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HIV, Antiretroviral Therapies, and the Brain

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Abstract While combination antiretroviral therapy (CART) has decreased the incidence of HIV-associated dementia, the severest form of HIV-associated neurocognitive disorders (HAND), mild neurocognitive disorder and asymptomatic neurocognitive impairment continue to persist, and there is evidence that neurocognitive deficits present even in acute HIV infection. Recent studies demonstrate that CART regimens with higher central nervous system (CNS) penetration effectiveness ranks may improve neurocognitive functioning. Considering these factors, earlier treatment initiation may be considered to protect the CNS. The functional impact of HAND on daily activities should be monitored. Areas that need further research are potential neurotoxicity of antiretrovirals, the eradication of potential latent reservoirs in the brain, when to start treatment to protect the CNS, and the neurological impact of HIV on the CNS in acute infection.

Keywords HIV-1 · CNS · Neurocognition · Impairment · Antiretroviral therapy

Introduction

Though the incidence of HIV-associated dementia (HAD) has decreased in response to combination antiretroviral therapy (CART), the presence of milder neurocognitive impairment continues to persist, most likely due to residual viral replication in the brain [1, 2]. Recent studies reveal the possible neurocognitive benefits of high central nervous system penetration effectiveness (CPE) ranking regimens and treatment initiation at CD4 cell counts more than 350/μL [3••, 4, 5]. However, research also describes the potential neurotoxic effects of ART, indicating that future treatment strategies featuring increased penetration or earlier initiation should proceed with some caution [6, 7•]. The following review discusses recent developments on the impact of CART penetration on HIV-associated neurocognitive disorders (HAND), treatment initiation and delivery, the functional complications associated with HAND, and emerging international profiles concerning subtype and HIV-related neurocognitive impairment.

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Nomenclature

Diagnostic definitions of HAD, mild neurocognitive disorder (MND), and asymptomatic neurocognitive impairment (ANI) were recently updated by Antinori et al. [1]. Clinically, HAD is diagnosed as performance of at least two standard deviations below the means of demographically corrected normative scores in two different cognitive domains, which include attention-information processing, language, abstraction-executive, complex perceptual motor skills, memory, and simple motor skills or sensory perceptual abilities. In addition, the patient should exhibit notable interruptions in activities of daily living (ADL). Neurocognitive impairment should not be associated with delirium or comorbid conditions. MND is characterized by one standard deviation below the means in at least two of the aforementioned cognitive areas and mild difficulties in ADL. Lastly, ANI is defined by the same criteria as MND, but without any deficits present in ADL.

ART Central Nervous System Penetration

Penetration of antiretrovirals (ARVs) into the central nervous system (CNS) is limited by the blood–brain barrier

(BBB) and blood cerebrospinal fluid (CSF) barriers, and may lead to ineffective treatment of virus in the CNS. To estimate CNS penetration, Letendre [8••] developed the CPE scale based on drug chemical properties, CSF concentration, and effectiveness in clinical studies. Highly penetrating drugs receive a rank of 4, high intermediate drugs a 3, low intermediate drugs a 2, and low penetrating drugs a 1. For ARV regimens, the rankings of each individual agent are summed for a total CPE score.

Several studies have validated the prior CPE ranking system and investigated the impact of regimen penetration on cognition [3••, 5, 6, 9]. Tozzi et al. [5] compared the CPE ranking system to the CNS penetration reference score and found that only CPE rankings significantly correlated with neurocognitive performance, with higher CPEs related to neurocognitive improvement. Similar to these results, the AIDS Clinical Trials Group (ACTG) Longitudinally Linked Randomized Trials (ALLRT) study found that subjects with higher penetrating CART regimens exhibited better neurocognitive outcomes [3••]. Patel et al. [9] also discovered that in comparison to low-ranked regimens, high CPE regimens were associated with a 41% reduction in incidence of pediatric HIV encephalopathy, though it was not statistically significant. These studies build on a previous study by Letendre et al. [10] based on the older CPE scale (high 1, intermediate 0.5, low 0) that demonstrated that CART regimens with CPE ranks at or below the 1.5 median increased the odds of detecting CSF viral loads by 88%. Marra et al. [6] also discovered trends between CPE regimens ranked≥2 (according to the older CPE rankings) and higher odds of CSF suppression. However, in comparison to subjects with CPE regimens ranked<2, subjects with CPE≥2 scored significantly lower on neurocognitive tests over the 52-week period. In addition, regimens with more drugs were related to poorer cognitive performance. Marra et al. [6] speculated that the unexpected results may be related to lack of adherence or the potential neurotoxicity of highly penetrating regimens. Differences in baseline neurocognitive impairment between studies may also affect outcomes, as subjects with greater baseline deficits tend to respond to ART with more improvement [11].

Novel ART Drugs

Recently, various novel agents have been approved for use in subjects who have developed multidrug resistance, including the CCR5 antagonists maraviroc and vicriviroc, the integrase strand transfer inhibitors (INSTIs) raltegravir and elvitegravir, the second-generation nonnucleoside reverse transcriptase inhibitor (NNRTI) etravirine, and the second-generation protease inhibitor (PI) darunavir [12]. Data on CNS penetration and influence on cognition have yet to be pursued for many of the drugs. However, the drugs have received CPE rankings based on the data available [8••]. Vicriviroc was given the highest rank of 4. Ritonavir-boosted darunavir, maraviroc, and raltegravir were ranked at 3. Etravirine received a low-intermediate rank of 2. Elvitegravir was not included in the revised CPE ranks.

In clinical studies, raltegravir achieved drug concentrations required to inhibit 50% of viral replication (IC50) in the CSF of about 50% of the CSF samples, though it was detectable in nearly all the samples [13]. Darunavir was detected in all of 14 CSF samples at or above IC50 [14]. Maraviroc exceeded the concentrations required to inhibit 96% of viral replication in 7/7 CSF samples [15]. However, previous studies indicate that maraviroc is a substrate of the drug efflux transporter Pgp, which may hinder the drug's successful penetration across the BBB [12, 16]. To our knowledge, CSF concentrations have not yet been specified for elvitegravir, vicriviroc, or etravirine. The neurocognitive impact of all the novel agents should also be assessed.

ART Drug Delivery Across the BBB

Since cognition is possibly impaired by continued HIV replication in the brain, ART drug delivery that increases penetration of the CNS may be neurocognitively significant. One method that exhibits potential is intranasal delivery of ARV drugs and other neuroprotective therapeutics. Intranasal delivery bypasses the BBB altogether by administering drugs directly into the brain through the olfactory and trigeminal neural pathways that innervate the nasal cavity. Since delivery occurs via extracellular routes and does not require receptor-binding or axonal transport, any ARV or therapeutic agent could be a candidate for intranasal delivery [17]. Past studies in HIV patients conducted with intranasal delivery of peptide T demonstrated reductions in integrated viral DNA and active CCR5-entry viral replication in the monocyte reservoir [18].

Another promising realm of drug delivery involves nanoparticles that facilitate passage across the BBB. Polymeric nanoparticles are promising in particular due to their retention in brain capillaries and potential to penetrate the BBB. In vitro studies have demonstrated the use of the polymeric nanoparticle polybutylcyanoacrylate in transporting lamivudine, zidovudine, delavirdine, and saquinavir across brain microvascular endothelial cells (BMVECs) [19]. Solid lipid nanoparticles (SLNs) have a hydrophobic core in which lipophilic drugs can be dissolved and delivered. SLNs may be effective due to their characteristic controlled drug release and biodegradable components. Atazanavir, delavirdine, and saquinavir have been delivered through SLNs to BMVECs in vitro [19–21]. In addition, recent research conducted by Bowman et al. [22] demonstrated that gold nanoparticles conjugated to SDC-1721, a component of

the HIV inhibitor TAK-779, were able to block HIV-1 fusion to human T cells.

The in vivo efficacy of these nanoparticles in BBB delivery however is more complex and may require host cell carriers [19]. Recently, indinavir nanoparticles loaded into bone marrow macrophages of a murine neuro-AIDS model were found in areas of HIVE that exhibited active astrogliosis, microgliosis, and neurodegeneration. Additionally, the indinavir nanoparticle treatment resulted in reduced viral replication in HIVE brain regions [23]. Further studies should be conducted on ARV nanoparticle delivery, especially through host cells that are capable of infiltrating the BBB.

Eradication of Latent Reservoirs

Despite the success of CART, research indicates the presence of latent reservoirs in the brain, which store viral variants and produce persistent, low-grade viral replication that may be responsible for impairing neurocognition [24, 25]. Though latent CD4+ cells were previously considered the main reservoir, recent studies demonstrate that infiltrating macrophages may be the most responsible for long-term viral replication in the brain [26, 27].

Immune activation therapy combined with CART has been suggested to induce HIV expression in latent cells while protecting infection of new cells. Possible candidates for immune activation, particularly in CD4+ cells, are histone deacetylase inhibitors, the kinase agonist hexamethyl bisacetamide, the kinase-C and NF-κB stimulating prostratin, and the cytokine interleukin-7 [28]. Archin et al. [29] discovered that class I histone deacetylase inhibitors, particularly MRKI, were capable of activating HIV promotor expression in J89 cells and viral outgrowth in resting CD4+ T cells from human HIV subjects. However, the potential toxicities involved with cellular activation coupled with CART intensification and the possible danger of a global immune response have hindered the immune activation therapy progress [24, 28]. Therapies that do not require viral gene activation, such as silencing the viral promoter via RNA interference, should be further pursued and refined for specificity and delivery [24]. So far, to our knowledge, there have not been immune activation therapy methods specifically created for potential non-CD4+ T-cell sources.

ART Neurotoxicity

Though higher CPE regimens have been associated with neurocognitive improvement, recent research demonstrates that ART may also have neurotoxic effects that adversely affect cognition. Robertson et al. [7•] found that the discontinuation of CART in experienced subjects actually improved neurocognition and those results were not attributed to practice effects. Additionally, subjects who re-initiated CART after discontinuation did not experience cognitive gains. ART neurotoxicity may be responsible for these unexpected results.

Previously, the injurious effects of ART on the brain were implicated through damage to peripheral tissues and MRI studies assessing neuronal integrity. Nucleoside reverse transcriptase inhibitors (NRTIs) were demonstrated to induce toxicity in peripheral tissues through mitochondrial dysfunction, and PIs were shown to damage proteasome function [30]. MRI studies by Schweinsburg et al. [31] revealed that subjects on didanosine and stavudine regimens exhibited decreased N-acetylaspartate (NAA) concentrations in frontal white matter, and longer treatment correlated with lower NAA levels. Despite this evidence, research had not yet been pursued on assessing the direct neurotoxic impact of ART.

Recently, Liner et al. [32•] presented studies assessing the direct effects of various ARVs on primary rat forebrain cultures. The studies have addressed the influence of five NRTIs (2′,3′-dideoxycytidine, 2′3′-dideoxyinosine, zidovudine, emtricitabine, and tenofovir), one NNRTI (efavirenz), and two PIs (ritonavir, atazanavir sulfate) on neuronal integrity and function. All of the ARVs tested except for DDI exhibited decreased intensity of tetramethylrhodamine methyl ester staining in mitochondrial membranes, indicating reduction of membrane potential. In addition, several ARVs destabilized neuronal intracellular calcium homeostasis, exhibiting a reduced acute response to glutamate. The ability of certain ARVs and ARV combinations to perturb neuronal calcium homeostasis and affect the mitochondrial membrane potential under conditions that produce little cell death indicates the early presence of neuronal dysfunction. Neurons treated with ARVs and stained for microtubule-associated protein-2 (MAP-2) exhibited dendritic beading and pruning, which have been linked to cognitive dysfunction [33]. Associations between ART treatment and loss of MAP-2 staining in the neuronal cultures illustrated the loss of cell density over a range of drug concentrations. The median toxic doses for several ARVs were well within the therapeutic concentration range in plasma of HIV-infected patients, and a few showed some signs of damage in the range of CSF concentrations. These initial observations highlight potential adverse effects of high concentrations of ARVs in the CNS and indicate that there may be some positive and negative tradeoffs to delivering therapeutic concentrations of ARVs to the CNS. Similar studies are being conducted to determine the in vitro effects of several of the most common ARV combinations.

Further in vitro and in vivo studies should be conducted, assessing ART neurotoxicity by adjusting for parameters such as CPE rank and time of exposure to ARVs.

CART Initiation and Treatment Guidelines

Previously, the benefits of treatment initiation at CD4 cell counts≤200/μL have been well documented [34]. However, current research supports treatment initiation at higher CD4 cell counts, especially since ART has become more tolerable than before [35]. Sterne et al. [4] analyzed data from 18 HIV cohort studies and found that subjects who initiated CART at CD4 cell counts between 351/μL and 450/μL exhibited decreased probability of progression to AIDS or death in comparison with subjects who initiated between 251/μL and 350/μL. A recent study by Kitahata et al. [36] revealed that compared with patients who initiated treatment at CD4 counts>500, the deferred-therapy group had a 94% increase in risk of death. Compared to patients who initiated in the 351 to 500 CD4 count range, the deferred-therapy group had a 69% increase in risk of death.

The US Department of Health and Human Services recently updated recommendations on CART treatment guidelines [35]. Regardless of CD4 cell count, ART should be initiated in patients with a history of an AIDS-defining illness or any of the following conditions: pregnancy, HIV-associated nephropathy, or hepatitis B co-infection with indicated hepatitis B treatment. All patients with CD4 cell counts<350 cells/mm^3 should start treatment, whereas the strength of the recommendation to initiate at counts between 350 and 500 or >500 is divided between strong to moderate and moderate to optional, respectively. The preferred regimens are as follows: NNRTI + two NRTIs (efavirenz + tenofovir + emtricitabine), ritonavir-boosted PI + two NRTIs (ritonavir-boosted atazanavir or ritonavir-boosted darunavir + tenofovir + emtricitabine), and INSTI + two NRTIs (raltegravir + tenofovir + emtricitabine).

Despite evidence supporting earlier initiation, the possibility of prolonged neurotoxic effects should also be carefully weighed, as recent studies indicate that ART could have potential damaging effects on neurocognition [6, 7•]. However, Cysique et al. [11] documented neurocognitive benefits associated with CART over the span of a year, with neuropsychological (NP) improvement most present at 24 weeks, 36 weeks, and 48 weeks after treatment initiation. Large, longitudinal studies should be conducted to assess the long-term effects of earlier ART initiation on neurocognition. One such study, START, is being conducted by the Insight Network, and the neurological substudy will assess potential gains in neurocognitive functioning with earlier versus delayed treatment initiation.

Neurological Problems in Acute Infection

Though the presence of neurocognitive deficits in HIV-seropositive individuals has been well-documented, the characteristics of cognitive deficits in acute HIV infection are less well understood. Ances et al. [37] conducted studies observing resting cerebral blood flow in acute and chronic HIV subjects and HIV-negative controls. Both acute and chronic HIV groups demonstrated decreased resting cerebral blood flow to the lenticular nuclei, while only chronic HIV patients exhibited reduced resting cerebral blood flow to the visual cortex. These results indicate the presence of subcortical deficits in acute HIV infection, which later progress to cortical areas.

Recent studies indicate the possible neurological benefits of CART initiation as early as acute infection. Marcondes et al. [38] initiated ART in rhesus monkeys upon diagnosis of acute SIV infection, which resulted in the prevention of early neurological symptoms, alterations in the brain's immune response to favor effector T cells, and decreased levels of interferon-α, a cytokine related to HAD pathology. Villar Del Saz et al. [39] also demonstrated the potential benefits of starting CART in individuals presenting with meningitis or meningoencephalitis during primary infection (n=10) or discontinuation of CART in sexually transmitted infection (n=3). Both groups of patients exhibited focal neurological signs, confusion, and agitation. A minority of them also experienced seizures. The early initiation of CART, mostly with CPE regimens≥2 (according to the older CPE ranking system), in 11 of 13 subjects may have contributed to the observed rapid recovery in severe neurological symptoms. Further studies assessing the long-term neurocognitive outcomes of CART initiation during acute HIV infection should be pursued. Schnell et al. [27] have demonstrated that there are compartmentalized variants of HIV in the CSF during primary infection, indicating that independent HIV replication can occur in the CNS early after transmission. Compartmentalized HIV variants in the CNS have been associated with HAD [40].

Functional Impact of Neurocognitive Deficits in Daily Living

HIV-associated neurocognitive disorders, whether MND or HAD, cause difficulties in performing everyday tasks. Cognitive deficits in the domains of executive functioning, memory, attention, visuospatial abilities, and fine motor control have been shown to hinder basic activities such as driving, shopping, medication adherence, and financial management. HIV-associated neurocognitive impairment, particularly in the areas of executive functioning, attention, and memory, has also been associated with unemployment.

Only a minority of HIV-positive individuals are able to maintain employment or find employment after losing a job [41]. Neuropsychiatric symptoms that can inhibit everyday functioning have also been documented, particularly apathy, depression, anxiety, mania, and psychosis [41, 42]. Additionally, ART drugs may play a role in affecting neuropsychiatric instability. Efavirenz in particular has been associated with hangover-like symptoms, impaired concentration, and hallucinations [43].

Recent studies have further specified the memory deficits exhibited in HAND and how they impact daily living. In a study conducted by Morgan et al. [44], HIV-seropositive subjects demonstrated deficits in source memory, an essential component of episodic memory encoding and retrieval, which correlated with impaired executive functioning. Difficulties related to memory encoding and retrieval may also contribute to impairment in prospective memory, the ability to carry out a future intention, which has also been observed in HIV subjects. Woods et al. [45] discovered that both impairment and self-reported difficulty in prospective memory correlated with increased risk of dependence in daily activities.

International Studies

Though the effects of CART on neurocognition have become better characterized in Western countries, work has just begun on understanding the neurocognitive effects of HIV and CART internationally, particularly in more resource-limited countries. Because resource-limited settings represent the areas most affected by the global HIV epidemic, research in these areas is important; however, it faces many challenges [46–48]. The ACTG 5199 study conducted by Robertson et al. [49•] indicated significant NP improvement after the initiation of CART over a 96-week period in Brazil, India, Malawi, Peru, South Africa, Thailand, and Zimbabwe. The magnitude of improvement varied by country and may be attributed to differences in HIV subtypes, populations, testing methods, or culture.

Recent HIV Neurocognitive Studies in Asia

Studies conducted by Heaton et al. [50] in a rural Chinese cohort found NP impairment in 34.2% of HIV-monoinfected subjects and 39.7% of HIV and hepatitis C virus (HCV) co-infected individuals. Both monoinfected and co-infected HIV groups showed deficits in processing speed, learning, memory, and motor skills. HCV co-infected subjects exhibited greater NP impairment and increased dependence in daily functioning. In addition, HIV-monoinfected and HIV–co-infected subjects experienced reduced employment or work time in the span of a year. These results build on previous studies conducted in China by Cysique et al. [51], which demonstrated significant NP deficits in HIV-positive individuals in comparison with HIV-negative controls.

Valcour et al. [52] conducted research in Thailand among subtype B-infected subjects and found cognitive improvement in both HAD and non-HAD groups after CART initiation. In addition, monocyte HIV DNA levels correlated with cognitive performance before and 48 weeks after highly active antiretroviral therapy (CART), with baseline HIV DNA counts greater than 3.5 log10 copies/10^6 monocytes distinguishing HAD from non-HAD cases. These findings support the possibility that incomplete cognitive recovery with CART may represent an active process related to the monocyte–macrophage reservoir.

Recent HIV Neurocognitive Studies in Sub-Saharan Africa

Studies currently being conducted in sub-Saharan Africa are especially important due to the high percentage of HIV-infected adults and children who reside there, approximately 67% of the global total. The region also endures a majority of the new HIV infections and deaths in the midst of limited resources. Recent research in Uganda by Sacktor et al. [53] on HIV-positive subjects revealed neurocognitive improvement in the areas of verbal memory and fluency, motor performance and psychomotor speed, and executive functioning in response to stavudine-based therapy. Subjects also experienced functional improvement, as measured by the Karnofsky scale. However, about 31% to 38% of patients developed peripheral neuropathy symptoms over the course of the study. The 2009 Neuro-AIDS in Africa Conference presented a number of studies underway from all across Africa, including Cameroon, Ethiopia, Kenya, Botswana, Malawi, Nigeria, South Africa, and Zambia [54]. As these studies come to fruition, more will be known about neurological disease in Africa.

HIV Clades/Subtypes and Neurocognitive Impairment

Recently, progress has been made in investigating whether some subtypes or clades are more neuropathogenic than others. Addressing subtypes A and D, studies by Sacktor et al. [55] in Uganda indicated that individuals with subtype D may be more likely to develop neurocognitive impairment than those with subtype A, building on previous knowledge of subtype D progressing more rapidly to AIDS and death than subtype A. Studies in South Africa and Zambia have revealed evidence of cognitive impairment in clade C [54]. These studies support previous evidence of NP impairment found in 60.5% of seropositive clade C individuals in South India [56]. Understanding neurocognitive differences in

clades can help to inform important decisions such as timing of CART initiation.

Despite differences across clades and populations, the international presence and profile of HAND in HIV-infected individuals appear to be relatively consistent, with deficits generally observed in areas of executive functioning, processing speed, and memory.

Conclusions

Though CART has been successful in reducing systemic viral load and the incidence of HAD, the continued presence of MND and ANI warrant further studies on the treatment parameters and potential neurotoxic effects of CART. The efficacy of optimal CNS penetration and the timing of treatment initiation are questions essential to improving the quality of life for HIV-infected individuals experiencing HAND, including acute/primary infection. Special attention should be given to international studies that reveal potential clade differences in neurological disease.

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