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# HIV-1 persistence in the central nervous system: viral and host determinants during antiretroviral therapy

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Despite remarkable therapeutic advances in the past two decades, the elimination of human immunodeficiency virus type 1 (HIV-1) from latent reservoirs constitutes a major barrier to eradication and preventing neurological disease associated with HIV/AIDS. Invasion of the central nervous system (CNS) by HIV-1 occurs early in infection, leading to viral infection and productive persistence in brain macrophage-like cells (BMCs) including resident microglia and infiltrating macrophages. HIV-1 persistence in the brain and chronic neuroinflammation occur despite effective treatment with antiretroviral therapy (ART). This review examines the evidence from clinical studies, *in vivo* and *in vitro* models for HIV-1 CNS persistence, as well as therapeutic considerations in targeting latent CNS reservoirs.

## Addresses

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## Introduction

Advancement in the treatment of HIV-1 ranks as one of the major achievements in medical care over the past century. The development of medications comprising antiretroviral therapy (ART) has transformed a once lethal diagnosis into a manageable chronic disease in both developed and developing countries [1]. Indeed, two patients have achieved sustained ART-free remission without evidence of viral replication through allogeneic bone marrow transplant [2,3<sup>\*\*</sup>]. Despite suppressed virus in plasma with efficient ART, chronic inflammation and

end-organ damage occur in patients living with HIV-1, possibly due to the presence of viral reservoirs in organs with limited ART penetrance. As patients with HIV-1 infection age, the long-term sequelae of chronic infection including renal failure, heart disease and brain disorders have come to the forefront of HIV-1 clinical care. Neurocognitive impairment occurs in approximately 20–30% of HIV/AIDS patients, and while ART has decreased the severity of these deficits, HIV-Associated Neurocognitive Disorders (HAND) remains an ongoing problem among patients despite adherence to optimal therapeutic regimens [4,5].

Beyond the impact of direct organ damage associated with infection, the establishment of tissue reservoirs represents a barrier to achieving eradication of HIV-1. Such so-called ‘safe-harbors’ for HIV-1 occur in multiple organs and tissues, including the gut, lymphoid tissue, adipose [6], skin [7], genital tract [8,9], and brain. Challenges in drug delivery to these tissues combined with unique cellular factors that support viral persistence are central to this problem. This review summarizes the present knowledge regarding the invasion, infection, and persistence of HIV-1 in the brain, and how these processes could potentially be targeted with future therapies as we continue to strive for an HIV/AIDS cure.

## Neuroinvasion and cellular reservoirs in HIV infection

Diminished immune defenses and accompanying opportunistic infections define the natural history of HIV-1 infection and the ensuing Acquired Immunodeficiency Syndrome (AIDS), which is characterized by depletion of CD4-expressing T-lymphocytes. During primary infection, HIV-1 infects CD4+ T cells using CD4 and chemokine co-receptors present on the surface of these cells, predominantly CCR5 but also including CXCR4 [10], CCR3, and CCR2b [11]. These receptors, which enable viral entry through interaction with HIV envelope proteins, are also present on non-lymphocytic cells such as macrophages, albeit at lower levels [12,13]. Nevertheless, macrophages infected in the periphery have been posited to play an important role in the dissemination of the virus [14,15,16<sup>\*</sup>], immunodeficiency or immune dysregulation, and the development of persistent viral reservoirs in the gut [17] and brain [18–21]. However, the notion that HIV-infected macrophages circulating in blood promote viral spread to other tissues, including the brain, is increasingly called into question by recent evidence suggesting that the viral evolution with time to adapt leads to infection of

other target cells such as BMCs that express low CD4 levels [22\*].

Though many neurologic manifestations of HIV-1 such as HAND are associated with late-stages of infection, invasion of the CNS is an early event that occurs during primary infection [23]. This supposition is fueled by reports of neurologic sequelae occurring at early stages of infection, including at or prior seroconversion [24,25]. In humans, actively replicating HIV-1 can be detected as early as eight days in the CSF and 15 days in brain tissue following primary infection [26]. Evidence of neuroinflammation has been observed in recently infected individuals through elevation of inflammatory molecules in cerebrospinal fluid (CSF) [27,28], magnetic resonance spectroscopy (MRS) [29–31], and structural neuroimaging [21,32].

### HIV-1 entry of the CNS

It has been theorized that HIV-1 dissemination in the brain occurs by the virus crossing the blood-brain barrier within circulating lymphocytes and macrophages. Interestingly, post-mortem studies of patients with HAND rarely detect HIV-infected T-cells in the brain [33]. Nonetheless, transmitter-founder (TF) viruses inefficiently infect macrophages despite being R5-tropic [12,34]; these viruses can only infect CCR5-expressing cells with concurrent high CD4 expression levels such as T-cells while macrophages and microglial cells express low levels of CD4 and may be less susceptible to infection by TF viruses. Thus, viruses evolving in the brain have the ability to infect macrophages and display show a unique property of infecting cells despite low levels of CD4 expression [35–37]. Studies comparing viruses from brain and CSF show a compartmentalization [38]. Indeed, genetic compartmentalization was also observed between viruses isolated from CSF versus plasma [39].

Brains from HIV-infected patients display detectable virus-encoded RNA, DNA and protein in myeloid lineage cells, including macrophages infiltrating from the periphery and resident microglia (yolk sac-derived); astrocytes have been shown to be permissive to HIV-1 infection but their capacity to support productive viral replication is minimal, though can be induced by inflammatory signals *in vitro* [40,41]. Of interest, recent studies suggest that macrophages from females are less susceptible to HIV-1 infection [42]. Indeed, the extent of neurologic disability correlates with the abundance of and activation of BMCs in patients with or without effective anti-retroviral treatment [23,42–47]. Increased permeability of the blood-brain barrier is a common feature of the later stages of HIV-1 infection [48,49]. Alteration of endothelial tight junctions mediated by the HIV-1 Tat protein [15,16\*] *in vitro*, and studies in non-human primate models [50] support the notion that disruption of the blood-brain barrier might contribute to HIV-1 neuro-invasion. The translocation of microbes, particularly proteobacteria,

perhaps from the gut into the bloodstream appears to be increased in HIV infection and likely a driver of chronic inflammation and monocyte activation in HIV-1 infection [51]. Serum levels of lipopolysaccharide (LPS), which modulate monocyte activation, are higher in HIV-infected patients compared to controls, and are notably higher in patients with HAND independent of viral load and CD4 count [52]. Of particular interest, the discovery of peptidoglycan in the brains of HIV/AIDS patients with and without neurocognitive deficits [53] has ignited interest in the role of microbial translocation into the brain in neurological disease [54,55], including HAND. A study by Branton *et al.* detected peptidoglycan and bacterial rRNA at similar levels in HIV-infected patients and other disease controls, with increased host immune responses in the CNS of the HIV group [53], suggesting that disruption and displacement of the host microbiome might contribute to chronic inflammation associated with end-organ damage during HIV infection.

Viral adaptation likely also contributes to the formation of a CNS reservoir during HIV-1 infection [13]. The primary co-receptor for HIV-1 infection of macrophages and microglia *in vitro* is CCR5, and viruses isolated from the CNS of patients depend on CCR5 for cell entry. Compared to virus isolated from the blood, brain-derived viruses are less dependent on CD4 for cell entry and are thus able to infect cells expressing lower levels of CD4, such as macrophages [38,56]. A rare brain-derived variant R5X4 contains a modified gp120 protein that efficiently and preferentially infects macrophages and microglia [13]. Macrophage-tropism of brain-derived HIV-1 variants correlates with neurotropism [57], underscoring the importance of myeloid lineage cells in viral persistence and pathology in the CNS.

Manipulation of cells by HIV-1 may also contribute to the virus' ability to invade and persist within the CNS. The population of CD16<sup>+</sup> and CD69<sup>+</sup> leukocytes expands throughout all stages of HIV/AIDS, and macrophages expressing CD16 are more susceptible to infection by HIV-1 compared to CD16<sup>-</sup> cells [58]. Expression of these surface proteins increase adherence to endothelium and support transmigration across tissue barriers, including those guarding the CNS. In non-human primate SIV models as well as *in vitro* studies of HIV-1, infected macrophages also increase their expression of CCR2, a receptor for the chemokine CCL2 [59], which is assumed to play a vital role in transmigration of cells across the blood-brain barrier, particularly during chronic inflammation. Undifferentiated monocytes do not appear to support viral replication *in vitro* due to the expression of restriction factors such as SAMHD1, which is discussed in subsequent sections. Monocytes in patients with HIV-1 rarely harbor viral DNA, particularly during ART [60,61]. Nevertheless, the activation of monocytes by infectious and pro-inflammatory stimuli is likely a requirement for invasion and productive infection of the CNS by HIV.

### Viral reservoirs and chronic inflammation

Upon invasion of the CNS, HIV-1 infects microglia and macrophages while evading the immune system and establishing intracellular reservoirs in the brain. Productive HIV-1 infection has been demonstrated in microglia and perivascular macrophages, as well as macrophage-like cells of the choroid plexus [62–64] in brains of patients with or without neurological disease [23]. These cell types are migratory, long-lived (weeks to years), and are important components of the blood-brain barrier [65]. *In vivo*, the virus does not productively infect neurons, astrocytes, oligodendrocytes, or brain endothelial cells. While HIV-1 infection drives the death of CD4+ T-cells, microglia/macrophages are more resistant to HIV-induced cell death, consistent with the observation of HIV-1 pro-viral DNA and mRNA detection in these cells in post-mortem analyses. Though microglia/macrophages support both latent and productive infection, HIV-1 can activate innate immune responses in BMCs that lead to neuronal injury and death through the release of inflammatory cytokines and toxic metabolites [66,67,68\*\*]. Notably, HIV-1 infection induces inflammasome activation with IL-1 $\beta$  release without ensuing inflammasome-associated cell death (pyroptosis) [69]. These neuroinflammatory and neurotoxic events are assumed to underlie the development of HAND and viral persistence.

The brains of HIV-infected patients display chronic neuroinflammation and persistent viral RNA and DNA despite effective ART [70\*]. Widespread reactive astrogliosis and activated macrophages are evident in post-mortem studies [71–73]. Understanding these cell processes, in addition to host-restriction factors, discussed in the next section, might be crucial to the control and eradication of HIV-1 in the CNS [48,74].

### Impact of host restriction factors on brain infection

HIV-1 infection has long been recognized to be modulated by Type 1 interferons [75]. Nonetheless, substantial evidence points to the impact of host restriction genes that limit and perhaps even prevent HIV-1 infection of lymphocytes and of macrophages in some cases. Prototypic host restriction factors include APOBEC3G, BST-2/Tetherin, TRIM5- $\alpha$ , TRIM22, MX2, SERINC3, and 5, SAMDH1 [76] and most recently the HUSH silencing complex [77,78]. Other less well-understood restriction factors include MARCH, SLFN11, and IFITM1, 2, and 3. The contribution of these genes to viral evolution and restriction in the CNS are uncertain, although BST-2 and SAMDH1 are highly expressed in macrophages. Predictably, SAMHD1 [79], and BST-2 [80] are implicated in HIV-1 infection of the CNS. Other potential regulators of HIV-1 infection include individual microRNAs that can act directly on the virus by targeting specific viral genes [81] as well as act on key host genes facilitating HIV-1 infection such as CD4 or CCR5 [82\*\*]. Several microRNAs have been implicated in HIV-1 infection of the brain [83–85].

### Mathematical modeling of Neuro-HIV

Modeling viral infections using mathematical tools has contributed to a deeper understanding of the underlying determinants influencing outcomes as well as predicting future directions of viral epidemics. Mathematical tools have also provided valuable guidance in the implementation of ART when it became available in the mid-1990's and continues to offer insights in the HIV/AIDS epidemic in different settings [86]. Modeling HIV-1 infection of the nervous system is challenging because of the limited availability of fluid (CSF) or tissue (brain) specimens for analyses of viral load and diversity. Thus, studies are largely restricted to cross-sectional reports using autopsied brain, although some prospective CSF studies exist with the caveat that viral dynamics in CSF might not fully recapitulate events in the brain parenchyma. Despite these challenges, studies show that ART controls viral replication within the CSF compartment and for the most part mirror circumstances in matched plasma specimens. In some instances, viral escape in CSF occurs with high levels of replication in the presence of virus suppression in plasma. The frequency of viral escape varies widely depending on the specific report, 4.4–38% of patients who receive suppressive ART, as well as variable correlations with neurocognitive impairment [87\*\*,88–90].

Using a mathematical model based on HIV-1 infection of brain macrophages, the dynamics of brain infection were modeled, and estimates indicated that HIV-1 integrated proviral DNA burden in brain increased slowly over time [91\*]. These studies indicated that the annual rate at which susceptible BMCs become HIV-infected was estimated to be  $2.9\text{--}48.7 \times 10^{-7}$ /year for ART-treated HIV-infected patients without comorbid neurological disorders. Assuming ART suppressed HIV-1 outside the brain, an improvement in therapy effectiveness (1.6–48%) could diminish HIV-1 brain infection in patients without neurological disorders. In those patients with advanced disease, major improvement in therapy effectiveness (~70%) might suppress HIV-1 provirus from the brain within 3–32 (interquartile range 3–9) years in patients without neurological disorders but 4–51 years of efficacious therapy was necessary for patients with evident neurological disease. Thus, a moderately effective therapy regimen could suppress HIV-1 brain infection depending on BMC lifespan and neurological comorbidity. These modeling results imply that an effective therapy has the capacity to suppress viral infection in the brain, although it does not account for the possibility that lingering viral infection of the brain could potentially reseed extra-CNS reservoirs.

### Models of Neuro-HIV

Over the past 30 years, multiple experimental models for HIV-1 infection of the brain have emerged to which different therapeutic interventions have been applied (Table 1). These models included humanized mice

Table 1

## Models of NeuroHIV

Model	Relevance
Non-human primates	
SIV-infected rhesus macaques and pigtail macaques	<ul style="list-style-type: none"> <li>• Neuropathology resembles HIV-1 encephalitis [115]</li> <li>• HAND-like syndrome develops in subset of infected animals [116]</li> <li>• Evidence that viral DNA persists in brain parenchyma despite suppression of viral RNA in blood, CSF, and brain tissue [117]</li> <li>• Studies of antiretroviral therapies [118*]</li> <li>• CD8+ T-cell depleted rhesus macaques develop SIV encephalitis [119]</li> </ul>
Rodents	
Transgenic mice	<ul style="list-style-type: none"> <li>• gp120: Develop motor and behavioral abnormalities typical of HAND with or without inducible transgenes [120]; indirect neurotoxicity through cytokine release and inflammation [121]</li> <li>• Tat: neuronal injury with behavioral deficits [122*]</li> <li>• Vpr: structural and functional CNS abnormalities similar to HAND [66]</li> </ul>
Transgenic full length HIV-1 genome rat Chimeric virus capable of infecting mice Viral proteins (e.g. Tat) implanted into CNS Immunodeficient mice, reconstituted with human hematopoietic stem cells	<ul style="list-style-type: none"> <li>• Transgenic full length HIV-1 genome rat develop neurological disease [123]</li> <li>• Studies of antiviral immune responses [124,125]</li> <li>• Study of neuropathogenesis and neuroprotective molecules [126,127]</li> <li>• Neuroinvasion through trafficking HIV-infected leukocytes localized in meninges and perivascular spaces [128,129]</li> <li>• Human myeloid (cell)-only mice (MOM) [61] and T-cell-only mice (TOM) [130**,131], infected with HIV-1 display persistent brain infection</li> </ul>
Feline	
FIV-infected cats	<ul style="list-style-type: none"> <li>• FIV neuroinvasion and replication early in primary infection; FIV infection predominantly in microglia, macrophages, and astrocytes [93]</li> <li>• Neuropathology and clinical features of HAND develop in susceptible animals [132]</li> <li>• Useful for study of antiretroviral therapies, anti-inflammatory and neurotrophic compounds (ex: insulin) [133]</li> </ul>

infected with HIV-1, SIV-infected non-human primates (NHP) such as different macaque species and other permissive NHPs, FIV-infected cats, and transgenic rodents. In addition, many *ex vivo* models of CNS HIV-1 infection continue to be implemented; these include cultured human primary and immortalized microglia, macrophages, astrocytes as isolated cell types as well as co-cultures with other relevant target cells including neurons and oligodendrocytes. Among the *in vivo* models, SIV-infected macaques (Rhesus, pigtail, and cynomolgus) and humanized (BLT, MOM) mice have achieved the widest recognition and use albeit with certain caveats that inevitably accompany all models. Nonetheless, humanized mice do not reconstitute all myeloid cells, especially those of embryonic origin such as microglia. Of note, SIV encodes an accessory protein, Vpx that counteracts SAMHD1, a restriction factor that plays a crucial role in limiting SIV infection of macrophages but HIV-1 does not encode a Vpx protein and is less efficient at infecting macrophages than SIV. Nonetheless, other models have also provided valuable and often more expedient insights into new concepts in pathogenesis and diagnosis [92] as well as therapeutic opportunities [93].

## Therapeutic implications

### Antiretroviral therapy (ART)

The selection of ART for treating HIV-associated neurological disorders has been influenced by the concept

termed CNS penetration-effectiveness (CPE), in which individual ART medications are assigned scores predicated on their relative cerebrospinal fluid:plasma distribution. The CPE score reflects the medication concentration in CSF [94\*]. ART regimens with high CPE have been associated with reduced CSF viral load; however, high CPE ART regimens are also associated with an increased risk of developing HAND [95]. The challenges of selecting the correct ART regimen are more complicated because multiple variables can influence a given medication's efficacy including its distribution across the blood-brain barrier which is different from the blood-CSF barrier that is likely more permeable. Additionally, the efficacy of some ART medications differs significantly depending on the targeted HIV-infected cell type in the brain such as microglia and/or infiltrating macrophage versus CD4+ T-cell in which most drugs are tested. In fact, several ART medications showed much higher EC<sub>50</sub> values in microglia compared to lymphocytes and macrophages [94\*]. In contrast, the CCR5 antagonist, maraviroc, was more efficient in microglia compared to T-cells which was supported by its ability to improve outcomes among patients with HAND [96\*]. Nonetheless, maraviroc also appears to have intrinsic neuroprotective properties due to its ability to block induced CCR5 expression on neurons [97]. It is important to recognize that despite viral suppression in blood for years, virus-encoded RNA, DNA and proteins remain detectable in the brains of

patients receiving ART [70\*,94\*]. It is unclear whether ART drugs effectively reach the brain in humans due to limited availability of brain tissue from patients receiving ART. Several ART drugs show very low concentrations in brain tissue with limited antiviral efficacy in microglia and macrophages compared to T cells [98,99]. Compounding this latter issue is that many ART drugs might be directly neurotoxic, making it challenging to distinguish HIV-mediated neurologic sequelae from iatrogenic neurological damage [100,101]. ART-resistance mutations in HIV-1 genomes contribute significantly to viral escape in the periphery, but the contribution of these mutations to the persistence of HIV in the brain has not been established. The severity of HIV-associated neurologic disease has improved in the era of ART; however, these therapies are insufficient to prevent the development of neurologic disability in chronic HIV-1 infection [4]. The potential application of nanotechnologies for enhanced delivery of ART to the brain and other organs portends promise for improving the likelihood of eradicating HIV-1 from different reservoirs [102,103]. The concurrent use of neuroimaging and a focus on macrophages as potential conduits for delivering ART has also advanced this field experimentally [104] and their application in the clinical setting [105].

### Immunotherapies

Recent reports have renewed enthusiasm regarding bone-marrow transplantation for HIV-1 infection coinciding with a second reported case of a patient treated with a HSCT from a donor with a homozygous mutation in CCR5 (CCR5 $\Delta$ 32/ $\Delta$ 32) [2,106]. This patient did not undergo radiation and HIV-1 was undetectable 18 months following transplantation. The long-term effectiveness, safety, and economic feasibility of this treatment are significant limitations to its mainstream application. Nonetheless, the apparent success in these two isolated cases highlights the potential of immunomodulation in the control and eradication of HIV.

Generating cells to detect and kill HIV-infected cells, an approach derived from the cancer literature, promises to be an additional therapeutic intervention for HIV/AIDS. Chimeric Antigen Receptor (CAR) T-cells against HIV/SIV are capable of engraftment in multiple lymphoid tissues where they can participate in viral-antigen activated memory-like immune responses to limit infection. In cancer, CAR-T cells are able to cross the blood-brain-barrier and thus by inference, their potential for targeting neurologic viral reservoirs. HIV-1/SIV-specific CAR-T cells derived from hematopoietic stem cells have shown promise in rhesus macaques in terms of reduced viral load, preserved CD4 T-cell counts, and limited viral rebound following withdrawal of antiretroviral therapy [107]. The ability of these cells to persist in human tissues, particularly in ART-suppressed patients with low viral loads, has not yet been established [108].

Monoclonal antibodies have shown early promise in both treatment of HIV-1 and in the development of vaccines and post-exposure prophylaxis. Therapeutic vaccines utilizing broadly neutralizing antibodies (bnAbs) targeting highly conserved epitopes of HIV-1 could potentially enhance the effectiveness of ART and reduce the pill burden of current regimens. The monoclonal antibody, 3BNC117, cloned from an HIV-infected viremic controller, showed potential in early clinical trials, where it significantly suppressed viral load [109] in infected individuals and during ART interruption [110]. Unfortunately, resistance rapidly developed in the majority of subjects in both Phase I and II clinical trials. Two antibody-mediated therapies for HIV are currently under clinical investigation and the role of bnAbs in combination therapy and as an adjunct to ART remains an exciting new frontier in HIV treatment. The long-term safety, efficacy, and access to CNS viral reservoirs by bnAbs is a subject of future study.

### Shock and kill strategies

Activation of latent viral reservoirs might be a strategy for their reduction and perhaps elimination from the body. This strategy, known as 'shock and kill' or 'kick and kill', uses latency reversal agents, such as vorinostat, in conjunction with a therapeutic vaccine that activates the host-immune response to HIV or intensive antiretroviral therapy (ART) [111]. The impact of this treatment strategy on viral rebound during planned ART interruption or long-term differences in viral control are an area of ongoing study. There are relevant concerns about the effectiveness and safety of latency reversal in CNS reservoirs. First, the ability of ART agents and immunotherapy to access infected BMCs is unknown. Second, inducing the expression of viral proteins in latently infected cells will likely lead to widespread BMC activation, further driving the inflammation associated with neurologic deterioration during HIV-1 infection [112]. Third, the established or potential neurotoxicity of several antiretroviral agents and immunotherapies is a substantial limitation to its therapeutic application [43,113]. In a recent SIV study, latency reversing agents reactivated latent virus that could be detected in the brain; one of the two macaques that received ART and latency reversing agents had severe neurological symptoms shortly after latency reversing agents were applied; this study emphasizes the need to carefully understand the effects of latency reversing agents in CNS reservoirs [114\*\*].

### Future perspectives

As the ability to control viral burden and prolong survival in HIV-1 infection has evolved, so has the understanding of how the virus invades tissues, and simultaneously evades and exploits the host immune system to achieve latency and drive chronic inflammation culminating in end-organ damage. Targeting the long-term sequelae of chronic HIV-1 infection through the elimination of latent

tissue reservoirs is a promising avenue of research. Indeed, strategies for safely eliminating CNS reservoirs might pose the greatest challenge to a future free from HIV/AIDS.

### Conflict of interest statement

Nothing declared.

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