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## The Impact of Cannabis Use on Cognition in People with HIV: Evidence of Function-Dependent Effects and Mechanisms from Clinical and Preclinical Studies

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### Abstract

**Purpose of Review**—Cannabis may have beneficial anti-inflammatory effects in people with HIV (PWH); however, given this population’s high burden of persisting neurocognitive impairment (NCI), clinicians are concerned they may be particularly vulnerable to the deleterious effects of cannabis on cognition. Here, we present a systematic scoping review of clinical and preclinical studies evaluating the effects of cannabinoid exposure on cognition in HIV.

**Recent Findings**—Results revealed little evidence to support a harmful impact of cannabis use on cognition in HIV, with few eligible preclinical data existing. Furthermore, the beneficial/harmful effects of cannabis use observed on cognition were function-dependent and confounded by several factors (e.g., age, frequency of use).

**Summary**—Results are discussed alongside potential mechanisms of cannabis effects on cognition in HIV (e.g., anti-inflammatory), and considerations are outlined for screening PWH that may benefit from cannabis interventions. We further highlight the value of accelerating research discoveries in this area by utilizing translatable cross-species tasks to facilitate comparisons across human and animal work.

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## Keywords

NeuroHIV; Cannabinoids; Cognition; HIV-associated neurocognitive disorders

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## Introduction

Approximately 38.4 million people live with human immunodeficiency virus (HIV) worldwide (UNAIDS, 2021). While advances in combination-antiretroviral therapy (cART) have reduced HIV progression, secondary effects of long-term infection arise, including self-reported [1–3] and clinically diagnosed neurocognitive impairment [NCI; 4–6]. NCI is estimated to affect 40–45% of people with HIV (PWH), typically impacting verbal fluency/language skills, attention/working memory, executive function, learning and memory, information-processing speed, and motor skills [7–11]. Treatment development is complicated by several factors. For example, while affected cognitive domains vary across PWH, HIV-associated NCI is diagnosed based on the *degree* of impairment, ranging from mild (i.e., asymptomatic neurocognitive impairment) to moderate (i.e., mild neurocognitive impairment) to severe (i.e., HIV-associated dementia) [12]. This means individuals often share the same categorical diagnoses, yet experience deficits in different functional domains. This approach is problematic given that distinct “cognitive trajectories” of HIV-associated-NCI are observed, suggesting discrete underlying network aberrations across PWH [13, 14, 15].

Moreover, worse NCI is observed in PWH who reported current [16–19] or past [20–22] substance use, necessitating considerations of the exacerbating effects of drug exposure. Cannabis, however, has anti-inflammatory and neuroprotective properties [23] which may combat the neuroinflammation and associated neurodegeneration thought to partly mediate HIV-associated NCI. Importantly, cannabis use (CU) is reported by PWH at two-to-three times the rate of the general population [24], driven in large part by self-medication (e.g., anxiety and pain management) [25, 26], but its interactions with HIV infection are not well understood.

Particularly, the interactive effects of CU and HIV infection on *domain-specific* cognition are required to facilitate development of targeted therapeutics for HIV-associated NCI.

## Cannabis and Interactions with the Endocannabinoid System

Cannabis acts primarily via the endocannabinoid (eCB) system, which comprises the G-protein coupled cannabinoid-1 and cannabinoid-2 receptors (CB<sub>1</sub>R and CB<sub>2</sub>R), and their endogenous ligands (i.e., *endocannabinoids*), N-arachidonylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG) [27]. AEA and 2-AG are retrograde signaling molecules that are synthesized on-demand following neuronal depolarization and decrease further neurotransmitter release by activating presynaptic eCB receptors [28].

CB<sub>1</sub>Rs are one of the most abundantly expressed receptors in the central nervous system (CNS), primarily expressed on neurons [29]. CB<sub>2</sub>Rs, while less abundant in the CNS, are expressed at higher levels on immune-activated glial cells and astrocytes and are largely

upregulated under pathological conditions, e.g., neuroinflammation [30]. The eCB system mediates widespread physiological and behavioral processes—including cognition [31]—and has therapeutic potential for HIV-associated neuropathology, e.g., blocking neuronal excitotoxicity (CB1R) [32, 33] and reducing neuroinflammation via attenuation of microglia activation (CB2R) [34]. Interestingly, AEA and related eCB ligands are decreased in PWH, suggesting dysregulation of the eCB system (although this result may be confounded by heavier drug use in the HIV cohort) [35]. The eCB system should, therefore, be further explored for potential biomarkers of HIV-related states, such as HIV-associated NCI.

Over 100 phytocannabinoids have been identified in the cannabis plant, each of which may contribute to its effects on cognition. Of these,  $\Delta^9$ -tetrahydrocannabinol (THC) and cannabidiol (CBD) are the best characterized. THC, the primary psychoactive constituent, is a partial agonist at both eCB receptors [36], although its cognitive effects are largely CB<sub>1</sub>R-mediated [37, 38]. The pharmacology of CBD includes antagonist/inverse-agonist activity at eCB receptors [36, 39], and agonist properties at several other non-eCB receptors [40–42]. Interestingly, THC and CBD can produce differential, or even opposing effects on cognition and associated brain activity [43–47]; thus, the THC:CBD ratio influences the pharmacological properties of cannabis, and likely its effects on cognition.

Essential to determining causal mechanisms of CU on HIV-associated NCI, including the role of the eCB system, is the use of neuroHIV animal models. NeuroHIV animal models enable well-controlled studies of cannabis and/or cannabinoid effects on HIV-associated NCI by minimizing confounds inherent to clinical HIV research (e.g., clinical demographics), as well as those relating to CU (e.g., inter-individual variation in dosing, THC/CBD content). Below we provide a brief overview of current animal models and their benefits and limitations in determining the effects of CU on cognition in HIV.

### Animal Models of HIV

Several transgenic (tg) animal models exist that incorporate HIV proteins into the host genome. For example, the glycoprotein (gp)120 tg mouse expresses the envelope protein gp120 in brain astrocytes and develops a similar neuropathology to that observed in humans with acquired immunodeficiency syndrome (AIDS) [48]. However, since gp120 is expressed constitutively from birth, generalizability to PWH is limited, apart from those born with HIV. Meanwhile, the inducible Tat (iTat) mouse expresses the HIV regulatory protein Tat only following additional treatment (doxycycline), thereby providing temporal control over viral exposure [49]. While the gp120 and iTat lines are useful in parsing the effects of individual HIV proteins on behavioral outcomes, they do not fully recapitulate the human disease, which entails exposure to several interacting viral proteins. The HIV-1tg rat partly addresses this limitation by constitutively expressing most of the HIV genome (excluding gag and pol) [50]. However, this model, too, is limited as it does not reproduce a key feature of viral pathogenesis—the replication and transmission of the infection to other host cells.

Other animal models recreate aspects of viral replication and propagation. For example, humanized mouse models comprising immunodeficient mice reconstituted with HIV-infected human cells enable the study of HIV transmission and chronic infection [51]. However, these mice have numerous drawbacks that limit their use in behavioral

assessments (e.g., longevity, cost, transmissibility concerns). A new approach utilizes EcoHIV, an injectable chimeric HIV virus in which the gp120 gene has been replaced with ecotropic gp80 (from murine leukemia virus), thus enabling viral entry into cells of healthy mice [52] and rats [53]. EcoHIV is sexually transmissible, virally suppressible with cART, and not transmissible to humans, making this model an ideal approach for recreating HIV in rodents.

Finally, simian immunodeficiency virus (SIV) and feline immunodeficiency virus (FIV)—lentiviruses found in non-human primates and felines, respectively [54, 55]—recreate aspects of HIV, though their species-specificity limits their translatability to the human disease. To address this, chimeric viruses (“SHIVs”) in which one or more HIV genes are inserted into the SIV viral genome have been developed [56]; however, given the complexity of utilizing larger animals in research, rodent models are far more commonly used to study neuroHIV.

## Objective

Here, we performed a systematic scoping review of the clinical (i.e., human) and preclinical (i.e., animal model) studies assessing the impact of cannabis exposure or manipulations of the eCB system on cognitive functioning in HIV. The aims of this review are to (1) summarize the existing literature on the effects of cannabinoids on individual cognitive domains; (2) highlight modulating factors of cannabinoid effects on cognition in HIV; and (3) discuss the use of cannabinoids, and alternative approaches in treating HIV-associated NCI.

## Methods

### Information Sources and Search Strategy

A systematic scoping review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [204]. Reports were identified by searching PubMed, EMBASE, PsycINFO, and Web of Science for articles published through May 2023. Studies with available data on aspects of cognition, cannabis or the eCB system, and HIV or non-human animal models of HIV. The full search strategies used for each database are provided in Supplemental File 1.

### Eligibility Criteria and Study Selection

Figure 1 summarizes the systematic scoping review results and applied inclusion/exclusion criteria used for study selection. Eligible studies required all three major components relevant to our review: (1) a study population of PWH or an appropriate model of HIV; (2) assessment of cognition; and (3) self-report of CU data (human studies), administration of cannabis, and measurement/manipulation of the eCB system. Only studies published or translated into the English language were included.

## Data Collection

Database search results were uploaded into EndNote to delete duplicated results. Unique articles were then uploaded to the systematic review software Rayyan QCRI. First and secondary assessments were performed by four reviewers, SA, BH, BR, and AHM, following a previously published systematic scoping review protocol [205, 206]. First and secondary assessments required reviews of the title and abstract, and full text review, respectively, based on the inclusion and exclusion criteria. Articles were approved by at least two reviewers to be considered eligible. Data was extracted from eligible reports using a standardized form, including: first author, publication year, gender distribution, sample-size, diagnoses/disease model, cognitive assessments, and CU criteria or relevant eCB measurement/manipulation method. Conflicts were resolved via discussion between the reviewers.

## Results

Table 1 summarizes eligible preclinical findings, including sample size, animal model, drug-administration, and cognitive task. Table 2 includes eligible clinical findings, including participant demographics, CU criteria, and cognitive tasks. It should be noted that articles may appear in several sections if they assessed multiple domains and may also reappear in beneficial, adverse, or null categories if reported findings were dependent on a varying factor (i.e., dose).

## Cognitive Domains

**Global Cognition**—As discussed, HIV-associated NCI affects various cognitive domains and is diagnosed based on overall NCI. Notably, several studies reported global NCI calculated from a comprehensive battery, such as the Global Deficit Score (GDS) [57, 58]. The GDS averages performance across tasks spanning the seven domains commonly affected in HIV, weighted such that no single exceptionally high-test score disproportionately influences the resultant value. While less useful for determining domain-specific CU/HIV interactions on cognition, this approach enables direct comparison across studies on global functioning. Our review identified 16 clinical studies examining associations between CU and global deficits among PWH. Of these, five studies found adverse effects [57, 59–62], six studies found beneficial effects [15, 58, 63–66], and the remaining studies reported null effects [62, 66–71].

Two studies reported adverse effects of CU on GDS in PWH enrolled in the NIH CHARTER initiative, a 12-year prospective observational study. One reported neurocognitive decline was unrelated to disease or treatment characteristics, possibly because most were virally suppressed on cART at follow-up assessment; however, lifetime (i.e., not current) history of CU disorder (CUD) predicted worsened global neurocognitive change overtime [57]. The other reported that lifetime CU was associated with worse GDS in PWH [59], suggesting CUD diagnoses was not necessary for the adverse CU effects observed in the previous study. Two additional studies described similar results utilizing composite scores other than the GDS. Cristiani et al. [60] reported that frequent CU was associated with greater NCI, an effect more pronounced in cognitively symptomatic versus asymptomatic PWH;

thus, disease state may influence the impact of CU on global cognition in PWH (although the negative impact of CU reported above were observed in cohorts that were virally suppressed). Similarly, CU was strongly associated with global impairment in a male cohort of PWH, but not people without HIV (PWoH) [61]. In contrast, in a female-only cohort of PWH, a specific cognitive impairment profile (deficits in executive function, learning, and processing-speed) was *less* likely in cannabis-using versus cannabis-abstinent PWH [15]; however, other impairment profiles incorporating these domains (e.g., the learning and memory profile) were not associated with CU. This divergence in cannabis effects on select cognitive impairment profiles emphasizes the importance of interpreting global deficit scores with caution. The protective effect of CU identified by this latter study may therefore contrast with the adverse effects reported above because of differences in definition of global deficit scores, and/or differences in gender distributions within the sample population.

Two studies suggested that dosage modulates the impact of CU on cognition in PWH. For example, PWH who engaged in moderate-to-heavy CU demonstrated greater NCI compared to those that reported light-to-no-use, underscoring the detrimental effects of heavier consumption patterns [62]. However, a subsequent study reported global NCI in non-using PWH versus PWoH, but no group differences when reported CU exceeded 1.43 g/week [66], suggesting a minimum threshold of exposure was required to mitigate observed NCI in PWH. Unreported frequency of CU patterns likely accounted for discrepant findings since this factor appears to modulate the beneficial effects of CU on GDS (see below).

The remaining studies identified indicated that CU may be beneficial for global cognition. Cannabis exposure in PWH was associated with better global cognition, an effect that did not vary by age [58], and a follow-up reported similar trends in daily users versus occasional or non-users [64], together suggesting more frequent use as beneficial. CU may be particularly favorable for global cognition in older PWH. For example, higher rates of lifetime CUD were observed in “super ager” PWH (i.e., above average performers on the GDS relative to their age) compared to cognitively normal and impaired PWH [63]. Surprisingly, these data were from a subset of participants in the CHARTER study, yet are at odds with the negative effects described by both studies described above [57, 59]. This divergence may be related to age of the samples since beneficial effects were observed in a sample that was over a decade older (~ 55 years old) [63]. CU frequency may mediate the beneficial CU effects in older PWH, as occasional ( $< 1 \times$  /week), but not frequent, use was associated with better global cognition in older PWH [65]. Furthermore, positive THC urine toxicology at cognitive assessment was linked to worse NCI, suggesting that time since last use also impacts CU effects on cognition in aging PWH. Together, these studies suggest that frequent-*previous* (i.e., CUD) [63], but not -*current* [65], CU benefits aging PWH, in addition to current moderate use. Frequency of CU and age may interact to differentially impact global NCI, warranting further investigation.

Overall, similar numbers of studies reported adverse effects of CU on global cognition in PWH as beneficial effects. Potential moderating factors included age, frequency of use, and disease severity, with a potential interaction between age and frequency of use. It is important to note that while these studies reported composite/summary measures of cognition, observed effects could have been driven by specific cognitive domains. Reporting

NCI in this manner therefore complicates identification of those domains most affected by CU, as well as developing targeted treatments. As such, the differential effects of cannabis on specific cognitive domains are reviewed below.

**Executive Function**—Our review yielded 21 clinical studies examining the effects of CU on executive function (EF) in PWH. These studies tested various aspects of EF, including problem solving, decision-making, cognitive-control, and inhibition. Five studies found beneficial effects [69–73], two reported adverse effects [62, 74], and the remaining studies reported null effects [58, 60, 62, 64, 66, 68, 75–83].

As with GDS, frequency of use may moderate cannabis' beneficial effects on EF. For example, PWH who reported frequent/occasional lifetime CU had better EF compared with non-users, with duration of CU correlating positively with task performance [71]. Chronicity of use was also a factor in Wang et al. [70], in which a non-significant trend indicated that PWH who engaged in regular ongoing CU ( $3 \times$ /week for  $> 2$  years) outperformed cannabis-abstinent PWH on tasks of EF. Furthermore, lifetime CUD history in PWH was associated with better EF performance, and also appeared to mitigate methamphetamine (METH)-induced EF impairments [69]; together suggesting chronic use may benefit EF, as well as prevent the deleterious effects of other substances on this domain. However, a different study suggested that chronic moderate-to-heavy ( $18 \times$ /week), but not light-to-moderate ( $14 \times$ /week), CU was associated with worse EF regardless of HIV status [62]. Therefore, while chronic CU appears to benefit EF in PWH, exceptionally high frequencies of use may be detrimental.

Beneficial effects of CU were also observed on neurological correlates of cognitive/inhibitory-control and related cognitive performance in PWH. Two studies utilized fMRI in combination with the error-awareness task (EAT), a modified go/no-go paradigm (with elements of the Stroop test) that required participants to (1) respond and inhibit responding to target versus non-target stimuli; and (2) report when they made an error. The first study found that lifetime CU was associated with reduced task-related brain activity in regions implicated in inhibitory-control in PWH, but not PWH; however, no group differences were detected in task performance [80]. The follow-up study reported impaired error-awareness and heightened rsFC in associated regions in cannabis-abstinent, but not cannabis-using, PWH [73]. Interestingly, an interactive effect of HIV and CU on cognition was observed such that PWH who used cannabis exhibited comparable error-awareness to that of controls. Finally, cannabis-using PWH exhibited similar magnetoencephalographic activity in task-relevant brain regions as PWH during performance of the Eriksen flanker task, although this activity was increased in cannabis-abstinent PWH; neither CU nor HIV status was associated with altered inhibitory-control, though CU *nonsignificantly* increased processing-speed in this EF-based task, selectively in PWH [72].

In contrast to the beneficial effects listed above, current CU predicted impaired risk-based decision-making in cognitively impaired and unimpaired PWH as measured by a mock gambling task (Game of Dice Task; GDT), irrespective of group differences in performance [74]. Interestingly, reported CU was higher in neurocognitively normal PWH compared to those diagnosed with HIV-associated NCI. However, as explained, HIV-associated NCI



diagnoses are based on global impairment. It should be noted that the GDT taps into *risk-based* decision-making, a facet of executive function, deficits of which have been observed in PWH [84] and cannabis-users [85]; this specific aspect of executive function may therefore be differentially affected by CU.

Our review also identified two preclinical studies assessing the relationship between eCB signaling and HIV in the context of EF. One study assessed behavioral inhibition in iTat mice using a go/no-go task, after which medial PFC (mPFC) CB<sub>1</sub>R expression was quantified and correlated with performance [86]. Inhibitory-control deficits were reported in female Tat<sup>+</sup> mice, though post hoc analyses revealed that this group only differed from male Tat<sup>+</sup> mice, and only arithmetically ( $p > 0.1$ ) from Tat<sup>-</sup> females. These data therefore do not describe a conclusive deficit relative to normal animals, though the study was likely insufficiently powered (3–4 animals/group). Importantly, CB<sub>1</sub>R expression was increased in the infralimbic (IL)-mPFC of Tat<sup>+</sup> females relative to all other groups. IL-mPFC CB<sub>1</sub>R expression in turn negatively correlated with overall task performance across all mice (likely driven by Tat<sup>+</sup> females), accounting for 30% of the total variance in inhibitory-control. Assuming a genuine effect of Tat expression on behavioral inhibition (sex-dependent or otherwise), these findings link subregion-specific increases in cortical eCB signaling to poor cognitive-control in the presence of Tat.

The other preclinical study assessed the effect of increased eCB signaling on reversal-learning in female iTat mice by inhibiting the degradative enzyme for 2-AG, monoacylglycerol lipase (MAGL) [87]. After learning the initial reward-predictive (target) stimulus in a spatial discrimination task, mice were treated with the MAGL inhibitor MJN110 prior to (and throughout) reversal training, in which the designations of the target and non-target stimuli were switched. Consistent with previous findings in Tat<sup>+</sup> mice [88] and HIV transgenic rats [89], Tat<sup>+</sup> mice acquired the original discrimination in fewer trials than controls, indicative of faster learning. *Reversal-learning* was also faster in Tat<sup>+</sup> mice, but was reduced to control levels by MAGL inhibition. However, no genotypic differences were evident in either treatment group, calling into question the functional significance of both the effect of genotype itself as well as its mitigation by MJN110 treatment. MAGL inhibition also increased 2-AG expression in Tat<sup>+</sup> and Tat<sup>-</sup> mice, and PFC AEA in Tat<sup>+</sup> mice, though eCB levels did not correlate with EF. Interestingly, response latency correlated with arachidonic acid (2-AG metabolite) and AEA levels in Tat<sup>+</sup> and MJN110-treated mice, respectively. While not directly related to EF per se, the relation of 2-AG metabolism to response-speed in Tat<sup>+</sup> mice is compelling given the reduction in Tat<sup>+</sup> reversal-learning and concomitant increase in 2-AG following MAGL inhibition. This study therefore provides preliminary evidence that manipulating eCB metabolism may produce functionally relevant, differential effects on both regional eCB levels and cognition in the context of HIV. Furthermore, the link between eCB metabolism and response latency may be relevant to the effects of CU on information-processing in PWH (see “Attention/Information-processing”). Extrapolation of these findings to the clinic remains difficult, however. For example, while the behavioral effects of MAGL inhibition were interpreted as mitigating Tat-induced neurocognitive alterations, the fact that this normalization was achieved by *impairing* reversal-learning hardly recommends MAGL inhibition as a treatment

for PWH. Additionally, lack of reversal-learning impairment in the iTat mouse indicates this line may not be the best model of HIV-associated EF deficits.

Overall, clinical studies indicate that there may be a beneficial effect of CU on EF in PWH. Furthermore, adverse consequences of CU on EF in PWH were either specific to heavier use patterns [62], or associated with deficits in a subdomain of EF (i.e., risky decision-making) [74]. Although few conclusive preclinical studies were identified, they suggested that expression of specific components of the eCB system (CB<sub>1</sub>R and 2-AG metabolites) may correlate with reversal-learning and cognitive-control in the context of HIV; therefore, cannabis may exert its effects on EF in PWH via eCB mechanisms.

**Attention/Information-Processing**—Our review identified 20 clinical studies examining associations between CU (or dronabinol exposure) and attention, information-processing, and/or processing-speed in PWH. Three studies found beneficial effects [65, 77, 83], five studies found adverse effects [62, 75, 78, 90, 91], two studies reported *nonsignificant* beneficial trends [64, 70], and the remaining studies reported no associations [58, 60, 62, 66, 68, 69, 71, 76, 81, 92, 93].

Dronabinol is a synthetic partial agonist of eCB receptors, like THC, and is used medicinally to enhance food intake and promote weight gain in AIDS. Three studies assessed the clinical efficacy of dronabinol on clinical outcomes and information-processing and/or attention in PWH who regularly smoked cannabis. In one study, acutely administered mid-to-high doses of dronabinol (20–30 mg), but not lower dronabinol doses or low-potency (0–3.9% THC) smoked cannabis, impaired divided attention and psychomotor speed in PWH [90]. A follow-up study reported that neither chronic administration (4 × /day for 4 days) of lower-dosed dronabinol (5–10 mg) nor low-potency cannabis (4 × /day for 4 days) affected attention and psychomotor speed in PWH [92], suggesting chronicity and dosage contributed to the formerly observed adverse effects of dronabinol. The null effect of low-potency cannabis on cognition in both studies should be cautioned; however, given these THC% do not reflect those found in modern markets [94, 95]. Nonetheless, when comparing longer-term administration, dronabinol (10 mg; 4 × /day) worsened processing-speed and attention after 9–16 treatment days [91]. The repeated findings that dronabinol, but not cannabis, impaired performance suggests dosing differences or the interaction of phytocannabinoid exposure (in cannabis but not dronabinol) could have contributed to their differential effects.

Cannabis-induced alterations were also observed in studies which utilized a composite score for information-processing. In one, moderate-to-heavy CU was associated with worse processing-speed compared to light-use and non-use cohorts, irrespective of HIV status [62], suggesting heavy-, but not light-, CU harms this function. In contrast, two studies reported a *nonsignificant* trend indicating that PWH who used cannabis performed better than non-users on information-processing and processing-speed [64, 70]. These results are seemingly contradictory; however, CU criteria varied substantially across studies. Particularly, negative effects were specific to heavier CU (up to 90 × /week) [62] whereas beneficial effects were reported in studies that defined CU as “moderate” and “daily” [64] or “chronic active-use” (see Table 2 for CU definitions) [70]; thus, frequency of CU likely contributed to discrepant

findings. Consistency in definitions of reported use would prove useful for collating findings in the future.

CU was also associated with worse performance in PWH using specific processing-speed outcome measures. For example, greater number of cannabis-using days were associated with worse performance in the Color Trails Test 2 (CMT2) in PWH [75]. Similarly, both daily and monthly CU in PWH was associated with worse performance in the Trail Making Test A (TMTA) compared to nonusers [78]. Importantly, the adverse effect of CU on processing-speed was observed both cross-sectionally [75] and longitudinally across 17 years [78]. However, the Okafor et al. [78] report demonstrated that each additional 5 years of CU significantly worsened processing-speed in PWH, but not PWH, which may indicate that PWH are less sensitive to the effects of *prolonged* CU exposure. These findings are consistent with interactive effects observed between CU and HIV wherein recent/current CU was associated with worse processing-speed in PWH, but not PWH [66]. In fact, PWH with a previous CUD diagnoses have performed better on the TMTA compared to those with no CUD history [77], supporting that a prolonged history of regular CU may instead confer a beneficial effect on this domain in PWH.

Age may also moderate CU effects on attention and information-processing. Few studies reported specific positive benefits; however, a recent study observed that in older PWH (mean = 56.2 years), occasional CU (< 1 × /week) was associated with better attention, compared to non-users [65]. The average age of CU onset within this study was 19.4 years [65], again indicating *chronic* CU may be particularly beneficial to EF in PWH. Similarly, in a younger cohort (mean = 36 years), PWH who initiated regular CU early in life (< 18 years old) were less likely to demonstrate impaired working-memory/attention compared to non-users [83]. However, these data are at odds with existing literature linking earlier age of CU onset with poorer cognitive function in healthy populations and PWH [83, 96, 97]. A final study linked CU with better processing-speed irrespective of HIV status, though after accounting for age, those effects were no longer significant [81]; once again highlighting that age may be an important moderating factor.

Overall, several studies associated CU or dronabinol administration with adverse effects on attention and information-processing in PWH, with processing-speed the most affected function. Although most studies reported null effects, broadly, the composite scores used to assess this domain make it difficult to ascertain the effects of CU on specific types of attention (i.e., sustained versus focused). Duration and dosage of CU were important moderating factors of processing-speed, with heavy, but not necessarily chronic, CU negatively impacting this function. Frequency of use may also be a moderating factor; however, inconsistent definitions for moderate, heavy, and light CU hinder comparison across studies. Interestingly, some studies indicated that CU impairs attention in PWH, but not PWH; therefore, research should determine whether PWH are indeed less sensitive to CU effects on attention and potential mechanisms underlying such effects. Importantly, and consistent with the reviewed literature, specific populations may uniquely benefit from CU such as aging PWH.

**Learning and Memory**—Our review identified 20 clinical studies that examined CU effects on learning and memory in PWH. Five studies reported adverse effects [60, 62, 83, 90, 98], three found beneficial effects [58, 69, 77], two studies reported *nonsignificant* beneficial trend effects [64, 65], and the remaining reported null effects [68, 70, 71, 75, 76, 79, 81, 91–93].

Age of CU onset appeared as a moderating factor in a study that reported PWH who initiated CU at an early age (< 18 years old) were eight times more likely to demonstrate learning impairment and four times more likely to demonstrate memory impairment compared to nonusers or later onset users [83]. These data contrast with the beneficial effects of early onset CU on attention (see above), suggesting this factor may differentially modulate CU impact on cognition dependent on functional domain. Thus, in the context of learning and memory functions, initiating CU during adolescence could have deleterious effects.

Disease state may have an important impact on the effects of CU on memory. For example, current CU was associated with poorer global cognition in PWH, an effect more pronounced in symptomatic versus asymptomatic PWH and driven by delayed memory impairments [60]. In another study, administration of 20-mg dronabinol to PWH with clinical muscle loss, but not those without muscle loss, decreased memory task performance [90]. Thus, PWH with advanced disease state may be particularly impacted by adverse CU effects on memory. Outside of health-related factors, recency of use may also modulate CU impact on memory; for example, a positive THC urine toxicology was associated with poorer global NCI, driven by poor memory/delayed-recall, despite reported CU not being associated with such impairments [65].

A study by Woods and colleagues [98] assessed a sub-type of memory, event-based prospective memory (PM), in a young-adult cohorts of PWH with and without comorbid substance use disorder (SUD). Here, reported SUD in PWH was associated with lower PM accuracy, which was driven by participants with CUD. These data contrast with a study in an older cohort that reported PWH with a past CUD diagnosis (i.e., not current) demonstrated better learning and memory compared to PWH with no history of CUD [77]. Similarly, and in an older cohort, lifetime history of cannabis dependence was associated with better learning and memory in PWH, and also appeared protective against the negative effects of lifetime METH dependence on cognitive performance in this domain (like the findings described in the EF section) [69]. Together, these studies suggest age may modulate the impact of CUD on memory in PWH, with adverse and beneficial effects observed in younger and older adults, respectively. However, beneficial effects were reported using composite domain scores in *previous* users, as opposed to the adverse effects that were reported in PM specifically in *current* users. Thus, task differences and recency of use may have also influenced discrepant findings.

The remaining studies suggest the beneficial effects of CU on this domain appear more specific to learning rather than memory tasks. For example, cannabis exposure (prior CUD or recent use) in PWH was linked to better learning performance [58], and two studies reported *nonsignificant* trend effects of CU in PWH to be associated with improved learning

functions [64, 65]. Instead, when a composite learning and memory score was reported, moderate-heavy CU (18–90 uses/week) was associated with impaired performance in PWH [62]. Thus, the latter study's discrepant finding could be due to tasks utilized or specific to the heavy CU reported in that cohort; however, this latter factor was difficult to interpret given the varied CU criteria used across all studies (refer to Table 2).

Our review also identified two preclinical studies assessing the effects of cannabinoid compounds on learning and/or memory. The first reported the individual and combined effects of THC (0.032–0.32 mg/kg) and SIV infection on repeated-acquisition performance [99]. Higher doses of acute THC decreased response-rate—but not accuracy—prior to SIV infection, both when learning new stimulus–response patterns and repeating old ones. This latter effect on learned behavior was also detected following SIV inoculation, with behavioral tolerance observed following chronic administration. Therefore, neither acute nor chronic THC differentially affected behavior in SIV<sup>+</sup> versus SIV<sup>-</sup> animals, and consistent with previous findings [100–102], higher doses of THC eliminated responding, severely limiting the assay's ability to detect explicit cognitive effects. Thus, THC-induced response-rate reductions were more likely indicative of the gross sedative-like effects of THC observed at such doses [103], rather than to alterations in information-processing. Importantly, the tendency for THC to more potently affect response-rate than accuracy in repeated-acquisition paradigms was also observed in the clinic, as was similar inter-individual variability [104], highlighting the cross-species predictive validity, and thus utility of repeated-acquisition paradigms. Nonetheless, these data suggest neither increased susceptibility to, nor benefit from, the effects of THC on learning and memory in HIV.

The other preclinical study identified by our search assessed spatial learning and memory. Male Sprague–Dawley rats were treated with a subchronic (3-day) course of the potent and non-specific cannabinoid receptor agonist Win55,212–2 prior to intra-hippocampal injection of the HIV envelope glycoprotein gp120 [105]. Rats were then assessed daily for 6 days in the Morris water maze, in which rodents learn to use spatial cues to navigate to an escape platform [106]. Gp120 treatment slowed escape latency, increased swimming distance, and decreased time spent in the target quadrant, suggestive of spatial learning impairment. This deficit was prevented by prophylactic (i.e., pre-gp120) Win55,212–2 in a CB<sub>2</sub>R-dependent manner, although the contribution of CB<sub>1</sub>R signaling was not assessed.

Overall, clinical studies indicate that CU variably affects learning and memory in PWH. Early age (< 18) of onset and more severe HIV disease state were associated with worse learning and memory, indicating that these factors may be critical in determining functional outcome for these domains. Differential effects of CU were also observed within the context of polysubstance use in which age and recency of use appeared to moderate the beneficial/adverse observed outcomes. Furthermore, limited data suggested memory functions may be more adversely affected in PWH than learning functions, which instead may be improved by cannabis exposure. The two animal studies identified were well-controlled in moderating factors and suggested null or beneficial effects of cannabinoid exposure on this cognitive domain. However, both preclinical studies were performed in males only, limiting generalizability of findings across sex.

**Language/Verbal-Fluency**—Our review identified 12 clinical studies that examined associations between CU and language and/or verbal-fluency domains in PWH. Four studies reported beneficial effects [58, 62, 68, 69], three studies reported beneficial trends [64, 65, 70], and eight studies reported null effects [60, 62, 64–66, 76, 77, 83].

Overall, CU tends to be associated with improved verbal-fluency in PWH. Watson et al. [58] reported that cannabis exposure, defined as a history of CUD or recent use, associated with better verbal-fluency in PWH. While such CU criteria cannot distinguish between current, or former chronic (i.e., CUD) CU, cannabis-exposed PWH reported an estimated 1724 g lifetime used suggesting they represented a sample with high exposure. These data somewhat align with a cross-sectional study that reported higher lifetime “dosage” of cannabis was correlated with improved verbal-fluency [68]. Here, “dosage” was achieved by multiplying standard cannabis units (undefined) used per day by the number of days used across periods of consistent CU. Similarly, PWH who reported chronic current CU ( $3 \times$  /week for 2 years) performed slightly, but *nonsignificantly*, better on verbal-fluency tasks than those who reported little-to-use [70]. Together, these data suggest high levels of CU in PWH, whether former or current, may benefit verbal-fluency.

Studies with defined variations in frequency of CU patterns also report beneficial effects, though frequency effects were not consistent across studies. For example, Watson et al. [64] reported a *nonsignificant* trend for better verbal-fluency in PWH who used cannabis daily compared to those who used occasionally ( $> 1 \times$  /month,  $< 3 \times$  /week) and compared to non-users, suggesting more frequent CU modulated beneficial CU effects. In contrast, better verbal-fluency was observed in PWH engaged in occasional ( $2\text{--}14 \times$  /week), but not more frequent ( $18\text{--}90 \times$  /week) CU, compared to PWH within the corresponding CU category [62]. However, CU definitions between studies were drastically different, and discrepant findings may be accounted for by the magnitude of CU, such that daily [64], but not necessarily excessive dosing of [62] CU may confer beneficial effects. In an older cohort, *nonsignificant* beneficial trend effects of occasional ( $<$  weekly), but not frequent ( $>$  weekly) CU was reported [65]; thus, as described in other sections, less frequent use in aging PWH may be beneficial for cognition.

A final study reported PWH with no lifetime CUD or METH-use disorder (CUD – /MUD –) performed worse than CUD + /MUD +, though no differences were found between other groups (CUD – /MUD + or CUD + /MUD –) [69]. Thus, the beneficial impact of CU on verbal-fluency only appeared in a cohort with concomitant MUD.

Overall, CU appeared to benefit language/verbal-fluency processes in PWH, and no data supported adverse effects of CU on this cognitive domain. Studies reported inconsistent CU frequency effects on language and verbal-fluency; however, it is difficult to draw coherent conclusions given the variable CU criteria across studies and insignificant trend effects. Finally, it is important to recognize that language and verbal-fluency domains cannot be measured in animals and therefore represent a domain whereby mechanistic animal literature will be inherently lacking.

**Motor Skills**—Our review identified 12 clinical studies that examined the association between CU and motor skills in PWH. One study reported beneficial effects [77], and one study reported adverse effects [107]. An additional study reported a *nonsignificant* association between daily CU and better motor task performance among PWH compared to abstinent PWH or PWH who moderately used (< 3 days/week) [64], suggesting more frequent use mediated this beneficial effect. Somewhat similarly, a history of CUD, indicative of *prior* frequent use, was associated with improved motor skill function in PWH, compared to PWH without prior CUD diagnoses [77]. However, a cannabis dependence history and HIV infection were associated with poorer motor function on procedural motor skill learning tasks among individuals with a history of polysubstance dependence [107]; thus, CU may interact with other substance use to impair motor function. The remaining studies reported null associations [58, 60, 68–70, 76, 79, 81, 83]. In all, there is a paucity of literature on the effects of cannabis on motor functioning in PWH, and more research is needed to guide interpretations.

## Discussion

### The Effects of Cannabis on HIV-Associated NCI Are Likely Function-Dependent

This review synthesized published data on the effects of CU and/or cannabinoid exposure on HIV-relevant cognitive domains. Results suggested that heavy or recent CU may have deleterious effects on global cognition in PWH, particularly in aging populations, though light-to-moderate use may confer beneficial effects. Otherwise, the effects of CU on cognition in PWH appeared function-dependent, and modulated by several factors (see Table 3 for a summary). For example, no studies reported adverse associations between CU and language/verbal-fluency in PWH, and similarly there is little support for adverse effects on motor functioning. CU tended to be associated with improved EF in PWH, particularly cognitive-control, and preliminary preclinical data supported that eCB ligands (i.e., 2-AG via MAGL inhibition) [87] and receptors (i.e., CB1) [86] relate to EF in HIV, suggesting that CU effects in PWH are likely mediated through eCB mechanisms. Furthermore, CU tended to be associated with adverse effects on attention/information-processing, driven by poor processing-speed, and in learning/memory domains, driven by memory impairment. Overall, the number of reported adverse effects were largely outnumbered by beneficial or null findings, providing insufficient support for the detrimental impact of CU on cognition in PWH.

Discrepant results between studies are likely be attributed to sparsely defined CU criteria. For example, many studies reported minimum CU criteria (e.g., > 3 × /week) and/or stratified CU by frequency groups (e.g., “occasional,” “moderate”), while few studies reported ranges of CU frequency (e.g., 6–37 days over the past 6 months) [64]. Only one study clearly accounted for independent daily instances of CU [66]. Additionally, age of CU onset appeared to have distinct effects on individual cognitive domains in PWH, however, was seldom reported.

Time of study may also account for inconsistencies reported across clinical data. As reviewed, cannabis dosing may alter its impact on cognition, and THC potency has steadily increased over the last decade [108]. Furthermore, given increased access to cART therapies,

more recent publications likely preclude participants with low nadir immunosuppression, a factor strongly associated with NCI in PWH [7, 8, 69, 109–113]. The legal status of cannabis at the time of the study completion may have also impacted participant self-report of cannabis or changed the proportion of cannabis-using PWH, including reasons for use (i.e., recreational versus medicinal), and the potential impact of using drugs gained illicitly versus legally.

Demographic and clinical differences between study participants further complicated the synthesis of results. Most clinical studies reported in this review consisted of largely male populations (see Table 2); though the sole study in which females were exclusively assessed [15] agreed with the group of literature suggesting a beneficial impact of CU on EF. Clinical studies also largely consisted of virally managed participants, limiting interpretations of CU-induced effects on cognition in advanced HIV stages. Future work must study more diverse populations to draw conclusions regarding potential sex- or gender- or clinical-based differences on observed effects.

Interpretation of clinical findings reviewed above would greatly benefit from animal studies that can precisely control for confounding conditions. Given the numerous existing cognitive tasks that are consistent across species [114, 115], future research utilizing such tasks should be prioritized.

### Importance of Utilizing Cross-Species Paradigms

To date, only one preclinical study has directly assessed the effect of a phytocannabinoid (THC) on cognition in HIV [99]; the remaining studies provide insight into how the eCB system interacts with HIV-related factors to regulate cognition [86, 87, 105]. While the reviewed preclinical literature describes limited differential impact of cannabinergic/eCB manipulations on HIV models versus controls, limitations of these studies exist, particularly those pertaining to the domain-specificity and/or clinical translatability of their cognitive tasks. For example, the finding that prophylactic Win55,212–2 prevented gp120-induced deficits in the Morris water maze (MWM) [105] is difficult to translate to the clinic. For one, there is no analogous human task. Additionally, central to the MWM is the element of stress [116, 117]; therefore, it is difficult to determine non-specific actions of Win55,212–2 on MWM performance given: (1) reported elevated corticosterone levels in naïve gp120 transgenic mice [118] and (2) the eCB system's role in regulating the stress response [119]. Nonetheless, between-sessions, learning occurs in the MWM, and therefore these findings merit confirmation using less aversive, and more translatable, assays (e.g., radial arm maze).

Many translational limitations of ethologically based assays like the MWM may be mitigated by operant conditioning paradigms, which enable assessment of several cognitive processes in a consistent manner across species [114]. For example, the cross-species go/no-go paradigm utilized to correlate PFC CB<sub>1</sub>R expression with behavioral inhibition in iTat mice represents a relative strength of this study [86]. Therefore, while lack of statistical power hindered interpretability of their findings (see above), sufficient sample sizes may identify a cognitive-control deficit in iTat mice that is directly relevant to the clinic, although translatability may yet be improved by utilizing the cross-species continuous performance task (CPT gold standard clinical assessment of vigilance and cognitive-control) [120].



Operant paradigms also enable large numbers of trials per session ( ~ 100). A major limitation of League and colleagues' study of the effects of Tat and MAGL inhibition on reversal-learning [87] was the lack of trials assessed due to task design. This dearth of trials precluded more detailed analyses that may have shed light on the specific processes impacted by Tat expression and MAGL inhibition, as afforded by operant paradigms. Increased trial numbers also permit the calculation of decision-making metrics (e.g., win-stay, lose-shift) [121] and thereby detection of more subtle differences in reversal-learning than could be gleaned from overall accuracy.

Operant-based cross-species reversal-learning tasks represent an opportunity to determine the effects of CU in PWH in a manner that would enable a subsequent preclinical mechanistic study. While reversal-learning paradigms (e.g., the probabilistic reversal-learning task; PRLT) consistently detect deficits in both neuropsychiatric populations [122–125] and relevant animal models [126–129], PWH have yet to be assessed in such a translational paradigm. Cognitive flexibility deficits are instead more commonly assessed using the Wisconsin Card Sorting Test in PWH, in which participants sort a deck of cards according to a rule that changes after every ten consecutive correct responses [130–132]; however, HIVtg rats detected rule shifts at the same rate as controls in the PRLT [89]. This divergence in preclinical and clinical findings demonstrates the need for consistent assessment of a given cognitive function (e.g., cognitive flexibility) across species. Importantly, the wide variety of cross-species translatable operant tasks means that this strategy may also be applied to the study of many other cognitive domains in addition to cognitive flexibility (e.g., vigilance, effort- and risk-based decision-making) [114].

### **Putative Mechanisms of HIV-Associated NCI and the Interactive Effects of Cannabis: Insights from Clinical Data**

Structurally, reduced cortical thickness and subcortical volumes, and the presence of white matter hyperintensities (found in aging and Alzheimer's disease), correlate with greater NCI in PWH [133–141]. However, data on the interactive effects of CU and HIV on brain structure are few and inconclusive. Larger caudate and cerebral white matter volumes have been linked to recent CU in PWH but not people without HIV (PWoH) [71]; however, duration of use *negatively* correlated with cortical volumes suggesting prolonged CU may exacerbate brain volumetric loss despite possible short-term benefits. Other studies reported interactive effects of CU and HIV on brain structure that were unrelated to cognition, or consistent structural changes across cannabis-using PWH and PWoH (null interactions) [66, 70].

Functional (f)MRI revealed increased brain activation in cognitively normal PWH relative to PWoH during decision-making [142] and memory task performance [143, 144], suggesting that hyperactivation in PWH may be compensatory, enabling comparable performance. Indeed, longitudinal assessments detected similar attentional ability and concomitant brain activity in PWH and PWoH at baseline, but an HIV-specific increase in brain activation a year later, with no change in performance [145]. In contrast, cognitively normal PWH demonstrated decreased task-dependent brain activation during an attention task, but enhanced activity in adjacent and contralateral regions [146]. Thus, elevated brain activity

may compensate for reduced network efficacy in PWH prior to detectable NCI. Meanwhile, studies in cognitively impaired PWH instead report *reduced* activation of task-dependent networks [147, 148], suggesting prolonged compensatory overactivation may result in NCI.

Interestingly, CU may normalize aberrant brain activity in PWH during cognitive performance. For example, CU in PWH was associated with normalization of elevated parietal-occipital gamma [76] and spontaneous frontocortical alpha activity [72] to control levels during visuospatial-processing, but performance behavior was not associated with, or directly compared to such changes. Instead, reduced theta oscillations have been linked to visuospatial-processing deficits in PWH, but chronic CU did not alter these findings [76, 149]. Meanwhile, HIV and CU were independently associated with abnormal insular-sensori-motor resting-state functional connectivity (rsFC), which in turn correlated with visuospatial-processing deficits; neither cannabis-using PWH nor cannabis-abstinent controls demonstrated these neurophysiological or cognitive deficits, supporting a beneficial effect of CU on these measures in PWH but a detrimental effect in PWOH [150]. However, CU did not affect salience-default mode network rsFC, which was elevated in PWH and correlated with deficient error-awareness in the same task [73]. Therefore, the beneficial effects of CU task-related brain activity in PWH appear dependent upon specific outcome measures (i.e., function-dependent).

Finally, additional studies reported null interactions between CU and HIV status on brain function [80, 151], or reported additive effects that do not relate to cognitive performance [71, 82]. Taken together, CU may partially remediate aberrant brain activity in PWH, though such effects were not always associated with cognition or relevant analyses were not conducted. Further studies are therefore required to determine the interactive effects of HIV and CU on co-occurring brain function and cognitive performance.

In addition to brain volume and activity, blood- and CSF-based biomarkers have been correlated to cognitive dysfunction in PWH. HIV-associated NCI is not always associated with viral loads [57, 152, 153], indicating that factors beyond the virus alone interact to contribute to the severity of NCI. Similarly, current immunosuppression indicators (i.e., CD4 + cell count) are not typically associated with cognition in PWH; however, lower *nadir* immunosuppression is linked to poorer cognitive outcomes [7, 8, 69, 109–113], suggesting delayed treatment as a significant risk factor for HIV-associated NCI. Low nadir immunosuppression has also been linked to cortical thinning and concomitant NCI in PWH [111]. Nonetheless, reported CU in PWH does not appear to be associated with changes to immune-related biomarkers in PWH [35, 83, 154, 155]. Furthermore, multiple studies observed no changes to viral-load or immune-related biomarkers in PWH following a 21-day low-dose (3.95% THC cigarette 3 × /day) cannabis intervention [156, 157]. Few studies have reported links between suppressed viral loads and better immune function in cannabis-using PWH; however, these effects were observed alongside NCI [62], or cognition was not measured [158]. Hence, there is little evidence to support direct viral/immunological mechanisms underlying the effects of CU on HIV-associated NCI.

In contrast, CNS proinflammatory markers tend to be linked to cognition in HIV [64, 159, 160]. Current and recent CU is consistently linked with reduced inflammation in PWH [64,

71, 154, 158, 161], including reductions in monocyte chemoattractant protein-1 (MCP-1), which mediates CNS leukocyte perturbation [162], and is associated with cognitive deficits arising from HIV [163], aging, and Alzheimer's populations [164, 165]. Specifically, lower MCP-1 and interferon gamma-induced protein (IP-10) levels were observed in cannabis-using PWH, which correlated with better learning task performance [64]. CU may therefore mitigate HIV-associated NCI through anti-inflammatory mechanisms, though more studies that directly relate such biomarkers to NCI are required to confirm this effect.

CU may also impact HIV-associated NCI through its interactions with the blood–brain barrier (BBB). Reduced BBB integrity is observed in PWH, which may facilitate entry of HIV-infected monocytes into the CNS [166, 167]. While BBB dysfunction has yet to be studied in the context of HIV-associated NCI, it has been associated with neuronal damage in PWH [168], indicating its potential to harm cognition. A recent study linked frequent CU to less BBB dysregulation in PWH [169]; however, explicit investigation of the interactions between CU, HIV, and the BBB on cognition is lacking and warranted.

Other risk factors for HIV-associated NCI include individual genetics [170], coinfections [171], and comorbid psychiatric [172], vascular [173–176], metabolic [74], and substance-use disorders (16, 17, 19, 21, 22), which are difficult to control for when studying human populations. Animal models, meanwhile, enable precise mechanistic study of cannabinoid effects on HIV-associated NCI by minimizing these confounds inherent to clinical HIV research, as well as those relating to CU (e.g., inter-individual variation in dosing, THC/CBD content). These models also permit determination of directionality of cannabis and HIV effects, thus elucidating causal mechanisms. Below, we provide a brief overview of current animal models as well as their benefits and limitations in determining the effects of CU on cognition in HIV.

### **Putative Mechanisms of HIV-Associated NCI and the Interactive Effects of Cannabis: Insights from Preclinical Models**

Cannabis may alter HIV-associated NCI by activating the eCB system to promote neurogenesis, and attenuate neuroinflammation and neurodegeneration associated with HIV viral exposure. Particularly, CB<sub>2</sub>R activation has attenuated gp120-induced neurodegeneration in vivo and in vitro across studies [177–180]. Interestingly, in vitro Tat-induced neurodegeneration was reduced by AEA, 2-AG, and WIN 55,212–2, which was prevented by CB<sub>1</sub>R, but not CB<sub>2</sub>R antagonism [32, 181]. These studies suggest the discrete HIV viral proteins Tat and gp120 have independent mechanisms (CB<sub>1</sub>R and CB<sub>2</sub>R, respectively) through which they produce neurodegeneration. Inhibition of AEA's degradative enzyme, fatty acid amide hydrolase (FAAH), is also protective against neurodegeneration and inflammatory responses induced by gp120 or Tat exposure [182–184]. Since proinflammatory markers are linked to NCI in PWH [64, 159, 160], and are reduced in cannabis-using PWH [64, 71, 154, 158, 161], the FAAH-induced reductions of inflammation may describe the mechanisms by which cannabis affects cognition in PWH. It should be noted that AEA is only one of several fatty acids degraded by FAAH [185, 186]; therefore, those molecules (e.g., OEA) and their respective receptor systems (e.g., PPAR $\alpha$ )

receptors) may also mediate the neuroprotective effects of FAAH inhibition on HIV-induced neurodegeneration and inflammation.

The eCB system may alleviate neuroinflammation and neurodegeneration induced by HIV-proteins through its ability to alter neurotransmission. Indeed, HIV-relevant proteins dysregulate neurotransmission, and the eCB system has a prominent role in regulating such processes. For example, Tat-induced attenuation of PFC inhibitory transmission was blocked by a CB<sub>1</sub>R in vitro [187]. In a follow-up study utilizing PFC slices from iTat mice, Tat-induction sex-dependently altered GABAergic activity and FAAH inhibition (i.e., a general increase in eCB signaling) suppressed GABAergic activity regardless of sex or Tat-expression [188], suggesting sex impacts the role of the eCB in modulating Tat effects.

Interestingly, application of Tat to rat hippocampal cultures reduced the magnitude of CB<sub>1</sub>R-mediated presynaptic inhibition of glutamatergic, but not GABAergic, neurotransmission [189]. The effects of Tat on neurotransmission may therefore also be dependent upon brain region (i.e., hippocampus versus PFC) and/or excitatory versus inhibitory signaling. Given the apparent sex-, region-, and neurotransmitter-specificity of Tat and/or eCB effects on neurotransmission, it is likely that any specific cognitive/behavioral outcomes of these mechanisms would be similarly context-dependent. For example, the sex-dependent effect of Tat expression on PFC eCB signaling [188] may partially account for the findings of poorer inhibitory-control in female versus male Tat + mice, especially given that females had higher CB<sub>1</sub>R expression, which also correlated with behavioral inhibition [86].

### **Recommendations for Treating HIV-Associated NCI with Cannabis/Cannabinoids**

This review has highlighted that CU may be detrimental or beneficial for HIV-associated NCI depending on the measured function. These results can be used as a starting guide for the individualized treatment of HIV-associated NCI with cannabis/cannabinoids. For example, medicinal cannabis may be particularly beneficial for PWH demonstrating EF or verbal-fluency impairments, but should be avoided in populations with impairments specific to information-processing and memory. In addition to the potential benefits for HIV-associated NCI, CU in PWH has been linked to lower inflammatory markers [59, 91–94], increased appetite [90, 92], and stronger BBB integrity [169]. In all, the number of beneficial or null effects of CU on cognition reviewed suggests cannabis and medications can be prescribed to PWH while posing little threat to cognitive function.

Despite this medicinal potential, certain phytocannabinoids, particularly THC, produce adverse side effects such as altered mobility, thermodyregulation, and anxiogenic responses [190–192]. The potential therapeutic effects of cannabis would also occur alongside its psychoactive properties, which could hinder daily functional ability (i.e., capacity to operate motor vehicles). Such adverse reactions can be avoided by using compounds known to elevate endogenous eCB tone by inhibiting eCB enzymatic degradation [193]. Both eCBs AEA and 2-AG are created on demand, and following eCB receptor binding, are rapidly degraded by their respective enzymes, FAAH (for AEA) and MAGL (for 2-AG). Thus, such enzyme inhibitors enhance/prolong naturally occurring eCB activity rather than artificially stimulating the eCB system via exogenous cannabinoid exposure (i.e., cannabis), produce fewer adverse side effects, and are devoid of psychoactive properties. FAAH inhibitors

are especially known for being well tolerated in healthy populations [194, 195] and in clinical trials [196, 197], and also increase other fatty acid signaling molecules known to have anti-inflammatory and neuroprotective effects (i.e., OEA and PEA). Therefore, FAAH inhibition may possess greater clinical potential for HIV-associated NCI.

Considering all articles discussed, few linked low-dose CU to cognitive dysfunction in PWH. Low potency cannabis is well tolerated in PWH [90, 92], but is not easily accessible in today's legal/illegal markets [94]. Ensuring prescribers and PWH which have access to low-dose medicinal cannabis for the potential treatment of HIV-associated NCI, or other HIV-related symptoms, should therefore be prioritized. Providing access to such low-dose cannabis may also reduce the number of PWH using high-dose, and likely harmful amounts of cannabis for self-medication.

In further relevance to the clinic, it will be important to consider interactions between CU and cART. Little data exists on the effects of CU on cART efficacy; however, phytocannabinoids and HIV medications share common metabolic pathways, thus concomitant use could lead to altered drug bioavailability and possible toxicity [198]. CU has also been linked to poorer cART adherence [199–203]; therefore, monitoring medication use patterns in PWH prescribed cannabis is of particular importance.

### Recommendations for Future Research

Our findings can be used as means to design future research to disentangle the impact of CU effects on HIV-associated NCI. Our summarized function-dependent findings highlight the importance of moving away from global cognitive scores to better define relationships between CU and HIV on cognition. Additionally, research is needed to better understand the specific effects of CU on motor functioning in PWH since the study of this domain is underrepresented in the literature, despite being integral to performance of cognitive tasks. We further recommend designing studies with explicit CU criteria, considering factors that impacted the beneficial/adverse effects on discrete cognitive domains in PWH reported in this review (e.g., dosage of CU on EF, disease state on CU-induced memory impairment). Such factors must also be clearly defined in future work, and preferably relative to previous published definitions to enhance the interpretation of study results and enable comparisons across studies.

Further investigation of low-dosed CU on HIV-associated NCI is particularly warranted given the majority of accessible cannabis contains high THC levels known to produce strong psychoactive and potentially adverse side effects. Additionally, given the adverse health consequences associated with cannabis smoke, future work should explore the impact of alternative CU methods (e.g., orally dosed) or compounds (eCB enzyme inhibitors) on cognition in the context of HIV. Since preclinical evidence support the neuroprotective effects of FAAH and MAGL inhibitors, and these compounds are tolerated in the clinic, their impact on HIV-associated NCI in human and animal studies is particularly warranted.

Undoubtedly, the use of cross-species cognitive tasks will permit the collection of translatable data on the effects of CU on cognition in PWH. Several cognitively based tasks can be completed in humans and animals, including the PRLT which measures

reinforcement learning and cognitive flexibility. Additionally, the cross-species Iowa Gambling Task, a measure of risk-based decision-making, could be utilized to further explore the adverse effects of CU on risk-based decision-making in PWH. Clinical studies should therefore utilize cross-species tasks to allow for future mechanistic determination of any effects observed while preclinical studies must similarly use such tasks to ensure data collected is translatable.

Future preclinical work will be essential for defining the impact of confounding factors since these can more easily be controlled for in animal studies. Furthermore, as highlighted by our review, specific exploration of phytocannabinoid impact on cognitive function in animal models of HIV is lacking and warranted. Particularly, future preclinical work should aim to increase face-validity by utilizing comparable cannabis administration methods used in humans (i.e., vapor or oral exposure) which would also expose the animal to the entirety of phytocannabinoids present in cannabis, rather than the administration of an individual component (i.e., CBD).

## Conclusions

This review revealed little support for the detrimental effects of CU on cognitive function in PWH. Further reviewed studies suggested beneficial/adverse effects of CU on cognition is function-dependent in the context of HIV, and modulated by several confounding factors. The scarcity of preclinical support for the interactions of cannabinoids and HIV on cognition is concerning since animal models of neuroHIV can help disentangle such effects in well-controlled experiments that allow for mechanistic explorations.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations

<b>2-AG</b>	2-Arachidonoylglycerol
<b>AEA</b>	N-Arachidonylethanolamine (anandamide)
<b>AIDS</b>	Acquired immunodeficiency syndrome
<b>BBB</b>	Blood-brain barrier
<b>cART</b>	Combination antiretroviral therapy
<b>CMT2</b>	Color Trails Test 2
<b>CPT</b>	Continuous performance task
<b>CUD</b>	Cannabis use disorder

<b>CB<sub>1</sub>R</b>	Cannabinoid-1 receptor
<b>CB<sub>2</sub>R</b>	Cannabinoid-2 receptor
<b>CBD</b>	Cannabidiol
<b>CNS</b>	Central nervous system
<b>CU</b>	Cannabis use
<b>EAT</b>	Error-awareness task
<b>eCB</b>	Endocannabinoid
<b>EF</b>	Executive function
<b>FAAH</b>	Fatty acid amide hydrolase
<b>FIV</b>	Feline immunodeficiency virus
<b>fMRI</b>	Functional magnetic resonance imaging
<b>GDS</b>	Global deficit score
<b>IL</b>	Infralimbic
<b>IP-10</b>	Interferon gamma-induced protein (IP-10)
<b>MAGL</b>	Monoacylglycerol lipase
<b>MCP-1</b>	Monocyte chemoattractant protein-1
<b>METH</b>	Methamphetamine
<b>mPFC</b>	Medial prefrontal cortex
<b>MRI</b>	Magnetic resonance imaging
<b>MWM</b>	Morris water maze
<b>NCI</b>	Neurocognitive impairment
<b>PFC</b>	Prefrontal cortex
<b>PL</b>	Procedural learning
<b>PM</b>	Prospective memory
<b>PRLT</b>	Probabilistic reversal learning task
<b>PWH</b>	People with HIV
<b>PWoH</b>	People with out HIV
<b>RPT</b>	Rotary pursuit task
<b>rsFC</b>	Resting-state functional connectivity

<b>SIV</b>	Simian immunodeficiency virus
<b>SMT</b>	Star mirror tracing task
<b>SUD</b>	Substance use disorder
<b>THC</b>	9-Tetrahydrocannabinol (THC)
<b>TMTA</b>	Trail Making Test A
<b>tg</b>	Transgenic
<b>WPT</b>	Weather prediction task

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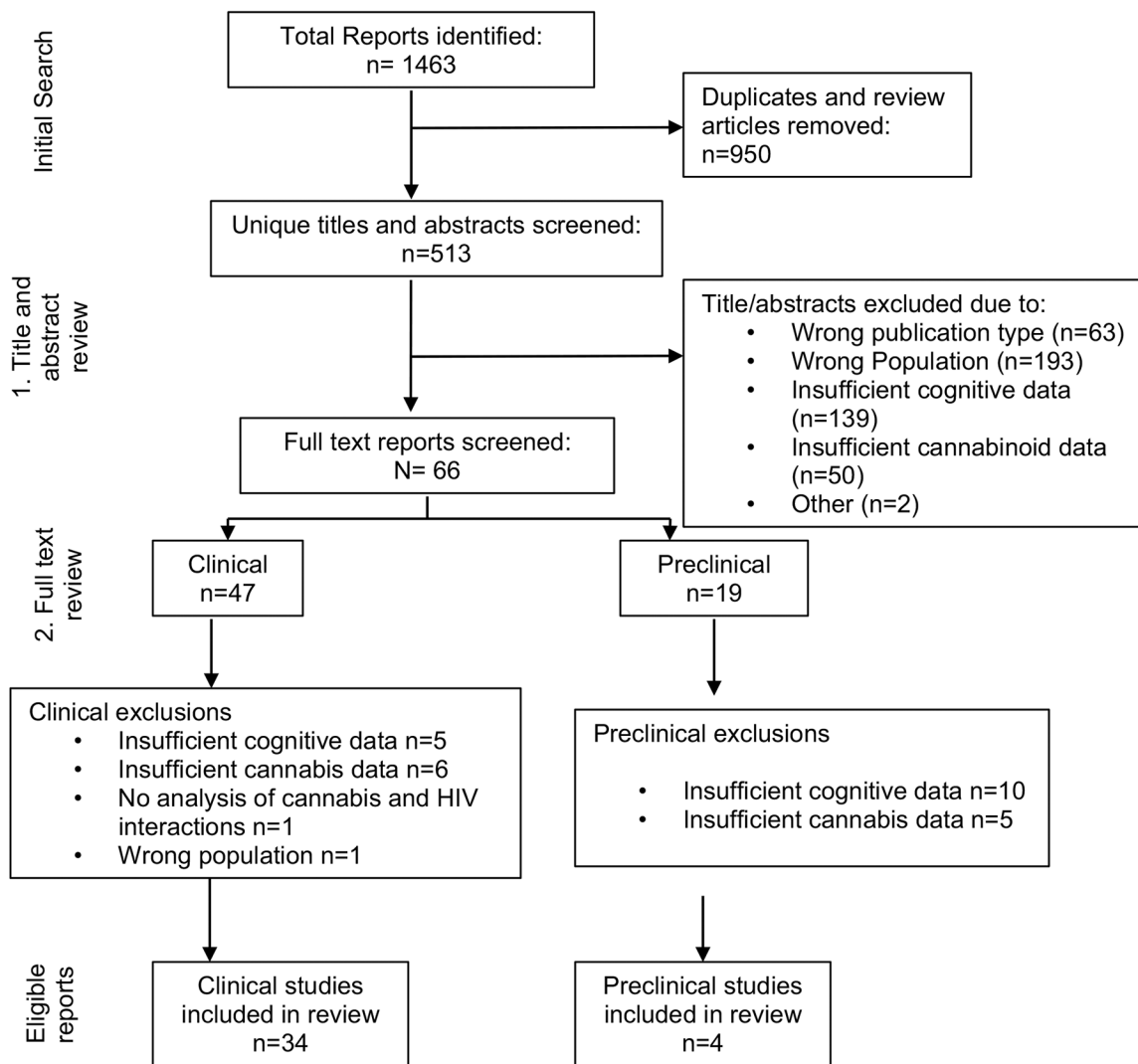
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**Fig. 1.** Flowchart of systematic scoping review results and inclusion/exclusion criteria

**Table 1** Data extraction from studies that examined the effects of cannabinoid exposure on cognition in the context of HIV in non-human animals

Author/year	HIV animal model and subject characteristics	Cannabinoid measure/manipulation	Cognitive assessments	Cognitive domains	Main findings
Jacobs et al. 2019	Mouse—iTat (50% female) 7/ Tat + /Tat –	Measured CB <sub>1</sub> R expression	Go/no-go task	Inhibitory-control	Female iTat + mice demonstrated less inhibitory-control compared to male iTat + mice and had higher CB <sub>1</sub> R expression in mPFC relative to all other groups; Higher infralimbic mPFC CB <sub>1</sub> R expression correlated with less inhibitory-control
League et al. 2021	Mouse—iTat (100% female)	MAG-L inhibition via MJN110	Discrimination and reversal-learning task	Learning and cognitive flexibility	Initial and reversal-learning was quicker in Tat + mice than in Tat – mice; MJN 110 slowed reversal-learning to Tat- levels
Wang et al. 2022	12/group: Tat +/Tat– Rat-hippocampal gp120 injection (100% male) 8–9/group: control, sham, gp120	eCB agonist WIN-55,212-2 (3 mg/kg) and/or CB <sub>2</sub> R antagonist AM630 (1.5 mg/kg) prior to gp120	Morris water maze	Learning and memory	Prophylactic WIN-55,212-2 treatment attenuated Gp120-induced spatial memory deficits; WIN-55,212-2 effects were blocked by CB <sub>2</sub> R antagonist treatment, which also prevented hippocampal gp120-induced inflammation and apoptosis
Winsauer et al. 2011	Rhesus monkeys (100% males)	Acute THC (0.032–0.32 mg/kg; IM); Chronic 28-day THC (2x/day; 0.32 mg/kg; IM)	Repeated acquisition task	Learning/working memory	Prior to SIV acute THC decreased response-rates without affecting %errors; tolerance developed to chronic THC irrespective of SIV. Chronic THC did not affect viral load but reduced neuropathology, opportunistic infections and inflammation in SIV + animals, and decreased hippocampal CB <sub>1</sub> R and CB <sub>2</sub> R expression across all animals (SIV + / –)

**Table 2**  
Data extraction from clinical studies examining associations between CU and HIV status in humans

Author/year	Sample characteristics (% male)	Cannabis use criteria	Cognitive assessments	Cognitive domains	Main findings
Attonito et al. 2014	370 PWH: > 50% CU + (49% M)	no. of days of CU in the past 3 months	AVLT, The Color Trails Test 2; Short Category Test	Executive function, attention, information-processing, memory	Higher number of CU days correlated with <b>worse</b> psychomotor speed and attention ( $p = 0.051$ )
Bedi et al. 2010	7 PWH: 100% current and chronic CU ( 2 × /week) (100% M)	16-day dronabinol (5–10 mg) + 16-day placebo (4×/day)	DSS, RAT, DAT, immediate and delayed DRT, 10-min rapid information-processing task	Attention, information-processing, verbal memory	Dronabinol was associated with <b>worse</b> processing-speed, latency (after 9–16 day treatment), and more false alarms (days 1–8), but <b>better</b> acquisition compared to placebo; <b>No effect</b> on information-processing or recall
Byrd et al. 2011	1284 PWH: 924 CU + (67% M)	Interview-Substance Abuse Module for frequent use ( 5×)	WAIS-III DS, WAIS-III SS, TMA, SMT, FMT, WCST, TMB, COWAT, CF, WAIS-III LNS, PASAT, GPT	Global cognition [executive function, attention, information processing, learning, memory, verbal-fluency, motor]; individual subdomain scores also reported	Lifetime “dosage” of cannabis was weakly associated with <b>better</b> verbal-fluency ( $p < 0.1$ )
Chang et al. 2006	PWH: 21 C – (81% M) 21 C + (86% M) PWoH: 30 C – (80% M) 24 C + (83% M)	C + : regular CU or history of chronic CU C – : < 1 joint per month or no use	Timed gait, RAVLT, GPT, Stroop, New adult reading test revised, TMA, TMB, SDM, CalCAP, Tests for working memory, and visual discrimination and response inhibition (degraded words with distracters, response reversal/visual scanning, and form discrimination tasks)	Executive function, information processing, verbal memory, motor function	CU, irrespective of HIV diagnosis, was associated with <b>better</b> executive function, information-processing and motor skills, but <b>no effects</b> on any cognitive function after age was included as a covariate
Christopher-Hayes et al. 2021	PWH: 22 C – (82% M) 18 C + (78% M) PWoH: 20 C – (55% M) 21 C + (57% M)	4 × CU/month; no other illicit substance use; no CU on test day	GPT, HVLTR, Phonemic and semantic verbal-fluency, WAIS-III DS, WAIS-III SS, TMA, Stroop, TMB	Executive function, attention, information-processing, learning, memory, verbal-fluency	<b>No effects</b> or interaction between cannabis and HIV on any cognitive functions; main effect of HIV on reaction time in visuospatial task (PWH slower than PWoH)
Cristiani et al. 2004	PWH: 46 asympt. C – 79 asympt. C + 29 sympt. C – 55 sympt. C + PWoH: 24 C – 49 C + No gender data	Past 12 month self-report; 1 × CU/week	WAIS-R, Selective Reminding Test, Wechsler Memory Scale-Revised, Verbal Concept Attainment Test, WCST, Verbal and figural fluency, TMA, TMB, GPT, PASAT	Global cognition [executive function, attention, information-processing, learning, memory, language, motor]	Cannabis related to worse overall impairment; driven by interaction effect on delayed memory; CU <b>worsened</b> delayed memory, particularly for those with more severe HIV disease)
Crook et al. 2021	PWH: 91 past CUD (79% M) 47 past CUD + (69% M)	Past CUD measured by DSM-IV interview; excluded current CUD	WAIS-III LNS, PASAT, TMA, WAIS-III DS, WAIS-III SS, TMB, WCST, COWAT, HVLTR, BVMT, GPT	Executive function, information-processing, attention, learning, memory, verbal-fluency, motor	CUD + associated with <b>better</b> processing-speed, visual learning, memory, delayed recall, and dominant hand motor ability compared to CUD–
Dastgheyb et al. 2021	929 PWH 717 PWoH 100% F	Self-reported CU	HVLTR, LNS, TMA, TMB, Stroop, SDMT, COWAT; Animal fluency; GPT	Neuropsychological “profiles” created using the following domains:	Current CU associated with <b>lower</b> likelihood of impairment “profile” consisting of learning, information-

Author/year	Sample characteristics (% male)	Cannabis use criteria	Cognitive assessments	Cognitive domains	Main findings
Flannery et al. 2021	PWH: 27 C – (67% M) 32 C + (91% M) PWoH: 22 C – (50% M) 28 C + (57% M)	1 × CU/week for 3 months; 20 × in the past year	EAT (go/no-go motor inhibition paradigm) during MRI; Cognitive Failures Questionnaire	Executive function, attention, learning, memory, language, motor Executive function	processing and executive function in women with HIV Greater lifetime CU associated with <b>worse</b> inhibition-related neural activity in PWoH but not PWH
Flannery et al. 2022	PWH: 28 C – (67% M) 32 C + (91% M) PWoH: 22 C – (50% M) 24 C + (57% M)	1 × CU/week for 3 months; 20 × in the past year	WAIS-IV, WCST, IGT, HVLTR, BVMIT, GPT, MST	Executive function, attention, information-processing, learning, memory, and motor	CU was associated with increased resting state functional connectivity in regions associated with executive function in PWH and PWoH, but <b>no effect</b> of CU on cognitive functions
Flannery et al. 2022	PWH: 28 C – (67% M) 32 C + (91% M) PWoH: 22 C – (50% M) 24 C + (57% M)	1 × CU/week for 3 months; 20 × in the past year	EAT (go/no-go motor inhibition paradigm) during MRI	Executive function	CU was associated with <b>better</b> executive function in PWH (error-awareness) relative to PWH who do not use cannabis
Gomez et al. 2017	138 neurocognitively normal (NN) PWH/C – 67 NN PWH/C + 69 NCI PWH/C – 14 NCI PWH/C + (84–90% M/group)	Patient chart review for the past cannabis abuse	Game of Dice Task (GDT), SDM, TMT-2/4, GPT, HVLIT, WCST	Executive function	CU predicted <b>worse</b> executive function (GDT net score)
Gonzalez et al. 2011	PWH: 25 C – 17 C + PWoH: 21 C – 23 C + Mostly men no gender data; polysubstance users	DSM-IV + Kreek-McHugh-Schluger-Kellog scale; lifetime history of cannabis dependence	Rotary pursuit task (RPT), Star mirror tracing task (SMT), weather prediction task (WPT)	Procedural learning of motor skills	History of cannabis dependence was not associated with procedural learning of motor skills; Motor skills performance on the RPT and SMT adversely affected among PWH with history of polysubstance dependence
Haney et al. 2005	15 PWH/C + with muscle loss (80% M) 15 PWH/C + no muscle loss (100% M) 100% current CU + 2×/ week for 4 weeks	Acute dronabinol (0, 10, 20, 30 mg) or cannabis (0.0, 1.8%, 2.8%, 3.9% THC)	DSS, RAT, DAT, Immediate and a delayed DRT	Attention, learning, memory	CU associated with <b>no effects</b> on performance in either group compared to placebo; 20-mg dronabinol associated with <b>worse</b> memory and attention in clinical muscle loss group; 30-mg dronabinol was associated with <b>worse</b> memory in normal muscle mass group
Haney et al. 2007	10 PWH/C + (90% M); 100% current cannabis users ( 2 ×/week) for the past 4 weeks	Chronic (4 day; QUID) dronabinol (0, 5, 10 mg) or cannabis (THC 0%, 2%, 3.9%)	DSS, RAT, DAT, immediate and a delayed DRT, 50-item visual analogue scale	Attention, information-processing, learning, memory	Cannabis or dronabinol was associated with <b>no effects</b> on cognitive performance compared to placebo



Author/year	Sample characteristics (% male)	Cannabis use criteria	Cognitive assessments	Cognitive domains	Main findings
Heaton et al. 2023	402 PWH 76% M	Past or present CUD	DVT, WAIS-III DS, WAIS-III SS, TMA, SMT, FMT, HCT, WCST, TMB, COWAT, CF, WAIS-R DS, WAIS-III LNS, PASAT, GPT	Global cognition [executive function, attention, information-processing, learning, verbal-fluency]	History of CUD was associated with <b>worse</b> neurocognitive decline (decrease from baseline after 12 years)
Kallianpur et al. 2020	PWH (85% M): 4 C – 25 recent C + 23 remote C + PWoH (73% M): 11 C – 9 recent C + 35 remote C +	Self-report of CU; recent use (use in the last 12 months), remote use (> 12 months ago); also reported 12-month CU frequency	CaICAP, RAVLT, RCF Copy and Recall, TMA, TMB, WAIS-R, WAIS-III LNS, GPT, Verbal-fluency test, Animal and Boston Naming tests, Delis-Kaplan Executive Function System, Stroop, Timed gait	Executive function, information-processing, learning, memory	Occasional CU was associated with <b>better</b> executive function in PWH compared to non-use; duration of CU <b>positively</b> correlated with psychomotor speed and executive function in PWH but not PWoH; recent CU was associated with <b>worse</b> psychomotor speed compared to remote CU in PWoH
Lorkiewicz et al. 2018	215 PWH 65% M	Lifetime CU history; current use: no. of days of use in the past 20 days); lifetime CU (no. of years use; 3×/week)	Montreal Cognitive Assessment (memory and attention)	Attention, memory	Current CU associated with <b>no effects</b> on cognitive function; <b>no significant association</b> between lifetime CU and cognitive function
Meade et al. 2018	PWH: 29 C – (72% M) 20 C + (75% M) PWoH: 19 C + (68% M) 25 C – (68% M)	4 days of CU in the past month and 1 year of regular CU	Stroop, Counting stroop (during fMRI)	Executive function	CU was associated with <b>no effects</b> on cognitive interference, but an HIV X cannabis interaction effect on fMRI activity in task-dependent brain regions. PWH/C + had the greatest activity in these regions
Murdoch et al. 2023	PWH: 33 C + 12 C – /cocaine + 22 C + /cocaine + 43 C – /cocaine – (58–91% M/group)	Lifetime history of regular use and 12 days of use in the past 90 days	PASAT, WAIS-IV DS, WAIS-IV LNS, TMA, TMB, WAIS-IV coding, Stroop, HVLT-R, CF, GPT	Global cognition [executive function, speed of information-processing, attention, learning, memory, verbal-fluency, motor function]	CU was associated with <b>no effect</b> on global score
Naveed et al. 2022	581 PWH-159 use cannabis 79% M	Self-reported CU	TMA, TMB, WCST, WAIS-III DS, WAIS-III SS WAIS-III LNS, PASAT, BVMT-R, HVLT-R, COWAT, GPT	global cognition [executive function, speed of information-processing, attention and working memory, learning, motor verbal-fluency, motor function]	Lifetime CU associated with <b>worse</b> neurocognitive decline
Okafor et al. 2019	PWH: 498 C – 290 C + PWoH: 755 C – 377 C + 100% M	Self-reported CU in the past 6 months; CU years = total days used during study; categorized “monthly,” “weekly,” “daily”	TMA, TMB, SDM	Executive functioning, attention, information-processing, psychomotor speed	Daily and monthly CU associated with <b>worse</b> processing-speed compared to non-users in PWH; <b>no association</b> between cumulative cannabis years and cognitive function in PWH men; each additional 5 years of CU was associated with worse in processing-speed in men without HIV
Rogers et al. 2023	PWH (82–92% M): 187 Meth –/C – 68 Meth –/C +	Timeline follow back and DSM-IV Interview for CUD	DVT, WAIS-III DS, WAIS-III SS, TMA, SMT, FMT, HCT, WCST, TMB, COWAT, CF, GPT	Global cognition [executive function, information-processing]	Meth +/C + performed <b>better</b> than Meth +/C– in executive function, learning, memory, working memory and <b>better</b>

Author/year	Sample characteristics (% male)	Cannabis use criteria	Cognitive assessments	Cognitive domains	Main findings
Saloner et al. 2019	All participants 50–64 years 734 PWH 123 PwOH PWH: 84% M PwOH: no gender distribution	Lifetime CUD	COWAT, CF, WAIS-R DS, WAIS-III LNS, PASAT, GPT	speed, learning, memory, verbal-fluency, motor]; individual subdomains also reported	than Meth – C – on verbal-fluency, but worse than Meth – /C – in learning and memory. Meth – /C + performed better than Meth – C – on executive function, learning, memory and working memory Higher rates of lifetime CUD among “super ager” PWH (participants with-above average GDS cognitive performance relative to their age) compared to cognitively impaired individuals PWH and cognitively normal PWH
Schantzell et al. 2022	33 PwOH/C – (48% M) 32 PwOH/C + (59% M) 17 PWH/C – (47% M) 18 PWH/C + (72% M)	2 ×CU/week for 6 months; other substance use < 1 ×/month	Eriksen flanker task during magnetoencephalography	Executive function	PWH/C – had larger flanker interference effect than PwOH/C + and PwOH/C –; PwOH/C + had smaller flanker interference effect relative to PWH/C +
Schouten et al. 2016	74 PwOH 103 PWH 100% M	Daily to monthly self-reported CU	CF, LF, TMB, WCST, Stroop, TMA, DS, SS, PASAT, LNS, RAVLT, Visual reproduction test, GPT	Global cognition [executive function, attention, information-processing, memory, fluency, and motor]	Cognitive impairment detected in 17% of men with HIV; CU was associated with worse cognitive performance among men with HIV
Skalski et al. 2018	PWH (67–75%): 42 C – 12EC + 15LC + EC + = early CU onset LC + = late CU onset (before/after age 18 respectively)	C + : 10 days/month 1 year or 3 ×/week of bingeing or problematic regular use	HVLT-R, BVMTR, TMA, TMB, GPT, COWAT, PASAT	Attention, information-processing, learning, memory, verbal-fluency, psychomotor ability	EC + more likely to have worse learning and memory compared to C – (learning, memory) but more likely to have better attention/working memory. No differences between LC + and C –
Thames et al. 2017	PWH (83% M): 24 PWH/C – 24 PWH/C + PwOH (52% M): 16 PwOH/C – 13 PwOH/C +	Average CU amount (in grams) smoked/day times no. of days/week of CU in the past month	WTAR, TMA, Stroop, WAIS-IV LNS, WAIS-IV DS, WAIS-IV SS, COWAT, BVMTR, HVLTR, TMB	Global cognition, [executive function, information-processing, attention, learning, memory, verbal-fluency] individual subdomains also reported	Higher levels of CU associated with worse global cognition in PwOH, no effect in PWH, driven by processing-speed and memory; simple effects: low CU (<1.43 g/week) was associated with worse global cognition in PWH vs. PwOH; no between group effects observed when CU > 1.43 g/week
Thames et al. 2016	PWH: 14 C – (85% M) 30 light C +(95% M) 31 heavyC +(54% M) PwOH: 32 C – (45% M) 12 light C +(75% M) 10 heavy C +(100% M)	Light C + : 2–14 ×/week > 12 months; Heavy C + : 18–90 ×/week > 12 months	WTAR, TMA, Stroop, WAIS – IV LNS, WAIS-IV DS, WAIS-IS SS, COWAT, BVMTR, HVLTR TMB	Executive function, attention, information-processing, learning, memory, verbal-fluency	Moderate to heavyC + associated with worse global cognition, processing-speed, learning/memory and executive function compared to LightC + and C – ; PWH/ HeavyC + performed worse in learning and memory compared to all groups, PWH/LightC + performed better in verbal-fluency than PwOH/LightC +
Wang et al. 2020	PWH: 23 C – (96% M) 21 C + (95% M) PwOH:	Chronic CU (> 3 ×/week for > 2 years)	RAVLT, RCFT, D-KEFS, Stroop, Trail-making (number-letter switching); WAIS-IV, Fluency test, COWAT, GPT	Executive function, attention, information-processing, learning, memory, design and verbal-fluency, motor	Nonsignificant trend indicating PWH/C + performed better than PWH/C – in executive function and verbal-fluency, executive function, and information processing

Author/year	Sample characteristics (% male)	Cannabis use criteria	Cognitive assessments	Cognitive domains	Main findings
Watson et al. 2020	24 C – (88% M) 22 C + (86% M) PWH: 573 C – (80% M) 106 C + (92% M) PWoH: 229 C – (60% M) 44 C + (79% M)	C + : history of CUD and/or CU in the past year	COWAT, CF, WCST, TMA, TMB, Stroop, WAIS-III DS, WAIS-III SS, WAIS-III LNS, HVLT-R, BVMTR-R, PASAT, GPT	Executive function, attention, information processing, learning, verbal-fluency, motor	PWH/C + associated with <b>better</b> performance in verbal-fluency, learning; <b>no effect</b> of cannabis in PWoH on any cognitive domain
Watson et al. 2021	PWH (82–95% M): 105 C – 62 moderate C + 31 dailyC + PWoH: 65 C – (68% M)	Moderate C + : 3 days of CU/week to 3 × of use within the past 6 months	HVLT-R, BVMTR, COWAT, VF, TMA, TMB, WCST, HCT, PASAT, GPT, WAIS-III DS, WAIS-III SS, WAIS-III LNS, Stroop	Executive function, attention, information-processing, learning, verbal-fluency, motor	PWH/Daily C + had <b>better</b> global cognition compared to PWH/moderate C + and PWoH/C – (ns); Similar trend in verbal-fluency, attention/working memory, processing-speed, learning and motor skills
Watson et al. 2023	PWH (81–92% M): 191 C – 83 Occasional C + 23 Frequent C +	Occasional: 1 ×/week to < 1 ×/month Frequent: 2–7 days/week	HVLT-R, BVMTR, COWAT, VF, TMA, TMB, WCST, HCT, PASAT, GPT, WAIS-III DS, WAIS-III SS, WAIS-III LNS, Stroop	Executive function, attention, information-processing, learning, verbal-fluency, motor	Occasional, but not frequent, CU was associated with <b>better</b> global cognition; driven by better performance in attention (significant), verbal-fluency (ns), and learning (ns). Recent THC use was associated with <b>worse</b> global cognition, driven by worse memory

AVLT, auditory verbal learning test; *WAIS-III DS*, Wechsler Adult Intelligence Scale Third Edition-III digit symbol; *WAIS-III SS*, *WAIS-III* symbol search; *TMA*, Trail Making Test Part A; *SMT*, Story Memory Test; *FMT*, Figure Memory Test; *WCST*, Wisconsin Card Sorting Task; *TMB*, Trail Making Test Part B; *COWAT*, Controlled Oral Word Association Test; *CF*, category fluency; *WAIS-III LNS*, *WAIS-III* letter-number sequencing; *PASAT*, paced auditory serial addition task; *GPT*, Grooved Pegboard Test; *RAVLT*, Rey Auditory Verbal Learning Test; *EAT*, error-awareness task; *Stroop*, Stroop Color Interference Test; *SDM*, symbol digit modalities; *CalCAP*, California Computerized Assessment Package; *HVLT-R*, Hopkins Verbal Learning Test-Revised; *WAIS-R*, Wechsler Adult Intelligence Scale-Revised; *BVMT-R*, Brief Visuospatial Memory Test-Revised; *MST*, Mirror Star Tracing Test; *TMT-2*, *TMT-4*, Trail Making Test 2 and 4; *HCT*, Halstead Category Test; *WTAR*, Wechsler Test of Adult Reading; *RCFT*, Rey-Osterreith Complex Figure Test; *DSS*, 3-min digit-symbol substitution task; *RAI*, 3-min repeated acquisition task; *DAT*, 10-min divided attention task; *DRT*, immediate and delayed digit-recall task; *D-KEFS*, Delis-Kaplan Executive Function System; *SUD*, substance use disorder; *QUID*, four times daily

**Table 3**

Summary of function-dependent effects of cannabis use in people with HIV

Functional domain	Beneficial CU effects (no. of reports)	Adverse CU effects (no. of reports)	Null findings (no. of reports)	Moderating factors	Conclusions from synthesized data
Global cognition	6 <sup>#</sup>	5 ~	7	Frequency of CU Age <sup>&amp;</sup> Disease severity	Inconsistent CU frequency effects, though heavy use appears detrimental CU may benefit aging PWH, particularly frequent previous use or current moderate use CU may be harmful in advanced disease stages
Executive functioning	5 <sup>#</sup>	2 ~	15	Chronicity of CU <sup>&amp;</sup> Frequency of CU	Chronic CU appears beneficial, but not when used at exceptionally high frequencies CU appears to have adverse consequences on risk-based decision-making
Attention and information-processing	5 <sup>##</sup>	5	11	Dosage Frequency of CU Chronicity of CU Age	CU appears to have adverse effects, particularly on processing-speed Dronabinol at high, but not low doses, appears adverse Heavy, but not necessarily chronic, CU appears detrimental, with some beneficial effects observed with moderate CU CU may be beneficial for older PWH
Learning and memory	5 <sup>##</sup>	5 ~	11	Age of CU onset Age Disease severity	CU may benefit learning functions, and hinder memory functions Early age of CU onset appears detrimental CU may be beneficial for older PWH, while having adverse effects in younger PWH CU may be harmful in advanced disease stages
Language and verbal fluency	7 <sup>##</sup>	0	8	Frequency of CU	CU appears beneficial No data to support adverse effects Inconsistent frequency of use effects
Motor skills	2 <sup>#</sup>	1	9		Little data to support beneficial or harmful effects of CU

CU, cannabis use

<sup>#</sup> indicates no. of beneficial trend effects included in total reports count

~ indicates no. of adverse effects selective to current heavy-use patterns (i.e., dose-dependency within the same study)

<sup>&</sup> moderated by frequency of CU