THE IMPACT OF EXECUTIVE FUNCTION ON MEDICATION
ADHERENCE IN PEOPLE LIVING WITH HIV

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by

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CHAPTER 1

INTRODUCTION

The advent of highly active antiretroviral therapy (HAART) has transformed the treatment of HIV, and, by substantially reducing morbidity and mortality, the prognosis for infected patients all over the world has been improved (Palella et al., 1998). The success of HAART, however, depends on the patients’ ability to adhere to complicated treatment regimens, with the many different medications requiring a different schedule and mode of administration (Hogg et al., 2002). Indeed, studies of HAART medication adherence have shown that not all patients are capable of managing the complex schedule of their medication regimens, thus running the risk of development of drug resistance (Bangsberg et al., 2000). A recent estimate suggested that approximately 40% of patients receiving antiretroviral therapy have difficulties with adherence (Bangsberg et al., 2001). Known predictors of poor adherence include mood disorders, polysubstance abuse, complexity of medication regimen, awareness of illness, and beliefs about medication efficacy and side effects (Gifford et al., 2000; Golin et al., 2002; Gordillo, del Amo, Soriano, & Gonzalez-Lahoz, 1999; Haubrich et al., 1999; Holzemer et al., 1999; Mannheimer, Friedland, Matts, Child, & Chesney, 2002; Paterson et al., 2000; Singh et al., 1999). The rate of cognitive impairment is relatively high in people with HIV and has been shown to have an impact on how well patients are able to adhere to their
medications (Cysique et al., 2009; Gorman, Foley, Ettenhofer, Hinkin, & van Gorp, 2009; Munoz-Moreno & Blanch Andreu, 2009). However, most studies studying its impact have focused on the cognitive domain of memory (Woods et al., 2009). The impact of impairment in other cognitive domains on medication adherence is just beginning to be explored (Ettenhofer et al., 2009). The present study aims to study the association between executive function, a specific aspect of cognitive function, and medication adherence in people infected with HIV.

Prevalance and Impact

Human immunodeficiency virus (HIV) is a retrovirus that can lead to acquired immunodeficiency syndrome (AIDS), a condition in humans in which the immune system begins to fail, leading to life-threatening opportunistic infections (DHHS-CDC, 2009). Infection with HIV occurs by the transfer of blood, semen, vaginal fluid, pre-ejaculate, or breast milk (DHHS-CDC, 2009). The four major routes of HIV transmission are unprotected sexual intercourse, contaminated needles, breast milk, and transmission from an infected mother to her baby at birth (DHHS-CDC, 2009). HIV infection in humans is now pandemic. In January 2006, the Joint United Nations Program on HIV/AIDS and the World Health Organization (WHO) estimated that AIDS has killed more than 25 million people since it was first recognized on December 1, 1981 (UNAIDS, 2006). About 0.6 percent of the world's population is infected with HIV (UNAIDS, 2006). In 2005, AIDS claimed an estimated 2.4–3.3 million lives, of which more than 570,000 were children (UNAIDS, 2005). A third of these deaths are occurring in sub-Saharan Africa, causing grave economic and social setbacks (UNAIDS, 2005). It
is estimated that HIV is set to infect 90 million people in Africa, resulting in a minimum estimate of 18 million orphans (Greener, 2002).

HIV infection has four stages: incubation period, acute infection, latency stage and AIDS (DHHS-CDC, 2009). The initial incubation period upon infection is asymptomatic and usually lasts between two and four weeks (DHHS-CDC, 2009). Acute infection of HIV lasts an average of 28 days and can include symptoms such as fever, lymphadenopathy, pharyngitis, rash, myalgia, malaise, and mouth and esophageal sores (DHHS-CDC, 2009). The latency stage shows few or no symptoms and can last anywhere from two weeks to twenty years and beyond (DHHS-CDC, 2009). Acquired immune deficiency syndrome or AIDS, the fourth and final stage of HIV infection manifests as symptoms of various opportunistic infections (DHHS-CDC, 2009). In 2007, an estimated 33.2 million people lived with AIDS worldwide, and it killed an estimated 2.1 million people, including 330,000 children (UNAIDS, 2007). Over three-quarters of these deaths occurred in sub-Saharan Africa (UNAIDS, 2008). Although treatments for AIDS and HIV can slow the course of the disease, there is currently no vaccine or cure (DHHS-CDC, 2009).

HAART is the current standard for treatment of HIV infection. Introduced in 1996, HAART has been highly beneficial to many HIV-infected individuals (Palella et al., 1998). Current optimal HAART options consist of combinations consisting of at least three drugs belonging to at least two types, or "classes", of antiretroviral agents (DHHS-CDC, 2009). Typical medication regimens consist of two nucleoside analogue reverse transcriptase inhibitors (NARTIs or NRTIs) and either a protease inhibitor or a non-
nucleoside reverse transcriptase inhibitor (NNRTI)(DHHS-CDC, 2009). HAART is available in most developed countries and clinicians assess viral load, CD4 cell count decline (a measure of a person’s immune function), and patient readiness (e.g. psychological conditions) when recommending treatment initiation (DHHS, 2005). Standard goals of HAART include improvement in the patient’s quality of life, reduction in complications, and reduction of the HIV virus itself below the limit of detection (Martinez-Picado et al., 2000). However, treatment does not cure the patient of HIV and needs to be continued throughout one’s life to prevent return of HAART resistant HIV (Dybul, Fauci, Bartlett, Kaplan, & Pau, 2002).

Despite the demanding nature of HAART regimens, many HIV-infected individuals have experienced remarkable improvements in their overall health and quality of life, which has led to the significant drops in HIV-associated morbidity and mortality (Chene et al., 2003; Palella et al., 1998; Woods et al., 2009). In the absence of HAART, progression from HIV infection to AIDS occurs at a median of between nine to ten years and the median survival time after developing AIDS is only 9.2 months (Morgan & Whitworth, 2001).

Adherence to (or compliance with) a medication regimen is generally defined as the extent to which patients take medications as prescribed by their health care providers (Osterberg & Blaschke, 2005). Rates of adherence for individual patients are usually reported as the percentage of the prescribed doses of the medication actually taken by the patient over a specified period (Osterberg & Blaschke, 2005). Some investigators have further refined the definition of adherence to include data on dose taking (taking the
prescribed number of pills each day) and the timing of doses (taking pills within a prescribed period) (Osterberg & Blaschke, 2005). Adherence rates are typically higher among patients with acute conditions, as compared with those with chronic conditions; Persistence among patients with chronic conditions is disappointingly low, dropping most dramatically after the first six months of therapy (Osterberg & Blaschke, 2005). The ability of physicians to recognize nonadherence is poor, and interventions to improve adherence have had mixed results (Osterberg & Blaschke, 2005). Furthermore, successful interventions generally are substantially complex and costly. Poor adherence to medication regimens accounts for substantial worsening of disease, death, and increased health care costs in the United States (Osterberg & Blaschke, 2005).

Adherence to HAART is the strongest predictor of HIV-related outcome (Mills et al., 2006). However, for more than fifty percent of patients, HAART is not efficacious due to medication intolerance in the form of side effects, prior ineffective antiretroviral therapy and infection with a drug-resistant strain of HIV (Nieuwkerk et al., 2001). Non-adherence and discontinuation of therapy are the major reasons why some people do not benefit from HAART (S. L. Becker, Dezii, Burcel, Kawabata, & Hodder, 2002). There are various reasons for non-adherence and discontinuation. Major psychosocial issues include poor access to medical care especially in developing countries, inadequate social support, depression and substance abuse (Gordillo et al., 1999; Paterson et al., 2000; Singh et al., 1999). HAART-specific regimens can involve taking a large number of pills, making the regimens complex and demanding (Kleeberger et al., 2001). Side effects, including lipodystrophy, dyslipidaemia, diarrhea, insulin resistance, an increase in
cardiovascular risks and birth defects can also be a major deterrent (Montessori, Press, Harris, Akagi, & Montaner, 2004; Saitoh, Hull, Franklin, & Spector, 2005).
Nonadherence to HAART is not only detrimental but dangerous as it can result in the development and transmission of HAART-resistant strains of the virus, amplifying challenges to treatment (Bangsberg et al., 2000). Given these findings, there is an urgent need for understanding factors that improve adherence in order to promote better adherence practices in this population.

Impact of HIV on Cognitive Function

Cognitive impairment is relatively common in HIV infection (Cysique et al., 2009; Gorman et al., 2009; Munoz-Moreno & Blanch Andreu, 2009). HIV infects macrophages and microglia, but not neurons, although neurons are injured and die by apoptosis (Fessel, 2009). The predominant pathway to neuronal injury is indirect through release of macrophage, microglial and astrocyte toxins, although direct injury by viral proteins might also contribute (Fessel, 2009). These toxins overstimulate neurons, resulting in the formation of free radicals and excitotoxicity, similar to other neurodegenerative diseases (Fessel, 2009).

HIV-associated cognitive impairment is found across all disease stages, with increasing rates of impairment in increasing systemic stage of HIV disease (Brew, Crowe, Landay, Cysique, & Guillemin, 2009; Hardy & Vance, 2009). Consequently, HIV-positive patients have higher rates of unemployment (Albert et al., 1995) and difficulty completing instrumental activities of daily living (Benedict, Mezhr, Walsh, & Hewitt, 2000). While persons with the greatest degree of immunological compromise
exhibit the most severe cognitive impairment, there is inconsistency regarding cognitive dysfunction in individuals in early and asymptomatic stages of the illness (Mandal et al., 2008). The most significant form of cognitive impairment presents as HIV associated dementia (HAD) and afflicts 10–15% of patients with advanced infection in the United States (Sacktor, 2002). HAD is a form of subcortical dementia—a type of dementia affecting the subcortical regions of the brain and characterized by impairment in attention, motivation and emotionality (Ghafouri, Amini, Khalili, & Sawaya, 2006). The risk factors for HAD include age, low CD4 cell count, high plasma viral load, low hematocrit/red blood cells, cocaine use, medication resistance/compromise, co-infection and gender (Ghafouri et al., 2006). There is moderate to severe impairment in two or more areas including slowed decision making, cognitive, motor, and behavioral problems, attention/concentration problems, abstraction/reasoning problems, visuospatial skill problems, memory/learning impairment and speech/language problems (Ghafouri et al., 2006). A person who has HAD usually complains of irritability and sadness. HAD may also manifest itself in poor balance, clumsiness and sloppy handwriting (Ghafouri et al., 2006). Early stage HAD is characterized by decreased attention and concentration, slowing, memory impairment and apathy (Ghafouri et al., 2006). Late stage HAD begins to affect the domains of language, visuospatial ability, executive functioning, disorders of movement and behavior (Ghafouri et al., 2006).

More common is a less severe pattern of HIV-related cognitive dysfunction labeled minor cognitive motor dysfunction (MCMD). In MCMD, persons show impaired attention, memory, motor function, irritability, and emotional lability (Ghafouri et al.,
The prevalence of MCMD is 20-30% for asymptomatic and 60%-90% for late stage HIV patients (Ghafouri et al., 2006). The primary risk factors for MCMD are age, late stage disease and viral load (Ghafouri et al., 2006). MCMD can result in occupational problems, problems with activities of daily living and reduced capacity to cope (Heaton et al., 1995; McArthur et al., 2003; Sacktor, 2002; Saykin et al., 1991).

A meta-analysis from 2002 compared cognitive function in asymptomatic, symptomatic and AIDS-diagnosed individuals (Reger, Welsh, Razani, Martin, & Boone, 2002). In comparison to controls, asymptomatic persons were three times more likely to exhibit cognitive impairment (Reger et al., 2002). In symptomatic persons, impairments were most frequently found on tests of motor functioning, executive function, processing speed and language (Reger et al., 2002). In individuals diagnosed with AIDS, severe impairments were found in motor functioning, executive function, processing speed, visual ability; moderate impairments were found in language and visual ability and mild impairments were found in attention (Reger et al., 2002). This pattern of impairment is consistent with other and more recent studies (Bornstein, Nasrallah, Para, Whitacre, & Fass, 1993; Heaton et al., 1995; McArthur et al., 1993; Sacktor, 2002; Saykin et al., 1991; Tozzi et al., 2005).

Impact of Cognitive Function on Adherence

While persons with the severe cognitive impairment of HAD would be expected to have poor adherence, it is likely that persons with subtler, though specific types of impairment may also be unable to manage their medications. However, few studies have examined the possible relationship between specific cognitive deficits and medication
adherence in persons with HIV. Although it has been widely assumed that memory would be the cognitive ability most closely related to adherence, findings are inconsistent across studies (Ettenhofer et al., 2009; Lovejoy & Suhr, 2009; Woods et al., 2009). Specifically, results of memory as a predictor of poor adherence has varied depending on the specific memory measures used (Norell, 1985) and the severity of cognitive impairment; in populations with greater cognitive impairment, memory has been found to be a weaker predictor of adherence than aspects of executive function, such as cognitive flexibility (Avants, Margolin & Warburton, et al., 2001).

A cognitive ability more likely to be linked to poor adherence in non-demented HIV patients is executive function. The pattern of symptoms of cognitive decline in persons with HIV is consistent with subcortical involvement with projections to the frontal lobe, the brain region most important for executive functioning (Chang et al., 2008). In a restrictive sense, executive function refers to the processes that are needed for completion of complex cognitive tasks requiring selection of the information to be processed, finding the rule to be applied, shifting mental sets, solving a multiple set problem, resisting cognitive inferences, sharing attentional resources and retrieving information from memory (Meltzer, 2007). Most of these processes are strongly correlated with working memory defined as the ability to maintain and manipulate a set of pertinent information during a brief period and to use this internal representation to produce a response (Meltzer, 2007). Many have argued that the coordination and integration of the storing and integration of the storage and processing aspects of a working memory task involve executive processes (Meltzer, 2007). One of these
processes is controlled attention, which prevents the forgetting of necessary information that would otherwise result from the interference caused by the task’s processing operation (Meltzer, 2007). Miyake et al. have highlighted that among the executive processes the unitary ones are 1) mental set shifting 2) information updating and 3) monitoring actions. In a broader sense, executive functions are those that are needed in novel or demanding situations that require goal-directed behaviors as opposed to more reflexive behavioral responses that can be easily activated by over-learned or routine situations (Miyake, Emerson & Friedman, 2000). To be correctly executed, these goal-directed behaviors require: 1) intentional defining of a goal (‘the will to act’); 2) selection of appropriate information 3) keeping and monitoring information within the working memory buffer 4) devising and performing the plan of action and 4) exerting a feedback control to maintain or shift the program of actions (Miyake, Emerson & Friedman, 2000). It has been commonly assumed that executive dysfunction, as inferred from the results of certain neuropsychological tests, implies lesions of the frontal lobes (McCloskey, 2008). However, research has shown that executive functions can be disturbed by damage not only to the frontal lobes but also to other related brain areas, particularly the basal ganglia (McCloskey, 2008). This underscores the close relationship between prefrontal cortex and other subcortical structures (McCloskey, 2008).

Evidence of executive dysfunction can be elicited by examining a person’s ability to function in real-life situations, including observing the person’s topic initiation and management, turn taking, verbal organization and ability to engage in active listening (NCLD, 2009). Examples of more formal testing are Trail Making Tests A and B which
are timed and structured versions of ‘connect the dots’ drawing and have been used extensively with HIV-infected populations to quantify and track cognitive impairment (J. T. Becker et al., 1997). Executive dysfunction is common in HIV-infected persons without HAD and likely impact critical health behaviors such as medication adherence (Dawes et al., 2008). Indeed studies have shown that executive dysfunction is associated with poor medication adherence in other populations (Stoehr et al., 2008). Some studies have demonstrated a strong relationship between the ability to comprehend medical information and frontal lobe and executive function (Stoehr et al., 2008). In a study of HIV-infected injection drug users starting methadone maintenance therapy, poorer executive function test performance predicted nonadherence, whereas memory performance did not. The strongest relationship between nonadherence and cognitive performance was observed for the Trail Making Test B, a test particularly sensitive to frontal lobe and executive function. However, this study constitutes one of very few to have demonstrated a possible relationship between frontal lobe functioning and adherence.

**Current Study**

Understanding the relationship between cognitive functioning and adherence is particularly important because of the association between the immune system and risk of cognitive impairment (Bangsberg et al., 2000). Poor adherence can result in increased viral resistance and immunosuppression (Bangsberg et al., 2000), which causes poorer cognition, which can further decrease adherence rates, and so on (Selnes, 2002). Executive function may be a key aspect of cognitive function in the context of adherence.
to HAART. Until now, studies examining the relationship between executive function and HAART have included HIV samples with advanced stage disease, and consequently, greater levels of cognitive impairment (Gonzalez, Bechara, & Martin, 2007; Gonzalez et al., 2005; Martin et al., 2007; Rothlind et al., 2005).

No study to date has examined the impact of mild to moderate executive dysfunction on adherence in a sample of relatively healthy asymptomatic and symptomatic HIV-infected individuals. As mentioned previously, executive dysfunction is common in HIV-infected individuals even in earlier stages of HIV disease but whether executive dysfunction at earlier stages is associated with adherence practices is not known (Stoehr et al., 2008).

In the current study we propose to examine executive function and its relationship with HAART adherence in a sample of asymptomatic and symptomatic HIV-infected individuals. A finding that executive dysfunction in a relatively healthy group can adversely affect adherence can have important clinical implications. In this regard, we believe this study will be an important step towards designing treatment programs based on these clinical implications. For instance, in addition to compensatory measures, specific ‘at-risk’ individuals can be targeted with less costly, preventative interventions designed to slow down cognitive decline, promote better adherence practices and in turn decrease morbidity and mortality. An additional innovation of the current study is found in the recruited sample. The majority of the current population is African-American, which is a particularly relevant group in the context of HAART adherence given that HIV-infected African Americans are likely to be less satisfied with their healthcare, have
poorer rates of adherence and are diagnosed later than their Caucasian counterparts (Gilbert, 2002). In addition, the primary mode of transmission in the current sample is sexual intercourse. This is an added advantage in the context of examining the impact of cognitive function on adherence as it reduces the confounding effect of cognitive impairment caused by drug use in a sample that is primarily composed of intravenous drug users.
CHAPTER 2

METHOD

The Louis Stokes Cleveland Department of Veterans’ Affairs (LSCDVAMC) Institutional Review Board approved the instruments described below, and informed consent was obtained from each participant prior to testing.

Participants

A total of 32 HIV-infected patients at the Infectious Diseases (ID) clinic from Louis Stokes Cleveland Department of Veterans’ Affairs (LSCDVAMC) were recruited. Study participation was open to English-speaking persons aged 18 and older and prescribed HAART. Exclusion criteria were chosen to maximize generalizability and included expressive aphasia, active psychotic symptoms and severe cognitive impairment as defined by falling below the cutoff on the Mini-Mental State Exam (MMSE) (described below). Patients were compensated with a $10 grocery store voucher for their participation in the study.

The age of participants ranged from 34-81 years (mean=51.8, s.d.=8.1). The majority of the sample was African-American (n=53.1%) and male (n = 90.6%). See Table 1 for demographic and medical variables.
Table 1. Demographic and Medical Characteristics (n=32)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Standard Deviation</th>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males (%)</td>
<td>90.6</td>
<td></td>
</tr>
<tr>
<td>Females (%)</td>
<td>9.4%</td>
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</tr>
<tr>
<td>Age (years)</td>
<td>51.8</td>
<td>8.1</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American (%)</td>
<td>53.1</td>
<td></td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>31.3</td>
<td></td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Asian (%)</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Clinical Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV without AIDS(%)</td>
<td>65.6</td>
<td></td>
</tr>
<tr>
<td>AIDS(%)</td>
<td>34.4</td>
<td></td>
</tr>
<tr>
<td>CD4 (Mean)</td>
<td>530</td>
<td>301.8</td>
</tr>
<tr>
<td>CAD(%)</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>Tobacco Use Disorder(%)</td>
<td>16.7</td>
<td></td>
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</table>

*Note.* *p*<.05, **p**<.01
Procedure

Participants were recruited for the proposed project during regular appointments with their medical care provider in the Infectious Diseases clinic at LSCDVAMC. At the end of the regularly-scheduled appointment, the care provider confirmed that the patient met the inclusionary/exclusionary criteria, described the study to the patient and asked whether the patient was interested in participating in the study.

If the patient indicated willingness to participate, he/she was approached by study staff who further described the study, read/had the patient read the consent form and obtained signed consent. The study was approved by the LSCDVAMC and Kent State University (KSU) Institutional Review Boards. The testing session was approximately 1.5 hours in duration and included brief cognitive testing and self-report questionnaires. Instructions and stimuli for the cognitive tasks were read aloud to the participant by the experimenter from a script. The experimenter recorded the participant’s response to items. Participants completed all self-report measures in the presence of the experimenter to ensure participants completed the forms correctly and no items were left blank. Consent to review participant medical charts was also obtained from the participant prior to testing.
Measures

Demographic Information

General demographic information was collected via a questionnaire for the purpose of describing the study sample and quantifying potential covariates (e.g., age, socioeconomic status, education).

Cognitive Function

The test battery was aimed at comprehensively assessing the key components of executive function, which are believed to be mediated primarily by the frontal lobe (Chang et al., 2008).

Instructions and stimuli for the cognitive tasks were read aloud to the participant by the experimenter from a script.

a) Digital Symbol Coding: This test has been shown as a sensitive measure of speed of processing and attention. People with HIV perform poorly on this test as compared to people without HIV (J. T. Becker et al., 1997). Further, performance on this test has been identified as a potential predictor of risk of developing HIV associated dementia (HAD) (Stern et al., 2001). The Digit Symbol Coding test asked participants to transpose a coded sequence. They were provided with a code at the top of the page (e.g. a ‘1’ means ‘+’) and asked to complete as many of the blank items as possible in 120 seconds. This measure has excellent test-retest reliability, with correlation coefficients in the .82 to .88 range.

b) Trail Making Tests: Trail Making Test A is a measure of attentional capacity and has been utilized heavily in the HIV literature (J. T. Becker et al.,
1997). It has also been shown to predict adherence (Hinkin, Castellon, Atkinson, & Goodkin, 2001), coping (Manly et al., 1997) and global impairment in this population (Sarter & Podell, 2000). Trail Making Test A is similar to the child’s game ‘Connect the dots’ and measures psychomotor speed and visual scanning. Participants were asked to connect a series of 25 numbered dots in ascending order as quickly as they could (e.g. 1-2-3 etc.). Trail Making Test B added a set-shifting component and required participants to alternate between numbers and letters in ascending order (e.g. 1-A-2-B etc.). Trail Making Test B is an easily administered test of scanning and visuomotor tracking, divided attention and cognitive flexibility. The Trail Making Tests are very sensitive to neurological injury with moderate to excellent reliability ranging from .60 – .90.

c) Wide Range Achievement Test-3 (WRAT-3) Reading subset: WRAT-3 test is a measure of reading ability, which provided an estimate of premorbid intellectual ability for the proposed study. This is the most popular test to assess premorbid intellectual ability in the HIV population (Moser et al., 2002). Participants were asked to read increasingly difficult words from a page.

d) Modified Mini Mental Examination: This test was administered to identify and exclude patients with severe cognitive impairment from the proposed study. This test is a brief screening measure of global cognitive function. It was comprised of several short tasks, including orientation (e.g. what is today’s date), counting backwards, learning and recall of a short list of target words, and copy of a simple geometric figure. This test has excellent test –retest reliability of .83 - .89 in
less severely impaired populations and nearly perfect test-retest reliability for populations with more severe impairment (Folstein, Folstein, & McHugh, 1975).

e) Frontal Assessment Battery: This test employed several short tasks to assess executive function abilities. More specifically, participants were asked to identify similarities among two words (e.g. automobile, boat), name as many words as they can, starting with a target letter (e.g. words that begin with ‘M’), and tap patterns with their right and left hands. Dubois, Slachevsky, et al., 2000 report good internal consistency and test-retest reliability of .70 and .89 respectively (Dubois, Slachevsky, Litvan, & Pillon, 2000).

f) Stroop Color-Word Test (SCWT): This is a task made up of three trials and is a measure of how well a person can suppress a habitual response for a novel one. In the first two trials, participants were asked to read names of colors and then the actual colors on the card. In the third trial, the person must ignore the word (name of a color) that is written and report the color of the ink that the word is written in, therefore suppressing a habitual response for a novel one (Golden, 1978).

Medication Adherence

Self-reported medication adherence was assessed during detailed structured interviews. The adherence assessment was prefaced with a non-judgmental instruction set acknowledging the difficulties of taking medications, based on instructions developed to increase the accuracy of self-reported adherence in the ACTG clinical trials (Chesney et al., 2000). Participants, guided by pill models, were asked to describe their knowledge of prescribed antiretroviral medications. After prompting with a calendar about recent
activities to cue their recall, participants indicated the number of antiretroviral medication pills in their prescribed regimen that they skipped on each of the past three days. To measure longer-term patterns of adherence, participants rated how frequently they skipped antiretroviral doses or took doses off-schedule for the past three months.

In prior research, these self-report measures of adherence were significantly related to HIV viral load, suggesting the validity of the self-report measure. For instance, in a pilot study, having a detectable viral load was significantly related to reporting any missed doses in the past two days, \( r = .22, p = .05 \), the past week, \( r = .29, p = .01 \), the past two weeks, \( r = .26, p = .05 \), and the past three months, \( r = .29, p = .01 \) (Bogart, Bird, Walt, Delahanty, & Figler, 2004; Delahanty, Bogart, & Figler, 2004). In a second pilot study by the same group, having a detectable viral load at baseline was significantly related to reports of greater nonadherence in the past three months, both cross-sectionally and prospectively (\( r = .31, p = .05 \) for baseline adherence and \( r = .72, p = .001 \) for three-month follow-up adherence), and reporting any nonadherence in the past week (\( r = .31, p = .05 \) for baseline and \( r = .54, p = .01 \) at three-month follow-up) (Bogart et al., 2004; Delahanty et al., 2004).

**Depression**

The Center for Epidemiological Studies – Depression Scale (CES-D: Radloff, 1977), a 20-item measure assessing cognitive, affective, and vegetative aspects of depression, was used to assess depression. This measure has been associated with HIV treatment adherence in prior work (Catz, Kelly, Bogart, Benotsch, & McAuliffe, 2000; Murphy, Moscicki, Vermund, & Muenz, 2000). One study has found satisfactory internal
consistency for this scale in a pilot study of HIV treatment adherence (alpha = .80) (Delahanty et al., 2004).

Substance Use

To assess alcohol use, participants were asked the number of standard drinks typically consumed and the number of drinking occasions during the past month (Czarnecki, Russell, Cooper, & Salter, 1990). This scale has had excellent test-retest reliability in prior research (r = .90) (Czarnecki et al., 1990) and is highly correlated with a diary measure of alcohol use (r = .92) (Webb, 1990). In addition, participants were asked about drugs typically used and the number of occasions they were used during the past month (e.g., marijuana, crack/cocaine, methamphetamine, etc.). This procedure is used in the ACTG assessment (Chesney et al., 2000), as well as other studies of individuals with HIV (Safren et al., 2001).

Medical Variables

Medical information, including HIV-related indices (i.e., HIV viral load, CD4+ cell count and medication prescriptions) was obtained from medical records. Participants’ signed medical release forms were kept in Division of infectious Diseases at LSCDVAMC, and study staff reviewed medical charts.
Correlations were employed to examine the relationships among study variables. The impact of demographic and covariates was also examined using correlations, and these variables were considered in analyses as needed. The association between cognition and adherence was examined using partial correlations while adjusting for age and education. Age was chosen as an important covariate as the increased age of HIV-infected patients using HAART presents unique adherence challenges as neurodegenerative diseases later in life begin to complicate the course of HIV/AIDS (Becker, Dew, Aizenstein, 2004). Education has been found to be a protective factor for cognitive impairment and non-adherence in people with HIV (Farmer, Kittner, Rae, Bartko & Regier, 1997). In HIV, the use of premorbid intelligence is consistently utilized as a method of determining overall cognitive functioning (Basso & Bornstein, 2000). Therefore, those with higher estimated premorbid intelligence have purportedly greater cognitive reserve capabilities, which affects the rate of decline in their cognitive abilities relative to disease progression (Basso & Bornstein, 2000). Finally, a multiple regression analysis was conducted to determine if cognitive performance overall was associated with medication adherence. Independent variables included premorbid intelligence (WRAT-3), information processing speed (Digit Symbol Coding),
psychomotor speed (Trail making test A), cognitive flexibility (Trail making test B), a frontal systems index measure (FAB) and inhibition (Stroop Color Word Test) and dependent variables included adherence at one week, adherence at one month and adherence at three months. All cognitive variables were simultaneously included in the regression analysis to predict if cognition predicted adherence.

Descriptive Analyses and Identification of Covariates

Distributions of all study variables met normality assumptions and thus no variables were transformed.

Demographic and medical characteristics for the sample are presented in Table 2.

Predictors of Cognitive Impairment

The prevalence of cognitive impairment in the sample ranged from 10% (Stroop Color Test) to 40% (Frontal Assessment Battery). Impairment was most common on tests measuring executive function and less common on tests measuring reading speed (Hinkin et al., 2001). This pattern is consistent with past studies of HIV patients and provides adequate power for subsequent analyses.

Zero-order correlations between demographic variables and cognitive test performance are presented in Table 2. Contrary to predictions, there was no statistically significant association between age, education and performance on any of the cognitive test performance. Speeded executive function (Trail Making Test B) score was negatively associated with unspeeded executive function (FAB) and attention (Trail Making Test A). (See Table 3).
Table 2. *Cognitive Test Data (n=32)*

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean (s.d.)</th>
<th>Range</th>
<th>Overall Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>WRAT 3</td>
<td>30.25 (7.15)</td>
<td>12-42</td>
<td>10%</td>
</tr>
<tr>
<td>FAB (Raw Score)</td>
<td>15.93 (2.40)</td>
<td>11-18</td>
<td>40%</td>
</tr>
<tr>
<td>TMT A</td>
<td>43.15 (16.96)</td>
<td>18-112</td>
<td>19%</td>
</tr>
<tr>
<td>TMT B</td>
<td>110.40 (59.64)</td>
<td>42-328</td>
<td>15%</td>
</tr>
<tr>
<td>Digit Symbol Coding</td>
<td>86.84 (19.93)</td>
<td>41-128</td>
<td>6%</td>
</tr>
<tr>
<td>Stroop Word</td>
<td>51.88 (11.45)</td>
<td>23-77</td>
<td>17%</td>
</tr>
<tr>
<td>Stroop Color</td>
<td>55.64 (17.98)</td>
<td>17-92</td>
<td>10%</td>
</tr>
<tr>
<td>Stroop Color Word</td>
<td>30.44 (8.44)</td>
<td>15-49</td>
<td>15%</td>
</tr>
</tbody>
</table>

*Note.* *p<.05,* *p<.01
Table 3. *Predictors of Cognitive Impairment (n=32)*

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<th>7.</th>
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<td>4. FAB</td>
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<td>6. Trails B</td>
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<td>-.60**</td>
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<td>-.59**</td>
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<td>.16</td>
<td>.33</td>
<td>.36*</td>
<td>-.32</td>
<td>-.42*</td>
<td>.49**</td>
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<td>9. Stroop Color</td>
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<td>-.23</td>
<td>-.23</td>
<td>.29</td>
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<td>10. Stroop</td>
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<td>-.14</td>
<td>0.38*</td>
<td>.47*</td>
<td>-.46*</td>
<td>-.41*</td>
<td>.43*</td>
<td>.60*</td>
<td>.64**</td>
</tr>
</tbody>
</table>

Color Word

*Note. *p<.05. **p<.01*
Adherence, Demographic and Medical Variables and Other Predictors

Relationships between adherence and demographic and other variables are presented in Table 4. Contrary to expectations, age and education were not associated with adherence in this sample. Surprisingly, depression also showed no association with adherence. Adherence in the past week was positively associated with adherence in the past month ($r=0.96$, $p<0.01$). However, adherence in the past three months was negatively associated with both adherence in the past week and adherence in the past month ($r=-0.69$ and -0.706 respectively, $p<0.01$).

Cognition and Adherence

Regarding the relationship between cognition and adherence, partial correlations after controlling for age and IQ showed that reading speed (Stroop Word) was positively associated with adherence in the past week and in the past month ($r=-0.38$ and -0.40 respectively, $p<0.05$). There was a trend for an association between speeded executive function (Trail Making Test B) and adherence in the past week ($r=-0.27$, $p=0.09$). No other variables were associated with adherence measures. (See Table 5).

Regression Analyses

Regression analyses were conducted while considering all cognitive tests simultaneously for reported adherence for past one week, past one month and past three months. Regression analyses are presented in Table 6, 7 and 8. When all cognitive tests were considered simultaneously, while the models did not fit the data well for adherence for the past week and past three months, the model fit the data well ($R^2=0.49$, adjusted
Table 4. *Predictors of Adherence (n=32)*

<table>
<thead>
<tr>
<th></th>
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<td>.16</td>
<td>-.09</td>
<td>-</td>
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<td>.19</td>
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<td>.08</td>
<td>.48</td>
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<td>8. CD4-3 months prior</td>
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<td>.16</td>
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<td>.09</td>
<td>.59</td>
<td>.96</td>
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<td>9. Adherence-Past Week</td>
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<td>-.08</td>
<td>-.12</td>
<td>-.05</td>
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<td>5. Adherence-Past month</td>
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<td>.07</td>
<td>.09</td>
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<td>-.05</td>
<td>-.11</td>
<td>.02</td>
<td>.96</td>
<td>-</td>
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<tr>
<td>6. Adherence-3 months</td>
<td>0.18</td>
<td>-.01</td>
<td>-.06</td>
<td>-.59</td>
<td>0.10</td>
<td>-.21</td>
<td>-.03</td>
<td>-.16</td>
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*Note.* *p<.05, **p<.01*
Table 5. *Cognition and Adherence (n=32)*

<table>
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<tr>
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<th>2</th>
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<th>7</th>
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<th>9</th>
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<td>1. FAB</td>
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<td>2. Trails A</td>
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<td>0.64**</td>
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<td>4. DSC</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Stroop Word</td>
<td>0.37*</td>
<td>-0.37*</td>
<td>-0.44*</td>
<td>0.47**</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6. Stroop Color</td>
<td>0.02</td>
<td></td>
<td></td>
<td>0.11</td>
<td>0.62**</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>7. Stroop Color Word</td>
<td>0.31</td>
<td>-0.42*</td>
<td>-0.29</td>
<td>0.26</td>
<td>0.51*</td>
<td>0.57**</td>
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<tr>
<td>8. Adherence-Past week</td>
<td>0.12</td>
<td>-0.22</td>
<td>-0.28</td>
<td>-0.15</td>
<td>-0.38*</td>
<td>-0.28</td>
<td>-0.19</td>
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<tr>
<td>9. Adherence-Past month</td>
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<td>-0.22</td>
<td>-0.28</td>
<td>-0.12</td>
<td>-0.40*</td>
<td>-0.31</td>
<td>-0.21</td>
<td>-0.96**</td>
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<td>10. Adherence-Past 3 months</td>
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*Note.* *p<.05, **p<.01
Table 6. *Cognition and Adherence at One Week (n=32)*

<table>
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<tr>
<th></th>
<th>B</th>
<th>SEB</th>
<th>B</th>
<th>T (p-value)</th>
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<tbody>
<tr>
<td>FAB</td>
<td>.62</td>
<td>.85</td>
<td>.18</td>
<td>.47</td>
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<td>TrailsA</td>
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<td>.11</td>
<td>-.15</td>
<td>.55</td>
</tr>
<tr>
<td>TrailsB</td>
<td>-.03</td>
<td>.03</td>
<td>-.26</td>
<td>.37</td>
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<tr>
<td>DSC</td>
<td>.19</td>
<td>.14</td>
<td>.34</td>
<td>.18</td>
</tr>
<tr>
<td>StroopWord</td>
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<td>.13</td>
<td>-.80</td>
<td>.01</td>
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<td>.14</td>
<td>.18</td>
<td>.50</td>
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<td>-.23</td>
<td>.25</td>
<td>-.24</td>
<td>.37</td>
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<tr>
<td>$R^2$</td>
<td></td>
<td></td>
<td>.43</td>
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</tr>
<tr>
<td>$F$</td>
<td></td>
<td></td>
<td>2.114 (p=.092)</td>
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</table>

*Note.* *p*<.05, **p**<.01
Table 7. *Cognition and Adherence at OneMonth (n=32)*

<table>
<thead>
<tr>
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<th>T (p-value)</th>
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<tbody>
<tr>
<td>FAB</td>
<td>3.02</td>
<td>3.25</td>
<td>.21</td>
<td>.92 (p=0.36)</td>
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<tr>
<td>TrailsA</td>
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<td>0.45</td>
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<td>-0.72 (p=0.47)</td>
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<td>0.14</td>
<td>-0.33</td>
<td>-1.22 (p=0.23)</td>
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<tr>
<td>DSC</td>
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<td>1.08 (p=0.29)</td>
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<tr>
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<td>.74 (p=.46)</td>
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<td>-.27</td>
<td>-1.08 (p=.29)</td>
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</table>

\[ R^2 \] 0.49  
\[ F \] 2.69* (p=0.04)  

*Note.* *p*<.05, **p**<.01
Table 8. *Cognition and Adherence at 3 Months (n=32)*

<table>
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<th>Test</th>
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<td>FAB</td>
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</tr>
<tr>
<td>TrailsA</td>
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</tr>
<tr>
<td>TrailsB</td>
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<td>.00</td>
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<td>-.02</td>
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<td>.93</td>
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<td>.22</td>
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<tr>
<td>Stroop Color Word</td>
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<tr>
<td>$F$</td>
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</table>

*Note. *p<.05, **p<.01*
$R^2=.31, F(2, 27)=2.69, p=0.04$; Table 6) for adherence for the past month. In addition, reading speed predicted adherence in the past month ($B=-1.56, S.E. B=.49, t=-3.13, p=0.00$), while tests of executive function (Trail making test B, Frontal Assessment Battery, Stroop Test - Color Word Trial) did not contribute appreciable predictive power to the model ($B=-1.06, S.E. B=-1.08, t=-.27, p=.29$).
CHAPTER 4

DISCUSSION

In the current, we did not find the expected significant association between demographic, medical and key psychological variables and adherence or cognitive function. In relation to our main hypothesis, while we did not find a significant association between executive function and adherence, we did find a significant association between an aspect of information processing speed and adherence. Several aspects of these findings warrant brief discussion.

Contrary to expectations, the current study found no association between demographic variables and performance on cognitive testing. Previous research indicates that older age and lower education levels are related to cognitive impairment in HIV samples (Hinkin et al., 2001). A likely explanation involves the limited variability in age and education levels, as most participants were middle-aged and college-educated. This pattern would attenuate the correlations and significant effects. Another possibility is that disease-related factors (e.g. low CD4 count, high plasma viral load) are more important contributors than demographic variables to cognitive function in persons with HIV. Some evidence for this possibility is already found in the literature (Gifford et al., 2000; Holzemer et al., 1999). National estimates of HIV prevalence show that the
majority of HIV cases are found in the age group 30-49 (DHHS-CDC, 2009). Future studies which recruit from samples with a larger range of age and education level could explore this hypothesis further.

Similarly, there was no association between reported rates of adherence and demographic and medical characteristics. This lack of association between age and education and adherence in this sample is not entirely surprising. Past studies show inconsistent effects of age on adherence, with significant findings typically indicating that younger age is associated with non-adherence in resource-rich settings (Gordillo et al., 1999; Haubrich et al., 1999; Mannheimer et al., 2002; Paterson et al., 2000). Educational level is generally not associated with adherence behavior in past studies (Gordillo et al., 1999; Haubrich et al., 1999; Mannheimer et al., 2002; Paterson et al., 2000). The null finding in this study with regard to demographic and medical characteristics may also be attributable to limited variability in age and education in this sample. Additional studies are needed that recruit samples with a larger range of demographic and medical characteristics to better determine the impact of these variables on adherence behavior in HIV patients.

It is interesting that depression was unassociated with adherence in our study. Earlier studies that have found depression to predict medication adherence (Carrieri et al., 2003) did not include cognitive measures. At least one other study that examined the relationship between cognitive performance and adherence also did not find a significant relationship between depression and adherence (Waldrop-Valverde, Ownby, Wilkie, Mack, Kumar & Metsch, 2006) It may be that impaired cognitive skills such as slowed
processing/psychomotor speed that often accompany depression accounted for the relationships reported earlier but were not directly tested. Additional exploration is much needed.

Another surprising finding is related to the negative correlation between adherence at past month and adherence at past three months. Self-reported measures of antiretroviral adherence vary greatly in recall time periods and response tasks. Discrepancy between accuracy of recent reports of adherence and adherence in the more distant past has been found, with higher rates of overreporting for more recent adherence behaviors (Lu et al., 2007). This is consistent with our finding in this regard—recent adherence was discrepant with adherence in the past. Specifically, reported adherence in the past month significantly higher than reported adherence three months previously in the current study, suggesting likelihood of overreporting of recent adherence behavior.

The current study investigated the relationship between executive function and medication adherence in an HIV-infected outpatient population. Study hypotheses were only partially supported, as treatment adherence at one month was associated with poorer performance on reading speed (Stroop Color Word Test—Word Trial). A non-significant trend also emerged between speeded executive function (Trail Making Test B) and reported rates of adherence at one month. Several aspects of these findings warrant brief discussion.

Persons with HIV in the current study reported high levels of adherence to their prescribed medication regimen, including 95% compliance in the past week and 85% in the past three months. These rates are higher than those typically found in the literature.
For example, typical adherence rates for medications prescribed over long periods of time are approximately 50-75% in HIV populations (DiMatteo, Giordani, Lepper, & Croghan, 2002). Given this pattern, it appears likely that the chosen measure overestimated the actual adherence rates of study participants. Self-report was chosen for the current study because of its low cost, ease of administration, and good correlation with other indirect adherence measures such as medical electronic monitoring system (MEMS) caps and pill count in past studies (Gifford et al., 2000; Haubrich et al., 1999). However, self-report is sometimes known to overestimate adherence rates in HIV populations relative to more objective measures like MEMS caps and pill counts (Wagner, 2002).

All adherence assessment methods have significant limitations, including self-report, clinician report, pill counts, pharmacy records, biological surrogate markers, and MEMS caps (Wagner, 2002). For example, while MEMS caps assess pill bottle opening events, they do not assess actual pill ingestion (Golin et al., 2002; Wagner, 2002). Furthermore, its relatively high cost and logistical complexities can also limit its usefulness in some research settings (Bova et al., 2005). Similar problems can also emerge when using pill counts (e.g. patients may simply throw medication away prior to a study visit) or journal recording (e.g. patient completes all medication entries at one sitting (Golin et al., 2002). Biological markers of antiretroviral medications have been significantly associated with adherence behavior and with virologic outcomes (Liechty et al., 2004). However, the disadvantage of this measure is that it does not necessarily add to the sensitivity of a composite adherence assessment that include self-report and
pharmacy data (Alcoba et al., 2003). Plasma concentrations are limited by their ability to detect only recent adherence behavior (Alcoba et al., 2003). Furthermore, low concentrations of antiretrovirals also may be caused by factors other than adherence, such as malabsorption, drug interactions, and individual metabolic differences (Alcoba et al., 2003). Future studies that employ a combination of adherence measures are needed to better clarify adherence to medication in patients with HIV.

Despite these potential concerns, finding an association between performance on a measure of executive function and reported adherence is noteworthy. Slowed reading speed was associated with reported nonadherence at one week and one month in the current sample. The exact reason for the strong association between this measure (Stroop Word) and reported adherence is unknown and has not been previously reported. In particular, the reason for this strong association and no association for other, more direct measures of executive function (e.g. Trail Making Test B, Frontal Assessment Battery) is unclear. One possible explanation is that this association is indicative of many patients being in the MCMD stage of HIV-related cognitive impairment. MCMD has subclinical and mild forms of which are characterized by slowed processing speed and reduced motor function, but the symptoms of which are not severe enough to qualify as a full blown dementia syndrome (Ghafouri et al., 2006). The reason for the null findings in relation to other tests of processing speed such as Digit Symbol Coding and Trail Making Test A may be because the Word Trial of the Stroop task yields a purer measure of processing speed by removing the motor function component from the test requirements. While tests like Digit Symbol Coding and Trail
Making Test A measure information processing speed, they also test motor ability and are more sensitive to a person’s overall impairment in this domain. To this end, Stroop-Word may have been a more specific measure of processing speed impairment in this sample.

The current study is limited in several ways. As mentioned previously, use of a self-report measure of adherence may have overestimated actual rates of adherence. While financial considerations encouraged use of this measure for the current study, future studies employing a combination of adherence measures (e.g. Mems caps, nurse ratings, pill counts) may yield a richer and more accurate estimate of adherence behavior. Another potential limitation is the relatively small and homogenous sample. It took over 15 months to recruit the current sample. Many individuals living with HIV or AIDS have unstable housing situations, are active substance users, or are disenfranchised or alienated from mainstream society, making recruitment of this population especially without significant compensation particularly challenging (Aidala, Lee, Abramson, Messeri, & Siegler, 2007). Future studies will benefit from using data collection techniques such as phone interviews and recruiting from multiple centers to recruit a larger and more diverse sample. While tracking individuals through telephone in resource-poor settings can be difficult because populations are mobile and infrastructure is poor, studies have shown that HIV-infected individuals have greater willingness to participate in the study if they are first contacted by telephone and provided initial information regarding the study (Juntunena, Hwaleka & Neale, 1999). A final consideration involves the cross-sectional design of the current study, as it precludes determining the direction of the relationship.
between adherence and cognitive function. It appears likely that poor adherence in the past might accelerate the adverse impact of HIV on the brain, producing greater cognitive impairment (Selnes, 2002). In turn, this greater level of cognitive impairment ultimately leads to future reductions in adherence levels (Selnes, 2002). Large, prospective studies are needed to better understand the short- and long-term association between adherence and cognitive function.

Despite these potential concerns, the current study provides information that may benefit clinicians. In consideration of the possibility that adherence was significantly overreported in the current study, it is important for clinicians to monitor adherence at each visit and utilize appropriate interventions as needed. For example, clinicians may make use of a variety of devices that may help patients organize their medication schedules and adhere to their treatment regimens better, such as pill boxes and reminder devices. Similarly, the current study found high rates of previously undetected cognitive impairment in middle-aged persons with HIV. For example, rates of impairment were particularly high across the sample for speeded executive functioning (Trail Making Test B) and processing speed (Stroop-Word trial). Given this finding, clinicians are encouraged to regularly screen for cognitive impairment and refer for complete neuropsychological evaluation as appropriate.

In summary, the current study examined the relationship between executive function and medication adherence in persons with HIV. While executive function did not predict adherence, processing speed was closely associated with reported adherence at one month. We found possible significant overreporting of adherence indicating the
need for clinicians to monitor adherence at frequent intervals. Furthermore, high levels of impairment in speeded executive functioning were also found across the group, which were previously undetected, encouraging care providers to regularly screen for impairment in this population.
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