

Viral Escape in Cerebrospinal Fluid—An Achilles Heel of HIV Therapy?

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(See the article by Edén et al, on pages 1819–1825.)

One of the ongoing challenges for human immunodeficiency virus (HIV) therapeutics is achieving optimal treatment for the infected brain. Structural and physiologic isolation of the brain, based on blood-brain and blood–cerebrospinal fluid (CSF) barriers, typically makes the treatment of infection of the brain challenging. Because HIV is present in this compartment throughout the course of infection, successful control of viral replication in the brain is essential to effective therapy, particularly therapy aimed at eradication of HIV, an increasingly discussed research goal. Edén and colleagues in this issue of the *Journal* [1] have made important observations from a series of patients with stable successful control of HIV in the plasma, documenting a surprisingly high proportion (10%) of patients with still detectable virus in the CSF. Although the virus infection did not appear symptomatic in these patients, extrapolation from past experience with HIV-associated cognitive impairment [2], and recent reports

of reversible symptomatic viral escape due to discordant virus [3], it is concerning that this ongoing viral presence represents a serious threat to the brain over the many years that these patients are expected to live. Additionally, it draws attention to the magnitude of the challenge that the brain is likely to represent for any eradication strategy.

Understanding the biology of this persistent viral population in the CSF will be important. The authors consider the possibility that the drugs effectively controlling virus in the plasma might be less effective in reaching the CNS and CSF compartments. CNS penetration effectiveness (CPE) scoring of HIV regimens has been proposed as a useful tool for researchers and clinicians to compare different drug regimens. Letendre and colleagues [4] created this tool, which continues to evolve with emerging new data and drugs, integrating observations that reflect viral and cognitive impact of therapies, as well as theoretical aspects of drug properties, to categorize the available antiretroviral drugs for their likely contribution to viral control within the central compartments. Although the tool is the best available means of analyzing such data, it requires additional validation and likely is limited by the dearth of data regarding the effectiveness and potential toxicity of HIV drugs in the brain. Differences in the CPE ranking of treatments

failed to provide an explanation for the escape of virus seen in this series, underscoring the fact that it does not provide a satisfactory understanding of this problem. Although it is critical to continue to prospectively evaluate the impact of CPE, it is clear that it is premature to make its application routine for selection of therapeutic regimens.

A second and related biologic theme links immune activation in the CSF with cognitive dysfunction. Before the highly active antiretroviral therapy (HAART) era, it appeared that cognitive status was linked with the degree of immune activation in the CNS [5–7]. One of the most attractive hypotheses for understanding the high frequency of neurocognitive dysfunction, routinely seen to be >50% of treated subjects in the current era [8], links ongoing low level viral replication in the central nervous system with a smoldering and detrimental inflammatory response. Observations in the Edén et al [1] report are consistent with association of ongoing viral presence in CSF with enhanced neuroinflammation, reflected by significantly higher neopterin levels in the CSF of subjects with viral escape in this compartment. This observation reinforces the potential importance of even low viral loads on the nervous system.

Perhaps the most challenging aspect of the current observations comes in the notable association of longer treatment or

Received 23 August 2010; accepted 23 August 2010; electronically published 4 November 2010.

Potential conflicts of interest: none reported.

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The Journal of Infectious Diseases 2010;202(12):1768–1769

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0022-1899/2010/20212-0002\$15.00

DOI: 10.1086/657343

more interruptions or relapses reported with the detection of CSF viral escape. Median duration of therapy was significantly longer in those that had viral escape, being 77 months in this group. Successful HIV therapy is now permitting extended lives for our patients, shifting the emphasis of research from survival to optimal quality of life. This topic also touches on the interaction of HIV with aging, particularly as it affects the brain and cognitive status. Observations in this article—that viral escape in the CSF is associated with longer treatment—underscores the concern that there might be an interaction of aging (requiring very long term therapy) with the biology of HIV as it affects the brain. The interaction is not simply one of age itself, since there was no difference in the age of the two cohorts studied, but rather with longer use of therapy. However, if control of virus in the brain becomes increasingly difficult to maintain over time, this implies that increasing neurologic symptoms associated with the virus might augment the cognitive decline of aging, resulting in much more serious late-life neurological issues for HIV-infected patients.

Finding that interruption of therapy or even “blips” in HIV replication may augment the risk of CSF viral escape adds one more argument for the emerging consensus that continuous therapy with modern antiretroviral drugs is superior to drug-sparing approaches, including delaying therapy or intermittent therapy [9]. If there is something about repeated virus replication cycles between drug regimens that supports the evolution of virus so that it may persist in the CNS, this would be an additional ominous consequence of inconsistent use of HIV therapy. The results of this investigation suggest this is possible. Both of these issues indicate that the technically challenging analysis of viral sequences of HIV from the brain compartment will deserve direct attention, as divergence of virus in the compartment could change its response to therapy independent of the plasma-derived virus.

The authors are to be congratulated on contributing these observations. CSF studies in asymptomatic subjects are challenging to perform yet essential to gain understanding of the complicated therapeutic challenges that are required to gain and maintain control of HIV. If these findings are replicated by others, suggesting 10% failure rate of current therapy in the critical CNS compartment, this would be a serious shortcoming for present therapy. The report by Eden et al [1] makes it clear that assessment of disease in the CNS should more routinely be performed as HIV therapeutics evolve. This report is timely because alternative strategies for therapy, including declining use of nucleoside antivirals that have been the backbone of most therapy to date, as well as early use of other antiretroviral drug classes, including CCR5 antagonist drugs and integrase inhibitors, will give opportunities to see if better outcomes for the CNS can be achieved.

However, it must be recognized that this study has some limitations. Samples were collected at sites recognized as referral centers for neurological cases, and indeed the population may have had more underlying neurologic disease than was appreciated. Systematic neurocognitive evaluations were not performed in the cohort as a whole, so the association of viral escape on cognitive functioning cannot be fully considered. Although the patients may have been asymptomatic, it is likely that more detailed testing would have revealed suboptimal performance on quantitative testing in many. Neurological examination helps reduce the probability of confounding conditions but is not sensitive to the prevalent mild cognitive changes that are most prevalent in the current era. Thus, more detailed neurologic performance studies paired with detailed virologic assessment seems necessary to fully understand the consequences of the observations noted. Additionally, the sample size is quite small, with further dilution of power because of the variety of drug com-

binations, duration of disease, and of treatment. Thus, the observations should be replicated in larger studies before the conclusions can be considered established. There are larger cohorts of HIV-infected patients where similar observations should be reported to further understand the generalizability of the report provided here. This article clearly supports ongoing efforts to study in detail the treatment of HIV infection as it relates to the brain.

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