Impact of Antiretroviral Therapy on HIV-Related Brain Injury

Richard W. Price
San Francisco General Hospital (SFGH), San Francisco, California

(See the article by Lescure et al, on pages 235–243.)

The report of Lescure et al [1] in this issue clearly documents the decrease in severe neurological disease associated with human immunodeficiency virus (HIV) infection in the era of combination antiretroviral therapy (cART). The authors matched each HIV-infected patient in Denmark by age and sex to 14 HIV-uninfected controls with use of the Danish population registry and compared the incidence of severe neurocognitive disorders (SNCDs) over three 4-year epochs. By the third of these epochs (2005–2008), the incidence of SNCDs among HIV-infected patients had decreased to a level similar to that of the control subjects. This confirms the impression of everyday clinical experience, extends previous reports of the salutary effects of cART on the incidence of the AIDS dementia complex (ADC) [2, 3], and places the magnitude of this therapeutic effect in a population-based perspective. The authors thus show that a nationwide program of treatment using international guidelines–based cART regimens had a profound impact on neurological morbidity.

Can we now conclude that beyond treating all HIV-infected individuals early enough in their course to prevent progression of immunosuppression, there is little more that needs to be done to assure protection of the brain from HIV-related injury? Perhaps. However, before we become complacent, we should address a number of additional questions raised by what we know of antiviral drug pharmacokinetics and by several clinical observations. Indeed, these questions have fostered a growing concern in the Neuro-AIDS community that insufficient attention is being directed to the effects of antiretroviral treatment on central nervous system (CNS) HIV infection and its consequences [4].

It is clear that many antiretroviral drugs do not reach inhibitory concentrations in the CNS, or at least in the cerebrospinal fluid (CSF) that provides a convenient surrogate for brain intracellular fluid in pharmacokinetic studies, although not without certain caveats [5]. Many of the currently favored drugs fail to achieve CSF concentrations shown to be effective in suppressing HIV replication in cell culture, and even those drugs that do penetrate the CNS barriers to drug entry characteristically achieve CSF concentrations considerably lower than those in blood [6]. This limited drug access has led to recommendations that more attention be paid to pharmacological CNS drug penetration, not only in treating symptomatic neurological disease, but more broadly in preventing CNS injury and, thus, perhaps in all patients [4]. To help clinicians address this problem, Letendre et al [6] developed a simplified system, the CNS penetration-effectiveness rank score. This provides a useful initial guide for clinicians but is also relatively crude, because it is based largely on the pharmacological properties rather than the demonstrated efficacy of the drugs in suppressing CNS infection and its consequences. In fact, it has proven to be difficult to evaluate individual CNS drug efficacy for a number of reasons, including the need to treat with multiple drugs making it difficult to single out the role of individual components, the reluctance of industry to incorporate CSF analysis in the early phases of drug testing when single agents might be used for a brief time, and uncertainty regarding the choice and interpretation of different study end points (eg, CSF HIV concentration, other CSF biomarkers, or neuropsychological test performance). Reports on the effects of the CNS penetration-effectiveness scores on CNS outcomes have been mixed [7–10].

Incorporating this into guidelines for therapy would also entail conflicts with drug toxicity and convenience and, thus, adherence.

In their study, Lescure et al [1] did not analyze the effect of different treatment regimens on the incidence of
SNCDs, and this likely would have been difficult with such a small group of afflicted patients \( (n = 32) \) and the presumed similarity of treatments in this nationally organized setting. The patients grouped under the definition of SNCDs were also likely heterogeneous. Indeed, one can ask whether it was useful to group together all SNCDs, as was done in this study. However, I agree with the authors’ approach. This designation, which identified patients with major neurological deficits regardless of cause (although excluding CNS opportunistic diseases), avoided the difficulties of diagnosing ADC from patient records. It also importantly allowed comparison of the HIV-infected and HIV-uninfected groups with respect to more severe neurological morbidity. Only 12 (37.5%) of the 32 received a diagnosis of AIDS dementia, and two-thirds were receiving treatment at the time of diagnosis, with 15 (71%) of these having undetectable plasma HIV RNA. They also differed from the HIV-uninfected group, because they were younger and had lower non-HIV co-morbidities and alcohol abuse. Thus, they may have been afflicted with a mixture of HIV-related and unrelated disorders. It might have been interesting to have more detail on the clinical diagnoses and presentations for the HIV-infected patients with SNCDs. The advantage of a population study such as this one is that it provides a broad and statistically sound overview of disease incidence and major risks. A disadvantage is that it does not provide a more detailed view of the individual patients and the reasons that they fell through the treatment safety net.

The ineffectiveness of CNS treatment has also been raised by reports of patients with discordant CSF treatment responses, compared with blood—also called CSF escape—in which CSF HIV RNA levels are elevated when plasma viral RNA concentrations are at or near the detection limit of contemporary assays [11, 12]. These patients, who comprised 10% of immunosuppressed patients in a recent study [12] may or may not have neurological symptoms and signs of CSF pleocytosis. If asymptomatic, it is not clear whether to assure that the CSF virus is treated to suppressive levels by substituting or adding drugs that reach the CNS or to continue a regimen that has preserved blood CD4\(^+\) cell counts. If symptomatic, it seems prudent to readjust treatment on the basis of virus susceptibility with inclusion of \( \geq 2 \) drugs that reach suppressive concentrations in the CSF, although there is little direct study to support this recommendation.

Another possible sign of incomplete CNS treatment effect is the persistence of mild elevations of the biomarker neopterin in the CSF in some patients [10, 13–15]. This pteridine biomarker of macrophage activation is produced in the CNS, elevated in the CSF during HIV infection with highest concentrations in ADC, and decreases with treatment. However, in immunosuppressed patients, CSF neopterin frequently remains above levels found in HIV-seronegative persons, although still below those of untreated infection. The reason for this is not clear. It may be a sign of persistent low-level CNS HIV infection despite inability to detect HIV RNA in CSF or a component of continued systemic immunooactivation that is common in treated patients [16]. Because macrophage activation is an important intermediary in brain injury in ADC and HIV encephalitis [17], an elevated CSF neopterin level might also indicate continued low-level brain injury.

Finally, an important source of concern that current therapy is not adequate for the CNS is the reported high prevalence of neurocognitive impairment in well-treated patients [9, 18]. Although cART has markedly reduced the incidence of more severe CNS disease, the prevalence of milder abnormalities detected by neuropsychological testing has been reported to remain high. For such cases, a revised nomenclature for HIV-related CNS impairment introduced 2 new terms to encompass this milder impairment: asymptomatic neurocognitive impairment and minor neurocognitive disorder, both with similar criteria for impairment on neuropsychological test, compared with norms, but differing in the absence or presence of symptoms and mild interference with daily function [19]. Together with more severe HIV-associated dementia that is largely parallel to the original ADC designation, these milder afflictions are grouped in the broad definition of HIV-associated neurocognitive disorders.

The study by Lescure et al [1] does not address the issue of milder disease but does suggest that such treated individuals infrequently experience more severe neurological impairment, at least at the age of the persons included and in the period spanned by the study. Although a population-based study of milder impairment structured like the one reported here would be invaluable in resolving this issue, it also would present formidable logistical and resource challenges. Therefore, alternative approaches are needed to prospectively study the effects of early treatment on these longer-term milder neurological outcomes. It would be particularly useful if the incidence or prevalence of these milder afflictions could be placed in a population-based context. This would require neuropsychological assessment of HIV-infected patients and matched HIV-uninfected control subjects, because these entities are otherwise difficult to recognize clinically. Unlike ADC, which as originally described had a core clinical phenotype and a consistent underlying neuropathology in HIV encephalitis [20, 21], asymptomatic neurocognitive impairment and minor neurocognitive disorder do not have clearly defined clinical presentations or consistent
neuropathology [22]. Moreover, there are no clear laboratory biomarkers of active brain disease in these individuals, and the underlying causes and patterns of CNS injury may be heterogeneous. Even in patients without alternative explanations, in whom HIV infection is the likely to be implicated, it is often unclear whether they experienced HIV-related brain injury in the past before therapy was begun or whether they continue to sustain active, although indolent, neurodegeneration despite immunosuppressive therapy. For this reason, defining disease activity in this context is one of the major requirements for rational therapeutic targeting.

One intriguing feature of the HIV-infected patients with SNCDS was their younger age, compared with the HIV-uninfected control subjects. This may relate to the inclusion of HIV-associated diseases, which afflict individuals earlier than most neurodegenerative conditions in the control population. Also, as the authors discuss, it may also relate to an interaction of HIV-related injury and the aging of the nervous system. Although there is little to support enhanced incidence of Alzheimer’s disease in the context of HIV infection [23], other additive or synergistic interactions between HIV and the aging brain may play a role. For example, subclinical HIV-related brain injury before treatment is initiated might predispose to earlier and more severe presentations of various CNS diseases that would only manifest later in the control population. Conditions now recognized to be more common with HIV infection but that are not traditionally AIDS related [24], including cerebrovascular diseases, may also be more common or progress more rapidly in these patients [25, 26].

In conclusion, the article by Lescure et al [1] is an important contribution to defining the impact of cART on neurological morbidity of HIV infection. It fits well with previous reports but adds a critical population context. Indeed, I urge the authors to extend their study over the coming decades to monitor whether the reduction in severe neurological disease by treatment is sustained. A population-based study such as the one by Lescure and colleagues should prove to be invaluable in clearly defining the impact of treated HIV infection on the aging nervous system as cART prolongs survival.

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References


