use in a sample of adolescents in substance abuse treatment (Chan et al., 2010). In another study by Mellins et al (2009), mental health predicted sex- and drug- risk behavior in perinatally HIV-exposed seropositive and seronegative youth (Mellins et al., 2009).

The relationship between medication adherence and HIV related drug- and sex-risk behavior has also been studied and PLWHA who are involved in risky behaviors tend to have poor adherence levels (Kalichman, 2008). In a sample of injecting drug users, Arnsten et al (2007) observed that no cocaine use, no sharing of needles and drug paraphernalia, and a greater sense of responsibility for protecting others were associated with good adherence. Studies have also investigated an association between NCI and risk behavior. Self reported sex- and drug- HIV related behavior was significantly related to prospective memory in a sample of substance dependent individuals (Martin et al. 2007) while implicit and spontaneous cognition independently predicted HIV risk behavior tendencies (Stacy et al. 2000; Stacy et al. 2006).

NEUROCOGNITIVE IMPAIRMENT

Both HIV and substance abuse can independently result in NCI symptoms. The HIV virus can enter the CNS and release toxins that can trigger pathological response in different brain cell types and lead to neuronal death. The virus can also activate processes in the CNS and affect normal neuronal pathways (Boisse, Gill, & Power, 2008; Kaul, 2008). There is evidence of reduced concentrations of certain neurotransmitters that are involved in normal cognitive functioning. Sailasuta et. al. (2009) observed reduced glutamate in the white matter of HIV+ patients while another study (Kumar et. al., 2007) showed that dopamine concentrations were significantly reduced in the basal ganglia of HIV+ post mortem brains and the regions with the lowest dopamine concentrations had the highest HIV RNA levels. Decreased dopamine levels in the different brain regions, however, did not correlate with the patients' NCI status and, in the Salisuta et al. study;

there was no difference in glutamate levels between patients on HAART and HAART naïve patients (Kumar et al., 2009; Sailasuta, Shriner, & Ross, 2009). Chang et al 2008, however, associated HIV related cognitive dysfunction with decreased dopaminergic functioning in the brain and Jernigan et al (2005) observed reduced volume of cortical, limbic, and striatal structures in seropositive individuals and this was more pronounced in older patients and was also associated with NCI (Jernigan et al., 2005).

HIV-associated NCI has been well documented since HIV was first discovered. NCI has been observed in patients with early stage HIV infection (Mandal et al., 2008) and is known to worsen with advancing stage of HIV infection (Njamnshi et al., 2009)..Cerebrospinal Fluid HIV-1 RNA levels were higher in more cognitively impaired patients (Stankoff et al, 1999) and in a cohort of PLWHA already on ARV, sustained and prevalent impairment was associated with a history of immunosuppression and current immune status (Robertson et al. 2007). A more recent study by Shiramizu et al. (2009) showed a directly proportional relationship between HIV related NCI and circulating HIV DNA.

The use of ART has resulted in a drastic reduction in HIV-associated dementia (HAD) and other NCI symptoms. In a study by Tozzi et al (1999), following 6 and 15 months of ART, patients with poor neuropsychological scores reduced from 81%, to 50%, and then to 22%. Prevalence of impaired memory also reduced from 50% to 9% after 15 months of treatment. Late stage HIV positive patients who were followed for 3 and 6 months after initiating ART not only showed an improvement in CD4 counts, but also in dementia, memory, psychomotor speed, executive functioning and functional activity (Sacktor et al., 2006). Munoz-Moreno et al (2010) compared patients who had

their ARV therapy interrupted to those who did not and found significantly lower levels of attention/working memory in the interrupted therapy group (Munoz-Moreno et al., 2010). In another study, patients who were successful on their HAART regimen had better speeds of mental processing (Parsons et al., 2006).

Severe forms of NCI have been greatly reduced since the use of ART but NCI symptoms, especially mild symptoms, still persist in the post-ART era (Joska, Gouse, Paul, Stein, & Flisher, 2010b). The persistence and increasing incidence of mild cognitive impairment has led to three major classifications of HIV associated NCI (Figure 1). HAD is the most severe form of HIV associated NCI and is characterized by disruptions in normal day to day functional activity. The other two categories are asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND) and are both characterized by no dementia. In MND, there is usually a mild interference with daily functioning while in ANI, there are usually no patient complaints and diagnosis is usually made after some form of neuropsychological testing (Antinori et al., 2007). All the above diagnoses are usually made after ruling out any other possible causes of dementia (as in HAD) or other NCI. A diagnosis of NCI can be made by neuropsychological testing (e.g., using the Halstead Impairment Index; Echardt & Matarazzo, 1981), neuroimaging (e.g., using MRI [magnetic resonance imaging]), or examining the cerebrospinal fluid (CSF) to rule out confounding etiologies (Ances & Ellis, 2007).

An interesting finding among PLWHA with undetectable viral loads was that although only 27% had cognitive complaints, upon more examinations, 74% of the sample was experiencing NCI including 64% of non-complaining patients (Simioni et al.,

2010). Thus, there are clearly weaknesses in the use of self-report measures alone to assess NCI.

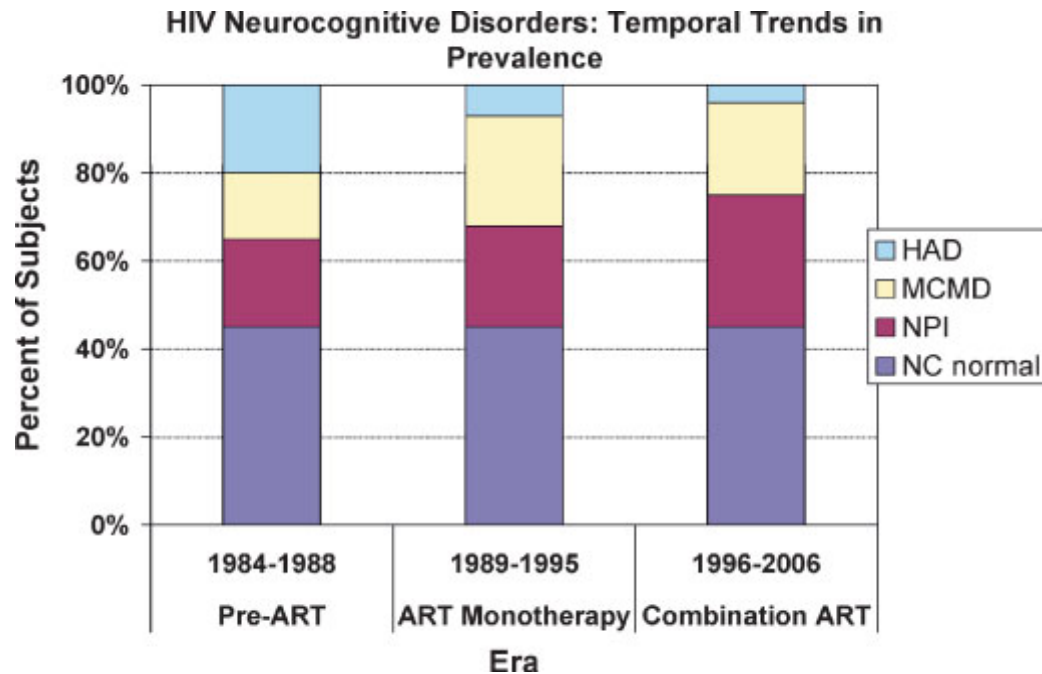


Figure 2: Schematic representation of changes in prevalence of different forms of HIV-related cognitive impairment in successive eras of antiretroviral therapy. MCMD, minor cognitive motor disorder; HAD, HIV-associated dementia; NPI, neuropsychologically impaired; NC normal, neurocognitively normal (Ances & Ellis, 2007).

The use of several substances of abuse has been linked to cognitive impairment in several studies. Heroin, alcohol, methamphetamines, marijuana, and cocaine use have all been associated with NCI (Aydin et al., 2009; Fishbein et al., 2007; Hanson & Luciana, 2010; Jovanovski, Erb, & Zakzanis, 2005; Rendell, Mazur, & Henry, 2009). Some studies have looked at the effect of duration of drug use on NCI and the results have not

been conclusive. Al Zahrani & Elsayed (2009) compared the effect of type of drug and duration of drug use on executive functioning. They compared drug dependent users of alcohol, opioids or amphetamines to a matched sample of healthy controls and they observed that overall, drug dependent individuals and those with a longer drug use history performed significantly worse (Al-Zahrani & Elsayed, 2009). On the contrary, in recently abstinent methamphetamine users who were free of HIV or HCV, there was not correlation between NCI and age of first use, years of use, or length of abstinence (Cherner et al., 2010). In another study, there was no difference in executive functioning and memory between current and former amphetamine and / or opiate users (Ersche, Clark, London, Robbins, & Sahakian, 2006).

In combination, HIV and substance abuse can have a profound effect on the CNS. In a study by Margolin et al (2002), in a sample of HIV positive injection drug users, 88% showed evidence of NCI with drug use and viral load being independent predictors of NCI. However the association of HIV and NCI, over and above the effect of substance use has also been shown. For example, compared to seronegative injection drug users, seropositive injection drug users had poorer attention and visual-motor abilities (Del Pesce, 1993) and among substance dependent individuals, prospective memory deficits were significantly higher in HIV positives compared to those who were HIV negative (Martin et al. 2007).

NCI can affect several cognitive domains including memory, learning, attention and executive functioning. It is not clear how these may cause decreased adherence or increased risk behaviors. Possible hypotheses point to the fact that good adherence to a reasonable extent depends on the sound functioning of the above mentioned cognitive

domains. Patients will have to remember to take their medications at the right time and in the right way (e.g., with or without food). The importance of sound cognition becomes more evident when patients are on cocktails with complex regimen that may have to be taken several times a day with different medication combinations.

Medication adherence, substance use, and neurocognitive impairment all appear to be interrelated (Anand, Springer, Copenhaver, & Altice, 2010). For example, Meade et al. (2010) observed that in addition to predicting adherence, neurocognitive functioning also partially mediated the relationship between cocaine dependence and poor adherence.

ASSESSING MEDICATION ADHERENCE, RISK BEHAVIOR, AND NCI

Self report, although subject to reporting bias, has been shown to be a valid and reliable measure of medication adherence and risk behavior in various HIV populations including drug involved PLWHA. Self reported medication adherence correlated with adherence measured using medication event monitoring system (MEMS) caps (Wagner, 2002; Walsh et al. 2002) and viral load measurements (Reynolds et al. 2007; Nieuwkerk & Oort, 2005; Godin et al. 2003). Self reported sexual behavior has been found to be valid in adolescents (Brener 1995; Orr 1997) but in an urban population with a high risk of STDs, self reported condom use did not correlate with STD incidence (Zenilman 1995). In IDUs risk behavior assessed using a clinical risk assessment showed good agreement with result of in depth interviews but there was consistent under-reporting in the clinical risk assessment (Morrison et al. 1995). The use of ACASI in self reported assessments can reduce bias (Langhaug, 2010; Estes et al. 2010) and the fact that subjects are assured of anonymity in these studies makes it more likely that subjects will

provide honest responses to questions regarding their medication adherence and sex risk behaviors.

There are several instruments used to measure NCI. Due to the multi faceted nature of neurocognition, standard neuropsychological tests are usually very long and extensive and require relatively significant professional assistance for them to be employed; for example the Halstead Impairment Index (Echardt & Matarazzo, 1981). For drug using populations, simple, brief but effective instruments to measure NCI are very useful. The Neuropsychological Impairment Scale (NIS, O'Donnell, Reynolds & De Soto, 1983) is an example of such an instrument. The NIS has been shown to have high validity, and has been employed successfully in PLWHA (O'Donnell, Reynolds & De Soto, 1984; Avants et al. 1997)..

NEUROCOGNITIVE IMPAIRMENT AND INTERVENTION OUTCOMES

Although the neurocognitive effects of HIV and substance abuse have been extensively studied and the potential role of neurocognitive impairment in medication adherence and HIV risk behaviors has been well documented, the specific effect of neurocognitive impairment on outcomes of interventions targeting drug-involved PLWHA remains unknown. These interventions typically place a high demand on cognitive domains that are known to be directly affected by both HIV infection and drug use, and this suggests that cognitive function at baseline may play an important role in how members of this target population respond to these interventions in terms of HIV risk reduction and medication adherence outcomes.

The role of neurocognitive impairment on treatment outcomes in substance abuse has been investigated in some studies. For example, in a sample of psychiatric, substance dependent patients, cognitive ability was found to be significantly associated with motivation to change substance abuse behavior (Blume et al., 1999). In another study involving substance users in an extensive 12-step treatment program, executive functioning, although not a significant predictor of poor treatment outcome, appeared to mediate the relationship between change processes and outcome. This study found that self-efficacy and a strong affiliation with Alcoholics Anonymous (change processes) were weakly associated with outcome in impaired subjects but very strongly associated with outcome in unimpaired subjects (Morgenstern & Bates, 1999). In a more recent study, Pasetti et al. (2008) investigated the neuropsychological predictors of treatment outcome in a sample of seronegative opiate dependent individuals after three months of treatment. The subjects received substitute opiate administration, had access to a psychologist and a discussion group. The study found that after 3 months of treatment, poor decision making, measured by the Iowa and Cambridge Gambling Tasks, was associated with non abstinence from illicit drugs in the past 30days and this was confirmed by urine drug screenings.

In another recent study, Flessner et al. (2010) examined the effect of neuropsychological functioning on Obsessive Compulsive Disorder (OCD) treatment outcomes in children aged 7-17years in a study designed to compare the efficacy of cognitive behavioral therapy (CBT) alone, pharmacotherapy alone, and combined CBT and pharmacotherapy. Neuropsychological assessment carried out before treatment showed that, for subjects receiving CBT treatment alone, non-responders were more

impaired than responders. This was not observed for subjects in the pharmacotherapy group, or those in the CBT and pharmacotherapy combined group (Flessner et al., 2010). The results of this study point to the potential of cognitive impairment in influencing treatment outcomes in CBT which is the basis for most behavioral interventions targeting drug involved PLWHA.

OBJECTIVES AND HYPOTHESES

Primary Objective 1: assess the relationship between NCI and change in medication adherence following the CHRP+ intervention.

Hypothesis: Subjects with lower cognitive functioning will have less improvement in medication adherence following the CHRP+ intervention.

Primary Objective 2: assess the relationship between NCI and change in sex- and drug-related HIV risk behavior following the CHRP+ intervention.

Hypothesis: Subjects with lower cognitive functioning will have less change in sex- and drug- related risk behavior following the CHRP+ intervention.

Other Objectives

1. To assess the relationship between NCI and medication adherence at pre and post intervention.
2. To assess the relationship between NCI and risk behavior at pre and post intervention.

METHOD

Design: This was a retrospective secondary analysis for a sample of drug-involved PLWHA who participated in the Community-Friendly Health Recovery Program (CHRP+; Copenhaver et al. 2010) in New Haven, Connecticut. Variables for HIV related drug- and sex-risk behavior had already been created in the primary study. Regression analysis was used to assess the association between these variables and treatment outcome with neurocognitive impairment measured using the neuropsychological impairment scale (NIS; O'Donnell et al 1983).

Sample: HIV infected individuals who were on prescribed antiretroviral medication and who were receiving methadone maintenance therapy participated in the CHRP+ study. Inclusion criteria included meeting DSM-IV opioid dependence criteria and self reported HIV risk behavior within the past month. For the purpose of the study, risk behavior was defined as having used IV drugs or having unprotected sex in the past three months. Participants were 64% African American, 18% Caucasian, and 15% Latino. 46% of them had contracted HIV through drug related behaviors and almost 80% had an annual income of less than \$10,000. 39 subjects enrolled, out of which 10 dropped out immediately after the pre-intervention assessment. All 29 remaining individuals were available for least one intervention session and 21 subjects participated in the post-intervention assessment. Participants were reimbursed for the time required for the assessments.

Measures: The Neuropsychological impairment scale (NIS; O'Donnell, Reynolds & De Soto, 1983) was used to assess NCI. The NIS comprises 95 items with a 5 point response

scale (0: not at all; 4: Extremely). The responses to the items are used to compute 7 subscale scores and 3 summary scores. There are also four validity checks.

Although the NIS requires professional interpretation, it can be self reported by the patient. In order to use the NIS, patients have to be 18 years or older and be able to read at 5th grade level or above. The NIS is generally used as a screening instrument and not a diagnostic tool for NCI. A clinical diagnosis will require the use of more comprehensive assessment instruments. The NIS has been shown to have strong sensitivity (.91) and specificity (.76) using the Halstead Impairment Index which is a standard, more comprehensive neuropsychological battery (O'Donnell, Reynolds & De Soto, 1984; Avants et al., 1997). In a study using the NIS to determine whether cocaine dependent patients differed by HIV status based on self awareness of cognitive impairment, HIV positive subjects were more likely to show impairment on several NIS subscales (Avants et al., 1997).

The NIS subscales assess Critical Items (CRIT), Cognitive Efficiency (COG), Attention (ATT), Memory (MEM), Frustration Tolerance (FRU), Learning Verbal (LV), and Academic Skills (ACD). These scores provide an indication of impairment for the different cognitive domains. Assessment of overall cognitive functioning is provided by the summary scores which are the Global Measure of Impairment (GMI), Total Items Circled (TIC), and Symptom Intensity Measure (SIM). Generally, high levels in any of these scores are an indication of NCI but too low scores can also indicate problems.

The validity scores provide a background for the interpretation of the other scores. Defensiveness (DEF) is an indication of the test takers attitude, Affective Disturbance (AFF) is an indication of emotional state of the subject at the time of the test, and

Response Inconsistency (INC) identifies inconsistent response pairs. NIS scores are usually expressed as T scores.

Summary Scores	Global Measure of Impairment (GMI)	Total of responses to 80 items on the instrument (excluding Defensiveness Scale and Affective Disturbance items). Provides and overall measure of impairment
	Total Items Circled (TIC)	Total number of items with non zero responses (excluding Defensiveness Scale and Affective Disturbance items).
	Symptom Intensity Measure (SIM)	Computed by dividing the GMI by the TIC
Subscales	Critical Items (CRIT)	Assesses the patient's history of neurological illness or injury
	Cognitive Efficiency (COG)	Assesses general symptoms of NCI
	Attention (ATT)	Assesses the patients ability to pay attention and concentrate
	Memory (MEM)	Assesses the patients memory
	Frustration Tolerance (FRU)	Assesses irritability, anger and temper
	Learning Verbal (LV)	Assesses learning and expressive speech
	Academic Skills (ACD)	Assesses ability to carry out daily activities involving computing and reading.

Table 1: Neuropsychological Impairment Scale Summary Scores and Subscales

Measures based on the Information, Motivation, and Behavior Skills (IMB; Fisher et al. 1994) model were used to assess medication adherence and risk behavior. These measures have been used in prior NIH-funded studies and show good psychometric properties (e.g., Copenhaver et al., 2010 in press; Copenhaver et al., 2009). According to the IMB model, HIV preventive behaviors are ultimately a product of an individual's level of information, motivation, and behavioral skills. This model has been successfully employed to reduce HIV risk behavior among college students (Fisher et al. 1996), predict condom use in STD patients and heroine addicts (Scott-Sheldon et al., 2010; Bryan et al., 2000), and improve medication adherence (Fisher et al., 2008).

Variables: NIS measurements comprising 7 impairment subscales, 3 validity scores, and 3 summary scores were taken at pre- and post-intervention assessment points. For the purpose of this study NIS scores <30T were considered low, scores >30T and <50T were considered average, a high score was >50T and < 60T, and any score above 60T was considered very high. Constructs for medication adherence and HIV related risk behavior were created based on the IMB model (Table 2). These were measured pre-intervention, post-intervention, and at a three month follow-up session. Change in treatment outcome was assessed by computing the difference between pre- and post- intervention scores for adherence and HIV risk behavior. Examples of questions used to compute the construct for adherence information were 'what should you do if you develop side effects?' and 'what should you do if you cannot remember how frequently to take your medication?' Drug use self and social motivation examples are 'in the next 6 months do you plan (intend) to stop using heroine completely?' and 'how important is being drug free to most of the people in your "social network"?' Examples of sex risk self efficacy and reported

behavior questions are ‘how confident are you that you would bring up the issue of condoms or safer sex in a conversation when sober’ and ‘how many sexual partners have you had in the past 30 days?’

Type of variable	Constructs
Antiretroviral adherence	Knowledge Motivation Self-efficacy
Drug use	Information Personal motivation, Social motivation Self-efficacy/difficulty, Reported behavior
Sex behavior	Information Personal motivation, Social motivation Self-efficacy, Reported safe sex

Table 2: Variables used (IMB constructs)

Intervention: The CHR+ intervention is a behavioral HIV risk reduction intervention consisting of four 45-minute weekly group meetings led by two graduate-level trained facilitators (Copenhaver et al. 2010). It was adapted from an evidence-based intervention - the Holistic Health Recovery Program (HHR+; Margolin et al. 2003) - and is tailored for IDUs in treatment.

Data Analysis: Pre-intervention (n=36) and post-intervention (n=21) data were included in the secondary analysis. First, simple correlations were carried out between all NIS scores and IMB construct scores and between all NIS scores and treatment outcome scores. This was done in order to narrow down the number of NIS scores such that only scores that were significant predictors of treatment outcomes were included in the final regression models. This was due to the limited sample size and large number of variables of interest. P values were set at <.05 and SPSS software was used for all statistical analyses described below.

RESULTS

There was no difference across participants between NIS scores at pre- and post-intervention; thus, the pre-intervention scores were used for this analysis. Mean NIS scores (Table 3) ranged from approximately 40T on the defensiveness subscale to 60T for critical items and cognitive efficiency subscales. Tables 4, 5 and 6 show the coefficient of determination (R^2) i.e. how much of the variance in each of the constructs was explained by their respective predictors. At pre-intervention, critical items (CRIT), cognitive efficiency (COG), frustration tolerance (FRU), memory (MEM), and global measure of impairment (GMI) were significantly associated with adherence self-efficacy while response inconsistency and affective disturbance were significantly associated with adherence motivation post intervention. 25.1% and 24.8% of the variance in adherence self efficacy and adherence motivation respectively was explained by the combination of their respective predictors.

At post intervention, drug use social motivation was predicted by learning verbal (LV) and response inconsistency (INC) while drug use self-efficacy was found to be significantly associated with LV, CRIT, MEM, DEF, ACD (academic skills). In combination, the respective predictors accounted for 24.4% and 81.3% respectively of the variance in drug use social motivation and drug use self-efficacy. Drug use reported behavior frequency was positively associated with CRIT and 21% of the variance of drug use reported behavior frequency was explained by CRIT.

Positive changes in adherence motivation from pre- to post-intervention was significantly associated with MEM and INC and together these explained 27.2% of the variance in change in adherence motivation whereas SIM (symptom intensity measure)

predicted negative changes in social motivation pertaining to drug use behavior, explaining 24.6% of the variance.

Predictor	Min	Max	Mean	SD
Validity Scores				
• Response Inconsistency	32.00	68.00	51.78	8.34
• Defensiveness Scale	31.00	56.00	40.08	6.26
• Affective Disturbance	32.00	72.00	56.75	11.56
Summary Scores				
• Global Measure	30.00	80.00	57.58	13.89
• Total Items Circled	30.00	80.00	55.51	16.75
• Symptom Intensity Measure	33.00	77.00	56.23	11.49
Impairment Subscales				
• Critical Items	38.00	80.00	57.97	13.18
• Cognitive Efficiency	35.00	76.00	57.97	12.78
• Attention	30.00	76.00	53.97	13.52
• Memory	30.00	75.00	56.06	12.46
• Frustration Tolerance	33.00	76.00	55.50	13.24
• Learning-Verbal	37.00	80.00	56.42	13.49
• Academic Skills	32.00	74.00	54.86	12.96
Summary of NIS scores (pre intervention) n=36.				

Table 3: Summary of NIS scores

Predictor	Adherence Efficacy	Self (pre)	Adherence (post)	Motivation (post intervention)
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	intervention) n=36	n=21
Validity Scores		
Response Inconsistency		-.434*
Defensive scale		
Affective Disturbance		-.444*
Summary Scores		
- Global Measure	-.362*	
- Total Items Circled		
- Symptom Intensity Measure		
Impairment Subscales		
- Critical Items	-.333*	
- Cognitive Efficiency	-.395*	
- Attention		
- Memory	-.351*	
- Frustration Tolerance	-.339*	
- Learning-Verbal		
- Academic Skills		
Total Variance explained (by combined significant predictors)	25.1%	24.8%

Table 4: Significant predictors (NIS scores) of adherence at pre and post intervention.
 *p<.05; **p<.01; ***p<.001

Predictor	Drug use self efficacy (post)	Drug use Social motivation (post)	Drug Use reported behavior
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	intervention) n=21	intervention) n=21	frequency (post intervention) n=21
Validity Scores			
Response Inconsistency		-.419*	
Defensive scale			
Affective Disturbance			
Summary Scores			
- Global Measure	-.475*		
- Total Items Circled			
- Symptom Intensity Measure			
Impairment Subscales			
- Critical Items	-.668***		.459*
- Cognitive Efficiency			
- Attention			
- Memory	-.420*		
- Frustration Tolerance			
- Learning-Verbal	-.513*	-.473*	
- Academic Skills	-.448*		
Total Variance explained (by combined significant predictors)	81.3%*	24.4%	21%*

Table 5: Significant predictors (NIS scores) of risk behavior at post intervention.
*p<.05; **p<.01; ***p<.001

Predictor	Adherence motivation (change) n=21	Drug use social motivation (change) n=21
Validity Scores • Response Inconsistency	-0.465*	
Summary Scores • Symptom Intensity Measure		-0.496*
Impairment Subscales • Memory	-0.489*	
Total Variance explained (by combined significant predictors)	27.2%	24.6%*

Table 6: Significant predictors (NIS scores) for change in outcome from pre to post
*p<.05; **p<.01; ***p<.001

The CHRP+ intervention produced significant improvements in adherence, sex behavior self-efficacy, and in reported sex behavior and drug use from pre-intervention to post-intervention (Copenhaver et al. 2010). This secondary analysis enables the results of the intervention to be viewed in light of NCI characteristics of the participants and how this could potentially have played a role in their performance in the intervention.

DISCUSSION

Consistent with other studies with this target population of HIV+ drug users (Margolin et al 2002; Del Pesce, 1993; Martin et al. 2007), moderate cognitive impairment was evident in this group of participants, as indicated by generally low scores on the NIS as well as relatively lower scores across specific subscales. Higher levels of cognitive impairment were associated with poorer adherence and higher levels of risk behavior, also consistent with other studies (Hinkin, Castellon, Durvasula, Lam et al., 2002; Hinkin et al., 2004; Martin et al. 2007). Global and specific impairment scales were negatively associated with adherence and drug use related constructs at pre- and post-intervention. This appears to be the first study assessing the potential association between neurocognitive impairment with adherence and risk reduction intervention outcomes in drug using PLWH. Following the intervention, improvements in adherence and drug risk reduction outcomes were negatively associated with cognitive impairment. Although most regression models did not reach conventional levels of significance – owing to the inclusion of a relatively small sample size, moderately large R^2 values that were observed (Table 7) suggest that more significant associations may have been observed given a much larger sample. The mean value for defensiveness suggests that participants did not

have a wrong attitude towards the test. On the other hand, the mean affective disturbance score was suggestive of some degree of emotional strain at the time testing which was not a surprising finding considering the nature of the sample. Drug involved individuals are typically socio-economically disadvantaged as evidenced by the very low annual income of the majority of our sample. The mean response inconsistency score also indicates some inconsistent answers to questions on the NIS.

There were more neurocognitive correlates – global and specific - with behavior skills constructs (self efficacy) and, interestingly, this was the area where significant changes were observed following the CHRP+ intervention (Copenhaver et al., 2010). Another interesting observation was that the CHRP+ did not observe any change in information constructs (Copenhaver et al., 2010) and there were no neurocognitive correlates with any of the information constructs or change in information from pre to post intervention. However, it was surprising to find that although the CHRP+ study did not observe any significant improvements in motivation constructs (Copenhaver et al., 2010), change in adherence motivation and drug use social motivation were negatively predicted by memory and symptom intensity measure respectively. There were also no neurocognitive correlates with sex-risk constructs before or after the intervention, or with change in sex risk constructs from pre to post intervention.

Model	Dependent variable	Predictors	R	R ²	Sig
1	Adherence	Self- CRIT,COG,FRU,MEM,GMI	.501	.251	.106

	efficacy(pre)				
2	Adherence Motivation (post)	AFF, INC	.498	.248	.077
3	Drug use Social motivation (post)	LV, INC	.494	.244	.081
4	Drug use Self-efficacy (post)	LV, CRIT, MEM, DEF, ACD, GMI	.813	.661	.009
5	Drug use Reported behavior frequency(post)	CRIT	-.459	.210	.036
6	Adherence Motivation (pre-post)	MEM, INC	.522	.272	.057
7	Drug use Social motivation (pre- post)	SIM	.496	.246	.022

Table 7: Regression Model Summaries

NCI appears to play an important role in how drug-involved PLWHA respond to secondary HIV risk reduction interventions targeting adherence and risk behavior. These interventions typically place a high demand on several cognitive domains such as memory, learning, and attention and NCI may be a potential confounding variable with regard to treatment outcomes. Adequate attention should be paid to NCI when designing and implementing interventions for this population (e.g., Copenhaver et al. 2003). This is particularly important in the post-ARV era where NCI symptoms are mostly mild and can very easily go undetected or be mistaken for other effects of active drug use such as hangovers or being ‘high’.

The results of this study should be viewed in light of a number of limitations. First, the sample size included in this secondary analysis was extremely small. It was not sufficiently large to generate enough power in the statistical analyses to adequately examine all the variables of interest. The observed R^2 values, however, suggest that the findings are worthy of follow up investigations. Secondly, the NIS, although a very user

friendly and convenient tool for difficult to reach populations such as drug users, it does not provide a comprehensive assessment of NCI and does not measure all possible cognitive domains. Thirdly, scores of adherence and risk behavior are highly correlated with one another, and we did not control for this due to the small sample size. It is possible that, with a larger sample, a multivariate analysis could be carried out which would allow us to control for such associations. Fourthly, all assessments were based on self-report, which is a challenge to the integrity of the responses provided, especially because the study seeks to examine mostly socially unacceptable behaviors. This may have been moderated, however, by the use of ACASI systems, which provided participants with a high level of privacy in addition to the assurance of anonymity. Finally, subjects with poor scores on the validity checks should have been excluded from this analysis for more accurate interpretation of results. Such an approach, however, would have further reduced statistical power due to a relatively small sample size.

It is important to note that the CHRP+ intervention employed cognitive remediation strategies designed to assist subjects who have cognitive difficulties. These involved multimodal (verbal, visual, and experiential) presentation of material, learning by doing (e.g. the use of role playing), structure and consistency (sessions were carried out at the same time and location every week), using simple language and reviewing material frequently. While this may have moderated the influence of NCI, its effect was not measured, and thus we are not aware of how the incorporation of cognitive remediateion strategies may have affected participants' outcomes. However, if cognitive remediation were indeed influential, the outcomes of this study may have been even more extreme since NCI was found to predict treatment outcome. That is, in the absence of

cognitive remediation strategies, the interventions would have been expected to be more challenging to the participants, and NCI would therefore have been more evident, thus its potential effects, more extreme.

CONCLUSION

Results of this study suggest that more attention should be paid to screening for NCI in this population, and potentially accommodating mild to moderate levels of NCI in the delivery of interventions for this target population as implied in prior work (Copenhaver et al., 2003). Controlling for NCI will provide more accurate interpretation of study results. It may also be necessary to assess the associations of NCI and intervention outcome variables at follow up. NCI may account for drop outs and may also explain some of the relapse often experienced in behavioral interventions. Future studies should utilize a larger sample, use more comprehensive and sensitive screening instruments for NCI, and objectively assess the contributions of cognitive remediation strategies. This would be consistent with several current NIH initiatives addressing this target population (e.g. NIDA RFA: PA-07-307; Drug Abuse aspects of HIV/AIDS).

Relatively high scores on affective disturbance observed were not unexpected in this sample considering the social and economic challenges faced by this population. It however suggests that those who administer neuropsychological test ought to be careful not to have activities that could add any more emotional strain to participants coinciding with test taking as this could potentially affect the reliability of test results. Although several behavioral risk reduction approaches such as the CHRP+ have been shown to be efficacious in this target population of HIV+ drug users, such interventions may not be

the first line of treatment for patients with cognitive difficulties, and it may still be necessary to explore other intervention approaches to improve adherence and reduce risk behavior in drug involved PLWHA. Substance use treatment such as methadone maintenance to address drug risk behavior, and the use of aids such as pill boxes to address medication adherence have, of course, been shown to play a helpful role. This study, as well as previous studies, suggests that there could be sub groups of patients within the larger group of drug involved PLWHA based on neurocognitive status. Recognizing this and tailoring treatment to meet their needs is an indispensable aspect of effective interventions targeting this population.

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