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An Update of the Review of Neuropsychological Consequences of HIV and Substance Abuse: A Literature Review and Implications for Treatment and Future Research

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Abstract

Neuropsychological dysfunction, ranging from mild cerebral indicators to dementia has been a consistent part of the medical picture of HIV/AIDS. However, advances in medical supervision, particularly as a result of antiretroviral (ARV) treatment, have resulted in some mitigation of the neuropsychological effects of HIV and necessitate re-evaluation of the pattern and nature of HIV-related cognitive or mental deficits. The associated enhancements in morbidity and mortality that have occurred as a result of ARV medication have led to a need for interventions and programs that maintain behaviors that are healthy and stop the resurgence of the risk of HIV transmission. Risk factors such as mental illness and substance use that may have contributed to the initial infection with HIV still need consideration. These risk factors may also increase neuropsychological dysfunction and impact observance of prevention for treatment and recommendations. Explicitly, a better comprehension of the role of substance use on the progression of HIV-related mental decline can enlighten management and evaluation of persons living with HIV with concurrent disorders of substance use. This review provides a summary of the neurophysiology of substance use and HIV and the existing research that has looked at the effects of both substance use and HIV disease on neurophysiological function and suggestions for future research and treatment.

Keywords

Future research; HIV; neuropsychology; substance abuse; treatment

INTRODUCTION

HIV/AIDS continues to be a global problem, with more than 40 million people worldwide living with the disease [¹]. In view of the fact that antiretroviral (ARV) regimens have extended the life expectancy of most HIV-infected individuals, it is critical to focus on the

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CONFLICT OF INTEREST

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physical and mental health of these patients. Many people with HIV are living longer, healthier lives thanks to ARV treatment. However, the neurocognitive effects of substance abuse, and the need for ongoing studies of HIV related neuropsychological dysfunction, particularly in substance abusers are still needed.

Additionally, an improved understanding of the neuropsychological sequelae of HIV disease, particularly in relation to substance abuse, is important to the evaluation and management of persons living with HIV (PLWH) with comorbid substance abuse disorders. The co-occurrence of HIV and substance abuse may compound medical and psychiatric problems, difficulties with HIV medication compliance, and poorer treatment outcomes (beyond those associated with HIV disease alone).

The medical and behavioral consequences of mental and substance abuse disorders in the HIV-infected population are a serious public health problem. Comorbid populations are more likely to participate in risky behaviors, making it difficult to contain the spread of the infectious disease [2, 3]. There is less likelihood of adhering to antiretroviral treatments, thereby worsening prognosis and increasing the probability of drug-resistant strains. Comorbid disease progression has been defined as an altered or presumptively accelerated disease progression due to the physiological interactions of HIV infection and substances of abuse [4]. HIV and substance abuse comorbidity presumably hastens disease progression *via* direct mechanisms by acting on common biological substrates in the brain, as well as by indirect actions mediated through alterations in central and peripheral immune and nervous systems.

Characteristically, an HIV infection can progress for ten years or more before the clinical syndrome (AIDS) occurs. The long latency period of the virus has contributed to many of the problems relating to diagnosis and control. Many factors, including genetics and behavioral determinants (*i.e.*, substance abuse), determine the speed at which the disease will progress in a given individual. Comprehensive neuropsychological assessments that consider both HIV disease and substance abuse may allow for the early detection of complications before irreversible neuronal damage occurs, which may facilitate the development and implementation of appropriate and targeted therapies and treatment.

However, in order to develop and implement appropriate and effective therapies and treatments for PLHW with comorbid substance abuse disorder, it is beneficial to review research conducted with this population thus far. Areas that will be examined in this review include the neuropsychology of HIV and substance abuse, and the potential interaction of HIV disease and substance abuse. In addition, implications for future research and treatments are discussed.

Pathophysiology

Shortly after seroconversion, HIV crosses the blood brain barrier *via* infected monocytes and CD4+ cells [1, 2]. These infected monocytes differentiate into macrophages, and ultimately infect microglia with HIV. At times, monocytes and microglia will fuse, and form multinucleated giant cells. These cells are distinct pathological hallmarks of HIV encephalopathy. Collectively, macrophages, microglia, and multinucleated giant cells serve

as pools from which HIV is replicated and expressed in the brain. Moreover, the blood brain barrier tends to resist ingress of antiretroviral medication, thereby increasing the likelihood that the virus may replicate unencumbered within the brain [3].

Despite the presence of HIV within the brain, there is little evidence of direct effects of the virus on the brain. In particular, HIV is tropic for glial cells, macrophages, and endothelial cells within the brain rather than neurons, and little HIV is typically detected in neurons [1]. Furthermore, the amount of neurologic damage is disproportionate to the presence of HIV in the brain [4], and cell loss may occur without overt neuronal infection.

Most evidence indicates that the neuropathogenesis of HIV happens indirectly [5]. Neurons lack a relevant receptor to mediate infection from HIV, but glial cells may be infected and emerge as the primary cerebral target of the virus. As HIV replicates, its presence triggers the release of inflammatory mediators which in turn adversely affect neurons. Agents such as cytokines, tumor necrosis factor, and granulocyte-monocyte colony-stimulating factors are toxic to neuronal activity and neurotransmitter function, and probably contribute to secondary inflammation (*e.g.*, encephalitis), cause leukoencephalopathy, or catalyze cell death through apoptosis [5–7]. Additionally, HIV infection yields release of a viral protein, transactivator of transcription (Tat). HIV Tat contributes to dysfunction of cellular mitochondria, dendritic degeneration, and neuronal death [9]. Sustained exposure to these toxic agents is possibly unnecessary, and a single episode of inflammation may be sufficient to damage tissue [2, 3]. Furthermore, these inflammatory processes are likely accelerated by presence of drug or alcohol abuse.

Gross Cerebral Changes—There is ample evidence that HIV infection may be associated with diffuse cerebral atrophy, multinucleated giant cells, leukoencephalopathy (myelin pallor), gliosis, axonal damage, and microglial nodules. Cortical atrophy and ventricular enlargement seem to correspond with immunocompromise and presence of opportunistic infections [9]. Synaptic and dendritic degeneration occurs frequently, and seems to coincide directly with cognitive impairment [10]. Subcortical gray matter in the limbic and striatal systems is also diminished. These abnormalities occur more often as the disease progresses, and they appear most often in people with AIDS [11–13].

Diffuse pathology notwithstanding, HIV seems to have an affinity for parenchymal regions of the brain. The virus tends to replicate most often in the basal ganglia, deep white matter, and in the brainstem [2]. At the cellular level, deep white matter density attenuates, astrocytes die, dendritic branches prune, and neurons die. Indeed, some studies show a 40% reduction of neuronal density in the frontotemporal region and as much as a 90% reduction in the hippocampus [3]. The simplification of dendritic branches is one of the most common changes associated with HIV at the cellular level. Ultimately, such changes manifest as diminished cerebral density, and this occurs most saliently within the frontal and temporal regions [2]. White matter changes are particularly prone to occur in circuits that link the frontal cortex with the basal ganglia and thalamus [14]. White matter degeneration tends to accumulate over time despite antiretroviral treatment [3]. The correlation of cerebral pathology with neuropsychological dysfunction is variable. Diffuse cerebral pathology does not correspond especially well with neuropsychological impairment. Most studies fail to

reveal a relationship between global pathology and neuropsychological impairment [15]. Additionally, global measures of cerebral activation (*e.g.*, evoked potential response, functional magnetic resonance imaging) are often abnormal in HIV infection, but are unrelated to neuropsychological impairment [16–18].

Although global brain abnormalities fail to correspond with neuropsychological deficits, structural and functional abnormalities involving the basal ganglia, hippocampus, and frontal lobes appear to correspond with cognitive impairment in HIV.

In an extensive literature review, Paul *et al.* [13] found that caudate atrophy was the brain region most consistently associated with neuropsychological dysfunction in HIV, and the basal ganglia are specifically diminished among seropositive individuals with cognitive impairment [19]. Similarly, Ances *et al.* [20] found that cognitively impaired HIV patients had smaller caudate volumes and less caudate blood flow than a control group, and such abnormalities coincide with poor cognitive function [14].

Additionally, reduced volumes in the putamen and hippocampus correlate with poor performance in HIV infection [21]. Other investigations have found that neuropsychological impairment correlates with diminished gray matter volume in the tissue bordering the basal ganglia and lateral ventricles as well as gray and white matter in the frontal lobes [22–24]. Furthermore, white matter degeneration in the basal ganglia and frontal lobes coincides with cognitive impairment. White matter degeneration is common in HIV, and frequently involves the frontal-subcortical circuits involving the basal ganglia [25]. Such degeneration becomes more pronounced as cognitive impairment worsens [19]. For instance, the total volume of white matter degeneration increases and becomes more diffuse throughout the brain in comparing individuals who have progressed to AIDS to those who are only seropositive [26]. Moreover, cognitive impairment worsened as white matter tracts involving the internal capsule, corpus callosum, and superior longitudinal fasciculus were diminished.

NEUROPSYCHOLOGY OF HIV AND AIDS

Clinical neuropsychology can be defined as an applied domain of neuroscience. It focuses upon the study of brain-behavior relationships that may be impacted by brain injury or disease, such as cognitive, sensorimotor, emotional, and general adaptive capacities of the individual [5, 6, 27, 28]. The discipline encompasses both neurocognitive and neurobehavioral processes. Neurocognitive processes include perceptual abilities, abstraction and conceptualization, reasoning and problem-solving, speed of information processing, perceptual motor integration, learning, remembering, and attention. Neuropsychological research also concerns related brain-mediated behaviors, such as mood and affect, personality, coping, and temperament. Some have theorized that declines in neurocognitive status are among the most sensitive indicators of underlying cerebral pathology, whereas changes involving mood or temperament can occur for many non-neuropathological reasons (*e.g.*, changes in mood brought on by unhappy news) [7, 29].

Because HIV appears to preferentially affect frontal-striatal circuits, certain neurobehavioral deficits may be expected. These cerebral circuits appear to be neural substrates of initiative,

motivation, impulse control, concept-formation, and problem-solving [30]. Consistent with this expectation, people with HIV often display deficits in conceptual reasoning, working memory and attention, memory, speed of information processing, and psycho-motor speed, and may appear apathetic, anhedonic, and amotivated [31]. Neurological examinations may also demonstrate abnormalities involving rapid limb movements and hyper-reflexia.

Neurocognitive impairment is classified according to its severity and impact on activities of daily living [32]. Inasmuch as mild cognitive impairment is present in two domains but daily function remains intact, a patient would be classified as having asymptomatic neurocognitive impairment (ANI). If mild cognitive impairment is present in two domains and daily function is compromised (*e.g.*, unemployment, inability to manage finances, *etc.*), a patient would be classified as having mild neurocognitive disorder (MND). If severe cognitive impairment (*i.e.*, performance falling below the 2nd percentile of normative performance) is present in two or more domains and two or more activities of daily living are compromised, a patient would be categorized as displaying HIV associated dementia (HAD).

Incidence of neurocognitive cognitive impairment has declined 75% with the advent of anti-retroviral therapies. Nonetheless, prevalence of cognitive impairment ranged from 15–50% of patients with HIV [3]. Among those with cognitive dysfunction, over 50% present with ANI, 20–40% display MND, and 1–7% manifest HAD [14]. Impairment tends to be mild and circumscribed among individuals presenting with ANI. Among those who manifest MND, deficits involving attention, working memory, mental slowing, memory impairment, or psychomotor slowing are most common. Obviously, deficits become more severe and generalized as patients progressing to HAD [3].

It should be noted that the American Psychiatric Association included dementia due to HIV in the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders [32]. Unfortunately, the DSM-IV criteria for this syndrome are modeled after the criteria for Alzheimer's disease. Consequently, the criteria for dementia emphasize abnormalities associated with cortical pathology such as apraxia and aphasia. HIV primarily affects subcortical structures, and does not typically yield such symptoms. Although cognitively impaired HIV seropositive patients may meet DSM-IV diagnostic criteria for dementia by virtue of criteria A1 (memory impairment) and A2d (executive dysfunction), the DSM-IV taxonomy fails to fully elaborate the nuances of HIV-related cognitive impairment.

Accordingly, many clinicians and researchers prefer to employ the nosology defined by the American Academy of Neurology [33], because it better captures the clinical realities and gradations of HIV-associated cognitive impairment. In addition, the AAN criteria more adequately describes the subcortical nature of the disorder through inclusion of key diagnostic criteria (*e.g.*, attentional impairment and cognitive slowing) not reflected in the DSM-IV criteria. A host of patient and clinical features seem to correspond with frequency and severity of neurocognitive impairment. For instance, regarding patient factors, increasing age, female sex, and history of injection drug use coincide with greater risk of cognitive dysfunction. Among disease factors, higher baseline viral load, low CD4 counts, comorbid medical illness, and low body mass index predict more impairment [3].

Disease status also corresponds with severity of cognitive dysfunction. Asymptomatic people display mild dysfunction on neuropsychological tests, whereas symptomatic individuals demonstrate moderate [34, 35]. It is estimated that 21–30% of individuals with asymptomatic HIV infection manifest ANI [36]. Mild problems with memory, attention, information processing speed, and motor skills may be present, but, overall, declines are apt to be subtle.

More severe cognitive dysfunction occurs as patients become symptomatic. MND occurs in 5–14% of cases with symptomatic HIV infection and in 25% of those who have progressed to AIDS [37]. The most common deficits observed in such patients involve verbal fluency, working memory, speed of information processing, verbal learning, visual spatial perception, and coordination. These problems are apt to be more severe than in those with ANI.

As the infection progresses, cognitive morbidity worsens. Approximately 6–30% of individuals diagnosed with AIDS are prone to manifest HAD [29]. Among these patients, moderate to severe deficits occur across all cognitive domains, but the most common form of deficit involves motoric slowing and slowed speed of information processing. This may be observed on measures of motor speed as well as those that do not involve a manual response. Other areas of morbidity include executive function, abstract reasoning, planning, mental flexibility, working memory, new-learning, and coordination. Notably, the memory difficulties in HIV seem to involve retrieval of new memories [35] as well as their acquisition [38]. This pattern of performance is consistent with other subcortical disorders. Indeed, in a discriminant function analysis [39] it was found that people with HIV manifest a pattern of dysfunction most similar to people with Huntington's disease.

Impairment is not entirely static. HIV-infected individuals may improve over time, worsen, retain a stable level of impairment, never become impaired, or fluctuate between varying levels of impairment [40, 41]. For instance, in a large prospective study of neurocognitive status in HIV 39% of patients presented with cognitive impairment at baseline. During a follow-up visit nearly 50 weeks later, 56% of these patients remained impaired, but 44% had improved. Among patients who were normal at baseline, 21% developed mild impairment over time. Baseline impairment was not correlated with immunological or viral indices, but declines in function occurred more frequently among patients whose CD4 levels declined [41]. However, unlike the early years of the HIV epidemic, drastic declines in function no longer occur with great frequency [3]. In a similar study [42], studied cognitive function across eight years, and found that the patients with greater illness and immunocompromise were most likely to deteriorate, and the most vulnerable neurocognitive domains included motor speed and speed of information processing.

Some variation in the course of HIV-related neurocognitive dysfunction may be attributable to the beneficial effects of CART. In addition to alleviating immunocompromise and HIV-associated illness, CART seems to slow, if not reverse, cognitive declines. In recent reviews of the literature [43–45], concluded that CART corresponds with stable neuropsychological function and a resistance to deterioration. Prevalence of severe cognitive impairment has diminished over time, and, when present, neuropsychological dysfunction tends to be mild. Some individuals actually demonstrate an improvement in function, and improvement

coincides with greater decreases in viral load. The neurocognitive benefits of CART seem most pronounced among patients who are medically-stable and maintain a non-detectable viral load. The medications that are most apt to cross the blood brain barrier exerted the most benefit on neuropsychological status. In a meta-analysis of CART and single medication anti-retroviral treatments, the magnitude of improvement in function was modest and most pronounced on measures of attention and motor function [46]. Such benefits notwithstanding, it remains uncertain whether CART medications post a meaningful risk of neurotoxicity or if accumulating resistance to the medications may yield neurocognitive relapse.

The impact of cognitive dysfunction upon the lives of HIV-infected individuals is considerable. In particular, neuropsychological impairment correlates with unemployment, and this occurs after controlling for medical and psychiatric illness, immune status, age, and education [47]. Intelligence, executive function, and new-learning are the factors that predict unemployment most potently [48]. Furthermore, neuropsychological function influences adherence to CART regimens. Nearly 50% of patients fail to adhere reliably to their treatment sufficiently to maintain its effectiveness. Cognitive dysfunction predicts poor treatment adherence, and executive function psychomotor speed, working memory, and new-learning are the most potent predictors [47, 49]. Likewise, deficits involving financial management and ability to drive an automobile is compromised in many people with HIV. Impairment in executive function, working memory, new-learning, and psychomotor speed predict poor financial management and driving ability [47].

SUBSTANCE USE AND HIV

Viral infections can cause continuing and ongoing changes in emotional and cognitive functions. While their systems of encounters vary, all substances of use are considered to share a mutual characteristic, which is the enhancement in mesolimbic dopamine levels [50]. The increased amount of dopamine is considered to facilitate most of the gratifying acts of drug use and gratifying actions in general. Thus, receptor and gene structures that are involved in reward-related neurocircuitry systems have long offered a preferred aspirant gene pool for research on addictions on psychiatry and have conventionally included primarily monoaminergic and opioid-related genes, but also hypothalamic-pituitary axis (HPA) and other stress regulating genes [50]. Through association and genetic linkage studies, single nucleotide polymorphisms (SNPs) analyses, and haplotype move toward numerous genes and chromosomal areas in monoaminergic and opioid-related systems have been recognized that can possibly elucidate in part phenotypes and disease progression facilitators immersed in drug use and possible psychiatric comorbid disease and HIV advancement [51].

As revealed in the aforementioned review, psychological dysfunction does not affect all individuals with HIV to the same extent. According to Kopkinsky, Bao & Lin, 2007 [50], different substances of abuse have varying HIV interactions in brain-derived cells or systems. These comorbidity factors include increased Tat-induced release of proinflammatory cytokines, increased Tat-induced oxidative stress and neurotoxicity, Tat-induced loss of DA terminals in striatum, synergic increase in HIV Tat striatal neurotoxicity,

exacerbates gp120 cytotoxicity, increased Tat-induced CCL2 positive astrocytes upregulates interfere inducible genes in HIV, potentiates gp10_{ma} neuronal apoptosis, interaction with gp120 and Tat that produces neurotoxicity, increases in Tat deaths of glial precursors and some astrocytes, increases in HIV expression up to 54%, increases Tat neurotoxicity assessed *via* CB and MAP2 IR, increases in Tat release and/or activation of MMPs, MA normalizes the decrease in glutamate in FIV cats, increase in gp 120 neurotoxicity, increased Tat decreases in striatal DA release and content, synergistically increases in Tat proinflammatory stimulation, increased Tat synergistically decreased striatal DA levels 65% and DAT 56%, increases I FIV astrocyte viral replication, and significantly increased Tat-induced neuronal death by two fold [50].

Accordingly, patient factors may exacerbate presence of cognitive impairment. In particular, substance misuse may contribute to greater neurocognitive morbidity in people with HIV. Indeed, people with HIV are prone to misuse drugs and alcohol more so than the general population. For instance, 40% of people with HIV acknowledge using illicit drugs, 18% admit to heavy alcohol misuse, and 12% report symptoms of substance dependence [52].

Ominously, abuse of certain drugs corresponds with cognitive dysfunction. Furthermore, some drugs of abuse may compromise immune function, which in turn may increase the likelihood of further neurobehavioral dysfunction through secondary infection (e.g., toxoplasmosis, CMV, *etc.*). Accordingly, many infected people with histories of substance misuse may manifest neuropsychological impairment more than their non-drug abusing counterparts. Yet, despite this possibility, there is relatively little research concerning the effect of co-morbid substance abuse and HIV infection. In the review that follows, we will survey the literature concerning the neurobehavioral and immunological effects of drugs that are popularly abused by individuals infected with HIV. Certain substances of abuse and the biological mediators of psychiatric illnesses reportedly interact in the brain and presumptively worsen HIV-related neuropathogenesis and survival measures [50]. Specifically, we will focus upon cocaine, opiates, alcohol, marijuana, and amphetamines. In doing so, we hope to suggest mechanisms by which abuse of these substances may exacerbate or contribute to neurobehavioral dysfunction in HIV infection.

Cocaine

Cerebral Morphology and Function—Although cocaine has a diffuse effect upon neurotransmitter systems, it affects the dopaminergic system especially. Cocaine is a dopaminergic agonist, and it stimulates dopamine production and inhibits its reuptake. It also inhibits the reuptake of serotonin and norepinephrine. After sustained use, this yields diminished dopamine availability on the presynaptic terminal and post-synaptic receptor supersensitivity. Resulting changes in dopaminergic response are thought to be most prominent in the basal ganglia, orbitofrontal cortex, and cingulate gyrus [53].

Cocaine abuse induces vasoconstriction, and increases the risk of a cerebrovascular accident [54]. These vascular changes correspond with decreased frontal lobe and basal ganglia activation [55] at rest, which may persist with abstinence [56–60]. Consequently, sustained cocaine misuse may yield durable changes in brain function. Acute intoxication likewise results in abnormal activation of the dopaminergic mesolimbic and mesocortical circuits,

which are associated with executive function, emotional responses, and reward responsivity [53]. Specifically, the caudate nucleus, ventral tegmental area and nucleus accumbens, subcortical regions that are innervated by dopaminergic neurons, increase in activation during acute cocaine intoxication. This presumably reflects the intense sensation of pleasure associated with cocaine [61]. Abnormal activation may persist in the medial and orbital frontal regions after 28-days of abstinence, and amount of cocaine used prior to abstinence correlated significantly with performance on a measure of concept formation and impulsivity [62]. Over periods of sustained abstinence (as long as 102 weeks), functional abnormalities involving the frontal lobe, cingulate gyrus, and cerebellum manifest while patients perform tasks that require self-control and restraint from impulsive responses. Curiously, such functional abnormalities occur without poor performance on cognitive tasks, as cocaine dependent patients performed as well as a control group [63].

Additionally, chronic cocaine use may also alter brain structure. Pascual-Leone *et al.* (1991b) [64] compared cerebral volumes in groups of cocaine users and drug-naïve subjects. Long-term use corresponded with cerebral atrophy, and there are indications that such atrophy may be especially pronounced in the frontal lobes [54]. More recent studies have also found evidence of tissue loss in the frontal and temporal lobes [65, 66], but other investigations have revealed no gross abnormalities [67]. Notably, however, Barros-Loiscertales *et al.* (2010) [68] compared a group of individuals diagnosed with cocaine dependence to a control group, and found subcortical gray matter loss, especially involving striatal structures. Generally, subcortical circuits innervated by dopaminergic tracts were diminished. This conforms with the primary neurotransmitter implicated in cocaine misuse. Ironically, Ersche *et al.* (2011) [68] found that striatal structures were larger in cocaine abusers, but orbital frontal cortex, cingulate gyrus and the cerebellum were reduced. These reductions correlated significantly with length of cocaine misuse and poor performance on measures reflecting impulse control. Yet, some evidence implies that after abstinence exceeding 30 days, structural abnormalities may dissipate [61].

Neuropsychological Function—Chronic cocaine misuse corresponds with poor executive function, new-learning and speed of information processing [65, 70–75]. In a meta-analysis that included 481 cocaine users and 586 control subjects [76], the largest effect sizes were observed on measures of attention, working memory, and visual memory. Modest effect sizes occurred on measures of executive function and sensory-perceptual function. Durability of neuropsychological abnormality seems to persist for at least several weeks of abstinence. For example, Pace-Schott *et al.* (2008) [77] studied a group of 17 inpatients seeking treatment for cocaine dependence repeatedly over several weeks. After two weeks of abstinence, the patients showed residual attention and new-learning deficits compared to normative estimates. Likewise, Fein *et al.* (2002) [78] found continued executive function deficits in cocaine dependent individuals after 6-weeks of abstinence, and this correlated with diminished pre-frontal cortex volumes. Additionally, deficits in memory, visuospatial perception, and attention have been reported despite several weeks of abstinence [70, 73], but some improvement occurs over longer periods of abstinence [79].

There are indications that cocaine-induced structural and functional abnormalities correlate with neuropsychological deficits [80]. Presence of neuropsychological dysfunction also

increases in association with lifetime amount of cocaine used [81]. Age seems to moderate the severity of cocaine-related working memory and executive function deficits [82]. Ironically, administration of cocaine to dependent individuals seems to alleviate cognitive dysfunction. Woicik *et al.* (2009) administered a battery of neuropsychological tests to a control group and to cocaine-dependent individuals who had recently used cocaine and to dependent participants who had been abstinent for several days [83]. Both patient groups performed worse than the control group on measures of working memory, executive function, and verbal memory, but those who had abstained performed worst.

Immune Function—Cocaine abuse suppresses T-cell response and various other immune cell interactions [84, 85], and the degree of immunosuppression may also be related to the amount of cocaine used [86]. In people infected with HIV, such morbidity may manifest with reductions in CD4 counts, faster progression to AIDS, and increased viral load [87–90]. For instance, in a sample of HIV-seropositive individuals that abused diverse illicit drugs, Rafie *et al.* (2011) [91] observed that CD4 counts diminished as cocaine use increased, and this occurred independently of antiretroviral treatment. Indeed, some investigations have shown that cocaine use corresponded with a decline of CD4 cells to AIDS levels, and this unfolded regardless of antiretroviral treatment adherence [92]. Moreover, there are indications that cocaine abuse exacerbates HIV replication [93]. Gaskill *et al.* (2009) [94] showed that release of dopamine facilitates HIV infection of macrophages. Because cocaine enhances dopamine availability, cocaine use may increase HIV proliferation. In addition, cocaine increases the susceptibility of the brain to infection by increasing permeability of the blood brain barrier to viral strains including HIV [95, 96].

HIV and Cocaine Use—Surprisingly little research has examined whether interactive or synergistic effects of HIV and cocaine misuse occur. The few studies available yield inconclusive results. Durvasula *et al.* (2000) [97] administered a battery of neuropsychological tests to nearly 240 African-American men, 172 of which were HIV seropositive. Most were either current or past cocaine users. Regardless of HIV status, moderate to heavy users of cocaine demonstrated psychomotor slowing. Worsening HIV status also corresponded with psychomotor slowing. Yet, there was no interaction of HIV status and cocaine misuse. Cocaine use did not seem to increase neuropsychological impairment in people with HIV. More recently, Levine *et al.* (2006) [98] examined vigilance performance in a sample comprised entirely of people with HIV, approximately half of who were abusers of cocaine and methamphetamine. Drug use corresponded with impaired vigilance, but there was no evidence that it exacerbated impairment in seropositive individuals. Meade *et al.* (2011) [99] conducted a similar study of 64 seropositive individuals, of which approximately half met DSM-IV criteria for cocaine dependence and were currently abusing the drug. Compared to normative values, the participants displayed abnormal neuropsychological performance. Furthermore, the current cocaine users had significantly worse neuropsychological performance than the non-users, and this was most saliently demonstrated on measures of verbal learning and visual-spatial construction. In a related study, Meade *et al.* (2011) [100] administered a measure of executive function that targeted self-control and impulsive choices while participants underwent functional MRI assessment. All subjects were HIV-seropositive, and were classified as currently using

cocaine, previously using, or cocaine-naïve. There was a trend for the currently abusing participants to display more impulsivity than the drug-naïve subjects, and they also showed less activation in frontal, parietal, and subcortical regions during performance of the executive function measure. Collectively, these data fail to reveal a synergistic effect of cocaine use and HIV status. Design limitations, namely the absence of a seronegative cocaine-naïve group from most of these studies, preclude revelation of a potential interaction effect. Regardless, the data show that cocaine exacerbates existing neuropsychological morbidity among patients with HIV.

Opiates

Cerebral Morphology and Function—Studies of opiate abuse on brain structure have produced inconsistent results. Indeed, a number of researchers acknowledge that relatively little is known concerning the long-term effects of opiate use on the brain [101]. Some studies have attempted to discern whether structural anomalies result from chronic opiate use. For instance, Pezawas *et al.* (1998) [102] compared cerebral volumes of opiate dependent men and age matched controls. The dependent group had smaller cortical volume than the control subjects, and atrophy in the frontal lobes was inversely associated with length of abstinence. With a small sample of opiate addicts (n=7), Strang and Gurling (1989) [103] identified definite abnormalities on CT scans, but there was no consistent brain region in which these lesions occurred across patients. In contrast to these investigations, Rose and colleagues [104] found no morphological abnormalities in their sample of 10 opiate dependent patients upon admission for rehabilitation treatment. In more recent research involving patients who uniformly abused only prescription-based opiates and had no other psychiatric disorder, Upadhyay *et al.* (2012) [105] found bilateral volume loss in the amygdala and white matter atrophy in circuits terminating in the amygdala and in the internal capsule. Length of opiate abuse correlated with this attenuation. Other recent studies of opiate dependent individuals have demonstrated diminished gray matter volumes in the frontal, temporal, and insula cortex [106–108]. Among opiate-dependent people who smoke heroin, studies have identified patterns of leukoencephalopathy. For example, Offiah and Hall (2008) and Bartlett and Mikulis (2005) [109, 110] found scattered lesions in such patients using structural MRI. Reports of such lesions in intravenous or orally ingested opiates are uncommon, suggesting they are due to method of drug administration than specific properties of the drug. Regardless, cause of structural anomalies in opiate dependent individuals is uncertain, but there are indications that pathological changes may be due to infections and illness that are co-factors with opiate use [110].

Apart from structural abnormalities, there are suggestions that chronic opiate use corresponds with functional anomalies. For example, Franken *et al.* (2004) [111] collected electroencephalograms (EEG) from abstinent heroin addicts and a control group. The heroin users showed abnormal EEG compared to the control group, and this occurred despite documented abstinence in the clinical group. Likewise, several studies demonstrate that cerebral metabolism is abnormally reduced in opiate dependent individuals. Such hypometabolism seems to occur in a diffuse pattern, but especially in the frontal, parietal, and temporal lobes [112–117]. In contrast, Galynker *et al.* (2000) [118] found that cingulate activation was higher among abstinent heroin addicts receiving methadone maintenance

treatment compared to control subjects. To some extent, activation levels may remain abnormal despite abstinence [114, 116, 118], but other studies suggest that it remits with abstinence [117]. More research is necessary to clarify this issue. Furthermore, functional anomalies observed in these studies may be non-specific to opiate use, as confounding variables (*e.g.*, pre-morbid health status, pre-morbid educational histories, *etc.*) may have been manifest.

Neuropsychological Function—Acute opiate intoxication has been studied with healthy control subjects who had no history of substance dependence. Ultimately, working memory, new-learning, and speed of information processing are diminished consequent to morphine [119, 120].

In early research concerning chronic opiate misuse, Fields and Fullerton (1975) [121] compared heroin addicts to a control group on a broad neuropsychological battery, and found no deficits. More recently, Gruber *et al.* (2007) [122] conducted a qualitative review of the literature. They concluded that chronic opiate misuse corresponds with dysfunction involving executive function, working memory, new-learning, psychomotor speed, and visual-spatial reasoning and perception. Effects of opiates can be observed across the spectrum of narcotics, including the illicit (heroin) and licit (*e.g.*, morphine), and they vary in severity between the drugs. It should be noted, however, that few investigations exist that depict the long term effects of chronic prescription-based narcotics. Thus, prescription-based medications may pose significant morbidity, but this is untested.

There is evidence that these deficits possess modest durability. Guerra *et al.* (1987) [123] evaluated neuropsychological function in heroin addicts at baseline and after one-week of abstinence. During the initial examination, the dependent patients performed worse than a control group across most measures, but these differences disappeared after one-week. Deficits involving executive function and impulse control have also been demonstrated after 18 months of abstinence [124]. Ultimately, few studies have conducted long-term evaluations of cognitive function among abstinent opiate abusers, but the available data implies that neurocognitive dysfunction ameliorates over time. Some abnormalities may remain, but their severity is lessened [125].

Curiously, there are indications that medical treatment of opiate addiction may sustain cognitive dysfunction. To alleviate withdrawal symptoms and narcotic craving, methadone or buprenorphine, opiate agonists, are often prescribed. Some data indicate that opiate users receiving methadone maintenance treatment may have significantly more neuropsychological impairment than those who are simply abstaining from any opiate or opiate agonist medication [126] compared methadone maintained opiate addicts to a control group and abstinent recovered opiate addicts. The methadone maintained patients performed worse on measures of executive function, visual working memory, and information processing speed, suggesting that methadone exacerbates cognitive dysfunction in opiate users. Gruber *et al.* (2006) and Verdejo, *et. al* (2005) [125, 126] evaluated opiate dependent individuals after two months of methadone treatment, and found significant improvement from pre-treatment levels on measures of verbal and visual learning, working memory, and psychomotor speed. These data indicate no deficits associated with methadone. In contrast,

Prosser *et al.* (2006) [127] compared 29 patients receiving methadone, 27 abstinent recovered addicts, and 29 control subjects on a battery of neuropsychological tests. The two patient groups were evaluated after they had passed at least 18-months without abusing opiates. The two patient groups performed significantly worse than the control group. Thus, deficits remain after 18-months, and there methadone does not increase neurocognitive morbidity over abstinence. Further complicating matters, Rapeli *et al.* (2011) [128] evaluated whether buprenorphine yields less neuropsychological impairment than methadone of 17 months of treatment. Separate treatment groups demonstrated equivalent impairment on measures of working memory and new learning at baseline compared to a control group. Over time, both groups showed residual deficits, but this was more pronounced in the methadone group than in the buprenorphine group. Similar findings were reported by Piratsu *et al.* (2006) [129], implying that buprenorphine poses less cognitive morbidity than methadone.

Immune Function—Accumulating data indicate that opiate abuse is immunosuppressive. For example, morphine and heroin reduce CD4 T lymphocyte counts and other indices of immune system integrity [130, 131]. Reductions in immune response can persist despite abstinence for several months [132].

Opiates and HIV Infection—The synergistic and immunosuppressive effects of opiates may be particularly significant in HIV infection. Opiate receptors appear on multiple immune cells including macrophages and CD4/CD8 cells. Administration of opiates modulates and suppresses the response of these cells [133]. Morphine stimulates the replication of the HIV virus [134, 135] including within the brain [136], and may accelerate progression to AIDS [137, 138]. Opiate abusing patients have higher rates of HIV-related encephalitis, and HIV disease progression slowed when patients abstained from illicit drug use [137]. Opiate misuse also seems to increase rates of symptomatic illness in people with HIV [139]. Furthermore, opiate abuse is apt to increase HIV viral load in the brain, and its presence facilitates secretion of neurotoxic proteins and cytokines (*e.g.*, Tat, gp 120) [136]. Given that HIV related illness and increasing viral burden corresponds with worsening neuropsychological function [140–144], opiate use may ultimately exacerbate neuropsychological dysfunction.

In this vein, some studies have examined the effects of opiate misuse among seropositive individuals. Remarkably, most early studies found no morbidity associated with opiate misuse [145–148]. Yet, the investigators only examined the main effects of substance abuse and infection, and the interaction of drug use and HIV status went unexamined. Later investigations have found that combined opiate and cocaine dependence corresponds with worsening neuropsychological function in people with HIV [149]. However, this research did not include seronegative individuals, thereby making it impossible to determine whether opiate misuse exacerbated cognitive deficits in HIV. More recently, Applebaum *et al.* (2010) [150] compared neuropsychological performance among opiate dependent individuals who were receiving methadone maintenance treatment. Half were seropositive, and the other half were seronegative. The seropositive patients performed worse than the healthy control group on measures of new-learning, working memory, and psychomotor speed. The investigators

assessed drug use frequency and recency, and found that opiate use had no significant effect on cognitive function. Gonzalez *et al.* (2008) [151] conducted a similar study design involving 96 patients with histories of cocaine and/or heroin misuse. Similar to Appelbaum *et al.* (2009), the seropositive patients performed worse than the seronegative participants. Yet, because non-drug users were excluded from this study, the design could not permit an evaluation of synergistic effects of drug use and HIV status.

In research that included seronegative opiate misusers, the results are similarly inconclusive. Vazquez-Justo *et al.* (2003) [152], compared seropositive and seronegative intravenous drug users to seronegative non-drug users. HIV seropositive drug users displayed impairment across multiple cognitive domains, but the seronegative drug users showed only mild neurobehavioral abnormalities. However, because no non-drug using seropositive individuals participated, the combined effect of opiate misuse and HIV status could not be examined. Rodriguez *et al.* (2006) [153] conducted a similar study, and found that intravenous drug use corresponded with cognitive impairment. However, some of their participants were abstinent whereas others were receiving methadone treatment. The HIV seropositive individuals performed worse than the seronegative patients. Moreover, compared to the seronegative opiate misusers and seropositive abstainers, the seropositive drug users who were maintained on methadone had higher rates of cognitive impairment. Consequently, these data agree with research involving HIV-seronegative individuals, implying that methadone seems to exacerbate neuropsychological dysfunction among opiate dependent individuals. Yet, because the methadone-maintained seropositive patients had lower education levels, this may have confounded the findings of this study.

Surprisingly, these investigations are among the few that have examined the effects of opiates and HIV status, but none have fully evaluated the synergistic effects of these factors. These findings fail to provide a consensus regarding the effects of opiate abuse on neuropsychological function in people with HIV. Despite the growing consensus that opiate abuse diminishes immune response, and may actually contribute to a more severe disease stage such as AIDS, there is little evidence that the combined effects yield amplified neurocognitive morbidity.

Alcohol

Lifetime prevalence of alcohol abuse and dependence is high in people with HIV, with prevalence estimates ranging 29–60% [155, 156]. Thus, alcohol misuse disorders are among the most common co-morbid disorders among people infected with HIV.

Cerebral Morphology and Function—Alcohol misuse exerts broad damage to multiple neurotransmitter systems including acetylcholine, dopamine norepinephrine, glutamate, and especially GABA [157, 158]. Presumably, alcohol misuse results in glutamate excitotoxicity and cellular inflammatory processes, resulting in cell death [159]. Alcohol may also weaken resistance of the blood brain barrier to leukocytes, the latter being a salient means of ingress for HIV into the brain [160]. Additionally, cortical atrophy over the frontal temporal, and parietal lobes [161] reduced subcortical volumes, diminished cortical thickness [162], and white matter abnormalities [163], have been reported. Indeed, somewhat paralleling the

pathology associated with HIV, sustained alcohol misuse corresponds with significant white matter degeneration [164], especially involving the frontal lobes [165]. Alcohol misuse also exerts damage upon the limbic structures and the cerebellum [164, 165]. Such structural anomalies correspond with diminished cognitive function and apathy [157, 168]. Furthermore, hypometabolism occurs in the frontal and parietal lobes [169–171], and remains despite abstinence [171, 172]. Salient abnormalities involving the mesolimbic circuits that mediate reward responses, and these structures appear to become hyper-reactive among individuals with alcoholism.

Neuropsychological Function—Prevalence of cognitive deficits is heightened in chronic alcohol misusers, and non-verbal intelligence, abstract reasoning, concept formation, memory, speed of information processing, attention, and visual-spatial perception are commonly impaired [172–178]. Some research to the contrary [179], cognitive difficulties may remain after several years of abstinence [180]. In one study, elderly individuals who had become abstinent before age 50 were compared to those who had ceased drinking later in life [181]. Those who had stopped drinking prior to age 50 generally performed normally, whereas those who became abstinent after that age continued to show poor performance across multiple domains. Notably, those who stopped drinking prior to age 50 continued to demonstrate abnormal auditory working memory performance.

Immune Function—Chronic alcohol misuse corresponds with immunosuppression [182–187] and this is manifest by suppressed monocytes, macrophages, and lymphocytes, including T-cell responses [185, 188]. T-cell apoptosis, mitochondrial damage, and phagocytic activity are each diminished in people who abuse alcohol [189]. Additionally, infection rates are higher in alcoholics [190]. Among seropositive individuals, alcohol misuse is associated with faster HIV replication, suppression of resistance to HIV, accelerated progression from asymptomatic to symptomatic illness, and greater permeability of the blood brain barrier to infectious agents [191–193]. Furthermore, seropositive individuals who abuse alcohol are less adherent to CART regimens, and are disinclined to achieve viral suppression or a resumption of immune function [194, 195]. There are indications that alcohol misuse exacerbates disease progression and hastens development of AIDS wasting syndrome [189, 196]. Hence, alcohol misuse in people with HIV may interact to exacerbate neuropsychological impairment beyond what might be expected of each factor independently.

HIV and Alcohol Misuse—The existing literature reveals that alcohol abuse impairs brain structure and function, neuropsychological performance, and immune response in seronegative individuals. Accordingly, alcohol abuse in HIV may exacerbate risk of neuropsychological deficit. Despite this suggestion, many imaging studies have shown no effect of alcohol abuse and HIV status [197, 198]. Unfortunately, owing to design limitations, these studies examined only the main effects of alcohol use and HIV status rather than their interaction (*e.g.*, comparing alcoholic and non-alcoholic seropositives).

Older investigations concluded that neurobehavioral abnormalities in HIV are not attributable to alcohol abuse alone [31, 199, 200]. Yet, these investigations only examined main effects of HIV status and alcohol misuse history; the interaction of these variables was

not addressed. More recent studies provide direct evidence of a synergistic or interactive relationship between HIV and alcohol use. Green *et al.* (2004) [201] compared four groups of homosexual men on a battery of neuropsychological tests. The men varied according to HIV status and history of alcohol misuse. History of alcohol misuse corresponded with diminished verbal intelligence, concept formation, auditory working memory, and reaction time. Compared to seronegative individuals, the seropositive participants performed worse on measures of verbal learning and motor speed. Notably, HIV status interacted with alcohol misuse history; HIV-seropositive participants with a history of alcohol abuse demonstrated poorer performance on measures of verbal intelligence, concept formation, and visual reaction time relative to other groups. Additionally, in the HIV negative group, history of alcohol abuse had no significant effect.

Other studies have reported similar outcomes. For example, Fama *et al.* (2009) [202] classified 164 participants according to HIV status and alcohol use history, and administered a computer-based neuropsychological test battery to them at baseline and one-year later. The individuals diagnosed with alcohol dependence had been actively abusing alcohol within three years of study participation. At study commencement, some were abstinent and some actively misused alcohol. Across both testing intervals, the individuals with co-morbid alcoholism and HIV infection performed in the impaired range on measures of new-learning, whereas normal controls, and individuals with HIV or alcoholism only performed normally. In further accordance with these findings, other investigations found a synergistic or interactive effect of alcoholism and HIV infection on measures of motor and visuomotor speed [203], and working memory [204, 205]. Such deficits remain despite controlling for potential confounds such as recency of alcohol misuse [206], age, education, history of head injury, and co-morbid drug misuse [207].

Although these domains of function seem most vulnerable to dysfunction due to alcoholism and HIV infection, other areas of cognition that are typically robust to brain damage also seem diminished. Notably, at least one study has shown that alcohol and HIV status interact to diminish intelligence. Penkower *et al.* (1995) [208] studied neuropsychological function of eighty gay and bisexual men who were categorized by HIV status and history of alcohol abuse, and an interaction emerged. In particular, history of alcohol misuse had no impact upon the men without HIV. In contrast, among those infected with HIV, those who had previously misused alcohol performed worse on measures of verbal intelligence, verbal reasoning, and reaction times. Similarly, Fama *et al.* (2011) [209] examined effects of alcoholism and HIV upon remote memory. Administering the Presidents' test to study long term-overlearned memories, they found that seropositive individuals with alcoholism displayed worse remote memory than a control group or individuals with either alcoholism or HIV alone. Viral load, depressive severity, and history of alcohol consumption correlated with remote memory performance, but education did not explain poor performance.

Collectively, these investigations suggest that heavy sustained alcohol use may interact with HIV status to exacerbate some aspects of neurobehavioral function. There is not accumulating evidence that [147, 201, 204, 207, 209, 210] that alcoholism and HIV disease status may act synergistically to increase neuropsychological impairment over and above the main effects of either alcohol or HIV alone. Memory, working memory, and speed of

information processing seem most saliently affected. Notably, imaging data have begun to emerge that parallel these neurocognitive findings. For instance, white matter degeneration is more pronounced among seropositive alcohol abusers compared to seronegative alcoholics [211]. At present, this literature continues to provide only tentative assertions, and additional research remains necessary to clarify matters.

Marijuana

Cerebral Morphology and Function—The principal psychoactive ingredient of marijuana (delta-9 tetrahydrocannabinol: THC) interacts with cannabinoid receptors (CB1), and these are distributed throughout the brain, most prominently in the basal ganglia, hippocampus, and cerebellum [70, 212]. Notably, these reveal that both HIV and marijuana implicate similar regions of dysfunction, namely the basal ganglia and striatum. There are indications that THC has an especially active effect upon hippocampal nuclei, posterior cingulate, superior frontal gyrus, and orbital-frontal cortex [213]. In studies involving functional imaging methods, marijuana use seems to correspond with general cerebral hypoactivation [214, 215]. A recent review of 33 functional neuroimaging studies concluded that abnormal pre-frontal and anterior cingulate activation occurs in marijuana users compared to control subjects, especially during the performance of cognitive tasks [216]. There is little evidence of structural abnormalities associated with marijuana use, and only three studies included in the review by Martin-Santos *et al.* (2010) [216] found significant abnormalities. Typically, studies that have demonstrated abnormal structural variations have included chronic users with long-histories of abuse. For instance, Solowij and Battisti (2008) [217] found significantly reduced hippocampal and amygdala volumes among individuals who had abused marijuana for over 20 years. Those who begin misuse before age 17 tend to have reduced brain volumes and increased resting brain activation compared to those who commenced use in late teens or early 20s [218].

Neuropsychological Function—There is little controversy concerning the effects of acute marijuana intoxication and post-acute intoxication on cognitive function. Impairments are clearly demonstrated on measures of new-learning, executive function, and working memory among heavy users and naïve users alike [158, 219], and these effects linger for several hours after drug administration [220]. Pope and colleagues have examined the effects of marijuana abuse after brief periods of abstinence, and found deficits involving memory, attention, concept formation, and psychomotor speed [221–223]. Over longer periods, however, effects are less certain. Fried *et al.* (2005) [224] followed a group of 113 children through from early childhood through early adulthood, and evaluated neurocognitive changes through development. Some of the cohort began to use marijuana, and Fried *et al.* examined the effects upon cognitive function. All participants were abstinent for at least 24 hours prior to testing. Fried *et al.* (2005) found that heavy users showed poor performance on measures of new-learning, information processing speed, and intelligence. Former users who had remained abstinent for at least three months showed no such deficits. In contrast, Jacobsen *et al.* (2004) [225] studied adolescents who had remained abstinent for 10 months, and found abnormal working memory and selective attention performance compared to a control group. Similarly, Pope *et al.* (2003) [226] found persistent memory and working memory deficits among chronic users after 28 days of abstinence, but only among those who

had commenced use prior to age 17. Such findings imply that age of onset for misuse may moderate the long-term effects of marijuana use on neurocognitive function.

Immune Function—Klein and colleagues have shown that marijuana misuse modulates T and B lymphocytes and cytokine response, decreases natural killer cell activity [227, 228], and diminishes immunity to infection [229, 230]. Thus, the likelihood that an HIV seropositive individual will become symptomatic or convert to AIDS will increase.

HIV and Marijuana Misuse—Few studies have examined whether marijuana use and HIV status pose a synergistic detriment upon cognitive function. Cristiani *et al.* (2004) [231] found that symptomatic seropositive individuals performed worse than a control group on measures of intellect, executive function, working memory, new-learning, speed of information processing, and motor speed. Compared to marijuana naïve participants, individuals who had misused marijuana demonstrated impaired new-learning and auditory working memory. Moreover, among marijuana users, the seropositive-symptomatic group performed significantly worse than the asymptomatic or seronegative groups. Among marijuana-naïve participants, there was no difference between individuals according to HIV status. Thus, marijuana use and symptomatic HIV-status acted synergistically to diminish neurobehavioral function. Subsequent studies have yielded less conclusive results. Chang *et al.* (2006) [232] compared neuropsychological performance of 42 seropositive individuals to a control group of 54 people. Approximately half reported histories of regular marijuana use, but most had not recently used the drug. After controlling for age and education, few differences existed between the groups, and there was no interaction of HIV and marijuana status. Gonzalez *et al.* (2011) [233] administered a battery of procedural memory tests to a group of 86 individuals 17 of whom were seropositive and had histories of past marijuana dependence, 25 who were seropositive only, 23 who had past marijuana dependence only, and 21 who had neither. Detrimental main effects of marijuana dependence and HIV status were found. Although no interaction of HIV and marijuana status emerged, additive effects manifested. Perhaps the absence of interaction in the studies by Chang *et al.* (2006) and Gonzalez *et al.* (2011) may be attributed to intra-group variability concerning recency and severity of marijuana use. In neither case were all of the participants in the marijuana groups currently using significant amounts of marijuana. Most of the research concerning marijuana effects on neurocognition reveals that the most salient detrimental effects occur among individuals who are heavy users and who have used recently. Regardless, the literature concerning synergistic effects of marijuana and HIV status upon neuropsychological function remains unsettled.

Amphetamine

Cerebral Morphology and Function—Amphetamines and methamphetamines act as agonists upon the norepinephrine and dopamine systems [234]. These substances have potential therapeutic value. When these medications are taken at therapeutic doses, there is no compelling evidence that cerebral abnormalities occur [235]. However, there is evidence that long-term abuse at super-therapeutic dosages results in pathological changes. Chronic abuse can deplete the amount of norepinephrine and dopamine activity in the brain, especially in the striatum and prefrontal cortex [236]. Much of the reduction seems due to

diminished dopamine receptors, depleted dopamine availability, and decreased transporters for dopamine and monoamines [237]. Despite abstinence of three years, amphetamine abusers continue to show abnormally depleted amounts of dopamine in the caudate and putamen [237]. In addition to abnormal dopamine levels, there are indications that glutamate may be affected by methamphetamine misuses. Sailasuta *et al.* (2010) [238] obtained magnetic resonance spectroscopy from methamphetamine dependent individuals who had been abstinent for at least three weeks. Compared to a control group, the methamphetamine abusers manifested excessive glutamate in the frontal region of the brain. Based on this finding, the authors hypothesized that methamphetamine misuse may yield neuronal damage through glutamate excitotoxicity.

Structural imaging methods reveal abnormal cerebral volumes, especially involving the striatum, temporal lobes, and hippocampus [239]. Reductions in hippocampal volume have been associated with poor performance on measures of new-learning [240, 241]. In contrast, other research found larger putamen and globus pallidus volumes in methamphetamine dependent patients than in methamphetamine naïve subjects [242]. These patients had been abstinent for two years at the time of imaging. A subset of patients had reduced volumes in these regions, and they showed impaired executive function and psychomotor speed, leading Chang *et al.* (2005) to hypothesize that the enlargement in these structures and normal cognitive function reflected some form of compensation to methamphetamine toxicity. Furthermore, among individuals who were abstinent for 18 months, white matter hyperintensities, suggestive of white matter degeneration, have been observed [243]. Such white matter changes are common, and have been reported in multiple studies involving methamphetamine dependent individuals [235]. Furthermore, amphetamine use results in vasoconstriction, thereby increasing the risk of vascular inflammation, hypertension, and stroke [158].

With functional imaging methods, amphetamine and methamphetamine abusers display abnormal patterns of activation in the frontal and temporal lobes, cerebellum, cingulate, and thalamus [245–249]. With periods of abstinence as brief as one week, methamphetamine dependent women showed hypoactivation in the cingulate and prefrontal cortex and hyperactivity in the amygdala, ventral striatum, and lateral orbitofrontal cortex [241]. With longer periods of abstinence up to 17 months, some normalization of function was observed in the thalamus, but continued hypoactivation in the striatum may be observed [250].

Neuropsychological Function—There are indications that long-term cognitive dysfunction may occur among individuals who misuse methamphetamine. Scott *et al.* [251] conducted a meta-analysis of 17 studies. They found that methamphetamine misuse found moderate to small effect sizes across all domains of neurocognition that was surveyed. The most potent effects were observed in the domains of new-learning, executive function, speed of information processing, and motor speed. They failed to find a significant effect of abstinence; effect sizes remained significant after controlling for whether patients were abstinent at the time of testing. This outcome is tenuous, because so few studies in their meta-analysis assessed this issue in a methodologically rigorous manner.

There is compelling evidence that patients who currently misuse methamphetamine are prone to demonstrate impairments on measures of concept formation, mental flexibility, speed of information processing, working memory, and new-learning [252]. There is also evidence that cognitive deficits persist despite abstinence.

Over relatively short periods of abstinence, methamphetamine dependence coincides with impaired function. For instance, Kalechstein *et al.* (2003) [253] found that methamphetamine dependent individuals who had been abstinent for at least 5-days displayed poor executive function, working memory, new learning, and psychomotor speed. Simon *et al.* (2010) [254] compared methamphetamine dependent individuals who had abstained for approximately one week to a control group. The drug dependent patients showed significant impairment, especially on measures of executive function, working memory, and new learning. Salo *et al.* (2009) [255] compared neuropsychological function of a healthy control group, methamphetamine dependent individuals who had abstained for an average of nearly three months, and methamphetamine dependent people who had abstained for 2.5 years. The long-term abstinent group performed as well as the control subjects, but the recently abstinent patients performed worse than these groups on the Stroop Color Word Test. After periods of abstinence as long as 18 months, Moon *et al.* (2007) [256] found that methamphetamine dependent individuals showed impaired visual memory and visual constructive skill, but their verbal memory was normal. Cherner *et al.* (2010) [257] examined cognitive function among methamphetamine dependent individuals who had been abstinent for an average of four months. These individuals had abused a variety of other drugs, and 61% of them met criteria for comorbid abuse or dependence. They were compared to a group comprised of at least some who had abused other drugs, but none had abused methamphetamine. The methamphetamine dependent group performed worse than the control group on measures of executive function, new learning, working memory, and psychomotor speed. Iudicello *et al.* (2010) [258] followed methamphetamine dependent individuals over one year. At baseline, all patients were abstinent for at least one month, and they displayed global impairment on a neuropsychological battery compared to a control group. Over one year, most of the patients relapsed. Those who remained abstinent performed as well as a healthy control group, but those who relapsed showed continued deficits. Moreover, the patients who were most impaired at baseline were most likely to relapse over time.

Immune Function—Research concerning the effects of amphetamine abuse upon immune response provides tentative conclusions. The available literature derives from animal and human studies, and shows that amphetamine use decreases T-lymphocyte response and increases permeability of the blood brain barrier to infection [259–263]. Chronic amphetamine abuse also corresponds with changes in hormonal and lymphocytic activity that reflects immunosuppression [264, 265]. With respect to cognitive dysfunction, Loftis *et al.* (2011) [266] evaluated the relationship between neuropsychological function and immune-associated cytokine activity among abstinent methamphetamine addicts and a control group. The methamphetamine dependent group showed greater cytokine activity, and this in turn correlated with diminished neuropsychological function.

HIV and Amphetamine Misuse—It is reasonable to expect that HIV and methamphetamine dependence would have synergistic effects on neurocognition. Both show a preference for subcortical structures, especially the basal ganglia. Both contribute to pathology through oxidative stress, glutamate toxicity, and diminished dopamine function. Existing data suggest that at least among stimulant abusers, there is some likelihood of an additive or interactive effect of drug use and HIV in NP functioning. Several mechanisms have been suggested to underlie this effect. In animal models, potentiation of HIV Tat protein mediated neurotoxicity by methamphetamine has been demonstrated, which can result in striatal proinflammatory cytokine stimulation and activation of redox-regulated transcription factors [82, 267]. Other mechanisms which have been suggested include mitochondrial dysfunction and subsequent oxidative stress. Dopaminergic, serotonergic, and glutamatergic systems are impacted by stimulant use and HIV, and dual vectors impacting these systems could result in additive neuropsychological effects [7, 8, 268, 269]. There are indications that these amphetamine-mediated effects on immune function may be exacerbated in people with HIV. For instance, there are indications that methamphetamine use may enhance the migration of HIV infected leukocytes across the blood brain barrier, thereby facilitating infection into the central nervous system [262]. Additionally, Marcondes *et al.* (2010) [270] examined the effects of methamphetamine upon immune function and viral replication in macaques which were infected with simian immunodeficiency virus. Compared to a seropositive control group, those who were administered methamphetamine had higher viral loads in the brain, and immune cells in the brain showed subtle dysfunction. Similar to this finding, Shoptaw *et al.* (2012) [88] showed that methamphetamine use increases immunocompromise in people infected with HIV.

With respect to effects of comorbid HIV infection and methamphetamine dependence on brain function, a number of studies have examined the interaction of HIV and methamphetamine use on cerebral structures and metabolites in the brain. Chang *et al.* (2005) [242] studied neurotransmitter metabolites among individuals who varied in their history of methamphetamine use and serostatus. Those who were HIV seropositive and were methamphetamine dependent showed significantly lower levels of metabolites, specifically N-acetylaspartate (NAA), particularly in the basal ganglia. This implies that HIV seropositive individuals who abuse methamphetamine will display greatest dysfunction involving the striatum. Taylor *et al.* (2007) [271] conducted a similar study. No significant interaction of methamphetamine and HIV status were observed. However, among those individuals who were HIV seropositive and methamphetamine dependent, lower levels of NAA in the frontal white matter. This relationship was not observed in other participant groups. NAA is a putative marker of neuronal integrity and can be related to neuropsychological functioning. Thus, there is modest evidence of exacerbated cerebral dysfunction in amphetamine using seropositive individuals.

Regarding cognitive performance, Weber *et al.* (2012) [272] evaluated neuropsychological performance among a group of patients who had become seropositive between 25 and 87 days before participating in the study. Compared to a control group, the seropositive group was significantly more likely to display cognitive impairment, especially involving new-learning and speed of information processing. Notably, equivalent rates of

methamphetamine misuse occurred in the HIV seropositive and control group, and the risk of manifesting impairment was increased among those seropositive individuals who had a history of abusing methamphetamine. Thus, serostatus and methamphetamine dependence acted in an additive fashion to exacerbate cognitive impairment. Rippeth *et al.* (2004) [272] examined the coincident effects of methamphetamine misuse and HIV status on neuropsychological function. Among the patients who were HIV seropositive and methamphetamine dependent, nearly 60% were impaired, whereas only 20% of the control group (HIV seronegative and non-methamphetamine dependent) were impaired. Among individuals who were HIV seropositive/non-methamphetamine dependent and those who were HIV seronegative/ methamphetamine dependent, approximately 40% were impaired. As such, there seems to be an interactive influence of HIV seropositivity and methamphetamine use on neuropsychological function. Likewise, Cherner *et al.* (2005) [274] examined the effects of HIV and methamphetamine dependence. These risk factors both yielded significant main effects upon cognitive impairment, but their combined effects exacerbated the severity of impairment. Similarly, Carey *et al.* (2006) [275] examined the effects of methamphetamine dependence and CD4 suppression on neuropsychological function. The combined effects of drug use and immunocompromise exacerbated impairment over the independent effects of either variable alone. Thus, the combined effects of methamphetamine dependence and HIV have greater neurobehavioral consequences than methamphetamine dependence or HIV infection alone.

With respect to neuroimaging, Jernigan *et al.* (2005) [11] obtained structural MRIs of individuals who were varied according to HIV status and presence of methamphetamine dependence. The methamphetamine dependent patients had been abstinent for an average of three months. Jernigan *et al.* found that the HIV seropositive group, regardless of methamphetamine dependence, displayed reduced volumes in the caudate, thalamus, hippocampus, and cerebral cortex, especially in the frontal and temporal lobes. Methamphetamine dependence, regardless of HIV status correlated with increased volumes in the caudate, nucleus accumbens, and lenticular nucleus as well as the parietal cortex. No interaction of HIV status and methamphetamine dependence was observed, but Jernigan *et al.* concluded that an additive effect was manifest. In those HIV seropositive individuals who were methamphetamine dependent, their caudate nuclei were of normal volume compared to the HIV and methamphetamine only groups. Ances *et al.* (2011) [276] conducted a similar study that examined overall cerebral blood flow during resting baseline and during a working memory task. No interaction of HIV status and methamphetamine dependence were observed, but significant main effects of HIV status and methamphetamine dependence occurred, leading Ances *et al.* (2011) to conclude that an additive effect of the variables occurs rather than an interaction.

Other Drugs

Other studies have examined the effects of polysubstance misuse on cognitive functioning. These studies have generally included patients who have abused various substances. They have typically demonstrated that seropositive individuals who have histories of substance misuse display impaired neuropsychological function compared to their seronegative counterparts who have abused drugs. In a series of studies [277–279], drug abusing

seropositive individuals have manifested impaired performance on measures reflecting executive function and working memory compared to drug abusers without HIV. Grassi *et al.* (1995) [280] likewise found that the combined effects of substance misuse and HIV seropositivity result in significantly lower performance. In this sample, there were no differences between the seronegative groups with respect to drug use history. Instead, cognitive function was affected by the chronic and current use of illicit substances, with the subsequent decline in cognitive function among the HIV-seropositive group being attributed to a chronic use of illicit substances rather than HIV infection [280].

In contrast to these effects, Mason *et al.* (1998) studied forty-two African American women with a history of poly-drug use [281]. They were classified according to disease severity (seronegative, asymptomatic seropositive, symptomatic seropositive, and AIDS). Although the symptomatic patients showed deficits involving psychomotor speed and verbal learning, there were no effects of drug use. More recently, Byrd *et al.* (2011) [282] reported similar results.

METHODOLOGICAL PITFALLS IN THE NEUROPSYCHOLOGICAL ASSESSMENT OF HIV AND SUBSTANCE USE

Many of the methodological and measurement issues that plague the accurate assessment of NP functioning in persons with HIV and concurrent substance use are not practicably addressable and require circumspection when interpreting findings. A key issue is in the assessment of substance use and abuse. The accurate assessment of drug and alcohol use is complicated by poor recall, intentional misreporting, and inconsistent patterns of drug/alcohol use (frequency, type, quantity) over time. Polysubstance use is often the norm, and over the course of many months and years, multiple drugs may be used simultaneously, or one drug may supplant another as the drug of choice. Periods of abstinence can punctuate periods of heavy use and “current” labels of drug use may not capture the myriad histories which preceded subjects’ current status.

The use of diagnostic categories (*e.g.*, abuse/dependence) to capture drug and alcohol use can result in slightly greater reliability as certain uniform requirements (*e.g.*, minimum period of use, impairments in social/occupational functioning, tolerance, withdrawal) imply a minimum level of use. However, categorizing participants solely on the basis of diagnosis can result in missing persons who recently began using heavily or who are recently abstinent. In addition, diagnostic interviews are also vulnerable to dissimulation and poor recall. More objective indices such as toxicology, while providing accurate indices of recent drug use (typically 72 hours), cannot provide useful data on past use. Because of these issues, interpretation of extant literature on the NP sequelae of HIV and substance use must remain aware of the operationalization of substance use that is employed when conclusions are drawn.

DISCUSSION

A review of the research indicates a plethora of studies documenting neuropsychological complications that are associated both with HIV disease and various substances of abuse.

However, the research focusing on the interaction or exacerbating effects of various substances of abuse on neuropsychological impairment among persons infected with HIV is much more limited. Of this research, the vast majority of the studies focused on the effects of methamphetamine use and alcohol use and HIV disease. Research examining the possible interaction effects of other substances was scarce. Among the available research, the study findings revealed mixed results with respect to HIV disease and substance-abuse interactions. While some studies show an effect of substance use on neuropsychological complications among HIV-infected persons, others do not. These discrepancies derive from several sources including type of drug used, measurement of substance use (use *vs* abuse), polysubstance use, pre *vs* post ARV, types of NP measures employed, and sociodemographic variables, such as socioeconomic status, age, and gender, which may play a role in cognitive functioning [117]. However, these findings, along with the neurological implications associated with HIV disease and substance abuse, suggest a number of future directions. While the separate effects of HIV disease and substance use on brain structure and functioning have been well-documented, more research is needed to address the effect of substance use on the severity and progression of HIV-associated psychoneurological complications. Currently, there is limited information to indicate whether a history of substance use either accounts for, or interacts with, HIV serostatus to facilitate the progression of neuropsychological impairment [4]. However, with respect to addiction treatment for HIV-positive drug users, there is growing evidence suggesting that, due to a variety of factors, a substantial proportion of HIV-positive drug users enter drug treatment with some degree of cognitive impairments in domains that could impede their ability to learn, retain, and execute HIV prevention behaviors [283].

Expanding inquiry in this area appears critical, considering the implications that comorbid substance abuse and HIV infection may have for treatment management, cognitive functioning, and ultimate morbidity. Evidence indicates that neuropsychological impairment and substance abuse are associated with an increased difficulty in adhering to medication for HIV-infected persons; as such, there is a critical need for expanded research in this area [118].

There seems to be a concerted need for developing a more comprehensive approach to the study of different substances of abuse, not only by type, but also by the frequency of their abuse among HIV-infected individuals. The importance of a factor in causing a disease or contributing to its progression is a function of both the frequency of the factor and the magnitude of its effect [119]. Age, gender, race, ethnicity, and a variety of geo-population differences also appear to be pivotal factors to examine in comorbidity studies.

Co-factors that frequently accompany drug use include lower socio-economic status, nutritional abnormalities, lower education levels, histories of head injury or other neurological compromises, and relatively higher rates of psychiatric disorder, all of which can complicate interpretation of the effects of drug use [120]. Longitudinal studies may allow a more robust evaluation of the neuropsychological effects of substance use and HIV disease. Such studies may help to elucidate whether aggressive substance abuse treatment can reduce the neuropsychological complications associated with HIV disease, which may

facilitate a “cognitive safety net”, both for individuals with a history of substance abuse and for current substance abusers who are living with HIV [283].

Finally, study design might profit by considering whether substance disorders are idiopathic or primary in nature and predate HIV infection, *vs* being syndromic. Such designs may discriminate between shared and independent contributors to comorbid disease progression. Ultimately, the primary goal of comorbidity research is to bring improved treatments (with a corresponding improved quality of life) to individuals suffering from multiple medical problems. The identification of the genetic, molecular, and cellular mechanisms that contribute to multiple medical illnesses appears to be a vital step in developing therapeutic interventions. The rational design of novel adjunctive therapies demonstrating both immunomodulatory and neuroprotective actions appear to be warranted. In pursuing this goal, interdisciplinary research directed to viral and emotional stress response systems and that utilize innovative approaches and study designs will be critical to advancing the field and overcoming the inherent limitations associated with patient and disease heterogeneity [4].

IMPLICATIONS FOR BEHAVIORAL AND PREVENTION SCIENCES

The implications of cognitive functioning and HIV-preventive behavior are of particular interest. Table 1 summarizes the association between cognitive functioning and HIV-preventive behavior among persons living with HIV (PLWH) [121].

There is a noted association between cognitive functioning and treatment outcome of which behavioral scientists and preventionists need to be aware when developing treatment interventions for drug-using PLWH. Traditional cognitive-behavioral treatment for substance users focus on the acquisition of skills needed to prevent relapse, including identifying high risk situations; understanding the antecedents and consequences of events; learning alternative coping strategies; correcting maladaptive thinking patterns; improving decision-making and problem-solving abilities; and planning for and coping with “slips.” [121, 122]. Learning, retaining, and generalizing these skills to daily life requires a wide array of cognitive capabilities that may be compromised in chronic drug users infected with HIV. To address the potential for cognitive dysfunction in HIV+ substance abusers, a number of cognitive remediation strategies have been suggested [284]. The use of a multimodal presentation of material stimulates interests and facilitates learning. The use of verbal, visual, and experiential modalities can be beneficial to achieving learning goals. Also, the frequent review of material facilitates learning and retention. In addition, fatigue, distractibility, and poor concentration impede learning and may be particularly problematic for cognitively impaired clients when they are attempting to learn new skills. Providing breaks during treatment sessions, using a multimodal presentation of materials, and holding groups in a quiet room with no outside distractions can help improve concentration. Providing consistency is a crucial component of a successful treatment program for cognitively impaired individuals. Meeting at the same time and place each week and following the same structured format can be beneficial in achieving consistency. The assessment of knowledge and skill acquisition provides cognitively-impaired individuals with the opportunity to evaluate the effectiveness of various learning strategies and to

receive feedback. Assessment also provides the opportunity for additional review of important material. Treatment groups can end with a post-session quiz to assess the acquisition of basic concepts covered in the groups, and counselors can provide immediate feedback to group members on their performance on the quiz. In addition, a comprehensive post-program quiz can be administered to assess longer-term skill acquisition. Also, knowledge and skills acquired in treatment need to generalize to the cognitively impaired individual's daily life. Counselors can provide real-world examples when group material is presented experientially, and clients can be encouraged to complete at-home exercises. In addition, counselors can seek the cooperation of clients' other health care providers and family and friends in order to provide an integrated team approach to improving clients' functioning in daily life.

A memory book system is a practical approach to helping individuals compensate for memory deficits. A client workshop can be based on a memory book system; it is designed not only to improve memory for group material, but also for organizing and remembering activities required for living a healthy lifestyle. Another effective strategy for dealing with cognitively impaired HIV+ drug users is that of learning by doing. Games provide a non-threatening context in which cognitively impaired individuals can practice skills. Immediate feedback during game playing can reinforce appropriate behavior and increase self-esteem and self-confidence. Lastly, management of stress is imperative for improving cognitive functioning. Stress can impair concentration, increase cognitive dysfunction, and potentially lead to relapse.

Group treatment is a preferred treatment modality when working with neuropsychologically impaired individuals because it permits generalizable pro-social behaviors to be practiced and strengthened. Group treatments can also reduce the isolation often experienced by individuals with HIV and can provide a source of interpersonal support from individuals with similar problems and life circumstances. Group treatment is cost-effective and readily incorporated into community-based drug treatment programs. In addition, participation of the client's significant other or a close friend/family member who is supportive of the client's recovery is recommended. Because rehabilitated peers can provide appropriate modeling of desired behaviors, it is also recommended that counseling groups include "peer guides" whenever possible. Peer guides should be HIV-positive individuals who are in recovery from addiction and have been abstinent from all illicit substances for at least 60 days [131]. They should be able and willing to demonstrate their knowledge and support of harm reduction strategies and have an interest in sharing this knowledge with others. Peer guides can be invited to every group meeting to deliver announcements (e.g., concerning NA meetings and community activities) and can provide assistance to the counselors by initiating games and experimental segments.

There are common clinical problems that may exist for members of this population, including continued high risk behavior, medical deterioration, psychiatric deterioration, and changes in cognitive functioning. Because changes in cognitive functioning (improvement or decline) during treatment is possible (e.g., due to continued drug use, abstinence, or HIV progression), clients should be monitored closely and treatment strategies modified, as necessary, to match clients' needs and cognitive abilities.

More research is needed to address the effect of substance use on the severity and progression of HIV-associated psychoneurological complications [283]. Expanding research in this area is important, considering the implications that comorbid substance use and HIV infection may have for treatment management, cognitive functioning and ultimate morbidity. There also appears to be a concerted need for the development of a comprehensive approach that could be used to study different substances of use, not only by type, but also by frequency of their use among HIV-positive individuals. The study should also include internal controls so that a maximum number of variables can be controlled. This would require the development of a variety of neuropsychological tools that could address problems associated with a given study population. In addition, future research efforts might be best focused on poly-drug abuse because this is becoming increasingly common; there is, at present, very little information on combined abuse. This may serve as a confounder that can complicate attribution of adverse drug effects to any single substance [284]. Longitudinal studies may allow a more powerful assessment of the neuropsychological effects of substance use and HIV disease. Furthermore, when the treatment team is faced with treatment issues such as poor compliance or missed appointments, the client's cognitive status should be considered carefully and treatment plans made accordingly.

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Table 1

Association between Cognitive Functioning and HIV-Preventive Behavior.

<u>Capacities required for HIV preventive behavior:</u>	
Acquire, retain, and use HIV preventive information and behavioral skills	
Motivation to engage in HIV preventive behavior	
Understand the antecedents and consequences of behavior	
Identify high-risk situations	
Self-regulation of psychological and physiological states	
Problem solving and decision making	
Negotiation with partners	
Know how to reduce harm in the event of a “slip”	
<u>Cognitive Deficits that may impede HIV preventive behavior:</u>	
Memory Deficits:	
Difficulty learning, retaining, and retrieving new information and skills	
Difficulty recalling details of high-risk situations	
Difficulty remembering treatment recommendations	
<u>Attention/Concentration Deficits:</u>	
Distractibility during information and skill acquisition	
Poor listening and communication skills	
Decreased ability to shift attention	
Attention limited to possibly tangential aspects of the situation	
<u>Deficits in Executive Functions:</u>	
Difficulty initiating action	
Difficulty self-correcting, self-regulating	
<u>Concreteness and Mental Inflexibility:</u>	
Decreased ability to appropriately generalize across experiences	
Decreased empathy	
Difficulty identifying alternative solutions to problems	
<u>Deficits in Insight, Reasoning, and Judgment:</u>	
Poor judgment in high risk situations	
Decreased ability to predict consequences of actions	
Decreased decision making ability	
Decreased ability for sequential concept formation and “logical” reasoning	