Chapter 17
Antiretroviral Therapy: Brain Penetration

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Core Message
In the era of combination antiretroviral therapy (cART), advanced neurologic complications of HIV infection are less common, than pre-cART. There is evidence that antiretroviral therapy prevents, delays, and may reverse neurocognitive complications of HIV infection. However, clinical trials leading to antiretroviral drug approval primarily measure HIV in the plasma as an indicator of therapy efficacy. In this chapter we assemble and present data on CNS exposure and penetration of antiretroviral drugs.

17.1 Introduction

Prior to the introduction of combination antiretroviral therapy (cART), neurologic complications of HIV infection were common, termed overall HIV-associated neurocognitive disorders (HAND). HAND ranges from asymptomatic neurocognitive impairment (ANI), to a mild neurocognitive disorder (MND), to full-blown HIV-associated dementia (HAD) and often exhibited as HIV encephalitis (HIVE) [1, 2]. The incidence of HAND decreased over time due to the use of cART. Especially, HAD is now less common, and it is rare in patients who are clinically stable on

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cART. The incidence of HAD per 1000 person-years reduced from 6.49 in 1997 to 0.66 during the years 2003–2006; this was associated with the introduction of highly active antiretroviral therapy (HAART) or cART, as mentioned [3]. HIV-1 invades the CNS early and can cause persistent infection and inflammation [4]. HAND shows decreased association with immune activation and has a more diffuse range of neuropsychological deficits that may overlap other brain diseases and, at times, with continued association with suppressed virus loads [4, 5]. Moreover, despite the advent of cART, an overall neurologic impairment is still prevalent, in some studies; for those patients on cART, it occurs greater than 80%, especially in its milder form. Reduction of HIV viral load in the CSF alone perhaps is not the only clinical indicator of treatment efficacy for HAND [4, 6–9]. For example, there was a lack of association between neurocognitive impairment with virologic and immunological factors that indicates ongoing neural injury regardless of the success of antiretroviral therapy based on these laboratory measures [8]. In addition to HIV load levels, several studies suggest other factors including immunological, aging, persistent HIV replication in the CNS including macrophages, evolution of highly neurovirulent HIV strains, and the long-term neurotoxicity of cART [9, 10].

In this chapter, we will discuss further the effects of antiretroviral therapy on HAND and the interaction between ARVs and the brain. Most data, when indicated, were studied in HIV-1 infection.

17.2 The CNS

17.2.1 The CNS Barriers

The CNS is surrounded by the BBB and the blood-cerebrospinal fluid barrier (BCB). These barriers prevent most molecules from entering the CNS and maintain a stable environment. The BBB inhibits the free diffusion of water-soluble molecules by complex tight junctions that interconnect endothelial cells within CNS microvessels. They lack intercellular pores and have low pinocytosis activity. The endothelial cells and pericytes are enclosed by basement membranes and are almost completely surrounded by astrocyte foot processes [11]. A functional BBB has numerous active transport systems, specifically expressed by brain capillary endothelial cells to ensure the transport of nutrients into the CNS and block potentially offending molecules from CNS entry. Moreover, BBB is the passage for HIV, viral products, infected cells, and activated immune cells to penetrate to the CNS [12]. On the other hand, the BCB is formed by *choroid plexus* epithelial cells and found at the apical tight junctions between the *choroid plexus* epithelial cells. The BCB inhibits paracellular diffusion of water-soluble molecules across this barrier. In addition, it has a secretory function and produces CSF. With CNS pathology, these barrier characteristics are disrupted, leading to edema and inflammation entry into the CNS [11]. Molecular diffusion and exchange can occur in both directions and additionally via the perivascular space as well as the CSF [13].

HIV is neurotropic, as indicated by neurocognitive impairment with HIV infection of the brain, on the one hand, and by decreasing neurocognitive impairment in patients with viral suppressions from cART, on the other hand. Moreover, HIV brain invasion results in neuronal loss, synaptic and dendritic damage, astrogliosis, microgliosis, and multinucleated giant cell formation [14, 15]. HIV infection of the CNS occurs by cell-free and HIV-infected cells that migrate from peripheral blood into the CNS. Cell-free HIV particles pass through the BBB using mannose-5-phosphate receptor and tight junction dissolution [16]. Moreover, HIV proteins and HIV infection activate T cells and monocytes resulting in immune cell trafficking across the BBB. Gp120 protein is a potent neurotoxin. Circulating gp120 increases BBB permeability by downregulating tight junction proteins [17]. Tat protein itself causes oxidative stress leading to compromised BBB integrity. Nef protein not only facilitates downregulation of CD4 and increases HIV replication; it also stimulates apoptosis and induces disruption of the BBB [18]. Lastly, viral protein R (Vpr) increases permeability of the BBB and recruits monocytes and macrophages into the CNS by dysregulating the astrocyte compartment [19].

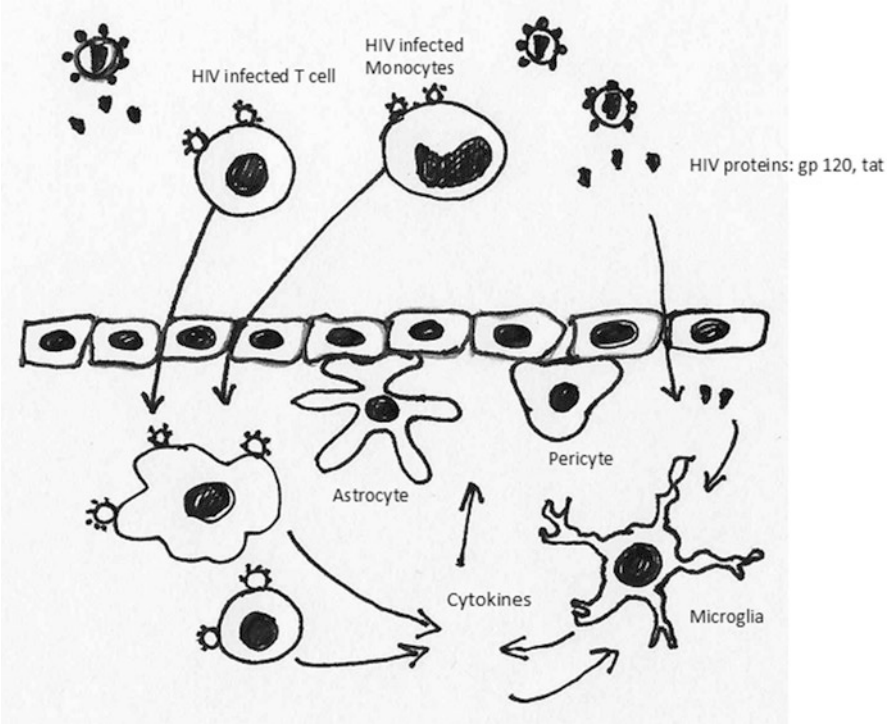

Fig. 17.1 Illustrates the mechanism of viral and cellular migration from peripheral blood into the brain. HIV, HIV proteins (gp120, tat), and HIV-infected cells can cross the BBB via transcytosis and infected microglia and astrocytes which then will be activated and release inflammatory cytokines, further activating microglia and astrocytes (Adapted from Hong and Banks [12])

Pericytes of the BBB endothelium secrete cytokines and increase HIV penetration of the BBB [16]. LPS stimulation, as a result of the increased gut microbial translocation [20], may facilitate HIV entry into the brain by inducing production and release of inflammatory mediators by brain endothelial cells. Additionally, cell-to-cell interaction facilitates HIV transmission from T lymphocytes to astrocytes. It was observed that virologic synapses formed by filopodial extensions binding of either cell type could be inhibited by anti-C-X-C chemokine receptor type 4 (CXCR4) antibody [18]. The interaction between HIV with the brain microvascular endothelial cells increases BBB leakiness, as a result, it increases brain-to-blood efflux of antiretroviral drugs [12, 18] (Fig. 17.1).

Penetrability of the ARVs across the BBB is facilitated by low molecular weight, high lipophilicity, degree of ionization, active transport pump, cerebral blood flow, and the degree of local inflammation [21, 22]. Many antiretroviral drugs, including protease inhibitors such as ritonavir and indinavir, are substrates for brain-to-blood transporters like P-glycoprotein (P-gp) [23]. Such transporters can pump the substrates out of the brain and prevent drugs from reaching therapeutic concentrations within the CNS [24].

17.2.2 The CNS as a Compartment

As mentioned above, the CNS is one of the compartments that HIV infects, and it provides sanctuary and allows independent replications. Occasionally, HIV escapes the CSF despite suppression in the plasma. It suggests that low-grade central nervous system infection may continue in treated patients and can cause further neurocognitive impairment [25, 26]. Different and inadequate penetration of antiretroviral agents can cause resistant mutations and distinct genetic profiles compared to HIV in plasma [27, 28].

17.3 cART

There seems to be an inverse correlation between concentration of antiretroviral agents in the CSF and the HIV CSF viral loads [22, 29]. Generally, the levels of ARVs in the CSF are low compared to plasma. There are questions if those ARVs in CSF are actually adequate to inhibit HIV replication. ARV concentration in the brain parenchyma is not uniform [30]. The ideal way to measure the ARV concentration in the CNS is the actual measurement of tissue concentration or the fluids (e.g., sinuses) from different parts of the brain. Such measurements are impractical in clinical settings. Most studies, however, use the ARV concentration in CSF as an indirect measurement of drug exposure, although it is unclear whether CSF concentrations accurately reflect parenchymal ARV concentrations [13].

Suppression of HIV replication requires a minimum drug concentration above the inhibitory concentrations (ICs). ICs are concentrations based on in vitro findings using HIV strains susceptible to the drug. For example, the concentration of the

drug necessary to inhibit 50% (IC50), 90% (IC90), or 95% (IC95) of viral replication is reported. For improved in vivo estimates, the corrected IC is derived by taking into account drug binding to plasma proteins, and the effective concentration (EC) is then calculated [31].

Frequently, IC50 of ARVs for wild-type HIV is often used as a reference and compared with half-maximal effective concentrations (EC50) to represent the plasma concentration [32]. However concentration of the drug necessary to inhibit 90% or 95% (IC90, IC95) offers greater accuracy. For example, for protease inhibitors, which are typically highly protein bound, the IC50 in CSF can be overestimated. It needs caution to compare IC50 values in plasma and in CSF [31, 33]. The measurement may vary depending on the methods to determine it, cell types, chronicity of infection, and HIV strains [34, 35]. Clinically, it also depends on the overall cART regimen, which may have additive or synergistic effects due to the use of multiple drugs. This rationale may be useful to treat CNS infection and to ensure that the cART regimen has adequate CNS drug levels. CNS escape, however, may occur as a result of inadequate treatment (suboptimal drug concentrations) of the CNS-compartmentalized HIV. Later, it may lead to the development of resistance mutations and additional neurologic complications [36–38]. Unfortunately, it is very difficult to compare drug levels and their IC values, because the results can vary with the protein concentrations as well as drug protein-binding ability [31]. Letendre et al. developed a quantification rank system of ARVs in CSF, which can be useful in selecting ARVs for patients with neurocognitive impairment [29, 39].

17.4 CNS Penetration and Effects of Current ARVs

17.4.1 Nucleoside/Nucleotide Reverse Transcriptase Inhibitors(NRTIs)

NRTIs are effective CSF concentrations because of their small molecular weights and low plasma protein-binding capacities; however, they have elevated hydrophilicity, which does not favor crossing the BBB. The optimum way to analyze the CNS concentration of NRTIs is to measure their intracellular triphosphate metabolites, which is not practical in the clinical setting [31]. Moreover, NRTIs are transported by organic anion transporter (OAT) at the *choroid plexus* [40]. Strazielle et al. studied delivery of ARVs and found that zidovudine (AZT) is the best among the NRTIs followed by stavudine, didanosine, and lamivudine [41]. Following is summary of the available data on CNS penetration of each NRTI.

17.4.1.1 Zidovudine (AZT)

AZT has the highest partition coefficient, which determines the ability of AZT to distribute, in the brain and CNS tissue [41]. It is the substrate for P-glycoprotein (P-gp), multidrug resistance-associated protein (MRP)-4 and MRP-5 [42]. Since it

was approved, pharmacokinetics of AZT was studied extensively [43–45]. In the largest study, Burger et al. had 39 patient participants and studied CSF concentrations of AZT. The CSF/plasma ratio increased linearly over time without significant relationship between AZT dose and CSF levels of AZT. This suggests that CSF penetration of AZT is dose independent. This finding may be an explanation for the efficacy of AZT in the prevention and treatment of HIV-related neurological diseases despite in low doses. Moreover, Burger et al. demonstrated that AZT reached therapeutic levels in CSF and was able to decrease CSF HIV viral load. Thus, it improved neurocognitive dysfunction as a single agent [43].

It is also associated with improved neuropsychological functioning in children with progressive encephalopathy by reduction of HIV viral load in CSF and improves neurocognitive performance in children with HIV encephalopathy as found early in the HIV epidemic to the present [46–49]. In addition, ART improves neurocognitive outcomes in HIV-infected children when applied early in their disease process [47, 49].

17.4.1.2 Stavudine (d4T)

The main side effect of d4T is mitochondrial toxicity; this led to a drastic reduction of d4T use in current clinical practice. However, in the early HIV epidemic, the CSF concentration of d4T was studied extensively [50, 51]. In patients with long-term use of d4T, its concentration in CSF ranged from 0 to 109.9 ng/ml with the mean d4T concentration of 51.6 ng/ml that exceeds the EC50 of clinical isolates of HIV (230 nM, 52 ng/ml) [50]. Stavudine uses organic anion-transporting polypeptide (OATP)-like transporter for its uptake [52].

17.4.1.3 Didanosine (ddI)

Didanosine chemical structure contains hypoxanthine. It has less than 5% protein binding [53]. In HIV-infected patients, ddI reaches a negligible level in the CSF. In patients who had been chronically taking ddI, average CSF concentration at 4 h after administration was 0.16 mumol/l in the CSF and 0.70 mumol/l in plasma. CSF concentration primarily uses the OATP-2-like transporter [53]. In one study, it had median CSF/plasma ratios of 0 in five patients [54]. However, unlike AZT, the use of ddI monotherapy did not reduce HIV viral load in CSF [55].

17.4.1.4 Lamivudine (3TC)

3TC has optimum uptake from blood to *choroid plexus* using the dioxin-sensitive transporters and organic cation transporters [56]. The concentrations of 3TC were studied in combination with either AZT or d4T. All subjects had detectable HIV viral load in CSF. However, there was no correlation between plasma and cerebrospinal fluid HIV-1 RNA concentrations; after 12 weeks of treatment, none of the

subject had detectable CSF HIV viral load even when the subjects did not achieve complete plasma HIV viral load suppression. In this study, 3TC had the highest CSF concentration followed by d4T and AZT. Drug concentrations in plasma declined rapidly, while drug concentrations in CSF reduced more slowly. CSF to plasma concentration for d4T, AZT, and 3TC increased over time, and the time-dependent CSF to plasma drug/penetration ratios was highest for AZT followed by d4T and 3TC. And the 3TC level was well above the IC50 (range 66–80 ng/ml) [57].

17.4.1.5 Abacavir (ABC)

ABC has optimum CSF penetration with moderate plasma protein binding and lipophilicity. In animal model, it crosses BBB without influence of other drugs [58]. A human study of 54 subjects demonstrated its CSF/plasma ratio that is enhanced by dose escalation, and the CSF concentration is adequate to inhibit HIV replication. Subjects received ABC 300 mg twice daily as part of cART. The median CSF ABC concentration was 128 ng/mL (range 37–384 ng/ml). Predicted CSF trough concentrations exceeded the IC50 (70 ng/mL) for 85% of the dose interval. The CSF/plasma ABC ratio is approximately 31–44% [59]. However, its lacking in the active efflux mechanism and having P-gp as its major transporter limit CNS penetration [60].

There are no studies to demonstrate a virological or clinical effect in the CNS. Adding high-dose ABC for HAD patients on stable cART did not improve performance scores or reduce CSF HIV RNA levels more than placebo [61].

17.4.1.6 Tenofovir

According to the DHHS guideline, tenofovir has been the preferred agent in cART component (www.aidsinfo.nih.gov). The initial FDA-approved formulation, tenofovir disoproxil fumarate (TDF), demonstrated efficacy and persistency, with concerns of nephrotoxicity, osteopenia, and osteoporosis [62, 63]. To minimize such concerns, tenofovir alafenamide (TAF) was developed. Both TDF and TAF are prodrugs of tenofovir diphosphate. And clinically, TAF has been replacing TDF in the existing combination formulas [63].

CSF tenofovir concentration has been described to be very low due to its limited uptake by membrane transporters [64]. A study to determine tenofovir CSF penetration using random plasma and CSF samples from 183 subjects who were on tenofovir found median plasma, and CSF tenofovir concentrations were 96 ng/mL and 5.5 ng/mL, respectively. Thirty-four of 231 plasma (14.7%) and 9 of 77 CSF samples (11.7%) were below detection. CSF/plasma concentration ratio from paired samples was 0.057. Median CSF to wild-type 50% inhibitory concentration ratio was 0.48 (IQR 0.24–0.98). Moreover, 77% of CSF concentrations were below the tenofovir wild-type IC50. The tenofovir concentrations in the CSF are only 5% of plasma concentrations, which suggest limited transfer into the CSF and possibly active transport out of the CSF. Therefore, tenofovir may not effectively inhibit viral replication in the CSF [65].

17.4.2 Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

17.4.2.1 Efavirenz (EFV)

Despite its common CNS side effects, it has limited CNS penetration. One of the reasons is that EFV bounded extensively by plasma albumin left a small fraction of unbound EFV passively penetrated into CNS. The CNS EFV is not bound well by CSF protein; both unbounded EFV concentrations are similar resulting in distortion of CSF/plasma EFV ratio [66]. The first published study of the CNS penetration of EFV of ten patients showed a mean CSF concentration of 11.1 ng/mL (range 2.1–18.6 ng/mL) and a CSF/plasma ratio of 0.61% [67]. A pharmacokinetic study of EFV showed its CSF penetration of 0.44% of plasma concentration [31]. A recent larger study of 80 CSF samples reported a median CSF EFV concentration of 13.9 ng/mL with all except two samples that were above the IC50 (0.51 ng/mL). Its CSF concentration is only about 0.5–1% of plasma concentration. However, the CSF concentration offers the CSF concentration above IC95 of HIV wild type. This suggests the potent ability of EFV in inhibiting HIV in the CSF in such a low CSF concentration [68]. Its efflux mechanism uses P-gp expression and function. It also concentration-dependently inhibits MRP-1, MRP-2, and MRP-3 [69]. Moreover, EFV major haptic metabolite, 8-hydroxyefavirenz, neither has significant association with EFV plasma concentration nor association with CYP2B6 genotype; therefore, it reaches the 0.01 μM toxicity threshold [54, 70]. There are increasing evidences of EFV-related CNS toxicities. We describe cART especially EFV toxicities in Sect. 17.6 of this chapter.

17.4.2.2 Nevirapine (NVP)

NVP crosses BBB well, has stable CSF concentration, has highest CSF/plasma penetrability rate, and offers the highest penetrability rank in Latendre classification [39, 54, 71, 72]. It has median CSF/plasma ratio of 0.63 [54]. In a study of nine HIV-infected patients, the median CSF NVP concentration was 932 ng/mL (range 219–1837 ng/mL), which exceed the CSF IC50 by tenfolds [72, 73]. Therefore, it is suitable to use in patients with neurocognitive impairment.

17.4.2.3 Etravirine (ETV)

ETV has a CSF/plasma ratio of 4%. In one study, all 17 CSF concentrations exceeded the wild-type IC50 by a median of 13.6-fold [31]. In another study of 12 patients, the median ETV concentration in plasma was 611.5 ng/mL with the median CSF concentration of 7.24 ng/mL, which was above the IC(50) range (0.39–2.4 ng/mL). The median ETV CSF/plasma ratio was 0.01. All but one patient had undetectable CSF viral load. This study suggested that ETV use was associated with virus suppression in CSF and plasma and may help control HIV in the CNS [31, 72, 74].

17.4.2.4 Rilpivirine (RPV)

RPV CSF drug penetration has been limitedly studied. In a NVP to RPV switch study, CSF drug concentration was measured. The mean plasma RVP trough concentration was 29.7 ng/mL with the mean CSF RVP concentration of 0.8 ng/mL (95% CI: 0.7–1.0), resulting in a CSF/plasma ratio of 1.4 the protein. It was shown that switching NVP to RVP was safe with reassuring drug levels both in plasma and in CSF [75].

17.4.3 Protease Inhibitors (PIs)

Due to their lipophilicity, PIs are expected to have good CNS concentrations but have low CSF concentrations due to the efflux mechanism (all PIs are P-gp substrates) and high protein-binding capacity (except indinavir) [76]. Using ritonavir to boost PIs also increases CSF penetrability [29].

17.4.3.1 Ritonavir (RTV)

Currently, RTV is used exclusively to pharmacokinetic enhance (aka boost) other PIs rather than as a primary antiviral drug. It is a cytochrome P450 3A isoenzyme inhibitor and increases plasma areas under the curve (AUC), drug half-lives, and trough concentrations (lowest drug concentration at steady state) of others. It has large molecular weight, is highly protein bound, and is also a P-gp inhibitor. Therefore RTV can enhance CSF levels of other drugs both by increasing plasma concentrations and by inhibiting efflux [23].

A cross-sectional study of 28 subjects on saquinavir/RTV therapy was evaluated and resulted in a strong correlation between plasma and CSF HIV viral loads. Low CSF drug levels of both saquinavir (<2 ng/ml) and ritonavir (<25 ng/ml) with low CSF/plasma concentration ratio of <0.005 suggested that CSF ritonavir and saquinavir levels are consistent with the estimated known fraction of unbound drug in plasma (<2%), and suppression of plasma viremia can indicate low CSF HIV RNA levels. Likewise, CSF virologic breakthrough was the result of plasma virology failure [77].

17.4.3.2 Indinavir (IDV)

Currently, IDV is only rarely used because of its dosing frequency and renal toxicity; however, it offers the best CNS penetrations among the PIs because of its low protein-binding capacity [78, 79]. It is the only PI that has a CSF concentration that attains its IC95 (18–71 ng/mL) [78, 80, 81]. It is also the only PI that achieves therapeutic concentrations in CSF without RTV boosting (dosing 800 mg three times daily). Using it in a boosted fashion with RTV, there are even higher CSF concentrations with mean CSF IDV concentrations of 203 ng/mL. This is well above the IC95 (18–71 ng/mL) [79]. Using IDV showed clinically improved neurocognitive dysfunction [81].

17.4.3.3 Lopinavir (LPV)

The median CSF concentrations of LPV were 11.2–17.0 ng/mL based on three studies with the CSF/plasma LPV ratio that was approximately 0.2% in all of them [82–84]. All the CSF samples were above the median IC50 (1.9 ng/mL) for wild-type virus. RTV-boosted LPV (LPV/r) has CSF levels that exceed the IC50 [82]. It has been shown that LPV/r both monotherapy and as a component of cART reduces CSF HIV replication and immune activation [84]. However, a recent study with patients on effective cART randomized to LPV/r monotherapy (n1/429) or continued treatment (n1/431) had to be terminated prematurely because of the high rate of failures in the monotherapy arm. A total of four out of six patients with plasma virologic failure developed neurological symptoms, and all of them were on monotherapy. In five of the failing patients, all had elevated CSF HIV RNA levels (3.1–5.1 log10 copies/mL). In addition, 8 of 25 patients who consented to a lumbar puncture at study termination had detectable HIV RNA in the CSF. All these patients were on monotherapy at the time of study termination, whereas none of 15 patients in the continued treatment arm had detectable HIV RNA in their CSF. The use of LPV/r may benefit patients with neurocognitive disorders as part of cART, not as monotherapy [38].

17.4.3.4 Amprenavir (APV) and Fosamprenavir (FPV)

Boosted APV and, its prodrug, FPV (both in unboosted and boosted forms) reaches their IC50 rapidly after oral administration. FPV is almost completely hydrolyzed to APV prior to reaching systemic circulation. A study of 119 matched CSF-plasma pairs from 75 subjects found that APV concentrations were 5.6 ng/ml compared to the IC50 for wild-type HIV. The APV concentrations in CSF exceeded the median IC50 for wild-type HIV in more than 97% of CSF specimens with detectable APV by a median of 4.4-fold (IQR, 2.9–7.9). This showed that FPV may control HIV replication in the CNS as a cART component [85]. With a single dose of 630 mg of APV, only one of five CSF samples collected from healthy males had detectable CSF APV levels [86].

In a study of boosted FPV monotherapy (FPV 700/RTV 100 mg twice daily), 20 patients entered the study with 9 patients (45%) had therapeutic failure. Hence, this study ended prematurely and the use of boosted FPV monotherapy was discouraged. The CSF APV concentration was well above the IC50. Despite virologic failure, APV levels and undetectable HIV RNA levels in CSF were documented in all samples evaluated [87].

17.4.3.5 Nelfinavir (NFV)

NFV did not reach therapeutic CSF concentration and was below the detection limit [88]. However, in two studies, NFV was quantifiable in 9 of 15 samples and 8 of 18 samples, respectively. Some of the concentrations were in the range of

the IC50, but most of them were below it. When used as a single agent for 17 days (in three patients), NFV failed to suppress the CSF viral load [89, 90]. Another study measuring NFV concentration in both plasma and CSF in 6 study subjects, even though NFV was not detected in any of the CSF specimen, there was a significant reduction of HIV RNA PCR in CSF of patients who were treated with NFV-containing regimen. This finding demonstrated that reduction of CSF HIV RNA correlated to the reduction in plasma HV RNA [91].

17.4.3.6 Saquinavir (SQV)

SQV did not reach therapeutic CSF concentration and was below the detection limit even with ritonavir boosting [39, 77].

17.4.3.7 Atazanavir (ATV)

CSF RTV concentrations increase when used with ATV boosting. In a study of 68 patients on a treatment regimen with boosted ATV (ATV 300–400 mg/RTV 100 mg once daily), the median CSF ATV concentration was 10.3 ng/mL (range, 5–38 ng/mL) and the CSF/plasma ratio was 0.9% [92]. Fifty-four percent of the samples were below the IC50 with plasma (11 ng/mL) and 24% were close to the IC50 determined without human proteins (1.0 ng/mL). The authors concluded that ATV did not reach therapeutic CSF concentration and that it might not protect against HIV replication in the CSF. Moreover, it has highly variable CSF concentrations and more than 100-fold lower than the plasma concentration even with RTV boosting. Its concentration did not consistently exceed the IC50 for the wild-type virus [39, 92]. To evaluate the effect of monotherapy with boosted ATV on the CSF viral load, lumbar punctures were performed on 20 patients who had received this regimen as maintenance therapy for 24 weeks. Two patients (7%) failed this regimen. Excluding failing patients, individual measurements of HIV RNA in patients showed occasional viral "blips" in five patients. Samples with elevated HIV RNA greater than 500 copies/ml in CSF were all wild type. The mean ATV drug concentration ratio was 0.9%. This finding supports potential use of PI-based mono-maintenance therapies. However, their results in CSF caution against the uncontrolled use of PI-based monotherapies that can lead to CSF escape [36].

17.4.3.8 Darunavir (DRV)

DRV has detectable and stable levels in the CSF that exceed levels needed to inhibit HIV replication. In a study of 14 samples from eight treatment-experienced HIV-infected patients receiving 600 mg/100 mg of DRV/RTV twice daily plus optimized background therapy, the median CSF DRV concentration was 34.2 ng/mL (range 15.9–212 ng/mL); all of them had CSF DRV levels well above the IC50. The finding suggests DRV contributes to viral suppression in the CNS [93].

DRV/RTV monotherapy was investigated in 225 patients, and three patients developed virologic failure on DRV/RTV monotherapy, and none failed on DTV/RTV triple-drug therapy. No resistance to protease inhibitor emerged in patients with plasma viral load above 50 copies/ml. The patients failing on DRV/RTV monotherapy had no emergence of new DRV resistance mutations preserving future treatment options [37]. Another study of DRV/RTV monotherapy at 48 weeks HIV RNA was less than 50 copies/ml – 86.2 versus 87.8% in the monotherapy and triple therapy arms, respectively. One patient per arm showed at least one protease inhibitor mutation, and one patient in the triple therapy arm showed an NRTI mutation. In both studies, switching to DRV/r monotherapy showed noninferior efficacy versus triple antiretroviral therapy [94]. The addition of two NRTIs led to improvements of symptoms and reductions of CSF viral load.

17.4.3.9 Tipranavir (TPV)

There was no published data on the CSF concentration of TPV.

17.4.4 Integrase Inhibitors (Integrase Strand Transfer Inhibitors, INSTIs)

Although raltegravir, elvitegravir, and dolutegravir are the three agents in this class that are currently approved by the FDA, there are limited published data available for CSF penetration.

17.4.4.1 Raltegravir (RAL)

RAL is a substrate for P-gp in vitro [95]. A study of 18 subjects who took RAL-containing regimens demonstrated a median concentration in plasma that was 260.9 ng/ml, with a median CSF/plasma ratio of 0.058. RAL concentrations in CSF exceeded IC50 for wild-type HIV-1 (3.2 ng/ml) by a median of 4.5-fold. Its presence in CSF was sufficiently high concentrations to inhibit wild-type HIV in all subjects [96]. Another study showed that in patients who were on RAL-based cART regimen, the median CSF/plasma ratio was 0.20 and correlated with plasma and CSF trough concentration. Despite variability of RAL penetration into CSF, the concentrations were well above wild-type HIV IC50s in all patients and above IC95 in 28.6% of the patients [97]. Moreover, in another study, 50% of the CSF specimens, concentrations exceeded the IC95 levels reported to inhibit HIV-1 strains without resistance to INSTIs [93]. Based on its CNS penetrability, as a component of cART, RAL likely contributes to the control of HIV replication in the nervous system as well as being neuroprotective by suppression of HIV-infected inflammatory cytokine, IL-8, production [98].

17.4.4.2 Elvitegravir (EGV)

An ongoing CSF pharmacokinetic study to determine the CSF concentrations of EGV along with tenofovir and TAF (NCT 02251236) has completed subject recruitment; data are not yet available (https://clinicaltrials.gov/ct2/show/record/NCT02251236).

17.4.4.3 Dolutegravir (DGV)

In 12 treatment-naive subjects, using 50 mg doses of DGV in combination of 3TC and ABC, the median DGV concentration in CSF was 13.2 ng/ml, 2–6 h post dose after 16 weeks of treatment. However, clinical relevance of this information is not established (https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Tivicay/pdf/TIVICAY-PI-PIL.PDF).

17.4.5 Entry Inhibitors

17.4.5.1 Enfuvirtide

Enfuvirtide is entry inhibitor acting on the process of fusion. Its chemical structure suggests that it would not reach effective drug concentrations in the brain due to high molecular weight (4492 Dalton), high protein binding (92%), and lack of lipid solubility [31, 99]. Its CSF concentrations were below the lower limit of quantification (25 ng/mL) in 18 out of 18 CSF samples [100]. A report of a patient who developed virologic failure while on enfuvirtide-containing regimen, using genotypic analysis of CSF-derived HIV RNA, V38A mutation was detected in the CSF but not in plasma. This finding illustrated the selection of enfuvirtide-resistant virus in CSF, causing subsequent loss of viral suppression in plasma [101].

17.4.5.2 Maraviroc

To date, maraviroc is the only approved CCR5 coreceptor antagonist for the treatment of HIV-1 infection. It is also a substrate for P-gp [102]. In one study, maraviroc was detectable in all seven CSF samples with a median concentration of 3.6 ng/mL (range 1.8–12.2 ng/mL) [93] and 2.6 ng/mL (range, 0.5–7.2 ng/mL) in another study [103] with median CSF/plasma ratios of 3% and 2.2%, respectively. All CSF samples contained ≥3-fold maraviroc concentration above the median EC90 (0.57 ng/mL) [103] (Table 17.1).

Table 17.1 Characteristics of ARVs based on available pharmacokinetic and pharmacodynamic data

Drug class	Drug	Molecular weight (Da)	Protein binding (%)	Lipid solubility	Protein-free IC 50(ng/ml)
Nucleoside/ nucleotide reverse transcriptase inhibitors	Zidovudine	267	34–48	low	5.3
	Abacavir	286	50	Low	457.6
	Emtricitabine	247	<4	Low	70
	Didanosine	236	<5	Low	1180
	Lamivudine	229	16–36	Low	549.6
	Stavudine	224	Negligible	Low	112
	Tenofovir	288	<7	Low	201.6
Non-nucleoside reverse transcriptase inhibitors	Nevirapine	266	60	Intermediate	32
	Efavirenz	316	9.5–99.8	High	1.3
	Etravirine	435	99.9	High	0.9
Protease inhibitors	Indinavir	712	60	Intermediate	4.3
	Darunavir	548	95	High	0.4
	Fosamprenavir	586	90	Intermediate	4.3
	Lopinavir	629	97–99	Not available	3.1
	Atazanavir	705	86	Intermediate	5.3
	Nelfinavir	664	>98	High	11
	Ritonavir	721	98–99	Not available	Not available
	Saquinavir	671	98	Intermediate	3.6
	Tipranavir	603	>99.9	High	53
CCR-5 inhibitor	Maraviroc	514	76	High	Not available[a]
Fusion inhibitor	Enfuvirtide	4492	92	Not available	Not available[a]
Integrase inhibitor[b]	Raltegravir	594	83	Low	3.6
	Elvitegravir	448	98	Not available	54
	Dolutegravir	419	98	Not available	2.7

Adapted from Yilmaz et al. [31]

[a]Data of protein-free IC50 of maraviroc and enfuvirtide were not available in the same way they were generated for other drugs

[b]Data for newer integrase inhibitors are limited; additional data from recent publications were added in the table [104–107]

17.5 The CNS Penetration Effectiveness (CPE) Score

The CNS penetration effectiveness (CPE) score has been proposed as a method for estimating the combined CNS effectiveness of cART regimens. The study was done as part of the CHARTER (CNS HIV Antiretroviral Therapy Effects Research) study. Eight hundred and thirty-three HIV-positive individuals had enrolled, and 467 (71%) met eligibility criteria for CPE analysis by ARV drug use report and HIV viral load in both plasma and CSF measured. ARVs were classified into three categories based on chemical properties (molecular weight, protein binding, lipophilicity, charge at physiological pH), pharmacokinetic data (mainly CSF concentrations compared

with inhibitory concentrations for wild-type HIV-1), and pharmacodynamic data (effectiveness in CNS in clinical studies). For this initial version of the *CPE score*, individual ARV drugs were assigned a penetration rank of 0 (low), 0.5 (intermediate), or 1 (high) based on their chemical properties, concentrations in CSF, and/or effectiveness in the CNS in clinical studies. The CPE rank was calculated by summing the individual penetration ranks for each ARV in the regimen. The findings noted that the median CPE rank was 1.5. Lower CPE ranks correlated with higher CSF viral loads even after adjusting for the total number of ARV drugs, ARV drug adherence, plasma viral load, duration and type of the current regimen, and CD4 count [29]. In the revised 2010 version of this ranking system, individual antiretroviral drugs are assigned a penetration score of 1 (none), 2 (low), 3 (intermediate), or 4 (high) [39]. CPE rank has been shown to correlate with improvements in cognitive performance and with CSF viral loads in some studies [29, 108], while other studies have found no correlation with neurocognitive improvement, detectable CSF viral loads, or level of intrathecal immune activation [25, 81, 109]. This suggests that using a simple categorical scale still has limitations that might not be sufficient in judging CNS efficacy. Moreover, data for some drugs is very limited and do not take into account possible genotypic resistance. A study of 64 subjects focusing on the effects of CPE score on neuropsychological performance showed that CPE score is not related to cognitive outcomes [110]. In recent studies, there was evidence of worsening neurocognitive function in patients who were on a high CPE regimen. For example, in the HIV-CAUSAL collaborative, 51,938 patients were followed, and they were compared based on high (>9) vs. low (<8) CPE regimens (with regimen CPE scores range 4–16). The patients who were on high CPE score regimens had increased risk of HAD (hazard ratio 1.74), while there was a difference in the risk of developing *cryptococcal* meningitis, CNS toxoplasmosis, and progressive multifocal leukoencephalopathy [111]. Other studies suggested that high CPE regimens may be neurotoxic. Using NRTIs can cause mitochondrial toxicities by inhibiting mitochondrial DNA polymerase gamma. N-acetyl-aspartate (NAA) was used as a surrogate marker for neuronal integrity and mitochondrial function and can be measured by magnetic resonance spectroscopy (MRS). Robertson et al. used this technique in 18 patients and found that patients who were on d4T and ddI had depleted NAA levels [112]. Efavirenz is also found to be neurotoxic and damaged dendritic cells [113]. The antiretroviral drug score (ΣCPE) was investigated in a small study for its potential correlation with brain atrophy. The investigators used ventricular/brain ratio, calculated by lateral ventricular area divided by the brain area at the same level in T2 transversal MRI slices, as an index of overall brain atrophy. The ΣCPE scores were done in 2010 and 2008 version. ΣCPE 2010 version was found to be correlated with atrophy than the 2008 version [114]. Future revision as more information available perhaps helps to better correlate with clinical findings (Table 17.2).

This table shows the CNS penetration effectiveness (CPE) ranking of the currently available antiretroviral. The initial CPE rank proposed by Latendre et al. was based on physiochemical characteristics, CSF concentrations, and efficacy data [29]. However, the recent cross-sectional data that included CSF vs. plasma viral load studies from the CHARTER cohort led to a revised CPE ranking system. The new

Table 17.2 ARVs that penetrate the blood-brain barrier (BBB)

Drug class	Drug	CPE 2010 rank	Transporter	References
Nucleoside/nucleotide reverse transcriptase inhibitors	Zidovudine	4	P-gp, BCRP substrate, ENT, CNT, and OAT	[56, 115–117]
	Abacavir	3	P-gp	[69]
	Emtricitabine	3	MRP	[69]
	Didanosine	2	ENT and CNT	[118, 119]
	Lamivudine	2	OCT, MRP	[56, 69, 120]
	Stavudine	2	CNT	[56]
	Tenofovir	1	MRP	[69]
Non-nucleoside reverse transcriptase inhibitors	Nevirapine	4	P-gp, MRP	[69, 121]
	Delavirdine	3	P-gp, MRP	[69, 121]
	Efavirenz	3	P-gp, MRP	[69, 121]
	Etravirine	2	Unknown	
Protease inhibitors	Indinavir/ritonavir	4	P-gp	[122]
	Darunavir/ritonavir	3	MRP	[123, 124]
	Fosamprenavir/ritonavir	3	P-gp	[125]
	Indinavir	3	P-gp	[122]
	Lopinavir/ritonavir	3	MRP	[126]
	Atazanavir	2	P-gp	[127]
	Atazanavir/ritonavir	2	P-gp	[127]
	Fosamprenavir	2	P-gp	[125]
	Nelfinavir	1	P-gp, BCRP	[23, 128]
	Ritonavir	1	P-gp, BCRP	[128, 129]
	Saquinavir	1	P-gp, MRP, BCRP	[122, 126, 128]
	Saquinavir/ritonavir	1	P-gp, MRP, BCRP	[122, 126, 128]
	Tipranavir/ritonavir	1	P-gp	[130]
CCR-5 inhibitor	Maraviroc[a]	3	P-gp	[131]
Fusion inhibitor	Enfuvirtide[b]	1	Unknown	
Integrase inhibitor[c]	Raltegravir	3	Unknown	

[a]Limited CNS distribution of CSF concentrations is about 10% of the free plasma concentration [131].
[b]Negligible CSF penetration [131]
[c]Data for new integrase inhibitors, elvitegravir and dolutegravir, are not yet available

system reflects stronger associations with CSF viral load analysis by incorporating recent pharmacokinetic and pharmacodynamic data. A higher number estimates better penetration in the CNS [39].

Drug transporters involved in each antiretroviral distribution at the BBB are mentioned. These transporters are ATP-binding cassette (ABC) superfamily includ-

ing P-glycoprotein (P-gp), multidrug resistance-associated protein (MRP), and breast cancer resistance protein (BCRP). Solute-carrier superfamily (SLC) includes organic anion-transporting polypeptide (OATP), organic anion transporter (OAT), and organic cation transporter (OCT). Nucleoside transporters include equilibrative nucleoside transporter (ENT) and concentrative nucleoside transporter (CNT) (adapted from Shapshak et al. [3]).

Gao et al. proposed a method to predict drug BBB permeability that can apply to both small compounds and macromolecules by various mechanisms besides passive diffusion. The curated drugs with known BBB permeability dataset were extracted from SIDER database. They built classification models with support vector machine (SVM) algorithms using data mining software, evaluated the performance of the model independently from the dataset, and conducted de novo prediction for each drug in the SIDER database. This method uses clinical phenotypes including drug side effects and indications, using dataset of 213 drugs, which has three antiretrovirals including EFV, AZT, and RTV. In this model it was found that it was predicted of BBB permeability in AZT but not EFV and RTV. This dataset is found to have an accuracy of 85.5% and can potentially serve as a point to commence further CNS drug repositioning and combinatorial research [132].

17.6 Nanobiology and CNS ARV Drug Delivery

To date, available antiretroviral drugs are effective primarily in decreasing the viral load in the peripheral system but do not as yet eradicate virus in the CNS reservoir. The primary impediment is the BBB; drug delivery is still a challenge. HIV neurotherapeutics through nanocarrier-based delivery of the antiretroviral drugs through the BBB is a promising methodology against HIV cure by possibly eradicating persistent and latent HIV infection in the CNS. Delivery systems experimented include liposomes and magnetic liposomes, nanoART, cationic trans-activating transcriptor (TAT) nanoparticles, and polymer-based nanoparticles. All of these approaches created an improved ARV delivery to the CNS and are potentially applied to all ARV classes [133]. The global call of HIV eradication promotes research in nanocarriers and noninvasive strategies to deliver drugs through BBB such as site-specific release of ARVs, nanoformulations to eradicate HIV reservoirs, and diagnostic tools to detect and monitor HIV infection. Such developments will help to develop personalized nanomedicines toward HIV cure [134].

17.6.1 Liposomes

Liposome-based nanoformulation was benchmarked by nanoformulation of foscarnet, which was also employed with other ARVs [135, 136]. However, this delivery method seems to have shorter half-life by reticuloendothelial cell sequestration [137].

17.6.2 NanoART

NanoART was explored by Kuo and Chen by incorporating AZT and 3TC into polybutylcyanoacrylate and methylmethacrylate-sulfopropylmethacrylate nanoparticles. This formulation increases BBB permeability [138]. Additionally, they investigated the electromagnetic field-regulated transport of cationic solid lipid nanoparticles across human brain endothelial cells. Using this technique, the permeability of SQV across the brain endothelial cell monolayer was increased about 17- to 22-folds [139]. Later, this strategy was exploited further to deliver IDV nanoparticle loaded into bone marrow macrophages in mice with HIV-1 encephalitis. IDV was detected in the brain suggesting nanoparticles deliver IDV across BBB [140]. ATV and RTV crystalline nanoART and nanoART using monocyte-derived macrophages as Trojan horses (ATV, RTV, IDV, and EFV) are proven to increase ARV penetration through BBB [141, 142]. Additionally, magnetic nanoART was developed using a magnetically guided layer-by-layer technique coloads TDF and vorinostat. This formulation provides sustained drug release with acceptable BBB penetrations [143].

17.6.3 TAT-Nanoparticles

TAT-nanopeptides are the most commonly used cell-penetrating peptides. This demonstrated delivery of RTV to the brain by escaping the P-glycoprotein efflux without disruption of BBB integrity [133].

17.6.4 Actively Targeting Nanoparticles

Actively targeting nanoparticles have been studied in ARV drug deliveries. These include (1) PEGylated albumin nanoparticles encapsulating AZT [144]; (2) methylmethacrylate-sulfopropylmethacrylate nanoparticle functionalized with the bradykinin analogue, RMP-7, to increase permeation of D4T, SQV, and delavirdine (DLV) across the BBB [145]; and (3) brain-specific nano-NRTIs decorated with the peptide apolipoprotein E receptor, which provided low neurotoxicity and enhanced anti-HIV activities [146].

17.6.5 Polymer-Based Nanoparticles

Poly(dl-lactide-co-glycolide) (PLGA) nanoparticles were demonstrated to increase the peak concentrations of RTV, LPV, and EFV in mice brain [147]. Enfuvirtide conjugated with iron oxide nanoparticles coated with an amphiphilic polymer increases enfuvirtide penetrations across the BBB and increases its efflux into brain parenchyma [148].

17.7 cART and CNS Toxicities

Among antiretroviral drugs, EFVs have been well known to cause neurological and neuropsychiatric adverse reactions. Patients treated with EFVs present a wide range of symptoms including nightmares, dizziness, insomnia, nervousness, lack of concentration, as well as more severe symptoms including depression, suicidal ideation, or even psychosis. Moreover, EFVs have recently been shown to associate with mild/moderate neurocognitive impairment.

In fact, neuropsychiatric side effects are the most common cause of EFV discontinuation [149–151]. These side effects can occur as early as the first dose of therapy and likely to subside within the first month. However, some patients might experience them several months or years post-therapy, requiring switching to alternative agents [151–156]. Although the mechanisms of these adverse reactions were unclear, there has been increased evidence of mitochondrial function disturbances in the brain and the bioenergetic systems [70].

In addition, potential EFV neurotoxicity mechanisms include the following:

1. Upregulation of pro-inflammatory cytokines (IL-1β and TNF-α) in blood cells exposed to pro-inflammatory stimuli. In animal models, this is associated with anxious behaviors and impaired cognitive performance, causing spatial memory deficits and increased stress susceptibilities. Moreover, EFVs upregulate these pro-inflammatory cytokines [157, 158].
2. Increase in 5-HT levels occurring in parallel to a reduced activity of tryptophan 2,3-dioxygenase. Apostolova et al. found that EFV-exposed rats showed downregulation of serotonin via tryptophan 2,3-dioxygenase resulting in increased serotonin activities [158].
3. EFV acting as a partial agonist of the serotonin receptors 5-HT2C and, particularly, 5-HT2A [159].
4. EFVs significantly inhibiting creatinine kinase activities in the cerebellum, hippocampus, striatum, and cortex in a mouse model. EFVs affect mitochondrial function of the brain by depleting ADP that leads to cognitive impairment as well as increased seizure susceptibilities in EFV-treated mice [160, 161];
5. It was also shown that EFV reduced creatinine kinase activity in the mouse brain by a specific inhibition of complex IV (cytochrome c oxidase) of the electron transport chain in the cerebral cortex, striatum, and hippocampus, but not in the cerebellum [162].
6. EFV, not other NNRTIs, increased endothelial permeability by inducing reduction in, and disrupting localization of, a tight junction protein, claudin-5 [163].
7. EFV impacts mitochondrial function and neural bioenergetics. EFV was found to increase soluble amyloid beta, promote increased β-secretase-1 expression, and decrease clearance of the amyloid beta peptides, resulting in mitochondrial stress [164].

In addition, the impact of EFV on biogenetics especially in the neurons and glial cells has been shown in in vitro studies. It disrupts mitochondrial function by direct inhibition of complex I activity of the mitochondrial electron transport chain, lead-

ing to a decrease in total oxygen consumption, an increase in the production of reactive oxidase species, and a decrease in mitochondrial membrane potential [165, 166]. The action of EFV on the mitochondria of glial cells and neurons is similar. EFVs directly inhibit complex I resulting in reduction of mitochondrial respiration both in neurons and glial cells. However, the bioenergetic responses of reduction of mitochondrial respiration in glial and neurons are different. In glial cells, the increase in the AMP/ATP ratio induced by mitochondrial dysfunction causes the activation of AMPK (by phosphorylation forming P-AMPK), leading to upregulation of glycolysis (increased extracellular lactate) and consequently to increased intracellular levels of ATP. Glycolysis activation is not observed in neurons causing reduction in intracellular ATP [166–168].

Bioenergetic interference also plays a role in nitric oxide synthesis in glial cells. The decrease in respiration and the increase in glycolysis and mitochondrial reactive oxygen species generation were partially reversed when inducible nitric oxide synthase activity was inhibited in glial cells. Additionally, while EFV produced a decrease in complex I activity in both neurons and glial cells, a slight inhibition of complex IV activity was detected only in glial cells, which is consistent with an inhibitory action of nitric oxide on this mitochondrial complex. EFV-treated mice display inhibition of complex IV activity in different areas of the brain in EFV-treated mice, and no alteration of complex I activity was observed [158, 162].

Direct toxicities from EFV primary metabolite, 8-hydroxyefavirenz, have been observed by stimulation of glycolytic flux and decreased mitochondrial oxygen consumption. Moreover, increase in calcium into cells mediated by L-type voltage-operated calcium channels damages dendritic spines and induces apoptosis [113].

17.8 Conclusions

Using cART helps to alleviate and prevent HAND. However, the efficacy of each ARV compound in the CNS should be considered specifically as well as in concert with others in choosing cART regimens. Early diagnosis of neurocognitive impairment is needed to appropriately select cART regimen with good CSF penetrability rank that proffers neuroprotection.

Another consideration of adequate suppression of HIV replication in the brain is to prevent CNS escape. Compartmentalization of HIV infection is associated with genetic differences between plasma and CSF strains in terms of resistance. Efficacy of cART in the CNS sanctuary requires awareness on ARV penetrability, resistance mutations in CSF, factors as modification of BBB, drug interactions, additive or synergistic effects of cART components, and comorbidities. Unfortunately, technology and data are helpful when assessing individual agents, but more difficult evaluating each regimen. Nanotechnologies are the promising areas to develop efficient drug delivery to eradicate HIV CNS reservoirs. Further studies are needed to discover improved assays to measure cART regimen efficacy in viral compartments

and to find drugs that can assure a good balance between therapeutic effect and neurotoxicity, leading to HIV eradication.

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