Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Mini-review: The therapeutic role of cannabinoids in neuroHIV

Barkha J. Yadav-Samudrala, Sylvia Fitting *

Department of Psychology and Neuroscience, University of North Carolina, Chapel Hill, NC, 27599, USA

ABSTRACT

In the era of combined antiretroviral therapy (cART), human immunodeficiency virus type 1 (HIV-1) is considered a chronic disease with an inflammatory component that specifically targets the brain and causes a high prevalence of HIV-1-associated neurocognitive disorders (HAND). The endocannabinoid (eCB) system has attracted interest as a target for treatment of neurodegenerative disorders, due to the potential anti-inflammatory and neuroprotective properties of cannabinoids, including its potential therapeutic use in HIV-1 neuropathogenesis. In this review, we summarize what is currently known about the structural and functional changes of the eCB system under conditions of HAND. This will be followed by summarizing the current clinical and preclinical findings on the effects of cannabis use and cannabinoids in the context of HIV-1 infection, with specifically focusing on viral load, cognition, inflammation, and neuroprotection. Lastly, we present some potential future directions to better understand the involvement of the eCB system and the role that cannabis use and cannabinoids play in neuroHIV.

1. Background

In the context of human immunodeficiency virus type 1 (HIV-1) infection, cannabis use is an important topic and is one of the most commonly used drugs among people living with HIV-1 (PWH). Cannabis use has been reported to be higher in PWH compared to the general population [178], potentially to manage HIV-1 symptoms such as pain, nausea, and appetite loss, despite the negative effects [20, 178, 240, see also Table 1]. Additionally, certain cannabinoids are emerging as therapeutically promising neuroprotective agents in several neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, and multiple sclerosis due to their anti-inflammatory, anti-oxidative, and anti-excitotoxic properties [156,226]. To enhance our understanding about the role of the endocannabinoid (eCB) system in neuroHIV, the current review focuses on how the eCB system is altered by neuroHIV and how cannabinoids affect HIV-1 infection and specifically HIV-1 associated neurocognitive disorders (HAND).

1.1. HIV-1 associated neurocognitive disorders (HAND)

HIV-1 associated neurocognitive disorders (HAND) was introduced in 2007 [9] and is an umbrella term for a group of neurocognitive disorders that include three subtypes; HIV-associated dementia (HAD), minor neurocognitive disorder (MND), and asymptomatic neurocognitive impairment (ANI) [72]. Before the availability of HIV-1 therapy, more than 15 % of infected patients developed the more severe form HAD and autopsy usually revealed pathological and inflammatory changes to the brain, also known as HIV encephalitis (HIVE) [47, 72]. With the introduction of combined antiretroviral therapy (cART), which is very effective in suppressing HIV-1 replication and restoring the immune system [12], HAD has significantly declined (< 5 %) and hardly any HIVE cases are reported at autopsy [72,96]. However, as ART medication does not eradicate the virus, low levels of viral replication and chronic immune activation still linger, specifically in the brain due to low brain penetration of cART [148]. The difficulty of efficient

---

Table 1

Human clinical findings.

Major effects	Species	HIV pathogen	ART	Target	Ligand	Effect	Reference
Neuroinflammation	Human (postmortem tissue)	HIV, encephalitis	Yes	CB_1RCB_2R	Anti- CB_1R and anti- CB_2R antibodies	• ↑ CB_1R in white matter microglia and perivascular cells • ↑ CB_2R microglia, astrocytes and perivascular macrophages	[52]
	Human	HIV-1	Yes	pDC	Δ^9-THC	• ↓ IFN-α by pDC	[99]
	Human	HIV-1	Yes	T-cell	Δ^9-THC	• IFN-α ↑ IL-7R-α expression in T cells • IFN-α ↑ IL7-induced phosphorylation of STAT5 in $CD4^+$ and $CD8^+$ cells • CD3/CD28/IFN-α-induced proliferation was ↑ by IL-7 and ↓ by THC	[98]
	Human and primary leukocytes (*in vitro*)	HIV-1		CD16 and IP-10 levels	Cannabis	• HIV+ users – ↓ circulating CD16 monocytes and plasma IP-10 than HIV- nonusers • HIV+ users – no CD16 expression when treated with *in vitro* IFNa • THC treatment of PBMC and purified monocytes ↓ IP-10 levels	[197]
Cognitive performance	Human	HIV-1	Yes	Effect on neurocognitive impairment	Cannabis	• Lower likelihood of neurocognitive impairment	[233]
	Human	HIV-1	No info	Effect on cognitive performance, CD4 count and viral loads	Cannabis	• HIV+ patients – lower neurocognitive performance than control • Moderate–to-heavy HIV+ users – low learning/memory performance than moderate-to-heavy HIV- users • HIV+ light users – more verbal fluency than HIV- light users • HIV+ cannabis users had lower viral loads and higher CD4 count than non-users	[228]
	Humans	HIV-1	No info	Effect on brain structure and cognitive performance	Cannabis	• Heavy users – smaller volumes in the entorhinal cortex and fusiform gyrus • HIV+/- smaller thickness of the cingulate • HIV- light-users had better cognitive performance than HIV+	[227]
	Humans	HIV-1	Some subjects on ART	Effects on cognition and brain metabolites	Cannabis	• No effect on cognition. • HIV+ non-users – ↓ N-acetyl aspartate in parietal white matter and ↑ choline compound in basal ganglia • Cannabis users (HIV+ and HIV-) – ↓ basal ganglia N-acetyl aspartate, choline compound, and glutamate, ↑ thalamic creatine • HIV+ cannabis users – ↓ glutamate in frontal white matter	[35]
	Humans	HIV-1	No info	Effects on cognitive function	Cannabis	• Frequent users reported more symptoms of depression and anxiety • No significant difference effects of marijuana on CD4 levels • Impact of marijuana was greater on delayed memory in severe HIV disease	[58]

2

Table 1 (*continued*)

Major effects	Species	HIV pathogen	ART	Target	Ligand	Effect	Reference
Viral load / Immune cells	Human	HIV-1	Yes (Indinavir or Nelfinavir)	HIV-1 RNA levels, $CD4^+$ and $CD8^+$ cells subset, PK analyses of protease inhibitor	Δ^9-THC	• No difference in attention, learning or memory due to marijuana use • Does not elevate viral load in patients on stable antiretroviral regimens • No effect on $CD4^+$ or $CD8^+$ cell counts • No clinical interaction of cannabinoid with protease inhibitors	[1]
	Human	HIV-1	Yes	HIV-1 RNA levels, $CD4^+$ and $CD8^+$ cells	Dronabinol or cannabis	• No negative changes • No changes in $CD4^+$ and $CD8^+$ cell levels	[29]
	Human	HIV-1	No	HIV-1 RNA viral loads	Cannabis	• ↓ Plasma HIV-1 RNA viral loads	[158]
	Human	HIV-1	Yes	HIV-1 viral suppression	Cannabis	• No viral suppression in daily or less than daily cannabis users	[175]
	Human	HIV-1	Yes	HIV-1 RNA levels in blood and semen	Cannabis	• ↑ HIV-1 RNA levels in semen	[83]
	Human	HIV-1	Yes	HIV-1 viral load	Cannabis	• Daily and nearly daily cannabis users show viral load suppression	[218]
	Human	HIV-1	Yes	Inflammatory immune cell frequency	Δ^9-THC	• ↓ Frequency of $HLA-DR^+$, $CD38^+$, $CD4^+$, and $CD8^+$ cells • ↓ Monocytes subset • ↓ IL-23 and TNF-α	[146]
	Human	HIV-1	Yes (Azidothymidine and/or Dideoxyinosine	Effects of marinol on HIV-1 progression	Marinol	• ↓ Clinical indicators, amylase, lipase, ALT and AST (not significant)	[236]
	Human	HIV-1	Yes	Effects of cannabis on inflammatory and circulating monocytes	Cannabis	• ↓ Inflammatory, nonclassical, activated classical and activated-inflammatory monocytes	[33]
	Human	HIV-1	Yes	Effects of cannabis use on BMI, $CD4^+$ cells and HIV-1 RNA suppression	Cannabis	• No changes in BMI and $CD4^+$ cell count • Cannabis users had detectable viral loads	[133]
	Human	HIV-1	No info	$CD4^+$ and $CD8^+$ cell counts	Δ^9-THC	• ↑ $CD4^+$ and $CD8^+$	[120]
ART adherence	Human	HIV-1	Yes	ART adherence and HIV-1 symptom	Cannabis	Cannabis dependent group - • Had low adherence than non-users and non-dependent users • Had higher viral loads • Had frequent and severe HIV symptoms/ ART side effects	[26]
	Human	HIV-1	Yes	ART adherence	Cannabis	• No relationship between cannabis use and adherence • Cannabis use for reducing nausea resulted in ART adherence	[62]
	Human	HIV-1	Yes	ART adherence	Cannabis	• Recreational users showed low ART adherence • Therapeutic users showed no association with ART adherence	[145]
	Human	HIV-1	Yes	Retention outcomes	Cannabis	• Not associated with IOM retention outcome • Associated with missing next appointment	[125]
	Human	HIV-1	Yes	ART adherence	Cannabis	• Use led to nonadherence	[231]
Appetite and/or Mood	Human	HIV-1	Yes	Effects on caloric intake	Dronabinol, Δ^9-THC	• ↑ Caloric intake • Minor effects on cognitive performance	[90]
	Human	HIV-1	No info	AIDS-related anorexia	Dronabinol	• ↑ Appetite above baseline • Mood improvement • ↓ Nausea	[16]
	Human	HIV-1	Yes		Dronabinol, Δ^9-THC	• ↑ Caloric intake • No cognitive impairment	[89]

Table 1 (*continued*)

Major effects	Species	HIV pathogen	ART	Target	Ligand	Effect	Reference
	Human	HIV-1	No info	Effects of caloric intake, mood, and sleep		• Only Δ^9-THC improved sleep	
				Effect on nutritional status	Dronabinol	• ↑ Percent body fat • ↑ Weight gain • ↑ Prealbumin • ↓ Symptom distress • Improved appetite	[222]
	Human	HIV-1	Yes	Effects of high dose	Dronabinol	• ↑ Food cravings • Improved sleep • Mood improvement	[18]
	Human	HIV-1	Yes	Effect on appetite hormones	Δ^9-THC	• ↑ Plasma levels of ghrelin, leptin • ↓ Plasma levels of PYY • No effect on insulin	[196]
	Humans	HIV-1	No info	Over all effects	Δ^9-THC	• ↓ Anxiety and/or depression • Improved appetite • Pain relief	[189]
	Human	HIV-1	Yes	Long-term effects of dronabinol	Dronabinol	• Safe to use for anorexia associated weight loss in patients with AIDS	[17]
	Human	HIV-1	Yes	HIV-1 wasting syndrome with anorexia	Dronabinol Megestrol acetate	• Dronabinol alone did not affect weight • High dose of megestrol acetate + dronabinol ↑ weight	[229]
	Human	HIV-1	Yes	Effect of appetite and weight gain	Dronabinol	• Improves appetite • Reverses weight loss	[63]
	Human	HIV-1	Zidovudine in 6 patients	Effects on weight	Dronabinol	• ↑ Body weight	[86]
	Human	HIV-1	N/A	Effects of HIV-1 symptoms	Δ^9-THC	• ↑ Appetite • ↓ Muscle pain • ↓ Nausea • ↓ Anxiety • ↓ Nerve pain • ↓ Depression • ↓ Paresthesia	[240]
Neuropathic pain	Human	HIV-1 and symptomatic HIV-SN	Yes	Effect of smoked cannabis on HIV-associated neuropathy	Δ^9-THC	• ↓ Chronic neuropathic pain from HIV-associated sensory neuropathy	[2]
	Human	HIV-DSPN	Yes	Effect of smoked cannabis on HIV-associated neuropathy	Δ^9-THC	• ↓ Pain • Improved mood and daily functioning	[73]

Abbreviations: AIDS, acquired immunodeficiency syndrome; ALT, alanine transaminase; ART, antiretroviral therapy; AST, aspartate transaminase; BMI, body mass index; CB_1R, cannabinoid type 1 receptor; CB_2R, cannabinoid type 2 receptor; CBR, cannabinoid receptor; Δ^9-THC, delta-9-tetrahydrocannabinol; HIV-SN, HIV-associated sensory neuropathy; HIV-DSPN, HIV-associated distal sensory predominant polyneuropathy; HLA-DR+, human leukocyte antigen – DR isotope; IFN-α, Interferon alpha; IL-7, interleukin 7; IL-23, interleukin 23; IL-7R-α, IL-7R-α receptor; IOM, Institute of Medicine; IP-10, IFN-γ-inducible protein 10; PBMC, peripheral blood mononuclear cells; pDC, plasmacytoid dendritic cells; PK, pharmacokinetics; PYY, peptide YY; STAT5, signal transducer and activator of transcription 5; TNF-α, tumor necrosis factor alpha.
Criteria for exclusion from this Table: (1) Studies on cannabinoids and HIV effects not directly related to the central nervous system. (2) Studies on the effects of cannabinoids on other diseases/disease pathogens.

delivery of cART to the central nervous system (CNS) [24,177,195] results in the prevalence of the milder forms of HAND to remain high. Up to 50 % of cART treated PWH exhibit MND or ANI that can interfere with daily life [9,69,72,80,96,206], involving problems in executive function, memory consolidation, decision-making, attention [60,82,91,96, 214], and/or mood [25,149,176].

The brain mechanisms underlying HAND involve two pathways, including HIV-1 induced neuroinflammation within the brain that indirectly affect neuronal health and continued production of neurotoxic HIV-1 proteins that can target neurons directly.

Chronic neuroinflammation within the brain appears to predominate and significantly contribute to the onset of HIV-1 associated neuronal injury and thus, HAND [81,92,118]. Shortly after infection, HIV-1 can enter the brain within infected macrophages, monocytes, and T cells [75,103,116,212,238] and as cell-free virus that establish central reservoirs by infecting microglia, brain endothelial cells or astrocytes [8, 28,44,95,127,131,134]. As the virus itself is not able to infect neurons the release and production of neurotoxic factors such as inflammatory

mediators from HIV-1 infected cells contribute indirectly to neuronal dysfunction and injury [3,44,84,104]. HIV-1 has been demonstrated to cause neurotoxicity by stimulating the production of proinflammatory cytokines and chemokines in the brain, inducing the release of TNF-α, RANTES/CCL5, and MCP-1/CCL2 from infected microglia and macrophages [71,217,235] and IL-8, IL-1ß, and TNF-α from infected astrocytes [37].

Additionally, HIV-1 contributes to HAND through the continued production of neurotoxic HIV-1 proteins from cellular reservoirs within the CNS that can target neurons directly [76,77,137,155,188]. HIV-1 proteins, such as the transactivator of transcription (Tat) and the envelope glycoprotein 120 (gp120) are likely agents of the observed neuronal loss in PWH and have been measured in the CNS of PWH under cART [97,115,153]. Besides their indirect effects on neurons via actions on microglia and astrocytes [38,70,119,123,130,136], Tat and gp120 have direct effects on neurons by activating glutamatergic NMDA receptors [76,77,94,142,151], altering chemokine receptor signaling [gp 120,101,154,155], and interacting with the lipoprotein receptor-related
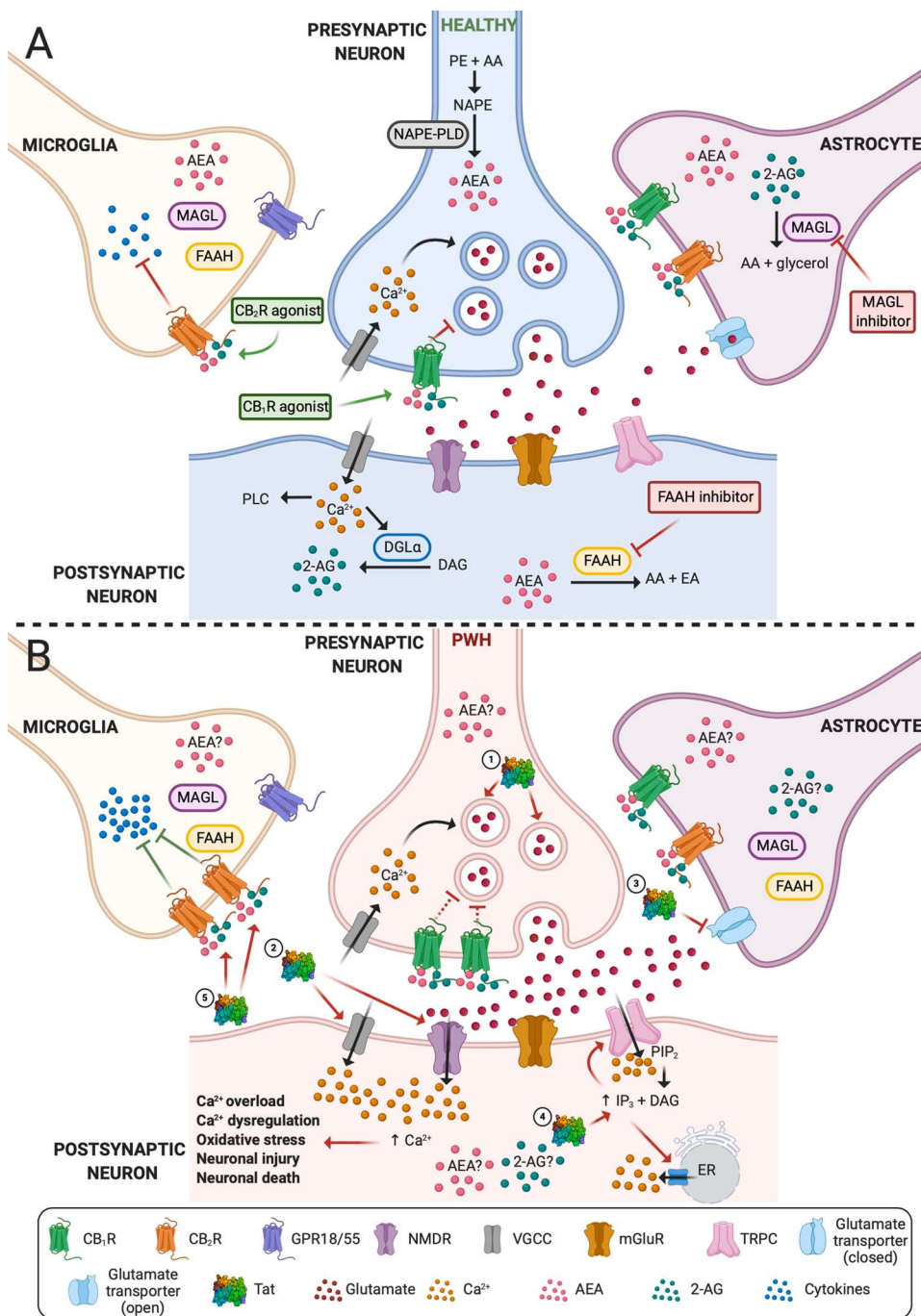
Fig. 1. A schematic presentation of the endocannabinoid (eCB) system. (A) Represents the eCB system in a healthy individual. CB_1Rs are present on presynaptic neurons. The influx of Ca^{2+} into the presynaptic neuron causes release of glutamate in the synapse and interacts with postsynaptic receptors (i.e. NMDR, mGluR). Excess of glutamate is taken up by the glutamate transporter present on astrocytes. CB_1R agonists block the release of glutamate and decrease excitotoxicity. CB_2Rs are predominantly expressed on microglia and their activation by CB_2R agonists decreases neuroinflammation by blocking the production of proinflammatory cytokines. It has been shown that neurons, but also glial cells, produce eCBs AEA and 2-AG which are hydrolyzed by the enzymes MAGL and FAAH, respectively. **(B)** Shows the possible mechanism of action of Tat and its effects on the eCB system in PWH. (1) Tat causes an excess of glutamate release into the synapse and (2) abnormally increases Ca^{2+} influx by acting on the NMDR, VGCC, and TRPC. (3) Tat blocks the glutamate transporter which further increases glutamate concentration in the synapse. TRPC channel is a nonselective cation channel that is also permeable for Ca^{2+}. (4) Tat increases the IP_3 concentration which activates the TRPC and leads to Ca^{2+} influx. Additionally, the increased IP_3 levels cause intracellular Ca^{2+} release from the ER. This excess of intracellular Ca^{2+} concentration causes Ca^{2+} overload, Ca^{2+} dysregulation, oxidative stress which leads to neuronal injury and eventually neuronal death. Tat also leads to the upregulation of CB_1Rs and CB_2Rs. Even though the CB_1R is upregulated in the presynaptic neuron, it is currently debated whether its inhibitory function is impaired or enhanced (represented by the broken inhibitor line). The negative effects of Tat are counteracted at the microglia as the overexpression of CB_2R blocks proinflammatory cytokines more effectively. Whether the endogenous ligands AEA and 2-AG are affected by Tat and their levels are upregulated in the brain of PWH is still not known (represented by?). Abbreviations; 2-AG, 2-arachidonoylglycerol; AA, arachidonic acid; AEA, arachidonoyl ethanolamine (anandamide); Ca^{2+}, calcium; DAG, diacylglycerol; DGL, diacylglycerol lipase; eCB, endocannabinoid; EA, ethanolamine; ER, endoplasmic reticulum; FAAH, fatty acid amide hydrolase; IP_3, inositol triphosphate; mGluR, metabotropic glutamate receptor; MAGL, monoacylglycerol lipase; NAPE-PLD, N-arachidonoyl phosphatidylethanolamine phospholipase D; NAPE, N-arachidonoyl phosphatidylethanolamine; NMDR, N-methyl-D-aspartate receptor; PE, phosphatidylethanolamine; PIP_2, phosphatidylinositol 4,5-bisphosphate; PLC, phospholipase C; PWH, people living with HIV; Tat, trans-activator of transcription; TRPC, transient receptor potential cation channel; VGCC, voltage-gated calcium channel. Created with BioRender.com.

protein [Tat; 137]. The effects of Tat on NMDA receptors in neuronal cultures has been demonstrated to potentiate glutamate-induced excitotoxicity [139], leading to increases in neuronal intracellular calcium levels, dendritic damage, and synapse loss [76,94,151,215]. Similarly, blocking chemokine receptor signaling has been shown to prevent gp120-induced neuronal apoptosis in the absence of non-neuronal cells

[155]. Thus, even though HIV-1 itself is not able to infect neurons, the release of HIV-1 proteins from HIV-1 infected cells can contribute to neurotoxicity via direct mechanisms on neurons.

The persistence of HAND in the era of cART has raised questions about the causes and treatment of HIV-1-related brain disorders and about the extent to which HAND and its underlying structural changes

are reversible.

1.2. The endocannabinoid (eCB) system

As HAND is a group of neurodegenerative cognitive disorders with an inflammatory component, the eCB system, which regulates both cognition and immune function, presents a promising therapeutic target for treating the consequences of HIV-1 infection on the CNS.

The eCB system, constituted of endogenous cannabinoids ('endocannabinoids'), cannabinoid receptors, and enzymes which synthesize or degrade cannabinoids, has attracted interest as a target for treatment of neurodegenerative disorders, due to the potential anti-inflammatory and neuroprotective properties of cannabinoids. A schematic presentation of the eCB system in a healthy individual is depicted in Fig. 1A. The two main eCB ligands are N-arachidonoylethanolamine (AEA, also known as anandamide) and 2-arachidonoylglycerol (2-AG). These ligands as well as exogenous cannabinoids, such as delta-9-tetrahydrocannabinol (Δ^9-THC) found in cannabis, act predominantly via cannabinoid type 1 and/or cannabinoid type 2 receptors (CB_1R and CB_2R, respectively), but can also activate the transient receptor potential vanilloid (TRPV) ion channels [102,117], peroxisome proliferator-activated receptors (PPARs) [174,224], and/or other G-protein-coupled receptors, including GPR55 and GPR18 [42,50,93,202].

The CB_1R is the most abundant G-protein-coupled receptor in the CNS, mainly expressed on neurons [150] and is responsible for the psychoactive effects of Δ^9-THC, which is a primary compound of cannabis [65,220]. CB_1R agonists have demonstrated promising protective effects, such as inhibiting excitotoxic neurotransmission by blunting presynaptic glutamate release [43,107,147] and decreasing intracellular calcium [173]. However, therapeutic use of direct CB_1R agonists is limited due to the psychoactive side effects associated with activation of CB_1Rs, including sensorimotor, affective and cognitive disturbances [65,162,220].

In turn, CB_2Rs are predominantly expressed by cells of the immune system [30,163,225] but can also be found in the CNS on immune-activated glia [163,221]. CB_2Rs represent a promising therapeutic target as their activation has been shown to induce anti-inflammatory signaling in astrocytes [219], regulate microglial migration and cytokine production [4,11,144], and reduce oxidative stress and apoptosis in neurons [232].

Another line of research has focused on the development of drugs targeting enzymes regulating the biosynthesis and degradation of AEA and 2-AG [6,135,187]. Because eCBs are neuromodulators that are synthetized locally on demand, the inhibition of their degradation is a therapeutic strategy that will cause their elevation only in locations where they are being actively produced to evoke their local neuroprotective effects, e.g. at the site of injury. Thus, in contrast to CB_1R or CB_2R agonists that are associated with side effects resulting from lack of site specificity and affecting receptors in the entire body, eCB catabolic enzyme inhibitors have high therapeutic potential as they are targeting 'on site' produced eCBs and inhibit eCB degradation [67,184]. There is strong preclinical evidence that selective inhibitors of the main AEA-metabolizing enzyme, fatty acid amide hydrolase (FAAH), and of the main 2-AG enzyme, monoacylglycerol lipase (MAGL) can ameliorate the unwanted effects in a variety of different laboratory animal models of neurodegenerative diseases [165,184]. Hydrolytic enzyme inhibitors of AEA (i.e. AM5206) and 2-AG (i.e. URB602, JZL184) have demonstrated to produce neuroprotective effects *in vitro* [41,165,209] and *in vivo* [124,165,166]. Additionally, the new generation of hydrolytic enzyme inhibitors, such as FAAH inhibitor PF3845 and MAGL inhibitors MJN110 and Abx-1431 show highly improved selectivity, potency and produce less side effects compared to previously available compounds [5,27,46,64,110,111,114,171,182].

Overall, targeting the eCB system appears to present a promising strategy to alleviate inflammatory and neurodegenerative consequences of HIV-1 infection on the CNS, which is reviewed in detail below.

2. The endocannabinoid (eCB) system in HAND

Most of what is known about the effects of HIV-1 infection on the eCB system is derived from protein expression studies for cannabinoid receptors, eCB ligands, and their enzymes, but little is known about the extent to which HIV-1 might disrupt their function. A schematic presentation of how the eCB system is potentially altered by HIV-1 Tat in PWH is depicted in Fig. 1B.

Effects on CB_1R expression in the context of neuroHIV have been variable, with reports ranging from no effects to upregulating effects. Brain tissue analysis from frontal cortex of simian immunodeficiency virus (SIV) rhesus macaques [21] or whole brain samples from HIV humanized mice [85] demonstrated no alterations in CB_1R protein or mRNA expression levels, respectively. However, when assessing cell-type specific changes, CB_1R upregulation levels have been reported [52,112,239]. CB_1R upregulation was noted in perivascular cells and white matter macrophages in brains of PWH with HIVE [52]. Further, CB_1R levels were reported to be increased in neurons in the infralimbic region in a HIV-1 Tat transgenic mouse model and was shown to be associated with behavioral deficits in an inhibitory control task [112]. The upregulation of CB_1R expression levels upon Tat exposure was also supported in mouse primary prefrontal cortex neuronal cultures *in vitro*, which demonstrated a time-course dependent linear increase of CB_1R protein expression over a 24 h time period [244]. Whether the upregulation of CB_1R expression levels observed in the female Tat(+) mice is a compensatory response to the Tat-induced observed behavioral deficits or contributes to the seen deficits in the behavioral Go-No-Go task needs to be further investigated [112]. Modified expression of CB_1R levels in other diseases has been negatively correlated with the prognosis of the symptoms [157]. For example, in neuropathic pain and multiple sclerosis, increases in CB_1R expression is associated with reductions of symptoms and/or dampened disease progression, suggesting a neuroprotective role [185], which is also confirmed in psychiatric disorders [169].

Most of the findings for changes of CB_2R expression levels provide evidence for increased expression levels of CB_2Rs in the context of neuroHIV [21,52,193]. Clinical postmortem studies demonstrated CB_2Rs upregulation in white matter microglia, astrocytes, and perivascular macrophages [52,193], which was specifically high in HIVE tissue and differed from HIV+ brains without HIVE [52]. This finding was confirmed in brain cortical tissue of SIV-infected rhesus macaques, demonstrating cell-type specific upregulation of CB_2Rs in perivascular monocytes/macrophages and microglia [21]. The increase of CB_2R expression levels in HIV-1 is suggested to be due to the inducible nature of CB_2R upon microglial cell activation under pathological conditions [10,15,23,49,157] and has been associated with an anti-inflammatory function in various disease models [10,113,179]. Interestingly, the upregulation of CB_2R expression appears to be specific to inflammation-driven neurodegeneration [48], as substantially more pronounced increases in CB_2R expression levels have been noted in response to HIV-1 infection or other bacterial/viral inflammatory mediators compared to direct neurotoxins that cause neuronal injury from within the cell, e.g. via oxidative stress [23,49].

Much less is known about changes of protein expression levels of eCB ligands and their degrading enzymes in the context of neuroHIV. Fatty acid amide hydrolase (FAAH) was found to be overexpressed in perivascular astrocytes and astrocytic processes of cortical SIV tissue samples [21]. It has been previously shown that the FAAH protein is selectively overexpressed in neuritic plaque-associated astrocytes in Alzheimer's disease brains [22]. FAAH upregulation in astrocytes appears to contribute to proinflammatory effects, as they are involved in converting AEA to arachidonic acid [56,152], thus, providing a potential source of inflammatory processes.

Further, it is not known if endogenous ligands such as AEA or 2-AG

are upregulated in the brain of PWH. A recent *in vitro* study, in primary prefrontal cortex neuronal cultures was unable to demonstrate a significant upregulation of AEA upon Tat exposure [100] but more clinical and preclinical studies are necessary to assess whether HIV-1 significantly alters eCB levels in the CNS.

Lastly, hardly any studies have investigated the effects of HIV-1 on eCB's regulatory function. It is not quite clear whether eCB signaling is diminished or enhanced in the context of neuroHIV. A recent study reported Tat-induced reduction of the inhibiting effects exerted on glutamatergic neurotransmission by cannabinoids in hippocampal cultures, including Δ^9-THC and 2-AG, due to impaired CB_1R-mediated presynaptic inhibition of glutamate release [241]. In turn, another study has shown that the downregulating effects of eCBs on glutamatergic transmission are enhanced in the context of neuroHIV [112]. Upregulating AEA via the FAAH enzyme inhibitor PF3845 demonstrated increased inhibition of glutamate release in prefrontal cortex brain slices of male Tat(+) transgenic mice compared to their control counterparts [112]. The discrepancy between results may be due to brain region-specific differences as the prefrontal cortex and hippocampus have been shown to display differential sensitivities to Tat [45].

Overall, additional studies are necessary to understand the effects of HIV-1 on the eCB system in more detail, specifically eCB signaling, and the underlying mechanisms involved.

3. Clinical and preclinical evidence of therapeutic properties of cannabinoids in HAND

3.1. Effects of cannabinoids on viral load

The effects of cannabinoids on viral load, HIV-1 replication, and $CD4^+$ cell count have been assessed over the last years [[1,29,83,133, 160,175,186,193,198,203,228,239], see also Tables 1 and 2].

Enhancing effects of cannabis use on HIV-1 replication and viral load are more observational in nature [26,83] and have been reported to be potentially due to low ART adherence [133], which has been demonstrated in a number of studies [61,141]; even though others have found no association with cannabis use [201] or even enhanced ART adherence if cannabis use was associated with medical use [62,145].

On the other hand, previous short-term randomized placebo-controlled studies reported no effects of cannabis, smoked or taken orally, on viral load, $CD4^+$, and/or $CD8^+$ cell counts in PWH [1,29], which has also been confirmed in some studies for recreational cannabis use in PWH [36,175,236].

Nevertheless, the vast majority of literature reports a downregulation of viral load and HIV-1 replication by cannabinoids, including clinical studies [158,228], and preclinical studies *in vivo* [160] and *in vitro* [186,193,198]. Clinical studies have found anti-viral effects of cannabinoids, with PWH cannabis users demonstrating lower viral load and higher $CD4^+$ counts than PWH non-users [228]. This has also been confirmed in PWH injection drug users that use cannabis at high intensities [158] or daily and near-daily use [218], as well as in an underrepresented group of black PWH [120]. Preclinical studies in SIV-infected rhesus macaques further support clinical findings [160]. Prolonged period of Δ^9-THC treatment prior to and during SIV infection resulted in lower viral load in lymph nodes and spleen as well as decreased inflammation (i.e. lower INF-γ and IL-6 protein in lymph nodes and spleen) [160,239].

Direct effects of cannabinoids on viral replication have been demonstrated *in vitro* by the reduced numbers of SIV-infected cells in culture incubated with Δ^9-THC prior to infection [161]. Interestingly, various preclinical *in vitro* studies have found CB_2Rs to be involved in inhibiting viral expression [186,193,198]. Specifically it has been shown that CB_2R activation with the agonists JWH144 and O-1966 decreased viral replication by affecting the long term repeat (LTR) of HIV-1 [193], potentially due to the CB_2R-induced

inhibition of cellular transcription factors involved in the transactivation of the HIV-1 LTR [193].

Another possible mechanism for suppression of viral replication includes the interaction of cannabinoids with HIV-1 coreceptors, CXCR4 and CCR5 [53,85,198], that are upregulated upon HIV-1 infection [132,203]. Whereas, CB_2R agonists JWH144 and O-1966 did not alter surface protein or gene expression of CXCR4 or CCR5 in HIV-1 infected monocyte-derived macrophages [193], other studies have shown an inhibitory effect of Δ^9-THC on CCR5 and CXCR4 in HIV-1 infected monocyte-derived macrophages [237], WIN55,212−2 inhibitory effects on CCR5 in microglia [198], and CB_2R agonist inhibitory effects in $CD4^+$ T cells on CCR5 [85] or CXCR4 [53]. Specifically, it has been suggested that CB_2R activation in $CD4^+$ T cells can inhibit actin reorganization with decreasing F-actin levels, which is an important contributor to productive HIV-1 infection [53].

Overall, findings indicate that the activation of CB_2Rs appear to potentially downregulate HIV-1 infection, with proposed mechanisms including CB_2R-induced inhibition of cellular transcription factors involved in the transactivation of the HIV-1 LTR or CB_2R cross-regulation of HIV-1 coreceptors, CXCR4 and CCR5, via inhibitory crosstalk.

3.2. Cannabinoid effects on cognition

A number of clinical studies have assessed cannabinoid effects in PWH. Specifically, cannabis use has been investigated and found to affect various biological processes, including cognitive performance [58,228,233], appetite [63,90,222], mood [16,18], and neuropathic pain [2,73,167]. More detailed information about these studies is provided in Table 1, with this subsection specifically focusing on cannabis effects on cognition. It is known that cannabis use, in general, has negative (psychoactive) effects on memory and executive functions in healthy individuals [57,194]; however, its effect in PWH remains unclear and divided.

The relationship between HIV-1 infection and cannabis use and their interactive effects on neurocognitive functioning is complex and various variables have been considered, including disease progression, the amount of cannabis use, and the cognitive domain assessed.

Some studies show that the effects of cannabis use in PWH depend upon disease stage [35,58]. Cannabis use resulted in cognitive dysfunction in PWH with an advanced stage of infection (symptomatic phase) but no effects were noted for HIV negative cannabis users or asymptomatic PWH cannabis users [58]. Additionally, frequency of cannabis use was associated with greater cognitive impairment among symptomatic PWH, which appeared to be primarily related to performance on memory tasks [58]. The lack of synergistic or interactive effects of HIV-1 and cannabis use on cognitive performance for the asymptomatic stage was confirmed in another study, which did not observe any significant abnormalities for neuroasymptomatic PWH cannabis users compared to PWH non-users on standard neuropsychological tests when correcting for group differences in age, education, or depression scores [35]. Since both, HIV-1 infection and cannabis use, have effects on the immune system, there is a likelihood that their interactions are specifically exacerbated in PWH with greater immune suppression.

Other studies have demonstrated that the amount of cannabis use determines what type of effects cannabis exhibits on cognition in PWH [26,227,228]. For example, significant negative effects for HIV-1 symptoms and ART side effects have been reported for cannabis dependent use, whereas no differences were noted between non-cannabis use and non-dependent cannabis use [26]. Similarly, a recent study found that independent of HIV-1 status moderate-to-heavy users consistently performed worse than light users on cognitive functioning tasks (global score) [228]. In a follow up study, the finding that the amount of cannabis use has significant effects on global cognition in PWH was not confirmed and based on their results the authors

Table 2

Preclinical animal studies (*in vivo*).

Major Effects	Species	HIV Pathogen	ART	Target	Ligand	Effect	Receptor Involved	Reference
Neuronal activity	Mice	HIV-1$_{IIIB}$ Tat$_{1-86}$	No		PF3845	• Tat(+) female mice –inhibitory control deficits, ↑ CB$_1$R in infralimbic cortex • Negative correlation between inhibitory control and infralimbic CB$_1$R expression • ↑ sEPSC in Tat(+) mice • PF3845 ↓ sEPSC	CB$_1$R	[112]
Neuroinflammation and Immune cells	Rhesus macaques	SIV$_{mac251}$, encephalitis	No info	CB$_1$R, CB$_2$R, FAAH	Anti- CB$_1$R & anti-CB$_2$R antibodies	• ↑ CB$_2$R microglia, perivascular macrophages and T–lymphocytes • ↑ FAAH in perivascular astrocytes and astrocytic processes	CB$_1$R, CB$_2$R	[21]
	Mouse	pVRCgp120	No info	Immune cells	Δ^9-THC	• ↑ or ↓ gp120 specific T cell responses depending on magnitude of IFN-γ response	No	[40]
	Mouse	pVRCgp120	No info	Immune cells	Δ^9-THC	• ↑ gp120 specific INF-γ and IL-2 response with gp120 derived peptide 81 • Δ^9-THC ↑ gp120-specific T cell activation in WT but not CB$_1^{-/-}$ and CB$_2^{-/-}$ mice	CB$_1$R, CB$_2$R	[39]
	Rhesus macaques	SIV	No info	CD4$^+$ and CD8$^+$ T lymphocytes	Δ^9-THC	Chronic administration • No difference in lymphocyte subtypes, proliferation or apoptosis • ↑ T lymphocyte CXCR4 expression of both CD4$^+$ and CD8$^+$ cells	No	[132]
	Rhesus macaques	SIV$_{mac251}$	No info	miR	Δ^9-THC	• No differences in plasma viral loads • ↑ Striatal BDNF • ↓ TNF-α mRNA expression in THC/SIV group • miRs modulation	No	[216]
Neurogenesis and Neuroinflammation	Mouse	GFAP/gp120	No	Deletion of FAAH gene	None	• ↑ Neurogenesis by ↑ expression of COX-2 and PGE-2 • ↓ Astrogliosis	No	[13]
	Mouse	GFAP/gp120	No	CB$_2$R	AM1241	• ↑ Neurogenesis in hippocampus • ↓ Astrogliosis and gliogenesis	CB$_2$R	[14]
Viral load and disease progression	Rhesus macaques	SIV$_{mac251}$	No	HIV-1 RNA levels CD4$^+$ and CD8$^+$ cells	Δ^9-THC	• No effect on disease progression, morbidity, and mortality • ↓ Plasma SIV-RNA viral load and lengthened survival • ↓ Classic markers of SIV disease	No	[161]
	Rhesus macaques	SIV$_{mac251}$	No	Effect of chronic Δ^9-THC on viral load and inflammation	Δ^9-THC	In lymph nodes and spleen • ↓ Viral replication • ↓ Viral gag RNA • ↓ INF-γ and IL-6	No	[160]
	Rhesus macaques	SIV$_{mac251}$	No	Effect of chronic Δ^9-THC on plasma viral load	Δ^9-THC	• Tolerance to disruptive effects of Δ^9-THC • ↓ CB$_1$R and CB$_2$R levels in the hippocampus • No effect on viral load in the plasma, CSF or brain tissue • ↓ Neuropathology and opportunistic infections • Lower expression of inflammatory cytokine MCP-1	No	[239]
	Mice (huPBL-SCID)	HIV-1$_{NL4-3}$	No	Effect of Δ^9-THC on HIV-1 progression	Δ^9-THC	• ↑ HIV-infected peripheral blood leukocytes • 50-fold ↑ viral load • Upregulation of CCR5 and CXCR4	No	[203]

(continued on next page)

Table 2 (*continued*)

Major Effects	Species	HIV Pathogen	ART	Target	Ligand	Effect	Receptor Involved	Reference
	Mice (huPBL/HIVE)	HIV-1$_{ADA}$	No	Effect of CB$_2$R agonist	Gp1a	• ↑ CB$_2$R expression in perivascular microglial cells and lymphocytes • Gp1a ↓ infiltration of human cells in the mouse brain and HLA DQ activation • Gp1a ↓ CCR5 expression on human cells in spleen • ↑ Fas ligand expression	CB$_2$R	[85]
	Rhesus macaques	SIV$_{mac251}$	No	Viral load, CD4$^+$ and CD8$^+$ cells, IgE$^+$ B cells	Δ^9-THC	• No difference in plasma viral load • ↓ CD4$^+$/CD8$^+$ ratio • ↓ IgE$^+$ B cells	No	[234]
BBB impairment	HBMEC and human astrocyte cocultures (*in vitro*), mouse (*in vivo*)	gp120$_{MN}$	No	TJ ZO-1, Claudin-5 expression	CP55,940, ACEA, URB597	• *In vitro* – CP55,940 and ACEA prevented BBB permeability and prevented ZO-1 and claudin-5 downregulation in HBMEC • *In vivo*– ACAE inhibited BBB permeability and prevented ZO-1 and claudin downregulation	CB$_1$R	[140]
Nociception	Rat	gp120$_{MN}$	No	FAAH	URB597, PF3845	• ↓ Nociception in rat HIV neuropathy model • ↓ Cold and tactile allodynia	CB$_1$R, CB$_2$R	[167]
	Rat	gp120$_{IIIB}$	No info	None	WIN55,212−2, AMD3100	• ↓ Analgesic effectiveness • AMD3100 restores the analgesic effects of WIN55,212−2	No	[180]

Abbreviations: BBB, blood-brain barrier; BDNF, brain derived neurotropic factor; CB$_1$R, cannabinoid type 1 receptor; CB$_2$R, cannabinoid type 2 receptor; CBR, cannabinoid receptor; COX-2, cyclooxygenase-2; CSF, cerebrospinal fluid; Δ^9-THC, delta-9-tetrahydrocannabinol; FAAH, fatty acid amide hydrolase; GFAP, glial fibrillary acidic protein; HBMEC, human brain microvascular endothelial cells; IFN-γ, Interferon gamma; IgE, immunoglobulin E; IL-2, interleukin 2; ; IL-6, interleukin 6; miR, microRNA; PGE-2, prostaglandin E2; SIV, simian immunodeficiency virus; sEPSC, spontaneous excitatory postsynaptic current; TJ ZO-1, tight junction zonula occludens-1; TNF-α, tumor necrosis factor alpha; WT, wild-type; ZO-1, zonula occludens-1.

Criteria for exclusion from this Table: (1) Studies on cannabinoids and HIV effects not directly related to the central nervous system. (2) Studies on the effects of cannabinoids on other diseases/disease pathogens.

concluded that cannabis use beyond 1.43 g/week had more adverse effects on neurocognitive performance in HIV negative users compared to PWH users [227]. However, caution should be exercised with this conclusion as a shortcoming of the study was that HIV negative non-users started out with significant higher cognitive performance compared to PWH non-users but then were significantly negatively affected by higher cannabis use (>1.43 g/week), which was not seen for PWH cannabis users [227]. Thus, baseline differences might have contributed to the seen adverse effects of high cannabis use in HIV negative individuals compared to PWH.

In addition to HIV-1 disease stage and the amount of cannabis use, the interactive effects of HIV-1 and cannabis also seem to depend on the cognitive domain assessed. Whereas moderate-to-heavy cannabis use significantly worsened overall cognitive performance independent of HIV-1 status (i.e. HIV negative individuals and PWH) PWH were most severely affected by moderate-to-heavy use for the learning and memory domain, displaying significantly lower scores in learning and memory performance compared to all other comparison groups [228]. It is known that the psychoactive effects of cannabis can be attributed to Δ^9-THC, which is known to negatively impact memory function [87,213], specifically at higher doses [109]. On the other hand, the study further reported that when the effects of light cannabis use were compared in PWH and HIV negative healthy controls, PWH light users outperformed HIV negative light users on verbal fluency [228]. This is an important finding as it indicates that depending on amount of cannabis use and the cognitive domain assessed, cannabis can have detrimental or beneficial effects on disease progression. The beneficial effects of cannabis use on verbal fluency find support in a recent study that demonstrated cannabis use, defined as history of cannabis substance use disorder and cannabis use in the past year, lowered odds of neurocognitive impairment in PWH regardless of age and viral levels or disease stage, with PWH cannabis use being specifically associated with higher performance in verbal fluency [233]. The differential cannabinoid receptor and/or ligand distribution across brain regions could contribute to the distinct effects seen for cannabis use depending on the cognitive domain assessed [79,181,210].

Overall, based on the studies outlined above interactive effects of cannabis use and HIV-1 infection on cognition appear to be specifically seen in PWH with more advanced symptomatic stages of HIV-1 infection, and further seem to depend on the amount of cannabis use and the cognitive domain assessed; with high cannabis use exhibiting more negative effects, specifically in the learning and memory domain, whereas light cannabis use might have some beneficial effects for domains such as verbal fluency. However, additional research is needed to investigate more in detail what role different cannabis types play on cognition in PWH, including cannabis use with high versus low Δ^9-THC content, as well as the components of cannabis that are non-psychoactive, including cannabinol or cannabidiol.

3.3. Anti-inflammatory properties of cannabinoids with neuroprotective benefits

The anti-inflammatory and immune modulatory properties of cannabinoids are well known [7,59,126,164,170] and have been reviewed in the context of HIV-1 infection [19, 54, 106, 242, see also Tables 1–3].

Table 3
Preclinical in vitro findings.

Major Effects	Species	Sample	HIV Pathogen	ART	Target	Ligand / Antibody	Effect	Receptor Involved	Reference
Neuronal activity	Rat	Hippocampal neurons	Tat_{1-86} (clade B)	No	Effects of Tat on eCB system	WIN55,212−2, 2-AG, JZL184, Δ^9-THC	• Tat ↓ DSE • 2-AG ↓ EPSCs • JZL184 did not affect 2-AG mediated EPSCs • WIN55,212−2 did not affect EPSC • Δ^9-THC ↓ EPSC	CB_1R	[241]
Neuronal damage and neuroinflammation	Mouse	PFC neuronal cultures	Tat_{1-86} (clade B)	No	FAAH	PF3845	• ↑ Neuronal survival • ↓ $[Ca^{2+}]_i$ • ↑ Dendritic volume • ↑ AEA, PEA	CB_1R	[100]
	Mouse	PFC neuronal cultures	Tat_{1-86} (clade B)	No	Neurons	AEA, 2-AG	• ↑ Neuronal survival • ↓ $[Ca^{2+}]_i$ • ↓ Dendritic injury • ↓ sEPSCs	CB_1R	[244]
	Human	Mesencephalic neuronal/glial culture	$gp120_{LAV/IIIB}$ (clade B)	No	Dopaminergic neurons	WIN55,212−2	• ↓ Neuronal damage • ↓ Microglial damage • ↓ Superoxide production • ↓ Chemokine and cytokine production	CB_2R	[105]
	Human	Primary Müller cell culture	Tat (clade B)	No	Müller glia	AEA, 2-AG	• AEA and 2-AG – • –Suppress Müller cell activation by ↓ inflammatory cytokines • –Control Tat-induced proinflammatory cytokines through MAPK phosphorylation • -Inhibit NF–KB signalosome • AEA induces MKP– independent of MEK necessary for ↑ anti–inflammatory and ↓ pro-inflammatory cytokines	CB_1R, CB_2R	[129]
	Human	Primary Müller cell culture	Tat (clade B) and Tat (clade C)	No	Müller glia	AEA	• HIV–1 clade Tat B and C act differently • Tat B suppresses through MKP–1 and Tat C through MEK–1 • ↑ PBMC attachment	CB_1R, CB_2R	[128]
GABA	Mouse	Mouse brain slices	Tat_{1-86} (clade B)	No	GABA	WIN55,212−2, AEA	• AEA ↓ GABAergic neurotransmission (mIPSCs) in PFC	CB_1R	[243]
	Rat	C6 glioma cells	Tat_{1-86}	No	NO synthase	WIN55,212−2, AEA	• ↓ Cytotoxicity	CB_1R	[74]
Cyto / Neurotoxicity	Human and murine	Human and murine NPCs	$gp120_{IIIB}$ (X4 strain) and $gp120_{Ba-L}$ (R5 strain)	No	CB_2R	AM1241	• ↓ Neurotoxicity and apoptosis • ↑ Differentiation of NPCs to neuronal cells • ↑ Neurogenesis *in vivo*	CB_2R	[14]
Synapse loss and neuroinflammation	Rat	Primary neuronal cultures	$gp120_{IIIB}$	No	MAGL	JZL184	• ↓ Synapse loss • ↓ Prostaglandins signaling • Blocks potentiation of NMDARs	CB_2R	[245]
	Rat	Hippocampal neuronal culture	$gp120_{IIIB}$	No	Synapse	WIN55,212−2	• Inhibits synapse loss • Blocks IL-1β release in microglia	CB_2R	[122]
Cell migratory and/or adhesion response	Human	Leukemic monocyte lymphoma cell line	Tat_{1-86}	No	Migration of U937 towards Tat	Δ^9-THC, CP55,940, O-2137	• ↓ Migration of U937 microphage-like cells towards Tat	CB_2R	[191]
	Human	Leukemic monocyte lymphoma cell line	Tat_{1-86}		Tat enhanced monocyte-like cell adhesion	Δ^9-THC, CP55,940	• ↓ Attachment of U937 cells to ECM proteins by altering b-integrin expression and distribution of polymerized actin	CB_2R	[192]
	Mouse	BV-2 microglial-like cells	Tat_{1-86}	No	Migration of BV-2	Δ^9-THC, CP55,940, 2-AG,	• ↓ Migration of BV-2 cells towards Tat	CB_2R	[78]
Inhibition of viral expression	Human	Microglial culture	None	No	HIV-1	WIN55,212−2	• ↓ HIV-1 viral expression	CB_2R	[198]
	Human	Primary monocytes	None	No	HIV-1	JWH133, GP1a, O-1966	• ↓ Activity of HIV-1 LTR • Partially ↓ expression of HIV-1 *pol*	CB_2R	[193]
	Human	HIV-1 infected $CD4^+$ lymphocyte and microglial cultures	None	No	HIV-1	WIN55,212−2	• ↓ Viral expression in both $CD4^+$ lymphocyte and microglial cultures		[186]
HIV infection	Human	$CD4^+$ T cells	HIV_{NL-GI}	No	CD4 + T cells			CB_2R	[53]

Table 3 (*continued*)

Major Effects	Species	Sample	HIV Pathogen	ART	Target	Ligand / Antibody	Effect	Receptor Involved	Reference
	Human	Primary human monocyte cell lines	None	No	HIV-1	JWH-133, JWH-150, AM630 Δ^9-THC	• CB_2R activation in $CD4^+$ cells inhibit actin reorganization which prevents infection of CXCR4-tropic HIV-1 in $CD4^+$ T cells • ↓ HIV-1 infection of macrophages • ↓ Cell surface receptors CD4, CCR5, and CXCR4 which ↓ viral entry	CB_2R	[237]
	Human	MT-2 cells	None	No	Syncytia formation	CP-55,940, Δ^9-THC, WIN-55,212,2, WIN-552,123	• Cannabimimetic drugs ↑ HIV-1 infection	CB_1R, CB_2R	[172]

Abbreviations: AEA, N-arachidonoylethanolamine; 2-AG, 2-Arachidonoylglycerol; ART, antiretroviral therapy; $[Ca^{2+}]_i$, intracellular calcium concentration; CB_1, cannabinoid type 1 receptor; CB_2, cannabinoid type 2 receptor; CBR, cannabinoid receptor; Δ^9-THC, delta-9-tetrahydrocannabinol; DSE, depolarization-induced suppression of excitation; ECM, extracellular matrix; eCB, endocannabinoid system; EPSC, excitatory postsynaptic currents; FAAH, fatty acid amide hydrolase; GABA, gamma aminobutyric acid; LTR, long terminal repeat; MAGL, monoacylglycerol lipase; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; MKP-1, mitogen-activated protein kinase phosphatase-1; NF-KB, nuclear factor kappa-light-chain-enhancer of activated B cells; NMDAR, N-Methyl-D-aspartic acid receptor; NO, nitric oxide; NPCs, neuronal progenitor cells; mIPSC, miniature inhibitory postsynaptic current; PBMC, peripheral blood mononuclear cells; PEA, palmitoylethanolamide; PFC, prefrontal cortex; sEPSC, spontaneous excitatory postsynaptic current.
Criteria for exclusion from this Table: (1) Studies on cannabinoids and HIV effects not directly related to the central nervous system. (2) Studies on the effects of cannabinoids on other diseases/disease pathogens.

Cannabis use has been reported to lower inflammatory responses in HIV-1 infection from immune cells [33,146,197] and the peripheral nervous system in PWH and animal models [34,160,239], with this section focusing on the effects of cannabinoids on neuroinflammatory processes and its consequence on neuronal health.

Various studies in the context of HIV-1 have demonstrated that the anti-inflammatory effects of cannabinoids in the CNS are related to the specific activation of CB_2R [14,32,53,105] which also has been reviewed previously [183,190]. A preclinical mouse study reported downregulation of astrogliosis and gliogenesis in the hippocampus of GFAP/Gp120 transgenic mice when treated with the CB_2R agonist AM1241 which was further accompanied by improved neurogenesis in the hippocampus [14]. *In vitro* studies demonstrated that cannabinoids, such as Δ^9-THC, CP55,940, and 2-AG, can inhibit the migration of mouse BV-2 microglial-like cells to viral products, such as HIV-1 Tat, which was linked functionally to the CB_2R potentially due to reducing CCR3 levels and altering its intracellular compartmentation [78]. Interestingly, recent studies have shown that CB_2R and chemokine CXCR4 are able to form heterodimers and display negative-crosstalk and cross-antagonism, thus, resulting in decreased CXCR4-mediated cell migration, invasion, and adhesion [168,211].

The downregulation of inflammatory responses derived from microglia by cannabinoids is specifically relevant as chronic activation of brain microglia is a major contributing factor for HIV-1 associated brain disease [159,199]. Using a culture model from human primary microglia, WIN55,212−2 inhibited the migration of gp120-activated microglia, thus suppressing the toxic activity of gp120 on the CNS [105]. Further, CB_2R activation inhibited gp120-induced superoxide production in purified human microglial cells and reduced gp120-induced production of chemokine and cytokine (CCL2, CX3CL1, IL-1β, CXCL10) in the human mesencephalic neuronal/glial cultures [105]. The protective effects of CB_2R activation are further supported in a neuronal/glial hippocampal culture model that reported inhibition of gp120-induced IL-1β production by WIN55,212−2, which subsequently let to reduced loss of synapses and was reversed by a CB_2R antagonist [122].

Cannabinoid-induced attenuation of neuroinflammation has also been demonstrated by upregulating eCB levels via the direct application of 2-AG or AEA or via enzyme inhibitors such as MAGL or FAAH [13,129,245]. The genetic deletion of the FAAH enzyme in GFAP/gp120 transgenic mice, and thus upregulation of AEA, but not 2-AG in whole brain, demonstrated downregulation of astrogliosis as well as enhanced neurogenesis [13]. As FAAH inhibition also upregulates levels of non-eCB-related lipids (i.e. palmitoylethanolamide, PEA; oleoylethanolamide, OEA) additional mechanisms beside AEA might be involved in the anti-inflammatory effects of FAAH inhibition, including PEA and OEA's effects on AEA metabolism by binding to PPAR-α or to TRPV1 [66,88,138]. In a different study the upregulation of 2-AG via the MAGL inhibitor JZL184 reduced gp120-induced prostaglandin E2 and IL-1β production, which prevented synapse loss and was attributed to CB_2R activation [245]. In contrast to AEA, which acts only as a weak partial agonist toward CB_1R and CB_2R, 2-AG has been shown to act as a full agonist toward both receptors, CB_1Rs and CB_2Rs [223].

I sum, the findings suggest that cannabinoids have anti-inflammatory effects with neuroprotective benefits in the context of neuroHIV, potentially via CB_2R activation, but additional mechanisms might be involved. Further, enzyme inhibitors targeting MAGL and FAAH have great therapeutic potential as they allow for selective elevation of eCB signaling, which enables investigation of physiological actions of particular eCBs as well as reveal therapeutic potential of such precise modulation [67,184].

3.4. Neuroprotective effects of cannabinoids via presynaptic mechanisms

Even though the anti-inflammatory properties of cannabinoids appear to be the predominant mechanism for the displayed neuroprotective benefits of cannabinoids in neuroHIV, some studies have demonstrated cannabinoids-regulating effects against HIV-1 protein toxicity directly on neurons via presynaptic mechanisms [100,244].

Direct neuroprotective effects of cannabinoids have been demonstrated in primary prefrontal cortex neuronal cultures that assessed the effects of eCB ligands against HIV-1 Tat toxicity [244]. Findings indicated that the two endogenous cannabinoid ligands 2-AG and AEA significantly decreased Tat-induced intracellular calcium, neuronal excitability, dendritic injury, and neuronal death [244]. The protective effects of both eCBs were attributed to CB_1R synaptic function with CB_1R but not CB_2R protein levels being significantly upregulated [244]. Similarly, a different study demonstrated that enhanced AEA levels via the FAAH enzyme inhibitor PF3845 displayed protective effects against Tat-induced intracellular calcium, dendritic injury, and neuronal death in prefrontal cortex neurons *in vitro* [100]. Importantly, whereas CB_1R played a role for downregulating the immediate effects of Tat on intracellular calcium production, CB_2R appeared to be involved in the more long-term PF3845-induced protective effects on dendritic changes and neuronal survival, potentially due to the 10 % astrocyte contribution in the neuronal culture model [100].

Additional cannabinoid-regulating effects on neuronal function in neuroHIV have been demonstrated on glutamatergic neurotransmission, including spontaneous, miniature, and evoked excitatory postsynaptic currents (sEPSCs, mEPSCs, and eEPSCs, respectively) [112,241,244]. The 2-AG- and AEA-induced downregulation of EPSCs has been shown to be related to a presynaptic CB_1R-related mechanism [241,244] with neuroprotective effects against excitations an neuronal injury [244]. It has been demonstrated that the mechanisms involved in Tat-induced synapse loss include calcium influx via NMDARs [121]. Interestingly, cannabinoid-induced glutamatergic hypofunction has been shown to involve coupling of CB_1Rs with NMDAR NR1 subunit by forming heterodimers [200,207,208]. Note however, whether CB_1R-related signaling is impaired or enhanced during neuroHIV is currently debated [112,241] and needs to be investigated in more detail.

For inhibitory neurotransmission, not much is known about the effect of eCBs on HIV-1/HIV-1 protein-induced alterations. In one study HIV-1 Tat-induced decreases in inhibitory gamma-aminobutyric acid (GABA)ergic neurotransmission in prefrontal cortex mouse brain slices were occluded by cannabinoids, such as WIN55,212−2 and AEA, via a presynaptic CB_1R-related mechanism [243]. Further, a recent study demonstrated normal CB_1R signaling at inhibitory synapses in the presence of Tat [241].

Overall, there is evidence that presynaptic CB_1R-related mechanisms contribute to neuroprotective effects against HIV-1 protein-induced toxicity. Additional studies are necessary to understand the underlying mechanisms involved in eCB's potential ability to attenuate or reverse HIV-1-induced synapse decline and altered neurotransmission on glutamatergic and potentially GABAergic neurons.

4. Conclusion and future directions

Here we have reviewed the specific involvement of the eCB system in HIV-1 disease progression and its potential use as a therapeutic target to decrease HAND pathology. The review shows the specific involvement of CB_2R in neuroHIV due to the inflammatory nature of the disease and indicates to be a promising therapeutic target via its anti-inflammatory effects on the immune and CNS systems, with additional beneficial effects on viral load potentially due to CB_2R and CXCR4 heterodimerization. Further alternative cannabinoid receptors, including GPR55 and GPR18, are worth investigating in more detail to understand their regulating effects on the CNS and how they may contribute to or attenuate HAND pathogenesis.

In contrast, CB_1R involvement in neuroHIV is less clear. Besides the known psychoactive effects via CB_1R, and thus limited therapeutic use, potential protective effects via inhibition of HIV-1-induced excitatory neurotransmission by presynaptic CB_1R mechanisms have been reported but more studies are necessary to assess the role of CB_1R and/or cannabinoids on the inhibitory system in neuroHIV, and whether CB_1R signaling is enhanced or inhibited. Additionally, as viral load and the distribution of the eCB system vary across brain regions, systematic studies are necessary to assess brain-region specific differences.

In turn, the use of eCB degrading enzyme inhibitors as a tool to alter eCB tone in neuroHIV seems a promising future avenue. Enhancing AEA or 2-AG via FAAH or MAGL enzyme inhibitors, respectively, has high therapeutic potential as they are targeting 'on site' produced eCBs and inhibit eCB degradation [67,184]. While there is debate about the safety of FAAH inhibition [68,108] the first-class MAGL inhibitor Abx-1431 [46,64,114] has entered clinical phase 2 for the study of Tourette syndrome or chronic motor tic disorder and indicates positive effects in these patients (www.clinicaltrials.gov). Moreover, the combination of different mechanisms of action to enhance eCB tone has started to receive attraction in other diseases [230] and is worth investigating in more detail in the context of neuroHIV.

Noteworthy, an important point to consider is the interaction of cannabinoids and cART medication. Not a lot of information is currently available but clinical studies are being conducted to investigate their interactive effects [55]. A past study has reported no clinical interaction of cannabinoid with protease inhibitors [1]. If these findings are confirmed in future studies cannabinoid-based treatment will have high therapeutic potential in the context of neuroHIV.

Further, evidence indicates that the eCB system appears to be altered in neuroHIV but more research is necessary to evaluate its impact on the CNS in PWH. Specific factors that should be taken into account are differences in HIV strains/variants, human/genetic variability, pharmacokinetics, and sex, which all could contribute to disease progression and degree of response to cannabinoid treatment. For example, inhibitory crosstalk between HIV-1 coreceptor CXCR4 and CB_2R has been reported to play a potential role in viral suppression, whereas CB_2R cross-regulation of CCR5 is less clear. Further, sex differences have been reported for the eCB system [51,205] as well as for the severity of neurocognitive impairments in HIV-1 [31,143,204], thus indicating the importance of including sex as a biological variable in clinical and preclinical studies. Lastly, when thinking about identifying components of the eCB system as useful biomarkers the use of *in vivo* neuroimaging studies, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), is highly encouraged and would provide very relevant data on eCB-related alteration in neuroHIV as well as cannabinoid treatment opportunities.

Funding

CRediT authorship contribution statement

Barkha J. Yadav-Samudrala: Conceptualization, Writing - original draft, Writing - review & editing. **Sylvia Fitting:** Conceptualization, Writing - original draft, Writing - review & editing, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no competing interests.

References

[1] D.I. Abrams, J.F. Hilton, R.J. Leiser, S.B. Shade, T.A. Elbeik, F.T. Aweeka, N. L. Benowitz, B.M. Bredt, B. Kosel, J.A. Aberg, S.G. Deeks, T.F. Mitchell, K. Mulligan, P. Bacchetti, J.M. McCune, M. Schambelan, Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial, Ann. Intern. Med. 139 (2003) 258–266.

[2] D.I. Abrams, C.A. Jay, S.B. Shade, H. Vizoso, H. Reda, S. Press, M.E. Kelly, M. C. Rowbotham, K.L. Petersen, Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial, Neurology 68 (2007) 515–521.

[3] H. Adle-Biassette, Y. Levy, M. Colombel, F. Poron, S. Natchev, C. Keohane, F. Gray, Neuronal apoptosis in HIV infection in adults, Neuropathol. Appl. Neurobiol. 21 (1995) 218–227.

[4] M. Aghazadeh Tabrizi, P.G. Baraldi, P.A. Borea, K. Varani, Medicinal Chemistry, Pharmacology, and Potential Therapeutic Benefits of Cannabinoid CB_2 Receptor Agonists, Chem. Rev. 116 (2016) 519–560.

[5] K. Ahn, D.S. Johnson, M. Mileni, D. Beidler, J.Z. Long, M.K. McKinney, E. Weerapana, N. Sadagopan, M. Liimatta, S.E. Smith, S. Lazerwith, C. Stiff, S. Kamtekar, K. Bhattacharya, Y. Zhang, S. Swaney, K. Van Becelaere, R. C. Stevens, B.F. Cravatt, Discovery and characterization of a highly selective FAAH inhibitor that reduces inflammatory pain, Chem. Biol. 16 (2009) 411–420.

[6] K. Ahn, M.K. McKinney, B.F. Cravatt, Enzymatic pathways that regulate endocannabinoid signaling in the nervous system, Chem. Rev. 108 (2008) 1687–1707.

[7] O. Almogi-Hazan, R. Or, Cannabis, the endocannabinoid system and immunity-the journey from the bedside to the bench and back, Int. J. Mol. Sci. 21 (2020).

[8] S.F. An, M. Groves, F. Gray, F. Scaravilli, Early entry and widespread cellular involvement of HIV-1 DNA in brains of HIV-1 positive asymptomatic individuals, J. Neuropathol. Exp. Neurol. 58 (1999) 1156–1162.

[9] A. Antinori, G. Arendt, J.T. Becker, B.J. Brew, D.A. Byrd, M. Cherner, D. B. Clifford, P. Cinque, L.G. Epstein, K. Goodkin, M. Gisslen, I. Grant, R.K. Heaton, J. Joseph, K. Marder, C.M. Marra, J.C. McArthur, M. Nunn, R.W. Price, L. Pulliam, K.R. Robertson, N. Sacktor, V. Valcour, V.E. Wojna, Updated research nosology for HIV-associated neurocognitive disorders, Neurology 69 (2007) 1789–1799.

[10] J.C. Ashton, M. Glass, The cannabinoid CB2 receptor as a target for inflammation-dependent neurodegeneration, Curr. Neuropharmacol. 5 (2007) 73–80.

[11] B.K. Atwood, K. Mackie, CB_2: a cannabinoid receptor with an identity crisis, Br. J. Pharmacol. 160 (2010) 467–479.

[12] B. Autran, G. Carcelain, T.S. Li, C. Blanc, D. Mathez, R. Tubiana, C. Katlama, P. Debre, J. Leibowitch, Positive effects of combined antiretroviral therapy on $CD4^+$ T cell homeostasis and function in advanced HIV disease, Science 277 (1997) 112–116.

[13] H.K. Avraham, S. Jiang, Y. Fu, E. Rockenstein, A. Makriyannis, J. Wood, L. Wang, E. Masliah, S. Avraham, Impaired neurogenesis by HIV-1-Gp120 is rescued by genetic deletion of fatty acid amide hydrolase enzyme, Br. J. Pharmacol. 172 (2015) 4603–4614.

[14] H.K. Avraham, S. Jiang, Y. Fu, E. Rockenstein, A. Makriyannis, A. Zvonok, E. Masliah, S. Avraham, The cannabinoid CB_2 receptor agonist AM1241 enhances neurogenesis in GFAP/Gp120 transgenic mice displaying deficits in neurogenesis, Br. J. Pharmacol. 171 (2014) 468–479.

[15] S. Basu, B.N. Dittel, Unraveling the complexities of cannabinoid receptor 2 (CB_2) immune regulation in health and disease, Immunol. Res. 51 (2011) 26–38.

[16] J.E. Beal, R. Olson, L. Laubenstein, J.O. Morales, P. Bellman, B. Yangco, L. Lefkowitz, T.F. Plasse, K.V. Shepard, Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS, J. Pain Symptom Manage. 10 (1995) 89–97.

[17] J.E. Beal, R. Olson, L. Lefkowitz, L. Laubenstein, P. Bellman, B. Yangco, J. O. Morales, R. Murphy, W. Powderly, T.F. Plasse, K.W. Mosdell, K.V. Shepard, Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia, J. Pain Symptom Manage. 14 (1997) 7–14.

[18] G. Bedi, R.W. Foltin, E.W. Gunderson, J. Rabkin, C.L. Hart, S.D. Comer, S. K. Vosburg, M. Haney, Efficacy and tolerability of high-dose dronabinol maintenance in HIV-positive marijuana smokers: a controlled laboratory study, Psychopharmacology (Berl.) 212 (2010) 675–686.

[19] C. Beji, H. Loucif, R. Telittchenko, D. Olagnier, X. Dagenais-Lussier, J. van Grevenynghe, Cannabinoid-induced immunomodulation during viral infections: a focus on mitochondria, Viruses 12 (2020).

[20] L. Belle-Isle, A. Hathaway, Barriers to access to medical cannabis for Canadians living with HIV/AIDS, AIDS Care 19 (2007) 500–506.

[21] C. Benito, W.K. Kim, I. Chavarria, C.J. Hillard, K. Mackie, R.M. Tolon, K. Williams, J. Romero, A glial endogenous cannabinoid system is upregulated in the brains of macaques with simian immunodeficiency virus-induced encephalitis, J. Neurosci. 25 (2005) 2530–2536.

[22] C. Benito, E. Nunez, R.M. Tolon, E.J. Carrier, A. Rabano, C.J. Hillard, J. Romero, Cannabinoid CB_2 receptors and fatty acid amide hydrolase are selectively overexpressed in neuritic plaque-associated glia in Alzheimer's disease brains, J. Neurosci. 23 (2003) 11136–11141.

[23] C. Benito, R.M. Tolon, M.R. Pazos, E. Nunez, A.I. Castillo, J. Romero, Cannabinoid CB_2 receptors in human brain inflammation, Br. J. Pharmacol. 153 (2008) 277–285.

[24] L. Bertrand, M. Nair, M. Toborek, Solving the blood-brain barrier challenge for the effective treatment of HIV replication in the central nervous system, Curr. Pharm. Des. 22 (2016) 5477–5486.

[25] E.G. Bing, M.A. Burnam, D. Longshore, J.A. Fleishman, C.D. Sherbourne, A. S. London, B.J. Turner, F. Eggan, R. Beckman, B. Vitiello, S.C. Morton, M. Orlando, S.A. Bozzette, L. Ortiz-Barron, M. Shapiro, Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States, Arch. Gen. Psychiatry 58 (2001) 721–728.

[26] M.O. Bonn-Miller, M.L. Oser, M.M. Bucossi, J.A. Trafton, Cannabis use and HIV antiretroviral therapy adherence and HIV-related symptoms, J. Behav. Med. 37 (2014) 1–10.

[27] L. Booker, S.G. Kinsey, R.A. Abdullah, J.L. Blankman, J.Z. Long, C. Ezzili, D. L. Boger, B.F. Cravatt, A.H. Lichtman, The fatty acid amide hydrolase (FAAH) inhibitor PF-3845 acts in the nervous system to reverse LPS-induced tactile allodynia in mice, Br. J. Pharmacol. 165 (2012) 2485–2496.

[28] R. Brack-Werner, Astrocytes: HIV cellular reservoirs and important participants in neuropathogenesis, AIDS 13 (1999) 1–22.

[29] B.M. Bredt, D. Higuera-Alhino, S.B. Shade, S.J. Hebert, J.M. McCune, D. I. Abrams, Short-term effects of cannabinoids on immune phenotype and function in HIV-1-infected patients, J. Clin. Pharmacol. 42 (2002) 82S–89S.

[30] N.E. Buckley, The peripheral cannabinoid receptor knockout mice: an update, Br. J. Pharmacol. 153 (2008) 309–318.

[31] R. Burlacu, A. Umlauf, A. Luca, S. Gianella, R. Radoi, S.M. Ruta, T.D. Marcotte, L. Ene, C.L. Achim, Sex-based differences in neurocognitive functioning in HIV-infected young adults, AIDS 32 (2018) 217–225.

[32] G.A. Cabral, L. Griffin-Thomas, Emerging role of the cannabinoid receptor CB_2 in immune regulation: therapeutic prospects for neuroinflammation, Expert Rev. Mol. Med. 11 (2009) e3.

[33] F.O.F. Castro, J.M. Silva, G.P. Dorneles, J.B.S. Barros, C.B. Ribeiro, I. Noronha, G. R. Barbosa, L.C.S. Souza, A.O. Guilarde, A. Pereira, R.F. Guimaraes, T.F. Oliveira, S.E.F. Oliveira, A. Peres, P.R.T. Romao, I.A.H. Pfrimer, S.G.D. Fonseca, Distinct inflammatory profiles in HIV-infected individuals under antiretroviral therapy using cannabis, cocaine or cannabis plus cocaine, AIDS 33 (2019) 1831–1842.

[34] L.C. Chandra, V. Kumar, W. Torben, C. Vande Stouwe, P. Winsauer, A. Amedee, P. E. Molina, M. Mohan, Chronic administration of Δ^9-tetrahydrocannabinol induces intestinal anti-inflammatory microRNA expression during acute simian immunodeficiency virus infection of rhesus macaques, J. Virol. 89 (2015) 1168–1181.

[35] L. Chang, C. Cloak, R. Yakupov, T. Ernst, Combined and independent effects of chronic marijuana use and HIV on brain metabolites, J. Neuroimmune Pharmacol. 1 (2006) 65–76.

[36] C. Chao, L.P. Jacobson, D. Tashkin, O. Martinez-Maza, M.D. Roth, J.B. Margolick, J.S. Chmiel, C. Rinaldo, Z.F. Zhang, R. Detels, Recreational drug use and T lymphocyte subpopulations in HIV-uninfected and HIV-infected men, Drug Alcohol Depend. 94 (2008) 165–171.

[37] N.C. Chen, A.T. Partridge, C. Sell, C. Torres, J. Martin-Garcia, Fate of microglia during HIV-1 infection: From activation to senescence? Glia 65 (2017) 431–446.

[38] P. Chen, M. Mayne, C. Power, A. Nath, The Tat protein of HIV-1 induces tumor necrosis factor-α production. Implications for HIV-1-associated neurological diseases, J. Biol. Chem. 272 (1997) 22385–22388.

[39] W. Chen, R.B. Crawford, B.L. Kaplan, N.E. Kaminski, Modulation of HIV_{GP120} antigen-specific immune responses in vivo by Δ^9-Tetrahydrocannabinol, J. Neuroimmune Pharmacol. 10 (2015) 344–355.

[40] W. Chen, B.L. Kaplan, S.T. Pike, L.A. Topper, N.R. Lichorobiec, S.O. Simmons, R. Ramabhadran, N.E. Kaminski, Magnitude of stimulation dictates the cannabinoid-mediated differential T cell response to HIVgp120, J. Leukoc. Biol. 92 (2012) 1093–1102.

[41] X. Chen, J. Zhang, C. Chen, Endocannabinoid 2-arachidonoylglycerol protects neurons against beta-amyloid insults, Neuroscience 178 (2011) 159–168.

[42] V. Chevaleyre, K.A. Takahashi, P.E. Castillo, Endocannabinoid-mediated synaptic plasticity in the CNS, Annu. Rev. Neurosci. 29 (2006) 37–76.

[43] A. Chiarlone, L. Bellocchio, C. Blazquez, E. Resel, E. Soria-Gomez, A. Cannich, J. J. Ferrero, O. Sagredo, C. Benito, J. Romero, J. Sanchez-Prieto, B. Lutz, J. Fernandez-Ruiz, I. Galve-Roperh, M. Guzman, A restricted population of CB_1 cannabinoid receptors with neuroprotective activity, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 8257–8262.

[44] M.J. Churchill, S.L. Wesselingh, D. Cowley, C.A. Pardo, J.C. McArthur, B.J. Brew, P.R. Gorry, Extensive astrocyte infection is prominent in human immunodeficiency virus-associated dementia, Ann. Neurol. 66 (2009) 253–258.

[45] T.J. Cirino, S.W. Harden, J.P. McLaughlin, C.J. Frazier, Region-specific effects of HIV-1 Tat on intrinsic electrophysiological properties of pyramidal neurons in mouse prefrontal cortex and hippocampus, J. Neurophysiol. 123 (2020) 1332–1341.

[46] J.S. Cisar, O.D. Weber, J.R. Clapper, J.L. Blankman, C.L. Henry, G.M. Simon, J. P. Alexander, T.K. Jones, R.A.B. Ezekowitz, G.P. O'Neill, C.A. Grice, Identification of ABX-1431, a selective inhibitor of monoacylglycerol lipase and clinical candidate for treatment of neurological disorders, J. Med. Chem. 61 (2018) 9062–9084.

[47] D.B. Clifford, B.M. Ances, HIV-associated neurocognitive disorder, the lancet, Infect. Dis. 13 (2013) 976–986.

[48] R.M. Concannon, E. Dowd, Central CB2 receptors in inflammation-driven neurodegeneration: dysregulation and therapeutic potential, Neural Regen. Res. 11 (2016) 1409–1410.

[49] R.M. Concannon, B.N. Okine, D.P. Finn, E. Dowd, Upregulation of the cannabinoid CB_2 receptor in environmental and viral inflammation-driven rat models of Parkinson's disease, Exp. Neurol. 283 (2016) 204–212.

[50] L. Console-Bram, E. Brailoiu, G.C. Brailoiu, H. Sharir, M.E. Abood, Activation of GPR18 by cannabinoid compounds: a tale of biased agonism, Br. J. Pharmacol. 171 (2014) 3908–3917.

[51] Z.D. Cooper, R.M. Craft, Sex-dependent effects of cannabis and cannabinoids: a translational perspective, Neuropsychopharmacology 43 (2018) 34–51.

[52] M.A. Cosenza-Nashat, A. Bauman, M.L. Zhao, S. Morgello, H.S. Suh, S.C. Lee, Cannabinoid receptor expression in HIV encephalitis and HIV-associated neuropathologic comorbidities, Neuropathol. Appl. Neurobiol. 37 (2011) 464–483.

[53] C.M. Costantino, A. Gupta, A.W. Yewdall, B.M. Dale, L.A. Devi, B.K. Chen, Cannabinoid receptor 2-mediated attenuation of CXCR4-tropic HIV infection in primary CD4+ T cells, PLoS One 7 (2012), e33961.

[54] C.T. Costiniuk, M.A. Jenabian, Cannabinoids and inflammation: implications for people living with HIV, AIDS 33 (2019) 2273–2288.

[55] C.T. Costiniuk, Z. Saneei, J.P. Routy, S. Margolese, E. Mandarino, J. Singer, B. Lebouche, J. Cox, J. Szabo, M.J. Brouillette, M.B. Klein, N. Chomont, M. A. Jenabian, Oral cannabinoids in people living with HIV on effective antiretroviral therapy: CTN PT028-study protocol for a pilot randomised trial to assess safety, tolerability and effect on immune activation, BMJ Open 9 (2019), e024793.

[56] B.F. Cravatt, D.K. Giang, S.P. Mayfield, D.L. Boger, R.A. Lerner, N.B. Gilula, Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides, Nature 384 (1996) 83–87.

[57] R.D.C. Crean, N. A, B.J. Mason, An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions, J. Addict. Med. 5 (2011) 1–8.

[58] S.A. Cristiani, N.D. Pukay-Martin, R.A. Bornstein, Marijuana use and cognitive function in HIV-infected people, J. Neuropsychiatry Clin. Neurosci. 16 (2004) 330–335.

[59] J.L. Croxford, T. Yamamura, Cannabinoids and the immune system: potential for the treatment of inflammatory diseases? J. Neuroimmunol. 166 (2005) 3–18.

[60] L.A. Cysique, P. Maruff, B.J. Brew, Prevalence and pattern of neuropsychological impairment in human immunodeficiency virus-infected/acquired immunodeficiency syndrome (HIV/AIDS) patients across pre- and post-highly active antiretroviral therapy eras: a combined study of two cohorts, J. Neurovirol. 10 (2004) 350–357.

[61] G. D'Souza, P.A. Matson, C.D. Grady, S. Nahvi, D. Merenstein, K.M. Weber, R. Greenblatt, P. Burian, T.E. Wilson, Medicinal and recreational marijuana use

among HIV-infected women in the Women's Interagency HIV Study (WIHS) cohort, 1994-2010, J. Acquir. Immune Defic. Syndr. 61 (2012) 618–626.

[62] B.C. de Jong, D. Prentiss, W. McFarland, R. Machekano, D.M. Israelski, Marijuana use and its association with adherence to antiretroviral therapy among HIV-infected persons with moderate to severe nausea, J. Acquir. Immune Defic. Syndr. 38 (2005) 43–46.

[63] E. DeJesus, B.M. Rodwick, D. Bowers, C.J. Cohen, D. Pearce, Use of dronabinol improves appetite and reverses weight loss in HIV/AIDS-infected patients, J. Int. Assoc. Physicians AIDS Care Chic. (Chic) 6 (2007) 95–100.

[64] H. Deng, W. Li, Monoacylglycerol lipase inhibitors: modulators for lipid metabolism in cancer malignancy, neurological and metabolic disorders, Acta Pharm. Sin. B 10 (2020) 582–602.

[65] V. Di Marzo, Targeting the endocannabinoid system: to enhance or reduce? Nat. Rev. Drug Discov. 7 (2008) 438–455.

[66] V. Di Marzo, T. Bisogno, L. De Petrocellis, D. Melck, B.R. Martin, Cannabimimetic fatty acid derivatives: the anandamide family and other endocannabinoids, Curr. Med. Chem. 6 (1999) 721–744.

[67] V. Di Marzo, N. Stella, A. Zimmer, Endocannabinoid signalling and the deteriorating brain, Nat. Rev. Neurosci. 16 (2015) 30–42.

[68] S. Dider, J. Ji, Z. Zhao, L. Xie, Molecular mechanisms involved in the side effects of fatty acid amide hydrolase inhibitors: a structural phenomics approach to proteome-wide cellular off-target deconvolution and disease association, NPJ Syst. Biol. Appl. 2 (2016) 16023.

[69] G.J. Dore, P.K. Correll, Y. Li, J.M. Kaldor, D.A. Cooper, B.J. Brew, Changes to AIDS dementia complex in the era of highly active antiretroviral therapy, AIDS 13 (1999) 1249–1253.

[70] N. El-Hage, A.J. Bruce-Keller, T. Yakovleva, I. Bazov, G. Bakalkin, P.E. Knapp, K. F. Hauser, Morphine exacerbates HIV-1 Tat-induced cytokine production in astrocytes through convergent effects on $[Ca^{2+}]_i$, NF-κB trafficking and transcription, PLoS One 3 (2008) e4093.

[71] N. El-Hage, M. Rodriguez, S.M. Dever, R.R. Masvekar, D.A. Gewirtz, J.J. Shacka, HIV-1 and morphine regulation of autophagy in microglia: limited interactions in the context of HIV-1 infection and opioid abuse, J. Virol. 89 (2015) 1024–1035.

[72] R. Ellis, D. Langford, E. Masliah, HIV and antiretroviral therapy in the brain: neuronal injury and repair, Nat. Rev. Neurosci. 8 (2007) 33–44.

[73] R.J. Ellis, W. Toperoff, F. Vaida, G. van den Brande, J. Gonzales, B. Gouaux, H. Bentley, J.H. Atkinson, Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial, Neuropsychopharmacology 34 (2009) 672–680.

[74] G. Esposito, A. Ligresti, A.A. Izzo, T. Bisogno, M. Ruvo, M. Di Rosa, V. Di Marzo, T. Iuvone, The endocannabinoid system protects rat glioma cells against HIV-1 Tat protein-induced cytotoxicity. Mechanism and regulation, J. Biol. Chem. 277 (2002) 50348–50354.

[75] T. Fischer-Smith, S. Croul, A.E. Sverstiuk, C. Capini, D. L'Heureux, E.G. Regulier, M.W. Richardson, S. Amini, S. Morgello, K. Khalili, J. Rappaport, CNS invasion by CD14+/CD16+ peripheral blood-derived monocytes in HIV dementia: perivascular accumulation and reservoir of HIV infection, J. Neurovirol. 7 (2001) 528–541.

[76] S. Fitting, P.E. Knapp, S. Zou, W.D. Marks, M.S. Bowers, H.I. Akbarali, K. F. Hauser, Interactive HIV-1 Tat and morphine-induced synaptodendritic injury is triggered through focal disruptions in Na$^+$ influx, mitochondrial instability, and Ca^{2+} overload, J. Neurosci. 34 (2014) 12850–12864.

[77] G. Fontana, L. Valenti, M. Raiteri, Gp120 can revert antagonism at the glycine site of NMDA receptors mediating GABA release from cultured hippocampal neurons, J. Neurosci. Res. 49 (1997) 732–738.

[78] D. Fraga, E.S. Raborn, G.A. Ferreira, G.A. Cabral, Cannabinoids inhibit migration of microglial-like cells to the HIV protein Tat, J. Neuroimmune Pharmacol. 6 (2011) 566–577.

[79] Y. Fukudome, T. Ohno-Shosaku, M. Matsui, Y. Omori, M. Fukaya, H. Tsubokawa, M.M. Taketo, M. Watanabe, T. Manabe, M. Kano, Two distinct classes of muscarinic action on hippocampal inhibitory synapses: M$_2$-mediated direct suppression and M$_1$/M$_3$-mediated indirect suppression through endocannabinoid signalling, Eur. J. Neurosci. 19 (2004) 2682–2692.

[80] P. Gannon, M.Z. Khan, D.L. Kolson, Current understanding of HIV-associated neurocognitive disorders pathogenesis, Curr. Opin. Neurol. 24 (2011) 275–283.

[81] S. Gartner, HIV infection and dementia, Science 287 (2000) 602–604.

[82] L.J. Garvey, D. Yerrakalva, A. Winston, Correlations between computerized battery testing and a memory questionnaire for identification of neurocognitive impairment in HIV type 1-infected subjects on stable antiretroviral therapy, AIDS Res. Hum. Retroviruses 25 (2009) 765–769.

[83] J. Ghosn, M. Leruez-Ville, J. Blanche, A. Delobelle, C. Beaudoux, L. Mascard, H. Lecuyer, A. Canestri, R. Landman, D. Zucman, D. Ponscarme, A. Rami, J. P. Viard, B. Spire, C. Rouzioux, D. Costagliola, M. Suzan-Monti, A.E.P.S. G. Evarist, HIV-1 DNA levels in peripheral blood mononuclear cells and cannabis use are associated with intermittent HIV shedding in semen of men who have sex with men on successful antiretroviral regimens, Clin. Infect. Dis. 58 (2014) 1763–1770.

[84] J.D. Glass, H. Fedor, S.L. Wesselingh, J.C. McArthur, Immunocytochemical quantitation of human immunodeficiency virus in the brain: correlations with dementia, Ann. Neurol. 38 (1995) 755–762.

[85] S. Gorantla, E. Makarov, D. Roy, J. Finke-Dwyer, L.C. Murrin, H.E. Gendelman, L. Poluektova, Immunoregulation of a CB2 receptor agonist in a murine model of neuroAIDS, J. Neuroimmune Pharmacol. 5 (2010) 456–468.

[86] R. Gorter, M. Seefried, P. Volberding, Dronabinol effects on weight in patients with HIV infection, AIDS 6 (1992) 127.

[87] I. Grant, R. Gonzalez, C.L. Carey, L. Natarajan, T. Wolfson, Non-acute (residual) neurocognitive effects of cannabis use: a meta-analytic study, J. Int. Neuropsychol. Soc. 9 (2003) 679–689.

[88] M. Guzman, J. Lo Verme, J. Fu, F. Oveisi, C. Blazquez, D. Piomelli, Oleoylethanolamide stimulates lipolysis by activating the nuclear receptor peroxisome proliferator-activated receptor α (PPAR-α), J. Biol. Chem. 279 (2004) 27849–27854.

[89] M. Haney, E.W. Gunderson, J. Rabkin, C.L. Hart, S.K. Vosburg, S.D. Comer, R. W. Foltin, Dronabinol and marijuana in HIV-positive marijuana smokers. Caloric intake, mood, and sleep, J. Acquir. Immune Defic. Syndr. 45 (2007) 545–554.

[90] M. Haney, J. Rabkin, E. Gunderson, R.W. Foltin, Dronabinol and marijuana in HIV+ marijuana smokers: acute effects on caloric intake and mood, Psychopharmacology (Berl.) 181 (2005) 170–178.

[91] D.J. Hardy, D.E. Vance, The neuropsychology of HIV/AIDS in older adults, Neuropsychol. Rev. 19 (2009) 263–272.

[92] J. Harezlak, S. Buchthal, M. Taylor, G. Schifitto, J. Zhong, E. Daar, J. Alger, E. Singer, T. Campbell, C. Yiannoutsos, R. Cohen, B. Navia, H.I.V.N. Consortium, Persistence of HIV-associated cognitive impairment, inflammation, and neuronal injury in era of highly active antiretroviral treatment, AIDS 25 (2011) 625–633.

[93] T. Harkany, K. Mackie, P. Doherty, Wiring and firing neuronal networks: endocannabinoids take center stage, Curr. Opin. Neurobiol. 18 (2008) 338–345.

[94] N.J. Haughey, C.P. Holden, A. Nath, J.D. Geiger, Involvement of inositol 1,4,5-trisphosphate-regulated stores of intracellular calcium in calcium dysregulation and neuron cell death caused by HIV-1 protein Tat, J. Neurochem. 73 (1999) 1363–1374.

[95] J. He, Y. Chen, M. Farzan, H. Choe, A. Ohagen, S. Gartner, J. Busciglio, X. Yang, W. Hofmann, W. Newman, C.R. Mackay, J. Sodroski, D. Gabuzda, CCR3 and CCR5 are co-receptors for HIV-1 infection of microglia, Nature 385 (1997) 645–649.

[96] R.K. Heaton, D.R. Franklin, R.J. Ellis, J.A. McCutchan, S.L. Letendre, S. Leblanc, S.H. Corkran, N.A. Duarte, D.B. Clifford, S.P. Woods, A.C. Collier, C.M. Marra, S. Morgello, M.R. Mindt, M.J. Taylor, T.D. Marcotte, J.H. Atkinson, T. Wolfson, B. B. Gelman, J.C. McArthur, D.M. Simpson, I. Abramson, A. Gamst, C. Fennema-Notestine, T.L. Jernigan, J. Wong, I. Grant, HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors, J. Neurovirol. 17 (2011) 3–16.

[97] L.J. Henderson, T.P. Johnson, B.R. Smith, L.B. Reoma, U.A. Santamaria, M. Bachani, C. Demarino, R.A. Barclay, J. Snow, N. Sacktor, J. McArthur, S. Letendre, J. Steiner, F. Kashanchi, A. Nath, Presence of Tat and transactivation response element in spinal fluid despite antiretroviral therapy, AIDS 33 (Suppl 2) (2019) S145–S157.

[98] J.E. Henriquez, M.D. Rizzo, R.B. Crawford, P. Gulick, N.E. Kaminski, Interferon-α-Mediated activation of T cells from healthy and HIV-Infected individuals is suppressed by Δ^9-Tetrahydrocannabinol, J. Pharmacol. Exp. Ther. 367 (2018) 49–58.

[99] J.E. Henriquez, M.D. Rizzo, M.A. Schulz, R.B. Crawford, P. Gulick, N.E. Kaminski, Δ^9-tetrahydrocannabinol suppresses secretion of IFNα by plasmacytoid dendritic cells from healthy and HIV-Infected individuals, J. Acquir. Immune Defic. Syndr. 75 (2017) 588–596.

[100] D.J. Hermes, C. Xu, J.L. Poklis, M.J. Niphakis, B.F. Cravatt, K. Mackie, A. H. Lichtman, B.M. Ignatowska-Jankowska, S. Fitting, Neuroprotective effects of fatty acid amide hydrolase catabolic enzyme inhibition in a HIV-1 Tat model of neuroAIDS, Neuropharmacology 141 (2018) 55–65.

[101] J. Hesselgesser, M. Halks-Miller, V. DelVecchio, S.C. Peiper, J. Hoxie, D.L. Kolson, D. Taub, R. Horuk, CD4-independent association between HIV-1 gp120 and CXCR4: functional chemokine receptors are expressed in human neurons, Curr. Biol. 7 (1997) 112–121.

[102] A. Higgins, S. Yuan, Y. Wang, B.D. Burrell, Differential modulation of nociceptive versus non-nociceptive synapses by endocannabinoids, Mol. Pain 9 (2013) 26.

[103] J.B. Honeycutt, A. Wahl, C. Baker, R.A. Spagnuolo, J. Foster, O. Zakharova, S. Wietgrefe, C. Caro-Vegas, V. Madden, G. Sharpe, A.T. Haase, J.J. Eron, J. V. Garcia, Macrophages sustain HIV replication in vivo independently of T cells, J. Clin. Invest. 126 (2016) 1353–1366.

[104] S. Hong, W.A. Banks, Role of the immune system in HIV-associated neuroinflammation and neurocognitive implications, Brain Behav. Immun. 45 (2015) 1–12.

[105] S. Hu, W.S. Sheng, R.B. Rock, CB$_2$ receptor agonists protect human dopaminergic neurons against damage from HIV-1 gp120, PLoS One 8 (2013), e77577.

[106] S. Hu, W.S. Sheng, R.B. Rock, Immunomodulatory properties of kappa opioids and synthetic cannabinoids in HIV-1 neuropathogenesis, J. Neuroimmune Pharmacol. 6 (2011) 528–539.

[107] C.C. Huang, S.W. Lo, K.S. Hsu, Presynaptic mechanisms underlying cannabinoid inhibition of excitatory synaptic transmission in rat striatal neurons, J. Physiol. (Paris) 532 (2001) 731–748.

[108] J.P. Huggins, T.S. Smart, S. Langman, L. Taylor, T. Young, An efficient randomised, placebo-controlled clinical trial with the irreversible fatty acid amide hydrolase-1 inhibitor PF-04457845, which modulates endocannabinoids but fails to induce effective analgesia in patients with pain due to osteoarthritis of the knee, Pain 153 (2012) 1837–1846.

[109] C.C. Hunault, T.T. Mensinga, K.B. Bocker, C.M. Schipper, M. Kruidenier, M. E. Leenders, I. de Vries, J. Meulenbelt, Cognitive and psychomotor effects in males after smoking a combination of tobacco and cannabis containing up to 69 mg delta-9-tetrahydrocannabinol (THC), Psychopharmacology (Berl.) 204 (2009) 85–94.

[110] B. Ignatowska-Jankowska, J.L. Wilkerson, M. Mustafa, R. Abdullah, M. Niphakis, J.L. Wiley, B.F. Cravatt, A.H. Lichtman, Selective monoacylglycerol lipase

inhibitors: antinociceptive versus cannabimimetic effects in mice, J. Pharmacol. Exp. Ther. 353 (2015) 424–432.

[111] B.M. Ignatowska-Jankowska, S. Ghosh, M.S. Crowe, S.G. Kinsey, M.J. Niphakis, R. A. Abdullah, Q. Tao, O.N. ST, D.M. Walentiny, J.L. Wiley, B.F. Cravatt, A. H. Lichtman, In vivo characterization of the highly selective monoacylglycerol lipase inhibitor KML29: antinociceptive activity without cannabimimetic side effects, Br. J. Pharmacol. 171 (2014) 1392–1407.

[112] I.R. Jacobs, C. Xu, D.J. Hermes, A.F. League, C. Xu, B. Nath, W. Jiang, M. J. Niphakis, B.F. Cravatt, K. Mackie, S. Mukhopadhyay, A.H. Lichtman, B. M. Ignatowska-Jankowska, S. Fitting, Inhibitory control deficits associated with upregulation of CB$_1$R in the HIV-1 Tat transgenic mouse model of hand, J. Neuroimmune Pharmacol. 14 (2019) 661–678.

[113] H. Javed, S. Azimullah, M.E. Haque, S.K. Ojha, Cannabinoid type 2 (CB$_2$) receptors activation protects against oxidative stress and neuroinflammation associated dopaminergic neurodegeneration in rotenone model of parkinson's disease, Front. Neurosci. 10 (2016) 321.

[114] M. Jiang, M. van der Stelt, Activity-based protein profiling delivers selective drug candidate ABX-1431, a monoacylglycerol lipase inhibitor, to control lipid metabolism in neurological disorders, J. Med. Chem. 61 (2018) 9059–9061.

[115] T.P. Johnson, K. Patel, K.R. Johnson, D. Maric, P.A. Calabresi, R. Hasbun, A. Nath, Induction of IL-17 and nonclassical T-cell activation by HIV-Tat protein, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 13588–13593.

[116] S.B. Joseph, K.T. Arrildt, C.B. Sturdevant, R. Swanstrom, HIV-1 target cells in the CNS, J. Neurovirol. 21 (2015) 276–289.

[117] M. Kano, Control of synaptic function by endocannabinoid-mediated retrograde signaling, Proc. Jpn. Acad., Ser. B, Phys. Biol. Sci. 90 (2014) 235–250.

[118] M. Kaul, G.A. Garden, S.A. Lipton, Pathways to neuronal injury and apoptosis in HIV-associated dementia, Nature 410 (2001) 988–994.

[119] M. Kaul, Q. Ma, K.E. Medders, M.K. Desai, S.A. Lipton, HIV-1 coreceptors CCR5 and CXCR4 both mediate neuronal cell death but CCR5 paradoxically can also contribute to protection, Cell Death Differ. 14 (2007) 296–305.

[120] L. Keen 2nd, A. Abbate, G. Blanden, C. Priddie, F.G. Moeller, M. Rathore, Confirmed marijuana use and lymphocyte count in black people living with HIV, Drug Alcohol Depend. 198 (2019) 112–115.

[121] H.J. Kim, K.A. Martemyanov, S.A. Thayer, Human immunodeficiency virus protein Tat induces synapse loss via a reversible process that is distinct from cell death, J. Neurosci. 28 (2008) 12604–12613.

[122] H.J. Kim, A.H. Shin, S.A. Thayer, Activation of cannabinoid type 2 receptors inhibits HIV-1 envelope glycoprotein gp120-induced synapse loss, Mol. Pharmacol. 80 (2011) 357–366.

[123] S. Kim, Y.K. Hahn, E.M. Podhaizer, V.D. McLane, S. Zou, K.F. Hauser, P.E. Knapp, A central role for glial CCR5 in directing the neuropathological interactions of HIV-1 Tat and opiates, J. Neuroinflammation 15 (2018) 285.

[124] S.G. Kinsey, L.E. Wise, D. Ramesh, R. Abdullah, D.E. Selley, B.F. Cravatt, A. H. Lichtman, Repeated low-dose administration of the monoacylglycerol lipase inhibitor JZL184 retains cannabinoid receptor type 1-mediated antinociceptive and gastroprotective effects, J. Pharmacol. Exp. Ther. 345 (2013) 492–501.

[125] A.M. Kipp, P.F. Rebeiro, B.E. Shepherd, L. Brinkley-Rubinstein, M. Turner, S. Bebawy, T.R. Sterling, T. Hulgan, Daily marijuana use is associated with missed clinic appointments among HIV-infected persons engaged in HIV care, AIDS Behav. 21 (2017) 1996–2004.

[126] T.W. Klein, Cannabinoid-based drugs as anti-inflammatory therapeutics, Nat. Rev. Immunol. 5 (2005) 400–411.

[127] S. Kramer-Hammerle, I. Rothenaigner, H. Wolff, J.E. Bell, R. Brack-Werner, Cells of the central nervous system as targets and reservoirs of the human immunodeficiency virus, Virus Res. 111 (2005) 194–213.

[128] G. Krishnan, N. Chatterjee, Differential immune mechanism to HIV-1 Tat variants and its regulation by AEA [corrected], Sci. Rep. 5 (2015) 9887.

[129] G. Krishnan, N. Chatterjee, Endocannabinoids affect innate immunity of Muller glia during HIV-1 Tat cytotoxicity, Mol. Cell. Neurosci. 59 (2014) 10–23.

[130] O. Kutsch, J. Oh, A. Nath, E.N. Benveniste, Induction of the chemokines interleukin-8 and IP-10 by human immunodeficiency virus type 1 Tat in astrocytes, J. Virol. 74 (2000) 9214–9221.

[131] J.H. Lane, V.G. Sasseville, M.O. Smith, P. Vogel, D.R. Pauley, M.P. Heyes, A. A. Lackner, Neuroinvasion by simian immunodeficiency virus coincides with increased numbers of perivascular macrophages/microglia and intrathecal immune activation, J. Neurovirol. 2 (1996) 423–432.

[132] N.J. LeCapitaine, P. Zhang, P. Winsauer, E. Walker, C. Vande Stouwe, C. Porretta, P.E. Molina, Chronic Δ-9-tetrahydrocannabinol administration increases lymphocyte CXCR4 expression in rhesus macaques, J. Neuroimmune Pharmacol. 6 (2011) 540–545.

[133] J.T. Lee, L.A. Saag, A.M. Kipp, J. Logan, B.E. Shepherd, J.R. Koethe, M. Turner, S. Bebawy, T.R. Sterling, T. Hulgan, Self-reported Cannabis use and changes in body mass index, CD4 T-Cell counts, and HIV-1 RNA suppression in treated persons with HIV, AIDS Behav. 24 (2020) 1275–1280.

[134] W. Li, L.J. Henderson, E.O. Major, L. Al-Harthi, IFN-γ mediates enhancement of HIV replication in astrocytes by inducing an antagonist of the β-catenin pathway (DKK1) in a STAT 3-dependent manner, J. Immunol. 186 (2011) 6771–6778.

[135] A.H. Lichtman, J.L. Blankman, B.F. Cravatt, Endocannabinoid overload, Mol. Pharmacol. 78 (2010) 993–995.

[136] S.A. Lipton, Human immunodeficiency virus-infected macrophages, gp120, and *N*-methyl-*D*-aspartate receptor-mediated neurotoxicity, Ann. Neurol. 33 (1993) 227–228.

[137] Y. Liu, M. Jones, C.M. Hingtgen, G. Bu, N. Laribee, R.E. Tanzi, R.D. Moir, A. Nath, J.J. He, Uptake of HIV-1 Tat protein mediated by low-density lipoprotein

receptor-related protein disrupts the neuronal metabolic balance of the receptor ligands, Nat. Med. 6 (2000) 1380–1387.

[138] J. Lo Verme, J. Fu, G. Astarita, G. La Rana, R. Russo, A. Calignano, D. Piomelli, The nuclear receptor peroxisome proliferator-activated receptor-α mediates the anti-inflammatory actions of palmitoylethanolamide, Mol. Pharmacol. 67 (2005) 15–19.

[139] F. Longordo, M. Feligioni, G. Chiaramonte, P.F. Sbaffi, M. Raiteri, A. Pittaluga, The human immunodeficiency virus-1 protein transactivator of transcription up-regulates *N*-methyl-D-aspartate receptor function by acting at metabotropic glutamate receptor 1 receptors coexisting on human and rat brain noradrenergic neurones, J. Pharmacol. Exp. Ther. 317 (2006) 1097–1105.

[140] T.S. Lu, H.K. Avraham, S. Seng, S.D. Tachado, H. Koziel, A. Makriyannis, S. Avraham, Cannabinoids inhibit HIV-1 Gp120-mediated insults in brain microvascular endothelial cells, J. Immunol. 181 (2008) 6406–6416.

[141] G.M. Lucas, M.L. Griswold, K.A. Gebo, J. Keruly, R.E. Chaisson, R.D. Moore, Illicit drug use and HIV-1 disease progression: a longitudinal study in the era of highly active antiretroviral therapy, Am. J. Epidemiol. 163 (2006) 412–420.

[142] D.S. Magnuson, B.E. Knudsen, J.D. Geiger, R.M. Brownstone, A. Nath, Human immunodeficiency virus type 1 tat activates non-*N*-methyl-D-aspartate excitatory amino acid receptors and causes neurotoxicity, Ann. Neurol. 37 (1995) 373–380.

[143] P.M. Maki, E. Martin-Thormeyer, HIV, cognition and women, Neuropsychol. Rev. 19 (2009) 204–214.

[144] N. Malek, K. Popiolek-Barczyk, J. Mika, B. Przewlocka, K. Starowicz, Anandamide, Acting via *CB2* receptors, alleviates LPS-Induced neuroinflammation in rat primary microglial cultures, Neural Plast. 2015 (2015), 130639.

[145] Z.L. Mannes, L.E. Burrell 2nd, E.G. Ferguson, Z. Zhou, H. Lu, C. Somboonwit, R. L. Cook, N. Ennis, The association of therapeutic versus recreational marijuana use and antiretroviral adherence among adults living with HIV in Florida, Patient Prefer. Adherence 12 (2018) 1363–1372.

[146] J.A. Manuzak, T.M. Gott, J.S. Kirkwood, E. Coronado, T. Hensley-McBain, C. Miller, R.K. Cheu, A.C. Collier, N.T. Funderburg, J.N. Martin, M.C. Wu, N. Isoherranen, P.W. Hunt, N.R. Klatt, Heavy Cannabis use associated with reduction in activated and inflammatory immune cell frequencies in antiretroviral therapy-treated human immunodeficiency virus-infected individuals, Clin. Infect. Dis. 66 (2018) 1872–1882.

[147] G. Marsicano, S. Goodenough, K. Monory, H. Hermann, M. Eder, A. Cannich, S. C. Azad, M.G. Cascio, S.O. Gutierrez, M. van der Stelt, M.L. Lopez-Rodriguez, E. Casanova, G. Schutz, W. Zieglgansberger, V. Di Marzo, C. Behl, B. Lutz, CB1 cannabinoid receptors and on-demand defense against excitotoxicity, Science 302 (2003) 84–88.

[148] J. Martinez-Picado, S.G. Deeks, Persistent HIV-1 replication during antiretroviral therapy, Curr. Opin. HIV AIDS 11 (2016) 417–423.

[149] M.J. Massie, Prevalence of depression in patients with cancer, J. Natl. Cancer Inst. Monogr. (2004) 57–71.

[150] L.A. Matsuda, S.J. Lolait, M.J. Brownstein, A.C. Young, T.I. Bonner, Structure of a cannabinoid receptor and functional expression of the cloned cDNA, Nature 346 (1990) 561–564.

[151] M.P. Mattson, N.J. Haughey, A. Nath, Cell death in HIV dementia, Cell Death Differ. 12 (Suppl 1) (2005) 893–904.

[152] M.K. McKinney, B.F. Cravatt, Structure and function of fatty acid amide hydrolase, Annu. Rev. Biochem. 74 (2005) 411–432.

[153] S. Mediouni, A. Darque, G. Baillat, I. Ravaux, C. Dhiver, H. Tissot-Dupont, M. Mokhtari, H. Moreau, C. Tamalet, C. Brunet, P. Paul, F. Dignat-George, A. Stein, P. Brouqui, S.A. Spector, G.R. Campbell, E.P. Loret, Antiretroviral therapy does not block the secretion of the human immunodeficiency virus tat protein, Infect. Disord. Drug Targets 12 (2012) 81–86.

[154] O. Meucci, A. Fatatis, A.A. Simen, T.J. Bushell, P.W. Gray, R.J. Miller, Chemokines regulate hippocampal neuronal signaling and gp120 neurotoxicity, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 14500–14505.

[155] O. Meucci, A. Fatatis, A.A. Simen, R.J. Miller, Expression of CX$_3$CR1 chemokine receptors on neurons and their role in neuronal survival, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 8075–8080.

[156] W.T. Milano, M.F. Capasso, A cannabinoids involvement in neurodegenerative diseases, Curr. Neurobiol. 8 (2017) 135–144.

[157] L.K. Miller, L.A. Devi, The highs and lows of cannabinoid receptor expression in disease: mechanisms and their therapeutic implications, Pharmacol. Rev. 63 (2011) 461–470.

[158] M.J. Milloy, B. Marshall, T. Kerr, L. Richardson, R. Hogg, S. Guillemi, J. S. Montaner, E. Wood, High-intensity cannabis use associated with lower plasma human immunodeficiency virus-1 RNA viral load among recently infected people who use injection drugs, Drug Alcohol Rev. 34 (2015) 135–140.

[159] A. Minagar, P. Shapshak, R. Fujimura, R. Ownby, M. Heyes, C. Eisdorfer, The role of macrophage/microglia and astrocytes in the pathogenesis of three neurologic disorders: HIV-associated dementia, Alzheimer disease, and multiple sclerosis, J. Neurol. Sci. 202 (2002) 13–23.

[160] P.E. Molina, A. Amedee, N.J. LeCapitaine, J. Zabaleta, M. Mohan, P. Winsauer, C. Vande Stouwe, Cannabinoid neuroimmune modulation of SIV disease, J. Neuroimmune Pharmacol. 6 (2011) 516–527.

[161] P.E. Molina, P. Winsauer, P. Zhang, E. Walker, L. Birke, A. Amedee, C.V. Stouwe, D. Troxclair, R. McGoey, K. Varner, L. Byerley, L. LaMotte, Cannabinoid administration attenuates the progression of simian immunodeficiency virus, AIDS Res. Hum. Retroviruses 27 (2011) 585–592.

[162] F.A. Moreira, M. Grieb, B. Lutz, Central side-effects of therapies based on CB$_1$ cannabinoid receptor agonists and antagonists: focus on anxiety and depression, Best Pract. Res. Clin. Endocrinol. Metab. 23 (2009) 133–144.

[163] S. Munro, K.L. Thomas, M. Abu-Shaar, Molecular characterization of a peripheral receptor for cannabinoids, Nature 365 (1993) 61–65.

[164] P. Nagarkatti, R. Pandey, S.A. Rieder, V.L. Hegde, M. Nagarkatti, Cannabinoids as novel anti-inflammatory drugs, Future Med. Chem. 1 (2009) 1333–1349.

[165] V. Naidoo, S.P. Nikas, D.A. Karanian, J. Hwang, J. Zhao, J.T. Wood, S. O. Alapafuja, S.K. Vadivel, D. Butler, A. Makriyannis, B.A. Bahr, A new generation fatty acid amide hydrolase inhibitor protects against kainate-induced excitotoxicity, J. Mol. Neurosci. 43 (2011) 493–502.

[166] A. Nallapaneni, J. Liu, S. Karanth, C. Pope, Pharmacological enhancement of endocannabinoid signaling reduces the cholinergic toxicity of diisopropylfluorophosphate, Neurotoxicology 29 (2008) 1037–1043.

[167] F. Nasirinezhad, S. Jergova, J.P. Pearson, J. Sagen, Attenuation of persistent pain-related behavior by fatty acid amide hydrolase (FAAH) inhibitors in a rat model of HIV sensory neuropathy, Neuropharmacology 95 (2015) 100–109.

[168] M.W. Nasser, Z. Qamri, Y.S. Deol, D. Smith, K. Shilo, X. Zou, R.K. Ganju, Crosstalk between chemokine receptor CXCR4 and cannabinoid receptor CB_2 in modulating breast cancer growth and invasion, PLoS One 6 (2011), e23901.

[169] F. Navarrete, M.S. Garcia-Gutierrez, R. Jurado-Barba, G. Rubio, A. Gasparyan, A. Austrich-Olivares, J. Manzanares, Endocannabinoid system components as potential biomarkers in psychiatry, Front. Psychiatry 11 (2020) 315.

[170] J.M. Nichols, B.L.F. Kaplan, Immune responses regulated by cannabidiol, Cannabis Cannabinoid Res. 5 (2020) 12–31.

[171] M.J. Niphakis, A.B. Cognetta 3rd, J.W. Chang, M.W. Buczynski, L.H. Parsons, F. Byrne, J.J. Burston, V. Chapman, B.F. Cravatt, Evaluation of NHS carbamates as a potent and selective class of endocannabinoid hydrolase inhibitors, ACS Chem. Neurosci. 4 (2013) 1322–1332.

[172] S.N. Noe, S.B. Nyland, K. Ugen, H. Friedman, T.W. Klein, Cannabinoid receptor agonists enhance syncytia formation in MT-2 cells infected with cell free HIV-1MN, Adv. Exp. Med. Biol. 437 (1998) 223–229.

[173] M.I. Nogueron, B. Porgilsson, W.E. Schneider, C.L. Stucky, C.J. Hillard, Cannabinoid receptor agonists inhibit depolarization-induced calcium influx in cerebellar granule neurons, J. Neurochem. 79 (2001) 371–381.

[174] S.E. O'Sullivan, An update on PPAR activation by cannabinoids, Br. J. Pharmacol. 173 (2016) 1899–1910.

[175] C.N. Okafor, Z. Zhou, L.E. Burrell 2nd, N.E. Kelso, N.E. Whitehead, J.S. Harman, C.L. Cook, R.L. Cook, Marijuana use and viral suppression in persons receiving medical care for HIV-infection, Am. J. Drug Alcohol Abuse 43 (2017) 103–110.

[176] M. Orlando, M.A. Burnam, R. Beckman, S.C. Morton, A.S. London, E.G. Bing, J. A. Fleishman, Re-estimating the prevalence of psychiatric disorders in a nationally representative sample of persons receiving care for HIV: results from the HIV Cost and Services Utilization Study, Int. J. Methods Psychiatr. Res. 11 (2002) 75–82.

[177] O. Osborne, N. Peyravian, M. Nair, S. Daunert, M. Toborek, The paradox of HIV blood-brain barrier penetrance and antiretroviral drug delivery deficiencies, Trends Neurosci. 43 (2020) 695–708.

[178] L.R.T. Pacek, S. L, A.L. Hobkirk, D. Nash, R.D. Goodwin, Frequency of Cannabis use and medical Cannabis use among persons living with HIV in the United States: findings from a nationally representative sample, AIDS Educ. Prev. 30 (2018) 169–181.

[179] J. Palazuelos, T. Aguado, M.R. Pazos, B. Julien, C. Carrasco, E. Resel, O. Sagredo, C. Benito, J. Romero, I. Azcoitia, J. Fernandez-Ruiz, M. Guzman, I. Galve-Roperh, Microglial CB_2 cannabinoid receptors are neuroprotective in Huntington's disease excitotoxicity, Brain 132 (2009) 3152–3164.

[180] J. Palma, M. Narasimhan, J. Guindon, K. Benamar, Supraspinal interaction between HIV-1-gp120 and cannabinoid analgesic effectiveness, Naunyn Schmiedebergs Arch. Pharmacol. 391 (2018) 1157–1161.

[181] V.A. Palomaki, M. Lehtonen, J.R. Savinainen, J.T. Laitinen, Visualization of 2-arachidonoylglycerol accumulation and cannabinoid CB_1 receptor activity in rat brain cryosections by functional autoradiography, J. Neurochem. 101 (2007) 972–981.

[182] L.A. Parker, M.J. Niphakis, R. Downey, C.L. Limebeer, E.M. Rock, M.A. Sticht, H. Morris, R.A. Abdullah, A.H. Lichtman, B.F. Cravatt, Effect of selective inhibition of monoacylglycerol lipase (MAGL) on acute nausea, anticipatory nausea, and vomiting in rats and Suncus murinus, Psychopharmacology (Berl.) 232 (2015) 583–593.

[183] Y. Persidsky, W. Ho, S.H. Ramirez, R. Potula, M.E. Abood, E. Unterwald, R. Tuma, HIV-1 infection and alcohol abuse: neurocognitive impairment, mechanisms of neurodegeneration and therapeutic interventions, Brain Behav. Immun. 25 (Suppl 1) (2011) S61–70.

[184] R.G. Pertwee, Elevating endocannabinoid levels: pharmacological strategies and potential therapeutic applications, Proc. Nutr. Soc. 73 (2014) 96–105.

[185] R.G. Pertwee, Emerging strategies for exploiting cannabinoid receptor agonists as medicines, Br. J. Pharmacol. 156 (2009) 397–411.

[186] P.K. Peterson, G. Gekker, S. Hu, G. Cabral, J.R. Lokensgard, Cannabinoids and morphine differentially affect HIV-1 expression in $CD4^+$ lymphocyte and microglial cell cultures, J. Neuroimmunol. 147 (2004) 123–126.

[187] S. Petrosino, V. Di Marzo, FAAH and MAGL inhibitors: therapeutic opportunities from regulating endocannabinoid levels, Curr. Opin. Investig. Drugs 11 (2010) 51–62.

[188] S.C. Piller, P. Jans, P.W. Gage, D.A. Jans, Extracellular HIV-1 virus protein R causes a large inward current and cell death in cultured hippocampal neurons: implications for AIDS pathology, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 4595–4600.

[189] D. Prentiss, R. Power, G. Balmas, G. Tzuang, D.M. Israelski, Patterns of marijuana use among patients with HIV/AIDS followed in a public health care setting, J. Acquir. Immune Defic. Syndr. 35 (2004) 38–45.

[190] V. Purohit, R.S. Rapaka, J. Rutter, Cannabinoid receptor-2 and HIV-associated neurocognitive disorders, J. Neuroimmune Pharmacol. 9 (2014) 447–453.

[191] E.S. Raborn, G.A. Cabral, Cannabinoid inhibition of macrophage migration to the trans-activating (Tat) protein of HIV-1 is linked to the CB_2 cannabinoid receptor, J. Pharmacol. Exp. Ther. 333 (2010) 319–327.

[192] E.S. Raborn, M. Jamerson, F. Marciano-Cabral, G.A. Cabral, Cannabinoid inhibits HIV-1 Tat-stimulated adhesion of human monocyte-like cells to extracellular matrix proteins, Life Sci. 104 (2014) 15–23.

[193] S.H. Ramirez, N.L. Reichenbach, S. Fan, S. Rom, S.F. Merkel, X. Wang, W.Z. Ho, Y. Persidsky, Attenuation of HIV-1 replication in macrophages by cannabinoid receptor 2 agonists, J. Leukoc. Biol. 93 (2013) 801–810.

[194] M. Ranganathan, D.C. D'Souza, The acute effects of cannabinoids on memory in humans: a review, Psychopharmacology (Berl.) 188 (2006) 425–444.

[195] K.S. Rao, A. Ghorpade, V. Labhasetwar, Targeting anti-HIV drugs to the CNS, Expert Opin. Drug Deliv. 6 (2009) 771–784.

[196] P.K. Riggs, F. Vaida, S.S. Rossi, L.S. Sorkin, B. Gouaux, I. Grant, R.J. Ellis, A pilot study of the effects of cannabis on appetite hormones in HIV-infected adult men, Brain Res. 1431 (2012) 46–52.

[197] M.D. Rizzo, R.B. Crawford, J.E. Henriquez, Y.A. Aldhamen, P. Gulick, A. Amalfitano, N.E. Kaminski, HIV-infected cannabis users have lower circulating $CD16^+$ monocytes and IFN-γ-inducible protein 10 levels compared with nonusing HIV patients, AIDS 32 (2018) 419–429.

[198] R.B. Rock, G. Gekker, S. Hu, W.S. Sheng, G.A. Cabral, B.R. Martin, P.K. Peterson, WIN55,212-2-mediated inhibition of HIV-1 expression in microglial cells: involvement of cannabinoid receptors, J. Neuroimmune Pharmacol. 2 (2007) 178–183.

[199] R.B. Rock, G. Gekker, S. Hu, W.S. Sheng, M. Cheeran, J.R. Lokensgard, P. K. Peterson, Role of microglia in central nervous system infections, Clin. Microbiol. Rev. 17 (2004) 942–964, table of contents.

[200] M. Rodriguez-Munoz, P. Sanchez-Blazquez, L.F. Callado, J.J. Meana, J. Garzon-Nino, Schizophrenia and depression, two poles of endocannabinoid system deregulation, Transl. Psychiatry 7 (2017) 1291.

[201] M.I. Rosen, A.C. Black, J.H. Arnsten, K. Goggin, R.H. Remien, J.M. Simoni, C. E. Golin, D.R. Bangsberg, H. Liu, Association between use of specific drugs and antiretroviral adherence: findings from MACH 14, AIDS Behav. 17 (2013) 142–147.

[202] G.R. Ross, A. Lichtman, W.L. Dewey, H.I. Akbarali, Evidence for the putative cannabinoid receptor (GPR55)-mediated inhibitory effects on intestinal contractility in mice, Pharmacology 90 (2012) 55–65.

[203] M.D. Roth, D.P. Tashkin, K.M. Whittaker, R. Choi, G.C. Baldwin, Tetrahydrocannabinol suppresses immune function and enhances HIV replication in the huPBL-SCID mouse, Life Sci. 77 (2005) 1711–1722.

[204] L.H. Rubin, G.N. Neigh, E.E. Sundermann, Y. Xu, E.P. Scully, P.M. Maki, Sex differences in neurocognitive function in adults with HIV: patterns, predictors, and mechanisms, Curr. Psychiatry Rep. 21 (2019) 94.

[205] T. Rubino, D. Parolaro, Sexually dimorphic effects of cannabinoid compounds on emotion and cognition, Front. Behav. Neurosci. 5 (2011) 64.

[206] N. Sacktor, M.P. McDermott, K. Marder, G. Schifitto, O.A. Selnes, J.C. McArthur, Y. Stern, S. Albert, D. Palumbo, K. Kieburtz, J.A. De Marcaida, B. Cohen, L. Epstein, HIV-associated cognitive impairment before and after the advent of combination therapy, J. Neurovirol. 8 (2002) 136–142.

[207] P. Sanchez-Blazquez, M. Rodriguez-Munoz, J. Garzon, The cannabinoid receptor 1 associates with NMDA receptors to produce glutamatergic hypofunction: implications in psychosis and schizophrenia, Front. Pharmacol. 4 (2014) 169.

[208] P. Sanchez-Blazquez, M. Rodriguez-Munoz, A. Vicente-Sanchez, J. Garzon, Cannabinoid receptors couple to NMDA receptors to reduce the production of NO and the mobilization of zinc induced by glutamate, Antioxid. Redox Signal. 19 (2013) 1766–1782.

[209] M.A. Sanchez-Rodriguez, O. Gomez, P.F. Esteban, D. Garcia-Ovejero, E. Molina-Holgado, The endocannabinoid 2-arachidonoylglycerol regulates oligodendrocyte progenitor cell migration, Biochem. Pharmacol. 157 (2018) 180–188.

[210] A.V. Savonenko, T. Melnikova, Y. Wang, H. Ravert, Y. Gao, J. Koppel, D. Lee, O. Pletnikova, E. Cho, N. Sayyida, A. Hiatt, J. Troncoso, P. Davies, R.F. Dannals, M.G. Pomper, A.G. Horti, Cannabinoid CB2 receptors in a mouse model of Aβ amyloidosis: immunohistochemical analysis and suitability as a PET biomarker of neuroinflammation, PLoS One 10 (2015) e0129618.

[211] K.A. Scarlett, E.Z. White, C.J. Coke, J.R. Carter, L.K. Bryant, C.V. Hinton, Agonist-induced CXCR4 and CB2 heterodimerization inhibits Gα13/RhoA-mediated migration, Mol. Cancer Res. 16 (2018) 728–739.

[212] G. Schnell, S. Joseph, S. Spudich, R.W. Price, R. Swanstrom, HIV-1 replication in the central nervous system occurs in two distinct cell types, PLoS Pathog. 7 (2011), e1002286.

[213] T. Schoeler, S. Bhattacharyya, The effect of cannabis use on memory function: an update, Subst. Abuse Rehabil. 4 (2013) 11–27.

[214] J.C. Scott, S.P. Woods, C.L. Carey, E. Weber, M.W. Bondi, I. Grant, H.I.V. Group, Neurocognitive consequences of HIV infection in older adults: an evaluation of the "cortical" hypothesis, AIDS Behav. 15 (2011) 1187–1196.

[215] A.H. Shin, H.J. Kim, S.A. Thayer, Subtype selective NMDA receptor antagonists induce recovery of synapses lost following exposure to HIV-1 Tat, Br. J. Pharmacol. 166 (2012) 1002–1017.

[216] L. Simon, K. Song, C. Vande Stouwe, A. Hollenbach, A. Amedee, M. Mohan, P. Winsauer, M. Molina, Δ9-tetrahydrocannabinol (Δ9-THC) promotes neuroimmune-modulatory MicroRNA profile in striatum of simian immunodeficiency virus (SIV)-Infected macaques, J. Neuroimmune Pharmacol. 11 (2016) 192–213.

[217] B.D. Sippy, F.M. Hofman, D. Wallach, D.R. Hinton, Increased expression of tumor necrosis factor-alpha receptors in the brains of patients with AIDS, J. Acquir. Immune Defic. Syndr. Hum. Retrovirol. 10 (1995) 511–521.

[218] D.E. Slawek, J. Arnsten, N. Sohler, C. Zhang, R. Grossberg, M. Stein, C. O. Cunningham, Daily and near-daily cannabis use is associated with HIV viral load suppression in people living with HIV who use cocaine, AIDS Care (2020) 1–8.

[219] S.R. Smith, C. Terminelli, G. Denhardt, Effects of cannabinoid receptor agonist and antagonist ligands on production of inflammatory cytokines and anti-inflammatory interleukin-10 in endotoxemic mice, J. Pharmacol. Exp. Ther. 293 (2000) 136–150.

[220] T.H. Smith, L.J. Sim-Selley, D.E. Selley, Cannabinoid CB$_1$ receptor-interacting proteins: novel targets for central nervous system drug discovery? Br. J. Pharmacol. 160 (2010) 454–466.

[221] N. Stella, Cannabinoid and cannabinoid-like receptors in microglia, astrocytes, and astrocytomas, Glia 58 (2010) 1017–1030.

[222] M. Struwe, S.H. Kaempfer, C.J. Geiger, A.T. Pavia, T.F. Plasse, K.V. Shepard, K. Ries, T.G. Evans, Effect of dronabinol on nutritional status in HIV infection, Ann. Pharmacother. 27 (1993) 827–831.

[223] T. Sugiura, S. Kondo, S. Kishimoto, T. Miyashita, S. Nakane, T. Kodaka, Y. Suhara, H. Takayama, K. Waku, Evidence that 2-arachidonoylglycerol but not N-palmitoylethanolamine or anandamide is the physiological ligand for the cannabinoid CB2 receptor. Comparison of the agonistic activities of various cannabinoid receptor ligands in HL-60 cells, J. Biol. Chem. 275 (2000) 605–612.

[224] Y. Sun, A. Bennett, Cannabinoids: a new group of agonists of PPARs, PPAR Res. 2007 (2007) 23513.

[225] A. Tahamtan, M. Tavakoli-Yaraki, T.P. Rygiel, T. Mokhtari-Azad, V. Salimi, Effects of cannabinoids and their receptors on viral infections, J. Med. Virol. 88 (2016) 1–12.

[226] R. Tanveer, N. Macguinness, S. Daniel, A. Gowran, V.A. Campell, Cannabinoid receptors and neurodegenerative diseases, WIREs Membr Transp Signal 1 (2012) 633–639.

[227] A.D. Thames, T.P. Kuhn, T.J. Williamson, J.D. Jones, Z. Mahmood, A. Hammond, Marijuana effects on changes in brain structure and cognitive function among HIV + and HIV- adults, Drug Alcohol Depend. 170 (2017) 120–127.

[228] A.D. Thames, Z. Mahmood, A.C. Burggren, A. Karimian, T.P. Kuhn, Combined effects of HIV and marijuana use on neurocognitive functioning and immune status, AIDS Care 28 (2016) 628–632.

[229] J.G. Timpone, D.J. Wright, N. Li, M.J. Egorin, M.E. Enama, J. Mayers, G. Galetto, The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. The DATRI 004 Study Group. Division of AIDS Treatment Research Initiative, AIDS Res. Hum. Retroviruses 13 (1997) 305–315.

[230] M. Toczek, B. Malinowska, Enhanced endocannabinoid tone as a potential target of pharmacotherapy, Life Sci. 204 (2018) 20–45.

[231] J.S. Tucker, M.A. Burnam, C.D. Sherbourne, F.Y. Kung, A.L. Gifford, Substance use and mental health correlates of nonadherence to antiretroviral medications in a sample of patients with human immunodeficiency virus infection, Am. J. Med. 114 (2003) 573–580.

[232] M.T. Viscomi, S. Oddi, L. Latini, N. Pasquariello, F. Florenzano, G. Bernardi, M. Molinari, M. Maccarrone, Selective CB2 receptor agonism protects central neurons from remote axotomy-induced apoptosis through the PI3K/Akt pathway, J. Neurosci. 29 (2009) 4564–4570.

[233] C.W. Watson, E.W. Paolillo, E.E. Morgan, A. Umlauf, E.E. Sundermann, R.J. Ellis, S. Letendre, T.D. Marcotte, R.K. Heaton, I. Grant, Cannabis exposure is associated with a lower likelihood of neurocognitive impairment in people living with HIV, J. Acquir. Immune Defic. Syndr. 83 (2020) 56–64.

[234] Q. Wei, L. Liu, Z. Cong, X. Wu, H. Wang, C. Qin, P. Molina, Z. Chen, Chronic Δ^9-Tetrahydrocannabinol administration reduces IgE$^+$B cells but unlikely enhances pathogenic SIV$_{mac251}$ infection in male Rhesus macaques of chinese origin, J. Neuroimmune Pharmacol. 11 (2016) 584–591.

[235] S.L. Wesselingh, K. Takahashi, J.D. Glass, J.C. McArthur, J.W. Griffin, D.E. Griffin, Cellular localization of tumor necrosis factor mRNA in neurological tissue from HIV-infected patients by combined reverse transcriptase/polymerase chain reaction in situ hybridization and immunohistochemistry, J. Neuroimmunol. 74 (1997) 1–8.

[236] R.M. Whitfield, L.M. Bechtel, G.H. Starich, The impact of ethanol and Marinol/marijuana usage on HIV+/AIDS patients undergoing azidothymidine, azidothymidine/dideoxycytidine, or dideoxyinosine therapy, Alcohol. Clin. Exp. Res. 21 (1997) 122–127.

[237] J.C. Williams, S. Appelberg, B.A. Goldberger, T.W. Klein, J.W. Sleasman, M. M. Goodenow, Δ^9-Tetrahydrocannabinol treatment during human monocyte differentiation reduces macrophage susceptibility to HIV-1 infection, J. Neuroimmune Pharmacol. 9 (2014) 369–379.

[238] K.C. Williams, S. Corey, S.V. Westmoreland, D. Pauley, H. Knight, C. deBakker, X. Alvarez, A.A. Lackner, Perivascular macrophages are the primary cell type productively infected by simian immunodeficiency virus in the brains of macaques: implications for the neuropathogenesis of AIDS, J. Exp. Med. 193 (2001) 905–915.

[239] P.J. Winsauer, P.E. Molina, A.M. Amedee, C.M. Filipeanu, R.R. McGoey, D. A. Troxclair, E.M. Walker, L.L. Birke, C.V. Stouwe, J.M. Howard, S.T. Leonard, J. M. Moerschbaecher, P.B. Lewis, Tolerance to chronic delta-9-tetrahydrocannabinol (Δ^9-THC) in rhesus macaques infected with simian immunodeficiency virus, Exp. Clin. Psychopharmacol. 19 (2011) 154–172.

[240] E. Woolridge, S. Barton, J. Samuel, J. Osorio, A. Dougherty, A. Holdcroft, Cannabis use in HIV for pain and other medical symptoms, J. Pain Symptom Manage. 29 (2005) 358–367.

[241] M.M. Wu, S.A. Thayer, HIV Tat protein selectively impairs CB$_1$ receptor-mediated presynaptic inhibition at excitatory but not inhibitory synapses, eNeuro 7 (2020).

[242] M.M. Wu, X. Zhang, M.J. Asher, S.A. Thayer, Druggable targets of the endocannabinoid system: implications for the treatment of HIV-associated neurocognitive disorder, Brain Res. 1724 (2019), 146467.

[243] C. Xu, D.J. Hermes, K. Mackie, A.H. Lichtman, B.M. Ignatowska-Jankowska, S. Fitting, Cannabinoids occlude the HIV-1 Tat-induced decrease in GABAergic neurotransmission in prefrontal cortex slices, J. Neuroimmune Pharmacol. (2016).

[244] C. Xu, D.J. Hermes, B. Nwanguma, I.R. Jacobs, K. Mackie, S. Mukhopadhyay, A. H. Lichtman, B. Ignatowska-Jankowska, S. Fitting, Endocannabinoids exert CB$_1$ receptor-mediated neuroprotective effects in models of neuronal damage induced by HIV-1 Tat protein, Mol. Cell. Neurosci. 83 (2017) 92–102.

[245] X. Zhang, S.A. Thayer, Monoacylglycerol lipase inhibitor JZL184 prevents HIV-1 gp120-induced synapse loss by altering endocannabinoid signaling, Neuropharmacology 128 (2018) 269–281.