Effects of Antiretroviral CNS Penetration on Procedural Learning Task Performance in HIV+ Drug Users

BY

MICHAEL WILSON
B.S., University of Maryland, College Park, 2006

THESIS

Submitted as partial fulfillment of the requirements for the degree of Master of Arts in Psychology in the Graduate College of the University of Illinois at Chicago, 2012

Chicago, Illinois

Defense Committee:

Eileen Martin, Chair and Advisor, Psychiatry
Robin Mermelstein
Jasmin Vassileva, Psychiatry
DEDICATION

This thesis is dedicated to my father, Richard A. Wilson.
ACKNOWLEDGMENTS

I would like to thank my thesis committee—Eileen Martin, Robin Mermelstein and Jasmin Vassileva—for their unwavering guidance and support in completing this project as well as in all areas of my professional development. Additionally, a number of my colleagues at the UIC HIV and Addictions Neuroscience Laboratory were extremely helpful to me throughout the development and completion of this thesis; I would like to thank Raul Gonzalez, Samantha DeHaan, Lorraine Gibbons, Leslie Ladd, Michelle Siroko and Samantha Wicks for their contributions.

MJW
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>CHAPTER</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. BACKGROUND AND RELATED LITERATURE</td>
<td>1</td>
</tr>
<tr>
<td>HIV-Associated Neurocognitive Disorder</td>
<td>1</td>
</tr>
<tr>
<td>Antiretroviral Medication and Neurocognition</td>
<td>2</td>
</tr>
<tr>
<td>Antiretroviral CNS Penetration Effectiveness</td>
<td>3</td>
</tr>
<tr>
<td>HIV-Associated Comorbidities</td>
<td>4</td>
</tr>
<tr>
<td>Medical Conditions</td>
<td>4</td>
</tr>
<tr>
<td>Substance Use Disorders</td>
<td>4</td>
</tr>
<tr>
<td>E. Neurocognitive Functioning of HIV+ Drug Users</td>
<td>5</td>
</tr>
<tr>
<td>Purpose of the Current Study</td>
<td>7</td>
</tr>
<tr>
<td>II. METHODS</td>
<td>8</td>
</tr>
<tr>
<td>Participants</td>
<td>8</td>
</tr>
<tr>
<td>Study Protocol</td>
<td>10</td>
</tr>
<tr>
<td>1. Assessment of substance use characteristics</td>
<td>10</td>
</tr>
<tr>
<td>2. Assessment of comorbid conditions</td>
<td>11</td>
</tr>
<tr>
<td>3. Assessment of antiretroviral CPE</td>
<td>11</td>
</tr>
<tr>
<td>4. Assessment of sedating medications</td>
<td>13</td>
</tr>
<tr>
<td>5. Neurocognitive Tasks</td>
<td>14</td>
</tr>
<tr>
<td>a. Rotary Pursuit Task</td>
<td>14</td>
</tr>
<tr>
<td>b. Weather Prediction Task</td>
<td>14</td>
</tr>
<tr>
<td>c. Immediate Memory Task</td>
<td>15</td>
</tr>
<tr>
<td>Data Analysis Plan</td>
<td>16</td>
</tr>
<tr>
<td>III. RESULTS</td>
<td>17</td>
</tr>
<tr>
<td>Group Characteristics</td>
<td>17</td>
</tr>
<tr>
<td>Rotary Pursuit Task Performance</td>
<td>18</td>
</tr>
<tr>
<td>Weather Prediction Task Performance</td>
<td>20</td>
</tr>
<tr>
<td>Immediate Memory Task Performance</td>
<td>21</td>
</tr>
<tr>
<td>Effects of Gender on Procedural Learning Task Performance</td>
<td>21</td>
</tr>
<tr>
<td>IV. DISCUSSION</td>
<td>23</td>
</tr>
<tr>
<td>Relationship to Previous Investigations of ARV CPE and Neurocognition</td>
<td>24</td>
</tr>
<tr>
<td>ARV CPE and Neurocognitive Status in Different Clinical Samples</td>
<td>24</td>
</tr>
<tr>
<td>Procedural Learning Performance in HIV+ SDIs</td>
<td>25</td>
</tr>
<tr>
<td>Potential Neurotoxic Effects of Highly Penetrant ARVs</td>
<td>26</td>
</tr>
<tr>
<td>Exploratory Findings of Gender Effects</td>
<td>27</td>
</tr>
<tr>
<td>Limitations</td>
<td>27</td>
</tr>
<tr>
<td>Implications for Future Research</td>
<td>28</td>
</tr>
<tr>
<td>Replication Studies</td>
<td>28</td>
</tr>
<tr>
<td>Longitudinal Monitoring of Procedural Learning Performance</td>
<td>29</td>
</tr>
<tr>
<td>Conclusion</td>
<td>29</td>
</tr>
<tr>
<td>CITED LITERATURE</td>
<td>31</td>
</tr>
<tr>
<td>DOCUMENTATION OF IRB APPROVAL</td>
<td>40</td>
</tr>
<tr>
<td>VITA</td>
<td>45</td>
</tr>
</tbody>
</table>
# LIST OF TABLES

<table>
<thead>
<tr>
<th>TABLE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. PARTICIPANT DEMOGRAPHICS</td>
<td>42</td>
</tr>
<tr>
<td>II. HIV+ PARTICIPANT CHARACTERISTICS</td>
<td>76</td>
</tr>
<tr>
<td>III. PARTICIPANT SUBSTANCE USE CHARACTERISTICS</td>
<td>78</td>
</tr>
<tr>
<td>IV. PARTICIPANT COMORBID CONDITIONS</td>
<td>79</td>
</tr>
<tr>
<td>V. CORRELATIONS OF POTENTIAL COVARIATES WITH TASK PERFORMANCE</td>
<td>81</td>
</tr>
<tr>
<td>VI. EXPLORATORY ANALYSIS GROUP DEMOGRAPHICS</td>
<td>82</td>
</tr>
<tr>
<td>FIGURE</td>
<td>PAGE</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
</tr>
<tr>
<td>1. Mean time on target during the Rotary Pursuit Task by HIV-seronegative, HIV+ Low CPE and HIV+ High CPE participants</td>
<td>18</td>
</tr>
<tr>
<td>2. Mean percentage of correct responses on the Weather Prediction Task by HIV-seronegative, HIV+ Low CPE and HIV+ High CPE participants</td>
<td>24</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>ANI</td>
<td>Asymptomatic Neurocognitive Impairment</td>
</tr>
<tr>
<td>ARV</td>
<td>Antiretroviral</td>
</tr>
<tr>
<td>BDI-II</td>
<td>Beck Depression Inventory-II</td>
</tr>
<tr>
<td>cART</td>
<td>Combination Antiretroviral Therapy</td>
</tr>
<tr>
<td>CD4</td>
<td>Cluster of Differentiation 4</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>CPE</td>
<td>Central Nervous System Penetration Effectiveness</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal Fluid</td>
</tr>
<tr>
<td>HAD</td>
<td>HIV-Associated Dementia</td>
</tr>
<tr>
<td>HAND</td>
<td>HIV-Associated Neurocognitive Disorder</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C Virus</td>
</tr>
<tr>
<td>IMT</td>
<td>Immediate Memory Task</td>
</tr>
<tr>
<td>MND</td>
<td>Mild Neurocognitive Disorder</td>
</tr>
<tr>
<td>PCL-C</td>
<td>Post-Traumatic Stress Disorder Checklist: Civilian Version</td>
</tr>
<tr>
<td>PL</td>
<td>Procedural Learning</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic Acid</td>
</tr>
<tr>
<td>RPT</td>
<td>Rotary Pursuit Task</td>
</tr>
<tr>
<td>WPT</td>
<td>Weather Prediction Task</td>
</tr>
<tr>
<td>WURS</td>
<td>Wender-Utah Rating Scale</td>
</tr>
<tr>
<td>SDI</td>
<td>Substance Dependent Individual</td>
</tr>
<tr>
<td>SRPS</td>
<td>Self-Report Psychopathy Scale</td>
</tr>
<tr>
<td>SSS-V</td>
<td>Sensation-Seeking Scale-V</td>
</tr>
<tr>
<td>STAI</td>
<td>State-Trait Anxiety Inventory</td>
</tr>
</tbody>
</table>
SUMMARY

HIV- and HIV+ substance dependent individuals (SDIs) were tested on motor and cognitive procedural learning (PL) tasks previously used to detect HIV-associated deficits and a control task of sustained attention. HIV- subjects were predicted to show superior performance to HIV+ subjects on PL tasks, while HIV+ subjects prescribed high CPE cART were expected to perform better on PL tasks than HIV+ subjects prescribed low CPE cART.

Results indicated no differences in PL task performance between HIV+ subjects as a function of cART CPE ranking. Contrary to expectation, only the High CPE subjects performed significantly worse than the HIV- group. No group differences were observed on the control task. The negative association between CPE ranking and PL performance may indicate possible neurotoxic effects of High CPE cART within an HIV+ SDI sample, although these data are not conclusive. Findings of HIV-associated deficits on PL task performance within SDIs are consistent with previous findings. The lack of group differences on the control task suggests that the observed deficits cannot be attributed to global neurocognitive impairment.
I. BACKGROUND AND RELATED LITERATURE

A. **HIV-Associated Neurocognitive Disorder**

HIV penetrates the central nervous system (CNS) early in the disease course, prior to the appearance of overt clinical symptoms. HIV infection results in neurological injury by multiple mechanisms that include the expression of toxic viral proteins and the induction of inflammatory responses (Hult et al., 2008). Although typically diffuse in its dispersal throughout the brain, HIV demonstrates a preferential affinity for the basal ganglia and hippocampus, and neuronal loss is prominent in prefrontal cortex (Berger et al., 2000; Cherner et al., 2002). Neurocognitive impairment is most common in processing speed, attention/working memory, learning and executive function (for reviews see Reger et al., 2002 and Woods et al., 2009).

The neuropsychological sequelae of HIV infection present significant problems for clinical management and quality of life. HIV-associated neurocognitive disorder (HAND) is associated with increased risk of death (Ellis et al., 1997; Tozzi et al., 2005) and decreased ability to carry out activities of daily living including job duties, driving and medication adherence (Heaton et al., 2004; Gorman et al., 2009). Recently developed criteria (Antinori et al., 2007) for HAND identify a spectrum of impairment: Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MND), and HIV-Associated Dementia (HAD). The criteria for both ANI and MND require impaired performance (below 1 SD of normative mean) in two or more of the following cognitive domains: verbal comprehension; working memory; executive function; memory; processing speed; visuospatial reading, and motor skills. A diagnosis of MND additionally requires evidence of mild day-to-day functional impairment, while criteria for HAD require marked impairment (below 2 SD of the normative mean) in two or more cognitive domains and at least moderate reductions in activities of daily living.
B. **Antiretroviral Medication and Neurocognition**

The clinical deployment of potent antiretroviral (ARV) combination therapy (cART) to treat HIV has resulted in increased life expectancies and quality of life for HIV+ individuals (e.g. Antiretroviral Therapy Cohort Collaboration, 2008; Detels et al., 1998). Although the prevalence of HAD has decreased in the era of cART, milder forms of HIV-associated neurocognitive impairment remain common (Sacktor et al., 2001a; Sacktor et al., 2002). Recent findings from the CNS HIV Antiretroviral Therapy Effects Research study (Heaton et al., 2010) indicate a prevalence rate of 33% for ANI, 12% for MND, and 2% for HAD, with notably higher rates of impairment in subgroups with comorbid conditions including psychiatric and substance use disorders.

The literature on the relationship between cART and neurocognitive function is inconsistent. Several studies have demonstrated improved neurocognitive functioning following cART initiation in HIV+ individuals (Sacktor et al., 2003; Marra et al., 2003; Letendre et al., 2004; Ferrando, Rabkin, van Gorp, Lin, & McElhinney, 2003), but such findings are not universal. Cysique, Maruff & Brew (2004b) found similar rates of neurocognitive impairment in an HIV+ cohort treated with ARV monotherapy compared with a cohort receiving cART. A recent study (Simioni et al., 2010) of aviremic HIV+ subjects reported that 84% of subjects reporting cognitive complaints and 68% of non-complaining subjects met criteria for HAND despite long-standing viral suppression. Findings from the AIDS Clinical Trials Group (Robertson et al., 2007) indicated that neurocognitive impairment persisted in a sample of previously significantly immunosuppressed (i.e. nadir CD4 count < 200) HIV+ subjects despite treatment with cART, while 21% of subjects developed neurocognitive impairment subsequent to cART initiation regardless of immunologic history. Cysique, Marruff & Brew (2006) also observed a relationship between history of immunosuppression and long-term neurocognitive impairment in cART-treated subjects. Tozzi et al. (2007) reported persistent neurocognitive deficits correlated with baseline neurocognitive impairment in a HIV+ cART-treated sample.
C. **Antiretroviral CNS Penetration Effectiveness**

The persistence of HIV-associated neurocognitive deficits despite marked improvement in systemic disease in the era of cART is difficult to interpret. One potential explanation is that although cART regimens may achieve viral suppression in the plasma and lymphatic tissue, HIV levels in the CNS are unaffected. Converging evidence from animal, clinical and post-mortem studies indicates that the CNS acts as a reservoir for HIV despite systemic ARV-induced viral suppression (Clements et al., 2005; Cunningham, et al., 2000; Petito, 2004; Schrager & D'Souza, 1998). ARV drugs with greater ability to penetrate the blood-brain barrier have been associated with greater reduction of HIV levels in the CNS (Letendre et al., 2004, 2008; Marra et al., 2009), suggesting that ameliorative effects of cART on HAND may be limited by the ability of ARV drugs to enter the brain.

Letendre et al. (2008) utilized available data on the pharmacokinetic and biochemical properties of widely used ARV drugs to create the CNS Penetration Effectiveness (CPE) Scale, a rating system that ranks individual ARV drugs by their relative ability to successfully pass through the blood-brain barrier that can be used to generate a total cART regimen CPE score. Higher total CPE rankings of cART regimens are associated with lower HIV RNA levels in the CNS (Letendre et al., 2004; Letendre et al., 2008; Marra et al., 2009). However, the relationship between CPE rank and neurocognitive function is less clear. Prospective studies have reported a range of outcomes in HIV+ subjects, including an association between high CPE cART regimens and improved neurocognition (Cysique et al., 2009; Cysique, Maruff, & Brew, 2006; Letendre et al., 2004); a positive association limited to a subset of participants with impairment at baseline (Cysique, Maruff & Brew, 2004a); no relationship (Simioni et al., 2010); or a negative relationship (Marra et al., 2009) between CPE rank and neurocognitive performance. The latter finding raises the possibility that cART regimens with high CPE ranks may exert detrimental neurocognitive deficits in some HIV+ individuals, possibly through neurotoxic injury (Robertson et al., 2010; Schweinsburg et al., 2005).
D. **HIV-Associated Comorbidities**

1. **Medical Conditions**

   In addition to the role of ARV CPE in determining neurocognitive status, comorbid conditions likely also contribute to neurocognitive deficits observed in HIV+ individuals treated with cART. Elevated rates of psychiatric disorders have been observed in HIV+ samples compared to other populations of medical patients (Lyketsos, Hanson, Fishman, Mchugh & Treisman, 1994; Dew et al., 1997). Comorbid medical problems are also common in HIV+ individuals, particularly hepatitis C (Danta et al., 2007; Kilbourne, Justice, Rabeneck, Rodriguez-Barradas, & Weissman, 2001) which has been associated with neurocognitive impairment in mono-infected HCV+ individuals (Forton, et al., 2002; Hilsabeck, Hassanein, Carlson, Ziegler, & Perry, 2003) and impairment is increased among individuals with HIV/HCV co-infection (Ryan, Morgello, Isaacs, Naseer & Gerits, 2004; Von Giesen, et al., 2004).

2. **Substance Use Disorders**

   Substance use disorders are also commonly seen in HIV and HIV/HCV co-infection and may contribute to HIV-associated neurocognitive deficits (Cherner et al., 2005; Martin et al., 2004). The terms “substance abuse” and “substance dependence” are generally employed for clinical diagnostic purposes. Experimental brain-based models of substance misuse typically focus on the construct of “addiction,” defined as a chronic relapsing brain disease characterized by compulsive drug seeking and use despite full knowledge of future negative consequences (Leshner, 1997). Such models typically define the addictive process conceptually as a loss of inhibitory control over substance use with exaggerated salience of substance reward properties due to pathological modulation of mesolimbic and prefrontal-striatal brain circuitry (Goldstein & Volkow, 2002). Briefly, mesolimbic reward circuitry projecting from the ventral tegmentum to the limbic system (including the ventral striatum, amygdala and hippocampus) become conditioned to produce hyperactive metabolic responses to drugs of abuse following repeated drug exposure. Neuroadaptations of mesolimbic and mesocortical circuitry yield pathological lasting changes in the activation of prefrontal-striatal circuitry such
that it is hyperactive in the presence of drugs of abuse and hypoactive during periods of withdrawal, leading to subjective experiences of craving and an inability to refrain from additional drug use (Kalivas & Volkow, 2005). All drugs of abuse result in these differential patterns of prefrontal-striatal activation. Additionally, substance-specific neurotoxicity may affect neurocognitive functioning (Verdejo-Garcia, Lopez-Torrecillas, Gimenez & Perez-Gracia, 2004). Individuals with histories of substance dependence show impaired executive functions; common deficits are seen on tasks of decision-making e.g. Iowa Gambling task, (Bechara et al., 2001; Bechara & Martin, 2004), delay discounting (Petry, 2003; Kirby & Petry, 2004) and behavioral inhibition, e.g. Go-No Go tasks (Fillmore & Rush, 2002; Fillmore, Rush & Hays, 2002).

Comorbid substance use disorders may play a significant role in neurocognitive deficits observed in HIV+ individuals. Rates of substance abuse are high in many HIV+ populations (e.g. Aceijas, Stimson, Hickman & Rhodes, 2004; Chander, Himelhoch & Moore, 2006; Martin et al., 2004), with comorbidity predicting more rapid HIV disease progression (Lucas et al., 2006). Substances of abuse and HIV cause synergistic neuronal damage through multiple mechanisms including immunosuppression, expression of inflammatory cytokines, facilitated HIV replication, and expression of viral proteins (for reviews, see Gonzalez & Cherner, 2008 and Martin & Paul, 2009). At the cellular level, striatal dopaminergic neurons are particularly vulnerable to the combined effects of drugs of abuse and HIV (Cass, Harned, Peters, Nath & Maragos, 2003; Theodor, Cass & Maragos, 2006).

E. **Neurocognitive Functioning of HIV+ Drug Users**

The neurocognitive effects of comorbid substance dependence and HIV infection have only recently begun to be explored systematically in order to identify their unique and additive deleterious effects (Basso & Bornstein, 2000). Such neurocognitive studies have demonstrated that compared to HIV- substance abusers, HIV+ substance-abusing individuals show impairment in verbal reasoning
(Green, Saveanu & Bornstein, 2004), attention (Schulte, Mueller-Oehring, Rosenbloom, Pfefferbaum & Sullivan, 2005), processing speed (Durvasula, Myers, Mason & Hinkin, 2006; Rothlind et al., 2004) and global cognitive function (Rippeth et al., 2004). Some studies have employed standard clinical neuropsychological tests; others have employed experimental cognitive measures to elucidate component cognitive processes affected by HIV (Woods, Moore, Weber & Grant, 2009). Such tasks are advantageous in that more specific neurocognitive functions can be targeted to test theory-driven hypotheses.

In a series of studies of neurocognitive effects of HIV and substance use, Martin and colleagues have systematically investigated the integrity of neurocognitive functioning critically dependent on prefrontal-striatal integrity among HIV+ and HIV- substance dependent individuals (SDIs) well matched on demographic, substance abuse and comorbidity characteristics (Bartok et al., 1997; Farinpour et al., 2000; Martin et al., 2001, 2003, 2004, 2007). Recent studies by this group have focused specifically on procedural learning (PL), a form of incremental non-declarative learning that is primarily dependent on integrity of the neostriatal rather than hippocampal memory systems (Packard & Knowlton, 2002; Squire & Zola, 1996). Tasks of PL such as motor skill learning and probabilistic classification have proven sensitive to detecting cognitive dysfunction in patients with basal ganglia disorders such as Parkinson’s disease (Jackson, Jackson, Harrison, Henderson & Kennard, 1995; Knowlton, Mangels & Squire, 1996; Sarazin et al., 2002) and Huntington’s disease (Heindel, Salmon, Shults, Walicke & Butters, 1989; Knopman & Nissen, 1991; Saint-Cyr, Taylor & Lang, 1988). Given the evidence for prefrontal-striatal dysfunction in both substance dependence and HAND, analysis of PL performance may further illuminate effects of HIV and substance use disorders on neurocognitive functions mediated by these neural systems. Previous investigations have revealed impaired performance on PL tasks among HIV+ individuals (A. Martin, Heyes, Salazar, Law & Williams, 1993; Gonzalez et al., 2008; Martin, Gonzalez, Vassileva & Maki, 2011) with and without a history of substance dependence.
F. **Purpose of the Current Study**

The purpose of the current study is to assess the effects of cART regimen CPE on PL performance and a control task of sustained attention in a sample of HIV+ individuals with histories of substance dependence and to compare overall task performance of HIV+ with HIV- SDIs. No published studies have compared the neurocognitive performance of HIV+ SDIs on high vs. low CPE cART regimens or specifically examined the effects of cART CPE on PL task performance. The current study will address these questions and contribute new knowledge of CNS effects of antiretroviral therapy among HIV+ individuals. HIV- subjects were hypothesized to show superior performance to HIV+ subjects on tasks of motor and cognitive PL performance, while HIV+ subjects prescribed high CPE cART would perform better on PL tasks than HIV+ subjects prescribed low CPE cART regimens. No performance differences on the control task of vigilance were expected due to predicted specificity of differential performance to the neurocognitive domain of PL.
II. METHODS

A. Participants

Participants were 86 male and 51 female HIV+ and 227 male and 83 female HIV- adults with lifetime DSM-IV diagnoses of substance dependence enrolled in a larger ongoing NIH-funded study of neurocognition and HIV among substance abusers. All HIV+ participants with a history of substance dependence and a current prescription of antiretroviral medication were selected for the current study; all HIV- individuals with a history of substance dependence were included. The sample was 84% African American, 12% Caucasian, 3% Hispanic and 29% female with a mean age of 42.5 (interquartile range, IQR = 11). Participants had completed an average of 11.6 years of education and had a demographically corrected mean premorbid verbal IQ of 87.4 as estimated by the Wechsler Test of Adult Reading. The relatively low demographically-corrected IQ scores of the participants relative to the general population may affect global neurocognitive performance; however, IQ scores did not differ significantly between participant groups and would not be expected to bias between-group comparisons of neurocognitive performance. Participants were recruited from the University of Illinois at Chicago (UIC) HIV/AIDS program, the Jesse Brown VA Medical Center Infectious Disease Clinic and Drug Dependence Treatment Program, Chicago community substance dependence treatment centers, and the general community via flyers and word of mouth. All participants provided informed consent. Study procedures were approved by the UIC and Jesse Brown VA Medical Center Institutional Review Boards. Demographic characteristics are listed in Table I.

HIV+ participants obtained current (i.e. from the past six months) CD4 lymphocyte counts and HIV RNA plasma viral load information from their physicians. Participants without recent CD4 count or plasma viral load results were tested at UIC as part of the study. The mean and median current CD4 cell counts for the HIV+ participants were 464.6 and 391 respectively (IQR = 395). Records of nadir CD4 counts (i.e. lowest clinically measured CD4 levels) were available from 86.4% of HIV+
participants. Mean and median nadir CD4 counts were 173.3 and 168 respectively (IQR = 205). Twenty-four percent of HIV+ participants met criteria for current immunologic AIDS (i.e. current CD4 < 200). All HIV+ participants were prescribed cART, defined as at least three separate ARV medications from two different ARV drug classes, including nucleoside analogue reverse transcriptase inhibitors (NRTI), non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs), or protease inhibitors. Medication adherence was indexed via the self-report Adult AIDS Clinical Trials Group (AACTG) Adherence Questionnaire (Chesney et al., 2000). Disease characteristics for the HIV+ subjects are presented in Table II.

Study exclusion criteria consisted of history of AIDS-defining or other neurological disorders, open head injury, seizure disorder, closed head injury with loss of consciousness exceeding 30 minutes, schizophrenia, current psychosis, current neuroleptic use, and acute substance withdrawal or intoxication. Participants were administered rapid urine toxicology screens (Visualine, SunBiomedica) and a breathalyzer (Intoxilyzer, CMI Inc.) on arrival for testing. Participants that tested positive for

---

### Table I

<table>
<thead>
<tr>
<th>PARTICIPANT DEMOGRAPHICS</th>
<th>HIV- (n=31)</th>
<th>HIV+ Low CPE (n=62)</th>
<th>HIV+ High CPE (n=56)</th>
<th>Test statistic</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in Years (Mean, SD)</td>
<td>42.2 (8.5)</td>
<td>42.6 (6.2)</td>
<td>44.4 (6.9)</td>
<td>F = 1.85</td>
<td>.16</td>
</tr>
<tr>
<td>Years Education (Mean, SD)</td>
<td>11.6 (1.7)</td>
<td>11.3 (2.1)</td>
<td>12.0 (2.0)</td>
<td>F = 2.29</td>
<td>.10</td>
</tr>
<tr>
<td>Estimated FSIQ (Mean, SD)</td>
<td>87.5 (9.9)</td>
<td>87.8 (10.1)</td>
<td>86.1 (8.9)</td>
<td>F = 0.55</td>
<td>.58</td>
</tr>
<tr>
<td>% African American</td>
<td>82</td>
<td>82</td>
<td>94</td>
<td>$\chi^2 = 5.46$</td>
<td>.24</td>
</tr>
<tr>
<td>% Female</td>
<td>27</td>
<td>39</td>
<td>32</td>
<td>$\chi^2 = 3.83$</td>
<td>.15</td>
</tr>
<tr>
<td>% Hepatitis C Seropositive</td>
<td>14</td>
<td>31</td>
<td>33</td>
<td>$\chi^2 = 17.67$</td>
<td>.001</td>
</tr>
</tbody>
</table>
Table II

<table>
<thead>
<tr>
<th>HIV+ PARTICIPANT DISEASE AND MEDICATION CHARACTERISTICS</th>
<th>HIV+ Low CPE (n=62)</th>
<th>HIV+ High CPE (n=56)</th>
<th>Test statistic</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma HIV Viral Load (% Undetectable i.e. &lt;100 copies/ml)</td>
<td>59</td>
<td>68</td>
<td>( \chi^2 = 1.21 )</td>
<td>.27</td>
</tr>
<tr>
<td>Current CD4 Count (Median, IQR)</td>
<td>386.5 (403)</td>
<td>404.5 (399)</td>
<td>( U = 1599.00 )</td>
<td>.46</td>
</tr>
<tr>
<td>Nadir CD4 Count (Median, IQR)</td>
<td>172 (203)</td>
<td>150 (213)</td>
<td>( U = 1282.00 )</td>
<td>.90</td>
</tr>
<tr>
<td>% HAART</td>
<td>92</td>
<td>95</td>
<td>( \chi^2 = 0.34 )</td>
<td>.56</td>
</tr>
<tr>
<td>log10 ACTG 4 Day ARV Adherence (Mean, SD)</td>
<td>0.06 (.16)</td>
<td>0.05 (0.12)</td>
<td>( F = 1.35 )</td>
<td>.25</td>
</tr>
<tr>
<td>% reporting at least one Adherence error</td>
<td>13</td>
<td>13</td>
<td>( \chi^2 = 2.45 )</td>
<td>.87</td>
</tr>
<tr>
<td>ARV Total Regimen CPE (Mean, SD)</td>
<td>6.6 (0.7)</td>
<td>9.2 (1.2)</td>
<td>( F = 9.58 )</td>
<td>.001</td>
</tr>
</tbody>
</table>

opiates, cocaine, methamphetamine or alcohol were rescheduled, while participants that tested positive solely for marijuana on urine screens (n = 32, 8%) were allowed to participate due to the long half-life of cannabis.

B. **Study Protocol**

All testing was conducted at the UIC Psychiatric Institute. The testing protocol included semi-structured medical and psychiatric interviews, paper and pencil self-report questionnaires, and a series of computerized laboratory-based cognitive neuropsychological tasks of motor and cognitive PL and inhibitory control. Trained bachelor's level technicians administered all study procedures under the supervision of a board-certified clinical neuropsychologist.

1. **Assessment of substance use characteristics**

Diagnoses of current and lifetime substance use disorder were obtained via the
Substance Abuse Module of the Structured Clinical Interview for DSM-IV (SCID-SAM; First, Spitzer, Gibbon, & Williams, 1995). A majority of participants met diagnostic criteria for more than one substance use disorder, including alcohol (70%), cannabis (59%), cocaine (78%), and opiates (49%). Past methamphetamine dependence among the population was comparatively minimal (10%). Severity of cocaine, alcohol and heroin use was indexed using the Kreek-McHugh-Schluger-Kellogg scale (KMSK; Kellogg et al., 2003), a self-report scale that queries the amount, frequency, duration of use and amount of money spent on drugs during the participant’s heaviest period of use. Possible KMSK scores for peak use range from 0-16 for cocaine and from 0-13 for both alcohol and heroin. Participant substance use history characteristics are reported in Table III.

2. **Assessment of comorbid conditions**

All participants completed a series of questionnaires that indexed personality traits and psychopathology frequently comorbid with substance use disorders with potentially confounding effects on neurocognitive performance. Symptoms of several psychiatric conditions were assessed, including current anxiety, major depression and post-traumatic stress disorder using the State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) and PTSD Checklist-Civilian Version (PCL-C; Weathers, Litz, Huska, & Keane, 1994). Childhood symptoms of Attention Deficit Hyperactivity Disorder were retroactively assessed via the Wender Utah Rating Scale (WURS; Ward, Wender, & Reimherr, 1993). Potentially confounding personality traits were assessed via the Self-Report Psychopathy Scale (SRPS; Levenson, Kiehl, & Fitzpatrick, 1995), a measure of psychopathic traits appropriate for use in non-incarcerated populations, and the Sensation-Seeking Scale-V (SSS-V Zuckerman, 1994) a robust self-report measure of the sensation-seeking personality construct. Participant scores on comorbid variables are listed in Table IV.
### TABLE III
PARTICIPANT SUBSTANCE USE CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>HIV- (n=310)</th>
<th>HIV+ Low CPE (n=62)</th>
<th>HIV+ High CPE (n=56)</th>
<th>Test statistic</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>% DSM-IV Past Substance Dependence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>67</td>
<td>77</td>
<td>75</td>
<td>$\chi^2 = 3.48$</td>
<td>.18</td>
</tr>
<tr>
<td>Cannabis</td>
<td>62</td>
<td>52</td>
<td>50</td>
<td>$\chi^2 = 4.12$</td>
<td>.13</td>
</tr>
<tr>
<td>Cocaine</td>
<td>75</td>
<td>85</td>
<td>88</td>
<td>$\chi^2 = 6.78$</td>
<td>.03</td>
</tr>
<tr>
<td>Opiates</td>
<td>54</td>
<td>37</td>
<td>36</td>
<td>$\chi^2 = 10.80$</td>
<td>.01</td>
</tr>
<tr>
<td>Years substance used (Mean, SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>19.6 (9.9)</td>
<td>20.6 (11.1)</td>
<td>22.0 (10.2)</td>
<td>$F = 1.29$</td>
<td>.28</td>
</tr>
<tr>
<td>Cannabis</td>
<td>12.3 (9.6)</td>
<td>14.4 (9.5)</td>
<td>14.9 (10.1)</td>
<td>$F = 2.22$</td>
<td>.11</td>
</tr>
<tr>
<td>Cocaine</td>
<td>13.4 (8.5)</td>
<td>15.1 (8.3)</td>
<td>15.2 (7.7)</td>
<td>$F = 1.65$</td>
<td>.19</td>
</tr>
<tr>
<td>Opiates</td>
<td>14.1 (9.7)</td>
<td>14.5 (10.0)</td>
<td>15.7 (9.8)</td>
<td>$F = 0.27$</td>
<td>.76</td>
</tr>
<tr>
<td>Days since last use (Median, IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>197 (1015)</td>
<td>184 (2042)</td>
<td>730 (2743)</td>
<td>$H= 4.19$</td>
<td>.12</td>
</tr>
<tr>
<td>Cannabis</td>
<td>2555 (7060)</td>
<td>2986 (7177)</td>
<td>5657.5 (8304)</td>
<td>$H= 1.51$</td>
<td>.47</td>
</tr>
<tr>
<td>Cocaine</td>
<td>187 (1090)</td>
<td>280 (2302)</td>
<td>518 (1205)</td>
<td>$H= 2.68$</td>
<td>.26</td>
</tr>
<tr>
<td>Opiates</td>
<td>183 (1160)</td>
<td>295 (2253)</td>
<td>518 (932)</td>
<td>$H= 3.20$</td>
<td>.20</td>
</tr>
<tr>
<td>KMSK score (Mean, SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>10.5 (2.2)</td>
<td>10.7 (2.1)</td>
<td>10.6 (2.0)</td>
<td>$F = 0.39$</td>
<td>.68</td>
</tr>
<tr>
<td>Cocaine</td>
<td>13.0 (3.0)</td>
<td>13.4 (2.7)</td>
<td>13.8 (3.0)</td>
<td>$F = 2.0$</td>
<td>.14</td>
</tr>
<tr>
<td>Opiates</td>
<td>10.0 (2.8)</td>
<td>9.8 (2.8)</td>
<td>10.0 (3.3)</td>
<td>$F = 0.06$</td>
<td>.94</td>
</tr>
</tbody>
</table>
TABLE IV

PARTICIPANT COMORBID CONDITIONSa

<table>
<thead>
<tr>
<th></th>
<th>HIV- (n=310)</th>
<th>HIV+ Low CPE (n=62)</th>
<th>HIV+ High CPE (n=56)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck Depression Inventory-II</td>
<td>10.5 (8.6)</td>
<td>15.9 (11.8)</td>
<td>12.2 (9.0)</td>
<td>9.03</td>
<td>.01</td>
</tr>
<tr>
<td>State-Trait Anxiety Inventory-State</td>
<td>32.6 (10.2)</td>
<td>36.9 (13.3)</td>
<td>35.6 (11.6)</td>
<td>4.83</td>
<td>.01</td>
</tr>
<tr>
<td>PTSD Checklist Civilian Version</td>
<td>36.1 (12.9)</td>
<td>40.4 (14.6)</td>
<td>35.3 (15.3)</td>
<td>2.87</td>
<td>.06</td>
</tr>
<tr>
<td>Wender Utah Rating Scale</td>
<td>31.7 (18.7)</td>
<td>34.6 (18.1)</td>
<td>35.8 (24.3)</td>
<td>1.41</td>
<td>.25</td>
</tr>
<tr>
<td>Self-Report Psychopathy Scale</td>
<td>51.5 (10.5)</td>
<td>53.9 (9.9)</td>
<td>52.8 (10.3)</td>
<td>1.60</td>
<td>.21</td>
</tr>
<tr>
<td>Sensation-Seeking Scale-V</td>
<td>14.8 (6.0)</td>
<td>14.2 (5.7)</td>
<td>14.7 (5.8)</td>
<td>0.30</td>
<td>.74</td>
</tr>
</tbody>
</table>

aAll test values are Mean (SD)

3. **Assessment of antiretroviral CPE**

   The total CPE rank of each participant's ARV medication regimen was computed using the revised CPE Scale (Letendre, Ellis, Ances & McCutchan, 2010). The CPE scale assigns a ranking to each individual ARV in a participant's regimen: a rank of 1 indicates a relatively low CNS penetration capability while a ranking of 4 indicates a relatively high penetration capability. A CPE regimen score is computed by summing the individual ranks of each ARV medication in a regimen. CPE regimen scores were employed as a grouping variable in data analysis. HIV+ participants were classified as High CPE (mean CPE = 9.2) and Low CPE (mean CPE = 6.6) groups via a median split.

4. **Assessment of sedating medication**

   In order to control for CNS effects of non-ARV medications on neurocognitive performance, each participant's medications were reviewed for potentially sedating side
effects. Use of a non-ARV medication with sedating properties (e.g. Benadryl, buspirone, citalopram, benzodiazepines, hypnotics) was tabulated for potential use as a covariate.

5. **Neurocognitive Tasks**

   a. **Rotary Pursuit Task**

   The Rotary Pursuit Task (RPT; Lafayette Instruments, Model 30014A) was employed to measure motor skill learning following methods employed in previous studies in this population (Gonzalez et al., 2008; Martin, Gonzalez, Vassileva, & Maki, 2011). Participants engaging in the task held a stylus over a patch of light that appeared to rotate repeatedly around the circumference of a circular disk and were instructed to keep the stylus directly over the light as it rotated. The rotation speed of the light was set at 55 revolutions per minute for all trials, an approach designed to minimize floor and ceiling performance effects in this clinical population. Ten trials lasting 20 seconds each were conducted for each participant, with a 20s rest period between each trial. The dependent variable was the total time that the stylus was kept on target per trial.

   b. **Weather Prediction Task**

   The Weather Prediction Task (WPT; Knowlton, Squire, & Gluck, 1994) is a computerized probabilistic classification paradigm, was utilized as a measure of cognitive PL. Test stimuli for the WPT consisted of 4 cards with unique designs. On each trial a display appeared with either one, two or three of the cards; a total of 14 distinct card combinations were possible. Participants were instructed to predict one of two possible weather outcomes (“rain” or “sunshine”) on each trial using the card display as a guide. Upon seeing the card combination, the participant pressed one of two keys on a keyboard to indicate their prediction and received immediate visual and auditory feedback indicating success or failure. Each card combination had a fixed probability of “rain” or “sunshine” which was not disclosed to the participant. Instead the participant was instructed to guess the weather outcomes at the beginning of the task and to anticipate future responses based on previous results. The procedure was
repeated over a total of four blocks of 50 trials each, utilizing a simpler probability structure (see Gluck, Shohamy and Myers, 2002) and a longer response latency per trial (10s instead of 5s; see Gonzalez et al., 2008 and Martin et al., 2011) than the original WPT (Knowlton et al., 1994) in order to adjust task demands for possible effects of low education and processing speed deficits common among both HIV+ and HIV- SDIs. A participant response was classified as correct if their weather prediction was the most likely outcome of the displayed card combination. Performance on the WPT was quantified as the percentage of correct responses per trial block.

c. **Immediate Memory Task**

The Immediate Memory Task (IMT; Dougherty, Marsh, & Mathias, 2002) is a computerized go/no go task designed to measure motor impulsivity and sustained attention. Substance users typically perform poorly on this task (Dougherty et al., 2003, 2007; Moeller et al., 2002, 2004; Thompson, Whitmore, Raymond & Crowley, 2006). On each trial a five-digit number display appeared for 500ms, followed by a second display that appeared 500ms after stimulus offset. Participants were instructed to respond by clicking a left mouse button if the target stimulus matched the immediately preceding cue stimulus and not to respond if the two displays were not identical. Four response types were possible: 1) a correct detection response given for a “target stimulus” identical to the preceding cue stimulus; 2) a commission error, when the subject responds to a “catch target” with four out of five digits matching the preceding stimulus; 3) an omission error, where a subject fails to accurately respond to a “target stimulus” and 4) a random error, when the subject responds to a “filler stimulus” with a completely different digit sequence from the preceding stimulus. The likelihood of either a target stimulus or a catch stimulus display was 33%, while the likelihood for a filler stimulus was 34%. All participants completed four blocks of 300 trials each. The performance measure was the d’ index of discriminability derived from the ratio of correct responses to correct responses + commission errors.
C. **Data Analysis Plan**

All variables were examined for violations of statistical assumptions of normality and non-normal data were transformed. Data reduction techniques were utilized to reduce variability of neuropsychological tasks. Specifically, performance on the ten trials of the RPT were reduced to five trial blocks with each RPT block representing average performance across two consecutive trials, while performance on the two hundred trials of the WPT were reduced to four trial blocks with each WPT block representing average performance across fifty consecutive trials.

A series of mixed design analyses of covariance (ANCOVAs) were employed to examine the relationship between serostatus, CPE regimen score and performance on the RPT and WPT tasks. Group categorization (HIV-, HIV+/Low CPE, HIV+/High CPE) was utilized as the between subjects factor. Task blocks were used as the within-subjects factor for both analyses. Time on target in seconds was the dependent variable for RPT analyses, while percentage of correct weather predictions per trial block was used as the dependent variable for WPT analyses. A univariate ANCOVA was conducted to examine the relationship between Group and $d'$, the IMT index of discriminability. Mixed design ANCOVAs were used to assess the percentage of correct responses per trial block and the percentage of commission errors per trial block, two subcomponents of IMT performance. Demographic, medical and psychological variables that differed significantly across groups were utilized as covariates in analyses. Post-hoc comparisons were conducted using the method of Bonferroni correction. The Jonckheere-Terpstra test was applied as a test of monotonic trend for ordinal data across Groups when indicated by preliminary analysis. As a validity check, the ANCOVAs were recalculated collapsing across the two HIV+ groups for each task to ensure that overall serostatus differences could be detected.
III. Results

A. Group Characteristics

Group demographic characteristics are listed on Table 1 of the Appendix. Participants were well-matched on age, $F(2,425) = 1.85$, $p > .05$, years of education, $F(2,425) = 2.29$, $p > .05$, and estimated verbal IQ, $F(2,424) < 1$. Group compositions did not vary significantly in terms of gender, $\chi^2(2) = 3.83$, $p > .05$ or ethnicity (African American, Caucasian, Other), $\chi^2(4) = 5.46$, $p > .05$. Positive Hepatitis C serostatus was significantly less common in the HIV- group (14%) than either the HIV+/Low CPE group (31%), $\chi^2(1) = 10.47$, $p < .005$ or the HIV+/High CPE Group (33%), $\chi^2(1) = 11.93$, $p < .005$. There were no significant group differences in history of past alcohol dependence, $\chi^2(2) = 3.48$, $p > .05$ or cannabis dependence, $\chi^2(2) = 4.12$, $p > .05$ (see Table III for substance use characteristics and test statistics). Prevalence of previous cocaine dependence was lower in HIV-subjects (75%) than HIV+/High CPE subjects (88%), $\chi^2(1) = 4.26$, $p < .05$. History of opioid dependence was more frequent in HIV-subjects (54%) than in either the HIV+/Low CPE group (37%), $\chi^2(1) = 6.05$, $p < .05$, or the HIV+/High CPE group (36%), $\chi^2(1) = 6.48$, $p < .05$. Groups did not differ in terms of total years of alcohol use, $F(2,402) = 1.29$, $p > .05$, cannabis use, $F(2,379) = 2.22$, $p > .05$, cocaine use, $F(2,355) = 1.65$, $p > .05$ or opioid use, $F(2,212) < 1$. The Kruskal-Wallis test was used to evaluate group differences in number of days since last drug use; no differences in recent drug use were detected for alcohol $H(2) = 4.19$, $p > .05$, cannabis, $H(2) = 1.51$, $p > .05$, cocaine, $H(2) = 2.68$, $p > .05$, or opioids, $H(2) = 3.20$, $p > .05$. Severity of past substance use as indexed by KMSK scores did not differ between groups for alcohol, $F(2,412) < 1$, cocaine, $F(2,376) = 2.00$, $p > .05$, or opioids, $F(2,376) < 1$ (see Table IV for comorbidity scores and test statistics).

In terms of comorbid psychiatric symptomatology and personality traits, group scores did not differ significantly on the WURS, $F(2,424) = 1.41$, $p < .05$, SRPS, $F(2,424) = 1.60$, $p > .05$, or SSS-V, $F(2,424) < 1$. Group differences reached a trend towards significance on the PCL-C, $F(2,424) = 2.87$, $p = .06$; however, Bonferroni-corrected pairwise comparisons revealed no significant differences.
between groups in severity of PTSD symptoms. HIV+/Low CPE subjects reported significantly elevated scores on the BDI-II ($M = 15.9$, $SD = 11.8$), and STAI ($M = 36.9$, $SD = 13.3$) relative to HIV-subject BDI-II ($M = 10.5$, $SD = 8.6$), $F(1,369) = 17.56$, $p < .001$, and STAI scores ($M = 32.6$, $SD = 10.2$), $F(1,352) = 7.84$, $p < .01$. Psychiatric and personality variables which differed significantly between groups and correlated significantly with neurocognitive performance dependent variables were included as covariates in analyses (see Table V).

**TABLE V**

<table>
<thead>
<tr>
<th></th>
<th>Mean RPT</th>
<th>Mean WPT</th>
<th>IMT $d'$</th>
<th>Mean IMT Correct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine Dependence</td>
<td>.00</td>
<td>-.08</td>
<td>-.05</td>
<td>-.03</td>
</tr>
<tr>
<td>Opioid Dependence</td>
<td>-.06</td>
<td>-.10</td>
<td>-.01</td>
<td>.10</td>
</tr>
<tr>
<td>STAI$^{b,c}$</td>
<td>-.16$^a$</td>
<td>.02</td>
<td>-.15$^a$</td>
<td>-.10</td>
</tr>
<tr>
<td>BDI$^b$</td>
<td>-.11$^a$</td>
<td>.01</td>
<td>-.08</td>
<td>-.02</td>
</tr>
<tr>
<td>Hepatitis C status$^b$</td>
<td>-.12$^a$</td>
<td>-.01</td>
<td>-.08</td>
<td>-.09</td>
</tr>
</tbody>
</table>

$^a p < .05$

$^b$Used as covariate in RPT analysis

$^c$Used as covariate in $d'$ analysis

**B. Rotary Pursuit Task Performance**

A 3 x 5 (Group x Block) mixed-model ANCOVA was conducted for RPT performance, using Hepatitis C serostatus and scores on the STAI and BDI as covariates. The analysis detected an expected significant main effect for Block, $F(4, 1516) = 9.90$, $p < .001$. A significant main effect for Group was observed, $F(2, 379) = 5.26$, $p < .01$, and post-hoc Bonferroni comparisons revealed that participants in the HIV+/High CPE group ($M = 8.25$, $SD = 4.42$) demonstrated significantly poorer task performance compared to the HIV- group ($M = 10.53$, $SD = 4.31$), $p < .01$ (see Figure 1). HIV+/Low CPE group RPT performance ($M = 9.24$, $SD = 4.55$) did not differ significantly from either the HIV-group, $p > .05$ or the HIV+/High CPE group, $p > .05$. No significant Block x Group interaction was
observed, $F(8, 1516) < 1$. A significant monotonic trend in RPT performance was observed across groups (Jonckheere-Terpstra statistic $= -3.77$, $p < .001$), meaning that HIV+ Low CPE subject performance may represent an intermediate level of ability between HIV- subjects and High CPE HIV+ subjects despite the lack of statistically significant pairwise differences between HIV+ Low CPE subjects and either comparison group. Collapsing across HIV+ groups, positive HIV serostatus was associated with poorer RPT performance ($M = 8.77$, $SD = 4.50$) than HIV- status ($M = 10.53$, $SD = 4.31$), $F(1,379) = 6.64$, $p < .05$.

Figure 1. Mean time on target during the Rotary Pursuit Task by HIV-seronegative, HIV+ Low CPE and HIV+ High CPE participants.
C. **Weather Prediction Task Performance**

A 3 x 4 (Group x Block) ANOVA of WPT performance was conducted; no variables that differed between groups correlated significantly with WPT performance, so no covariates were included. An expected significant main effect of Block was observed across WPT trials, \( F(3,1266) = 13.59, p < .001 \). A significant main effect of Group on WPT performance was also observed, \( F(2,422) = 6.76, p < .005 \). Post-hoc Bonferroni comparisons of the Group main effect indicated that HIV+/High CPE group WPT performance (\( M = 12.84, SD = 2.04 \)) differed significantly from HIV- WPT performance (\( M = 13.98, SD = 2.36 \)), \( p < .005 \) (see Figure 2). HIV+/Low CPE group WPT performance (\( M = 13.40, SD = 2.01 \)) did not significantly differ from the HIV+/High CPE group, \( p > .05 \), but showed a trend toward poorer performance compared with the HIV- group, \( p < .08 \). The test of Group x Trial Block interaction yielded no significant results, \( F(6,1266) < 1 \). Collapsing across HIV+ groups detected a significant

![WPT](image)

Figure 2. Mean percentage of correct responses on the Weather Prediction Task by HIV-seronegative, HIV+ Low CPE and HIV+ High CPE participants.
main effect of HIV Serostatus, $F(1,420) = 5.73$, $p < .05$, with HIV- subjects ($M = 13.98, SD = 2.36$) demonstrating better WPT performance than HIV+ subjects ($M = 13.14, SD = 2.04$). Jonckheere-Terpstra test results indicated a significant monotonic trend in mean WPT performance across groups (Jonckheere-Terpstra statistic = -3.80, $p < .001$), indicating that HIV+ Low CPE subject performance may be at an intermediate level between HIV- subjects and High CPE HIV+ subject performance despite a lack of significant pairwise differences between the HIV+ Low CPE group and comparison groups.

D. **Immediate Memory Task Performance**

A between-subjects ANCOVA was conducted for IMT discriminability with Groups as the factor, d' as the dependent variable and STAI scores as a covariate. The analysis revealed no Group effect on discriminability, $F(2,402) < 1$. Additionally, two 3 x 4 (Group x Block) mixed model analyses were conducted with either percentage of correct IMT responses per trial block or percentage of commission errors per trial block as the dependent variables. No potential covariates correlated significantly with IMT correct responses, so the analysis was conducted as an ANOVA. For the analysis IMT commission errors, an ANCOVA was conducted including Past Opioid Dependence and scores on the STAI and BDI as covariates. No significant main effect for Trial Block or was observed during analyses of either correct responses, $F(3,1272) < 1$, or commission errors, $F(3,1200) < 1$. Analyses of Group effects detected no significant main effects for correct responses, $F(2,424) < 1$, or commission errors, $F(2,400) < 1$. Additionally was not a significant Block x Group interaction for either correct responses, $F(6,1272) < 1$, or commission errors, $F(6,1200) = 1.71, p > .05$.

E. **Effects of Gender on Procedural Learning Task Performance**

An exploratory analysis was conducted in an effort to replicate previous findings of gender differences in RPT and WPT performance in a larger sample of HIV+ SDIs (Martin et al., 2011). The analyses described above were repeated with Gender and HIV Serostatus utilized as between-subject factors instead of the CPE grouping factor. Trial Block was the between-subject factors in all mixed-
model ANCOVAs. Gender groups were well-matched on demographic variables (see Table VI). Variables which differed significantly between Gender groups and which correlated significantly with neurocognitive performance variables were included as covariates in analyses.

### TABLE VI

**EXPLORATORY ANALYSIS GROUP DEMOGRAPHICS**

<table>
<thead>
<tr>
<th></th>
<th>Male HIV- (n=227)</th>
<th>Male HIV+ (n=76)</th>
<th>Female HIV- (n=83)</th>
<th>Female HIV+ (n=42)</th>
<th>Test statistic</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in Years (Mean, SD)</td>
<td>42.3 (8.7)</td>
<td>44.1 (6.4)</td>
<td>40.8 (8.0)</td>
<td>42.8 (6.6)</td>
<td>$F = 2.05$</td>
<td>.11</td>
</tr>
<tr>
<td>Years of Education (Mean, SD)</td>
<td>11.6 (1.6)</td>
<td>11.6 (2.1)</td>
<td>11.7 (2.0)</td>
<td>11.3 (1.6)</td>
<td>$F = 0.82$</td>
<td>.48</td>
</tr>
<tr>
<td>% African American</td>
<td>84</td>
<td>88</td>
<td>77</td>
<td>88</td>
<td>$\chi^2 = 4.31$</td>
<td>.23</td>
</tr>
</tbody>
</table>

A 2 x 2 x 5 (Gender x HIV Serostatus x Block) mixed-model ANCOVA (covarying for Hepatitis C serostatus and STAI scores) indicated that RPT performance of female subjects ($M = 8.10$, $SD = 4.21$) was significantly poorer than male subjects ($M = 10.82$, $SD = 4.27$), $F(1,379) = 26.03$, $p < .001$. There was a significant main effect of Block, $F(4,1516) = 10.11$, $p < .001$. There were no significant interactions of Gender x HIV Serostatus, $F(1,379) < 1$, Block x Gender, $F(4,1516) < 1$, or Block x HIV Serostatus, $F(4,1516) < 1$. A 2 x 2 x 4 (Gender x HIV x Block) mixed-model ANCOVA of WPT performance (covarying for SSS-V) detected no significant main effect for Gender, $F(1,420) = 1.58$, $p > .05$. The expected significant main effect for Block was not observed, $F(3,1260) = 1.09$, $p > .05$, although removing SSS-V scores as a covariate resulted in the expected Block main effect $F(3,1263) = 17.58$, $p < .001$. No significant interactions were detected for Block x Gender, $F(3,1260) = 1.19$, $p > .05$, or Block x HIV Serostatus, $F(3,1260) < 1$. A trend towards significant Gender x HIV Status interaction was observed, $F(1,420) = 3.05$, $p < .09$. 
IV. Discussion

In this study the PL task performance of HIV+ subjects on ARV drug regimens with high CNS penetration capability was compared to the performance of HIV+ subjects on drug regimens with relatively low CNS penetrance capability and HIV- controls. Participant groups consisted entirely of individuals with histories of substance dependence and were well-matched on most demographic variables. HIV+ groups were well-matched on disease characteristics, and numerous potential confounds associated with neurocognitive performance in HIV+ and substance-dependent populations were controlled for. No evidence was found of significant differences in PL task performance between HIV+ subjects subdivided by scores on the CPE scale (Letendre et al., 2010) which ranks current antiretroviral therapy regimens according to level of CNS penetrance. Specifically, HIV+ subjects prescribed high CPE cART regimens demonstrated significantly poorer performance than HIV- subjects, but subjects prescribed lower CPE regimens did not differ significantly from either comparison group. Follow-up analyses indicated a monotonic decrement across groups in both RPT and WPT performance. Contrary to expectation, the HIV+ High CPE group mean performance ranked lower than the HIV+ Low CPE group mean performance.

Both RPT and WPT performance significantly improved over trial blocks for all groups, indicating successful task learning. A two-group comparison according to serostatus showed the HIV+ subjects performed both tasks significantly more poorly compared to controls, consistent with previous reports (Gonzalez et al., 2008; Martin et al., 2011). There were no significant interactions between group status and trial block for either RPT or WPT performance, indicating that rates of learning did not differ between groups; therefore any group differences cannot be attributed to differences in PL per se, but rather indicate deficits on tasks involving a PL component. Performance accuracy and discriminability on the IMT task did not differ across groups, indicating that observed RPT and WPT deficits cannot be attributed to global neurocognitive impairment within the high CPE subsample.
A. Relationship to Previous Investigations of ARV CPE and Neurocognition

1. ARV CPE and Neurocognitive Status in Different Clinical Samples

Previous findings on the relationship between ARV CPE and neurocognitive performance in have been mixed. Although there was no evidence supporting the hypothesis that higher cART CPE rankings would be associated with higher PL task performance in the current sample of HIV+ SDIs, the literature on CPE and neurocognition has not produced consistent results across various HIV+ samples. High CPE medication has previously been demonstrated to predict lower CNS HIV RNA levels in a cross-sectional analysis (Letendre et al., 2008). Cysique and colleagues (2004a) conducted a cross-sectional comparison of two HIV+ groups treated with either neuroactive cART or cART regimens of comparatively low neuropenetrance and found no relationship between neuropenetrance and performance in seven standard clinical neurocognitive domains (attention, psychomotor speed, motor coordination, verbal memory, visual memory, visuospatial ability) across all subjects. However, comparisons of cognitively impaired subsets from both HIV+ groups revealed significantly better memory performance in the subset treated with neuroactive cART. Two longitudinal analyses have replicated findings of associations between High CPE and lower HIV levels in the CNS (Letendre et al., 2004; Marra et al., 2009) and several longitudinal studies have demonstrated positive associations between CPE and global neurocognitive performance (Cysique et al., 2006, 2009; Letendre et al., 2004). However, recent evidence has also emerged in the neuropsychological literature suggesting ARV-related cognitive deficits. A recent cross-sectional study by Ciccarelli et al. (2011) established a link between use of the highly neuropenetrant ARV Efavirenz and neurocognitive impairment in otherwise asymptomatic HIV+ subjects. Results from an ACTG prospective treatment study (Marra et al., 2009) indicated that cART regimens with high CPE were associated with more effective suppression of CSF HIV but poorer neurocognitive performance compared with low CPE ARVs. An ACTG study of subjects with preserved immune function demonstrated improved neurocognitive ability that was maintained for up to ninety-six weeks following elective
discontinuation of cART, indicating possible remediation of ARV-related neurotoxicity (Robertson et al., 2010). However, the majority of study participants from these investigations did not have an explicitly identified history of substance dependence, and the effects of past substance dependence on relationships between CPE, HIV CNS levels, and global neurocognitive functioning have yet to be evaluated.

2. **Procedural Learning Performance in HIV+ SDIs**

The present results support earlier reports indicating that a positive HIV serostatus is related to deficits in motor and cognitive PL task performance in SDIs. Gonzalez et al. (2008) reported HIV-associated deficits of RPT task performance in HIV+ SDIs which are replicated in the current study. As in the current report, Gonzalez et al. (2008) found significant main effects in group RPT performance but no group x block interactions, indicating differences in complex motor performance but not non-declarative learning. Martin et al. (2011) also reported a marginally significant HIV-associated deficit in RPT performance within a sample of HIV+ SDIs. These findings taken with the current study indicate the RPT is a strong experimental task for detecting motor performance deficits within HIV+ SDIs.

Gonzalez et al. (2008) did not detect an HIV serostatus effect on WPT task performance. An exploratory analysis of the current sample examining the effects of gender and HIV serostatus on PL performance indicated significantly lower performance of HIV+ subjects across CPE levels. This finding of an HIV-associated WPT performance deficit replicates findings reported by Martin et al. (2011). The variability of WPT task performance across these three studies may owe partly to the fact that although the WPT is incrementally acquired, learning the task may not be solely a function of the non-declarative memory systems hypothesized to be impaired in HIV+ individuals. Individual variability in subject cue strategies has been reported on the WPT, indicating possible recruitment of different neuroanatomical memory systems during task acquisition (Gluck, Shohamy & Myers, 2002). Functional neuroimaging results have shown that individuals with basal ganglia disease
experience activation of the medial temporal lobe and regions of the prefrontal cortex associated with explicit memory retrieval while engaging in the WPT (Moody, Bookheimer, Vanek & Knowlton, 2004). Variable WPT findings within this population may therefore be due to the variety of neuroanatomical regions potentially activated by task performance, some of which may not be as compromised by deleterious effects of HIV and/or substance dependence. Despite these considerations, two out of the three studies utilizing the WPT as a probe for neurocognitive deficits in HIV+ SDIs have revealed HIV-associated impairment, suggesting that this task deserves future consideration for use within this population.

3. **Potential Neurotoxic Effects of Highly Neuropenetrant ARVs**

The current findings indicate impaired performance within substance dependent subjects on High CPE cART regimens on tests of motor and cognitive PL, a finding which is not inconsistent with reports of neurocognitive impairment associated with ARV neuropenetrance but does not provide conclusive evidence of neurotoxicity. Converging findings from the HIV literature suggest that at least some ARV drugs may cause neurotoxic effects that are detectable via neurocognitive assessment. ARV medications have been implicated in toxic syndromes including myopathy (Dalakas et al., 1994; Gerschenson et al., 2000), hepatic dysfunction (Carr, Miller, Law & Cooper, 2000; Lai, Gang, Zawacki & Cooley, 1991), lipodystrophy (Carr et al., 1998, 1999) and distal sensory neuropathy (Feng et al., 2001, Moyle & Sadler, 1998). Convergent evidence for ARV-associated CNS toxicity is emerging. Recent in vitro findings have demonstrated that a combination of the commonly prescribed ARV medications Zidovudine and Indinavir damage human blood-brain barrier endothelial cells (Manda, Banerjee, Banks & Ercal, 2010). Therapeutic doses of the protease inhibitors Nelfinavir and Saquinavir have been shown to inhibit human proteasome function (Piccinini et al., 2005). Magnetic resonance spectroscopy data indicate mitochondrial disruption in frontal white matter of HIV+ subjects treated with the nucleoside reverse transcriptase inhibitors Didanosine and Stavudine (Schweinsburg et al., 2005). Liner, Robertston & Meeker (2009) recently presented preliminary findings indicating that fifteen commonly used ARV medications
are neurotoxic to fetal rat cortical tissue cultures at concentrations above 10µg/ml; several of the studied ARVs showed median toxic doses at concentrations typically seen in the plasma and CSF of patients treated with cART. Taken together, this body of neurobiological research suggests the potential for deleterious effects of neuropenetrant ARV medications in HIV+ individuals.

4. **Exploratory Findings on Gender Effects**

In addition to the primary analysis of CPE effects, an exploratory analysis of the effects of gender and HIV serostatus on PL task performance was conducted. The purpose of this analysis was to replicate findings of female-specific performance deficits in HIV+ SDIs observed in a previous study (Martin et al., 2011). Martin et al. (2011) reported that HIV-females performed better than HIV+ females on both the RPT and WPT, but performance of HIV+ and HIV+ males did not differ significantly. In the current study, male subjects performed better on the RPT than female subjects collapsing across serostatus, while HIV-subjects outperformed HIV+ subjects. No significant interactions between gender and serostatus or gender and trial block were observed. Similar to the findings of Martin et al. (2011), HIV- individuals in the current study performed better on the WPT than HIV+ individuals, and no WPT performance differences between males and females were evident. However, the current findings diverge from those of Martin et al. (2011) in that rates of WPT improvement did not differ within genders as a function of serostatus. The disparities in WPT performance across these studies may owe to high individual variability in cue strategies used by subjects to solve the task (Gluck, Shohamy & Myers, 2002). Additional replication trials are required to understand possible causes of the discrepancies in WPT results between these two reports.

B. **Limitations of the Current Study**

The present study had several limitations. HIV medication adherence information was obtained via a brief self-report measure with no independent verification, so no firm conclusions can be drawn
about actual medication use. Although HIV biomarkers were obtained including current and nadir CD4 counts and systemic HIV RNA viral load, cerebrospinal fluid (CSF) samples were not available, so the association of CNS viral burden with CPE rankings or neurocognitive performance could not be evaluated. However, the relationship between CSF HIV levels and neurocognition is unclear, with studies of cART-treated individuals reporting either associations between high CSF viral load and neurocognitive impairment (Ellis et al., 1997, 2002) or no relationship between CSF viral levels and neurocognitive status (McArthur et al., 2004; Sevigny et al., 2004). The inconsistent nature of these findings may be due to cART-induced suppression of CSF HIV (Sevigny et al., 2004), which may limit the utility of CSF HIV levels as a predictor of neurocognitive status in cART-treated individuals. Due to the cross-sectional nature of the current study, longitudinal predictions of neurocognitive status based on baseline measures of pre-existing cognitive deficits were not possible. Cross-sectional designs have previously been established in the literature as a viable method of successfully demonstrating differences in neurocognitive performance between groups treated with ARV therapy vs. no treatment (Martin et al., 1998, 1999) or High vs. Low CPE cART (e.g. Ciccarelli et al., 2011; Cysique et al., 2004) even though causal factors for observed differences cannot be drawn from these research designs.

C. Implications for Future Research

1. Replication Studies

This is the first study to investigate potential association between PL task performance and CNS penetrance. Additionally, the present investigation is the first to explicitly examine the association between neurocognitive performance and CPE in an entirely substance-dependent HIV+ sample. Therefore the present findings awaits replication with non-substance dependent HIV+ individuals. This study targeted the specific cognitive domains of PL and attention/behavioral inhibition, so it is possible that the observed association of high CPE and neurocognitive deficits in these domains may not conflict with previous reports of positive associations between high CPE cART regimens and superior performance on test batteries assessing standard clinical neurocognitive domains. The experimental measures administered have not been previously studied among clinical
populations of HIV+ SDIs, so conjecture about the relationship between the PL impairment observed in the current study and global neurocognitive status is not possible. Future investigations assessing PL task performance in addition to more globalized assessments of neurocognition (including clinical determinants of HAND) will clarify how CPE effects on PL performance relate to global neurocognitive status. HIV+ individuals prescribed high CPE ARV regimens may have been suffering from more severe (and perhaps more clinically overt) neurocognitive deficits prior to initiation of cART, and thus high CPE medication may serve as a proxy measure for greater baseline cognitive impairment within the current sample.

2. **Longitudinal Monitoring of Procedural Learning Performance**

   Should findings of PL deficits associated with high CPE cART be replicated, future longitudinal examinations of the effects of CPE on PL performance in HIV+ subjects are recommended. Prospective studies could determine how pre-existing cognitive impairment, HIV disease course, and initiation/change of cART regimens of varying CPE levels affect PL performance deficits. Clinical status at time of initiating cART has been shown to influence CPE score (Garvey et al., 2011), so prospective measurement of clinical variables could lead to clarification of potential third variables that might confound associations between CPE and neurocognitive performance. Neuroimaging studies that specifically address the question of prefrontal-striatal integrity in HIV+ SDIs on high and low CPE medications could help determine if the observed PL task performance deficits can be attributed to ARV-related toxic injury to neuroanatomical substrates of non-declarative memory. Future longitudinal research carefully evaluating cognitive function prior to cART initiation would be helpful in illuminating potential selective effects of ARV CPE on PL performance.

D. **Conclusion**

   The current study is the first effort to understand the impact of ARV neuropenetrance on the neuropsychological status of HIV-infected individuals with histories of substance dependence. HIV and substance dependence are two chronic sources of potential neurological insult that frequently co-
occur in clinical populations and may represent a particular vulnerability for impairment of frontostriatal-mediated neurocognition, represented in the current study by tests of non-declarative learning. Among the entire study sample of HIV+ and HIV- drug users, HIV infection was associated with significantly lower performance on both a task probabilistic classification and a task of complex motor skills, replicating previous results of additive deleterious effects of HIV in substance dependent samples. Additionally, higher CPE cART regimens were found to predict significantly worse performance on frontostriatal-mediated tasks than seen in HIV- SDIs, suggesting a clustering of neurocognitive deficits within this segment of the HIV+ sample. Although the cross-sectional design of the current study limits interpretation of these findings, both high and low CPE HIV+ groups were well-matched on HIV disease characteristics, suggesting that increased severity of HIV disease in the high CPE group cannot solely account for the observed differences. Additionally, all participant groups were well-matched on demographic and psychiatric characteristics, and no differences between any groups were detected on a test of attention and motor impulsivity, indicating that the observed deficits on non-declarative learning tasks within HIV+ SDIs may not be attributed to global neurocognitive impairment.

The current results are suggestive of additive deleterious effects of HIV and substance dependence on frontostriatal neurocircuitry, and the relative clustering of neurocognitive impairment with HIV+ SDIs prescribed high CPE medications may indicate a vulnerability to potential neurotoxic effects of ARVs within this patient population. Further longitudinal research on the effects of cART CPE on HIV+ SDIs is recommended including examination of both frontostriatal-mediated memory tasks and standard clinical neurocognitive domains and careful measurement of baseline medical, psychiatric and neurocognitive status.


exposed in utero to 3'-azido-3'-deoxythymidine. *AIDS Research and Human Retroviruses*, 16, 635-644.


Approval Notice
Continuing Review (Response To Modifications)

March 7, 2011

Eileen M. Martin, PhD
Psychiatry
1601 W. Taylor St.
583 P.I., M/C 912
Chicago, IL 60612-4310
Phone: (312) 996-9373 / Fax: (312) 413-8147

RE: Protocol # 2006-0044
“Cognitive Neuropsychology of HIV and Drug Abuse Phase II”

Please note that due to the over enrollment of subjects, the informed consent documents will be released with the approval notice for Amendment #8, which is the request to increase the subject enrollment number.

Dear Dr. Martin:

Your Continuing Review (Response To Modifications) was reviewed and approved by the Expedited review process on March 4, 2011. You may now continue your research.

Please note the following information about your approved research protocol:

Approved Subject Enrollment #: 600 (612 subjects enrolled)
Additional Determinations for Research Involving Minors: These determinations have not been made for this study since it has not been approved for enrollment of minors.
Performance Sites: Jesse Brown VAMC, UIC
Sponsor: NIDA - National Institute on Drug Abuse
PAF#: 2005-03681
Grant/Contract No: 2 RO1 DA012828-06
Grant/Contract Title: Cognitive Neuropsychology of HIV and Drug Abuse Phase II
Research Protocol:
   a) "Cognitive Neuropsychology of HIV and Drug Abuse", Version 4, 05/18/2010
Recruitment Materials:

a) "Research Participants Needed" Flyer, Version 2.5, 01/29/2009
b) "Interested in a paid memory research study?", UIC Protocol # 2006-0044 P2, Version 1.0, 04/26/2010
c) "Paid Memory Research Study", Text Only Ad--for newspaper Help Wanted and Advertisement/Classified sections #2006-0044, Version 1.0, 04/26/2010

Informed Consents: Due to the over enrollment of subjects, the informed consent documents will be released with the approval notice for Amendment #8.

HIPAA Authorizations: Please continue to use the following documents, once Amendment #8 has been approved, as they have previously been approved and have not expired:

a) VA Authorization: Cognitive Neuropsychology of HIV and Drug Abuse Phase II, Version 2, 03/12/2010
b) UIC Authorization: Neuropsychology of HIV and Drug Abuse Phase II, Version 3, 03/12/2010

Your research meets the criteria for expedited review as defined in 45 CFR 46.110(b)(1) under the following specific categories:

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows: (a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or (b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.,

(3) Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.,

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis),

(7) Research on individual or group characteristics or behavior (including but not limited to research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Please note the Review History of this submission:

<table>
<thead>
<tr>
<th>Receipt Date</th>
<th>Submission Type</th>
<th>Review Process</th>
<th>Review Date</th>
<th>Review Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>02/04/2011</td>
<td>Continuing Review</td>
<td>Expedited</td>
<td>02/15/2011</td>
<td>Modifications Required</td>
</tr>
<tr>
<td>02/22/2011</td>
<td>Response To Modifications</td>
<td>Expedited</td>
<td>03/04/2011</td>
<td>Approved</td>
</tr>
</tbody>
</table>
Please remember to:
 Use your research protocol number (2006-0044) on any documents or correspondence with the IRB concerning your research protocol.
 Review and comply with all requirements on the enclosure, "UIC Investigator Responsibilities, Protection of Human Research Subjects" "JBVAMC Investigator Responsibilities for Performing Research Involving Human Subjects"

Please note that the IRB has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 413-8457. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Barbara Corpus
Assistant Director, IRB # 4
Office for the Protection of Research Subjects

Enclosures:
1. UIC Investigator Responsibilities, Protection of Human Research Subjects
2. JBVAMC Investigator Responsibilities for Performing Research Involving Human Subjects
3. VA Form 10-1223 - Report of Subcommittee on Human Studies

cc: Anand Kumar, Psychiatry, M/C 912
    Israel Rubinstein, M.D, JBVAMC, Mail Point 151, M/C 977
    OVCR Administration, M/C 672
March 22, 2011

Eileen M. Martin, PhD
Psychiatry
1601 W. Taylor St.
583 P.I., M/C 912
Chicago, IL 60612-4310
Phone: (312) 996-9373 / Fax: (312) 413-8147

RE: Protocol # 2006-0044
“Cognitive Neuropsychology of HIV and Drug Abuse Phase II”

Dear Dr. Martin:

Members of the Collaborative JBVAMC/NU/UIC Institutional Review Board (IRB #4) have reviewed this amendment to your research and/or consent form under expedited procedures for minor changes to previously approved research allowed by Federal regulations [VHA Handbook 1200.05, 38 CFR 16.110(b), and 45 CFR 46.110(b)(2)]. The amendment to your research was determined to be acceptable and may now be implemented.

Please note the following information about your approved amendment:

Amendment Approval Date: March 21, 2011

Amendment:
Summary: UIC Amendment #8, dated February 18, 2011 and received in OPRS on February 22, 2011 (modification response received on March 15, 2011), is an investigator-initiated amendment including the request to increase the subject enrollment number from 600 to 750 and the submission of a revised UIC and JBVAMC consent documents.

Approved Subject Enrollment #: 750

Informed Consent:

a) VA Consent: Neuropsychology of HIV and Drug Abuse Phase II, Version 6, 02/21/2011
b) UIC Consent: Neuropsychology of HIV and Drug Abuse Phase II, Version 3, 02/21/2011
Please note the Review History of this submission:

<table>
<thead>
<tr>
<th>Receipt Date</th>
<th>Submission Type</th>
<th>Review Process</th>
<th>Review Date</th>
<th>Review Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>02/22/2011</td>
<td>Amendment</td>
<td>Expedited</td>
<td>03/04/2011</td>
<td>Modifications Required</td>
</tr>
<tr>
<td>03/15/2011</td>
<td>Response To Modifications</td>
<td>Expedited</td>
<td>03/21/2011</td>
<td>Approved</td>
</tr>
</tbody>
</table>

Please be sure to:

→ Use only the IRB-approved and stamped consent documents enclosed with this letter when enrolling subjects.

→ Use your research protocol number (2006-0044) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure, "UIC Investigator Responsibilities, Protection of Human Research Subjects" "JBVAMC Investigator Responsibilities for Performing Research Involving Human Subjects"

Please note that the IRB has the right to ask further questions, seek additional information, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact the OPRS at (312) 996-1711 or me at (312) 413-8457. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Barbara Corpus
Assistant Director, IRB # 4
Office for the Protection of Research Subjects

Enclosures:

1. UIC Investigator Responsibilities, Protection of Human Research Subjects
2. JBVAMC Investigator Responsibilities for Performing Research Involving Human Subjects
3. Informed Consent Document:
   a) VA Consent: Neuropsychology of HIV and Drug Abuse Phase II, Version 6, 02/21/2011
   b) UIC Consent: Neuropsychology of HIV and Drug Abuse Phase II, Version 3, 02/21/2011

cc: Anand Kumar, Psychiatry, M/C 912
Israel Rubinstein, M.D, JBVAMC, Mail Point 151, M/C 977
VITA

NAME: Michael Wilson

EDUCATION: B.S., Biology, University of Maryland, College Park, 2006
B.S., Psychology, University of Maryland, College Park, 2006

TEACHING: Dept. of Psychology, University of Maryland, College Park, 2006-2007
Dept. of Psychology, University of Illinois at Chicago, 2010-2012

PROFESSIONAL EXPERIENCE: Dept. of Psychology, University of Maryland, College Park, 2006-2008
Dept. of Psychology, University of Maryland School of Medicine, 2008-2010

ABSTRACTS:


PUBLICATIONS:
