Commentary

Targeting chronic central nervous system HIV infection

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Central nervous system (CNS) HIV infection is a nearly universal facet of systemic infection. Although antiretroviral therapy is generally effective in suppressing this infection and reducing its severe complications, reports of continued neurological abnormalities have questioned whether treatment developed for systemic efficacy is optimized for CNS infection. Shikuma et al. report that a ‘monocyte efficacy’ score based on cell culture studies and applied to antiretroviral drugs correlated with neuropsychological performance in a previously reported cohort. Although there are important questions regarding the theoretical underpinnings of both this score and its application, the findings present a novel slant on therapy.

Background: CNS antiretroviral therapy

The past few years have witnessed heightened interest in central nervous system (CNS) HIV-1 infection, its long-term consequences and, in particular, its effective treatment. This is not a new issue. It has long been evident that CNS infection – or as more commonly documented, the presence of virus in cerebrospinal fluid (CSF) – is a nearly universal facet of systemic infection that begins shortly after initial virus exposure and continues through the course of untreated systemic infection [1–3]. Although most often clinically silent and seemingly innocent despite local inflammatory reactions, it can evolve in some patients to frank HIV encephalitis presenting clinically as HIV-associated dementia (HAD) with synaptic and dendritic alterations and neuronal loss [4], most often in the context of advanced systemic infection and immunosuppression [5]. The effective treatment and prevention of this severe end point has long been an important objective of clinical research, and the introduction of suppressive antiretroviral therapy (ART) has generally been very successful in both arresting established disease and reducing the incidence of HAD [6,7].

Recent attention to CNS infection has been provoked by a number of observations and potential treatment issues, including reports of a high prevalence of neuropsychological test impairment in treated patients [8], potential interactions of HIV-related brain injury with brain aging as patients survive longer with effective therapy [9], pharmacological limitations in treating compartmentalized CNS infection as a result of the blood–brain and blood–CSF barriers that restrict antiviral drug exposure [10], reports of symptomatic and asymptomatic CNS (or CSF) viral escape in treated patients [11,12], the potential for CNS infection to serve as a viral reservoir that may be a source for virological failure and limit viral eradication [13,14], and the possibility that antiretroviral drugs may have CNS toxicity [15].

These considerations have led to more careful scrutiny of the CNS effects of therapy and, in particular, to drug combinations that might be more effective in suppressing CNS infection and its consequences [10]. This effort has centred principally on the capacity of different drugs to reach CNS targets. Prominent in these efforts has been the development of a CNS penetration effectiveness (CPE) score by Letendre et al. [16]. This defines an aggregate score for a drug regimen based on the sum of a three-level scale (0, 0.5 and 1) [16], or in its more recent iteration, a four-level scale (1–4) [17] for each drug based on available data – mainly on CSF pharmacokinetics, but where available also on measures of drug effect (mostly on CSF HIV RNA concentrations). The utility of this aggregate score in predicting treatment response has been supported by some studies, although not by others [17–21]. Importantly, most of these studies involve observational cohorts...
or retrospective analysis of trials structured for other purposes rather than randomized trials designed specifically to address CNS drug efficacy.

Whatever the precision and utility of this simplified score, its rationale is clear – it aims to better treat infection within the CNS and, more precisely, the compartmentalized CNS infection that is genetically distinct from the systemic infection measured in plasma [22]. Efforts at special CNS drug targeting assume that current antiviral regimens, which have been developed and refined on the basis of systemic efficacy in suppressing plasma virus and sustaining blood CD4+ T-cell counts, are not optimized for preventing or treating CNS infection. Without drug 'penetration’, it is inferred that CNS infection may persist and continue to cause CNS injury despite systemic control. In most patients there is little evidence for this, although there are clear exceptions. Notably, Canestri et al. [11] reported a group of 11 patients with new CNS disease despite suppression of plasma virus to near or below the clinical detection level who had higher HIV RNA concentrations in CSF than in plasma. These patients improved clinically after treatment was modified taking into account CSF viral genotypic resistance and CNS drug entry. Although additional reports have documented similar cases [23], this neuro-symptomatic CSF escape nonetheless appears to be rare. The Canestri et al. [11] cases were gathered over a 5-year period from clinics that had followed approximately 6,000 HIV-infected patients per year. A second type of CSF escape was documented by Edén et al. [12] in a retrospective series reporting low levels of CSF HIV RNA in 7 of 69 neurologically asymptomatic or stable patients with suppressed plasma virus. The clinical significance of this more common CSF escape is not yet clear: whether innocent and equivalent to plasma ‘blips’ or indicative of persistent compartmentalized CNS infection with eventual neuropathogenic potential is an important question that needs to be addressed in the current setting of suppressive therapy. This study also showed no relationship between CSF escape and CPE score. Mild elevation of CSF neopterin, a marker of macrophage activation, in the escaped group suggests that there was an active host immunological response in these subjects.

How do these virological observations relate to the more common issue of neurological symptoms or neuropsychological test impairment in seemingly well-treated patients? This relationship is to a large extent uncertain. Many factors can contribute to test impairment, beginning with normal variation in performance that assures ≥16% of individuals will be 'impaired’, and a larger number may be so classified as the number of tests expands [24]. Confounding CNS diseases, drug use, depression and the like are also important contributors to clinical symptoms and test impairment [20]. Where HIV infection appears to be the only evident cause, the critical unanswered question is whether the underlying brain injury was sustained before treatment initiation resulting in static residual damage, or whether the neuropathological process actually continues despite systemically suppressive treatment. If the former, then the remedy is earlier initiation of treatment, but if injury continues despite plasma viral suppression additional treatment strategies are needed.

Treating monocyte infection

In this issue of Antiviral Therapy, Shikuma et al. [25] outline a different approach to treating CNS infection and preventing CNS injury, one that proposes to target HIV replication in cells of the monocyte-macrophage lineage. This uses a monocyte efficacy (ME) score for different drugs derived from cell culture studies, reviewed by their co-authors Gavegnano and Schinazi [26], to predict CNS treatment effect. They report that this ME score predicted aggregate test performance (NPZ8 score) in a previously reported cohort, whereas the CPE score did not.

This approach targets a different pathogenetic schema than the CPE score. Rather than drug accessibility to CNS infection, it focuses on HIV replication in monocytes and macrophages outside of the CNS. It is predicated on the hypothesis that infected monocytes may be relatively impervious to some standard therapies and may continue to seed the brain despite treatment that suppresses plasma virus. After entering the CNS, these infected cells differentiate into macrophages where they assume a pathogenic role. However, there is little evidence that such a cycle of monocyte–CNS macrophage entry and infection, in fact, takes place in treated patients. In this hypothetical cycle, when are these cells initially infected and in what ontogenetic state? Is it as monocyte progenitors, as circulating monocytes as the authors seem to favour, or as macrophages within the brain? The authors cite their own work [27] and, in fact, correlate detection of HIV DNA in peripheral blood mononuclear cells (PBMCs) with lower ME score [25]. However, circulating monocytes express only low levels of CD4 [28], and it is generally accepted that monocytes are difficult to infect prior to differentiation into macrophages [29–31]. Although CNS macrophages are infected in overt HIV encephalitis, it is not clear that they are already infected when they enter the CNS rather than acquiring and propagating infection in situ in the absence of drug therapy. In one recent report using sensitive methods the authors failed to find viral DNA in the blood monocyte population [32], while in another report viral DNA was rare and markedly lower than in CD4+ T-cells [33]; similar results have
also been seen but not reported by others (R Koup, personal communication). These types of studies crucially rely on the quality of the cell sorting step, and it is essential to carefully define the level of contaminating T-cells in the sorted monocyte pool. Finally, in our own work we noted that the presence of macrophage-tropic HIV in the CSF/CNS did not predict the presence of virus with this entry phenotype in the blood [34]. Thus, although CNS macrophages are key cells in the pathogenesis of overt HIV encephalitis, evidence that infected blood monocytes play a role in evading systemic antiviral therapy and seeding the CNS in the face of treatment has little direct support.

Additionally, the applicability of the in vitro system used to derive the monocyte score requires scrutiny. This score is based on a cell culture system in which donor primary monocytes are first allowed to differentiate into macrophages before undergoing what they term ‘acute infection’, in which antiviral drugs are added to the system before viral inoculation in order to inhibit the initial cycle of replication. The ME score is the reciprocal of the median effective concentration (×1,000) in this system. It does not otherwise directly integrate human dosing or in vivo levels achieved for each drug. Because of the differentiation of these cells in culture, the system likely better tests susceptibility of macrophages rather than monocytes. Moreover, because of differences in donor cell properties, in vivo tissue-specific macrophage variation and viral isolate tropism, the applicability of this score to patient populations cannot be taken for granted.

To illustrate some of the practical issues, Table 1 compares CPE and ME scores for regimens included in the current DHHS Guidelines as initial therapy [35] for which monocyte scores can be calculated from the data presented by Shikuma et al. [25]. Because many of the drugs used to treat their cohort are no longer commonly used and data for many of the contemporary drugs are not available, this list is small and difficult to apply to current therapies. However, it shows that the commonly used combination of tenofovir disoproxil fumarate/emtricitabine/efavirenz and the alternative regimens using abacavir/lamivudine with either efavirenz or fosamprenavir/ritonavir have ME scores above the means of the neurologically normal or asymptomatic abnormal test groups reported by Shikuma et al. [25]. The table also shows that ‘conflicts’ between CPE and ME scores exist in some regimens, for example with the high CPE and low ME score of abacavir/lamivudine/nevirapine. More generally, if the ME score predicts effectiveness at suppressing a component of systemic infection, then one may ask why it would not also predict higher systemic efficacy. If monocyte–macrophage infection can select for drug resistance, one might expect spread of resistance to other cell types including CD4+ T-lymphocytes.

The authors discuss combining their score with some adaptation of the CPE to take into account both brain exposure and macrophage exposure to account for more direct treatment of infected brain macrophages, although this is not included in the presented analysis. As perhaps implied by the comparisons in Table 1, this might involve compromise of one or more treatment properties in designing such regimens.

**Evaluating central nervous system drug efficacy**

While one may question some of the scientific underpinnings of the ME score and the authors’ view that the results support the group of underlying hypotheses, it is still important to take into account the empirical evidence that the ME score correlated with the neuropsychological test outcome, even if as a step in refining both these hypotheses and the score. The authors...
report a correlation of the ME score with neuropsychological test outcomes both as a normalized continuous variable (the NPZ8 score) and by diagnostic categories determined by score definitions and clinical information, although oddly many of the NPZ8 scores of the subjects categorized as ‘neuropsychologically abnormal’ and of mild cognitive motor disorder were within the range of -1 to 1, considered normal in most studies [25]. Importantly, they also analyse outcomes in the subset of patients with suppressed plasma viral loads, in whom the confounding outcomes of the weaker systemic effects of some regimens and of drug resistance are thereby reduced. Although the effect of the ME scored is not profound, it is statistically significant.

The main study uses cross-sectional analysis of a cohort and assumes that the antiviral regimen they had been taking at study entry exerted a therapeutic or preventative effect on their neurological performance over the duration of therapy, in this study a mean of 2.1 years. The analysis does not take into account the patients’ pretreatment status. Because the treatments were prescribed by their care providers, the individual drugs and their combinations were varied and, of course, not randomized. This type of observational cohort makes it difficult to discern the effect of an individual drug or combination, and underscores the attractiveness of an aggregate score such as the CPE or ME score that attempts to represent a shared, though variable drug property across this range of regimens. By contrast, such scores fail to take into account many of the other properties of the regimen that contribute to systemic and likely CNS efficacy and that have been evaluated over the course of an extensive body of clinical trials and other studies. In observational studies such as this one, other important clinical factors may contribute to drug selection, and need to be taken into account in the analysis [36]. Hence the application of either CPE or ME scores needs to be tempered by the broader picture of systemic drug experience. Unfortunately, this study did not measure CSF HIV RNA levels, so this more direct assessment of the effect on CNS infection is unknown.

Conclusions

Current recommendations for systemic antiretroviral therapy are based on a large body of data, and represent the product of continuous refinement that has led to improved systemic virological control and immune preservation along with reduced side effects. Clearly, there is room for further improvement – for better restoration of CD4+ T-cells and reduction in the residual immune activation associated with an array of ‘non-AIDS’ morbidities and reduced longevity. Is more effective treatment of monocyte and macrophage HIV infection a helpful step in this direction? Will focus on treating this component of infection attenuate the continued CNS morbidity beyond that conferred by early treatment initiation, more effective systemic infection control and reduced immune activation?

The contribution of Shikuma et al. [25] suggests one approach, albeit limited by questions regarding the underlying hypothetical framework. What next then? As can be seen from Table 1, the available data cannot readily be used to judge contemporary preferred treatments, so this hypothesis needs to be supported by broader and more robust cell culture data using consistent methods as a basis for this score. The resultant predictive value of the ME score will need to be examined in other cohorts both cross-sectionally as in this initial study, but also using a prospective longitudinal design. While this has generally proved difficult in purely neurologically-directed trials, studies that ‘piggy-back’ on prospective randomized clinical trials where regimens have different ME (and CPE) scores should be considered. End points for such studies should include not only neuropsychological test outcomes but biological measures including CSF HIV RNA (viral load, genetic compartmentalization and macrophage entry phenotype) and markers of macrophages involvement such as the activation marker neopterin, or the chemokine CCL2/MCP-1 [37]. Using these combined strategies, it should be possible to further test this score and reflect on the underlying theoretical framework.

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References


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