

HIV-associated neurocognitive disorders: a changing pattern

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Combination antiretroviral therapy has dramatically decreased the incidence of HIV-related mortality and serious opportunistic diseases, among which is HIV-associated dementia. However, minor forms of cognitive dysfunction have not disappeared and may even have increased in frequency. Aging of HIV⁺ patients, insufficient penetration of antiretroviral drugs into the brain with continuous low-grade viral production and inflammation may play a role. A putative neurotoxicity of combination antiretroviral therapy is controversial. In this article, we will discuss these aspects, as well as clinical and pathophysiological features shared by HIV-associated neurocognitive disorders and other neurodegenerative diseases, especially Alzheimer's disease. This article will briefly summarize the current clinical trials on neuroprotective agents, and the management of patients with neurocognitive disorders will be discussed.

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Learning objectives

Upon completion of this activity, participants should be able to:

- Describe changes in the epidemiology of HIV-associated dementia and HANDs
- Describe the pathophysiology underlying HANDs
- Describe the management of patients with HANDs and clinical trials on neuroprotective agents

Keywords

- combination antiretroviral therapy neurotoxicity
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The survival prognosis of HIV infection has dramatically improved in western countries thanks to the introduction of combination anti-retroviral therapy (cART). Moreover, the incidence of the classical neurological complications of HIV (e.g., cryptococcal meningitis, cerebral toxoplasmosis, progressive multifocal leukoencephalopathy or primary CNS lymphoma) has also decreased [1]. Nevertheless, despite these notable improvements in immune outcomes, HIV-associated neurocognitive disorders (HANDs) still remain an important issue.

The aim of this article is to discuss the causes and pathogenic mechanisms of the persistence of HANDs in cART-treated patients in order to provide an update on possible therapies and to propose an algorithm for the management of HIV-infected patients susceptible to developing HANDs.

Modification of the spectrum of cognitive disorders in HIV-infected patients

At the beginning of the AIDS epidemic, the most severe form of HAND, HIV-associated dementia (HAD), typically occurred in immunosuppressed patients with low CD4⁺ T cells counts [2]. Onset was insidious and the clinical syndrome mimicked subcortical dementia, characterized by mental slowness, forgetfulness, poor concentration and behavioral abnormalities such as lethargy, decreased spontaneity and decreased emotional responses. However, the spectrum and the severity of HANDs seem to have changed in the cART era. To account for this evolution, the diagnostic criteria first developed by the American Academy of Neurology (AAN) in 1991 [3] were refined in 2007 [4] to recognize three conditions, given here in order of increasing severity: HIV-associated asymptomatic neurocognitive impairment (ANI),

corresponding with mild-to-moderate cognitive deficits in two or more cognitive domains without difficulties in activities of daily living; HIV-associated mild neurocognitive disorders, corresponding with mild-to-moderate cognitive deficits in two or more cognitive domains accompanied by mild difficulties in activities of daily living; and HAD, corresponding with moderate-to-severe cognitive deficits in two or more cognitive domains and moderate-to-severe difficulties in activities of daily living.

While the incidence of HAD has significantly decreased in the cART era [1], its prevalence, as well as the incidence and prevalence of milder forms of HANDs, seem to have remained relatively stable and may even have increased [5]. Overall, the prevalence of HANDs has been reported to range from 15 to more than 50% according to some studies [5–8], with higher rates reported in patients showing greater comorbidities. For example, coinfection with hepatitis C virus was associated with greater neuropsychological impairment and increased difficulties in learning, executive functioning and processing speed [9]. However, cART-treated HIV/hepatitis C virus-coinfected patients do not seem to have a worse course of HANDs than HIV monoinfected patients on cART [10].

Furthermore, the CD4⁺ T-cell counts among the individuals diagnosed with HAD appear to be higher than those reported before the introduction of cART [11], and the proportion of HAD among the AIDS-defining illnesses has also been reported to have increased [12].

One explanation for these apparently paradoxical phenomena might be retrieved from epidemiological data. In fact, the number of HIV⁺ patients older than 65 years of age has increased tenfold between 1994 and 2004 in the USA, due in part

to the prolonged survival of HIV-infected patients with advanced immune deficiency as a result of cART [13]. In addition, between 1991 and 1996, the number of new AIDS cases rose twice as fast in persons aged 50 years or older than it did in younger people (22 vs 9%, respectively) [13]. However, the risk of developing HAD increases in parallel with the aging HIV population; it has been reported that 25% of HIV⁺ patients aged 50 years or older do exhibit such a neurological condition versus 14% under the age of 40 years ($p < 0.04$) [14].

The presence of HANDs has also been studied in stable patients with undetectable viremia and has shown controversial results. In a cross-sectional study, such patients were reported to have normal performance on a scale screening for HAND (International HIV Dementia Scale [HDS]) [15]. Furthermore, in a 5-year longitudinal study, no decline was observed in long-term asymptomatic HIV⁺ patients in measures of psychomotor speed [16]. By contrast, other studies reported HANDs despite HIV virological control. We recently estimated that up to 69% of HIV-infected patients with undetectable plasma HIV viral load might present at least mild cognitive deficits, the majority of those deficits being ANI [8]. Consistent with our data, a study examining cognitive functioning over 27 months, regarding HIV⁺ patients treated with cART, reported a cognitive decline over time in 8–34% of patients with undetectable viremia [17]. A second study reported a lack of association between incident neurocognitive impairment and virological and immunological measures, thus implying that neural injury continues in some patients despite success of cART [18]. Finally, a cohort study of patients with AIDS reported that 21% of aviremic patients progressed to HAD [19]. The prevalence of HANDs was quite different among the above studies. These differences probably reflect methodological issues related to the size of the neuropsychological batteries that were used and to the statistical definition of cognitive impairment. Nevertheless, most of the results demonstrate that mild forms of HANDs remain the most prevalent in the cART era, in line with results obtained in the early 1990s, before the ANI diagnostic category was formalized [20,21].

These observations seem to indicate that cART fails to fully prevent cognitive impairment. Thus raising the question as to why are HANDs persist in cART-treated patients. Is the access of cART in the CNS insufficient, thus allowing a chronic low-grade viral replication within the CNS? Is cART toxic for the brain? Is there a mechanism occurring

independently of cART? These questions are currently under investigation. Before reviewing them, a re-examination of the neuropathology of HIV infection might help in understanding the mechanisms at play in HANDs.

Physiopathology of HIV infection in the cART era

Evidence for persistent neuroinflammation in cART-treated patients

HIV enters the CNS early after primary infection [22]. As its neurotropism is strong, there is concern that it might establish latent viral reservoirs in which the virus could continue low-grade replication despite cART [23], thus leading to a ‘sanctuary’ effect in the CNS and to a chronic inflammation typical of HIV encephalopathy.

HIV encephalopathy, the neuropathological correlate of more severe forms of HANDs [24], classically results from the invasion of the brain by HIV-infected mononucleated cells from the peripheral blood. HIV infects perivascular macrophages, microglial cells and astrocytes, with the latter being infected only nonproductively [22,25]. Its neuropathological aspect is characterized by multinucleated giant cells and multiple microglial nodules, reactive astrocytosis and diffuse myelin pallor. By contrast, HIV does not infect neurons or oligodendrocytes. The infection of microglial cells triggers an inflammatory reaction, with subsequent release of viral proteins, proinflammatory cytokines, chemokines, nitric oxide, neopterin, arachidonic acid, glutamate and quinolinic acid, among others.

These inflammation mediators may lead to cell loss via excitotoxic mechanisms, as well as injury to the synaptodendritic complex, leading to disturbed synaptic transmission mediated by the glutamatergic, dopaminergic and cholinergic systems [26,27]. However, HIV infection can also affect cell functioning by interfering directly with intracellular mechanisms. Autophagy and the immunoproteasome system (ubiquitin proteasome system) are the major intracellular pathways for the degradation and recycling of proteins and cytoplasmic organelles. These systems are disturbed by chronic HIV infection, which may lead to the accumulation of cellular waste and ultimately neuronal degradation [28,29].

In the pre-cART era, HIV encephalopathy could be detected particularly in the basal ganglia and the central white matter. The neocortical grey matter, brainstem and cerebellum were sometimes involved, but to a lesser extent [30]. In cART-treated patients, neuroinflammation

has not diminished, but its pattern has changed: pronounced inflammation is now found in the hippocampi and adjacent parts of the entorhinal and temporal cortices in the autopsied brains of cART-treated patients [30]. These findings correlate with clinical observations in cART-treated patients that suggest an increasing involvement of the hippocampus in HIV-related cognitive dysfunction, as characterized by decreased memory learning [7,11].

Other neuropathological findings described in cART-treated patients share several features with neurodegenerative diseases. These will be described below.

Neurodegenerative mechanisms related to HIV infection

According to some authors, HIV infection might speed up the natural process of aging. Indeed, the cognitive profile of HIV-infected patients appears quite similar to that observed in normal aging. In particular, cognitive abilities such as learning, attention, working memory and processing speed are affected in both conditions, whereas language, remote memory and visuospatial skills remain preserved [31]. From a histopathological point of view, HIV infection and normal aging both lead to white matter atrophy preferentially involving the frontostriatal tracks, diminished production of myelin by the oligodendrocytes located in the frontal lobes, hippocampal neuronal loss and alteration of the BBB [31].

The longer duration of HIV disease combined with the increasing age of HIV-infected patients may also play a role in the development of several neurodegenerative diseases [31]. Indeed, there are neuroimmunopathological similarities between HIV infection and neurodegenerative disorders, such as activation of microglia and astrocytes [32], increases of proinflammatory cytokines (e.g., TNF- α and IL-6) [33] and chemokines (MCP-1) in both serum and cerebrospinal fluid (CSF) [34] or decreased immune surveillance [35].

More specifically, HIV has common features with Parkinson's disease and Alzheimer's disease (AD). In fact, both Parkinson's disease and HIV diseases affect substantia nigra and induce dopaminergic [31] and testosterone deficits [36]. With regard to AD, cART-treated HIV⁺ patients also share several risk factors with patients suffering from this pathology, such as insulin resistance, testosterone deficit or increase of cholesterol [31]. In one series, apoE4, an accepted risk factor for AD, was expressed twice as much in HIV-infected individuals with dementia compared with infected individuals without dementia [37].

Some evidence also suggests that the location of selective neuronal loss described in HAD mimics that of AD, with larger degrees of hippocampal neuronal cell loss in the earlier stages. Amyloid plaques have been identified in the brains of AIDS patients, with a significantly higher frequency in older compared with younger individuals. In addition, amyloid- β precursor protein (APP) was detected in the brains of 27% of asymptomatic HIV⁺ patients, demonstrating that there is an early deposit of this neurotoxic protein in these patients [38]. Tat, the regulatory protein of HIV, inhibits neprilysin, a neuronal endopeptidase known to degrade amyloid- β . This may be the reason why amyloid- β deposition increases in HIV⁺ patients [39]. Finally, prolonged exposure to cART (e.g., to ritonavir, which is known to inhibit amyloid clearance from the brain) and aging may account for the overall increase of amyloid deposition in HIV⁺ patients [40]. Contrasting with these findings, Ances *et al.* assessed amyloid deposition in older cognitively unimpaired HIV⁺ patients (mean age: 52 years) by using *in vivo* amyloid imaging with ¹¹C-PiB PET technology and reported that HIV patients did not have more fibrillar brain amyloid deposition [41]. However, these authors did find a diminished level of the neuropathological form of amyloid- β , A β 1-42, in the CSF, similar to those patients with AD.

Are there specific biomarkers of HIV-associated neurocognitive disorders?

Based on some similarities between AD and HANDs, the validity of biomarkers described initially in AD has been assessed in HAND patients. In AD, typical CSF changes include a decrease in A β 1-42 and an increase in tau protein [42]. Similar to AD, a low level of the toxic form of A β 1-42 was found in the CSF of patients with HANDs [43] together with a normal CSF level of A β 1-40, indicating brain amyloid deposition and not just death of neurons [44]. However, the results regarding tau are discordant between studies: some found an increase of tau in the CSF of patients with HANDs, similar to those with AD [43], whereas others found no increase of CSF tau, either in its total form or its phosphorylated one [44-46], thus offering a distinct profile of HAND as compared with AD. Recently, Gisslen *et al.* carried out a comprehensive study of several biomarkers and found that the CSF combination of a low level of soluble APPs (sAPPs)- α and - β and a normal level of phosphorylated tau allowed the discrimination of patients with HAD from both HIV⁺ and HIV⁻ neuroasymptomatics and from AD patients, but not from those

HIV⁺ patients with opportunistic infections [47]. They concluded that parallel reductions of CSF sAPP- α and sAPP- β in HAD and opportunistic CNS infections suggest an effect of CNS immune activation or inflammation in neuronal amyloid synthesis or processing [47].

Taken together, these data point to a multifactorial etiology of HANDs, located at the interface between infection, inflammation and neurodegeneration. Considering this complex situation, is it possible to successfully treat, and even prevent, HANDs?

Current knowledge on cART efficacy for the brain

cART penetration-effectiveness in the CNS

A number of mechanisms affect the CNS concentration of cART by limiting the access to drugs into and within CNS compartments. In particular, anatomical barriers such as the BBB, the blood-CSF barrier and the CSF-brain barrier play a crucial role.

In the current anti-HIV armamentarium, nevirapine, indinavir, lopinavir, amprenavir, abacavir, zidovudine, stavudine, emtricitabine, darunavir and raltegravir are the only drugs found to have CSF levels that are sufficient to inhibit HIV replication in the brain [48].

In 2008, based on the actual knowledge on cART pharmacokinetic characteristics, CSF concentrations and effectiveness in suppressing CNS viral replication as reported in previously published studies, Letendre *et al.* designed a score to measure the CNS penetration-effectiveness (CPE) of antiretroviral therapies [49]. The CPE score for a targeted cART regimen is obtained by summing individual drug scores. By computing the CPE rank, it becomes possible to evaluate the CNS efficacy of a given cART regimen. Letendre *et al.* found that lower CPE scores were associated with higher CSF viral loads [49]. Other recent publications confirmed that antiretroviral drugs with higher CPE score were the most efficient in suppressing HIV replication in the CSF [50,51].

With regard to HANDs, the value of the CPE score is more controversial. In a recent longitudinal study in which the authors followed up cognitively impaired patients initiating a new cART regimen for 48 weeks, Cysique *et al.* found that cognition gradually improved after initiating cART, with a peak at approximately 24–36 weeks [50]. In addition, they showed that a high CPE score significantly predicted neuropsychological improvement. Along the same lines, another follow-up study of patients

changing or initiating cART reported that CPE scores correlated with greater improvement in neuropsychological measures of concentration, speed of mental processing and mental flexibility after 20 and 39 months. Higher CPE scores were also associated with an improvement in global neuropsychological scores after 39 months [52]. By contrast, other studies did not report a beneficial effect of cART with high CPE scores [8,51]. This CPE ranking system has been recently revised to integrate new drugs (TABLE 1).

In conclusion, the CPE score is certainly an interesting concept, but prospective studies are needed in order to validate it as a clinical tool. An added level of complexity comes from the fact that new drugs are regularly arriving on the market and thus this score will have to be updated often, which may render comparison between studies complicated.

In the meantime, the question remains as to whether the lack of cognitive improvement in some cART-treated patients might be related to CNS toxicity of cART, which might hide or limit the cognitive benefit of the treatment.

Might cART be neurotoxic?

The literature reports some cases of worsening of CNS pathologies under cART [53], but given the large cohort of treated patients, these reports are quite rare. In addition, these phenomena seem to result from a transient worsening of pre-existing pathologies paradoxically attributable to the so-called immune reconstitution inflammatory syndrome (IRIS) more than from any direct toxicity of cART [54,55]. The frequency of IRIS is disputed, ranging from 0.9 to 35% of patients on cART within the first months of therapy [56–57]. In any case, IRIS plays a role in the expression of several AIDS-related CNS disorders such as tuberculosis, cryptococcal disease, cytomegalovirus retinitis and progressive multifocal leukoencephalopathy [55,56]. Indeed, beginning cART soon after the diagnosis of an opportunistic infection might increase the risk of a reactivation [55]. Recently, the detection of the following features were proposed as guidelines for the diagnosis of CNS IRIS [56]:

- A worsening of neurological status after initiation of cART;
- New neuroradiological findings that are suggestive of inflammation, as illustrated by contrast-enhanced lesions on MRI;
- A decrease in plasma HIV viral load of greater than or equal to 1 log₁₀;

Table 1. CNS penetration-effectiveness scores of antiretroviral agents.

Agent type	CNS penetration-effectiveness score			
	4 (very good)	3 (good)	2 (fair)	1 (poor)
NRTI	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir Zalcitabine
NNRTI	Nevirapine	Delavirdine Efavirenz	Etravirine	
PI	Indinavir/r	Darunavir/r Fosamprenavir/r Indinavir Lopinavir/r	Atazanavir Atazanavir/r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir/r Tipranavir/r
Entry inhibitors		Maraviroc		Enfuvirtide
Integrase inhibitors		Raltegravir		

*NNRTI: Non-nucleoside reverse transcriptase inhibitor; NRTI: Nucleoside reverse transcriptase inhibitor;
 PI: Protease inhibitor.
 Data taken from [91].*

- Symptoms that are not explained by a newly acquired disease or by the unusual course of a pre-existing disease;
- Histopathology that is demonstrative of T-cell infiltration.

There is currently little evidence that cART in itself may be neurotoxic. Some studies reported that nucleoside reverse transcriptase inhibitors may disturb mitochondrial function [58] and that protease inhibitors may affect proteosomal function [59], leading to neuropathy. In neuroimaging studies using magnetic resonance spectroscopy (MRS), decreased N-acetylaspartate levels were reported in HIV⁺ patients treated with stavudine and didanosine compared with HIV⁺ patients taking other antiretrovirals or no cART, revealing possible neuronal damage [60]. Finally, long-term cART regimens were shown to be associated with abnormal blood oxygen level-dependent functional MRI responses during the performance of attention tasks, pointing to the possible exacerbation by cART of HIV-associated brain injury in the frontal lobes [61]. By contrast, other neuroimaging studies suggest that cART is beneficial. Indeed, some authors have reported improved brain function after longer periods of treatment [62] and a decreased amplitude of the blood oxygen level-dependent functional MRI response in patients treated with high CPE score regimens, thus reflecting a reduction of the metabolic demand owing to decreased viral replication within the CNS [63].

The impact of cART on cognitive functioning was also assessed in some studies, leading to controversial results. A longitudinal study by

Cysique *et al.* reported a negative effect of cART regimens combining ritonavir and another protease inhibitor on motor function and hypothesized that the interaction of ritonavir with other protease inhibitors might enhance their capacity to enter the CNS and induce neurotoxicity [64]. But the most convincing and surprising data suggesting that cART may indeed be detrimental to cognitive functions were recently published by Robertson *et al.* [65]. Neurocognitive function was assessed as part of the AIDS Clinical Trials Group (ACTG) 5170 study, a multicenter, prospective observational study of HIV-infected subjects who elected to discontinue cART. Following 167 HIV⁺ patients over 96 weeks, these authors demonstrated a gradual neurocognitive improvement in patients who did not resume cART, whereas there were no significant changes in neurocognitive function in the 46 subjects who restarted cART prior to week 96. In an accompanying editorial, Clifford writes that this study raises the concern that the therapy may have toxicity that was not appreciated before and that this report “provides a critical warning that even as therapies are used earlier and longer, greater attention to the impairment that they may generate will be essential.” [66]. However, he also emphasizes the fact that the overall effect of cART is largely beneficial for HIV⁺ patients, as has been demonstrated recently [67], and to not prescribe cART based on these results is simply not an option.

Indeed, several other studies support a beneficial effect of cART on HANDs. The improvement of HANDs was found to be proportional to the duration of cART [50]. Along the same lines, we reported that HIV-infected patients with a longer duration of cART treatment tended to have better

cognitive performances [8]. In a randomized controlled study, Winston *et al.* recently focused on the beneficial effects of specific antiretroviral agents [68]. Treatment-naïve patients were randomly assigned to three different cART regimens of tenofovir–emtricitabine plus efavirenz, atazanavir–ritonavir or zidovudine–abacavir.

They were assessed with neuropsychological examinations and MRS at baseline and after 48 weeks. Results showed greater improvement in neuronal recovery on MRS for patients receiving tenofovir–emtricitabine plus efavirenz, whereas patients receiving tenofovir–emtricitabine plus zidovudine–abacavir demonstrated a greater improvement in cognitive functioning.

In conclusion, the data presented in the literature generally suggest that cART alleviates HANDs. The question of neurotoxicity of cART warrants further studies, but overall, the picture that emerges is that cART is not always sufficient to completely relieve HANDs.

Diagnosis & management of HIV-infected patients with HIV-associated neurocognitive disorders

At present, how should we manage patients with HANDs? Certainly, one important challenge relates to the early detection of HANDs in stable and cART-treated patients, and this is especially true for the physicians taking care of HIV⁺ patients in their daily practice.

Recently, Cysique *et al.* proposed a brief algorithm to identify patients at risk of HANDs [69]. This algorithm was developed on a sample of patients with advanced HIV (stage C3 according to the Centers for Disease Control and Prevention [CDC] classification) and based on variables that have been documented as risk factors for HANDs: age, educational level, plasma viral load, past history of CNS opportunistic infection, hemoglobin levels, HIV duration, cART CNS penetration characteristics and duration of current cART [69]. The reported sensitivity and specificity of this algorithm were 78 and 70%, respectively, for the identification of patients with HANDs [69].

To determine whether HIV⁺ patients do indeed suffer from HAND, ideally, a full neurocognitive battery should be administered to each patient who obtains a significant score from the aforementioned algorithm or who simply complains of cognitive dysfunction. Unfortunately, this option is not realistic as these examinations are time-consuming and are not available in every center. Thus, a screening method to detect HANDs is essential. Currently, a few

cognitive screening procedures exist for the detection of HANDs, but none of them are validated to detect minor cognitive disorders in HIV⁺ patients. In the pre-cART era, the HDS was developed to identify HAD, quickly assessing learning, attention, psychomotor speed and visuospatial skills. This scale demonstrated a sensitivity of 80% when the score was 10 points or less from a maximum of 16 [70]. However, the accuracy of the HDS to detect minor cognitive deficits in cART-treated patients was found to be inappropriate when using the classical cutoff of less than or equal to 10 points [71,72]. We recently administered the HDS to 100 aviremic HIV⁺ patients and reported that a cutoff of less than or equal to 14 points was associated with a sensitivity of 83%, and a predictive value of 92% to detect mild forms of HANDs, despite a somewhat decreased specificity (63%) [8].

We propose that patients who complain of cognitive disorders and who have an HDS score of less than 14 should undergo a comprehensive neuropsychological examination. Normative cutoffs and neuropsychological tests should be selected as recommended in the new nosology for HANDs [4].

In cases where cognitive deficits are ascertained, it is important to rule out confounding factors that may mimic or worsen HANDs, in particular other developmental or neurologic conditions such as opportunistic infections/tumors of the CNS, major depression or recent drug or alcohol dependence. Indeed, the observed cognitive deficits and functional limitations should not be explained on the basis of other conditions unrelated to HIV. Follow-up visits may sometimes be mandatory to disentangle the effects of multiple disorders on cognition. The practitioner should rely on the algorithm by Antinori *et al.* for a detailed procedure of differential diagnosis [4].

In the presence of HANDs in a cART-treated patient without significant confounding factors, one might face two situations. In the first one, plasma HIV viral load may be detectable. In this case, the physician should change cART to a more appropriate regimen, look for genotype resistances or check the patient's compliance. Only in selected cases (suspicion of intracranial process) should ancillary examinations such as brain MRI or lumbar puncture be considered.

In the second situation, plasma HIV viral load may be undetectable. In this case, additional investigations such as brain MRI and lumbar puncture to measure CSF HIV viral load are warranted. If CSF viral load is detectable (>20 copies/ml), whereas viral load is

Table 2. Review of studies that have assessed the efficacy of neuroprotective drugs.

Agents	Sample	Design	Main findings	Ref.
Antioxidants				
OPC-14117 (240 mg/day)	30 patients with cognitive impairment	12-week double-blind, placebo-controlled, randomized study; follow-up with neuropsychological tests	Only a trend towards improvement in cognitive scores	[74]
Selegiline (2.5 mg 3-times/week <i>per os</i>)	36 patients with cognitive impairment on stable antiretroviral regimen	10-week randomized, double-blind, placebo-controlled trial; follow-up with neuropsychological tests	Cognitive improvement on verbal memory ($p = 0.002$); only a trend towards improvement of psychomotor speed	[75]
Transdermal selegiline (1.0 mg/cm ² × 15 cm ² patch)	14 patients with cognitive impairment on stable antiretroviral regimen	10-week placebo-controlled study; follow-up with neuropsychological tests	Improvement in verbal learning ($p = 0.03$) and motor/psychomotor function ($p = 0.03$)	[76]
Transdermal selegiline (6 mg/24 h or 3 mg/24 h)	128 patients with cognitive impairment	24-week placebo-controlled study; follow-up with neuropsychological tests and proton MRS	No cognitive or functional benefit; no MRS change	[77,79]
Transdermal selegiline (6 mg/24 h or 3 mg/24 h)	86 patients with cognitive impairment	24-week open-label treatment phase offered to patients having completed the 24-week placebo-controlled study above; follow-up with neuropsychological tests	Improvement in a cognitive global score (NPZ-8; $p = 0.03$) and in psychomotor ($p < 0.01$), fine motor/nonverbal ($p = 0.02$) and frontal system ($p < 0.01$) function domains	[77,78]
Antiapoptotic drugs				
Lithium (maintenance of 12-h trough concentrations between 0.4–0.8 mEq/l)	8 patients with cognitive impairment	Single-arm, open-label 12-week pilot study; follow-up with neuropsychological tests	Improvement in a clinical global deficit score ($p = 0.008$)	[80]
Lithium (300 mg 2-times/day)	13 patients with cognitive impairment	10-week open-label study; follow-up with neuropsychological tests and MRI (MRS, diffusion tensor imaging and functional MRI)	No change in cognitive performance; changes in MRS metabolite ratios in the frontal gray matter, suggestive of improvement ($p < 0.03$)	[81]
Calcium channel blockers				
Nimodipine (60 mg 5-times/day or 30 mg 5-times/day)	41 patients with mild-to-severe AIDS dementia complex or HIV-associated neuropathy	Phase I and Phase II trial, 16-week placebo-controlled study; follow-up with neuropsychological tests	No significant cognitive change; only a trend for an improvement on the higher dose	[82]
CCR5 antagonists				
Intranasal peptide T (2 mg 3-times/day)	215 patients with cognitive impairment	6-month double-blind, placebo-controlled trial; follow-up with neuropsychological tests	No cognitive benefit	[83]
PAF antagonists				
Lexipafant (500 mg/day)	30 patients with cognitive impairment	10-week randomized, placebo-controlled trial; follow-up with neuropsychological tests	Only a trend toward cognitive improvement, especially for verbal memory	[84]
TNF antagonists				
CPI-1189 (50 or 100 mg/day)	64 patients with cognitive impairment	10-week randomized, double blind, placebo-controlled trial; follow-up with neuropsychological tests	No cognitive benefit, except for a slight improvement in motor function on higher doses ($p = 0.01$)	[85]
cART: Combination antiretroviral therapy; MRS: Magnetic resonance spectroscopy; NMDA: N-methyl-D-aspartate; NPZ-8: Neuropsychological composite z-score of eight cognitive subtests.				

Table 2. Review of studies that have assessed the efficacy of neuroprotective drugs.

Agents	Sample	Design	Main findings	Ref.
NMDA antagonists				
Memantine (40 mg/day)	140 patients with mild-to-severe AIDS dementia complex on stable cART	16-week Phase II randomized, double-blind, placebo-controlled trial; follow-up with neuropsychological tests and MRS	No cognitive benefit; increase in the NMDA:creatinine ratio in the frontal white matter ($p = 0.04$) and parietal cortex ($p = 0.02$) on MRS	[86]
Memantine (40 mg/day)	99 patients with mild-to-severe AIDS dementia complex on stable cART	Up to 60-week open-label treatment phase offered to patients having completed the 16-week placebo-controlled study above [86]; follow-up with neuropsychological tests	Cognitive improvement at week 12 for patients randomized to memantine in previous study as compared with those randomized to placebo. No benefit during the 48-week extension	[86,87]

cART: Combination antiretroviral therapy; MRS: Magnetic resonance spectroscopy; NMDA: N-methyl-D-aspartate; NPZ-8: Neuropsychological composite z-score of eight cognitive subtests.

undetectable in the plasma, physicians should assume that the chosen cART regimen is not optimal. The CPE score might be useful in this case to improve cART CPE [49]. Nevertheless, when both plasma and CSF viral loads are undetectable, a change in cART medication may be useless. In this context, and based on what is known of the physiopathology of HANDs, several neuroprotective and/or anti-inflammatory approaches have been attempted.

Focusing on new therapeutic approaches

Current data on anti-inflammatory & neuroprotective drugs

Several putative neuroprotective agents with different modes of action were administered to patients with HANDs but did not provide strong evidence of efficacy (TABLE 2). Only the most significant trials are summarized here. For an exhaustive review on this topic, we refer the reader to the review by Rumbaugh *et al.* [73].

Antioxidants were tried in an attempt to reduce oxidative stress-induced neuronal injury due to the toxic interactions between HIV-infected macrophages and neurons. One study was conducted using OPC-14117, a lipophilic antioxidant, but this showed only a trend toward cognitive improvement [74]. Two studies conducted using selegiline and transdermal selegiline showed significant efficacy on HANDs [75,76], but in larger trials, neither cognitive benefit [77,78] nor changes in brain metabolism were observed [79]. Antiapoptotic drugs (e.g., lithium), which are supposed to prevent or delay neural injury, were also studied. No clear benefit was observed in neuropsychological measures [80,81]. However, in one study, neuroimaging revealed a decrease

in the glutamate:glutamine ratio peak in the frontal grey matter, increased fractional anisotropy and decreased mean diffusivity in several brain areas, as well as changes in brain activation patterns, thus suggesting improvement of the HIV-associated CNS injury [81].

Calcium channel blockers (e.g., nimodipine) [82], CCR5 antagonists (e.g., peptide T) [83], PAF antagonists (e.g., lexipafant) [84] and TNF antagonists (e.g., CPI-1189) [85] did not allow clear cognitive improvement.

Finally, in a Phase II study, memantine, an N-methyl-D-aspartate antagonist, did not induce significant improvement in the neuropsychological tests of patients with moderate-to-severe neurocognitive impairment during the 16-week treatment duration. However, MRS demonstrated potential neuroprotective effects, as reflected by an improvement of the neuronal metabolism in the frontal white matter and parietal cortex of treated patients [86]. In a subsequent open-label trial, long-term use of memantine for up to 60 weeks did not provide clear evidence of cognitive benefit [87]. In addition to current treatment approaches, agents such as minocycline or valproic acid are under consideration. A putative favorable effect of cholinesterase inhibitors has been hypothesized [88] based on the similarities between HANDs and AD and based on the fact that choline acetyltransferase, a major enzyme in the synthesis of acetylcholine, is markedly diminished in the putamen and hippocampus of simian immunodeficiency virus-infected monkeys early in the course of simian immunodeficiency virus infection [89].

Do all of these treatment trial failures mean that such anti-inflammatory and/or neuroprotective drugs are pointless? This is probably

not the case. A major pitfall that is common to all kinds of trials studying a neuroprotective agent (not only in the HIV field) is that often these trials are too short to see a putative beneficial effect. Another problem is that we lack precise biomarkers. Finally, it is likely that several of the physiopathological pathways leading to HANDs are redundant, meaning that the future might demonstrate the need for a cocktail of neuroactive drugs, together with optimal neuro-cART [73].

Conclusion

HIV-associated neurocognitive disorders still occur in HIV-infected patients despite cART, even though HANDs and their functional impacts on patients' daily living appear to be less severe than in the pre-cART era. With the prolonged survival of cART-treated patients, there is concern that HIV speeds up the natural process of aging and may facilitate the expression of several neurodegenerative disorders. The occurrence of HANDs is probably determined by both persistent inflammation within the CNS and neurodegenerative mechanisms that might be similar to those occurring in other neurodegenerative conditions, such as AD. One

unsolved question concerns the role of cART in inducing or maintaining HANDs. To date, the data favoring a beneficial effect of cART on HANDs largely outweigh its putative neurotoxic effects; nevertheless, since in the near future patients will probably be treated earlier in the course of their HIV infection (with CD4 >350/ μ l) [90], there should be heightened awareness of the possible long-term neurotoxic side effects of antiretroviral drugs. Clearly, large clinical trials are now needed to answer this question. Finally, as cART is sometimes insufficient to cure or prevent HANDs, the research on immunomodulatory and neuroprotective therapies should be strongly encouraged.

Future perspective

In the future, drug research will probably continue to focus on three main questions. The first one will be to determine which cART regimen is optimal in terms of preventing and curing HANDs. A concomitant question will be to examine whether cART has neurotoxic effects, and if this is the case, which are the culprit compounds. These questions will not be easily solved, as they will probably require large randomized controlled trials.

Executive summary

Modification of the spectrum of cognitive disorders in HIV-infected patients

- The incidence of HIV-associated dementia has decreased in the combination antiretroviral therapy (cART) era but its prevalence has increased.
- The incidence and prevalence of milder forms of HIV-associated neurocognitive disorders (HANDs) have increased.

Evidence for persistent neuroinflammation in cART-treated patients

- HIV probably reaches the CNS very early upon infection and may trigger a long-lasting low-grade inflammation that is relatively insensitive to cART.
- In cART-treated patients, neuroinflammation does not diminish, but sites of neuroinflammation change towards involvement of the hippocampus and adjacent parts of the entorhinal and temporal cortices.

Neurodegenerative mechanisms related to HIV infection

- HIV shares histopathological similarities with neurodegenerative diseases, in particular Alzheimer's disease.
- ApoE4 was expressed twice as much in HIV-infected individuals with dementia compared with infected individuals without dementia.
- Amyloid plaques have been identified in the brains of AIDS patients.
- Amyloid- β precursor protein was detected in the brains of 27% of asymptomatic HIV⁺ patients.

cART penetration effectiveness in the CNS

- Many antiretroviral agents seem to penetrate the CNS poorly.
- The CNS penetration-effectiveness score might help in measuring the CNS efficacy of a given cART regimen, but further studies are needed to assess its validity.

Might cART be neurotoxic?

- There are significantly more data supporting a favorable effect of cART on HANDs than a detrimental effect. Nevertheless, recent data are troubling and call for greater attention to their putative impairment on cognitive functions.

Management of HIV-infected patients with HIV-associated neurocognitive disorders

- For now, cART remains the best treatment for HANDs.
- An algorithm for the management of patients with HANDs has been designed.

Current data on neuroprotective drugs

- Several putative neuroprotective agents were tested for the treatment of HANDs but without reaching strong evidence of efficacy.

The second major point concerns the development of new therapies attempting to reduce or prevent neuronal damage. Until now, the results that were obtained with several anti-inflammatory and/or neuroprotective agents were quite disappointing. Newer compounds, possibly given in combination, in large and long-term studies,

are needed. Third, it will certainly become more and more important to identify biomarkers that allow for differentiation between patients developing HANDs and those developing other neurodegenerative diseases. Such biomarkers may also be useful for detecting changes in clinical trials testing new compounds for HANDs.

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.

	1	2	3	4	5
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. Which of the following statements about the epidemiology of HIV-associated dementia and HIV-associated neurocognitive disorders (HANDs) is most likely correct?

- A In the combined antiretroviral therapy (cART) era, the incidence of HIV-associated dementia has increased
- B In the cART era, the prevalence of HIV-associated dementia has decreased
- C In the cART era, the prevalence of milder HANDs has decreased
- D In the cART era, the incidence of milder HANDs has increased

2. A 62-year-old man has been treated with cART and now has evidence of mild cognitive impairment. Which of the following statements about the underlying pathophysiology of his cognitive dysfunction is most likely correct?

- A cART has been proven to have no neurotoxic effects
- B HIV may speed up the natural process of aging and facilitate the expression of neurodegenerative disorders
- C The putative neurotoxic effects of cART clearly outweigh its beneficial effect on HANDs
- D Neuroinflammation in cART-treated patients is decreased and shifted toward the occipital cortex

3. Which of the following statements most likely applies to the management of the patient described in question 2?

- A cART should be discontinued because of neurotoxicity
- B It is well known which cART regimen is optimal for preventing and curing HANDs
- C Most existing antiretroviral agents have good central nervous system (CNS) penetration
- D Results with existing anti-inflammatory and/or neuroprotective agents used to treat HANDs have been disappointing

Author Proof