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Clinical Treatment Options and Randomized Clinical Trials for Neurocognitive Complications of HIV Infection: Combination Antiretroviral Therapy, Central Nervous System Penetration Effectiveness, and Adjuvants

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Abstract

The etiology and pathogenesis of human immunodeficiency virus type-I (HIV)-associated neurocognitive disorders (HAND) remain undetermined and are likely the produce of multiple mechanisms. This can mainly include neuronal injury from HIV, inflammatory processes, and mental health issues. As a result, a variety of treatment options have been tested including NeuroHIV-targeted regimens based on the central nervous system (CNS) penetration effectiveness (CPE) of antiretroviral therapy (ART) and adjuvant therapies for HAND. NeuroHIV-targeted ART regimens have produced consistent and statistically significant HIV suppression in the CNS, but this is not the case for cognitive and functional domains. Most adjuvant therapies such as minocycline, memantine, and selegiline have negligible benefit in the improvement of cognitive function of people living with HIV (PLWH) with mild to moderate neurocognitive impairment. Newer experimental treatments have been proposed to target cognitive and functional symptoms of HAND as well as potential underlying pathogenesis. This review aims to provide an analytical overview of the clinical treatment options and clinical trials for HAND by focusing on NeuroHIV-targeted ART regimen development, CPE, and adjuvant therapies.

Keywords

Clinical trials; CPE; HIV; associated neurocognitive impairment; Treatment options

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1 NeuroHIV-Targeted Combination Antiretroviral Therapy

Although combination antiretroviral therapy (ART) has markedly reduced morbidity and mortality among people living with HIV (PLWH) (Cysique et al. 2004; Deutsch et al. 2001), the prevalence of HIV-associated neurocognitive disorders (HAND) remains high, with current estimates ranging from 35% to greater than 50% depending on disease stability and viral suppression status (Brouillette et al. 2015; Calcagno et al. 2018). Several etiological factors may be responsible for such a high prevalence of HAND.

Besides well-studied contributing factors such as lower nadir CD4+ T-cell count, substance use disorders, cardiovascular diseases (CVD), mood disorders, education, and hepatitis C virus (HCV) coinfection, the importance of underlying mechanisms has been increasingly recognized including patient-related (e.g., age and inflammation), virus-related (e.g., persistent viral replication in the central nervous system (CNS) and microglia/perivascular macrophage infection), and treatment-related (e.g., suboptimal ART distribution in the CNS and neurotoxicity) (Ellis and Letendre 2016; Lanman et al. 2019; Letendre 2011). Since people with HAND have a lower quality of life, are more frequently unemployed, and have poor medication adherence and impairment in other activities of daily living in addition to a higher risk of death (Ellis et al. 1997; Sevigny et al. 2007), development of ART with higher CNS penetration effectiveness (CPE or referred more generally as NeuroHIV-targeted ART in this chapter) and optimization of ART for neurocognitive outcomes remain critically needed for the long-term HIV management.

Despite the high prevalence of HAND and the importance of healthy cognition to the quality of life in PLWH, consensus treatment guidelines for NeuroHIV-targeted ART have yet to be formulated, as they require a high level of clinical evidence. In particular, controversy remains about whether antiretroviral penetration into the CNS is clinically important for treating HAND. One of the major hurdles for the development and optimization of NeuroHIV-targeted ART is the accessibility of antiretrovirals across the blood–brain barrier (BBB). The BBB can limit the distribution of ART in the CNS, creating a distinct pharmacologic compartment (Letendre 2011). Differences between antiretrovirals in crossing the BBB and brain concentrations may partially explain inter-individual variances in susceptibility to HAND among treated individuals (Decloedt et al. 2015).

In addition, the CNS can serve as a virologic compartment (Marban et al. 2016), providing potential targets for interventions, in particular, most adjuvant therapies for HAND (Fig. 1). Viral proteins can cross the BBB via transcytosis or paracellularly followed by infections of astrocytes and microglia. HIV-infected T cells and monocytes can also migrate into the brain to induce chronic inflammation, in which inflammatory cytokines further activate astrocytes and microglia. The astrocytes/microglia activation leads to an increased permeability of BBB and release of glutamine and other neurotoxic cytokines, eventually causing neuronal injuries and contributing to HAND (Letendre 2011; Bougea et al. 2019; Hong and Banks 2015). Despite successful peripheral suppression, HIV remains detectable in the cerebrospinal fluid (CSF) in ~5 to 15% individuals receiving ART (Perez Valero et al. 2014), which has been referred as “CSF viral escape” (Eden et al. 2010), suggesting that ART with a better penetration might be associated with a better control of viral replication in the CNS.

One of the major practical attempts to target NeuroHIV is the development and validation of the CPE score system for ART from the CHARTER (Ellis and Letendre 2016; Letendre 2011). The CPE was first established in 2008 (CPE 2008), and antiretroviral drugs were assigned into three ranks from 0 (low), 0.5 (intermediate), to 1 (high) mainly based on their penetration profiles (Letendre et al. 2008). In 2010, CPE was revised to 1, 2, 3, and 4 with larger numbers reflecting better penetration and CNS effectiveness (CPE 2010) (Letendre et al. 2010). The CPE ranks antiretroviral agents according to their physicochemical properties (e.g., molecular weight, protein binding, and octanol-water partition coefficient), CSF concentrations, and efficacy based on CSF virologic suppression (Table 1) (Letendre 2011; Letendre et al. 2008). The score of a combination ART regimen is calculated by summing the values of individual agents. The objective of this review is to provide an analytical overview of relevant data and accumulating evidence on the clinical trials of NeuroHIV-targeted ART regimens with a particular reference to CPE and adjuvant therapies tested as potential options to prevent and treat HAND.

2 Association Between CPE and HIV Suppression in the CSF

The 12 clinical studies with detailed data on ART regimens and viral load in the plasma and CSF were selected to determine if higher CPE was associated with a better HIV control in the CSF (Table 2). The majority of the clinical studies (n = 9, 75%) concluded with positive findings. For instance, among 401 participants from the CHARTER cohort followed up for 34 months, ART regimens with lower CPE were significantly associated with detectable HIV RNA levels in the CSF over time (Livelli et al. 2019). An early study in 142 patients, who underwent lumbar punctures due to neurological complications, demonstrated that low CPE (<2, CPE 2008) was linked with detectable HIV RNA in the CSF despite aviremia (Rawson et al. 2012). These clinical studies included prospective, longitudinal ones with a relatively small sample size and large retrospective and cross-sectional analyses that consistently demonstrated an association between CPE and HIV suppression in the CSF.

Among the three studies showing no association, two were cross-sectional with a relatively small sample size. Eden et al. reported similar mean CPE between 7 CSF viremia and 62 CSF aviremia (7.3 vs. 7.4, CPE 2010), all of whom had undetectable concentrations of HIV RNA in plasma, and concluded that CPE is not a predictor for CSF viremia (Eden et al. 2010). The other study retrospectively analyzed 155 patients from the Frankfurt HIV Cohort, among whom 131 received ART with high CPE (mean 7.3, CPE 2010) versus 24 on boosted dual protease inhibitors (bdPI) with low CPE (mean 4.2, CPE 2010). Although the proportion of undetectable CSF HIV virus was lower in the bdPI group, the median CSF viral load was significantly higher (600 vs. 50 copies/mL, p = 0.027), suggesting viral replication in the CNS over time due to the low CPE of dbPI regimens; however, no significant correlation was noted between CPE and quantitative HIV-1 RNA in the CSF (Donath et al. 2016). The only well-designed randomized clinical trial (RCT) of NeuroHIV-targeted ART in 49 patients with HAND was prematurely interrupted due to slow accrual and imbalance among study arms. After 16 weeks follow-up, the use of a NeuroHIV-targeted ART regimens (n = 26, mean CPE 2.5, CPE 2008) resulted similar plasma and CSF HIV viral suppression in comparison to that with the non-targeted ones (n = 23, mean CPE 1.0, CPE 2008) (Ellis et al. 2014). Importantly, significant limitations

presented in these studies, such as relatively small differences in CPE between groups, the cross-sectional nature, complex NeuroHIV-targeted regimens, and the small sample size in the randomized clinical trial, which made interpretations of study findings challenging.

In summary, the majority of the observational studies demonstrated that ART regimens with high CPE were associated with better HIV suppression in the CSF. Therefore, optimization of ART regimens based on CPE remains a practical approach for HIV management in the CNS.

3 Association Between CPE and Neurocognitive Improvement

Controversies have mostly centered on the associations between CPE and neurocognitive improvement. Although mounting evidence indicated that higher CSF HIV virus load predicted the progression of neurocognitive impairment, it remains largely unclear if the use of ART regimens with high CPE to achieve better HIV control in the CNS would lead to subsequent improved neurocognitive performance (Ellis et al. 2002). Among 18 studies assessing the association between CPE and neuropsychological performance (Table 3), 8 (44%) concluded higher CPE associated with neurocognitive improvement, 3 (17%) showed an inverse relationship, and the rest 7 (39%) showed no interaction. Except for two RCTs, 16 studies (89%) were observational without control, including 8 prospective cohort and 8 cross-sectional analyses. In the AIDS Clinical Trials Group (ACTG) A5175 study, 860 treatment naïve participants were randomized to three groups receiving lamivudine-zidovudine-efavirenz (CPE = 9, CPE 2010, $n = 289$), atazanaviremtricitabine-didanosine (CPE = 7, CPE 2010, $n = 293$), and emtricitabinetenofovir-disoproxil fumarate-efavirenz (CPE = 7, CPE 2010, $n = 278$). At week 192 follow-up, neurocognitive performance significantly improved, but no differences were observed between treatment regimens (Robertson et al. 2012). The other RCT with only 49 participants did not show a significant improvement of neurocognitive performance at week 16 in CNS-targeted ART group with high CPE (Ellis et al. 2014).

The largest prospective study was conducted in ACTG Longitudinal Linked Randomized Trials (ALLRT) cohort involving a total of 2636 aviremic participants, who received neurocognitive tests every 48 weeks. After a median 4.7 years of follow-up, the ALLRT study demonstrated that higher CPE was associated with better neurocognitive functioning (Smurzynski et al. 2011). Another French prospective study included 96 participants with a median viral load of 10,760 c/mL at the baseline, 71 (74%) without HAND and 25 (26%) with HAND at baseline, with a median 22 months follow-up. The neurocognitive tests revealed that 6 (6%) improved, 31 (32%) worsen, and 59 (61%) stable. Lower CPE at baseline (6.9 vs. 8.1, CPE 2010) and at the end of follow-up (7.2 vs. 7.8, CPE 2010) were independently associated with clinical neurocognition deterioration (Vassallo et al. 2014). In contrast to the findings from most prospective studies (5 positive, 1 no interaction), Marra et al. reported that high CPE (≥2, CPE 2008) was associated with poor neurocognitive performance, despite better HIV viral suppression in the CSF among 79 participants with advanced HIV disease beginning or changing a new ART, who received neurocognitive tests at baseline, week 24, and week 52. One possible and appealing explanation for such a discrepancy was that ART with high CPE exhibited more neurotoxicity in advanced HIV

disease (Marra et al. 2009). In fact, neurotoxicity of ART, as summarized in Table 1, has become an increasing concern especially for HAND and elderly PLWH. A theoretical model has been proposed that predicts a cognitive deterioration after an initial improvement due to the inhibition of viral replication, most likely dictated by long-term ART neurotoxicity (Underwood et al. 2015).

In addition to the conflicting results from these prospective studies, the findings from several large cross-sectional analyses are inconclusive. For instance, one Swiss cohort study involving 909 aviremic participants concluded that CPE was not associated with neurocognitive improvement (Santos et al. 2019). In another study from Italy, 660 participants demonstrated that higher CPE was associated with poor neurocognitive performance (Libertone et al. 2014). More recently, HIV-CAUSAL Collaboration (1998–2013) has concluded that initiation of ART with high CPE increases the risk of HIV dementia, but not of other NeuroHIV conditions after evaluating a total of 61,938 individuals followed for a median of 37 months (Caniglia et al. 2014). Unfortunately, this conclusion suffered significantly from several pitfalls, such as obsolete ART regimens evaluated, focusing on the most severe form of HAND (i.e., HIV-associated dementia, HAD), and a small gap in the CPE scores among different groups. These findings nevertheless provided some useful information, particularly from both the analytical and pharmacological perspectives.

In summary, the association between CPE and neurocognitive performance remains questionable, and many factors might contribute to such an inconclusiveness. First, most studies were observational, and none of them evaluated integrase strand transfer inhibitor (INSTI)-based ART regimens. Second, the inclusion criteria varied significantly (e.g., with and without HAND at baseline, treatment naïve and experienced, and plasma/CSF viremic and aviremic), which makes interpretation and comparison challenging. In addition, the neurocognitive test used were inconsistent across these studies, and there was no consistent CPE cut-off score used across the studies either. Despite all these limitations, the findings in general supported the concept that high CPE was associated with better HIV suppression in the CNS and possible benefit of neurocognitive improvement, but with the caution of potential neurotoxicity from ART due to high CNS concentrations. Thus, large RCT and prospective studies, especially those focusing on INSTI-based regimens, are warranted to further evaluate clinical utility of CPE.

4 Adjuvant Therapies

Because of the persistence of HAND in many individuals despite the use of ART, numerous therapeutic strategies and adjuvant therapies have been investigated. With the discovery of the inferred mechanisms through which HIV might cause HAND (Fig. 1), predominantly neuroprotective strategies have been evaluated (Table 4). A total of 22 trials on various adjuvant therapies are identified and assessed, mostly double-blind RCTs with small sample sizes. Early investigations of potent anti-oxidants including OPC-14117 and CPI-1189 failed to show a significant improvement in cognitively impaired patients with advanced HIV disease (The Dana Consortium on the Therapy of HIV Dementia and Related Cognitive Disorders 1997; Clifford et al. 2002). Likewise, selegiline, a monoamine oxidase B inhibitor

with anti-oxidant properties, did not show significant benefit in an initial trial despite some verbal memory improvement at week 10 (Dana Consortium on the Therapy of HIV Dementia and Related Cognitive Disorders 1998). The other potential neuroprotective agent, peptide T, a short peptide derived from HIV envelop protein (gp 120), only showed negligible cognitive improvement in patients with mild impairment at the baseline (Heseltine et al. 1998). The results from clinical trials testing experimental approaches against neuronal apoptosis were mostly disappointing as well. Lexipafant, a platelet-activating factor (PAF) antagonist, showed no significant impact on neurocognition except some trends toward improvement of timed gait and learning in the Rey Auditory Verbal Learning Test (RAVLT) (Schifitto et al. 1999). Valproic acid, which inhibited neuronal apoptosis induced by PAF and glycogen synthesis kinase (GSK)-3β, only showed a weak trend toward improvement in neurocognitive performance (Schifitto et al. 2006). Two single-arm open-label trials on lithium, a mood stabilizer widely used to treat bipolar disorder and a neuroprotectant, providing neurons protection from apoptosis, also yielded inconsistent results (Letendre et al. 2006; Schifitto et al. 2009a).

Because of the initial promising results on selegiline, five additional RCTs were conducted for the transdermal formulation of this agent (Evans et al. 2007; Schifitto et al. 2007a, 2009b), but unfortunately, all showed no significant benefit, except one demonstrating some better performance in RAVLT and Grooved Pegboard Test (dominant hand) (Sacktor et al. 2000). In addition, because of excitotoxicity in the HAND pathogenesis, memantine, a neuroprotectant and first-generation N-methyl-D-aspartate (NMDA) receptor antagonist that is commonly used for moderate to severe Alzheimer's disease, was once considered a promising candidate for HAND treatment. However, a placebo-controlled study of memantine in HAND indicated no association with overall neurocognitive improvement, but only transit and moderate changes (Schifitto et al. 2007b; Zhao et al. 2010).

In the last 10 years, other new adjuvant therapies have been tested, also based on neuroprotection and anti-inflammation strategies. Minocycline, which has both anti-inflammatory and neuroprotective effects, however, showed no benefit in two RCTs (Sacktor et al. 2011; Nakasujja et al. 2013). Rivastigmine, a cholinesterase inhibitor commonly used for Alzheimer's disease, had no overall effects on neurocognition except some improvement in processing speed (Simioni et al. 2013), similar to that observed with lithium (Munoz-Moreno et al. 2017). Paroxetine, a selective serotonin reuptake inhibitor typically used for the treatment of depression, was compared to fluconazole, an anti-fungal agent with potent anti-inflammatory effect, in HAND. Unlike fluconazole that showed no benefit, paroxetine demonstrated some improvement in the neurocognitive test, although the clinical relevance for such a modest improvement remained questionable (Sacktor et al. 2018). Ketogenic diet (KD), which was associated with an improvement in brain metabolism due to its potent anti-inflammatory and antioxidant effects, was tested in HAND, which demonstrated significant better executive function and processing speed; however, the cognitive gains were not sustained after the usual diets resumed (Morrison et al. 2019). Despite those mostly negative, more promising and better-tolerated neuroprotective therapies are being developed. For instance, intranasal insulin therapy, targeting insulin signaling defect-related metabolic dysregulation in the brain, demonstrated a potential benefit by reversing hippocampal dendritic injury and cognitive impairment in

a mouse model, and a clinical trial (NCT03277222) is currently ongoing as a treatment for HANDs (Kim et al. 2019). Tesamorelin, a growth hormone-releasing hormone (GHRH), was approved as an injectable medication to treat abdominal fat accumulation in HIV. A randomized clinical trial conducted in PLWH with mild cognitive impairment and healthy elderly showed favorable effect on cognition improvement (Baker et al. 2012). Further phase 2 clinical trial of tesamorelin for cognition in the elderly PLWH is currently ongoing (NCT02572323).

Among age-related comorbidities, cardiovascular disease (CVD) and metabolic syndrome were strongly and independently associated with poor cognitive performance in PLWH (Foley et al. 2010; Wright et al. 2010). Even among the wellcontrolled with a long-term viral suppression, current CVD risk, past CVD, and age were independent risk factors for neuronal injury and inflammation, suggesting that vascular changes in the CNS lead to cognitive impairment (Cysique et al. 2013). Thus, potential interventions targeting CVD have been tested in different model systems without consistent findings. In HIV-1 transgenic rats, an experimental model for HAND, chronic low-dose aspirin, reduced neuroinflammatory markers and oxidative stress (Blanchard et al. 2015). In vitro studies found that statin treatment decreased CD14+/CD16+ inflammatory monocyte subpopulation, which played a central role in the pathogenesis of HAND (Yadav et al. 2016). However, the analysis of 658 HIV+ patients in CHARTER showed that statin use was not associated with better neurocognitive performance (Letendre et al. 2007). A longitudinal analysis of a cohort nested from the Multicenter AIDS Cohort Study indicated that higher total cholesterol and low-density lipoprotein cholesterol were associated with faster rate of cognition decline. In addition, among patients with elevated cholesterol, statin use was associated with slower rate of cognition decline (Mukerji et al. 2016). In ACTG ALLRT cohort of 3949 participants, neither statin (a median 133-week use) nor angiotensin-converting enzyme inhibitors (ACEI)/ angiotensin receptor blockers (ARB) (a median 180-week use) showed a significant effect on neurocognitive function (Erlandson et al. 2017). Future studies are needed for neurocognitive effects of these agents for CVD treatment among PLWH.

ART intensification with maraviroc has been recently suggested as an option for the clinical management of HAND in the context of viral suppression (Carroll and Brew 2017). The rationales behind this suggestion include: (1) CCR5 receptor interactions with CNS reservoir cells are linked with CNS HIV and HAND; (2) Maraviroc, a CCR5 receptor antagonist, has adequate CNS penetration, with low rates of resistance, inhibitory effects on CNS viral replication in monocyte/ macrophage cells (Kelly et al. 2013), and anti-inflammatory properties. A recent prospective, open-label pilot randomized controlled trial in participants with viral suppression and stable ART for 12 months found that maraviroc-intensified ART improved global neurocognitive performance without significant side effects (Gates et al. 2016; Robertson et al. 2016). The other study compared standard and maraviroc/raltegravir-intensified ART regimens in 62 acute HIV infection that showed improved CNS-related outcomes but no difference between the two regimens at week 24, suggesting large randomized controlled studies would be necessary to confirm this option as a treatment for HAND in the future (Valcour et al. 2015). ACTG A5324 (https://clinicaltrials.gov/ct2/show/NCT02519777) is an ongoing double-blinded RCT to compare maraviroc (MVC) and dolutegravir (DTG) intensification to the standard ART regimens

in aviremic participants with neurocognitive impairment. Cenicriviroc, a dual CCR2 and CCR5 antagonist, demonstrated potent anti-inflammatory effects by decreasing monocyte activity maker (sCD14) (Thompson et al. 2016). A single-arm, open-label clinical trial of cenicriviroc for 24 weeks showed a sizable improvement in the neurocognitive test (D'Antoni et al. 2018).

In summary, although multiple adjuvant therapies have been developed to target various mechanisms of action and studied in small-scale trials, none have shown clear positive effects on HAND. Yes, with a better understanding of the pathogenesis and therapeutic targets, newer and effective interventions would become available in the near future.

5 Reservoirs Eradication

Although invasion of CNS is an early event that occurs during primary HIV infection (Thompson et al. 2011; Valcour et al. 2012), the brain displays chronic neuroinflammation and persistent viral RNA and DNA despite of effective ART. The CNS can serve a reservoir of ongoing HIV replication (Churchill et al. 2006), which limits the opportunity for HIV cure or eradication. While T-cell populations are the main source of CNS HIV in early HIV infection, perivascular macrophage and microglia are considered the primary cells that harbor HIV replication in chronic phase (Joseph et al. 2015). In addition to brain parenchyma, choroid plexus, CSF, and meninges are considered distinct reservoir sites in brain (Petito et al. 1999). Clearance of both latent and productive HIV from the brain would determine successful viral eradication. Numerous approaches have been developed to reduce these HIV reservoirs (e.g., early initiation of ART during acute infection (NCT00796146), gene and cell base therapy for HIV cure (Wang and Cannon 2016), nanotechnology (Cao and Woodrow 2019), and broadly neutralizing HIV antibody (bNAb)) (Lu et al. 2016). Most of these approaches remain experimental, and their effects on the HIV reservoirs in the CNS remain largely unknown. For instance, although the newly developed bNAbs represent a promising treatment entity for viral eradication, due to the large molecular weights, their CSF concentrations are 100-fold to 1000-fold lower than those in the plasma (Prabhakaran et al. 2020). Thus, additional studies are warranted to evaluate the effects of bNAbs on viral eradication in the CNS and their implications in HAND management.

6 Conclusion

HAND remains one of the ongoing challenges for the care of PLWH in the modern ART era, in addition to aging, multimorbidity, polypharmacy, and drug–drug interactions. This review tends to provide an overview of completed studies, understanding of the association between CPE, HIV viral suppression in the CNS, and neurocognitive performance, and status of adjuvant therapy for HAND management.

While the majority of the studies demonstrated that higher CPE was associated with better HIV control in the CSF, the relationship between CPE and neurocognitive performance is largely unclear. The possible reasons for this lack of clarity include neurotoxicity from ART and polypharmacy, lack of standard neurocognitive assessment, variations in study populations, and lack of newer ART regimens. Unfortunately, most of the tested adjuvant

therapies showed no significant benefit for HAND, suggesting a better understanding of pathogenesis and therapeutic targets remains warranted.

6.1 Clinical Implications

Since lower nadir CD4+ T-cell count and late presentation are strong predictors for HAND, early ART initiation should be recommended with a NeuroHIV-targeted regimen to reduce CNS reservoir and prevent HIV-associated neurocognitive impairment. In addition, psychosocial interventions may be beneficial because illicit drug use and psychiatric illness are significant risk factors. More evidence has suggested a critical role of age and CVD in the pathogenesis of HAND; thus, conventional approaches such as blood pressure control and statin use should be considered especially for those with a high risk, although the benefit for neurocognitive improvement remains to be determined. Since no specific biomarkers for HAND diagnosis currently are available, nor standard neurocognitive tests for follow-up, practicing physicians particularly HIV specialists should be aware of the high prevalence of HAND and the mild asymptomatic subtypes, and routine neurocognitive and mental health screenings should be recommended. From a practical perspective, in patients presenting with significant neurological symptoms of HAND, ART regimens with high CPE should be recommended to better control the HIV in the CNS.

6.2 Further Perspectives

In the combination ART era, the neurocognitive performance evaluation has been challenged to identify subtle deficits. Therefore, development of biomarkers in combination with neuroimaging and neurocognitive testing should be developed. PLWH are living longer under stable viral suppression, and they are more likely experiencing multimorbidity and polypharmacy. In the context of HAND, this means that a comprehensive management plan for multimorbidity especially CVD, diabetes, and metabolic syndrome should also be recommended. Although largely unknown, polypharmacy, typically resulting from multimorbidity, may likely contribute to the pathogenesis of HAND, in particular, for the medications with high neurotoxicity. The interactions between aging, polypharmacy, neurotoxicity, and HAND are currently under evaluation. Finally, a growing number of bNAbs are now in development. The CSF penetration profiles of these bNAbs and their effects on viral reservoirs, especially in the CNS, remain largely unknown and warrant further evaluation. The eradication of CNS reservoirs not only is a challenge but also might be the key to the future free of HAND.

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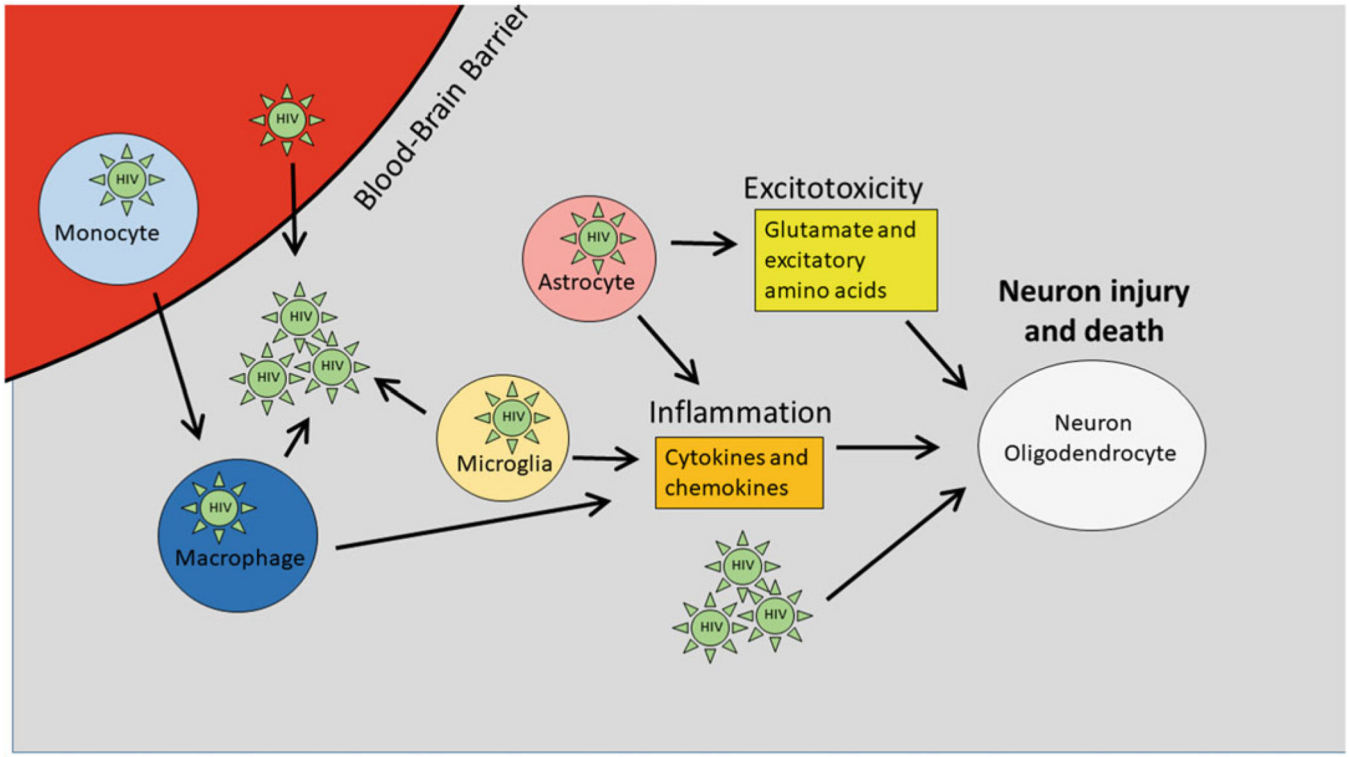

Fig. 1.

The effects of HIV in the central nervous system. *HIV entry*: HIV enters the CNS through the blood–brain barrier (BBB) directly or within infected monocytes. This process involves HIV-induced monocyte and endothelial activation, astrocyte dysfunction, and structural impairment of the BBB. *Viral replication*: HIV infects and activates macrophages and microglia followed by viral replication. *Inflammation*: HIV-induced activation of microglia, macrophages, and astrocytes leads to the release of proinflammatory cytokines and chemokines, which cause further influx of immune cells and mediate neuronal injury. *Excitotoxicity*: HIV induces release of glutamate and other excitatory amino acids from neurons and astrocytes, which together with HIV and HIV-induced chemokines, overstimulate N-methyl-D-aspartate (NMDA) receptors, leading to excitotoxicity. *Neuronal injury*: Insults from HIV, excitotoxicity, and inflammation lead to axonal injury and neuronal apoptosis. HIV also affects neural progenitor cells, impeding repair and growth

Table 1

Ranking of commonly prescribed antiretroviral drugs as for CNS penetration effectiveness (CPE) scores and in vitro neurotoxicity

	Abbreviation	Approval year	CPE	In vitro neurotoxicity
NRTI				
Zidovudine	AZT/ZDV	1987	4	+/−
Didanosine	ddI	1991	2	+
Stavudine	d4T	1994	2	+/−
Lamivudine	3TC	1995	2	+/−
Abacavir	ABC	1998	3	++
Tenofovir disoproxil fumarate	TDF	2001	1	+/−
Emtricitabine	FTC	2003	3	+/−
Tenofovir alafenamide fumarate	TAF	2015	1	
NNRTI				
Nevirapine	NVP	1996	4	+
Delavirdine	DLV	1997	3	
Efavirenz	EFV	1998	3	++
Etravirine	ETR	2008	2	+
Rilpivirine	RPV	2011	-	+
Doravirine	DOR	2018	-	
Protease inhibitors				
Saquinavir mesylate	SQV	1995	1	+
Indinavir	IDV	1996	3	+
Nelfinavir mesylate	NFV	1997	1	
Lopinavir	LPV	2000	3	+
Atazanavir sulfate	ATV	2003	2	+
Fosamprenavir calcium	FOS	2003	2	+
Tipranavir	TPV	2005	1	
Darunavir	DRV	2006	3	-
Fusion inhibitors				
Enfuvirtide	T-20	2003	1	
CCR5 co-receptor antagonists				
Maraviroc	MVC	2007	3	-
INSTIs				
Raltegravir	RAL	2007	3	+/−
Dolutegravir	DTG	2013	-	
Elvitegravir	EVG	2014	-	+/−
Bictegravir	BIC	2018	-	
Post-attachment inhibitors				
Ibalizumab	IBA	2018	-	

	Abbreviation	Approval year	CPE	In vitro neurotoxicity
Pharmacokinetic enhancers				
Ritonavir	RTV	1996	1	+/−
Cobicistat	COBI	2014	-	

NRTIs nucleoside reverse transcriptase inhibitors, NNRTIs non-nucleoside reverse transcriptase inhibitors, INSTIs integrase strand transfer inhibitors, CPE 2010

Table 2

Association between CPE and HIV suppression in the CNS

						HIV RNA (log c/mL)		CPE			
Year	***n***	**Design**	**Patient selection**	**Age (years)**	**CD4 cell count (c/mL)**	**Plasma**	**CSF**	**Baseline**	**Cut-off**	**CPE and CSF HIV association**	**Ref**
2002	50	Longitudinal	LP due to neurologic signs or research purpose	37	59	5.25	3.16	Nil	Nil	ART with higher CSF penetration correlated with a more profound CSF HIV-1 viral load reduction	De Luca et al. (2002)
2002	75 (cross-sectional), 29 (longitudinal)	Cross-sectional, longitudinal	LP due to neurologic signs (37% ART naive)	39	131	5	3.5	Number of CSF penetrating drug: 2	Nil	A significant difference in CSF HIV-1- RNA reduction was observed according to the use of three or more drugs penetrating the blood-brain barrier	Antinori et al. (2002)
2008	467	Cross-sectional	Receiving ART and having HIV VL measured in both plasma and CSF. LP for research purpose	44	406	1.7	1.7 (CSF detectable group = 2.5)	1.5[a]	1.5[a]	Lower CPE ranks was associated with detectable CSF VL	Letendre et al. (2008)
2009	79	Longitudinal	Initial ART or changing to a new ART. LP for research purpose	39	111	4.89	3.33	2.0[a]	2[a]	CPE score ≥ 2 was associated with 4.10-folds CSF HIV suppression	Marra et al. (2009)
2010	69	Cross-sectional	Neurological asymptomatic, ART >6 months with plasma HIV VL < 50 c/mL. LP for research purpose	CSF viremia: 46, control: 45	CSF viremia: 620, control: 525	<50 c/mL	CSF viremia: 121 c/mL, control: <50 c/mL	CSF viremia: 7.3, control: 7.4	Nil	CPE rank was not a predictor of detectable CSF virus	Eden et al. (2010)
2012	142	Retrospective, cross-sectional	LP due to clinical CNS events	45	395	48% detectable	54% detectable	1.5[a]	2[a]	Even with plasma HIV RNA <50 copies/mL, CPE <2 was significantly associated with detectable CSF HIV RNA	Rawson et al. (2012)
2013	83 (CSF undetectable),	Longitudinal	ART for at least 6 months and plasma HIV <50 cop-	44	520 (CSF undetectable);	<50 c/mL	Undetectable vs. detectable	CSF undetectable:	2[a], 7	The CPE score was significantly lower in patients with	Cusini et al. (2013)

						HIV RNA (log c/mL)		CPE			
Year	***n***	**Design**	**Patient selection**	**Age (years)**	**CD4 cell count (c/mL)**	**Plasma**	**CSF**	**Baseline**	**Cut-off**	**CPE and CSF HIV association**	**Ref**
	4 (CSF detectable)		ies/mL. LP for research purpose		369 (CSF detectable)			2.3[a], 8; CSF detectable: 1.0[a], 6		detectable CSF HIV RNA	
2014	49	RCT	Initial or change ART. LP for research purpose	CNS- T = 44.9, non-CNS- T = 43.6	CNS-T = 214, non-CNS- T = 306	CNS- T = 4.2, non-CNS- T = 3.5	CNS-T = 3.1, non-CNS- T = 3.1	CNS-T = 2.5[a], non-CNS- T = 1[a]	Nil	CSF viral suppression rate was similar for the 2 arms	Ellis et al. (2014)
2016	155	Cross-sectional, retrospective	Boosted dual protease inhibitor (bdPI) regimen, or any 2NRTI-containing ART. LP for clinical purpose	46.85	174.5	bdPI 115, ART 173	bdPI 600, ART 50	bdPI 4.29, ART 7.53	Nil	No significant correlation between quantitative HIV-1 RNA in CSF and CPE score	Donath et al. (2016)
2017	220	Retrospective, cross-sectional (*n* = 220), longitudinal (*n* = 55)	HIV in plasma and CSF < 50 copies/mL. LP for research purpose	44	503	65.2% plasma RNA > 1c/mL (low-level viremia)	CSF VL > 1: *n* = 93, CSF VL < 1: *n* = 127	CSF VL > 1:6.8, CSF VL < 1:7.2	7	Lower CPE values were associated with CSF HIV-1 RNA loads of ≥1 copy/mL	Anderson et al. (2017)
2018	71	Retrospective	Under stable ART, plasma HIV VL < 1000 copies/mL, neurological symptom. LP for clinical reason	38	361	71.8% undetectable	4250 c/mL in CSF/plasma HIV discordance	91.5%, ≥6	6	CPE values <6 were more likely to develop CSF/plasma HIV discordance	Dravid et al. (2018)
2019	401	Longitudinal	Under stable ART, HIV VL measurable in plasma and CSF. LP for clinical purpose	44	446	60%, <50 c/mL	87%, <50 c/mL	7.5	Nil	Detectable HIV RNA concentrations in CSF were associated with decreased CPE value	Livelli et al. (2019)

[a]CPE 2008 vision (rank from 0, 0.5, to 1)

CPE central nervous system penetration effectiveness, *LP* lumbar puncture, *ART* antiretroviral therapy, *CSF* cerebrospinal fluid, *CNS* central nervous system, *VL* viral load, *RCT* randomized clinical trial

Table 3

Association of CPE and neurocognitive performance

Year	*n*	Design	Patient selection	Follow-up	Age (years)	CD4 cell count (c/mL)	Plasma HIV RNA (log c/mL)	CPE		Neurocognitive performance (NP) test	CPE and neurocognition association	Ref
								Baseline	Cut-off			
2009	37	Prospective cohort	Mild to moderate NP impairment, untreated or planned initiation of anew ART	Baseline, wl2, w24, w36, w48	40	196	4.90	1.4[a]	2[a]	GDS (based on 6 NP measures)	CPE (≥2) independent factor for NP improvement	Cysique et al. (2009)
2009	185	Prospective cohort	With or suspected HAND, CD4 + <200, initial or change ART	Baseline, 20 months, 39 months	39	293	4.14	1.65[a]	Nil	Composite NP test z scores (6 NP measures)	Higher CPE scores correlated with greater improvements in NP test	Tozzi et al. (2009)
2009	79	Prospective cohort	CD4+ <200, plasma and HIV >2000 copies/mL, or HIV >50,000 c/mL, initial or change ART	Baseline, w24, w52	39	111	4.89	2.0[a]	2[a]	Composite z score for the short battery (NPZ4) and the longer battery (NPZ8)	Higher CPE associated with poorer neurocognitive performance	Marra et al. (2009)
2011	101	Cross-sectional	Stable ART >3 months, plasma HIV <50 c/mL, no neurological symptoms	NP test once	53	525	<50 c/mL	1.5[a], 7.0	Nil	Computerized cognitive test (CogState)	CPE not associated with NP impairment	Garvey et al. (2011)
2011	2,636	Prospective cohort	ART ≥6 weeks, plasma HIV <50 c/mL	Baseline, every 48 weeks	40	244	<50 c/mL	2.0[a]	Nil	NPZ3	Higher CPE associated with better neurocognitive functioning	Smurzynski et al. (2011)
2012	860	RCT	CD4+ <300, treatment naive	Baseline, every 24 weeks till wl92	34	173	5	7.0 vs. 9.0	Nil	Grooved pegboard, timed gait, semantic verbal fluency, and finger tapping	No differences in neurological and neuropsychological functioning between regimens with different CPE	Robertson et al. (2012)
2013	111	Prospective cohort	Age 18– 35 years, treatment naive	Baseline, 1 year later	18–35	<350	Nil	>7 (*n* = 38), ≤7 (*n* = 31)	7	GDS	No significant difference in cognitive outcomes between higher and lower CPE regimens	Cross et al. (2013)

Year	*n*	Design	Patient selection	Follow-up	Age (years)	CD4 cell count (c/mL)	Plasma HIV RNA (log c/mL)	CPE		Neurocognitive performance (NP) test	CPE and neurocognition association	Ref
								Baseline	Cut-off			
2013	101	Cross sectional cohort	ART, plasma HIV <50 c/mL	NP test once	47	620	<50 c/mL	1.5[a], 6	1.5[a], 6	18 NP measures	CPE ≥ 6 showed a decreased risk of cognitive impairment	Ciccarelli et al. (2013)
2013	54	Cross sectional cohort	ART for 4– 7 years with a stable CPE	NP test once	42	460	Nil	1[a] (*n* = 14), 1.5–2[a] (*n* = 18), 2.5[a] (*n* = 25)	1[a], 1.5–2[a], 2.5[a]	Short neuropsychological battery (4 NP measures)	High CPE scores associated with poorer NP performance	Kahouadji et al. (2013)
2014	49	RCT	Initial ART or change ART regimen	Baseline, weekl6	CNS-T 45, non-CNS-T 44	CNS-T 214, non-CNS-T 306	CNS-T 4.2, non-CNS-T 3.5	CNS-T 2.5[a], non-CNS-T 1[a]	Nil	GDS	No evidence of neurocognitive benefit for a CNS-targeted strategy	Ellis et al. (2014)
2014	96	Prospective cohort	>18 years, but no limit set for CD4+ count or HIV VL	Baseline, 2 years later	48	551	10,760 c/mL	7.8 (without HAND 7.6, with HAND 8.1)	Baseline: 6.9 vs. 8.1; at f/u 7.2 vs. 7.8	8 NP measures	Clinical deterioration associated with lower CPE at baseline and at the end of follow-up	Vassallo et al. (2014)
2014	229	Cross-sectional	Stable ART >12 months, plasma HIV <50 c/mL > 6 months	NP test once	45	325	<50 c/mL	6.93	7	Global NPZ-4	CPE <7 was associated with a trend to worse neurocognitive performance	Casado et al. (2014)
2014	660	Retrospective, cross-sectional	ART-treated	NP test once	49	586	84%, <40 c/mL	6.6	Nil	14 NP measures	Higher CPE values associated with poor NP performance	Libertone et al. (2014)
2015	64	Cross-sectional	Stable ART for >3 months	NP test once	38	227	1.3	Low CPE (*n* = 29); high CPE (*n* = 35)	7	NPZ-4	No significant differences between different CPE groups	Baker et al. (2015)
2016	417	Prospective, cross-sectional	ART for >90 days	NP test once	47	215	382 c/mL	7	Nil	GDS (6 NP measures)	Higher CPE values correlated with lower prevalence of neurocognitive impairment	Carvalhal et al. (2016)
2017	220	Retrospective, cross-sectional (*n* = 220), longitudinal cohort (*n* = 55)	ART, plasma and CSF HIV <50 c/mL	NP test once	44	503	65.2% plasma RNA > 1 c/mL (low level viremia)	7.1, (CSF VL > 1: 6.8, CSF VL < 1 : 7.2)	7	Global neurocognitive performance	Worse neurocognitive performance not associated with CPE	Anderson et al. (2017)

Year	*n*	Design	Patient selection	Follow-up	Age (years)	CD4 cell count (c/mL)	Plasma HIV RNA (log c/mL)	CPE		Neurocognitive performance (NP) test	CPE and neurocognition association	Ref
								Baseline	Cut-off			
2017	94	Prospective cohort	>18 years but no limit set for CD4 count or HIV VL	Baseline, 2 years later	46	552	69%, <200 c/mL	7.72 (HAND: 7.62, non-HAND: 8)	Nil	8 NP measures	Lower CPE at baseline independent risk factors for cognitive deterioration	Vassallo et al. (2017)
2019	909	Cross sectional and retrospective	ART, plasma HIV <50 c/mL	NP test once	53	638	<50 c/mL	6.66	7	9 NP measures	No association between neurocognitive impairment and CPE	Santos et al. (2019)

[a]CPE 2008 vision (rank from 0, 0.5, to 1)

CPE central nervous system penetration effectiveness, *NP* neurocognitive performance, *ART* antiretroviral therapy, *GDS* global deficit score, *VL* viral load

Table 4

Adjuvant therapies for HAND

Year	Design	Patient selection	Adjuvant	Dosage	Study arm	*n*	Follow-up neurocognitive performance change outcome	Main findings	Ref
1997	RCT	Cognitive impairment and under ART for 6 weeks	O PC-14117	OPC-14117:120 mg daily for the initial 6 weeks of the study and 240 mg daily for the remaining 6 weeks	OPC-14117 ($n = 15$), placebo ($n = 15$)	30	Baseline to wl2	No benefit	The Dana Consortium on the Therapy of HIV Dementia and Related Cognitive Disorders (1997)
1998	RCT, double-blind	Cognitive impairment and under stable ART for 6 weeks	Deprenyl, thioctic acid	Deprenyl 2.5 mg three times a week oral; thioctic 600 mg twice daily oral	Placebo ($n = 9$), deprenyl ($n = 9$), thioctic acid ($n = 9$), both ($n = 9$)	36	Baseline to wlO	1. Subjects receiving deprenyl performed significantly verbal memory improvement2. Thioctic acid: no benefit	Dana Consortium on the Therapy of HIV Dementia and Related Cognitive Disorders (1998)
1998	RCT, double-blind	Cognitive deficit (either no ART for 4 weeks or stable ART use for 12 weeks before study entry)	Peptide T	Peptide T, 2 mg, intranasally 3 times a day for 6 months	Peptide ($n = 66$), placebo ($n = 77$)	143	Baseline to month 6	Peptide T treatment was associated with overall cognitive improvement in patients with baseline global deficit scores (GDS) of at least 0.5	Heseltine et al. (1998)
1999	RCT, double-blind	Cognitive impairment and under ART for 6 weeks	Lexipafant	Lexipafant 250 mg, orally, twice daily	Lexipafant ($n = 16$), placebo ($n = 14$)	30	Baseline to wlO	There were trends toward improvement in the Rey auditory verbal learning test and timed gait test	Schifitto et al. (1999)
2000	RCT, double-blind	Cognitive impairment and under stable ART for 6 weeks	Selegiline transdermal system (STS)	STS 3.1 mg per 24 h	STS ($n = 9$), placebo ($n = 5$)	14	Baseline to wlO	The selegiline group performed better on the Rey auditory verbal learning test (RAVLT) delayed recall and the grooved pegboard dominant hand test	Sacktor et al. (2000)
2002	RCT, double-blind	HIV-associated cognitive-motor disorder and under stable ART for 8 weeks	CPI-1189	CPI-1189 50 mg/ day, CPI-1189 100 mg/day	CPI-1189 50 mg/day ($n = 21$), CPI-1189 100 mg/day ($n = 22$), placebo ($n = 21$)	64	Baseline to w6 and wl0	No benefit	Clifford et al. (2002)
2006	RCT, double-blind	With and without cognitive impairment	Valproic acid (VPA)	VPA 250 mg twice daily	VPA ($n = 11$), placebo ($n = 11$)	22	Baseline to wlO	With the exception of the mean reaction time and trial 5 of the Rey auditory verbal memory, all neuropsychological	Schifitto et al. (2006)

Year	Design	Patient selection	Adjuvant	Dosage	Study arm	*n*	Follow-up neurocognitive performance change outcome	Main findings	Ref
								measures favored the impaired subjects in the VPA group	
2006	Single-arm, open-label	Cognitive impairment and under ART for 12 weeks	Lithium	Oral lithium was initiated at 300 mg daily and was titrated to maintain 12-h trough concentrations between 0.4 and 0.8 mEq/L	Lithium (*n* = 8)	8	Baseline to wl2	Six of the eight individuals improved sufficiently to reduce their GDS from the impaired to the normal range	Letendre et al. (2006)
2007	RCT, double-blind	Nil	Selegiline transdermal system (STS)	STS 3 mg/24 h, 6 mg/24 h	Nil	86	Baseline to w24	No benefit	Evans et al. (2007)
2007	RCT, double-blind	Cognitive impairment and under ART for 6 weeks	Memantine	Memantine 10 mg per day for 1 week, escalated by 10 mg in weekly increments to 40 mg per day by week 4, or up to the maximum tolerated dose	Memantine (*n* = 70), placebo (*n* = 70)	140	Baseline to wl6	No benefit	Schifitto et al. (2007b)
2007	RCT, placebo-control	Cognitive impairment and under stable ART	Selegiline transdermal system (STS)	STS 3 mg/24 h patch daily, STS 6 mg/24 h patch daily	STS 3 mg/24 (*n* = 42), STS 6 mg/24 (*n* = 43), placebo (*n* = 43)	128	Baseline to w24	No benefit	Schifitto et al. (2007a)
2009	RCT, placebo-control	With cognitive impairment	Selegiline transdermal system (STS)	STS 3 mg/24 h patch daily, STS 6 mg/24 h patch daily	STS 3 mg/24 (*n* = 19),"STS 6 mg/24 (*n* = 18), placebo (*n* = 25)	62	Baseline to w12, w24	No benefit	Schifitto et al. (2009b)
2009	Single-arm, open label	Cognitive impairment and under ART for 8 weeks	Lithium carbonate	Lithium carbonate 300 mg PO bid	Lithium carbonate (*n* = 15)	15	Baseline to w10	No benefit	Schifitto et al. (2009a)
2010	RCT, double-blind	With or without ART, ADC (AIDS dementia complex) stage ≥1	Memantine	Memantine up to 40 mg/day	Memantine (*n* = 51), placebo (*n* = 48)	99	Baseline to w20 (double-blind phase), w48 (open- label phase)	During the initial 12-week, memantine arm had a statistically significant higher NP test improvement compared to placebo. No statistically significant NP changes were detected during the 48-week extension	Zhao et al. (2010)
2011	RCT, double-blind	Cognitive impairment and under ART for 16 weeks	Minocycline	Minocycline 100 mg orally every 12 h	Minocycline (*n* = 52), placebo (*n* = 55)	107	Baseline to w24	No benefit	Sacktor et al. (2011)

Year	Design	Patient selection	Adjuvant	Dosage	Study arm	*n*	Follow-up neurocognitive performance change outcome	Main findings	Ref
2013	RCT, double-blind	With undetectable plasma and CSF VL and with HAND	Rivas tigmine	Rivas tigmine 1.5 mg/day and was progressively increased every 2 weeks (3, 4.5, 6, 9, and 12 mg/day)	Rivastigmine (n = 9), placebo (n = 8)	17	Baseline to w20	Processing speed improved on rivastigmine	Simioni et al. (2013)
2013	RCT, double-blind	Naïve to ART, with CD4 + T cell 250–350/μL, AIDS dementia scale stage 0.5– 1, international HIV dementia scale score < 10	Minocycline	Minocycline 100 mg orally every 12 h	Minocycline (it = 36), placebo (n = 37)	73	Baseline to w24	No benefit	Nakasujja et al. (2013)
2016	RCT, double-blind	Diagnosis of HAND, under stable cART with plasma and CSF HIV VL ≤ 50 copies/mL	Maraviroc	Maraviroc 150 mg/300 mg/ 600 mg twice daily according to background therapy	Maraviroc (n = 9), control (n = 8)	17	Baseline to month 6, 12	Improved global neurocognitive functioning in maraviroc arm	Gates et al. (2016)
2017	RCT	Age 20– 75 years, with cognitive impairment, under stable cART at least 6 months, and undetectable plasma HIV viral load	Rivastigmine, lithium	Rivastigmine (started at 4.6 mg daily and increased to 9.5 mg daily at week 4), lithium (400 mg twice daily, titrated progressively to ensure plasma drug concentrations of between 0.4 and 0.8 mEq/ L)	Rivastigmine (n = 10), lithium (n =11), control (n = 8)	29	Baseline, wl2, w48	Better cognitive outcomes were observed in all groups, although there were no significant differences between the arms. The rivastigmine group showed the highest positive trend	Munoz-Moreno et al. (2017)
2018	RCT, double-blind	Age 18– 65 years, with cognitive impairment, under	Paroxetine, fluconazole	Paroxetine 20 mg orally every evening per day.	Placebo (n = 11, paroxetine (n =11),	45	Baseline to w24	1. HIV+ individuals receiving paroxetine showed improved summary	Sacktor et al. (2018)
		stable cART at least 3 months		fluconazole 100 mg orally every 12 h per day	fluconazole (n = 11), paroxetine + fluconazole (n = 12)			scores2. Fluconazole: No benefit	
2018	Single-arm, open-label, clinical trial	Age 18– 70 years, under stable ART>1 year, with plasma HIV VL < 50 copies/ mL, below-normal cognitive performance (<—0.5 SD)	Cenicriviroc (CVC)	Cenicriviroc (CVC) dosage adjusted by each participant's ART regimen	CVC (n = 17)	17	Baseline to w24	NP test improvements over 24 weeks	D'Antoni et al. (2018)
2019	RCT	Age > 50 years, stable HIV (CD4 + >350, ART ≥6 months), mild to	Ketogenic diet (KD)	Low carbohydrate (<50 g/day) and high-fat diet for 12 weeks	KD (n = 7), control (n = 1)	14	Baseline, wl2, wl8	At week 12, the KD group performed significantly better on trails A and trails B assessments	Morrison et al. (2020)

Year	Design	Patient selection	Adjuvant	Dosage	Study arm	*n*	Follow-up neurocognitive performance change outcome	Main findings	Ref
		moderate cognitive impairment							

ART antiretroviral therapy, *cART* combined ART, *GDS* global deficit score, *RCT* randomized clinical trial, *VL* viral load, *NP* neuropsychological