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## **Cognitive Functioning in Adults Aging with HIV: Exploring Cognitive Subtypes and Influential Factors**

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COGNITIVE FUNCTIONING IN ADULTS AGING WITH HIV:  
EXPLORING COGNITIVE SUBTYPES AND INFLUENTIAL FACTORS

by

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A DISSERTATION

Submitted to the graduate faculty of The University of Alabama at Birmingham,  
in partial fulfillment of the requirements for the degree of  
Doctor of Philosophy

BIRMINGHAM, ALABAMA

2012

# COGNITIVE FUNCTIONING IN ADULTS AGING WITH HIV: EXPLORING COGNITIVE SUBTYPES AND INFLUENTIAL FACTORS

PARIYA L. FAZELI

LIFESPAN DEVELOPMENTAL PSYCHOLOGY

## ABSTRACT

Research suggests that individuals with HIV may be at risk for declines in cognitive functioning. Cluster analytic studies have suggested that there may be unique cognitive subgroups in HIV, with some individuals exhibiting normal cognitive performance, some with global cognitive deficits, and some with unique cognitive deficits in specific domains. The purpose of the current study was to perform a cluster analysis in a sample of adults ( $N = 78$ ;  $M_{age} = 46.61$ ) with HIV and to compare these clusters with an HIV-negative reference group ( $N = 84$ ;  $M_{age} = 47.93$ ) on cognitive, functional, demographic, and mental and physical health variables. Two-Step cluster analysis was used to examine cognitive subtypes using six cognitive measures (Useful Field of View Test<sup>®</sup>, Complex Reaction Time, Letter and Pattern Comparison, Finger Tapping Test, Wisconsin Card Sorting Test, and Hopkins Verbal Learning Test). MANOVA and chi-square analyses were used to examine the differences between the HIV-positive clusters and the HIV-negative reference group. Results revealed a two cluster solution, with Cluster 1 ( $n = 32$ ; 41% of HIV-positive group) exhibiting lower performance across all cognitive and functional measures except the Finger Tapping Test, and Cluster 2 ( $n = 46$ ; 59% of HIV-positive group) displaying “normal” performance across the cognitive and functional measures compared to the HIV-negative reference group. The most influential factor to cluster membership was age, with Cluster 1 participants being significantly older on average than Cluster 2 and the HIV-negative

reference group. There were no other significant differences between Clusters 1 and 2 on any of the HIV-specific, demographic, or mental and physical health variables. However, there was a trend for years with HIV, percentage currently employed, and percentage with hepatitis C, with Cluster 1 containing participants with a longer HIV diagnosis, fewer employed participants, and more participants with hepatitis C. The findings of this study suggest that in this sample there do not appear to be unique cognitive subtypes; rather, there is a subset with overall “normal” cognitive performance and a subset with lower cognitive performance compared to an HIV-negative group. Implications for future research and practice are provided.

Keywords: HIV, aging, cognition, everyday functioning, cluster analysis

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## LIST OF ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
ANI	asymptomatic neurocognitive impairment
CDC	Centers for Disease Control and Prevention
CRT	Complex Reaction Time
HAART	highly active antiretroviral therapy
HAD	HIV-associated dementia
HAND	HIV-associated neurocognitive disorder
HIV	human immunodeficiency virus
HNRC	HIV Neurobehavioral Research Center
HVLT	Hopkins Verbal Learning Test
MND	mild neurocognitive disorder
OTDL	Observed Tasks of Daily Living
TIADL	Timed Instrumental Activities of Daily Living
UFOV	Useful Field of View
WCST	Wisconsin Card Sorting Test

## INTRODUCTION

### Background and Demographics

Research suggests that there are over one million people in the United States living with HIV, with approximately 21% of these individuals unaware of their status (Centers for Disease Control and Prevention (CDC), 2006). Since its emergence in the United States in 1981, the incidence, or number of new HIV diagnoses per year, has gradually leveled off since the mid 1980's and now remains relatively stable. In contrast with the lack of growth in HIV incidence, there has been a continued increase in the prevalence of individuals living into older age with HIV, with more than 25% of people in the United States living with HIV/AIDS over the age of 50 (60% increase since 2001)(CDC, 2008b). This demographic change is primarily due to the life extending effects of highly active antiretroviral therapy (HAART) medications that were introduced in 1996. While this trend of increased life expectancy is promising, it also indicates a concern, as these individuals may experience the possible synergistic effects of normal aging as well as HIV, which are currently not well understood. Furthermore, although the overall incidence of new HIV infections has decreased over time, there has been an increase in the number of new HIV diagnoses among adults and older adults. Research indicates that adults age 50 and older represent 15% of new HIV cases in the United States per year (CDC, 2008a). Given that by 2015 over half of the HIV/AIDS population in the United States will be over 50 (Smith, 2006), there is a need to study the effects of HIV among individuals who are reaching older adulthood with this disease.



## Cognitive Impairment in HIV

Several studies have provided evidence of lower cognitive performance for HIV-positive individuals compared to their HIV-negative counterparts. In general, these cognitive decrements appear to be in the domains of psychomotor functioning, attention, processing speed, executive functioning, and memory, reflecting a pattern of dysfunction of frontal-subcortical circuitry (Lojek & Bornstein, 2005; Murji et al., 2003; Navia, Jordan, & Price, 1986; Reger, Welsh, Razani, Martin, & Boone, 2002; van Gorp et al., 1993). One study found that in late stage HIV and AIDS patients, 36% displayed subcortical deficits, 3% had cortical deficits, and 61% had no deficits (Becker et al., 1995). The cognitive declines in HIV are similar to those observed in normal aging (Craik & Salthouse, 2000). Specifically, it seems as though the core abnormality is a generalized slowness in performing mental operations, with those with HIV performing slower on timed tasks, translating to poorer performance in cognitive tests that have a speeded component (Hardy & Hinkin 2002). Given that cognitive abilities underlie performance of many everyday activities in individuals with HIV such as medication management and driving (Hinkin et al., 2002; Hinkin et al., 2004; Marcotte et al., 2004), examining cognitive functioning in HIV is particularly important.

In addition to relative agreement on the aforementioned affected domains, there is also evidence that cognitive dysfunction in HIV is associated with disease severity, with those in later stages being more vulnerable to cognitive declines (Baldewicz et al., 2004; Hardy et al., 1999; Reger et al., 2002). However, there is much heterogeneity in the literature on the cognitive patterns and prevalence of cognitive impairment in those with

HIV. This is likely due to both differences in methodology (inclusion of HIV-negative reference groups versus examination of HIV-positive samples only) and criteria used to define impairments. While the definition of impairment varies across studies, the most current and preferred diagnostic criteria are the HIV Neurobehavioral Research Center (HNRC) definitions which include three categories of HIV-associated neurocognitive disorders (HAND): HIV-associated asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), and HIV-associated dementia (HAD) (Antinori et al., 2007) (Table 1). ANI is defined as performance of at least one standard deviation below the mean for age-education-appropriate norms in at least two cognitive domains. MND is defined as performance of at least one standard deviation below the mean in at least two cognitive domains; this impairment must at least mildly interfere with daily functioning (as indicated by self-report or observation). Finally, an HAD diagnosis is given in the presence of performance at least two standard deviations below the mean in at least two cognitive domains, as well as more pronounced impairment in daily functioning. Fortunately, the incidence of the more severe form of HAND (i.e., HAD) has decreased significantly in the HAART era. In contrast, its prevalence, as well as the incidence and prevalence of milder forms of HAND seem to be increasing despite potent antiretroviral therapy, with an estimated 30% - 50% of HIV-positive individuals exhibiting some form of HAND in their lifetime. One recent large study found that 52% of the total sample had some form of HAND, with ANI being the most common and HAD being the least common (ANI = 33%, MND = 12%, HAD = 2%) (Heaton et al., 2010). Thus, the current nosology for HAND provides more sensitivity to

detect subclinical cognitive declines that may signal the need to monitor or intervene with neurocognition in those with HIV.

In addition to heterogeneity in the literature on methods of defining cognitive impairment in HIV, there are also differences across studies in the nature of the samples used. Specifically, there are various co-factors such as age, education, and depression that may cause some individuals with HIV to be at a higher risk for poorer cognitive performance and the examination of these and other co-factors varies across studies. When examining cognitive functioning in HIV, it is necessary to include these factors in order to understand the unique contribution of HIV to cognition and the moderating influence of various co-factors. Additionally, it is ideal to have an HIV-negative reference group that is demographically similar to the HIV-positive sample for more accurate comparisons. Given that some individuals with HIV may have no cognitive deficits and that there are vast individual differences in co-factors that may affect performance, examining cognitive profiles in adults with HIV is an important area for research. Specifically, it is important to examine whether there is one prototypical pattern of impairment in HIV with lower global cognitive functioning compared to HIV-negative controls, or whether there are variable patterns with distinct domains affected. Furthermore, using cluster analysis to find subgroups with varying patterns of performance in HIV-positive samples may be more useful than comparisons of group means in HIV-positive individuals as a whole, which may obscure detection of these meaningful subgroups who share similar patterns of performance and composition of co-factors.

## Cluster Analyses

Cluster analytic studies offer a useful method for examining cognitive subtypes in HIV. Currently there are only three studies using this method in adults with HIV. A study by van Gorp and colleagues (1993) was the first known attempt using this technique to examine whether unique cognitive subtypes existed in HIV. The study included a sample ( $N = 298$ ;  $M_{age} = 38.9$ ) of HIV-positive males who were screened and excluded for substance abuse, psychosis, learning disabilities, migraines, head injury involving loss of consciousness, and other pre-existing neurological conditions. Participants were administered a comprehensive cognitive and behavioral battery, including a depression and anxiety measure. After factor analyzing the cognitive and behavioral measures, five factors emerged: psychomotor speed, mood and affect, visuospatial ability, verbal ability, and verbal memory. Results of the K-Means cluster analysis yielded the following three-cluster solution: Cluster 1 (39% of the sample) was defined as the normal participants who performed above their peers across all cognitive domains; Cluster 2 (28% of the sample) was defined as depressed participants with psychomotor slowing and lowered verbal memory; and Cluster 3 (33% of the sample) was defined as participants with lowered overall cognitive performance and normal mood. While the clusters did not differ on current CD4+ lymphocyte count, Cluster 1 had significantly higher education than the other two clusters. Furthermore, Cluster 1 had more clinically asymptomatic participants (72%) than Clusters 2 and 3 (39% and 48%, respectively). Finally, Cluster 2 participants were significantly older ( $M_{age} = 41.1$ ) than Clusters 1 and 3 ( $M_{age} = 37.6$  and  $M_{age} = 37.4$ , respectively). To further examine these demographic differences between clusters, a discriminant function analysis was

used to determine if age and education predicted cluster membership. Results revealed that 64% of Cluster 1 participants, 40% of Cluster 2 participants, and 41% of Cluster 3 participants were correctly classified. Given that these predictors did not correctly classify all participants, this suggests that cluster membership was not primarily determined by age and education. While this study did not explicitly provide data for comparisons of the HIV clusters versus an HIV-negative control group on the neuropsychological measures, the researchers briefly note that 87% of the Cluster 1 participants did not score within the impairment range (defined as performance two or more standard deviations below the mean of a demographically matched HIV-negative control group) on any of the neuropsychological measures examined, while 61% in Cluster 1 and 63% in Cluster 2 did exhibit performance in the impairment range on at least one of the measures.

There are several important points to note in this study. First, this study occurred before HAART was developed; thus, results may not apply to current HAART-treated populations. Second, this is a younger adult sample, which limits the application of these results to older adults with HIV. While Cluster 2 members were statistically significantly older, they were only about four years older on average, which may not have real-world implications. Third, the sample only included male participants. Lastly, nadir CD4+ lymphocyte count (i.e., lowest ever CD4+ lymphocyte count) was not gathered, which may be more influential than current CD4+ lymphocyte count. While this study does have limitations, the implication of varying subtypes of cognitive impairment in HIV is important. Furthermore, the normal participants (Cluster 1) being more highly educated implies that education may serve as a protective factor. While current CD4+ lymphocyte

count did not differ between clusters, Cluster 1 contained more participants who were clinically asymptomatic which highlights two important points. First, while CD4+ lymphocyte count is often used as an index of disease severity, whether or not one is clinically free of HIV symptoms (as determined by a clinical assessment) may be more relevant to cognition. Second, since Cluster 1 had significantly more asymptomatic participants than the other clusters, this implies that once an individual reaches the symptomatic stages of HIV he/she may be at more of a risk for cognitive impairment. Nonetheless, Clusters 2 and 3 did contain some participants who were asymptomatic, albeit a smaller percentage than Cluster 1, indicating that declines in cognitive performance can occur in this relatively healthy population. Lastly, identification of a group with subcortical-like poorer performance (Cluster 2) in this study is supportive of other findings (Navia, Jordan, & Price, 1986).

Another cluster analytic study by Lojek and Bornstein (2005) sought to identify patterns of cognitive functioning in a sample of HIV-positive ( $N = 217$ ;  $M_{\text{age}} = 34.3$ ) and HIV-negative ( $N = 55$ ;  $M_{\text{age}} = 33.1$ ) men, and to examine the stability of these patterns over one year. Participants were excluded if they had non-HIV related neurological disorders, psychiatric disorders, head injuries with loss of consciousness, and current or past substance abuse. Participants completed a broad battery of cognitive measures which were factor analyzed to yield the following seven factor solution: memory and learning, reaction time, processing speed, psychomotor speed, categorical thinking, attention, and language. The K-Means cluster analysis yielded a four cluster solution of patterns of cognitive performance. Cluster 1 (7.4%) consisted of those with psychomotor speed dysfunction as the central characteristic. Cluster 2 (29.6%) included those with

memory and learning dysfunction as the dominant pattern. Cluster 3 (10.4%) included those with multiple cognitive domains affected, in which performance on all cognitive factors was impaired. Cluster 4 (50.6%) included those with no cognitive deficits or subclinical deterioration, with performance comparable to the HIV-negative controls at baseline. Clusters 1-3 and the HIV-negative control group showed relative stability over the year study period, while Cluster 4 showed lack of stability, with deterioration occurring over the year period, despite their comparability to the controls at baseline. The clusters did not differ on level of anxiety and depression, age, current CD4+ lymphocyte count, or type of anti-HIV medication being used. The Cluster 4 participants had higher levels of education, and were mostly asymptomatic HIV and AIDS-free. Thus, while certain factors such as education and well-controlled HIV infection may protect against cognitive dysfunction in HIV, a subsyndromic or subclinical deterioration may occur nonetheless.

While the clusters did not differ on age, the relatively young age of this sample is a limitation when applying these results to older adults with HIV. Another limitation, as with the previous study, is the male-only sample. Overall this study indicates that there is not one prototypical pattern of cognitive dysfunction in HIV, and the patterns suggested here are in line with the 1993 van Gorp study. Also congruent with the van Gorp study is the finding that a majority of the sample was classified as unimpaired or “normal” (or had subclinical deficits only). Furthermore, both studies imply that the subcortical or frontal-subcortical circuitry is vulnerable in HIV infection. Another parallel finding with the van Gorp study was detection of a cluster with lowered overall cognitive performance. Lastly, both studies did not find current CD4+ lymphocyte count to differ between

clusters, and in both studies the unimpaired cluster had more asymptomatic participants. This may be due to the fact that these studies did not examine nadir CD4+ lymphocyte count. The fact that the normal cluster had more asymptomatic participants implies that normal cognitive functioning is observed in those with well-controlled HIV.

A final cluster analysis by Dawes and colleagues (2008) used a larger sample size to examine cognitive patterns among HIV-positive adults ( $N = 553$ ;  $M_{\text{age}} = 40.68$ ). Participants were not excluded for current substance use disorders, or a diagnosis of major depression, as these co-morbidities are common in HIV and examining the influence of these confounds was of interest. Participants completed a battery of cognitive measures which were factor analyzed to yield the following domains: processing speed, verbal episodic memory, executive functioning, visual episodic memory, motor functioning, and working memory/attention. Hierarchical and K-Means cluster analysis was employed and yielded six clusters or profiles. In contrast to the two aforementioned cluster analytic studies, the current study used ipsative scoring on the cognitive factors to define clusters based on pattern (not overall level) of performance. Cluster 1 (17.7% of sample) consisted of a relative strength in executive functioning, in contrast to Cluster 6 (23.9% of the sample), which consisted of the opposite pattern: weakness in executive functioning and relative strength in verbal memory. Cluster 2 (15% of the sample) consisted of relative strength in motor skills but weakness in verbal memory and executive function, while Cluster 4 (15.2% of the sample) showed the opposite pattern of weakness in motor function and relative strength in verbal memory. Cluster 3 (14.3 % of the sample) reflected a relative strength in processing speed and



weakness in visual memory and executive functioning, while Cluster 5 (13.9% of the sample) reflected a relative strength in working memory.

No cluster differences were found for age, education, gender, AIDS status, current or nadir CD4+ lymphocyte count, percentage with detectable viral load, percentage taking HAART, hepatitis C status, subjective cognitive complaints, or current rates of major depression or substance use disorders, suggesting that these variables did not influence cluster membership. Clusters did differ on verbal IQ (measure by the Wide Range Achievement Test-Third Edition), with those in Clusters 4 and 5 exhibiting higher verbal IQ than the remaining clusters. While Cluster 1 had the highest prevalence of global cognitive impairment (72%) (determined by using the Global Deficit Score), all six clusters contained substantial numbers of cognitively impaired and unimpaired individuals, suggesting there is no single pattern of performance that characterizes HIV-related cognitive impairment. Furthermore, congruent with the previous two studies is evidence of a frontal-subcortical pattern of impairment. In addition, this study is in agreement with the other studies with the detection of a cluster characterized by motor speed deficits and a cluster with lower performance across all domains. While this sample was slightly older than the previous two studies, the general lack of older adult participants makes these results less applicable to older adults with HIV and thus more cluster analytic studies are needed using older samples. Furthermore, the methodology used in the cluster analysis in this study yielded results that may be cumbersome to interpret as they are relative to pattern, rather than level of performance, which may be more important when the goal is isolating those with cognitive impairment. Also, this

approach to cluster analysis yielded twice the amount of clusters as the other two studies, which may be difficult to interpret due to lack of parsimony.

Overall, the three cluster analytic studies on the cognitive subtypes in adults with HIV yielded some consistent findings. First, these studies suggest that there is not one prototypical pattern of cognitive impairment in HIV. In fact, some individuals may not have any cognitive deficits, some may exhibit declines in specific domains, while others may have more global impairment with lowered overall performance across multiple domains. Second, these studies suggest that while there may be variable patterns, the affected domains seem to be those involving frontal-subcortical circuitry. Finally, there are several co-factors such as education and age that may influence cluster membership. Unfortunately, the samples used in these studies were relatively younger adults, with the highest mean age being 40.68 years in the study by Dawes and colleagues (2008). Furthermore, two of the studies only used male samples. Also, only one of the studies examined nadir CD4+ lymphocyte count. Additionally, only one of the studies explicitly compared their HIV-positive clusters to an HIV-negative reference group. Thus, there is a need for more cluster analyses of the cognitive subtypes in HIV using older samples, including both males and females, including an HIV-negative reference group, and examining more co-factors including nadir CD4+ lymphocyte count (See Table 2 for a comparison of the cluster analytic studies).

## Potential Moderating Co-Factors

### *Age*

With the demographic increase in the prevalence of adults over age 50 with HIV, there is a need to examine whether there is a synergistic effect of HIV and age on cognition. Given that both age and HIV are independently associated with cognitive declines, it would be reasonable to hypothesize that older adults with HIV may be at an increased risk for cognitive impairment compared to their HIV-negative counterparts. There are mixed findings in the literature on aging and HIV on cognition. Several studies have suggested that there may be a synergistic effect of HIV and age on cognition (Hardy et al., 1999; Fazeli, Marceaux, Vance, Slater, & Long, 2011; Sacktor et al., 2010; Vance, Wadley, Crowe, Raper, & Ball, 2011). Furthermore, studies have suggested that older HIV-positive adults may be specifically at an increased risk for cognitive impairment in the face of greater disease severity (Cherner et al., 2004; Hardy et al., 1999). In contrast, other studies have not found an increased vulnerability for cognitive impairment among older adults with HIV (Kissel, Pukay-Martin, & Bornstein, 2005; Vance, Woodley, & Burrage 2007; Wilkie et al., 2003). More research is needed to explore this growing population of adults aging with HIV. Additionally, given that older adults and adults aging with HIV may have more medical co-morbidities (due to either side effects of HIV medications or aging alone) such as diabetes and hypertension, which may further affect cognition above age, this also adds to the hypothesis that there may be a combined effect of older age and HIV on cognition. Furthermore, as a result these individuals may thus take more prescription medications, which may also have effects on cognition. Thus, older age as well as the neuromedical co-morbidities that are common in aging combined

with the cognitive side effects of medications for their treatment may particularly compromise cognition in individuals aging with HIV.

### *Cognitive Reserve/Education*

Cognitive reserve is a theory referring to the threshold of brain insults that must be reached in order for impaired functioning to occur (Stern, 2009). Cognitive reserve is often measured by education or educational quality, intelligence, and engagement in cognitively stimulating work/leisure activities (Vance, 2010). Higher cognitive reserve capacity has been shown to be predictive of better cognitive functioning in HIV-negative individuals (Le Carret et al., 2003); thus, cognitive reserve capacity is expected to be correlated to cognitive functioning in HIV-positive samples. Basso and Borstein (2000) examined whether intelligence mediated cognitive performance in executive functioning over one year in an HIV-positive sample of men ( $N = 113$ ) and an HIV-negative control group ( $N = 54$ ). Intelligence was estimated by using a demographically based regression equation and was used to classify the participants as either average or above average intelligence (Wechsler Adult Intelligence Scale-Revised Full-Scale IQ Scores of 110 and greater = above average), after comparison with controls. Results revealed that regardless of disease stage (asymptomatic HIV, symptomatic HIV, and AIDS), those with above average intelligence either improved over the year period or remained stable on the cognitive measures. In contrast, among the participants with average intelligence, those with both symptomatic HIV and AIDS declined over time. These findings suggest that higher intelligence may mediate preservation of cognitive function in individuals with stable HIV. Thus, this study supports a theoretical model of the protective value of

increased cognitive reserve capacity, with intelligence serving as a protective factor for cognition in HIV.

Another study examined the impact of cognitive reserve on cognitive performance in a sample of HIV-positive adults without AIDS ( $N = 100$ ;  $M_{\text{age}} = 33.5$ ) and an HIV-negative control group ( $N = 63$ ;  $M_{\text{age}} = 29.8$ ) (Pereda et al., 2000). Cognitive reserve was measured by creating a Cerebral Reserve Score which was derived from educational level, vocabulary knowledge, and occupational achievement. Initial analyses yielded no significant differences between the HIV-positive and HIV-negative individuals on the traditional cognitive measures used. However, the HIV-positive group did perform slower than the control group on two reaction time measures. Furthermore, those HIV-positive participants with a low Cerebral Reserve Score showed the poorest performance on the cognitive measures. In addition, regressions revealed that older age and lower Cerebral Reserve Score were predictive of lower global cognitive scores and of cognitive impairment. Thus, in line with the Basso and Bornstein (2000) study, these findings support the cognitive reserve hypothesis, suggesting that HIV-positive individuals with a lower cognitive reserve capacity may be more vulnerable to presumed underlying neuropathology in HIV.

### *Substance Abuse*

Reports have shown higher levels of substance abuse in HIV-positive individuals compared to HIV-negative counterparts (Ferrando et al., 1998). Thus, it is important to consider the combined effects of aging and substance abuse on cognition. One of the most commonly abused drugs in HIV is methamphetamine. One study compared the

effect of methamphetamine on cognitive performance among HIV-positive and HIV-negative individuals by dividing the sample into four groups (HIV-positive/meth dependent, HIV-positive/non-dependent, HIV-negative/meth dependent, and HIV-negative/non-dependent) (Rippeth et al., 2004). Results revealed the following rates of global cognitive impairment: HIV-positive/meth dependent (58%), HIV-negative/meth dependent (40%), HIV-positive/non-dependent (38%), and HIV-negative/non-dependent (18%). Thus, the HIV-positive meth users had the worst functioning of the four groups, and the rates of impairment were very similar and quite high for the HIV-positive non-users and HIV-negative meth users. Overall, these results imply that HIV and methamphetamine use are each associated with cognitive impairment, and also suggest that together these factors may be associated with additive deleterious cognitive changes.

In addition to methamphetamine, high rates of alcohol abuse have been reported in HIV-positive individuals compared to the general population (Petry, 1999). Rothlind and colleagues (2005) examined the effect of HIV and alcohol abuse on cognitive functioning by comparing performance across four groups (HIV-positive light or non drinker, HIV-positive heavy drinker (> 100 drinks per month), HIV-negative light or non drinker, and HIV-negative heavy drinker). Results indicated significant main effects for both HIV and heavy drinking on cognitive performance, with the HIV-positive heavy drinkers having the worst performance and the HIV-negative light or non drinkers having the highest performance. When further examining only the heaviest drinkers (> 6 drinks per day) in the sample, there was a synergistic effect with HIV on measures of psychomotor skills. This study also found better cognitive performance in those HIV-positive individuals on treatment and with lower viral burdens, suggesting the protective

effect of these factors. Altogether, these findings suggest that HIV and heavy drinking are independent risk factors for cognitive impairment, and there may be an interactive effect of HIV and heavy drinking.

### *Depression*

Like substance abuse, rates of depression are higher in HIV-positive individuals compared to their HIV-negative counterparts. Individuals with HIV show higher rates of depressive symptomatology as well as clinical depression (e.g., Major Depressive Disorder), particularly among older adults with HIV (Justice et al., 2004). Depression in HIV may either be directly caused by the virus (primary effect of HIV in the brain) or indirectly caused by the stressors (i.e., stigma, financial problems, and social problems) of living with HIV. Either way, there is a concern that depression may exacerbate cognitive impairments in HIV. Furthermore, depression and cognition may have a bidirectional relationship, with depression leading to poorer cognition, and in turn subjective cognitive complaints leading to further depression. This relationship is not completely understood, as some studies suggest depression and cognition are unrelated in individuals with HIV (Grant et al., 1993; Hinkin et al., 1992), while others suggest that depression may lead to poorer cognitive performance (Castellon, Hinkin, Wood, & Yarema, 1998; Castellon et al., 2004).

Two pre-HAART studies of note found that depression and cognitive performance seem to be unrelated in HIV. One study by Hinkin and colleagues (1992) examined whether participants who were classified as either depressed or non-depressed using the Beck Depression Inventory differed on cognitive performance. Results

revealed no significant differences between groups on any of the cognitive measures, indicating that depression in HIV infection does not necessarily lead to cognitive impairment. Similarly, Grant and colleagues (1993) examined whether depressed mood (measured by the Profile of Mood States) was related to cognitive performance in HIV-positive participants and a HIV-negative control group. Results revealed that while the HIV-positive group displayed more depressive symptoms and cognitive impairment, there were no systematic relationships detected between depression and cognitive impairment. Both of these studies imply that perhaps depression and cognitive impairment may have independent associations with HIV infection.

In contrast, Castellon and colleagues (1998) examined the relationship of depression to cognition in HIV by further examining the components of the Beck Depression Inventory as well as the construct of apathy, which consists of impairment of motivation and goal-directed behavior. HIV-positive and HIV-negative participants completed reaction time and working memory tasks, in addition to the depression and apathy measures. Results revealed that apathy, not depression, was related to working memory impairment in the HIV-positive group compared to the HIV-negative group, suggesting that motivational deficits can affect cognitive performance. In contrast, the cognitive-affective component of the Beck Depression Inventory, but not apathy, was related to poorer performance on the reaction time measures in the HIV-positive group, while total Beck Depression Inventory scores showed a less consistent relationship to cognition. Another study by Castellon and colleagues (2004) further examined the dimensionality of the Beck Depression Inventory by performing a principal components analysis to yield distinct factors of this measure. Three factors emerged: Mood-



Motivation Disturbance, Somatic Disturbance, and Self Reproach. After examining the relationship of these factors with cognitive performance, results revealed that the most influential factor was the Mood-Motivation Disturbance factor, which was related to verbal memory, executive functioning, and motor speed performance. Results from these studies yielded three important findings. First, mental health factors other than just depression, such as apathy, may be more influential on cognition than depression alone. Second, perhaps various mental health constructs (i.e., apathy, depression) have differential effects on cognitive performance, with such constructs affecting different cognitive domains. Finally, examining various components of depression measurements may be more sensitive to cognitive performance than total scores for depression scales.

### *Hepatitis C*

Along with substance abuse disorders and depression, rates of hepatitis C infection are more prevalent in HIV-positive individuals than the general population, with an estimated 25%-30% of HIV-positive individuals in the United States also co-infected with hepatitis C (CDC, 2005). There is evidence that hepatitis C infection is independently associated with a risk for cognitive impairment (Forton et al., 2005); thus, it is reasonable to hypothesize exacerbated cognitive impairments with HIV and hepatitis C co-infection. Hinkin, Castellon, Levine, Barclay, and Singer (2008) examined this synergistic effect by comparing cognitive performance between HIV-positive participants and HIV-positive participants who were co-infected with hepatitis C. As hypothesized, results revealed that the co-infected participants were more likely to be classified as impaired than the HIV mono-infected participants. Specifically, rates of global cognitive

impairment were 63% for the co-infected participants compared to 43% for the HIV mono-infected participants. Furthermore, the co-infected participants were three times more likely to be classified as impaired in the domains of learning and memory.

In contrast, Perry and colleagues (2005) examined cognitive performance between a hepatitis C infected group and an HIV and hepatitis C co-infected group. Their results showed no significant differences between the groups on measures of attention, concentration, and psychomotor speed, implying that HIV may not necessarily interact with hepatitis C to impair cognition. Von Giesen and colleagues (2004) further examined cognitive impairment in HIV and hepatitis C co-infection; however, unlike the previous studies they included an HIV-negative control group, in addition to an HIV-positive only group, hepatitis C only group, and the co-infected group. While they found no significant differences between the three infected groups on intellectual and cognitive measures, these groups did differ from the HIV/hepatitis negative control group on tests of psychomotor abilities, with the infected groups presenting poorer performance. Altogether the results of the effects of HIV and hepatitis C co-infection on cognitive functioning have mixed findings. The inconsistent results are likely due to the confounders that complicate the interpretations. For example, HIV severity and substance use must be considered. Nonetheless, it appears that whether one is co-infected, or mono-infected with either disease, they will likely show some cognitive decrements compared to non-infected controls. More studies are needed to explore whether there is a synergistic effect of these diseases on cognition.

*CD4+ Lymphocyte Count and Viral Load*

In addition to the aforementioned co-factors that may moderate cognitive performance among HIV-positive persons, there are HIV-related factors that have been shown to be related to cognitive impairment. CD4+ lymphocyte count has been shown to be related to cognitive impairment, especially in the pre-HAART era when depleted immune function was more prevalent. As previously mentioned, several studies have provided evidence of increased cognitive impairment with increasing clinical HIV stage as indicated by CD4+ lymphocyte counts (asymptomatic HIV, symptomatic HIV, and AIDS) (Baldewicz et al., 2004; Reger et al., 2002). In the era of HAART, nadir CD4+ lymphocyte count has become a more robust predictor than current CD4+ lymphocyte count (Heaton et al. 2011). Nadir refers to the lowest CD4+ lymphocyte count that an HIV-positive person has reached and nadir CD4+ lymphocyte counts < 200 (indicative of AIDS) seem to be particularly deleterious to cognition. One study found nadir CD4+ lymphocyte count to be a consistent predictor of cognitive impairment in both the pre and post-HAART eras, while viral load, duration of infection and current CD4+ lymphocyte count were only predictive in the pre-HAART era (Heaton et al., 2011). However, one study found that among older adults with HIV, those with detectable levels of virus in the cerebral spinal fluid had twice the prevalence of cognitive impairment than those without detectable levels (Cherner et al., 2004), suggesting that older adults may manifest cognitive impairment in the face of poor viral suppression more so than younger adults. Nonetheless, some studies have failed to find a relationship between plasma and cerebral spinal fluid viral load and cognitive impairment and have in fact shown that the prevalence of at least mild cognitive impairment in HIV is high even in those with

undetectable HIV viral load (Cysique, Maruff, & Brew, 2006; Simioni et al., 2010).

Given that nadir CD4+ lymphocyte count may be a more robust predictor of cognition than viral load, and cognitive impairment can exist in the face of suppressed viremia, this suggests that perhaps blood and cerebral spinal fluid viral load are not completely accurate indices of HIV RNA in the brain. A history of severe immunosuppression as indicated by low nadir CD4+ lymphocyte count may be more reflective of cognitive impairment. Given that the course of HAND may be evolving in the HAART era with at least mild cognitive impairment occurring in the face of less opportunistic infection and higher current CD4+ lymphocyte counts, nadir CD4+ lymphocyte count may be a particularly important predictor of incident cognitive impairment.

### *HAART*

CD4+ lymphocyte count and HAART adherence are closely related co-factors in that in order to avoid severe immune decline, HAART is crucial. Given that the most severe form of cognitive impairment seems to have decreased in the HAART era, this implies that HAART has some beneficial effects on cognitive impairment. Several studies have shown improved cognitive abilities among those who are taking HAART (Brouwers et al., 1997; Martin, Pitrak, Novak, Purcell, & Mullane, 1999; Suarez et al., 2001). However, medication adherence must be considered. A 90-95% adherence rate is optimal to avoid drug resistance and for viral suppression (Bangsberg et al., 2000; Paterson et al., 2000; Wainberg & Friedland, 1998). In other words, when HIV-positive persons are not adherent to their medication, they face the risk of the virus becoming resistant to their medications which may lead to disease progression that can contribute to

cognitive impairment. While older HIV-positive adults may in general have better medication adherence than their younger HIV-positive counterparts, in the face of cognitive impairments they may be at a risk for suboptimal adherence (Ettenhofer et al., 2009; Hinkin et al., 2004). Furthermore, there is likely a bidirectional relationship between medication adherence and cognitive impairments in HIV. Poor adherence may perpetuate cognitive impairments, and in turn, cognitive impairments may further contribute to suboptimal adherence. While there are many neuromedical side-effects of HAART medications such as diabetes and hypertension (Montessori, Press, Harris, Akagi, & Montaner, 2004) that may have a negative effect on cognitive functioning, in general remaining adherent to these medications is currently the best way to control HIV disease and avoid severe cognitive impairments. Given that nadir CD4+ lymphocyte count is a consistent predictor of cognitive impairment, adhering to HAART allows HIV-positive persons to avoid the substantial declines in CD4+ lymphocyte count that may put them at risk for cognitive impairment.

Given that cognitive impairment can still persist even in HAART treated patients with viral suppression, recently researchers have begun to examine whether different HAART regimens with a greater ability to penetrate the central nervous system are more beneficial in improving or preserving cognition. These studies have yielded mixed findings. Smurzynski and colleagues (2011) examined whether antiretroviral drugs with better brain penetration were related to better cognitive performance. Results revealed that higher central nervous system penetration was related to higher cognitive performance, but only among those subjects taking more than 3 antiretroviral drugs. This implies that some HIV+ individuals may require more than three drugs in their regimen

in order to achieve the optimal neural benefits of HAART. In contrast, Marra and colleagues (2009) found that a higher central nervous system penetration score was related to poorer cognitive performance. While this may have been due to confounds and sample differences between studies, nonetheless this implies that results are not yet conclusive on the neuroprotective effects of HAART regimens with higher central nervous system penetration. Furthermore, recent research suggests that HAART may have a direct neurotoxic effect (Robertson et al., 2010), in addition to the indirect neurotoxic effects of many of the side effects of HAART such as diabetes and hypertension (Carr & Cooper, 2000). Overall, the findings on medication adherence and HAART indicate that further research is needed on this new topic before any generalizations can be made. Whether HAART is neurotoxic via only its side effects or its primary effects in the brain remains to be seen. Furthermore, there is much more evidence on the efficacy of HAART in improving longevity and even in improving cognitive abilities to some degree. Thus, until there is more conclusive evidence in research, clinicians should monitor their patients HAART regimens for any cognitive complaints as well as encourage optimal adherence in order to avoid resistance and immune decline.

## PURPOSE

### Rationale Summary

Research suggests that individuals with HIV may be at risk for poorer cognitive functioning than their HIV-negative counterparts. In addition to the possible direct effect of HIV on cognition, HIV-positive individuals are also at risk for a number of co-factors

that may increase their risk for cognitive dysfunction. These factors include, but are not limited to, the synergistic effects of aging, neuromedical co-morbidities, substance use, and depression and anxiety. While there is some general consistency in the literature on the affected cognitive domains in HIV, the use of cluster analyses indicate that there is not one prototypical pattern of cognitive performance in HIV. In fact, some individuals may not have any cognitive declines. Furthermore, the profile or pattern of cognitive dysfunction is likely influenced by the aforementioned co-factors, resulting in vast cognitive profiles determined by individual differences in this heterogeneous population. These various co-factors will help facilitate the examination of these cognitive subtypes by serving as risk and protective factors to cognitive impairment. **Thus, the purpose of the current study is to examine cognitive subtypes in a sample of adults with HIV and to determine if these subtypes differ based on various co-factors. Furthermore, this study seeks to examine the differences in cognitive and functional performance between the HIV-positive clusters and a demographically similar HIV-negative reference group.**

#### *Aim 1*

To examine cognitive subtypes in a sample of HIV-positive adults.

*Hypothesis 1.* There will not be a single pattern of cognitive impairment in HIV. Rather, several clusters will emerge. Specifically, there will be a “normal” or unimpaired cluster(s) and the remaining clusters will likely be characterized by processing speed and/or executive function deficits. There will also be a cluster with global cognitive decrements, with lower performance across all cognitive measures.

### *Aim 2*

To examine the differences in performance on cognitive and everyday functioning measures between the HIV-positive clusters and an HIV-negative reference group.

*Hypothesis 2.* The “normal” or unimpaired cluster(s) will have similar performance on these cognitive measures as the HIV-negative reference group, while the impaired clusters will exhibit poorer performance. Similarly, cognitive performance will translate to everyday functioning, with the lower functioning cluster(s) exhibiting poorer performance on these measures while the “normal” or unimpaired cluster will perform similarly to the HIV-negative reference group.

### *Aim 3*

To determine whether the clusters differ on HIV-specific co-factors (i.e., years with HIV, medication adherence, current and nadir CD4+ lymphocyte count, plasma viral load) and to compare the clusters to an HIV-negative reference group on non-HIV specific co-factors (i.e., age, education, depression, stressful life events, neuromedical co-morbidities, number of medications, employment status, hepatitis C co-infection, and substance use).

*Hypothesis 3.* The impaired or lower functioning clusters will be comprised of those who are older, have lower education, more depression and stressful life events, poorer medication adherence, lower nadir CD4+ lymphocyte count, higher plasma viral load, greater number of co-morbidities, and greater substance use. In contrast, the “normal” or unimpaired group will be comprised of those who are younger, with higher



education, lower levels of depression and stressful life events, better medication adherence, higher nadir CD4+ lymphocyte counts, lower plasma viral load, fewer number of neuromedical co-morbidities, and less frequency of substance use.

#### *Aim 4*

To examine the prevalence of ANI in the overall HIV-positive sample, and stratified by the HIV-positive clusters. Furthermore, the prevalence of ANI in the HIV-negative group will be examined and compared with the HIV-positive group.

*Hypothesis 4.* The more impaired cluster(s) will be composed of a higher percentage of individuals with ANI than the cognitively “normal” cluster(s).

Additionally, the HIV-negative group will exhibit a lower prevalence of ANI than the HIV-positive group

## METHOD

### Participants

Three-hundred and forty-seven adults recruited from the Birmingham, Alabama, metropolitan area were telephone screened for this study. Participants with HIV were recruited from a university HIV/AIDS clinic with flyers and brochures. Participants without HIV were recruited from flyers, brochures, university newspaper advertisements, and word-of-mouth. Interested participants responded to a flyer posted in the clinic and called the research center and a telephone screening interview was conducted to determine eligibility. HIV-positive participants must have known about their HIV diagnosis for at least one year. This screening was done in order to eliminate the

potential confounds of reactive anxiety and depression that may accompany an initial HIV diagnosis. Additional exclusion criteria for the entire sample included being homeless, pregnant, blind, deaf, having a developmental disability, undergoing chemotherapy or radiation, not being proficient in speaking and reading English, past brain injury involving a loss of consciousness for longer than 30 minutes, or having a severe neurological condition (e.g., schizophrenia, bipolar disorder, or HIV encephalopathy, dementia). In addition to the self-report information on the presence of these neurological co-morbidities, this information was verified with the HIV clinic medical charts for the HIV-positive participants; when there was a discrepancy with their self-report information, these participants were excluded. After excluding those who met the exclusion criteria, 78 HIV-positive participants ( $M_{age} = 46.61$ ; 24% female) and 84 HIV-negative participants ( $M_{age} = 47.93$ ; 60% female) remained. The HIV-negative participants were included in the current study in order to have a reference group for comparisons between HIV-positive participants. These participants were subject to the same exclusion criteria as the HIV-positive group, when applicable. This HIV-negative group was recruited to be demographically similar to the HIV-positive group with regard to age and education.

### Procedure

All participants completed a 2 ½ hour battery consisting of demographic, mental and physical health, cognitive, and functional measures. Participants were compensated \$50 for their time. Testers were experienced in administering these measures as well as avoiding drift.

## Measures

### *Demographic Questionnaire*

This measure was used to acquire demographic information such as age, education level (e.g., 12 = completed high school, 13 = some college, 14 = associates degree, etc.), employment status (1 = working part-time or full-time, 0 = not working), and annual income (e.g., 1 = \$0 - \$10,000 and 8 = over \$70,000).

### *Health Questionnaire*

Information on various health aspects was gathered using an adapted version of the measure used in the Cardiovascular Health Study (1989). A list of several medical conditions (e.g., diabetes, hypertension, cataracts, high cholesterol) was given to determine the presence (0 = no, 1 = yes, has or has had the condition) of these conditions over the participant's lifetime. Given that many of these conditions were not expected to affect cognition (e.g., chronic skin conditions) a composite was created for the total number of neuromedical conditions only (i.e., mood problems, diabetes, hypertension, stroke, and hepatitis C). In subsequent analyses, both the total number of neuromedical conditions and the dichotomies for each of these conditions were examined. Participants also reported the total number of prescription medications they were currently taking. In order to adapt this questionnaire for the HIV-positive participants, questions regarding self-reported current CD4+ lymphocyte count and HIV plasma viral load were added.

### *CD4+ Lymphocyte Count and Viral Load*

Since participants were recruited from the university HIV/AIDS clinic, computerized chart extraction of their most recent laboratory values for current and nadir CD4+ lymphocyte count and viral load was available. Clinic values were always used in subsequent analyses rather than self-reported values, unless otherwise stated below. For 75 participants who had both self-reported and corresponding clinic values for their current CD4+ lymphocyte count, there was a high level of agreement ( $r = .73, p < .001$ ). Thus, current CD4+ lymphocyte count values for the three participants whose values were missing from the clinic were imputed using their self-reported values since the correlation between self-reported and actual values was high. For 32 participants who had both self-reported and corresponding clinic values for plasma viral load, there was a low level of agreement ( $r = .01, p = .92$ ); thus, only clinic values of plasma viral load were used and for the four cases that were missing this information, imputation was not deemed appropriate. Clinic values for nadir CD4+ lymphocyte count were available for 70 participants; since the correlation between nadir CD4+ lymphocyte count and current clinic values for CD4+ lymphocyte count was high ( $r = .67, p < .001$ ), for the remaining eight cases, their current CD4+ lymphocyte count was used to impute this missing value in subsequent analyses.

### *Addiction Severity Index*

The Addiction Severity Index is a widely used, gold standard measure of alcohol and drug use (McLellan et al., 1992). Separate scores are created for alcohol and drug

use and can be used in analyses as an indicator of alcohol and drug use severity. Higher scores indicate greater severity of substance use.

#### *Simplified Medication Adherence Questionnaire*

This 6-item questionnaire measures how consistently participants take their HIV medications as prescribed (e.g., Over the past 3 months, how many days have you not take any medicine at all?). Higher scores indicate poorer adherence to HIV medications (Knobel et al., 2002).

#### *Social Readjustment Rating Scale*

The Social Readjustment Rating Scale is a proxy measure of stressful life events (Holmes & Rahe 1967). It includes a list of 30 life events in which the participants are instructed to indicate whether each event has happened to them over the past 12 months by putting a check mark beside each item. Each item has a predetermined value, with more stressful events given a higher value. Total scores were created by summing all the values for which there was a check mark, with higher scores reflective of a greater amount of stressful events.

#### *Profile of Mood States (POMS)*

This self-administered questionnaire is a measure of affective mood state and psychological distress (McNair, Lorr, & Droppelman, 1992). Using a five-point Likert scale, participants are instructed to indicate the frequency (0 = not at all; 4 = extremely) with which they have had 65 different feelings (e.g., friendly, tense, angry) over the past

week, including that day. To create a total mood disturbance score, the scores for all negative items (e.g., tense, unhappy) were summed, and the scores for all positive items (e.g., friendly, lively) were subtracted from this sum. Higher scores for the total mood disturbance score reflect more negative affect and poorer mood. Additionally, the subscales that were comprised from these negative items (i.e., tension, depression, anger, fatigue, and confusion) were used to create a negative affect composite. Similarly, the subscale that was comprised of the positive items (i.e., vigor) was used to represent positive affect. Higher scores on the negative affect composite reflect more negative affect and higher scores on the positive affect composite reflect more positive affect.

#### *Useful Field of View Test<sup>®</sup> (UFOV)*

The UFOV<sup>®</sup> test is a measure of visual attention and processing speed (Edwards et al., 2005). It is a computerized measure utilizing a touch screen response mode. There are four subtests that increase in difficulty as participants progress through the test. In each subtest participants must attend to central and peripheral (or both) visual stimuli and the presentation time lengths (17-500ms) of the stimuli become shorter, and thus more difficult, as they progress. This allows for quantification of processing speed by using display duration threshold as the score. Using a double-staircase method, scores are generated for each subtest which reflects the presentation speed in which 75% accuracy has been achieved. These scores were combined to create a total Useful Field of View<sup>®</sup> score, with lower scores indicating fewer milliseconds needed to correctly perceive the stimuli, and thus better processing speed.

### *Complex Reaction Time Test (CRT)*

The CRT test is a measure of everyday processing speed and reaction time (Ball et al., 2002; Ball & Owsley, 2000). It is a computerized measure using a mouse response mode. Participants were presented with several road signs (left and right turn arrows, pedestrian, and bicycle) and instructed to react as quickly as possible in a specific way (either a single click or moving the mouse right or left). There are two trials of 12 presentations (the first presents three signs at a time, while the second presents six). Participants' average reaction time in seconds was used as the score for this test, with lower scores indicative of faster processing speed.

### *Letter and Pattern Comparison*

The letter comparison task is a commonly used paper-and-pencil measure of processing speed (Salthouse, 1991). This version of the test consisted of 192 pairs of letters with three (e.g., NLH, NLZ), six (e.g., HCLZXL, HCLZXL), and nine (e.g., RZRLNLNFL, RZRLNLNFL) segments (64 pairs per set). For each set, participants were instructed to determine whether the pairs of letter sequences were the same or different by writing either an "S" or "D" beside each pair. In this timed test, participants were given 20 seconds per page (32 pairs per page for a total of 6 pages) to complete as many pairs as possible and were asked to do so as quickly as possible. Total scores were calculated by adding the total number of correct responses from all six pages, with larger scores indicating better processing speed. Just like the letter comparison task, the pattern comparison task is a paper-and-pencil measure of processing speed, except in this version the test consisted of 96 pairs of patterns containing three, six, and nine line segments (32

pairs per set). Again, participants were instructed to determine if the pairs of patterns were the same or different by writing either an “S” or a “D” beside each pair. Total scores were calculated by summation of the total number of correct responses from all three sections, with larger scores reflective of better processing speed. Total scores for the Letter and Pattern Comparison task were combined to create a total Letter and Pattern score, with higher scores indicative of better performance.

### *Finger Tapping Test*

In this measure of psychomotor speed, participants were instructed to tap their index finger as rapidly as possible on a button for 10 seconds (Reitan & Wolfson, 1985). The Finger Tapping Test device automatically records the number of taps per 10 seconds. A total of 10 trials were conducted; five on the right hand and five on the left, starting with the dominant hand. The five trials for each hand were averaged to create an average total score for both hands. Higher scores are indicative of better psychomotor skills.

### *Wisconsin Card Sorting Test (WCST) Computer Version 4*

This is a computerized measure of executive functioning using a mouse response mode (Heaton, Chelune, Talley, Kay, & Curtiss, 1993; Heaton, 2003). Participants are required to sort the cards on the screen according to different principles (color, form, or number) during the test administration. However, for this test there are no formal instructions, rather, they are simply told to match the cards and the computer will inform them if they are right or wrong. After matching a response card to a stimulus card, participants are told whether their choice is correct or incorrect. Participants continue



card matching until 10 cards in a row are matched, and the computer then surreptitiously changes the sorting principle for the participant to figure out the principle; six matches are possible. In this version, the test ends when participants complete all 6 categories, and if they do not, 128 trials are administered. For the current study, number of categories completed and percentage of correct responses were used. Higher values on both scores indicate better executive functioning.

#### *Hopkins Verbal Learning Test (HVLTL)*

The HVLTL is a test of verbal recall and consists of 12 words that are presented, four from each of 3 semantic categories (Brandt, 1991). There are three learning/free-recall trials. For this study, the total number of correctly recalled words from the three learning trials was used, with higher scores reflective of better memory functioning.

#### *Timed Instrumental Activities of Daily Living (TIADL)*

The TIADL is a measure of everyday functioning (Owsley, Sloane, McGwin, & Ball, 2002). It measures both the speed and accuracy in which five typical everyday activities are completed (e.g., finding two food items on a shelf of food, using coins to count out correct change, finding the telephone number of a person in a telephone book, finding and reading the directions on a medicine bottle, and finding ingredients on a can of food). The amount of time (seconds) necessary to complete each task is used as the score. If the task is not completed within the time limit (e.g., two minutes), the task is then terminated and the participant is given the maximum time limit as the score for that task. If the task is completed within the pre-set time limit but is performed incorrectly, a

time penalty is added. This penalty is equal to one standard deviation of time that is derived from the scores of those who performed that task within the time limit. The final scores are transformed into a  $z$ -score for each of the five tasks in order to provide a TIADL composite score; this standardization ensures that the tasks are equally weighted. Since  $z$ -scores are used, composite scores can be reflected in negative and positive coefficients; lower composite scores indicate better performance on this test. This measure has evidence of good test-retest reliability ( $r = .64$ ; Owsley, Sloane, McGwin, & Ball, 2002).

#### *Observed Tasks of Daily Living (OTDL)*

This measure is composed of 28 observational tasks that simulate complex and instrumental activities of daily living that require inferential thinking and have observable elements allowing objective scoring of performance (Diehl, Willis, & Schaie, 1995). The tasks include medication, telephone, and financial-related activities. Participants are given stimulus items (e.g., medicine bottles) and a card with a question on it for each activity. This is not a timed task; rather, accuracy is recorded (yes - performed correctly, or no – performed incorrectly), and whether or not a prompt was needed. Total scores are calculated based on accuracy and use of prompts; higher scores reflect better everyday functioning. The mean kappa across tasks for all three domains is 0.93.

## Data Analysis

### *Aim 1*

Preliminary analyses included examining the data for missing values and substantial outliers, and handling any issues accordingly. Furthermore, descriptives and group differences on the demographic and mental and physical health variables as well as the cognitive and functional measures were conducted between the HIV-negative and HIV-positive samples using ANOVA and chi-square analyses. In order to determine whether unique cognitive subtypes exist in a sample of adults with HIV, cluster analysis was employed. Formann (1984) suggest a sample size of no less than  $2^k$  ( $k$  = number of variables). With this relatively small sample size ( $N = 78$ ), a maximum of six variables can be entered into the cluster analysis. As highly correlated variables are not recommended for cluster analysis, in order to examine whether there was any multicollinearity among the six cognitive measures to be entered into the cluster analysis (UFOV<sup>®</sup>, CRT, Letter and Pattern Comparison, WCST (percentage of correct responses), HVLT, and the Finger Tapping Test), correlations were conducted. It is suggested that correlations below 0.90 are appropriate to enter into a cluster analysis (Mooi & Sarstedt, 2011).

While some prior cluster analytic studies factor analyzed their measures to reduce the amount of variables in order to avoid redundancy, this was deemed as inappropriate in the current study for several reasons. First, factor analysis is preferred when the sample size is greater than 200 (Tabachnick & Fidell, 2006). Second, factor analysis is performed most optimally when there are a large number of variables entered; in the current study with six measures, this was considered insufficient to include in a factor

analysis. Third, in factor analysis, there is always a certain amount of variance not explained; thus, it was not considered ideal for the interpretation of the results. Lastly, interpreting factor scores can be cumbersome compared to examining the actual variables themselves. Thus, factor analysis was not considered appropriate in the current study. SPSS contains three clustering techniques: Hierarchical, K-Means, and Two-Step. The Hierarchical clustering method is a nesting procedure in which the two nearest cases/clusters are identified based on proximity to the group centroid and combined until all cases are nested or until a preselected number of clusters are reached. In other words, the Hierarchical clustering method begins with a number of clusters equal to the sample size and continues until all cases are joined into a single group. However, a limitation of this approach is that there is no measurement of the most appropriate cluster solution that best fit the data. In the K-Means clustering technique, the investigator specifies the desired number of clusters prior to the procedure and the software package creates clusters to optimize between-group differences for the desired number of clusters. Thus, the K-Means procedure is only appropriate when the investigator has a conceptual, a priori justification for selecting a specific number of clusters. However, as with Hierarchical clustering, there are no fit statistics available for the K-Means approach, thus making both of these approaches very subjective to the researcher's goals for determining the appropriate number of clusters.

The Two-Step method, a newer clustering approach, is a variant of the Hierarchical clustering technique (Chiu, Fang, Chen, Wang, & Jeris, 2001). However, in the Two-Step procedure, cases are "pre-clustered" in the first step, then after the pre-cluster, a Hierarchical cluster analysis is employed as described previously. Since the

measures used in the current study are all continuous and display a normal distribution, the log-likelihood was used as the method of determining distance between clusters. All cognitive measures were standardized to  $z$ -scores by default in the Two-Step procedure. This is necessary for cluster analysis to produce optimal results when variables are measured on different scales. The advantage to the Two-Step clustering method is that it provides a measure of the most appropriate number of clusters using the Schwarz Bayesian Information Criterion, a general measure of the overall fit of a solution based upon the mean square error. The Schwarz Bayesian Information Criterion is provided for all possible solutions, from the pre-clustered phase until all cases are converged into a single group, and compared to determine the best solution. The appropriate number of clusters was determined by the cluster solution where the Schwarz Bayesian Information Criterion was small and the Schwarz Bayesian Information Criterion change between adjacent clusters was also small. This clustering method is preferred when the most appropriate number of clusters to fit the data is not known prior to the clustering procedure. Additionally, in order to demonstrate the stability of the cluster solution yielded from the Two-Step method, a Hierarchical and a K-Means cluster analysis were also employed using the number of clusters yielded from the Two-Step approach. Agreement between the different approaches implies that the original cluster solution is stable across methods. Furthermore, as the ordering of cases in the dataset can sometimes affect clustering, the different approaches were performed numerous times after sorting by different variables. After determining the optimal number of clusters, the variables in the analysis were examined to determine which variables were actually important in determining cluster membership.

### *Aim 2*

After employing the cluster analysis, comparisons were conducted between the HIV-positive clusters and the HIV-negative reference group on the six cognitive measures used to form the clusters as well as two measures of everyday functioning. These measures included: UFOV<sup>®</sup>, CRT, Letter and Pattern Comparison, WCST (percentage of correct responses and number of categories completed), HVLT, the Finger Tapping Test, TIADL, and OTDL. MANOVA was used to control for multiple comparisons and Bonferonni's post-hoc test was used to for follow-comparisons. By examining the translation of cognitive performance to everyday performance, this aim demonstrated the validity of the cluster solution. In order to present these findings graphically, average *z*-scores with a mean of zero and a standard deviation of one were plotted for each measure by group (each HIV-positive cluster and the HIV-negative group). In order for visual clarity, *z*-scores for UFOV<sup>®</sup> and CRT were reversed, so that higher *z*-scores represented better performance across the measures.

### *Aim 3*

In order to determine whether clusters differed on HIV-specific co-factors (i.e., years with HIV, medication adherence, current and nadir CD4+ lymphocyte count, and plasma viral load) and to compare the clusters to an HIV-negative reference group on non-HIV specific co-factors (i.e., age, education, income, race, sexual orientation, gender, depression, stressful life events, neuromedical co-morbidities, medications, employment status, hepatitis C co-infection, and substance use), MANOVA was used for

continuous variables and chi-square analyses were used for dichotomous variables (i.e., race, sexual orientation, gender, and employment status). In addition to examining the composite for total number of neuromedical co-morbidities, each of these conditions (i.e., self-reported presence/absence of mood problems, diabetes, hypertension, stroke, and hepatitis C) were also examined separately. In order to comply with the assumptions of MANOVA, all continuous variables were examined for violations of normality and handled accordingly.

#### *Aim 4*

To further examine the validity of the cluster solution, the clusters were examined for psychometrically defined ANI, using similar methods as Antinori and colleagues (2007). Using the mean and standard deviations of the demographically similar HIV-negative reference group for each of the six cognitive measures, z-scores were created for the HIV-positive group. Participants whose performance was one or more standard deviations in the impaired direction for two or more measures were classified as “impaired” or as having ANI. Percentages were calculated for the composition of impairment in the clusters as well as for the total HIV-positive sample and the total HIV-negative sample. As our study did not contain self-report questions on impairments in daily functioning and since it would have been cumbersome to quantify frank “impairment” in daily functioning from our two functional measures (TIADL and OTDL), it was not considered appropriate to classify participants with anything beyond ANI (i.e., MND and HAD).

## RESULTS

One data point was missing for the following cognitive tests: Finger Tapping Test, CRT, UFOV<sup>®</sup>, and WCST. Based on the remaining cognitive scores, linear regression was used to impute these missing values. There were no violations of normality nor were there any substantial outliers on any of the cognitive measures, after inspection of  $z$ -scores and skewness and kurtosis values. Preliminary analyses indicated that the HIV-positive group and the HIV-negative reference group were demographically similar (Table 3). There were no significant differences between the groups on age, percentage over age 50, race, income, education, depression, stressful life events, and drug and alcohol use. The HIV-negative group had a significantly higher proportion of heterosexuals and currently employed participants. The HIV-positive group had significantly more males and individuals with hepatitis C. Furthermore, the HIV-positive group reported more neuromedical conditions and prescribed medications, as would be expected in this clinical population. In addition to having higher frequency of hepatitis C infection, the HIV-positive group also had a significantly higher frequency of self-reported mood problems (depression or anxiety) than the HIV-negative group. Regarding the cognitive and functional measures, the HIV-positive group performed significantly worse than the HIV-negative group on the CRT, Letter and Pattern Comparison, and the TIADL.

Descriptive analyses were also performed on the HIV-positive sample for HIV-specific variables (Table 4). Results revealed that 87% of the sample was currently taking some type of HAART regimen. Fifteen percent of the sample had a current CD4+ lymphocyte count below 200, which is indicative of AIDS. Forty-two percent of the



sample had a nadir CD4+ lymphocyte count below 200. Nadir CD4+ lymphocyte count represents the lowest CD4+ lymphocyte count ever reached during the course of one's illness. Finally, 38% of the sample had an undetectable plasma viral load. Viral load represents the number of HIV copies per milliliter of blood. A viral load of 48 copies/mL is considered "undetectable".

Correlations revealed that for all of the cognitive measures (UFOV<sup>®</sup>, CRT, Letter and Pattern Comparison, Finger Tapping Test, WCST, HVLIT), correlation coefficients did not exceed 0.51, indicating that there was no multicollinearity (Table 5). This finding implied that each of the measures represented relatively different constructs; thus, it was not deemed appropriate to create composite scores between any of these measures. For example, UFOV<sup>®</sup> and CRT are moderately correlated ( $r = 0.51$ ) and this would be expected as they are both measures tapping into the broad domain of processing speed; however, UFOV<sup>®</sup> captures visual processing speed while CRT taps more into reaction time. In order to examine whether the outcome of the cluster analysis would be affected by including different combinations of variables, the cluster analysis was performed numerous times including different combinations of the variables (i.e., including only three, four, and five variables). In no situation was the cluster solution (number of clusters yielded) any different than the original analysis including all six measures. Thus, all six measures were entered into the cluster analysis.

Results of the Two-Step cluster analysis of the HIV-positive sample yielded a two cluster solution as the most appropriate, as determined by the lowest Schwarz Bayesian Information Criterion and Schwarz Bayesian Information Criterion change values (357.18 and -16.49, respectively). Cluster 1 contained 32 participants while Cluster 2

contained 46. In order to examine the stability and consistency of this cluster solution, several follow-up analyses were performed. A K-Means and Hierarchical cluster analysis were performed with a specified solution of two clusters. Results revealed that 83% of the participants in the K-Means analysis, and 90% of those in the Hierarchical analysis were correctly classified in the two clusters yielded from the initial Two-Step procedure. Additionally, as cluster analysis may be influenced by the ordering of variables, the Two-Step cluster analysis was repeated multiple times after sorting the data by differing variables, and 100% agreement was found between each sorting method and the original Two-Step, two-cluster solution.

In order to examine the differences in cognitive and functional performance between the HIV-positive clusters and the HIV-negative reference group, MANOVA was conducted on the cognitive and functional variables. Results revealed that Cluster 1 performed significantly worse than Cluster 2 and the HIV-negative reference group on each measure except for the Finger Tapping Test, for which there were no group differences. Furthermore, Cluster 2 performed similarly to the HIV-negative group on every measure except the HVLT, where Cluster 2 actually had significantly better performance than the HIV-negative group. Similarly, for the OTDL and TIADL, Cluster 1 performed significantly worse than both Cluster 2 and the HIV-negative group, while Cluster 2 and the HIV-negative group did not perform significantly different from each other (Table 6; Figure 1).

In order to examine any potential factors that were influential to cluster membership, differences in demographic and mental and physical health variables between the two clusters, as well as the HIV-negative group, were examined. MANOVA

was conducted for each continuous variable with Bonferroni post-hoc analyses, while chi-square analyses were conducted on dichotomous variables. Results revealed that Cluster 1 was significantly older than Cluster 2. Furthermore, Cluster 1 and the HIV-negative group had a significantly higher percentage of participants over age 50 than Cluster 2. Clusters 1 and 2 both had a significantly higher proportion of males and a significantly lower proportion of heterosexuals than the HIV-negative group. Regarding employment status and hepatitis C infection, Clusters 1 and 2 had significantly more participants with hepatitis C and significantly fewer participants who were currently working than the HIV-negative group. There was a trend for these two variables between Clusters 1 and 2, with a trend towards Cluster 1 having fewer participants who were employed and having a higher prevalence of hepatitis C infection. Cluster 1 reported significantly more neuromedical conditions than Cluster 2 and the HIV-negative group, while Clusters 1 and 2 both reported significantly more medications than the HIV-negative group. Of these medical conditions, Cluster 1 had a significantly higher frequency of both stroke and hypertension than Cluster 2 and the HIV-negative group. There were no significant differences between Clusters 1 and 2 and the HIV-negative group on proportion of Caucasians, income, education, mood, stressful life events, alcohol use, and drug use (Table 7). With regard to HIV-specific variables, Clusters 1 and 2 did not significantly differ on any of these variables; however, there was a trend for years with HIV, with those in Cluster 1 on average having a longer diagnosis of HIV (Table 8).

To address aim four, the clusters were examined for psychometrically defined ANI, using similar methods as Antinori and colleagues (2007). Participants whose

performance was one or more standard deviations in the impaired direction of the demographically similar HIV-negative reference group for two or more measures were classified as having ANI. Results revealed that 91% ( $n = 29$ ) of Cluster 1 participants were classified as having ANI, compared to 17% ( $n = 8$ ) of Cluster 2 (Figure 2). Furthermore, in Cluster 2, of those who were classified as impaired, all but one of these participants (who exhibited lower performance on three tests) only exhibited lowered performance in two tests, while Cluster 1 contained participants who performed worse on between three and six measures. Additionally, when considering the HIV-positive sample as a whole regardless of cluster membership, 47% ( $n = 37$ ) of the sample was classified as having at least ANI. Regarding the HIV-negative group, 30% ( $n = 25$ ) of the sample was classified with ANI.

## DISCUSSION

When examining the differences between the HIV-positive and HIV-negative samples, the fact that age and education were similar between the groups was of the most importance, as these variables are known to affect cognitive performance (Lezak, 1995). Thus, the HIV-positive and HIV-negative sample were demographically similar on the variables relevant to cognitive functioning. This similarity highlights the validity of the findings of this study. While the HIV-positive sample did have more participants who were men, homosexual/bisexual, unemployed, had hepatitis C co-infection, reported more medical conditions, and were prescribed more medication, this is representative of the current population of adults with HIV. Furthermore, those variables that were of interest due to their potential relationship to cognition (i.e., employment status, hepatitis

C, medical conditions, and medications) were examined in subsequent analyses, as they were aims of this study. It was surprising that the number of stressful life events and depressed mood was not significantly different between groups. However, there were raw mean differences in the expected direction, with HIV-positive participants exhibiting more depressive symptomatology and a higher occurrence of stressful life events. Nonetheless, the finding that there was no significant difference on these two variables between the HIV-positive and HIV-negative group is promising and implies that this is perhaps due to the groups being similar on age, education, and income; thus these demographic factors may be more related to the occurrence of stressful events and depressed mood than HIV itself.

The resulting two-cluster solution to the Two-Step cluster analysis is both in parallel and inconsistent to the literature, and our hypotheses. It is in parallel because this study's findings are congruent with the literature suggesting that there is a subset of HIV-positive individuals with global lower performance and a subset with global higher performance ("normals"). It is incongruent because prior cluster analyses have yielded cluster solutions of three or more clusters, with some clusters defined as having relative decrements in specific cognitive domains only (e.g., psychomotor only). There are two major explanations for this. First, these prior cluster analytic studies had much larger sample sizes, which may have made it possible to detect these distinct subgroups in the data. Second, as these prior studies used factor analysis, their cognitive "factors" were forced to be orthogonal (uncorrelated), making it possible for them to detect distinct subgroups rather than only groups with overall lower/higher performance. However, as

previously mentioned, the limitations of factor analysis outweighed the benefits in the current study.

When comparing the HIV-positive clusters to the HIV-negative reference group on the cognitive and functional measures, the validity of the two-cluster solution was confirmed. Individuals in Cluster 1 (the lower performing cluster), performed significantly worse on all of the measures except the Finger Tapping Test (for which there were no group differences) than individuals in Cluster 2 (the “normal” performance cluster) and individuals in the HIV-negative group. The lack of a significant difference for the Finger Tapping Test suggests that psychomotor speed may be spared in the face of well-controlled HIV. Cluster 2 and the HIV-negative group did not differ on any of the measures except for the HVLT, where individuals in Cluster 2 actually had better performance on the average. However, while statistically significant, the fact that on average Cluster 2 participants recalled two more words than the HIV-negative group may not have everyday implications. The results of these comparisons of group differences on the cognitive and functional measures is promising because it suggests that those high functioning individuals with HIV are performing no differently than a demographically similar HIV-negative group.

The finding that Cluster 1 was significantly older than Cluster 2 upheld our hypothesis regarding a relationship between age and cluster membership. This finding suggests that there may be a synergistic relationship between age and HIV on cognition. While examining a statistical interaction between age and HIV on cognition was not the goal of the current study, this research question was addressed in this sample in a previous study (Vance, Fazeli, & Gakumo, in press). This previous study compared

younger ( $< 50$  years old) and older ( $\geq 50$  years old) adults with and without HIV on cognitive and functional measures and found main effects for age and HIV on many of the cognitive measures while there were no significant age by HIV interactions. However, there was a trend ( $p < .10$ ) for an age by HIV interaction on the TIADL measure. Furthermore, the older HIV-positive group performed worse than the younger HIV-positive group and both the younger and older HIV-negative groups on all of the cognitive measures, although these differences were not statistically significant. Thus, in the current sample prior analyses suggest there does not seem to be a synergistic relationship of age and HIV on cognition. Given these previous findings, the results of the current study suggest that perhaps age was the primary reason why the Cluster 1 participants performed poorly, while the Cluster 2 participants had higher performance. While Cluster 2 was not significantly younger than the HIV-negative group, they were about four years younger on average, suggesting that this may have been an explanation for their comparability to the HIV-negative group. This is further implicated by the fact that Cluster 1 and the HIV-negative group had a significantly higher proportion of individuals over age 50 (59% and 49%, respectively) than Cluster 2 (26%) despite not having significantly different mean ages. Furthermore, while Cluster 1 was not significantly older than the HIV-negative group, they were about three years older on average, which again suggests that age was the most influential factor to cluster membership. Additionally, since Cluster 1 had a significantly higher proportion of individuals who had hypertension and a prior stroke than Cluster 2 and the HIV-negative group, this implies that these conditions could have been the primary reason why age emerged as a significant predictor. Lastly, while Clusters 1 and 2 had significantly more

men and individuals who were homosexual or bisexual, this was inherent in the HIV-positive sample as a whole and was not considered to be related to cognition.

Regarding the percentage of individuals who were employed either full or part-time and who had hepatitis C, Clusters 1 and 2 had a significantly higher proportion of individuals who were unemployed and had hepatitis C, which was also inherent in the HIV-positive sample. However, that there was a trend for these two variables between Cluster 1 and 2, with Cluster 1 having fewer individuals who were employed and more individuals with hepatitis is an interesting finding and suggests that perhaps hepatitis C co-infection and being unemployed may be related to their poorer performance. Regarding employment, the direction of this relationship is not known (i.e., are they performing worse because they are not employed and thus experiencing negative neuroplasticity due to a lack of mental stimulation, or are they not employed because of initial cognitive problems?); however, there may be a bidirectional relationship. Causal inferences cannot be made with the current analyses. For total number of reported medical conditions, since Cluster 1 reported significantly more conditions than the HIV-negative group and Cluster 2 this implies that this variable was related to cluster membership, and as previously mentioned, this variable may have been the primary reason why age emerged as a predictor. For number of prescribed medications, the finding that Clusters 1 and 2 both had significantly more medications than the HIV-negative group was not surprising as this difference was also inherent in our HIV-positive sample and is expected given the pill regimens of HAART.

Regarding the differences between the Clusters on HIV-specific variables, the finding that there were no significant differences between the clusters on current CD4+



lymphocyte count was congruent with prior cluster analytic studies. However, it was surprising that nadir CD4+ lymphocyte count (which was only examined in one prior study) was not related to cluster membership. This indicated that disease severity did not seem to be related to cognitive performance (as defined by cluster membership). While the lack of relationship between disease severity indices and cognitive performance may suggest that HAART may be neurotoxic, examining HAART neurotoxicity was not the goal of this study and this inference should be taken with caution. Furthermore, the finding that prescribed HIV medications and medication adherence were not related to cognitive performance was surprising; however this sample contained a large majority of individuals who were prescribed HIV medications and were largely adherent to these medications. Thus, in this sample there was likely not enough variability to examine the effect of these variables on cognitive performance. While not statistically significant, the trend for years with HIV, with those in Cluster 1 having been diagnosed with HIV for about three years more on average than Cluster 2 may suggest at first glance that individuals who have had HIV longer may be at an increased risk for cognitive declines; however, since years with HIV and age were moderately correlated ( $r = 0.42$ ), it may be that age is the true reason for this relationship, as years with HIV is inherently confounded by age.

Results of the final analysis confirmed the validity of the cluster solution, with a majority of Cluster 1 participants psychometrically defined as having ANI, and a majority of Cluster 2 being defined as cognitively “normal” compared to the HIV-negative reference group. While it may seem surprising that any of the Cluster 2 members were defined as having ANI, the participants in Cluster 2 who were classified

as impaired were those who had lower performance on the fewest number of measures (i.e., one participant had lower performance on three measures while for the rest it was only on two measures). In contrast, the majority of those in Cluster 1 had lowered performance on between three and six measures. Thus, these findings confirm the validity of the cluster analysis as the participants who exhibited the poorest performance were correctly classified to Cluster 1 while the higher performing participants were correctly classified to Cluster 2. Furthermore, the finding that 47% of the sample exhibited at least ANI is congruent with the findings on the prevalence of ANI in the HAART era (Heaton et al., 2010). The finding that 30% of the HIV-negative group exhibited ANI suggests that individuals with HIV are at a higher risk for cognitive declines than HIV-negative individuals. However, as this sample included adults and older adults, it was not surprising that there was such a high percentage of ANI in the HIV-negative group.

### Implications

Overall, the results of this study are congruent with the literature and have promising findings. Perhaps the most salient finding of this study is that when compared to a demographically similar HIV-negative reference group, higher functioning HIV-positive participants showed no differences in cognitive and functional performance. This is promising as it implies that cognitive declines in HIV may not necessarily occur in all HIV-positive persons. Furthermore, the fact that age was associated with cluster membership implies that age and the co-morbid conditions of aging and HIV may have a synergistic effect on cognition in some individuals. The fact that education and income

were not significantly different between the clusters and the HIV-negative group implies that socioeconomic status was not influential to cognitive performance. The finding of overall lowered performance on the cognitive and functional measures in Cluster 1 illustrates the validity of the cluster solution as well as the translation of cognitive performance to everyday performance. Given that there are currently few studies using cluster analytic statistical techniques, this study is quite relevant. Clinicians and researchers should be aware of potential cognitive declines in adults with HIV, even if these declines are subtle. This study also indicates the importance of using a demographically similar HIV-negative reference group when examining cognitive dysfunction in HIV-positive samples in order to avoid overestimation of cognitive dysfunction in HIV. Additionally, the finding that 47% of the HIV-positive sample had some form of HAND (i.e., ANI) was in parallel with the current HIV literature, and thus underscores that although HIV-associated dementia (HAD) is decreasing, more subtle cognitive decrements are still prevalent and should be taken seriously and monitored by individuals with HIV as well as their healthcare team.

#### Strengths, Limitations, and Directions for Future Research

The strengths of the current study include: a higher mean age than prior studies; inclusion of females compared to prior studies; using the more modern Two-Step clustering method that includes fit indices for determining the appropriate number of solutions to fit the data; the inclusion of a demographically similar HIV-negative reference group; including measures such as medication adherence and nadir CD4+ lymphocyte count. The only significant limitation of the current study was the relatively

small sample size. Future studies should examine cognitive subtypes in HIV using very large sample sizes (i.e., thousands of participants) in order for more optimal performance of the cluster analysis technique. Since in cluster analysis, the larger the sample, the more variables that can be included, larger sample sizes would allow for more variables to be entered, and thus more distinct clusters may potentially be discovered.

Additionally, more studies are needed that include older samples (i.e., aged 50 and above). While participants in this age group may have been scarce in years prior to the advent of HAART, with the increase in the prevalence and incidence of HIV in adults over age 50, these individuals will be more available to examine in the coming years. Similarly, longitudinal studies are needed that examine the trajectory of cognitive functioning and cognitive change in adults with HIV as they age into older adulthood.

In addition to the need for future research examining cognitive declines associated with HIV, intervention strategies to ameliorate such cognitive declines are needed. Research in older adults without HIV has suggested that computerized cognitive remediation therapy may be an effective intervention strategy to help improve or maintain cognition, especially in the domain of processing speed (Ball et al., 2002). Pilot research has also utilized this technique in a sample of adults with HIV and it was found to be effective in improving processing speed and performance of a speeded everyday functioning task compared to a no-contact control group (Vance, Fazeli, Ross, Wadley, & Ball, in press). Additionally, future research is needed to examine the efficacy of preventative strategies to avoid cognitive dysfunction in HIV. For example, Vance and colleagues (2011) have posited the concept of theoretical “cognitive prescriptions” which are individualized behavioral plans given by clinicians to help promote habits that may

increase positive neuroplasticity (e.g., healthy diet, exercise, intellectual stimulation), and reduce habits that may increase negative neuroplasticity (e.g., substance abuse, depression). While these healthy and unhealthy behaviors are commonly acknowledged by individuals, many may not be aware of the potential relationship of these lifestyle habits to cognition and thus performance of everyday activities. Thus, educating individuals with HIV (especially those with subjective cognitive complaints) about this relationship may make them more inclined to adjust their behaviors to promote better cognitive functioning.

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## APPENDIX A

## TABLES

Table 1  
HNRC Definitions of HAND

HAND Diagnostic Category	Cognitive Criteria	Functional Criteria
HIV-associated asymptomatic neurocognitive impairment (ANI)	Performance of at least 1 SD below the mean of demographically corrected scores in at least 2 of the following cognitive domains: verbal/language, attention/working memory, abstraction/executive function, memory, processing speed, sensory/perceptual skills, and psychomotor skills.	No functional impairment
HIV-associated mild neurocognitive disorder (MND)	Performance of at least 1 SD below the mean of demographically corrected scores in at least 2 of the following cognitive domains: verbal/language, attention/working memory, abstraction/executive function, memory, processing speed, sensory/perceptual skills, and psychomotor skills.	Mild functional impairment as indicated by at least one of the following: <ol style="list-style-type: none"> <li>1. Self-report declines in mental acuity, inefficiency in work, homemaking, or social function</li> <li>2. Observation by knowledgeable person of declines in mental acuity, inefficiency in work, homemaking, or social function</li> </ol>
HIV-associated dementia (HAD)	Performance of 2 SD or greater below the mean in at least 2 of the following cognitive domains: verbal/language, attention/working memory, abstraction/executive function, memory, processing speed, sensory/perceptual skills, and psychomotor skills.	Marked interference in daily functioning as indicated by both self-report and observation by a knowledgeable person. (Must be more pronounced than the mild functional impairment in MND)

*Note.* The clinician should ensure that for ANI and MND the cognitive impairment is not reflective of dementia, delirium, or any other preexisting cause. Likewise, for HAD the impairment should not reflect delirium, or any other preexisting cause (i.e., other non-HIV related CNS disorders, severe substance abuse disorders, major depression).

Table 2  
Comparison of Cluster Analytic Studies on Cognitive Subtypes in Adults with HIV

Study	Sample	HIV-Negative Group	Cluster Method	Cluster Results	Significant Predictors	% Impaired*	Limitations
van Gorp et al., 1993	HIV-positive men ( $N = 298$ ; $M_{age} = 38.90$ )	Yes, but did not provide data for cognitive comparisons. Only used this reference group to classify impairment within clusters	K-Means	Cluster 1 (cognitively “normal”); Cluster 2 (depressed w/ psychomotor slowing & lowered verbal memory); Cluster 3 (lowered overall cognitive performance)	Education, age, HIV symptom status	Cluster 1 (13%); Cluster 2 (61%); Cluster 3 (63%)	Male-only sample; study was before the advent of HAART; nadir CD4+ lymphocyte count not examined
Lojek & Bornstein, 2005	HIV-positive men ( $N = 217$ ; $M_{age} = 34.30$ ); HIV-negative men ( $N = 55$ ; $M_{age} = 33.10$ )	Yes	K-Means	Cluster 1 (low psychomotor speed); Cluster 2 (memory/ learning dysfunction); Cluster 3 (lowered overall cognitive performance); Cluster 4 (cognitively “normal”)	Education, HIV symptom status	Did not examine	Relatively young sample; male-only sample; nadir CD4+ lymphocyte count not examined
Dawes et al., 2008	HIV-positive adults ( $N = 553$ ; $M_{age} = 40.68$ )	No	Hierarchical & K-Means	Cluster 1 (strength in executive functioning); Cluster 2 (strength in motor skills/weakness in verbal memory & executive function); Cluster 3 (strength in processing speed/weakness in visual memory & executive function); Cluster 4 (weakness in motor skills & strength in verbal memory); Cluster 5 (strength in working memory); Cluster 6 (weakness in executive function/strength in verbal memory)	Verbal IQ	Cluster 1 (72%); Cluster 2 (53%); Cluster 3 (47%); Cluster 4 (62%); Cluster 5 (44%); Cluster 6 (42%)	No HIV-negative group; interpretability of clusters is cumbersome (i.e., large number of clusters & focuses too much on pattern rather than level of performance)

Note. \*Methodology used to define impairment varied across study

Table 3  
Group Differences Between the HIV-Positive and HIV-Negative Samples ( $N = 162$ )

Variable	HIV-Positive ( $n = 78$ )		HIV-Negative ( $n = 84$ )		$p$ -value
	$n$ (%)	$M$ ( $SD$ )	$n$ (%)	$M$ ( $SD$ )	
Age		46.61 (10.40)		47.93 (13.06)	0.48
No. Over Age 50 (%)	31 (40%)		41 (49%)		0.25
No. Men (%)‡	59 (76%)		33 (39%)		0.00
No. Heterosexuals (%)‡	39 (50%)		78 (93%)		0.00
No. Caucasians (%)*	48 (62%)		55 (65%)		0.73
No. Working (%)‡	12 (15%)		35 (42%)		0.00
Income		1.74 (1.35)		1.98 (1.53)	0.31
Education (years)		12.77 (2.48)		12.79 (1.68)	0.96
No. Med. Conditions‡		1.59 (1.14)		1.06 (0.99)	0.00
No. w/ Hepatitis C (%)‡	26 (33%)		6 (7%)		0.00
No. w/ Mood Prob. (%)†	44 (56%)		33 (39%)		0.03
No. w/ Stroke (%)	7 (9%)		5 (6%)		0.46
No. w/ Hypertension (%)	38 (49%)		32 (38%)		0.17
No. w/ Diabetes (%)	9 (12%)		10 (12%)		0.94
No. Medications‡		4.83 (3.39)		2.18 (2.74)	0.00
POMS Total		35.47 (40.29)		28.26 (37.89)	0.24
POMS-Positive		17.73 (6.68)		19.27 (6.52)	0.14
POMS-Negative		53.21 (36.55)		47.54 (34.87)	0.31
Stressful Life Events		268.29 (139.58)		238.51 (164.16)	0.22
ASI - Alcohol Use		0.23 (0.60)		0.24 (0.45)	0.90
ASI - Drug Use		0.03 (0.07)		0.02 (0.04)	0.12
UFOV® Test		737.73 (361.48)		638.45 (334.64)	0.07
CRT†		1.93 (0.56)		1.75 (0.47)	0.02
Letter & Pattern†		76.67 (17.36)		82.75 (17.28)	0.03
WCST % Correct		50.54 (18.26)		54.35 (18.84)	0.19
WCST Cat. Completed		2.52 (2.20)		3.07 (2.25)	0.12
Finger Tapping Test		50.52 (7.73)		48.63 (8.27)	0.14
HVLT		23.53 (6.28)		24.12 (6.21)	0.55
TIADL†		0.65 (3.44)		-0.61 (2.65)	0.01
OTDL		68.10 (7.59)		69.71 (7.38)	0.17

*Notes.*  $M$  = Mean; No. = number;  $SD$  = standard deviation; Working = currently working either part-time or full-time; For income, 1 = \$0 - \$10,000 and 8 = over \$70,000; No. Med. Conditions = total number of neuromedical conditions; Mood prob. = self-reported mood problems (depression or anxiety); POMS Total = Profile of Mood States total mood disturbance score; Stressful life events = Social Readjustment Scale score; ASI = Addiction Severity Index; UFOV = Useful Field of View; CRT = complex reaction time; Letter & Pattern = Letter & Pattern Comparison task total; WCST = Wisconsin Card Sorting Test; WCST Cat. Completed = Wisconsin Card Sorting Test categories completed; HVLT = Hopkins Verbal Learning Test; TIADL = Timed Instrumental Activities of Daily Living; OTDL = Observed Tasks of Daily Living. \* = All others were African American except one who was Native American who was HIV-positive. † $p < .05$ ; ‡ $p < .01$ .

Table 4  
Descriptives for HIV+ Sample on HIV-Related Variables ( $N = 78$ )

Variable	n (%)	$M$ ( $SD$ )	Range
Years with HIV		12.93 (7.34)	1.00 - 26.10
No. Taking ART (%)	68 (87%)		
Medication Adherence		3.19 (4.31)	0.00 - 17.00
Current CD4+ count		471.30 (274.40)	11.00 - 1,140.00
Nadir CD4+ count		276.39 (236.60)	1.00 - 1,037.00
Current Viral Load		14,780.82 (67,501.02)	48.00 - 549,000.00
No. with Current CD4+ count < 200 (%)*	12 (15%)		
No. with Nadir CD4+ count < 200 (%)	33 (42%)		
No. with Undetectable Viral Load (%)	28 (38%)		

*Note.*  $N$  for medication adherence = 67.  $N$  for current viral load = 74. \*CD4+ counts below 200 are indicative of AIDS. Current CD4+ Count = Current CD4+ lymphocyte count (cells/ $\mu$ L); Nadir CD4+ Count = Nadir CD4+ lymphocyte count (cells/ $\mu$ L); Current Viral Load = Current Viral Load (copies/ml).

Table 5  
Correlations for Cognitive Measures ( $N = 78$ )

Variables	1	2	3	4	5	6
1. Useful Field of View	1.00					
2. Complex Reaction Time	0.51**	1.00				
3. Letter & Pattern Comparison	-0.44**	-0.44**	1.00			
4. WCST Percentage Correct	-0.32**	-0.31**	0.33**	1.00		
5. Finger Tapping Test	-0.25*	-0.13	0.33**	-0.03	1.00	
6. HVLТ	-0.47**	-0.41**	0.30**	0.40**	0.15	1.00

*Note.* WCST = Wisconsin Card Sorting Test; HVLТ = Hopkins Verbal Learning Test.

\* $p < .05$ ; \*\* $p < .01$

Table 6  
Cognitive and Functional Test Scores of the HIV+ Clusters and the HIV-Negative Reference Group (Total  $N = 162$ )

Test	Cluster						<i>p</i>
	Cluster 1		Cluster 2		HIV- Group		
	<i>(n = 32)</i>		<i>(n = 46)</i>		<i>(n = 84)</i>		
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	
UFOV® Test	1039.78	279.19	527.61	244.72	638.45	334.64	< .0001 <sup>a,b</sup>
Complex Reaction Time	2.36	0.53	1.64	0.34	1.75	0.47	< .0001 <sup>a,b</sup>
Letter & Pattern Comparison	67.81	16.83	82.83	15.04	82.75	17.28	< .0001 <sup>a,b</sup>
WCST Percent Correct	40.83	15.83	57.30	16.85	54.35	18.84	< .0001 <sup>a,b</sup>
WCST Categories Completed	1.19	1.67	3.45	2.06	3.07	2.25	< .0001 <sup>a,b</sup>
Finger Tapping Test	49.08	7.91	51.52	7.52	48.63	8.27	<i>ns</i>
HVLT	18.69	5.90	26.89	3.90	24.12	6.21	< .0001 <sup>a,b,c</sup>
TIADL	2.95	3.86	-0.95	1.90	-0.60	2.65	< .0001 <sup>a,b</sup>
OTDL	63.41	7.56	71.37	5.72	69.71	7.38	< .0001 <sup>a,b</sup>

*Note.* UFOV<sup>®</sup> Test = Useful Field of View Test; WCST = Wisconsin Card Sorting Test; HVLT = Hopkins Verbal Learning Test; TIADL = Timed Instrumental Activities of Daily Living; OTDL = Observed Tasks of Daily Living.

<sup>a</sup> Cluster 1 differs from Cluster 2 at  $p < .05$

<sup>b</sup> Cluster 1 differs from HIV- Group at  $p < .05$

<sup>c</sup> Cluster 2 differs from HIV- Group at  $p < .05$



Table 7  
Demographic and Mental and Physical Health Differences of the HIV+ Clusters and the HIV-Negative Reference Group (Total  $N = 162$ )

Variable	Cluster						
	Cluster 1		Cluster 2		HIV- Group		
	(n = 32)		(n = 46)		(n = 84)		
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>p</i> -value
Age	51.27	10.84	43.36	8.83	47.93	13.06	< .05 <sup>a</sup>
No. Over Age 50 (%)	19 (59%)		12 (26%)		41 (49%)		< .01 <sup>a, c</sup>
No. Men (%)	22 (69%)		37 (80%)		33 (39%)		< .05 <sup>b, c</sup>
No. Heterosexuals (%)	20 (63%)		19 (41%)		78 (93%)		< .05 <sup>b, c</sup>
No. Caucasians* (%)	8 (25%)		21 (46%)		29 (36%)		<i>ns</i>
No. Working (%)	2 (6%)		10 (22%)		35 (42%)		< .001 <sup>b, c, †</sup>
Income	1.56	0.84	1.87	1.61	1.98	1.53	<i>ns</i>
Education (years)	12.66	2.51	12.85	2.49	12.79	1.68	<i>ns</i>
No. Med. Conditions	1.94	1.24	1.34	1.02	1.06	0.99	< .01 <sup>a, b</sup>
No. w/ Hepatitis C (%)	14 (44%)		12 (26%)		6 (7%)		< .001 <sup>b, c, †</sup>
No. w/ Mood Prob. (%)	18 (56%)		26 (57%)		33 (39%)		<i>ns</i>
No. w/ Stroke (%)	6 (19%)		1 (2%)		5 (6%)		< .05 <sup>a, b</sup>
No. w/ Hypertension (%)	20 (63%)		18 (39%)		32 (38%)		< .05 <sup>a, b</sup>
No. w/ Diabetes (%)	4 (13%)		5 (11%)		10 (12%)		<i>ns</i>
No. Medications	5.25	3.85	4.54	3.04	2.18	2.74	< .001 <sup>b, c</sup>
POMS Total	35.59	32.94	35.39	45.05	28.26	37.89	<i>ns</i>
POMS-Positive	16.94	6.43	18.28	6.87	19.27	6.52	<i>ns</i>
POMS-Negative	52.53	30.55	53.67	40.53	47.54	34.87	<i>ns</i>
Stressful Life Events	263.56	151.71	271.59	132.10	238.51	164.16	<i>ns</i>
ASI-Alcohol Use	0.07	0.15	0.35	0.75	0.24	0.45	<i>ns</i>
ASI-Drug Use	0.03	0.06	0.03	0.08	0.02	0.04	<i>ns</i>

*Notes.* *M* = Mean; No. = number; *SD* = standard deviation; Working = currently working either part-time or full-time; For income, 1 = \$0 - \$10,000 and 8 = over \$70,000; No. Med. Conditions = total number of neuromedical conditions; Mood prob. = self-reported mood problems (depression or anxiety); POMS Total = Profile of Mood States total mood disturbance score; Stressful life events = Social Readjustment Scale score; ASI = Addiction Severity Index. \* = All others were African American except one who was Native American who was HIV-positive.

<sup>a</sup> Cluster 1 differs from Cluster 2 at  $p < .05$

<sup>b</sup> Cluster 1 differs from HIV- Group at  $p < .05$

<sup>c</sup> Cluster 2 differs from HIV- Group at  $p < .05$

<sup>†</sup>  $p < .10$  for Cluster 1 versus Cluster 2

Table 8  
Differences Between Clusters on HIV-Related Variables (Total N = 78)

Variable	Cluster 1 (n = 32)			Cluster 2 (n = 46)			p
	n (%)	M	SD	n (%)	M	SD	
Years with HIV		14.68	7.91		11.72	6.73	0.08
No. Taking ART (%)	27 (84%)			41 (91%)			0.39
Medication Adherence		2.44	3.43		3.70	4.78	0.25
Current CD4+ Count		498.50	247.20		452.37	293.00	0.47
Nadir CD4+ Count		329.72	225.33		239.28	239.54	0.10
Current Viral Load		5395.70	17159.16		21179.77		0.33
No. w/ Current CD4+ count < 200 (%)*	4 (13%)			8 (17%)	86216.81		0.40
No. with Nadir CD4+ count < 200 (%)	11 (34%)			22 (48%)			0.17
No. with Undetectable Viral Load (%)	14 (47%)			14(32%)			0.15

*Note.* N for medication adherence = 67. N for current viral load = 74. \*CD4+ counts below 200 are indicative of AIDS. Current CD4+ Count = Current CD4+ lymphocyte count (cells/ $\mu$ L); Nadir CD4+ Count = Nadir CD4+ lymphocyte count (cells/ $\mu$ L); Current Viral Load = Current Viral Load (copies/ml).

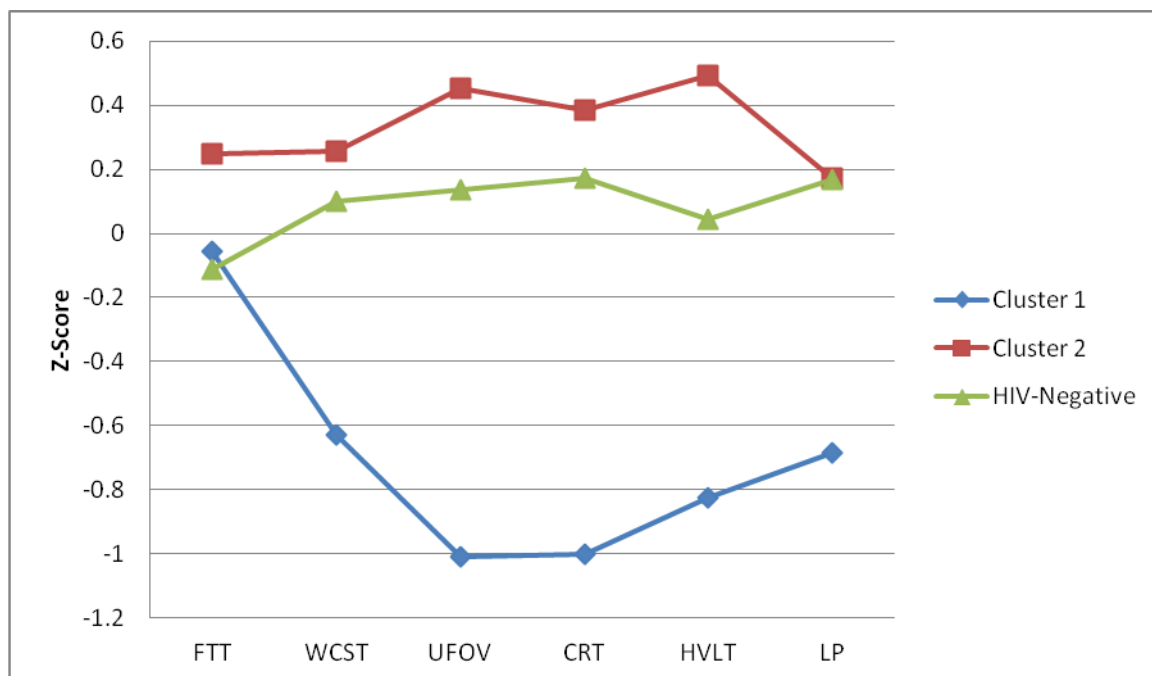


Figure 1. Z-scores for Cognitive Test Performance for Clusters 1 and 2, and the HIV-Negative Group.

*Note.* FTT = Finger Tapping Test; WCST = Wisconsin Card Sorting Test; UFOV® = Useful Field of View; CRT = Complex Reaction Time; HVL = Hopkins Verbal Learning Test; LP = Letter and Pattern Comparison. For the purpose of clarity, higher z-scores reflect higher performance for all variables.

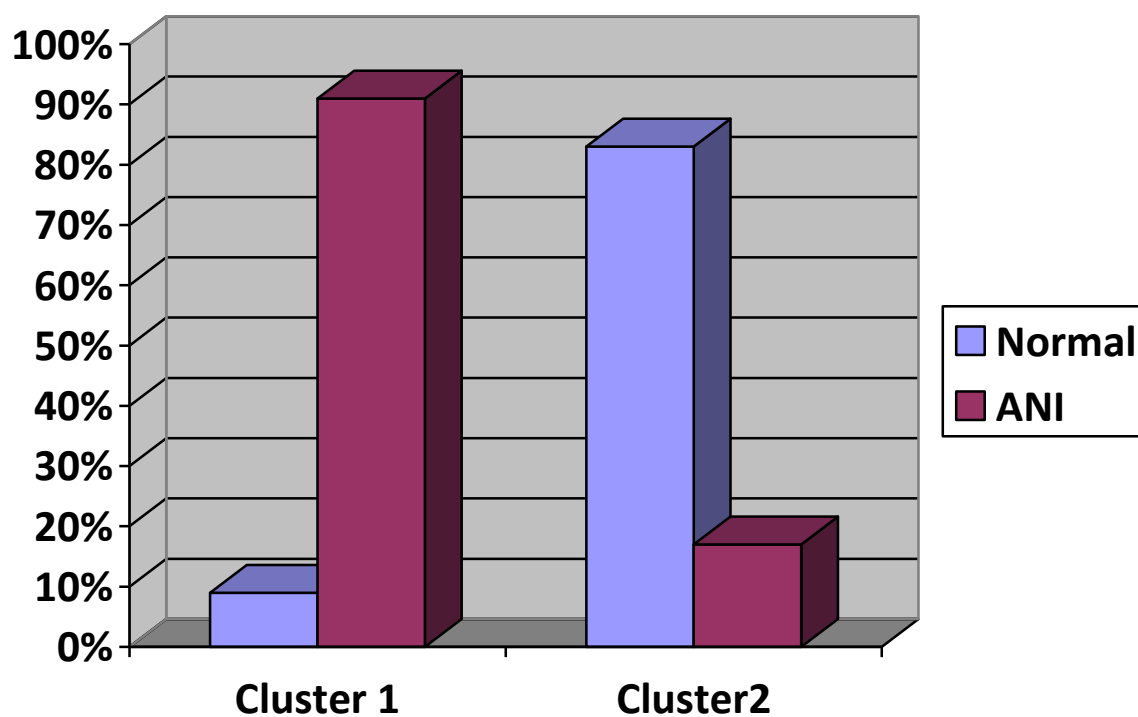


Figure 2. Percentages of HIV+ Participants with Psychometrically Defined HIV-Associated Asymptomatic Neurocognitive Impairment (ANI).

APPENDIX B  
IRB PROJECT APPROVAL FORM

Form 4: IRB Approval Form  
Identification and Certification of Research  
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The Assurance number is FWA00005960 and it expires on September 29, 2013. The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56.

Principal Investigator: FAZELI, PARIYA

Co-Investigator(s):

Protocol Number: **E110825007**

Protocol Title: *Cognitive Functioning in Adults Aging with HIV: Exploring Cognitive Subtypes*

The above project was reviewed on 9-7-11. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This project qualifies as an exemption as defined in 45CF46.101, paragraph 4.

This project received EXEMPT review.

IRB Approval Date: 9-7-11

Date IRB Approval Issued: 9-7-11



Marilyn Doss, M.A.

Vice Chair of the Institutional Review  
Board for Human Use (IRB)

Investigators please note:

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.