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# RELATIONSHIP BETWEEN IMMUNE FACTORS AND CNS PENETRATIVE EFFECTIVENESS OF HAART ON COGNITION AND NON-VERBAL PROCESSES IN AN HIV POSITIVE SAMPLE

By

Nickolas Arion Dasher, M.S.

A dissertation

submitted in partial fulfillment

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**Committee Approval**

To the Graduate Faculty:

The members of the committee appointed to examine the dissertation of Nickolas A. Dasher, M.S. find it satisfactory and recommend that it be accepted.

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RE: Your application dated 4/17/2013 regarding study number 3916: HIV Neurocognitive Dementia Screening

Dear Mr. Dasher:

Thank you for your response to requests from a prior review of your application for the new study listed above. Your study is eligible for expedited review under FDA and DHHS (OHRP) 4. Routine clinical data designation.

You are granted permission to conduct your study as most recently described effective immediately. The study is subject to continuing review on or before 4/26/2014, unless closed before that date.

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Sincerely,

Ralph Baergen, PhD, MPH, CIP
Human Subjects Chair

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Abstract

While advances in HIV-treatment have lowered the mortality of those infected exponentially, neurocognitive deficits remain prevalent due in part to medications' variability in reaching the central nervous system. Neuropsychological impairments associated with infection involve poor processing speed, cognitive flexibility, strategy use, and learning and free recall. Much of the research exploring these executive and memory deficits relied on measures mediated by verbal processes while little work has been done on nonverbal mechanisms. In addition, although mixed, previous literature is trending that medications that are better at penetrating the blood-brain barrier are more effective at mitigating the virus within the CNS and reducing neurocognitive deficits. However, much of this research has focused only on the most recent medications used versus patients' larger use history. Hence, the present study assessed the impact of medication history of CNS-penetrative effectiveness (CPE Ratio) and Nadir CD4+ count on broad cognitive abilities, nonverbal fluency, and nonverbal memory. Results indicated that patients with a history of using medications with a lower CPE demonstrated slower processing speed and produced fewer figural designs, and this relationship was mediated by producing fewer and smaller design clusters. CPE Ratio did not predict broad performance on a nonverbal memory task, however, errors were consistent with a subcortical profile. Implications of the potential clinical and empirical utility of this new ratio score are discussed.

# CHAPTER ONE

## Relationship Between Immune Factors and CNS Penetrative Effectiveness of HAART on Cognition and Non-Verbal Processes in an HIV Positive Sample

Since its discovery in 1981, it is estimated that approximately 40 million people worldwide are infected with human immunodeficiency virus (HIV), a retrovirus that undermines the body's immune system that can result in Acquired Immune Deficiency Syndrome (AIDS) (Ellis, Calero, & Stockton, 2009; Ellis, Langord, Masliah, 2007; Heaton et al., 1995). Those infected are at increased risk for opportunistic infections, cancers, and cognitive and motor impairments (Mandell, Bennett, & Dolan, 2009; Reger, Welsh, Razani, Martin, & Boone, 2002; Shiller, Foley, Burns, Sellers, & Golden, 2009; Woods, Moore, Weber, & Grant, 2009). Neuropsychological research has shown that compared to those without infection, HIV positive individuals can show greater impairments in several domains including attention, working memory, cognitive processing speed, and motor function (e.g., bradykinesia) (Heaton et al., 1995; Millikin, Trepanier, & Rourke, 2004; Reger et al., 2002; Stout et al., 1995; Woods et al., 2009; Woods et al., 2004). The amalgamation of these heterogeneous neuropsychological impairments is broadly known as HIV-Associated Dementia (HAD) (Grant & Martin, 1994; Woods et al., 2009).

The advent of highly active anti-retroviral therapy (HAART) for the treatment of HIV infection in the 1990s has resulted in a reduction in the prevalence and severity of HAD over the past three decades; however, the occurrence of cognitive and motor impairments related to HIV still remains (Ellis, Langford, & Masliah, 2007, Paul, Sacktor, Valcour, Tashima, 2008; Richardson et al., 2002). In addition, an area that has

received little attention within the neuropsychological literature is the effect that HIV has on nonverbal learning processes and nonverbal strategy use. Thus, the present study sought to elucidate HIV's impact on these processes and how it relates to the broad neuropsychological impairments associated with HIV infection. Before elaborating further on these cognitive and motor impairments, however, the general pathology of HIV infection on both the body and central nervous system will be reviewed.

## HIV Pathogenesis Primer

Over the past three decades, considerable efforts have gone into identifying the particular mechanisms that are involved in HIV pathogenesis. In general, two hypotheses that have received the most support are: 1) that HIV causes direct loss of a subgroup of immune cells known as CD4+ T-lymphocytes by infecting and killing those cells directly and 2) that HIV infection indirectly impairs cells function via an abnormal reaction to the infection by the host's immune response (Stevenson, 2003). These processes compromise the immune system via direct infection of CD4+ cells and secondary infection to macrophages, which serve many functions but are particularly crucial in eliminating cellular debris and pathogens as well as stimulate lymphocytes to respond to infectious pathogens (Gonzalez-Scarano & Martin-Garcia, 2005).

At initial infection, HIV's envelope proteins known as gp120 and gp41 interact with the host cell's chemokine receptors, CCR5 and CXCR5, to infiltrate the target cell. Once breached, the virus immediately releases two viral RNA strands, reverse transcriptase, and the replication enzymes integrase and protease into the cytoplasm and cell nucleus (Ellis, Calero, & Stockton, 2009; Gonzalez-Scarano & Martin-Garcia, 2005). Reverse transcriptase converts the single viral RNA strand to a double helix DNA strand

and integrase then cleaves a dinucleotide strand from each end of the viral DNA, which allows it to be integrated into the host cell's genome (Mandell, Bennett, & Dolan, 2009; Stevenson, 2003). Activation of the host cell induces transcription of proviral DNA into viral mRNA and this strand enters into the cytoplasm of the host cell. Once there, viral mRNA undergoes translation into long polypeptide chains, which are cleaved into smaller core proteins by protease (Mandell, Bennett, & Dolan, 2009). These smaller proteins then assemble near the body of the host cell and merge with two viral RNA strands and the replication enzymes to form a viral capsid, which is released from the host cell to infect other cells and repeat the process.

If left untreated, HIV will almost always cause progressive destruction to the infected immune system as demonstrated by the reduction in the quantity of CD4+ T-lympohcytes (Ellis, Calero, & Stockton, 2009; Mandell, Bennett, & Dolan, 2009). Once an infected individual's CD4+ cells fall to 14% or less of total T-lymphocytes or to a count of less than 200 cells/μL, the individual would be diagnosed with AIDS due to the immune system's inability to ward off opportunistic infections at such levels (Centers for Disease Control and Prevention, 1992). Luckily, with the introduction of HAART, patients who maintain strong adherence to the treatment often achieve reduction of the virus to undetectable levels and a substantial rebound to their immune system by curbing the destruction of CD4+ T-lymphocytes (Hammer et al., 2008). The use of HAART, however, does not result in complete destruction of the virus, as it will reemerge once HAART treatment has ceased.

HIV is an insidious and destructive pathogen on the body's immune system. The immune system is not the only victim of this virus, however, as the virus also penetrates

the central nervous system (CNS) as well and has the capacity to induce several neurological and psychological impairments such as cognitive disorders, aseptic meningitis, and sensory neuropathies (McArther, Brew, & Nath, 2005; Miller & Cummings, 2007). A review of the neuropathogenesis of HIV in the central nervous system is discussed next.

## HIV Infection and the Central Nervous System

HIV infection invades the CNS shortly after initial infection by crossing the blood-brain barrier (BBB) as passengers in infected monocytes (i.e., Trojan Horse method) that circulate in the blood (Grant & Martin, 1994). Once established in the CNS, infection can disrupt neural functioning through two primary mechanisms: viral factors and host factors (Gonzalez-Scarano & Martin-Garcia, 2005; Kumar et al., 2003; McArthur, Brew, & Nath, 2005). Viral factors are derived from the virus itself and host factors derive indirectly from the subsequent infection and can cause damage to uninfected cells and neurons (Ellis, Calero, & Stockton, 2009; Gonzalez-Scarano & Martin-Garcia, 2005). As discussed below, both of these factors converge to cause severe damage to the intricate network of neural connectivity that can eventually lead to HAD.

### Viral Factors

HIV does not infect neurons directly, but does infect perivascular macrophages, astrocytes (glial cells that provide nutritive support and repair for neurons), and microglia (primary immune defense of the central nervous system) in the brain (Gonzalez-Scarano & Martin-Garcia, 2005; Schoenberg & Scott, 2011). These infected cells are responsible for producing not only more HIV but also a variety of proteins that have been shown to be toxic to neuronal cells and interfere with CNS function (Stevenson, 2003). One of

most toxic of these proteins is called gp120, which as mentioned earlier is the virus's protein envelope that binds to the host cell's receptors to gain entry. This protein interacts with the host cell's cellular response to alter glutamate signaling and it is hypothesized that gp120 can cause neural degeneration via glutamate-mediated excitotoxicity inducing neural apoptosis (Ellis, Calero, & Stockton, 2009; Thomas, Mayer, & Sperber, 2009). A second highly toxic protein produced by the infected cells is transcriptional transactivator (Tat). Tat derived from HIV infected cells has been shown to cause dendritic atrophy, cellular necrosis, mitochondrial dysfunction, oxidative stress, and neurotoxicity, which can all impair neural function and cellular communication (Ellis, Calero, & Stockin, 2009; Gonzalez-Scarano & Martin-Garcia, 2005; King et al., 2006; Pocemich et al., 2005). So despite the lack of direct neural infection by HIV, the toxic proteins produced in the brain via infected cells are believed to be the direct proponents of neural degeneration.

**Host Factors**

In addition to the more direct damage induced by the production of neurotoxic cell proteins, HIV can also impair the CNS via its secondary effects on the immune system. The presence of HIV infection in the brain has been associated with irregular immune activation that can result in neural damage (Gonzalez-Scarano & Martin-Garcia, 2005). In particular, both infected and immune-activated macrophages and microglia in the brain can secrete pro-inflammatory cytokines known as tumour necrosis factor (TNF) and interleukin-1β (IL-1β), which can cause severe cranial swelling, impairing neural transmission, and potentially induce neural death (Brabers & Nottet, 2006; Gonzalez-Scarano & Martin-Garcia, 2005). In addition, certain infected macrophages can also

increase the permeability of the BBB promoting further invasion of HIV-infected monocytes into the brain (Brabers & Nottet, 2006) Lastly, infected macrophages and astrocytes have been shown to inhibit vital functions of astrocytes in maintaining neural health, such as the uptake of the excitatory neurotransmitter (glutamate) thereby increasing the likelihood of neural excitotoxicity (Gonzalez-Scarano & Martin-Garcia, 2005).

While these are just some of the processes hypothesized to be involved with the direct and indirect neural damage associated with HIV infection, more research is needed to further elucidate the causal mechanisms. What has been broadly demonstrated, however, is the complexity of HIV infection and the multiple modalities available for the virus to impact neural function leading to the cognitive and motor impairments seen in many afflicted individuals. In addition, the available neuropsychological and imaging research indicates that HIV does not appear to impair all affected neural systems equally. Therefore, a review of the cortical and subcortical systems that appear to be primarily impacted by HIV infection is discussed below.

## Neuroanatomy of HIV Infection

Unlike some neurodegenerative disorders where the neuropathology of the illness has a more definitive pathological trajectory (i.e., Huntington's Disease), once HIV crosses the BBB, the virus can inflict synaptodendritic injuries to multiple cortical and subcortical regions indiscriminately. There is available evidence implicating HIV's direct involvement in the degeneration of temporal, occipital, limbic, and parietal regions (Ances et al., 2009; Thompson et al., 2005). Despite this lack of general predictability in the path of HIV associated neural damage, there is significant evidence that HIV has a

particular affinity for the basal ganglia, frontal lobes, and the subcortical white matter tracts that connect them (Aylward et al., 1995). Thus, a review of the function of these systems is discussed next as well as the consequences of HIV infection to these regions.

**Basal Ganglia Function and HIV Infection**

The basal ganglia are a collection of gray matter nuclei residing deep within the white matter of the brain and are comprised of four primary structures: the striatum, the globus pallidus, the substantia nigra, and the subthalamic nucleus (STN) (Table 1) (Rubin & Safdieh, 2007). The striatum can be further divided into the dorsal striatum (comprised of caudate nucleus and putamen) and the ventral striatum (comprised of the nucleus accumbens, septum, and olfactory tubercle) (Rubin & Safdeih, 2007). The globus pallidus is further divided into its external (GPe) and internal segment (GPi) as well as ventral pallidum. Lastly, the substantia nigra can be divided into the pars compacta (SNc) and pars reticulata (SNr) (Rubin & Safdieh, 2007). Each of these systems has distinct afferent and efferent connections that relay information from the cortex and the thalamus.

In general, the basal ganglia function in two primary ways to regulate cortical activity: direct and indirect neural circuits. The direct pathway serves to increase cortical activity while the indirect pathway inhibits cortical activity (Schoenberg & Scott, 2011). In other words, direct excitatory signals project from the cortex to the striatum and discharges its firing of inhibiting signals to the thalamus (via the GPi), which then releases the desired behavior (e.g., move the right index finger). Indirect pathways cause the STN to increase the tonic inhibitory activity of the Gpi, which suppresses closely related, but unwanted behavior (move the right index finger but not the adjacent fingers) (Kolb & Whishaw, 1996; Koziol & Budding, 2010). Thus, the basal ganglia is involved

extensively in the coordination of desired, executed behavior and inhibition of irrelevant behaviors.

While traditionally relegated to strictly motor processes, the basal ganglia's excitatory and inhibitory "gating" system for cortical activity has implications for cognitive processes as well. In addition to the motor pathway, the basal ganglia also relays parallel but separate information via channels from several frontal and prefrontal cortical regions (Table 2). These four remaining circuits are the 1) dorsolateral prefrontal pathway, 2) lateral orbitofrontal pathway, 3) oculomotor pathway, and 4) limbic pathway (anterior cingulate, hippocampus, and amygdala) (Schoenberg & Scott, 2011). As is elaborated below, the cortical origins of these circuits are hypothesized to be extensively involved with processing higher-order cognitions and emotions, particularly the dorsolateral, lateral orbitofrontal, and limbic pathways and the basal ganglia is involved in mediating some of these functions (Miller & Cummings, 2007). For instance, Chang et al. (2007) linked specific regions of the basal ganglia to the encoding, maintenance, and response phase of a working memory task. There is also evidence that the basal ganglia is involved in contextual, instrumental learning and categorization (Seger & Cincotta, 2006). Thus, given the basal ganglia's "gating" processes essentially modulate "when" certain cortical regions should become active, it has the capacity to exert a substantial influence on not only motor functions but also modulate and coordinate activation of higher-order cognitive processes as well (i.e., planning and strategy formation).

With regard to HIV infection, research has shown that production of HIV is most prevalent within the basal ganglia and that this either directly or indirectly impairs its structure and functionality (McArthur, Brew, & Nath, 2005). For instance, Ances and

colleages found that neurosymptomatic HIV-positive individuals demonstrated significant reductions in caudate volume and blood flow when compared to controls, and that greater decrease in flow and volume was associated with greater cognitive impairment (Ances et al., 2006). Stout et al. (1998) conducted a longitudinal study to measure progressive cerebral atrophy in HIV-positive individuals and found significant atrophy of the caudate nucleus, which was related to the rate of decline in CD4+ T-lymphocyte levels. Additional research has found similar results in regard to reduced subcortical blood flow and volume of the basal ganglia associated with HIV infection, and HAD in particular (Ances et al., 2009; Aylward et al., 1993). Given the extensive cortical connections that relay through the basal ganglia, particularly the afferent connections received by the caudate nucleus from multiple cognitive and motor processing regions, it can be seen how HIV-associated damage to this subcortical region can lead to several neurocognitive difficulties. Before elaborating on these specific types of impairments, however, it is important to also review other regions often affected by HIV infection.

**Frontal Cortex Functions and HIV Infection**

The frontal cortex of the human brain represents 40% of the neocortex and as mentioned above is hypothesized to be involved in higher-order processes and motor functions (Miller & Cummings, 2007). It is made up several functionally distinct regions: 1) Motor, 2) Premotor, 3) Dorsolateral prefrontal cortex (dlPFC), 4) Orbitofrontal cortex (OFC), and 5) Anterior Cingulate Gyrus (ACC) (Kolb & Whishaw, 1996; Schoenberg & Scott, 2011). Figure 1 provides an overview of these structures.

Projections from the motor cortex (BA 4) connect to the basal ganglia and extend to the thalamus. This route it is hypothesized to be the primary processor of fine motor coordination, correction, and motor planning (Kolb & Whishaw, 1996). The premotor cortex (BA 6 & 8) projects axons to the primary motor cortex and is hypothesized to be involved in motor planning behavior (Kolb & Whishaw, 1996). The dlPFC (BA 9 & 46) is believed to be involved in what are called "traditional" executive functions including reasoning, problem solving, sequencing, working memory, and maintenance of behaviors (i.e., self monitoring and sustained attention) (Schoenberg & Scott, 2011). The OFC (BA 10, 11, & 47) is hypothesized to be the site of neural circuitry associated with behavioral inhibition, emotional regulation, forming emotional responses, and reinforced associations towards stimuli. Normal OFC function is broken down into four parts: it detects the salience of both tangible and cognitive reinforcers, detects changes in the value of those reinforcers, rapidly reprograms the association between a stimulus and its value, and lastly facilitates rapid shifts in behavior as a result of altered reward contingencies (Kringelbach & Rolls, 2004; Rule, Shimamura, & Knight, 2002). Lastly, the ACC (BA 24, 32, & 33) lies on the medial surface of the cingulate gyrus and is hypothesized to also be associated with sustained attention and behavioral inhibition as well as initiation of behavior, motivation, empathy, error detection, and reward-based learning (Allman et al., 2001; Miller & Cummings, 2007; Schoenberg & Scott, 2011). Taken together, each of these regions function through an integrated network to process higher-order cognitive abilities and motor functions.

In regard to HIV infection, reductions in the cortical thickness and atrophy have been found in the frontal cortex. Using magnetic resonance imaging (MRI), Thompson et

al. (2005) found that the primary motor and premotor cortices were up to 15% thinner in patients with AIDS relative to aged-matched, healthy controls. There is also evidence that HIV is associated with decreased regional cerebral blood flow (rCBF) in the lateral frontal cortices in the early stages of infection (Chang et al., 2000). In addition, there is evidence of neuronal loss due to HIV infection, particularly in the prefrontal cortices (Everall, Luther, & Lantos, 1991; Ketzler, Weis, Haug, & Budka, 1990). Hence, there is evidence to indicate that HIV can induce synaptodendritic injury and neuronal loss to those regions of the frontal cortex predominately responsible for motor control, precision, and higher-order executive abilities.

Following this review of the neuropathogenesis of HIV infection and the subsequent damage that the virus can have on the CNS, it is important to also outline the efficacy of HAART, particularly its impact on the brain. As noted above, since the advent of HAART, HIV has become a manageable and treatable affliction and has substantially reduced the prevalence and severity of HAD. Over the past two decades since these treatments became available, however, there is increasing evidence indicating that while medications are effective at reducing viral loads in the broader immune system, the CNS is not as easily treated.

## HAART and the Central Nervous System

The blood brain barrier (BBB) is a structure of the vasculature that restricts passage of most toxins from the blood into the CNS. It is composed of a tissue that does not exist in the broader circulatory system, consisting of tight junctions throughout all surrounding capillaries (Cysique & Brew, 2009). The role of these tighter junctions is to prevent microscopic bacteria and large molecules from gaining access to the brain and

cerebral spinal fluid (CSF) in order to protect it from infection, while still allowing smaller molecules to enter (i.e., oxygen). HIV manages to bypass this barrier by "sneaking" in on infected monocytes, thus enabling direct infections of macrophages and glial cells within the brain.

The difficulty with treating HIV that has managed to cross the BBB lies in the fact that many of the antiretroviral agents are hampered by the BBB and are therefore unable to mitigate effectively the viral load in the CNS (Cysique & Brew, 2009). Although some agents developed over the years have demonstrated some mobility across the BBB, the reported efficacy of these drugs have been mixed. CSF measurements used to determine the concentrations of the active agents are only a surrogate for the concentration in the brain so estimates may be flawed (Valcour, Sithinamsuwan, Letendre, & Ances, 2011). In addition, some have also argued that once the antiretroviral agent is able to cross the BBB, it may be promptly pumped back out into circulation by efflux transporters (Ellis et al., 2009). Thus, the restricted mobility of HAART to cross the BBB allows for continued viral replication, despite broader peripheral suppression, and some have reported this creates a sort of "viral sanctuary" that perpetuates virological resistance and the manifestation of HAD (Ellis et al., 2009; Valcour et al., 2011; Varatharajan & Thomas, 2009).

Recently, a practical method of quantifying the penetrative effectiveness of HAART regiments was developed, which classified drugs as either low, medium, or high in regard to their CNS penetrative effectiveness (CPE) (Letendre et al., 2008). This form of classification has demonstrated validity in that lower CPE drugs appear to allow greater HIV replication in the CNS (indicated by higher CSF viral loads) when compared

to higher CPE drugs (Letendre et al., 2008). Despite these promising results, however, more research is needed to determine the effectiveness of higher CPE in mitigating neurocognitive deficits and how effective these higher CPE drugs are at allowing the brain to repair damage induced by HIV infection of the CNS. At present, the available research on the impact of lower CNS-penetrative treatment on neurocognitive functioning remains somewhat mixed (Cysique & Brew, 2009; Ellis et al., 2014; Letendre et al., 2008) but broadly trends toward the conclusion that use of high CNS-penetrative medications is associated with better neuropsychological performance.

Furthermore, there have been reports that HAART itself may have detrimental effects on the brain and subsequent cognition. In recent studies, the use of HAART has been associated with persistent inflammation of the hippocampus, mitochondrial toxicity, and CNS hyperstimulation (Carr, 2003; Squire, Stark, & Clark, 2004). A longitudinal study by Cardenas and colleagues (2009) examined structural changes in the brain in HIV-positive individuals over a period of two years and found that these participants demonstrated significant losses in white matter volume compared to HIV-negative controls, and this was not mediated by degree of viral suppression. So despite the broader improvements in immune strength with the use of HAART, HIV can still have detrimental effects on the brain even with treatment. In fact, recent meta-analysis on the effectiveness of HAART on improving cognition found only a modest improvement with treatment: 85% to 92% of HIV patients treated with HAART still performed at levels comparable to non-medicated HIV patients, and only minor improvements were found in attention, executive functions, motor speed, and verbal memory (Al-Khindi, Zakzanis, & van Gorp, 2011). Therefore, although significant advances in the fight against HIV/AIDS

have lead to immunological enhancing treatments, the advances have had only minor success at reducing HIV-associated neurotoxic effects.

It is important now to turn to the particular neurobehavioral detriments associated with HAD. As mentioned previously, HIV in the CNS does not necessarily follow a predictable pattern of neurological infection and neuropsychological sequelae, as some common neurodegenerative diseases do such as Huntington's. Some have argued that HIV primarily infects the subcortical grey matter (i.e., basal ganglia) initially, and that the cortex becomes infected only in the later stages of the disease, but support for that hypothesis is mixed (Dennis, Houf, Han, & Schmitt, 2011; Moore et al., 2006; Thompson et al., 2005). The research cited thus far, however, has demonstrated that HIV has a propensity towards infecting the cells of the basal ganglia, frontal cortices, and white matter tracts. These regions, collectively, form the frontostriatal region. Impairments in this neurological region can have substantial adverse effects on one's cognitive and motor abilities.

## HIV Infection and Neuropsychological Function

Early observations of the neuropsychological profile of HAD demonstrated that it was remarkably similar to that of other frontosubcortical dementias (e.g., Parkinson's disease) and based on this conceptual framework there has been a burgeoning amount of research to support this dementia model (Woods et al., 2009). For instance, Sadek and colleages compared Huntington's patients (HD; subcortical pathology), Alzheimer's patients (AD; cortical pathology), and HIV patients in regard to their performance on retrospective recall of information from previous decades (Sadek et al., 2004). They found significant differences in the pattern of results of the AD patients compared to HIV

and HD patients. In all three groups, free recall of verbal material was impaired but when presented with recognition cues, the performance of the HD and HIV groups improved significantly whereas the AD group did not benefit from cueing. This finding indicates that AD is marked by a distinct encoding deficit, HIV dementia resembles subcortical dementias (such as HD), which are marked by retrieval deficits. Therefore, it is important to outline the distinct neuropsychological impairments associated with the subcortical dementia known as HAD.

**Motor Skills and Cognitive Processing Speed**

Empirical research has demonstrated significant impairments in motor skills, including psychomotor processing and motor dexterity, in HIV infected individuals that is believed to be primarily the result of reduced dopaminergic activity in the basal ganglia (Lezak et al., 2012; Saint-Cyr, 2003). A meta-analysis found that motor function and processing speed (in addition to executive functions) are the most impaired by HIV infection (Reger et al., 2002). Overall, the more severe forms of motor impairment such as chorea, myoclonus, dyskineasia, and dystonia are rare, manifesting during the later stages of HIV infection and with co-occurring opportunistic infection (Dennis et al., 2011). What is more common and seen as an early symptom of neurological impairment is bradykinesia (i.e., slowed movement) (Woods et al., 2009). Motor slowing due to HIV infection has been seen via impaired gait velocity, slow finger tapping speed, and impaired manual dexterity (Carey et al., 2004; Heaton et al., 1995; Robertson et al., 2006). Although there is available evidence indicating that motor speed can improve with the initiation of HAART therapy, impairments in this domain continues to be a primary

complaint among HIV infected individuals both on and off treatment (Grant & Adams, 2009; Saktor et al., 2000).

Bradyphrenia (i.e., slowed information processing speed) is also considered an early symptom of neurological impairment (Woods et al., 2009). Although there is some dispute that this impairment may be exacerbated by other impairments such as poor attention, motor slowing, and co-morbid substance abuse, slowed information processing speed associated with HIV infection has been demonstrated via impairment on tasks of timed sequencing (i.e., Trails A), WAIS Digit-Symbol, and Color-Word Interference (i.e., Stroop) (Reger et al., 2006; Sassoon et al., 2007; Woods et al., 2009). Therefore, given bradykinesia and bradyphrenia have also been demonstrated in other neurodegenerative diseases such as Parkinson's and Huntington's disease, this evidence provides further support for HAD as a fronto-subcortical dementia via degradation of the basal ganglia and its frontostriatal circuits (Grant & Adams, 2009).

**Learning and Recall**

Memory and learning deficits are also commonly seen in HIV infected individuals (Dennis et al., 2011). It is estimated that episodic memory impairments are seen in roughly 40%-60% of infected individuals in both free recall of verbal (i.e., list learning and story passages) and visual tasks (i.e., Rey-Osterrieth Complex Figure; RCFT) (Heaton et al., 1995; Reger et al., 2002). The general level of impairment in this domain ranges from the mild-moderate range but as the disease progresses to advanced HIV or AIDS, impairments can become moderate to severe (Reger et al., 2002).

As mentioned earlier, the general pattern of memory and learning deficits seen in HIV individuals, however, is not typical of that seen in neurological disease characterized

by medial-temporal pathology, such as Alzheimer's (Grant & Adams, 2009). The pattern of episodic memory impairments associated with HIV is most consistent with a poor encoding and retrieval profile but do not typically exhibit signs of rapid forgetting as exhibited by relatively better recall performance via recognition or cueing (Delis et al., 1995; Sadek et al., 2004; Woods et al., 2009). Although there has been some evidence that a small proportion of HIV infected individuals have displayed signs of rapid forgetting, this is more often seen in later stages of HIV infection when many argue that the infection has spread from the basal ganglia to the cortical regions (i.e., temporal) responsible for memory consolidation (Reger et al., 2002). In addition, evidence of rapid forgetting during the early to middle stages of the disease is often attributed to shallow encoding as indicated by elevated recency effects and poor encoding strategies (Gongvatana et al., 2007; Scott et al., 2006). Evidence thus far is consistent with the hypothesis that HAD memory impairments generally stem from inefficient encoding and retrieval strategies that result in a low learning slope but not rapid decay of memory (Woods et al., 2009).

**Attention and Working Memory**

Attention, particularly simple attention appears relatively preserved in early stages, but deficits seem to appear in the later stages of the disease (Dennis et al., 2011; Reger et al., 2002). In particular, HIV infected patients have demonstrated significant impairment in more complex tasks that require divided attention, selective attention, and response inhibition in these later stages (Hinkin, Castellon, & Hardy, 2000; Hinkin et al., 1999; Sorenson, Martin, & Robertson, 1994). While there may be mild deficits in

automatic attentional processes, the evidence indicates these become amplified when demands on controlled processes are increased.

Impaired divided and controlled attention tasks may also contribute to the significant impairments that HIV infected individuals have demonstrated on both visual and verbal working memory (WM) tasks, but predominantly only in the later stages of the disease (Grassi et al., 1999; Hinkin et al., 2002; Weber et al., 2010). Working memory has been proposed as a tripartite model composed of two slave systems (phonological loop and visuo-spatial sketchpad) that are coordinated by a master system known as the central executive (Baddely & Hitch, 1974). Most have argued that the central executive acts as the mental faculty that maintains information in a conscious, active state in order to manipulate information for present use (Baddely, 2003; Miyake & Shah, 1999). So in this regard, WM is less of a memory system and more about the use of attention to maintain information in an active, retrievable state while suppressing intrusive or repetitive information (Hofmann et al., 2008). HIV-related impairments in working memory tasks may result from an impaired ability to sustain controlled attention on a mental task while simultaneously preventing interference from intrusive material. Indeed, this WM hypothesis is consistent with the fronto-subcortical hypothesis of HAD, particularly regarding the degradation of the frontostriatal white matter tracts between the basal ganglia and dorsolateral prefrontal cortex (dlPFC), as evidence exists that implicates the dlPFC as the neural basis of the central executive (Hunt & Ellis, 2003).

**Executive Functioning**

Executive functions are a heterogeneous construct but generally include the abilities to plan, organize, strategize, solve complex problems, formulate concepts and

abstract ideas, and flexibly shift tasks appropriately (Dennis et al., 2011; Mega & Cummings, 1994). As mentioned above, the available evidence indicates that executive functions rely predominately on the prefrontal cortex, particularly the dorsolateral PFC, as well as the basal ganglia and posterior parietal cortex (Miller & Cummings, 2007; Stuss & Levine, 2002). The most common deficits in executive functioning seen in HIV-infected individuals have been found in the domains of abstract concept formation, novel problem solving, cognitive flexibility, and verbal fluency (Reger et al., 2002; Woods et al., 1999). In fact, recent research has linked impaired executive functioning as a significant component to other neurocognitive impairments in HIV patients, indicating that executive functioning deficits are central to the profile of HAD (Dawes et al., 2008). For instance, as mentioned earlier, the episodic memory impairments seen in HIV patients is arguably due to shallow and inefficient use of encoding and retrieval strategies (i.e., executive processes), rather then poor retention of information (Delis et al., 1995). Thus, executive functioning deficits are a common symptom of HAD and linked to deficits in other, non-executive processes as well (i.e., memory). Given that similar executive dysfunctions have been demonstrated in other basal ganglia and frontostriatal diseases or impairments, this evidence of executive dysfunction again supports the hypothesis that HAD is primarily a fronto-subcortical dementia (Grant & Adams, 2009; Lezak et al., 2012).

**Prospective Memory**

Prospective memory is generally defined as one's ability to successfully execute a future intention (i.e., remember to remember) (Wood et al., 2009). Prospective memory differs from the classic model of memory (i.e., Atkinson & Schifrin, 1967) in that it

involves a level of continual maintenance, retrieval, and execution of a future intention rather than retrieving information that has been stored in long-term memory (McDaniel & Einstein, 2000). While certain demands are placed on retrospective memory for prospective memory to function properly (i.e., recalling the intended action), it is arguably linked to executive functioning. Evidence shows that tasks that rely on prospective memory show increased activation in the prefrontal cortex versus the medial temporal lobe (Kolb & Whishaw, 1996; Simons et al., 2006).

Empirical evidence has found that that persons infected with HIV demonstrate significant impairment on performance-based tests of prospective memory compared to non-infected controls, and prospective memory failures have been documented as a frequent complaint among the infected (Martin et al., 2007; Woods et al., 2007). Linked to this impairment is an additional deficit in what cognitive psychologists call "meta-memory." Meta-memory refers to the ability to accurately reflect upon the integrity of one's own thoughts, memories, and knowledge and is also highly linked with the prefrontal cortex (Metcalfe & Shimamura, 1994; Shimamura, 2000). HIV infected individuals have demonstrated impaired insight into the integrity of their memory. Additionally, different problem areas have been associated with different subjective complaints. Specifically, those who exaggerate memory problems tend to suffer from depression while those who under-report tend to exhibit greater executive impairment (Rourke, Halman, & Bassel, 1999).

**Visuoperception and Spatial Cognition**

The last cognitive domain of HIV-related neurocognitive impairment is that involving visual perception and spatial cognition. Overall, evidence of impairment in this

domain is mixed. There is a general consensus in the literature thus far that during the early stages of HIV-related neurocognitive impairment, visuospatial ability is relatively spared but deficits can emerge with disease progression (Heaton et al., 1995; Reger et al., 2002). These deficits tend to be more subtle in nature but there is some evidence to implicate impairment in perceptual span, mental rotation tasks, and visuoconstructional tasks (Hardy et al., 2004; Olesen et al., 2007; Poutianinen et al., 1988). Indeed, neuroimaging evidence indicates HIV can result in cortical thinning of the parietal lobe, which may increase the likelihood of constructional apraxia and spatial orientation deficits (Lezak et al., 2012; Thompson et al., 2005). The difficulty in attributing these impairments to spatial cognitive dysfunction, however, is that other cognitive domain impairments more common to HAD (i.e., working memory and attention) may account for visuospatial difficulties (Woods et al., 2009). For now it appears that if visuospatial deficits are uniquely present due to HIV infection, they are subtle, but more research is needed.

**Summary of HAD Profile**

HIV can cause a variety of neurobehavioral impairments that are generally in accordance with the fronto-subcortical profiles typical of neuropathologies that affect the frontostriatal system. Early in the disease course, subtle deficits in executive abilities, information processing speed, and motor skills are the most prevalent, followed by subsequent complex attention, greater executive dysfunction, and memory retrieval impairments as the disease progresses (Reger et al., 2002).

## Direction of Research

Strategy use is a multi-faceted executive function that can impact performance on a variety of different tasks and has been largely linked to frontal-lobe processes. For instance, individuals who have suffered severe frontal damage can exhibit disorganized behaviors, poor memory, and problem solving deficits, which have been shown to stem from poor use of organizational and retrieval strategies (Godefroy, 2003). Given HIV's affinity for infecting the frontostriatal network, investigating the impact that HIV has on strategy use has received growing attention, particularly in the domain of verbal fluency.

Verbal fluency tasks require individuals to say as many different words that belong to either a particular category (category fluency) or start with a particular phoneme (letter fluency) in a limited time span. This ability is largely viewed as an executive function because adequate performance requires fluidity of thought and an organized approach to producing answers from one's lexical memory. Within the HIV-literature, several authors have found that those with HIV produce significantly fewer words than healthy controls, particularly when shifting between different clusters of subcategories within the task (i.e., shifting between nautical birds and exotic birds during the Animal Category) (Iudicello et al., 2008; Millikin et al., 2004; Woods et al., 2009). Thus, these verbal fluency deficits in HIV+ patients appear to be due to executive deficits in set shifting, which is largely consistent with frontostriatal pathology. Consistent with these findings, imaging research has demonstrated that fluency performance with HIV patients can be predicted by degree of atrophy of the basal ganglia (Thames et al., 2012).

Despite the extensive available evidence on verbal fluency deficits associated with HIV, an area that has received little attention is the impact of HIV on nonverbal

fluency task performance. Like verbal fluency, nonverbal design or figural fluency is also an executive ability but one that requires participants to produce as many different drawn, abstract patterns/designs in a limited time span instead of words recalled from semantic memory. Although figural fluency was originally created to assess for right-hemispheric integrity following injury, research has indicated that performance on figural fluency tasks may not be lateralized (Baldo et al., 2001; Tucha, Smelly, & Lange, 1999). At present, the only available study that has examined the relationship between HIV and figural fluency performance is by Basso and Bornstein (2003) who found that the HIV+ group produced fewer designs than those without infection, but had not examined the mechanisms involved in the reduced performance (e.g., set-shifting and/or poor strategic clustering).

The present study sought to fill this empirical void by assessing the executive/cognitive components that drive design fluency performance in adults with HIV. Though sparse, empirical literature on clinical populations with similar afflictions known to undermine frontostriatal functioning implies strategic clustering is a primary component of poor performance. In nonverbal fluency tasks, strategic clustering is multi-factorial. The first component involves identifying the type of strategy to initiate, which include the graduate addition or subtraction of lines (i.e., quantitative) or a rotational strategy. Once this strategy has been exhausted, the second component involves the participant switching to a new strategy while simultaneously monitoring his or her performance as to prevent repetition of previously used designs.

Tucha et al. (2005) compared clustering and switching ability on verbal and figural fluency tasks with adults diagnosed with attention deficit hyperactivity disorder

(ADHD) and found those with ADHD produced significantly fewer figural designs, compared to adults without ADHD, driven by poor strategic clustering. In another study, set shifting impairments were also observed in patients with Parkinson's disease (Saint-Cyr, 2003). Given the evidence that strategic clustering and switching is impaired in patients with compromised frontostriatal systems, the current study hypothesized that switching will be a significant component of reduced performance on nonverbal fluency tasks among patients with HIV.

In order to assess the impact of infection on nonverbal fluency performance, these outcomes were regressed on their medication history, particularly the penetrative effectiveness of HAART. As indicated earlier, one problem with HAART is its limited mobility in passing through the BBB, however, certain agents have been shown to be more effective at reaching the CNS and poorer penetration has been associated with higher CSF viral loads (Letendre et al., 2008). In turn, recent longitudinal evidence indicates that patients treated with a HAART regiment of higher CPE scores are at a lower risk for clinical worsening of cognitive symptoms (Vassallo et al., 2014). Hence, the present study continued this approach through the use of a CPE ratio score as a predictor of nonverbal fluency performance. A description of the calculation of this ratio score is in Chapter 2.

In line with this penetrative index score, as previously discussed, the broader cognitive domains of executive/inhibition, attentional processes, and cognitive processing speed all appear to be particularly sensitive to the detrimental effects of HIV infection on the central nervous system. While there is empirical evidence of the typical sequela of cognitive deficits associated with progressive infection (Reger et al., 2002), little is

known about what domains are most sensitive to the effects of HIV-infection in those individuals with a varied history of CNS penetrative HAART. Therefore, the present study examined the relationship between participants' CPE ratio score and performance on composite scores of processing speed, executive/inhibition, and attention.

The last domain that was explored was examining learning acquisition performance on a nonverbal procedural memory tasks in HIV+ individuals. As expressed earlier, the "subcortical" dementia profile associated with HIV is characterized by slow learning, ineffective use of encoding or retrieval strategies, and improved recall performance on recognition trials (Woods et al., 2009). A substantial amount of research demonstrating this pattern, however, comes from neuropsychological tests of verbal memory leaving a dearth of empirical literature exploring if the same pattern emerges on a non-verbal/visuospatial memory task.

Theorists have argued that individuals can use two organizational mechanisms to encode and subsequently retrieve verbal information: primary organization (serial-order clustering) and secondary organization (semantic or subjective clustering) (Stricker, Brown, Wixted, Baldo, & Delis, 2002). The use of secondary organization strategies on verbal tasks require retrieval of temporally stored information that enables one to organize the material based on common or generated associations and has been shown to be a superior strategy over primary organization in aiding memory (Hunt & Ellis, 2003; Stricker et al., 2002). The reliance on primary organizational strategies tends to produce a slow learning slope, poor recall, and increased primary or recency effects. Given that this is a common cognitive phenomenon with HIV+ populations on verbal memory tasks, it may be that these individuals are only using primary organization strategies due to

impaired rule guided lexical and semantic search strategies (i.e., lack of secondary organizational strategies) (Gongvatana et al., 2007; Woods et al., 2004).

In regard to nonverbal memory, studies conducted thus far have been limited strictly to recall and recognition performance of visual stimuli but have not examined the specific roles of nonverbal encoding, recall, error types, and learning rate acquisition. For instance, Odiase, Ogunrin, & Ogunniyi (2007) found significant visual memory deficits in symptomatic HIV patients compared to asymptomatic patients, but stopped short of examining the encoding or retrieval components that may have impaired performance. In addition, Morgan et al. (2009) found that HIV+ patients demonstrated impaired source memory for visual/non-verbal information but not for the visual item itself. In other words, there was no significant difference in recall performance of the specific item to be remembered between the HIV+ and healthy control groups, but those with infection showed a significant deficit in remembering where they learned of the material. Given source monitoring of memories is particularly attributed to frontal processes (Johnson, Kounios, & Nolde, 1997), this supports the frontostriatal pathology hypothesis of HIV but it does not provide insight into the specific learning characteristics and strategies involved while encoding non-verbal material.

Thus, while empirical evidence does indicate that visual memory deficits exist within HAD, it is unknown as to whether this "sub-cortical" pattern of poor encoding, poor free retrieval, error types, and slow learning acquisition found with verbal memory will translate to a nonverbal, serial memory task as well. For example, verbal memory is enhanced by secondary strategies that organize material in ways salient to the individual and facilitate recall. Nonverbal/visual organizational strategies may operate differently by

relying on arbitrary patterns or pieces of visual information and "chunking" them together based on conceptual or subjective clusters. In other words, lexical-semantically based secondary organization strategies are not as readily available to nonverbal/visual tasks. Indeed, there is evidence from imaging research to support different neural networks involved in verbal versus nonverbal encoding strategies. Examination of individual differences in encoding strategies found that those who self-reported using verbal elaboration strategies showed increased left middle temporal (associated with semantic processing) and left inferior prefrontal activity while in contrast, self-reported use of visual inspection strategies was associated with left striatal (associated with object processing) and right inferior prefrontal (associated with encoding and retrieval of visual stimulation) activity (Kirchhoff, 2009). Thus, neuroimaging evidence supports a theory that not all forms of encoding strategies rely on one central processor. Therefore, the present study utilized an experimental nonverbal procedural memory measure known as the Northwest Trail Learning Test (NWTLT; Legaretta, 2012), which is a nonverbal analog to verbal list-learning tests (e.g., California Verbal Learning Test- 2nd Edition; CVLT-II) (Delis, Kramer, Kaplan, & Ober, 2000). Utilizing this measure, the CPE ratio score and Nadir CD4+ count were used as predictors to assess the effect of history of poor CNS penetrative HAART use and immune functioning have on learning characteristics, recall, and recognition performance in those with HIV infection.

## Summary and Hypotheses

In summary, HIV is an insidious virus that causes substantial harm to the immune and central nervous system. Although advances in antiretroviral treatments have relegated HIV as a manageable disease, HIV's detrimental impact on the brain,

particularly the frontostriatal white matter tracts, and subsequent cognitive processes continues to be prevalent due to the variable permeability of HIV treatment across the BBB. The present study examined the impact that history of lower-penetrative index HAARTs has on performance across several different cognitive domains through the utilization of a novel CPE ratio score. The neurobehavioral deficits associated with HIV tend to follow a progressive pattern of slowed psychomotor speed, executive dysfunction, and impaired memory. Despite the extensive literature demonstrating this deficit profile, there is a relative dearth of literature on HIV's effects on nonverbal cognitive processes including design fluency and visual memory. Therefore, to examine what cognitive domains are most sensitive to the effects of HIV-infection in those individuals with a varied history of CNS penetrative HAART and its impact on nonverbal abilities, this study recruited a sample of HIV-infected individuals and tested the relationship between neurocognitive measures and estimates of HIV penetration into the CNS. CNS penetration was based on 1) Nadir CD4+ count, 2) the estimated CNS Penetration Effectiveness (CPE) of medications, and 3) interaction between CD4+ count and medication CNS penetration (CD4+ x CPE). The following hypotheses were made:

**Hypothesis 1**: Cognitive functioning (Executive/Inhibition, Process Speed, and Visual Scanning) will depend on medication permeability and Nadir CD4+ status. As CPE and Nadir CD4+ count decrease, cognitive performance will decrease.

**Hypothesis 2:** Cognitive switching and clustering ability will mediate relationship between CPE Ratio and Nadir CD4+ to verbal and figural fluency.

**Hypothesis 3:** HIV CNS indicators (CPE Ratio and Nadir CD4+) will be related to learning and recall scores on a visual procedural memory task.

# CHAPTER TWO

## Method

### Participants

Twenty-five, adult HIV+ participants were recruited for the present study. Demographic information can be found in Table 3.

### Procedure

The procedure was carried out with the approval of the Idaho State University Human Subjects Committee. The study was explained to each participant and participants were given time to ask questions prior to signing the informed consent form. Upon signing the consent, participants completed a neuropsychological test battery, given the intake questionnaire to complete, and thanked for their contribution to the study. Each participant was given a unique identification number and all data collected was stored separately from any identifying information.

All HIV+ participants were recruited from the Pocatello Family Medicine (PFM) HIV integrative healthcare team. Prospective HIV+ participants received a letter from their primary care physician (PCP) that informed them of the clinic's desire to provide a voluntary cognitive evaluation, at no cost to them, as part of their standard care. Patients were given the option to respond either by mail (via a pre-paid return envelope) or in person during their next clinic visit. Those who indicated interest in the evaluation were referred to the study investigators (Dr. Vik or Mr. Dasher). A member of the clinical research team met with the individual during his or her next scheduled appointment at PMC or phone to schedule a separate appointment for the neurocognitive evaluation.

Testing was conducted either at the ISU Psychology Clinic (for those in Pocatello) or at the Regional District Health Office (for those in or around Idaho Falls). Prior to the clinical evaluation, the individual completed ISU Psychology Clinic informed consents as part of their clinical care. Next, patients were provided additional written consent for their cognitive test results to be used in this study.

The test battery and questionnaire took approximately 2-3 hours to complete. The order of the administration of the cognitive test battery was standardized across all participants to ensure testing consistency and to ensure that all participants receive sufficient delays for the memory tests as well as avoid interference from common cognitive domains that could impair recall (i.e., verbal fluency not administered during CVLT-II delay). The administration order can be seen in Table 4.

All test reports were written by the investigator (Mr. Dasher) or a doctoral student under the supervisor of the project supervisor, Dr. Peter Vik. These reports were accompanied with a personalized feedback session with the investigator, project supervisor, or doctoral practicum student. During the feedback session, participants were provided with an explanation of their results at a language level suitable for their understanding and given ample time to discuss and questions or concerns.

**Calculation of Ratio Score**

The CPE Ratio score was calculated by summing the penetrative scores of the most effective medication the participant was reportedly taking since diagnosis. This score was then divided by the total number of years the participant was diagnosed. If the participant was taking multiple HAART medications, the most penetrative score was used in the calculation. CNS penetrative-effectiveness for each medication was based on

the rankings outlined by Letendre & colleagues (2010). The CPE ratio score ranges from 0 to 4 (higher is more penetrative) with a score of 0 assigned for years untreated after diagnosis. An example of the ratio score is below for a participant diagnosed for 10 years, untreated for 3 years, and on Aricept for the remaining 7 years:

$$\frac{(0\ x\ 3) + (3\ x\ 7)}{10} = CPE\ Ratio\ of\ 2.10$$

**Measures**

**Intake Questionnaire.** This measure collected participant's demographic information including age, sex, ethnicity, educational background, and marital status. Additionally, this questionnaire inquired about the participant's substance use history, psychiatric history (e.g., bipolar disorder), and medical history, including neuromedical events (e.g., TBI; stroke). Information regarding estimated duration of HIV infection, current CD4+ count (cells/μL), Nadir CD4+ count (cells/μL), and HIV medications were obtained from patient medical records at Pocatello Family Medicine in Pocatello, ID.

**Northwest Trail Learning Test (NWTLT).** The Northwest Trail Learning Test was designed to measure separately encoding and recall of visuospatial information. It was designed specifically to minimize the impact of verbal mediation during encoding and to provide visual/non-verbal data in context to standard verbal learning tasks. Examinees have up to 15 trials to learn a predetermined trail connecting 13 of the nodes. The trail is considered to have been learned when the examinee completes two consecutive error-free trials (learning criterion). The stimulus is an 8.5" x 11" white card with 20 nodes (19 circles and one FINISH mark) printed on it.

At the beginning of trial 1, the examiner demonstrates the Trail Test. After the examiner demonstrates the entire trail sequence, the examinee attempts the trial. As the

examinee attempts the trial, the examiner provides feedback at each decision node as to whether the node next selection is correct or incorrect. If correct, the examiner says, "okay", and then makes the next selection. If incorrect, the examinee is told to "go back" to the previous node and choose again. If the examinee does not choose the correct node after five subsequent errors, the examiner demonstrates the correct choice to the participant and is instructed to continue the trial from the next correct node. Prior to the participant trying the second trial, the examiner again demonstrates the trail, after which the examinee again attempts the trail with the same corrective feedback. On subsequent trials (3 onward), the examiner does not demonstrate the trail but does provide corrective feedback as the examinee attempts the trial. If the participant does not reach learning criterion after the 15$^{th}$ trial, the individual is considered to not have learned the trial.

After a 30-minute delay, the Free Recall (FR) component is administered. The participant is presented with the original stimulus card and instructed to re-create the trail once more. During FR, the examiner does not provide corrective feedback at each decision node. Following the free-recall component, the examinee completes a "Forced Choice" procedure. In the forced choice, the examinee is presented with a copy of the stimulus pattern, which has been modified to include three lines emanating from the "start" position. One line connects to the correct first node; the other two connect to incorrect choices. If the examinee selects an incorrect choice, he or she is told to go back and select another node. If he or she makes a correct choice, the examinee flips the page to a second stimulus card in which three lines emanate from the current node. The examinee continues to select the correct node until he or she has reached the end of the

trial. The total correct score on the forced choice is the number of correct choices made on each node without an error.

After completion of the forced choice, a segment recognition component is administered in which the participant is shown a flipbook of 32 patterns. A pattern is defined as three or four line segments connecting a series of nodes together. The examinee is given two seconds to view the pattern before it is hidden from view. The examinee is then asked if the pattern was part of the originally presented trail (in the correct sequential order). Half of the items (16) reflect the learned trial, and the other half is not part of the trail. Pattern recognition generates two scores: correct hits and false positives.

**Rey-Osterrieth Complex Figure Test (RCFT).** The RCFT is a widely used measure of non-verbal memory, but one that relies on a number of other cognitive and motor skills, to complete it correctly, including visuospatial cognition, attention, planning, and graphomotor dexterity (Meyers & Meyers, 1995). The task requires participants to copy and then recall a complex geometric figure twice from memory that is presented on a sheet of paper presented in a landscape fashion. Following two free recall trials (immediate recall and delayed recall), a recognition task follows. The Recognition part presents several geometric designs that were part of the original complex figure, along with geometric design distractors that were not part of the original figure. The participant circles those pieces that were part of the original figure. The copy condition was administered to participants as a means to measure their use of visual organizational abilities outlined by Savage et al. (1999) that has shown strong validity and reliability (Deckersbach et al., 2000). In sum, examinees receive organization points

for constructing individual elements as an unfragmented unit, receiving a total score ranging from 0 to 6 (Savage et al., 1999).

**Wechsler Adult Intelligence Scale – 4th Edition (WAIS-IV) – Coding.** The WAIS-IV Coding subtest consists of several rows containing small blank squares that are each paired with a randomly assigned number from one to nine. Above these rows at the top of the page is printed key, which pairs each number with an abstract symbol. The participant is given a practice trial to pair the first nine empty squares on the top row with its associated symbol indicated on the key. Following this practice, the participant is instructed to fill in the remaining blank spaces with the correct symbol-number pair. The participant is told to stop after two minutes has passed. The test measures cognitive processing speed and is relatively unaffected by intellectual capacity and educational background (Hoyer, Stawski, Wasylyshyn, & Verhaeghen, 2004) Roughly half of the score value is contributed by copy speed, however, so controlling for motor speed and dexterity is important to tease out the overlapping variance (Lezak et al., 2012). The test has demonstrated particular sensitivity to detect impaired cognitive processing speed in cases of cortical (i.e., Alzheimer's) and subcortical (Huntington's) dementia early in disease progression, including HIV (Devanand et al., 2007; Gomez-Anson et al., 2007; Mandal et al., 2008).

**Wechsler Adult Intelligence Scale – 4th Edition (WAIS-IV) – Letter-Number Sequencing (LNS).** The LNS subtest is a measure of attention, concentration, and working memory (Crowe, 2000). Participants hear a list of jumbled numbers and letters (in alternating order) of increasing trial length (two to eight digits). Subjects are asked to recite back the numbers and letters they heard in ascending order beginning with the

numbers first and letters second. The task is completed when the participant completes all trials or errors on reciting the letters and digits in three consecutive trials.

**Delis-Kaplan Executive Function System (D-KEFS) – Verbal Fluency.** The D-KEFS Verbal Fluency test is an oral verbal fluency test, which measures fluid and divergent thinking and cognitive flexibility (Delis et al., 2001). The test contains three task conditions: Letter Fluency, Category Fluency, and Category Switching. For Letter Fluency, the participant is instructed to name as quickly as possible in a 60 second time limit, as many different words that begin with that letter. Examinees cannot use names of people, places, or numbers. Letter Fluency consists of three trials involving a different letter each time (F, A, and S). Similarly, the Category Fluency condition requires participants to name as many different words they can think of that belong to two different categories: Animals and Boy's Names. Both categories are administered one at a time in 60-second increments. In the final condition, Category Switching, the participant is asked to alternate between items that belong to two different categories (Fruit and Furniture) within a 60-second time limit. Production of phonetically similar letters and switching has been linked to frontal and left hemispheric processing while production of semantically related words and semantic clustering has been linked to temporal processes (Cerhan et al., 2002; Troyer et al., 1998).

Performance on this test is based on several items: total number of novel words produced in either the letter, category, or switching condition. Phonetic and semantic clustering strategies and switching was scored using procedures described by Tucha et al. (2005) and Troyer et al. (1998). Letter Fluency Clusters are defined as at least 3 words starting with the same first two letters (i.e., sea and seen), differing only by one vowel

(i.e., fear and far), that rhymed (i.e., flight and fright), and homonyms (i.e., feat and feet). Homonyms were only accepted if the participants make the distinction during testing, otherwise they were considered repetitions. Category Fluency Semantic Clusters are defined as successive generation of words with an obvious relationship (i.e., zebra, gazelle, and elephant with in the Animals condition are "African/Safari"). Lastly, switches are counted when the participant moves from using one cluster strategy to another cluster strategy. In order to maintain consistent scoring reliability, two independent raters separately scored the use of cluster strategies and switching on a subsample of protocols to test inter-rater reliability.

**Delis-Kaplan Executive Function System (D-KEFS) – Color-Word Interference.** The D-KEFS Color-Word interference task is designed to broadly assess one's ability to inhibit a proponent, overlearned response in order to generate a conflicting response (Delis et al., 2001). The test consists of four conditions, each assessing a different cognitive skill. The first condition asks the participant to name the color of a series of color patches (red, blue, or green) presented in several rows on a display, as quickly as possible, and without skipping any. The second condition asks the participant to read the words (red, blue, or green) printed in black ink on a similar display in the same manner. The combined time it takes the participants to complete both conditions is considered their automatic reading speed as well as been implicated as a sensitive measure of processing speed (Denney, Gallagher, & Lynch, 2011). The third condition is based on the original Stroop (1935) task designed to measure inhibition, which asks the participant to say the ink color of words printed in dissonant ink colors (e.g., the word "red" printed in green ink). Lastly, the fourth condition assesses both

inhibitory ability and cognitive flexibility by asking the participant to switch back and forth between naming the dissonant printed ink colors and reading the printed words.

**Delis-Kaplan Executive Function System (D-KEFS) – Sorting.** The D-KEFS Sorting test is a direct adaptation of the original California Card Sorting Test and is a measure of concept formation, problem solving, and cognitive flexibility (Delis et al., 2001). The test consists of two testing conditions: Free Sorting and Sort Recognition. The present study only administered the Free Sorting condition because the variables of interest are spontaneous initiation of concept formation and cognitive flexibility demonstrated though creation of novel perceptual or verbal sorts. In the Free Sorting condition, the participant is presented with six cards that have different perceptual and verbal features. The participant is asked to sort the cards into two groups of three cards each and describe the rule or concept they used in creating the sort. This test has shown to be sensitive to frontal and subcortical functioning and may be useful in dissociating between verbal and nonverbal concept formation and processes (Crouch, Greve, & Brooks, 1996; Delis, Squire, Bihrle, & Massman, 1992; Dimitrov, Grafman, Soares, Clark, 1999).

**Delis-Kaplan Executive Function System (D-KEFS) – Trails.** The D-KEFS Trails test consists of five separate conditions that are designed to isolate the basic components of performance (Delis et al., 2001). The first condition is a visual cancellation task. Participants are presented with an 11” x 17” sheet of paper with an array of circles printed on it. Within each circle is a number. Participants are instructed to locate and cross out all circles containing of the number “3s” on the sheet and is designed to assess for deficits in attention, perception, spatial cognition, and processing speed. The

second and third conditions ask participants to sequence a series of numbers (condition 2) or letters (condition 3) by drawing lines connecting the numbered circles in ascending order. These conditions assess attention and visuomotor tracking. The fourth condition, also a sequencing task, asks participants to draw lines connecting circles, but they must alternate between numbers and letters in ascending order. This switching condition assesses divided attention and cognitive flexibility. The last condition, which asks participants to trace a dotted line that connects several empty circles is designed to assess motor speed. Every task is timed and participants are encouraged to work as quickly, but as accurately, as possible. Previous research has shown condition 4 (i.e., switching) to be a sensitive measure of frontal lobe pathology in those with focal damage and frontal lobe epilepsy (McDonald, Delis, Norman, Tecoma, & Iraqui-Madozi, 2005; Yochim et al., 2009).

**Ruff 2 & 7 Selective Attention Test.** The Ruff 2 & 7 Test is cancellation test designed to assess differences between automatic and controlled selective attention while measuring aspects of sustained attention (Ruff & Allen, 1996). The test consists of 20 horizontal rectangles that contain 3 smaller rows within them. These smaller rows contain either a combination of 2s, 7s, and letters (automatic condition) or all numbers (1-9; controlled condition). These conditions are alternated down the page in a random sequence. The participant is asked to cross out only the 2s and 7s as quickly as possible, in serial order without skipping any, beginning with the top rectangle. Every 15 seconds, the examiner says “next”, requiring the participant the move to the next rectangle and repeat the process again. Performance is scored on speed and accuracy.

**Ruff Figural Fluency Test (RFFT).** The RFFT is a nonverbal measure of fluid, divergent thinking and cognitive flexibility. It is an adaptation from the original Design Fluency test by Jones-Gotman and Milner (1977) and the Five Dot Test (Regard, Strauss, & Knapp, 1982), which were intended as counterparts to verbal fluency tasks. The test consists of five sheets of paper (one for each condition), each containing 40 squares. Each square contains five dots. The dots are arranged symmetrically in the first three conditions (the second and third add visual distractors). The dots in the fourth and fifth conditions do not contain distractors, but the dots are arranged asymmetrically. The instructions for the participant are the same for each condition: they are to create as many different novel designs as quickly as possible by connecting at least two dots together in a 60 second period.

Performance is based primarily on the total number of unique designs produced and for the number of repetitions. In addition to this method; however, the use of strategy clusters and switching is accounted for as well. A strategy cluster is a sequence of at least three consecutive responses in which each successive figure is either rotated or changed quantitatively (Gardner, Vik, & Dasher, 2013; Vik & Ruff, 1988) while a switch is defined as shifting from one cluster strategy to a different cluster.

**North American Adult Reading Test (NAART).** The NAART is the North American adaptation by Blair and Spreen (1989) of the National Adult Reading Test (NAART), originally developed for British populations. It contains a list of 61 words that progressively become less familiar (i.e., are more rare in common English American and Canadian dialect) that the participant is instructed to read out loud to the examiner. Errors are based on mispronunciations and skipped items and the total score is tallied based on

all words pronounced correctly. The NAART correlates with the WAIS-R VIQ score (Lezak et al., 2012). It is used to estimate premorbid intelligence, and has shown a high internal consistency (Uttl, 2002).

**California Verbal Learning Test – 2nd Edition (CVLT-II).** The CVLT-II is a word-learning test that measures one's ability to encode and recall orally presented verbal material (Delis et al., 2000; Lezak et al., 2012). Over five learning trials, sixteen words (List A) are read to the examinee with instructions to recall the words in any order. Within the list of words are four conceptual categories (animals, modes of transportation, vegetables, and furniture) that each cluster four words together. Participants are not told about the category composition of the list but are expected to recognize it after a few trials and to use the categories to facilitate recall (Lezak et al., 2012). After the five initial trials, the examiner reads an interference list (List B). This list consists of four words from two overlapping categories (e.g., more animals and vegetables) and eight words from two non-overlapping categories. Following List B, participants are asked to freely recall any words they can remember from List A. Next they are administered a cued recall trial for List A based on the conceptual categories (e.g., "tell me all the words from the first list that were animals"). Twenty minutes after these Short-Delay Free and Cued Trials, participants are asked again to freely recall as many words they can from List A, followed by another cued recall (Long Delay Free and Cued Recall). Finally, subjects complete a recognition task in which they are read a list of 48 words and after each word they must say "YES" or "NO" as to whether or not the word was present on the original list (List A). The oral presentation of the recognition list consists of all words from Lists A and B, eight novel items from List A categories, and eight unrelated words. This

measure has been found to have high construct and internal validity and reliability (Delis et al., 2000).

**Wisconsin Card Sorting Test (WCST).** The WCST tests multiple domains of executive functioning including concept formation, rule learning, and cognitive flexibility. Modified by Heaton et al. (1993) from an original card-sorting task developed by Berg (1948), it consists of four key cards and two decks of 64 cards each. The present study only utilized one deck of cards for purposes of research. The four key cards are placed next to each other in front of the participant and in a standardized format. The participant's task is to place a card from the deck, one at a time, below the key cards (one red triangle, two green stars, three yellow crosses, and four blue circles) accordingly to an unspoken principle that the participant must deduce from the examiner's responses to their placement of the cards. For instance, if the determining principle is color then placing a deck card below a key card of matching color would be correct. The participant simply begins placing the cards and the examiner states whether each placement is correct or incorrect. After a run of ten consecutive correct placements, the examiner changes the principle without telling the subject. The participant must detect the shift and determine the new guiding principle through the examiner's feedback. The shift is standardized and follows the sequence: color-form-number-color-form-number. The examiner continues until the participant has made six runs of ten correct placements or until all of the cards have been placed.

**Grooved Pegboard.** The grooved pegboard is test of motor dexterity and speed that test consists of a small board containing a 5x5 set of slotted holes angled in different orientations (Kløve, 1963). At the top of the board lies a dish containing several metal

pegs that each has a ridge along one side, requiring it to be rotated into positions for correct insertion. The participant is instructed to place a peg into the holes in sequential order starting at the top row until each row is filled. Performance is measured by time to completion. The test has demonstrated sensitivity to detecting general motor slowing due to progressive neurodegenerative diseases, including HIV (Matthews & Haaland, 1979; Miller et al., 1990).

# CHAPTER THREE

## Results

All analyses were conducted using the IBM Statistical Package for the Social Sciences (SPSS). Prior to testing the study hypotheses, neuropsychological test scores were submitted to an exploratory principal components analysis (PCA) to reduce scores to relevant latent constructs. PCA was conducted with nine variables (T-scores) using varimax rotation. Results of the PCA revealed three component scores with Eigenvalues greater than 1. Together the three factors accounted for over 72% of the variance (Table 5). Three variables that loaded onto the first component reflected *Executive/Inhibition* (WAIS Letter-Number Sequencing, Errors on DKEFS Color-Word Inhibition, and Errors on DKEFS Color-Word Inhibition/Switching). Three variables that loaded onto the second component reflected *Visuospatial Processing* (Ruff 2&7 Total Accuracy, Ruff Figural Fluency Errors, and Errors on DKEFS Trail Making Test – switching condition). Lastly, the three variables that loaded onto the third component reflected *Processing Speed* (DKEFS Combined Color-Word Reading, Ruff 2&7 Total Speed, and WAIS Coding). These tests were chosen from the broader neuropsychological battery because of their verified construct validity in measuring abilities related to the broader cognitive domains of processing speed, executive functioning, and attention (Lezak et al., 2012).

**Hypothesis 1**: **Broad Cognitive Domains**

Hypothesis 1 stated that cognitive ability (Executive/Inhibition, Visuospatial Processing, & Processing Speed) would depend on medication permeability (CNS Penetration Effect; CPE) and Nadir CD4+ status. Specifically, Hypothesis 1 predicted that as CPE and Nadir CD4+ count decreased, cognitive performance would decline.

Conducting Pearson correlations among Nadir CD4+ count and CPE Ratio to the cognitive domains first tested hypothesis 1. The bivariate correlations between Executive/Inhibition were not significant for both CPE (r = 0.066, $p$ = 0.755) and Nadir CD4+ (r = 0.141, $p$ = 0.501) as well as with Visuospatial Processing for CPE (r = 0.157, $p$ = 0.454) and Nadir CD4+ (r = 0.214, $p$ = 0.304). As for Processing Speed, Nadir CD4+ also came out non-significant (r = 0.162 $p$ = 0.438), but there was a moderate and positive, significant relationship found for CPE (r = 0.483, $p$ = 0.014). A partial correlation was then computed between CPE Ratio and Processing Speed, controlling for age, verbal intelligence, and years diagnoses. If age, verbal intelligence, and years of diagnosis are the principle determinants of processing ability then than the partial correlation should be non-significant. The results suggest that the CPE Ratio is related to Processing Speed in the hypothesized direction. Table 6 presents the partial correlations.

Hypothesis 1 was next tested using a model comparison approach (Judd, McClelland, & Ryan, 2009; Vik, 2014). In the model comparison approach, Model 1 (the null hypothesis model) predicted the dependent variable with covariates only (age, NAART, Years Diagnosed), and Model 2 added the hypothesized predictors (CPE Ratio, Nadir CD4+ count, and their interaction term). Comparing the sum of squared errors produced by each model revealed whether the added variables, as well as which variables in particular (CPE ratio, Nadir CD4+, and CPE x Nadir), improved prediction of the dependent variable. This model comparison approach was conducted separately for each dependent variable. For the first analysis, the dependent variable was the Executive/Inhibition composite. Of the covariates, premorbid verbal intelligence significantly predicted Executive/Inhibition (p = .011). None of the predictors that were

added to create model 2 were significant after controlling for the covariates: CPE ratio (*b* = -5.674, t = -.701, *p* = 0.492), Nadir CD4+ (*b* = 0.003, t = 0.089, *p* = 0.930), and CPE x Nadir CD4+ (*b* = 0.092, t = 1.934, *p* = 0.068).

For the second analysis, the dependent variable was the composite score of Visuospatial Processing. None of the covariates predicted Visuospatial Processing. After controlling for these covariates, none of the hypothesized individual predictors was statistically significant: CPE ratio (*b* = 1.690, t = 0.162, *p* = 0.873), Nadir CD4+ (*b* = 0.037, t = 1.012, *p* = 0.324), and CPE x Nadir (*b* = 0.011, t = 0.186, *p* = 0.854).

The third analysis used Processing Speed as the dependent variable. None of the covariates predicted the composite score. After controlling for the covariates, CPE ratio significantly predicted Processing Speed (*b* = 21.53, t = 2.399, *p* = 0.03). According to this finding, as CNS penetration effect increased, Processing Speed improved. Neither the Nadir CD4+ (*b* = -0.005, t = -0.145, *p* = 0.886) nor the interaction between Nadir CD4+ and CPE (*b* = -0.013, t = 0.-0.227, *p* = 0.823) was statistically significant. This finding partially supported the hypothesis that HIV+ individuals receiving HAART with a higher CNS permeability performed better on tasks designed to measure cognitive processing speed. In summary, findings regarding Hypothesis 1 revealed that CPE Ratio was related to Processing Speed but not Visuospatial Processing or Executive Inhibition. Nadir CD4+ was not related to any of the cognitive outcome composite scores.

**Hypothesis 2: Strategic Cluster Use on Fluency**

The second hypothesis postulated that the relationship between HIV CNS indicators (CPE and Nadir CD4+ count) and figural fluency production would be mediated by the use of figural fluency strategic clusters. Strategic clusters were measured

in two ways: (a) average cluster size (ACS; number of figures included in a strategic cluster), and (b) the number of times a person used a strategic cluster (NSC). Two approaches were used to test this mediation hypothesis: procedures described by Baron and Kenny (1986), and calculation of the Sobel Test.

Barron and Kenny (1986) procedures required three steps. In Step 1 the outcome score (Ruff Figural Fluency Test Total Score; RFFT) was regressed on one of the HIV indicators (either the CPE ratio score or Nadir CD4+) while controlling for age, verbal intelligence (NAART), and years living with HIV. This step established an association between the predictor (HIV indicator) and outcome (RFFT Total) variables. In Step 2, the mediator (strategic cluster score) was regressed on the predictor. This step demonstrated an association between predictor and mediator. Finally, in Step 3, RFFT Total Score was regressed on both the mediator and the predictors simultaneously. Support for this mediation hypothesis would be found if the mediator (strategic cluster) remained significantly related to RFFT Total Score, but predictor (either the CPE ratio or Nadir CD4+) no longer predicted RFFT Total Score.

In addition to the classic Baron and Kenny (1986) approach, a Sobel statistic was conducted to assess the significance of the indirect relationship between either the CPE Ratio or Nadir CD4+ count to the total score on the RFFT. This analysis is conceptualized in Figure 2. The direct path between predictor and outcome is designated as "c." The mediated relationship between predictor and outcome is designated as "c'." The relationship between predictor and mediator is designated "a," and the relationship between mediator and outcome is designated "b." The formula for the Sobel Test is:

$$\frac{ab}{\sqrt{b^2S_a^2 + a^2S_b^2}}$$

The Sobel test produces a Z-score; therefore, a Sobel score higher than 1.96 is regarded as statistically significant at .05 level.

Eight mediation effects were tested for Hypothesis 2. The first four analyses examined HIV indicators (CPE Ratio and Nadir CD4+) in relationship to nonverbal fluency. Analyses five to eight repeated the first four hypotheses using verbal fluency (instead of figural fluency) as the outcome. The first evaluation of Hypothesis 2 tested the Average Strategic Cluster size (ACS) as a mediator between CPE and RFFT Total Score. All three mediation conditions were met, demonstrating that ACS mediated between CPE and RFFT total score. First, the path between CPE Ratio and RFFT Total Score was statistically significant ($b$= 7.785, $t$ = 2.154, $p$ = 0.043), thus meeting condition 1 for mediation. Next, a relationship between CPE Ratio and ACS was significant ($b$= 1.865 $t$ = 3.761, $p$ = 0.001), thus meeting condition 2 for mediation. Finally, when RFFT Total Score was regressed on both CPE and ACS, ACS continued to predict RFFT Total Score ($b$= 3.976, $t$ = 3.944, $p$ = 0.001), but CPE no longer predicted RFFT Total Score ($b$= 0.477, $t$ = 0.118, $p$ = 0.907). Figure 2 shows this meditational effect. The Sobel test also supported this mediation effect ($z$ = 2.722, $p$ < 0.001).

The second evaluation of this hypothesis tested the Number of Strategic Clusters (NSC) as a mediator between CPE ratio and RFFT Total Score. Again, all three conditions were met for mediation. Condition 1 was established in the previous mediational analysis. Regression analysis revealed a statistically significant relationship between CPE Ratio and NSC ($b$= 3.663 $t$ = 0.610, $p$ = 0.002), thus meeting condition 2 for mediation. When simultaneously regressing RFFT Total Score on CPE and NCS, ACS remained significantly related to RFFT Total Score ($b$= 1.364, $t$ = 2.417, $p$ = 0.024),

but the relationship between the CPE Index and Total Score on the RFFT was no longer significant ($b$= 1.027, $t$ = 1.387, $p$ = 0.181). Figure 3 shows this mediation effect. The Sobel test further supported the mediation model ($z$ = 1.992, $p$ = 0.046).

The third evaluation of this hypothesis tested the ACS as a mediator between Nadir CD4+ and RFFT Total Score. The path between Nadir CD4+ and RFFT Total Score was statistically significant ($b$= 0.035, $t$ = 3.164, $p$ = 0.005), thus meeting condition 1 for mediation; however, the relationship between Nadir CD4+ and ACS was not significant ($b$= 0.003, $t$ = 1.504, $p$ = 0.148). A Sobel test was conducted and did not support the mediation model ($z$ = 1.402, $p$ = 0.161). Thus, condition 2 for mediation was not achieved.

The relationship between Nadir CD4+ and NCS was also assessed in the fourth evaluation, which also yielded a non-significant result ($b$= 0.005, $t$ = 1.143, $p$ = 0.266). A Sobel test was also conducted, which did not support the mediation model ($z$ = 0.969, $p$ = 0.332). Hence, no evidence was found that fewer strategic clusters (proxy for set-shifting) or cluster size explains the relationship between reduced Nadir CD4+ count and figural fluency performance. In summary, CPE Ratio predicted figural fluency performance, and use of strategic clusters mediated the relationship. Nadir CD4+ also predicted figural fluency; however, strategic clusters did not mediate that relationship.

The fifth evaluation of this hypothesis tested whether verbal fluency strategic clusters mediated between CPE and total verbal (phonetic) fluency. The direct path between CPE Ratio ($b$= 1.372, $t$ = 0.439, $p$ = 0.665) and DKEFS Letter Fluency Total Score was not statistically significant. Thus, condition 1 for mediation was not met.

In addition to this approach assessing the mediation of NSC and ASC on CPE Ratio and Nadir CD4+ to RFFT, the significance of the indirect effects was also assessed using bootstrapping procedures. Unstandardized indirect effects were computed for each of 10,000 bootstrapped samples, and the 95% confidence interval was computed by determining the indirect effects at the 2.5th and 97.5th percentiles.

Compared to the Baron and Kenny method, this subsequent analysis yielded mixed results for CPE Ratio but were consistent with Nadir CD4+. For CPE Ratio and ACS, the bootstrapped unstandardized indirect effect was 18.66, and the 95% confidence interval ranged from 5.54, 43.53. However, for CPE and NSC, the bootstrapped unstandardized indirect effect was 10.67, and the 95% confidence interval ranged from -1.16, 31.33. Thus, the indirect effect was still statistically significant for ACS but not NSC. In regard to Nadir CD4+ and RFFT, the 95% confidence interval for both mediators passed through zero (NSC: -0.017, 0.075; ACS: -0.01, 0.07), demonstrating a non-significant indirect effect.

Analysis six of Hypothesis 2 tested whether verbal fluency strategic clusters mediated between Nadir CD4+ and total verbal fluency score. The direct path between Nadir CD4+ ($b$= 0.007, $t$ = 0.707, $p$ = 0.488) and DKEFS Letter Fluency Total Score was not statistically significant. Thus, condition 1 for mediation was not met.

Since direct effects between HIV predictors and verbal fluency outcomes were not found, analysis seven (NSC as mediator) and analysis eight (ACS as mediator) were not conducted as condition 1 for mediation had not been met. Hence, no evidence was found that fewer strategic clusters (proxy for set-shifting) or cluster size explains the relationship for both HIV indicators and letter fluency performance.

Similar to the subsequent analysis for the first four mediations, the mediation of NSC and ASC on CPE Ratio and Nadir CD4+ to Letter Fluency Total Scores was also tested with bootstrapping. Unstandardized indirect effects were computed for each of 10,000 bootstrapped samples, and the 95% confidence interval was computed by determining the indirect effects at the 2.5th and 97.5th percentiles. Four all four mediations, the 95% confidence interval passed through zero, demonstrating a non-significant indirect effect that was consistent with the Baron and Kenny method.

In conclusion, partial support was found for the second hypothesis with regard to figural but not verbal fluency. Individuals with a history of being treated with lower CPE HAARTs produced fewer figures on a fluency measure and the mechanism behind this was due to smaller cluster sizes. However, bootstrapping and Baron and Kenny yielded mixed results with regard to NSC. This discrepancy may be because NSC only partially mediates the relationship between CPE and RFFT. In regard to Nadir CD4+ count, although evidence was found in support of a direct effect, the mechanism behind this relationship remains unknown, as Nadir CD4+ count was not predictive of fewer strategic clusters or cluster size. No direct or mediated effect was found for these HIV CNS indicators and letter fluency performance.

**Hypothesis 3: HIV CNS Indicators and Nonverbal Memory**

Hypothesis 3 stated that HIV CNS indicators would be related to learning and recall scores on an experimental visuospatial memory task. Table 6 presents the partial correlations between the HIV indices (CPE and CD4+) and the NWTLT memory scores, controlling for age, NAART, and years diagnosed. CPE and CD4+ were not correlated with any of the learning and recall scores; however, CPE correlated with two NWTLT

error scores: Learning Repetition errors (-.476, p = .029) and Forced Choice Target (number) errors (-.446, p = .043). Learning Repetition Errors occurred when a subject selected an incorrect next step after having already selected that node and receiving feedback that it was incorrect. Forced Choice Target Errors occurred when a subject inserted a response that was part of the trail but was selected out of sequence. Essentially, this type of error was an intrusion of a correct item at the wrong place in the sequence. Free Recall Node Omission errors approached statistical significance (-.421, p = .057). Nadir CD4+ only correlated with a single error score: Forced Choice Target (number) errors (-.434, p = .049).

Hypothesis 3 was next tested using the model comparison used in Hypothesis 1 (CPE, Nadir CD4+, and their interaction, after controlling for age, NAART, years diagnosed). In contrast to the partial correlations, only one of the regression models revealed an association between HIV indicators and NWTLT scores (see Table 7). To understand why partial correlations yielded several associations while these effects did not remain for the regression analyses, collinearity diagnostics were conducted. Tolerance was low for all three HIV predictors in the model: CPE (.584), Nadir CD4+ (.608), and the interaction term (.703). Collinearity between HIV predictors likely masked the relationship between predictors (predominantly CPE) and NWTLT scores.

In sum, partial support was found for the third hypothesis in regard to error types associated with HIV indicators. Although collinearity between the HIV predictors likely masked the relationship between these variables and measures of the NWTLT in the regression equation, partial correlations were consistent with hypothesis.

# CHAPTER FOUR

## Discussion

The aim of this study was to investigate the potential relative effects of HAART drugs with lower versus higher CNS penetrative-effectiveness on cognitive functioning. An index of CNS drug penetration effectiveness (CPE) was created to estimate the degree of neurpenetration across a patient's medication history. Three hypotheses were developed to investigate these relationships. Hypothesis One predicted that HIV+ individuals with a lower CPE Ratio score would perform poorer on composite neurocognitive scores (Visuospatial Processing, Processing Speed, and Executive/Inhibition) than those with higher CPE Ratios, and that this relationship would be modified by Nadir CD4+ count. Hypothesis Two predicted that HIV+ individuals with a lower CPE Ratio score and lower Nadir CD4+ count would perform worse on a measure of figural fluency and that this relationship will be mediated by number of strategic clusters (i.e., their ability to effectively use cluster strategies) and cluster size (i.e., their ability to maximize the use of their present clustering strategy). This hypothesis was designed to extend upon previous findings regarding verbal fluency strategic clusters among persons with HIV to comparable non-verbal (figural) fluency performance. Hypothesis Three predicted that HIV+ individuals with a lower CPE Ratio score and Nadir CD4+ would perform worse on an experimental measure of nonverbal learning and recall. Evidence that early HIV-related neurological effects are seen in sub-cortical regions (Gongvatana et al., 2007; Scott et al., 2006; Woods et al., 2009) suggests that HIV patients would display a "sub-cortical" type of memory profile that is marked

by poor learning characteristics, increased repetitive errors, poor free recall, but intact recognition.

In regard to the first hypothesis, support was found for CPE Ratio to predict processing speed. Individuals whose medication history included a higher proportion of HIV drugs with lower CNS penetrative effect demonstrated slower cognitive processing. In contrast, no support was found for CPE Ratio, Nadir CD4+, or their interaction to predict performance on two of the three composite measures: executive/inhibition and visuospatial processing.

For the second hypothesis, partial support for a mediated effect was found for CPE Ratio as predictor of figural fluency performance (i.e., lower ratio was associated with fewer figures). Specifically, the most parsimonious interpretation of findings suggests that CPE relates to figural fluency performance by limiting the use of planning strategies. Using two mediation approaches, ACS was a robust mediator but NSC was found to be a significant mediator in the Baron and Kenny approach but only approached significance with bootstrapping. This may due to only a partial mediation existing for NSC, however, more research is needed to reconcile this discrepancy. In contrast, while Nadir CD4+ also predicted figural fluency performance (lower count predicted fewer designs), strategic clusters did not mediate this relationship. This finding was hypothesized based on prior findings linking HIV to verbal fluency via strategic clustering. It was surprising therefore, that verbal fluency was not related to the HIV indicators in this study.

For the third hypothesis, some evidence supported a “sub-cortical” learning and memory profile on an experimental measure of visuospatial learning and memory.

Although regression model comparison findings were null, these findings were likely due to high colinearity observed between predictors (CPE and CD4+). When, partial correlations controlling for age, years diagnosed, and verbal IQ were used, lower CPE Ratio score was associated with greater repetition errors during learning and greater intrusion errors on cued recall. Errors during learning and recall are common among people with fronto-subcortical difficulties (Delis et al., 1995). Such a pattern is characteristic of HIV patients who are beginning to evidence neurocognitive difficulty.

**Implications**

One implication of these findings regards the concept and utility of the CPE Ratio score developed in the present study. The evidence provided in this study supported the CPE Ratio as an indicator of HIV neurological risk. In the age of HAART, individuals infected with HIV now have access to a multitude of different treatments that can effectively mitigate the viral load of the disease. These treatments, however, are not equal in their ability to cross the blood-brain barrier (BBB) and thereby reduce the virus in the CNS. Differences in drugs and use histories produce individual differences in risk for neurocognitive difficulties. Patients fluctuate between drugs that may differ in CNS penetrativeness, and they vary in the length of time using particular medications. The CPE Ratio was hypothesized as a more sensitive indicator of neurological risk than either the Nadir CD4+ count or years diagnosed because it takes into account a patient's comprehensive (and often complicated) medication history. Findings here supported the value of the CPE ratio index.

The CPE Ratio score provides clinical psychologists, physicians, nurses, and other medical staff directly involved with patient care a potentially effective means to

identify those at neurocognitive risk. Neuropsychological deficits associated with HIV infection can be subtle during years of initial infection and in treated populations (Reger et al., 2002; Woods et al., 2009). As a result, during a medical or psychological evaluation it is plausible that an HIV-infected patient may appear cognitively intact during an office visit, yet in actuality she or he already experiences subtle cognitive changes. This scenario has the potential to negatively impact patient care in several ways, including the presumption that a patient can follow complex instructions related to medication adherence or attend to activities of daily living. The CPE Ratio may offer an effective gauge to alert healthcare providers to subtle patient vulnerability or needs.

Another implication surrounds the study's supporting evidence of HIVs affinity for impacting the frontostriatal system (i.e., basal ganglia and prefrontal cortex), the cognitive domains associated with this neural network, and the typical neuropsychological sequela associated with infection. The results of the first hypothesis corroborates previous research that processing speed as an initial domain compromised by HIV-infection of the CNS (Reger et al., 2002; Woods et al., 2009). The fact that performance on the composite score of visuospatial processing/attention and executive/inhibition were not related to either HIV indicators (CPE Ratio and Nadir CD4+ count) or their interaction is consistent with prior research that basic attention, concentration skills, and executive dysfunction surrounding cognitive flexibility remain relatively intact until the later stages of disease progression (Brew, 2004, Reger et al, 2002; Woods et al., 2009). Given that the mean Nadir CD4+ was above the clinical threshold for an AIDS diagnosis (i.e., >200 cells/μL), it can be argued that the majority of

the present sample was relatively healthy and currently at less neurocognitive risk than individuals with more progressed infection or an AIDS-defining condition.

In regard to the second hypothesis, the resulting evidence provided empirical support that HIV-associated nonverbal fluency difficulties may involve cognitive processes that are similar to those observed with verbal fluency performance. In fact, current findings suggest that nonverbal difficulties may emerge earlier than verbal problems. Previous research found that the ability to effectively utilize strategic clusters during verbal fluency tests was impaired in patients with compromised frontostriatal systems . Hence, the present results extend HIV's purported frontrostriatal affinity (Iudicello et al., 2008; Woods et al., 2009) to nonverbal fluency as well. Despite these nonverbal fluency findings, which were hypothesized based upon prior verbal fluency results, the current study did not replicate those prior verbal fluency effects (Thames et al., 2012; Milikan et al., 2004; Woods et al., 2004). An implication of this outcome is that the nonverbal frontal issues may emerge earlier in the cognitive progression than do verbal issues.

The role of strategic clusters to mediate between HIV indicators and nonverbal fluency outcome was found only for CPE Ratio and not for Nadir CD4+ count, which deviates slightly from previous research on findings linking verbal fluency and HIV. Millikin, Trepanier, and Rourke (2004) concluded that poor phonetic fluency performance was associated with impaired switching (not clustering), but only in those with more advanced HIV-infection. As stated above, given that the mean Nadir CD4+ was above 200 cells/μL, the present sample should not be characterized as having advanced HIV-infection. As such, finding that both switching and cluster size mediated

the relationship between CPE and total figures produced offers further support for the CPE Ratio as a sensitive index for detecting cognitive risk.

A possible explanation for the failure to replicate verbal fluency effects could be the general health status of the sample. The implication of this explanation would be that nonverbal fluency is susceptible to HIV-associated changes earlier in the disease process than verbal fluency is. Prior research on the neurological correlates of fluency lends support that both verbal and nonverbal modalities rely predominately on bilateral frontal processes in both healthy and clinical populations (Fama et al., 2000; Tucha, Smelly, & Lange, 1999). There is evidence, however, that some degree of lateralized processing still differentiates these modalities. For example, Baldo and colleagues (2001) found that individuals with left frontal lesions performed slightly worse on verbal fluency tests (compared to right frontal patients) while design fluency impairment was found for right, left, and bilateral impairment. Figural fluency may detect difficulties arising from diverse frontal regions whereas verbal fluency is predominantly left frontal. Although HIV shows a propensity of frontostriatal impairment, its impact on specific regions of the frontal cortex may vary. Given the varied frontal-subcortical regions that HIV may initially target, a test such as figural fluency, which may be impacted by damage to various brain regions, may cast a broader screening net and therefore detect impairment earlier than a test such as verbal fluency that is sensitive to more specific brain regions.

It is also plausible that this disassociation may be due to design fluency being a relatively pure executive task given that verbal fluency also involves drawing from language stores that are often relatively preserved in early subcortical and frontal-variant pathologies (Hodges et al., 1999). Indeed, drawing from a crystalized, language store

(verbal fluency) versus self-generation of abstract stimuli (nonverbal fluency) does involve distinct neural regions (Robinson et al., 2012). Although prior research and current findings lend broad support that strategic deficits in clustering and switching are associated with poor fluency performance, the generation of abstract designs may be a more difficult task compared to the production of verbal items. It may be that subtle nonverbal fluency difficulties and subsequent set-shifting and clustering problems surface more readily versus verbal analogs. Given HIV's propensity for infecting the frontostriatal network and subsequent executive, strategic abilities (discussed above), future neuropsychological research with integrated neuroimaging should examine this differential.

Finally, with regard to memory issues (Hypothesis 3), the CPE Ratio and Nadir CD4+ failed to predict a robust sub-cortical memory profile characterized by shallow encoding, poor retrieval, and intact recognition on the NWTLT when tested using multiple regression analyses. One problem detected was the statistical colinearity of the two predictors. Subsequent partial correlation analyses revealed an association between error scores and the CPE Ratio in accordance with both the hypothesis and previous research on verbal memory. As Delis and colleagues (1994) found in examining the verbal memory pattern of HIV, Parkinson's (PD), and Alzheimer's (AD) patients, both the HIV and PD patients demonstrated an increased number of repetition and cued intrusion errors compared to normal controls and AD patients. These types of errors are consistent with the types of errors found in the present study to correlate with CPE (learning repetitions and forced-choice target intrusions). These partial correlations imply that the CPE Ratio is sensitive to memory impairment consistent with frontostriatal function – specifically,

errors were consistent with the learning and recall errors characteristic of sub-cortical disease.

**Limitations**

There are several limitations of this study to consider. First, difficulty recruiting HIV-infected adults from a rural and small population reduced the sample size. As a result, it is possible that some analyses lacked sufficient power to detect a true effect. For example, omission errors approached but did not meet statistical significance. Nevertheless, it is important to note the robust nature of the present findings, specifically the utility of the CPE Ratio as an effective predictor of neurocognitive risk, in light of this statistical power. Distance, time, and expense were some barriers to participation. Others may not have perceived a personal value of the evaluation or might have wished to avoid learning about any potential cognitive changes. To the extent possible, given resources available for the study, these barriers were addressed (e.g., examiners traveled to sites more easily accessible for testing). Further studies might offer financial compensation for time and travel expense.

Secondly, although the CPE Ratio score was calculated via chart review of each participant's medical record in the primary care clinic, there were five participants who did not have a complete medical history documented since the time of their diagnosis. As a result, data from these participants were based upon their recall of the medications they were prescribed during the early years following diagnosis. The negative impacts that recall bias has on the validity of research are well documented (Hassan, 2006) and important to take into consideration with the present findings given the sample size. In addition, degree of medication compliance since infection was not assessed and as a

result, calculation of the CPE Ratio score was made under the assumption that participants were compliant with their HAART regiment. Given that prospective memory impairments have been associated with HIV-infection (Odiase, Ogunrin, & Ogunniyi, 2007; Woods et al., 2007; Woods et al., 2009), which can impact ones' ability to remember to take regular medication, it is unknown how variability of non-compliance within the sample impacted the present results.

Furthermore, although the CPE Ratio score appeared to be a more sensitive indicator of neurological risk than either Nadir CD4+ or years of diagnosis, CD4+ was not given the same degree of estimation as was the CPE. CPE reflected fluctuations and duration of medication use. Similar attention to fluctuations and duration of various CD4 levels may lead to a more sensitive indicator of disease progression and / or neurocognitive risk than merely noting the Nadir level. Hence, it is possible that a similar quotient score of Nadir CD4+ and years of diagnosis may also be of utility and provide a useful indicator for rate of disease progression. This hypothesis warrants further examination.

Lastly, although attempts were made to create a neuropsychological battery that assessed most cognitive domains, its breadth was limited out of desire to keep the administrative time under three hours. As a result, certain neuropsychological domains were either omitted or limited, such as prospective memory, visual working memory, and simple motor ability (e.g., finger tapping). In addition, examiner error resulted in missing data for some measures for some subjects, which made certain tests unavailable for the exploratory PCA for the first hypothesis. These included the Wisconsin Card Sorting Test, DKEFS Sorting task, and Grooved Pegboard. Given the sorting measures are

designed to assess cognitive flexibility via degree of perseveration and Grooved Pegboard assess motor dexterity and speed, it is unknown how well these measures would have loaded onto the composite scores, specifically Executive/Inhibition and Processing Speed.

**Future Research**

While several studies have examined the impact that the use of lower CNS-penetrative HAARTs have on neurocognitive functioning (Cysique & Brew, 2009; Ellis et al., 2014; Letendre et al., 2008), this is the first study to create and utilize a CPE Ratio score. These findings lend additional support for the hypothesis that use of high CNS-penetrative HAARTs is associated with better neuropsychological performance. Hence, first and foremost it is important that the validity of the CPE Ratio for neurocognitive risk in HIV-infected populations continued to be studied in an expanded population. The CPE Ratio score demonstrates potential as an effective, clinical gauge of neurocognitive risk in HIV-infected populations and warrants further research to test the utility of this calculation.

HIV treatments not only vary in their ability to cross the blood-brain barrier, but also in their mechanism to prevent viral replication. These differing classes include entry inhibitors (interferes with the virus's ability to bind to receptors on the outside of a cell), fusion inhibitors (interferes with the virus's ability to fuse with a cellular membrane), reverse transcriptase (RT) inhibitors (prevents the virus's enzyme from converting single stranded RNA into DNA), integrase and protease inhibitors (interferes with the subsequent enzyme's ability to function), and multi-class (a combination of these functions). The use of HIV medications have been shown to come with varying risk of

CNS toxicity and subsequent neural impairment, independent of the virus (Carr, 2003; Squire, Stark, & Clark, 2004). Hence, given the variability in type of medications available and risk of toxicity, future research should further examine the utility and efficacy of the CPE Ratio in the context of neurotoxicity risks to assess potential differences in measuring neurocognitive vulnerability based on treatment class.

Furthermore, although the present study lends initial support for the hypothesis that a lower CPE Ratio score is associated with poorer performance on certain neuropsychological domains (i.e., processing speed, nonverbal fluency, and nonverbal learning and recall errors), CPE was treated as a continuous scale. Further research is needed to explored whether the CPE ratio may have a clinical cutoff that establishes neurocognitive risk. Within the context of a healthcare setting, face-to-face time between provider and patient can be limited; establishing a threshold that optimizes sensitivity and specificity potentially holds tremendous clinical utility in ascertaining which patients warrant further attention and evaluation for risk of neurocognitive decline.

Lastly, due to demographic and regional limitations of the population, the majority of the sample was male (80%). Although limited, available neuropsychological research has found evidence for neuropsychological impairments to differ according to sex (Failde-Garrido, Alvarez, & Simon-Lopez, 2008). Thus, subsequent research on a broader population demographic should assess for potential gender effects on impacting the efficacy and utility of the CPE Ratio score in measuring neurocognitive risk.

**Summary**

In conclusion, this is the first study to demonstrate the utility of a new quotient score (CPE Ratio), taking into account broad medication history with years of infection,

as a measure of neurocognitive risk. In addition, these results provided additional empirical support for HIV's affinity for infecting and impairing the frontostriatal network as demonstrated through impairments in neuropsychological domains (e.g., processing speed, nonverbal fluency, and effective strategy use) that are commonly seen in other subcortical disease. Interestingly, similar impairments were not found on verbal fluency tasks, which raise a question as to whether nonverbal processes are more sensitive than verbal to neurocognitive sequelae early in HIV infection. Given that these findings were found in light of low power due to recruiting challenges and in a relatively healthy HIV+ population (average CD4+ > 200), the findings demonstrate the robustness and potential of CPE as a predictor to identify patients at neurocognitive risk, even in asymptomatic stages of the disease. Hence, future research should seek to expand upon these findings with a larger population as well as examine the ecological utility of this score to determine its clinical significance in predicting everyday functioning and identifying those who may benefit from early health-related interventions to mitigate HIV-associated impairments.

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# Appendix A: Tables & Figures

Table 1

*Overview of the Basal Ganglia Divisions*

| Basal Ganglia Structure | Primary Subdivision | Secondary Subdivision |
|---|---|---|
| Striatum | Dorsal Striatum | Caudate |
| | | Putamen |
| | Ventral Striatum | Nucleus Accumbens |
| | | Septum |
| | | Olfactory Bulb |
| Globus Pallidus | External Segment (Gpe) | |
| | Internal Segment (Gpi) | |
| | Ventral Pallidum | |
| Substantia Nigra | Pars Compacta (SNc) | |
| | Pars Reticula (SNr) | |
| Subthalamic Nucleus (STN) | | |

Table 2

*Diagram of Fronto-Thalamo-Striatal Circuitry*

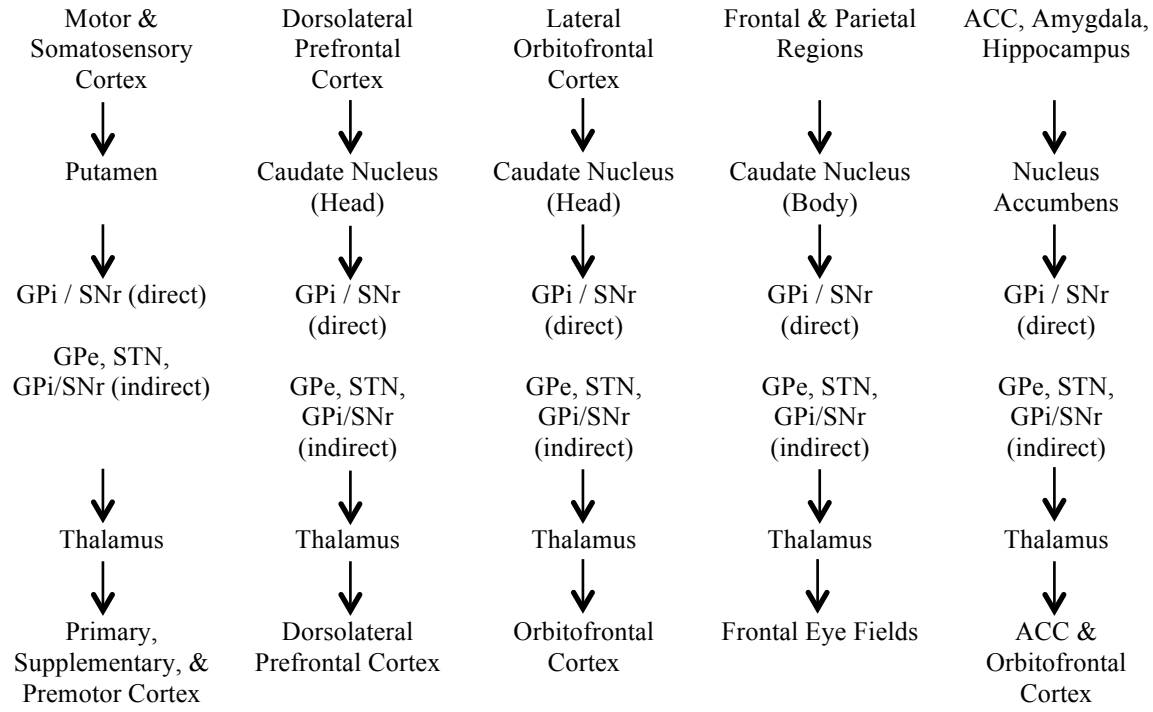


Table 3

*Demographic Information*

| Item | Frequency | Percentage |
|---|---|---|
| Sex | | |
| Male | 20 | 80% |
| Highest Degree | | |
| Less/Equal 12 years | 10 | 40% |
| More than 12 years | 15 | 60% |
| Ethnicity | | |
| White | 22 | 88% |
| Hispanic | 2 | 8% |
| Native American | 1 | 4% |
| Marital Status | | |
| Single | 9 | 36% |
| Married/Co-Habitating | 13 | 52% |
| Divorced/Separated | 3 | 12% |
| Handedness | | |
| Right | 23 | 92% |
| Left | 2 | 8% |

| Item | Mean | Std Deviation |
|---|---|---|
| Age | 45.08 | 9.01 |
| NAART | 105 | 10.29 |
| Years Diagnoses | 10.72 | 8.69 |
| CPE Ratio | 2.62 | 0.61 |
| Nadir CD4+ | 277 | 187.25 |

Table 4

*Administration Order of Neuropsychological Battery*

| Neuropsychological Test | Estimated Administration Time |
|---|---|
| Northwest Trails Learning Trial | 15 Minutes |
| WAIS-IV Coding | 3 Minutes |
| Wisconsin Card Sorting Test | 15 Minutes |
| D-KEFS Verbal Fluency | 10 Minutes |
| Ruff 2 & 7 Selective Attention Test | 6 Minutes |
| **** 30 Minute Delay Since Idaho Trails Learning Trial **** | |
| Northwest Trails Free Recall Trial | 5 Minutes |
| Northwest Trails Pattern Recognition | 5 Minutes |
| CVLT-II Learning Trial | 15 Minutes |
| D-KEFS Trails | 5 Minutes |
| Ruff Figural Fluency Test | 7 Minutes |
| Grooved Pegboard Test | 5 Minutes |
| Rey Complex Figure Test Copy Trial | 3 Minutes |
| NAART | 3 Minutes |
| Rey Complex Figure Test – Immediate Recall | 5 Minutes |
| **** 20 Minute Delay Since CVLT-II Learning Trial **** | |
| CVLT-II Recall Trial | 5 Minutes |
| WAIS-IV Letter-Number Sequencing | 5 Minutes |
| D-KEFS Sorting Test | 15 Minutes |
| D-KEFS Color-Word Interference Test | 5 Minutes |
| **** 30 Minute Delay Since RCFT Learning Trial **** | |
| Rey Complex Figure Test – Delayed Recall | 5 Minutes |
| Rey Complex Figure Test – Recognition | 3 Minutes |

Table 5

*Varimax Rotation Principle Component Analysis (PCA) Matrix*

| Item | Component 1 | Component 2 | Component 3 |
|---|---|---|---|
| Construct 1: Executive/Inhibition | | | |
| WAIS Letter-Number Sequencing | **0.620** | 0.134 | 0.044 |
| Errors DKEFS Color-Word Inhibition | **0.873** | 0.017 | 0.168 |
| Errors DKEFS Color-Word Inhibition/ Switching | **0.855** | 0.096 | 0.122 |
| Construct 2: Visuospatial Processing | | | |
| Ruff 2&7 Total Accuracy | 0.345 | **0.885** | -0.042 |
| Ruff Figural Fluency Total Errors | -0.426 | **0.782** | 0.034 |
| Errors DKEFS Letter-Number Sequence | 0.327 | **0.689** | 0.141 |
| Construct 3: Processing Speed | | | |
| DKEFS Combined Color-Word Reading | 0.055 | 0.399 | **0.742** |
| Ruff 2&7 Total Speed | 0.044 | -0.233 | **0.882** |
| WAIS Coding | 0.236 | 0.096 | **0.840** |

Table 6

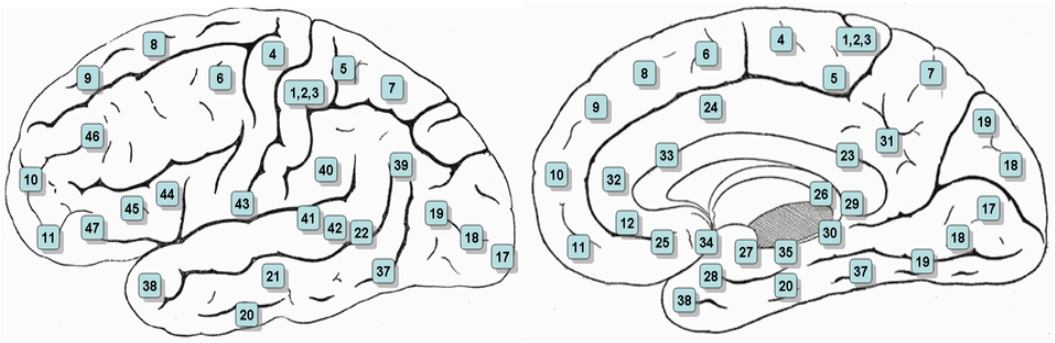
*Partial correlation between HIV indicators and neuropsychological variables*

| **Test Score** | **CPE** | **(*p*)** | **Nadir CD4+** | **(*p*)** |
|---|---|---|---|---|
| Hypothesis One | | | | |
| Executive/Inhibition | -.066 | (.776) | .094 | (.685) |
| Visuospatial Processing | .112 | (.630) | .280 | (.219) |
| Processing Speed | **.533** | **(.013)** | .243 | (.288) |
| Hypothesis Three | | | | |
| NWTT Total | .243 | (.289) | .256 | (.263) |
| NWTT Free Recall | .275 | (.227) | .354 | (.115) |
| NWTT Forced Choice | .327 | (.148) | .186 | (.418) |
| NWTT Segment Hits | -.043 | (.854) | .198 | (.389) |
| NWTT Segment False Positives | -.185 | (.421) | .158 | (.494) |
| NWTT Errors: | | | | |
| Learning Repetitions | **-.476** | **(.029)** | -.344 | (.127) |
| Learning Perseverations | -.309 | (.173) | -.345 | (.125) |
| Free Recall Insertions | -.285 | (.210) | -.143 | (.537) |
| Free Recall Omit Connects | -.276 | (.225) | -.321 | (.156) |
| Free Recall Omit Nodes | -.421 | (.057) | -.193 | (.403) |
| Forced Choice Letter errors | -.211 | (.359) | -.047 | (.839) |
| Forced Choice Number errors | **-.446** | **(.043)** | **-.434** | **(.049)** |

Table 7

*Semi-partial correlations between HIV Indicators and Northwest Trail Test scores*

| **Test Score** | **CPE** | **Nadir CD4+** | **CPE X CD4+** |
|---|---|---|---|
| NWTLT Learning/Recall | | | |
| Total Learning | .131 | .139 | .024 |
| Free Recall | .179 | .179 | .218 |
| Forced Choice Recall | .312 | -.024 | .197 |
| Segment Recognition, Hits | -.073 | .164 | .239 |
| Segment Recognition, False + | -.390 | .369 | **-.412** |
| NWTLT Error Scores | | | |
| Learning Repetitions | -.286 | -.174 | .172 |
| Learning Perseverations | -.155 | -.193 | -.031 |
| Free Recall Connect Omissions | -.186 | -.150 | -.185 |
| Free Recall Node Omissions | -.374 | .053 | -.154 |
| Forced Choice, Target (letter) | -.216 | .074 | -.060 |
| Forced Choice, Non-Target | -.292 | -.170 | -.183 |




Lateral View Medial View

*Figure 1.* Brodmann maps of functionally distinct regions of the frontal cortex: Primary Motor Cortex (BA 4), Premotor Cortex (BA 6 & 8), Dorsolateral Prefrontal Cortex (BA 9 & 46), Orbitofrontal Cortex (BA 10, 11, & 47), and Anterior Cingulate Gyrus (BA 24, 32, & 33).

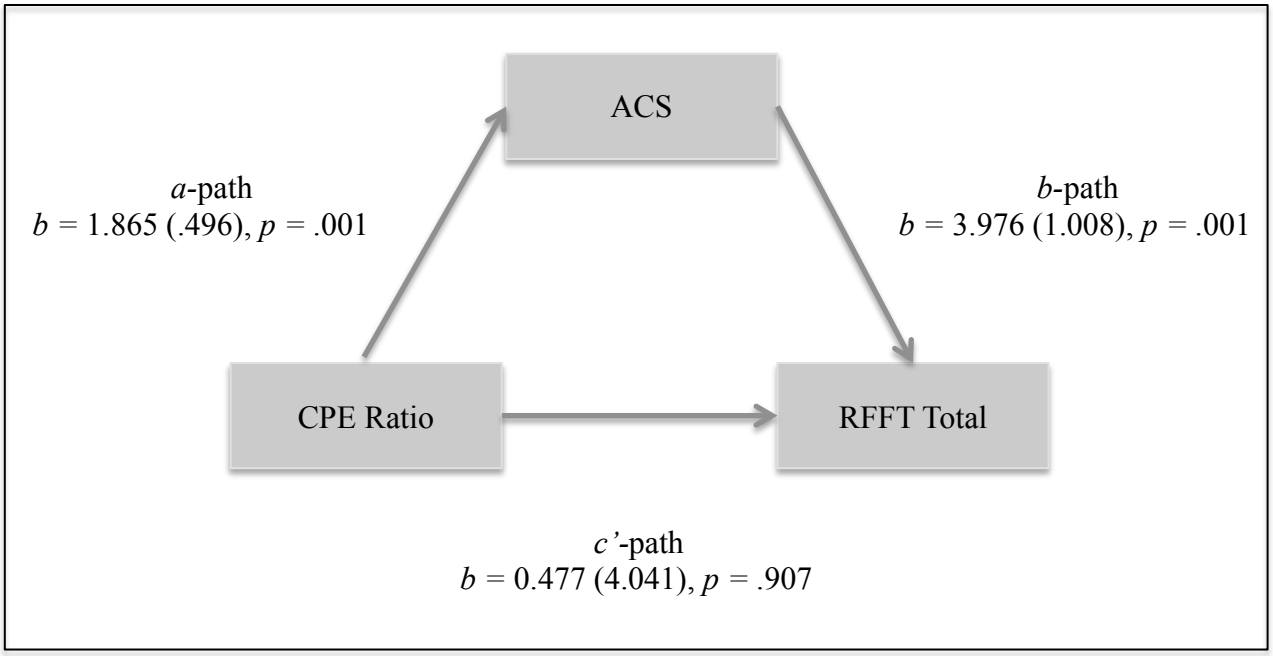



*Figure 2.* Controlling for age and premorbid intelligence, Average Cluster Size (ACS) significantly mediates the relationship between CPE Ratio and total score on the Ruff Figural Fluency Test (RFFT).

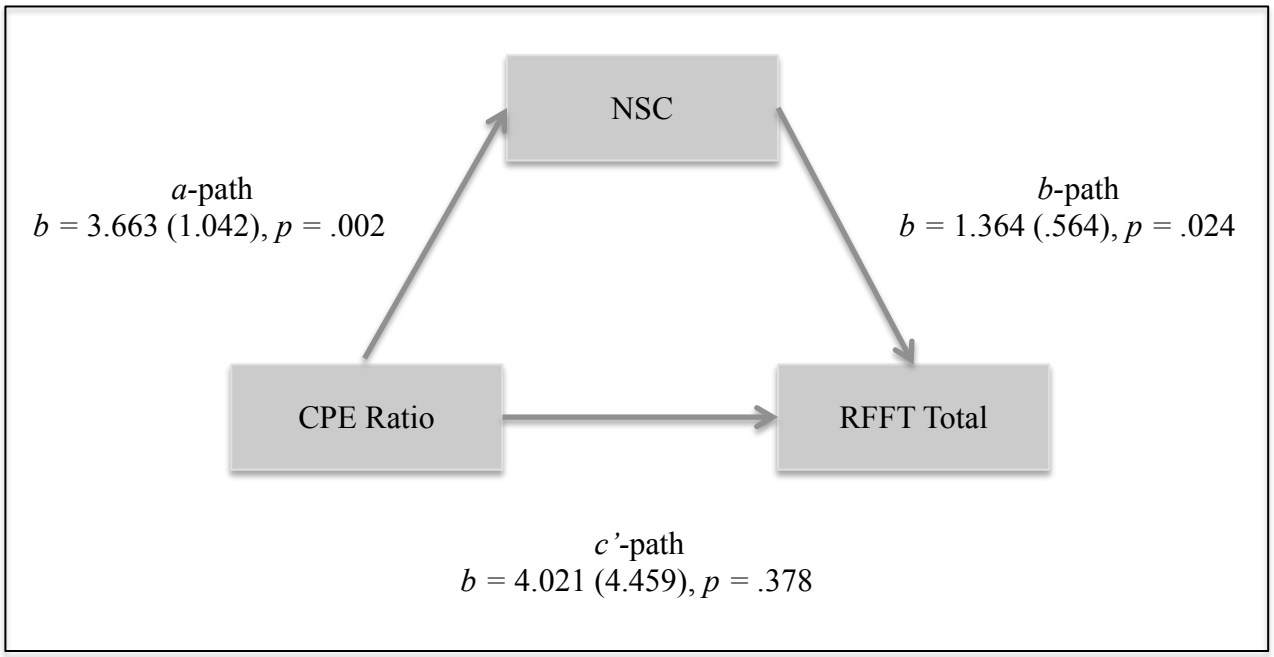



*Figure 3.* Controlling for age and premorbid intelligence, Number of Strategic Clusters (NSC) significantly mediates the relationship between CPE Ratio and total score on the Ruff Figural Fluency Test (RFFT).

# Appendix B: Forms & Measures

## Consent Form

### *Neurocognitive Evaluation of HIV-Positive Patients*

We are asking you to be in a research study.

You do not have to be in this study.

If you say yes, you may quit the study at any time.

Please take as much time as you want to make your choice.

**Why is this study being done?**

Dr. Peter Vik, a Professor of Psychology at Pacific University and Dr. David Hachey, Associated Professor of Pharmacy at Idaho State University are conducting a study to examine effective ways to assess mental ability among persons living with HIV. We want to learn more about brain functioning and thinking process of people who are HIV-positive.

We are asking people like you to participate by completing a 3 hour assessment. The assessment involves completing a number of cognitive (mental) tasks, much like puzzles. Some tasks you will find easy, some will be difficult. Most of the tests used are part of the routine cognitive assessment we are providing to patients who attend the Family Practice clinic. There are three measures, however, that we are using on an experimental basis: a visual memory test and two questionnaires.

**What happens if I say yes, I want to be in the study?**

If you say yes, we will:

- Someone from Dr. Vik's research group will contact you and arrange an appointment to conduct the testing.
- When you come for testing, a research team member will present detailed information about the study and what you can expect, and then she or he will ask if you are willing to participate in the project.
- The researcher will begin the testing, which will take about 3 hours.
- After completing testing, you will have an opportunity to ask any questions you may have.
- The researcher and Dr. Vik will score your results and write a report about your brain functioning that will be provided to the clinical staff at the Family Residency HIV clinic.

**How long will the study take?**

This study will take about 3 hours, including testing and participation paperwork.

**Where will the study take place?**

The study will take place at one of three possible places, depending on what is most convenient for you. Possible places are: the ISU Psychology Clinic, Family Practice Residency (HIV Clinic), or District 7 Health Department.

**What happens if I say no, I do not want to be in the study?**

No one will treat you any differently. You will not be penalized.

**What happens if I say yes, but change my mind later?**

You may stop being in the study at any time. You will not be penalized. Your relationship with the HIV Clinic will not change.

**Who will see my test information?**

The only people who will see your test results will be the people who work on the study, the clinical staff at the HIV Clinic, and those legally required to supervise our study.

Your test results, health information, and survey information, and a copy of this document will be locked in our files.

When we share the results of our study in professional journals, at conferences, or as part of workshops, we will not include your name. We will do our best to make sure no one outside the study will know that you are a part of the study.

**Will it cost me anything to be in the study?**

No.

**Will being in this study help me in any way?**

As a result of being in this study you will receive a free comprehensive cognitive evaluation that will become part of your medical record at the Family Practice Residency HIV Clinic. This information may help your clinical staff make decisions about your treatment.

**Will I be paid for my time?**

You will not be paid; however, you will receive a free cognitive evaluations.

**Is there any way being in this study could be bad for me?**

Yes, there is a chance that someone could find out that you were in this study and learn something about you that you do not want them to know.

We will do our best to protect your privacy.

**What if I have questions?**

Please call the head researcher of the study, Nickolas Dasher, M.S. (208-282-2462) or Dr. David Hachey (208-282-5763) , if you:

- Have questions about the study.
- Have questions about your rights.
- Feel you have been injured in any way by being in this study.

You can also call the Idaho State University Human Subjects Committee office at 208-282-2179 to ask questions about your rights as a research subject.

**Do I have to sign this document?**

No. You only sign this document if you want to be in the study.

**What should I do if I want to be in the study?**

You sign this document. We will give you a copy of this document to keep.

By signing this document you are saying:

- You agree to be in the study.
- We talked with you about the information in this document and answered all your questions.

_____
Your Name (please print)

_____ _____
Your Signature Date

**Intake Questionnaire**

This interview is ***completely confidential*** – You ***cannot*** be identified by your answers.

**PART I: Demographics**

1. How old are you? _____

2. Sex? M F (circle one)

3. What is your ethnicity? (circle one):

(1) European-American (2) White Hispanic (3) Latino

(4) Asian/Pacific Islander (5) African American (6) Native American

(7) Other/Multi-racial

4. How many years of education did you complete? (circle one):

(1) Less than 12 years (2) High School Diploma/GED

(3) Associates/Technical Degree (4) College Degree (undergraduate)

(5) Masters Degree (6) Doctorate

5. Are you (circle one):

(1) Right Handed (2) Left Handed (3) Both Hands Used Equally

6. What is your current marital status? (circle one):

(1) Single (2) Married (3) Co-Habitating

(4) Divorced (5) Widowed (6) Other

**PART II: Health Status**

7. Have you experienced or has a doctor ever told you that you have any of the following conditions? (**circle all that apply**)

(1) Encephalitis (2) HIV Positive (3) Huntington's Disease

(4) Stroke/TIA (5) Seizures (6) Alzheimer's Disease

(7) Dementia (8) Brain Tumor (9) Parkinson's Disease

(10) Depression (11) Anxiety (12) Learning Disability

(13) Diabetes (14) Migraines (15) Multiple Sclerosis

(16) Schizophrenia (17) Psychosis (18) Concussion

(19) Bipolar Disorder (20) Sleep Apnea (21) Migraine/Persistent Headaches

(22) Loss of Consciousness

- If yes, how long? (circle one) > 5 minutes > 20 minutes

(23) Severe Head Injury

- If yes, OPEN or CLOSED head injury (circle one)

**Intake Questionnaire**

This interview is ***completely confidential*** – You ***cannot*** be identified by your answers.

8. Have you ever been told by a doctor that you have had permanent brain damage or loss due to a head injury?
Yes No

9. Please list any serious accidents that required hospitalization:

_____

_____

10. Please describe any head injuries including when it happened and points of impact (e.g. frontal injury).

_____

_____

**PART III: Alcohol and Drugs**

11a. How old were you when you began drinking **alcohol** regularly _____ Age_____ Never

11b. On the days you do drink, approximately how much alcohol did you drink? _____ Drinks
(Drink = 1oz liquor; 4oz wine; 12oz beer)

11c. How many days ago did you last drink alcohol? _____ Days ago

12a. How old were you when you began using **marijuana** regularly? _____ Age _____ Never

12b. How many days ago did you last use marijuana? _____ Days ago

13a. How old were you when you begain using **methamphetamine** regularly? _____ Age _____ Never

13b. When was the last time you used methamphetamine? _____ Days ago

14a. How old were you when you began using **cocaine** regularly? _____ Age _____ Never

14b. When was the last time you used cocaine? _____ Days ago

**PART IV: Medications**

15. Have you taken any medication TODAY? (circle one) YES NO

15b. If yes, please answer questions below

| Name of Medication | Time Taken | Dosage | Reason for Medication |
|---|---|---|---|
| _____ | _____ | _____ | _____ |
| _____ | _____ | _____ | _____ |
| _____ | _____ | _____ | _____ |
| _____ | _____ | _____ | _____ |
| _____ | _____ | _____ | _____ |