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CENTRAL NERVOUS SYSTEM INFECTIONS (J LYONS, SECTION EDITOR)

HIV-associated Neurocognitive Disorders and Antiretroviral Therapy: Current Concepts and Controversies

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Abstract Antiretroviral drugs may help prevent neurological decline in individuals with HIV infection by suppressing viral replication and associated chronic immune activation in the central nervous system. However, HIV control in the brain may come at the price of drug-induced neurotoxicity. Herein, we review recent advances in the balance between adequate viral suppression in the nervous system and adverse effects of the medications used in HIV treatment.

Keywords Antiretroviral toxicity · HIV-associated neurocognitive disorder · HIV dementia · CSF escape encephalitis · CNS penetration effectiveness

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Introduction

HIV can affect the nervous system in a multitude of ways. Collectively, the HIV-associated neurologic disorders are termed neuroAIDS and classically include malignancies such as central nervous system (CNS) lymphoma, opportunistic infections such as cerebral toxoplasmosis, and HIV-associated neurocognitive disorder (HAND) [1]. Combination antiretroviral therapy (cART) reduces the risk of AIDS-associated CNS malignancies and opportunistic infections. However, HAND persists or develops in many HIV-infected individuals despite cART [2]. The persistence of HAND in the cART era has prompted concerns that cART regimens may not adequately suppress HIV in the nervous system or that antiretrovirals themselves may be neurotoxic and thus promote HAND. Here, we review current concepts and controversies about the relationship between HAND and cART.

HIV-Associated Neurocognitive Disorder

HAND consists of three diagnoses on a spectrum of severity, ranging from asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND) to HIV-associated dementia (HAD) [3]. Individuals with ANI demonstrate mild impairment on neuropsychological testing but have normal daily functioning; in MND, minor impairment in daily functioning is also present. The distinction between ANI and MND in clinical practice is subjective; patients may lack awareness of or fail to report functional limitations that would confer a diagnosis of MND. In one study, more objective functional assessments in those with ANI showed impairments comparable to those seen in MND [4].

HAD represents the most debilitating type of HAND and is defined by severe deficits in both neuropsychological testing and daily functioning. HAD classically presents as a subcortical dementia characterized by psychomotor slowing, poor concentration, inattentiveness, depression, and anxiety [1, 5]. Whereas cortical signs such as aphasia, apraxia, neglect, and agnosia were not commonly observed in the past, cortical findings are now increasingly recognized in patients with HAD, and some affected individuals have disease that is similar to Alzheimer's, with prominent deficits in memory and executive functioning [1, 2]. In advanced cases of HAND, magnetic resonance imaging may show generalized atrophy and diffuse white matter changes (Fig. 1).

Epidemiologic data on the effect of cART on HAND have yielded nuanced results. On the one hand, the advent of cART has been associated with a decline in HAD. In the Multicenter AIDS Cohort Study, a longitudinal cohort of men who have sex with men in the USA, the incidence of HIV dementia decreased by approximately half with the introduction of cART, from 21.1 cases per 1000 person-years in 1990–1992 to 10.5 cases per 1000 person-years in 1996–1998 [6]. The Multicenter European EuroSIDA study of 17 countries also showed a similar reduction in HAD during this period [7].

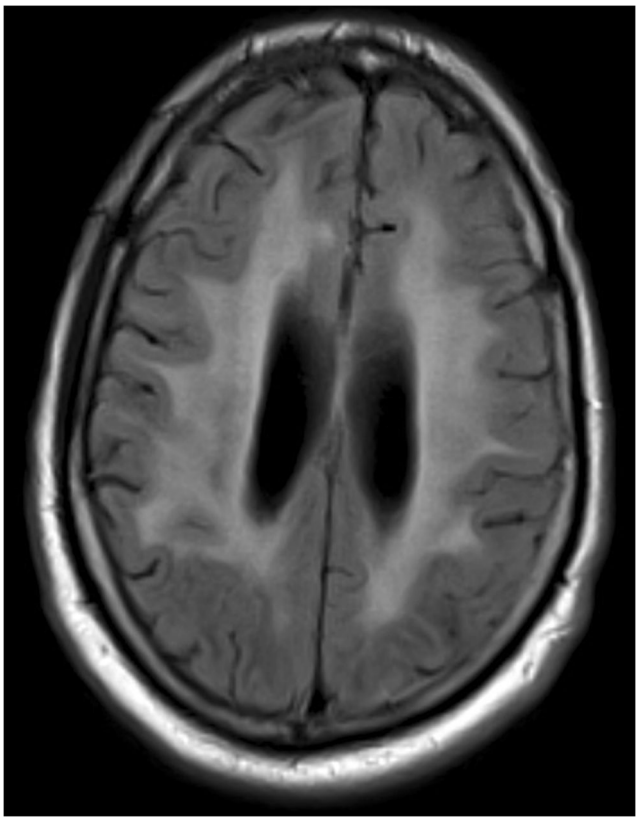

Fig. 1 Axial T2 FLAIR-weighted magnetic resonance imaging in a 49-year-old man with a 12-year history of AIDS without opportunistic infections which demonstrates generalized atrophy, ventricular dilation, and diffuse, confluent subcortical white matter hyperintensities that spare the association fibers

These associations indicate that cART may prevent or delay the most severe forms of HIV-associated neurocognitive impairment. On the other hand, while HAD has become less common in the cART era, the prevalence of HAND has remained stable due to persistence of the less severe forms of the disease [2, 8], suggesting that current antiretrovirals are insufficient to eliminate the neurocognitive effects of HIV.

CSF Viral Escape and Antiretroviral CNS Penetration

In a subset of HIV-infected individuals, there is active HIV replication within the cerebrospinal fluid (CSF) despite virologic suppression in the peripheral blood. Clinical manifestations of this entity, called CSF viral escape, range from a lack of symptoms to acute meningoencephalitis to subacute neurologic deterioration [9, 10•] that is clinically distinct from HAND. The prevalence of CSF viral escape is unknown, but in one small study of asymptomatic individuals with suppressed viral loads in the blood, 7 of 69 subjects (10 %) had detectable HIV RNA in the CSF [10•]. Discordance between CSF and plasma HIV RNA levels can be pronounced. In one study of 10 patients, the median CSF HIV RNA level was 3900 copies/mL, while the median plasma HIV RNA level was 62 copies/mL [9]. Antiretroviral resistance mutations can arise in this context; in two small case series, resistance-associated mutations in the CSF were detected in 6 of 7 and 7 of 8 patients undergoing resistance testing [9, 11].

Recognition of CSF viral escape, coupled with the persistence of HAND in the cART era, has led to speculation that standard antiretroviral regimens may not penetrate the blood-brain barrier well and thus may not effectively treat HIV in the CNS. Moreover, the principal cells that harbor HIV in the CNS, macrophages, may require higher levels of some antiretrovirals in order to prevent viral replication as compared to the primary peripheral reservoir, the CD4+ T lymphocyte [12]. Studies characterizing individual antiretrovirals have shown highly variable CSF levels irrespective of drug class [13]. For example, concentrations of tenofovir, one of the most commonly used antiretroviral drugs, were only 5 % of plasma concentrations in one study [14]. Conversely, the frequently prescribed antiretroviral efavirenz achieves near equivalent protein-free levels in CSF and blood [15].

Recognition of the heterogeneity of antiretroviral CNS penetration led to the development of the CNS penetration effectiveness (CPE) rank, a numerical score for each antiretroviral based on measured CSF concentrations, pharmacodynamic properties, and the results of clinical studies assessing the ability of antiretrovirals to reduce the CSF viral load or improve cognition [16, 17]. CPE scores for commonly used antiretrovirals are listed in the table below (Table 1). Because CPE scores are derived from multiple data sources,

Table 1 CPE scores and reported CNS toxicities in humans for commonly used antiretrovirals

Drug class	Drug	CPE score	Reports of CNS adverse effects
Nucleoside/nucleotide reverse transcriptase inhibitors	Tenofovir	1	Case report describing the development of neuropsychiatric symptoms in 9 patients who switched from efavirenz-containing regimens without tenofovir to efavirenz-containing regimens with tenofovir [18]
	Lamivudine	2	Case report of 2 patients with reversible acute dystonia being treated with lamivudine for hepatitis B infection [19]
	Emtricitabine	3	Retrospective study of patients switching from lamivudine to emtricitabine in which 8 of 158 reported neuropsychiatric symptoms (headache, paresthesias, confusion) soon after the switch [20]
	Abacavir	3	Case reports of 3 patients with neuropsychiatric symptoms (depression, hallucinations, headaches) after switching to abacavir-containing cART regimens [21, 22]
Non-nucleoside reverse transcriptase inhibitors	Efavirenz	3	Twofold increase in suicidality in 5332 patients randomized to efavirenz-containing regimens in four clinical trials [23]; longitudinal follow-up of 86 patients taking efavirenz in a clinical trial showed an increase in bad dreams and anxiety over time [24]; cross-sectional analysis of 146 asymptomatic patients showed an increased risk for HAND with efavirenz use [25]
	Nevirapine	4	Case reports of 3 patients developing psychotic symptoms [26] and 4 patients experiencing vivid dreams [27] after initiating nevirapine
	Rilpivirine	–[a]	None reported
Protease inhibitors	Atazanavir/ritonavir	2	None reported
	Darunavir/ritonavir	3	None reported
	Lopinavir/ritonavir	3	None reported
Integrase inhibitors	Raltegravir	3	Case report of 4 patients with worsening depression after starting raltegravir [28]; case reports of 5 patients with insomnia associated with raltegravir use [29, 30]
	Dolutegravir	–[a]	Increased risk of insomnia compared to an efavirenz-containing regimen in a randomized trial [31]
	Elvitegravir	–[a]	None reported

[a] Not classified in the 2010 CPE ranking system

equivalent CPE scores for different antiretrovirals do not necessarily reflect the same properties or strength of evidence, and no CPE score directly represents intracellular drug concentrations in the CNS [32]. While cART regimens with higher CPE scores are associated with undetectable CSF HIV RNA, the clinical utility of the CPE score remains unclear as studies have produced conflicting results, and the chronicity by which HAND develops may preclude adequate longitudinal evaluation [33].

Studies Comparing High Versus Low CPE Regimens

Several studies have compared the risk of developing neuroAIDS or HAND alone between high and low CPE regimens, with disparate results. The UK Collaborative HIV Cohort estimated incidence of neuroAIDS and all-cause mortality among 22,365 HIV-infected individuals on low (<4) versus high (>10) CPE regimens [34]. Although statistically nonsignificant, a trend was observed toward increased risk of neuroAIDS and mortality among those taking low CPE regimens. A limitation of this study was that a subclass analysis of the individual diseases comprising neuroAIDS was not performed.

In contrast, Caniglia et al. followed 51,938 HIV-infected, initially treatment-naïve individuals in the HIV-CAUSAL collaboration for four neuroAIDS conditions on low (<8) compared to high (>9) CPE regimens [35•]. While there was no significant difference between the groups in the incidence of cryptococcal meningitis, toxoplasmosis, or progressive multifocal leukoencephalopathy, there was an increased risk of HAD (hazard ratio 1.74) in those taking high CPE regimens.

Neither of these studies rigorously evaluated the less severe forms of HAND, which are now more common than HAD or CNS opportunistic infections in areas where cART is available. Research investigating the effect of antiretrovirals on HAND has generally shown a neuroprotective effect, although the influence of CPE score has varied. In a randomized trial of HIV-infected adults initiating cART in seven resource-limited countries, neurocognitive function improved with antiretroviral therapy, with no difference in improvement among regimens with different CPE scores [36]. Another randomized trial also showed no effect of higher CPE regimens on neurocognitive function, but it was stopped early by its data safety and monitoring board due to poor accrual of subjects and thus had limited power to detect a difference [33]. In contrast, Tozzi et al. found in 185 HIV-infected individuals with or at risk for HAND that cART regimens with higher CPE scores were associated with greater gains in neurocognitive performance [37]. The timing of cART initiation may influence the effect of therapy on neurocognitive function; in one study of 101 individuals with advanced HIV who were starting antiretrovirals, higher CPE regimens were linked to poorer results on neuropsychological testing at 1 year [38].

Antiretroviral CNS Toxicity

The suggestion of worse neurocognitive function in some studies of high CPE regimens has prompted concerns that antiretrovirals themselves may be neurotoxic, thus contributing to the persistence of HAND in the cART era. Some in vitro investigations have supported these concerns. For instance, using MAP-2 staining, dendritic arborization complexity, and neuronal response to exogenous calcium as markers for neuronal damage, Robertson et al. showed neuronal toxicity from 15 different antiretrovirals from different drug classes [39].

In vivo studies in both humans and animals have also demonstrated adverse neuronal effects of antiretroviral therapy. Nucleoside reverse transcriptase inhibitors (NRTIs) are thought to cause mitochondrial toxicity due to inhibition of mitochondrial DNA polymerase gamma and subsequent depletion of mitochondrial DNA [40]. N-acetylaspartate (NAA) is an amino acid derivative found only in neurons and synthesized by mitochondria; NAA levels can therefore be employed as a surrogate for neuronal integrity and mitochondrial function, and they can be measured by magnetic resonance spectroscopy (MRS). Using MRS in 18 HIV-infected individuals, NAA levels were found to be reduced in subjects receiving the NRTIs stavudine and didanosine [41]. Moreover, in a macaque model of HIV infection, a cART regimen of tenofovir, saquinavir, atazanavir, and the integrase inhibitor L870812 reduced hippocampal synapse number [42]. While many of these studies have used antiretrovirals that are no longer commonly prescribed in clinical practice in resource-rich settings (e.g., stavudine, didanosine, and saquinavir), patients with long-standing HIV infection may have taken these drugs in the past and thus may have been exposed to neuronal toxicities.

Some contemporary, first-line antiretrovirals also appear to have deleterious effects on the nervous system. In particular, efavirenz, a component of one of the most commonly prescribed cART regimens, damages dendritic spines in neuronal culture and is associated with abnormalities on neuropsychological testing [25, 43]. Data on the neurotoxicity in humans of other first-line antiretrovirals is mostly limited to case reports and case series describing the development of side effects soon after initiating or switching therapy; some of these reports are summarized in the table. In a study of cART treatment interruption in 167 individuals with CD4 counts greater than 350 cells/mm^3, average neuropsychological test scores improved with cessation of cART regimens [44]. However, treatment interruption increases the risks of opportunistic infections and death and is thus not recommended [45].

Conclusions

HIV-infected individuals benefit from cART for multiple reasons, one of which is a decrease in the overall risk of neuroAIDS. cART has rendered HAD uncommon, but the milder forms of HAND are prevalent, and CSF viral escape may occur in individuals who are otherwise successfully treated for HIV. These observations have raised questions about the ability of antiretroviral drugs to penetrate the blood-brain barrier and prevent viral replication in the CNS. An attempt to quantify the CNS penetration of different antiretrovirals through the CPE ranking system has uncertain clinical import. Higher CPE regimens have not shown a clear advantage to lower CPE regimens and, in some cases, have been associated with worse neurocognitive outcomes. These data suggest that antiretroviral toxicity may contribute to neurocognitive decline; in vivo and in vitro studies lend credence to this conclusion by documenting antiretroviral-induced neuronal damage.

Nevertheless, we favor antiretroviral treatment of all HIV-infected individuals with the goal of an undetectable plasma HIV viral load due to the preponderance of health benefits associated with this approach. However, practitioners must maintain a high index of suspicion for HAND, even in patients who are effectively treated with cART. If concern for this disorder arises, neuroimaging and CSF fluid analysis may be warranted, with consideration given to switching to a higher CPE regimen if CSF viral escape is present.

Compliance with Ethics Guidelines

Conflict of Interest Jennifer Lyons, Mark Etherton, and Kevin Ard have no relevant disclosures.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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