The Impact of Marijuana Use on Memory in Patients with HIV/AIDS

by

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Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor
of Philosophy in the Department of
Psychology & Neuroscience in the Graduate School
of Duke University

2015

ABSTRACT

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Abstract

The most robust neurocognitive effect of chronic marijuana use is memory impairment. Memory deficits are also high among persons living with HIV/AIDS, and marijuana use among this population is disproportionately common. Yet research examining neurocognitive outcomes resulting from co-occurring marijuana and HIV is virtually non-existent. The primary aim of this case-controlled study was to identify patterns of neurocognitive impairment among HIV patients who used marijuana compared to HIV patients who did not use drugs by comparing the groups on domain T-scores. Participants included 32 current marijuana users (≥3 times per week for at least 1 year) and 37 non-drug users. A comprehensive battery assessed substance use and neurocognitive functioning. Among the full sample, marijuana users performed significantly worse on verbal memory tasks compared to non-drug users and significantly better on attention/working memory tasks. A secondary aim of this study was to test whether the effect of marijuana use on memory was moderated by HIV disease progression, but these models were not significant. This study also examined whether the effect of marijuana use was differentially affected by marijuana use characteristics. Results indicated that earlier age of initiation was associated with worse memory performance. These findings have important clinical implications, particularly given increased legalization of this drug to manage HIV infection.

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1. Introduction

Marijuana use among HIV-infected individuals is disproportionately common. In a recent study of >3000 patients receiving HIV care in four cities in the United States (US), 24.3% reported marijuana use in the past 3 months (Mimiaga et al., 2013). In comparison, the most recent national prevalence study of adults aged 26 or older in the general population reported 5.6% used marijuana in the past month (SAMHSA, 2014). Some HIV-infected individuals report smoking marijuana to alleviate HIV-related symptoms by stimulating appetite and reducing nausea, but many also use for recreational purposes (Woolridge et al., 2005). Given the legalization of medicinal marijuana in 23 U.S. states and the District of Columbia, with most explicitly citing HIV/AIDS as a condition appropriate to manage with medicinal marijuana (National Organization for the Reform of Marijuana Laws, 2014), it is important to understand the effects of regular marijuana use in this population.

1.1 HIV infection and memory impairment

HIV infiltrates the central nervous system and causes neurocognitive impairment (Valcour, Sithinamsuwan, Letendre, & Ances, 2011). Although the introduction of highly active antiretroviral therapy (HAART) in 1996 has significantly changed the course of HIV-related neurocognitive impairment, including a sharp decline in the incidence of dementia (Antinori et al., 2007), milder forms remain a significant public health concern. The CHARTER, a large multi-site study that enrolled >1,500 HIV-infected adults in the

US, found 52% of HIV-infected adult participants to have HIV-associated neurocognitive impairment with the greatest impairments in learning, memory, attention/working memory, and executive functioning (Heaton et al., 2010; Heaton et al., 2011). A meta-analysis reported that neurocognitive deficits worsen as HIV disease progresses, and when HIV infection has progressed to AIDS, effect sizes of verbal and visual memory impairment are moderate to large (Reger, Welsh, Razani, Martin, & Boone, 2002).

Individuals infected with HIV have more difficulty recalling word lists (Maki et al., 2009; Moore et al., 2011; Rippeth et al., 2004; Schiller, Foley, Burns, Sellers, & Golden, 2009; Scott et al., 2011; Scott et al., 2006; Woods et al., 2007; Woods et al., 2005; Wright et al., 2011), stories (Scott et al., 2011), and completing tasks of visual memory (Maki et al., 2009; Martin et al., 2007; Moore et al., 2011; Rippeth et al., 2004; Schiller et al., 2009). There is evidence that HIV-related impairment becomes more pronounced as task difficulty increases. For instance, recognition abilities often remain intact despite impaired recall (Carey, Woods, Rippeth, Heaton, & Grant, 2006; Maki et al., 2009; Morgan et al., 2012; Schiller et al., 2009; Woods, Dawson, Weber, & Grant, 2010; Woods et al., 2005; Zogg, Woods, Weber, Doyle, & Grant, 2011).

Memory impairment may increase in the context of advanced HIV disease progression. A significant trend emerged when comparing performance between patients with acute/early HIV infection and patients chronically infected with HIV

(Moore et al., 2011). Specifically, individuals with chronic HIV infection demonstrated the greatest impairment, those with acute/early HIV demonstrated intermediate performance, and HIV-negative individuals the least impairment. Despite evidence of a relationship between HIV disease progression and severity of memory deficits, however, some studies did not find correlations between current CD4 count or viral load and memory performance (Martin et al., 2007; Waldrop, Ownby, & Kumar, 2004; Woods et al., 2010). Thus, it may be that these markers of HIV disease progression are not the most accurate means of predicting task performance. Few researchers measured nadir CD4 (i.e. the lowest CD4 count), a reflection of the most severe immune suppression, which may more accurately reflect the extent to which brain functioning has been affected by HIV (Ellis et al., 2011; Heaton et al., 2011). It has been hypothesized that when immune suppression is lowest the HIV virus is better able to penetrate and cause significant and long-lasting neurocognitive damage. (D'Amico et al., 2005; Valcour et al., 2006). Thus, it may be that the virus causes more damage during a short period of severe immunosuppression than over longer periods of time when CD4 count is higher and the immune system is stronger.

1.2 Marijuana use and memory impairment

The most robust neurocognitive effect of marijuana use is memory impairment, and memory problems are the most frequently reported cognitive complaint of marijuana users (Ranganathan & D'Souza, 2006; Solowij & Battisti, 2008). Compared to

non-drug users, marijuana users perform significantly worse on both verbal (Battisti et al., 2010; M. Becker, Collins, & Luciana, 2014; Block et al., 2002; Hermann et al., 2007; Meier et al., 2012; Messinis, Kyprianidou, Malefaki, & Papathanasopoulos, 2006; Pope et al., 2003; Pope, Gruber, Hudson, Huestis, & Yurgelun-Todd, 2001; Solowij et al., 2002; Wadsworth, Moss, Simpson, & Smith, 2006) and visual (Bolla, Brown, Eldreth, Tate, & Cadet, 2002; Hadjiefthyvoulou, Fisk, Montgomery, & Bridges, 2011; Hermann et al., 2007; McHale & Hunt, 2008; Meier et al., 2012; Nestor, Roberts, Garavan, & Hester, 2008) memory tasks.

Several studies found that the age at which a person first begins to use marijuana is an important variable that impacts cognitive functioning (Battisti et al., 2010; Meier et al., 2012; Pope et al., 2003). In the Dunedin Study birth cohort, participants who initiated marijuana use before age 18 demonstrated a broad decline in cognitive performance whereas those who started using after age 18 did not (Meier et al., 2012). These results were corroborated with cross-sectional studies (Battisti et al., 2010; Pope et al., 2003). Pope and colleagues (2003) reported that only individuals who began using marijuana before age 17 exhibited memory impairment, and Battisti and colleagues (2010) found age of first use to be correlated with brain alterations measured by event-related potentials, despite no impact on task performance. Two studies that did not find an effect of age of first use were both limited by minimal variability in this factor (B. Becker, Wagner, Gouzoulis-Mayfrank, Spuentrup, & Daumann, 2010; Tait, Mackinnon, &

Christensen, 2011). In one study, participants were split at the median age of onset (age 15) into two subgroups with the "late-onset" group having a mean initiation age of 17 (B. Becker et al., 2010), and in the other study all participants had begun using before age 18 (Tait et al., 2011).

Memory deficits also are correlated with longer duration of regular marijuana use (Meier et al., 2012; Messinis et al., 2006; Solowij et al., 2002; Wadsworth et al., 2006). For example, Solowji and colleagues (2002) found that long-term users with an average of 24 years of regular marijuana use performed worse on almost every measure of memory compared to short-term users with an average of 10 years of regular use. Despite nearly daily marijuana use, short-term users did not significantly differ from controls, which led the authors to conclude that duration of marijuana use may be a more salient contributor to memory impairment than quantity or frequency of use. There were similar findings when researchers compared individuals with an average of 16 years of regular use to individuals with an average of 7 years' regular use (Messinis et al., 2006).

Frequency of marijuana use also affects performance. Specifically, greater memory impairment has been correlated with an increased frequency of use within an individual's lifetime (Hadjiefthyvoulou et al., 2011; Indlekofer et al., 2009; Jager et al., 2007; Pope et al., 2003), the past week (Bolla et al., 2002), month or 30 days (Hadjiefthyvoulou et al., 2011; Tait et al., 2011), or year (Jager et al., 2007). This

association between frequency of use and memory is robust, and there is evidence that it persists even after an extended period of abstinence. For example, Bolla and colleagues (2002) found that number of joints smoked per week predicted memory performance more strongly than duration of use, and that the association between frequency of use and memory deficits persisted even after 28 days of abstinence.

1.3 HIV, marijuana, and memory: A compensatory model hypothesis

Because the brain of an individual infected with HIV is particularly susceptible to neural injury, it is hypothesized that the effects of marijuana on memory functioning will be more pronounced in this population. It has been well documented that HIV causes direct damage to brain structure and functioning (Valcour et al., 2011). In one of the only studies utilizing imaging technology to examine brain functioning during memory processing in persons with HIV infection, Castelo and colleagues (2006) observed disrupted neural activation. The pattern of underactivation in task-specific regions typically activated in healthy individuals coupled with a greater recruitment of frontal regions is strikingly similar to neural activation patterns observed as the brain ages (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008).

A "compensatory hypothesis" has been posited to explain age-related changes in neural activation (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008). During cognitive tasks, older adults demonstrate neural activation in brain regions similar to their younger counterparts, but with different degrees of activation. Specifically, the

older brain demonstrates decreased neural activity in regions typically activated during cognitive tasks, which is thought to reflect age-related deficits in brain functioning (Reuter-Lorenz & Cappell, 2008). At the same time, older adults engage additional frontal and prefrontal regions that are not typically utilized by their younger counterparts. This overactivation is thought to be adaptive, reflecting the brain's attempt to compensate for cognitive impairment by engaging additional neural circuits. In fact, there is evidence that successfully engaging in these neural compensatory strategies can be associated with comparable task performance and that older adults can effectively compensate for age-related cognitive decline by engaging additional neural networks.

This hypothesis maps well onto the HIV-infected brain. Castelo and colleagues (2006) observed normal performance on memory tasks among HIV-infected individuals despite altered neural activation. This population had relatively high CD4 counts, which may indicate that in early stages of the disease the brain is able to effectively compensate for cognitive impairment through compensatory strategies. However, there may be a threshold beyond which the brain is unable to provide sufficient resources to compensate for decline, and then performance suffers. This decline in performance could occur when the task requires more cognitive resources than the brain is able to provide, either because the task is overly difficult or because impairment is too significant for the brain to fully compensate for it. Figure 1 presents a theoretical model of how marijuana use may affect brain functioning in HIV-infected individuals.

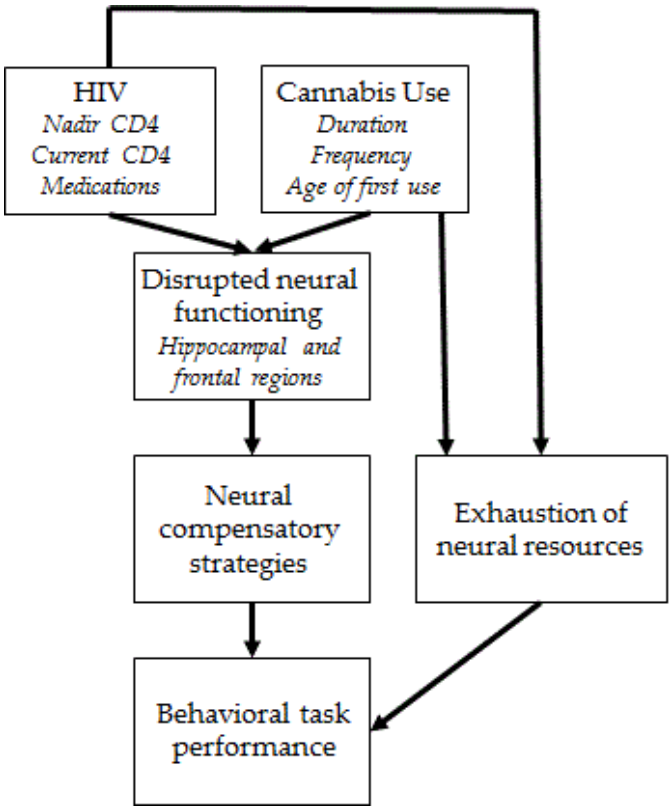

Figure 1 Theoretical model of how marijuana use among persons living with HIV/AIDS affects neurocognitive functioning.

Marijuana use may be associated with disrupted neural functioning during memory tasks in similar brain regions as HIV-infected individuals, including hippocampal and frontal regions (B. Becker et al., 2010; Block et al., 2002; Jager et al., 2007; Nestor et al., 2008). Underactivation in frontal regions is congruous with observations of lower resting blood flow in the frontal lobe of marijuana users (Lundqvist, Jonsson, & Warkentin, 2001), which provides additional evidence that marijuana use may be associated with less efficient frontal processing. In healthy individuals, these disruptions in memory

processing may not be associated with memory decline (Jager et al., 2007; Nestor et al., 2008). It is hypothesized that the added neural strain caused by co-occurring marijuana use is likely to exhaust neural resources in persons with HIV infection, resulting in more significant memory impairment.

This hypothesis is consistent with findings from one of the only published articles to examine this topic empirically. Cristiani and colleagues compared the neurocognitive performance of HIV-positive and HIV-negative individuals, stratified by disease stage and frequency of marijuana use (Cristiani, Pukay-Martin, & Bornstein, 2004). They reported an interaction effect, finding that current marijuana use was associated with greater global neurocognitive impairment among individuals with symptomatic HIV infection. Furthermore, they found that this effect was primarily driven by performance on a delayed memory task. Interpreting these results through the compensatory hypothesis suggests that marijuana users who are in the early stages of HIV are able to draw upon neural reserves to compensate for marijuana-related impairment. As HIV disease progresses and HIV-related impairment exhausts neural resources, however, the brain may no longer be able to compensate for marijuana-related brain injury. Consequentially, the cognitive effects of marijuana on memory may be exacerbated in the context of advanced HIV disease progression.

This underscores the need for research examining how marijuana use may affect neurocognitive functioning among individuals already experiencing HIV-associated

decline. Since Cristiana and colleagues published their compelling findings in 2004, no subsequent studies could be identified that examine memory outcomes resulting from co-occurring marijuana and HIV infection. This study aimed to empirically test how marijuana use impacts memory among HIV-infected individuals.

1.4 Specific aims and hypotheses

This was a case-controlled study of HIV-infected adults with and without marijuana use. The specific aims and hypotheses were as follows:

Specific Aim 1 (primary): Identify patterns of neurocognitive impairment among HIV patients who use marijuana compared to HIV patients who do not use drugs.

Hypothesis 1: Marijuana users will demonstrate increased impairment on memory tasks compared to non-drug users.

Specific Aim 2 (secondary): Test whether the effect of marijuana use on memory is moderated by HIV disease progression.

Hypothesis 2: It is expected that there will be an interaction between marijuana use and HIV disease progression such that marijuana's effect on memory will be stronger among individuals with more advanced HIV disease progression. It is expected that nadir CD4 count will be more strongly associated with memory as compared to other biomarkers of HIV disease progression (i.e., viral load, current CD4 count).

Specific Aim 3 (secondary): Test whether the effect of marijuana use on memory is differentially affected by marijuana use characteristics.

Hypothesis 3: It is hypothesized that age of first use will be the most robust predictor of memory. Specifically, initiating marijuana at a young age will be associated with increased memory impairment. It is also hypothesized that after taking into account age of first use, other characteristics of use (i.e., frequency of use, duration) will not be associated with memory.

2. Methods

2.1 Participants and procedures

2.1.1 Eligibility

The sample included HIV-positive men and women of all races who were ≥18 years old and used or did not use marijuana. *Marijuana* use was defined as a positive urine screen for marijuana, ≥10 days of marijuana use in the past 30 or ≥30 days of marijuana use in the past 90, and ≥1 year of regular marijuana use. *Non drug* use was defined as a negative urine drug screen for marijuana, 0 days of marijuana use in the past year, and no history of regular marijuana use. Individuals who fell between these selection criteria were excluded to ensure sufficient differentiation between the study groups. Individuals were also excluded for a positive urine drug screen for any other drug (unless verified by prescription) and any other drug use in the past year. Past alcohol dependence was permitted in both groups if in sustained full remission, and

marijuana users were permitted to have a history of other drug dependence in sustained full remission if marijuana dependence had always been their principal diagnosis. Exclusion criteria were: <8th grade education; English non-fluency or illiteracy; serious neurological disorders and events (e.g., seizure disorder, multiple sclerosis, brain embolism); severe head trauma with loss of consciousness requiring medical intervention; physical disabilities impeding participation (e.g., blindness); severe mental illness (e.g., bipolar or psychotic disorders); use of mood stabilizers or antipsychotics; acute psychiatric distress (e.g., severe suicidality); and impaired mental status. To eliminate potential confounds, it was also required that individuals be diagnosed with HIV for >3 months and be on a stable antiretroviral medication regimen for >3 months.

2.1.2 Recruitment

Participants for this study were recruited December 2012 through November 2014. This data was supplemented by data from participants who completed a different protocol in the Meade Lab June 2010 through November 2012 who met the same inclusion criteria. Recruitment strategies included both the Infectious Disease clinic at Duke University Medical Center and community-based strategies. To facilitate clinician referrals in the Infectious Disease clinic, study staff queried the electronic medical record to identify eligible participants. Patients were flagged as potentially eligible if they were infected with HIV and did not have any comorbid medical conditions that were grounds for exclusion (e.g. serious neurological disorders, severe mental illness) or indications of

drug abuse other than marijuana. Once an individual was identified, the date of their next clinic visit was determined. On the day of the visit, study staff went to clinic and informed the provider that their patient might be eligible and asked that the provider inquire if the patient was interested in learning more about a research study. If the patient was interested, research staff met with the patient to explain they were recruiting for a study comparing individuals with HIV-infection who did or did not use marijuana. If the patient was still interested, research staff administered a brief prescreening assessment (described below).

In addition to clinician referrals, brochures were placed in the waiting room and flyers on the wall of the clinic. Participants were also recruited from the community via newspaper and online advertisements (e.g., JobFinderUSA, craigslist.com), brochures and/or fliers in other community-based clinics (e.g., Lincoln Community Health Center) and sites that serve individuals with HIV infection (e.g., Alliance, CAARE). Interested patients contacted study staff via phone to complete the prescreening assessment. Participants also were encouraged to refer their peers.

2.1.3 Prescreening

All interested individuals completed the same prescreening assessment to determine preliminary eligibility (e.g., current and past substance use, medical history) regardless of group (See Appendix A). For most individuals, this occurred over the

telephone. For individuals recruited directly from Duke Infectious Disease clinic, this occurred in-person at the clinic.

2.1.4 In-person assessments

Participants were asked to refrain from using marijuana for ≥6 hours prior to all visits, and each visit began with a breathalyzer to ensure no participant was acutely intoxicated.

2.1.5 Visit 1: Eligibility screening

Potentially eligible participants were invited to complete a 3 hour screening to verify eligibility criteria. The following assessments were administered:

2.1.5.1 General

Participants reported age, gender, race, sexual orientation, education, and income. The Wechsler Test of Adult Reading (WTAR), in which participants read aloud 50 words with atypical grapheme to phoneme translations, was used to assess premorbid intellectual functioning (Wechsler, 2001). Raw scores were translated into age-corrected T-scores.

2.1.5.2 Substance use

The Timeline Follow-back (TLFB) method was used to assess substance use in the past 3 months (Sobell & Sobell, 1996). The Addiction Severity Index-Lite (ASI-Lite), a semi-structured interview, assessed lifetime and past month frequency of substance use and current functioning in the following domains: drug, alcohol, medical, employment,

legal, social, and psychiatric (McGahan, Griffith, Parente, & McLellan, 1986; McLellan et al., 1992). To determine whether drug use other than marijuana occurred within the past year (an exclusion), additional items were added to the ASI-Lite that assessed past year drug use. Module E of the Structured Clinical Interview for DSM-IV (SCID-E) identified current and lifetime substance use diagnoses (First, Spitzer, Gibbon, & Williams, 1996). Urine toxicology screens were performed to verify recent use of amphetamines, barbiturates, benzodiazepines, cocaine, methamphetamine, opioids, methadone, marijuana, and oxycontin.

2.1.5.3 Mental health

The Mini International Neuropsychiatric Interview (MINI), a structured clinical interview, was used to identify DSM-IV-TR psychiatric diagnoses, including mood, anxiety, and psychotic disorders (Sheehan et al., 1998). The MINI is the most widely used diagnostic instrument in the world and has been validated against the Structured Clinical Interview for DSM and the Composite International Diagnostic Interview (Lecrubier et al., 1997; Sheehan et al., 1997).

2.1.5.4 HIV disease

Participants completed module 3 of the HIV Cost and Services Utilization Study (HCSUS) baseline questionnaire, which provided information on HIV testing, staging, and treatment (RAND Corporation, 2007). Participant reported date diagnosed with HIV and lab results (i.e. current CD4 count, nadir CD4 count, viral load) relevant to their

HIV infection. They were also asked to report HIV medications. Medical records were reviewed to corroborate self-report.

2.1.6 Visit 2: Neurocognitive assessment

Participants who were eligible for Part 2 based on the Part 1 screening were invited back on a separate day for an in-depth assessment. All participants had a urine toxicology screen to verify self-reported use of benzodiazepines, cocaine, methamphetamine, opioids, and marijuana. Participants then completed an assessment battery that included the following measures:

2.1.6.1 Substance use

The TLFB methodology was again utilized to assess substance use that may have occurred since the screening visit (Sobell & Sobell, 1996). Participants who used marijuana also completed a computerized Assessment of Marijuana questionnaire that assessed marijuana use habits (e.g., number of hours high per day, dollars spent on marijuana per week), for the past 90 days and lifetime (See Appendix B).

2.1.6.2 Neurocognition

This 75-minute battery assessed functioning in 7 domains: learning, memory, processing speed, attention/working memory, verbal fluency, motor ability, and executive functioning. All tests had excellent clinical validity with large national norming samples and were scored using standard procedures.

Hopkins Verbal Learning Test-Revised (HVLT-R) measured immediate recall (i.e., learning) and delayed recall (Brandt & Benedict, 2001). Across 3 trials, participants were read a list of 12 words. After each repetition, they recalled as many words as they could. After a 25-minute delay, they recalled the words again.

Brief Visuospatial Memory Test-Revised (BVMT-R) measured immediate recall (i.e, learning) and delayed recall (Benedict, Schretlen, Groninger, & Dobraski, 1996). Across 3 trials, participants were presented with 6 geometric figures. After each viewing, they drew as many figures in their correct location as possible. After a 25-minute delay, they drew the figures again.

Trail Making (TMT) Part A measured processing speed (Lezac, 1995). Participants connected a series of 25 numbered circles in order as quickly and accurately as possible.

TMT Part B measured executive functioning (Lezac, 1995). It was similar to Trails A, but the circles contained both letters and numbers (i.e., 1-A-2-B-3-C, etc).

Paced Auditory Serial Addition Test (PASAT-50) measured attention and working memory (Gronwall, 1977). Participants computed serial addition of pairs of consecutive numbers at varying interval rates across 50 trials.

Digit Span Forwards and Backwards assessed attention and working memory (Stern & White, 2003). Participants were orally presented with a series of digits and were asked recall them forward and in reverse order.

Controlled Oral Word Association Test (COWAT) measured verbal fluency (Benton, Hamsher, & Sivan, 1983). Participants retrieved and verbally reported as many exemplars of specific semantic categories as possible in 60 seconds. Specifically, they retrieved words starting with the letters F, A, and S (phonemic fluency) and animals (semantic fluency).

Grooved Pegboard Test (GPT) measured fine motor coordination and speed (Heaton, Grant, & Matthews, 1991). Participants placed pegs in 25 holes with randomly positioned slots as fast as they could with their dominant and nondominant hands.

Stroop Color and Word Task (Stroop) measured executive functioning (Golden, 1978). Participants' read a list of items across 3 conditions: word reading, color naming, and color word naming. In the color word naming trial, participants were presented with a list of colors (i.e., green, blue, and red) that were printed in a different color (e.g. "green" was printed in blue ink) and instructed to read the name of the color while ignoring the printed word.

Digit Symbol Test measured processing speed (Wechsler, 1997). Participants paired novel symbols with numbers using a reference key, making as many pairings as possible in 90 seconds.

2.1.6.3 Psychological distress

A computerized survey included the 6-item depression subscale and 6-item anxiety subscale of the Brief Symptom Inventory 18 (BSI) (Derogatis, 1993). Participants rated past week depression using a 5-point scale (not at all to extremely).

2.2 Statistical analyses

2.2.1 Transforming raw scores to T-scores

Raw scores were converted to demographically corrected T-scores (M=50, SD=10) using published norms. Specifically, raw scores on TMT, COWAT, PASAT, and GPT were converted to T-scores adjusted for gender, education, age, and race using the Revised Comprehensive Norms for an Expanded Halstead-Reitan Battery (Heaton, Miller, Taylor, & Grant, 2004). Calculation of T-scores for the HVLT-R, BVMT-R, and Stroop also adjusted for gender, education, age, and race (Norman et al., 2011). Raw scores on Digit Span were converted to T-scores adjusted for sex, age, and education using the Neuropsychological Assessment Battery: Administration, Scoring, and Interpretation Manual (Stern & White, 2003). Raw scores on Digit Symbol Test were converted to age-corrected T-scores using the Wechsler Adult Intelligence Scale manual (Wechsler, 1997).

2.2.2 Calculating outcome variables

Domain scores were created by averaging individual T-scores assessing the same domain as follows: *Learning/Short-term Memory* (HVLT-R trials 1-3, BVMT-R trials 1-3),

Memory/Delayed Recall (HVLT-R delayed recall, BVMT-R delayed recall), *Processing Speed* (TMT Part A, Digit Symbol Test), *Executive Functioning* (TMT Part B, Stroop interference), *Attention/Working Memory* (PASAT, Digit Span Forward, Digit Span Backward), *Verbal Fluency* (COWAT FAS, COWAT animals), and *Motor Ability* (GPT dominant hand, GPT nondominant hand). A global neurocognitive T-score was created by taking the average of performance across these 7 domains. Summing scores on individual T-tests and dividing by the total number of tests administered is a common strategy for determining overall neurocognitive functioning in HIV patients (Applebaum, Otto, Richardson, & Safren, 2009; B. Becker, Thames, Woo, Castellon, & Hinkin, 2011; Meade, Conn, Skalski, & Safren, 2011).

Post hoc analyses also examined Domain Deficit Scores (DDS) and Global Deficit Score (GDS). These scores reflect the severity of test performance and gives relatively less weight to performances that are within normal limits. To calculate, T-scores for each test were converted to a 0-5 deficit rating: T ≥40= 0 (no impairment), 35-39= 1, 30-34= 2, 25-29=3, 20-24= 4, and <20= 5. The DDS scores were calculated by adding deficit scores for each domain and divided by the number of tests. All DDS were added together and divided by total number of domains to determine GDS. Global impairment on the GDS was defined as ≥0.5 and impairment within a domain was defined as >0.5 (Carey et al., 2004).

2.2.3 Hypothesis testing

First, descriptive statistics were used to characterize the sample in terms of demographics, other substance use, and HIV disease characteristics. To test specific aim 1 *(identify patterns of neurocognitive impairment among HIV patients who use marijuana compared to HIV patients who do not use drugs)* marijuana and non-drug users were compared on domain-specific and global T-scores using t-tests. To examine specific aim 2 (*test whether the effect of marijuana use on memory is moderated by HIV disease progression***)**, nadir CD4 cell count was dichotomized at 200 cells/mm^3 and current cell CD4 count at 500 cells/mm^3. Plasma viral load was "detectable" or "undetectable" based on a sensitivity of < 48 copies/ml. Variables were created that captured the interaction between marijuana group and these biomarkers of HIV disease progression (i.e., current CD4, nadir CD4, viral load), and separate linear regressions were conducted for each biomarker, marijuana group, and the interaction term. Outcome variables were T-scores in the domains of memory, learning, and global functioning. Linear regression was used for specific aim 3 (*test whether the effect of marijuana use on memory is differentially affected by marijuana use characteristics).* Age of first use was a continuous variable indicating the age at which an individual began to use marijuana regularly (≥3 days per week), and because responses were not normally distributed participants were grouped into early-initiation (≤ age 18) and late-initiation (> age 18) groups. Duration was the cumulative number of years in which a participant used marijuana regularly. Frequency was the

number of days a participant reported using marijuana within the past 90 days, and because this variable also was not normally distributed participants were categorized into daily/almost daily users (≥ 6 times per week) or non-daily users (< 6 times per week). Multicollineary diagnostics were conducted to determine whether age of first use, duration, and frequency were too highly correlated to be included in the same regression model, and because the variance inflation factor (VIF) was < 3.0 for all variables they were entered into a multivariable model together. Separate analyses examined T-scores in the domains of memory, learning, and global functioning.

2.2.4 Power analyses

Power analyses were conducted to determine the minimum sample size needed for each aim. Power to detect differences was calculated in G*Power 3.1.7 (Faul, Erdfelder, Buchner, & Lang, 2009) with an alpha set to .05, 80% power, and a medium effect size ($f^2 = .15$). This effect size was chosen because although no studies examining marijuana use in HIV-infected individuals provided enough information to calculate effect size, several studies of marijuana use among healthy individuals suggest that when present the effect is medium to large (Battisti et al., 2010; Pope et al., 2001; Solowij et al., 2002). In Aim 1, the two-group independent sample t-test required a sample size of 29 per group. In Aim 2, linear regression with the addition of the biomarker variable and its interaction term required a sample size of 77. In Aim 3, including all three characteristics of marijuana use in the same model again required a sample size of 77.

This study was designed to be powered for the primary hypothesis (Aim 1), and Aims 2 and 3 were exploratory.

3. Results

3.1 Description of sample

The sample include 69 HIV-infected adults. Table 1 presents demographic, psychiatric, and HIV characteristics of the sample by group. The majority (72%) were male and African American (75%). Most participants had a high school degree or GED (90%) and about a quarter (28%) had completed college. Participants had been living with HIV for an average of 11 years, ranging from 4 months to 32 years. Although half (49%) had a nadir CD4 count below 200, only 14% had a current CD4 count that low. Marijuana users were more likely to be Caucasian and younger in age. There were no group differences on any other demographics, HIV disease characteristics, depression, or anxiety.

Table 1 Demographic, psychiatric, and HIV disease characteristics of the sample

	Marijuana n=32	Non-drug n=37	Statistic	p-value
Demographic				
Male sex (%)	71.9%	72.2%	χ^2 (1) = 0.00	0.593
Age, years (M, SD)	**38.1 (11.1)**	**47.0 (10.3)**	**t(66) = 3.45**	**0.001****
Education, years (M, SD)	13.3 (2.8)	14.0 (2.3)	t(66) = 1.21	0.228
Caucasian (%)	**28.1%**	**5.6%**	**χ^2 (1) = 6.36**	**0.013***
Heterosexual (%)	37.5%	44.4%	χ^2 (1) = 0.34	0.370
Yearly income < $15,000 (%)	51.6%	41.7%	χ^2 (1) = 0.66	0.285
WTAR verbal IQ (M, SD)	91.3 (18.1)	85.9 (17.9)	t(66) = -1.25	0.215
HIV disease				
CD4 cell count (M, SD)	581.6 (266.4)	530.6 (311.5)	t(63) = -0.70	0.485
Nadir CD4 cell count (M, SD)	263.7 (218.8)	200.3 (195.7)	t(64) = -1.24	0.219
Detectable viral load (n, %)	41.9%	50.0%	χ^2 (1) = 0.44	0.340
AIDS diagnosis (n, %)	32.3%	41.7%	χ^2 (1) = 0.63	0.295
Years HIV infected (M, SD)	10.3 (8.8)	12.2 (8.3)	t(65) = 0.94	0.353
Psychiatric				
Anxiety (BSI) (M, SD)	0.55 (0.68)	0.45 (0.68)	t(65)= -0.60	0.552
Depression (BSI) (M, SD)	0.60 (0.70)	0.59 (0.83)	t(65)= -0.05	0.964

Note. WTAR = Wechsler Test of Adult Reading; BSI = Brief Symptom Inventory
* $p < 0.05$, ** $p < 0.01$

Marijuana use among the sample is presented in Table 2. On average, individuals in the marijuana group were chronic users who used multiple times per day and had been using for 15 years. More than half (63%) used daily or almost daily (≥ 6 days per week). One-fifth (20%) indicated that they had tried to stop or limit their marijuana use within the past 90 days. Two participants in the marijuana group met criteria for another drug dependence disorder in the past (cocaine), but clinical interview determined that

marijuana dependence had always been primary. There were no group differences on number of days consuming alcohol in the past 90 days or past alcohol dependence.

Table 2 Marijuana use characteristics of the sample

	Marijuana n=32
Age first tried (M, SD, range)	16.2 (3.9), 8 - 25
Age first regular use (M, SD, range)	19.8 (4.4), 13 - 34
Began to use regularly ≤ 18 years old	51.6%
Duration, years (M, SD, range)	15.6 (9.0), 1 - 36
Frequency, days/past 90 (M, SD, range)	71.7 (22.4), 16 - 90
Daily/near daily (%)	62.5%
Hours high per day (M, SD, range)	5.3 (4.7), 0 - 16
Current dependence (%)	50%

Note. Daily/near daily = ≥ 6 days/week.

3.2 Specific Aim 1

Identify patterns of neurocognitive impairment among HIV patients who use marijuana compared to HIV patients who do not use drugs

Raw scores and T-scores by group are presented in Table 3. Comparison of domain T-scores indicated that marijuana users trended towards worse performance compared to non-drug users in the domain of memory, specifically driven by worse performance on the verbal task. They performed better than non-drug users in the domain of attention. Both groups demonstrated substantial neurocognitive impairment defined as T-scores ≥1 SD below the mean (Table 4). Marijuana users were more likely to

demonstrate impairment on the learning/short-term verbal memory task (HVLT-R) and less likely to demonstrate impairment on some attentional tasks (Digit Span forward, Digit Span backwards).

To further understand why groups did not significantly differ on memory or learning domain T-scores, post hoc analyses were conducted. First, rather than grouping verbal and visual memory tasks together to create learning (i.e., short-term recall) and memory (i.e. delayed recall) domains, verbal tasks and visual tasks were instead grouped together to create verbal (HVLT-R trials 1-3, HVLT-R delayed recall) and visual (BVMT-R trials 1-3, BVMT-R delayed recall) domain scores. T-tests indicated that marijuana users performed significantly worse in the domain of verbal memory [$t(67) = 2.05$, $p = 0.044$], but there were no group differences in visual memory.

Additionally, post hoc analyses examined DDS and GDS scores. Findings were similar to impairment T-scores with marijuana users demonstrating more learning/short-term memory impairment and less attentional impairment (Table 5). When again re-grouping verbal and visual memory separately as described above to create DDS scores, marijuana users demonstrated greater verbal memory impairment ($t(67) = -2.12$, $p = 0.038$), but there were no group differences on visual impairment.

A third post hoc analysis re-ran the primary models but restricted the sample to individuals aged 30 to 50 in order to reduce heterogeneity and to account for group differences in age. The new groups were comparable in age, including 20 marijuana

users (M = 39.6, SD = 6.4) and 18 non-drug users (M = 40.7, SD = 6.2). T-tests found that the marijuana group performed worse in the domain of memory [$t(36) = 2.44$, $p = 0.020$] and trended towards worse performance in the domain of learning [$t(36) = 1.86$, $p = 0.071$]. There were no group differences in attention or any other cognitive domain.

Table 3 Raw scores and T-scores for each individual test and by cognitive domain

	Raw				T-score			
	Marijuana (n=32)	Non-drug (n=37)	t-test	p-value	Marijuana (n=32)	Non-drug (n=37)	t-test	p-value
Learning								
HVLT-R trials 1-3	21.84 (5.00)	22.30 (4.56)	-0.394	0.695	**37.46 (8.60)**	**40.88 (7.81)**	**1.735**	**0.087†**
BVMT-R trials 1-3	19.81 (8.61)	18.05 (8.71)	0.841	0.403	44.02 (9.93)	45.82 (10.35)	0.734	0.465
Domain T-score	---	---	---	---	40.74 (7.64)	43.35 (6.76)	1.508	0.136
Memory								
HVLT-R delayed recall	7.13 (2.37)	7.46 (2.49)	-0.569	0.571	**38.12 (7.33)**	**41.99 (8.60)**	**1.999**	**0.050†**
BVMT-R delayed recall	8.16 (3.44)	7.51 (3.75)	0.737	0.463	46.79 (12.05)	50.43 (13.62)	1.169	0.247
Domain T-score	---	---	---	---	**42.45 (7.78)**	**46.21 (9.20)**	**1.817**	**0.074†**
Processing speed								
TMT, part A	30.56 (20.11)	32.00 (14.10)	-0.347	0.729	50.53 (12.96)	52.68 (12.57)	0.697	0.488
Digit Symbol Test	71.78 (18.38)	66.89 (20.03)	1.050	0.297	49.44 (10.27)	48.89 (11.95)	-0.202	0.841
Domain T-score	---	---	---	---	49.98 (9.40)	50.78 (10.90)	0.324	0.747
Executive function								
TMT, part B	81.56 (51.77)	96.35 (59.89)	-1.088	0.280	50.75 (11.51)	50.84 (12.26)	0.031	0.976
Stroop interference	6.06 (15.83)	0.81 (10.94)	1.579	0.120	57.59 (15.92)	53.89 (11.87)	-1.081	0.284
Domain T-score	---	---	---	---	54.17 (10.57)	52.36 (8.03)	-0.805	0.424
Verbal fluency								
COWAT FAS	40.28 (13.23)	38.68 (11.21)	0.546	0.587	50.66 (9.76)	49.95 (9.33)	-0.309	0.759
COWAT animals	20.88 (5.49)	19.62 (5.98)	0.902	0.371	51.81 (10.22)	51.32 (11.40)	-0.186	0.853
Domain T-score	---	---	---	---	51.23 (8.53)	50.64 (8.79)	-0.286	0.776
Attention								
PASAT-50	33.91 (10.69)	32.00 (11.03)	0.717	0.476	46.87 (10.32)	48.40 (10.91)	0.587	0.559
Digit Span forward	**8.44 (2.06)**	**7.11 (2.46)**	**2.411**	**0.019***	**46.88 (9.10)**	**40.97 (10.76)**	**-2.439**	**0.017***

Digit Span backward	**4.41 (2.56)**	**2.86 (1.99)**	**2.810**	**0.006****	**47.03 (11.00)**	**38.81 (9.88)**	**-3.270**	**0.002****
Domain T-score	---	---	---	---	**46.93 (8.93)**	**42.59 (8.46)**	**-2.071**	**0.042***
Motor abilities								
GPT dominant hand	71.31 (13.39)	80.35 (31.86)	-1.494	0.140	47.59 (9.79)	48.73 (10.96)	0.451	0.653
GPT nondominant hand	79.19 (19.93)	95.86 (63.97)	-1.421	0.160	48.03 (10.87)	48.76 (11.57)	0.267	0.790
Domain T-score	---	---	---	---	47.81 (9.69)	48.74 (10.36)	0.383	0.703
Global Functioning								
Average T-score	---	---	---	---	46.96 (5.77)	46.89 (6.45)	-0.045	0.964

† $p < 0.10$, * $p < 0.05$, ** $p < 0.01$

Table 4 Percent impaired (T-score ≤40) on individual tests

	Marijuana (n=32)	Non-drug (n=37)	χ^2	p-value
Learning				
HVLT-R trials 1-3	**71.9%**	**43.2%**	**5.724**	**0.015***
BVMT-R trials 1-3	43.8%	29.7%	1.460	0.169
Memory				
HVLT-R delayed recall	62.5%	48.6%	1.331	0.181
BVMT-R delayed recall	31.3%	21.6%	0.825	0.263
Processing speed				
TMT, part A	9.4%	8.1%	0.035	0.591
Digit Symbol Test	15.6%	21.6%	0.404	0.374
Executive function				
TMT, part B	18.8%	13.5%	0.351	0.395
Stroop interference	9.4%	10.8%	0.039	0.583
Verbal fluency				
COWAT FAS	6.3%	10.8%	0.450	0.409
COWAT animals	12.5%	18.9%	0.528	0.348
Attention				
PASAT-50	25.0%	22.9%	0.042	0.531
Digit Span forward	**12.5%**	**51.4%**	**11.655**	**0.001****
Digit Span backward	**18.8%**	**45.9%**	**5.711**	**0.016***
Motor abilities				
GPT dominant hand	21.9%	18.9%	0.093	0.496
GPT nondominant hand	18.8%	13.5%	0.351	0.395

* $p < 0.05$, ** $p < 0.01$

Table 5 Deficit scores for each cognitive domain and global functioning

	Marijuana (n=32)	Non-drug (n=37)	t-test	p-value
Learning	**1.02 (0.87)**	**0.68 (0.77)**	**1.731**	**0.088†**
Memory	0.86 (0.84)	0.61 (0.79)	1.275	0.207
Processing Speed	0.25 (0.61)	0.26 (0.56)	-0.048	0.962
Executive Functioning	0.28 (0.49)	0.24 (0.47)	0.330	0.743
Verbal Fluency	0.13 (0.31)	0.23 (0.48)	-1.089	0.280
Attention	**0.39 (0.73)**	**0.82 (0.75)**	**-2.450**	**0.017***
Motor Abilities	0.41 (0.90)	0.42 (1.12)	-0.051	0.959
Global Functioning	0.47 (0.38)	0.47 (0.44)	0.094	0.925

† $p < 0.10$, * $p < 0.05$, ** $p < 0.01$

3.3 Specific Aim 2

Test whether the effect of marijuana use on memory is moderated by HIV disease progression

In multivariable models, there was no main effect of current CD4, nadir CD4 or viral load nor did these variables interact with marijuana group to affect memory. Post hoc analyses re-ran the models by re-grouping verbal and visual memory together, using DDS scores as the outcome, and restricting the sample to individuals aged 30-50 and all models remained nonsignificant.

3.4 Specific Aim 3

Test whether the effect of marijuana use is on memory differentially affected by marijuana use characteristics

Age of first use, duration, and frequency were not significantly correlated. Multivariable models including all three predictors together found younger age of first use to be associated with lower performance in learning and memory (Table 6). There were no associations with duration or frequency of use.

Table 6 Multivariate regression examining marijuana use characteristics' impact on learning, memory, and overall functioning

Marijuana	B	SE(B)	β	T	p-value
Learning/short-term memory					
Age of first use	**7.767**	**2.398**	**0.516**	**3.239**	**0.003****
Duration	-0.156	0.134	-0.191	-1.160	0.256
Frequency	1.991	2.477	0.132	0.804	0.429
Memory					
Age of first use	**6.670**	**2.581**	**0.427**	**2.584**	**0.015***
Duration	-0.226	0.145	-0.267	-1.563	0.130
Frequency	1.317	2.665	0.084	0.494	0.625
Global functioning					
Age of first use	2.766	2.095	0.247	1.320	0.198
Duration	-0.005	0.117	-0.008	-0.040	0.968
Frequency	0.435	2.163	0.039	0.201	0.842

* $p < 0.05$, ** $p < 0.01$

4. Discussion

Despite the increased legalization of medicinal marijuana and the high prevalence of use among HIV-infected individuals, this is among the first studies to examine the effects of co-occurring marijuana use and HIV infection on memory. Although planned analyses did not find significant group differences on domain T-scores, post hoc analyses suggest marijuana does exacerbate memory impairment. For instance, when verbal and visual tasks were grouped together rather than grouping by short- and long-delay conditions, marijuana users' composite verbal memory score was significantly lower than non-drug users. There was a similar trend when DDS was the outcome. This is consistent with extant literature because although there is evidence that marijuana use can be associated with visual memory problems (Bolla et al., 2002; Hadjiefthyvoulou et al., 2011; Hermann et al., 2007; McHale & Hunt, 2008; Meier et al., 2012; Nestor et al., 2008), many studies found verbal memory impairment in the context of intact visual memory (M. Becker et al., 2014; Indlekofer et al., 2009; Pope et al., 2003; Pope et al., 2001; Rodgers, 2000; Tait et al., 2011).

Across both groups, a substantial percentage of participants were impaired (T-score ≤1 SD below the mean). A greater percentage of marijuana users were impaired on the short-term verbal memory task but not in the delayed condition. Failure to find group differences on the delayed verbal memory task may be due to the high (nearly half) impairment in the non-drug group that could have washed out the effects of

marijuana when examining a dichotomous outcome. HIV-associated impairment this high is consistent with prior research, as the CHARTER study reported nearly 50% memory impairment (Heaton et al., 2011). In contrast, marijuana users in this sample had significantly less attention/working memory impairment than the non-drug use group, which not consistent with prior research (Heaton et al., 2010; Heaton et al., 2011; Woods, Moore, Weber, & Grant, 2009). Marijuana users in this sample may have unusually strong attentional abilities, but this discrepancy also may be explained by a limitation in calculation of T-scores for Digit Span tasks that took into account gender, education, and age, but not race. Failure to consider race is particularly problematic for this sample because a higher proportion of marijuana users were Caucasian whereas the non-drug group was comprised of more African Americans, and it has been shown that neurocognitive tasks are often biased against racial minorities (Diehr et al., 2003; Heaton et al., 2004; Manly, Schupf, Tang, & Stern, 2005; Norman et al., 2011). With regards to the Digit Span task specifically, there is evidence that among low SES populations and African Americans literacy, rather than education, is associated with task performance (Dotson, Kitner-Triolo, Evans, & Zonderman, 2009). Given that this was a largely low SES sample, comparison of T-scores may have inflated the performance of the predominantly Caucasian marijuana use group.

Further, restricting the sample to individuals whose ages ranged from 30-50 led to findings consistent with the primary hypothesis, despite being underpowered.

Specifically, marijuana users performed significantly worse in the domain of memory and trended towards worse performance in learning with no group differences in attention or any other cognitive domain. Although calculation of T-scores for learning and memory domains did account for age, marijuana users were much younger than non-drug users and overall the study sample demonstrated significant heterogeneity with participants ranging in age from 21 to 70. Additionally, it is well known that neurocognitive functioning declines with age (Yankner, Lu, & Loerch, 2008) and it is hypothesized that HIV/AIDS may accelerate aging (Desai & Landay, 2010; Pathai, Bajillan, Landay, & High, 2014). Age-corrections normalized in healthy samples may not adequately take into account the accelerated aging process among HIV-infected individuals, inflating the performance of the younger marijuana group. Restricting the age range so that groups were more closely matched on this demographic rather than relying on T-score corrections may have provided more accurate results.

The potential of marijuana to exacerbate already high levels of memory impairment among HIV-infected persons has concerning real-world implications. The clearest example is the relationship between memory impairment and medication non-adherence (Andrade et al., 2005; Contardo, Black, Beauvais, Dieckhaus, & Rosen, 2009; Ettenhofer, Foley, Castellon, & Hinkin, 2010; Hinkin et al., 2002; Hinkin et al., 2004; Zogg et al., 2010), which in addition to serious negative health consequences for the individual is concerning from a public health perspective because it can lead to drug-resistant

mutations (Harrigan et al., 2005) and increases the likelihood of transmitting the virus during sexual activities (Cohen et al., 2011). Further, memory abilities are among the strongest neuropsychological predictors of obtaining employment (van Gorp et al., 2007) and may be predictive of an HIV-infected individual's ability to abstain from high-risk sexual and injection practices (Martin et al., 2007).

The proposed theoretical model, hypothesizing there would be an interaction between marijuana use and HIV disease progression, did not reach significance. However, it is important to note that this was an underpowered secondary aim and that with a larger sample size significant findings may have emerged. Failure to find an interaction may also be explained by the inability to find a main effect of HIV disease progression. Although there is evidence of a relationship between severity of HIV disease and memory impairment (Moore et al., 2011), lab measures of CD4 count and viral load taken at a single time-point are not consistently associated with memory performance (Martin et al., 2007; Waldrop et al., 2004; Woods et al., 2010), suggesting they are not the most accurate measures of HIV disease severity. Understanding the impact of HIV on brain functioning may require consideration of multiple variables (i.e., viral load, CD4 count, length of infection) to form a composite score rather than examining each variable in isolation. For instance, utilization of an algorithm that took into consideration age, current CD4 count, past central nervous system HIV-related diseases, and current treatment duration was found to have clinical utility in helping

clinicians more effectively identify individuals at advanced stages of HIV-infection who were at greater risk for cognitive impairment (Cysique, Murray, Dunbar, Jeyakumar, & Brew, 2010). Although it can be logistically very difficult to obtain lab results over time, researchers have also proposed examining "copy-years viremia," a measure of cumulative viral load calculated by adding the area under a patients' charted viral load over time, thus taking into account both the level of viral replication and the duration of replication (Cole et al., 2010). Associations between copy-years viremia and neurocognitive impairment have not yet been examined, but this longitudinal measure of HIV disease progression has been found to be more strongly associated with AIDS and mortality than cross-sectional measures (Cole et al., 2010). A more accurate measure of HIV disease progression may have been needed for the proposed theoretical model to obtain significance, and future research should examine whether copy-years viremia is associated with neurocognitive outcomes.

The hypothesis that beginning to use marijuana at an earlier age would be associated with greater memory impairment was supported. Frequency and duration of use were not associated with memory outcomes, but it should be noted that this was a sample of heavy users and lack of variability may have precluded finding a relationship with these variables. The significant association between age of initiation and memory is consistent with prior literature (Meier et al., 2012; Pope et al., 2003) and has significant clinical implications. First, as the legalization of marijuana becomes more widespread, it

will be important to carefully consider strategies for preventing adolescent use. This should be a public health priority in order to protect youth from incurring memory deficits that can persist into adulthood. Second, it suggests that using marijuana in adulthood to manage HIV-related symptoms may not be as significant a risk factor for memory decline. In fact, the vast majority of marijuana users in this sample (88%) initiated their marijuana use prior to contracting HIV, suggesting that many individuals are using for recreational reasons rather than medicinal ones. However, future research with greater variability is needed to determine whether frequency of use impacts memory among those who initiate in adulthood before patients with health conditions such as HIV can be confident that managing symptoms with marijuana will not have iatrogenic effects on memory. This information would allow physicians who prescribe medicinal marijuana to provide more precise recommendations to patients, which is urgently needed because currently there are no guidelines regarding appropriate doses for managing symptoms associated with HIV infection (Hoffmann & Weber, 2010).

Despite the strengths of this study, including multiple measures of drug use and HIV disease progression combining both self-report and objective assessments, there were also notable limitations. First, as discussed above, cross-sectional measures of HIV disease progression were utilized rather than longitudinal measures such as copy-years viremia or a composite measure that included multiple biomarkers. Second, the cross-sectional design did not allow for conclusions regarding causality. Without having

established baseline memory functioning prior to initiation of marijuana use, it is possible individuals who chose to initiate marijuana may have had preexisting differences in brain functioning. Unfortunately, longitudinal studies that assess baseline neurocognitive functioning require large sample sizes because it can be difficult to predict who will initiate marijuana use, particularly when marijuana use begins before HIV seroconversion. Third, as discussed above, the marijuana group was limited in variability and predominantly comprised of heavy users. Fourth there was no HIV-negative control group to identify the unique contributions of HIV-infection to memory impairment.

In sum, findings suggest that HIV-associated memory impairment is prevalent and that it may be exacerbated by marijuana use, particularly when marijuana use begins at a young age. This is concerning because memory impairment can have devastating real-world consequences, including antiretroviral medication non-adherence and difficulty with independent living. Given that the prevalence of marijuana use among this population is already high, and it is likely to increase given increased legalization of the drug, educating patients of the potential harmful neurocognitive consequences of using marijuana should be a public health priority.

Appendix A

Prescreening Assessment

"I would like to ask I would like to ask you some questions that would help us determine if you qualify to be in one of our research studies. This will take between 5 to 10 minutes. These questions will involve your giving information about your medical history. Answering these questions is voluntary. You are under no obligation to answer them, and not answering them will have no effect on your health care at Duke. Not answering the questions, however, means that you will not be eligible to participate in this research study. If at any time during this prescreening you would like to stop and not participate or if you have any questions, just let me know.

Here is some information about the confidentiality of the information I collect today. If you do not qualify for the study or decide not to participate, we will not keep the information we collect today. If you do qualify for the study and decide to participate, we will ask you to sign a consent form at your first appointment. The personal information you give me today will become part of your research record and will be reviewed by Dr. Christina Meade and the research staff. Your name will not appear on this screening information. We will assign a code number and the key to the code will be kept in a locked file separate from the other information I collect today. If you change your mind at any time and decide that you do not want to participate, you can call us and we will immediately destroy the private information that we collect today."

*Would you like to continue now with the screening questions? Yes No

**If you are not eligible for current studies, would you like us to keep your name and contact information only on file and contact you about future studies? Yes No

Gender: Female Male
Age: _____
Ethnicity: _____
Handedness: Left Right

Sexual Orientation: _____
Years of Education before GED: _____
Able to read English? Yes No
Smoking status: Current Past Never

HIV Medical History

1. Have you ever tested positive for HIV? Yes No If yes, when? _____
2. Where do you receive your medical care? _____

Substance Abuse

I am going to ask you some questions about your history of alcohol and drug use. Please remember that everything you tell me is confidential; try to be as honest as possible.

	Ever?	Current/last use	Heaviest use	Years?
Marijuana				

Do not record any answers for individual items – only a "yes" if one or more of the exclusions are met and "no" if no exclusions met.

	Ever?	Past year use	Heaviest use
Alcohol		Exclude if abuse/dependence within year	n/a
Cocaine		Exclude if any use within year	Exclude if any lifetime abuse/dependence
Stimulants		Exclude if any use within year	Exclude if any lifetime abuse/dependence
Heroin		Exclude if any use within year	Exclude if any lifetime abuse/dependence
Other opiates		Exclude if any use within year	Exclude if any lifetime abuse/dependence
Sedatives		Exclude if any use within year	Exclude if any lifetime abuse/dependence
Other		Exclude if any use within year	Exclude if any lifetime abuse/dependence

**Drug use history precluding participation?* *Yes No*

Medical History

3. Have you lost consciousness, had a concussion, or been in a coma? Yes No
   - If yes, about how long ago? _____
   - Describe, including length: _____
   - Treatment: _____

**Severe head trauma precluding participation?* *Yes No*

4. Do you have any other medical conditions? Yes No
**Seizures, multiple sclerosis, or severe neurological condition precluding participation? Yes No*

5. Do you have any physical handicaps, like immobility, blindness, or hearing impairment?
**Impairments that may impede participation? Yes No*

6. Are you currently taking any medications? Yes No
- Which ones/for what? _____

7. Have you ever been treated for psychological/mental health problems or taken any medications for psychological/mental health problems? Yes No
- About how long ago? _____
- Which medications? _____

8. Have you ever been diagnosed with a psychological or psychiatric disorder (e.g., major depression, bipolar disorder, psychotic disorder)? Yes No
- What diagnosis? _____

**Severe mental illness precluding participation? Yes No*

Appendix B

Marijuana Assessment

We would like to ask you about your experiences with marijuana.

These questions will be asking about the past 90 days.

1) When did you last use any kind of marijuana?
   Please list day and time of last use: _____
   __ __ hours ago

2) During the past 90 days, on average, how much money did you spend per week on marijuana?
   $_____per week

3) During the past 90 days, when you smoked, how many hours per day did you feel high on average?
   _____ hours per day

4) During the past 90 days, on a typical day when you smoked, how many times per day did you get high on average (at least a 90 minute time interval is necessary to count as separate "times")?
   _____ times per day

5) During the past 90 days, what was your typical source of marijuana (select one)?
   ___ (1) I bought it
   ___ (2) Prescription from a doctor
   ___ (3) I grew it myself
   ___ (4) I received it as a gift
   ___ (5) Other (please specify)_____

6) During the past 90 days, when did you typically smoke? (please check all that apply)
   ___ (1) Mornings (6am - noon)
   ___ (2) Afternoons (noon - 6pm)
   ___ (3) Evenings (6pm - midnight)
   ___ (4) Nights (midnight - 6am)

7) What was the major reason you **first** started smoking marijuana?
   ___ (1) To relieve physical pain

___ (2) To get high/for euphoria
___ (3) To improve sleep
___ (4) To relieve depression, sad feelings
___ (5) To relieve nervousness, anxiety
___ (6) Other (please specify)_____

8) What is the major reason you **continue** to smoke marijuana?
___ (1) To relieve physical pain
___ (2) To get high/for euphoria
___ (3) To improve sleep
___ (4) To relieve depression, sad feelings
___ (5) To relieve nervousness, anxiety
___ (6) To avoid withdrawal
___ (7) Other (please specify)_____

9) During the past 90 days, did you purposefully stop, try to stop, cut down or try to limit your use of marijuana? (We are not referring to times that you stopped or cut back because you were pressured to or unable to get marijuana [like if there was mandatory drug testing, if you were someplace where you couldn't get marijuana, etc.], but rather because you purposefully stopped smoking.)
___ (1) Yes
___ (2) No

10) How accurate do you think you have been in estimating your marijuana use? I'm not asking if you got everything exactly right. But overall, how accurate is this information in describing your marijuana use?

1	2	3	4	5	6	7
Not at all Accurate			Fairly Accurate			Very Accurate

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Biography

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