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Marijuana use, heavy drinking, and cognitive dysfunction in people with Human Immunodeficiency Virus-infection

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Thesis

MARIJUANA USE, HEAVY DRINKING, AND COGNITIVE DYSFUNCTION IN PEOPLE WITH HUMAN IMMUNODEFICIENCY VIRUS -INFECTION

by

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B.S., Loyola University Chicago, 2012

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MARIJUANA USE, HEAVY DRINKING, AND COGNITIVE DYSFUNCTION IN PEOPLE WITH HUMAN IMMUNODEFICIENCY VIRUS -INFECTION

SARA LORKIEWICZ

ABSTRACT

Aims: Substance use and dependence is very common among people living with HIV-infection. Since substances like alcohol and marijuana as well as the HIV virus itself are believed to have negative effects on cognition and the brain, our aim was to test the hypothesis that current and lifetime marijuana and heavy alcohol use are associated with cognitive dysfunction in people with HIV-infection.

Methods: Boston ARCH cohort participants consisted of 215 HIV-infected adults with substance dependence or current or past injection drug use. In cross-sectional, regression analyses we tested the association between current marijuana use (number of days marijuana was used in the past 30 days), current heavy alcohol use (number of heavy drinking days in the past 30 days defined as ≥4 drinks for women and ≥ 5 for men in 24 hours), lifetime marijuana use (number of years marijuana was used ≥ 3 times per week), lifetime alcohol use (total Kg), duration of heavy alcohol use (# of years alcohol was use > 84 grams or > 6 drinks per day), and three measures of cognitive dysfunction: i) memory and ii) attention domains of the Montreal Cognitive Assessment (MoCA), and iii) 4-item cognitive function scale (CF4) from the Medical Outcomes Study HIV Health Survey (MOS-HIV, range 0-100). Eight multivariable models were fit comparing: 1. current marijuana use by each cognitive outcome, 2. current heavy alcohol use by each

cognitive outcome, 3. lifetime marijuana use by each cognitive outcome, 4. lifetime alcohol use (Kg) by each cognitive outcome, 5. lifetime marijuana use, duration of heavy alcohol use, current heavy alcohol use, and current marijuana use by each cognitive outcome, 6. lifetime marijuana use, lifetime alcohol use (Kg), current heavy alcohol use, and current marijuana use by each cognitive outcome, 7. the interaction between current marijuana and heavy alcohol use by each cognitive outcome, and 8. the interaction between lifetime marijuana and lifetime alcohol use (Kg) by each cognitive outcome. Analyses were adjusted for demographics, primary language, comorbidities, depressive symptoms, anxiety, antiretroviral therapy, HIV-viral load, CD4 count, lifetime cocaine use, cocaine use in the past 30 days, illicit opioid use in the past 30 days, and any prescribed opioids.

Results: Participant characteristics were as follows: Mean age 49 yrs., 35% female, 20% white, 66% ≥ 12 years of education, 86% English as primary language, 82% unemployed, mean Charlson comorbidity score 2.9, 28% scored ≥ 3 on the PHQ-2 indicating depressive symptoms, 44% scored ≥ 8 on OASIS indicating symptoms of anxiety, 58% had Hepatitis C infection at some point in their life, 86% were on HAART, 72% had an HIV-viral load < 200 copies/mL, CD4 cell count/mm^3 was 10% <200 and 33% 200 - <500, mean HIV duration was 16 years, lifetime cocaine use was 9 years, 30% used cocaine in the past 30 days, 25% used illicit opioids in the past 30 days, and 61% were prescribed opioids. Current marijuana use was significantly associated with a lower MOS-HIV CF4 score in three of the fully adjusted models (1,5, and 6) listed previously

with a decrease in 0.30 points for every day of use, but neither MoCA score. Current heavy alcohol use was also associated with a higher MOS-HIV CF4 score in model 5, increasing 0.36 points for every day of use. This finding did not confirm our hypothesis and in fact was opposite our projections. Lifetime marijuana use and lifetime alcohol use were not associated with any measure of cognitive dysfunction, and there was no interaction between lifetime marijuana use and lifetime alcohol use with cognitive dysfunction, and no interaction between current marijuana use and current alcohol use with cognitive dysfunction.

Conclusion: Current marijuana use may be associated with cognitive dysfunction. We also detected an unexpected association between current heavy alcohol use and better cognitive function, but it is not biologically plausible. However, we did not detect associations between lifetime alcohol or marijuana use and cognitive dysfunction among people with substance dependence and HIV-infection. Further research, particularly on long-term exposure to substances, should include subtler measures of cognitive dysfunction and consider whether or not cognitive dysfunction that may be the consequence of marijuana and alcohol use is detectable among those who have many other factors effecting cognition. These results suggest that marijuana use should not be considered benign for individuals with substance dependence and HIV-infection.

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LIST OF ABBREVIATIONS

ANI……...Asymptomatic Neurocognitive Impairment

ARD……Alcohol Related Dementia

ASI……..…..Addiction Severity Index

ATP ……..Adenosine Triphosphate

BBB……Blood Brain Barrier

CBF……..Cerebral Blood Flow

CNS…….Central Nervous System

CSF……Cerebrospinal Fluid

DSM-5 …….Diagnostic and Statistical Manual of Mental Disorders

DTI ……..…….Diffusion Tensor Imaging

ELISA……..Enzyme Linked Immunosorbent Assay

HAART……...Highly Active Anti-Retroviral Therapy

HANDs…….HIV-Associated Neurocognitive Disorders

HCV……...Hepatitis C Virus

HIV……Human Immunodeficiency Virus

HIV-D……..……...HIV-related dementia

MCP-1……...…….Monocyte Chemoattractant Protein-1

MND……..Minor Neurocognitive Deficit

MoCA…….Montreal Cognitive Assessment

MOS-HIV CF4…….……Medical Outcomes Study HIV Health Survey Cognitive Function (4 Questions)

MRI ……...Magnetic Resonance Imaging

MRS ……..Magnetic Resonance Spectroscopy

NAA……..N-Acetyl Aspartate

NMDA……N-Methyl-D-Aspartate

OASIS ……Overall Anxiety Severity and Impairment Scale

PCr ……..……Phosphocreatine

PDE ……Phosphodiesterase

PHQ-2……...Patient Health Questionnaire 2

rCBF……Regional Cerebral Blood Flow

TLFB……..Timeline Follow Back

WKS……Wernicke-Korsakoff Syndrome

Δ^{9}-THC……..……Delta-9-Tetrahydrocannabinol

≥……...……Greater than or equal to

>…….Greater than

<……...……Less Than

INTRODUCTION

The prevalence of people living with the human immunodeficiency virus (HIV) is estimated to be around 1.2 million people in the United States and 35 million people worldwide[91,92]. With the advent of highly active anti-retroviral therapy (HAART), individuals with HIV are living longer, healthier lives than they have in the past. Despite overall improvements in HIV viral load, CD4 cell counts, symptomology, and general suppression of the virus in the periphery in those treated with HAART, cognitive effects of the virus can still be observed, in part due to continued infection of the central nervous system (CNS)[2,10]. At the same time, use of and dependence on substances such as alcohol and marijuana is particularly high in HIV-infected people despite documented effects of both on cognition[19]. Since the HIV virus, alcohol, and marijuana all have potential deleterious effects on the brain and cognition, it is important to determine whether there is a negative, synergistic effect of all three. Cognitive dysfunction lowers an individual's quality of life and can hinder one's ability to maintain the complicated medication regimens required to suppress HIV-infection. This can ultimately increase the risk for worse disease outcomes and higher rates of mortality.

Effects of the HIV Virus on the Brain and Cognition

The brain is believed to serve as a reservoir for the HIV virus, entering the central nervous system (CNS) via a "Trojan horse" mechanism early on in infection[4,5,7]. The virus is able to cross the blood brain barrier (BBB) undetected in immature monocytes

and lymphocytes, which then become activated in the brain with the ability to spread the virus and induce neuronal injury[4,5,7]. HIV can infect microglia and astrocytes in the CNS.[7] Microglia are the main reservoirs for the virus, while astrocytes are infected to a lesser extent.[7] Neurons have not been found to harbor the virus[7]. Neuronal damage due to HIV-infection can be caused directly by the virus or indirectly through activation of the innate immune system. Infected lymphocytes and macrophages release neurotoxic and pro-inflammatory chemicals causing astrocytosis, neuronal injury, and inflammation[4,5,7]. Astrocytosis increases the permeability of the BBB, which may cause further propagation of infection into the brain[4,5,7]. Neuronal injury is worsened by the release of glutamate and oxidative stress which is induced by neurotoxic chemokines and inflammation[4,5,7]. The HIV viral envelope protein, gp120, is also known to inhibit neuronal growth and induce apoptosis of neurons[13]. In both direct and indirect brain injury, damage to the dendrites and synapses of neurons appears to be more detrimental to cognitive function than the loss of neurons[11]. It is thought that complement, a main player of the innate immune system, plays a role in the indirect damage of neural tissue[8]. Neurons are known to be particularly susceptible to the membrane attack complex (MAC), or end result of the complement cascade, which induces apoptosis in cells[8]. While levels of complement in the CNS are normally very low, they are found to be elevated in individuals with HIV[8]. Complement regulatory factors are also shown to be downregulated in CNS tissue of those with HIV, which would cause an increased susceptibility to MAC[8].

The major site of HIV-infection in the brain appears to be the basal ganglia, as it normally contains the highest concentration of the virus[1,9-11]. However, HIV also has

effects on other subcortical gray matter structures, deep white matter tracts, and the frontal cortices[1,9,11,20]. There appears to be more gray than white matter involvement[20]. Pathophysiological signs of HIV-infection in the brain include myelin loss, giant, multinucleated cells (infected perivascular macrophages), gliosis, and microglial nodules[4,9,11]. Cerebral atrophy and a decreased resting cerebral blood flow (CBF) are the most salient alterations of HIV-infection to brain morphology and metabolism, both of which appear to worsen with disease progression[7,10]. Cardenas et al found that HIV-infected people on HAART show a significantly greater loss of global white matter than those not infected with the virus and that a worse disease progression (lower CD4 cell counts and increased viral load) correlates with greater tissue loss[10]. There is also thought to be a decrease in N-acetyl aspartate (NAA), a marker of mature neurons and their processes, and an increase in choline and myoinositol, markers of cell membrane breakdown and inflammation respectively, in the brains of those with HIV-infection[7].

HIV-infection of the brain typically presents with a triad of behavioral, motor, and cognitive symptoms[3,5,7,9,11]. Eventually, behavior becomes apathetic and there is a decrease in spontaneity[9]. A loss of fine motor control is seen accompanied with postural instability and bradykinesia that resembles Parkinson's disease without the resting tremor[9]. HIV affects a number of cognitive domains that are primarily associated with subcortical damage: learning and memory, attention, executive function, and language[1,21].

HIV-associated neurocognitive disorders (HANDs) are becoming the most common form of young-age dementia worldwide and are present in around 30% of individuals living with the virus[1,7]. HAND is a spectrum of organic neurocognitive

disorders induced by the HIV virus itself (excluding opportunistic infections of the brain, active drug use, and psychiatric disorders) ranging from mild impairment of cognition and daily functioning to debilitating dementia[1,3-5]. Generally, five major areas of cognitive function must be assessed when diagnosing HAND including: executive function, learning and memory, complex attention, language, and perceptual-motor function[1,21]. Since the onset of HAART, the most debilitating form of HAND, HIV-associated dementia (HIV-D), has decreased in prevalence, but more mild forms still persist, with 27% of HIV-infected individuals with suppressed viral loads having cognitive complaints concerning memory, mental slowing, and attention[1,7].

HAND is thus a general term encompassing asymptomatic neurocognitive impairments (ANIs), mild neurocognitive deficits (MNDs) and HIV-D[1,3-5]. ANIs include cognitive deficits in at least two of the cognitive domains stated previously with no interference in everyday functioning[1,3]. It is believed that 21-30% of asymptomatic HIV-infected individuals are affected by ANIs as well as up to 50% of individuals diagnosed with HAND[1]. ANI can be considered a pre-symptomatic form of HAND[7]. MNDs include cognitive deficits in two domains of cognitive function with mild interference in daily functioning and a prevalence of 5-20% of HIV-infected people and 30-50% of individuals diagnosed with HAND[1]. HIV-D is defined as having deficits in two cognitive domains as well as marked interference in daily functioning with a prevalence of 1-2% of people living with HIV[1]. In general, HAND appears to be more prevalent in symptomatic individuals, regardless of whether they realize that cognitive impairments exist[1]. Likewise, any severity of HAND appears to be predictive of abnormal brain morphology,

a decrease in daily functioning, and early mortality[1,6]. Heaton et al found that those with neuropsychological impairments in executive function, attention, and working memory were more likely to fail laboratory simulated tests representative of medication management, financial management, and work assessment, revealing a potential decline in everyday functioning[6].

HIV disease severity, age, vascular risk, cognitive reserve, Hepatitis C infection, and substance use disorders are all shown to worsen the progression of HAND[13,17]. Sacktor et al conducted a study looking at the additive effects of age and HAND on cognition in a cohort of older individuals. They found that older individuals with HIV-D tested worse in areas of executive function than their younger counterparts and that older individuals with MNDs tested worse in areas of executive function, memory, and motor speed than younger individuals[14]. Foley et al extended the work of Sacktor et al, finding that cardiovascular disease, or "vascular risk," is a predictor of cognitive dysfunction in the domain of processing speed and also interacts in a negative, additive way with age in the domain of verbal fluency[15]. In a study looking at whether high cognitive reserve may mask signs of neurodegeneration, Thames et al found that higher cognitive reserve was associated with greater atrophy in the basal ganglia despite similar levels of neurocognitive functioning across participants[16]. This means that individuals with a higher cognitive reserve won't present with a form of HAND until they have greater brain damage.

Hepatitis C infection has become an important comorbidity to HIV-infection. The hepatitis C virus (HCV) has been shown to create cognitive impairment in its own right

in a similar subcortical fashion to HIV[22]. HCV is thought to cross the BBB after infection and individuals that are HCV positive were shown to have HCV antigens and antibodies present in the central nervous system, revealing that the brain is a site for viral replication of HCV as well[18,19]. It is plausible, then, that HCV augments the cognitive dysfunction and neuronal damage already induced by HIV. Letendre et al showed that 33% of individuals co-infected with HCV and HIV progressed to HIV-D and 62% showed signs of MND, which is a higher prevalence than that found in those infected with HIV alone[18].

Effects of Marijuana Use, Alcohol Use, and Their Interaction with HIV on the Brain and Cognition

Substance use and substance use disorders are extremely common in HIV-infected individuals, with 40 – 74% of HIV-infected people reporting past or current substance use[17]. Half of people living with HIV/AIDS report the use of recreational marijuana and around one third report therapeutic marijuana use[23]. Likewise, individuals who use recreational marijuana have also been found more likely to drink alcohol[23]. Traditionally, alcohol use among HIV-infected people has been very high. Alcohol use and drinking at hazardous levels is around twice the prevalence in HIV-infected people than in that of the general population, with 37% of HIV-infected individuals drinking alcohol, and one third of those who drink doing so at hazardous levels[24,25]. It is well documented that alcohol and marijuana effect cognitive function, and it is also believed that these substances can have a negative, additive effects on the brain when combined with HIV-infection.

Effects of Marijuana Use on the Brian and Cognition

Marijuana is arguably one of the most widely used illicit drugs in the United States and is thought by some laypersons to be a benign, recreational substance. Thus, it is important to understand what types of effects this drug may have on cognition and the brain. The major psychoactive ingredient in marijuana is a cannabinoid by the name of delta-9-tetrahydrocannabinol (Δ^{9}-THC)[26]. Δ^{9}-THC can cross the BBB where it binds to its primary CNS receptor, CB1, one of the most abundant receptors in the brain[26]. CB1 receptors are found in highest concentration in the basal ganglia, cerebellum, and hippocampus[26,27]. In the hippocampus, marijuana can inhibit long-term potentiation, a process involved in memory formation[26]. Likewise, it can induce cell death in specific cells in the hippocampus during neuronal development[26]. CB1 receptors are also known to co-exist with dopamine receptors in the basal ganglia, and may inhibit dopamine action and thus have a potential effect on motor and psychomotor control[26]. Δ^{9}-THC is stored in adipose tissue and has a long half-life because it can be slowly released into the system from these fat stores[26.27]. The psychoactive effects of marijuana begin after about 30 minutes post ingestion and last for up to four hours[27].

According to the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; *DSM–5*; American Psychiatric Association, 2013), marijuana intoxication is shown to induce behavioral and psychological changes including impaired motor coordination, euphoria, anxiety, sensation of slowed time, impaired judgment, and social withdrawal. Individuals exposed to Δ^{9}-THC report subjective increases in: relaxation, deep thought, sensory perception, laughter, dizziness, feeling withdrawn, hunger, paranoia, anxiety,

drowsiness, and depression[27]. Marijuana is thought to interfere with cognitive function in a temporal fashion, from the time of acute intoxication to what may be long after cessation of use. Thus, acute effects, residual effects, withdrawal effects, and long-term, persistent CNS effects of Δ^{9}-THC have been observed. Acute, residual, and long-term cognitive effects also appear to be dependent on whether or not marijuana is being used chronically and what concentration of Δ^{9}-THC the individual is being exposed to. Users who have used marijuana the longest are thought to perform worse on cognitive tasks, and as the amount or potency of Δ^{9}-THC increases during acute exposure, neurocognitive performance is also thought to decrease[33,35,48,49].

Acute Effects of Marijuana Use on the Brain and Cognition

Acute effects of marijuana use are those occurring from the time of intoxication up to four hours afterward[27]. Acute marijuana use has been shown to alter brain metabolism, presumably leaving the brain's architecture intact. Changes in cerebral blood flow (CBF) have been observed, most notably increases in the frontal, limbic, paralimbic, and cerebellar areas of the brain[27]. Correlations have been found between these regional CBF (rCBF) changes and the subjective feelings of intoxication reported by users of marijuana[27]. For instance, increases in rCBF in the orbital/mesial frontal lobes and paralimbic areas are thought to be correlated with the mood effects of marijuana while decreases in rCBF in the temporal auditory and attention areas of the brain are thought to be associated with the perceptual effects of marijuana[29]. O'Leary et al reported an increase in rCBF in the cerebellum after acute marijuana intoxication. Since the

cerebellum plays a role in timing of actions and perceived time, it is believed that this change in brain metabolism can be related to marijuana altering one's sense of time.

There are mixed opinions on precisely which cognitive domains are affected by acute marijuana use and intoxication. The most commonly reported cognitive impairment appears to be in memory, particularly in the area of recall, but some studies have reported deficits in attention and executive function[27-29,33]. Recall has been shown to decrease when information is presented to an individual while intoxicated, but there is no deficit in recall of information presented pre or post-intoxication[27,31,35]. Retrieval cues can help recall the information learned under the influence, so it appears that Δ^{9}-THC disrupts access and organization of memories, or the retrieval of memories and not necessarily encoding[31].

In an evidence review looking at the acute and residual effects of marijuana on cognition, Crean et al found that attention and executive functions such as information processing, inhibition and impulse control, and working memory were impaired due to acute use, but subsided after the initial period of intoxication[26]. Ramaekers et al extended these findings, reporting that high-potency marijuana caused deficits in impulse control during acute marijuana use[33]. Similarly, Lundqvist et al reported deficits in attention with relation to selection of relevant stimuli and filtering out irrelevant stimuli as well as a deficits in memory[29]. On the other hand, Kelleher et al found no effect of acute marijuana use on information processing[32]. Hart et al also did not find any deficits of accuracy on neurocognitive tests regarding executive function, but did find that acute Δ^{9}-THC

intoxication increased the time taken to complete these tasks and that premature responses were increased[34]. This could indicate deficits in inhibitory control.

Residual Effects of Marijuana Use on Cognitive Function

Residual effects of marijuana include any effects on cognition that persist after intoxication (over four hours post-intoxication) and remain while Δ^{9}-THC is leaving the system[39]. These effects are caused by any active Δ^{9}-THC metabolites that remain in the CNS post acute marijuana intoxication[39]. While Δ^{9}-THC has a half-life of 2-60 hours, its effects can still persist well after acute intoxication due to the redistribution of Δ^{9}-THC from the plasma into the tissues[39]. It accumulates in the fat of chronic users and can build up in the system. Thus, residual effects can range from 12-24 hours post intoxication to days or weeks later depending on how often an individual smokes marijuana[39].

There is still much debate concerning the residual effects of marijuana on cognition[28]. In a meta-analysis of the non-acute, cognitive effects of marijuana use, Schreiner et al found a negative impact of marijuana in the domains of executive function, attention, language, perceptual-motor, and learning and memory in individuals abstinent for less than 25 days[40]. In another meta-analysis looking at the residual effects of marijuana, Grant et al found that there were small but significant residual effects of marijuana on learning and forgetting with evidence of an increased recency effect when learning new material[41]. They also found a small negative global effect in chronic marijuana users, all of which were abstinent from marijuana for at least 24 hours[41]. Pope et al found evidence of impaired memory in heavy marijuana users for up to 7 days post-

cessation in two consecutive studies, and Battisti et al furthered these findings showing that heavy marijuana users show deficits specifically in memory recall after 12 hours of cessation[42-44]. Battisti et al also showed that chronic marijuana users show a decrease in accuracy of the Stroop task 12 hours post-cessation of marijuana, which could reveal deficits in executive function such as inhibition control[45]. Solowij et al reported that long-term, heavy marijuana users showed deficits on memory and attention tasks in the areas of learning, retrieval, and retention[48]. These deficits were found to worsen with years of use and persist despite marijuana cessation for at least 12 hours prior to participating in the study[48]. Chronic marijuana users have also been shown to make more errors and need more time when completing neurocognitive assessments upon cessation of marijuana use[48]. It is thought that these compensation strategies could be masking an even worse cognitive dysfunction. Alternatively, Chang et al and Kanayama et al found no significant difference on any neuropsychological tests in chronic marijuana users who were abstinent from marijuana for at least 4 hours prior to administration of the tests[47,52].

Marijuana Withdrawal

In addition to the inconsistent findings regarding the residual effects of marijuana use, it is oftentimes unclear whether the residual effects mentioned previously are due to withdrawal symptoms or the actual effects of Δ^9-THC metabolites remaining in the system since the period of marijuana abstinence in many studies is extremely variable, ranging from hours to weeks. The DSM-5 has defined a cluster of symptoms termed "cannabis withdrawal" which can include: irritability, anger, aggression, anxiety, sleep

disturbance, decreased appetite or weight loss, restlessness, depressed mood, stomach pain, tremors, sweating, fever, or headache. The onset of symptoms is found to appear 1-2 days after abrupt cessation in 50% of marijuana users[38]. Some symptoms such as sleep disturbances and irritability appear to persist longer than others[38]. It is reasonable to suspect, then, that these documented withdrawal symptoms may be confounding the residual effects of marijuana on cognition.

Long-Term, Persistent Effects of Marijuana Use on Cognitive Function

Long-term, persistent effects of marijuana include any cognitive deficits that remain after all of the Δ^{9}-THC and its metabolites have left the system[39]. As with residual effects of marijuana, there is still conflicting evidence as to whether lasting CNS effects exist and what domains of cognitive function may be affected. In a meta-analysis looking at the residual effects of marijuana, Schreiner et al found that while marijuana was shown to produce global, residual effects on cognition in individuals abstinent for less than 25 days, all deficits subsided after one month of abstinence[40]. Simiarly, Pope at al. found that deficits in memory were present on days 0-7-post abstinence in heavy marijuana users, but all negative effects on cognition subsided by 28 days. Jager et al also found that there were no long-term deficits of marijuana in working memory or selective attention after one week of abstinence[42,43,51]. On the other hand, Gonzalez et al reported that the very small, negative effect that marijuana use has on memory is only present in heavy, long-term users upon cessation of marijuana use[27]. In support of the findings of Gonzalez et al, Bolla et al found that heavy marijuana use was associated with worse performance

on language, visual learning and memory, executive functions, psychomotor speed, and manual dexterity even after 28 days of abstinence[49].

Effects of Long-Term Marijuana Use on the Brain

Despite mixed evidence of marijuana's cognitive effects beyond those of acute use and intoxication, there is evidence that long-term, persistent marijuana use effects brain activity and metabolism even when all of the Δ^9-THC has left the system. An altered brain activity pattern is probably the most common feature of marijuana's influence on the brain. Lundqvist et al reported that marijuana users show 9% lower brain activity than non-users[29]. Kanayama et al also reported that marijuana users displayed more widespread brain activation during working memory task performance in which supplementary brain regions were recruited[47]. Chronic marijuana users have also been shown to have an altered brain activation pattern in attentional neural networks with a decrease in activation in normal attention areas, and an increase in smaller, compensatory regions[33]. All of these findings support the hypothesis that marijuana use induces a recruitment of alternate neural networks and neuroadaptation to compensate for subtle neural deficits caused by frequent marijuana use[29]. A decrease in rCBF in memory related areas of the prefrontal cortex, an increase in rCBF in cerebellar memory regions (with decreased activation upon cessation), and altered lateralization of activity in the hippocampus have also all been observed[29,46]. Upon intoxication however, experienced marijuana users show an increase in brain metabolism and a dose related increase in CBF[29].

These findings are important because while cognitive deficits might subside upon abstinence from marijuana, there are still notable differences in brain metabolism and activation in heavy marijuana users using marijuana for long periods of time. This raises the question of whether comorbid conditions like HIV-infection may exacerbate these underlying brain disturbances and cause them to possibly reach a threshold where they will become manifested clinically.

Marijuana and HIV

Despite any deficits in cognition that may be induced by marijuana use, marijuana is thought to have potential therapeutic benefits. Marijuana has been legalized for medicinal use in 23 states in the United States with four states having legalized recreational marijuana use[93]. Marijuana is thought to possess anti-nociceptive qualities by acting at the level of the thalamus in the brain[26]. Through injecting cannabinoids into the peri-aqueductal grey area of the brain, a region that sends afferent nerves reporting noxious stimuli from the spinal cord to the thalamus, researchers were able to diminish pain[26]. It is thought that Δ^{9}-THC activates inhibitory neurons projecting from the brain stem to spinal cord to inhibit pain[26]. Δ^{9}-THC has also been shown to enhance the anti-pain effects of opioids[26].

Pain is one of the symptoms of HIV-infection that has the potential to be mitigated by medicinal marijuana use. In a study of pain frequency in women living with HIV and AIDS, it was found that 20% of individuals reported that they were often in pain, with peripheral neuropathy, tingling, numbness, musculoskeletal, and abdominal

pain being the most frequent types[26,27]. Other symptoms associated with HIV-infection can occur as a direct or indirect result of the disease or in reaction to HAART treatments. These can include: nausea/vomiting, reduced appetite, weight loss, headaches, anxiety, and depression[27]. 27% of HIV-infected individuals use marijuana to treat HIV-related symptoms, with pain and decreased appetite relieved the most by marijuana use[27]. Richardson et al has reported that frequency of pain is associated with a higher frequency of marijuana use[89].

In light of studies reporting deleterious effects of marijuana on cognitive function, and evidence that individuals are using marijuana as a therapeutic agent, it is important to know if there is a negative, additive effect of marijuana use and HIV-infection on cognitive function, especially if it will negatively impact an individual's daily functioning, particularly their ability to abide by complicated medication regimes[50]. Fisk et al reported that marijuana use may create deficits in real-world memory function and other areas of executive function which correlated closely to daily functioning abilities[50].

Despite this pressing question, few studies have looked at the interaction of HIV and marijuana on cognitive function. Chang et al reported that there was no negative interaction of marijuana use and HIV on cognitive function[52]. However, Cristiani et al found that marijuana use is associated with greater cognitive dysfunction in symptomatic HIV-infection, mostly in the domain of delayed memory, which is similar to what is seen in acute marijuana use[90]. The findings of Cristiani et al lend support to the idea that minor cognitive deficits caused by marijuana use that are not necessarily manifested clinically are exacerbated when combined with the comorbid condition of HIV-infection.

The Effects of Alcohol Use on the Brain and Cognition

It is widely accepted that alcohol causes cognitive dysfunction ranging from acute intoxication to an assortment of dementias. Ethanol, the compound contained in alcoholic beverages, is believed to affect the brain directly and indirectly. While there is still a debate as to what the molecular targets of ethanol might be in the brain, it is believed that ethanol interacts with proteins, such as enzymes and ion-channels, on neurons to cause its cognitive and behavioral effects[56]. In the neurotoxicity hypothesis, ethanol is thought to directly induce neuronal loss and dysfunction through glutamate excitotoxicity, oxidative stress, and disruption of neurogenesis[53]. Ethanol is thought to inhibit N-methyl-D-aspartate (NMDA) receptors, which ultimately increases glutamate, and the excitotoxic response in neurons[53,54]. Ethanol has also been found to cause damage to DNA in neurons[54].

Indirect damage of ethanol to the CNS can be caused by malnutrition commonly accompanied by alcohol use disorders as well as metabolism disturbances caused by alcohol use. Alcoholics are known to consume less thiamine (Vitamin B1), with ethanol also compromising thiamine metabolism[53]. This lowers the concentration in the plasma, causing acute neurological disorders[53]. Also, increased ethanol consumption is associated with increased homocysteine residues in the brain, which are found to intensify excitotoxic damage[55].

Ethanol is also believed to induce a pro-inflammatory state in the brain that can contribute to the indirect damage of alcohol on cognitive dysfunction. Zhao et al found that intermittent ethanol exposure increased the number of activated microglia and pro-

inflammatory cytokines in the hippocampus, parietal association cortex, and entorhinal cortex which was associated with cognitive deficits in memory[58]. He et al also found that there was an increase in monocyte chemoattractant protein 1 (MCP-1) in the ventral tegmental area, substantia nigra, hippocampus, and amygdala[59]. MCP-1 is thought to mediate CNS inflammation and possibly drinking behavior, and has been shown to be related to the neurodegeneration found in brains of alcoholics[59]. Dysfunction of the cingulate cortex has been shown to be related to attentional dysfunction[59].

Overall, deleterious effects of alcohol are shown to be most prominent in the frontal lobe, with abnormalities in different regions of the frontal lobe being associated with different cognitive deficits[54]. Cortical atrophy, ventricular enlargement or increased CSF, meningeal thickening, cell loss, and architectural disruption of cortical laminae have all been reported in the frontal lobes[54,55]. Cortical atrophy has been shown to be proportional to the amount of alcohol consumed in a lifetime[54,55]. Changes in both white and gray matter have been observed, with white matter showing more striking negative effects due to myelin loss than loss of grey matter due to neurotoxicity[76]. However, loss of grey matter is most associated with cognitive deficits[76]. Dendritic and synaptic changes are believed to produce cognitive deficits that precede severe structural changes[54]. A decrease in glucose metabolism, NAA, choline (a marker of membrane integrity), and creatine (a measure of cell energy) have also been found in the frontal lobes of alcoholics[54]. All frontal lobe abnormalities have been shown to improve after prolonged abstinence[54,55].

Other areas of the brain that have been shown to have pathologies are the corpus callosum, cerebellum, hypothalamus, and hippocampus[53]. Despite observed effects of alcohol on memory, the hippocampus has not shown to be subject to neuronal loss, but to have dendrite and axonal damage[82].

Alcohol can be thought to effect cognition on a continuum ranging from mild cognitive impairment to the more severe Wernike-Korsakoff's syndrome (WKS) and alcohol related dementia (ARD)[67]. The main domains of cognition affected by alcohol appear to be memory, attention, psychomotor, and executive function, with alcoholics showing deficits and lower efficiency on neurocognitive tests[67]. The cognitive effects of alcohol also depend on what type of exposure an individual has had. For instance, acute effects of alcohol could be due to social or binge-drinking, while chronic effects on cognition may arise due to prolonged, heavy use. Withdrawal from alcohol has also been known to cause and worsen cognitive deficits.

Effects of Acute Alcohol Use on Cognition

Acute exposure to alcohol includes the time-period when alcohol is in an individual's system. The acute effects of alcohol on cognition are thought to vary depending on if an individual is drinking at "moderate levels", or at hazardous levels seen in episodes of binge-drinking. Binge-drinking is defined as consuming hazardous amounts of alcohol in a limited period of time followed by a period of abstinence. Typically, ≥ 5 drinks for men and ≥ 4 drinks for women in a span of 24 hours is considered hazardous[62]. According to the DSM-5, alcohol intoxication is accompanied by

slurred speech, incoordination, unsteady gait, nystagmus, impaired attention and memory, and stupor or coma. Weissenborn et al found that in general, acute alcohol use impairs executive functions such as planning and spatial recognition with binge-drinking effecting spatial working memory[60]. Townshend et al furthered these findings, reporting that binge-drinking impairs not only spatial working memory but motor impulsivity, sustained attention, and impulse control[61]. Both findings from Weissenborn et al and Townshend et al reveal deficits in executive function, which is known to be represented in the frontal lobes.

It seems that the predictor of cognitive dysfunction due to moderate, acute use of alcohol and binge-drinking is not necessarily the amount of alcohol an individual drank in a given time, but the magnitude of the effect that that amount of alcohol had on each person specifically since variables like age and gender can influence one's sensitivity to the effects of alcohol[61,108]. Therefore, the acute effects of alcohol on cognition can be extremely variable, and it is difficult to generalize the type of consequences drinking may have on cognition[62,108].

Related to binge-drinking is alcohol withdrawal, since binge-drinking by definition includes a period of alcohol abstinence. According to the DSM-5, withdrawal can occur several hours to a few days post alcohol cessation. Symptoms include autonomic hyperactivity, increased hand tremor, insomnia, nausea, hallucinations, psychomotor agitation, anxiety, tonic-clonic seizures as well as cognitive impairments[21]. Repeated alcohol withdrawal has been shown to increase the risk of withdrawal associated seizures and cognitive deficits[62,66]. In a study by Duka et al looking at the

effects of previous ethanol withdrawal on cognition, they found that impulsivity, specifically the inhibition of motor responses, was negatively affected[66]. This again, is an executive function controlled by the frontal lobe.

Effects of Chronic Alcohol Use on Cognition

Excessive, prolonged alcohol use, as occurs with alcoholism and alcohol dependence also causes cognitive deficits associated with frontal lobe damage exemplified in WKS and ARD. ARD is defined as persistent cognitive and functional decline following cessation of alcohol as a direct result of the neurotoxic effects of alcohol on the brain[53]. ARD accounts for 1.4% of all dementia patients, but 22% of all dementia patients under the age of 65[53]. Neurocognitive deficits associated with ARD appear to be both cortical and subcortical, with visuospatial, working memory, motor speed, and executive function being the most prominent areas with deficits[53]. WKS is defined as an alcohol induced persisting amnestic disorder with characteristic memory disturbances and is the result of thiamine deficiency and most likely some degree of neurotoxicity due to ethanol[53]. Wernicke's encephalopathy is the direct result of decreased thiamine, which is followed by a triad of oculomotor, cerebellar, and mental state abnormalities[53]. This is then followed by memory impairment termed Korsakoff's Syndrome[53]. WKS syndrome is prevalent in about 1-2% of the general population and 10% of those with alcohol use disorders[53]. Neurocognitive deficits associated with WKS are mostly manifested as memory impairments, represented by anterograde amnesia and

impaired recall[53]. Impaired visuoperception, executive function, and working memory have also been reported[53].

The period of time and amount of alcohol required for ARD and WKS to manifest is inconsistent in the literature due to there being many different definitions for standard drinks and what is considered heavy drinking across different cultures[101]. Generally, in the United States, a "standard drink" is considered 14 grams of pure alcohol or 12 ounces of regular strength beer, 5 ounces of wine, and 1.5 ounces of hard liquor. There have been reports that consuming 70-80 grams (the equivalent of 5-6 standard drinks) of alcohol per day will cause mild cognitive dysfunction[101]. It is also been reported that after five years of consuming 35 standard drinks a week for men and 28 standard drinks a week for women, the risk of ARD is significant due to an increased neurotoxicity[101]. In general, it is believed that there is a U-shaped relationship between alcohol use and dementia, with low to moderate levels possibly causing a decrease in risk for cognitive dysfunction and heavy drinking causing an increased risk[101].

The Effects of Alcohol Use on Cognition May be Reversible

In general, the cognitive deficits found in sober individuals with previous alcohol use disorders (that do not have ARD or WKS) have been shown to be mitigated, if not reversed, by abstinence. Abstinence of one week or more can resolve much of the cognitive dysfunction in individuals with alcohol related disorders[53,65,67]. In a study of abstinent alcoholic men and women, Fein et al only found mild deficits in spatial processing in long-term, abstinent alcoholic individuals[65]. Deficits in executive function, working memory, and perceptual and motor impairments appear to last longer than verbal

and visual-spatial impairments[53]. Female sex, increased age, and decreased education level all appear to be related to worse cognitive outcomes and worse recovery of cognitive dysfunction in chronic alcoholics[53,66]. Recovery also appears to be related to the amount of recent alcohol use and duration of abstinence rather than lifetime use[53,66]. Multiple withdrawals also appear to be associated with worse cognitive outcomes[53].

Alcohol and HIV

As stated previously, alcohol use among HIV-infected individuals is particularly high. An increased prevalence of alcohol use among HIV-infected people is dangerous for a number of reasons. Alcohol increases sexual risk behavior, with 33% of individuals having consumed alcohol before engaging in sexual activities[68]. Thus, it is likely that alcohol may contribute to the spread of HIV. Also, hazardous drinking decreases an individual's adherence to HAART regimens[71,73,77]. Since any adherence less than 95% decreases the benefit of HAART, it is essential that it is maintained[71]. In a study examining the effects of alcohol consumption on life expectancy in HIV-infected individuals, Braithwaite et al showed that a 33% decrease in treatment success decreased an individual's life expectancy by 3.3 years[71].

Not only does alcohol possibly facilitate worse disease outcomes in those with HIV-infection, there is evidence to show that alcohol and HIV act synergistically in the CNS to produce negative effects on cognition and brain pathology. Alcohol has been shown to mainly affect the frontal lobes while HIV mainly affects central white matter and subcortical structures like the basal ganglia with there being little overlap in the

structures involved in the pathology of either condition separately. However, affects on central white matter, subcortical gray matter, and the frontal cortex have been shown to be exacerbated due to the comorbid conditions[82]. Pfefferbaum et al, in two separate studies looking at the additive effects of alcohol and HIV on the ventricles, corpus collosum, and white matter, showed that the comorbid conditions combine to effect the structural integrity of the brain as seen in neuroimaging techniques such as Magnetic Resonance Spectroscopy (MRS), Magnetic Resonance Imaging (MRI), and Diffusion Tensor Imaging (DTI)[83,84]. These effects cannot be described in those with HIV-infection or alcoholism separately[83,84]. These deficits were mainly reflected in altered mirco and macro structural integrity of the corpus collossum[83,84]. There have also been documented synergistic effects on cell membrane metabolism in the brain as can be seen in a decrease in phosphodiesterase (PDE), phosphocreatine (PCr), and adenosine triphosphate (ATP)[83,84].

There are many different cognitive domains that are thought to be affected by the additive effects of alcohol and HIV-infection, some of which include: motor, visuomotor, verbal reasoning, reaction time, auditory processing, associative learning, attention, memory, and executive function[13,20,22,72,74,75,76,78-82]. Memory has specifically been shown to be influenced in the areas of free recall and sequencing[78]. These cognitive impairments are thought to be the product of a threshold effect. The impairments of alcohol and HIV-infection on cognition separately may not be detected, but over time the comorbid conditions act synergistically, crossing a threshold of brain damage that manifests clinically as cognitive dysfunction[78]. In a study on attentional control in HIV-infected

individuals who also had alcohol use disorders, Schulte et al found that separately, HIV-infected individuals without alcohol use disorders and individuals without HIV-infection with alcohol use disorders performed the same as controls on neurocognitive tests of attention[80]. However, the deficits became apparent in alcoholics with HIV-infection[80].

SPECIFIC AIMS

The present study looks at the association of current and lifetime marijuana and heavy alcohol use on cognitive function in HIV-infected individuals. There is quite a bit of evidence showing that HIV-infection, marijuana use, and alcohol use all affect cognition individually. Similarly, there is some support that HIV-infection in combination with marijuana use, as well as HIV-infection in combination with alcohol use also affects cognition in a negative, additive manner. However, there is a lack of data considering the effects of the combination of alcohol, marijuana, and HIV-infection on cognitive function. It is reasonable to hypothesize that individuals who use marijuana, drink heavily and have HIV-infection may be subject to additive, negative or even synergistic effects of all three conditions on the brain, cognition, and ultimately daily functioning. Our main objectives were as follows:

Among individuals with current substance dependence or ever injection drug use and HIV-infection:

1.) To test if current marijuana use is associated with cognitive dysfunction;

2.) To test if current heavy alcohol use is associated with cognitive dysfunction;

3.) To test if lifetime marijuana use is associated with cognitive dysfunction;

4.) To test if lifetime, heavy alcohol use is associated with cognitive dysfunction;

5.) To test if lifetime marijuana use and lifetime heavy alcohol use are synergistically associated with cognitive dysfunction;

6.) To test if current marijuana use and current heavy alcohol use are synergistically associated with cognitive dysfunction.

METHODS

Design and Human Subjects Approval

Using cross-sectional, regression analyses, we attempted to determine whether or not there are associations between current and lifetime marijuana use, heavy alcohol use, and cognitive dysfunction in HIV- infected individuals. The Institutional Review Board (IRB) of Boston Medical Center reviewed and approved all study procedures.

Sample

Participants were a part of the Boston ARCH cohort which is comprised of 250 HIV-infected individuals affected by multiple substances and is one of three cohorts that make up the URBAN ARCH (Uganda Russia Boston Alcohol Network for Alcohol Research Collaboration on HIV/AIDS) consortium. Recruitment and data collection took place between September of 2012 and November of 2014. For this analysis, participants were required to have completed the lifetime drug and alcohol data assessments, taking place 6 months or more after the baseline assessment. This resulted in a loss of 35 individuals for a final sample of 215. Participants were recruited from clinical sites of HIV care in Boston, Massachusetts including the Center for Infectious Disease at Boston Medical Center and the Boston Healthcare for the Homeless program.

Inclusion criteria for Boston ARCH included documentation of HIV-infection in participants' medical records which could consist of: an ELISA testing for HIV antibodies confirmed by Western blot, having a viral load of > 10,000, a 4^{th} generation

ELISA (Enzyme Linked Immunosorbent Assay) confirmed by "Multi-Spot" rapid test, or nucleic acid testing for HIV-1. Participants were required to have current drug or alcohol dependence in the 12 months prior to entering the cohort or current or past injection drug use. They were required to speak fluent English, be 18 years or older, and be able to provide contact information for one person who knew of their whereabouts to assist in locating them for follow up interviews. Exclusion criteria were pregnancy, plans to leave the Boston area within the year, and cognitive impairment that could inhibit an individual from being able to give informed consent or understanding interview questions as assessed by trained research staff.

Data Collection

Data were collected by research assistants by interview and collection of urine and blood samples. An initial baseline screening interview was administered to each participant after obtaining oral consent to view their medical records to confirm HIV-infection. The baseline screener included all inclusion and exclusion criteria. Next, a baseline assessment questionnaire was administered by in person interview. All data used for analyses herein were obtained by the screening interview, the baseline assessment, and electronic medical record review except for the lifetime alcohol and marijuana use data which were obtained at a six month or one year follow up contact.

Independent Variables

There were five independent variables also depicted in Figure 1 below: current marijuana use, current heavy alcohol use, lifetime marijuana use, and two measure of lifetime heavy alcohol use. Current use variables were defined as number of days of marijuana use in the past 30 days for marijuana and number of heavy drinking days in the past 30 days for alcohol. Current marijuana use was measured using questions adapted from the validated, 30-Day Drug Addiction Severity Index (ASI) (See Appendix A) [99,100]. The Interviewer read, "Now I am going to ask you some questions about your drug use in the past 30 days. How many days in the past 30 days have you used…" and participants were to report how many days they had used a number of different drugs, including marijuana. Current heavy alcohol use was measured using the 30-day Timeline Follow-Back method (TLFB) (See Appendix B). This is a self-report calendar measure that looks at an individual's drinking patterns and behavior on each of the past 30 days and has been validated for use in people with HIV-infection[85]. Research assistants asked participants about their use of alcohol on each day for the 30 days prior to the interview. If alcohol was used, subjects reported the type and quantity of standard drinks for each day, with "standard drinks" meaning 12 ounces of regular strength beer, 5 ounces of non-fortified wine, and 1.5 ounces of 80 proof liquor. These quantities were then converted to the gram equivalent of 14 grams of pure alcohol. A heavy drinking day was defined as ≥ 5 drinks in 24 hours for males and ≥ 4 drinks in 24 hours for females.

Lifetime variables were defined as follows: number of years marijuana was used ≥ 3 times per week, lifetime alcohol consumption in kilograms (kg), and duration of

heavy drinking in years. Lifetime marijuana use was measured at the six-month assessment and at any following appointments if the six-month assessment was missed using selected questions from the ASI (See Appendix C). The portion of the ASI included in the follow up appointments was adapted from the 30 day Drug ASI to measure how many years participants regularly used a variety of drugs ≥3 times per week, including marijuana. Participants were asked, "How many years in your life have you regularly used…" and were to report this number for each drug. Lifetime alcohol consumption in Kg was measured starting at the six-month assessment and at any follow up appointments if the six-month assessment was missed using the validated lifetime drinking history (LDH) self-report questionnaire (See Appendix D)[102,103]. Participants were asked to recall their drinking patterns throughout life starting at the point when they began to drink regularly up until the day of the interview. Specifically, they were asked when they began to drink regularly, if there were any events that led their drinking behavior to change, and the frequency of drinking during any periods of regular drinking. Periods of regular drinking were considered to be any time participants had at least one standard drink a month, with "standard drink" still defined as 12 ounces of regular strength beer, 5 ounces of non-fortified wine, and 1.5 ounces of 80 proof liquor. These data were then converted to total lifetime alcohol exposure in kilograms (Kg). Duration of heavy drinking was taken from the same assessment, but was defined as the number of years a participant drank > 84 grams of alcohol or > 6 drinks per day throughout their life.

Dependent Variables

All three dependent or outcome variables measured cognitive dysfunction as depicted in Figure 1 below and included: the Montreal Cognitive Assessment (MoCA) memory score, MoCA attention score, and Medical Outcomes Study HIV Health Survey (MOS-HIV) CF4 sore. The MoCA is a rapid screening measure for cognitive dysfunction that takes approximately 10 minutes to administer. It assesses various aspects of cognition including attention and concentration, executive function, memory, language, visuocontructional skills, conceptual thinking, calculations, and orientation. It has been validated for use in HIV-infected people and its different domains have also been shown to be positively correlated with other neuropsychological tests in similar areas of cognition[86,87]. In this study, we used the memory and attention domains of the MoCA (See Appendix E). The memory portion tested participants' recall. The interviewer read each participant a list of words that they had to recall directly after the first two trials and again five minutes later. Participants could recall a maximum of five words in each trial. For each word recalled correctly, they received a "1" and for each word not recalled they received a "0," yielding a minimum of 0 and a maximum of 5 points per trial. The attention portion tested individuals on their ability to repeat a sequence of numbers exactly as the interviewer read them in the first trial and then to repeat a different set of numbers backwards in the second trial. Participants either received a "1" for repeating each sequence correctly or a "0" for repeating them incorrectly, resulting in a minimum of 0 and maximum of 2 points for both trials combined.

The MOS-HIV is a brief, validated measure looking at the health-related quality of life of those with HIV-infection[89]. It is comprised of 35 questions that make up 11 separate domains including: general health perceptions, pain, physical functioning, role functioning, social functioning, energy/fatigue, mental health, health distress, cognitive functioning, quality of life, and health transition. The raw scores are linearly transformed to a 1-100 point scale with higher scores indicating better health. In the present study, only the domain of cognitive function was used (CF4). This section is composed of four questions related to cognitive function (See Appendix F).

Independent Variables *Current and Lifetime marijuana and heavy alcohol use measures*	**Dependent Variables** *Measures of Cognitive Dysfunction*
Current Marijuana Use • *# of days of marijuana use in the past 30 days*	**MoCA Memory Score** • *Memory section of the MoCA testing recall of five words directly after hearing them and five minutes later.* • *Two trials were ran using the same five words, after the second participants were asked to recall those five words five minutes later* • *Participants received 0 for each word not recalled and 1 for each word recalled with a range of 0-5 possible points for each trial*
Current Alcohol Use • *# of heavy drinking days in the past 30 days*	**MoCA Attention Score** • *Attention section of the MoCA consisting of two trials requiring participants to repeat a sequence of 5 numbers exactly as the interviewer said them in the first, and then repeat a sequence of 3 numbers in reverse in the second* • *Participants received 0 if the sequences were repeated incorrectly and 1 if repeated correctly for a range of 0-2 points between both trials*
Lifetime Marijuana Use • *# years marijuana was used* ≥ 3 times per week	**MOS-HIV CF4 Score** • *4 Questions regarding cognitive function taken from the MOS-HIV* • *Scores were converted to a 0-100 point scale with a higher score indicated better health.*
Lifetime Alcohol Use • *Lifetime Alcohol Consumption (Kg)*	
Lifetime Alcohol Use • *Duration of Heavy Drinking* • *# of yrs. participants drank > 6 drinks or >84 grams/day*	

Figure 1. Independent and Dependent Variables used in Analyses
Left column: Independent variables used for current and lifetime marijuana and heavy alcohol use and how each variable was measured listed in italics.
Right column: Dependent variables used for cognitive dysfunction and how each were measured listed in italics.

Analysis

Descriptive statistics were calculated for the independent variables, dependent variables and all covariates as shown at the beginning of the results section in Table 1. This included the median, mean, standard deviation, range, upper, and lower percentiles for any continuous variables and frequencies and proportions for any dichotomous variables.

Analyses consisted of unadjusted, core-adjusted, and fully adjusted models. Covariates adjusted for included a group of "core" covariates to definitively be included in the analyses and those determined after considering a Spearman correlation matrix and bivariate analyses, creating a full list of covariates. The Spearman correlation matrix was generated for all covariates and independent variables to check for co-linearity. If any variables were correlated > 0.40, only one of them was included in the regression models. Bivariate analyses were used to assess any associations between all covariates or independent variables and all cognitive outcomes. (see Table 2 in results section). Core covariates included: age, biological sex, race, education level, primary language, employment status, and depressive symptoms taken from the patient health questionnaire (PHQ-2). The full group of covariates chosen included the core plus: the Charlson Comorbidity Index Score obtained from participants' medical records, anxiety symptoms from the overall anxiety severity and impairment scale (OASIS), hepatitis C infection (ever) determined by a positive antibody test or a viral load of > 0, whether or not participants were currently on HAART, HIV viral load, current CD4 cell count, duration of HIV-infection, lifetime cocaine use (years of regular use equivalent to 2 binges per

week) taken from the adapted lifetime ASI, past 30 day cocaine use from the 30-Day Drug ASI, past 30 day sedative or opioid use from the 30-Day Drug ASI, and whether or not participants had a current prescription for opioids. The Charlson Comorbidity Index is a validated way to predict the risk of mortality in one year based on 19 predetermined comorbidities that have been assigned weights of 1,2,3, and 6[94,95]. These are then added together for a total score which takes into account the number and seriousness of comorbid conditions, with higher scores indicating a higher risk for mortality[94,95]. The PHQ-2 is a validated, two-item questionnaire which assesses depression severity[96]. A score of ≥ 3 indicates symptoms of depression[96]. The OASIS is a validated, five-item questionnaire used primarily to identify anxiety disorders, but also to assess the frequency and intensity of anxiety symptoms and any functional impairment related to these symptoms[97,98]. A score of ≥ 8 indicates symptoms related to an anxiety disorder[97,98].

Multivariable logistic and linear regression models were then fit to test the associations between all five independent variables and all three dependent variables. All independent variables were modeled as continuous as they represented a range of marijuana use and heavy alcohol consumption for both current and lifetime use. The MoCA memory score and MOS-HIV CF4 score were also modeled as continuous variables since participants were able to score between 0-5 and 0-100 on each test respectively. The MoCA attention score was dichotomized between individuals who scored either a 0 or a 1 or those who scored a 2. Linear regression was used in all models testing an association between the independent variables and both the MoCA memory and MOS-HIV CF4 outcomes while logistic regression was used when testing an

association between the independent variables and the MoCA attention outcome. Adjusted and unadjusted models were fit using the covariates listed previously. All models were first core-adjusted, and then fully adjusted using only the core covariates and then all covariates respectively.

There were 8 different groups of multivariable regression models fit, 6 of which are described in Figure 2 below. In Group 1, we tested associations between current marijuana use and each cognitive outcome. In Group 2, we tested associations between current heavy alcohol use and each cognitive outcome. In Group 3 we tested associations between lifetime marijuana use and each cognitive outcome. In Group 4, we tested associations between lifetime alcohol use (kg) and each cognitive outcome. In Group 5, lifetime marijuana use, duration of heavy drinking, current heavy alcohol use, and current marijuana use were tested for associations with each cognitive outcome. In Group 6, lifetime marijuana use, lifetime alcohol use (kg), current heavy alcohol use, and current marijuana use were tested for associations with each outcome. In Group 7, the interaction between current heavy alcohol and current marijuana use was tested for each cognitive outcome. In Group 8, the interaction between lifetime marijuana and total lifetime alcohol use was tested for each cognitive outcome. All groups were fit using unadjusted, core-adjusted, and fully-adjusted models as stated previously.

	Independent Variables				
Group Number of Multivariable Regression Models	Current Marijuana Use	Current Heavy Alcohol Use	Lifetime Marijuana Use	Lifetime Alcohol Use (Kg)	Duration of Heavy alcohol Use
1	+				
2		+			
3			+		
4				+	
5	+	+	+		+
6	+	+	+	+	

Figure 2. Multivariable Linear and Logistic Regression Models

Figure 2 depicts 6 of the multivariable regression models fit to assess associations between the five continuous independent variables and dependent variables. The MoCA Memory score and MOS-HIV CF4 score were continuous while the MoCA Attention score was dichotomous. Not shown in the table are Groups 7 and 8 which tested the possible interactions of current and lifetime marijuana and heavy alcohol use with each cognitive outcome respectively. Multivariable linear regression analyses were used when assessing associations between the independent variables and MoCA memory score and MOS-HIV CF4 score. Multivariable logistic regression analyses were used when assessing associations between the independent variables and the MoCA attention score. All analyses used unadjusted, core-adjusted, and fully-adjusted models.

RESULTS

Descriptive Statistics

Demographics

The mean age of participants was 49 years, 65% were male, and 20% were white. 66% of participants completed high school or a high school equivalent, 17% were employed, and 86% reported English as their primary language. The mean Charlson comorbidity score was 2.9 with 59% having tested positive for HCV ever in their lifetime. Participants scored ≥ 3 on the Patient Health Questionnaire 2 (PHQ-2) 28% of the time indicating substantial depressive symptoms and 45% scored ≥ 8 on the Overall Anxiety Severity and Impairment Scale (OASIS) indicating potential anxiety disorders. Participants currently on HAART were 87%, 71% had an HIV viral load of < 200 copies/mL, CD4 cell count/mm^3 was 10%: <200 and 33%: 200-<500, and the mean duration of HIV-infection of 16 years. The mean years of cocaine use was 9.3, with 31% of people reporting that they had used the drug in the past 30 days. Illicit opioid use in the past 30 days was 26%, with 39% of participants reporting a current opioid prescription. Demographic statistics for all variables are reported in Table 1 below.

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Table 1. Descriptive Statistics for Independent Variables, Dependent Variables, and Covariates
Descriptive statistics calculated for continuous variables included the mean, median, range, standard deviation (SD), upper quartile (UQ), and lower quartile (LQ). Descriptive statistics calculated for dichotomous variables were frequencies and percentages. Categories that dichotomous variables were dichotomized as are listed in italics underneath the variable name. Frequencies and percentages correspond to the fist, second, and third category respectively.

		Continuous Variables										
	Current Marijuana Use (Days)	Current Alcohol Use (Days)	Lifetime Marijuana Use (Years)	Lifetime Alcohol Use (Kg)	Duration of Heavy Alcohol Use (Years)	Charlson Comorbidity Index Score	Age (Yrs)	HIV Duration (years)	HIV Viral Load (copies/ mL)	Lifetime Cocaine Use (Years)	MoCA Memory Score (1-5)	MOS-HIV CF4 Score (1-100)
N	215	215	214	215	215	215	215	213	215	215	215	215
Mean	6.5	4.8	9.8	720.7	6.4	2.9	48.6	16	1.56	9.3	3.2	68.8
Median	0	1	5	326	1.1	2	50	16	1	7	3	70.8
Range	30	30	48	6529.8	51.9	13	45	32.8	6.23	47	5	83.4
UQ	7	6	16	812.2	11.1	4	56	23	2.7	15	4	83.3
LQ	0	0	0	78	0	1	43	9	0	1	2	58.3
SD	10.5	8.1	11.8	1079.8	9.5	2.5	9.5	8.4	1.7	9.8	1.3	18.9

Table 1 cont. Descriptive Statistics for Independent Variables, Dependent Variables, and Covariates

Descriptive statistics calculated for continuous variables included the mean, median, range, standard deviation (SD), upper quartile (UQ), and lower quartile (LQ). Descriptive statistics calculated for dichotomous variables were frequencies and percentages. Categories that dichotomous variables were dichotomized as are listed in italics underneath the variable name. Frequencies and percentages correspond to the fist, second, and third category respectively.

Dichotomous Variables														
	MoCA AttentionScore *0-1 or 1-2***	Race *White or non-White*	Education *Finished High School or Did Not*	Primary Language *English or non-English*	Employed *Yes or No*	Sex *Male or Female*	PHQ-2 Score *< 3 or ≥ 3*	OASIS Score *0-7 or ≥ 8*	HCV infection (ever) *Yes or No*	Currently on ART *Yes or No*	CD4 count *< 200, 200-<500, ≥ 500*	Illicit Opioid Use in the Past 30 days *Yes or No*	Cocaine use in the Past 30 days *Yes or No*	Prescribed Opioids *Yes or No*
N	215	215	215	215	215	215	214	215	214	215	215	215	215	215
Freq.	73, 142	43, 172	143, 72	184, 31	37, 178	140, 75	154, 60	119, 96	126, 88	187, 28	22, 71, 122	55, 160	66, 149	84, 131
%	34, 66	20, 80	66.5, 33.5	86, 14	17, 83	65, 35	72, 28	55, 45	59, 41	87, 13	10, 33, 57	26, 74	31, 69	39, 61

Table 2. Bivariate Analysis

Table 2 describes the results of the bivariate analysis used to assess any associations between covariates or independent variables and each outcome in order to determine a full list of covariates. OR means odds ratio from logistic regression analyses and CI means confidence interval.

Independent Variable	MoCA Attention Score n	MoCA Attention Score OR (95%CI)	MoCA Attention Score P-Value	MoCA Memory Score n	MoCA Memory Score β (95% CI)	MoCA Memory P-Value	MOS-HIV CF4 Score n	MOS-HIV CF4 β (95% CI)	MOS-HIV CF4 P-Value
Lifetime Drinking (Kg)	215	1.0 (1.0, 1.0)	0.7	215	0 (-0.0001, 0.0002)	0.6	215	-0.0004 (-0.003, 0.002)	0.8
Duration of Heavy Drinking	215	1.01 (1.0, 1.04)	0.7	215	0.004 (-0.01, 0.02)	0.6	215	-0.03 (-0.3, 0.2)	0.8
Lifetime Marijuana	214	1.02 (1.0, 1.04)	0.2	214	0.01 (-0.003, 0.03)	0.1	214	0.01 (-0.2, 0.2)	0.9
Current Alcohol	215	1.01 (1.0, 1.04)	0.8	215	-0.01 (-0.03, 0.01)	0.3	215	0.06 (-0.2, 0.4)	0.7
Current Marijuana	215	1.01 (0.98, 1.04)	0.4	215	0.007 (-0.097, 0.02)	0.4	215	-0.2 (-0.3, 0.4)	0.3
Age	215	1.0 (0.9, 1.00)	0.05	215	-0.03 (-0.05, -0.01)	0.0003	215	0.08 (-0.2, 0.3)	0.6
Sex	215	0.8 (0.4, 1.4)	0.5	215	0.006 (-0.4, 0.4)	1.0	215	1.1 (-4.2, 6.4)	0.7
Race	215	1.4 (0.7, 3.0)	0.3	215	0.3 (-0.1, 0.8)	0.2	215	-2.9 (-9.2, 3.5)	0.4
Education	215	0.4 (0.2, 0.8)	0.004	215	-0.5 (-0.9, -0.1)	0.007	215	-6.7 (-12, 1.4)	0.01
Primary Language	215	3.8 (1.7, 8.4)	0.009	215	0.5 (-0.02, 0.99)	0.06	215	5.8 (-1.4, 13)	0.1
Employment Status	215	0.4 (0.2, 0.8)	0.01	215	-0.2 (-0.7, 0.2)	0.3	215	1.5 (-5.2, 8.3)	0.6
Charlson Comorbidity Index	215	0.9 (0.8, 1.0)	0.08	215	-0.04 (0.1, 0.02)	0.2	215	-0.3 (-1.4, 0.7)	0.5
PHQ-2 Score	214	1.6 (0.8, 3.1)	0.1	214	-0.3 (-0.7, 0.07)	0.4	214	-17.2 (-22.4, -12)	<0.001

Table 2 cont. Bivariate Analysis
Table 2 describes the results of the bivariate analysis used to assess any associations between covariates or independent variables and each outcome in order to determine a full list of covariates. OR means odds ratio from logistic regression analyses and CI means confidence interval.

OASIS Score	215	1.0 (0.5, 1.7)	0.9	215	-0.1 (-0.5, 0.2)	0.7	215	-14.8 (-19.2, -9.7)	<0.001
HCV (ever)	214	1.0 (0.6, 1.8)	1.0	214	-0.05 (-0.4, 0.3)	0.2	214	2.5 (-2.7, 7.7)	0.3
Currently on HAART	215	0.4 (0.1, 1.0)	0.06	215	-0.3 (-0.8, 0.2)	0.05	215	7.4 (-0.1, 14.9)	0.05
HIV viral load	215	1.1 (0.9, 1.3)	0.2	215	0.1 (0.003, 0.2)	0.8	215	-1.4 (-2.9, 0.03)	0.05
CD4 count	215	0.6 (0.2, 1.7)	0.5	215	0.2 (-0.4, 0.9)	0.008	215	0.3 (-8.8, 9.5)	0.9
HIV Duration	213	1.0 (0.9, 1.0)	0.05	213	-0.03 (-0.05, 0.007)	0.2	213	0.2 (-0.1, 0.5)	0.2
Lifetime Cocaine	215	1.0 (1.0, 1.04)	0.7	215	-0.01 (-0.03, 0.006)	0.5	215	-0.1 (-0.4, 0.1)	0.3
Cocaine Past 30 Days	215	1.7 (0.9, 3.3)	0.09	215	-0.1, (0.5, 0.2)	0.09	215	-6.7 (-12.2, -1.3)	0.01
Opioids Past 30 Days	215	1.9 (1.0, 3.9)	0.06	215	0.3 (-0.05, 0.7)	0.5	215	-2.4 (-8.3, 3.4)	0.4
Prescribed Opioids	215	1.5 (0.8, 2.7)	0.2	215	0.1 (-0.2, 0.5)	0.1	215	0.8 (-4.4, 6.0)	0.7

Main Independent Variables

The distributions for current marijuana and heavy alcohol use are shown in Figure 3 below, and descriptive statistics can be found in Table 1. Participants reported a mean of 6.5 days of marijuana use in the past 30 days with a standard deviation of 10.5. The

mean number of heavy drinking days in the past 30 days was 4.8 with a standard deviation of 8.1.

The distributions for lifetime marijuana and heavy alcohol use are shown in Figure 4 below and descriptive statistics can be found in Table 1. Participants used marijuana ≥3 times per week for a mean of 9.8 years with a standard deviation of 11. The mean duration of heavy alcohol use was 51.9 years with a standard deviation of 9.5 and the mean lifetime alcohol consumption of 720.7 Kg with a standard deviation of 1,079.

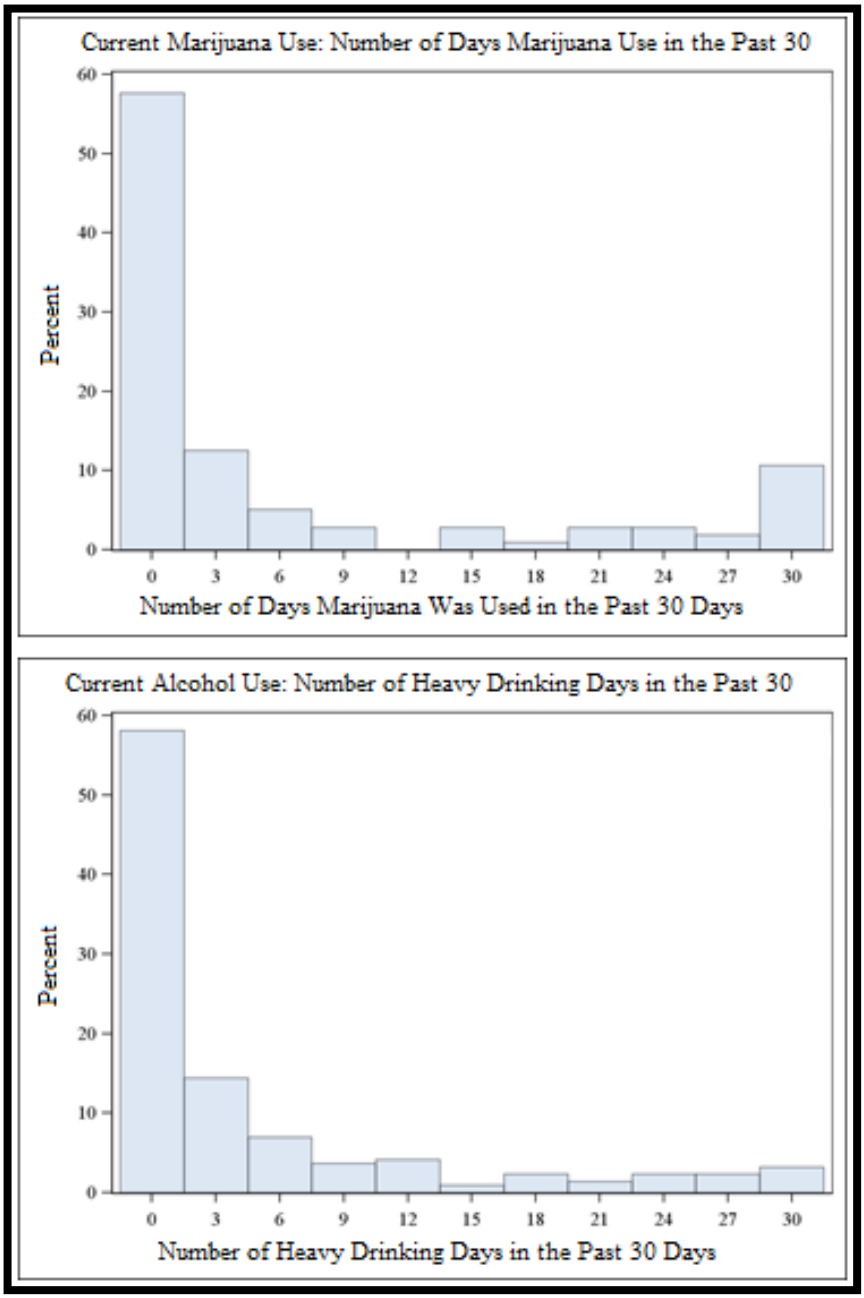


Figure 3. Distributions for Current Marijuana and Heavy Alcohol Use
Top Graph: X-axis measures number of days marijuana was used in the past 30 days or current marijuana use and Y-axis measures the percentage of the sample. Bottom Graph: X-axis measures number of heavy drinking days in the past 30 days or current heavy alcohol use and the Y-axis measures the percentage of the sample.

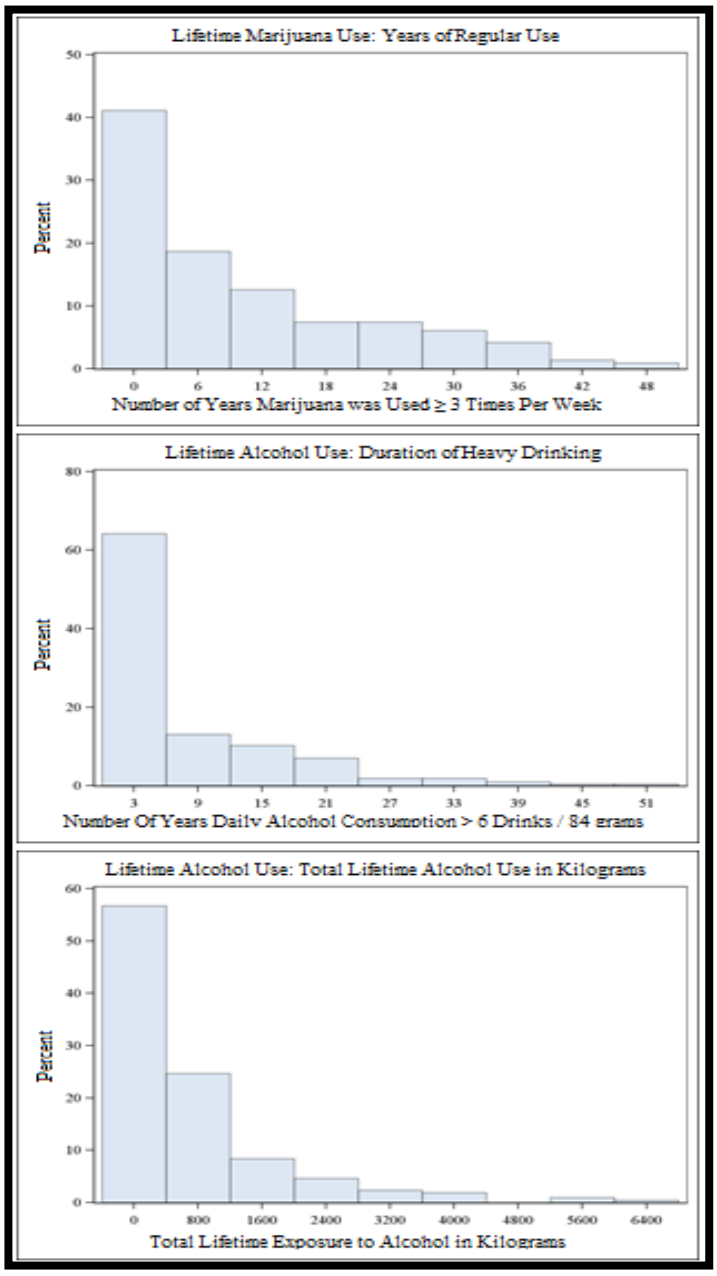
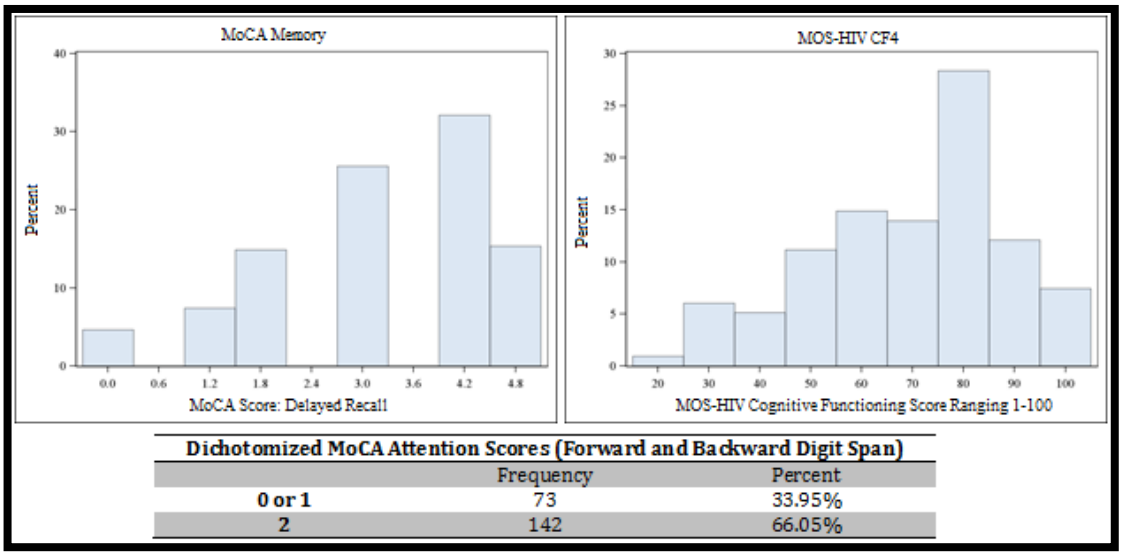


Figure 4. Distributions for Lifetime Marijuana and Heavy Alcohol Use
Top graph: X-axis measures how many years marijuana was used ≥ 3 times per week or lifetime marijuana use and the Y-axis measures the percentage of the sample. Middle graph: X-axis measures the number of years participants drank >5 drinks/ 84 grams of alcohol per day or duration of heavy alcohol use and the Y-axis measures the percentage of the sample. Bottom graph: X-axis measures the total lifetime exposure to alcohol in kilograms or lifetime alcohol and the Y-axis measures the percentage of the sample.

Dependent Variables

Distributions and frequencies for cognitive dysfunction outcomes are listed in Figure 5 below and descriptive statistics can be found in Table 1. On the MoCA memory measure, participants scored a mean of 3.2 with a standard deviation of 1.3, revealing that they recalled over half of the words presented to them on average. Participants correctly repeated sequences in the MoCA attention measure 66% of the time, and the mean score on the MOS-HIV CF4 was 68.8 out of 100 with a standard deviation of 18.9.



Dichotomized MoCA Attention Scores (Forward and Backward Digit Span)

	Frequency	Percent
0 or 1	73	33.95%
2	142	66.05%

Figure 5. Distributions and Frequencies for Dependent Variables (Measures of Cognitive Dysfunction)
Left Graph: Distribution of MoCA Memory Score, with the score (1-5) listed on the X-axis and the percent of the sample listed on the Y-axis.
Right Graph: MOS-HIV CF4 Score (1-100) listed on the X-axis and the percent of the sample listed on the Y-axis.
Bottom table: Frequencies and percentages from the MoCA attention score dichotomized for scoring of either 0 or 1 or 2.

Results of Regression analyses

Out of the 8 different regression models fit, Group 1, Group 5, and Group 6 revealed significant associations between the independent and dependent variables.

In Group 1, we used unadjusted, core-adjusted, and fully-adjusted regression models to test the association between current marijuana use all three cognitive outcomes. Current marijuana use was significantly associated with the MOS-HIV CF4 score, but neither the MoCA memory or MoCA attention scores as shown in Table 3 below.

Table 3. Significant Association Between Current Marijuana Use and MOS-HIV CF4 Score

Table 3 shows the p-values, confidence intervals, β-values, and odds ratios for the Group 1 regression analyses using unadjusted, core-adjusted, and fully-adjusted models. Linear regression was used for the MOS-HIV CF4 and MoCA memory outcomes and logistic regression was used for the MoCA attention outcome. Current marijuana use was significantly negatively associated with the MOS-HIV CF4 score in the core-adjusted and fully-adjusted models.

Group 1: Independent Variable: Current Marijuana (# days Marijuana was used in the past 30 days)									
Dependent Variables	Unadjusted			Core-Adjusted			Fully-Adjusted		
	p-Value	Confidence Interval (95%)	β-Value	p-Value	Confidence Interval (95%)	β-Value	p-Value	Confidence Interval (95%)	β-Value
MOS-HIV CF4 Score (range 1-100)	0.3	-0.4, 0.1	-0.1	0.03	-0.5, -0.02	-0.2	0.01	-0.5, -0.07	-0.30
MoCA Memroy Score	0.4	-0.01, 0.02	0.007	0.8	-0.01, 0.02	0.002	0.8	-0.01. 0.02	0.002
MoCA Attention Score	0.4	0.9, 1.0	Odds Ratio 1.0	0.4	0.9, 1.0	Odds Ratio 1.0	0.3	0.9, 1.0	Odds Ratio 1.0

In Group 2, we used unadjusted, core-adjusted, and fully-adjusted regression models to test the association between current heavy alcohol use and all three cognitive outcomes. No significant associations were found between current heavy alcohol use and any of the cognitive outcomes as shown in Table 4 below.

Table 4. No Association between Current Heavy Drinking and Cognitive Outcomes
Table 4 shows the p-values, confidence intervals, β-values, and odds ratios for the Group 2 regression analyses using unadjusted, core-adjusted, and fully-adjusted models. Linear regression was used for the MOS-HIV CF4 and MoCA memory outcomes and logistic regression was used for the MoCA attention outcome. No significant associations were found between current heavy drinking and any cognitive outcome.

Group 2: Independent Variable: Current Heavy Drinking (# heavy drinking days in the past 30 days)									
Dependent Variables	Unadjusted			Core-Adjusted			Full-Adjusted		
	p-Value	Confidence Interval (95%)	β-Value	p-Value	Confidence Interval (95%)	β-Value	p-Value	Confidence Interval (95%)	β-Value
MOS-HIV CF4 Score (range 1-100)	0.7	-0.2, 0.4	0.06	0.3	-0.1, 0.4	0.1	0.2	-0.09, 0.6	0.2
MoCA Memroy Score	0.3	-0.03, 0.01	-0.01	0.6	-0.03, 0.02	-0.005	0.6	-0.02, 0.02	-0.006
MoCA Attention Score	0.8	0.9, 1.0	Odds Ratio 1.0	0.6	0.5, 1.05	Odds Ratio 1.0	0.7	0.9, 1.01	Odds Ratio 1.0

In Group 3, we used unadjusted, core-adjusted, and fully-adjusted regression models to test the association between lifetime marijuana use and all three cognitive outcomes. No significant associations were found between lifetime marijuana use and any cognitive outcome as shown in Table 5 below.

Table 5. No Association between Lifetime Marijuana Use and Cognitive Outcomes
Table 5 shows the p-values, confidence intervals, β-values, and odds ratios for the Group 3 regression analyses using unadjusted, core-adjusted, and fully-adjusted models. Linear regression was used for the MOS-HIV CF4 and MoCA memory outcomes and logistic regression was used for the MoCA attention outcome. Lifetime marijuana use was not significantly associated with any cognitive outcome.

Group 3: Independent Variable: Lifetime Marijuana Use (# years marijuana was used ≥ 3 times per week)									
Dependent Variables	Unadjusted			Core-Adjusted			Full-Adjusted		
	p-Value	Confidence Interval (95%)	β-Value	p-Value	Confidence Interval (95%)	β-Value	p-Value	Confidence Interval (95%)	β-Value
MOS-HIV CF4 Score (range 1-100)	0.9	-0.2, 0.2	0.01	0.1	-0.3, 0.05	-0.1	0.2	-0.3, 0.06	-0.1
MoCA Memroy Score	0.1	-0.002, 0.03	0.01	0.2	-0.006, 0.02	0.009	0.2	-0.005, 0.03	-0.005
MoCA Attention Score	0.2	1.0, 1.04	Odds Ratio 1.0	0.2	0.9, 1.0	Odds Ratio 1.0	0.2	1.0, 1.05	Odds Ratio 1.0

In Group 4 we used unadjusted, core-adjusted, and fully-adjusted regression models to test the association between lifetime alcohol use in kilograms and all three cognitive outcomes. No significant associations were found between lifetime alcohol use (kg) and any cognitive outcome as seen below in Table 6.

Table 6. No Association between Lifetime Alcohol Use (Kg) and Cognitive Outcomes
Table 6 shows the p-values, confidence intervals, β-values, and odds ratios for the Group 3 regression analyses using unadjusted, core-adjusted, and fully-adjusted models. Linear regression was used for the MOS-HIV CF4 and MoCA memory outcomes and logistic regression was used for the MoCA attention outcome. Lifetime alcohol use measured in Kg was not significantly associated with any cognitive outcome.

Group 4: Independent Variable: Lifetime Alcohol Use (Total Kg)									
Dependent Variables	Unadjusted			Core-Adjusted			Full-Adjusted		
	p-Value	Confidence Interval (95%)	β-Value	p-Value	Confidence Interval (95%)	β-Value	p-Value	Confidence Interval (95%)	β-Value
MOS-HIV CF4 Score (range 1-100)	0.8	-0.003, 0.002	-0.0004	0.9	-0.002, 0.002	-0.002	1.0	-0.002, 0.002	0
MoCA Memroy Score	0.6	-0.0001, 0.002	0	0.2	-0.0001, 0.0003	0.0001	0.3	-0.0001, 0.0003	0.0001
MoCA Attention Score	0.7	1.0, 1.0	Odds Ratio	0.9	1.0, 1.0	Odds Ratio	0.8	1.0, 1.0	Odds Ratio
			1.0			1.0			1.0

In Group 5 we used unadjusted, core-adjusted, and fully-adjusted regression models to test the association between lifetime marijuana use, duration of heavy drinking (years), current marijuana use, and current heavy alcohol use and each cognitive outcome adjusting for all covariates. Current marijuana use was again significantly associated with the MOS-HIV CF4 score, but neither MoCA score. Current heavy alcohol use was also significantly associated with the MOS-HIV CF4 score in this model, but it was in the opposite direction of what was hypothesized. Current heavy alcohol use was not associated with either MoCA score. Likewise lifetime marijuana and heavy alcohol use were not associated with any cognitive outcome. See Table 7 below.

Table 7. Significant Associations between Current Marijuana, Heavy Alcohol Use (kg) and the MOS-HIV CF4 Score

Table 7 shows the p-values, confidence intervals, β-values, and odds ratios for the Group 3 regression analyses using unadjusted, core-adjusted, and fully-adjusted models. Linear regression was used for the MOS-HIV CF4 and MoCA memory outcomes and logistic regression was used for the MoCA attention outcome. Current marijuana and heavy alcohol use (kg) were both significantly associated with the MOS-HIV CF4 score, with current marijuana having a negative association and current heavy drinking having a positive association. Both were only significant in the fully adjusted model. Duration of heavy drinking and lifetime marijuana use were not significantly associated with any cognitive outcome. First, second, third, and fourth values in the table correspond to lifetime marijuana, duration of heavy drinking (years), current marijuana use, and current heavy drinking

Group 5: Independent Variables: Lifetime Marijuana use, duration of heavy drinking (years), current marijuana use and current heavy drinking									
Dependent Variables	Unadjusted			Core-Adjusted			Full-Adjusted		
	p-Value	Confidence Interval (95%)	β-Value	p-Value	Confidence Interval (95%)	β-Value	p-Value	Confidence Interval (95%)	β-Value
MOS-HIV CF4 Score (range 1-100)	0.4 0.5 0.4 0.2	-0.1, 0.4 -0.4, 0.2 -0.2, 0.5 -0.5, 0.09	0.1 -0.09 0.1 -0.2	0.8 0.3 0.08 0.05	-0.3, 0.2 -0.4, 0.1 -0.03, 0.6 -0.5, -0.003	-0.03 -0.1 0.3 -0.3	0.8 0.2 0.03 0.01	-0.2, 0.3 -0.5, 0.1 0.03, 0.7 -0.6, -0.08	0.03 -0.2 0.4 -0.4
MoCA Memroy Score	0.2 0.3 0.1 0.8	-0.007, 0.03 -0.009, 0.03 -0.04, 0.006 -0.02, 0,02	0.01 0.01 -0.02 0.003	0.3 0.007 0.2 0.8	-0.008, 0.03 -0.002, 0.04 -0.04, 0.009 -0.02, 0.02	0.01 0.02 -0.01 -0.002	0.2 0.2 0.3 0.7	-0.006, 0.03 -0.008, 0.04 -0.04, 0.01 -0.03, 0.02	0.01 0.01 -0.01 -0.004
MoCA Attention Score	0.3 0.7 0.9 0.9	1.0, 1.05, 1.0, 1.04 1.0, 1.04, 1.0, 1.04	Odds Ratio 1.0 1.0 1.0 1.0	0.4 0.2 0.8 0.7	1.0, 1.05 1.0, 1.06 1.0, 1.04 1.0, 1.05	Odds Ratio 1.0 1.0 1.0 1.0	0.3 0.5 1.0 0.8	1.0, 1.06 1.0, 1.05 1.0, 1.05 1.0, 1.01	Odds Ratio 1.0 1.0 1.0 1.0

In Group 6 we used unadjusted, core-adjusted, and fully-adjusted regression models to test the association of lifetime marijuana use, lifetime heavy alcohol use measured in kg, current marijuana use, and current heavy alcohol use and each cognitive outcome adjusting for all covariates. Again, current marijuana use was significantly

associated with the MOS-HIV CF4 score but neither the MoCA memory or MoCA attention scores. Current heavy drinking, lifetime marijuana use, and lifetime heavy alcohol use (kg) were not significantly associated with any cognitive outcomes. See Table 8 below.

Table 8. Significant Association Between Current Marijuana Use and MOS-HIV CF4 Score

Table 8 shows the p-values, confidence intervals, β-values, and odds ratios for the Group 3 regression analyses using unadjusted, core-adjusted, and fully-adjusted models. Linear regression was used for the MOS-HIV CF4 and MoCA memory outcomes and logistic regression was used for the MoCA attention outcome. Current marijuana use was significantly negatively associated with the MOS-HIV CF4 score in only the fully-adjusted model. Current heavy drinking, lifetime marijuana use, and lifetime heavy alcohol use (kg) were not significantly associated with any cognitive outcome. First, second, third, and fourth values in the table correspond to lifetime marijuana, duration of heavy drinking (years), current marijuana use, and current heavy drinking

Group 6: Independent Variables: lifetime marijuana use, lifetime heavy alcohol use (Kg), current marijuana use, and current heavy drinking									
Dependent Variables	Unadjusted			Core-Adjusted			Full-Adjusted		
	p-Value	Confidence Interval (95%)	β-Value	p-Value	Confidence Interval (95%)	β-Value	p-Value	Confidence Interval (95%)	β-Value
MOS-HIV CF4 Score (range 1-100)	0.4 0.5 0.4 0.2	-0.1, 0.4 -0.003, 0.002 -0.2, 0.5 -0.5, 0.09	0.1 -0.0008 0.1 -0.1	0.8 0.5 0.09 0.05	-0.3, 0.2 -0.003, 0.001 -0.05, 0.6 -0.5, 0.0007	-0.03 -0.0008 0.3 -0.3	0.8 0.5 0.05 0.01	-0.2, 0.3 -0.003, 0.002 -0.006, 0.6 -0.6, -0.07	0.03 -0.008 0.3 -0.4
MoCA Memroy Score	0.2 0.4 0.2 0.8	-0.007, 0.03 -0.0001, 0.0003 -0.04, 0.007 -0.02, 0.02	0.01 0.0001 -0.02 0.003	0.2 0.2 0.3 0.8	-0.008, 0.03 0, -0.0003 -0.03, 0.01 -0.02, 0.02	0.01 0.0001 -0.01 -0.003	0.2 0.2 0.3 0.7	-0.007, 0.03 -0.0001, 0.0003 -0.04, 0.01 -0.03, 0.02	0.01 0.0001 -0.01 -0.005
MoCA Attention Score	0.3 0.6 0.7 0.9	1.0, 1.05 1.0, 1.00 1.0, 1.05 1.0, 1.04	Odds Ratio 1.0 1.0 1.0 1.0	0.3 0.9 0.7 0.9	1.0, 1.05 1.0, 1.00 1.0, 1.05 1.0, 1.04	Odds Ratio 1.0 1.0 1.0 1.0	1.3 0.7 0.7 0.9	1.0, 1.1 1.0, 1.0 1.0, 1.1 1.0, 1.05	Odds Ratio 1.0 1.0 1.0 1.0

In Group 7, we used unadjusted, core-adjusted, and fully-adjusted regression models to determine if there was an interaction between current marijuana and heavy alcohol use on all three cognitive outcomes. Likewise, in Group 8, we used unadjusted, core-adjusted, and fully-adjusted regression models to determine if there was an interaction between lifetime marijuana and heavy alcohol use (kg) on all three cognitive outcomes. There were no significant interactions found between current or lifetime marijuana and heavy alcohol use with any measure of cognitive dysfunction.

DISCUSSION

We examined the effects of marijuana and heavy alcohol use on cognitive function in people with HIV-infection. Regression analyses revealed a significant, negative association between current marijuana use and the MOS-HIV CF4 score. A significant positive association between current heavy drinking and the MOS-HIV CF4 score was also found, but was in the opposite direction of what was expected. Current marijuana use was not associated with either the MoCA memory or MoCA attention score. Likewise, we did not find any associations between lifetime marijuana or either measure of lifetime heavy alcohol use and any measures of cognitive dysfunction. There were no interactions between current marijuana and heavy alcohol use or lifetime marijuana and heavy alcohol use with any cognitive outcome.

Our finding that current marijuana use has a negative impact on cognitive function is consistent with other reports in the literature that acute use of marijuana has negative effects on memory, executive function, and attention with some residual effects reported in the same cognitive domains[27-29,33,40-45,48]. Similarly, the results that current, but not lifetime, marijuana use is associated with cognitive dysfunction are consistent with previous findings indicating that any effects of marijuana use diminish or are absent after around a month of abstinence, and that the long-term persistent effects of marijuana on cognition are still under debate[40,42,43,51]. Over 55% of participants reported no marijuana use in the past 30 days, indicating that many had abstained for at least one month. This would theoretically be enough time for most cognitive impairments to

subside. It is believed that after abstinence of one month, all cognitive impairments caused by marijuana will remit[42,43]. Therefore, it is possible that our lifetime marijuana measure was not associated with any cognitive dysfunction because a good portion of our study population had abstained for a long enough period of time for cognitive dysfunction to abate.

On the other hand, our finding that current heavy drinking is associated with an increase in cognitive function is inconsistent with the literature. Heavy alcohol use has been shown to have negative effects on executive function, attention, and memory[53,60,61,66]. While these findings could be causal (some studies have found that moderate drinking at low levels is associated with better cognitive function[104-107]), this finding most likely represents a Type I error or a failure to adequately adjust for confounders. This finding also only appears in the Group 5 multivariable regression model (whereas the finding that current marijuana is associated with cognitive dysfunction appears in 3 models) revealing that it is not very robust.

In general, it is well documented that what may be considered hazardous exposure to alcohol over long periods of time can lead to severe cognitive deficits such as ARD and WKS. In a review of cognitive functioning among sober, social drinkers, Parksons et al found that 5-6 standard drinks per day over time created some cognitive deficits, 7-9 drinks per day caused mild cognitive deficits, and 10 or more drinks per day caused cognitive deficits such as those seen in individuals with alcohol use disorders[109]. These levels of drinking are consistent with hazardous drinking as defined in the current study. However, the threshold at which alcohol consumption becomes harmful is unclear and

most-likely variable from person to person, with the effects on cognition potentially U-shaped in nature meaning low amounts of alcohol can be beneficial and high amounts harmful[101,108]. Therefore, we may have not detected any significant associations of lifetime alcohol use and cognitive dysfunction despite individuals drinking at hazardous levels due to the fact that the effects of alcohol on cognition are variable and cognitive dysfunction may not be occurring in all participants even when exposed to alcohol at that level.

Despite marijuana, alcohol, and HIV-infection having their main affects on different areas of the brain, certain similarities would indicate that synergistic effects could be encountered, but this was not found in our study. HIV-infection, marijuana use, and alcohol use have all been shown to affect the basal ganglia and frontal lobes, which are involved in executive functions[1,9-11,20,26,27,54,59]. The HIV-virus as well as the CB1 receptor, which binds Δ^{9}-THC, have been shown to have the highest concentration in the basal ganglia[1,9-11,20,26,27]. Likewise, there has been shown to be an increase in MCP-1, a measure of inflammation in the brains of alcoholics, in the basal ganglia[59]. This suggests that there is a potential for marijuana, alcohol, and HIV to have negative synergistic effects on the basal ganglia and frontal cortices, manifesting as deficits in executive function, but this was not found in the present study. Likewise, hippocampal damage has been reported in the brains of alcoholics, and the CB1 receptor has been shown to induce hippocampal cell death, also suggesting a synergistic effect of these two on perhaps memory function[27].

It is well documented that marijuana causes deficits in recall, manifesting as acute and residual cognitive dysfunction[27-29,31,33,35]. The MoCA directly tests recall, as participants must recall a list of words directly after hearing them, and five minutes later, so the finding that current and lifetime marijuana use was not associated with it is opposite of what was expected. One reason for this, and a limitation of our study, may have been that the MoCA as a whole has been validated for use in HIV-infected people, but its domains have only been validated in populations such as individuals with varying forms of dementia. The domains individually may not be sensitive enough to test mild cognitive dysfunction among specific domains of cognition in those with HIV-infection and comorbid substance use. This may also be why there was no association found between the MoCA attention score and recent marijuana use, since there is also some support to show that acute marijuana use impairs attentional function[28,29]. The MOS-HIV takes executive function into consideration (as well as attention and memory) which is known to be impaired in HIV-infection and to some extent with marijuana use[1,9-11,21,28,29,33]. Current marijuana use showed a significant correlation with the MOS-HIV but neither MoCA score, which may be reflective of the MOS-HIV being more sensitive to executive function impairment and more global cognitive dysfunction in general.

On the other hand, a strength of this study was that we included many covariates in the analyses to adjust for potential confounders. All of these variables have been shown to influence cognition in their own right[1,7,10,12,13,22]. Similarly, since we fit a variety of different multivariable regression models, we were able to see that the association between number of days of marijuana use in the past 30 days and MOS-HIV

CF4 score was found in all models in which it was included, suggesting that it was a very robust association not accounted for by any of the confounding factors we measured and adjusted for.

Since the MOS-HIV in general is utilized as a brief screening tool to assess functional status and well-being in those with HIV-infection, our findings suggest that increasing current marijuana use may actually decrease an individual's level of functioning and well-being. We found that for every day that an individual uses marijuana, their MOS-HIV CF4 score decreases by 0.3 points. This is significant since optimal daily functioning is necessary for optimal HIV suppression. Therefore, even if marijuana may have proven therapeutic qualities, they will need to be weighed against the risks of cognitive dysfunction.

CONCLUSION

In summary, current marijuana use appears to be associated with lower cognitive function. We did not find an association between lifetime marijuana use and any measure of cognitive dysfunction, nor did we find an association with lifetime alcohol use and any measure of cognitive dysfunction. Current alcohol use was associated with better cognitive function, but this was opposite of what we hypothesized. Likewise, no interactions were found between current marijuana use and heavy drinking on cognitive function or between lifetime marijuana use and lifetime heavy drinking on cognitive function. Future research should utilize measures more specific to HIV-infected people as well as measures that are sensitive to more subtle forms of cognitive dysfunction and possibly a wider range of cognitive dysfunction other than that of memory and attention. Future studies should also consider whether or not the effects of alcohol and marijuana are detectable as significant agents of cognitive decline in individuals who have many competing risks for cognitive dysfunction.

APPENDIX A

30 Day Drug ASI

Now I am going to ask you some questions about your use of drugs in the past 30 days:

Note to Interviewer: Record numbers of days subject reported using non-prescription drugs (i.e., heroin, methamphetamine) and numbers of days subject reported using prescription drugs used without a doctor's prescription of in amounts greater than prescribed.

*Note the usual or most recent route of administration for each drug. For more than one route, choose the most severe. The routes are listed from least severe to most severe. Ask if subject is currently prescribed each prescription drug/category **after** assessing number of days of misuse and route of administration for **all** drugs.*

How many days in the past 30 days have you used…?

	Number of Days	**Route of Administration** *(Oral, Nasal, Smoking, Injection, IV)*	
Cocaine	_____	_____	
Heroin	_____	_____	
Hallucinogens	_____	_____	
Phencyclidines	_____	_____	
Cannabis/ Marijuana	_____	_____	**Are you Currently Prescribed…?**
Stimulants/ Amphetamines	_____	_____	☐ **Yes** ☐ **No**
Buprenorphine	_____	_____	☐ **Yes** ☐ **No**
Methadone	_____	_____	☐ **Yes** ☐ **No**
Other Prescription Opioids	_____	_____	☐ **Yes** ☐ **No**
Tranquilizers/ Sedatives	_____	_____	☐ **Yes** ☐ **No**
Inhalants	_____	_____	
Miscellaneous	_____	_____	
More than One Drug	_____	_____	
No Drugs	_____	_____	

APPENDIX B

30-Day TLFB Alcohol

Interviewer Prompt: Administer TLFB
Use a calendar for the preceding 30 days starting from yesterday, to recor the subject's use of alcohol.

If alcohol is used, record the number of standard drinks for each day. Consider a "drink" to be a can or bottle of beer (12 ounces), a glass of wine (5 ounces), a wine cooler (12 ounces), or a shot of hard liquor like gin, vodka, or whiskey (1.5 ounces).

Please enter the number of drinks per day rounded to the nearest whole number. The 30th day on the Timeline Follow-Back should be entered as Day 1. "Yesterday" (i.e. the day prior to the date the TLFB was administered) should be recorded as Day 30.

Day	Alcohol Use Number of Drinks	Day	Alcohol Use Number of Drinks
Day 1		Day 16	
Day 2		Day 17	
Day 3		Day 18	
Day 4		Day 19	
Day 5		Day 20	
Day 6		Day 21	
Day 7		Day 22	
Day 8		Day 23	
Day 9		Day 24	
Day 10		Day 25	
Day 11		Day 26	
Day 12		Day 27	
Day 13		Day 28	
Day 14		Day 29	
Day 15		Day 30	

APPENDIX C

Lifetime ASI

This next section will focus on questions about your alcohol and/or drug use. By "drug use" we mean drugs that you use either without a doctor's prescription, in larger amounts that prescribed, or for longer periods that prescribed.

Note the usual or most recent route of administration for each drug. For more than one route, choose the most severe. The routes are listed from least to most severe: Oral, Nasal, Smoking, Injection, IV

How many <u>years</u> in your life have you regularly used…? (3x/week or more)
How do you use it?
How old were you the first time you used…?

	Lifetime Use: ≥ 3x/week (Number of Years)	Route of Administration	Age of Onset
Cocaine	_____	_____	_____
Heroin	_____	_____	_____
Hallucinogens	_____	_____	_____
Phencyclidines	_____	_____	_____
Cannabis/ Marijuana	_____	_____	_____
Stimulants/ Amphetamines	_____	_____	_____
Buprenorphine	_____	_____	_____
Methadone	_____	_____	_____
Other Prescription Opioids	_____	_____	_____
Tranquilizers/ Sedatives	_____	_____	_____
Inhalants	_____	_____	_____
Miscellaneous	_____	_____	_____
More than One Drug	_____	_____	_____
No Drugs	_____	_____	_____

APPENDIX D

Lifetime Drinking History

I'm going to ask you about your drinking history. I'd like to start with the year that you began to drink regularly and work forward to the present. Please give me information as accurately as you can about what type of beverage you were drinking, how much, and how often.

Note to interviewer: Why the timing overlaps with the age that the subject found out that they were HIV-infected, ask question B. Continue through phases until current phase is reached. Use additional forms as needed

How old were you the first time you had a drink? By "first drink" I mean the first full drink of alcohol excluding tastes or small sips.

_____ (age in years)

☐ **Never had a drink SKIP TO NEXT SECTION**

<u>Phase 1 of Drinking</u>

Now I am going to ask you about your drinking during the first year that you began to have at least one drink per month. Consider a "drink" to be a 12oz can or a bottle of beer, a 5oz glass of wine, a 120z wine cooler, or a 1.5oz shot of hard liquor (like scotch, gin, or vodka).

1A. How old were you when you began to drink at least one drink per month (regular drinking?)

_____ Age of phase 1 of drinking (years)

☐ **Never had more than one drink SKIP TO NEXT SECTION**

1B. How many drinks would you have on a typical day when you were drinking?

_____ typical # of drinks/day (quantity)

(If participant answers in anything other than # of drinks, convert later)

1C. How many days per month would you generally drink at this level (i.e. typical # of drinks)?

_____ days/month (frequency)

1D. What is the maximum number of drinks that you <u>would have</u> in any one day?

_____ maximum # of drinks/day (quantity)

(This is the maximum # of drinks the subject actually drank, <u>not his/her potential</u>. If participant answers in quantity other than # of drinks, convert later)

You just told me about your drinking habits at the point when you first began to drink regularly. You said you began to drink when you were _____ years old, that you typically drank _____ drinks per occasion, _____ times per month.

<u>EVENT that changed drinking</u>

Now I want you to think about when your drinking behavior changed in a significant way from this time. This change in your drinking might have occurred 6 months after you started drinking regularly or perhaps 2 or 5 years later. Can you think of any event or events in your life that may have changed your drinking habits? Examples of events could be the death of someone close to you, marital or family problems, medical problems, jail, or any other event that affected your drinking.

Event that changed subject's drinking pattern: _____

1E/2A. How old were you when this event happened, and your drinking changed?

_____ age when drinking changed (years)

Phase 2 of Drinking

2B. After this event or events happened, and your drinking changed, how many drinks would you have on a typical day when you were drinking?

_____ typical # of drinks/day (quantity)

2C. How many days per month would you generally drink at this level (typical # of drinks)?

_____ days/month (frequency)

2D. What is the maximum number of drinks that you <u>would have</u> in any one day?

_____ maximum # drinks/day (quantity)

(This is the maximum # of drinks the subject actually drank, <u>not his/her potential</u>)

How long did you continue to drink at this level (on average _____ drinks per day, _____ days a month) until your drinking changed in a significant way? Did any important event or events occur during this period that changed your usual drinking habits? Examples of events could be the death of someone close to you, marital or family problems, work problems, medical problems, jail, or any other event that affected your drinking.

Even that changed subject's drinking pattern: _____

2E/3A. How old were you when this event happened, and your drinking changed?

_____ age when drinking changed (years)

Phase 3 of Drinking

3B. After this even or events happened, and your drinking changed, how many drinks would you have on a typical day when you were drinking?

_____ typical # of drinks/day (quantity)

3C. How many days per month would you generally drink at this level (typical # of drinks)?

_____ days/month (frequency)

3D. What is the maximum number of drinks that you <u>would have</u> in any one day?

_____ maximum # drinks/day (quantity)

(This is the maximum # of drinks the subject actually drank, <u>not his/her potential)</u>

How long did you continue to drink at this level (on average _____drinks per day _____ days a month) until your drinking changed in a significant way? Did any important event or events occur during this period that changed your usual drinking habits?

Event that changed subject's drinking pattern: _____

3E/4A. How old were you when this even happened, and your drinking changed?

_____ age when drinking changed (years)

<u>Phase 4 of Drinking</u>

4B. After this even or events happened, and your drinking changed, how many drinks would you have on a typical day when you were drinking?

_____ typical # of drinks/day (quantity)

4C. How many days per month would you generally drink at this level (typical # of drinks)?

_____ days/month (frequency)

4D. What is the maximum number of drinks that you <u>would have</u> in any one day?

_____ maximum # drinks/day (quantity)

(This is the maximum # of drinks the subject actually drank, <u>not his/her potential)</u>

How long did you continue to drink at this level (on average _____drinks per day _____ days a month) until your drinking changed in a significant way? Did any important event or events occur during this period that changed your usual drinking habits?

Event that changed subject's drinking pattern: _____

4E/5A. How old were you when this even happened, and your drinking changed?

_____ age when drinking changed (years)

Phase 5 of Drinking

5B. After this even or events happened, and your drinking changed, how many drinks would you have on a typical day when you were drinking?

_____ typical # of drinks/day (quantity)

5C. How many days per month would you generally drink at this level (typical # of drinks)?

_____ days/month (frequency)

5D. What is the maximum number of drinks that you would have in any one day?

_____ maximum # drinks/day (quantity)

(This is the maximum # of drinks the subject actually drank, not his/her potential)

How long did you continue to drink at this level (on average _____drinks per day _____ days a month) until your drinking changed in a significant way? Did any important event or events occur during this period that changed your usual drinking habits?

Event that changed subject's drinking pattern: _____

5E/6A. How old were you when this even happened, and your drinking changed?

_____ age when drinking changed (years)

Phase 6 of Drinking

6B. After this even or events happened, and your drinking changed, how many drinks would you have on a typical day when you were drinking?

_____ typical # of drinks/day (quantity)

6C. How many days per month would you generally drink at this level (typical # of drinks)?

_____ days/month (frequency)

6D. What is the maximum number of drinks that you would have in any one day?

_____ maximum # drinks/day (quantity)

(This is the maximum # of drinks the subject actually drank, not his/her potential)

How long did you continue to drink at this level (on average _____drinks per day _____ days a month) until your drinking changed in a significant way? Did any important event or events occur during this period that changed your usual drinking habits?

Event that changed subject's drinking pattern: _____

6E/7A. How old were you when this even happened, and your drinking changed?

_____ age when drinking changed (years)

Phase 7 of Drinking

7B. After this even or events happened, and your drinking changed, how many drinks would you have on a typical day when you were drinking?

_____ typical # of drinks/day (quantity)

7C. How many days per month would you generally drink at this level (typical # of drinks)?

_____ days/month (frequency)

7D. What is the maximum number of drinks that you <u>would have</u> in any one day?

_____ maximum # drinks/day (quantity)

(This is the maximum # of drinks the subject actually drank, <u>not his/her potential)</u>

How long did you continue to drink at this level (on average _____drinks per day _____ days a month) until your drinking changed in a significant way? Did any important event or events occur during this period that changed your usual drinking habits?

Event that changed subject's drinking pattern: _____

7E/8A. How old were you when this even happened, and your drinking changed?

_____ age when drinking changed (years)

Phase 8 of Drinking

8B. After this even or events happened, and your drinking changed, how many drinks would you have on a typical day when you were drinking?

_____ typical # of drinks/day (quantity)

8C. How many days per month would you generally drink at this level (typical # of drinks)?

_____ days/month (frequency)

8D. What is the maximum number of drinks that you <u>would have</u> in any one day?

_____ maximum # drinks/day (quantity)

(This is the maximum # of drinks the subject actually drank, <u>not his/her potential)</u>

How long did you continue to drink at this level (on average _____drinks per day _____ days a month) until your drinking changed in a significant way? Did any important event or events occur during this period that changed your usual drinking habits?

Event that changed subject's drinking pattern: _____

8E/9A. How old were you when this even happened, and your drinking changed?

_____ age when drinking changed (years)

LDH WEB FORM FOR DATA ENTRY

Note to Interviewer: Record age of first drink in the table below. Beginning with the earliest phase, record the subject's age when this phase of drinking began and ended, the typical number of drinks the subject reported having per occasion (drinking day), the average number of days per month the subject reported drinking at this level (i.e. typical number of drinks) and the maximum number of drinks the subject reported having in any one day. Record this information in below for each phase of drinking reported by the subject.

Age Range (younger to older) **Frequency (days/month)** **Quantity (drinks/day)**

First drink: _____

0. OR

☐ Never had a drink

From age: _____

1A. OR

☐ Never had more than one drink a month **1C**. _____ days/month **1B**. Typical # drinks/day_____

1E. To age: _____ **1D.** Maximum # drinks/day: ___

2A. From age: _____ **2B.** Typical # drinks/day: _____

2C. _____ days/ month

2E. To age: _____ **2D.** Maximum # drinks/day: ___

3A. From age: _____ **3B.** Typical # drinks/day: _____

3C. _____ days/ month

3E. To age: _____ **3D.** Maximum # drinks/day: ___

4A. From age: _____ **4B.** Typical # drinks/day: _____

4C. _____ days/ month

4E. To age: _____ **4D.** Maximum # drinks/day: ___

5A. From age: _____ **5B.** Typical # drinks/day: _____

5C. _____ days/ month

5E. To age: _____ **5D.** Maximum # drinks/day: ___

6A. From age: _____ **6B.** Typical # drinks/day: _____

6C. _____ days/ month

6E. To age: _____ **6D.** Maximum # drinks/day: ___

7A. From age: _____ **7B.** Typical # drinks/day: _____

7C. _____ days/ month

7E. To age: _____ **7D.** Maximum # drinks/day: ___

8A. From age: _____ **8B.** Typical # drinks/day: _____

8C. _____ days/ month

8E. To age: _____ **8D.** Maximum # drinks/day: ___

APPENDIX E

MoCA Memory and Attention Sections

1. Memory:

To Interviewer: Read list of words at the rate of 1 per second. Subject must repeat them. Do 2 trials, even if the first trial is successful. You will ask the subject to recall again after the next section. Mark a check in the allocated space for each word the subject produces on this first trial. When the subject indicates that (s)he has finished (has recalled all words), or can recall no more words, read the list a second time giving the following instructions:

A. This is a memory test. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn't matter in what order you say them.

	FACE	VELVET	CHURCH	DAISY	RED
1st Trial					

B. I am going to read the same list for a second time. Try to remember and tell me as many words as you can, including words you said the first time

	FACE	VELVET	CHURCH	DAISY	RED
2nd Trial					

To Interviewer: Put a check in the allocated space for each word the subject recalls after the second trial. At the end of the second trial, inform the subject that (s)he will be asked to recall these words again by saying:

I will ask you to recall those words again in about 5 minutes.

2. Attention:

A. I am going to say some numbers and when I am through, repeat them to me exactly as I said them.

To Interviewer: Read the five number sequence at a rate of one digit

per second

2 1 8 5 4

Score: 0 or 1

B. Now I am going to say some more numbers, but when I am through you must repeat them to me in the backwards order.

To interviewer: Read the three number sequence at a rate of one digit per second. Subject has to repeat them in backward order

7 4 2

Score: 0 or 1

Scoring: Allocate one point for each sequence correctly repeated

APPENDIX F

MOS-HIV CF4 (Taken from Section B of the Boston ARCH Baseline Screener)

10. How much of the time during the past 4 weeks:

a. Did you have difficulty reasoning and solving problems, for example, making plans, making decisions, learning new things?

All of the time
Most of the time
A good bit of the time
Some of the time
A little of the time
None of the time
Refused

b. Did you forget things that happened recently, for example, where you put things and when you had appointments?

All of the time
Most of the time
A good bit of the time
Some of the time
A little of the time
None of the time
Refused

c. Did you have trouble keeping your attention on any activity for long?

All of the time
Most of the time
A good bit of the time
Some of the time
A little of the time
None of the time
Refused

d. Did you have difficulty doing activities involving concentration and thinking?

All of the time
Most of the time
A good bit of the time
Some of the time
A little of the time
None of the time
Refused

LIST OF JOURNAL ABBREVIATIONS

Addict Behav	Addictive Behaviors
AIDS Behav	AIDS and Behavior
AIDS Patient Care ST	AIDS Patient Care and STDs
Alcohol Clin Exp Res	Alcoholism- Clinical and Experimental Research
Alcoholism Drug Depend	Journal of Alcoholism and Drug Dependence
Alcohol Res Health	Alcohol Research and Health
Alzheimers Res Ther	Alzheimer's Research and Therapy
Am J Drug Alcohol Ab	American Journal of Drug and Alcohol Abuse
Am J Addict	American Journal on Addictions
Am J Epidemiol	American Journal of Epidemiology
Am J Psychiat	American Journal of Psychiatry
Ann Neurol	Annals of Neurology
Arch Gen Psychiat	Archives of General Psychiatry
Behav Brain Res	Behavioral Brain Research
Biol Psychiat	Biological Psychiatry
Clin Neuropsychol	Clinical Neuropsychologist
Curr Addict Rep	Current Addiction Reports
Curr Drug Abuse Rev	Current Drug Abuse Reviews
Curr HIV/AIDS Rep	Current HIV/AIDS Report
Curr Opin Neurol	Current Opinion in Neurology
Depress Anxiety	Depression and Anxiety

Drug Alcohol Depend	Drug and Alcohol Dependence
Exp Clin Psychopharm	Experimental and Clinical Psychopharmacology
Exp Neurol	Experimental Neurology
JAMA	JAMA: The Journal of the American Medical Association
J Addict Med	Journal of Addiction Medicine
J Am Geriatr Soc	Journal of American Geriatrics Society
J AIDS Clinic Res	Journal of AIDS and Clinical Research
J Acquir Immune Defic Syndr	Journal of Acquired Immune Deficiency Syndromes
J Chron Dis	Journal of Chronic Diseases
J Clin Epidemiol	Journal of Clinical Epidemiology
J Clin Exp Neuropsychol	Journal of Clinical and Experimental Neuropsychology
J Clin Pharmacol	Journal of Clinical Pharmacology
J Gerontol A Biol	Journals of Gerontology Series A- Biological Sciences And Medical Sciences
J Infect Dis	Journal of Infectious Diseases
J Int Neuropsychol Soc	Journal of the International Neuropsychological Society
J Neuroimmune Phar	Journal of Neuroimmune Pharmacology
J Neuropsychiatry Clin Neurosci	Journal of Neuropscyhiatry and Clinical Neurosciences
J Neurovirol	Journal of Neurovirology
J Psychiatr Res	Journal of Psychiatric Research

J Pharmacol	Journal of Pharmacology
J Stud Alcohol	Journal of Studies on Alcohol
J Study Alcohol Drugs	Journal of Studies on Alcohol and Drugs
J Subst Abuse Treat	Journal of Substance Abuse Treatment
Int J STD AIDS	International Journal of STDs and AIDS
Medcare	Medical Care
Neuropsychol Rev	Neuropsychology Review
Pharmacol Biochem Be	Pharmacology Biochemistry and Behavior
Philos Trans R Soc Lond B Biol Sci	Philosophical Transactions of Royal Society London Biological Society
Prog Neurobiol	Progress in Neurobiology
Psychol Addict Behav	Psychology of Addictive Behaviors
Psychpharmacology (Berl)	Psychopharmacology (Berlin)
Qual Life Res	Quality of Life Research
Semin Neurol	Seminars in Neurology
Sci Signal	Science Signaling
Top Antivir Med	Topics in Antiviral Medicine

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CURRICULUM VITAE

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Born: 1990
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Education:

2013 – Present **Boston University School of Medicine**
Pursuing an M.S. in Medical Sciences
Relevant Courses Completed:
◆ Medical Physiology, Biochemistry, Intro to Pathology, Intro to Neuroscience

2008- 2012 **Loyola University Chicago**
B.S. in Molecular Biology
B.S. in Psychology
Relevant Courses Completed:
◆ Brain and Behavior, Cognitive Psychology, Abnormal Psychology, Research Methods, Molecular Genetics, Immunology

Research Experience:

◆Thesis work with Dr. Richard Saitz- *Boston University School of Public Health, Boston, MA*

- June 2014 – present
- Master's Student in the MAMS program at Boston University School of Medicine
- Researching the association of marijuana, alcohol, and cognitive dysfunction in patients with HIV/AIDS using data from the BOSTON ARCH cohort.

◆ Molecular Genetics lab with Dr. Eric Schroeter - *Loyola University Chicago, Chicago, IL*

- January – May 2011
- Assisted graduate students and Dr. Schroeter in studying how specific neurons make synaptic connections in the retina through various molecular biology techniques such as PCR, gel electrophoresis, florescence in situ hybridization

◆ Social psychology research lab with Dr. Fred Bryant – *Loyola University Chicago, Chicago IL*

- August – December 2009

- Assisted graduate students and Dr. Bryant in studying the effects of positive and negative emotions on gratitude through proctoring surveys which student participants took and inputing data into SPSS.

Volunteering Experience:

- bWell Center – *Boston Medical Center, Boston, MA*
  - May 2014 – Present
  - Our aim is to promote health and wellness through fun, educational activities with children and their parents who are being seen in the pediatrics department

- Northwestern Rehabilitation Institute of Chicago – *Northwestern University Chicago, Chicago, IL*
  - November 2011 – May 2012
  - Assisted physical therapists in an in-patient setting with group therapy sessions to help rehabilitate patients with a wide range of histories including car accidents, surgeries, and broken bones.

- Loyola EMS – *Loyola University Chicago Chicago IL*
  - November 2010 – May 2012
  - Responded to emergency situations of students on Loyola University's campus as well as took part in training new EMT students in the program

- Global Medical Brigades – *Loyola University Chicago, Chicago IL*
  - November 2010 – August 2011
  - Traveled to Honduras, helping to prepare and set up medical clinics which offered free health care to the citizens of the rural towns we traveled to.