EDITORIAL COMMENT

HIV cure strategists: ignore the central nervous system at your patients' peril

Stephen A. Spector[a,b] and Jay Rappaport[c]

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Early in the AIDS epidemic, numerous investigators determined that central nervous system (CNS) disorders including dementia were common among persons infected with HIV. Moreover, it has been established that infected persons without clearly identified dementia can have mild HIV associated neurological disorders [1]. HIV can be identified within cerebrospinal fluid (CSF) of almost all HIV-infected persons not receiving antiretroviral therapy (ART) and post-mortem brain tissues have readily detectable viral expression primarily within resident microglial cells and macrophages [2,3]. Furthermore, in patients with undetectable viral load in both plasma and CSF, HIV DNA was detectable in all subjects in brain autopsy tissue [4]. Further, experimental animal models in which $CD4^+$ T cells are depleted or absent emphasize the importance of the macrophage reservoir [5,6]. Thus, it is somewhat surprising that the CNS as an important reservoir in persons receiving treatment remains hotly debated.

Numerous publications in the era of effective ART have continued to identify subtle neurological deficits in HIV-infected persons despite what appears to be effective long-term viral suppression. This could be due to immune activation rather than infection of the CNS per-se. However, low-level replication leading to chronic inflammation remains possible. The existence of areas of persistent virus is supported by the multiple pattern decay kinetics of virus in the CNS in patients with neurological disease suggesting differences in the cellular reservoirs in these patients [7]. The association of slower decaying virus in CSF, with low $CD4^+$ T-cell tropism, is suggestive of viral reservoirs within macrophages/microglia, rather than $CD4^+$ T cells. If the slow decline of virus within the CNS is indeed even only partially due to macrophage infection, then curative strategies that ignore this reservoir will fail.

The article by Gama *et al.* [8] in this issue of *AIDS* provides additional support in a macaque model for the persistence of virus [in this case simian immunodeficiency virus (SIV)] within the CNS despite what appears to be effective ART suppression of virus for more than a year. In their study, one of three macaques showed increases in activation markers within CSF, and SIV transcripts were identified within the occipital cortex of resident $CD68^+$ macrophages (likely microglia cells). Virus could be reactivated from plasma and tissues including brain. Notably, reactivation in peripheral tissues and the CNS occurred independently and viral genotypes could be distinguished between the CNS and the periphery based on phylogeny. The investigators could also show increasing levels of SIV RNA in the brain resulting from what appears to have been focal viral reactivation. It is important to note that only one of three animals showed this pattern of select CNS latency and reactivation, and it is possible that not all macaques (or humans) will harbor viral reservoirs within the CNS.

[a]Department of Pediatrics, University of California San Diego, La Jolla, [b]Rady Children's Hospital San Diego, California, and [c]Department of Neuroscience and Comprehensive NeuroAIDS Center, Temple University School of Medicine, Philadelphia, Pennsylvania, United States.

Correspondence to Stephen A. Spector, Department of Pediatrics, University of California San Diego, La Jolla, USA or Jay Rappaport, PhD, Department of Neuroscience and Comprehensive NeuroAIDS Center, Temple University School of Medicine, Philadelphia, Pennsylvania, United States.

E-mail: saspector@ucsd.edu; jayrapp@temple.edu
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The data from the study by Gama *et al.* [8] are consistent with recent findings from other groups, strongly suggesting that the CNS can serve as an isolated and independent reservoir of HIV during ART. Several lines of reasoning argue that the CNS should not be ignored when developing a cure strategy for HIV including the CNS is seeded early following initial HIV infection [9,10]; ART penetration into the CNS is known to be poor for many antiretrovirals, thus establishing an environment with inadequate drug levels to fully suppress virus [11,12]; despite prolonged viral suppression on ART, markers of immune activation persist within CSF [13]; neuroimaging studies provide additional evidence for persistent inflammation in patients fully suppressed on ART [14,15]; viral RNA can be detected in the CSF of some patients but not in blood when using the same sensitive assays (CSF escape) [16–18]; and discrete viral sequences can be identified within CSF and plasma supporting the notion that compartmentalized HIV infection occurs independently within the CNS [7,19].

It is interesting to note that only a single patient has been cured after receiving a stem cell transplant from a CCR5-Δ32 homozygous donor [20]. In other patients receiving similar transplants, the time to rebound appears to be elongated, suggestive of a smaller reservoir of infection. It is important to fully characterize this reservoir. Long-lived cells, such as macrophages with slow turnover kinetics, may be particularly resistant to eradication strategies. Moreover, cure strategies should be more inclusive when approaching HIV reservoirs rather than exclusive in devising approaches to eradicate virus. The study by Gama *et al.* [8] adds additional information in the rhesus macaque model to the increasing accumulated data supporting the CNS, as well as the macrophage/microglia as an occult reservoir of HIV. For those HIV cure strategists, we warn that you ignore the CNS as an HIV reservoir at your patients' peril.

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Conflicts of interest

There are no conflicts of interest.

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