Antiviral Therapy 2013; **18:**149–151 (doi: 10.3851/IMP2561)

Commentary

A light in the cognitive fog?

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HIV escape in the central nervous system (CNS) despite undetectable viral load in the plasma has been observed and may contribute to HIV-associated neurocognitive disorders. Favouring the use of HIV drugs with a good penetration into the CNS has been advocated, leading to the establishment of the CNS penetration-effectiveness (CPE) score. However, the relevance of this score is not fully established. Ciccarelli *et al*. compared two versions of the CPE scores in their capacity to predict cognitive dysfunction in HIV-infected individuals. The revised CPE score, but not the original one, showed an improved association with cognitive impairment. Prospective studies are warranted to assess the validity of the CPE score.

Thanks to combination antiretroviral therapy (cART), HIV-associated dementia has decreased over the past decades, but minor cognitive disorders seem to be present in a substantial proportion of the patients. To account for this evolution, the diagnostic criteria first developed by the American Academy of Neurology in 1991 were refined in 2007 [1] to recognize three conditions: HIV-associated asymptomatic neurocognitive impairment (ANI), corresponding to deficits to ≥1 standard deviation below age-appropriate norms in ≥2 cognitive domains without difficulties in activities of daily living; HIV-associated mild neurocognitive disorders (MND), corresponding to the same criteria as ANI but accompanied by mild difficulties in activities of daily living; and HIV-associated dementia corresponding to moderate to severe cognitive deficits in ≥2 cognitive domains and moderate to severe difficulties in activities of daily living. Yet, even if minor, HIV-associated neurocognitive disorders (HAND) can be deleterious since these disorders are associated with diminished quality of life, decreased compliance to treatment and ultimately increased morality [2,3].

Is it possible to avoid or minimize HAND? It has been suspected for more than a decade that the different antiretroviral drugs have unequal efficacy in terms of HIV containment in the central nervous system (CNS). Indeed, keeping HIV in check in the periphery is not always synonymous with good control of the virus in the CNS. Peluso *et al*. [4] identified 10 virologically controlled HIV-infected patients who developed new onset neurological abnormalities, including cognitive ones. Although, the median HIV viral load was 62 copies/ml in the plasma, it was 3,900 copies/ml in the cerebrospinal fluid (CSF). Almost all patients improved with a switch towards drugs that have a better access into the CNS [4]. Precisely, in an attempt to rank antiretroviral drugs, in 2008, Letendre *et al*. [5] established a CNS penetration-effectiveness (CPE) score, which is based on the physicochemical, pharmacokinetic and pharmacodynamic properties of the different antiretroviral compounds. Although there is a relative agreement that a high CPE score is inversely correlated with the HIV viral load in the CSF, there is more dispute as to whether this score is associated with a better cognitive outcome in HIV-infected people [6,7], or not [8,9]. Others have examined the mortality due to opportunistic infections of the CNS and found that if it was inversely correlated with the CPE score in the early years of cART (before 1998), this correlation was lost in the more recent years, suggesting that the newest powerful antiretroviral drugs are sufficient to keep the virus under control, independently of the CPE score [10].

A revised version of the CPE score, containing new drugs and a refined classification of those previously included, was proposed in 2010 by Letendre *et al*. [11]. Although not published so far, this revised version of the CPE score is being used by different groups, and thus independent studies assessing the respective values of these two CPE scores need to be performed.

Accordingly, in this cross-sectional single cohort study, Ciccarelli *et al*. [12] administered a neuropsychological

battery to 101 HIV-infected patients on effective antiretroviral therapy as reflected by an undetectable plasma viraemia. In an attempt to avoid overestimation of cognitive impairment, they compared the scores of the HIV-infected patients to 30 age-, gender-, education- and nationality-matched HIV-negative control subjects. They found that ANI was present in as many as 50% of the HIV-infected cohort. Interestingly, in a multivariate analysis, they showed that the 2010 (revised) CPE score ≥6 – but not the 2008 (original) CPE score – as well as a self-reported antiretroviral treatment adherence of ≥80%, were associated with better cognition [12]. Although it awaits confirmation, this study is promising as it suggests that the revised CPE score may be of higher value than the original one and may thus provide a better guide to the clinicians dealing with patients with HAND.

Another salient aspect of this article is that it adds to the growing body of evidence showing that even virologically controlled HIV patients, without severe comorbidities frequently present neurocognitive impairment when carefully assessed by neuropsychologists [13–15]. Somewhat surprisingly, and contrasting with previous studies, Ciccarelli *et al*. [12] identified a high percentage of patients with ANI (50%), but no patients with MND. One can wonder whether ANI was over-diagnosed or, on the contrary, whether some of these ANI patients were in fact affected by MND. We do not think that the diagnosis of ANI was exaggerated. Indeed, this study encompassed a control group of matched HIV-uninfected subjects, making it unlikely that HIV-infected patients diagnosed with ANI were just a variant of the norm. However, it is still surprising that such a high percentage of patients with ANI were identified, contrasting with the absence of MND. Yet, ANI and MND are not differentiated by their impairment in cognition, but by, respectively, the absence or presence of functional impairment. To assess such a functional impairment, the Instrumental Activities of Daily Living functional scale was administered [16]. Although administering this scale is better than relying on mere subjective impression of the examiner, one can wonder whether this scale, which was designed to detect Alzheimer's disease in HIV-negative older subjects, is always sensitive enough to capture mild functional impairment in the younger HIV-infected working population. Thus, it can be hypothesized that some of the ANI subjects reported here were actually MND patients. This hypothesis is further supported by the fact that in the study by Ciccarelli *et al*. [12], patients' self-reported adherence <80% was independently associated with cognitive disorders. This lower adherence may be due, at least in part, to memory losses, suggesting that these patients suffered from functional impairment, thus reaching the MND definition. This point emphasizes the importance of designing an adapted functional scale to assess, specifically, HIV-infected subjects in the future.

Although suggesting that the revised CPE score may be valuable in helping to choose the optimal cART for a given patient, the data reported by Ciccarelli *et al*. [12] must not be overemphasized. Indeed, this is an observational study, thus biases in the clinician's treatment choices cannot be ruled out. Illustrating this point, other authors have shown that, at cART initiation, subjects with advanced HIV disease or previous lower adherence are more likely to be prescribed regimens with low CPE scores [17]. Moreover, one does not know how many times the patients switched regimens prior to enrolment into the current study, nor how long they were on each regimens, all factors that may have played a significant role in the results. These points underline the need to perform longitudinal prospective studies in order to establish firmly the value of the revised CPE score. However, such longitudinal studies would have many more advantages. For example, they would allow determination of the incidence of ANI and its true clinical meaning: is it an irremediable process leading to more cognitive impairment or is it reversible with an optimal cART? Hopefully, some of these questions will be answered by the ongoing START trial assessing immediate versus delayed HIV treatment in patients with a $CD4^+$ T-cell count >500 cells/μl. For instance, one will learn whether early HIV treatment averts the appearance of ANI in a large HIV population without neurocognitive impairment at baseline. Even if there are still many questions in the complex field of HAND, it is important for patients to see that there is plenty of ongoing work, such as the study by Ciccarelli *et al*. [12] reported here, which should eventually disperse this cognitive fog.

Disclosure statement

MC has received an unrestricted research grant from Gilead and MSD, and his institution has received an honorarium for advisory boards from BMS, Gilead, MSD and Janssen-Cilag. RADP has received an unrestricted research grant from Abbott and Gilead.

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Accepted 1 November 2012; published online 13 March 2013