HIV persistence in the CNS: the final frontier for a cure?

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Understanding how often, where, and by which mechanisms HIV persists in the central nervous system (CNS) in individuals on antiretroviral therapy (ART) is critical for preventing and managing CNS-related HIV complications and for designing strategies to achieve a cure of HIV infection. In this issue of the *Journal of Virus Eradication*, Joseph *et al.* [1] report on a ground breaking meeting convened by the National Institutes of Mental Health on 'Cerebrospinal fluid (CSF) HIV-1 Escape' with the goals of elucidating key knowledge gaps about this newly recognised entity, establishing a research agenda and assembling a 'Global HIV-1 CSF Escape Consortium' to fill these gaps.

Twenty-three investigators from the US, Europe, India, Uganda and Australia attended the meeting and presented findings from their clinical cohorts of individuals on ART with CSF viral escape. Joseph *et al.* [1] clearly summarise the questions and strategies needed to accelerate research in this area. An important theme was that CSF escape has been variably defined and inconsistently evaluated across different studies making it very difficult to draw firm conclusions about its epidemiology, pathogenesis, and implications for clinical management and for HIV cure strategies.

There appear to be two general contexts in which CSF escape occurs: one associated with incomplete suppression of viral replication, manifest by detectable plasma HIV-1 RNA; and the other associated with complete suppression of viraemia by ART. In addition, CSF escape in either context can be clinically asymptomatic or symptomatic (i.e. neurological dysfunction). Differentiating between complete and incomplete virological suppression and between symptomatic and asymptomatic escape should be a high research priority because pathogenesis and management strategies are likely to be quite different, although some overlap between the scenarios undoubtedly occurs in some individuals.

CSF escape in the context of incomplete suppression of viraemia is likely to result from continual seeding of the CNS by infected cells that traffic into the brain and/or by ongoing, cycles of viral replication in cells within the CNS. Inadequate potency of ART from incomplete medication adherence, suboptimal systemic and CNS pharmacokinetics, or HIV drug resistance, is likely to be a major mechanism of CSF escape. Standardised assessments of medication adherence, drug levels in blood and CSF (when possible), and HIV drug resistance will be critical for elucidating the causes of incomplete viral suppression. Switching or intensifying the ART regimen may improve viral suppression and reduce or eliminate CSF escape.

In low-income settings, CSF escape remains understudied and further work is needed given the burden of HIV disease in these countries. Presentations at the meeting from Rakai in Uganda, Pune in India and Bucharest in Romania all showed that sustained suppression on ART was far less frequent than in high-income countries, less potent and more toxic ART regimens were commonly used, and symptomatic CNS disease was far more frequent.

Symptomatic CNS escape is a major challenge clinically and for which there are limited therapeutic options. Symptomatic disease may be the result of local inflammation from uncontrolled viral replication. Common co-infections, particularly those that affect the CNS, including cryptococcosis, tuberculosis, and herpes virus or polyomavirus reactivation may increase the risk of symptomatic CSF escape and requires further investigation. In children, symptomatic CSF escape remains a very significant challenge as HIV-related CNS damage can be permanent and have profound developmental impact. A global collaborative network would be particularly useful to develop case definitions, ensure appropriate collection of samples and access to specialised testing, and to investigate better management strategies.

In the setting of complete virological suppression, determining if the CNS is indeed an important reservoir of HIV is a high priority for the cure agenda but it remains an extremely challenging area to study. The limited ability to sample the CNS with the sensitivity required to detect the persistence of rare, HIV-infected cells with intact (replication-competent) proviruses is a major obstacle to progress. Reasonably large volumes of CSF (i.e. up to 25 mL) can be safely obtained, but CSF contains very few cells and has few to no virus particles in individuals on long-term suppressive ART. Antemortem tissue sampling is prohibited except in rare circumstances in which a diagnostic biopsy is required, and then the sample obtained may not be representative of other regions of the brain. Greater effort to rapidly obtain and store brain tissue after death from individuals on suppressive ART for in-depth analysis of HIV persistence is critical for progress and such efforts have already begun, providing a much needed resource.

Recent cohort studies suggest that in individuals with high CD4 T cell counts, sustained virological suppression and no prior AIDS-defining illnesses or HIV drug resistance, CSF escape is rare, potentially in the range of 1–5% or even lower, especially since the introduction of simpler and more potent ART regimens [2]. However, does this mean that there is no residual viral reservoir in the CNS? Although studies of CSF show infrequent detection of HIV RNA, but this does not exclude the persistence of infected cells in brain parenchyma, which some would argue is very likely. To test this latter thesis, more sensitive assays are needed to quantify and characterise very low levels of virus particles or virus-infected cells in CSF or brain and to determine if virus sequences are intact [3], as are more sensitive CNS imaging methods to detect the persistence of immune activation and inflammation that could be driven by HIV persistence. Analysis of viral protein or cells in the CSF and markers of inflammation or neuronal damage as indirect indicators of HIV persistence could be informative [4]. A multidisciplinary approach that includes investigations of both CSF and brain tissue, combined with comprehensive measures of systemic HIV persistence, are needed to answer the key question whether the CNS is a major sanctuary for HIV persistence; and, if so, what cells in which regions of the brain are the sites of persistence. Indeed, the CNS looms large as an unknown frontier in the efforts to cure HIV infection.

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