# New horizons in HIV neuropathogenesis: thinking beyond the brain

*Thomas A. Angelovich*[a,b,c], *Kathleen Busman-Sahay*[d], *Janna Jamal Eddine*[a], *Melissa J. Churchill*[a,b], *Afam A. Okoye*[d,e] *and Jacob D. Estes*[d,e]

**Purpose of review**
Neurocognitive disorders and neuropathology continue to affect a subset of people with HIV (PWH) despite long-term viral suppression with antiretroviral therapy (ART). The mechanisms driving persistent neuropathology remain incompletely defined, and current therapeutic options are largely nonspecific and patient-dependent. This review analyses emerging evidence on HIV-associated neuropathology in ART-suppressed PWH, with a particular focus on the role of the gut–brain axis.

**Recent findings**
Recent studies demonstrate that the CNS is a stable and transcriptionally active tissue reservoir, which may sustain chronic microglial activation, pro-inflammatory signalling, and synaptic injury. In parallel, accumulating evidence implicates systemic inflammation and gut barrier dysfunction as key contributors to neuroinflammation, linking microbial translocation and gut–brain axis perturbations to cognitive decline in PWH. Furthermore, persistent gut inflammation may result in enteric nervous system (ENS) dysfunction and aberrant signals that directly results in neuroinflammation and neuropathology. These mechanistic insights have driven evaluation of adjunctive strategies targeting HIV transcription and inflammatory pathways as potential approaches to limit neuropathogenesis.

**Summary**
Neuropathology in ART-suppressed PWH arises from convergent processes involving CNS HIV reservoirs, myeloid-driven neuroinflammation, systemic immune activation and gut-derived injury, rather than residual brain infection alone. Defining the relative contribution of these pathways in PWH and developing CNS-penetrant interventions that silence viral transcription, restore gut integrity and dampen systemic inflammation, will be critical to preventing and treating HIV-associated neuropathology.

**Keywords**
antiretroviral therapy, gut–brain axis, HIV neuropathogenesis, HIV-associated brain injury, neuroinflammation

## INTRODUCTION

Despite viral suppression of HIV in the blood, a subset of antiretroviral therapy (ART)-suppressed people with HIV (PWH) develop HIV-associated neurocognitive disorders and are impacted by legacy effects. These disorders can lead to memory, cognitive and motor function deficits that affect a person's ability to live and function independently [1–5]. Several potential mechanisms of neuropathology in ART-suppressed PWH exist, ranging from legacy effects of acute infection and/or periods of poor viral suppression, ongoing viral activation within the brain, ongoing viral activation in peripheral reservoirs, and long-term gut damage and dysfunction [3–7,8,9–13,14▪]. Emerging evidence suggests that neuropathogenesis in ART-suppressed PWH should no longer be viewed as an isolated CNS process, but rather as a systemic inflammatory disorder involving bidirectional communication between the brain and peripheral tissues. In this review, we describe current understanding of the discrete impact of each pathway on neuropathology, current efforts to limit neuropathology, and the role of targeting sources outside

[a]ATRACT Research Centre, School of Health and Biomedical Sciences, Royal Melbourne Institute of Technology (RMIT) University, [b]Life Sciences, Burnet Institute, [c]Department of Infectious Diseases, The University of Melbourne at The Peter Doherty Institute for Infection and Immunity, Melbourne, Victoria, Australia, [d]Vaccine and Gene Therapy Institute and [e]Oregon National Primate Research Center, Oregon Health & Science University, Beaverton, Oregon, USA

Correspondence to Jacob D. Estes, Vaccine and Gene Therapy Institute, Oregon Health & Science University, Beaverton, Oregon, USA.
Tel: +1 503 418 2727; e-mail: estesja@ohsu.edu

**Curr Opin HIV AIDS** 2026, 21:364–371

DOI:10.1097/COH.0000000000001052



Copyright © 2026 Wolters Kluwer Health, LLC. All rights reserved.

## KEY POINTS

- HIV-associated cognitive impairment/injury and chronic neuroinflammation remain a significant issue for ART-suppressed PWH.
- The brain is a stable reservoir of transcriptionally active HIV, which partly, but not fully, accounts for the neuroinflammation and brain injury observed in ART-suppressed PWH.
- Gut barrier dysfunction, microbial translocation and ENS activation are likely contributors to systemic inflammation and CNS neuroinflammation, implicating the gut–brain axis in neuroinflammation in ART-suppressed PWH.
- Therapeutic strategies targeting persistent transcription in CNS and non-CNS reservoirs as well as gut-directed anti-inflammatory interventions represent promising adjuncts to ART to limit neuropathogenesis in PWH.

the brain on improving neurocognitive outcomes in ART-suppressed PWH.

## EVIDENCE OF ONGOING NEUROPATHOLOGY DESPITE LONG-TERM ANTIRETROVIRAL THERAPY

### Clinical evidence

Despite long-term ART, ~30% of PWH experience some form of neurocognitive impairment. These conditions include HIV-associated neurocognitive disorders, and HIV-associated brain injury, which consist of both long-term chronic all-cause neurocognitive impairment, as well as HIV-associated legacy effects from acute unsuppressed infection [2–5]. As the number of people aging with HIV continues to increase, delineating the mechanisms by which HIV-related factors drive neurocognitive decline independent of other traditional risk factors including smoking and substance abuse remains a critical challenge. Importantly, valuable preclinical translational nonhuman primate (NHP) models can provide direct mechanistic insight into the role novel and traditional risk factors play in HIV, Simian Immunodeficiency Virus (SIV) and neurologic disease. Neuropsychological testing has shown that PWH score lower in attention/working memory, motor function and information processing speed despite over 15 years of ART compared to HIV seronegative individuals [13]. In addition, PWH also self-report a higher number of cognitive difficulties in daily life [13]. Structural MRI analysis has demonstrated reduced proportions of subcortical grey and white matter [13,15,16], a pathology also observed in individuals with Alzheimer's diseases. Further MRI and PET scanning has demonstrated a lower synaptic density in the fronto-striato-thalamic circuits of ART-treated individuals [17] as well a chronically activated brain innate immune response and microglia activation [18]. Collectively, these observations suggest that effective plasma viral suppression does not equate to complete neurological recovery, and that ongoing subclinical brain injury may persist despite decades of ART.

### Cellular evidence of persistent neuroinflammation

Studies in CSF and autopsy brain tissue from both PWH and NHP models have revealed increased measures of neuroinflammation during ART suppression [8,11,19–24▪] (Fig. 1). Specifically, plasma and CSF analysis studies have detected heightened levels of interferon-stimulated gene expression, pro-inflammatory cytokines and chemokines linked to neurodegeneration in PWH [23,25]. At the cellular level, we have demonstrated that frontal cortex brain tissue from both ART-suppressed and non-ART-suppressed PWH contain significantly higher frequencies of astrocytes and myeloid cells expressing the interferon stimulated gene *Mx1* and the proinflammatory cytokine TNFα relative to HIV-seronegative individuals [8▪]. Importantly, the frequency of $Mx1^+$ myeloid cells correlated with levels of HIV DNA within the brain, suggesting that persistent local viral reservoirs may contribute to ongoing neuroinflammation even in the context of viral suppression [8▪]. Consistent with these observations, analysis of postmortem human brain tissue have identified prominent microglial nodules distributed throughout both grey and white matter in PWH with symptomatic neurocognitive disorders [26▪]. These neuropathological features are associated with ongoing HIV RNA expression in myeloid cells [26▪], implicating local viral activity in contributing to chronic neuroinflammatory processes in the brain. Of note, a recent preprint characterizing gene expression across multiple brain regions from PWH using single nuclei sequencing also demonstrated heightened cell activation linked to HIV transcripts [27▪].

These findings are further supported by recent studies using brain organoid models [28–30]. In these systems, HIV infection of microglia elicits a pro-inflammatory response, characterized by elevated levels of key cytokines and chemokines, including IL-6, IP-10, TNFα, IL-8, MCP1, IFNα, IL-1β and IFNβ [28]. Transcriptomic analysis further substantiates this inflammatory phenotype. Differential gene expression profiling demonstrated significant upregulation of caspase-5 and DTHD1, which has recently been



Copyright © 2026 Wolters Kluwer Health, LLC. All rights reserved.

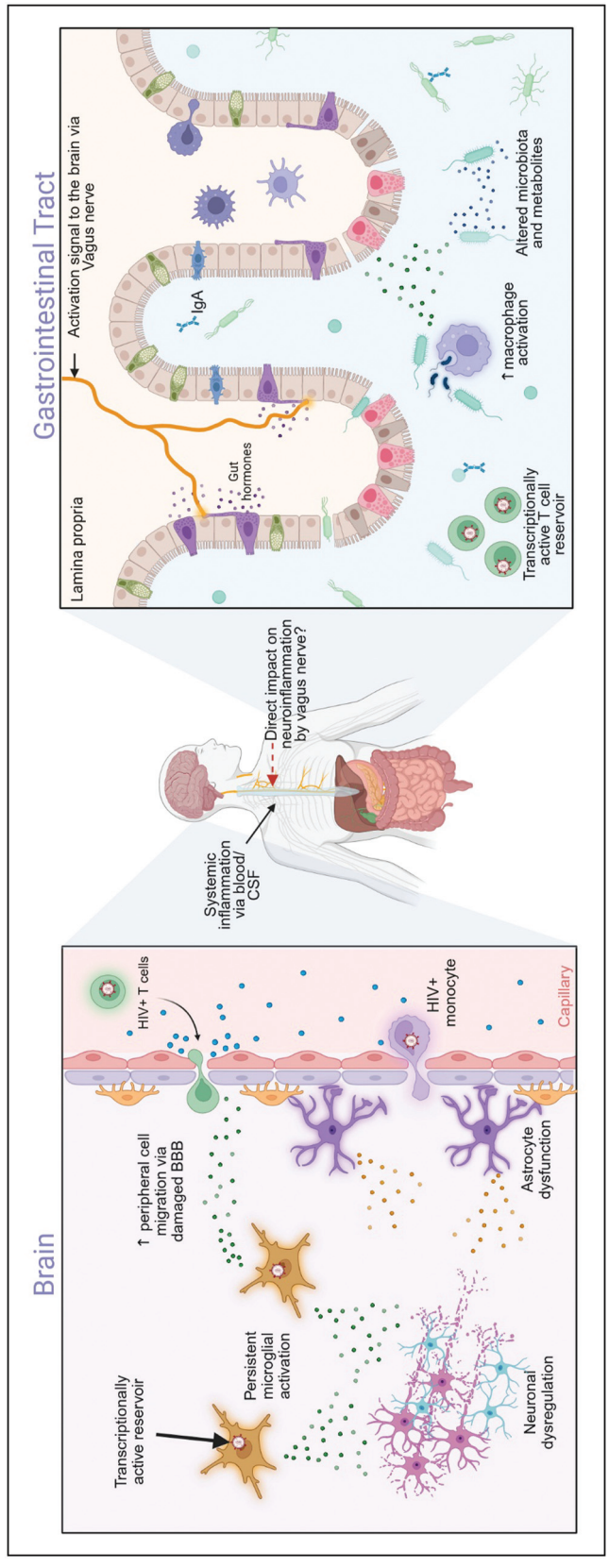


**FIGURE 1.** Gut–brain interactions in HIV-associated neuroinflammation. Schematic overview of bidirectional crosstalk between the gastrointestinal tract and central nervous system (CNS) during HIV infection. In the brain (left), HIV enters via infected T cells and monocytes crossing a compromised blood–brain barrier (BBB), establishing reservoirs in resident cells, particularly microglia. Despite antiretroviral therapy (ART), reservoirs persist that are transcriptionally, and potentially, translationally activate driving persistent microglial activation, astrocyte dysfunction, and inflammatory mediator release, leading to neuronal dysregulation despite viral suppression with ART. In the gut (right), the lamina propria harbours transcriptionally active HIV-infected T cells, which may drive viral induced cellular activation. HIV-associated damage to the epithelial barrier, dysbiosis and altered microbial products and metabolites also disrupt mucosal immunity and promote local inflammation and can enter the blood. Gut-derived signals (microbial products, cytokines and hormones) influence the brain via ENS activation and local neuroinflammation, systemic and cerebrospinal fluid inflammation leading to BBB dysfunction. It is hypothesized that direct signals can also propagate via the vagus nerve to the CNS, driving neuroinflammation. Together, gut-derived signals and CNS infection amplify systemic inflammation and contribute to HIV-associated neurocognitive impairment. Created in BioRender.



Copyright © 2026 Wolters Kluwer Health, LLC. All rights reserved.

reported to be active and highly expressed in the brains of individuals with Alzheimer's disease [31] and multiple sclerosis lesions [32].

In-vivo evidence further supports a role for myeloid-driven neuroinflammation. In rhesus macaque models of SIV encephalitis, infection leads to marked alterations in brain myeloid cell populations, including the emergence of microglia-like cells that express high levels of chemo-attractants capable of recruiting CNS-associated macrophages [33]. Using a model of chronic ART-suppressed SIV infection, we further showed heightened measures of microglial and astrocyte cell activation persists despite no detectable SIVE, indicating the presence of cell activation and BBB dysfunction even in the presence of suppressive ART [7]. Interestingly, cell activation was not correlated with levels of SIV DNA+ or RNA+ cells, suggesting non-CNS intrinsic factors were associated with brain cellular activation.

Taken together, these studies position the CNS as a site on ongoing cellular activation that is not resolved by suppressive ART.

## POTENTIAL MECHANISMS OF NEUROPATHOLOGY

### HIV reservoirs in the central nervous system

Recently, the brain parenchyma has been comprehensively defined as a stable reservoir of both intact and defective HIV DNA despite long-term, effective ART, which has been proposed as a contributor of ongoing neuropathology [6,9,11,14,34–37▪]. HIV persists within microglia, perivascular macrophages and astrocytes [14,34,38–41▪], with microglia identified as the major CNS viral reservoir. We and others have demonstrated the presence of intact and defective HIV DNA and also the detection of p24+ cells in the brain of ART-suppressed PWH [6,8▪,9,11,12], suggesting the potential of replication competent genomes despite viral suppression. Two studies have further demonstrated that microglia isolated from the parenchyma of both untreated and ART-treated PWH harbour intact replication-competent viruses [14▪,34], with the ability to recover infection virions from these cells that were able to infect CD4+ T cells and monocyte-derived microglia *ex vivo*[34]. These studies indicate that the persistence of intact proviral HIV genomes within ART suppressed PWH is significant as these viral reservoirs represent a potential source of ongoing low-level viral production during ART and a potential source of replication competent virus that could lead to viral rebound is ART was stopped. While these cells can harbour HIV genomes, they can also contribute to chronic immune activation and neuroinflammation, thereby playing a central role in HIV-associated neuropathogenesis. Importantly, we have demonstrated that higher levels of intact HIV proviral DNA in the brain is associated with increased frequencies of Mx1-expressing and TNFα-expressing astrocytes and myeloid cells even in ART-suppressed PWH [8▪].

In addition to the persistence of viral reservoirs with replication-competent proviral HIV DNA, ongoing HIV transcription has been well documented within the CNS despite systemic viral suppression. HIV transcripts have been detected in both CSF and parenchymal brain tissue of ART-suppressed PWH [12,42–44], indicating ongoing viral transcriptional activity. 'CSF escape' is a well documented example, defined by detectable or elevated HIV RNA levels in the CSF despite undetectable plasma viral loads, which can occur with or without neurological symptoms [43,45–49]. Within the parenchyma, we have recently demonstrated persistent transcription in ART-suppressed PWH [12], including the presence of full length and multiply spliced transcripts. These findings raise important questions regarding the significance of viral persistence during ART, and whether ongoing transcription, and possibly even undetectable low-level replication, sustains chronic neuroinflammation and contributes to the development of neurocognitive impairment during suppressive therapy. Importantly, the impact of HIV infection in the CNS may extend beyond cell-intrinsic responses. Infected microglia that were co-cultured with brain organoids induced increased phosphorylation of NF-κB in astrocytes, neurons and neural stem cells, indicating that localized microglial infection is sufficient to activate inflammatory signalling across multiple brain cells in their local cellular neighbourhoods [29]. In addition, microglial infection induced increased expression of CCL2/MCP-1, which was not abrogated under ART conditions [28–30]. MCP-1 has been implicated in the development of HIV-associated dementia in viraemic individuals, and other neurodegenerative diseases such as Alzheimer's disease [50,51].

Together, these findings support a model in which the CNS functions as a biologically active HIV reservoir during suppressive ART rather than a transcriptionally silent compartment. Further, we propose that persistent low-level HIV transcription and viral production within long-lived CNS reservoirs may provide a sustained inflammatory stimulus capable of perpetuating neuroimmune dysfunction independently of overt viral replication.

### Systemic inflammation and the gut–brain axis

While HIV persistence within the CNS is likely a key contributor to HIV neuropathogenesis, it is important to note that the size or transcriptional activity of viral reservoirs within the CNS does not fully account for



Copyright © 2026 Wolters Kluwer Health, LLC. All rights reserved.

the level of neuroinflammation and neuropathology observed alone. Therefore, other factors likely contribute, at least in part, to cell activation in the brain. Accumulating evidence demonstrates that systemic inflammation, including stimuli originating from the gastrointestinal tract plays a critical and independent role in the development of neuroinflammation and neurocognitive disorders (Fig. 1). Gastrointestinal tract damage is also a hallmark of acute HIV infection and leads to microbial translocation where bacterial products cross the compromised intestinal barrier and enter gastrointestinal and gastrointestinal-draining tissues, and ultimately within the systemic circulation [52]. Microbial translocation triggers persistent local and systemic inflammation and immune activation, which has been correlated with disease pathogenesis in PWH [53]. In one study, they showed microbial molecules were detected in the brains from both PWH and SIV-infected NHPs, principally in microglia and astrocytes with increased bacterial burden in humans and animals displaying neurological disease [54]. Notably, we have demonstrated in both SIV-infected and SIV-uninfected rhesus macaques (RMs) with experimentally induced colitis that gut damage can induce neuroinflammation [7], further highlighting the potential role of the gut–brain axis in neuropathology in ART-suppressed PWH. RMs demonstrated both cell activation within the gut but also heightened measures of systemic inflammation and the loss of blood–brain barrier integrity. These findings support a mechanism by which systemic inflammatory analytes travel to the CNS from peripheral sources, including the gut, leading to BBB breakdown, enhanced peripheral cell trafficking into the brain and neuroinflammation.

Alternatively, emerging evidence from neurodegenerative disease research demonstrates that the gut–brain axis plays a fundamental role in driving CNS pathology, with enteric nervous system (ENS) dysfunction serving as a critical mediator linking gastrointestinal damage to neuroinflammation. In Parkinson's disease, α-synuclein pathology originates in the ENS and spreads to the CNS via vagal pathways [55,56], while in Alzheimer's disease, gut microbiome dysbiosis triggers systemic inflammation that activates microglia and promotes neurodegeneration [57]. Importantly, a recent study demonstrated that modulation of gut–brain signalling due to myeloid cell activation in the gut induced by changes in the microbiome can impair signalling and lead to cognitive decline [58▪]. These insights reveal that ENS dysfunction is not merely a consequence of neurological disease, but rather an active driver of central neuroinflammation through complex mechanisms that require high-dimensional spatial analysis to fully understand.

Whether these pathways are similarly a source of neuropathogenesis in PWH is unclear. Direct intracolonic administration of HIV Tat in a rat model was demonstrated to enhance enteric neuronal excitability [59] and activated an enteric glial-mediated neuroinflammatory response consisting of glial cell activation in the within the colonic wall that extended to the spinal cord and frontal cortex [60], demonstrating the ability of viral proteins in the gut to induce both local gut and CNS neuroinflammation. One study in NHPs demonstrated that SIV-infection-induced activation of enteric neurons during acute infection [61]; however, the long-term impact of sustained ART suppression of SIV/HIV, and the impact of the timing of ART initiation on related pathology remains unclear. As the gut of ART-suppressed PWH and SIV-infected NHPs harbours transcriptionally and translationally active reservoirs [10,62], it is likely that viral activation in the gut contributes to damage and inflammation (both local and systemic) that can drive ENS activation and neuroinflammation. These findings support an emerging paradigm in which gastrointestinal tract dysfunction and microbial translocation contribute directly to CNS immune activation, linking peripheral tissue injury with chronic neuropathology in ART-suppressed PWH.

Another potential mechanism linking systemic inflammation to neuropathology is the role of peripheral immune cells trafficking into the brain during infection. The CNS is seeded early during acute infection, likely through the infiltration of infected T cells and monocytes, which are known reservoirs of HIV [63–65]. However, the role of peripheral cells, including CD8+ T cells and natural killer cells, into the brain in either targeting or modulating viral reservoirs and inflammation is unclear. A recent study that treated SIV-infected RMs with anti-IL15 antibody prior to infection showed no reduction in the number of SIV $RNA^+$ cells, and clonal SIV RNA populations were detected within the brain, indicating the successful establishment of a local viral reservoir. However, anti-IL15 treatment was associated with reduced T cells in the brain and microglial expression of the proinflammatory cytokine IL-6, and increased expression of the anti-inflammatory cytokine TGF-β in brain macrophages [66▪]. These changes were accompanied by a global reduction in inflammatory signalling and upregulation of macrophage activation pathways. Of note, animals started anti-IL-15 treatment prior to infection and the impact of treatment when ART is initiated during chronic SIV infection was not assessed. Collectively, these findings suggest that a reduction of T-cell influx into the CNS reduces neuroinflammation during acute infection without preventing reservoir seeding. Modulating immune cell recruitment into the CNS may therefore represent a promising strategy



Copyright © 2026 Wolters Kluwer Health, LLC. All rights reserved.

to reduce neuroinflammation without necessarily eliminating established viral reservoirs.

## THERAPEUTIC STRATEGIES TO REDUCE NEUROPATHOGENESIS

While effective systemic viral suppression occurs with adherent ART, HIV continues to exert a persistent impact on the CNS with increased risk of neurocognitive decline and chronically elevated inflammatory profiles within the brain demonstrating the need for CNS-specific therapeutic approaches. While ART prevents infection of new target cells, it does not uniformly suppress viral transcription from integrated proviral DNA or the production of virions, particularly within CNS myeloid populations and gut reservoirs [7,8▪,10,12,46,62,67]. Persistent HIV transcription has been linked by our group and others to chronic inflammation and immune activation, which may contribute to neuroinflammation and other HIV-associated comorbidities [8▪,11,12,68]. Importantly, this may relate to transcriptionally and translationally active defective HIV proviruses, which form the bulk of the reservoir, which may also contribute to neuroinflammation [69–71]. These observations highlight the need for adjunctive strategies that specifically target ongoing viral activity and inflammatory pathways contributing to neuropathogenesis, beyond standard ART intensification.

Small molecule inhibitors have shown promise in reducing HIV transcription, including compounds targeting the Janus kinase/signal transducers and activators of transcription (JAK/STAT) signalling. JAK/STAT signalling is central in regulating immune responses and inflammation by activating STAT-dependent transcription of pro-inflammatory cytokines and chemokines [72]. In a SCID mouse model of HIV neuropathology, treatment with the JAK1/2 inhibitor baricitinib reduced neuroinflammation, glial activation, p24 production and reversed behavioural abnormalities [73]. Consistent with these findings, a clinical trial of the JAK1/2 inhibitor ruxolitinib in ART-suppressed PWH demonstrated good tolerability and reductions in cellular markers of viral persistence and immune activation, although effects on CNS outcomes remain to be defined [74].

Transcription-associated cyclin-dependent kinases (tCDKs) inhibitors have also been shown to suppress HIV proviral expression [75,76]. tCDKs regulate RNA polymerase II activity and are therefore critical for transcriptional elongation of the HIV genome [72]. Inhibition of factors such as CDK9 and CDK8/19 have established proviral latency in in-vitro T-cell models, with latency persisting for several days following discontinuation of CDK8/19 inhibition, suggesting sustained transcriptional repression [75,76]. Although these data are derived primarily from peripheral T-cell systems, they raise the possibility that CNS-penetrant tCDK inhibitors could similarly stabilize latency within brain and gut reservoirs and attenuate downstream inflammatory cascades.

Targeting systemic inflammation is another approach to limiting neuroinflammation; however, results have been largely unsuccessful. Treatment with statins and minocycline have not resolved cognitive decline while having modest effects on systemic inflammation [77,78], indicating that more effective measures are needed to suppress chronic inflammation. Treatment of ART-suppressed PWH with Ruxolitinib did show some reduction in markers of inflammation, albeit with no significant impact on IL-6 levels [74].

Finally, therapeutic targeting gut inflammation and particularly the gut microbiota may be an important and novel strategy to reduce neuroinflammation and cognitive impairment. Several studies have shown evidence of altered microbiota in the gastrointestinal tract from PWH with neurocognitive impairment, although this has not been observed consistently across all cohorts [79–82]. These findings support a potential role for the gut–brain axis in HIV-associated neurocognitive dysfunction and suggest that the gut microbiota may be a therapeutically targetable contributor to disease pathogenesis. However, further studies are needed to determine whether interventions that modify the gut microbiota can effectively reduce systemic and neuroinflammation and, ultimately, improve cognitive outcomes in PWH.

Collectively, suppression of HIV transcription represents a promising avenue to limit chronic immune activation and neuroinflammation in the brain. However, rigorous evaluation of CNS pharmacokinetics, durability of transcriptional silencing and potential off-target effects on host transcription is required before these agents can be widely adopted. In parallel, there is a pressing need to develop and test interventions targeting gut barrier integrity, microbial translocation and systemic inflammation, which may synergize with transcription-targeting therapies to improve brain health in ART-suppressed PWH. Future therapeutic strategies will likely require combined targeting of persistent viral transcription, maladaptive myeloid activation and systemic inflammatory pathways across both CNS and peripheral tissue reservoirs.

## CONCLUSION

Despite dramatic reductions in HIV-associated dementia in the ART era, milder forms of HIV-associated cognitive disorders remain common and clinically important in aging PWH. Emerging data show that



Copyright © 2026 Wolters Kluwer Health, LLC. All rights reserved.

neuropathogenesis in this setting is driven by convergent mechanisms involving persistent CNS HIV reservoir activation, myeloid-driven neuroinflammation, systemic immune activation and gut-derived injury, rather than by residual brain infection alone. Defining how these processes interact in PWH will be essential for risk stratification and for designing targeted interventions. Longitudinal studies integrating advanced neuroimaging, cerebrospinal fluid and plasma biomarkers of HIV transcription, microglial activation and gut barrier dysfunction are needed to disentangle 'legacy' from ongoing injury and to identify novel therapeutic targets.

Importantly, novel therapeutics that silence HIV transcription may offer a plausible route to reducing reservoir-driven inflammation, but require careful assessment of CNS penetration, long-term safety and clinical benefit. In parallel, adjunctive strategies aimed at restoring gut integrity, modulating the microbiome and attenuating systemic inflammation may further mitigate neuroinflammation and should be prioritized for clinical evaluation. Ultimately, moving beyond a brain-centric view of HIV neuropathogenesis may be essential for developing effective strategies to prevent and treat HIV-associated neuroinflammation and cognitive impairment in the ART era.

## Acknowledgements

*None.*

## Financial support and sponsorship

*The authors were supported by funding by the National Institutes of Health (grants AI149672, 1 UM1AI164560, and MH130197 to J.D.E.), the Oregon National Primate Research Center (grant P51OD0110925 to J.D.E. and A. A.O.) and the Australian National Health and Medical Research Council (NHMRC; GNT2020633 to M.J.C., J. D.E. and T.A.A.).*

## Conflicts of interest

*There are no conflicts of interest.*

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Heaton RK, Clifford DB, Franklin DR, *et al.* CHARTER Group. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology 2010; 75:2087–2096.
2. Simioni S, Cavassini M, Annoni JM, *et al.* Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. AIDS 2010; 24:1243–1250.
3. Sacktor N, Skolasky RL, Seaberg E, *et al.* Prevalence of HIV-associated neurocognitive disorders in the Multicenter AIDS Cohort Study. Neurology 2016; 86:334–340.
4. Antinori A, Arendt G, Becker JT, *et al.* Updated research nosology for HIV-associated neurocognitive disorders. Neurology 2007; 69:1789–1799.
5. Nightingale S, Ances B, Cinque P, *et al.* Cognitive impairment in people living with HIV: consensus recommendations for a new approach. Nat Rev Neurol 2023; 19:424–433.
6. Angelovich TA, Cochrane CR, Zhou J, *et al.* Regional analysis of intact and defective HIV proviruses in the brain of viremic and virally suppressed people with HIV. Ann Neurol 2023; 94:798–802.
7. Byrnes SJ, Busman-Sahay K, Angelovich TA, *et al.* Chronic immune activation and gut barrier dysfunction is associated with neuroinflammation in ART-suppressed SIV+ rhesus macaques. PLOS Pathogens 2023; 19:e1011290.
8. ■ Byrnes SJ, Jamal Eddine J, Zhou J, *et al.* Neuroinflammation associated with proviral DNA persists in the brain of virally suppressed people with HIV. Front Immunol 2025; 16:1570692.

This study demonstrates a role for defective HIV proviral DNA as a contributor to ongoing neuroinflammation in ART-suppressed PWH.

9. Cochrane CR, Angelovich TA, Byrnes SJ, *et al.* Intact HIV proviruses persist in the brain despite viral suppression with ART. Ann Neurol 2022; 92: 532–544.
10. Estes JD, Kityo C, Ssali F, *et al.* Defining total-body AIDS-virus burden with implications for curative strategies. Nat Med 2017; 23:1271–1276.
11. Gabuzda D, Yin J, Misra V, *et al.* Intact proviral DNA analysis of the brain viral reservoir and relationship to neuroinflammation in people with HIV on suppressive antiretroviral therapy. Viruses 2023; 15:1009.
12. Jamal Eddine J, Angelovich TA, Zhou J, *et al.* HIV transcription persists in the brain of virally suppressed people with HIV. PLoS Pathog 2024; 20: e1012446.
13. McMahan C, Dietrich DK, Horne EF, *et al.* Neurocognitive dysfunction with neuronal injury in people with HIV on long-duration antiretroviral therapy. Neurology 2023; 100:e2466–e2476.
14. ■ Nühn MM, Gumbs SBH, Schipper PJ, *et al.* Microglia exhibit a unique intact HIV reservoir in human postmortem brain tissue. Viruses 2025; 17:467.

This study demonstrates the presence of HIV proviral DNA in microglia isolated from the brain of ART-suppressed PWH, confirming microglia as a site of both intact and defective HIV proviruses.

15. Nichols MJ, Gates TM, Soares JR, *et al.* Atrophic brain signatures of mild forms of neurocognitive impairment in virally suppressed HIV infection. AIDS 2019; 33:55–66.
16. Pfefferbaum A, Zahr NM, Sassoon SA, *et al.* Accelerated and premature aging characterizing regional cortical volume loss in human immunodeficiency virus infection: contributions from alcohol, substance use, and hepatitis C coinfection. Biol Psychiatry Cogn Neurosci Neuroimaging 2018; 3:844–859.
17. Weiss JJ, Calvi R, Naganawa M, *et al.* Preliminary in vivo evidence of reduced synaptic density in human immunodeficiency virus (HIV) despite antiretroviral therapy. Clin Infect Dis 2021; 73:1404–1411.
18. Vera JH, Guo Q, Cole JH, *et al.* Neuroinflammation in treated HIV-positive individuals: a TSPO PET study. Neurology 2016; 86:1425–1432.
19. Mohammadzadeh N, Roda W, Branton WG, *et al.* Lentiviral infections persist in brain despite effective antiretroviral therapy and neuroimmune activation. mBio 2021; 12:e0278421.
20. Branton WG, Zhang N, Cohen EA, *et al.* Brain RNA profiling highlights multiple disease pathways in persons with HIV-associated neurocognitive disorder. AIDS 2025; 39:496–507.
21. Edén A, Marcotte TD, Heaton RK, *et al.* Increased intrathecal immune activation in virally suppressed HIV-1 infected patients with neurocognitive impairment. PLoS One 2016; 11:e0157160.
22. Guha D, Mukerji SS, Chettimada S, *et al.* Cerebrospinal fluid extracellular vesicles and neurofilament light protein as biomarkers of central nervous system injury in HIV-infected patients on antiretroviral therapy. AIDS 2019; 33:615–625.
23. Tavasoli A, Gelman BB, Marra CM, *et al.* Increasing neuroinflammation relates to increasing neurodegeneration in people with HIV. Viruses 2023; 15:1835.
24. Borjabad A, Morgello S, Chao W, *et al.* Significant effects of antiretroviral therapy on global gene expression in brain tissues of patients with HIV-1-associated neurocognitive disorders. PLoS Pathog 2011; 7:e1002213.
25. Burdo TH, Weiffenbach A, Woods SP, *et al.* Elevated sCD163 in plasma but not cerebrospinal fluid is a marker of neurocognitive impairment in HIV infection. AIDS 2013; 27:1387–1395.
26. ■ Dos Reis RS, Ignatz LA, Selvam S, *et al.* Microglial reactivity and nodule formation are associated with synaptodendritic damage in the brains of people with HIV-1. Brain Pathol 2025; 36:e70064.

This study demonstrated that microglial activation and related synaptic damage was associated with poorer cognitive outcomes, supporting a role for microglia dysregulation as a contributor to neuropathogenesis in ART-suppressed PWH.

27. ■ Yang J, Agrawal K, Stanley J 3rd, *et al.* Multiomic characterization of HIV effects at single cell level across human brain regions. bioRxiv 2025.

This non peer-reviewed preprint described comprehensive viral and cellular responses across brain tissue at the single cell level, demonstrating a chronic inflammatory state in the brain.

28. Narasipura SD, Zayas JP, Ash MK, *et al.* Inflammatory responses revealed through HIV infection of microglia-containing cerebral organoids. J Neuroinflammation 2025; 22:36.
29. Martinez-Meza S, Premeaux TA, Cirigliano SM, *et al.* Antiretroviral drug therapy does not reduce neuroinflammation in an HIV-1 infection brain organoid model. J Neuroinflammation 2025; 22:66.



Copyright © 2026 Wolters Kluwer Health, LLC. All rights reserved.

**30.** Kong W, Frouard J, Xie G, *et al.* Neuroinflammation generated by HIV-infected microglia promotes dysfunction and death of neurons in human brain organoids. PNAS Nexus 2024; 3:gae179.
**31.** McInnis JJ, Sood D, Guo L, *et al.* Unravelling neuronal and glial differences in ceramide composition, synthesis, and sensitivity to toxicity. Commun Biol 2024; 7:1597.
**32.** Elkjaer ML, Hartebrodt A, Oubounyt M, *et al.* Single-cell multi-omics map of cell type-specific mechanistic drivers of multiple sclerosis lesions. Neurol Neuroimmunol Neuroinflamm 2024; 11:e200213.
**33.** Xu X, Niu M, Lamberty BG, *et al.* Transformation of brain myeloid cell populations by SIV in rhesus macaques revealed by multiomics. Commun Biol 2025; 8:100.
**34.** Tang Y, Chaillon A, Gianella S, *et al.* Brain microglia serve as a persistent HIV reservoir despite durable antiretroviral therapy. J Clin Invest 2023; 133:e167417.
**35.** Oliveira MF, Pankow A, Vollbrecht T, *et al.* Evaluation of archival HIV DNA in brain and lymphoid tissues. J Virol 2023; 97:e0054323.
**36.** Zhang Z, Reece MD, Roa S, *et al.* The identification of intact HIV proviral DNA from human cerebrospinal fluid. Neurotherapeutics 2024; 21:e00373.
**37.** Sun W, Rassadkina Y, Gao C, *et al.* Persistence of intact HIV-1 proviruses in the brain during antiretroviral therapy. Elife 2023; 12:R89837.
**38.** Bertrand L, Cho HJ, Toborek M. Blood-brain barrier pericytes as a target for HIV-1 infection. Brain 2019; 142:502–511.
**39.** Churchill MJ, Wesselingh SL, Cowley D, *et al.* Extensive astrocyte infection is prominent in human immunodeficiency virus-associated dementia. Ann Neurol 2009; 66:253–258.
**40.** Churchill MJ, Gorry PR, Cowley D, *et al.* Use of laser capture microdissection to detect integrated HIV-1 DNA in macrophages and astrocytes from autopsy brain tissues. J Neurovirol 2006; 12:146–152.
**41.** Ko A, Kang G, Hattler JB, *et al.* Macrophages but not astrocytes harbor HIV DNA in the brains of HIV-1-infected aviremic individuals on suppressive antiretroviral therapy. J Neuroimmune Pharmacol 2019; 14:110–119.
**42.** DeMarino C, Denniss J, Cowen M, *et al.* HIV-1 RNA in extracellular vesicles is associated with neurocognitive outcomes. Nat Commun 2024; 15:4391.
**43.** Suzuki K, Zaunders J, Gates TM, *et al.* Elevation of cell-associated HIV-1 transcripts in CSF CD4+ T cells, despite effective antiretroviral therapy, is linked to brain injury. Proc Natl Acad Sci 2022; 119:e2210584119.
**44.** Jamal Eddine J, Chalmers EK, Zhou J, *et al.* HIV promoters isolated from brain and peripheral tissue of virally suppressed PWH are phylogenetically and functionally similar. Int J Mol Sci 2026; 27:3185.
**45.** Wang M, Yoon J, Reisert H, *et al.* HIV-1–infected T cell clones are shared across cerebrospinal fluid and blood during ART. JCI Insight 2024; 9:e176208.
**46.** Farhadian SF, Lindenbaum O, Zhao J, *et al.* HIV viral transcription and immune perturbations in the CNS of people with HIV despite ART. JCI Insight 2022; 7: e160267.
**47.** Livelli A, Vaida F, Ellis RJ, *et al.* CHARTER Group. Correlates of HIV RNA concentrations in cerebrospinal fluid during antiretroviral therapy: a longitudinal cohort study. Lancet HIV 2019; 6:e456–e462.
**48.** Spudich S, Robertson KR, Bosch RJ, *et al.* Persistent HIV-infected cells in cerebrospinal fluid are associated with poorer neurocognitive performance. J Clin Invest 2019; 129:3339–3346.
**49.** Wagner TA, Tierney C, Huang S, *et al.* Prevalence of detectable HIV-DNA and HIV-RNA in cerebrospinal fluid of youth with perinatal HIV and impaired cognition on antiretroviral therapy. AIDS 2024; 38:1494–1504.
**50.** Corrêa JD, Starling D, Teixeira AL, *et al.* Chemokines in CSF of Alzheimer's disease patients. Arq Neuropsiquiatr 2011; 69:455–459.
**51.** Sokolova A, Hill MD, Rahimi F, *et al.* Monocyte chemoattractant protein-1 plays a dominant role in the chronic inflammation observed in Alzheimer's disease. Brain Pathol 2009; 19:392–398.
**52.** Brenchley JM, Price DA, Schacker TW, *et al.* Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med 2006; 12: 1365–1371.
**53.** Vázquez-Castellanos JF, Serrano-Villar S, Latorre A, *et al.* Altered metabolism of gut microbiota contributes to chronic immune activation in HIV-infected individuals. Mucosal Immunol 2015; 8:760–772.
**54.** Branton WG, Fernandes JP, Mohammadzadeh N, *et al.* Microbial molecule ingress promotes neuroinflammation and brain CCR5 expression in persons with HIV-associated neurocognitive disorders. Brain Behav Immun 2023; 107: 110–123.
**55.** Chandra R, Sokratian A, Chavez KR, *et al.* Gut mucosal cells transfer α-synuclein to the vagus nerve. JCI Insight 2023; 8:e172192.
**56.** Holmqvist S, Chutna O, Bousset L, *et al.* Direct evidence of Parkinson pathology spread from the gastrointestinal tract to the brain in rats. Acta Neuropathol 2014; 128:805–820.
**57.** Cattaneo A, Cattane N, Galluzzi S, *et al.* INDIA-FBP Group. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. Neurobiol Aging 2017; 49:60–68.
**58.** ■ Cox TO, Devason AS, de Araujo A, *et al.* Intestinal interoceptive dysfunction drives age-associated cognitive decline. Nature 2026; 652:442–450.
This recent study demonstrates a key role of the gut–brain axis in age-associated cognitive decline, which may have significant implications in the content of HIV.
**59.** Ngwainmbi J, De DD, Smith TH, *et al.* Effects of HIV-1 Tat on enteric neuropathogenesis. J Neurosci 2014; 34:14243–14251.
**60.** Esposito G, Capoccia E, Gigli S, *et al.* HIV-1 Tat-induced diarrhea evokes an enteric glia-dependent neuroinflammatory response in the central nervous system. Sci Rep 2017; 7:7735.
**61.** Orandle MS, Veazey RS, Lackner AA. Enteric ganglionitis in rhesus macaques infected with simian immunodeficiency virus. J Virol 2007; 81:6265–6275.
**62.** Telwatte S, Lee S, Somsouk M, *et al.* Gut and blood differ in constitutive blocks to HIV transcription, suggesting tissue-specific differences in the mechanisms that govern HIV latency. PLoS Pathog 2018; 14:e1007357.
**63.** Veenhuis RT, Abreu CM, Costa PAG, *et al.* Monocyte-derived macrophages contain persistent latent HIV reservoirs. Nat Microbiol 2023; 8:833–844.
**64.** Albalawi Yasmeen A, Narasipura Srinivas D, Olivares Leannie J, *et al.* CD4dim CD8bright T cells home to the brain and mediate HIV neuroinvasion. J Virol 2022; 96:e00804–e00822.
**65.** Fischer-Smith T, Bell C, Croul S, *et al.* Monocyte/macrophage trafficking in acquired immunodeficiency syndrome encephalitis: lessons from human and nonhuman primate studies. J Neurovirol 2008; 14:318–326.
**66.** ■ Ram DR, Gopalakrishnan RM, Aid M, *et al.* Anti-IL-15 treatment reduces acute lentivirus inflammation and signaling in the brain. Cell Rep Med 2026; 7: 102567.
Pretreatment of SIVmac293x-infected nonhuman primates with IL-15 antibodies prior to infection was demonstrated to impact T-cell recruitment and modulate microglial activation, demonstrating a role of IL-15 in modulating neuroinflammation during acute infection.
**67.** Yukl SA, Kaiser P, Kim P, *et al.* HIV latency in isolated patient CD4(+) T cells may be due to blocks in HIV transcriptional elongation, completion, and splicing. Sci Transl Med 2018; 10:eaa9927.
**68.** Guha D, Misra V, Yin J, *et al.* CSF inflammation markers associated with asymptomatic viral escape in cerebrospinal fluid of HIV-positive individuals on antiretroviral therapy. Viruses 2023; 15:1829.
**69.** Imamichi H, Smith M, Adelsberger JW, *et al.* Defective HIV-1 proviruses produce viral proteins. Proc Natl Acad Sci U S A 2020; 117:3704–3710.
**70.** Buchholtz N, Hermans LE, Umunnakwe CN, *et al.* Defective proviruses significantly impact viral transcription and immune activation in men and women with HIV-1 subtype C in rural South Africa. Front Immunol 2024; 15:1484358.
**71.** Singh K, Natarajan V, Dewar R, *et al.* Long-term persistence of transcriptionally active 'defective' HIV-1 proviruses: implications for persistent immune activation during antiretroviral therapy. AIDS 2023; 37:2119–2130.
**72.** Hu X, li J, Fu M, *et al.* The JAK/STAT signaling pathway: from bench to clinic. Signal Transduct Target Ther 2021; 6:402.
**73.** Gavegnano C, Haile WB, Hurwitz S, *et al.* Baricitinib reverses HIV-associated neurocognitive disorders in a SCID mouse model and reservoir seeding in vitro. J Neuroinflammation 2019; 16:182.
**74.** Marconi VC, Moser C, Gavegnano C, *et al.* Randomized trial of ruxolitinib in antiretroviral-treated adults with human immunodeficiency virus. Clin Infect Dis 2022; 74:95–104.
**75.** Horvath Riley M, Brumme Zabrina L, Sadowski I. Small molecule inhibitors of transcriptional cyclin-dependent kinases impose HIV-1 latency, presenting "block and lock" treatment strategies. Antimicrob Agents Chemother 2024; 68:e01072–e01123.
**76.** Horvath RM, Brumme ZL, Sadowski I. CDK8 inhibitors antagonize HIV-1 reactivation and promote provirus latency in T cells. J Virol 2023; 97: e0092323.
**77.** Nakasujja N, Miyahara S, Evans S, *et al.* Randomized trial of minocycline in the treatment of HIV-associated cognitive impairment. Neurology 2013; 80: 196–202.
**78.** Sacktor N, Miyahara S, Evans S, *et al.* ACTG A5235 team. Impact of minocycline on cerebrospinal fluid markers of oxidative stress, neuronal injury, and inflammation in HIV-seropositive individuals with cognitive impairment. J Neurovirol 2014; 20:620–626.
**79.** Hua S, Peters BA, Lee S, *et al.* Gut microbiota and cognitive function among women living with HIV. J Alzheimers Dis 2023; 95:1147–1161.
**80.** Borgognone A, Prats A, Sharma AAA, *et al.* Interactions between gut microbiota, plasma metabolome and brain function in the setting of a HIV cure trial. Front Cell Infect Microbiol 2025; 15:1629901.
**81.** Dong R, Lin H, Chen X, *et al.* Gut microbiota and fecal metabolites associated with neurocognitive impairment in HIV-infected population. Front Cell Infect Microbiol 2021; 11:723840.
**82.** Zhang F, Yang J, Ji Y, *et al.* Gut microbiota dysbiosis is not independently associated with neurocognitive impairment in people living with HIV. Front Microbiol 2018; 9:3352.


1746-630X Copyright © 2026 Wolters Kluwer Health, LLC. All rights reserved.


Copyright © 2026 Wolters Kluwer Health, LLC. All rights reserved.