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HIV-Associated Neurocognitive Disorders: Perspective on Management Strategies

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Abstract

Potent combination antiretroviral therapy (ART) has resulted in dramatic improvement in AIDS associated morbidity and mortality. Although combination ART has resulted in a significant reduction in HIV associated dementia, the most severe form of HIV associated neurocognitive disorders (HAND), the overall prevalence of HAND among this population is estimated at 40%. It has been recognized that the central nervous system (CNS) serves as a reservoir for HIV, and neuronal damage begins at the time of acute infection and persists due to chronic infection of microglial and perivascular macrophages. Although combination ART has resulted in virologic control in the plasma compartment, virologic breakthrough can potentially ensue within the CNS compartment due to limited ART drug exposure. The purpose of this review is to discuss the definition, clinical spectrum and risk factors associated with HAND, review the pathogenesis of HAND, and address the pharmacologic challenges associated with ART drug exposure in the CNS compartment.

Keywords

HIV associated neurocognitive disorders; ARV pharmacology

I. Background

The World Health Organization estimates that over 40 million people worldwide are living with human immunodeficiency virus (HIV)[1]. While HIV is most known for its devastating effects on the immune system and the resulting acquired immunodeficiency syndrome (AIDS), it can also cause several neurocognitive disorders, collectively known as HIV-associated neurocognitive disorders (HAND).

Since the introduction of combination antiretroviral therapy (ART) there has been a profound decrease in mortality rates of people infected with HIV. Potent therapy has directly resulted in virologic suppression, preserved immune function, and decreased risk of opportunistic infections. Likewise, it has had a dramatic improvement on neurocognitive decline associated with high virus burden and opportunistic infections in the central nervous system. The incidence of HIV-associated dementia, the most severe form of HAND, has

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also significantly decreased since the widespread availability of combination ART. Despite this dramatic shift, the prevalence of HAND is increasing, tipping the balance of the spectrum of collective disorders of HAND in HIV towards milder cognitive disturbances. HAND remains a major concern for HIV-infected individuals because it can result in impaired daily living and a reduced quality of life. In severe instances, HAND can contribute to increased mortality in HIV-infected individuals because their cognitive dysfunction could contribute to ART non-adherence.

The causes of continuing high rates of HAND in the ART era are uncertain. As ART-treated patients survive into older age, there could be a rise in HAND due to interactive effects of chronic immune activation and aging on the central nervous system (CNS)[2]. Multiple etiologies have been proposed including i) irreversible brain injury prior to initiating ART, ii) poor CNS penetration of some commonly used antiretroviral drugs (ARVs) leading to incomplete viral suppression in the CNS, iii) the presence of drug-resistant viral strains in the CNS, and iv) neuronal injury and dysfunction due to prolonged exposure to low levels of viral replication in the CNS[3], neurotoxicity of ART itself, and exposure to other conditions that may affect cognition[4] Finally, acute or subacute neurological manifestations may be associated with discordance of viral suppression between the plasma and cerebrospinal fluid (CSF) compartments. One study demonstrated a mean CSF HIV ribonucleic acid (RNA) of 880 copies/mL in the setting of well controlled HIV plasma viremia in patients receiving combination ART and experiencing neurologic abnormalities. The authors suggested that this discordance may be linked to neurocognitive impairment [5]. Although neurocognitive impairment is not universal among HIV individuals, clinically mild cognitive disease affects up to 30% of otherwise asymptomatic HIV persons and up to 50% of individuals with AIDS[4, 6]. This review will focus on the diagnosis and management of HAND in the era of potent combination ART with an emphasis on the pharmacology of ARVs within the CNS. A comprehensive literature search of PubMed was performed with no time limit defined using the key words: HIV-associated neurocognitive disorders HAND, HIV associated dementia (HAD), AIDS dementia and neurocognitive impairment. We did a focused literature review of all newly licensed antiretroviral agents and cross referenced it with search terms that included pharmacokinetics, CSF penetration, and CNS penetration effectiveness (CPE).

I. HIV-Associated Neurocognitive Disorders (HAND): Definition and Clinical Spectrum of Disease

HIV-associated neurocognitive disorders (HAND) is an umbrella term used to describe neurodegenerative disease caused by chronic HIV infection. In 2007 the National Institute of Mental Health (NIMH) and the National Institute of Neurological Diseases and Stroke (NINDS), commissioned the development of an updated, working research criteria for HAND. The previous criteria, first established in 1991, described two categories of neurocognitive disorders associated with HIV infection—HIV-associated dementia (HAD) and the less severe minor cognitive motor disorder. With the advent of combination ART, the progression of HIV-associated neurocognitive disorders has been modified, leading the working group to conclude that the two existing categories no longer encompassed all forms of HIV-associated neurocognitivedisorders [7]. The resulting criteria defined three conditions: asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), and HAD. Individuals meeting criteria for delirium or dementia, and impairment that can be explained by comorbid conditions are excluded from these definitions.

The three conditions comprising HAND—ANI, MND, and HAD are classified using a variety of specific clinical and laboratory-based diagnostic methods. On one end of the

spectrum, ANI is the mildest form of HAND and is characterized by asymptomatic or unrecognized neurocognitive impairment. These individuals typically do not have abnormality in everyday functioning. Their neurologic deficits occur in one or more cognitive areas, such as memory or executive function. Typically the cognitive impairment is considered mild and defined as at least one standard deviation below the mean of demographically adjusted normative scores in two or more areas[7]. In addition to the criteria associated with ANI, MND requires that there be impairment in everyday function and activities of daily living, which may be mild to moderate. For example, by self-report or observation, individuals may have reduced mental acuity and inefficiency in work, homemaking or social functioning. On the severe end of the spectrum, HAD describes individuals with documented moderate to severe deficits in two or more cognitive areas similar to the other 2 categories of HAND. However, individuals with HAD display substantial impairment in everyday functioning resulting in inability to live independently. Oftentimes, individuals are incapable of caring for themselves and as a result have difficulty with medication compliance and routine follow-up appointments[7]. HAD has become a rare entity and is strongly associated with low CD4 T lymphocyte count and high plasma viral RNA[8].

The diagnosis of HAND may be classified using a variety of specific clinical and laboratory methods but is clearly dependent upon the availability of resources such as neuropsychological testing. Criteria required for interpretation and classification of patients with HAND depend on the following determinations: 1) the presence and severity of neurocognitive impairment, 2) the presence and severity of functional decline, and 3) the degree to which cognitive impairment or functional decline are likely to have been influenced by comorbid conditions[7]. Notably, HIV care providers must be aware of the clinical manifestations of neurocognitive complications of HIV infection. As HAND is often a diagnosis of exclusion, the HIV practitioner must first perform a diagnostic work-up that excludes opportunistic infections and malignancies of the CNS, neurosyphilis, CNS vascular disease, as well as metabolic co-morbidities that can affect neurocognitive function. Screening for depression, other psychiatric disorders, and substance abuse must also be performed. In the aging HIV population, neurodegenerative disorders such as Alzheimer's dementia may also concurrently be present but do not manifest with similar symptoms. For example, deficits including pronounced amnesia with rapid forgetting and integrating new information, including difficulty in comprehension and naming objects are findings more consistent with Alzheimer's rather than HAND. Notably, extrapyramidal motor signs can be increased in HIV in the ART era and the impact of HIV on extrapyramidal motor signs is exacerbated by aging[9].

II. HAND: Risk Factors

Risk factors which have been associated with the development of HAND include virologic factors, immunologic factors, and patient demographics and comorbidities. The virologic factors include virus clade, uncontrolled plasma viremia and a high CSF virus burden[10]. Although high plasma and CSF virus burdens have historically been associated with HAND[3], work by Sevigny et al. demonstrates a weakened association between baseline HIV RNA levels and the incidence of HAD as a result of alterations in CSF viral dynamics in persons receiving ART[11]. Host immune related factors such as current and nadir CD4 counts have also been reported as risk factors[12–14]. Increased age is an important risk factor for HAND, specifically HAD. In the Hawaii Aging with HIV cohort study, HAD was approximately three times more common in the greater than 50-year age group as compared to the younger cohort after controlling for education, race, substance dependence, antiretroviral medication status, viral load, CD4 lymphocyte count, and Beck Depression Inventory score[15].

The number of potential confounders and comorbid conditions associated with HAND is exceedingly large. Thus it is imperative to identify comorbidities in order to help differentiate these disorders from HAND. Comorbid conditions may exacerbate HAND and therefore there is strong rationale to treat these comorbidities, including cardiovascular disease, metabolic disorders, and major depressive disorders, in order to reduce the severity of neurocognitive disease in HIV-infected patients[16, 17]. Metabolic complications associated with HIV and antiretroviral treatment such as central obesity and diabetes in older HIV patients has been associated with increased risk for neurocognitive impairment[18]. It has also been reported that co-infection with hepatitis C results in a more severe form of HAND and is associated with increased mortality[19] and this may eventually become an important contributor as 30 percent of HIV infected individuals are coinfected with hepatitis C[20]. Evaluation and management of these comorbidities has become exceedingly important as the HIV population is aging, and the proportion of newly diagnosed HIV patients greater than the age of 50 has increased over the past decade[21].

III. Pathogenesis of HAND

Viral entry into the CNS

HIV-1 invades the CNS early in its disease course and can cause persistent infection and inflammation. HIV-1 can enter the CSF as early as 2 weeks after infection[22]. Within the CNS the virus establishes its reservoir within the perivascular macrophages. Entry of HIV into the CSF has been the subject of many studies using animal models and tissue-culture preparations that mimic the blood brain barrier (BBB). While the mechanism of viral entry into the CNS remains a debatable topic, a commonly accepted theory is the “Trojan horse” mechanism[23]. This process of CNS entry was classically described years ago for lentiviruses such as Visna virus of sheep[24]. Using the sheep-specific lentivirus Visna virus as a model of HIV infection, Haase et al. first proposed that HIV and other lentiviruses enter the CNS as passengers in monocytes that later differentiate into macrophages trafficking to the brain. Subsequent infection and activation of neighboring cells occurs via direct contact with infected cells. Cells directly contacted by infected ‘Trojan horse’ cells include perivascular macrophages, astrocytes, and microglia[6, 25]. In theory, the five main cell types of the CNS are susceptible to retroviral infection including astrocytes, oligodendrocytes, neurons, perivascular macrophages and microglia. Of these five, the latter two are the most commonly infected by HIV since microglia and macrophages are the only CNS cells to possess both CD4 and C-C chemokine receptor type 5 (CCR5)[26]. Thus, perivascular macrophages and microglia are the only resident CNS cells capable of promoting HIV infection in the brain. While there is little evidence to suggest that the virus infects neurons, significant neuronal dysfunction including axonal and dendritic pruning is prevalent throughout the CNS[27–29]. It is therefore believed that infected cells release viral proteins, particularly glycoprotein 120 (Gp120) and Tat protein, which are toxic to neurons. For example, Gp120 is the envelope surface protein of HIV and can bind C-X-C chemokine receptor type 4 (CXCR4) and CCR5, even in the absence of CD4, on the surface of neurons and trigger neuronal apoptosis[30].

The inflammation associated with acute and chronic HIV infection is an important contributor to HAND and likely mediates the CNS damage in neurocognitively impaired HIV-infected individuals. Other factors that contribute to neuronal damage include oxidative stress and excitotoxicity of N-methyl–D-asparate (NMDA)-subtype glutamate receptors resulting in apoptosis[31]. Before the introduction of ART, robust neuro-inflammation was frequently observed in brain autopsies from HIV-infected patients and the severity of inflammation generally increased throughout clinical disease progression from the early asymptomatic stage to AIDS[32] suggesting a spectrum of pathologic changes. In a study by Masliah et al., antemortem neuropsychological performance was correlated with postmortem

neuropathological changes, and it was noted that the degree of neurocognitive impairment was related to the amount of dendritic simplification[29]. The apparent net effect of chronic inflammation and the production of virus related neurotoxic substances results in neuronal damage and dendritic pruning throughout the CNS. The pathological changes of multinucleated giant cells, microglial nodules, gliosis, myelin pallor, and neuronal loss is seen in HAND, and commonly seen in the most severe form of this illness[33].

Clinical Diagnosis and Follow-up of HAND

DIAGNOSTICS—Diagnosis of HAND is difficult to assess in clinical practice and often relies on recognition of the clinical syndrome and exclusion of alternative diagnoses, rather than on specific laboratory-based findings. A key challenge in the diagnosis and monitoring of HAND is the lack of both specific symptoms and lack of reliable and practical methods of screening for and evaluating neurocognitive impairment. Early infection with HIV is typically asymptomatic. However if symptoms do occur they are often subtle and range from headaches to subclinical symptoms of encephalitis.

Cerebrospinal fluid (CSF) analysis and magnetic resonance spectroscopy (MRS) imaging can detect CNS abnormalities during the early period of infectivity. MRS measures metabolites in targeted tissues, and has demonstrated abnormal concentrations and ratios of metabolites in HIV infected persons with neurocognitive dysfunction[32–34]. Magnetic resonance imaging (MRI) suggestive of HAD include diffuse cerebral atrophy and subcortical or periventricular white matter changes that appear hypodense on computed tomography or bright on T2 sequences on MRI. However, neuroimaging in this setting is most useful as a means to exclude other common neurological conditions in individuals with AIDS, because neither atrophy nor white matter changes are sensitive or specific for HAND[34]. Infection of the CNS by HIV-1 can be detected and monitored by measurement of viral RNA in CSF. Quantitative testing for HIV-1 in the CSF is available in commercial labs. For appropriate handling and testing, at least 3 milliliters (mL) of CSF should be collected in a sterile screw-capped container. Heparin tubes should not be used for collection as heparin inhibits polymerase chain reaction (PCR). The CSF specimen should be transported to the commercial lab frozen, as this increases specimen stability for up to 35 days[35].

Several groups have reported a positive correlation between CSF viral RNA and the observed degree of cognitive dysfunction in patients with HAND[36–38], with the highest concentrations of virus observed in those subcortical structures most frequently affected in patients with severe HAND[39]. However in the post-ART era this correlation appears to be diminished[11].

Many screening tools have been utilized for detecting HAND. However no single tool has been approved for detection of all forms of HAND. For example, the HIV dementia scale[40] and the International HIV dementia Scale[41] are designated primarily for screening HAD. Conversely, the Montreal Cognitive Assessment is more appropriate for patients on ART with immunologic and virologic control[42]. Although this review will not focus on these screening tools, in general they have been useful in screening for the diagnosis of HAND. While these tools are helpful and rapid, screening tests for disease such as the International HIV dementia scale (IHDS), have a sensitivity of 80% and specificity of 57%[41]. A few of the shortcomings include the lack of a good single tool suitable for use across all practice settings, availability of a clinician suitably trained to administer and interpret each tool, and the need for multiple detection methods to establish diagnosis.

To date, there has not been a consensus on the approach and monitoring of HAND. No single screening tool has been proven to be consistently superior but several groups such as

the European AIDS Clinical Society and the Mind Exchange program have provided guidance. Recently, the international consensus guidelines developed by the Mind Exchange Working Group[10]. It is recommended that all patients with HIV be screened to assess neurocognitive function using standardized tools (as described above), ideally during the first 6 months after an HIV diagnosis is made. It would be optimal for initial screening to occur before initiation of ART. The frequency of follow-up screening is dependent on several factors which include: those with lower nadir CD4+ T lymphocyte counts less than 200 cells/mm3, high plasma HIV RNA, high CSF HIV RNA, HIV-related CNS disease or history thereof, and those with HIV for longer duration. The aforementioned criteria present a higher risk group and should be monitored closely, at least every 6 to 12 months[10]. Frequency of monitoring should be increased in patients with neurocognitive decline, those not on ART, and those with poor immunologic response and incomplete virologic suppression.

A comprehensive neurocognitive or neuropsychiatric evaluation is the accepted standard for evaluation of HAND. Neuropsychiatric evaluation should address five neurocognitive domains including verbal/language, attention/working memory, abstraction/executive function, learning/recall, speed of information processing, and motor skills. Differentiating HAND from other neurodegenerative disorders may prove difficult as oftentimes non-HAND neurocognitive disorders may occur concurrently. Also accompanying the neuropsychiatric evaluation should be an evaluation of prior substance abuse.

ANTIRETROVIRAL STRATEGIES FOR HAND

Antiretroviral CNS pharmacokinetics: In the pre-ART era several studies showed that CSF HIV RNA levels correlated with severity of HIV-associated dementia[13]. Inhibition of HIV replication in the CNS is probably critical in treating patients who have HIV-associated neurocognitive disorders. The development of novel agents has expanded antiretroviral treatment choices, improving the survival and quality of life of patients infected with HIV. But despite potent suppression of HIV RNA in the plasma, low-level viral replication in the CNS may still persist[3]. As a sequestered viral ‘sanctuary’ site, it is well known that viral replication in the CNS may be sub-optimally controlled due to limited penetration of ARVs. Treatment with ARVs that have greater distribution into the CNS (CNS penetration) has been associated with better neurocognitive outcomes in some trials. Although there has been conflicting data[43], most recently a large cohort study demonstrated better neurocognitive outcomes after 6 weeks of combination ART that contained ARVs with higher CNS penetration[44]. Accordingly, the behavior of ARVs in the CNS has been an area of immense research for over 20 years. The interaction of these agents with the blood-brain barrier (BBB) and blood-CSF barrier is rather complex, and there is still much to be understood. The degree to which individual agents permeate the CNS is dependent on multiple elements including the drug’s degree of ionization, lipophilicity, protein-binding, molecular size, and affinity for specific transmembrane carriers[45]. Letendre et al. have proposed a scoring system of CNS penetration effectiveness for individual agents[46, 47]. With some exception, nucleos(t)ide reverse transcriptase inhibitors (NRTIs) have the most favorable scores as a class. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have moderate penetration, and protease inhibitors (PIs) have the least[45]. For treatment of patients with HIV-related dementia, CNS opportunistic infections, and other HIV encephalopathy, it may be prudent to select an ARV combination with favorable CNS properties. The ensuing review will discuss pertinent pharmacokinetic properties of ARV agents, the ARV and CNS interface, and summarize the existing data on ARV CNS pharmacokinetics with special focus on newer agents.

Scoring System for ARV CNS properties: Favorable properties for drug transit across the BBB would be low molecular weight, neutral or low degree of ionization, high lipophilicity, and low protein binding. Additionally, cerebral blood flow and degree of inflammation are patient-specific factors that influence drug transport across the BBB. Evidence shows there is a direct correlation between CNS drug levels and viral suppression in this sequestered anatomical site[46, 48, 49]. Letendre et al. suggest a scoring system of 1 to 4 points assigned to each antiretroviral to characterize the degree of CNS activity, known as the CPE score (see table 1). A higher CPE score indicates more favorable CNS activity, and has been shown to have strong correlation with control of CNS viral RNA. Indeed, this system has been used by various researchers as a basis for clinical investigations[49]. Although ARV drug levels in CSF are much lower compared to levels in plasma, the pivotal issue is whether these low levels are still sufficient to inhibit HIV replication in the CNS. Unlike the plasma which contains copious amounts of the binding proteins albumin and alpha 1-acid glycoprotein (AAG), it should be noted that nearly all of drug in CNS is protein-unbound and therefore pharmacologically active.

Drug Movement across the CNS: In characterizing drug movement across the CNS, a series of complex interactions take place at the BBB and blood-CSF barrier which may further inhibit antiretroviral entry. In general, ARVs enter via passive diffusion or active transport. In passive diffusion, ARV medications with low protein binding, low molecular size and higher lipid solubility tend to penetrate more easily. It should be mentioned however, that extremely high lipophilicity of certain compounds may actually cause the agent to become entrapped within the lipid bilayer and prevent it from becoming pharmacologically active. The BBB is comprised of cerebral capillaries. Capillary endothelial cells are joined together by tight junctions that allow selective entry of drugs and other molecules. Similarly, the blood-CSF barrier is mainly composed of tight junctions residing on the apical surface of the choroid plexus epithelial cells, separating circulating blood from ventricular CSF flow[45, 50]. As the integrity of these barriers is compromised during inflammation, they become more porous to both HIV infected cells and antiretroviral drugs[50].

Working in conjunction with the BBB to limit passage of nutrients, drugs, and other molecules are various known transport proteins. Most important for restricting the carriage of ARVs across are the active efflux transporters (AET)[50]. These efflux transporters are capable of targeting multiple drugs. Of these, P-glycoprotein (P-gp) has been well-described and is the best understood. It functions as a transmembrane efflux protein found in sites such as the liver, kidney, small intestine, lymphocytes, microglia, and the BBB[50]. Interestingly, P-gp expression is altered by acute inflammation in the setting of common CNS diseases[51]. In an experimental model, downregulation of P-gp was seen following administration of bacterial endotoxin-lipopolysaccharide into rat ventricles[52]. But in a separate study, these authors later demonstrated that after the initial inflammation stage and P-gp downregulation, what follows is a rebound increase in P-gp expression and efflux activity[53]. These findings suggest that acute CNS inflammation presents a small window of opportunity for drug passage, but as chronic inflammation takes hold, P-gp substrates will later have limited ability to cross the BBB. Furthermore, in vitro and in vivo experiments have indicated that most ARVs tend to alter CNS barrier transporter activity via either inhibition or induction. This is particularly evident in protease inhibitors[54]. Knowledge about P-gp and other transporters (i.e. MRPs, OATs, OATPs, BRCP, OCTs) has prompted further research in examining methods to modulate these proteins and drug entry.

Nucleos(t)ide Reverse Transcriptase Inhibitors: As a class, the nucleoside reverse transcriptase inhibitors (NRTIs) have shown favorable CNS pharmacokinetics. Zidovudine, stavudine, didanosine, abacavir, and lamivudine have all proven to achieve good CSF

levels[55]. Early experience with zidovudine from 1987 to 1997 demonstrated that its use improved neuropsychological symptoms of HIV disease. A number of studies have shown that zidovudine significantly improves cognition, motor skill function, and reduces p24 antigen in CSF. This benefit seems to be dose-related, with hematologic toxicity being the most frequent dose-limiting problem[55]. The duration of this benefit persists for only 6–12 months in most patients, but these studies used zidovudine monotherapy to treat HIV. Additionally, several autopsy studies examining brain tissue of patients treated with zidovudine showed less parenchymal injury (multinucleated giant cells, diffuse myelin pallor, diffuse white matter damage, or microglial nodules). This difference was most pronounced when patients took zidovudine for over 1 year and until shortly before death[55]. The notable exception in this class of antiretroviral agents is tenofovir which does not consistently reach the half maximal inhibitory concentration (IC50) for the wild-type virus, and therefore is not ideal for treating CNS viral replication[45]. In a recent multicenter study, 77% of CSF levels drawn from 183 patients did not meet the wild-type IC50. Median CSF to plasma ratio was 0.057 (range 0.03–0.1; n=38)[56]. The NRTI emtricitabine (which is available in various co-formulations with agents such as tenofovir, efavirenz, rilpivirine, and elvitegravir) has not undergone extensive study in regard to CNS pharmacokinetics. In a pilot study of 21 patients taking emtricitabine/tenofovir combination, Calcagno et al. found that emtricitabine levels reached a median of 68 ng/ml (range 2.5–98) in the CSF, exceeding the wild-type IC50. The CSF to plasma ratio was 0.26 (range 0.05–0.41). It should be mentioned that 9 (42.8%) of the 21 patients studied had some degree of BBB damage as evidenced by altered CSF albumin and immunoglobulin G (IgG), findings that would favor drug transport. Interestingly, tenofovir levels achieved a median 6 ng/ml (range of <2–8), and CSF to plasma ratio was 0.05 (0–0.13). Though tenofovir is not expected to reach adequate CSF concentrations, this study showed that a compromised BBB could increase tenofovir penetration[57].

Non-Nucleoside Reverse Transcriptase Inhibitors: Studies among the non-nucleoside reverse transcriptase inhibitors (NNRTIs) have shown that this class exhibits moderately good CSF penetration. Of the commonly used agents, nevirapine achieves the highest levels, followed by efavirenz, and followed by etravirine[47]. Data on the newest agent rilpivirine is not yet available. The level of efavirenz in CSF only measures 0.5% that of plasma, but this value still exceeds the wild-type IC50[58]. Etravirine CNS pharmacokinetics was recently studied in 12 treatment-experienced patients. The median treatment period was 34 weeks (range 4–140 weeks). In all CSF samples drawn, the median etravirine CSF concentration was 7.24 ng/ml (range 3.59–17.9) surpassing the IC50 range of 0.39–2.4 ng/ml. Correspondingly, the CSF to plasma ratio was 0.01 (range 0.005–0.03), and CSF to free plasma level yielded an impressive ratio of 12.06. Despite etravirine being 99.9% protein-bound in plasma, this study shows that effective levels are still achievable in CSF. This finding is further supported by the fact that etravirine is not a substrate of P-gp, and consequently is not susceptible to efflux by this transport protein[59]. In contrast, Nguyen et al. discovered that only a very small proportion of unbound etravirine reaches the CNS, which is consistent with its characteristic high protein binding. They found that 98.4% of this agent was bound to protein in the CSF. Though total CSF levels exceeded the IC50 for all 17 samples tested, the unbound portion fell below IC50 for all 17 CSF samples[60]. Hence this study shows that etravirine perhaps behaves differently than other ARVs in that it remains predominantly bound even in the CSF.

Protease Inhibitors: The HIV protease inhibitors (PIs) generally are poor candidates for transport across the BBB and blood-CSF barrier. They have good lipid solubility but despite this, are generally over 95% protein-bound (indinavir is the exception). Among ARVs, they also have the highest molecular size which significantly hinders CNS penetration. Finally,

their high affinity for P-gp means they seldom achieve high concentrations in the CNS compared to other antiretroviral compounds. Ritonavir is a potent inhibitor of P-gp and therefore improves CNS levels of other PIs when used as a booster. Indinavir is only 60% protein-bound and achieves the highest CSF concentrations of all PIs, surpassing the IC95 (concentration at which 95% of virus is inhibited)[45]. Newer PIs that have been studied include lopinavir, atazanavir, fosamprenavir, and darunavir. Several studies have concluded that ritonavir-boosted lopinavir consistently exceeds wild-type IC50 in the CNS[61–63]. On the other hand, results of studies using boosted atazanavir have been underwhelming. In 117 patients on atazanavir, ritonavir boosting did little to improve CNS concentrations. Median levels with and without ritonavir were 10.3 (range <5–38) and 7.9 (range <5–40), respectively. The CSF to plasma ratio was only 0.74%. In fact, 24% of CSF samples was completely undetectable for drug (<5 ng/ml). And 54% of all CSF atazanavir samples were below the IC50 of 11 ng/ml[64]. The authors concluded that when atazanavir is chosen as part of an ART regimen to target the CNS, other agents with superior CNS penetration should be included as well. The prodrug fosamprenavir undergoes phosphorylation into amprenavir, for which the IC50 of wild-type HIV is 5.6 ng/ml. In a study of 75 patients, amprenavir achieved a level 24.8 ng/ml (range 16.2–44.0) in the CNS, equating to a 0.012 median CSF to plasma ratio (range 0.008–0.018). Over 97% of all CSF samples in these patients exceeded the IC50. Ritonavir boosting was associated with higher plasma amprenavir concentrations, but not with higher CSF levels. The authors classified amprenavir with an intermediate ranking in relation to other PIs in terms of CNS penetration[65]. Darunavir is a very potent PI that effectively suppresses virus in both treatment-naïve and heavily treated patients. Recent data indicates that it effectively penetrates the CNS to inhibit virus there. In a study of 16 patients dosed at 600 mg twice daily with ritonavir 100 mg twice daily, darunavir had a median total level of 55.8 ng/ml (range 39.5–79.1). When examining only unbound CSF levels, the median was 50.2 ng/ml (range 35–72.6). The corresponding median CSF to plasma ratios were 0.014 and 0.085 for bound and unbound, respectively. CSF protein-binding was calculated to be 6.5% (range 3.0–9.3%). These resulting unbound CSF concentrations far exceeded IC50 and concentration at which 90% of virus is inhibited (IC90) of wild-type HIV by over 20-fold. The authors concluded that darunavir has intermediate penetration into CSF based on fractional penetrance, reaching higher levels than atazanavir, lopinavir, and amprenavir, but lower than indinavir[66]. Yilmaz et al. had similar findings in their study of 8 patients on darunavir with ritonavir boosting as part of combination ART. Median CSF to plasma ratio was 0.9% (range 0.3 to 1.8%). All samples collected had concentrations within the protein-adjusted IC50 range of 12 to 55 ng/ml, or exceeded it[67]. Another question is whether once-daily or twice-daily dosing of darunavir provides superior CSF levels. In clinical practice, once-daily is preferred for treatment-naïve patients, while twice-daily is recommended for treatment-experienced patients. This was addressed in a comparative study of 41 patients. All subjects received ritonavir concomitantly either once-daily or twice-daily with darunavir. Results showed that darunavir/ritonavir once-daily produced significantly lower CSF darunavir trough concentrations compared to twice-daily therapy [10.7 ng/ml (range 6.7–23) vs. 38.2 (range 30.2–52.3); P=0.0004]. Comparison of CSF to plasma ratios favored the twice-daily group as well (median 0.9% vs. 0.32%). Furthermore, CSF viral escape, defined as HIV RNA undetectable in plasma, but detectable in CSF, was seen in 5 of 25 (20%) patients in the once-daily arm, compared to only 1 of 13 (7.7%) in the twice-daily arm[68]. Tipranavir, which is indicated for HIV patients who have failed prior PI based regimens, has no data available yet on CSF pharmacokinetics. However, like predecessors in its class, its overall pharmacokinetic profile does not predict extensive CNS penetration.

Fusion and Entry Inhibitors: Enfuvirtide is a fusion inhibitor which is indicated for HIV patients who have failed prior ART regimens and has limited data on CNS pharmacokinetics. 2 small case series showed similar results. In a brief report, van Lelyveld et al. presented a highly treatment-experienced patient who was started on maraviroc, enfuvirtide, tenofovir, zidovudine, and lamivudine salvage therapy. Rapid immunologic recovery was seen and his CD4 count increased from 38 cells/mm3 to 579 cells/mm3. In contrast, HIV RNA decline was much slower, but did eventually reach undetectable levels in plasma. After several months on this regimen, the patient then developed sensory and gait disturbances prompting a full neurological workup. Analysis of the CSF revealed HIV RNA of 2780 copies/ml, indicating low-level replication. Enfuvirtide levels were 3.74 and 0.055 mcg/ml in plasma and CSF, respectively. Genotypic testing revealed the enfuvirtide-related V38A mutation in CSF HIV RNA. Paradoxically, full analysis of the concurrent plasma sample did not show any enfuvirtide mutations. In fact, only when ARV therapy failed 11 months later did genotypic testing finally detect the V38A mutation in plasma. The authors concluded that continued CSF viral replication in the presence of inadequate enfuvirtide levels resulted in selection of drug-resistant virus in the CSF. The patient developed enfuvirtide-resistant HIV-1 in the CSF first and then proceeded to have resistant virus in the plasma.[69] Likewise, another small patient study found low CSF levels of enfuvirtide that did not reach the assay detection limit, and the authors concluded that this agent is not ideal in clinical situations where CNS drug exposure is critical[70].

Enfuvirtide is also limited because it is only available as a subcutaneous injection, and is associated with injection site reactions. Maraviroc is a novel CCR5 co-receptor antagonist and blocks HIV entry into cells that express CCR5 co-receptors. A number of pharmacokinetic studies have examined the disposition of this agent in the CSF[71–74]. It is a substrate of P-glycoprotein, which might limit its transport across the CNS. In a small study of 7 patients, the median CSF concentration was found to be 3.63 ng/ml (range 1.83–12.2). All samples collected surpassed the median effective concentration at which 90% of virus is inhibited (EC90) of 0.57 ng/ml. Median CSF to plasma ratio was 0.03 (0.01–0.10). 2 patients on concomitant ritonavir exhibited the highest CSF maraviroc levels despite being on low doses of maraviroc. Ritonavir not only boosts maraviroc levels via cytochrome P450 (CYP) 3A4 interaction, but is also a potent inhibitor of P-gp. The authors also noted an increase in the maraviroc CSF levels with increased sampling time, suggesting that this agent may have a longer elimination half-life in the CNS[71]. In a separate study, this agent was part of a salvage combination ART regimen in 12 treatment-experienced HIV patients who underwent CSF drug analysis. The median CSF concentration was 2.585 ng/ml (range <0.5–7.22) which exceeded the median plasma-adjusted EC90 of 0.57 ng/ml. All but 1 CSF sample exceeded the aforementioned median EC90. The corresponding CSF to free plasma ratio was 0.094, indicating that maraviroc has good CSF penetrating ability[72]. A third study similarly confirmed that median maraviroc CSF concentration was 2.4 ng/ml and CSF to free plasma ratio was 0.19[73].

Integrase Inhibitors: Among the newer agents, raltegravir is a novel integrase inhibitor which prevents viral DNA insertion into the human cell genome. It has lower plasma protein binding (83%) compared to other ARVs and is believed to be a substrate of P-gp transport. The CNS pharmacokinetics of 16 treatment-experienced patients was studied. The IC95 of raltegravir is 15.0 ng/ml and was used as the reference to measure *in vitro* activity. All 25 CSF samples taken had detectable raltegravir levels, but only 13 (52%) of them reached levels above the IC95. The overall median concentration was 18.4 ng/ml (range <2.0 to 126.0)[75]. A later study also examined raltegravir in the CNS, but used the lower IC50 threshold of 3.2 ng/ml. In 17 patients, 21 CSF and plasma sample pairs were drawn. The median concentration in CSF was 14.5 ng/ml (range 9.3–26.1). Median CSF to plasma ratio was 0.058 with higher ratios seen later in the dosing interval[76]. Results in this study were

comparable to those achieved by Yilmaz et al. It is worth noting that two different inhibitory concentration standards were used in these 2 studies. Yilmaz et al. used the more rigorous IC95, rather than the more commonly used IC50. If IC50 had been the reference, then 80% of CSF samples in the Yilmaz et al. study would have exceeded this value. At the time of this writing, there is no available CNS data on the newly approved combination ARV containing the integrase inhibitor elvitegravir, combined with cobicistat, tenofovir, and emtricitabine.

Targeted Therapies for HAND

Recent and past clinical therapeutic trials for the treatment of HAND have focused on drugs as adjuncts to current ART, and although only modest success with adjunctive therapies has been achieved, the need for more effective protection against HAND has clearly been recognized. Some adjunctive therapies to HAART studied thus far include NMDA antagonists, calcium channel blockers, antioxidants, and anti-inflammatory drugs that either specifically or non-specifically target suspected key pathways in HIV-induced neuronal injury. The focus will be on previously used non-ART therapies: selegiline, memantine, minocycline, and nimodipine.

Selegiline is a monoamine oxidase B inhibitor capable of decreasing oxygen-free radicals, increasing the formation of the antioxidant enzymes superoxide dismutase and catalase, and providing additional neuroprotection by enhancing the synthesis of neurotrophic factors.

Previously trials had suggested improvements of verbal memory and motor/psychomotor performance, warranting a larger study[77]. Clinical Trial A5090 results demonstrated no significant benefit in either cognitive or functional outcome in subjects treated with selegiline compared with those who received placebo[78]. However, it is possible that the exposure to selegiline in A5090 was too short to translate into a measurable cognitive or functional effect. The open-label extension of A5090 did not fully address this issue. A substudy of A5090 was conducted using magnetic resonance spectroscopy and CSF protein carbonyl concentration nas biomarkers of CNS injury. The study found that the selegiline transdermal system (STS) had no effect on either improvement in brain metabolites (as measured by MRS) or decreases in oxidative stress levels (as measured by CSF protein carbonyl concentrations) when compared with placebo[79].

Memantine is a voltage-dependent, open channel uncompetitive low affinity antagonist of theNMDA receptor that decreases prolonged conductance of calcium via a simple uncompetitive bimolecular reaction with the receptor that does not appear to interfere with physiological function[80]. It is currently approved by the US Food and Drug Administration (FDA) for treating Alzheimer’s disease[81] and has been shown to be neuroprotective against HIV neurotoxicity *in vitro* and in animal models[82].

ACTG trial 301 results were reported by Zhang et al. to evaluate the long-term safety and efficacy of memantine use as treatment of HIV-associated cognitive impairment. While there was a statistically significant improvement in cognitive scoring using the Global Z scores (NPZ-8) in the memantine arm as compared to placebo. During the initial 12 week period, the difference in NPZ-8 was not sustained at the 48 week follow-up[83].

Minocycline is a second-generation tetracycline antibiotic derivative. In addition to the antibiotic properties of this molecule, it also potentially has protective and anti-inflammatory effects in the CNS. Its affects has been observed in both brain injury models and in vitro suppression of HIV. In addition, its excellent penetration of the BBB and relative safety profile make it a favorable therapy for use. In a study by Sacktor et al., HIV-1-infected individuals with progressive neurocognitive decline were enrolled in a

double-blind, placebo-controlled study of minocycline. Participants were randomized to receive minocycline 100 mg or matching placebo orally every 12 hours. The primary efficacy measure was change in a neuropsychological test composite *z* score from baseline to week 24. The investigators concluded at the end of 24 weeks of therapy that while minocycline was safe and well-tolerated in individuals with HIV-associated cognitive impairment, cognitive improvement was not observed compared to placebo[84].

Increased amounts of calcium in the cytoplasm cause disruption of mitochondrial function and activation of a number of cellular and apoptotic pathways[85]. Thus, nimodipine, a voltage-activated calcium-channel blocker, was theorized to prevent HIV-related neuronal injury and possibly provide a novel form of treatment for HIV related neurocognitive disease. Small clinical trials of nimodipine suggested some therapeutic benefit but were not conclusive[86]. While the above targeted treatments for HAND appeared to be well tolerated, sustained neurocognitive improvement was not achieved in any of the trials. Currently no targeted therapies other than ART is recommended for routine treatment of HAND[87].

Current and future directions—As the understanding of ARV pharmacokinetics in the central nervous system continues to evolve, the proper selection of agents can be optimized. The complexity of the interaction between the drug, BBB, and blood-CSF-barrier makes it difficult to predict which agents will cross adequately into the CNS. Powerful transporters located on the surface of these barriers inhibit drug entry and can be difficult to overcome. Current research in the field of nanotechnology will hopefully provide answers to improve drug transport across physiologic membranes like the CNS. Advanced nanomedicines using polymeric nanoparticles, liposomes, lipid nanoparticles, and micelles can facilitate drug transport across the CNS[88]. Nanoparticles loaded with various protease inhibitors have already been shown to improve drug bioavailability to the brain[50].

To date, there are no studies that demonstrate superiority of a specific combination ART regimen for the prevention or treatment of HAND. Additionally, it is unclear whether virologic suppression in the CNS compartment translates into a clinical benefit with regard to management of HAND. It is the opinions of the authors that it is reasonable to use combination ART regimens that include agents that have a favorable CNS pharmacokinetic profile in the setting of a HAND diagnosis–as long as the HIV genotype in the plasma compartment supports the use of these agents. Based on the data provided above, it appears that most of the NRTIs are “appropriate”; however, taking into consideration toxicity profiles (such as peripheral neuropathy), recommended NRTIs would include zidovudine, abacavir, lamivudine, and emtricitabine. Most notably, tenofovir which is commonly prescribed as a co-formulation with emtricitabine appears to have a less favorable CNS pharmacokinetic profile. In combination with other classes, the NNRTIs are considered potent agents in serologic viral efficacy. Nevirapine may be considered as an option as part of a combination ART regimen for HAND. It is not surprising that despite etravirine being highly protein bound, it does not achieve optimal CSF levels. Efavirenz, which is often prescribed as a co-formulation with tenofovir and emtricitabine does have acceptable CSF levels. The significant CNS side effects associated with efavirenz could be problematic in the setting of HAND, and probably should be used cautiously in this patient population. Due to protein binding and large molecular size, the PIs as a class may not reach adequate CNS levels; however ritonavir boosting appears to improve drug exposure in this compartment. Of the newer PIs, twice daily dosing darunavir with ritonavir boosting and the co-formulation lopinavir/ritonavir appear to reach acceptable levels in the CNS compartment. Atazanavir which is commonly prescribed due to its convenient once daily dosing, may not be the optimal PI based regimen in patients with HAND, especially since other PIs demonstrate better CNS drug exposure. Likewise, once daily darunavir was inferior to twice

daily darunavir with regard to CNS drug exposure (both with ritonavir boosting). Although indinavir has the most favorable CNS pharmacokinetic profile for the PIs, its use has been largely replaced by the newer and better tolerated PIs. With regard to the newer agents, raltegravir may be a reasonable option; however maraviroc has demonstrated consistent CSF levels and should warrant consideration in patients who have HAND and R5 virus phenotype.

Clearly, the most important aspect of HIV management is durable virologic control within the plasma compartment which is achieved by effective agents, good adherence, tolerance of ART, and close monitoring. As stated previously, some studies have correlated virologic escape within the CSF compartment with neuro-cognitive abnormalities. It is reasonable for the HIV practitioner to re-evaluate the patient's current combination ART regimen, and consider optimizing ART CSF drug exposure in patients with a clinical syndrome compatible with HAND. The prospect for HIV has improved dramatically as better control of HIV plasma virus burden is achieved. Nevertheless, the incidence of HAND continues to rise and is associated with decreased quality of life, poor ART adherence, and increased mortality. Without compromising adequate virologic control and ability to adhere to an ART regimen, strategic treatment efforts should be made to decrease direct and indirect effects of HIV replication within the CNS.

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Table 1

CNS penetration effectiveness ranking 2010 (Reproduced with permission from IAS–USA[47])

	4 points	3 points	2 points	1 point
NRTI	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir Zalcitabine
NNRTI	nevirapine	Efavirenz Delavirdine	Etravirine	
PI	Indinavir/RTV	Darunavir Fosamprenavir/RTV Indinavir Lopinavir/RTV	Atazanavir Atazanavir/RTV Fosamprenavir	Nelfinavir Ritonavir saquinavir Saquinavir/RTV Tipranavir/RTV
Entry/fusion inhibitor		Maraviroc		Enfuvirtide
Integrase strand transfer inhibitors		Raltegravir		

Note: larger numbers reflect estimates of better CNS penetration or effectiveness (i.e. ranking of 4 indicates highest penetration/effectiveness). RTV = ritonavir; PI = protease inhibitor; NRTI = nucleos(t)ide reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor.

Table 2

Pharmacokinetic properties of antiretroviral agents

Agent	Molecular weight	Protein binding	CSF:plasma ratio	Does unbound CSF drug concentration exceed IC50?
NRTIs				
Zidovudine	267.2	< 38%	0.6	Yes
Lamivudine	229.3	< 36%	0.23	Yes
Stavudine	224.2	negligible	0.2–0.4	Yes
Didanosine	236.2	<5%	0.2	Yes
Abacavir	286.3	50%	0.36	Yes
Tenofovir	519.4	7%	0.05	No
Emtricitabine	247.24	<4%	0.26	Yes
NNRTIs				
Nevirapine	266.3	60%	0.29–0.63	Yes
Efavirenz	315.7	99.5%	0.005	Yes
Etravirine	435	99.9%	0.01	No
Rilpivirine	402.9	99.7%	unknown	unknown
PIs				
Indinavir	613.8	60%	0.11	Yes
Ritonavir	721	99%	0	No
Nelfinavir	567.8	>98%	0	No
Saquinavir	670.9	98%	0	No
(Fos) Amprenavir	585.6	90%	0.012	Yes
Lopinavir	628.8	99%	0.0023	Yes
Atazanavir	704.9	86–89%	0.01	variable
Darunavir	548	95%	0.09	Yes
Tipranavir	602.7	>99.9%	Unknown	No
Other				
Enfuvirtide	446.2	92%	0.015	No
Maraviroc	514	76%	0.03–0.19	Yes
Raltegravir	444	83%	0.03–0.058	Yes
Elvitegravir	447.9	98%	Unknown	Unknown

IC50 = half maximal inhibitory drug concentration; PI = protease inhibitor; NRTI = nucleos(t)ide reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor.