Pathogenesis of HIV in the brain

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HIV enters the brain early after infection and can persist there for years, even when antiretroviral therapy keeps plasma viremia suppressed. In the pre-antiretroviral therapy (ART) era, neurological effects of brain infection were commonly evident, most notably HIV encephalitis and resulting HIV-associated dementia. In the ART era, those symptoms are rare; however, impacts on the brain remain. The field has shifted towards a more difficult question: why signs of neuroinflammation, brain injury, or cognitive change persist in some ART-suppressed people with HIV despite long-term systemic viral control.

The articles in this section approach that question from different angles, but they converge on the same broad message. HIV neuropathogenesis can no longer be understood through a narrow, central nervous system (CNS)-only model. It is now understood that CNS viral persistence, chronic activation of myeloid cells, transcription from both intact and defective proviruses, and inflammatory processes can arise beyond the brain and impact neurological outcomes. Just as importantly, these ongoing biological processes develop in an ageing population where vascular disease, metabolic illness, psychiatric burden, and other comorbidities increasingly impact the boundaries of what can be labelled as CNS-driven HIV-specific brain injury.

Zuidmeer and colleagues (pp. 386–392) place microglia at the centre of this story. Their review captures one of the clearest advances in the field: microglia are now understood not simply as markers of past infection, but as a durable HIV reservoir within the brain. The evidence they assemble shows that microglia can harbour intact, largely macrophage-tropic and potentially inducible proviruses despite long-term ART, underscoring that viral persistence in the CNS is biologically relevant rather than merely residual. But the significance of microglia goes beyond reservoir status alone. HIV infection appears to push these cells toward an inflammatory state while also disrupting their normal roles in synaptic maintenance and neuronal support. ART attenuates some of those effects, yet does not fully restore microglial biology to an HIV-uninfected baseline, a point that may help explain why virological success does not always translate into neurological recovery.

Angelovich and colleagues (pp. 364–371) widen the frame further by arguing that treated HIV neuropathogenesis should not be seen as a self-contained CNS disorder. Their review makes a persuasive case that the gut-brain axis and systemic inflammation belong within the same pathogenic model. In this account, microbial translocation, chronic gut barrier dysfunction, and inflammatory signals generated in the periphery can feed into blood–brain barrier disruption, myeloid activation, and neuroinflammation within the CNS. This is an important shift in emphasis because it suggests that persistent brain injury may depend not only on what remains in the brain, but also on what continues to impact it. The therapeutic implication is equally important: controlling plasma virus, or even reducing CNS reservoir activity alone, may not be sufficient if peripheral inflammatory drivers remain active.

Chalmers and colleagues (pp. 372–378) address another question that has become increasingly difficult to ignore, what defective proviruses are doing in the brain and other tissues. For years, the field largely treated defective genomes as inert by-products because they could not produce replication-competent virus. Their review shows why that view is now too simple. Defective proviruses make up most of the proviral reservoir across blood and tissues, including the CNS, and many remain capable of transcription, with some also able to generate viral proteins or aberrant transcripts that may still engage immune sensing pathways. This matters especially in the brain, where tissue access is limited and where most studies identify a reservoir dominated by defective genomes. If those genomes continue to produce RNA or inflammatory signals, then reducing rebound-competent virus alone may not be enough to reduce neuropathogenesis. In that respect, the review sharpens a key conceptual point: HIV persistence in the brain may not be as silent as first thought.

Brew and Cysique (pp. 379–385) bring the discussion from mechanism to clinical interpretation. Their review is valuable because it does not try to erase the tension between competing frameworks, but instead clarifies why the tension exists. The

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traditional HAND criteria have been criticised for overcalling impairment, particularly through the asymptomatic neurocognitive impairment category and through the migration of research criteria into routine clinical use. Yet abandoning HIV-specific framing altogether risks ignoring evidence that low-level viral activity, inflammatory signalling, and potentially reversible injury may still matter in some virally suppressed patients. Their conclusion is measured and convincing: the HAND framework remains useful, but only if applied carefully, longitudinally, and in proper clinical context. Their emphasis on tiered assessment, functional change over time, and the distinction between active and legacy injury is an important reminder that classification is never separate from biology.

Read together, these studies argue for a more integrated account of HIV pathogenesis in the brain. Microglia appear central, both as reservoir and as effector cell. Viral transcription, including from defective proviruses, may continue to matter even when productive replication is tightly constrained. Inflammatory inputs generated outside the CNS, particularly in the gut, may amplify or sustain brain injury. And the clinical picture that follows is shaped not only by these processes, but also by ageing, resilience, comorbidity, and the limitations of the tools used to define impairment. Across the section, one message is especially clear: an undetectable plasma viral load should not be mistaken for biological quiet in the brain.

At the same time, these reviews also show why the field remains difficult to resolve. Evidence of HIV DNA, HIV RNA, or neuroinflammatory activation in the CNS does not map neatly onto symptoms or outcomes. Some individuals remain clinically stable despite measurable reservoir persistence or inflammatory signatures, whereas others develop cognitive, behavioural, or motor change over time. That mismatch makes it difficult to distinguish active injury from accumulated damage, and harder still to identify who is most likely to benefit from targeted intervention. It also complicates attribution, since in older people with HIV, the effects of vascular disease, psychiatric illness, substance use, metabolic dysfunction, and age-related neurodegeneration increasingly coexist with HIV rather than simply confound it. The challenge, then, is not merely to show that HIV still matters in the brain, but to determine when, how, and in whom it matters most.

Several unresolved issues now sit at the centre of that effort. It remains uncertain how much impairment in virally suppressed people reflects active HIV-driven biology as opposed to legacy injury. The pathogenic importance of defective proviruses is still being defined, particularly in the CNS where it remains technically difficult to separate transcription from intact genomes and transcription from defective ones. It is also not yet clear how much ongoing neuropathogenesis is governed by local CNS reservoirs and how much is sustained by systemic inflammation and gut-derived signals. Finally, the field still lacks robust tools to identify active, potentially reversible brain injury in individual patients or to monitor CNS risk during cure-directed interventions that perturb latent reservoirs. These are no longer peripheral questions that now define the landscape of NeuroHIV research.

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