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REVIEW ARTICLE

Treating HIV Infection in the Central Nervous System

A. Calcagno[1] · G. Di Perri[1] · S. Bonora[1]

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Abstract Combination antiretroviral treatment is associated with clear benefits in HIV-positive subjects, and is also effective in the central nervous system (CNS), meaning HIV-associated dementia is now an uncommon event. Nevertheless, a significant number of patients show symptoms of neurocognitive impairment which may negatively affect their quality of life. Although several risk factors for HIV-associated neurocognitive disorders have been identified, there is no clear recommendation for their prevention and management. In this review, the penetration of drugs into the cerebrospinal fluid/CNS is discussed as well as the viral and clinical consequences associated with higher/lower compartmental exposure. We also review the potential interventions according to the currently identified underlying mechanisms, including persistent CNS immune activation, legacy effects, low-level viral replication and escape, co-morbidities, and antiretroviral-associated direct and indirect 'neurotoxicity'. Adjunctive therapies and interventions (including neuro-rehabilitation) are then briefly discussed. The treatment of HIV infection in the CNS is a complex area of therapeutics requiring multidisciplinary interventions and further study.

Key Points

HIV affects the central nervous system and may cause neurocognitive function impairment (memory, attention, fine motor skills), usually called 'HAND' (HIV-associated neurocognitive disorder).

Neurocognitive impairment is associated with HIV persistence, immune system dysregulation, vascular abnormalities and, potentially, with the toxic effects of certain medications.

Specific interventions including tailoring of antiretroviral treatment, adjunctive therapies and rehabilitation need to be addressed in prospective studies as significant uncertainty still exists regarding the appropriate management of HIV-positive patients with HAND.

1 Introduction

The evolution of antiretroviral therapy has led to extraordinary success in the treatment of HIV-positive subjects—with the introduction of combination antiretroviral treatment (cART), the prognosis changed from a death sentence to a chronic stable disease. Besides enormous beneficial effects in terms of survival and quality of life, the incidence of opportunistic infections in efficaciously treated HIV-positive subjects reduced to approximately zero; thus, age- and inflammation-associated disorders emerged as leading causes of morbidity in these patients. Before the introduction of antiretroviral drugs (ARVs) the central nervous system (CNS) was often affected by HIV and patients

✉ A. Calcagno
andrea.calcagno@unito.it

[1] Unit of Infectious Diseases, Department of Medical Sciences, University of Torino, c/o Ospedale Amedeo di Savoia, C.so Svizzera 164, 10159 Torino, Italy

presented a so-called 'subacute encephalitis'; 20–30% of untreated subjects developed AIDS dementia complex, now termed HIV-associated dementia (HAD) [1]. With appropriate combinations of ARVs, the incidence of HAD has become rather infrequent but less severe forms are still highly prevalent and significantly affect patients' quality of life [2]. The exact prevalence of non-confounded HIV-associated neurocognitive disorder (HAND), its clinical course and appropriate management are still debated [3, 4]. However, acute neurological symptoms may emerge in cases of selective viral replication in the cerebrospinal fluid (CSF), a rare event termed 'symptomatic CSF escape'. Several factors may influence the effectiveness of ARVs in the central compartment, thus highlighting the need for a better understanding of HIV infection in the CNS.

2 Untreated HIV Infection of the Central Nervous System (CNS)

Following HIV infection, the virus reaches the CNS and may be detected both in the CSF and brain tissue as early as 8 days post-infection [5]. Besides being associated with acute neurological symptoms similar to viral meningoencephalitis, HIV neuroinvasion leads to a high CSF viral load, local immune activation (including higher CSF pleocytosis and neopterin, a macrophage-derived marker of immune activation), changes in magnetic resonance imaging (MRI) (such as putamen volume) and partially reversible neurocognitive impairment in a few patients [6–8]. In the months following HIV neuroinvasion, these inflammatory-mediated perturbations seem to increase and may pave the way to chronic neuronal damage—several pieces of evidence support the relationship between advanced immune depletion (after years of uncontrolled HIV infection) and the incidence of HAND [9].

Viral particles may enter the CNS directly or through HIV-infected lymphocytes and, potentially, monocytes; once there, they have been shown to infect microglia, perivascular macrophages and, although through a restricted infection, astrocytes [10]. Early CNS entry seems to be dependent on α4 integrin, and natalizumab blocks viral trafficking in macaques; brain tissue analysis shows superior benefits of this approach when used early after infection [11]. Neuronal damage seems to be indirect following the production of neurotoxic products (such as free radicals and reactive oxygen species) by infected cells. HIV proteins influence several functions of the CNS immune system and the permeability of the blood–brain barrier (BBB). HIV trans-activating regulatory protein (TAT) has been extensively studied and it has been associated with several pathogenic pathways that may explain HIV-associated neuronal damage [12]. Years after primary infection, CSF HIV replication persists at lower levels. Although genetically distinct CSF viruses have been described, viral evolution over time does not seem to be relevant, suggesting that continuous virus replication is not the major cause of viral persistence in the CNS [13]. Simultaneously, several markers of neuronal damage increase with advanced immune suppression and HAD—neurofilament and tau protein seem to increase with disease progression [14].

While only 5–10% of astrocytes are infected and mature viral particles are not produced, the involvement of these cells seems relevant as they participate in the neurovascular unit and affect the permeability of the BBB. HIV may alter the stability of tight junctions, thus affecting BBB permeability [15, 16]. An altered BBB was observed in almost 100% of patients with HAD but also in severely immune-suppressed patients without neurocognitive disorders; furthermore, an altered BBB may refuel HIV replication in the CNS by enhancing viral trafficking from and to the systemic circulation [17, 18].

The clinical consequence of these processes is dementia, which is now defined as a marked acquired impairment in cognitive functioning involving at least two ability domains and producing relevant interference with day-to-day functioning (work, home life, social activities) [19]. An alternative diagnosis has to be sought in cases of active delirium, untreated major depression, active substance abuse or in the presence of pre-existing causes of dementia.

3 Antiretrovirals and HIV Infection in the CNS

After the introduction of cART, CSF HIV RNA declines and usually parallels the plasma viral load: CSF replication is undetectable in 90% of adequately treated patients. This compartmental efficacy leads to a decrease in all markers of immune activation and neuronal damage, although it is still higher than that observed in HIV-negative subjects [20]. Dementia is now observed in late presenters and in elderly patients with several co-morbidities. Neuropathological studies suggest significant changes in brain tissue after the introduction of cART; although microglial activation and neuroinflammation were, surprisingly, not reduced, they are now observed in different brain areas. While pre-cART examinations showed basal ganglia involvement, post-cART specimens suggest pronounced inflammation in the hippocampus and adjacent parts of the entorhinal and temporal cortex; in contrast, lymphocyte infiltration is now rarely observed with the exception of patients with immune reconstitution inflammatory syndrome (IRIS) or CD8 encephalitis [21, 22].

However, cART is not completely effective in the CNS: low-level compartmental replication, CSF escape, mild

neurocognitive symptoms and, potentially, neurotoxicity have all been described.

3.1 Low-Level Cerebrospinal Fluid (CSF) Replication

CSF HIV RNA is usually 1 Log_{10} lower than plasma levels and with antiretroviral treatment it rapidly decreases to below the limit of detection of conventional methods (20–50 copies/mL). Using sensitive methods (including the single copy assay) low-level replication has been demonstrated in 17–60% of patients with an undetectable plasma viral load: the lowest prevalence was observed in patients with 10 years of efficacious antiretroviral treatment [23, 24]. In these papers [23, 24] the lowest CSF viral load strata was the one associated with the lowest, and almost normal, concentrations of neopterin. These data suggest that the strictest viral control is associated with the lowest immune activation. The origin of this low-level HIV RNA is still debated: controversy regarding the'ongoing replication' versus 'dismissal from reservoirs' origin hypotheses exists. An interesting study showed that intensification with drugs crossing the BBB or remaining in the systemic circulation had no effect on CSF residual HIV RNA [25].

3.2 CSF Escape

CSF escape is defined as a detectable CSF HIV RNA with undetectable plasma HIV RNA or a CSF HIV RNA 1 Log_{10} (0.5 Log_{10} in some papers) higher than plasma HIV RNA. CSF escape has been observed in approximately 10% of patients but its clinical relevance is still unknown. Preliminary data suggest that 25% of patients may have detectable CSF HIV RNA without clinical progression, resembling what happens with plasma viral blips [26, 27]. Nightingale et al. [28] observed a significantly higher prevalence of CSF/plasma discordance (18%) in patients with unexplained episodes of low-level HIV RNA in plasma in the previous 12 months.

CSF escape may be asymptomatic, symptomatic or 'secondary' (i.e. in association with a concomitant non-HIV infection such as neurosyphilis or herpesvirus as a consequence of the local inflammatory response) [29]. The most relevant cases are those with symptomatic CSF escape, which present acute neurological symptoms varying from headache to coma. True to form, CSF replication with associated resistance-associated mutations has been observed [30, 31]. This event is rare (there are less than 30 published cases) and it is reversible with optimised antiretroviral therapy. Recent unpublished data suggest that it may be far more common in intermediate- and low-income countries: in a case series from India, the incidence of symptomatic CSF escape was 1% and worrisome resistance patterns were described in the CSF of these subjects [32]. The rarity of this event does not allow analysis of the predictors of symptomatic CSF escape; however, a low CD4 nadir and the presence of resistance-associated mutations in plasma (thus limiting the efficacy in both compartments) have been reported. Incomplete penetration of ARVs in the CNS might be an issue and are discussed in Sect. 4. There is no evidence of a higher prevalence of CSF escape or neurocognitive function decay over time in patients on protease inhibitor (PI) monotherapy [33]. However, treatment failures have been observed (both in plasma and CSF) in patients with a CD4 nadir below 200 cells/μL and cases of symptomatic CSF escape have been described, which suggests that the less powerful antiretroviral strategies in patients with large compartmental infection (secondary to severe immune depletion) might be a risk factor [34, 35]. CSF replication in these cases is usually low (typically below 10^4 Log_{10} copies/mL) but MRI shows a significant involvement of white matter with acute inflammatory changes; therefore, CSF HIV RNA may be the trigger for immune-mediated changes in brain tissue [31, 36].

3.3 Factors Associated with HIV-Associated Neurocognitive Disorder (HAND)

The exact prevalence of milder forms of neurocognitive impairment is still debated: while dementia is rare (<2%), mild neurocognitive disorders (MNDs) or asymptomatic neurocognitive impairment (ANI) are observed in 15–50% of treated patients [37, 38]. Patients with ANI report normal results in the Independence Activity in Daily Living test as opposed to those diagnosed with MND; however, they score poorly on performance-based tests (rather than self-reported perception of their own disability) and there is a significant risk of progression to more severe forms of impairment over time [39–41]. One of the performance-based tests that patients with ANI scored poorly on (the Medication Management Test-Revised [MMT-R]) was clearly associated with adherence to medication in a large group of HIV-positive subjects [42].

Besides sociodemographic features and alcohol/substance abuse, two groups of factors have been constantly associated with the prevalence of HAND: advanced immune depletion and vascular abnormalities [3]. A recent study prospectively followed 99 subjects on suppressive cART, measuring CSF biomarkers on two occasions: the authors observed that mild HAND (ANI and MND) was associated with increased intrathecal immune activation. Furthermore, the authors reported a correlation between neopterin and neurofilament that supports an association between neurocognitive impairment, CNS inflammation and neuronal damage [43].

Advanced immunosuppression before treatment (as testified by a low CD4+ nadir cell count) is usually associated with persistent immune and glial cell activation, BBB damage and the incidence of HAND. Peripheral blood mononuclear cell (PBMC) HIV DNA, usually considered a marker of the amount of HIV in body reservoirs, is inversely correlated with CD4 nadir and has been associated with HAND prevalence, neurocognitive worsening and cortical atrophy on brain MRI [44–46]. Hepatitis C virus (HCV) infection has been associated with worse neurocognitive performance, although its effect in HIV-positive individuals is controversial [47, 48].

On the other hand, an increasing amount of data have highlighted the higher cardio- and cerebrovascular risk in HIV-positive patients: chronic inflammation, viral replication and the effects of drugs have been shown to interact with age and traditional risk factors [49]. Cardiovascular risk factors, central obesity, insulin resistance, diabetes mellitus and atherosclerosis (as measured by a higher intima media thickness on carotid ultrasound examination or by ophthalmic artery resistance) have been associated with neurocognitive impairment in HIV-positive subjects [50–52]. Standard and perfusion brain MRI confirm the high prevalence of cerebrovascular abnormalities in symptomatic and asymptomatic HIV-positive patients [53]. With the longer life expectancy of cART-treated HIV-positive patients, a differential diagnosis needs to be performed in older subjects to exclude Alzheimer's and vascular dementias (among others) [54].

3.4 Neurotoxicity

Neurological adverse effects have been demonstrated for several ARVs, such as thymidine analogues (peripheral neuropathy), efavirenz (neuropsychiatric symptoms including dizziness and insomnia) and integrase inhibitors (headache and sleep disturbances), among others. Several in vitro pieces of evidence support the theory of a neuronal toxicity induced by certain ARVs, as demonstrated in cell cultures and in macaques [55]. After 14 days of incubation, foetal rat cortical neuron cultures showed some degree of functional injury with all drugs, with no additive effect, and with efavirenz having the highest toxicity and the lowest toxicity being for emtricitabine, tenofovir, darunavir and maraviroc [56]. Furthermore, ARVs can induce oxidative stress in neuronal cultures, PIs disrupt astrocytic glutamate transporter function (and alter neurobehavioural performance in rats) and β-amyloid metabolism may be impaired by efavirenz and PIs [57, 58].

Efavirenz, besides its well-known adverse effects, has been associated with a higher prevalence of HAND [59, 60]. Although still debated, the adverse drug effects (which seem to be dose dependant and susceptible to dose optimisation) and in vitro data suggest that efavirenz should be avoided in patients with neurocognitive disturbances. A prospective study of patients who elected to discontinue cART showed that there was an improvement in two neuropsychological tests (Trail-Making Test A & B and the Wechsler Adult Intelligence Scale-Revised Digit Symbol subtest) for up to 96 weeks; this effect was higher in efavirenz recipients but was still significant in those who were on different ARVs [61]. Vague neuropsychiatric symptoms (including worsening depression), headache and sleep disturbances have been reported with dolutegravir. US Department of Health and Human Services guidelines suggest that the use of efavirenz and rilpivirine in patients with psychiatric illnesses and efavirenz in those with HAD should be avoided [62].

The last point to be considered is the potential endothelial toxicity caused by ARVs. In a post-mortem brain tissue gene array study, two different pictures of impairment were observed: a rare (<10%) inflammatory pattern with strong immune response and a common (>35%) pattern with upregulated genes of endothelial origin (such as *JAG1*, *PECAM1* and *TFRC*) [63]. PIs have been associated with severe lipid metabolism abnormalities and lopinavir/ritonavir has been associated with a higher cumulative incidence of cardiovascular disorders. In another autoptic study, cerebral small vessel disease was observed in more than 60% of brains and was associated with PI-based cART and the presence of diabetes [64, 65].

4 Determinants of the Efficacy of Antiretrovirals in the CNS

cART initiation has beneficial effects on CSF HIV RNA, immune activation, compartmental inflammation and neurocognitive function. Nevertheless, none of the CSF biomarkers has been found to normalise despite antiretroviral treatment. The number of ARVs does not seem to affect CNS efficacy since three-drug and intensified regimens do not seem to differ substantially: provided patients are accurately selected, even less drug regimens seem to be comparably efficacious [66]. While the START (Strategic Timing of Antiretroviral Therapy) trial provided no strong evidence for a beneficial effect on neurocognitive function with early initiation of cART (above or below 500 CD4+ T lymphocytes/μL), preliminary data support the use of ARVs in patients with primary HIV infection (PHI). In an as-yet unpublished study, ARV treatment during acute HIV infection was associated with a reduction in CSF neopterin to levels comparable with those observed in HIV-negative subjects [67, 68]. In another study, most individuals had normal neuropsychiatric performance during PHI and early cART improved their psychomotor function; however,

approximately 25% had impaired neuropsychiatric performance that did not improve with early cART, possibly indicating limited reversibility of cognitive impairment in a subset of PHI individuals [8].

There is considerable uncertainty regarding the differential neuroefficacy of ARVs—reasons exist both in favour and against such a hypothesis, and these have been reviewed recently [3].

4.1 Targets of Antiretroviral Therapy in the CNS

In order to understand the pharmacodynamics of antiretroviral treatment in the CNS it is necessary to establish the markers of compartmental efficacy. However, this is particularly difficult given the complexity and multifactorial nature of HAND pathogenesis, the non-linear relationship between these markers and the possible emergence of drug-associated neurotoxicity (Table 1). Each of these targets may warrant study into specific interventions.

Some of these markers are purely hypothetical and biopsies are not feasible except in cases of unexplained rapid worsening of cognitive function. Those markers normally used in clinical practice have significant pitfalls, including the low sensitivity and practice effect of neurocognitive tests, the lack of validation of CSF biomarkers, the non-reversibility of brain atrophy and white matter abnormalities on MRIs [69]. The use of CSF as a surrogate marker for brain tissue needs further discussion; its composition has been deemed to originate both from brain extracellular fluid (two-thirds) and plasma (one-third) [70]. In the pre-cART era, autoptic brain tissue HIV RNA showed significant regional variations but good correlation with CSF HIV RNA; compartmental efficacy is currently based on this biomarker [71]. The most interesting tissue data in the cART era have been published by Gelman and colleagues [72]: brain HIV RNA was higher in subjects with HAND plus HIV encephalitis (HIVE) but not in those without HIVE or microglial nodule encephalitis (MGNE) [72]. Interestingly, worse neurocognitive scores correlated significantly with higher HIV RNA in brain specimens but not with HIV RNA levels in pre-mortem blood plasma or CSF.

The optimal level of viral suppression is, however, uncertain: low-level CSF HIV RNA has been associated with a higher prevalence of neurocognitive impairment and higher neopterin concentrations (as discussed in sect. 3.1) but its relevance and targeted interventions are not known. For instance, guidelines provide recommendations if CSF escape occurs, but no recommendation is provided for symptomatic patients with suppressed CSF HIV RNA when receiving cART [73].

4.2 Pharmacokinetics and the Concentration Penetration Efficacy (CPE) Score

Antiretrovirals reach the CSF with significant variability, and concentrations of some antiretrovirals do not exceed the inhibitory concentration for wild-type HIV replication in CSF. Several factors may influence the passage of ARVs in the CSF. Some are patient related (age, meningeal inflammation, CSF flow alterations and BBB damage) and some are drug related (molecular size, lipophilicity, binding to plasma proteins, ionisation and affinity to transporter enzymes) or variable according to patients and drugs (plasma concentrations and concomitant drugs) [74].

Several attempts have been made to create a score relating to the neuropenetration/neuroeffectiveness of ARVs following the observation that drugs estimated to have good effectiveness on the CNS are associated with

Table 1 Targets for the treatment of HIV in the central nervous system and markers for assessing the efficacy of specific interventions

Target	Marker	Surrogate marker
Stop HIV RNA replication in brain tissue	HIV RNA on brain biopsy (?)	Cerebrospinal fluid HIV RNA
Stop tissue viral protein production	Immune-staining for viral proteins on brain biopsy (?)	CSF viral protein levels (?)
Stop neuronal damage	Cyto-morphology on brain biopsy (?)	CSF (neurofilament, tau-protein, etc.) and plasma (neurofilament) biomarkers
Reduce compartmental immune activation	Brain functional imaging (PET scan with cell-specific ligands)	CSF biomarkers (neopterin, MCP-1 and other cytokines)
Reverse brain atrophy (?) and connectivity	Brain MRI, fMRI, EEG	Brain MRI, fMRI, EEG
Normalise cognitive function	Neurocognitive tests	Neurocognitive tests

CSF cerebrospinal fluid, *EEG* electroencephalography, *fMRI* functional magnetic resonance imaging, *PET* positron emission tomography, *MCP-1* monocyte chemoattractant protein-1, *MRI* magnetic resonance imaging, *(?)* hypothetical markers that have not been used in clinical practice or in studies conducted in humans

lower levels of HIV RNA in CSF and better cognitive function [75]. The largest and most structured analysis was performed by the CHARTER (CNS HIV Antiretroviral Therapy Effects Research) group, a large US-based collaborative research group that enrolled more than 1000 patients and followed them prospectively. The last version of the Concentration Penetration Efficacy (CPE) score ranked ARVs into four categories (from 1 to 4), where those in the higher group are associated with the highest efficacy in the CSF (Table 3): this was obtained using the properties of the drugs, CSF concentrations and, in a few cases, compartmental viral response in monotherapy studies. This scoring system was published in 2014 and a few co-factors were found to be associated with an undetectable CSF HIV RNA—plasma HIV RNA levels, ethnicity, ongoing depression, incomplete adherence and duration of cART [76]. All of these modifiers are associated with socioeconomic status, adherence to medication and the amount of HIV in body reservoirs and they had already been identified in previous studies as determinants of HAND and CSF escape. Besides the initial CHARTER analysis, several other studies have found an association between a higher CPE score and a lower prevalence of CSF viral replication; in contrast, an association with better neurocognitive function is still controversial [74]. Two longitudinal studies found a protective effect of cART, with higher CPE scores on the prospective changes in neurocognitive function [77, 78]. The aggregate results of four randomized clinical trials that compared regimens with different CPE scores suggest better or equal neurocognitive outcomes with more "neuroefficacious" drugs and worse ones with efavirenz-containing regimens [79–81]. In the prevention trial, conducted in China, the magnitude of neurocognitive decline was directly associated with efavirenz CSF concentrations (suggesting potential neurotoxicity) and inversely associated with tenofovir CSF concentrations (implying incomplete drug penetration) [82].

A single study (involving 61,938 individuals) found an unexpected result: patients starting antiretroviral treatment with high CPE regimens had a higher incidence of dementia [83]. However, the large sample size is counterbalanced by some methodological pitfalls such as a substantial channelling bias and an arbitrary CPE cut-off (10; not achieved by currently recommended regimens). A large body of evidence supports the usefulness of this approach, even if some controversies regarding its use need to be acknowledged (Table 2).

Two further issues also exist: CSF HIV RNA is a surrogate marker of tissue replication and the optimal inhibitory concentration has not been clearly defined. As opposed to bacterial meningitis (where bacteria or fungi replicate in the CSF and meninges), CSF contains viral particles released from cells in 'deep' brain parenchyma. Furthermore, concentrations are judged as adequate according to their ability to overcome the 50% inhibitory concentration (IC_{50}), although a theoretical risk of residual viral production exists. Our group found that individual concentrations (as opposed to drugs' ranks) above the 95% inhibitory concentration (IC_{95}) (as opposed to IC_{50}) were associated with a lower prevalence of CSF escape: this observation supports potential benefits with higher CSF concentrations in some patients [87].

4.3 Cell Types

While the major target of ARVs is the pool of activated and resting lymphocytes, all cells in the CNS are macrophage derived (microglia, perivascular macrophages and astrocytes). Several pieces of evidence support a major role of microglial activation and astrocytosis in the pathogenesis of HAND and BBB damage. An in vivo study using positron emission tomography with [^{11}C]-PK11195, a marker of translocator protein (TSPO) expressed by activated microglia, found several areas of activated microglia despite optimal antiretroviral treatment [88]. Furthermore, greater [^{11}C]-PK11195 binding in certain brain areas (anterior cingulate, corpus callosum and posterior cingulate) was associated with poorer executive function performance. The role of astrocytosis in the pathogenesis of BBB damage has already been discussed—an additional study found that patients with higher CSF S100β protein had a deficit in their verbal fluency [89].

In vitro data suggest that ARVs may have different activity (and intracellular concentrations) in activated and resting macrophages. This may be due to the different pattern of protein expressed (according to the cellular state) and to the endogenous nucleotide pool (lower than that measured in lymphocytes) [90]. Interestingly Shikuma et al. [91] found that drugs with a lower macrophage activity score (calculated according to their in vitro macrophage inhibitory concentration) were associated with a higher prevalence and severity of neurocognitive disorders. This line of research is very interesting but data are limited and standardised macrophage activity scores are mostly unavailable (Table 3). A recent study applied patients' withdrawn CSF to three cell lines (PBMCs, neuro-derived glial [U87] and astrocyte [373] cells) and developed an infectivity model with IC_{50} [92]. Antiviral efficacy was higher in patients receiving tenofovir/emtricitabine plus lopinavir/ritonavir plus maraviroc than in those receiving tenofovir/emtricitabine/rilpivirine: the antiviral effect on astrocyte cell lines directly correlated with rilpivirine and lopinavir CSF concentrations. These data support the idea that compartmental efficacy with

Table 2 Controversies on the use of the Concentration Penetration Efficacy score

Pros	Cons
Easy to use scoring system	Score based mostly on physio-chemical characteristics or CSF concentrations: limited pharmacodynamic data available
In cases of CSF escape, cART modification according to RAMs and CPE led to clinical improvement and viral suppression	Wild-type viruses considered: better prediction of neurocognitive function in a study using RAM-adjusted CPE [84]
Large available data (both retrospective and prospective) on the association between CPE score and CSF HIV RNA	Insufficient data on regimens with fewer drugs (mono- and dual therapies)
Preliminary data on the use of higher CPE score drugs and improvement of neurocognitive function in patients with HAND [78, 85]	Needs to be integrated with clinically relevant variables (age, nadir CD4, co-morbidities, duration of viral suppression, adherence, substance abuse, etc.)
Association of higher CPE score with better mood [86]	Interpatient variability in drug exposure not considered

cART combination antiretroviral treatment, *CPE* Concentration Penetration Efficacy, *CSF* cerebrospinal fluid, *HAND* HIV-associated neurocognitive disorders, *RAM* resistance associated mutations

Table 3 Comparison of central nervous system activity scores for currently available antiretroviral drugs

Drug	CPE score [76]	95% inhibitory quotients [87]	Macrophage efficacy score [91]
NRTIs			
Abacavir	3	NA	3
Emtricitabine	3	NA	12.5
Lamivudine	2	NA	50
Tenofovir disoproxil fumarate	1	NA	50
Zidovudine	4	NA	50
NNRTIs			
Nevirapine	4	NA	20
Efavirenz	3	6.4	100
Etravirine	2	5.1	NA
Rilpivirine	NA	NA	NA
PIs			
Atazanavir	2	0.4	NA
Atazanavir/r	2	2.8	NA
Darunavir/r	3	8.2–18.5	NA
Lopinavir/r	3	1.5	NA
INIs			
Raltegravir	3	0.7	NA
Elvitegravir/r	NA	NA	NA
Dolutegravir	NA	NA	NA
EIs			
Maraviroc	3	NA	NA
Enfuvirtide	1	NA	50

CPE Concentration Penetration Efficacy, *EIs* entry inhibitors, *INIs* integrase inhibitors, *NA* not available, *NNRTIs* non-nucleos(t)ide reverse transcriptase inhibitors, *NRTIs* nucleos(t)ide reverse transcriptase inhibitors, *PIs* protease inhibitors, */r* boosted with ritonavir

currently available drugs may be incomplete, as already suggested in lymph nodes [93]. Further data suggest that some ARVs may have reduced inhibitory effects in infected astrocytes: lamivudine, stavudine and, surprisingly, zidovudine had insufficient HIV-1 inhibitory activity, with 90% effective concentrations that were significantly greater than the achievable CSF concentrations [94] (Table 3).

5 Adjunctive Therapies

Several adjunctive treatments have been tested in HIV-positive patients with neurocognitive impairment, although none had a significant effect. The most striking results have been observed with cART initiation in patients with dementia. In the early period of the HIV epidemic, the introduction of zidovudine was able to improve severe

neurological conditions [95]. To date, two studies have demonstrated non-ARV drugs to provide some benefit in HIV-positive patients. A randomized, double-blind, placebo-controlled crossover trial tested the use of oral rivastigmine (up to 12 mg/day for 20 weeks) in 17 aviraemic patients with HAND [96]; although no effect was observed on the primary endpoint (Alzheimer's Disease Assessment Scale-Cognitive subscale), patients taking rivastigmine showed improvements in processing speed and executive functioning. In addition, a recently presented trial compared the effect of adding paroxetine, fluconazole or both in 24 highly adherent cART-treated individuals with HAND: paroxetine was associated with neurocognitive improvements (after adjusting for depression) while fluconazole was associated with a decrease in inflammatory markers [97].

In addition to its antiviral activity, maraviroc, a CCR5 antagonist, has several favourable immunological properties; preliminary evidence supports further study in the setting of progressive multifocal leukoencephalopathy and CNS inflammatory disorders [98]. In HIV-positive patients, the effect of maraviroc is partially mediated by entry inhibition since most CSF viruses are R5-tropic; cellular interactions are, however, more complex and HIV-loaded lymphocytes may infect astrocytes via CXCR4 [99, 100]. Maraviroc treatment has been found to be protective for CNS infection in Simian immunodeficiency virus in macaques [101]. In addition, maraviroc intensification has been associated with better neuronal integrity (increase in spectroscopy-MRI N-acetylaspartate to creatine ratio [Naa/Cr]), lower CSF immune activation (lower interferon-γ-induced protein 10 [IP-10] and CD16+ monocytes), lower monocyte-associated HIV DNA and better cognitive function in HIV-infected subjects and with the improvement of CNS MRI abnormalities in an HIV-positive child: better effects were reported in patients with higher maraviroc plasma concentrations [102–105]. Finally, a recent small randomised controlled trial has been conducted in 14 virally suppressed (blood and CSF) HIV-positive males receiving stable cART who had recent progression to HAND: patients in the maraviroc arm showed significant cognitive improvement [106]. However, no neurocognitive benefit was found in naïve patients starting a maraviroc versus a tenofovir-based regimen [107].

Given the incomplete effectiveness of these interventions, cognitive rehabilitation protocols have been developed. Three studies have used a restorative approach (which aims to restore the neural circuits underlying impaired cognitive processes by means of practice and focused training exercises)—they reported positive effects on visual learning and speed of information processing [108–111]. In a recent study, our group developed a cognitive rehabilitation treatment for HAND in HIV-positive adults, combining a restorative and compensatory approach. We reported significant improvements in patients with HAND undergoing the rehabilitation protocol; furthermore, such benefits persisted for at least 6 months after the end of the intervention [112].

6 Conclusions

The pathogenesis of neurocognitive disorders in HIV-positive patients is complex and multifactorial. Although current knowledge does not allow clear recommendations to be formulated, we propose a pragmatic flowchart of potential management strategies (Fig. 1). In the future we will probably observe a different clinical scenario involving universal testing and early access to ARVs, thus preventing late presentation and the observed neurological effect of years of immune depression and viral replication. The identification and treatment of patients with PHI will theoretically be beneficial, although it will remain a challenging task. The prevention and treatment of HAND will also be part of a comprehensive care of HIV-positive patients going forward: managing age-, virus- and drug-associated co-morbidities is a primary objective of HIV outpatient management due to the 'greying' of the HIV epidemic. Vascular abnormalities are common in HIV-infected patients for several reasons (lifestyle, viral-associated chronic inflammation, drug-induced toxicities) and have been recognised as a key risk factor for HAND. Small-vessel cerebral disease and vascular abnormalities need to be assessed and managed adequately. Reducing the direct and indirect toxicities of antiretrovirals is now possible with the availability of efficacious, well-tolerated and safe drugs and should be actively pursued. The contribution of HCV to neurocognitive disorders has been recognised but we still have no data on the consequences of eradicating this infection; however, given the undeniable benefits of directly active anti-HCV agents it is imperative to treat as many patients as possible. No evidence is currently available on the consequences of interventions targeted at co-morbidities on neurocognitive function in HIV-positive subjects.

However, despite all of these efforts, we will still observe patients with acute neurological symptoms, CSF escape and HAND. Besides optimising antiretroviral regimens according to resistance-associated mutations (both in plasma and CSF) and enhancing patients' adherence to medication, no other clear recommendation can be formulated. Several factors may affect cognitive function in those patients with undetectable plasma and CSF HIV RNA, including residual viral replication, immune activation and, potentially, neurotoxicity of ARVs; further

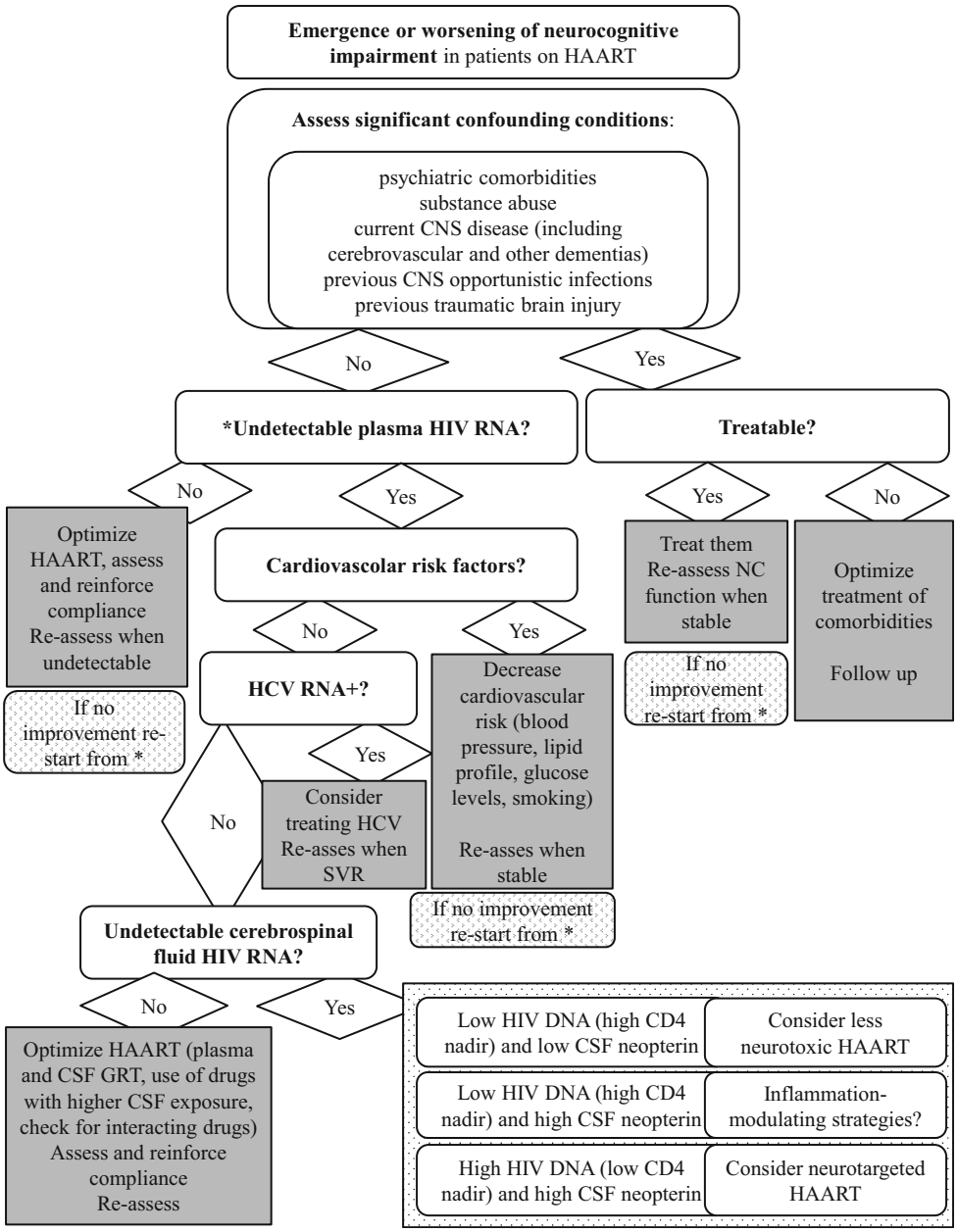

Fig. 1 Flowchart of potential management in HIV-positive subjects diagnosed with HIV-associated neurocognitive disorders (HAND). Although the suggested interventions are derived from studies identifying risk factors for HAND, no randomised clinical trial has proven their efficacy. The management of patients with controlled plasma and cerebrospinal fluid HIV RNA is controversial and the interventions proposed in the *grey box* are based on the authors' expert opinion. *CNS* central nervous system, *CSF* cerebrospinal fluid, *GRT* genotype resistance test, *HAART* highly active antiretroviral therapy, *SVR* sustained virological response

studies are needed in order to understand the efficacy of targeted interventions in this complicated scenario.

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Compliance with Ethical Standards

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Conflict of interest AC has received honoraria from Abbvie, BMS, Gilead, Janssen-Cilag, MSD and Viiv and is currently receiving research grants from BMS, Gilead and Viiv. GDP and SB have received honoraria from Abbvie, BMS, Gilead, Janssen-Cilag, MSD and Viiv.

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