

# Mechanisms underlying HIV-associated cognitive impairment and emerging therapies for its management

Ronald J. Ellis<sup>1,2</sup>✉, María J. Marquine<sup>3,4</sup>, Marcus Kaul<sup>5</sup>, Jerel Adam Fields<sup>2</sup> & Johannes C. M. Schlachetzki<sup>6</sup>

## Abstract

People living with HIV are affected by the chronic consequences of neurocognitive impairment (NCI) despite antiretroviral therapies that suppress viral replication, improve health and extend life. Furthermore, viral suppression does not eliminate the virus, and remaining infected cells may continue to produce viral proteins that trigger neurodegeneration. Comorbidities such as diabetes mellitus are likely to contribute substantially to CNS injury in people living with HIV, and some components of antiretroviral therapy exert undesirable side effects on the nervous system. No treatment for HIV-associated NCI has been approved by the European Medicines Agency or the US Food and Drug Administration. Historically, roadblocks to developing effective treatments have included a limited understanding of the pathophysiology of HIV-associated NCI and heterogeneity in its clinical manifestations. This heterogeneity might reflect multiple underlying causes that differ among individuals, rather than a single unifying neuropathogenesis. Despite these complexities, accelerating discoveries in HIV neuropathogenesis are yielding potentially druggable targets, including excessive immune activation, metabolic alterations culminating in mitochondrial dysfunction, dysregulation of metal ion homeostasis and lysosomal function, and microbiome alterations. In addition to drug treatments, we also highlight the importance of non-pharmacological interventions. By revisiting mechanisms implicated in NCI and potential interventions addressing these mechanisms, we hope to supply reasons for optimism in people living with HIV affected by NCI and their care providers.

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A full list of affiliations appears at the end of the paper. ✉e-mail: [roellis@ucsd.edu](mailto:roellis@ucsd.edu)

## Key points

- The pathogenesis of neurocognitive impairment (NCI) in people living with HIV is complex, and no disease-modifying therapies are currently available.
- Neuroinflammatory and metabolic changes are hallmarks of HIV-associated NCI and are potential therapeutic targets.
- The neuropathogenesis of HIV-associated NCI in diverse ethnic and racial groups warrants further exploration.
- Examples of promising targets for the treatment of NCI in people living with HIV include human growth hormone-releasing hormone (hGHRH) and the enzyme phosphatidylinositol-glycan-specific phospholipase D (also known as GPLD1).
- Non-pharmacological interventions that might enhance cognitive function in people living with HIV include increased physical activity, improved quality of sleep and nutritional treatments.

## Introduction

Acquired neurocognitive impairment (NCI) affects 30–50% of the 38 million people living with HIV worldwide<sup>1,2</sup>. Persistent NCI is a major concern for the ageing population of people living with HIV who are affected by the chronic, negative consequences of this condition<sup>3</sup>. By highlighting interventions that treat or prevent HIV-associated NCI, we hope to supply reasons for optimism in affected individuals. Among the general mechanisms that underlie HIV-associated NCI are chronic inflammation, oxidative stress and direct neurotoxicity of viral proteins. In subsequent sections, we specifically and precisely describe these potentially targetable mechanisms.

HIV infects and replicates in immune cells, particularly in CD4<sup>+</sup> T cells, macrophages and microglia. It causes cellular dysfunction and disease by a variety of mechanisms, such as progressive CD4<sup>+</sup> T cell depletion and inflammation. The prognosis for people living with HIV has made great strides forward over the past two decades as effective, well-tolerated antiretroviral therapies (ART) have evolved. In most people living with HIV, these combination drug regimens suppress viral replication, restore CD4<sup>+</sup> T cell numbers, slow, stop and even partially reverse disease progression, reduce the likelihood of opportunistic diseases and cancer, and greatly extend lifespan. While ART has not been specifically approved to ameliorate NCI by the European Medicines Agency or the US Food and Drug Administration (FDA), individuals initiating ART often demonstrate substantial, clinically significant improvements in cognitive performance<sup>3,4</sup>, particularly when ART is initiated early, before substantial immunosuppression occurs<sup>5</sup>. Nevertheless, some degree of NCI persists in many individuals and does not appear to improve in the long term<sup>6</sup>. While frank dementia is now very uncommon, milder HIV-associated NCI persists in the context of suppression of viral replication. The remaining lingering mild NCI is associated with poor health outcomes and quality of life in people living with HIV<sup>1,7,8</sup>. Several ART trials designed specifically to target HIV-associated NCI have shown little effectiveness<sup>3,9</sup>, and numerous plausible explanations for the lack of effectiveness have been advanced. For example, an intensification trial that added abacavir, a drug with good, predicted CNS penetration, to existing background

ART, did not show neurocognitive benefit. Subsequent assays found that two-thirds of patients had baseline resistance to abacavir, probably because of prior exposure to other drugs in the same class (for example, HIV nucleoside reverse transcriptase inhibitors).

The clinical literature on NCI in HIV is characterized by numerous areas of debate, controversy and inconsistent findings. These include concerns about nomenclature and varying reports on the prevalence and incidence of NCI. In our discussion of these various areas of study, we highlight several sources of disagreement. Discrepancies arise from factors such as differences in NCI prevalence depending on the selection of neurocognitive test instruments, variations in cohort composition (for example, proportions of men versus women, different racial or ethnic groups, differential access to care, and specific antiretroviral treatment regimens), the rapid evolution of specific antiretroviral combinations resulting in long-term group trends, and differences in the thresholds for designating impaired performance (for example, one standard deviation in two domains versus two standard deviations).

## Nomenclature, epidemiology and clinical impact of HIV-associated NCI

In 2007, a multinational consensus document outlined the terminology for HIV-associated neurocognitive disorders, including HIV-associated dementia, mild neurocognitive disorder and asymptomatic neurocognitive impairment (ANI)<sup>10</sup>. Diagnosis of these conditions is based on impaired performance in multiple neurocognitive domains in combination with a clinical history including premorbid or ongoing conditions, impact on activities of daily living, medical and neurological examination, and laboratory testing designed to identify conditions other than HIV ('confounds') that contribute to or in some cases fully account for NCI and functional impairments. However, with the rapid advancement of ART and the ageing of people living with HIV, the patterns of neurocognitive dysfunction are evolving. The classification terminology is debated, particularly the importance of ANI<sup>11–13</sup>. Some investigators suggest that isolated test results showing NCI (ANI) might represent false positives or artefacts of inadequate normative corrections that are clinically insignificant, are related to comorbidities rather than HIV itself, and have no basis in neuropathogenesis. Counter arguments include observations that ANI often progresses to symptomatic impairment and is associated with blood, cerebrospinal fluid (CSF) and neuroimaging biomarkers of neuronal injury and neuroinflammation that have plausible connections to HIV itself<sup>14–16</sup>. Recognizing the continuing debate in this area, we have chosen to use the broader term HIV-associated NCI.

Despite sustained ART and viral suppression, HIV-associated NCI affects 30–50% of people living with HIV<sup>1,17–19</sup>. Key symptoms are difficulties with attention and sustained focus, forgetfulness, and loss of the ability to perform some cognitive tasks that the person previously managed with relative ease. Additionally, depression often accompanies this condition. HIV-associated NCI adversely impacts ART adherence<sup>20</sup>, driving<sup>20</sup>, quality of life<sup>21–24</sup>, independence in daily activities<sup>11,16,17</sup> and life expectancy<sup>25</sup>. The risk of HIV-associated NCI significantly increases in people living with HIV aged 50 years and older, who now comprise the largest and fastest-growing age group of people living with HIV in Europe and the USA<sup>26–29</sup>. Legacy effects contribute to the high prevalence of NCI in people living with HIV. This concept is supported by the well-established observation that lower nadir levels of CD4<sup>+</sup> T cells, which reflect a history of advanced immunosuppression, are associated with an increased risk of NCI<sup>30,31</sup>. Additionally, people living with HIV show premature and accelerated neurocognitive ageing<sup>23,24</sup>, leaving them vulnerable to functional decline<sup>25,26</sup> and impaired quality of life<sup>27</sup>.

Unlike Alzheimer disease (AD) and many other neurodegenerative disorders, HIV-associated NCI is not inexorably progressive<sup>32</sup>, but the cumulative effect of decades of neurocognitive disability is profound.

Ethnic and racial disparities in HIV-associated NCI have received increasing attention over the past few years. In the USA, new HIV infection rates are eight and four times higher, respectively, among Black and Latino people than in non-Latino white people. Black and Latino people account for 65% of the national population of people living with HIV<sup>33</sup>. These groups are underserved clinically and under-represented in research. Despite inconsistent findings across studies, some have reported that Black people living with HIV have cognitive impairment more frequently than white people living with HIV in the USA<sup>34–36</sup>. Similarly, Latino people living with HIV of diverse heritage (Mexican and Puerto Rican) and language use (speaking primarily English and Spanish), and who live in different geographical regions in the USA<sup>37–40</sup>, show more frequent NCI and faster longitudinal neurocognitive decline than non-Latino white people living with HIV.

In 2021, 38.4 million people were living with HIV worldwide, with the vast majority in low-income and middle-income countries, including 53% in eastern and southern Africa<sup>7</sup>. Although estimates vary according to the viral clade (subtype), regional subpopulations and assessment methods, HIV-associated NCI is quite prevalent in these regions<sup>41–43</sup>. Notable disparities in access to ART and other medical resources are likely to drive at least part of the increased risk of HIV-associated NCI<sup>42</sup>, yet there are important gaps in our understanding

of the underlying mechanisms and management of HIV-associated NCI in these settings.

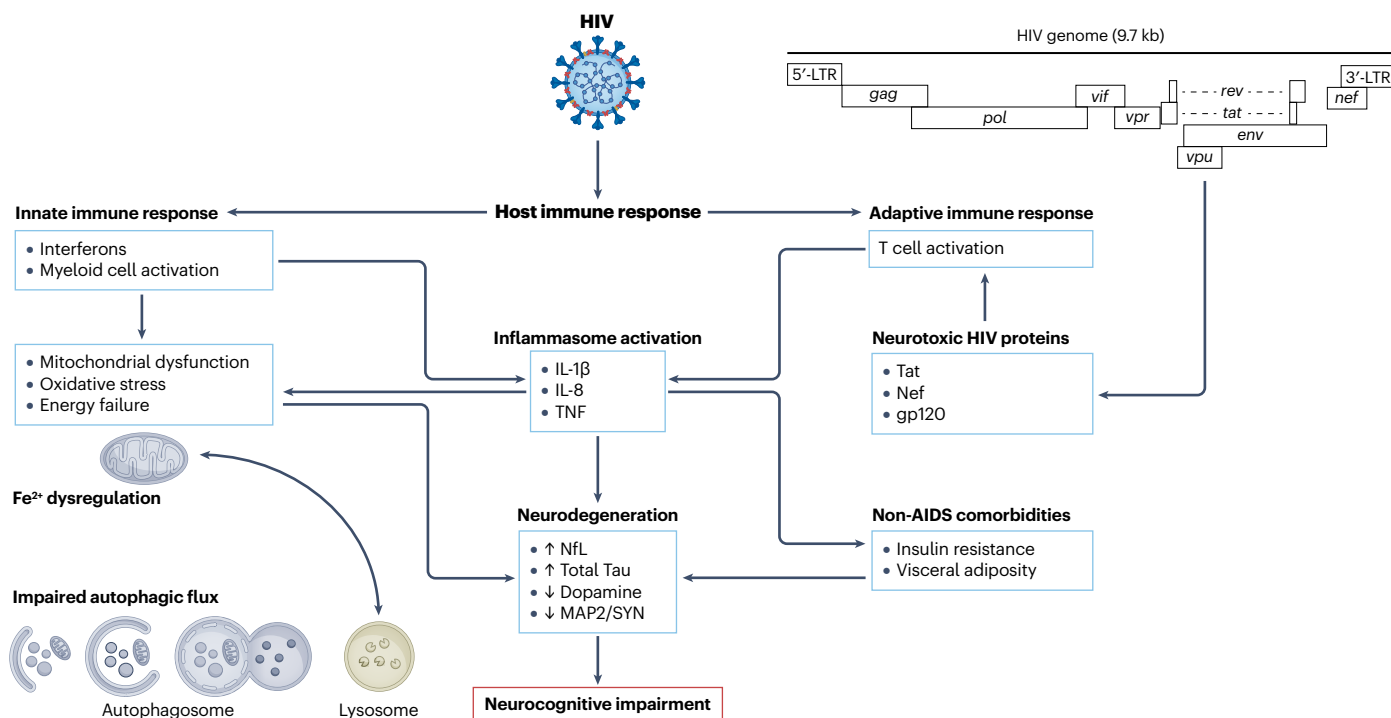
## Neuropathogenesis of HIV-associated NCI

A variety of molecular mechanisms contribute to HIV-associated NCI; we focus on the direct and indirect effects related to HIV infection. Because the number of neuropathogenic mechanisms is large, we focus on a subset of mechanisms for which robust experimental support exists. Figure 1 presents an overview of some of the key contributing causes of HIV-associated NCI.

### HIV persistence in the brain

Despite ART-mediated suppression, HIV proviruses are detectable in the brain and CSF of people living with HIV. As such, the brain presents a major challenge for viral eradication<sup>44–47</sup>, and HIV persistence directly or indirectly contributes to HIV-associated NCI.

Although CSF viral loads (HIV RNA) do not always provide a reliable surrogate for brain viral loads, CSF escape is well described in people living with HIV on ART. CSF escape is a condition in which HIV RNA is detectable in the CSF but undetectable in blood or is significantly higher in CSF than in blood (usually by 0.5 log<sub>10</sub> [copies per millilitre]). Most studies report a prevalence of CSF escape of 5–15%, but this prevalence varies depending on the characteristics of the cohort studied and has generally declined over the past 15 years as ART regimens have become increasingly effective, convenient and well tolerated<sup>48–50</sup>.



**Fig. 1 | Overview of factors contributing to neurocognitive impairment in people living with HIV with viral suppression.** HIV proteins, such as Tat, which continue to be produced even when HIV replication is suppressed by antiretroviral therapy, are toxic to neurons and glial cells. In addition, HIV interacts with the host to produce deleterious immune responses. Particularly important here is the innate immune response, mediated in large part by interferon signalling and myeloid cell activation, which results in the production of neurotoxic inflammatory mediators, mitochondrial dysfunction and oxidative

stress, impaired autophagy and ultimately neurodegeneration, leading to neurocognitive impairment. Additional contributing factors are comorbidities, such as insulin resistance, and visceral adiposity as well as toxicities of antiretroviral medications. Addressing these alterations might influence the long-term course of brain disease associated with HIV. LTR, long terminal repeat; NfL, neurofilament light; MAP2, microtubule associated protein 2; SYN, synaptophysin; TNF, tumour necrosis factor.

Although most instances of CSF escape are asymptomatic, clinical presentations are non-specific and include encephalopathy, seizures and stroke-like symptoms. In some cases, antiretroviral drug resistance mutations have been found in CSF but not in blood, although this finding is confounded by technical limitations in assessing resistance at low viral loads. Reports exist of individuals whose antiretroviral regimens were changed in response to CSF escape and drug resistance profiles, with a subset of these cases showing clinical improvement<sup>49,51</sup>. However, whether these improvements were spontaneous or related to the regimen changes is unclear.

Intact and defective HIV DNA provirus has been detected in post-mortem brain tissue from people with HIV who had been on ART<sup>52,53</sup>. Transcriptomic analyses of brain tissue showed increased HIV RNA levels accompanied by elevated interferon signalling compared with uninfected controls. Conversely, the expression of genes linked to synaptic and neuronal function was downregulated compared with uninfected controls<sup>54</sup>. HIV RNA transcripts have also been measured in the CSF of people living with HIV, predominantly in CD4<sup>+</sup> T cells<sup>55</sup>. High levels of intracellular HIV RNA transcription in CSF CD4<sup>+</sup> T cells have been associated with ongoing neuronal injury as measured by proton magnetic resonance spectroscopy<sup>56</sup>. Another study showed that HIV-infected cells (HIV DNA) persist in the CSF of almost half of individuals on sustained ART and that the presence of these cells is correlated with decreased neurocognitive performance<sup>57</sup>. Consistently, HIV transcription occurs in infected cells even under sustained ART<sup>58,59</sup>. Chronic transcription and translation could potentially induce chronic immune activation<sup>60</sup>. The factors driving HIV transcription despite ART are not well defined. Interestingly, HIV transcripts and proteins, such as Nef, Tat and Env, are present in exosomes – small vesicles carrying proteins and RNAs from the originating cells – secreted from infected cells<sup>61–63</sup>. Therefore, exosomes continue to be an evolving topic for improved understanding of HIV infection and the associated NCI<sup>64,65</sup>. Exosomes are being studied for their suitability in providing HIV and NCI biomarkers<sup>64,66,67</sup> but also as functional players in the promotion<sup>63,64,66,67</sup> of infection and NCI and as delivery vehicles for therapeutics<sup>61,62,66–68</sup>. Exosomes from HIV-infected cells modulate the gene expression and function of uninfected immune cells, for instance, via activation of NF- $\kappa$ B<sup>69,70</sup>. Vice versa, exosomes from uninfected cells can modulate the transcription of HIV in infected cells, leading to an increased release of HIV RNA from infected cells<sup>71</sup>. Comorbidities such as substance use disorders have also been shown to modulate HIV transcription<sup>72</sup>. Specifically, the use of benzodiazepines, at least in a subset of people living with HIV, is linked to NCI<sup>73,74</sup>. The benzodiazepine alprazolam increases HIV RNA transcription and might thus indirectly contribute to neuronal dysfunction<sup>75</sup>. The precise mechanisms by which drugs modulate HIV transcription in T cells and myeloid cells are not well understood.

Long-term HIV infection can induce neuronal damage that could have been triggered before starting ART, commonly referred to as a legacy effect<sup>76</sup>. Concerted efforts such as the 'Last Gift' study, which follows people living with HIV who were diagnosed with a terminal illness during the last months of their lives and agreed to donate their bodies to HIV research, provide the unprecedented opportunity to deeply profile all anatomical niches, including the brain, where HIV plays hide and seek<sup>77</sup>.

## Neuropathogenesis in diverse ethnic and racial groups

An understanding of the sociocultural, behavioural and biological factors that underlie HIV-associated NCI is crucial to achieving

treatment benefits. Most human studies in the USA have included primarily non-Latino white people and have not investigated differences in neuropathogenesis across diverse ethnic and racial groups. However, evidence exists that key pathophysiological mechanisms of HIV-associated NCI might differ across ethnic and racial groups. For example, a higher score on the Veterans Aging Cohort Study Index was significantly associated with worse global neurocognition in white and Black people living with HIV but not among Latino people living with HIV in southern California<sup>78</sup>. Age and lower current CD4 T cell counts were the most important predictors among Black people. For Latino people, age and hepatitis C virus (HCV) status were most important. In a multisite study at six medical centres in the USA<sup>78</sup>, comorbidity status was a unique and important predictor of higher NCI in participants of Mexican and Puerto Rican heritage. Among those of Mexican heritage, lower nadir CD4 T cell count was also a notable predictor, as was being on ART, in people living with HIV of Puerto Rican origin<sup>78</sup>. A study of Spanish-speaking people living with HIV in southern California showed that, among those without a history of lifetime substance use disorder, more years of ART exposure were significantly associated with decreased rates of global NCI, while those not meeting criteria for a lifetime substance use disorder showed no such association<sup>40</sup>. A post-mortem study of people with HIV on ART showed that alterations in triggering receptor expressed on myeloid cells 2 (TREM2) were an important marker of HIV-associated NCI among Latino people and a potential therapeutic target for intervention<sup>79</sup>. One genetic association study found that a common mitochondrial DNA haplogroup within this population (haplogroup B) was linked with decreased risk for NCI among Latino people living with HIV<sup>80</sup>.

## Evidence of neuronal injury in HIV-associated NCI

The final common cause of HIV-associated NCI is neuronal dysfunction. Comprehensive neuropathological analyses of post-mortem brain samples from people with HIV with NCI report reductions in synapses and dendrites, weakening the functional connectivity between neurons upon which cognition depends<sup>81–83</sup>. Imaging studies of people living with HIV with NCI suggest that neuronal dysfunction is associated with brain atrophy<sup>14</sup> and abnormal brain white matter connections<sup>84</sup>. Functional measures, such as PET and functional MRI, show additional abnormalities. CSF, serum and plasma levels of neurofilament light and Tau – both major structural elements of large-calibre myelinated axons – increase in many neurodegenerative disorders<sup>85–90</sup>, including HIV<sup>91</sup>, indicating progressive axonal and neuronal degeneration. A study conducted in 2022 showed that increasing levels of neurofilament light, total Tau and phosphorylated Tau 181 were associated with worse neurocognitive performance<sup>16</sup>. These clinical findings reinforce the neuropathological data linking neurodegeneration with NCI in people living with HIV. Again, minority racial and ethnic groups are under-represented in these studies.

HIV neuropathogenic mechanisms can be classified into two broad categories: direct toxic effects of the virus itself and toxic effects related to host response to the virus and its downstream consequences. Because HIV does not infect neurons, most proposed mechanisms of neuronal injury are indirect.

## Animal models used in research on HIV in the brain

Numerous animal models of HIV neuropathogenesis have been developed, ranging from chimpanzees and other non-human primates to cats and rodents (rats and mice)<sup>92–97</sup>. Only non-human primates, cats and rodents have been found to be suitable for the study of HIV



neuropathogenesis, neurological sequelae and behavioural impairment (reviewed elsewhere<sup>98</sup>). Non-human primates, cats and rodents are not permissive to HIV infection; however, some monkey species can contract simian immunodeficiency virus (SIV), and cats can be infected with a lentivirus called feline immunodeficiency virus (FIV)<sup>99–101</sup>. Both SIV and FIV induce AIDS-like disease with neuropathology or encephalitis, and thus macaques and cats have been used to study the pathogenesis of AIDS and NeuroAIDS<sup>99–105</sup>. However, there are substantial differences between these viruses and HIV, limiting the translation of the findings into the human system.

As rodents cannot be productively infected with wild-type HIV, two chimeric HIV mutants have been generated in which the viral envelope protein gp120 is replaced with the gp80 of ecotropic murine leukaemia virus (EcoHIV)<sup>106</sup>. This pseudo-typing approach enabled the establishment of a lasting and neuroinvasive lentiviral infection in mice with an associated immune response, and thus provides a model suitable for research on HIV in the brain<sup>107</sup>.

An earlier experimental approach for research on HIV in the brain used intracranial injection of HIV-infected human monocyte-derived macrophages into the brains of mice with severe combined immunodeficiency<sup>108–111</sup>. This model system provided evidence that HIV-infected macrophages cause key features of the neuropathology observed in post-mortem brains from patients with HIV dementia. Alternatively, a human haematopoietic system can be established in some immunocompromised mouse strains, resulting in ‘humanized mice’ that are permissive to HIV infection and provide a small animal model for research on HIV in the brain<sup>97,112</sup>.

Mice and rats have the important advantage that they can be genetically modified; several transgenic mice and a rat that express an entire HIV genome develop AIDS-like diseases<sup>93,113–116</sup>. Transgenic mouse models expressing the entire HIV genome or single components of the virus, such as gp120, Tat or Vpr, in the brain develop various degrees of behavioural deficiencies and neuropathology, including loss of synapses, neuronal dendrites and entire neurons, as well as glial activation; these models thus recapitulate key pathological features of people living with HIV who have neurocognitive impairment<sup>117–124</sup>. Moreover, the brains of HIV-gp120 transgenic mice share a considerable fraction of differential gene regulation with brains from people with HIV or HIV encephalitis who did and did not have NCI when alive<sup>125</sup>.

## Direct neurotoxic mechanisms

Although HIV does not infect neurons, these cells are directly exposed to neurotoxic HIV proteins from infected myeloid cells. Low-level expression of HIV proteins in the brain and periphery continues in the presence of suppressed viral replication in the brain<sup>126–128</sup> and might explain the neuronal dysfunction and damage that underlie many of the clinical neuronal complications associated with HIV infection. *In vitro*, the HIV proteins Tat, gp120, Vpr and Nef trigger neuronal oxidative stress, altered mitochondrial transport and autophagic flux, induction of apoptosis, and abnormal Ca<sup>2+</sup> signalling in cellular and animal models<sup>129–136</sup>. The involvement of HIV proteins in mitochondrial dysfunction in the brain was highlighted in a study that found alterations in the electron transport chain, glycolytic pathways, mitochondrial trafficking proteins and proteins involved in various energy pathways in a rat model of HIV-induced neurotoxicity<sup>137</sup>.

## Indirect mechanisms of neurotoxicity

The concept of indirect mechanisms of neurotoxicity refers to the observations that HIV-infected cells, specifically macrophages and

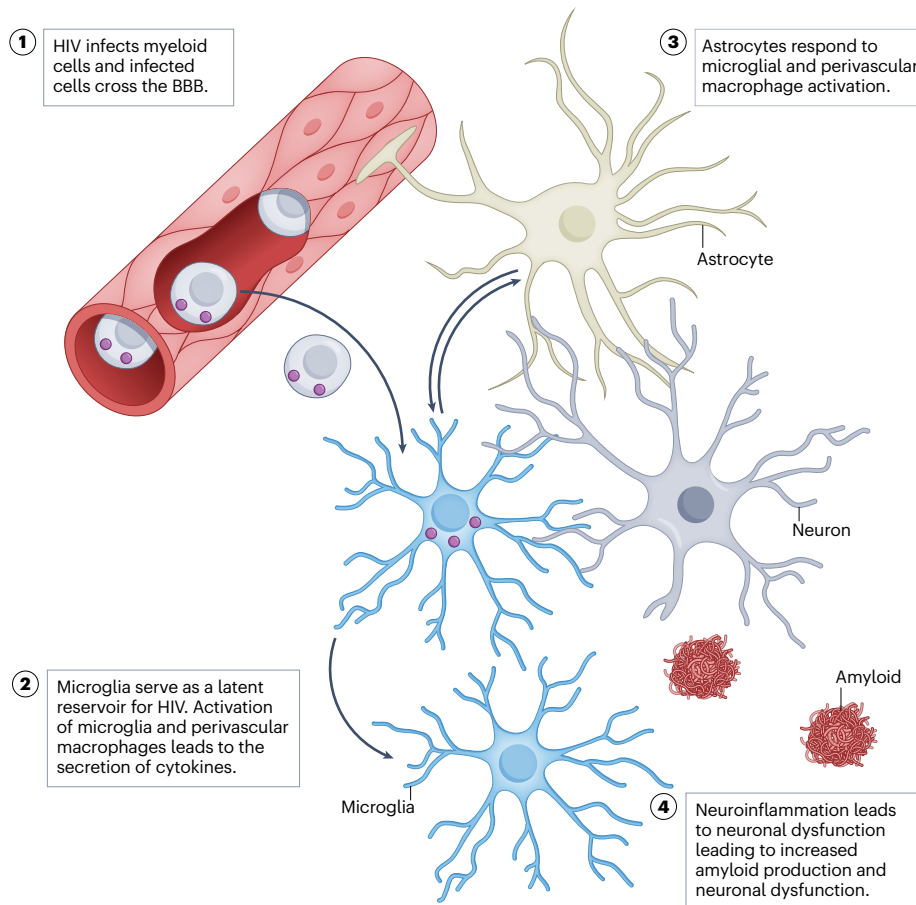
microglia, secrete neurotoxins in conjunction with HIV virions or viral components and host proteins as well as other toxic molecules that damage neurons. The neurotoxicity of macrophages and microglia is in line with the notion that HIV infects and persists in myeloid cells.

**Persistence of HIV in brain myeloid cells.** HIV enters the brain within days after infection, infecting myeloid cells through chemokine receptors and sustaining productive infection (replication and assembly of infectious virions)<sup>138</sup>. The earliest descriptions of HIV encephalitis identified fused macrophages (multinucleated giant cells) and microglial nodules reflecting direct infection<sup>139,140</sup>. Modern neuropathological studies of decedents who had HIV infection and were virally suppressed find predominantly synaptodendritic pruning<sup>141,142</sup>. This shift in neuropathology has paralleled the clinical shift from frank dementia to milder forms of NCI. Astrocytes can also be infected but are resistant to productive infection<sup>143,144</sup>. Brain myeloid cells can constitute a ‘latent’ reservoir and are associated with chronic neuroinflammation<sup>145</sup>, although viral genes continue to be transcribed and translated<sup>128</sup>. Latent HIV in brain myeloid cells is associated with chronic neuroinflammation<sup>146</sup> and neuronal dysfunction<sup>147,148</sup> (Fig. 2). Several lines of evidence suggest that macrophages and microglia can injure neurons by releasing excitotoxic substances that lead to excessive activation of glutamate receptors, primarily of the *N*-methyl-D-aspartate subtype (NMDARs), including a metabolite of the tryptophan–kynurenine pathway, quinolinic acid<sup>149–152</sup>. Quinolinic acid concentrations are increased even in the brains of people living with HIV with viral suppression and have been linked to prospective memory impairment<sup>151,153</sup>, providing a potential explanation for persistent NCI despite viral control. Moreover, neurotoxicity can also be mediated by macrophage-derived and microglial-derived inflammatory cytokines (such as IL-1 $\alpha$  and tumour necrosis factor (TNF)), arachidonate and its metabolites (including the closely related platelet-activating factor (PAF), the biosynthesis of which shares a precursor source with arachidonic acid and eicosanoids), certain chemokines, and the release of viral proteins such as gp120, Tat, Nef or Vpr<sup>143,149,151,152,154</sup>.

HIV-associated NCI is characterized by distinct microglial phenotypes. Microglia respond to pathogens, injury and neurodegeneration by changing morphology, migrating to the site of damage and destroying pathogens. Microglia possess sensing mechanisms, such as TREM2, to detect CNS damage<sup>79</sup>. Transcriptomic analyses of brain tissue revealed dysregulated genes implicated in immune functioning and synaptic transmission<sup>155</sup>, and pathway analyses identified genes involved in immune responses, neurotransmission and cell signalling<sup>156–158</sup>. *In vitro*, exposure to HIV Tat protein resulted in microglial activation and induced the NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome<sup>159</sup>.

**Type I interferons.** In contrast to interferon- $\alpha$  (IFN $\alpha$ ), a product of activated microglia and macrophages, IFN $\beta$  exerts anti-inflammatory effects and is able to control HIV and SIV infection in the periphery and brain<sup>160,161</sup>. Studies of SIV-infected macaques show that IFN $\beta$  is the main type I interferon that is produced by the brain during acute infection, and its expression is associated with viral control in the brain<sup>160</sup>.

In the classical model of type I interferon signalling, IFN $\beta$  controls the time course of IFN $\alpha$  production<sup>162</sup>. However, SIV infection induces a protective antiviral IFN $\beta$  response in the brain without the production of IFN $\alpha$ <sup>163</sup>. The suppression of IFN $\alpha$  during SIV infection depends on CCL2, which is predominantly produced by astrocytes upon viral infection<sup>164</sup>.



**Fig. 2 | Hypothetical model of HIV-mediated myeloid cell and neuronal dysfunction in HIV-associated NCI.** HIV-infected monocytes transigrate from the peripheral blood to the brain. HIV-infected perivascular macrophages and microglia respond by releasing cytokines that further activate microglia and astrocytes. This eventually leads to neuronal dysfunction, as evidenced by impairment of synaptic transmission, disturbed mitochondrial bioenergetics and, eventually, neurocognitive impairment (NCI). BBB, blood–brain barrier.

Similar to the observation in SIV-infected macaques, transiently increased expression of *Ifnb1* mRNA (encoding IFN $\beta$ ) is seen in the brains of HIV-gp120 transgenic mice<sup>165</sup>. This transgenic mouse model of HIV in the brain expresses viral gp120 of the HIV isolate lymphadenopathy-associated virus (LAV) under the control of a modified glial fibrillary acidic protein (*Gfap*) promoter in astrocytes in the CNS and recapitulates key features of brain injury seen in patients living with HIV or AIDS<sup>118</sup>. Moreover, as mentioned previously, HIV-gp120 transgenic mouse brains share a considerable number of differentially expressed genes with patients with human HIV and HIV encephalitis, including evidence of an endogenous interferon response<sup>125,166</sup>. Most interestingly, treatment of HIV-gp120 transgenic mice with exogenous recombinant IFN $\beta$  via intranasal delivery results in neuroprotection, at least in the cortex and hippocampus<sup>165</sup>, whereas, in the absence of exogenously supplied IFN $\beta$ , IFNAR1 critically contributes to the neurotoxicity of gp120 (ref. 167).

Because of its pronounced antiviral activity<sup>168,169</sup>, IFN $\alpha$  has been investigated for HIV treatment in several settings: before the introduction of combination ART, as part of a structured treatment interruption strategy, in acute HIV infection, as a component of salvage therapy and, most recently, in attempts to eradicate viral reservoirs<sup>170,171</sup>. Early attempts at treating established HIV infection were disappointing or inconclusive, in part because of a lack of understanding that the effects of the endogenous interferon system and exogenously supplied interferons depend on the stage of the HIV infection<sup>172–174</sup>. Moreover,

chronically elevated IFN $\alpha$  eventually compromises the immune system and facilitates viral persistence and progression to AIDS<sup>171</sup>. Accordingly, one study suggested that blocking type I interferon (IFN $\alpha$ ) signalling during chronic HIV infection with an antibody against IFNAR2 enables the restoration of immune function<sup>175</sup>. However, other investigations related to HIV eradication suggest that non-IFN $\alpha$ 2 type I interferons, such as IFN $\epsilon$ , or type III interferons along with combination ART as well as viral reactivation agents can support the elimination of HIV reservoirs<sup>172,173,176–178</sup>. As the brain constitutes an HIV reservoir in the majority of people living with HIV, even in those on virally suppressive ART<sup>53</sup>, it presents a potential challenge for viral eradication<sup>44–46</sup>. Additionally, it will be important to assess whether therapeutic modulation of the interferon system can remediate NCI. Unfortunately, prior clinical trials of interferon treatment for HIV did not evaluate cognitive endpoints. The timing and duration of interferon treatment might be critical factors for the successful eradication and treatment of NCI<sup>179,180</sup>. IFN $\beta$  induces expression of antiviral C-C motif chemokine receptor 5 (CCR5) ligands<sup>165,181</sup> and, as a therapeutic tool, it seems to cause fewer adverse effects than IFN $\alpha$ <sup>179</sup>. Moreover, owing to its immunomodulatory effect, IFN $\beta$  is approved by the FDA for the treatment of the inflammatory neurodegenerative autoimmune disease multiple sclerosis.<sup>179,180</sup> Thus, on the basis of the available data, it is reasonable to further develop human IFN $\beta$  and IFN $\alpha$  isoforms to therapeutically control chronic HIV infection and delay or prevent the development of HIV-associated NCI.

**Lipocalin 2.** Lipocalin 2 (LCN2) is a component of the innate immune system that counteracts bacterial infection by sequestering iron and regulates biological processes such as cellular energy metabolism and apoptosis<sup>182–186</sup>. LCN2 has been implicated in the regulation of anxiety, emotional and contextual discrimination, and cognition<sup>182,187–190</sup>. In addition, it regulates inflammation<sup>125,129,130</sup> and modulates microglial activation<sup>191,192</sup> and possibly neurodegeneration<sup>125,193,194</sup>. Knockout of the *Lcn2* gene in HIV-gp120 transgenic mice reduced behavioural impairment and neuronal damage<sup>195</sup>. Elevated levels of LCN2 may be neurotoxic and override neuroprotection mediated by CCR5 and its chemokine ligands. Increased plasma and serum levels of LCN2 in people living with HIV correlate with worse processing speed and motor function<sup>196</sup>. Further studies are needed to clarify whether LCN2 can serve as a therapeutic target for HIV-associated NCI<sup>195</sup>.

## BBB dysfunction in HIV

The blood–brain barrier (BBB) consists of vascular endothelial cells welded together via tight junctions surrounded by pericytes and astrocyte end-feet. The BBB is important in selectively filtering substances from the peripheral blood supply into the brain parenchyma. Increased BBB permeability allows harmful products from the systemic circulation to enter the CNS, including both HIV and activated immune cells<sup>197</sup>. HIV affects the function, structure and multicellular components of the BBB, including subcellular structures such as mitochondria, all of which contribute to the regulation of tight junctions and BBB permeability<sup>197</sup>. HIV affects the BBB largely through infection of monocytes and macrophages, which affect the BBB upon crossing<sup>198–201</sup>. HIV also infects astrocytes<sup>202–204</sup> and pericytes<sup>205</sup>, although to a smaller extent than the aforementioned myeloid-lineage cells, as astrocytes and pericytes are resistant to productive infection<sup>143,144</sup>. In people living with HIV with viral suppression on ART, the BBB can also be affected by HIV protein expression and ART-induced inflammation<sup>198,206</sup> as well as by drugs of abuse<sup>207</sup>. Studies on the triggers of BBB breakdown consistently report a decrease in tight junction proteins, with a critical role for HIV proteins<sup>208–211</sup>. Although a comprehensive review of HIV-induced and ART-induced BBB dysfunction is beyond the scope of this Review, mounting evidence suggests that further investigation into this area is warranted.

## Neuroinflammation and inflammasome activation

Neuroinflammation is a major indirect contributor to synaptodendritic degeneration. HIV infection induces an inflammatory state that alters the homeostasis of cytokines in both plasma and CSF<sup>212–215</sup>. Cytokines are immunomodulatory proteins with a variety of functions, including recruiting immune cells to sites of infection and regulating their functions, to resolve infections and repair injured tissues. However, chronic expression of cytokines is harmful. As most neural cells express cytokine receptors<sup>216–219</sup>, cytokines affect and mostly impair neuronal function. Several key biomarkers of inflammation and their clinical correlations in people living with HIV are described below.

Macrophages secrete TNF, which binds lymphotoxin- $\alpha$ <sup>220</sup>. Soluble TNF receptor II (sTNFR<sub>II</sub>) is the cell membrane-bound receptor for TNF and modulates its biological function. Concentrations of sTNFR<sub>II</sub> in plasma correlate strongly with the clinical stage and progression of disease<sup>221,222</sup>. Neopterin is a marker of myeloid cell activation and a biochemical product of the guanosine triphosphate pathway. Neopterin is elevated in people living with HIV and strongly predicts disease progression<sup>223</sup>. Neopterin levels correlate strongly with reactive oxygen species released by myeloid cells, which contribute to

oxidative stress and neurodegeneration. In addition, neopterin induces pro-inflammatory signal transduction<sup>224</sup>. ART reduces CSF neopterin levels; however, neopterin often remains mildly elevated despite suppression of plasma and CSF HIV RNA, raising the important question of whether neopterin elevation is caused by continued CNS infection or persistent CNS injury<sup>224</sup>.

## The NLRP3 inflammasome

Recent studies show that HIV alters NLRP3 inflammasome signalling in CNS microglia, astrocytes and neurons<sup>159,225–229</sup>, suggesting a role for this pathway in HIV neuropathogenesis. The *NLRP3* gene encodes the NALP3 protein (cryopyrin), a member of the NLRP3 inflammasome complex. This complex is an intracellular sensor that detects microbial motifs and endogenous danger signals such as reactive oxygen species and lysosomal damage<sup>230</sup>, resulting in the assembly and activation of the inflammasome<sup>231</sup>. Inflammasome activation leads to caspase 1-dependent release of the pro-inflammatory cytokines IL-1 $\beta$  and IL-18 as well as to pyroptosis, a rapid, inflammatory form of lytic programmed cell death. NLRP3 remains activated in people living with HIV with viral suppression<sup>232,233</sup>. Inflammatory cytokines regulated by NLRP3 (refs. 234–236) are elevated in the blood and CSF of people living with HIV. High IL-1 $\beta$  and IL-18 deplete synaptic serotonin, dopamine and norepinephrine<sup>237</sup>. Both IL-1 $\beta$  and IL-18 affect dendritic sprouting, synaptic plasticity, long-term potentiation, growth factors and neurogenesis<sup>238–240</sup>.

## mTOR and NCI in HIV

Mammalian target of rapamycin (mTOR) is the catalytic subunit of two structurally distinct multiprotein complexes, mTOR complex 1 (mTORC1) and mTORC2 (ref. 241). The functions of mTORC1 include initiation of translation, protein synthesis and autophagy, while mTORC2 orchestrates cytoskeletal organization and cell survival<sup>242</sup>. mTOR regulates the metabolic machinery necessary for glucose, lipid, amino acid and nucleic acid metabolism<sup>243,244</sup>. HIV enhances mTORC1 activity to favour its replication, contributing to dysregulated apoptosis, autophagy and inflammation<sup>245,246</sup>. However, inhibition of mTOR is neuroprotective<sup>247,248</sup> and has beneficial effects relevant to HIV, including improved immune function<sup>249,250</sup> and metabolism<sup>251</sup>, preserved insulin sensitivity<sup>252</sup>, and suppression of T and B cell activation<sup>253,254</sup>.

## AD-like pathogenic mechanisms in HIV

As the mortality rate of HIV has decreased as a result of ART, people living with HIV reach the age when their risk of AD increases. Indeed, histological studies using post-mortem brain tissue suggest that increased interaction of HIV neuropathogenesis with age-dependent neurological diseases might contribute to the pathogenesis of HIV-associated NCI<sup>255–257</sup>. For example, post-mortem studies of the brains of individuals with HIV-associated NCI revealed that the intracellular and extracellular presence of  $\beta$ -amyloid is a common pathological feature<sup>255,257</sup>. Dysfunctional clearance of  $\beta$ -amyloid was shown to correlate with increased levels of HIV RNA and neuroinflammation in the brain<sup>82</sup>. HIV can lead to the accumulation of amyloid in the brain through several mechanisms, including neuroinflammation. Infected microglia release inflammatory cytokines, such as TNF and IL-1 $\beta$ , which increase the production of amyloid precursor protein and its cleavage by  $\beta$ -secretase and  $\gamma$ -secretase, resulting in the release of amyloid that can accumulate in brain tissue<sup>258–261</sup>. Studies have shown that HIV-associated NCI and AD share common pathogenic pathways, including signs of immune activation, decreased levels of microglial receptors involved in the



clearance of protein aggregates and dying brain cells, and compromised neuronal functioning<sup>79,82,156,256</sup>. These findings have led some researchers to postulate that HIV may promote accelerated ageing of the brain<sup>262,263</sup>. For example, multiple studies have indicated reduced levels of microglial-bound TREM2 in the CNS of people living with HIV with NCI<sup>79,264</sup>. This finding might be important because TREM2 dysfunction has been implicated in AD neuropathogenesis, suggesting that HIV neuropathogenesis might share mechanisms with AD, consistent with findings of HIV-associated premature ageing. However, there is evidence that HIV-induced neuropathogenesis is distinct from that of AD. For example, some studies did not detect increased brain  $\beta$ -amyloid in people living with HIV compared with controls<sup>265</sup>. As will be discussed, disruptions in metabolic homeostasis, including autophagy and mitochondrial dysfunction, are also potential common aetiologies of HIV and AD. The prospect of HIV-associated AD-like pathogenesis is the subject of many ongoing studies. Mackiewicz et al.<sup>266</sup> have published a thorough review of the current findings on this topic.

## Comorbidities as sources of NCI in HIV

Ageing people living with HIV have an excess burden of comorbidities, such as diabetes mellitus and depression<sup>267,268</sup>, and these comorbidities have a substantial adverse effect, including frailty<sup>269</sup>, poor adherence to ART and virological failure<sup>270,271</sup>, NCI<sup>272</sup>, poor quality of life<sup>22,273–275</sup>, and early death<sup>276–279</sup>. Comorbidities tend to appear at younger ages in people living with HIV than in the general population and accumulate at a faster rate as people living with HIV age, phenomena often referred to as premature and accelerated ageing<sup>280–282</sup>. Numerous cross-sectional and some short-term longitudinal studies have shown that comorbid medical conditions predispose both people living with HIV and people without HIV to worse neurocognitive outcomes<sup>283–286</sup>. Additionally, an increased burden of comorbidity in people living with HIV with viral suppression is associated with increased brain white matter abnormalities, reduced grey matter volume and loss of neuronal integrity, illustrating continuing effects on the brain even with virally suppressive ART<sup>287</sup>. It is plausible that comorbidities are now the chief source of brain injury and NCI in people living with HIV, rather than HIV disease itself or its treatment with ART<sup>284</sup>.

Various comorbidity indices have been developed to predict the risk of poor cognitive outcomes in people living with HIV<sup>288–292</sup>. These indices incorporate data such as medical history, medication use, laboratory testing and, in some cases, demographic characteristics. In a study of people living with HIV followed for 7 years on average<sup>293</sup>, more rapid neurocognitive worsening correlated with worse average cumulative comorbidity scores and lower nadir CD4<sup>+</sup> T cell count. Poorer visit-specific neurocognition was related to worse comorbidity scores, detectable HIV viral load and higher CD4<sup>+</sup> T cell counts. The impact of comorbidities on neurocognitive decline exceeded that of HIV disease factors. In a second study, a simple comorbidity index composed of the presence or absence of chronic lung disease, hypertension and depression predicted significantly worse cognitive decline over 12 years. HIV infection increases the prevalence of all three of these conditions<sup>294–299</sup>. Treatments for these comorbidities were at best partially effective, and more successful treatment or prevention of these comorbidities might improve neurocognitive outcomes. Effective treatment of comorbidities in people living with HIV may require different strategies from those for comorbidities in people without HIV. For example, depression in people living with HIV is often refractory to typical anti-depressant medications such as serotonin reuptake inhibitors<sup>300–302</sup>. Because chronic inflammation persists

despite viral suppression, it might be that inflammation drives depression in people living with HIV to a greater extent than in people without HIV. Inflammation in people living with HIV also confers an increased risk of hypertension and chronic lung disease<sup>303–306</sup>. Improvement in hypertension can be achieved with exercise, dietary interventions and anti-hypertensive medications<sup>307,308</sup>. Abundant evidence in other clinical situations has shown that successful treatment of comorbidities does indeed benefit neurocognition<sup>309,310</sup>. Treatment of comorbidities associated with cognitive decline is particularly important in middle age<sup>311–314</sup>.

## Abdominal obesity, metabolic syndrome and HIV-associated NCI

Abdominal obesity is a central component of metabolic syndrome, a very common comorbidity in people living with HIV. Metabolic syndrome was present in 20% of 2,247 antiretroviral-naïve individuals entering ART clinical trials and developed de novo in an additional 27% after 2.8 years<sup>315</sup>. The frequency of the metabolic syndrome increases with age and is associated with increased risk for and severity of NCI in people living with HIV<sup>316</sup>. The severity of NCI in people living with HIV correlates with waist circumference (a measure of abdominal obesity<sup>317</sup>), as also occurs in HIV-negative populations<sup>318</sup>. Abdominal obesity is a major risk factor for systemic inflammation, which is mediated by an influx of M1 pro-inflammatory macrophages that replace resident M2 anti-inflammatory macrophages<sup>319</sup> in lipid-laden adipocytes. In older people with obesity and living with HIV, more than 70% had elevated serum TNF, insulin resistance and impaired endothelial function<sup>320</sup>.

## CNS insulin resistance

Preclinical data implicate insulin resistance in the CNS in HIV-associated brain injury and suggest that insulin treatment might be beneficial. Neurons in the hippocampus, cerebellum and cerebral cortex express insulin receptors<sup>321–324</sup>. Insulin treatment of HIV-infected primary human microglia suppressed HIV p24 levels and reduced *CXCL10* and *IL6* transcript levels<sup>325</sup>. Insulin treatment of primary human neurons prevented HIV Vpr-mediated cell process retraction and death<sup>325</sup>, suggesting that insulin acts as a neurotrophic factor to improve survival. In a mouse model of HIV-associated NCI, NCI correlated with reductions in hippocampal dendritic arbours and downregulation of neuronal function genes; intranasal insulin reversed these changes and completely reversed NCI. Intranasal insulin treatment also reduced brain HIV DNA in mice<sup>326</sup>. Clinical data supporting the use of insulin for HIV-associated NCI and other conditions, such as mild cognitive impairment, have recently emerged<sup>327–329</sup>. A randomized, double-blind, placebo-controlled study of intranasal insulin for people living with HIV with mild-to-moderate cognitive impairment (NCT03277222) was recently completed, and the results are being analysed.

## Co-infections

People living with HIV frequently present with co-infections. Although some co-infections might not markedly impact HIV disease, others affect the natural history of HIV infection and vice versa<sup>330–332</sup>. Several common co-infections, such as HCV, tuberculosis, cryptococcal meningitis and malaria, have been linked with worse NCI in people living with HIV<sup>333–337</sup>. The mechanisms underlying this increased risk of NCI in people with HIV co-infections vary by type of co-infection, and many remain unclear. Evidence is emerging that herpesviruses, including cytomegalovirus (CMV) and Epstein–Barr virus (EBV), can also contribute to NCI in people living with HIV. For example, higher anti-CMV



IgG titres were associated with worse HIV-associated NCI<sup>338–341</sup>. Higher anti-CMV IgG concentrations in blood were associated with higher CSF viral load and higher sCD163 (a marker of activated monocytes), suggesting that the CMV-related immune response at least indirectly influences pathological events in the CNS, perhaps by increased migration of activated monocytes, increased sCD163 or by infected CD4<sup>+</sup> T cell-derived HIV RNA into this protected compartment. CMV is likely to contribute to HIV-associated NCI through metabolic<sup>317,342,343</sup> and vascular disease<sup>284,344</sup> and by replicating in vascular endothelial and smooth muscle cells, leading to macrophage infiltration of vessel walls and promoting atherogenesis<sup>345,346</sup>. An ongoing clinical trial (NCT04840199) is testing whether the potent anti-CMV drug letermovir can reduce inflammation and atherosclerosis in people living with HIV, with the aim of improving neurocognitive performance. Detection of EBV DNA in CSF was associated with increased levels of biomarkers of neuronal damage and inflammation<sup>347</sup>.

## Mitochondrial dysfunction

Mitochondrial dysfunction has downstream effects on autophagy, metal ion signalling, and other pathways and vice versa; intracellular and intercellular communication must be kept in mind when establishing research paradigms. Thus, targeting metabolism is promising for therapeutic discovery, and such discoveries might not only lead to help for people living with HIV but also for people with other CNS disorders.

### Mitochondria in HIV CNS dysfunction

Mitochondrial dysfunction has long been implicated in the pathogenesis of HIV-associated NCI<sup>348–351</sup>. Neurons require high levels of mitochondrial activity to maintain and form new synapses and are thus highly dependent upon energy substrate from blood and a healthy network of mitochondria. In a healthy brain, astrocytes transport glucose across the BBB into the brain parenchyma and provide an energy substrate to neurons in the form of lactate and glutamine<sup>352,353</sup>. Perivascular macrophages and microglia primarily rely on oxidative phosphorylation to generate ATP to fuel their functions in immune surveillance of the brain parenchyma. During brain injury, such as occurs with HIV infection, astrocytes and microglia shift their metabolic profiles to oxidative phosphorylation and glycolysis, respectively<sup>354,355</sup>. These metabolic shifts in glia might lead to metabolic stress and mitochondrial dysfunction in neurons<sup>355–362</sup>. Thus, the metabolic interplay between

neurons, astrocytes and macrophages might impair brain health in HIV-associated NCI.

Almost every aspect of mitochondrial function is negatively affected by HIV or ART. Mitochondrial biogenesis, mitochondrial fission and fusion, and mitophagy are altered in the brains of people living with HIV and HIV-associated NCI<sup>358,363,364</sup>. Mitochondrial biogenesis proteins are reduced in neurons and increased in astrocytes in the brains of people living with HIV on ART and in *in vitro* and *in vivo* models for HIV-induced and ART-induced neurotoxicity<sup>358,359</sup>. Mitochondrial fission and fusion are compromised by gp120 but possibly also by other HIV proteins, and the trafficking of mitochondrial proteins along neuronal microtubules is also compromised, resulting in damaged and elongated mitochondria in neurons<sup>135,136,364,365</sup>. Inflammatory cytokines induce increased glycolysis and oxidative phosphorylation in astroglia and confer neurotoxicity<sup>358</sup>. Several studies have shown that blocking this increase in metabolic activity in stimulated astroglia, for example, by using cannabinoid receptor agonists and caloric restriction mimetics, might be neuroprotective<sup>358,366–368</sup>. Mitochondria are key regulators of the sequestration and signalling of metal ions, particularly calcium and iron, both of which are dysregulated by HIV proteins, including Tat, nef and VPR<sup>369–374</sup>. Animal models expressing gp120 in the brain induce mitochondrial biogenesis in astroglia while concomitantly reducing it in neurons<sup>359–362</sup>. Inflammatory cytokines induce increased glycolysis and oxidative phosphorylation in astroglia and confer neurotoxicity<sup>358</sup>. Several studies have shown that blocking this increase in metabolic activity in stimulated astroglia might be neuroprotective<sup>358,366–368</sup>. In line with the neuroprotective properties of caloric restriction mimetics, exercise is a potential intervention (discussed below) that might provide neuroprotection in part through improved mitochondrial function in neurons, which might help to ameliorate HIV-associated NCI<sup>375–380</sup>.

### Autophagy and lysosomal biology

As the molecular processes of autophagy and the lysosomal systems were deciphered in detail<sup>381–386</sup>, it became clear that HIV might affect this important process for cellular renewal during times of physiological stress<sup>129,247</sup>. Although autophagy often plays a defensive role in viral infections, some viruses can hijack these cellular processes to facilitate infection and replication. The number of autophagosomes in the brain is increased in people living with HIV compared with control individuals<sup>247</sup>. HIV gp120 and Tat alter autophagosome,

**Table 1 | Neurotoxicity of currently used antiretrovirals**

Drug class	Examples	Clinical findings	Proposed mechanism of toxicity
NRTIs	Tenofovir alafenamide, abacavir	Psychosis, mania <sup>457</sup> , chronic kidney disease <sup>458,459</sup>	Inhibition of mitochondrial DNA polymerase- $\gamma$ <sup>460</sup> , energy depletion and oxidative stress <sup>461–463</sup> , ER stress <sup>464</sup> , mitochondrial DNA depletion <sup>465,466</sup>
NNRTIs	Efavirenz, rilpivirine	Dizziness, insomnia, vivid dreams, headache, hallucinations, mania, depression <sup>467</sup> , anxiety <sup>468</sup>	Increased ER stress and mitochondrial toxicity <sup>469</sup>
Protease inhibitors	Ritonavir, lopinavir, darunavir	Nausea, insomnia, circumoral paraesthesias <sup>470</sup>	Reduced oligodendrocyte maturation <sup>471</sup> , astrocyte glutamate homeostasis <sup>472</sup> and synaptic acetylcholine <sup>473</sup> , worse small vessel disease <sup>474</sup> , oxidative stress <sup>475</sup>
INSTIs	Dolutegravir, bictegravir, raltegravir, elvitegravir	Diarrhoea, nausea, headache <sup>476</sup> , neural tube defects <sup>477</sup> , insomnia <sup>478,479</sup> , depression, anxiety <sup>480</sup>	Increased production of reactive oxygen species in astrocytes <sup>480</sup> , integrated stress response (elvitegravir) <sup>475</sup>
Entry inhibitors	Maraviroc, cenicriviroc, ibalizumab	Bronchitis, nasopharyngitis, oesophageal candidiasis <sup>481</sup>	No notable CNS toxicity reported <sup>482–485</sup>

ER, endoplasmic reticulum; NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; INSTIs, integrase strand transfer inhibitors. <sup>a</sup>Dolutegravir and bictegravir have a greater effect than raltegravir and elvitegravir<sup>486–489</sup>.

**Table 2 | Selected past and ongoing human clinical trials for HIV-associated NCI illustrating mechanisms described in this Review**

Drug (NCT number)	Targeted mechanism(s)	Sample and design	Status	Key findings	Ref.
Memantine (00000867)	Reduce glutamate toxicity	n=99; placebo controlled	Completed	Ineffective	490
Selegiline (00013585)	Reduce oxidative stress	n=128; placebo controlled	Completed	Ineffective	411
Intranasal insulin (03081117)	Neuroprotection	n=21; placebo controlled	Completed	Improved performance on neuropsychological tests related to memory and attention	491
Statins (01600170)	Reduce inflammation	n=11; crossover	Completed	No normalization of monocyte gene expression patterns; no changes in monocyte surface markers or plasma mediators	492
Minocycline (00855062)	Reduce inflammation	n=73; placebo controlled	Terminated	No change in HIV-associated NCI	413
Fluconazole/paroxetine (01354314)	Neuroprotection	n=45; placebo controlled	Completed	Fluconazole showed no benefit in cognition and an increase in multiple markers of cellular stress; paroxetine showed improvement in a summary neuropsychological test measure	415
Tesamorelin (02572323)	Reduce inflammation, neuroprotection	n=100; crossover	Recruiting and ongoing	Results not yet published. Outcomes: change in neuropsychological performance, change in IGF1, MRS neuroinflammation, hippocampal volume	423

IGF1, insulin-like growth factor 1; NCI, neurocognitive impairment; NCT, National Clinical Trial; MRS, magnetic resonance spectroscopy.

lysosome and endosome function in mouse models and neuronal cultures<sup>387–389</sup>. Pharmacological compounds, such as rapamycin, an mTOR inhibitor, show neuroprotective properties that coincide with the normalization of autophagy markers and levels of astrogliosis and microgliosis<sup>388</sup>. Gene delivery of the autophagy nucleation protein, beclin 1, also showed promising results in the gp120 transgenic mouse model, reducing neurodegeneration markers and gliosis while enhancing autophagy proteins<sup>387</sup>. Thus, targeting autophagy might be worth further investigation as a therapeutic avenue for people living with HIV.

### Iron regulation in HIV CNS dysfunction

Several studies have implicated disruptions in iron regulation and signalling as an aetiology of HIV-induced neurological dysfunction<sup>373,374,390,391</sup>. These findings are particularly important because iron ions regulate the intracellular redox state, which modulates the function of mitochondria, autophagosomes, lysosomes and practically all cellular signalling<sup>370,371,392</sup>. Intracellular iron levels affect HIV replication by enhancing Tat escape from endolysosomes, which might be a mechanism that promotes neurotoxicity in people living with HIV<sup>393</sup>.

### The gut microbiome

The gut is an important reservoir for HIV and acts as a hub for its dissemination<sup>310</sup>. Some gut microbes produce metabolites such as short-chain fatty acids (for example, acetic acid, propionic acid and butyric acid) and neurotransmitters (for example, acetylcholine, GABA and serotonin). These metabolites can communicate to the brain via the bloodstream and vagus nerve. Changes in gut microbial composition and metabolites have been associated with altered neurotransmitter signalling, neurogenesis, microglial development and response, myelination, neurogenesis, and diseases including Parkinson disease, AD and amyotrophic lateral sclerosis<sup>394–396</sup>. Interestingly, experimentally induced colitis in rhesus macaques resulted in a neuroinflammatory profile like that observed in SIV-infected rhesus macaques, highlighting the importance of the gut–brain axis<sup>397</sup>. For example, inflammatory cytokines, including interferon, activate indolamine dioxygenase, an enzyme that metabolizes tryptophan, ultimately lowering serum tryptophan concentrations. Indeed, tryptophan levels are lower in

people living with HIV compared to people without HIV<sup>398</sup>. Further studies investigating treatments targeting the gut microbiota in people living with HIV are needed.

### Antiretroviral medication neurotoxicity

Although ART has been transformative in the management of HIV infection, antiretroviral drugs can induce neurotoxicity directly or indirectly, contributing to cognitive impairment<sup>399–401</sup>. The neurotoxic effects of currently used antiretroviral drugs are summarized in Table 1. Notably, the ‘greying’ (shifting age of the population) of people living with HIV on virally suppressive ART is linked to polypharmacy that includes both ART and non-ART drugs, increasing the risk of drug–drug interactions that could worsen neurotoxicity and NCI<sup>402,403</sup>. Age-related changes in drug distribution, binding proteins, metabolism and elimination can lead to increased CNS drug exposure in older people living with HIV<sup>404–406</sup>, further predisposing to NCI. In addition, ageing causes structural and functional changes in the BBB that result in increased BBB permeability, which can affect ART CNS pharmacokinetics<sup>407–409</sup>. Information on ethnic and sex disparities in this area is scant.

### Experimental treatments for HIV-associated NCI

Examples of past and current human clinical trials of treatments for HIV-associated NCI – selected to illustrate mechanisms discussed in this Review – are listed in Table 2. Some of these treatments have already been approved for other neurodegenerative diseases (for example, selegiline and memantine)<sup>410,411</sup> or represent re-purposing of treatments for other conditions (for example, minocycline, fluconazole, intranasal insulin (NCT03277222), statins (NCT01600170))<sup>412–417</sup> and antioxidants (coenzyme Q<sub>10</sub>, haem oxygenase 1 and dimethyl fumarate)<sup>418–420</sup>. A comprehensive list is beyond the scope of this Review, but a summary of the interventions that are most relevant to the mechanisms discussed here is also provided (Table 3).

### Tesamorelin

Tesamorelin, an analogue of human growth hormone-releasing hormone (hGHRH), has been approved by the FDA to treat HIV-related abdominal obesity but has not been tested for the treatment of NCI in

people living with HIV. Tesamorelin stimulates physiological growth hormone (GH) secretion and restores the normally pulsatile nocturnal rhythm of GH release that is seen in GH-deficient conditions such as HIV<sup>421</sup>. In addition to reducing abdominal obesity, tesamorelin also reduced C-reactive protein (CRP), an inflammatory mediator released from the liver<sup>422,423</sup>. A second mechanism by which tesamorelin might benefit neurocognition is by stimulating the production of insulin-like growth factor 1 (IGF1), a neurotrophic hormone. IGF1, in turn, stimulates brain blood flow and angiogenesis, improves neurogenesis, neurite out-growth and synaptic complexity, and is neuroprotective against oxidative stress<sup>424</sup>. Blood IGF1 levels correlate with overall cognitive performance<sup>425</sup>, including perceptual motor performance, fluid intelligence and processing speed<sup>426,427</sup>. In animals, when IGF1 levels are increased in the hippocampus by treatment with IGF1, deficits in cognitive functions are corrected<sup>428</sup>. An ongoing clinical trial (NCT02572323) hypothesizes that tesamorelin will attenuate systemic inflammation and immune activation in people living with HIV with viral suppression and cognitive impairment.

## GPLD1

GPLD1, an enzyme also known as phosphatidylinositol-glycan-specific phospholipase D, can mimic the beneficial effects of exercise (discussed below). Levels of GPLD1 are increased by physical activity, improving antioxidant systems<sup>429</sup> and anti-inflammatory responses<sup>430</sup>. Novel mechanistic associations have been reported between physical activity, cognition and GPLD1 levels<sup>431</sup>. GPLD1 from the liver cleaves glycosylphosphatidylinositol and glycosylphosphatidylinositol-anchored proteins to regulate mitochondrial function and regulate inflammation, clotting and vascular integrity<sup>432–434</sup>. GPLD1 also ameliorates oxidative stress and inflammation<sup>435,436</sup>. In mice, systemic administration of GPLD1 recapitulated the neurogenic and cognitive benefits of physical activity<sup>431</sup>. Furthermore, in mice, higher GPLD1 levels dampened inflammation and normalized coagulation, factors shown to be fundamentally

dysregulated in people living with HIV and to predict declines in cognition, mood and other outcomes even in people living with HIV with viral suppression<sup>437</sup>. By mimicking the effects of physical activity, exogenous administration of GPLD1 or other interventions to modify this pathway might be beneficial for HIV-associated NCI and are currently being tested in animal models.

## Effectiveness of pharmacological therapy for HIV-associated NCI

A consistently efficacious treatment or prevention for HIV-associated NCI has not yet been discovered, for multiple reasons. Clinical trials for NCI frequently fail despite promising preclinical results owing to inadequate participant recruitment and/or retention, fundamental differences between animal models and human participants, and unforeseen adverse effects. More specifically, the pathogenesis of HIV-associated NCI remains unclear. HIV-associated NCI can result from legacy effects, inadequate viral suppression in the CSF, persistent inflammation, direct or indirect neurotoxicity from antiretroviral drugs, combinations of these factors, or other uncharacterized factors. Without a clear pathological target, developing specific treatment modalities becomes exceptionally challenging, and the impetus for the many prior clinical trials came either from medications that showed neuroprotection in other diseases or from incidental findings in the clinic. Pathophysiological mechanisms of NCI in people living with HIV might vary between ethnic and/or racial groups, and sociocultural and behavioural factors might interact with the pathophysiological mechanisms underlying NCI. To properly confront this disease entity, more research to provide answers to preclinical questions about NCI is essential. Furthermore, future studies incorporating culturally relevant psychosocial, environmental, biomedical and genetic factors might best inform the identification of therapeutic targets and the development of clinical interventions to promote the neurocognitive health of the diverse population of people living with HIV.

**Table 3 | Examples of potential treatment strategies for HIV-associated NCI illustrating mechanisms described in this Review**

Intervention	Proposed mechanism	Status of research	Effectiveness
Iptakalim	Reduced neuroinflammation	In vivo studies	Inhibited microglia-mediated neuroinflammation in rats <sup>493</sup>
Antibody to IFNAR2	Blocks downstream interferon-stimulated cascade	In vivo studies	Reduced inflammation in animals <sup>494</sup>
Intranasal IFNβ	IFNβ has antiviral effects and anti-inflammatory effects	In vivo study in model system	Neuroprotection in vivo <sup>465</sup>
Interferons with or without ART	Type I interferons reduce viral replication and prevent infection of new targets	Human clinical trials (NCT02471430, NCT02767193, NCT01935089, NCT02227277)	Ongoing, aiming at reduced HIV reservoir <sup>495</sup>
Letermovir	Antiviral against cytomegalovirus, reducing inflammation	Proposed secondary end point in ongoing human clinical trial (NCT04840199)	Ongoing
Physical exercise	Improved mitochondrial biogenesis, hippocampal neurogenesis <sup>a</sup>	In vivo studies	In mice, exercise is associated with mitochondrial biogenesis and hippocampal neurogenesis <sup>496</sup>
Mindful meditation	Improved function in brain networks supporting attention and emotion regulation <sup>a</sup>	Human clinical trial (NCT02936401)	Not yet published
Ketogenic diet	Antioxidant increases mitochondrial biogenesis <sup>a</sup>	Human clinical trial	Ketogenic drink improved cognition in mild cognitive impairment <sup>497</sup>

ART, antiretroviral therapy. <sup>a</sup>Non-pharmacological interventions.



## Non-pharmacological interventions

Pharmacological therapeutics are important, but non-pharmacological approaches are also needed. These therapies can affect metabolism and inflammatory processes in ways that drugs cannot. Despite advances in our understanding of HIV-associated NCI pathogenesis, the translation of findings into the clinical setting has been disappointing. Medical approaches targeting different mechanisms have not resulted in better primary outcomes. Owing to comorbidities, people living with HIV already require several medications. Thus, attention should be placed on non-pharmacological interventions for HIV-associated NCI, including sleep, physical exercise, diet and cognitive training interventions.

More than half of people living with HIV with NCI report symptoms of insomnia<sup>438–441</sup>. Compromised sleep quality and duration are often connected to drug or alcohol use and other comorbidities such as depression or obstructive sleep apnoea<sup>442,443</sup>. Poor sleep health leads to reduced cognitive performance in memory, learning and concentration. In healthy individuals,  $\beta$ -amyloid levels in the brain on PET imaging were elevated after a single night of sleep deprivation<sup>444</sup>. Reduced sleep can also activate the immune system and increase the production of inflammatory mediators<sup>445,446</sup>.

The benefits of caloric restriction, ketogenic diets, intermittent fasting and physical activity – all of which improve metabolic function – need to be investigated for therapeutic efficacy. One trial (NCT02936401) is currently assessing the use of mindfulness-based stress reduction as a method to improve function in people living with HIV with NCI who are older than 60 years. Another trial (NCT03483740) is testing cognitive remediation group therapy in a similar cohort of older people living with HIV with NCI.

As mentioned above, physical activity has a plethora of positive effects at the molecular level in the brain by increasing levels of neurotrophins and growth factors and by modulating synaptic plasticity, neurogenesis and blood flow<sup>447</sup>. Physical activity improves cognition, mood and general health status in the general population, and we and others have published findings showing correlations between greater physical activity and better cognition in people living with HIV<sup>448–454</sup>.

Cognitive training is another non-pharmacological intervention that has been associated with improvements in cognition and daily function in people living with HIV. Some computerized cognitive training programmes might improve cognition in people living with HIV<sup>455</sup>. The domains of speed of information processing and attention and/or working memory seem the most likely to show improvement<sup>456</sup>. However, there are gaps in understanding the type and dose of cognitive training that might be most beneficial. There is a need to consider socio-cultural factors in the development of all types of non-pharmacological interventions for people living with HIV to assure their acceptability and utility among diverse people living with HIV, particularly those living in regions of the world where health-care access is limited and resources scarce.

## Conclusions

Findings from preclinical and clinical studies suggest that HIV-associated NCI is a heterogeneous disease with a complex multi-system pathogenesis. Several mechanisms can contribute to neurodegeneration and NCI in people living with HIV, including mitochondrial toxicity, endoplasmic reticulum stress, oxidative species and neurotoxicities of specific antiretroviral medications. A substantial number of experimental therapies, including anti-inflammatory drugs, are not beneficial in the treatment of NCI in people living with HIV. We have presented promising avenues for the improvement of cognition in the ageing cohort

of people living with HIV. Lastly, we delineated non-pharmacological treatments that could be readily implemented in the daily lives of people living with HIV. We think that, with the current rapid scientific advances in the field of HIV-associated NCI, more treatment options will be available for people living with HIV and NCI.

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<sup>1</sup>Department of Neurosciences, University of California San Diego, La Jolla, CA, USA. <sup>2</sup>Department of Psychiatry, University of California San Diego, La Jolla, CA, USA. <sup>3</sup>Department of Medicine, Duke University, Durham, NC, USA. <sup>4</sup>Department of Psychiatry and Behavioral Sciences, Duke University, Durham, NC, USA. <sup>5</sup>School of Medicine, Division of Biomedical Sciences, University of California Riverside, Riverside, CA, USA. <sup>6</sup>Department of Cellular and Molecular Medicine, University of California San Diego, La Jolla, CA, USA.