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Memory impairment in HIV-infected individuals with early and late initiation of regular marijuana use

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Abstract

Marijuana use is disproportionately prevalent among HIV-infected individuals. The strongest neurocognitive effect of marijuana use is impairment in the domain of memory. Memory impairment is also high among HIV-infected persons. The present study examined 69 HIV-infected individuals who were stratified by age of regular marijuana initiation to investigate how marijuana use impacts neurocognitive functioning. A comprehensive battery assessed substance use and neurocognitive functioning. Findings indicated early onset marijuana users (regular use prior to age 18), compared to non-marijuana users and late onset marijuana users (regular use at age 18 or later), were over 8 times more likely to have learning impairment and nearly 4 times more likely to have memory impairment. A similar pattern of early onset marijuana users performing worse in learning emerged when examining domain deficit scores. The potential for early onset of regular marijuana use to exacerbate already high levels of memory impairment among HIV-infected persons has important clinical implications, including increased potential for medication non-adherence and difficulty with independent living.

Keywords

Marijuana; cannabis; HIV/AIDS; memory; neurocognitive functioning

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%

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Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

reported marijuana use in the past 3 months [1]. In comparison, the most recent national prevalence study in the general population found 19.6% of adults aged 18–25 and 6.6% of adults aged 26 and older to have used marijuana in the past month [2]. Some HIV-infected individuals report smoking marijuana to alleviate HIV-related symptoms such as loss of appetite and nausea and to cope with the psychological stress of their disease [3], but many also use marijuana for recreational purposes [3,4]. Given the legalization of medicinal marijuana in 29 US states and the District of Columbia, with most explicitly citing HIV/AIDS as a condition appropriate to manage with medicinal marijuana [5], it is important to understand the effects of regular marijuana use in this population.

HIV can infiltrate the central nervous system and cause neurocognitive impairment [6]. Although the introduction of highly active antiretroviral therapy (HAART) in 1996 significantly changed the course of HIV-related neurocognitive impairment, including a sharp decline in the incidence of dementia [7], milder forms remain a significant public health concern. The CHARTER study, a large multi-site study of >1,500 HIV-infected adults in the US, found that 52% had HIV-associated neurocognitive impairments, primarily in learning, memory, attention/working memory, and executive functioning [8,9]. In the domain of memory, individuals infected with HIV have demonstrated impairment on both verbal and visual tasks [10–14].

Memory impairment may increase in the context of advanced HIV disease, suggesting that HIV biomarkers may moderate the impact of HIV on cognitive functioning [13,15,16]. However, some studies did not find correlations between current CD4 count, a marker of the degree of immunosuppression, or HIV viral load and memory performance [17–19]. It may be that these markers of HIV disease progression are not the most accurate means of predicting task performance. Nadir CD4 (i.e., the lowest CD4 count), a reflection of the most severe immune suppression, may more accurately capture the extent to which brain functioning has been affected by HIV [9,20]. 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 [21,22]. 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.

Outside the field of HIV, several reviews of the literature have concluded that marijuana use is associated with neurocognitive impairment across multiple domains [23–26]. The most robust neurocognitive effect is on memory impairment, and memory problems are the most frequently reported cognitive complaint of marijuana users [27,28]. A recent meta-analysis found current marijuana users to demonstrate worse performance compared to non-marijuana users on tasks of both short- and long-delayed recall within the first 25 days of abstinence [26]. However, the effect size was small, and when analyses were limited to studies of marijuana users who had been abstinent for 25 days or longer group differences were no longer significant. Importantly, results also indicated there was significant variability between studies included in the review, which makes it difficult to draw firm conclusions given that the severity of cognitive impairment is affected by factors such as duration of use, frequency, age of onset of marijuana use, and length of abstinence [29,30]. In particular, there is robust evidence that initiating marijuana use at a younger age is

associated with worse neurocognitive outcomes [31–33]. 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 [31]. Two other studies examining the impact of age of first use on memory did not find an effect, but both were limited by minimal variability in participants' ages [34,35]. 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 [35], and in the other study all participants had begun using before age 18 [34]. Memory deficits have also been correlated with longer duration of regular marijuana use [31,36–38] and greater frequency of use [34,39–42].

Little research has examined whether marijuana and HIV infection have a synergistic effect on memory functioning and findings are not consistent. One of the earliest studies to examine this question empirically compared the neurocognitive performance of HIV-infected and HIV-uninfected individuals, stratified by disease stage and frequency of marijuana use [43]. They reported an interaction effect, finding that current marijuana use was associated with greater global neurocognitive impairment among individuals with symptomatic HIV infection and that this effect was primarily driven by performance on a delayed memory task. These results suggest that marijuana use may exacerbate memory impairment among HIV-infected individuals already experiencing memory decline. However, Cristiani and colleagues did not consider age of first marijuana use in their analyses, nor did they present descriptive information on age of first use. In contrast, a more recent study also examining interaction effects of marijuana and HIV on cognitive functioning did not find marijuana use to exacerbate memory impairment among HIV-infected individuals. Instead, they suggested marijuana use more adversely impacts HIV-uninfected than HIV-infected individuals [44]. In this study, age of first marijuana was reported but not considered in analyses due to no significant group differences. In fact, to date no studies to our knowledge have considered how age of marijuana initiation impacts neurocognitive outcomes among HIV-infected populations.

To address this important gap in the literature, the present study of HIV-infected adults who were stratified based on age of initiation of regular marijuana use investigated how marijuana use impacts neurocognitive functioning. We hypothesized the following: (1) individuals who initiated regular marijuana use at an early age would demonstrate increased impairment on memory tasks compared to both individuals who initiated regular marijuana at a later age and non-marijuana users; (2) there would be an interaction between marijuana use and HIV disease progression such that marijuana's effect on memory would be stronger among individuals with more advanced HIV disease progression.

METHODS

Participants

HIV-infected adults were recruited via advertisements in local newspapers and websites, flyers posted and brochures distributed at community-based organizations and infectious diseases clinics, and participant referrals. Interested individuals completed a structured telephone pre-screen to assess preliminary eligibility (e.g., HIV infection, drug use history). If eligible, participants were invited for an in-person screening visit.

The sample included HIV-infected adults 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 per month, and 1 year of regular marijuana use. Consistent with the Addiction Severity Index-Lite (ASI-Lite), regular use was defined as three or more times per week, binges, or problematic irregular use in which normal activities are compromised [45]. Our decision to consider age of regular marijuana use rather than age of experimentation is common in the literature when examining the impact of marijuana use on neurocognitive functioning [33,46]. Given that frequency of use is known to moderate the severity of a drug's impact on cognitive functioning, regular use is expected to impact brain functioning more profoundly than infrequent experimentation. Early onset was defined as regular use beginning <18 years of age, and late onset was defined as regular use beginning 18 years of age. This cutoff of age 18 was previously used in the Dunedin Study birth cohort study and found to predict broad decline in cognitive functioning [31]. *Non-marijuana 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. Frequency of drug use was assessed by self-report. Individuals were also excluded for a positive urine drug screen for any other illicit drug, other illicit drug use in the past 90 days, or regular use of any other illicit drug in the past year. Past alcohol dependence as defined by the Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision [47](DSM-IV-TR) was permitted in both groups if in sustained full remission (i.e., 12 months without meeting any criteria for dependence or abuse). Exclusion criteria were: <8th grade education; English non-fluency or illiteracy; serious neurological disorders and events (e.g., seizure disorder, multiple sclerosis, brain embolism); pregnancy; 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 related to acute psychiatric distress or initiation of new medication, it was also required that individuals be diagnosed with HIV for >3 months and be on a stable antiretroviral medication regimen for >3 months. Participants were drawn from two protocols with shared procedures that recruited HIV-infected adults from the Raleigh-Durham area between June 2010 and April 2015. All procedures were approved by the institutional review board at Duke University Health System.

Procedures

At the initial in-person screening visit, participants provided written informed consent. They completed clinical interviews and questionnaires, and provided a urine sample to screen for pregnancy and drug tests. We used the CLIAwaived, Inc. 9-Panel Rapid Dip Drug Test which was run onsite during the study visit. Eligible participants returned on another day to complete neurocognitive testing, additional questionnaires, and another urine drug test. Participants were asked to refrain from using marijuana for 6 hours prior to both visits, and each visit began with a breathalyzer to ensure no participant was acutely intoxicated from alcohol. Participants were paid \$35 for the screening, regardless of eligibility, and \$65 for the testing visit.

Measures

Demographics—Participants reported age, gender, race, sexual orientation, and education. The Wechsler Test of Adult Reading (WTAR) was used to assess premorbid intellectual functioning [48].

Substance use—The Timeline Follow-back (TLFB) method was used at both study visits to assess frequency of recent substance use in the past 90 days [49]. Heavy alcohol use was defined as 4 drinks for women and 5 drinks for men in one episode [50]. The ASI-Lite, a semi-structured interview, assessed lifetime substance use [45,51]. Module E of the Structured Clinical Interview for DSM-IV-TR identified current and lifetime substance use disorder diagnoses [52]. Participants who used marijuana also completed a computerized questionnaire that assessed characteristics of marijuana use, including age of first use and age beginning to use regularly (3 times per week), and whether there were attempts to stop or limit use.

Mental health—The Mini International Neuropsychiatric Interview (MINI), a structured clinical interview, was used to identify DSM-IV-TR psychiatric diagnoses [53]. Depression and anxiety were measured using the Brief Symptom Inventory 18 (BSI) [54].

HIV disease—Medical records were reviewed to obtain date diagnosed with HIV and lab results (i.e., current CD4 count, nadir CD4 count, viral load) relevant to HIV infection. Self-report was used when medical records were incomplete or unavailable. Nadir CD4 cell count was dichotomized at 200 cells/mm³ and current cell CD4 count at 500 cells/mm³. Plasma viral load was “detectable” or “undetectable” based on a sensitivity of < 50 copies/mL.

Neurocognitive functioning—A 60-minute neurocognitive battery assessed functioning across seven domains:

1. *Learning (immediate recall)*: Hopkins Verbal Learning Test-Revised—total number of words recalled on trials 1–3 [55]; and Brief Visuospatial Memory Test-Revised—total score for figures correctly recalled on trials 1–3 [56].
2. *Memory (delayed recall)*: Hopkins Verbal Learning Test-Revised—number of words recalled on trial 4 [55]; and Brief Visuospatial Memory Test-Revised—total score for figures correctly recalled on trial 4 [56].
3. *Executive function*: Trail Making Test Part B—number of seconds to completion [57]; and Stroop Color and Word Test—interference score [58].
4. *Processing speed*: Trail Making Test Part A—number of seconds to completion [57]; and Digit Symbol Test—number correct [59].
5. *Motor abilities*: Grooved Pegboard Test dominant and non-dominant hand—number of seconds to completion [60].
6. *Verbal fluency*: Controlled Oral Word Association Test phonemic fluency—number of FAS words generated; and Controlled Oral Word Association Test semantic fluency—number of animals generated [61].

7. *Attention/working memory*: Paced Auditory Serial Addition Test-50—number correct [62]; and NAB Digit Span Forwards and Backwards—number correct [63].

Using up-to-date published norms, raw scores were converted to demographically corrected T-scores ($M=50$, $SD=10$) [59,64–67]. Each case was scored independently by two research assistants. Any discrepancies were resolved by a third research assistant re-scoring the case.

Domain T-scores were created by averaging individual T-scores from tests assessing the same cognitive domain. T-score impairment was defined as 1 SD below the mean. We also computed Domain Deficit Scores (DDS), which reflect the severity of impairment in test performance and give relatively less weight to performances that are within normal limits [68]. T-scores for each test were converted to a 0–5 deficit rating: $T \geq 40 = 0$ (no impairment), $35–39 = 1$, $30–34 = 2$, $25–29 = 3$, $20–24 = 4$, and $<20 = 5$. The DDS were calculated by adding deficit scores for the tests within each of the seven domains and dividing by the number of tests within the domain. Impairment within a domain was defined as ≥ 0.5 [69].

Data analysis

Descriptive statistics were used to characterize the sample. We used ANOVA and chi-square to identify group differences in terms of demographics, mental health, alcohol use, and HIV disease characteristics, followed by post-hoc analyses to probe significant group means. A series of bivariate logistic regressions were used to predict T-score impairment status (< 40 vs. ≥ 40) in each cognitive domain as a function of early and late marijuana onset, with non-marijuana users as the reference group. Then, ANOVAs were used to examine group differences in DDS, again followed by post-hoc analyses to probe significant group means. Finally, we examined whether the effect of marijuana use on memory was moderated by HIV disease progression. Separate 3 (marijuana use group) $\times 2$ (HIV biomarker) ANOVAs were conducted for each of the three relevant HIV biomarkers (i.e., CD4, nadir CD4, and viral load) to determine whether there was an interaction between HIV disease progression (e.g., detectable vs. undetectable viral load) and marijuana use (early onset of regular use vs. late onset of regular use vs. no drug use).

RESULTS

The sample included 69 HIV-infected adults. Table I presents demographic, mental health, substance use, and HIV disease characteristics of the sample by group. The majority were male (73%) and African American (77%). Most had a high school degree or GED (90%), and about a quarter (28%) had completed a 4-year college. Non-marijuana users were more likely to be older in age than early onset [$F(1, 52) = 8.02$, $p = 0.007$] and late onset [$F(1, 55) = 7.98$, $p = 0.007$] marijuana users. Early onset users had fewer years of education than late onset users [$F(1, 25) = 5.62$, $p = 0.026$] and non-marijuana users [$F(1, 52) = 7.98$, $p = 0.007$]. Participants had been living with HIV for an average of 11 years, ranging from 4 months to 32 years. Half (46%) had a nadir CD4 count < 200 , and 38% had a current CD4 count < 500 . Both early and late marijuana users were diagnosed with HIV infection at a younger age than non-marijuana users. Most marijuana users (82%) began using marijuana

prior to their HIV diagnosis. There were no group differences in mental health or alcohol use.

On average, individuals in the marijuana groups were chronic users who had been using regularly for 15.63 years (SD = 9.15, range 1 – 36). They used an average of 73.96 days out of the last 90 (SD = 20.82, range 22 – 90) with more than half (67%) reporting daily or almost daily (≥ 6 days per week) use. One-fifth (22%) indicated that they had tried to stop or limit their marijuana use within the past 90 days, and approximately half met criteria for marijuana dependence (48%). The average age of first use was 16.19 (SD = 3.94, range 8 – 25), and the average age of beginning to use regularly was 19.81 (SD = 4.36, range 13 – 34). Comparison of early onset and late onset groups indicated that, aside from age of first regular use [$F(1, 25) = 28.18, p = 0.000$], there were no significant group differences on any other characteristics of marijuana use.

Rates of neurocognitive impairment and deficit scores

In logistic regressions predicting impairment, the early onset group was more likely to demonstrate impairment compared to non-marijuana users in the domains of learning (OR = 8.46, 95% CI = 1.93–37.02, $p = 0.005$) and memory (OR = 3.95, 95% CI = 1.04–15.04, $p = 0.044$), and less likely to demonstrate impairment in the domain of attention/working memory (OR = 0.11, 95% CI = 0.01–0.93, $p = 0.043$) (Table II). There were no differences in impairment between the late onset group and non-marijuana users. Examination of deficit scores revealed similar patterns, with the early onset group having the highest deficit scores in learning and memory and lowest scores in attention/working memory, but the differences were only significant between the early onset group and non-marijuana users in the domain of learning [$F(1, 52) = 6.54, p = 0.014$] (Table III). The effect size was large ($d = 0.79$).

HIV disease progression as moderator

There were no main effects of current CD4, nadir CD4, or HIV viral load on memory functioning, nor were there interaction effects between these biomarkers and marijuana use group (all $p > 0.05$).

DISCUSSION

Despite the increased legalization of medicinal and recreational marijuana and the high prevalence of use among HIV-infected individuals, this is the first study to our knowledge to examine how age of initiating regular marijuana use impacts memory functioning in a sample of HIV-infected individuals. Findings revealed that individuals who initiated regular marijuana use prior to age 18, compared to non-marijuana users, were over 8 times more likely to have learning impairment and nearly 4 times more likely to have memory impairment. A similar pattern of early onset users performing worse than non-marijuana users in the domain of learning emerged when examining deficit scores. In contrast, individuals who initiated regular marijuana use after age 18 did not significantly differ from non-marijuana users on any outcome measure.

Surprisingly, the early onset group demonstrated less impairment compared to non-marijuana users in attention/working memory. Nearly half (45%) of the non-marijuana users

in our sample were impaired in this domain, which was almost double the impairment rate for this group in any other domain we measured, whereas only a minority (8%) of early onset users demonstrated impairment in attention/working memory. Extant literature does not support a relationship between marijuana use and improved attention or working memory functioning, but rather comprehensive reviews suggest marijuana can be associated with impairment in these domains [25,70]. Conclusions should be made with caution as more research is needed in this area.

The hypothesis that there would be an interaction between marijuana use and HIV disease progression was not substantiated in this sample. This contrasts with prior research that found the effects of marijuana use to be stronger in the context of advanced HIV infection [43], and may be explained by low immunosuppression in our sample. The prior study found the interaction effect to be most pronounced among individuals with symptomatic HIV-infection whose average CD4 counts were under 300 (i.e., 182 for marijuana users and 273 for non-marijuana users). In our study, immunosuppression was much lower, with average CD4 counts over 500 (i.e., 631 for marijuana users and 547 for non-marijuana users), potentially because all were receiving antiretroviral medications. In over a decade since Cristiani et al. (2004) published their findings, medications for the treatment of HIV have improved dramatically, transforming HIV infection from an acute life-threatening disease to a chronic health condition that if well-managed allows for a life-expectancy close to normal [71,72]. The evolution of antiretroviral medications may also explain why Cristiani et al. (2004) found a main effect of HIV disease stage on neurocognitive outcomes whereas we did not find any relationship between markers of HIV disease progression and memory. The effect of HIV infection on neurocognitive functioning may be more pronounced at later stages of infection when immunosuppression is high, and it is only at this time when cognitive resources are lower that marijuana use interacts with HIV.

The significant association between age of onset and memory in our sample of HIV-infected individuals is consistent with studies conducted in general samples [31,32] and has significant clinical implications. First, as the legalization of marijuana becomes more widespread, it will be important to educate the public regarding the potentially harmful neurocognitive consequences of marijuana use, particularly when regular use begins at a younger age. Second, it suggests that using marijuana in adulthood to manage HIV-related symptoms may not be as significant a risk factor for memory decline. However, future research with greater variability is needed to determine whether frequency of use impacts memory among those whose regular use begins in adulthood before patients with health conditions such as HIV can be confident that managing symptoms with marijuana will not have iatrogenic effects on cognitive functioning. 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 [73].

The potential of regular marijuana use initiated prior to age 18 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 [74–79], 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 [80] and increases the likelihood of transmitting the virus during sexual activities [81]. Further, memory abilities are among the strongest neuropsychological predictors of obtaining employment [82] and may be predictive of an HIV-infected individual's ability to abstain from high-risk sexual and injection practices [17].

Despite the strengths of this study, including multiple measures of drug use and HIV disease progression that combined both self-report and objective assessments, there were also notable limitations. First, our sample size of 69 may have limited our power to detect small effects and precluded examination of possible moderators, such as duration of marijuana use and co-occurring heavy alcohol use. Future research with larger sample sizes is warranted. Second, analyses of deficit scores were limited in variability due to fairly low scores overall and many individuals having no impairment. Third, the cross-sectional design did not allow for conclusions regarding causality. Without having established baseline memory functioning prior to initiation of regular marijuana use, it is possible individuals who chose to initiate regular marijuana use may have had preexisting differences in neurocognitive functioning. For instance, impulsivity is a well-established risk factor for substance use [83,84], and it is possible that individuals who initiate regular marijuana use early may demonstrate other high risk behaviors (e.g. truancy, aggression) related to impulsivity that could have further reduced neurocognitive functioning. Further, a recent review found that poor performance on tasks of working memory and inhibition predicts substance use initiation among adolescents [85], which highlights the difficulty of teasing apart to what extent neurocognitive impairment associated with marijuana use is a preceding vulnerability factor or a consequence of use. Unfortunately, longitudinal studies that assess baseline neurocognitive functioning require large sample sizes because it can be difficult to predict who will initiate regular marijuana use, particularly when marijuana use begins before HIV seroconversion. Fourth, the marijuana group was limited in variability and predominantly comprised of heavy users by design, which prevented us from examining whether occasional use of marijuana has a similar effect on neurocognitive functioning as frequent use. Finally, there was no HIV-uninfected control group to identify the unique contributions of HIV infection to memory impairment.

In summary, findings suggest that HIV-infected adults who initiate regular marijuana use in adolescence have higher levels of memory impairment compared to non-marijuana users and individuals who initiate regular marijuana use later in life. This is concerning because memory impairment can have serious real-world consequences, including antiretroviral medication non-adherence and difficulty with independent living. Given that the prevalence of marijuana use among HIV-infected patients 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.

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Table 1
Demographic, psychiatric, and HIV disease characteristics of the sample (N=69)

	Early onset n=12	Late onset n=15	Non-marijuana n=42	Statistic	p-value
<u>Demographic characteristics</u>					
Male, %	75%	67%	74%	$\chi^2 (2) = 0.33$	0.848
Age in years, M (SD)	36.17 (9.00) ^a	36.60 (10.92) ^a	45.57 (10.43) ^b	$F(2, 66) = 6.49^{**}$	0.003 ^{**}
Education in years, M (SD)	12.00 (2.09) ^a	14.33 (2.85) ^b	14.02 (2.21) ^b	$F(2, 66) = 4.10^*$	0.021 [*]
Caucasian, %	33%	27%	10%	$\chi^2 (2) = 4.83$	0.089
Heterosexual, %	42%	27%	41%	$\chi^2 (2) = 1.00$	0.608
Premorbid verbal IQ (WTAR), M (SD)	88.00 (17.51)	90.13 (17.98)	88.40 (18.90)	$F(2, 66) = 0.06$	0.943
<u>Mental health and alcohol use</u>					
Anxiety symptoms (BSI), M (SD)	0.61 (0.96)	0.52 (0.50)	0.46 (0.71)	$F(2, 65) = 0.22$	0.807
Depression symptoms (BSI), M (SD)	0.53 (0.87)	0.67 (0.68)	0.60 (0.80)	$F(2, 66) = 0.10$	0.901
Lifetime alcohol dependence, %	16.7%	20.0%	4.8%	$\chi^2 (2) = 3.49$	0.174
Any heavy alcohol use, %	33.3%	20.0%	14.3%	$\chi^2 (2) = 2.23$	0.328
Days of use, M (SD)	1.50 (1.00)	2.67 (2.08)	2.83 (2.79)	$F(2, 10) = 0.45$	0.648
<u>HIV disease characteristics</u>					
Years since HIV diagnosis, M (SD)	9.63 (7.55)	8.60 (9.01)	11.51 (7.92)	$F(2, 66) = 0.81$	0.451
Nadir CD4 cell count, M (SD)	299.08 (211.50)	306.67 (305.04)	215.24 (198.75)	$F(2, 66) = 1.24$	0.297
Current CD4 cell count, M (SD)	624.58 (254.86)	636.27 (356.34)	546.98 (309.84)	$F(2, 65) = 0.60$	0.554
Current HIV viral load < 50 copies/mL, %	58%	67%	49%	$\chi^2 (2) = 1.51$	0.471
<u>Marijuana use characteristics</u>					
Initiated prior to HIV diagnosis, %	92%	73%	–	$\chi^2 (1) = 1.49$	0.240
Age of first use, M (SD)	15.24 (1.88)	16.80 (5.02)	–	$F(1, 25) = 0.82$	0.375
Age of first regular use, M (SD)	16.33 (1.44)	22.60 (3.87)	–	$F(1, 25) = 28.18^{**}$	0.000 ^{**}
Duration in years, M (SD)	18.33 (9.03)	13.47 (8.95)	–	$F(1, 25) = 1.96$	0.174
Marijuana use days in past 90, M (SD)	82.50 (27.02)	81.93 (20.50)	–	$F(1, 25) = <0.01$	0.950
Heavy marijuana use days in past 90, M (SD) ^a	56.67 (40.89)	61.67 (30.25)	–	$F(1, 25) = 0.13$	0.718
Current marijuana dependence, %	50%	48%	–	$\chi^2 (1) = 0.03$	0.585
Tried to cut down/stop in past 90 days, %	25%	20%	–	$\chi^2 (1) = 0.10$	0.557

Note. Values within a row that do not share the same superscript differ significantly at $p < .05$.

^aHeavy marijuana use defined as 2 joints per day.

p < .001

**
p < .01,

*
p < .05,

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Table II

Series of logistic regression models predicting neurocognitive impairment by domain (N=69)

	Percent impaired	Odds Ratio (95% CI)	p-value
<u>Learning</u>			
Early onset	75%	8.46 (1.93–37.02)	0.005 **
Late onset	20%	0.71 (0.17–2.97)	0.634
Non-marijuana	26%		
<u>Memory</u>			
Early onset	58%	3.95 (1.04–15.04)	0.044 *
Late onset	27%	1.03 (0.27–3.90)	0.971
Non-marijuana	26%		
<u>Executive Function</u>			
Early onset	8%	0.67 (0.07–6.38)	0.730
Late onset	0%	0.00 (0.00–0.00)	1.000
Non-marijuana	12%		
<u>Processing Speed</u>			
Early onset	25%	4.33 (0.75–25.12)	0.102
Late onset	13%	2.00 (0.30–13.32)	0.474
Non-marijuana	7%		
<u>Motor Abilities</u>			
Early onset	17%	1.20 (0.21–6.88)	0.838
Late onset	13%	0.92 (0.17–5.16)	0.927
Non-marijuana	14%		
<u>Verbal Fluency</u>			
Early onset	17%	1.20 (0.21–6.88)	0.838
Late onset	7%	0.43 (0.05–3.89)	0.451
Non-marijuana	14%		
<u>Attention/Working Memory</u>			
Early onset	8%	0.11 (0.01–0.93)	0.043 *
Late onset	27%	0.44 (0.12–1.61)	0.215
Non-marijuana	45%		

*
p < .05,**
p < .01,***
p < .001

Table III

Group comparisons on domain deficit scores (N=69)

	Early onset n=12	Late onset n=15	Non-marijuana n=42	Omnibus F-test	p-value	Cohen's d	
						Early initiator vs. Non-marijuana	Late initiator vs. Non-marijuana
Learning	1.33 (0.91) ^a	0.73 (0.62) ^{ab}	0.67 (0.76) ^b	F(2, 66) = 3.63 [*]	0.032 [*]	0.79	0.09
Memory	0.96 (0.94)	0.70 (0.65)	0.58 (0.75)	F(2, 66) = 1.13	0.328	0.45	0.17
Executive function	0.21 (0.50)	0.27 (0.50)	0.27 (0.52)	F(2, 66) = 0.08	0.925	-0.12	0.00
Processing speed	0.29 (0.45)	0.30 (0.80)	0.18 (0.40)	F(2, 66) = 0.43	0.653	0.26	0.20
Motor abilities	0.38 (0.74)	0.40 (1.07)	0.29 (0.78)	F(2, 66) = 0.13	0.883	0.12	0.12
Verbal fluency	0.17 (0.39)	0.10 (0.28)	0.29 (0.52)	F(2, 66) = 1.03	0.364	-0.26	-0.45
Attention/working memory	0.28 (0.51)	0.56 (0.94)	0.82 (0.75)	F(2, 66) = 2.54	0.086	-0.84	-0.31

*
p < .05,**
p < .01,***
p < .001

Note. Values within a row that do not share the same superscript differ significantly at p < .05