2015-03-31

Characterizing HIV-Associated Neurocognitive Disorder in Two Underserved Sociodemographic Groups

Julia S. Seay
University of Miami, julia.s.seay@gmail.com

UNIVERSITY OF MIAMI

CHARACTERIZING HIV-ASSOCIATED NEUROCOGNITIVE DISORDER IN TWO UNDERSERVED SOCIODEMOGRAPHIC GROUPS

By

Julia S. Seay

A DISSERTATION

Submitted to the Faculty
of the University of Miami
in partial fulfillment of the requirements for
the degree of Doctor of Philosophy

Coral Gables, Florida

May 2015

UNIVERSITY OF MIAMI

A dissertation submitted in partial fulfillment of
the requirements for the degree of
Doctor of Philosophy

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Julia S. Seay

Approved:

_____ Michael H. Antoni, Ph.D. Professor of Psychology	_____ Erin Kobetz-Kerman, Ph.D., M.P.H. Associate Professor of Public Health
_____ Gail Ironson, M.D., Ph.D. Professor of Psychology	_____ Hector Bolivar, M.D. Assistant Professor of Medicine
_____ Neil Schneiderman, Ph.D. Professor of Psychology	_____ M. Brian Blake, Ph.D. Dean of the Graduate School

_____
Dominique Musselman, M.D.
Associate Professor of Psychiatry

SEAY, JULIA S. (Ph.D., Psychology)
(May 2015)

Characterizing HIV-Associated Neurocognitive Disorder in Two Underserved Sociodemographic Groups

Abstract of a dissertation at the University of Miami.

Dissertation supervised by Professor Michael H. Antoni.
No. of pages in text (76)

The purpose of this project is to characterize neurocognitive functioning and correlates of neurocognitive functioning, as well as to examine the diagnostic accuracy of relatively promising neurocognitive tests in two underserved sociodemographic groups living with HIV: monolingual Spanish-speaking Hispanics and English-speaking African-Americans, in order to better understand HIV-Associated Neurocognitive Disorder (HAND) within these groups. Examining HAND in underserved groups is paramount to the development of effective HAND screening and treatment algorithms in clinics that serve these groups, such as the AIDS Clinical Research Unit (ACRU) at the University of Miami. The current project was drawn from an initiative to develop a HAND screening algorithm for this clinic, such that patients with milder forms of HAND can be identified.

The current study examined the performance of convenience samples of English-speaking African-Americans (n = 38) and monolingual Spanish-speaking Hispanics (n = 50) on a variety of easy-to-use, sensitive neurocognitive tests we previously collected at the ACRU: Grooved Pegboard (GP), Trail Making Test (TMT), Action Fluency (AF), and the Hopkins Verbal Learning Test-Revised (HVLT-R). I used these tests and medical chart review to classify HAND via the 2007 Frascati diagnostic criteria, the most

up-to-date criteria for classifying HAND. Furthermore, I examined the association between an array of psychosocial, medical, and behavioral factors and HAND classification, which may aid in informing HAND screening and testing algorithms. Finally, I also examined the sensitivity and specificity of promising measures, Action Fluency (which tests the ability to generate novel verbs) and Trail Making Test, in detecting HAND, in order to elucidate whether these free and easy-to-administer measures should be added to screening batteries to detect HAND within these groups.

Using logistic regression analyses, I analyzed associations between medical, behavioral, and psychosocial correlates and HAND. Perceived stress and poorer sleep quality were found to be at least marginally associated with increased odds of HAND, while social support from friends was found to be associated with decreased odds of HAND. Using HAND diagnosis via GP, HVLT-R, and medical chart review as the gold standard, I calculated the sensitivity and specificity of the AF and TMT, as well as performed ROC analyses to evaluate the overall diagnostic accuracy of these measures. Both the AF and TMT measure did not demonstrate adequate sensitivity (> 70%) in detecting HAND in the overall sample, as well as within each of the sociodemographically distinct groups. Furthermore, the AF and TMT demonstrated poor AUC estimates (> .70), indicating poor overall diagnostic accuracy.

Though the sample size was limited, results indicate that psychosocial factors such as stress, sleep quality, and social support from specific sources may aid in identifying individuals at risk for or living with HAND. These results also indicated poor diagnostic accuracy for the AF and TMT in the study samples. Future work should evaluate these measures using larger samples and more extensive testing batteries.

TABLE OF CONTENTS

LIST OF TABLES v

LIST OF FIGURES vi

Chapter

1 INTRODUCTION 1
Prevalence of HAND in the Post-HAART Era 3
Health Disparities and HAND 4
Risk Factors for HAND 6
Development and Symptoms of HAND 13
Assessment and Treatment of HAND 15
Current Study 23

2 METHOD 27
Participants 27
Procedure 27
Measures 29
Neurocognitive Measures 29
Functional Status Measures 30
Psychosocial Measures 31
Medical and Behavioral Measures 33
Data Analysis Plan 33

3 RESULTS 37
Descriptive Analyses 37
Relationships between Psychosocial Variables and HAND 40
Diagnostic Accuracy of the Trail Making Test and the Action Fluency Test 42

4 DISCUSSION 44
Psychosocial Correlates of HAND 47
Diagnostic Accuracy of the Trail Making Test and the Action Fluency Test. 50
Limitations 53
Conclusion 55

TABLES……..… 57

FIGURES ……..…..... 62

REFERENCES……..... 65

LIST OF TABLES

TABLE 1: Descriptive Statistics (Mean (SD); Frequency (Percent)) for Sociodemographic, Medical, and Behavioral Variables. 57

TABLE 2: Descriptive Statistics (Mean (SD); Frequency (Percent)) for Psychosocial Variables 58

TABLE 3: Univariate Odds Ratios for Associations between Sociodemographic, Medical, and Behavioral Variables and HAND 59

TABLE 4: Univariate Odds Ratios for Associations between Psychosocial Variables and HAND 60

TABLE 5: Multivariate Odds Ratios for Associations between Significant Variables and HAND 61

LIST OF FIGURES

FIGURE 1: ROC Analyses Examining the Diagnostic Accuracy of the TMT and Action Fluency Test for the Overall Sample 62

FIGURE 2: ROC Analyses Examining the Diagnostic Accuracy of the TMT and Action Fluency Test for the African-American Sample 63

FIGURE 3: ROC Analyses Examining the Diagnostic Accuracy of the TMT and Action Fluency Test for the Hispanic Sample 64

CHAPTER 1: INTRODUCTION

During the era of Highly Active Antiretroviral Therapy (HAART), people living with HIV (PLWH) who are adherent to their medication live nearly as long as the non-infected population (Samji et al., 2013). With this advance, these individuals are experiencing lower rates of mortality due to AIDS-related illnesses such as pneumocystis pneumonia and toxoplasmosis; however, PLWH demonstrate higher prevalence of other life-threatening chronic illnesses such as cardiovascular disease, diabetes, and certain types of cancer, including non-Hodgins lymphoma and Kaposi's sarcoma (Worm et al., 2009; NCI, 2011). Researchers hypothesize that although HAART regimens allow for viral control within the bloodstream, HIV may still proliferate through the formation of latent reservoirs within tissues. Additionally, chronic inflammation caused by HIV infection and its sequelae may also contribute to increased rates of these chronic illnesses (Chun et al., 1997; Alexaki et al., 2008).

Recently, researchers and clinicians have noticed a new chronic syndrome that is likely due to HIV proliferation: HIV-Associated Neurocognitive Disorder (HAND). HAND is an umbrella term, encompassing multiple levels of neurocognitive impairment including asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated Dementia (HAD; Antinori et al., 2007). Individuals living with HAND can experience progressive functional deficits, which can limit ability to perform activities of daily living, such as working, driving, and running a household. While HIV-Associated Dementia (HAD), commonly characterized by severe neurocognitive impairment within the context of end-stage AIDS, has decreased

significantly with the advent of HAART, the milder forms of HAND, ANI and MND, have increased as HIV-positive individuals in the post-HAART era age (Antinori et al, 2007; Heaton et al., 2004).

With increasing numbers of middle-aged and elderly PLWH, HAND is increasing, even in those who are adherent to HAART regimens (Gannon et al., 2011). However, unlike the pre-HAART era, most of the individuals who are living with HAND are classified as either ANI or MND, rather than HAD. Both ANI and MND involve milder neurocognitive and functional deficits that are less pronounced than those in HAD, thus making HAND more difficult to diagnose. Both clinicians and researchers have noted a variety of challenges in understanding HAND, including estimating the prevalence of HAND, identifying risk factors for HAND, and developing neurocognitive testing batteries that are both sensitive and specific for detecting HAND (Mind Exchange Program, 2013; Antinori et al., 2007; Heaton et al., 2004). Furthermore, these challenges may be compounded in certain sociodemographic minority groups, such as African-Americans and Spanish-speaking Hispanics, who traditionally have performed more poorly on neurocognitive tests despite being neurologically normal (Morgan et al., 2008; Norman et al., 2011; Chu et al., 2008; Gasqoine et al., 2007). Thus, research is needed to characterize HAND in sociodemographic minority groups specifically. Moreover, given that culture and ethnicity have been found to moderate disease outcomes within a variety of diseases, including HIV, it is plausible that these factors may significantly influence the development and assessment of HAND. Thus, the prevalence of HAND, risk factors for HAND, and the neurocognitive measures that are both sensitive and specific for

detecting HAND may differ between sociodemographic groups that are ethnically and culturally unique.

Given the aforementioned deficits in our current understanding of HAND, my dissertation aims to characterize HAND, identify correlates of neurocognitive functioning, and examine the diagnostic accuracy of a promising neurocognitive test in detecting HAND in two understudied sociodemographic groups living with HIV: monolingual Spanish-speaking Cubans and low-SES English-speaking African-Americans. This investigation will aid in our understanding of HAND within these groups, as well as aid in developing HAND screening algorithms and interventions that are tailored to these groups. Below I provide background on issues surrounding HAND, including its prevalence, risk factors, its development and diagnosis, as well as potential HAND-related health disparities, before outlining the current study.

Prevalence of HAND within the Post-HAART Era

The largest study of HAND to date, the CHARTER Study, examined neurocognitive impairment in individuals living with HIV across multiple sites within the United States. The CHARTER Study revealed the prevalence of ANI, MND, and HAD to be 33%, 12%, and 2%, respectively (Heaton et al., 2010). Another large study that examined neurocognitive functioning in individuals living with HIV classified 39% of their sample as having at least mild neurocognitive impairment, however, these researchers did not classify their participants using the updated diagnostic criteria for HAND (Robertson et al., 2007; Antinori et al., 2007). The prevalence of both HAND and neurocognitive impairment reported by these studies is alarming, given that they were both conducted within the HAART era. Given the CDC's estimate of 1,144,500

individuals living with HIV in the U.S., these estimates imply that over 300,000 of these individuals are living with ANI and over 100,000 of these individuals are living with MND (CDC, 2013).

Furthermore, while both of these studies recruited over 1000 individuals living with HIV, both samples may not be representative of all individuals living with HIV, especially those who may be the most susceptible to developing HAND. For instance, both study samples had relatively high education levels with large proportions of participants having a high school education or above (Heaton et al., 2010; Robertson et al., 2007). However, lower education level has been identified as a potential risk factor for HAND (Cross et al., 2013). Furthermore, both of these study samples did not include significant proportions of Hispanic participants (Heaton et al., 2010; Robertson et al., 2007). Hispanic individuals, especially recent immigrants, may be at higher risk for HAND due to lack of access to healthcare and other resources (Rajabiun et al., 2008). Thus, the prevalence of HAND may be even higher in these disadvantaged groups. In fact, the two studies that have examined prevalence of HAND in Hispanics specifically (albeit with very small sample sizes) have demonstrated prevalence estimates of 70% or greater in this group (Wojna et al., 2006; Mindt et al., 2009). All in all, more research is needed to understand the development, features, and prevalence of HAND across diverse groups, so that HAND interventions may reach those that need them most.

Health Disparities and HAND

Throughout the HIV epidemic, multiple sociodemographic minority groups have been at disparate risk for both acquiring HIV and experiencing poorer HIV-related outcomes once infected. Minority groups, especially African-Americans, Hispanics, and

men who have sex with men (MSM) experience rates of HIV that are disproportionate to their representation within the general U.S. population (CDC, 2014; CDC, 2014b; CDC, 2014c). Once infected, these groups may experience poorer health outcomes with regard to HIV disease progression, as well as disparities in the development of other co-morbidities such as HIV nephropathy and cardiovascular disease (Chu & Selwyn, 2008). A multitude of factors may contribute to the existence of these disparities among minority and vulnerable groups, including lack of health education, lack of access to resources, exorbitant cost of healthcare and health insurance, stigma, and discrimination (Chu & Selwyn, 2008; Bogart et al., 2010; Bogart et al., 2013; Wohl et al., 2010).

These disparities persist within the HAART era, and given that these groups may be susceptible to faster HIV progression, these disparities may confer greater risk of developing HAND as well. While the aforementioned sociopolitical and disease progression factors may increase the risk for HAND, a lack of focus on these groups in research studies may aid in increasing risk for HAND within these groups as well. For example, there have been very few studies that have focused on HAND and/or neurocognitive impairment within Hispanic individuals. Even the CHARTER study, the largest study of HAND to date, gathered a sample that was only nine percent Hispanic (Heaton et al., 2010). One study that focused on neurocognitive impairment in Hispanic individuals living with HIV suggested that Hispanics may experience poorer executive functioning ability than their non-Hispanic white counterparts (Mindt et al., 2008), reflecting a possible HAND-related disparity, and highlighting a need to focus on Hispanics. While other studies have gathered samples with more adequate proportions of minority groups (e.g. African-Americans, MSM, drug users, etc) living with HIV, few

studies of HAND within the U.S. have focused on these at-risk groups specifically (Mindt et al., 2008; Mindt et al., 2003; Durvasula et al., 2006; Durvasula et al., 2000; Mason et al., 1998; Manly et al., 1998).

Even within studies that recruit substantial numbers of participants from minority groups, results may be distorted through analyzing individuals from minority groups together with individuals from majority groups. Many studies seek to include minority group status as a covariate or risk factor, rather than delving into a more nuanced understanding of HIV and its resulting sequelae, including HAND, within minority groups. While this approach may be more parsimonious, it may also be biased, in that it may mask the possible unique challenges these groups face, as well as fail to elucidate how health disparities within these groups may be eliminated. Given that HAND is likely to have a more significant and deleterious impact in at-risk minority groups, more work is needed to understand HAND, its assessment, and its risk factors within minority groups specifically.

Risk Factors for HAND

Researchers and clinicians have sought to identify correlates of neurocognitive decline in individuals living with HIV, in order to better understand various processes underlying the development of HAND, as well as to identify patients most at risk for HAND. Most studies examining possible risk factors for HAND have focused on medical factors, such as biomarkers and co-morbidities, however, more recently researchers have noted a variety of psychosocial and behavioral factors which may significantly influence neurocognitive functioning in individuals living with HIV.

Medical Risk Factors. Within the pre-HAART era, PLWH developed HAD when experiencing significant CD4 T-cell decline (Heaton et al., 2010). Within the post-HAART era, multiple studies have revealed nadir CD4 count (the lowest CD4 count measured) to be a significant predictor of neurocognitive functioning in PLWH, as lower nadir CD4 counts are associated with poorer neurocognitive functioning (Munoz-Moreno et al., 2008; Robertson et al., 2007; Tozzi et al., 2005; Ellis et al., 2011; McCombe et al., 2013). This finding is salient, given that with adherence to HAART, HIV patients may recover CD4 count to be within normal range. Interestingly, one study found that the relationship between nadir CD4 count and neurocognitive impairment was the strongest in individuals whose HIV was well-controlled on HAART (Ellis et al., 2011). Certainly, immune decrements incurred in early, undiagnosed, and/or poorly managed HIV infection may have significant implications for HAND even after stabilization on HAART treatment.

HIV viral load has also been identified as a correlate of neurocognitive impairment in individuals living with HIV. Studies have shown that higher HIV viral load in cerebrospinal fluid, detectable HIV viral load in the plasma, and higher baseline viral load are associated with increased impairment in neurocognitive functioning (Letendre et al., 2005; Letendre et al., 2004; Giesbrecht et al., 2014; McCombe et al., 2013). Furthermore, Letendre and colleagues (2004) demonstrated that reductions in HIV viral load within CSF were associated with improvements in cognitive functioning. While little research has examined the specific intermediary pathways by which nadir CD4 count and HIV viral load are associated with neurocognitive decline, these measures may reflect the development of HIV latent reservoirs which may impact HIV

proliferation in the CNS (Van Lint et al., 2013; Thompson et al., 2011). One study demonstrated that HIV latent reservoirs in the CNS are found in individuals who do not yet exhibit neurocognitive impairment, and that increased infected macrophage proliferation in the brain may be associated with immunosuppression (Thompson et al., 2011). Thus, nadir CD4 count and HIV viral load may be reflective of HIV proliferation within the brain, which may stimulate the development of HAND.

In addition to immune-related risk factors, certain medical co-morbidities may increase an individual's risk for developing HAND. Hepatitis C, obesity, cardiovascular disease, hypercholesterolemia, and hypertension have all been associated with neurocognitive impairment and/or HAND in previous studies (Wright et al., 2010; Vivithanaporn et al., 2012; Giesbrecht et al., 2014; Letendre et al., 2005; Ryan et al., 2004; Valcour et al., 2005; Foley et al., 2010). Hepatitis C has been found to negatively impact neurocognitive functioning independently of effects attributed to HIV, and may impair neurocognitive functioning via harmful viral proteins and pro-inflammatory sequelae (Letendre et al., 2005). Cardiovascular and metabolic risk factors, such as CVD, hypertension, obesity, and hypercholesterolemia may be linked to neurocognitive impairment in HIV via vascular changes and insulin resistance, similar to the connections hypothesized between these factors and other types of dementia (e.g. vascular dementia, Alzheimer's disease; Wright et al., 2010). Additionally, the APOE4 genotype, known to predispose individuals to developing metabolic syndrome, has been found to be associated with neurocognitive decline in HIV, however, results have been mixed (Spector et al., 2010; Morgan et al., 2013).

Understanding these medical risk factors for HAND within the context of health disparity is critical. Some ethnic minority groups, such as African-Americans, demonstrate HIV-related disparities in these risk factors, which may confer greater risk for HAND. For example, African-Americans are more likely to be diagnosed later in the disease, making this group more likely to have lower nadir CD4 counts and higher peak HIV viral loads (CDC, 2014). Additionally, both African-Americans and Hispanics are more likely to develop obesity, which may confer greater risk for HAND (CDC, 2009). Thus, it is crucial to examine HAND and its risk factors within these groups specifically.

Sociodemographic Risk Factors. Multiple sociodemographic factors have been found to be associated with poorer neurocognitive functioning and/or the incidence of HAND in individuals living with HIV. Older age, lower education level, African-American ethnicity, and female gender have been identified as possible risk factors for the development of HAND (Cross et al., 2013; Gandhi et al., 2010; McCombe et al., 2013; Munoz-Moreno et al., 2013). While these factors are also predictors of other types of dementia (Azad et al., 2007; Brayne et al., 2010; Green et al., 2003), some of these factors may be confounded. For example, while African-Americans may be at greater risk for HAND due to higher prevalence of medical risk factors for HAND in this population (e.g. lower nadir CD4 counts, etc), research has also demonstrated that healthy African-Americans tend to score more poorly than their white counterparts on standard neurocognitive tests, despite being neurologically normal (CDC, 2014; Heaton et al., 2004b). Researchers have developed sociodemographically-corrected norms to attempt to account for these discrepancies, however, these norms do not exist for every test, nor does every researcher employ these norms when evaluating African-American patients

for neurocognitive impairment (Norman et al., 2011; Heaton et al., 2004b). Thus, the incidence of HAND among African-Americans may be artificially inflated (Antinori et al., 2007; Norman et al., 2011). Certainly, more work is needed in African-Americans, as well as other ethnic minority groups, to understand the relationships between ethnicity and HAND.

Psychosocial and Behavioral Risk Factors. In addition to medical and sociodemographic factors, researchers have hypothesized that psychological, social, and behavioral factors may relate to the development of HAND. Depression has been theorized to be both a risk factor and a confounding co-morbidity in relation to HAND. Multiple studies have revealed significant correlations between higher depressive symptoms and poorer neurocognitive functioning in PLWH (Fialho et al., 2013; Shimizu et al., 2011; Giesbrecht et al., 2014; Cross et al., 2013; Sassoon et al., 2012), however, findings have been inconsistent (Cysique et al., 2007; Nakasujja et al., 2010). Differences in findings pertaining to the relationship between depression and neurocognitive functioning in HIV may be attributed to differences in the measurement of depression between studies. For example, one study found that only mood/motivation disturbance symptoms were associated with neurocognitive functioning in individuals living with HIV (as compared with self-reproach and somatic disturbance symptoms; Castellon et al., 2006). However, another study found that non-depressed patients experienced greater improvement in neurocognitive function over time as compared with depressed patients, suggesting that depression may impact the course of neurocognitive functioning over time (Gibbie et al., 2006). Other psychosocial factors that have been examined within the context of neurocognitive functioning in HIV include stress, sleep,

and social support. Higher stress, poorer sleep, and lower social support have been correlated with either poorer neurocognitive function or higher cognitive burden in individuals living with HIV (Gamaldo et al., 2013; Atkins et al., 2010; Pukay-Martin et al., 2003).

In addition to psychosocial risk factors, various behavioral factors may contribute to the development of HAND. Researchers have studied the relationship between prior substance abuse and HAND, and revealed that previous histories of cocaine, methamphetamine, heroin, and alcohol abuse increase risk of developing HAND (Gill & Kolson, 2014). Certain substances, such as methamphetamine, cocaine, and opiates, may increase risk for HAND through enhancing HIV proliferation within macrophages (Wang et al., 2012; Reynolds et al., 2012; Dhillon et al., 2007). In addition, substance abuse may increase dopamine within the brain, which has been shown to be associated with enhanced HIV replication within macrophages, as well as harmful alterations in cytokine production within the CNS (Gaskill et al., 2009; Gaskill et al., 2013). Furthermore, stimulants such as cocaine and methamphetamine are associated with the degradation of the blood-brain barrier within animal models, suggesting another pathway by which substance abuse may increase risk for HAND (Martins et al., 2011; Dhillons et al., 2008; Gill & Kolson, 2014). Finally, HAART non-adherence represents another significant behavioral risk factor for the development of HAND. HAART non-adherence has been shown to be related with neurocognitive impairment in multiple studies (Ettenhofer et al., 2009; Solomon & Halkitis, 2008). Certainly, non-adherence to HAART regimens can lead to an increase of HIV in the bloodstream and a decrease in healthy CD4 cells, both

of which may allow for increased HIV within the CNS and thus increased risk for HAND (Ettenhofer et al., 2009; Solomon & Halkitis, 2008).

Again, these psychological and behavioral factors may differ between different sociodemographic groups, each of which may experience unique challenges in relation to living with HIV. For example, both African-American and Latina women have been found to be more likely than white women to discontinue HAART in a previous study (Anastos et al., 2005). Certainly, these types of disparities may confer greater risk of developing HAND in these groups, and warrant further investigation within these groups specifically.

Reciprocal Relationships between Risk Factors and HAND. Some of the aforementioned risk factors for HAND, such as education level and gender, clearly precede the development of neurocognitive impairment in individuals living with HIV. However, most of the risk factors associated with HAND may possibly demonstrate a reciprocal relationship with neurocognitive impairment (Anand et al., 2010). For instance, individuals who are non-adherent to HAART may develop HAND, yet once HAND has developed individuals may be even less adherent to HAART due to neurocognitive impairment (e.g. issues with memory and executive functioning). Similarly, individuals who are depressed may be at increased risk for developing HAND, however, HAND may also contribute to the development of mental health problems. For example, one study found that individuals living with HAND exhibited decreased emotional processing ability, suggesting that the degradation of fronto-cortical pathways in HAND may increase risk for mood problems (Lane et al., 2012). All in all, it may be difficult to isolate a linear temporal connection between these types of risk factors and

HAND, given that these relationships are likely to be reciprocal. However, understanding these risk factors may allow for the development of interventions to prevent or improve HAND symptoms.

Development and Symptoms of HAND

Neuropathogenesis of HAND. The development of HAND within HAART-adherent patients occurs less rapidly than in the pre-HAART era. However, similar neuropathological mechanisms may impact the development of HAND in both HAART adherent and non-adherent patients (Lindl et al., 2012; Gannon et al., 2011). While HIV may be controlled in the bloodstream via HAART medication, HIV accumulates in latent reservoirs of inactive CD4 cells, and is thought to maintain low-level viremia through the activation of these infected reservoir cells (Chun et al., 1997). Thus, even in the context of viral suppression, HIV may exist throughout the body, infecting not only CD4 cells but also other types of immune cells, including monocytes and macrophages (Chun et al., 1997; Alexaki et al., 2008).

Researchers have revealed that one such latent HIV reservoir develops in the central nervous system (CNS), even prior to the progression to AIDS in many PLWH (Thompson et al., 2011). Interestingly, the latent CNS reservoir may form during acute HIV infection (Chun et al., 1998). The mechanisms underlying the formation of HIV latent reservoirs within the CNS have been poorly understood until recently, given that HIV cannot typically cross the blood-brain barrier. Researchers have now identified HIV-infected monocytes as a mechanism by which the virus is able to cross the blood-brain barrier and infect brain cells. Infected monocytes become macrophages, which then can infect other macrophages, astrocytes, and microglia, ultimately leading to neuronal

damage (Lindl et al., 2012; Albright et al., 2003; Williams & Hickey, 2002; Gonzalez-Scarano & Martin-Garcia, 2005). Lindl and colleagues (2012), outlined two possible ways infected macrophages and microglia may cause neuronal damage associated with HAND. Firstly, viral proteins released from these infected cells may directly cause neuronal damage. Additionally, the cellular inflammatory immune response to viral proteins may also cause neuronal damage via chemokine/cytokine production, excitotoxicity, and oxidative stress-mediated pathways (Lindl et al., 2012; Gonzalez-Scarano & Martin-Garcia, 2005; Kaul et al., 2005). Furthermore, viral protein-associated pro-inflammatory cytokine/chemokine production and excitotoxicity may also cause neuronal degeneration through synaptic disruption (Lindl et al., 2012).

HAND-associated neuronal damage may occur in specific structures of the brain, in addition to spreading diffusely throughout the cortex. Researchers have identified subcortical, fronto-striatal, and white matter areas of the brain as areas commonly affected by HAND (Jernigan et al., 2011). HAND is associated with degradation of specific brain structures, as well as degradations in the functional connectivity between these structures. Degradation of the basal ganglia and/or pathways associated with the basal ganglia are common in HAND, with deficits in the putamen having been identified even in non-demented individuals living with HIV (Castelo et al., 2007). In addition, deficits in pre-frontal connectivity have been identified in non-demented individuals living with HIV (Melrose et al., 2008).

Symptoms of HAND. The neurocognitive deficits associated with HAND are reflective of the aforementioned areas of the brain targeted by HIV. Individuals living with HAND can exhibit multiple neurocognitive deficits, including a slowing and

impairment of motor coordination, as well as impairments in verbal fluency, processing speed, executive function, learning, and memory. Interestingly, during the pre-HAART era, motor, fluency, and processing speed deficits were more commonly seen in individuals with HAND. In the post-HAART era, individuals with HAND are now demonstrating deficits in learning, memory, and executive function more commonly. However, a broad range of neurocognitive deficits can be seen across all stages of HAND (Heaton et al., 2011).

In addition to objectively-measured neurocognitive deficits, individuals with HAND may experience difficulties performing activities of daily living, which can progress to the inability to care for oneself as an individual develops HAD. Individuals with MND or HAD may experience problems in a variety of activities including housekeeping, work responsibilities, driving, cooking, and general self-care. Additionally, individuals living with any form of HAND may report subjective cognitive deficits, such as problems with forgetting, difficulties paying attention and concentrating, and problem-solving difficulties, which may or may not interfere with activities of daily living (Antinori et al., 2007; Heaton et al., 2004).

Assessment and Treatment of HAND

Diagnostic Criteria. Antinori and colleagues (2007) outlined new diagnostic criteria for HAND, known as the Frascati criteria, that are more consistent with the neurocognitive sequelae PLWH experience within the post-HAART era. This publication described specific criteria for each stage of HAND (ANI, MND, and HAD), as well as addressed common challenges that may arise in the diagnosis of HAND. These new diagnostic criteria have now been accepted broadly by both researchers and

clinicians seeking to diagnose HAND in PLWH (Mind Exchange Program, 2013; Heaton et al., 2010).

The diagnostic criteria for each stage of HAND are as follows: ANI involves impairment in cognitive function within at least two ability domains, as defined by scores of greater than one standard deviation below the mean for sociodemographically adjusted norms on standardized tests of cognitive function. This impairment does not affect activities of daily living or a patient's functional capacity, and is not due to delirium, dementia, or any other pre-existing condition. The criteria for neurocognitive impairment in MND are the same as those for ANI (scores >1SD below in two domains, not due to other conditions), except that MND also involves either self or observer-reported minor decrements in functional status which may impact activities of daily living (working, driving, homemaking, etc). Finally, HAD involves impairment in cognitive function within at least two ability domains that is defined by scores of greater than two standard deviations below the mean on standardized tests, as well as major decrements in functional status which are evidenced by significant impairment in activities of daily living. As with ANI and MND, the cognitive impairment cannot be attributed to other causes (e.g. delirium, other neurological disorders, etc; Antinori et al., 2007).

There are a number of issues that may arise when attempting to diagnose an individual with HAND. Firstly, the diagnostic criteria state that co-morbidities that may impact neurocognitive functioning must be ruled out before HAND can be diagnosed. This may be incredibly difficult within the context of HIV, given that many PLWH experience substantial medical and psychiatric co-morbidities that may impact cognitive functioning. Antinori and colleagues (2007) outlined guidelines for the consideration of

co-morbidities as they relate to HAND diagnosis. Neurological disorders, such as other forms of dementia or CNS infections, preclude a diagnosis of HAND, and such diagnoses are considered to be "confounding co-morbidities." However, other types of medical issues that may work synergistically with HIV to impact cognitive functioning, such as previous substance abuse, may be considered "contributing co-morbidities," and may not necessarily preclude HAND diagnosis. Psychiatric conditions, such as major depression and substance dependence, may also impede HAND diagnosis. While these conditions are relatively common in individuals living with HIV, Antinori and colleagues (2007) recommend that individuals meeting DSM-IV criteria for these disorders be tested after the disorder(s) remit. This may be difficult, however, in the context of clinical care, given that many PLWH struggle with long-term psychiatric illnesses (Bing et al., 2001).

Neurocognitive Testing. There are a variety of neurocognitive tests that have been used in the assessment of HAND, however, researchers and clinicians have not yet identified an optimal screening battery to be used in the common clinical setting. One of the most significant challenges in the assessment of HAND in the post-HAART era has been the mediocre to poor performance of traditional cognitive functioning measures in detecting the earlier stages of HAND (ANI and MND; Mind Exchange Research Group, 2013). Both the HIV Dementia Scale and International HIV Dementia Scale have been criticized by researchers as demonstrating inadequate sensitivity and specificity for detecting the earlier stages of HAND (Haddow et al., 2013; Zipursky et al., 2013). Some researchers have attempted to raise the cutoff scores of these scales in order to attempt to capture individuals exhibiting the earlier stages of HAND, however, the majority of studies have recommended either using other neurocognitive measures or adding other

neurocognitive measures to these traditional measures to increase diagnostic accuracy (Mind Exchange Group, 2013; Charlermchai et al., 2013; Sakamoto et al., 2013; Carey et al., 2004; Moore et al., 2012).

Thus, researchers have begun to examine the sensitivity and specificity of other neurocognitive measures and batteries for detecting HAND. While researchers have not yet identified an optimal battery to be disseminated through routine clinical practice, a number of measures have showed promise for increasing diagnostic accuracy within the context of HAND. Carey and colleagues (2004) found that batteries that included both the Hopkins Verbal Learning Test and the Grooved Pegboard Test (non-dominant hand), as well as the Hopkins Verbal Learning Test-Revised and the WAIS-III Digit Symbol Test demonstrated superior sensitivity to the HIV Dementia scale, with sensitivity estimates of greater than .70 for each combination. Similarly, Moore and colleagues (2012) found that combinations of the Hopkins Verbal Learning Test-Revised, the Stroop Color Test, and the Paced Auditory Serial Addition Test exhibited adequate sensitivity in detecting HAND. In addition, these researchers found that the Action Fluency Test significantly increased the specificity of these batteries (Moore et al., 2012), and this test has also been shown to be associated with both cognitive and functional impairment within the context of HIV (Woods et al., 2005; Wood et al., 2006). Finally, both the Trail Making Test and the Grooved Pegboard have been shown to improve diagnostic accuracy when added to traditionally used measures (Chalermchai et al., 2013; Ku et al., 2014).

In addition to these specific measures, computer-based brief neurocognitive batteries such as the CogState battery have also shown some promise in improving diagnostic accuracy for HAND. The CogState battery covers a variety of cognitive areas

including reaction time, learning, and working memory and takes only 10 to 15 minutes to complete (Cysique et al., 2006; Zipursky et al., 2013). However, the dissemination of these batteries may be limited, especially within resource-poor settings. Furthermore, one study revealed low agreement between a computerized cognitive battery and a standard neurocognitive battery in classifying impairment in PLWH, suggesting that computerized cognitive batteries may not be interchangeable with standard neurocognitive batteries (Gonzalez et al., 2003).

Assessment of Functioning. According to Antinori and colleagues (2007), researchers and clinicians must assess functional status in addition to neurocognitive function in order to classify HAND. Assessment of functional status involves the evaluation of basic functional abilities, including abilities to perform activities of daily living, as well as subjective cognitive abilities (e.g. ability to remember, plan, problem-solve, etc). Assessment of functional status is crucial in classifying HAND, as ANI does not involve functional deficits, MND involves minor functional deficits, and HAD involves significant functional deficits. Functional status may be assessed through self-report and/or observer report. Minor decrements in functional status may include at least two of the following: 1) increased difficulties or need for assistance with instrumental activities of daily living (cooking, shopping, driving, etc.); 2) inability to perform aspects of a job that were previously performed; 3) subjective difficulties in thinking, reasoning, and concentrating or increased errors or effort in performing tasks; 4) problems with memory, planning, or problem solving; and/or 5) performance of greater than one standard deviation below the mean in standardized tests of functional ability. Major decrements in functional status may include at least two of the following: 1) dependence

on assistance within two instrumental activities of daily living; 2) inability to work (that is not due to another condition); 3) subjective difficulty with at least four aspects of cognition (thinking, reasoning, concentrating, problem solving, effort, etc); and/or 4) performance of greater than two standard deviations below the mean in standardized tests of functional ability (Antinori et al., 2007).

Many researchers have used and modified established functional ability measures such as the Lawton and Brody Instrumental Activities of Daily Living Scale (Lawton & Brody, 1969) and the Medical Outcomes Study-HIV measure (Wu et al., 1997) to assess functional status in individuals living with HIV in order to classify HAND (Heaton et al., 2004; Zipursky et al., 2013). These measures may be useful in assessing HAND, especially if they have been modified to assess change in functional ability (Heaton et al., 2004). However, these self-reported measures can be subject to bias, especially within the context of depression (Thames et al., 2011; Blackstone et al., 2012). More thorough assessments of functional ability, including more extensive interviews, informant interviews, and standardized tests have been developed (Heaton et al., 2004), however, these more comprehensive measures may not be feasible to employ within brief clinical screenings.

Clinical Biomarkers. Given that the assessment of HAND can be complicated, researchers are attempting to identify clinical biomarkers that may classify individuals currently experiencing or at risk for neurocognitive impairment within the context of HIV. Morris and colleagues (2010) presented an array of biomarkers that may show promise in the assessment of HAND. Although various cytokines, chemokines, and other immune-related biomarkers have been shown to be associated with neurocognitive

impairment in HIV, developing a biomarker testing protocol that is specific to detecting HAND remains challenging (Morris et al., 2010). Firstly, many immune-related markers that denote dysregulation in the CNS are best measured through cerebrospinal fluid (CSF). However, it would not be clinically feasible to collect CSF from patients as part of routine screening practice (Morris et al., 2010). In addition, many of the immune biomarkers identified by Morris and colleagues (2010) may be increased within the context of HIV infection and/or other medical co-morbidities and may not necessarily denote the presence and/or risk of HAND.

Challenges in HAND Assessment in Minority Groups. As cultural factors are known to impact neurocognitive testing, assessment of HAND may be challenging in ethnic minority groups (Antinori et al., 2007). There are many challenges in characterizing HAND in Hispanics, especially in monolingual Spanish-speakers. Firstly, not all neurocognitive tests have been translated into Spanish. Additionally, most neurocognitive tests have not been normed using Spanish-speaking populations, and the tests that have been normed using Spanish-speaking populations were normed with mostly Mexican or Spanish populations (Gasquoine et al., 2007). Given that Spanish-speakers come from a variety of cultural backgrounds, all of which may influence neurocognitive testing, these Spanish-speaking norms may be less than ideal to use for Spanish-speaking individuals who are not Mexican or Spanish (Gasquoine et al., 2007). Each of these issues poses a significant concern, and indeed, many of the researchers who examine HAND in ethnic minority groups use the "best norms available," implying that testing bias may exist in their assessment (Heaton et al., 2010; Mindt et al., 2008). While there are active research projects currently aimed at addressing these limitations, there is

not yet a "gold standard" test battery for detecting HAND, nor are there multicultural sociodemographic norms for neurocognitive tests in Spanish-speaking Hispanics. More work is needed to understand the performance of Spanish-speaking Hispanics on neurocognitive tests that have been found to be sensitive to detecting HAND in other populations, in order to elucidate how to screen these individuals for HAND, as well as to understand any possible impacts of culture and/or acculturation on HAND screening in these groups.

Additionally, many other groups are underrepresented in the HAND literature. African-American individuals may have the highest risk for many HIV-associated comorbidities, however many studies of HAND have not focused on the unique challenges this group may face. While there have been testing norms developed that are specific to English-speaking African-Americans, these norms do not exist for all neurocognitive tests (Heaton et al., 2004b). However, these norms provide researchers opportunity to assess HAND in African-Americans, albeit not perfectly, with less testing bias.

Treatment of and interventions for HAND. Given the alarming proportions of individuals living with HAND reported in previous studies, researchers are attempting to identify interventions and treatments to prevent and/or slow the progression of HAND. One such treatment may be to prescribe HAART medications that have high CNS penetrance, in order to attempt to control viral proliferation in the brain (Letendre et al., 2008). Letendre and colleagues (2008) developed a rating system to classify the level of CNS penetrance for HAART medications, known as the CNS Penetration Effectiveness Rank. This ranking refers to the overall CNS penetrance of a particular HAART regimen

and has been found to be significantly correlated with HIV viral load within cerebrospinal fluid, such that higher CNS penetrance is related with lower HIV viral load in CSF. However, evidence for the efficacy of high-CNS penetrance regimens in preventing HAND has been mixed, with one study finding no difference in cognitive deficits in individuals taking high vs. low penetrance regimens (Cross et al., 2013b). Certainly HAART regimens with high CNS penetrance should be considered in individuals experiencing symptoms of HAND, even though these regimens may not reverse current HAND symptoms (Letendre et al., 2008).

In addition to the modification of HAART regimens, clinicians and researchers are examining the effects of anti-inflammatory and neuroprotective drugs in improving neurocognitive function, within both animal and human models. Currently, there are no adjuvant therapies that have demonstrated substantial effects on cognitive functioning in human models. Valproic acid, methotrexate, and statins may show some promise in future studies, however, there are no recommended adjuvant treatments for HAND currently (Clifford & Ances, 2013).

Current Study

The prevalence of HAND within the United States is alarmingly high, affecting hundreds of thousands of individuals living with HIV. The prevalence may be even higher in sociodemographic minority groups (Wojna et al., 2006; Mindt et al., 2008), many of whom have experienced disparities in both HIV and HAND-related risk factors (Chu & Selwyn, 2008). This HAND disparity is compounded by the aforementioned challenges in assessing neurocognitive functioning in ethnic minority groups—the ability to adequately address potential HAND-related disparities within these groups depends on

our capability to effectively screen these groups for HAND. The current study was designed to inform HAND screening within an HIV clinic, the University of Miami AIDS Clinical Research Unit, serving primarily minority groups in Miami, Florida. I aim to examine neurocognitive functioning, correlates of neurocognitive functioning, and the diagnostic accuracy of two promising brief neurocognitive tests in monolingual Spanish-speaking Hispanics and English-speaking African-Americans within this clinic. While the ACRU provides care to individuals from a variety of ethnic and cultural backgrounds, these two groups are the most commonly seen in the clinic, and I aim to evaluate these two groups specifically in this preliminary study in order to provide this clinic with data that will aid in developing HAND screening algorithms for these groups.

More generally, examining test performance on sensitive neurocognitive tests, using these tests to assess HAND, as well as understanding how HAND relates to a variety of psychosocial, medical, and behavioral factors in disadvantaged minority groups specifically may improve clinicians' ability to classify HAND and understand the impact of HAND in those who may be at disparate risk. Furthermore, although early identification of HAND may be critical in preserving functional capacity and slowing neurocognitive decline in HIV+ individuals, researchers and clinicians have not yet solidified a gold-standard test battery that is both sensitive and specific in detecting HAND. While some neurocognitive measures have shown promise in previous studies, these measures have not been examined in all sociodemographic groups. Examining the sensitivity and specificity of free, easy-to-administer neurocognitive tests in underserved sociodemographic groups may lead to the improvement of current testing batteries to detect HAND for all people living with HIV.

Aims and Hypotheses

Aim 1: To understand the relationship between HAND and psychosocial, medical, and behavioral factors within these two sociodemographic groups.

1) I conducted univariate and multivariate logistic regression analyses to determine the associations between medical (CD4 count, viral load, years post HIV-diagnosis), psychosocial (depressive symptoms, sleep, stress, social support), and behavioral (HAART adherence) factors and HAND within an overall sample. My main hypothesis was that individuals with greater depressive symptoms, higher stress, lower social support, and more sleep problems are more likely to have HAND.
2) As an exploratory analysis I also examined whether these associations vary between groups via moderated regression analyses. As almost half of the Hispanic group in the sample is Cuban, we compared Cubans vs. African-Americans in addition to the aggregated Hispanic group vs. African-Americans.

Aim 2. To examine the diagnostic accuracy of two promising neurocognitive measures, Action Fluency and Trail Making Test, in detecting HAND in both groups.

1) I computed the sensitivity and specificity of the Action Fluency and Trail Making Test measures in the overall sample, as well as within each group (African-Americans and Hispanics), using the diagnosis of HAND as the gold standard (see Data Analysis Plan for more detail). Given the relative simplicity of both of these tests, my main hypothesis was that, consistent with the previous literature, both the Action Fluency test and the Trail Making Test would demonstrate

adequate sensitivity and specificity for detecting HAND in both sociodemographic groups.

2) I also evaluated the diagnostic accuracy of this test via separate Receiver Operating Curve (ROC) analyses (please see Data Analysis Plan for more detail).

CHAPTER 2: METHODS

Participants

I recruited a convenience sample of 88 men and women living with HIV from the AIDS Clinical Research Unit (ACRU) at the University of Miami. Among these were English-speaking African-Americans (n = 38) and monolingual Spanish-speaking Hispanics (n = 50). Participants were recruited through flyers, study screeners, and clinic staff while attending their ACRU appointments. Participants were screened for eligibility by the ACRU study screeners and were scheduled for a study visit if they were interested in the study and eligible. Participants were eligible if they were: 1) between ages 18 and 65 2) HIV-positive 3) self-reported their primary language as either Spanish or English. Participants were excluded if they 1) self-reported any active neurological problems, such as seizures, brain infections, and/or stroke 2) were unable to provide informed consent. Study screeners screened 93 English-speakers for eligibility. Out of these 93, 8 were found to be ineligible on initial screen and 2 were found to be ineligible upon medical chart abstraction post study completion. Most of the English-speakers who were screened but did not enroll in the study failed to enroll in the study due to scheduling conflicts. Study screeners screened 62 Spanish-speakers, all of whom were eligible for the study. Those Spanish-speakers who did not complete the study failed to complete the study due to scheduling conflicts.

Procedure

Two study coordinators who were trained in research and the administration of neuropsychological tests managed the study visits. One of the coordinators, a bilingual Infectious Diseases physician, collected the data for the Spanish-speaking participants,

and the other coordinator, a master's level Psychology graduate student, collected the data for the English-speaking participants. Upon their arrival at the study visit, participants were greeted by one of the study coordinators and ushered into a private interview room within the ACRU. Study coordinators confirmed participant eligibility and completed the informed consent with the participant. The informed consent was translated into Spanish by a certified translator, and all study participants received study documents and measures in their primary language. After completing informed consent, the neurocognitive measures were administered in the following order to minimize verbal interference: Grooved Pegboard, Action Fluency, Trail Making Test, and Hopkins Verbal Learning Test-Revised (Rourke et al., 1973; Woods et al., 2005; Reitan, 1958; Shapiro et al., 1999). After completing the neurocognitive measures, the study coordinator administered a modified version of the Lawton & Brody Instrumental Activities of Daily Living scale in interview format (Lawton & Brody, 1969). The participants then began to complete the self-administered questionnaires. The study coordinators allowed the participants to work on completing the self-administered questionnaires for approximately 15-20 minutes, and then asked the participants to pause the questionnaires, in order to complete the recall portion of the HVLT-R. The participants then resumed completing the self-administered questionnaires after completing the recall portion of the HVLT-R. After completing the self-administered questionnaires, participants were remunerated with $25 cash and signed a receipt form. All study procedures were approved by the University's Institutional Review Board.

Measures

The Grooved Pegboard, Trail Making Test, Hopkins Verbal Learning Test-Revised, and Marin Acculturation Scale were previously translated and validated in Spanish by other researchers (Rosselli et al., 2001; Cherner et al., 2008, Cherner et al., 2007; Marin et al., 1987). All other study measures were translated into Spanish and back-translated into English by bilingual study staff. Any discrepancies were discussed among study staff and final translated measures were agreed upon. All study measures, both in Spanish and English, as well as the translation procedures were approved by the University's Institutional Review Board.

Neurocognitive Measures

Grooved Pegboard. The Grooved Pegboard measures fine motor speed by having participants place pegs into a board as quickly as possible, turning the pegs in order to fit them into the slots on the board. Participants are allowed to use only one hand while completing this task, and are asked to place the pegs in sequential order. The time (in seconds) to complete the task with each hand is recorded, and participants complete the task with their dominant hand first, before completing the task again with their non-dominant hand (Rourke et al., 1973).

Action Fluency. The Action Fluency task measured participant ability to generate novel verbs within 60 seconds. Participants are instructed to generate as many novel verbs as possible, being careful not to generate different conjugations of the same verb. The participant's responses within 60 seconds are recorded, and the number of novel verbs generated, the number of verbs repeated, and the number of non-verbs generated is tabulated from the participant's responses (Woods et al., 2005).

Trail Making Test. The Trail Making Test is divided into two parts. Part A measured processing speed and Part B measured executive functioning. For Part A, participants are asked to draw a line between numbers that are randomly distributed across a page, moving in ascending sequential order and not lifting the pen from the paper. For Part B, participants are asked to draw a line between numbers and letters, alternating between numbers and letters (e.g. 1-A-2-B), in ascending sequential order. Participants are given a practice exercise before completing each part, in order to ensure understanding. Time (in seconds) to complete each part is recorded (Reitan, 1958).

Hopkins Verbal Learning Test-Revised. The Hopkins Verbal Learning Test-Revised measures verbal learning and memory. Participants listen to a list of 12 words derived from 3 semantic categories and are asked to generate as many words as they can remember immediately following the reading of the list. There are 3 learning trials in which the list is read and participants generate the words from the list. Participant responses are recorded and the number of correct words is tallied for each trial. The number of correct responses for each trial are summed to generate the learning trial total score. Twenty to twenty-five minutes after the third learning trial is given, participants are asked to spontaneously recall as many words from the list as they can. The number of correct responses is tallied to generate the recall score (Shapiro et al., 1999).

Functional Status Measures

Modified Lawton & Brody Instrumental Activities of Daily Living Scale. The Lawton & Brody Instrumental Activities of Daily Living Scale (IADL) measures participant ability to independently perform the following activities: using the telephone, shopping, food preparation, housekeeping, laundry, transportation (driving and/or taking

public transportation), taking medications, and handling finances. Similar to Heaton and colleagues (2004), we modified the scale to ascertain participant's highest ever level of functioning in each of these activities, in addition to their current level of functioning, in order to discern any changes in functional status. The modified IADL scale is administered in a semi-structured interview format (Heaton et al., 2004; Lawton & Brody, 1969).

Medical Outcomes Study-HIV Functional/Cognitive Subscale. The Medical Outcomes Study-HIV Functional/Cognitive Subscale measures subjective cognitive difficulties, including difficulties with reasoning/problem solving, remembering, paying attention, and concentration, and has been found to be associated with objective measures of neurocognitive impairment in a previous study (Knippels et al., 2002). The MOS-HIV Functional Cognitive subscale is composed of four Likert-type questions, and is self-administered (Wu et al., 1997).

Psychosocial Measures

Sociodemographic Questionnaire. Participants completed a self-administered questionnaire that asked for the following sociodemographic characteristics: age, gender, ethnicity, nationality, number of years in the U.S. (for Hispanic participants), education level, and income. This questionnaire was composed by our study staff. Our Spanish-speaking Hispanic group also completed the Marin Acculturation Scale, which is a 12-item Likert-type scale that measures acculturation to American culture (Marin et al., 1987).

Beck Depression Inventory. The Beck Depression Inventory is a 21-item self-administered questionnaire. The BDI measures both cognitive and somatic symptoms of

depression using a Likert-type scale. Because we aimed to measure current levels of depressive symptoms, we limited the BDI questions to target only the past week (including the day of the study visit). Items are summed to create a total score, with higher scores indicating greater depressive symptoms (Beck et al., 1996).

Perceived Stress Scale. The Perceived Stress Scale is a 14-item self-administered questionnaire that measures levels of perceived stress over the past month using a Likert-type scale. The PSS includes both negatively-worded items (e.g. "How often have you been upset because of something that happened unexpectedly?") and positively-worded items (e.g. "How often have you dealt successfully with irritating life hassles?"). After the positively-worded items are reversed coded, all items are summed to create a total score, with higher scores indicating greater perceived stress (Cohen et al., 1983).

Pittsburgh Sleep Quality Index. The Pittsburgh Sleep Quality Index (PSQI) is a 10-item self-administered questionnaire. The PSQI measures overall sleep quality as well as the following subscales: sleep latency, sleep duration, habitual sleep efficacy, sleep disturbance, sleep quality, daytime dysfunction, and the use of sleep medication over the past month (Buysse et al., 1989). The PSQI is scored using the algorithm outlined in Buysse et al. (1989)—briefly, each of the subscales is scored 0 to 3, then the subscale scores are summed to create a total composite score.

UCLA Social Support Scale. The UCLA Social Support Scale (UCLASSI) is a 9-item self-administered questionnaire. The UCLASSI measures informational, tangible, encouragement, and listening support from partners, friends, family, groups/organizations, religious communities, and healthcare providers using a Likert-type

scale. Additionally, the UCLASSI measures satisfaction with each of the four types of support using a Likert-type scale. Items can be summed across type of support (e.g. informational, tangible, etc.) and/or across source of support (e.g. friends, family, etc; Schwarzer et al., 1994).

Medical and Behavioral Measures

HAART Adherence and HIV Symptoms. HAART adherence, including 4 day recall and time since last dose missed, was measured via the ACTG self-reported questionnaire. Additionally, the questionnaire measured reasons for missing medications and HIV symptoms (fatigue, fever, neuropathy, etc), using a Likert-type scale (Chesney et al., 2000).

Medical Chart Abstraction. I abstracted participant's medical charts for information pertinent to HAND diagnosis. I collected data regarding most recent CD4 count and HIV viral load, AIDS status, and years post HIV diagnosis, as well as any neurological and psychiatric history (including substance abuse history).

Data Analysis Plan

HAND Assessment. I scored all neurocognitive tests using sociodemographically corrected (by age, gender, education, ethnicity, and/or language) norms as available. Consistent with the Frascati criteria, individuals scoring at greater than one standard deviation away from the normative mean on a test (e.g. T-score of < 40) were classified as having a deficit on that test. Additionally, the global deficit rating system was used to assign the magnitude of such deficits, such that those that are severe (e.g. > 2 SD away from mean) can be distinguished (Carey et al., 2004b).

I also examined the two functional measures (Modified Lawton Activities of Daily Living Scale and MOS-HIV Functional/Cognitive subscale) to evaluate participants for functional deficits. Consistent with the Frascati criteria, I categorized participants as having minor functional deficits if they demonstrated minor decrements in functional ability on at least 2 activities of daily living AND they reported any subjective cognitive deficits on the MOS-HIV. I did not anticipate any of participants would have major functional deficits, however, to be classified as having major functional deficits participants would have complete dependence on others for at least 2 activities of daily living and report significant deficits in all 4 of the subjective cognitive areas measured by the MOS-HIV.

After scoring the neurocognitive tests and evaluating functional status for each of the participants, I then classified each participant according to level of HAND: normal, ANI, MND, or HAD, using the 2007 Frascati criteria. To be classified as having ANI, a participant must have demonstrated neurocognitive deficits in at least 2 ability domains (ability domains: motor (GP) or learning/memory (HVLT-R)) as indicated by T-scores of less than 40, while demonstrating no functional deficits (per the aforementioned functional status evaluation). To be classified as having MND, a participant must have demonstrated neurocognitive deficits in two ability domains, as well as demonstrated minor functional deficits (as previously defined). To be classified as having HAD, a participant must have demonstrated severe neurocognitive deficits in two ability domains, as well as demonstrated severe functional deficits (as previously defined).

Aim 1. I performed regression analyses to address the first aim. I used logistic regression to explore the univariate and multivariate relationships between a variety of

psychosocial variables (depressive symptoms, sleep quality, social support, and perceived stress) and HAND in the overall sample. Possible covariates considered included sociodemographic characteristics (income, age, etc), medical (CD4 count, HIV viral load, AIDS status, etc), and behavioral variables (HAART adherence, substance abuse history). All variables significantly associated with HAND in the univariate analyses were included in the multivariate analysis. I centered all continuous variables in the multivariate analysis to protect against multicollinearity. I also explored whether these relationships differed between sociodemographic groups via moderated regression analyses. Any significant interactions were decomposed using the procedures outlined in Holmbeck (2002). As no more than 5% of the data is missing, overall sample mean substitution was used to account for missing values.

Aim 2. For our second aim, I examined the sensitivity (the test's ability to identify individuals with HAND) and specificity (the test's ability to distinguish individuals who are negative for HAND) of the Action Fluency test and the Trail Making Test within the overall sample, as well as in both of the sociodemographic groups separately. I used a diagnosis of HAND (via the Grooved Pegboard, HVLT-R, functional status measures, and medical chart abstraction) as a gold standard when computing the sensitivity and specificity estimates. Given that I was aiming to determine whether the Action Fluency test is an accurate screening tool for HAND, I considered sensitivity values of 70% or greater to be adequate.

Additionally, I examined these parameters using receiver operating characteristic (ROC) curves. ROC curves allow for the examination of the overall performance of a diagnostic test via area under the curve (AUC) analyses. The AUC analyses determine

the probability that a test accurately distinguishes between disordered and non-disordered individuals. These analyses expand upon traditional sensitivity and specificity analyses by allowing for the examination of diagnostic accuracy while moving along the continuum of possible cutoff score (rather than just using one cutoff score via traditional sensitivity and specificity analyses). AUC values of greater than .70 are considered to be adequate, with values of .90 and over indicating high diagnostic accuracy. These analyses allowed me to determine whether the Action Fluency test and Trail Making Test are better than random at classifying HAND in each of the study samples (Pintea & Moldovan, 2009).

CHAPTER 3: RESULTS

Descriptive Analyses

Sociodemographic Characteristics. As shown in Table 1, I computed the descriptive statistics (either mean/standard deviation or frequency/percentage) for the overall sample as well as for our study groups. I then used independent samples t-tests and Chi-square analyses to examine any potential differences in sociodemographic characteristics between the study groups. The overall sample of 88 participants had a mean age of 48.21 years (SD = 9.11 years; range = 23-63 years), and age did not significantly differ between African-American and Hispanic participants. Only 26 (29.5%) of our participants were female, which is similar to the gender distribution of HIV nationally (23%; CDC, 2013), as well as the gender distribution within the patient population attending the ACRU. However, there was a significantly larger proportion of female participants within the African-American participants (42.1%) than within the Hispanic participants (20%) $p = .024$. The mean years of education was 12.74 (SD = 1.97 years), and Hispanic participants reported significantly greater years of education than did African-American participants (13.16 years vs. 12.18 years; $p = .016$). The modal income was $5,001-$10,000 per year in the overall sample, and income did not significantly differ between African-American and Hispanic participants. While all African-American participants were American, the Hispanic participants were of a broad array of nationalities, including the Caribbean, Central America, and South America (see Figure 1.).

Medical and Behavioral Characteristics. As shown in Table 1, the overall sample of participants had a mean CD4 count of 630.31 cells/μL (SD = 333.37 cells/μL),

and a mean log HIV viral load of 1.71 copies (SD = 0.91 copies). HIV viral load was highly skewed and was thus log-transformed, 64 (72.7%) of participants had undetectable HIV viral load, indicating viral control. Overall, 30 (34.1%) of participants had AIDS, and the mean number of years post HIV-diagnosis was 10.73 (SD = 6.34 years). In the overall sample, 45 (51.1%) of participants indicated never missing HAART medications. Additionally, 26 (29.5%) of participants had a previous substance abuse history as documented in their medical charts.

As shown in Table 1, we conducted independent samples t-tests and Chi-square analyses to analyze potential differences between in both medical and behavioral variables. Hispanic participants had significantly lower log HIV viral load ($p = .011$) and significantly greater viral control ($p = .031$), but not significantly higher CD4 counts than African-American participants. Our groups did not significantly differ with respect to years post HIV diagnosis, however, a greater proportion of African-American participants had AIDS compared with Hispanic participants ($p = .022$). Additionally, while HAART adherence did not differ between our study groups, a greater proportion of African-American participants had histories of substance abuse than did Hispanic participants ($p < .001$).

Psychosocial Characteristics. As shown in Table 2, in the overall sample the mean Beck Depression Inventory score was 8.48 (SD = 8.41), which corresponds to minimal depressive symptoms. The mean PSQI Total Score was 6.85 (SD = 4.24), which is below the clinical cutoff score of 7. The mean PSS score was 20.68 (SD = 9.48). Finally, the mean social support scores from each source were as follows: Partner: 6.14

(SD = 7.12), Friend: 7.95 (SD = 5.72), Family: 7.97 (SD = 5.79), Group/Organization: 7.42 (SD = 6.23), Religious: 6.11 (SD = 5.55), Healthcare Provider: 13.53 (SD = 6.24).

Independent samples t-tests were conducted to determine any possible differences in these psychosocial characteristics between African-American and Hispanic participants. African-American and Hispanics did not differ in depressive symptoms (BDI), sleep quality (PSQI), and stress (PSS). However, African-Americans reported significantly greater social support from every source (partner, friend, family, group, religious, and healthcare provider) than did Hispanic participants.

Proportion of HAND. In the overall sample, 33 (37.5%) of participants were classified as having HAND using the aforementioned diagnostic criteria. Of the participants classified as having HAND, 31 (93.9%) had Asymptomatic Neurocognitive Impairment (ANI), 2 (6.1%) had Mild Neurocognitive Disorder, and no participants had HIV-Associated Dementia (HAD). Interestingly, Hispanic participants had significantly greater proportion of HAND (50.0% vs. 21.1%, $p = 0.005$). However, both participants with MND were African-American, and thus all Hispanic participants with HAND were classified as ANI.

Potential Covariates of HAND. As shown in Table 2, univariate logistic regression analyses were conducted to determine potential relationships between sociodemographic, medical, and behavioral variables and HAND. The only significant sociodemographic correlate of HAND was ethnicity, with Hispanic participants being nearly twice as likely to be diagnosed with HAND as African-American participants (OR = 0.267, 95% CI: 0.102- 0.694, $p = .007$). All other sociodemographic variables were non-significant, however, as the neurocognitive test scores were sociodemographically-

adjusted for age, years of education, language, and/or gender, it is understandable that these variables would not be associated with HAND in the overall sample. Interestingly, none of the medical and behavioral variables including CD4 count, log HIV viral load, years post HIV diagnosis, AIDS status, HAART adherence, and substance abuse history, were associated with HAND in the univariate analyses. Thus, ethnicity was the only covariate used in the multivariate analyses below.

Relationships between Psychosocial Variables and HAND

Univariate Analyses. As shown in Table 3, the relationship between each psychosocial variable (depression, sleep, social support, and stress) was evaluated via univariate logistic regression analyses. Stress (PSS) was significantly associated with HAND (OR = 1.072, 95% CI: 1.015-1.131, p = .012), such that individuals experiencing higher levels of stress were more likely to be diagnosed with HAND. Overall sleep quality (PSQI) and social support from friends (UCLASSI) were marginally associated with HAND (OR = 1.100, 95% CI: 0.989-1.224, p = .078 and OR = 0.922, 95% CI: 0.849-1.002, p = .055), such that individuals with poorer sleep and lower social support from friends were more likely to be diagnosed with HAND. For psychosocial variables that were at least marginally associated with HAND, we examined the interaction between ethnicity and these psychosocial variables (stress, sleep, social support from friends) in predicting HAND. None of these interactions were significant. Given that nearly half of the Hispanic sample was of Cuban nationality, as an exploratory analysis we examined the relationship between ethnicity for this group (Cubans only vs. African-Americans) and the aforementioned psychosocial variables. None of these interactions were significant as well.

Multivariate Analyses. As shown in Table 4, we included all covariates (ethnicity) and psychosocial variables (stress, sleep, social support from friends) found to be at least marginally significant ($p < .10$) in the univariate analyses in our multivariate model. In the multivariate analyses, only ethnicity remained significantly associated with HAND (OR = 0.296, 95% CI: 0.097-0.908, p = 0.033), with stress, sleep, and social support from friends dropping to marginal significance or non-significance. However, the directionality of the relationships between these variables and HAND did not change in the multivariate analysis.

Additionally, I examined the relationships between each marginally significant psychosocial variable and HAND, controlling for ethnicity only. Higher levels of perceived stress remained significantly associated with increased odds of HAND (OR = 1.076, 95% CI: 1.018-1.138, p = 0.010). Furthermore, after controlling for ethnicity only, poorer sleep quality was significantly associated with increased odds of HAND (OR = 1.145, 95% CI: 1.020-1.285, p = 0.021). Social support from friends was not significantly associated with HAND when controlling for ethnicity only.

Exploratory Analyses. As an exploratory analysis, I examined the interaction between stress and social support as well as the interaction between stress and sleep in relation to HAND in our overall sample, as both social support and good sleep quality may buffer against the detrimental effects of stress. Neither of these interactions were significant, however. Additionally, I examined the univariate relationship between acculturation and HAND in our Hispanic participants. Acculturation was marginally associated with HAND, such that participants with higher acculturation to American

culture were less likely to be diagnosed with HAND (OR = 0.916, 95% CI: 0.835-1.006; p = .068).

Additionally, given that both perceived stress and poor sleep quality were associated with HAND when controlling for ethnicity, I examined the relationships between these psychosocial variables and scores on the individual neurocognitive tests (Grooved Pegboard, Trail Making Test, Action Fluency, and HVLT-R) via regression analyses. Higher levels of perceived stress were associated with both poorer learning (β = -0.305, p = 0.001) and memory (β = -0.264, p = 0.009) on the HVLT-R. Perceived stress was not significantly associated with any of the other neurocognitive test scores. Poor sleep quality was also associated poorer learning (β = -0.265, p = 0.006) and memory (β = -0.329, p = 0.001) on the HVLT-R, and not significantly associated with any of the other neurocognitive test scores.

Diagnostic Accuracy of the Trail Making Test and the Action Fluency Test

Sensitivity and Specificity. I calculated the sensitivity and specificity for the TMT and Action Fluency Tests in our overall sample, as well as within our study groups separately. The overall sensitivity and specificity for TMT-A (processing speed) were 24.2% and 89.1%, for TMT-B (executive functioning) were 57.5% and 78.1%, and for Action Fluency were 48.5% and 74.5%, respectively. Each of these tests did not reach adequate sensitivity (> 70%) in the overall sample. For the Hispanic participants, the sensitivity and specificity for TMT-A were 24.0% and 88.0%, for TMT-B 60.0% and 64.0%, and for Action Fluency were 52.0% and 60.0%, respectively. For the African-American participants, the sensitivity and specificity for the TMT-A were 25.0% and 90.0%, for TMT-B were 50.0% and 90.0%, and for Action Fluency were 37.5% and

86.7%, respectively. Each of these tests did not reach adequate sensitivity in the individual study groups as well.

Receiver Operating Curve (ROC) Analyses. ROC analyses were conducted to examine the overall diagnostic accuracy of each measure via area under the curve (AUC) analyses using the overall sample, as well as within each study group. In the overall sample, as well as in each study group, each of the measures (TMT-A, TMT-B, and Action Fluency) performed poorer than random at classifying HAND (see Figures 1-3). Area under the curve (AUC) estimates for the overall sample for TMT-A, TMT-B, and Action Fluency were .261, .198, and .324, respectively. Each of these estimates is significantly poorer than the recommended estimate of > .700. In the Hispanic participants the AUC estimates for the TMT-A, TMT-B, and Action Fluency were .238, .270, and .370, respectively. In the African-American participants the AUC estimates for the TMT-A, TMT-B, and Action Fluency were .349, .185, and .315, respectively. Within our study groups, each of these estimates is significantly poorer than the recommended estimate of > .700, as well.

CHAPTER 4: DISCUSSION

For the current study, I examined potential psychosocial correlates of HAND, as well as the diagnostic accuracy of specific neurocognitive measures for HAND in two sociodemographic groups commonly seen in the ACRU at the University of Miami: African-Americans and monolingual Spanish-speaking Hispanics, in order to inform HAND screening practices within the clinic. Additionally these low-SES groups seen the in ACRU have been understudied in the previous literature examining HAND and risk factors for HAND. I found proportions of HAND in our participants that were similar to those found in the previous literature. Over a third of the overall participants demonstrated HAND based on our diagnostic algorithm. While this proportion mirrors those found by Heaton and colleagues (2010) and Robertson and colleagues (2007), it is alarming, given that many clinics like the ACRU in Miami do not currently have a HAND screening protocol in place. Clearly, many HIV patients are demonstrating impairment on neurocognitive tests, even when adjusted for sociodemographically-corrected norms.

Furthermore, HAND proportions differed significantly by ethnicity, with over two-thirds of Hispanic participants being diagnosed with HAND, while only about one-third of African-American participants were diagnosed with HAND. This potential disparity has been reported in the previous literature, with two prior studies finding the proportion of HAND in Hispanic participants to be approximately 70% (Wojna et al., 2006; Mindt et al., 2009). Interestingly, African-American participants experienced significantly greater immune decrements than did Hispanic participants, with higher HIV viral loads and a greater proportion of participants with AIDS. Given the relationship

between immune decline and neurocognitive dysfunction evidenced in the previous literature (Munoz-Moreno et al., 2008, Tozzi et al., 2005; Ellis et al., 2011), it is peculiar that the Hispanic participants, who had significantly better values on some of the immune parameters, had a higher proportion of HAND. However, even though the proportion of participants with AIDS and HIV viral loads were greater in African-Americans, the two groups did not differ in CD4 count.

Interestingly, no medical variables (CD4 count, HIV viral load, AIDS status, years post HIV diagnosis) were associated with HAND in the overall sample. While some medical variables such as HIV viral load have been associated with HAND in prior studies (Munoz-Moreno et al., 2008; Tozzi et al., 2005; Ellis et al., 2011), the limitations of the current study may in part explain the lack of associations. Firstly, I was unable to collect some key immune parameters such as nadir CD4 count for the participants, as this information was unknown for most of the participants, although multiple studies have shown nadir CD4 count to be a more promising predictor of HAND than current CD4 count (Munoz-Moreno et al., 2008; Tozzi et al., 2005; Ellis et al., 2011). Peak CD4 count is a strong predictor of HAND because it may be associated with the formation of latent HIV reservoirs early in infection, significantly impacting HIV proliferation within the CNS and the development of HAND (Van Lint et al., 2013; Thompson et al., 2011). Additionally, while AIDS status is a bit more indicative of nadir CD4 count (as individuals with AIDS must have had at least one CD4 count under 200 cells/μL), it is also a dichotomous variable, and thus may lack the variability needed to determine a significant relationship. Finally, while I collected number of years post-HIV diagnosis, this variable does not indicate immune status at the time of diagnosis, nor does it reflect

the inherent variability in HIV treatment and other outcomes that may also influence the development of HAND, and this variability may explain why this variable was not related to HAND.

Additionally, the behavioral variables were not found to be significantly associated with HAND. Given that HAART adherence has been found to be associated with neurocognitive functioning in multiple prior studies (Ettenhofer et al., 2009; Solomon & Halkitis, 2008), this null finding is somewhat surprising. However, the composition of the HAART regimen may also influence the development of HAND, as the CNS penetrance of a HAART regimen has been found to be a significant correlate of HIV virus in CSF (Letendre et al., 2008). Thus, variance in HAART regimens could possibly explain the null result, as individuals taking non-CNS penetrative regimens may not have had as great a benefit from HAART adherence as those who did. Unfortunately, I was unable to collect HAART regimen information for the current study.

Furthermore, a history of substance abuse was not associated with HAND in the overall sample. However, this was a dichotomous variable, as I was unable to abstract specific substances abused for many participants. Prior studies have shown a strong link between the use of certain substances such as cocaine, methamphetamine, and opiates and HAND (Wang et al., 2012; Reynolds et al., 2012; Dhillon et al., 2007). Thus, the inability to examine associations between specific substance use and HAND may explain our null result. All in all, both HAART adherence and history of substance abuse may be associated with HAND in our study populations, however, a more nuanced approach that involves collecting objective behavioral data may be needed to elucidate these associations.

Psychosocial Correlates of HAND

As hypothesized, multiple psychosocial variables demonstrated at least marginally significant relationships with HAND in the overall sample of participants. Interestingly, perceived stress was found to have the strongest relationship with HAND, with higher levels of stress associated with greater likelihood of HAND. While there has been one prior study examining the potential relationship between stressful life events and cognitive functioning in individuals living with HIV, compared with other psychosocial factors such as depression, perceived stress has not received a significant amount of attention in the previous literature (Pukay-Martin et al., 2003). Stress has been shown to be a significant prognostic indicator in many chronic conditions, including HIV (Leserman, 2000). Stressful life events have been associated with decreased natural killer cells, increased HIV viral load, and more rapid CD4 cell decline, each of which may influence HIV progression and increase the risk for neurocognitive impairment and HAND in individuals living with HIV (Leserman, 2000). Thus, stress may be a key variable to screen for when evaluating HIV-positive individuals for HAND.

In addition to stress, global sleep quality was found to be marginally associated with HAND, such that individuals with poorer sleep were more likely to have HAND. While this association was not as strong as the association between stress and HAND, associations between sleep and cognition in HIV have been shown in prior work (Gamaldo et al., 2013). Furthermore, prior studies have shown that HIV may target dopamine pathways in the brain specifically, attacking the basal ganglia and degrading fronto-cortical connections (Castelo et al., 2007; Kumar et al., 2011). These degradations in dopamine pathways due to neural HIV may have a detrimental impact on sleep. One

prior study found sleep disturbances to be independently associated with lower dopamine levels in African-American women living with HIV (Seay et al., 2013). While the association was modest, my results suggest that screening for subjective sleep quality may aid in identifying individuals with early stage HAND.

Furthermore, social support from friends was found to be marginally associated with HAND, such that individuals who reported higher levels of social support were less likely to be diagnosed with HAND. While social support has been found to be associated with HAND in one prior study (Atkins et al., 2010), no studies to date have examined social support from specific sources (e.g. friends, family, groups, etc). Interestingly, friends were the only source of social support that emerged as associated with HAND, with family, partner, groups/organizations, religious, and healthcare provider support shown to be non-significant. While this finding is unexpected, prior studies have highlighted the importance of social support from friends specifically in individuals living with HIV. For instance, Fekete and colleagues (2014) found social support from friends to significantly relate to sleep quality in African-American women living with HIV. Certainly, the relative importance of sources of social support may differ between individuals and populations living with HIV. I was limited in that I only assessed quantity of social support from various sources, without assessing the importance of these sources to the individual. Investigating the relative importance of each source of support in future may elucidate why certain sources may be more strongly associated with HAND. All in all, social support may be important to assess when evaluating patients for HAND.

Interestingly, depressive symptoms were not associated with HAND in the overall sample. However, the current evidence for the association between depression and HAND is mixed, and the current study may reflect this ambiguity. In addition to studies linking depressive symptoms with poorer cognitive functioning (Fialho et al, 2013; Giesbrecht et al., 2014; Cross et al., 2013), other prior studies have found that only particular depressive symptoms are associated with neurocognitive impairment (Castellon et al., 2006) and that depressive symptoms were associated with change in neurocognitive impairment over time (Gibbie et al., 2006). As an exploratory analysis, I examined the association of the cognitive and affective subscales of the BDI with HAND separately, however, neither of these analyses was significant. I am limited in that my study was cross-sectional, and thus I could not examine the impact of depressive symptoms on HAND over time in an attempt to replicate the results of Gibbie and colleagues (2006).

Additionally, as an exploratory analysis we examined potential interactions between significant psychosocial correlates and ethnicity in relating to HAND. I hypothesized that the relationships between these correlates and HAND may differ according to ethnic group, given potential cultural and linguistic differences between the study groups. However, none of these interactions were significantly associated with HAND. Furthermore, I examined the interaction between stress and social support from friends, as well as the interaction between stress and sleep quality in relating to HAND, as both of these variables could possibly moderate the association between stress and neurocognitive impairment. Neither of these interactions were significant, however the small sample size may have contributed to these null findings.

Furthermore, given that both perceived stress and sleep quality were significantly associated with HAND when controlling for ethnicity, we examined the relationships between these variables and the individual neurocognitive test scores as a post-hoc analysis. Interestingly, both higher levels of perceived stress and poorer sleep quality were associated with poorer learning and memory scores on the HVLT-R, but were not significantly associated with any of the other neurocognitive test scores. These results suggest that these psychosocial variables may influence learning and memory in particular, which is important not only within the context of HAND, but also within the context of other HIV-related health concerns, such as HAART adherence. These results suggest that patients who are experiencing high stress and/or sleep problems may be particularly at risk for developing issues with learning and memory, and may help inform HAND screening practices.

Diagnostic Accuracy of the Trail Making Test and the Action Fluency Test

I expected that both the Trail Making Test and the Action Fluency Test would demonstrate adequate sensitivity to HAND as defined by sensitivity estimates of greater that 70%, however, for the overall sample both of these tests performed relatively poorly, with sensitivity estimates of under 60% for each test. The sensitivity of each test was also poor within each ethnic group, and interestingly, each ethnic group demonstrated relatively similar sensitivity estimates for each test (TMT-A, TMT-B, and Action Fluency). The best-performing test in terms of sensitivity was the TMT-B, which tests executive functioning. This test may have exhibited the best performance as prior work has shown deficits in executive functioning to be more common in individuals living with HAND in the post-HAART era (Heaton et al., 2011). The specificity, or ability to

distinguish HAND-negative individuals, was relatively good for each test, with most estimates over 70%. However, my hypothesis pertained to the sensitivity of these tests, because the primary goal of giving these tests within clinical care is to identify HAND-positives rather than HAND-negatives.

Additionally, I examined the overall diagnostic accuracy of each test over a range of cutoff scores using ROC analyses. I found that over the full range of possible cutoff scores, each of the tests (TMT-A, TMT-B, and Action Fluency) performed poorly in the overall sample, as indicated by area under the curve (AUC) estimates of below .70. When I conducted the ROC analyses within each study group the results were similar, with poor AUC estimates for each measure within each group. The ROC analyses indicate that there is no cutoff score for each measure that represents an optimal sensitivity to detecting HAND.

Even though the sensitivity of the TMT and Action Fluency tests was poor in both the overall and individual sociodemographic groups, the specificity of each of these test was good (> 70%) in the overall sample, as well as in the African-American participants. Prior studies have found the specificities of tests selected for optimal HAND batteries to be relatively good as well, with specificity estimates of 70% or higher (Carey et al., 2004; Moore et al., 2012). However, with the exception of the TMT-A (processing speed), the specificity of each test examined was not adequate in the Hispanic group, with specificity estimates of approximately 60%. This is important to note because specificity refers to a test's ability to distinguish HAND negatives, which may be instrumental in resource allocation when screening for HAND in the common clinical setting. Even though sensitivity is similar between each sociodemographic group, these differences in

specificity may indicate that these tests are less useful in screening for HAND in monolingual Hispanics.

There may be multiple explanations for why these tests did not demonstrate adequate diagnostic accuracy as hypothesized. Firstly, while study samples in the prior literature have demonstrated some ethnic diversity, very few studies have examined HAND in low-SES monolingual Spanish-speaking Hispanics (Mindt et al., 2003). Additionally, while many studies have examined HAND in African-Americans, the African-American sample may have been more transient and of lower SES than African-American samples in prior work. My results may suggest that although the TMT and Action Fluency Test have shown promise in prior samples (Moore et al., 2012; Chalermchai et al,. 2013), these instruments may not demonstrate equivalent efficacy in detecting HAND in all sociodemographic groups living with HIV.

However, the results of the current study should be interpreted with caution, given that the instruments used in determining our gold standard HAND diagnosis were limited. Some prior studies examining tools to evaluate HAND have used more extensive testing batteries as the gold standard battery by which to evaluate diagnostic accuracy of particular tests (Carey et al., 2004; Moore et al., 2012). However, some of these studies used flawed methodology, evaluating single tests against broader batteries within which the test in question was included, artificially inflating sensitivity estimates (Carey et al., 2004; Steve Woods, personal communication). The current standard for the evaluation of diagnostic accuracy is to compare particular instruments to batteries that they are not a part of. While this method is less biased than those used in the past, it limits the measures that can be included in gold standard batteries (Steve Woods,

personal communication). Thus, if we were able to give more measures, results may have differed. However, of note, despite inconsistencies across studies with respect to gold standard batteries, our ROC analysis indicates that the TMT and Action Fluency Test, two free and easy-to-administer measures, may not be interchangeable with the Grooved Pegboard and HVLT-R, the gold-standard measures that may incur cost. Thus, these analyses may help inform HAND battery decision-making in resource-limited settings.

Limitations

The current study has a number of limitations that should be acknowledged. Firstly, the study was intended to be an initial investigation into HAND in the two major clinic populations at the ACRU, African-Americans and monolingual Spanish-speaking Hispanics. As such, the sample size of the current study is limited, and thus may limit the generalizability of the results. Through power analysis, I determined that while the current study was powered (> .80) to detect medium to large effect sizes in the overall sample, there was considerably less power to detect group differences and small effect sizes. Although over a third of the participants had HAND, a larger study may have allowed me to investigate variability between the forms of HAND (ANI, MND, HAD). Future studies of HAND in these populations should recruit larger samples in order to conduct more nuanced investigations.

Furthermore, the neurocognitive battery I utilized for the current study was limited. I chose tests that had previously been found to be sensitive to detecting HAND in other populations, as well as were easy-to-administer, such that the battery might be more externally valid given the limitations associated with screening for HAND in

standard HIV clinical care. However, an ideal HAND battery would be one that included two or more tests per cognitive domain examined. While HAND test batteries are not yet unified or standardized in research and clinical care, studies and clinics that utilize a more extensive testing battery may have higher quality information to work with when characterizing HAND in their patient populations. Indeed, because my gold standard HAND battery was limited, I may be limited in the inferences I can draw, and the generalizability of our results may be limited as well.

Moreover, the addition of a matched HIV-negative control group may have aided in isolating deficits in neurocognitive function associated with HIV, versus deficits in neurocognitive function that may have been pre-morbid or due to other factors. While the neurocognitive deficits found in our participants are relative to HIV-negative normative populations, having a matched control group may have allowed us to affirm that these deficits were indeed due to HIV infection rather than other factors. Future studies may include HIV-negative control groups and/or evaluate pre-morbid cognitive functioning in participants in order to better isolate the diagnosis of HAND.

Additionally, while our study aimed to examine HAND in African-American and monolingual Spanish-speaking patients, our results may not be generalizable to other sociodemographic groups. Many groups within Miami are socioculturally unique and distinct from similar groups in other parts of the country. For example, the monolingual Spanish-speakers in our study we primarily from South America and the Caribbean. Thus, our results may not be generalizable to other Spanish-speaking groups, such as monolingual Spanish-speakers on the US-Mexico border. We attempted to examine potential differences between our Cuban participants specifically and African-Americans

in terms of potential relationships between psychosocial variables and HAND. We did not find any of these interactions to be significant, and given our small sample size, we were unable to adequately examine potential differences between Spanish-speaking individuals of different nationalities. Future studies and clinical protocols examining HAND should take into account potential sociocultural variation that may exist between individuals that may fall into the same broader ethnic category.

Moreover, given that both of our study groups were of low socioeconomic status and underserved, it is likely that these groups experience poorer psychosocial status (e.g. higher stress, poorer sleep, etc), than more privileged sociodemographic groups. Thus, the addition of a non-Hispanic white HIV+ group may have allowed for a more nuanced understanding of the connection between psychosocial variables and HAND, and may have allowed for the comparison of groups at varying levels of socioeconomic status. Future studies may include more diverse groups of individuals living with HIV in order to better understand these relationships.

Conclusion

For the current study, we examined HAND within an HIV clinic that does not currently have a HAND screening protocol, evaluating neurocognitive functioning in the two largest clinic populations: African-Americans and monolingual Spanish-speaking Hispanics. Additionally, our study is among the first studies to examine HAND in monolingual Spanish-speakers. We found that stress and poor sleep quality are associated with increased odds of HAND, while social support from friends was associated with decreased odds of HAND. Screening that includes each of these psychosocial variables may aid in identifying individuals at risk for or living with

HAND. Unfortunately, we also found that the TMT and Action Fluency tests did not demonstrate adequate sensitivity in detecting HAND within our overall sample, as well as within each sociodemographic group. While further work is needed to evaluate the diagnostic accuracy of these measures, our analyses suggest these measures alone may not be sufficient for screening for HAND in our clinic populations. In future research efforts within these populations, clinicians may focus on examining neurocognitive performance on more extensive testing batteries using larger samples. Additionally, researchers may examine the utility of screening for psychosocial factors such as stress, sleep quality, and social support alongside neurocognitive testing in effort to understand how best to identify HAND in these underserved groups.

Tables

Table 1. Descriptive Statistics (Mean (SD); Frequency (Percent)) for Sociodemographic, Medical, and Behavioral Variables

	Overall Sample	Hispanic Sample	African-American Sample	p-value
Age (years)	48.21 (9.11)	48.46 (8.06)	47.90 (10.43)	0.783
Gender (female)	26 (29.5%)	10 (20.0%)	16 (42.1%)	0.024
Modal Income (per year)	$5,001-$10,000	$5,001-$10,000	$5,001-$10,000	0.311
Education (years)	12.74 (1.97)	13.16 (2.12)	12.18 (1.61)	0.016
Years Post HIV Diagnosis	10.73 (6.34)	9.70 (6.09)	12.10 (6.05)	0.070
CD4 Count (cells/μL)	630.31 (333.47)	671.68 (280.15)	575.87 (357.96)	0.162
Log HIV Viral Load	1.71 (0.91)	1.48 (0.46)	2.01 (1.16)	0.011
Viral Control	64 (72.7%)	41 (82.0%)	23 (60.5%)	0.031
AIDS Status	30 (34.1%)	12 (24.0%)	18 (47.4%)	0.022
HAART Adherence	45 (51.1%)	30 (62.5%)	15 (42.9%)	0.076
Substance Abuse History	26 (29.5%)	4 (8.0%)	22 (57.9%)	<0.001

Table 2. Descriptive Statistics (Mean (SD); Frequency (Percent)) for Psychosocial Variables

	Overall Sample	Hispanic Sample	African-American Sample	p-value
Depression	8.48 (8.41)	8.01 (8.70)	9.11 (7.97)	0.546
Sleep	6.85 (4.24)	6.25 (4.17)	7.63 (4.13)	0.127
Stress	20.68 (9.48)	20.54 (10.47)	20.86 (7.51)	0.874
Social Support				
Partner Support	6.14 (7.12)	4.58 (6.28)	8.18 (7.71)	0.022
Friend Support	7.95 (5.72)	5.74 (4.69)	10.87 (5.70)	<0.001
Family Support	7.97 (5.79)	6.06 (5.16)	10.47 (5.59)	<0.001
Group Support	7.42 (6.23)	5.02 (4.56)	10.58 (6.76)	<0.001
Religious Support	6.11 (5.55)	4.70 (4.36)	7.97 (6.41)	0.009
Healthcare Provider Support	13.53 (6.24)	11.70 (6.47)	15.94 (5.04)	0.001

Table 3. Univariate Odds Ratios for Associations between Sociodemographic, Medical, and Behavioral Variables and HAND

	Odds Ratio	95% CI	p-value
Age	1.018	0.970-1.069	0.469
Gender (female)	0.658	0.248-1.744	0.400
Income	1.114	0.780-1.589	0.554
Education (years)	1.189	0.951-1.486	0.129
Years Post HIV Diagnosis	1.005	0.936-1.078	0.900
CD4 Count	1.001	1.000-1.002	0.158
Log HIV Viral Load	0.923	0.552-1.542	0.759
AIDS Status	0.761	0.302-1.916	0.562
HAART Adherence	0.875	0.360-2.128	0.768
Substance Abuse History	0.658	0.248-1.744	0.400

Table 4. Univariate Odds Ratios for Associations between Psychosocial Variables and HAND

	Odds Ratio	95% CI	p-value
Depression (BDI)	1.005	0.954-1.058	0.862
Sleep (PSQI)	1.100	0.989-1.224	0.078
Stress (PSS)	1.072	1.015-1.131	0.012
Social Support (UCLASSI)			
Partner Support	0.963		0.247
Friend Support	0.922	0.849-1.002	0.055
Family Support	0.972	0.900-1.050	0.470
Group Support	0.969	0.902-1.042	0.398
Religious Support	0.968	0.892-1.050	0.433
Healthcare Provider Support	0.973	0.909-1.043	0.444

Table 5. Multivariate Odds Ratios for Associations between Significant Variables and HAND

	Odds Ratio	95% CI	p-value
Ethnicity	0.296	0.097-0.908	0.033
Sleep	1.071	0.931-1.231	0.338
Stress	1.068	0.998-1.143	0.055
Friend Support	0.925	0.838-1.022	0.125

Figures

Figure 1. ROC Analyses Examining Diagnostic Accuracy of the TMT and Action Fluency Test for the Overall Sample

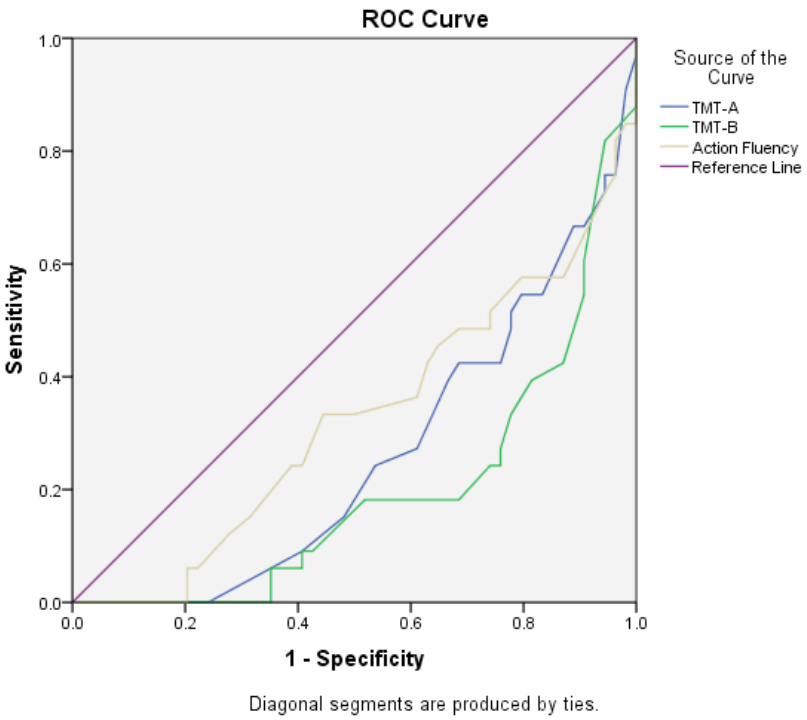


Figure 2. ROC Analyses Examining Diagnostic Accuracy of the TMT and Action Fluency Test for African-American Participants

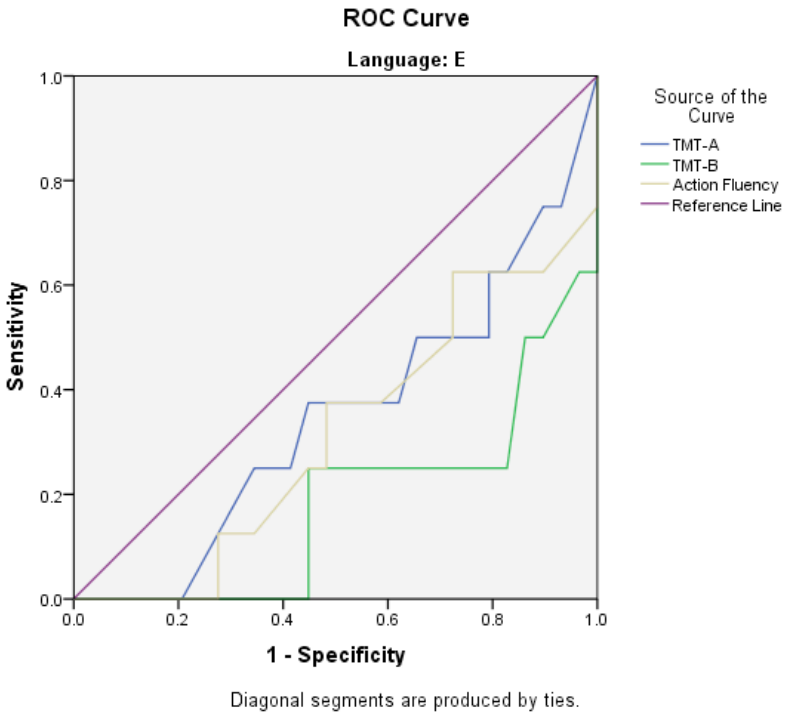
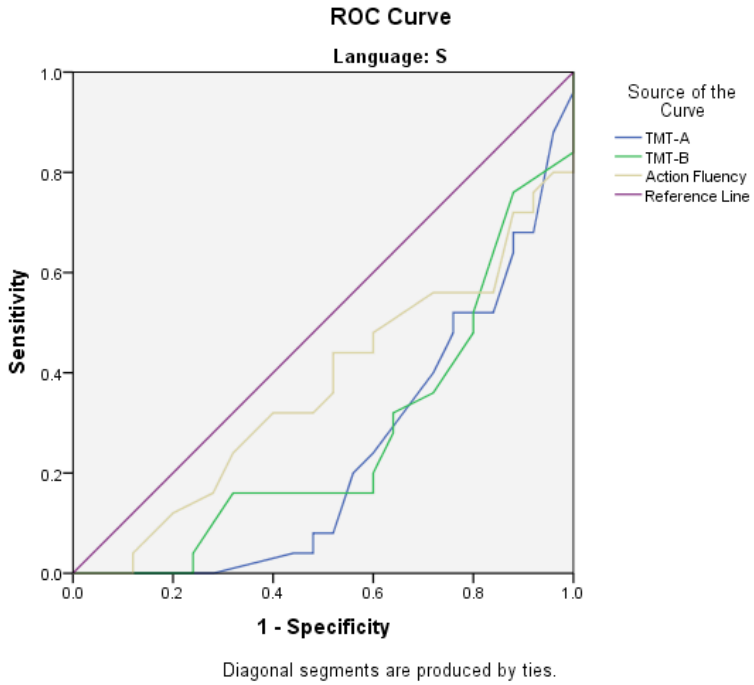


Figure 3. ROC Analyses Examining Diagnostic Accuracy of the TMT and Action Fluency Test for Hispanic Participants



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