Published in final edited form as:

Neuropsychol Rev. 2009 June ; 19(2): 215–231. doi:10.1007/s11065-009-9101-6.

Drug Abuse and Hepatitis C Infection as Comorbid Features of HIV Associated Neurocognitive Disorder: Neurocognitive and Neuroimaging Features

Eileen M. Martin-Thormeyer and

University of Illinois and Jesse Brown VA Medical Center, Chicago IL USA
emartin@psych.uic.edu

Robert H. Paul

University of Missouri, St Louis MO USA

Washington University St Louis, MO, USA

Abstract

Substance abuse and co-infection with hepatitis C (HCV) are two highly relevant determinants of neurocognitive and neuroimaging abnormalities associated with HIV. Substance abuse and HCV are common in the HIV population and there is increasing evidence that the CNS is directly compromised by these comorbid conditions via additive or synergistic processes. In this article we review the current literature regarding mechanisms of neuronal injury as well as the neuropsychological and neuroimaging signatures associated with substance abuse and HCV status among HIV patients. We discuss specific methodological challenges and threats to validity associated with studies of HIV and comorbid substance use disorders or HCV and review potential strategies for minimizing their confounding effects. Efforts to understand the interactions between HIV, substance abuse and HCV co-infection will lead to more complete models of neuropathogenesis of HIV and a greater understanding of the variability in neuropsychological expression of HIV Associated Neurocognitive Disorder.

Keywords

HIV; Drug abuse; Hepatitis C; Addiction; Neurocognition; Neuroimaging; Dementia

Overview

Comorbid medical and psychiatric conditions frequently complicate the clinical presentation and neural mechanisms of HIV-associated Neurocognitive Disorder (HAND). HIV can compromise the capacity to carry out a range of critical life tasks (Heaton et al. 2004) such as driving (Marcotte et al. 1999), maintaining employment (Heaton et al. 1994), adhering to complex medication regimens (Hinkin et al. 2004), and possibly abstaining from high risk sexual and injection practices. Comorbid substance dependence or hepatitis C virus (HCV) infection in the HIV-infected individual will increase the risks of morbidity, mortality, and serious personal, social and economic consequences including incarceration, additional psychiatric and medical hospital admissions, financial problems, and family discord.

In this article we review neurocognitive and neuroimaging studies of substance use disorders (SUDs) and HCV infection, two disorders that are highly prevalent among HIV+ individuals, focusing primarily on investigations conducted since the introduction of highly active antiretroviral therapy (HAART). We discuss specific methodological challenges and threats to validity associated with studies of HIV and comorbid SUDs or HCV and review potential strategies for minimizing their confounding effects. This article focuses primarily on comorbidity issues; we refer the interested reader elsewhere in this special issue and to a recent comprehensive text (Kalechstein and van Gorp 2007) for more extensive reviews of HAND or neurocognitive aspects of substance dependence, respectively

HIV and the Brain: A Brief Review

HIV disease is associated with a spectrum of neurocognitive impairment ranging from mild but clinically silent performance deficits on neurocognitive testing to frank dementia. HIV-1 typically invades the brain within 2 weeks of initial infection, most likely via trafficking of infected monocytes (Kanmogne et al. 2002), and facilitated by compromise of the blood brain barrier. The virus infects directly supportive cells of the brain, such as microglial cells, astrocytes, and macrophages (Garden 2002) and the term “HIV encephalitis” refers specifically to a constellation of neuropathological changes including microgliosis, multinucleated giant cells, and myelin pallor associated with direct CNS infection (e.g., Budka et al. 1991). The distribution of central neuropathology due to direct or indirect effects of primary HIV infection is not limited to distinct brain regions, however neuropathology is preferentially distributed, with primary involvement of deep white matter and subcortical nuclei. Neuronal loss is evident in prefrontal cortex and in hippocampus, but cortical involvement is typically less severe than damage to basal ganglia, particularly to caudate and putamen, where high levels of viral aggregation are known to occur (Berger and Arendt 2000). Initial reports of HIV-associated dementia (the “AIDS dementia complex” (Navia et al. 1986), now termed “HIV Associated Dementia,” or HAD) emphasized the behavioral and neurological consequences of the virus’s predilection for basal ganglia and white matter; these included prominent mental and motor slowing, impaired attention, defects in memory retrieval, and relative sparing of higher cortical functions; and positive neurological findings such as bradykinesia, tremor, and postural instability (Berger and Arendt 2000; Beckley et al. 1998). Initial studies employing structural MRI were able to detect CNS abnormalities (Aylward et al. 1995), but primarily among individuals with advanced disease. Advances in neuroimaging technology and data analytic methods, such as morphometric analysis (e.g. Jernigan et al. 2005) and magnetic resonance spectroscopy (MRS) have enabled investigators to detect more subtle and nonlinear trends in brain changes (e.g., Castelo et al. 2007) associated with HAND among individuals with milder disease (for reviews see Paul et al. 2002; Tucker et al. 2004; Pfefferbaum et al. 2002). A recent paper by Paul et al. (2008) demonstrated that ratios of key brain metabolites detected subtle basal ganglia abnormalities in a group of nondemented HIV+ subjects, but MRI did not, suggesting that MRS can be more sensitive to early CNS changes compared among HIV + individuals without dementia. Finally, examination of the microstructural integrity of the brain using diffusion tensor imaging (DTI) has detected subtle changes in neuronal myelination and axonal integrity and these highly sensitive scans may have the resolution to reveal more consistent brain changes that occur early in the disease (Filippi et al. 2001; Pomara et al. 2001; Chang et al. 1999).

Since the introduction of HAART the incidence of HAD has declined but rates of milder cognitive impairment have not, indicating that currently available antiretroviral regimens do not eradicate virus in brain completely, perhaps due to insufficient CNS penetrance (Langford et al. 2006). Post-HAART studies (e.g., Cysique et al. 2004) have reported more variable features of HAD, with fewer cases characterized primarily by psychomotor

slowing. Impairments in learning and memory, attention, motor and executive functions are common in HAND but there is no signature pattern of cognitive deficits (Dawes et al. 2008). Similarly, more variability has been observed in clinical course; cognitive deficits can progress, improve, fluctuate, or remain static over time (Nath et al. 2008).

Neurocognitive function in persons living with HIV/ AIDS is affected by many factors in addition to direct infection of the CNS (see Table 1 for a representative listing of known and potential risk factors). Comorbid substance dependence and hepatitis C disease are significant contributing factors to neurocognitive impairment, but additional factors such as aging have assumed increased importance as persons with HIV live longer. These issues are addressed elsewhere in this special issue.

HIV and Substance Dependence: Clinical and Scientific Challenges

Investigators of neurocognition among both HIV+ and HIV– substance dependent individuals (SDIs) must contend with multiple methodological difficulties. In North America, the majority of SDIs abuse multiple substances and “pure” dependence on a single substance is rare, providing significant impediments to targeting effects of specific drugs of abuse on the human CNS. Analysis of neurocognitive findings is complicated significantly by direct and indirect medical consequences of drug abuse, such as head injury, cerebrovascular abnormalities and malnutrition (e.g. Bell et al. 2006). Additionally, SUDs are accompanied in turn by a spectrum of neuropsychiatric conditions, including mood disorders, anxiety disorders such as PTSD and social phobia, ADHD and learning disabilities, and personality disorders (Grant et al. 2004a, b; Chilcoat and Breslau 1998; Compton et al. 2007; Biederman et al. 1998); Neurobiological personality traits prevalent among SDIs, such as sensation-seeking and antisociality (Zuckerman 1996; Gonzalez et al. 2005a; Vassileva et al. 2007a, b) influence both neurocognitive function and risk behavior. Concurrent psychoactive medication and opioid substitution therapies such as methadone are associated with impaired cognitive performance (Mintzer and Stitzer 2002). Finally, combined antiretroviral therapy and methadone can increase HIV disease severity and decrease methadone effectiveness (Bruce et al. 2006, 2008 [thereby increasing SDIs’ disinclination to adhere with treatment regimens]).

Empirical attempts to distinguish cognitive changes associated with substance dependence from HAND are complicated further by the absence of a gold standard to index substance use. The majority of neurocognitive studies of drug addiction employ the SCID-Substance Abuse Module (First et al. 1996), the well-established Addictions Severity Index (McLellan et al. 1985) or the newer Kreek-McHugh-Schluger-Kellogg Scale (Kellogg et al. 2003). However, clinical diagnostic systems such as DSM-IV criteria do not provide an ideal proxy for brain exposure to alcohol and illicit substances; a clinical diagnosis of “abuse” or even “dependence” does not readily describe the chronicity or amount/frequency of dose. Timeline-follow back interviews have been used to obtain finer-grained estimates of dosage and substance quantity but administration time for these very detailed inquiries can be prohibitive. Consequently, investigators have employed numerous potential predictor variables, including estimated total exposure, age of onset, duration of use, length of abstinence, route of administration, and number of detoxifications, in efforts to capture addiction severity.

Cellular Effects of HIV and Substances of Abuse

In a recent review, Bell et al. noted that, “Given the immune modulatory effects of some major classes of drugs, together with the effects of drugs themselves on brain tissue, it would be surprising if drug abuse did not influence HIV– related brain disease” (2006, p. 187). Numerous in vitro and animal studies have reported multiple common mechanisms by

which HIV and drugs of abuse confer harmful effects at the cellular level. A range of substances of abuse, including opiates, cocaine, methamphetamine, and alcohol are all known to increase immunosuppression and enhance viral replication (e.g., Liang et al. 2008; Dhillon et al. 2007). Interactions between viral proteins such as gp120 and tat and substances of abuse facilitate breakdown of blood-brain barrier, release of TNF- α and other neurotoxic cytokines, upregulate CCR5 expression and increase oxidative stress (Hauser et al. 2006; Khurdayan et al. 2004; Liang et al. 2008; Flora et al. 2003, 2005; Flores and McCord 1998; Theodore et al. 2006; Hu et al. 2005; Shiu et al. 2006). However, despite clear laboratory evidence that HIV and substances of abuse in combination result in significant cellular damage that can exceed effects of one or the other, this pattern of activity does not necessarily translate to human clinical or epidemiological studies (Kapadia et al. 2005).

CNS Effects of HIV Among Substance Dependent Individuals

Neurological and epidemiological studies have typically (but not invariably) reported more rapid disease progression, higher prevalence of dementia and more common postmortem HIV encephalitis among injection drug users (IDUs) compared with other risk groups (Bell et al. 1998; Bouwman et al. 1998; Nath et al. 2001, 2002; Langford et al. 2003; Lucas et al. 2006) but findings from neurocognitive studies of HIV+ IDUs have been more variable, particularly investigations conducted prior to the introduction of HAART. Some investigators reported significant cognitive impairment among HIV+ compared with HIV-IDUs (Egan et al. 1992; Marder et al. 1992; Starace et al. 1998), while others did not (Concha et al. 1992; Hestad et al. 1993; Selnes et al. 1992). Virtually all studies reported higher prevalence of abnormal neuropsychological test scores among IDUs, regardless of serostatus, compared to the general population (e.g. Hestad et al. 1993). It was hypothesized that cognitive impairment was present in only a subset of HIV+ IDUs that was not apparent from overall group comparisons, or that the test batteries had not included measures with adequate sensitivity to HIV-associated cognitive deficits. Active drug use may have also contributed to subjects' inconsistent performance; many of these studies recruited both in- and out-of-treatment subjects and urine toxicology screening was not routinely conducted.

Because recruitment for these early studies was based on risk factors, opiates were the drug of choice for the vast majority of participants, and many were also infected with hepatitis C. More recent studies have recruited additional groups of SDIs characterized by heavy use of substances other than opiates, including cocaine, methamphetamine, and cannabis and who do not necessarily inject drugs (Basso and Bornstein 2003) in study samples characterized by a broader range of age, education, and ethnic characteristics. However, even in the post-HAART literature there has been a relative paucity of well controlled cognitive studies of neuroAIDS among SDIs (e.g., Basso and Bornstein 2003; Chang et al. 2005; Cristiani et al. 2004; Durvasula et al. 2000; Green et al. 2004). Additionally, few studies (e.g., Rippeth et al. 2004; Jernigan et al. 2005; Schulte et al. 2005) have employed experimental designs that permitted comparisons of neurocognition among both HIV+ and HIV- subjects with and without a history of substance dependence, which hindered tests of hypothesized additive or synergistic effects. Further, essentially no studies to date have evaluated the neurocognitive performance among HIV+ individuals who abuse prescription drugs (e.g., opioids or anxiolytics); club drugs such as MDMA (Ecstasy), ketamine, and GHB; steroids; or investigate cognitive deficits among HIV+ individuals receiving opioid substitution therapies such as methadone or buprenorphine.

In this section we review the available neurocognitive studies of HIV that have included substance dependence characteristics as independent variables of interest, with special attention to evidence of additive or interactive effects. For convenience these studies are

grouped according to substance of primary interest in a given investigation, but the majority of subjects abused multiple substances, so inferences regarding the effects of specific drugs of abuse are limited.

Alcohol

Neurocognitive investigations have demonstrated significant impairment of multiple cognitive domains among HIV+ individuals with comorbid alcohol dependence. Rothlind et al. (2005) administered a comprehensive battery of neurocognitive tasks to groups of HIV+ and HIV- individuals classified as either light or heavy alcohol drinkers. They reported significant main effects of serostatus and drinking level on overall neurocognitive function; additionally, synergistic effects of HIV serostatus and alcohol were apparent on measures of psychomotor and visuomotor speed among individuals with heaviest drinking rates. Green et al. (2004) tested well-matched groups of HIV+ and HIV- men with and without a past history of SCID-diagnosed alcohol use disorder with a comprehensive neurocognitive test battery; they reported that HIV+ subjects with a positive alcohol diagnosis performed measures of verbal reasoning, reaction time and auditory processing significantly more poorly compared with HIV+ subjects without alcohol disorder, but this pattern of differences was not evident among the HIV- groups. Durvasula et al. (2006) evaluated neurocognitive performance of a sample of 497 African-American males grouped by HIV serostatus and alcohol history. Consistent deficits in motor and mental speed were apparent among HIV+ individuals with a recent (12-month) history of alcohol use, however the investigators cautioned that their findings should be interpreted with care because complete data regarding potential confounds such as drug use and head injury were not available.

Investigators have also reported evidence of synergistic effects of HIV and alcohol on performance of theory-driven experimental cognitive tasks. Sassoon et al. (2007) administered a modified version of the Digit Symbol task that permitted isolation of cognitive and motor components of task performance, including associative learning, visual perception and psychomotor speed, to groups with varying HIV serostatus and alcohol history. They reported that HIV+ persons with alcohol dependence were impaired on multiple components of the task compared with subjects with one risk factor. Similarly, Schulte et al. (2005) examined multiple cognitive components of attention using a match to sample version of the Stroop task to HIV+ and HIV- groups with and without a history of alcohol dependence. Their findings paralleled those of Sassoon et al., in that a positive HIV serostatus in the context of alcohol dependence impaired attentional function but deficits were not observed among subjects with HIV disease or alcohol dependence alone.

In comparison to the number of neuroimaging studies focused specifically on HIV, fewer studies have examined the combined effect (additive/synergistic) of HIV and alcohol or substance abuse on neuroimaging indices. Pfefferbaum and colleagues have been the most productive in this area of study. Pfefferbaum et al. (2007) reported reductions in the neuronal metabolite n-acetyl aspartate (NAA) in the superior parietal-occipital cortex among nondemented HIV patients with histories of alcoholism, while no similar effects were evident among individuals with HIV alone or diagnosis of alcoholism alone. Of interest is that no such effect was observed when a ratio of NAA to creatine (Cr) was examined because of a significant reduction in Cr among the groups (thus Cr was not a stable reference marker). Similarly Meyerhoff et al. (1995) reported decreased levels of phosphodiester and phosphocreatine metabolites (both are indices of energy) in the superior white matter among alcoholic HIV patients.

Pfefferbaum et al. (2006) also reported significantly larger ventricle volume among HIV patients with histories of alcoholism, and this effect was particularly strong in the frontal and body regions of the lateral ventricles. Interestingly, this group also reported that patients

with alcoholism exhibited significantly greater white matter hyperintensities (WMHs) compared to HIV patients without alcoholism or seronegative individuals with alcoholism. This finding is of particular interest because other studies have not reported significant differences in WMHs among HIV alone patients relative to healthy controls (Bornstein et al. 1992), suggesting that a comorbid alcohol history may significantly change the natural history of WMHs associated with HIV.

Most recently, Pfefferbaum et al. (2007) utilized DTI to examine the impact of HIV and alcoholism on the micro-structural integrity of the white matter. In this study, HIV patients with histories of alcoholism exhibited significantly lower fractional anisotropy (FA) in the corpus callosum compared to HIV patients without alcoholism. In addition, patients with HIV and alcoholism exhibited significantly greater mean diffusivity (MD) in the body and genu of the corpus callosum compared to the comparison groups. When subdivided by AIDS vs. nonAIDS status, the lower FA and increased MD in the corpus callosum were most pronounced among individuals with AIDS. Collectively the studies conducted by Pfefferbaum and colleagues demonstrate that a comorbid history of alcoholism significantly influences the macrostructural and microstructural integrity of the brain as defined by in vivo MRS, MRI and DTI in a manner that is not observed among HIV patients without a history of alcoholism.

Cannabis

Studies of the neurocognitive effects of cannabis in general have reported variable results: primarily minimal cognitive impairment, with evidence of neuroprotective effects in some instances (Grant et al. 2003). Concurrent cannabis use does not typically increase neurocognitive risk among users of other substances, such as methamphetamine (Gonzalez et al. 2004). Neurocognitive effects of cannabis and HIV serostatus have not been well-studied and available results are similarly inconsistent. Cristiani et al. (2004) evaluated the effects of a positive history of cannabis use among a sample of 282 HIV+ individuals, and reported that cognitive impairment (primarily memory deficits) was most prominent among cannabis users with symptomatic HIV disease. Chang et al. (2006) studied groups of HIV+ and HIV- individuals with and without a history of cannabis use using MRS and neurocognitive testing. They reported evidence of additive and interactive effects of HIV serostatus and cannabis use on brain metabolites, but cognitive deficits were apparent only among HIV+ individuals, regardless of cannabis use. Collectively, these studies suggest that although cannabis effects on neurocognition are minimal among uninfected individuals or those at early stages of HIV infection, the risk for cognitive deficits among HIV+ cannabis users increases with disease progression.

Stimulants: Cocaine

Surprisingly, relatively few studies have evaluated neurocognitive performance among HIV + and HIV- users of crack or powder cocaine, and available studies have reported inconsistent results. Durvasula et al. (2000) reported that both HIV disease and cocaine use were associated independently with cognitive defects, especially on psychomotor tasks, in a sample of 237 African American males, but there was no evidence that cocaine use combined with a positive HIV serostatus increased neurocognitive risk. Levine et al. (2006) studied the integrity of sustained attention in 40 HIV+ individuals that included a mixed group of 17 cocaine and methamphetamine users and 23 non drug using controls. Groups were well matched on demographics, current mood, and measures of global neurocognitive function. They reported that stimulant users performed significantly more erratically and made more errors on the Continuous Performance Test, a standardized measure of vigilance, compared to HIV+ controls and to age and education appropriate norms. Similarly, few neuroimaging studies have investigated the combined effects of HIV and cocaine use. A

recent PET study using C¹¹-labeled receptor imaging reported that abnormally decreased dopamine transporter density (DAT) in basal ganglia was detectable among HIV+ subjects with or without a positive cocaine history; however, these abnormalities were most prominent among cocaine users regardless of serostatus (Chang et al. 2008).

Stimulants: Methamphetamine

Neurotoxic effects of methamphetamine use have been well documented (Kalechstein et al. 2003; Chang et al. 2007; Nordahl et al. 2003). Investigators at the University of California-San Diego have published a comprehensive series of reports that have documented the additive and synergistic effects of methamphetamine abuse and HIV on neurocognition and structural, biochemical and functional neuroimaging. Rippeth et al. (2004) administered a comprehensive battery of neurocognitive tests to groups of HIV+ and HIV- subjects with and without a history of methamphetamine abuse. They reported that either risk factor was associated with cognitive impairment, with the highest rate among HIV+ methamphetamine users. In a follow up study, Carey et al. (2006) examined the influence of HIV disease severity on methamphetamine associated neurocognitive impairment and reported that neurocognitive impairment was significantly higher among HIV+ methamphetamine users with advanced disease compared with subjects without significant disease progression.

Taylor et al. (2004) reported a clear “dose dependent” relationship between HIV and stimulant abuse risk group and NAA levels in the anterior cingulate, with the highest levels observed among healthy controls and the lowest levels (i.e., greater injury to mature neurons) among stimulant abusing seropositive individuals. No additive effects were observed for NAA in the caudate and neither myo-inositol (mI) nor choline (Cho) differed by group status. In terms of morphometry, Jernigan et al. (2005) reported significant reductions in the caudate, thalamus, hippocampus and both frontal and temporal cortical volume among HIV-positive individuals whereas, methamphetamine abuse in the absence of HIV was associated with significant *increases* in caudate, lenticular nucleus and nucleus accumbens volume. Individuals with both HIV and methamphetamine exhibited no significant difference in caudate volume relative to healthy controls, a finding driven by the opposing effects of both HIV and methamphetamine. These results underscore the need to consider both direct and opposing effects of stimulant abuse when defining morphometric indices of the basal ganglia (particularly the caudate) among HIV-positive individuals.

Postmortem studies of potential cellular mechanisms of combined effects of HIV and methamphetamine have reported evidence of selective damage to frontal cortical interneurons that are immunoreactive (IR) for the calcium-binding protein calbindin (CB) (Langford et al. 2003). This cellular damage was most prominent in the brains of HIV+ methamphetamine users with evidence of HIV encephalitis at autopsy. In a follow up study, Chana et al. (2006) reported that global neurocognitive impairment and memory scores were significant predictors of severity of CB-IR neuronal damage, which was significantly more extensive for HIV+ methamphetamine users with HIV encephalitis compared with methamphetamine users without HIV encephalitis and with HIV+ non methamphetamine users without HIV encephalitis. These effects were selective for CB-IR neurons rather than the result of generalized cellular damage

Polysubstance Dependence

The first author's group has conducted a series of cognitive neuropsychological studies in Chicago with a large cohort of crack and heroin users.¹ These studies have been designed to minimize variability by matching HIV+ and HIV- groups carefully on demographics, SUD parameters, and potentially confounding comorbid disorders (e.g., PTSD, ADHD). Abstinence at testing was verified in all subjects by rapid urine toxicology screening and

breathalyzer testing. These studies have reported consistent evidence that compared to HIV– controls, HIV+ SDIs show increased vulnerability to specific cognitive deficits associated with abnormalities of prefrontal-striatal networks. Impaired representative or “working” memory, which requires online information processing, storage, monitoring or updating, appears to constitute a signature deficit among HIV+ drug abusers. In a series of studies, HIV+ SDIs performed consistently more poorly than matched HIV– SDIs on measures that stressed working memory by a variety of means, including increase in information load, time delay, and task complexity (Bartok et al. 1997; Farinpour et al. 2000; Martin et al. 2001, 2003). Similar additive effects have been demonstrated on decision making performance as captured on the Iowa Gambling Task (Martin et al. 2004a) and on time-driven prospective memory, a type of memory for future intentions that requires active self-generated cueing for successful retrieval (Martin et al. 2007).

Our current investigations have moved forward from studies targeting aspects of “executive functions” toward evaluating the integrity of nondeclarative memory functions that are dependent primarily on integrity of striatal and (in some instances) cerebellar systems. Surprisingly few studies have investigated the effects of either a positive HIV serostatus or substance abuse on these functions, despite their common effects on striatum (cf. A. Martin et al. 1993; van Gorp et al. 1999). Recently we reported evidence of additive effects of HIV on SDIs’ performance of two motor skill learning tasks, the Pursuit Rotor and the Star Mirror Tracing Task (Gonzalez et al. 2008). This initial investigation found no evidence of impairment of probabilistic learning measured by the Weather Prediction Task (Knowlton et al. 1996), however the study sample was primarily male; follow up analyses have indicated possible gender effects on vulnerability to impaired performance on this cognitive procedural learning task (Martin, unpublished data 2008).

Nicotine

Durazzo et al. (2007) reported that HIV-positive individuals who smoke and drink heavily exhibited significantly lower volumes in the frontal, temporal and parietal cortices compared to healthy controls, while nonsmoking HIV patients who were heavy drinkers exhibited significantly smaller volumes only in the frontal lobe. Further, HIV-positive individuals with histories of smoking and heavy drinking performed significantly worse on tests of learning, memory and cognitive efficiency compared to HIV-positive individuals with histories of drinking but not smoking. These findings indicate that chronic cigarette smoking, like alcohol and stimulants, alter the anatomical and functional health of the brain in the context of HIV. These are critically important findings; rates of cigarette smoking have been estimated at up to 88% among individuals in substance abuse treatment (Richter et al. 2002). These findings emphasize the need to include a smoking cessation component in substance abuse treatment programs, as this intervention might facilitate cognitive recovery among abstinent SDIs.

Overall these studies have facilitated greatly our progress toward an understanding of the neurocognitive effects of HIV and substance dependence, particularly by delineating the conditions under which additive or synergistic effects are most likely to occur. Both HIV disease severity and substance type appear critically important: some cognitive deficits are apparent primarily among HIV+ SDIs with symptomatic infection or who specifically abuse alcohol or methamphetamine, although there is no selective impairment of specific cognitive functions. Additional detailed studies of cocaine are necessary, particularly given the very high prevalence of crack among HIV+ SDIs, and nicotine addiction. Neurocognitive studies

¹These studies included only SDIs in order to demonstrate that additive effects of HIV could be detected reliably by theory-driven cognitive measures. These findings have paved the way for additional cognitive studies of non-SDI samples that are currently in progress in our laboratory.

of HIV+ SDIs must also be broadened to include potential effects of club drugs and abuse of prescription drugs including steroids.

Hepatitis C as a Comorbidity in HIV

Hepatitis C (HCV) has only recently been recognized as an important “cognitive” comorbidity to HIV infection yet in the last few years interest among clinicians and researchers regarding co-infection has developed at a rapid pace. The interest in HCV-HIV co-infection is based in part on observations that the prevalence of co-infection is very high in some populations of HIV patients, co-infected individuals exhibit more severe cognitive impairment than individuals with mono-infection, and the mechanisms that drive these cognitive symptoms largely remain unknown. Below we review the extant literature in these areas and provide recommendations for future studies that aim to delineate the additive/synergistic effects of HCV-HIV co-infection.

Frequency of HIV-HCV Coinfection

HCV is a member of the Flaviviridae family of viruses (along with yellow fever, dengue virus, and tick-borne viruses). The prevalence of HCV infection among the general population is nearly two times the prevalence of HIV, likely due to an increased probability of percutaneous transmission of HCV compared to HIV (Alter et al. 1999). World-wide, it is estimated that more than 170 million individuals are infected with HCV, including nearly 3 million individuals in the United States (Armstrong et al. 2006). Unfortunately the vast majority of patients face a chronic infection and many develop hepatic and extrahepatic complications (Vassilopoulos and Calabrese 2005).

Given the high rate of transmission through percutaneous exposure it is not surprising that individuals infected with HIV through injection drug use (IDU) are at an exceptionally high risk of being co-infected with HCV compared to individuals infected with HIV through sexual activity, although HCV can be transmitted by sexual contact. Estimates of the prevalence of co-infection among IDUs ranges from 44% as reported in the Johns Hopkins HIV Clinical Cohort to as high as 90% in some European countries (Sulkowski et al. 2002; Verucchi et al. 2004). These numbers translate to approximately 300,000 individuals in the US that are co-infected. Clearly, the possibility that HIV-positive patients with histories of IDU are co-infected with HCV is very high and the clinical needs of these individuals require attention.

HCV and the Brain

There is a wealth of data generated in the field of HCV mono-infection describing impairment in brain function associated with HCV mono-infection. This literature is relevant as it hints towards mechanisms that may interact with or add to well-defined models of HIV neuropathogenesis (to be discussed in detail elsewhere in this issue). For a more detailed review of the HCV-monoinfection literature readers are referred to Forton et al. (2001, 2002, 2005).

HCV crosses the blood-brain-barrier and is present in both the CSF and brain tissue (Laskus et al. 2002; Maggi et al. 1999; Murray et al. 2008). Further, some of the HCV sequences observed in the peripheral mononuclear cells and lymph nodes and the brain are very similar, suggesting that the virus effectively crosses the BBB (perhaps by via infected leukocytes; Forton et al. 2004; Laskus et al. 2004). However, diversification has also been noted (Murray et al. 2008).

The specific brain targets infected by HCV remain a matter of debate. Letendre et al. (2007) reported the presence of HCV proteins in brain astrocytes using Western blotting and immunostaining among co-infected patients. More recently, Wilkinson et al. (2008) examined sections of frontal cortex and subcortical white matter from 12 HCV infected patients (six of whom were co-infected with HIV) and found HCV presence in CD68 cells (macrophages and microglia) and less involvement within brain astrocytes. Of interest is that the HCV phenotype was identical between HCV mono-infected samples and co-infected samples. These findings are consistent with Letendre et al. (2007) in that both studies demonstrated evidence of HCV antigens in the brain, but they differ in terms of the primary cell populations infected. As described by Wilkinson et al. (2008), these differences may be associated with the difference in patient populations or in the differences in methods to determine which cells were primarily infected (use of polyclonal antibodies against the NS5A protein vs. monoclonal antibodies against the NS3 protein).

Nevertheless, the presence of HCV antigens in the brain along with evidence of HCV diversification in the brain (Bagaglio et al. 2005) suggest that the brain may represent a site of persistent HCV viral replication among co-infected patients. For example, Adair et al. (2005) demonstrated down-regulation of oxidative phosphorylation genes in the brains of HCV-infected patients. Functionally this finding is of significance as oxidative phosphorylation is a critical source of cell energy and neurons are susceptible to reduced energy sources due to high metabolic rates. As described by Adair, high levels of free radicals in the brain may be produced as a consequence of disruption in energy-dependent calcium homeostasis. The data suggested above suggest that brain infection with HCV could potentially lead to free radical damage. Alternatively, it is possible that presence of HCV in the brain could produce an inflammatory cascade not very different from HIV (Forton et al. 2008; Morgello 2005; Paul et al. 2007).

A number of MRS studies have demonstrated metabolite abnormalities associated with HCV mono-infection. For example, Forton et al. (2008) revealed elevations in the myo-ml/creatine (Cr) ratio in the frontal white matter among patients with chronic HCV mono-infection. Increased ml is believed to represent microglial activation and astrogliosis (Bitsch et al. 1999), and therefore elevations in the ml/Cr ratio may reflect consequences of proinflammatory reactions to the presence of HCV in the brain (Forton et al. 2008). Of interest is that Forton et al. (2008) also demonstrate a significant inverted relationship between elevated ml/Cr ratios and working memory performance among patients infected with HCV suggesting that the MRS metabolite disturbance may underlie functional properties of the brain.

Evidence of HCV-mediated inflammation in the brain has been observed by Letendre et al. (2005). Specifically, HCV serostatus was found to associate with a range of inflammatory indices (e.g., MCP-1, TNF-alpha and TNFR-II). When all of the inflammatory indices were considered together, HCV status was most strongly associated with increased levels of sTNFR-II levels, and these relationships remained significant after controlling for substance abuse history and HIV serostatus. Collectively these findings suggest a model of HCV-mediated brain involvement characterized by HCV presence in the brain, disruption in metabolic processes/oxidative stress, and pro-inflammatory reactions that lead to impaired neuronal function.

The model defined above is intriguing but it is not without limitations. As described by Letendre et al. (2007) identification of HCV presence in the brain has proven difficult and this may relate to low rates of viral replication in the brain or the development of antibody complexes or other immunological reactions. Thus the level of HCV in the brain may not be sufficient to drive sustained brain damage, or the virus is present but undetectable. Further, a

number of studies of HCV-mono-infected patients have revealed relationships between liver disease and cognition raising the possibility that liver dysfunction may also be related either directly or indirectly to CNS compromise in this population. As noted previously, Perry et al. (2005) reported a significant relationship between neuropsychological performance and liver fibrosis stage. In addition, Hilsabeck et al. (2002, 2003) reported that poor cognitive function among HCV mono-infected patients is associated with increased severity of liver fibrosis.

Most recently, Morgello et al. (2005) contrasted neuropsychological performance between HIV patients from the MHBB with evidence of HCV in the brain and liver, patients with evidence of HCV only in the liver, and patients with no evidence of HCV in either the brain or the liver. Results revealed that individuals with evidence of HCV in the brain performed significantly worse on Trail Making B compared to individuals without evidence of HCV sequences in the brain. However, neuropathological results revealed a high level of abnormalities among individuals with HCV sequences in the brain *and* among individuals with HCV only in the liver. Specifically, both groups exhibited Alzheimer type 2 gliosis in the brain regardless of whether HCV was present in the brain. This latter finding suggests that the brain does not have to be directly infected with HCV to develop significant neuropathological dysfunction. Further, with the exception of a single neuropsychological measure (Trails B), performance on neuropsychological tests was similar between individuals with and without evidence of HCV in the brain.

A number of other studies have demonstrated significant neuropsychological impairment among individuals infected with HCV alone. Interestingly, these studies have revealed significant cognitive compromise in the absence of either substance abuse or cirrhosis, suggesting a possible direct impact of HCV on the brain. Interested readers are referred to Perry et al. (2008) for a recent review though we provide a brief review in this section. Hilsabeck et al. (2002, 2003) have reported significant impairments among HCV mono-infected patients on tests of psychomotor speed, sustained attention, and working memory with impairment rates (defined as performance more than one standard deviation below that of controls) exceeding 80% on some measures. Neuropsychological performances were generally more impaired among individuals with greater liver damage but individuals with only mild liver compromise also demonstrated impaired neuropsychological functions.

Similar results were reported by Fontana et al. (2005) using data obtained from a large clinical trial for the treatment of HCV (the HALT-C trial). In this study, more than one third of the sample met criteria for neuropsychological impairment as defined by performances at least one standard deviation below that of controls on at least four neuropsychological tests. Verbal memory and working memory were most likely impaired in this cohort and no significant correlations were observed between performances in these domains and liver severity. Most recently, Huckans et al. (2009) examined neuropsychological function among HCV mono-infected patients with and without histories of substance abuse compared to healthy controls with no HCV and no substance abuse history. Collectively individuals with HCV performed significantly more poorly than individuals without HCV on tests of verbal memory, attention, processing speed and mental flexibility. Further, HCV mono-infected individuals without substance abuse histories performed significantly more poorly than healthy controls most of the same cognitive measures.

The studies above demonstrate that HCV mono-infection is associated with significant impairment in neuropsychological domains typically characterized as “subcortical” in nature, with predominant impact on attention, information processing speed, and verbal memory. Further, evidence of neuropsychological impairment among HCV mono-infected

individuals exists independent of comorbid substance abuse and severe liver disease, raising the possibility of direct brain involvement from HCV.

HIV-HCV Co-infection and Everyday Functioning

There has been limited research conducted to date regarding the impact of HIV-HCV co-infection on aspects of everyday living yet this is an important area of study given the synergistic effects of the viruses on psychological and medical outcomes. Most studies have focused on quality of life (QOL) among individuals with co-infection, with HCV-HIV comorbidity resulting in more deleterious self-reported QOL compared to individuals with HIV mono-infection (Baum et al. 2008; Braitstein et al. 2005; Marcellin et al. 2007; Tillmann et al. 2006; Tsui et al. 2007; Vigil et al. 2008) and compared to individuals co-infected with HIV and hepatitis B co-infection (Tillmann et al. 2006). Predictors of reduced QOL among co-infected patients include depressive symptoms, high levels of fatigue, poverty, and substance abuse (Baum et al. 2008; Braitstein et al. 2005; Marcellin et al. 2007; Tsui et al. 2007). In addition, Vigil et al. (2008) reported that compromised information processing speed and depressive symptoms among HIV-HCV co-infected individuals were associated with decline in instrumental activities of daily living while compromised fine motor speed and dexterity predicted decline in physical activities of daily living.

Individuals infected with both HIV and HCV utilize healthcare services significantly more frequently than individuals with HIV mono-infection (Baum et al. 2008) and healthcare utilization, along with depression, physical symptoms and limited access to HCV treatment, predicted lower QOL in this population. These findings clearly indicate that comorbid HCV infection in the context of HIV results in significant individual burden and this translates into additional utilization of healthcare resources. Studies are needed that more completely describe the impact of co-infection on other aspects of everyday function such as medication adherence, employment, and driving ability in order to understand the degree to which co-infection interrupts independence in these areas as well as the disease and host mechanisms that underlie the effects.

Contribution of Substance Abuse and Depression

Individuals co-infected with HIV and HCV tend to report greater illicit alcohol and substance abuse (e.g., Ryan et al. 2004; Cherner et al. 2005) and as warned by van Gorp and Hinkin (2005) higher levels of abuse of these substances may influence the prevalence of cognitive impairment in co-infected patients.

To address this issue the second author's group examined a cohort of co-infected patients compared to HIV mono-infected patients on a computerized battery of neuropsychological tests (Paul et al. 2008). In addition we examined substance and alcohol use with a self-report measure that quantified the duration, amount and frequency of use of each alcohol, stimulants, heroin, and marijuana. Consistent with previous studies we observed significantly poorer cognitive function among co-infected patients, particularly on tests of information processing speed and psychomotor speed, relative to HIV mono-infected patients. In addition, while the co-infected patients reported significantly more heroin use than mono-infected patients, correlational analyses revealed no significant relationships between the quantified exposure of each substance and performance on any cognitive test among the co-infected group. These findings, along with other studies that have controlled for illicit substance abuse in analyses, suggest that differential degrees of illicit substances and alcohol among co-infected patients likely does not account for the greater degree of neuropsychological impairment evidence in this population.

Some studies have also reported that co-infected patients experience more severe symptoms of depression or other psychiatric conditions relative to HIV mono-infected patients in several studies. This raises the possibility that psychiatric disturbance may underlie the greater degree of cognitive impairment in this population. Indeed, Clifford et al. (2005) reported that 57% of the co-infected patients reported depressive symptomatology in comparison to 32% of HIV mono-infected patients. However, not all studies have reported greater degrees of psychiatric symptoms among co-infected patients. For example, Ryan et al. (2004) provided detailed psychiatric results based on a structured interview and reported no difference in current psychiatric diagnoses between 62 co-infected individuals and 45 HIV mono-infected individuals. Further, studies that have identified more severe depressive symptoms among co-infected patients have reported increased cognitive impairment even after controlling for obvious psychiatric symptoms. Thus, as in the case of substance abuse, it appears that psychiatric symptoms do not provide sufficient explanatory power to account for the neuropsychological symptoms of co-infection

Interactions Between HIV and HCV: Focus on Neuropsychological Status

A number of studies have demonstrated significant interactions between HIV and HCV in terms of disease morbidity and clinical outcomes. For the most part these studies fall outside of the scope of this article, and readers interested reviewing the impact of HIV on HCV disease progression or the influence of HCV morbidity among HIV patients are referred to Strider (2005) and Vassilopoulos and Calabrese (2005). More directly related to this article is the interaction of HCV and HIV on the central nervous system (CNS) and more specifically, neuropsychological function. As noted above, individuals infected with both HCV and HIV express more severe neuropsychological impairment than individuals with HIV alone but the mechanisms underlying these effects remain unclear.

To date a handful of studies have examined neuropsychological function among individuals co-infected with HCV and HIV. Among these studies there is notable variability in the methods to examine neuropsychological function, the use of various comparison groups (e.g., HCV alone, HIV alone, both mono-infected groups compared to co-infected patients), and the focus on various laboratory indices of disease burden. These methodological differences require some caution when drawing conclusions regarding the impact of co-infection on cognitive outcome. For example, a number of studies did not involve a comprehensive neuropsychological assessment, and therefore, conclusions regarding the neuropsychological pattern associated with co-infection remains premature. With that caveat noted, there is some suggestion in the literature that several domains of cognitive function are more likely impacted by co-infection than others.

Decreased processing speed and psychomotor speed among co-infected individuals is a commonly reported outcome of the studies. For example von Giesen et al. (2004) observed significantly slower reaction times among co-infected patients compared to individuals with either HIV or HCV mono-infection. A similar finding was reported by Martin et al. (2004b), using a computerized version of the Stroop task. In this study, co-infected individuals recorded slower reaction times on the task compared to mono-infected individuals and these results were observed after controlling for differences in intelligence and substance abuse histories. Of interest is that the study relied on a voice-activated response system, and therefore the reduced reaction times among co-infected patients were not confounded by complications in peripheral motor function. Analyses also revealed that HCV status was associated with slower performances on all conditions of the Stroop task while HIV was associated with poorer performance on the incongruent condition, suggesting a specific deficit in slower processing speed associated with co-infection.

Other studies have also demonstrated slower processing speed among co-infected patients. Hilsabeck et al. (2005) reported that 80% of a co-infected sample met criteria for cognitive impairment compared to 69% of a HIV mono-infected group that met criteria for impairment. Further, the primary cognitive domain affected among the co-infected group was psychomotor slowing, with 84% of the co-infected group impaired in this domain compared to 56% of the mono-infected group. A similar finding was reported by Clifford et al. (2005). In this study, co-infected patients performed significantly more poorly on the Symbol Digit Modalities Test (SDMT) and Trail Making B, but no differences were noted between the groups on Trail Making A or the Symbol Search test.

Evidence of selective impairment in psychomotor speed/information processing is not universal. Ryan et al. (2004) reported nearly identical rates of impairment (44% vs. 43%) in psychomotor speed as measured by Trail Making A, Digit Symbol and Symbol Search between co-infected patients and HIV mono-infected patients respectively. The two groups also performed similarly across other domains with the exception of executive function which was measured by Trail Making B and Perseverative Responses on the Wisconsin Card Sorting Test. Specifically, 43% of the co-infected patients were impaired in the domain of executive function versus 29% of the mono-infected patients. Of further interest is that the group difference in this domain was largely driven by poor performances on the WCST which requires a low demand of motor and processing speed. In addition, Cherner et al. (2002) recently reported that HCV serostatus was a significant predictor of performance among HIV-infected individuals in the domains of learning, abstraction, and motor skills, with only a trend noted for information processing speed (and delayed recall). Of further interest is that HCV status did not predict performance in the area of attention/working memory or verbal fluency. Similar results were recently reported by Hinkin et al. (2008).

Not all studies have reported greater cognitive impairment among co-infected patients. For example, Perry et al. reported no significant differences between co-infected patients and a comparison group of HCV mono-infected patients. In this study, 29 co-infected patients and 47 HCV mono-infected patients completed Trail Making A and B, Symbol Search, and the SDMT. Both groups demonstrated poor performances when compared to expected values of healthy control subjects, but the percentages of impaired patients on the three tests did not differ by co-infection status. Comparisons of the raw scores indicate that co-infected patients performed worse than mono-infected patients on the SDMT, and mono-infected patients performed more poorly on Symbol Search, but neither difference was statistically significant. When the two groups were combined, there was a statistically significant relationship between liver fibrosis stage and neuropsychological impairment but since the groups were aggregated it is not clear if the relationship was driven by one group more so than the other. Further, the strongest correlation was observed between Symbol Search performance and liver fibrosis stage (coefficient = 0.66) and this test was the only one of the four on which HCV mono-infected patients were *more* likely to be impaired than co-infected patients.

When taken collectively the majority of studies have reported more severe neuropsychological impairment among co-infected patients than mono-infected patients. The one exception did not include a HIV mono-infected group and the neuropsychological battery was limited in scope, with no measures of attention, working memory, learning and memory and only one test of executive function. Other studies have demonstrated select impairments in these domains (Hinkin et al. 2008), and therefore the battery administered by Perry et al. may not have been of sufficient breadth to capture impairments associated with co-infection.

Future Directions for Studies of HIV and HCV Co-infection

A number of open questions remain among studies of HIV-HCV co-infection. The neuropsychological pattern, if a specific pattern exists, has not been fully defined. In part this is due to that fact that many studies conducted to date have been based on retrospective data. This does not discount the value of these studies, but it does create limitations to the available neuropsychological tests administered in the parent study, and therefore, the opportunity to identify a complete neuropsychological pattern. Clearly, large studies are needed that include comprehensive neuropsychological batteries. Studies are also needed that examine inflammatory markers in the brain, as well as evidence of HCV sequences present in the central compartment. Combined with more sensitive measures of liver status and neuroimaging indices, these studies will help elucidate the mechanisms associated with cognitive impairment in co-infected patients.

To our knowledge only one study has examined DTI findings among co-infected patients. Stebbins et al. (2007) reported a trend toward lower whole-brain fractional anisotropy (FA) and a highly significant increase in whole-brain mean diffusivity (MD) among co-infected patients relative to HIV mono-infected patients. Lower FA and higher MD values typically refer to reduced neuronal integrity, and as such the results of this study are consistent with brain compromise among co-infected patients. However, substance abuse was also much more common among this sample and it is possible that substance abuse histories influenced the outcomes.

Future studies are needed to identify the neuroimaging signatures of co-infection. A number of studies have employed MRS to examine white matter abnormalities in HCV-mono-infection and DTI represents an alternate approach because FA provides a robust marker of white matter integrity. Our lab (RP) is currently conducting a NIDA-funded study of cognition, liver disease, and multimodal neuroimaging (including DTI) among co-infected and HIV mono-infected patients. Results from this study are expected to shed new light on the putative mechanisms involving CNS injury associated with co-infection.

Strategies for Approaching the Problem of Comorbid Substance Dependence

In recent articles, investigators of neuroAIDS have emphasized the importance of developing a systematic approach with empirically defined organizing principles to address the inevitable confounds associated with neurocognitive aspects of HIV. In 2005 a group of international neuroAIDS experts was convened and charged with reviewing the existing AAN guidelines (Janssen et al. 1991) for classifying HIV-associated neurocognitive disorders and recommending updates to reflect advances in neuroAIDS research in the era of HAART (Antinori et al. 2007). Their report includes a series of empirical guidelines for estimating the influence of a particular confound (e.g., cerebrovascular disease, depression, substance abuse) as either compatible with HAND; contributing to HAND; or confounding the assessment of HAND (e.g., precluding the judgment that neurocognitive abnormalities can be attributed to direct effects of HIV). The recommendations for evaluating the contribution of comorbid substance use were formulated using multiple variables, including DSM-IV criteria; recency of drug use; ability to maintain employment or independent living; and the presence or absence of withdrawal or intoxication at testing. These guidelines are promising and await longitudinal evaluation of their utility and validity.

In the Chicago studies led by the first author, both exclusion criteria and research procedures are designed to address potential confounding conditions. On recruitment, exclusion criteria are restricted to a minimum number of “deal breakers,” including 1) central neurological

disorders; 2) closed head injury with more than 30 min loss of consciousness; 3) open head injury of any type; 4) seizure disorder; 5) schizophrenia; or 6) current neuroleptic or narcotic medication. [In our experience, study candidates are most commonly excluded for history of head injury or psychoactive medication]. All subjects are required to pass a rapid urine toxicology screen and breathalyzer testing; otherwise their study visit is terminated with no payment. In addition to hypothesis-driven neurocognitive tasks, participants are administered measures of ADHD symptoms (Stein et al. 1995), reading (Wechsler 2001), PTSD (Keane et al. 1987), antisociality (Levenson et al. 1995), sensation seeking (Zuckerman 1996) and current psychological distress (Beck et al. 1996). Scores on these measures can be employed both as covariates and as independent variables of interest. For example, a recent study by our group demonstrated that sensation seeking and decision making both affected the tendency to engage in high risk behavior but the patterns of predictors were different for the HIV+ and HIV- groups (Gonzalez et al. 2005b).

Our experimental approach to comorbidity problems is also influenced significantly by models that postulate that in addition to substance-specific effects, all drugs of abuse activate common neural circuitry that includes orbitofrontal cortex, anterior cingulate and ventral striatum (Goldstein and Volkow 2002; Kalivas and Volkow 2005) resulting in a loss of inhibitory control. These inhibitory deficits contribute to behavioral features displayed by all SDIs, including continuing drug use even after loss of any pleasurable effects and despite full knowledge of future consequences, features that persist among abstinent SDIs. These deficits are readily demonstrable with measures of decision making that require the subject to refrain from choosing attractive but risky options in order to optimize future outcomes (Bechara et al. 2001; Grant et al. 2000; Rogers et al. 1999; Brand et al. 2008), go/no-go (Forman et al. 2004; Kaufman et al. 2003) and stop-signal reaction time tasks (Fillmore et al. 2002; Fillmore and Rush 2002) which require the subject to inhibit ongoing motor responses but only under certain conditions; and measures of delay discounting (Kirby and Petry 2004; Petry 2001), which index the individual's ability to tolerate delayed reward. Consequently, one would predict that all SDIs should be vulnerable to deficits on inhibitory tasks, regardless of HIV or HCV serostatus. These deficits might serve as a proxy for "nonspecific" effects of drug dependence and employed as control tasks for comparison with measures of specific aspect of cognition.

The HIV and addictions neuroscience literature has reported a number of potentially significant influences on vulnerability and clinical features of HAND among drug users that remain to be studied. As an example, converging evidence shows consistent evidence of sex differences throughout different stages of the addictive process (Wetherington 2007). Compared to men, escalation of drug use and progression to addiction are more rapid, vulnerability to relapse is higher and withdrawal symptoms are more severe among women (Becker and Hu 2008). Additionally, neural mechanisms of addictive behavior among women are often distinct or even opposite of those reported in men (e.g., Wang et al. 2007). For example, Kilts et al. (2004) reported that amygdala activation decreased with cue-induced craving for women but increased among men, suggesting that additive or interactive effects of drug abuse and HAND might result in dissimilar patterns of brain activity and neurocognitive function for men and women. Studies of interactions between estrogen, HAND, and drug abuse will have critical translational implications for treatment of substance dependence and for management of HIV disease.

Conclusions

Comorbid influences on neurocognition and neurobehavioral function are highly prevalent among individuals living with HIV/AIDS. We have attempted to provide the reader with a clearer understanding of the sequelae of comorbid substance use disorder or HCV disease.

Many questions remain to be answered, but the field of comorbidity and neuroAIDS research has moved steadily forward and will continue to benefit from ongoing advances in neurocognitive, neuroimaging and addiction neuroscience.

Acknowledgments

We thank Raul Gonzalez and two anonymous reviewers for their helpful comments on this article; and Edie Sullivan for her very gracious assistance with our timeline.

Supported by grants R01 DA12828 to EMT and 1R03 DA022137 and 5R01 NS052470 to RHP.

References

- Adair DM, Radkowski M, Jablonska J, Pawelczyk A, Wilkinson J, Rakela J, et al. Differential display analysis of gene expression in brains from hepatitis C-infected patients. *AIDS*. 2005; 3:S145–S150. [PubMed: 16251812]
- Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *The New England Journal of Medicine*. 1999; 341(8):556–562. [PubMed: 10451460]
- Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. 2007; 69:1789–1799. [PubMed: 17914061]
- Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Annals of Internal Medicine*. 2006; 144:705–714. [PubMed: 16702586]
- Aylward EH, Brettschneider PD, McArthur JC, Harris GJ, Schlaepfer TE, Henderer JD, et al. Magnetic resonance imaging measurement of gray matter volume reductions in HIV dementia. *American Journal of Psychiatry*. 1995; 152:987–994.
- Bagaglio S, Cinque P, Racca S, Pedale R, Grasso MA, Lazzarin A, et al. Hepatitis C virus populations in the plasma, peripheral blood mononuclear cells and cerebrospinal fluid of HIV/hepatitis C virus-co-infected patients. *AIDS*. 2005; (Suppl 3):S151–S165. [PubMed: 16251813]
- Bartok J, Martin EM, Pitrak DL, Novak RM, Pursell KJ, Mullane KM, et al. Working memory deficits in HIV-seropositive drug users. *Journal of the International Neuropsychological Society*. 1997; 3:451–456. [PubMed: 9322404]
- Basso MR, Bornstein RA. Effects of past noninjection drug abuse upon executive function and working memory in HIV infection. *Journal of Clinical and Experimental Neuropsychology*. 2003; 25:893–903. [PubMed: 13680438]
- Baum MK, Jayaweera DT, Duan R, Sales S, Lai S, Rafie C, et al. Quality of life, symptomatology and healthcare utilization in HIV/HCV co-infected drug users in Miami. *Journal of Addictive Disorders*. 2008; 27:37–48.
- Bechara A, Dolan S, Denburg N, Hindes A, Anderson SW, Nathan PE. Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. *Neuropsychologia*. 2001; 39:376–389. [PubMed: 11164876]
- Beck AT, Steer RA, Ball R, Ranieri WF. Comparison of Beck Depression Inventories-IA and -II in psychiatric outpatients. *Journal of Personality Assessment*. 1996; 67:588–597. [PubMed: 8991972]
- Becker JB, Hu M. Sex differences in drug abuse. *Frontiers in Neuroendocrinology*. 2008; 29:36–47. [PubMed: 17904621]
- Beckley DJ, Bloem BR, Martin EM, Panzer VP, Remler MP. Postural reflexes in patients with HIV-1 infection. *Electroencephalography and Clinical Neurophysiology/Electro-myography and Motor Control*. 1998; 109:402–408.
- Bell JE, Brettle RP, Chiswick A, Simmonds P. HIV encephalitis, proviral load and dementia in drug users and homosexuals with AIDS: Effect of neocortical involvement. *Brain*. 1998; 121:2043–2052. [PubMed: 9827765]
- Bell JE, Arango J-C, Anthony IC. Neurobiology of multiple insults: HIV-1-associated brain disorders in those who use illicit drugs. *Journal of Neuroimmune Pharmacology*. 2006; 1:1557–1890.

- Berger JR, Arendt G. HIV dementia: The role of the basal ganglia and dopaminergic systems. *Journal of Psychopharmacology*. 2000; 14:214–221. [PubMed: 11106299]
- Biederman J, Wilens TE, Mick E, Faraone SV, Spencer T. Does attention-deficit hyperactivity disorder impact the developmental course of drug and alcohol abuse and dependence? *Biological Psychiatry*. 1998; 44:269–273. [PubMed: 9715358]
- Bitsch A, Bruhn H, Vougioukas V, Stringaris A, Lassmann H, Frahm J, et al. Inflammatory CNS demyelination: histopathologic correlation with in vivo quantitative proton MR spectroscopy. *American Journal of Neuroradiology*. 1999; 20:1619–1627. [PubMed: 10543631]
- Bornstein RA, Chakeres D, Brogan M, Nasrallah HA, Fass RJ, Para M, et al. Magnetic resonance imaging of white matter lesions in HIV infection. *The Journal of Neuropsychiatry and Clinical Neurosciences*. 1992; 4:174–178. [PubMed: 1627978]
- Bouwman FH, Skolasky RL, Hes D, Selnes OA, Glass JD, Nance-Sproson N, et al. Variable progression of HIV-associated dementia. *Neurology*. 1998; 50:1814–1820. [PubMed: 9633733]
- Braitstein P, Montessori V, Chan K, Montaner JS, Schechter MT, O'Shaughnessy MV, et al. Variable progression of HIV-associated dementia. *AIDS Care*. 2005; 17:505–515. [PubMed: 16036236]
- Brand M, Roth-Bauer M, Driessen M, Markowitsch HJ. Executive functions and risky decision-making in patients with opiate dependence. *Drug and Alcohol Dependence*. 2008; 97:64–72. [PubMed: 18485620]
- Bruce RD, Altice FL, Gourevitch MN, Friedland GH. Pharmacokinetic drug interactions between opioid agonist therapy and antiretroviral medications: Implications and management for clinical practice. *Journal of Acquired Immune Deficiency Syndrome*. 2006; 163:412–420.
- Bruce RD, Altice FL, Friedland GH. Pharmacokinetic drug interactions between drugs of abuse and antiretroviral medications: implications and management for clinical practice *Expert Review of Clinical Pharmacology*. 2008; 1:115–127.
- Budka H, Wiley CA, Kleihues P, Artiga J, Asbury AK, Cho ES, et al. HIV-associated disease of the nervous system: Review of nomenclature and proposal for neuropathology-based terminology. *Brain Pathology*. 1991; 1:143–152. [PubMed: 1669703]
- Carey CL, Woods SP, Rippeth JD, Gonzalez R, Heaton RK, Grant I, et al. Additive deleterious effects of methamphetamine dependence and immunosuppression on neuropsychological functioning in HIV infection. *AIDS and Behavior*. 2006; 10:185–190. [PubMed: 16477511]
- Castelo JMB, Courtney MG, Melrose RJ, Stern CE. Putamen hypertrophy in nondemented patients with Human Immunodeficiency Virus infection and cognitive compromise. *Archives of Neurology*. 2007; 64:1275–1280. [PubMed: 17846265]
- Chana G, Everall IP, Crew L, Langford D, Adame A, Grant I, et al. Cognitive deficits and degeneration of interneurons in HIV+ methamphetamine users. *Neurology*. 2006; 67:1486–1489. [PubMed: 17060582]
- Chang L, Ernst T, Leonido-Yees M, Walot I, Singer E. Cerebral metabolite abnormalities correlate with clinical severity of HIV-1 cognitive motor complex. *Neurology*. 1999; 52:100–108. [PubMed: 9921855]
- Chang L, Cloak C, Yakupov R, Ernst T. Combined and independent effects of chronic marijuana use and HIV on brain metabolites. *Journal of Neuroimmune Pharmacology*. 2006; 1:1–12.
- Chang L, Daniel A, Ernst T, Volkow N. Structural and metabolic brain changes in the striatum associated with methamphetamine abuse. *Addiction*. 2007; 102:16–32. [PubMed: 17493050]
- Chang L, Ernst T, Speck O, Grob CS. Additive effects of HIV and chronic methamphetamine use on brain metabolite abnormalities. *American Journal of Psychiatry*. 2005; 162:361–369. [PubMed: 15677602]
- Chang L, Wang GJ, Volkow ND, Ernst T, Telang F, Logan J, et al. Decreased brain dopamine transporters are related to cognitive deficits in HIV patients with or without cocaine abuse. *Neuroimage*. 2008; 42:869–878. [PubMed: 18579413]
- Cherner M, Masliah E, Ellis RJ, Marcotte TD, Moore DJ, Grant I, et al. Neurocognitive dysfunction predicts postmortem findings of HIV encephalitis. *Neurology*. 2002; 59:1563–1567. [PubMed: 12451198]

- Cherner M, Letendre S, Heaton RK, Durelle J, Marquie-Beck J, Gragg B, et al. Hepatitis C augments cognitive deficits associated with HIV infection and methamphetamine. *Neurology*. 2005; 64:1343–1347. [PubMed: 15851720]
- Chilcoat HD, Breslau N. Posttraumatic stress disorder and drug disorders: Testing causal pathways. *Archives of General Psychiatry*. 1998; 55:913–917. [PubMed: 9783562]
- Clifford DB, Evans SR, Yang Y, Gulick RM. The neuropsychological and neurological impact of hepatitis C virus co-infection in HIV-infected subjects. *AIDS*. 2005; 19:S64–S71. [PubMed: 16251830]
- Compton WM, Thomas YF, Stinson FS, Grant BF. Prevalence, correlates, disability and comorbidity of DSM-IV drug abuse and dependence in the United States. *Archives of General Psychiatry*. 2007; 64:566–576. [PubMed: 17485608]
- Concha M, Graham NMH, Munoz A, Vlahov D, Royal W, Updike M, et al. Effect of chronic substance abuse on the neuropsychological performance of Intravenous Drug Users with a high prevalence of HIV-1 seropositivity. *American Journal of Epidemiology*. 1992; 136:1338–1348. [PubMed: 1362630]
- Cristiani SA, Pukay-Martin ND, Bornstein RA. Marijuana use and cognitive function in HIV-infected people. *Journal of Neuropsychiatry and Clinical Neurosciences*. 2004; 16:330–335. [PubMed: 15377740]
- Cysique LA, Maruff P, Brew BJ. Prevalence and pattern of neuropsychological impairment in human immunodeficiency virus-infected/acquired immunodeficiency syndrome (HIV/AIDS) patients across pre- and post-highly active antiretroviral therapy eras: a combined study of two. *Journal of Neurovirology*. 2004; 10:350–357. [PubMed: 15765806]
- Dawes S, Suarez P, Casey CY, Cherner M, Marcotte TD, Letendre S, et al. Variable patterns of neuropsychological performance in HIV-1 infection. *Journal of Clinical and Experimental Neuropsychology*. 2008; 30:613–626. [PubMed: 18608689]
- Dhillon NK, Williams R, Peng F, Tsai Y, Dhillon S, Nicolay B, et al. Cocaine mediated enhancement of virus replication in macrophages: Implications for human immunodeficiency virus-associated dementia. *Journal of Neurovirology*. 2007; 13:483–495. [PubMed: 18097880]
- Durazzo T, Rothlind J, Cardenas V, Studholme C, Weiner M, Meyerhoff D. Chronic cigarette smoking and heavy drinking in human immunodeficiency virus: consequences for neurocognition and brain morphology. *Alcohol*. 2007; 41:489–501. [PubMed: 17923369]
- Durvasula RS, Myers HF, Satz P, Miller EN, Morgenstern H, Richardson MA, et al. HIV-1, cocaine, and neuropsychological performance in African American men. *Journal of the International Neuropsychological Society*. 2000; 6:322–335. [PubMed: 10824504]
- Durvasula RS, Myers HF, Mason K, Hinkin C. Relationship between alcohol use/abuse, HIV infection and neuropsychological performance in African American men. *Journal of Clinical and Experimental Neuropsychology*. 2006; 28:383–404. [PubMed: 16618627]
- Egan V, Brett RP, Goodwin GM. The Edinburgh cohort of HIV-positive drug users: pattern of cognitive impairment in relation to progression of disease. *British Journal of Psychiatry*. 1992; 161:522–531. [PubMed: 1393340]
- Farinpour R, Martin E, Seidenberg M, Pitrak DL, Pursell KJ, Mullane KM, et al. Verbal working memory in HIV-seropositive drug users. *Journal of the International Neuropsychological Society*. 2000; 5:548–555. [PubMed: 10932474]
- Filippi CG, Ulug AM, Ryan E, Ferrando SJ, van Gorp W. Diffusion tensor imaging of patients with HIV and normal-appearing white matter on MR images of the brain. *American Journal of Neuroradiology*. 2001:277–283. [PubMed: 11156769]
- Fillmore MT, Rush CR. Impaired inhibitory control of behavior in chronic cocaine users. *Drug and Alcohol Dependence*. 2002; 66:265–273. [PubMed: 12062461]
- Fillmore MT, Rush CR, Hays L. Acute effects of oral cocaine on inhibitory control of behavior in humans. *Drug and Alcohol Dependence*. 2002; 67:157–167. [PubMed: 12095665]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JB. Structured clinical interview for DSM-IV Axis I disorders. New York: Biometrics Research Department; 1996.

- Flora G, Lee YW, Nath A, Hennig B, Maragos W, Toborek M. Methamphetamine potentiates HIV-1 tat protein-mediated activation of redoxsensitive pathways in discrete regions of the brain. *Experimental Neurology*. 2003; 179:60–70. [PubMed: 12504868]
- Flora G, Pu H, Lee YW, Ravikumar R, Nath A, Hennig B, et al. Proinflammatory synergism of ethanol and HIV-1 tat protein in brain tissue. *Experimental Neurology*. 2005; 191:2–12. [PubMed: 15589507]
- Flores SC, McCord JM. Oxidative stress and human immunodeficiency virus. *Advances in Molecular and Cell Biology*. 1998; 25:71–94.
- Fontana RJ, Bieliauskas LS, Back-Madruga C, Lindsay KL, Kronfol Z, et al. Cognitive function in hepatitis C patients with advanced fibrosis enrolled in the HALT-C trial. *Journal of Hepatology*. 2005; 43:614–622. [PubMed: 16237784]
- Forman SD, Dougherty GG, Casey BJ, Siegle GJ, Braver TS, Barch DM, et al. Opiate addicts lack error-dependent activation of rostral anterior cingulate. *Biological Psychiatry*. 2004; 55:531–537. [PubMed: 15023582]
- Forton DM, Allsop JM, Main J, Foster G, Thomas H, Taylor-Robinson S. Evidence for a cerebral effect of the hepatitis C virus. *Lancet*. 2001; 358:38–39. [PubMed: 11454379]
- Forton DM, Thomas HC, Murphy CA, Allsop JM, Foster GR, Main J, et al. Hepatitis C and cognitive impairment in a cohort of patients with mild liver disease. *Hepatology*. 2002; 35:433–439. [PubMed: 11826420]
- Forton DM, Karayiannis P, Mahmud N, Taylor-Robinson SD, Thomas HC. Identification of unique hepatitis C virus quasiespecies in the central nervous system and comparative analysis of internal translational efficiency of brain, liver, and serum variants. *Journal of Virology*. 2004; 78:5170–5183. [PubMed: 15113899]
- Forton DM, Allsop JM, Cox IJ, Hamilton G, Wesnes K, Thomas HC, et al. A review of cognitive impairment and cerebral metabolite abnormalities in patients with hepatitis C infection. *AIDS*. 2005; (Suppl 3):S53–S63. [PubMed: 16251829]
- Forton DM, Hamilton G, Allsop JM, Grover VP, Wesnes K, O'Sullivan C, et al. Cerebral immune activation in chronic hepatitis C infection: A magnetic resonance spectroscopy study. *Journal of Hepatology*. 2008; 49:316–322. [PubMed: 18538439]
- Garden GA. Microglia in human immunodeficiency virus-associated neurodegeneration. *Glia*. 2002; 40:240–251. [PubMed: 12379911]
- Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. *American Journal of Psychiatry*. 2002; 159:1642–1652. [PubMed: 12359667]
- Gonzalez R, Jacobus J, Martin EM. Investigating neurocognitive features of hepatitis C virus infection in drug users: Potential challenges and lessons learned from the HIV literature. *Clinical Infectious Diseases*. 2005a; 41:S45–S49. [PubMed: 16265613]
- Gonzalez R, Vassileva J, Bechara A, Grbesic S, Sworowski L, Novak RM, et al. The influence of executive functions, sensation seeking, and HIV serostatus on the risky sexual practices of substance dependent individuals. *Journal of the International Neuropsychological Society*. 2005b; 11:121–131. [PubMed: 15962700]
- Gonzalez R, Rippeth JD, Carey CL, Heaton RK, Moore DJ, Schweinsburg BC, et al. Neurocognitive performance of methamphetamine users discordant for history of marijuana exposure. *Drug and Alcohol Dependence*. 2004; 76:181–190. [PubMed: 15488342]
- Gonzalez R, Jacobus J, Vassileva J, Quartana P, Amatya A, Martin E. Deficits in complex motor functions, despite no evidence of procedural learning deficits, among HIV+ individuals with history of substance dependence. *Neuropsychology*. 2008; 22:240–251.
- Grant S, Contoreggi C, London ED. Drug abusers show impaired performance in a laboratory test of decision making. *Neuropsychologia*. 2000; 38:1180–1187. [PubMed: 10838152]
- Grant I, Gonzalez R, Carey CL, Natarajan L, Wolfson T. Non-acute residual neurocognitive effects of cannabis use: A meta-analytic study. *Journal of the International Neuropsychological Society*. 2003; 9:679–689. [PubMed: 12901774]

- Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders. *Archives of General Psychiatry*. 2004a; 61:807–816. [PubMed: 15289279]
- Grant BF, Stinson FS, Dawson DA, Chou SP, Ruan J, Pickering RP. Co-occurrence of 12-month alcohol and drug use disorders and personality disorders in the United States. *Archives of General Psychiatry*. 2004b; 61:361–368. [PubMed: 15066894]
- Green JE, Saveanu RV, Bornstein RA. The effect of previous alcohol abuse on cognitive function in HIV infection. *American Journal of Psychiatry*. 2004; 161:249–254. [PubMed: 14754773]
- Hauser KF, El-Hage N, Buch S, Nath A, Tyor WR, Bruce-Keller WR, et al. Impact of opiate-HIV-1 interactions on neurotoxic signaling. *Journal of Neuroimmune Pharmacology*. 2006; 1:98–105. [PubMed: 18040795]
- Heaton RK, Velin RA, McCutchan JA, Gulevich SJ, Atkinson H, Wallace MR, et al. Neuropsychological impairment in human immunodeficiency virus-infection: Implications for employment. *Psychosomatic Medicine*. 1994; 56:8–17. [PubMed: 8197319]
- Heaton RK, Marcotte TD, Mindt MR, Sadek J, Moore DJ, Bentley H, et al. The impact of HIV-associated neuropsychological impairment on everyday functioning. *Journal of the International Neuropsychological Society*. 2004; 10:317–331. [PubMed: 15147590]
- Hestad K, Aukrust P, Ellertson B, Kløve H, Wilberg K. Neuropsychological deficits in HIV-1 seropositive and seronegative intravenous drug users. *Journal of Clinical and Experimental Neuropsychology*. 1993; 15:732–742. [PubMed: 8276932]
- Hilsabeck RC, Hassanein TI, Carlson MD, Ziegler EA, Perry W. Cognitive functioning and psychiatric symptomatology in patients with chronic hepatitis C. *Journal of the International Neuropsychological Society*. 2003; 9:847–854. [PubMed: 14632243]
- Hilsabeck RC, Castellon SA, Hinkin CH. Neuropsychological aspects of coinfection with HIV and hepatitis C virus. *Clinical Infectious Diseases*. 2005; 41:S38–S44. [PubMed: 16265612]
- Hilsabeck RC, Perry W, Hassanein TI. Neuropsychological impairment in patients with chronic hepatitis C. *Hepatology*. 2002; 35:440–446. [PubMed: 11826421]
- Hinkin CH, Hardy DJ, Mason KL, Castellon SA, Durvasula RS, Lam MN, et al. Medication adherence in HIV-infected adults: Effect of patient age, cognitive status, and substance abuse. *AIDS*. 2004; 18:S19–S25. [PubMed: 15075494]
- Hinkin CH, Castellon SA, Levine AJ, Barclay TR, Singer EJ. Neurocognition in individuals co-infected with HIV and hepatitis C. *AIDS*. 2008; 27:11–17.
- Hu S, Sheng WS, Lokensgard JR, Peterson PK. Morphine potentiates HIV-1 gp120-induced neuronal apoptosis. *Journal of Infectious Disease*. 2005; 191:886–889.
- Huckans M, Seelye A, Parcel T, Mull L, Woodhouse J, Bjornson D, et al. The cognitive effects of hepatitis C in the presence and absence of a history of substance abuse disorder. *Journal of the International Neuropsychological Society*. 2009; 15:69–82. [PubMed: 19128530]
- Janssen RS, Cornblath DR, Epstein LG, Foa RP, McArthur JC, Price RW. Nomenclature and research case definitions for neurological manifestations of human immunodeficiency virus type-1 (HIV-1). Report of a Working Group of the American Academy of Neurology AIDS Task Force. *Neurology*. 1991; 41:778–785.
- Jernigan TL, Gamst AC, Archibald SL, Fennema-Notestine C, Mindt MR, Marcotte TL, et al. Effects of methamphetamine dependence and HIV infection on cerebral morphology. *American Journal of Psychiatry*. 2005; 162:1461–1472. [PubMed: 16055767]
- Kalechstein AD, Newton TF, Green M. Methamphetamine dependence is associated with neurocognitive impairment in the initial phases of abstinence. *Journal of Neuropsychiatry and Clinical Neurosciences*. 2003; 15:215–220. [PubMed: 12724464]
- Kalechstein, A.; van Gorp, W. *Neuropsychology and substance use*. New York: Taylor & Francis; 2007.
- Kalivas PW, Volkow ND. The neural basis of addiction: pathology of motivation and choice. *American Journal of Psychiatry*. 2005; 162:1403–1413. [PubMed: 16055761]
- Kanmogne GD, Kennedy RC, Grammas P. HIV-1 gp120 proteins and gp160 peptides are toxic to brain endothelial cells and neurons: Possible pathway for HIV entry into the brain and HIV

- associated dementia. *Journal of Neuropathology and Experimental Neurology*. 2002; 61:992–1000. [PubMed: 12430716]
- Kapadia F, Vlahov D, Donahoe RM, Friedland G. The role of substance abuse in HIV disease progression: reconciling differences from laboratory and epidemiologic investigations. *Clinical Infectious Diseases*. 2005; 41:1027–1034. [PubMed: 16142670]
- Kaufman JN, Ross TJ, Stein EA, Garavan H. Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. *Journal of Neuroscience*. 2003; 23:7839–7843. [PubMed: 12944513]
- Keane TM, Wolfe J, Taylor KL. Post-traumatic stress disorder: Evidence for diagnostic validity and methods of psychological measurement. *Journal of Clinical Psychology*. 1987; 43:32–43. [PubMed: 3558840]
- Kellogg SH, McHugh PF, Bell K, Schluger JH, Schluger RP, LaForge KS, et al. The Kreek-McHugh-Schluger-Kellogg scale: A new, rapid method for quantifying substance abuse and its possible applications. *Drug and Alcohol Dependence*. 2003; 69:137–150. [PubMed: 12609695]
- Khurdayan VK, Buch S, El-Hage N, Lutz SE, Goebel SM, Singh IN, et al. Preferential vulnerability of astroglia and glial precursors to combined opioid and HIV-1 Tat exposure in vitro. *European Journal of Neuroscience*. 2004; 19:3171–3182. [PubMed: 15217373]
- Kilts CD, Gross R, Ely TD, Drexler KPG. The neural correlates of cue-induced craving in cocaine-dependent women. *American Journal of Psychiatry*. 2004; 161:233–241. [PubMed: 14754771]
- Kirby KN, Petry NM. Heroin and cocaine abusers have higher discount rates for delayed rewards than alcoholics or non-drug-using controls. *Addiction*. 2004; 99:461–471. [PubMed: 15049746]
- Knowlton BJ, Mangels JA, Squire LR. A neostriatal habit learning system in humans. *Science*. 1996; 273:1399–1402. [PubMed: 8703077]
- Langford D, Adame A, Grigorian A, Grant I, McCutchan JA, Ellis RJ, et al. Patterns of selective neuronal damage in methamphetamine-user AIDS patients. *Journal of the Immune Deficiency Syndrome*. 2003; 34:467–474.
- Langford TD, Letendre SL, Larrea GJ, Masliah E. Changing patterns in the neuropathogenesis of HIV during the HAART era. *Brain Pathology*. 2006; 13:195–210. [PubMed: 12744473]
- Laskus T, Radkowski M, Bednarska A, Wilkinson J, Adair D, Nowicki M, et al. Detection and analysis of hepatitis C virus sequences in cerebrospinal fluid. *Journal of Virology*. 2002; 76:10064–10068. [PubMed: 12208987]
- Laskus T, Radkowski M, Jablonska J, Kibler K, Wilkinson J, Adair D, et al. Human immunodeficiency virus facilitates infection/replication of hepatitis C virus in native human macrophages. *Blood*. 2004; 103:3854–3859. [PubMed: 14739225]
- Letendre SL, Cherner M, Ellis RJ, Marquie-Beck J, Gragg B, Marcotte T, et al. The effects of hepatitis C, HIV, and methamphetamine dependence on neuropsychological performance: Biological correlates of disease. *AIDS*. 2005; 19:S72–S78. [PubMed: 16251831]
- Letendre S, Paulino AD, Rockenstein E, Adame A, Crews L, Cherner M, et al. Pathogenesis of hepatitis C virus coinfection in the brains of patients infected with HIV. *Journal of Infectious Disease*. 2007; 196:361–370.
- Levenson MR, Kiehl KA, Fitzpatrick CM. Assessing psychopathic attributes in a non institutionalized population. *Journal of Personality and Social Psychology*. 1995; 68:151–158. [PubMed: 7861311]
- Levine AJ, Hardy DJ, Miller E, Castellon SA, Longshore D, Hinkin CH. The effect of recent stimulant use on sustained attention in HIV-infected adults. *Journal of Clinical and Experimental Neuropsychology*. 2006; 28:29–42. [PubMed: 16448974]
- Liang H, Wang X, Chen H, Song L, Ye L, Wang S-H, et al. Methamphetamine enhances HIV infection of macrophages. *American Journal of Pathology*. 2008; 172:1617–1624. [PubMed: 18458095]
- Lucas GM, Griswold M, Gebo KA, Keruly J, Chaisson RE, Moore RD. **Illicit drug use and HIV-1 disease progression: A longitudinal study in the era of Highly Active Antiretroviral Therapy.** *American Journal of Epidemiology*. 2006; 163:412–420. [PubMed: 16394200]

- Maggi F, Giorgi M, Fornai C, Morrica A, Vatteroni ML, Pistello M, et al. Detection and quasispecies analysis of hepatitis C virus in the cerebrospinal fluid of infected patients. *Journal of Neurovirology*. 1999; 5:319–323. [PubMed: 10414523]
- Marcellin F, Preau M, Ravaux I, Dellamonica P, Spire B, Carrieri MP. Self-reported fatigue and depressive symptoms as main indicators of the quality of life (QOL) of patients living with HIV and Hepatitis C: Implications for clinical management and future research. *HIV Clinical Trials*. 2007; 8:320–327. [PubMed: 17956833]
- Marcotte TD, Heaton RK, Wolfson T, Taylor MJ, Alhassoon O, Arfaa K, et al. The impact of HIV-related neuropsychological dysfunction on driving behavior. *Journal of the International Neuropsychological Society*. 1999; 5:579–592. [PubMed: 10645701]
- Marder K, Stern Y, Malouf R, Tang M-X, Bell K, Dooneief G, et al. Neurologic and neuropsychological manifestations of Human Immunodeficiency Virus Infection in intravenous drug users without Acquired Immunodeficiency Syndrome; Relationship to head injury. *Archives of Neurology*. 1992; 49:1169–1175. [PubMed: 1444884]
- Martin A, Heyes MP, Salazar AM, Law WA, Williams J. Impaired motor-skill learning, slowed reaction time, and elevated cerebrospinal fluid quinolinic acid in a subgroup of HIV-infected individuals. *Neuropsychology*. 1993; 7:149–157.
- Martin E, Pitrak DL, Weddington W, Rains NA, Nunnally G, Nixon H, et al. Cognitive impulsivity and HIV serostatus in substance dependent males. *Journal of the International Neuropsychological Society*. 2004a; 7:931–938. [PubMed: 15803556]
- Martin EM, Sullivan TS, Reed RA, Fletcher TA, Pitrak DL, Weddington W, et al. Auditory working memory in HIV-1 infection. *Journal of the International Neuropsychological Society*. 2001; 7:20–26.1. [PubMed: 11253838]
- Martin EM, Pitrak DL, Rains MA, Grbesic S, Pursell K, Nunnally G, et al. Delayed non match to sample performance in HIV-seropositive and HIV-seronegative polydrug abusers. *Neuropsychology*. 2003; 17:283–288. [PubMed: 12803434]
- Martin EM, Novak RM, Fendrich M, Vassileva J, Gonzalez R, Grbesic S, et al. Stroop performance in drug users classified by HIV and hepatitis C virus serostatus. *Journal of the International Neuropsychological Society*. 2004b; 10:298–300. [PubMed: 15012850]
- Martin EM, Nixon H, Pitrak DL, Weddington W, Rains NA, Nunnally G, et al. Characteristics of prospective memory deficits in HIV-seropositive substance dependent individuals. *Journal of Clinical and Experimental Neuropsychology*. 2007; 29:496–504. [PubMed: 17564915]
- McLellan AT, Luborsky L, Cacciola J, Griffith J, Evans F, Barr HL, et al. New data from the Addiction Severity Index: Reliability and validity in three centers. *Journal of Nervous and Mental Disease*. 1985; 173:412–423. [PubMed: 4009158]
- Meyerhoff DJ, MacKay S, Sappey-Mariner D, Deicken R, Calabrese G, Dillon WP, et al. Effects of chronic alcohol abuse and HIV infection on brain phosphorus metabolites. *Alcoholism: Clinical Experimental Research*. 1995; 19:685–692.
- Mintzer MZ, Stitzer ML. Cognitive impairment in methadone maintenance patients. *Drug and Alcohol Dependence*. 2002; 67:41–51. [PubMed: 12062778]
- Morgello S. The nervous system and hepatitis C virus. *Seminars in Liver Disease*. 2005; 25:118–121. [PubMed: 15732003]
- Morgello S, Estanislao L, Ryan E, Geritis P, Simpson D, Verma S, et al. Effects of hepatic function and hepatitis C virus on the nervous system assessment of advanced-stage HIV-infected individuals. *AIDS*. 2005; (Suppl. 3):S116–S122. [PubMed: 16251806]
- Murray J, Fishman SL, Ryan E, Eng FJ, Walewski JL, Branch AD, et al. Clinicopathologic correlates of hepatitis C virus in brain: A pilot study. *Journal of Neurovirology*. 2008; 14:17–27. [PubMed: 18300072]
- Nath A, Maragos WF, Avison MJ, Schmitt FA, Berger JR. Acceleration of HIV dementia with methamphetamine and cocaine. *Journal of Neurovirology*. 2001; 7:66–71. [PubMed: 11519485]
- Nath A, Hauser KF, Wojna V, Booze RM, Maragos W, Prendergast M, et al. Molecular basis for interactions of HIV and drugs of abuse. *Journal of Acquired Immune Deficiency Syndromes*. 2002; 31:S62–S69. [PubMed: 12394784]

- Nath A, Schiess N, Venkatesan A, Rumbaugh J, Sacktor N, McArthur J. Evolution of HIV dementia with HIV infection. *International Review of Psychiatry*. 2008; 20:25–31. [PubMed: 18240060]
- Navia BA, Jordan BD, Price RW. The AIDS dementia complex: I. Clinical features. *Annals of Neurology*. 1986; 19:517–524.
- Nordahl TE, Salo R, Leamon M. Neuropsychological effects of chronic methamphetamine use on neurotransmitters and cognition: A review. *Journal of Neuropsychiatry and Clinical Neurosciences*. 2003; 15:317–325. [PubMed: 12928507]
- Paul R, Cohen R, Navia B. Neuroimaging relationships to cognition in patients with HIV. *Neurosciences and Biobehavioral Reviews*. 2002; 26:353–359.
- Paul R, Letendre S, Dearborn J. Impact of hepatitis C coinfection on cognitive outcomes in HIV infected individuals. *Current Hepatitis Reports*. 2007; 6:145–152.
- Perry W, Carlson MD, Barakat F, Hilsabeck RC, Schiehser DM, Mathews C, et al. Neuropsychological test performance in patients co-infected with hepatitis C virus and HIV. *AIDS*. 2005; 19(Suppl 3):S79–S84. [PubMed: 16251832]
- Perry W, Hilsabeck RC, Hassanein TI. Cognitive dysfunction in chronic hepatitis C: A review. *Digestive Diseases Sciences*. 2008; 53:307–321.
- Petry NM. Delay discounting of money and alcohol in actively using alcoholics, currently abstinent alcoholics, and controls. *Psychopharmacology*. 2001; 154:243–250. [PubMed: 11351931]
- Pfefferbaum A, Rosenbloom M, Sullivan EV. Alcoholism and AIDS: Magnetic resonance imaging approaches for detecting interactive neuropathology. *Alcoholism: Clinical and Experimental Research*. 2002; 26:1031–1046.
- Pfefferbaum A, Rosenbloom MJ, Rohlfing T, Adalsteinsson E, Kemper CA, Deresinski S, et al. Contribution of alcoholism to brain dysmorphology in HIV infection: effects on the ventricles and corpus callosum. *Neuroimage*. 2006; 33:239–251. [PubMed: 16877010]
- Pfefferbaum A, Rosenbloom MJ, Adalsteinsson E, Sullivan EV. Diffusion tensor imaging with quantitative fibre tracking in HIV infection and alcoholism comorbidity: Synergistic white matter damage. *Brain*. 2007; 130:48–64. [PubMed: 16959813]
- Pomara N, Crandall DT, Choi SJ, Johnson G, Lim KO. White matter abnormalities in HIV-1 infection: a diffusion tensor imaging study. *Psychiatry Research*. 2001; 28:15–24. [PubMed: 11231096]
- Richter KP, Ahluwalia HK, Mosier MC, Nazir N, Ahluwalia JS. A population-based study of cigarette smoking among illicit drug users in the United States. *Addiction*. 2002; 97:861–869. [PubMed: 12133125]
- Rippeth JD, Heaton RK, Carey CL, Marcotte TD, Moore DJ, Gonzalez R, et al. Methamphetamine dependence increases risk of neuropsychological impairment in HIV infected persons. *Journal of the International Neuropsychological Society*. 2004; 10:1–14. [PubMed: 14751002]
- Rogers RD, Everitt BJ, Baldacchino A, Blackshaw R, Swainson R, Wynne K, et al. Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: Evidence for monoaminergic mechanisms. *Neuropsychopharmacology*. 1999; 20:322–339. [PubMed: 10088133]
- Rothlind JC, Greenfield TM, Bruce AV, Meyerhoff DJ, Lindgren JA, Weiner MW. Heavy alcohol consumption in individuals with HIV infection: Effects on neuropsychological performance. *Journal of the International Neuropsychological Society*. 2005; 11:70–83. [PubMed: 15686610]
- Ryan EL, Morgello S, Isaacs K, Naseer MG, Gerits P. Manhattan HIV Brain Bank. The neuropsychiatric impact of hepatitis C on advanced HIV. *Neurology*. 2004; 62:957–962. [PubMed: 15037699]
- Sassoon SA, Fama R, Rosenbloom MJ, O'Reilly A, Pfefferbaum A, Sullivan EV. Component cognitive and motor processes of the Digit Symbol Test. *Alcoholism: Clinical and Experimental Research*. 2007; 31:1315–1324.
- Schulte T, Mueller-Oehring EM, Rosenbloom MJ, Pfefferbaum A, Sullivan EV. Differential effect of HIV infection and alcoholism on conflict processing, attentional allocation, and perceptual load: Evidence from a Stroop match-to-sample task. *Biological Psychiatry*. 2005; 57:67–75. [PubMed: 15607302]

- Selnes OA, McArthur JC, Royal W, Updike L, Nance-Sproson T, Concha M, et al. HIV-1 infection and intravenous drug use: Longitudinal neuropsychological evaluation of asymptomatic subjects. *Neurology*. 1992; 42:1924. [PubMed: 1407574]
- Shiu C, Barbier E, Di Cello F, Choi HJ, Stins M. HIV-1 gp120 as well as alcohol affect blood-brain barrier permeability and stress fiber formation: Involvement of reactive oxygen species. *Alcoholism: Clinical and Experimental Research*. 2006; 31:130–137.
- Starace F, Baldassare C, Biancolili V, Fea M, Serpelloni G, Bartoli L, et al. Early neuropsychological impairment in HIV-seropositive intravenous drug users: evidence from the Italian Multicentre Neuropsychological HIV Study. *Acta Psychiatrica Scandinavica*. 1998; 97:132–138. [PubMed: 9517907]
- Stebbins GT, Smith CA, Barta RE, Kessler HA, Adeyemi OM, Martin E, et al. HIV-associated alterations in normal-appearing white matter: A voxel-wise diffusion tensor imaging study. *Journal of the Acquired Immune Deficiency Syndrome*. 2007; 46:564–573.
- Stein MA, Sandoval R, Szumowski E, Roizen N, Reinecke MA, Blondis TA, et al. Psychometric characteristics of the Wender Utah Rating Scale (WURS): Reliability and factor structures for men and women. *Psychopharmacology Bulletin*. 1995; 31:425–433. [PubMed: 7491401]
- Strider DB. Coinfection with HIV and hepatitis C virus in injection drug users and minority populations. *Clinical Infectious Disease*. 2005; 4:S7–S13.
- Sulkowski MS, Moore RD, Mehta SH, Chaisson RE, Thomas DL. Hepatitis C progression of HIV disease. *Journal of the American Medical Association*. 2002; 288:199–206. [PubMed: 12095384]
- Taylor MJ, Letendre SL, Schweinsburg BC, Alhassoon OM, Brown GG, Gongvatana A, et al. Hepatitis C virus infection is associated with reduced white matter N-acetylaspartate in abstinent methamphetamine users. *Journal of the International Neuropsychological Society*. 2004; 10:110–113. [PubMed: 14751013]
- Theodore S, Cass WA, Maragos WF. Methamphetamine and human immunodeficiency virus protein Tat synergize to destroy dopaminergic terminals in the rat striatum. *Neuroscience*. 2006; 137:925–935. [PubMed: 16338084]
- Tillmann HL, Kaiser T, Claes C, Schmidt RE, Manns MP, Stoll M. Differential influence of different hepatitis viruses on quality of life in HIV positive patients. *European Journal of Medical Research*. 2006; 11:381–385. [PubMed: 17101461]
- Tsui JJ, Bangsberg DR, Ragland K, Hall CS, Riley ED. The impact of chronic hepatitis C on health-related quality of life in homeless and marginally housed individuals with HIV. *AIDS and Behavior*. 2007; 11:603–610. [PubMed: 17028996]
- Tucker K, Robertson K, Lin W, Smith JAH, Chen Y, Aylward S, et al. Neuroimaging in human immunodeficiency virus infection. *Journal of Neuroimmunology*. 2004; 157:153–162. [PubMed: 15579293]
- van Gorp WG, Hinkin CH. Triple trouble: cognitive deficits from hepatitis C, HIV, and methamphetamine. *Neurology*. 2005; 64:1328–1329. [PubMed: 15851716]
- van Gorp WG, Wilkins JN, Hinkin CH, Moore LH, Hull J, Horner MD, et al. Declarative and procedural memory functioning in abstinent cocaine abusers. *Archives of General Psychiatry*. 1999; 56:85–89. [PubMed: 9892260]
- Vassileva J, Gonzalez R, Bechara A, Martin E. Are all drug addicts impulsive? Effects of antisociality and extent of multidrug use on cognitive and motor impulsivity. *Addictive Behaviors*. 2007a; 32:3071–3076. [PubMed: 17507173]
- Vassileva J, Petkova P, Georgiev S, Martin EM, Tersyski R, Raycheva M, et al. Impaired decision-making in psychopathic heroin addicts. *Drug and Alcohol Dependence*. 2007b; 86:287–289. [PubMed: 16930861]
- Vassilopoulos D, Calabrese LH. Extrahepatic immunological complications of hepatitis C virus infection. *AIDS*. 2005; 19(Suppl. 3):S123–S127. [PubMed: 16251807]
- Verucchi G, Calza L, Manfredi R, Chiodo F. Human immunodeficiency virus and hepatitis C virus coinfection: Epidemiology, natural history, therapeutic options and clinical management. *Infection*. 2004; 32:33–46. [PubMed: 15007741]

- Vigil O, Posada C, Woods SP, Atkinson JH, Heaton RK, Perry W, et al. Impairments in fine-motor coordination and speed of information processing predict declines in everyday functioning in hepatitis C infection. *Journal of Clinical and Experimental Neuropsychology*. 2008; 4:1–11.
- von Giesen HJ, Heintges T, Abbasi-Boroudjeni N, Kücüköylü S, Köller H, Haslinger BA, et al. Psychomotor slowing in hepatitis C and HIV infection. *Journal of Acquired Immune Deficiency Syndrome*. 2004; 35:131–137.
- Wang JH, Liu XF, Chen YM, Sun HY, Fu Y, Ma MX, et al. Heroin impairs map-picture-following and memory tasks dependent on gender and orientation of the tasks. *Behavioral Neuroscience*. 2007; 121:653–644. [PubMed: 17663591]
- Wechsler, D. Wechsler Test of Adult Reading. San Antonio, TX: The Psychological Corporation; 2001.
- Wetherington CL. Sex-gender differences in drug abuse: A shift in the burden of proof? *Experimental and Clinical Psychopharmacology*. 2007; 15:411–417. [PubMed: 17924775]
- Wilkinson J, Radkowski M, Laskus T. Hepatitis C virus neuroinvasion: Identification of infected cells. *Journal of Virology*. 2008; 83:1312–1319. [PubMed: 19019968]
- Zuckerman M. The psychobiological model for impulsive unsocialized sensation seeking: A comparative approach. *Neuro-psychobiology*. 1996; 34:125–129.

Table 1

Factors affecting HIV-associated neurocognitive disorder

Age
Education
Substance Dependence and complications
Neuropsychiatric disorders
Head injury
Aging-related conditions: vascular disease, diabetes
Antiretroviral therapy
Psychoactive and other medications
Toxoplasmosis and other CNS opportunistic conditions
Additional infections: hepatitis C, syphilis