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Pharmacologic Approaches to HIV-Associated Neurocognitive Disorders

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Abstract

Antiretroviral therapy in people living with HIV can achieve potent, long-term suppression of HIV plasma viremia and has increased life expectancy. The central nervous system is infected early after virus acquisition and remains a reservoir for HIV. HIV-associated neurocognitive disorders (HAND) are an end-organ manifestation of HIV infection. The need to address neurological complications caused by HAND is significant as approximately 50% of people living with HIV on suppressive antiretroviral therapy are estimated to have some form of HAND. This review discusses the pathophysiology of HAND, CSF/CNS penetration and clinical pharmacology of antiretrovirals including pharmacokinetic/pharmacodynamic relationships, the persistence of HIV in the brain, and future therapeutic approaches to preserve and improve sustained viral suppression in the brain.

Keywords

HIV; HIV-associated neurologic complications; Antiretroviral therapy

Introduction

In this 5th decade of the HIV epidemic, and despite the success of combination antiretroviral therapy (ART) in achieving potent, long-term HIV suppression, HIV-associated neurocognitive disorders (HAND) remain common in persons living with HIV-infection (PLWH) and increase the risks of morbidity and mortality. Approximately 50% of PLWH on ART are estimated to have some form of HAND. HAND is an end-organ manifestation of HIV infection and refers to a constellation of disorders in memory, concentration, attention

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

and motor skills. In the current ART era, there has been an increase in milder forms of HAND [mild neurocognitive disorder (MND) and asymptomatic neurocognitive impairment (ANI)] and a decrease in HIV-associated dementia. Recent data suggest that even in the setting of long-term viral suppression, there is evidence for ongoing progression of HAND [1].

Within one to two weeks after acquisition of HIV, the virus disseminates throughout the body and establishes multiple reservoir sites including the central nervous system (CNS), adipose tissue, male and female reproductive tracts, the secondary lymph nodes (LN) and gut-associated lymphoid tissue (GALT). The persistence of latent virus in cells of these reservoirs is a major obstacle to virus eradication. Furthermore, these same anatomical sites may be pharmacologic sanctuaries, as evidenced by concentrations of antiretroviral drugs (ARVs) lower than those in peripheral blood, and in some cases associated with evidence for low-level ongoing virus replication [2,3].

In this review, we will discuss pharmacologic approaches to HIV-associated neurocognitive disorders (HAND) and focus on the CNS as a pharmacologic sanctuary highlighting data on penetration of newer ARVs into the CSF and CNS (pharmacokinetics, PK) and ARV-associated responses (pharmacodynamics, PD), and close with comments on future therapeutic approaches.

Antiretroviral Penetration into the CNS

Blood-Brain Barrier (BBB)

The BBB is a semipermeable border of endothelial cells that prevents entry of drugs from the blood stream into the CNS. It is comprised of endothelial cells and HIV susceptible astrocytes and pericytes. The BBB restricts entry of pathogens, diffusion of solutes and large or hydrophilic molecules into the CSF, while allowing diffusion of hydrophobic and small polar molecules [4].

Drug Penetration

The degree of drug CNS penetration is dependent on the brain's permeability attributes and various drug characteristics that include molecular weight, protein binding, ionization, and lipid-water partition coefficient [5]. A highly protein-bound drug will have a slower penetration rate. The blood-CSF barrier can play a role in CNS penetration. An in-depth description of the blood-CSF barrier has been published by Nau [6]. Higher penetration of ARVs into LN, gut and brain tissues of the BALB/c mouse model was associated with higher dissociation constant (pKa), higher lipophilicity (logP) and increased hydrophobicity [7]. The transporters, p-glycoprotein (P-gp), organic anion transporters (OAT 1,2,3) breast cancer resistance protein (BCRP), found at the BBB also influence drug penetration due to transporter-mediated efflux. This mechanism has been implicated in some refractory CNS disorders (i.e., refractory epilepsy) [8]. Transporter expression may be influenced by genetic polymorphisms.

Animal models have shown ARV CSF penetration does not always correlate with brain tissue penetration [9]. Discrepancies have been attributed to ARV affinity for drug uptake

and efflux at the BBB and blood-CSF barrier. Protein-binding plays a role as active transport of ARVs across the BBB and blood-CSF barrier disturbs the equilibrium of passive unbound drug movement (the “free drug hypothesis”), which may result in differences of ARV concentrations in plasma, CSF and brain tissues [9]. The CNS has low binding protein concentrations compared with plasma and studies of ARVs in the CSF have found the drug present is mostly unbound. However, in 17 PLWH, efavirenz had higher protein-binding in CSF (98.4%) than in plasma (96%) [10]. A methodological challenge for ARV quantitation in CSF was described by Winchester who showed non-polar ARVs can adsorb to polypropylene collection tubes [11]. This suggests some re-examination of ARV concentrations in CSF in PLWH who are/are not virologically-suppressed may be warranted.

ARV Classes and CNS Penetration

Table 1 gives a summary of select CSF penetration characteristics of ARV that are recommended for first-line regimens for treatment-naïve PLWH. Highlights of select features follow.

Nucleoside reverse transcriptase inhibitors (NRTIs).—Zidovudine has the best CNS penetration rank in brain and CSF and remains used today in PLWH who have symptomatic CSF escape [12,13]. Tenofovir can be given as tenofovir disoproxil fumarate (TDF) or as tenofovir alafenamide (TAF). TDF achieves higher CSF concentrations than TAF, based on a single PLWH who switched from a TDF- to a TAF-containing regimen and tenofovir CSF concentrations decreased from 3.30 to 0.46 ng/mL [14]. NRTIs are transported via OATs and changes in their activity due to co-administered drugs (e.g., probenecid) or genetic polymorphisms can affect the CSF concentrations of certain NRTIs [15].

Protease Inhibitors (PI).—As a class, PIs achieve poor CSF exposure, although some, for example lopinavir, achieve CSF concentrations above the IC_{50} . PI CSF penetration can be increased with low-dose ritonavir or cobicistat co-administration [16,17]. Atazanavir CSF concentrations increased with ritonavir (from 7.9 to 10.3 vs. ng/mL), but did not always exceed the IC_{50} [18]. A study in PLWH showed darunavir CSF concentrations were comparable when co-administered with either cobicistat or ritonavir (15.9 ng/mL vs. 16.4 ng/mL, $P=0.58$) [17]. PIs are substrates for P-gp, OAT1 and OAT2; similar to NRTIs, this can decrease their CSF penetration [19–21].

Non-nucleoside reverse transcriptase inhibitors (NNRTIs).—Among the class, nevirapine has the highest CSF penetration [22]. Efavirenz CSF concentrations are generally sufficient to suppress HIV in the CSF [23]. Srinivas found CSF concentrations of 6 ARVs (tenofovir, emtricitabine, raltegravir, maraviroc, atazanavir and efavirenz) were >13-fold lower than brain tissue in nonhuman primates, with poor agreement between CSF and brain tissue except for efavirenz ($r=0.91$, $P<0.001$) [9]. Efavirenz CSF concentrations were $>IC_{50}$ in twelve PLWH and viral suppression was achieved in both plasma and CSF [12]. A recent study in PLWH receiving intramuscular rilpivirine (and cabotegravir) found CSF concentrations were 1.1–1.3% of plasma and exceeded the IC_{50} [24].

Integrase strand transfer inhibitors (INSTIs).—Raltegravir CSF concentrations exceed the IC_{95} and is used in regimens designed for improved CSF penetration. The fractional CSF penetration of dolutegravir is low, though concentrations were above the IC_{50} [5]. This scenario is similar for bictegravir, with CSF concentrations above the IC_{50} in 15 PLWH [25]. There are limited CSF penetration data on injectable cabotegravir (not FDA approved as of May 1, 2020). Cabotegravir CSF concentrations were 0.3% of plasma and exceeded the IC_{50} in 16 PLWH, who all had HIV-RNA <50 copies/mL in plasma and CSF [24].

Antiretroviral Clinical Pharmacology in the CNS

A goal of ART is to inhibit HIV replication throughout the body and maintain an undetectable viral load. This is achieved by optimizing PK/PD parameters such that sufficient concentrations are achieved to inhibit viral replication and minimize emergence of viral resistance, and so that the drug is safe and well-tolerated. The inhibitory quotient (IQ) is a useful concept to achieve the former; it is the ratio of drug concentration achieved to the in-vitro inhibitory concentration. The inhibitory concentration is commonly the level at which 50, 90 or 95% (IC_{50-95}) of in-vitro viral replication is inhibited utilizing wildtype viruses. These in-vitro concentrations are often obtained in protein-free conditions, which for clinical translation of highly protein-bound drugs to concentrations necessary in plasma, requires protein-binding adjustment. Binding in the CSF, however, may be different from plasma. CNS PK/PD endpoints are further complicated as no clear exposure thresholds have been identified. CSF HIV-RNA is used as a marker of antiviral activity given its established dose-concentration-response relationship for ARVs in plasma. Further, it is been shown to correlate with cognitive improvements in patients with HAND [5].

CNS Penetration-Effectiveness Score (CPE)

The CPE was developed in 2008 to classify ARV penetration and effectiveness in the CNS. Methodologically, each drug is given a rank from 1 to 4 based on PK/PD data, drug characteristics, clinical studies, and effectiveness in reducing CSF viral load or improving cognition. The composite CPE score for an ART regimen is the sum of ranks for each drug. Regimen scores are classified as low (<8), medium (8–9), or high (>9). Conceptually, the CPE is an attractive tool, however, limitations exist [5]. Studies have shown a higher CPE score results in lower CSF HIV-RNA and a correlation between CPE score and CSF escape; however, these associations have not been uniformly observed [5].

CNS Toxicity of ART

A complete understanding of the CNS toxicity profiles for most ARVs is lacking. In-vivo data have shown ARVs, such as tenofovir, ritonavir, saquinavir, and atazanavir can produce neuronal damage due to accumulation of reactive oxidative species [26]. Other studies have shown the potential for ARV to reach toxic concentrations without additive effects with combinations used clinically [5].

PLWH are at increased risk for ischemic cerebrovascular disease, brain opportunistic disease, cardiac embolisms, and hypercoagulopathy. Cerebral small vessel disease (CVSD)

has been associated with ischemic stroke and cerebral infarction. Mild/moderate/severe small vessel diseases has been associated with PI-based ART and HAND was associated with mild CSVD [27]. The clinical CNS adverse effects of efavirenz are well characterized. Efavirenz has been associated with the diagnosis of HAND in PLWH [27]. A recent study in PLWH found associations among ARV use and aging-related brain changes [28]. Darunavir and ritonavir were associated with an increased risk of aging-related changes; TDF with a lower likelihood of B-amyloid plaque deposition in the frontal cortex; and there was a trend between emtricitabine use and CSVD. PLWH had greater improvement of cognitive function when coming off efavirenz versus other ARVs [5]. 36% (108/300) of Ugandan patients on efavirenz were affected by persistent nervous system/psychiatric adverse reaction for a median duration of 22 months [29]. Even asymptomatic PLWH had improved neuropsychological parameters associated with decreased CNS oxidative stress, excitatory neuronal activity, and decreased immune activation when switched off efavirenz [30]. There are emerging CNS toxicity data with INSTIs. High discontinuation rates have been observed with dolutegravir due to insomnia, sleep disturbances, and other neuropsychiatric adverse effects compared with other INSTIs. 61,938 ARV-naïve individuals who started ART were followed for a median of 37 months for the occurrence of four neuroAIDS conditions [31]. Those with a high CPE regimen had an increased risk for developing dementia (HR, 1.74; CI, 1.15–2.65). Zidovudine and efavirenz were commonly used in high CPE regimens; both are associated with high rates of treatment-limiting side effects and neither are recommended first-line regimens in most ART-naïve persons. The extrapolation of these findings to a contemporary high CPE regimen is questionable.

HIV Persistence in the CNS/CSF

HIV infects perivascular macrophages, microglial cells and astrocytes at an early stage of infection [32]. Several lines of evidence suggest the brain represents a persistent and stable HIV reservoir. CSF viral escape is the presence of quantifiable CSF HIV-RNA in persons with undetectable plasma HIV-RNA or levels of CSF HIV-RNA that exceed plasma [33]. A recent study detected CSF viral escape in 55 (4.4%; 95% CI, 3.4–5.6) of 1264 PLWH who had plasma HIV-RNA <50 copies/mL [34]. CSF viral escape was independently associated with use of ritonavir-boosted PIs and unboosted atazanavir. There were similar rates of neurocognitive impairment in those with (38.2%) and without (37.%) CSF escape. Not all cases of CSF viral escape are symptomatic; however, those that are would seem to provide strong evidence of a CNS viral reservoir containing replication competent virus [13].

The extent and significance of HIV persistence in the CSF in PLWH who have long-term plasma HIV-RNA suppression has not been well-described. HIV persistence and biomarkers of immune activation in CSF and neuropsychological evaluations were performed in 69 PLWH on long-term (median of 8.6 years) ART with viral suppression (67/69 with plasma HIV-RNA <40 copies/mL; 2 <100 copies/mL). HIV-DNA was detected in CSF in 48% [35]. The presence of CSF HIV-DNA was associated with significantly poorer neurocognitive dysfunction. CSF levels of immune activation (e.g., neopterin) were not associated with CSF HIV-DNA detection. Animal models provide important evidence on HIV replication and establishment of viral reservoirs in the brain. In SIV-infected rhesus macaques (RM), in-vivo imaging showed vRNA-positive cells were higher in brain tissues, likely due to poor ARVs

penetration [2]. After six-months of ART, only two-fold decrease in vRNA-positive cells was observed in brain versus >30-fold decrease in vRNA-positive cells in other LT compartments [2]. In SIV-infected pigtailed macaques (PTMs) receiving ART, 56% developed lymphocyte dominant encephalitis and meningitis due to infiltration of B and T immune cells [36]. These findings suggest that dysregulated immune responses in PLWH might contribute to the development of HAND. Recently, the majority of ART-treated, virally-suppressed PTMs were shown to have replication-competent SIV in brain macrophages [37]. These data strongly indicate presence of a macrophage latent reservoir in the brain that could reestablish infection after treatment interruption. Collectively, these data argue the CNS has continued viral replication, is a viral reservoir and pharmacologic sanctuary, and therefore, an obstacle to overcome to optimize neurocognitive function and achieve HIV eradication.

Future Therapeutic Approaches

Therapeutically, one, of several challenges, is how to improve ARV activity and outcomes in the brain without causing unacceptable side effects. A partial list of pharmacologic strategies includes early ART, simplification, treatment intensification and reversal of HIV latency.

Early ART

The benefit of early ART initiation during acute HIV-infection (AHI) was investigated in persons who started ART a median of 17 days from estimated time of infection [38]. Most (64.4%) received a regimen of efavirenz/TDF and either lamivudine or emtricitabine. Some (34.7%) also received maraviroc and raltegravir for the first 24 weeks. At weeks 24 and 96 of ART, CSF HIV-RNA was <80 copies/mL in 100% and 95%, respectively, and plasma was <50 copies/mL in 91.1% and 98.6%, respectively. CSF markers of immune activation (e.g. neopterin) decreased from baseline to week 96 to levels not different from HIV-negative controls. In contrast, plasma levels of the same markers, with the exception of IL6, while lower than baseline, remained significantly elevated compared with HIV-negative controls. The authors concluded a likely explanation for the different responses was because early ART reduced the size of the CNS latent reservoir. There was also evidence of a greater reduction in immune activation with the addition of maraviroc and raltegravir. It is unknown, but worthy of investigation whether early ART might prevent development of HAND.

Simplification

Adherence, side effects and quality of life are major factors contributing to long-term ART success. For PLWH who have HAND, a regimen easier to adhere to, that reduces side effects and improves quality of life might improve virologic control. There are efforts to simplify ART regimens, as evidenced by approval of two-drug regimens, dolutegravir/lamivudine and dolutegravir/rilpivirine and the anticipated approval of once-monthly intramuscular cabotegravir/rilpivirine. These two-drug combinations were non-inferior to three-drug regimens in plasma HIV-RNA suppression. However, little is known about long-term activity in other compartments, including the CNS and until data are available, these two-drug combinations might not be optimal choices for PLWH and HAND [39–41].

Intensification: regimen intensification, higher CPE, and CNS-targeted therapy

Accumulating evidence suggests increasing the CNS-activity of ART is associated with improved clinical outcomes. Maraviroc has good CSF-penetration and anti-neuroinflammatory properties. A small, randomized study compared maraviroc-intensified ART with an existing regimen in men with plasma HIV-RNA <50 copies/mL and HAND [42]. At 6- and 12-months of therapy, those who received maraviroc-intensified ART had clinically-relevant improvements in neurocognition, but there were no changes in CSF neopterin and β 2-microglobulin (37). Other strategies to enhance drug activity in the CSF include brain-targeted drug delivery. Nanoformulated elvitegravir was shown to achieve improved BBB penetration and anti-HIV activity in an in-vitro BBB model [43]. Nanoformulations are an exciting future approach to enhance CNS drug delivery and a comprehensive review has been published by Saxena [44].

Separate from the single-drug intensification strategy is ART regimen CSF intensification. 401 PLWH taking ART underwent 2207 assessments including neurocognitive and lumbar puncture (not done in all) over an average of 2.5 years. Failure to achieve plasma HIV-RNA <50 copies/mL was the strongest predictor of detectable CSF HIV-RNA. Other significant predictors were a lower CPE score for the ART regimen and PI-containing ART [45]. These data provide some guidance for ART regimen design for PLWH and HAND.

Reversal of HIV latency

Reversal of HIV latency with latency-reversal agents (LRAs) is an investigational strategy to reduce or eliminate viral reservoirs in PLWH [46]. Work to date with histone deacetylase inhibitors, including in combination with therapeutic vaccination, has not reduced the HIV reservoir [47]. Recently, AZD5582, which activates non-canonical NF- κ B signaling pathway, showed activation of latent proviruses in peripheral blood and in tissues including LT of ART-suppressed HIV-infected BLT mice and SIV-infected RMs. An 8.7-fold increase in viral gag RNA was observed in the brain of BLT mice [48]. LRAs that penetrate brain tissues may provide an important approach to clear the brain viral reservoir, reduce HAND and pave a pathway to eradicate HIV-infection.

Conclusions

HAND remains a significant problem in PLWH. ART CSF/CNS penetration is an important consideration to maximize virologic suppression and optimize neurocognitive function. The use of newer ARVs with enhanced CNS penetration/activity should be assessed in prospective studies. Continued work on drug delivery strategies to target the CSF/CNS is essential. Finally, approaches to reduce or clear viral reservoirs must include a focus on the brain and thereby, have the potential to optimally treat HAND.

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Table 1.

CSF Pharmacologic Characteristics of Antiretroviral Drugs

Drug Class	Protein Binding (%)	Protein Free IC ₅₀ (ng/mL)	CSF Concentration (ng/mL) Median values	CSF IQ	CPE
NRTIs					
Abacavir [5,49]	50	72	128	1.78	3
Lamivudine [5]	16–36	21	95	4.5	2
Emtricitabine [50]	<4	70	68	0.97	3
Tenofovir Disoproxil Fumarate * [50]	<7	11.5	6	0.52	1
Tenofovir Alafenamide * [51]	80	1.4	0.46	0.64	NA
NNRTIs					
Doravirine	76	1.74	NA	NA	NA
Efavirenz [5,52]	99.78	1.3	18.8	14.5	3
Rilpivirine [24,53]	>99	0.27	0.8	3.0	NA
INSTIs					
Bictegravir [54]	>99	1.1	6.9	34.5	NA
Dolutegravir [5]	>98.9	0.2	18.2	91	NA
Raltegravir [5,55]	83	3.6	31	8.6	3
Cabotegravir (IM admin) [24]	>99	0.10	Q4: 12.7 Q8: 10.6	127	NA
PIs					
Atazanavir [56]	86	1.7	7.9	4.65	2
Darunavir [56]	95	0.4	30	75	3
CCR5I					
Maraviroc [57]	76	0.26	2.4	9.2	3

Abbreviations: NRTIs, Nucleoside reverse transcriptase inhibitors; NNRTIs, Non-nucleoside reverse transcriptase inhibitors; INSTIs, Integrase Strand Transfer Inhibitor; IM, Intramuscular; PIs, protease inhibitors; CCR5I, C-C chemokine receptor type 5 inhibitor; IC₅₀, inhibitory concentration at which 50%, of in-vitro viral replication is inhibited; CSF, cerebrospinal fluid, EC₅₀, concentration of a drug that gives 50% response; IQ, inhibitory quotient; CPE, CNS penetration effectiveness score; NA, not available.

* Based on active moiety of TFV