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Solving the Blood-Brain Barrier Challenge for the Effective Treatment of HIV Replication in the Central Nervous System

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Abstract

Recent decades mark a great progress in the treatment of HIV infection. What was once a deadly disease is now a chronic infection. However, HIV-infected patients are prone to develop comorbidities, which severely affect their daily functions. For example, a large population of patients develop a variety of neurological and cognitive complications, called HIV associated neurological disorders (HAND). Despite efficient repression of viral replication in the periphery, evidence shows that the virus can remain active in the central nervous system (CNS). This low level of replication is believed to result in a progression of neurocognitive dysfunction in infected individuals. Insufficient viral inhibition in the brain results from the inability of several treatment drugs in crossing the blood-brain barrier (BBB) and reaching therapeutic concentrations in the CNS. The current manuscript discusses several strategies that are being developed to enable therapeutics to cross the BBB, including bypassing BBB, inhibition of efflux transporters, the use of active transporters present at the BBB, and nanotechnology. The increased concentration of therapeutics in the CNS is desirable to prevent viral replication; however, potential side effects of anti-retroviral drugs need also to be taken into consideration.

Keywords

HIV; Blood brain barrier; anti-retroviral drugs; central nervous system; viral reservoir; nanoparticles

1. INTRODUCTION

Natural progression of HIV disease is associated with a gradual exhaustion of the immune system and a rise in complications such as opportunistic infections or other comorbidities. HIV can also cross the blood brain barrier and infect the central nervous system (CNS), which results in a wide array of complications, ranging from HIV associated dementia

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Conflict of Interest

Nothing to report

(HAD) to asymptomatic neurocognitive impairment (ANI) [1]. The introduction of highly active anti-retroviral therapy (HAART) has drastically reduced the severity of neurological diseases, but has not reduced their prevalence [2]. This indicates a need for a comprehensive treatment approach to ameliorate current therapies to target HIV replication in the CNS.

The blood brain barrier (BBB) is a highly selective barrier that restricts the passage of elements from the circulatory system to the CNS. This restriction prevents toxic molecules, viruses, bacteria and inflammatory cells from reaching the CNS, which could damage the brain. While BBB is important in preventing CNS infection, it also hinder the treatment of brain pathology. Crossing the BBB has proved to be a major obstacle in treatment of a variety of brain diseases, from viral and bacterial infections to cancer or brain metastasis [3, 4].

The successful delivery of drugs to the CNS is highly dependent on the structure of the molecule. In the treatment of HIV, several anti-retroviral drugs have been analyzed to identify their ability to cross the BBB. While some demonstrate a relatively high CNS penetration-effectiveness (CPE), a high proportion of therapeutics show low to poor CPE (see table 1). This hinders the efficiency of treatment and increases the probability of drug resistance due to CNS HIV replication at sub-optimal drug levels [5].

1.1. Blood brain barrier

The BBB is mainly composed of brain microvascular endothelial cells (BMEC) that form a highly sealed layer around the brain circulatory system to control the exchange of charged molecules of more than 400 Da [6]. This restricts the passage of proteins and nutrients, but also of drugs used in the treatment of neuroinfections. The tightness on this barrier is controlled by multiple proteins implicated in the formation of tight junctions. The main effectors in the BBB tight junctions are claudins (especially claudin-5), which are transmembrane proteins that are implicated in sealing of paracellular space. This structure is also composed of intracellular proteins which regulate tight junction tightness and its link with the cytoskeleton. Proteins such as zona occludens-1, 2, and 3, along with cingulin, act as adaptor molecules between membrane proteins and the cytoskeleton. In addition, occludin, junctional adhesion molecules (JAMs), and adherens junction proteins (PECAM-1, VE-cadherin and caveolin-1) play a role in tight junction regulation [7].

Due to the highly restrictive nature of BBB, several transport mechanisms are present to supply the CNS with nutrients and preserve tissue homeostasis. Several transporters are expressed on the surface of BMEC. GLUT1 is responsible for the transport of glucose and is tightly regulated in response to metabolic needs in the CNS, as demonstrated by the distinct and dynamic distribution of this transporter on both sides of the endothelium [8]. In addition, several amino acid transporters are expressed on both apical and basolateral sides of BMEC [9]. Ion equilibrium across the BBB is maintained using ion transporters for sodium, potassium and chloride. Several transporters in the BBB also function to protect the CNS from toxic substances. Some amino acid transporters are exclusively expressed on the basolateral side to remove excess amino acids from the CNS [10]. BMEC also express ABC transporters, such as P-glycoprotein 1 (P-gp), that pump drugs and other harmful substances back into the circulation [11]. The harmonious action of these transporters preserves CNS

microenvironment integrity, supplies it with nutrients and prevents the entry of toxic molecules.

The layer formed by brain endothelial cells is surrounded by a basement membrane that primary functions to maintain the integrity of the BBB. The luminal layer consists of collagen (mainly isoform IV) and laminins (mainly α4β1γ1 and α5β1γ1 to a lesser degree). The abluminal layer is associated with the brain parenchyma and is produced by astrocytes. It is mainly composed of laminin α1β1γ1 and α2β1γ1. The equilibrium between the luminal and abluminal layers is essential to restrict leukocyte migration [12]. The two layers are linked by the small matrix proteins called nidogen and perlecan [13–15]. The ensemble maintains BBB integrity by providing an anchor substrate for cells of the neurovascular unit (BMEC, astrocytes and pericytes) and a region for cell-cell interaction [16, 17]. This anchoring is imparted using integrins, which can result in intracellular signaling by the FAK and MAPK pathways, affecting cellular proliferation and differentiation [18].

On the brain (i.e., parenchymal) side of the basement membrane, astrocytes and pericytes are the main components of the BBB. They are adjacent to BMEC and have an important role in regulating TJ tightness and the basement membrane integrity. Astrocytes are in direct contact with BMEC using their end-feet projections and cover almost the entire brain side of the BBB [19]. This expanse is discontinuous in only few areas to allow interactions of other cells, such as microglial, neurons and other glial cells, with the BBB. Astrocytes act as a second layer of restriction to molecules transported across this layer and also secrete factors of their own (TGF-β, bFGF and GDNF) to influence BMEC functions [20]. Disruption of this cell-cell communication, often observed in infections and inflammation, can lead to BBB disruption, highlighting the importance of this mechanism in the maintenance of its integrity [21].

Another cells of the neurovascular unit are pericytes. They play an important role in cerebral blood flow via their contractile ability, and are important in maintaining BBB integrity by affecting differentiation of BMEC and angiogenesis [22–24]. Pericytes also influence maturation of brain microvessels. The loss of pericytes results in the accumulation of toxic molecules in the CNS, arteriovenous malformation, and promotes the development of neurodegenerative disease [25, 26]. Evidence demonstrates that pericytes have a regulatory effect on transcytosis, TJ integrity, and vessel structure, which could all be linked to an impact on BBB integrity.

1.2. BBB and HIV infection

There are over 35 million people in the world living with AIDS, and of those around 1.5 million per year succumb to AIDS related illnesses [27]. Disease burden was highly alleviated by the introduction of HAART in 1990s, shifting HIV from a deadly disease to a chronic infection. While some complications related to HIV infections, such as immunodepletion, can be prevented, HIV-infected patients still demonstrate a high incidence of various comorbidities, including neurological disorders [1, 28–30].

HIV is a neuroinvasive virus that can cross into the CNS causing inflammation and neurotoxicity. The crossing of the virus across the BBB is still not fully elucidated; however,

most evidence points to a “Trojan horse” model, in which infected immune cells migrate to the CNS, releasing virus into the brain tissue allowing the subsequent infection of microglial cells and astrocytes [31–33]. Our recent studies indicate that BBB pericytes are also permissible to HIV infection [34, 35]. While HIV-associated dementia (HAD) is rare in patients under HAART, milder neurodegenerative diseases, such as asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND), are still present in 40 to 60% of patients [36, 37]. Typical symptoms of MND are confusion, forgetfulness, and problems with cognition and movement, effecting daily life and work duties. The main cause of HIV associated neurocognitive disorders (HAND) is mainly associated with HIV-encephalitis; however, other factors, such as neurotoxic viral proteins or BBB disruption can play a significant role in cognitive decline and HAND progression.

HIV-induced disruption of the BBB is an important part neuropathogenesis induced by the virus. While HIV does not infect endothelial cells, it can directly infect astrocytes and pericytes, i.e., cells important in maintaining BBB integrity [35, 38, 39]. This process affects a variety of cellular functions important for the maintenance of the barrier integrity, such as the secretion of growth factors and tight junction regulation. The presence of cell-cell communication channels, formed by connexin43 and gap junctions, extends the reach of HIV infection, affecting a wider area and bystander cells. In addition, the ensuing immune responses exacerbate BBB disruption by the secretion of matrix metalloproteinases (MMPs) [40] and decreased expression of tight junction proteins due to pro-inflammatory molecules, such as TNF-α, IL-1β or IFNγ [41–43].

Several HIV proteins exhibit high level of toxicity, which may also induce vascular and neuronal pathology. Exposure of neurons to gp120, even at picomolar levels, is highly toxic and has been linked to HIV-associated sensory neuropathy [44, 45]. Furthermore, gp120 can bind the viral co-receptors, CCR5 and CXCR4, present on BMEC and lead to an increase in monolayer permeability due to downregulation of tight junction proteins and an increase in the levels of MMPs [46]. HIV Tat is another viral protein that has potent toxicity. It can affect BBB integrity and TJ assembly in BMEC, via a process that has been linked to signaling via small GTPases [47]. In addition, Tat exposure can lead to elevated intracellular ROS levels and cause apoptosis [48]. Finally, viral proteins Nef and Vpr have also been shown to be associated with BBB permeability and neurotoxicity [49, 50].

2. TARGETING THE CNS RESERVOIRS

The confined nature of the CNS is highly effective at protecting it from pathogens. However, in the event of failure of this system and established brain infection, the BBB becomes an obstacle that can severely obstruct treatment efficacy. While therapeutic levels of drugs can be achieved in the plasma, several factors can lead to a low degree of penetration into the CNS leading to hindered viral inhibition. As a result, the CNS can act as a viral reservoir where HIV can replicate and increasing the number of latently infected cells [51]. In the event of HAART interruption, virus may cross back into circulation and restore high levels of viremia. Furthermore, the sub-optimal concentrations of antiretroviral drugs (ARVd) in the brain can result in the selection of resistant mutations that lead to loss of treatment efficacy [52]. Finally, HIV replication in the brain stimulates neurodegeneration and

cognitive disorders. These facts highlight the need for drugs that can efficiently cross the BBB to achieve therapeutic concentrations in the CNS to prevent HIV replication.

The efficiency of ARVd in crossing the BBB varies greatly. Efavirenz and atazanavir demonstrate low CSF concentrations, averaging 0.5% and 1% of plasma levels, respectively [53, 54]. In comparison, nevirapine can reach CSF concentration that represent 29–63 % of plasma levels [55, 56]. To further enhance this problem, the ratio of CSF to plasma drug concentration can vary greatly between individuals and over time, in part in association with BBB permeability [57].

It has been demonstrated that treatment of patients with drugs demonstrating low BBB penetration is associated with higher prevalence of neurocognitive disorders. A CHARTER study of 300 individuals demonstrated that 26% of patients with undetectable HIV RNA levels (below 2 copies per ml) had detectable CSF viremia [58]. This study also indicated that patients treated with drug regimen with low BBB penetration levels demonstrate poorer performance on neuropsychological tests. These findings indicate that uncontrolled low levels of CNS HIV replication could lead to nervous system injury leading to HAND. This report is supported by other studies that evaluated patients who developed neurocognitive disorders despite stable antiretroviral treatment and undetectable blood HIV RNA levels [59, 60].

3. STRATEGIES IN CROSSING THE BBB

Several factors can influence CNS drug concentration. Drug efflux pumps, such as P-gp and organic anion transporters can actively shuttle drugs out of the CNS. In addition, several characteristics of the drugs can impact BBB penetration. Molecules highly bound by plasma proteins are less likely to cross the BBB. On the other hand, low molecular weight and hydrophobicity are factors that promote BBB penetration, while ionization has a negative effect.

Multiple mechanisms can play a role in a drug’s ability to cross into the brain parenchyma. They include paracellular aqueous pathway, transcellular lipophilic pathway, transport proteins, receptor mediated transcytosis and adsorptive transcytosis.

3.1. Efflux pump

Numerous drugs, including ARVds, are able to cross the BBB, but are actively pumped out from the brain parenchyma by efflux transporters. For example, protease inhibitors (PI) are mostly large lipophilic drugs that can cross into the brain but bind with high affinity to P-gp [61]. One strategy to overcome this mechanism is to add into the treatment regimen ritonavir (another PI), which demonstrates even higher affinity for P-go and thus reduces PI translocation [62, 63]. An alternate method is to block these transport proteins by co-administration of specific inhibitors along with treatment. Several of such compounds are being developed and are in various stages of clinical development. The use of the first generation of P-gp inhibitors, such as verapamil and cyclosporine A, was compromised by their low affinity and toxicity. The use of the second generation inhibitor valspodar successfully increased treatment efficacy of paclitaxel, who is a substrate of P-gp, and

significantly reduced tumor size in a nude mouse model of glioblastoma [64]. However, the translation to clinical trial had limited success [65]. The use of third generation P-gp inhibitors proved much more successful. For examples, elacridar increased brain concentration of the drug paclitaxel 5-folds and reduced tumor size by 90% [66]. Inhibition of other transporters such as MRP (by sulfinpyrazone and probenecid) and BCRP (by fumitremorgin C) was reported, but their effectiveness in clinical settings has yet to be demonstrated. While promising, these inhibitors demonstrated limited success up to now. In addition, the potential side effects of long term administration of these compounds are unknown, but need to be evaluated given the important role played the efflux transporters in brain homeostasis [67, 68]. A potential alternative is to bypass the efflux transporters without inhibition. Several strategies are being developed, with the most promising being based on masking the drug and transferring it across the brain endothelium without exposure to the ABC transporters. One such mechanism uses immunoliposomes which are coupled with molecules that actively transport it across the BBB to the brain parenchyma.

Testing for transporter activity is useful as a screening tool for identification of drugs with high CNS penetration. However, inconsistencies are observed between BBB models both in vitro and in vivo. These problems, additionally coupled with the population variations in expression and polymorphism of efflux transporters, makes the prediction of drug efficacy difficult and not fully reliable [69, 70].

3.2. Increasing BBB translocation

Because several mechanisms are present at the BBB to actively transport substrates across the BBB, a possible approach is to employ these intrinsic transporters to actively import therapeutics into the CNS. A well explored strategy is to use the transferrin transporter, normally used for iron transport into the CNS [71]. The conjugation of a drug to monoclonal antibody against this receptor has been used experimentally both in vitro and in vivo [72–74]. The strategy demonstrated a significant increase in drug delivery to the CNS in a brain tumor model, leading to a significant reduction in tumor size and increased animal survival [75]. Despite its efficacy, the feasibility of this method is compromised by potential side effects linked to hemolytic anemia associated with the antibody [76]. A new approach, based on a non-competitive peptide that binds to the transferrin receptor, demonstrated low toxicity while retaining the translocation capacity [77–79]. However, it should be added that the binding to the transferrin receptor is influenced by coating density on the therapeutic agent [80].

Other receptors present at the BBB have also been used to increase translocation of therapeutics into the CNS. The low density lipoprotein receptor-related protein-1 (LRP-1) has been demonstrated as a suitable candidate for the translocation of IgG antibody to the CNS, through a process that does not involve vesicle acidification [81]. A monoclonal antibody against the insulin receptor (HIRMAb) coupled with an enzyme was successfully transported to the CNS [82]. In addition, studies have screened potential candidates for receptor mediated transcytosis and identified several target receptors, such as basign, Glut1 and CD98hc in mice [83], transthyretin [84], melanotransferrin [85, 86], apoE [87], RAGE [88], Fcγ [89] and SCAR [90].

In addition to using active transporters, therapeutic agents can also be coupled with cell-penetrating peptides (CPPs) to translocate across the BBB by triggering endocytosis. Several of these peptides have been identified and characterized for their ability to deliver cargo to the CNS, mostly in vitro [91–93]. The first and the most studied group of these peptides was derived from Antp (antennapedia transcription factor from Drosophila Melanogaster) and from the HIV protein TAT [94–96]. A second group of CPP peptides was identified from chimeric molecules, such as transpotan, composed of a segment of galanin and mastroparan, a wasp venom [97]. The third group of this family has been composed of synthetic peptides identified mainly through phage display. The effectiveness for CNS delivery has been demonstrated for several CPPs, such as Tat, RDP, FGF4, RVG, Penetratin, SynB1/3 and Angiopep. They were able to mediate successful delivery of proteins, nucleic acids and/or small molecules [98–104].

The use of nanoparticles also proved to be a suitable method to increase BBB penetration. Nanoparticles can be used in conjunction with the above mentioned approaches to target drug delivery to the CNS or alone to exploit an increase in BBB permeability observed in brain diseases. Several types of nanoparticles can be used, such as nanotubes, liposomes, solid lipid nanoparticles, nanospheres, nanocapsules, polymeric mycelles and dendrimers. They vary greatly in structure and composition. Several of these strategies have been successfully used to deliver compounds to the CNS [105–108]. Dendrimers have demonstrated their ability to translocate small molecules, such as the chemotherapeutic agent doxorubicin, and nucleic acids across the BBB using the transferrin receptor. The strategy resulted in a 2–3 fold increase in CNS concentration as compared to free drug and increased survival time in a mouse brain tumor model [109, 110]. Regarding HIV treatment, a group observed that encapsulation of atazanavir in solid lipid nanoparticles increases uptake by endothelial cells up to 3 folds [111]. Another group tested delivery of stavudine, delavirdine and saquinavir (nuncleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI) and PI respectively) linked to several nanoparticle carriers, observing enhanced delivery across an in vitro BBB model by up to 16 folds compared to drug alone [112]. In a SCID rat model of intracranial HIV-1 infection, it was demonstrated that coupling of zidovudine to a nanogel matrix increased treatment efficacy, leading to lower HIV levels in the CNS [113]. Finally, enfuvirtide, a fusion inhibitor that does not cross the BBB, when coupled with iron oxide nanoparticles coated with amphiphilic polymer, significantly increased translocation and anti-viral activity [114].

Varieties of magnetic nanocarriers (MNCs) have been developed in recent years for target-specific drug delivery. As such, BBB translocation ability of magnetic (Fe3O4/Fe2O3) nanocarrier for anti-HIV and anti-addiction efficacy has been intensively studied [114–122]. However, drug release from this nanocarrier is manually uncontrollable, and depends on pathology-specific cellular responses (e.g. variation temperature, pH, intracellular Ca2+ level, etc.). To overcome this constraint, a novel electro-magnetic carrier (MENCs) was developed. Unlike MNC, MENC possess both magnetic and electric fields at physiological temperature range. The alternating current (AC) trigger on these particles breaks the symmetry of charge distribution i.e. ionic bonding between drugs and nanocarriers which provide control over drug release as and when required [123–126]. A ~3 fold higher transendothelial translocation of AZTTP could be achieved using MENCs, and HIV-p24

inhibition efficacy of AC-triggered released drug remained unaffected [123]. Similarly, mRNAs could be delivered across BBB using MENCs [125], and mice undergoing MENCs treatment to brain did not show signs of negative neuro-modulation [126]. Thus, MENCs possess unique ability to provide control over field-mediated drug release and can be applied to treating many CNS disorders, including HIV infection.

3.3. Bypassing the Blood-brain barrier

A potential way to circumvent the obstacles of the BBB is to enter the CNS using alternative routes of delivery. Several experiments, conducted mainly in rodents, demonstrated that intranasal drug administration increases uptake of drugs to the brain parenchyma as opposed to oral or peritoneal delivery [127–129]. The effectiveness of this delivery has been observed even for large and charged molecules such as insulin [130, 131]. The drugs are routed to the CNS along the olfactory pathway by the nasal cavity extension of the subarachnoid space. While this technique demonstrates promising results, a high variability is observed in various published reports [132–134]. In addition, the differences in nasal physiology between rodents and human make the translation of this technique difficult [135].

Direct delivery to the CNS using physical methods such as intracerebral or intrathecal administration has proved to be effective in several clinical trials, raising a potential of implanting an infusion system to facilitate repeated delivery [136–139]. While this technique bypasses any barriers to drug delivery, its implementation in a large population such as the HIV cohort is not feasible. In addition, the lifelong need for therapy in HIV patients makes the maintenance of this method very challenging and complications have been observed [140, 141].

Finally, a possible delivery route through the BBB is to disrupt it, enabling drugs to cross into the CNS. Several approaches have been tested; however, they rely mainly on osmotic methods that dilate tight junctions by inducing cell shrinkage using chemicals such as mannitol and polydixylitol [142–144]. While they are currently used in the clinic, their delivery methods strongly affects their efficiency in disrupting the BBB. In addition, these compounds may act nonspecifically. A new technique that is rising in popularity for CNS delivery is the use of focused ultrasounds (FUS). This non-invasive method was first discovered in the 1950s [145] but its employment in drug delivery was first studies in the 1990s [146]. The local disruption of the BBB is achieved by focusing ultrasounds at a specific site of the brain and injecting microbubbles into the circulation [147]. When they reach the target area, there is an increase in reagents crossing the BBB due to sonoporation. While this method has been extensively studied in rodents, the translation to non-human primates proved challenging since the thicker skull made it harder for acoustic pressure to reach the brain. While a group was able to use this technique for effective delivery of agents to the CNS [148], there remains the need for further testing to evaluate long term safety and tissue damage [149]. In addition, successful implementation of this treatment approach in a large population may not be feasible.

4. DRUG EFFICACY AND TOXICITY IN CNS CELLS

An important consideration for ARVd efficacy in the CNS is metabolism of cells involved in HIV infection of the brain, which can be substantially different from the cellular targets of HIV infection in the periphery, namely T cells and macrophages. Cells susceptible to HIV infection in the CNS are primarily microglial cells, perivascular monocytes, and astrocytes [35, 150, 151]. It is well known that a cell type plays a central role in determining the inhibitory concentration (IC) of drugs. For example, relatively low levels of nucleotides present in monocytes or astrocytes can increase the effectiveness of NRTIs and NNRTIs [152]. At the same time, a lower activity of cellular kinases needed for the phosphorylation of NRTIs, such as lamivudine or zidovudine, can reduce the effectiveness of these drugs [153].

The microenvironment in the CNS is also quite different than in the serum, affecting drug efficacy. Drugs that are highly protein bound, for example PI and NNRTIs, have diminished activity in the presence of serum [154]. On the other hand, CSF albumin concentration (8–50 mg/L) is lower than in blood (34–54 g/L), allowing for increased efficacy of these therapeutics. In fact, it was shown that darunavir is mainly unbound in CSF [155]. All of these factors need to be taken into consideration when identifying the concentrations needed in the CNS to inhibit HIV replication. This is critical because subtherapeutic levels of drugs allow the development and selection of drug resistance variants of HIV, affecting treatment of infection both in the brain as in periphery.

On the other hand, the neurotoxicity of ARVds also needs to be taken into account when discussing their entry into the CNS. The lack of drug elimination by liver and kidneys once ARVds cross the BBB can lead to their accumulation. This phenomenon can be further amplified by lower activities of enzymes that degrade these compounds in cellular targets of the CNS. For example, a correlation has been observed between efavirenz-associated toxicity and the presence of specific cytochrome alleles, such as CYP2B6*6, implicated in its elimination [156]. This association has also been linked to alterations of mitochondrial functions, disruption of autophagy, and cell stress responses in neurons [157, 158] and other cell types [159, 160]. Moreover, efavirenz and PIs disrupt glucose metabolism [28, 161], and drugs, such as zidovudine and ritonavir, can induce the production of reactive oxygen species, leading to increased cellular oxidation [162, 163]. All these observations highlight the importance of balancing the need for CNS delivery of ARVds with potential side effects that could worsen neurological complications associated with the infection.

5. CONCLUSION

The development of HAND in a large proportion of HIV infected patients highlights the need for comprehensive treatment approaches that can prevent viral replication on both sides of the BBB. Limited activation of specific NRTIs in the brain requires enhanced delivery to reach inhibitory concentrations. At the same time, careful consideration must be applied to identify potential consequences of higher levels of drugs in the CNS. Indeed, neurotoxicity of specific ARVds can be observed at the levels that are therapeutic in the periphery.

Several methods are being explored to overcome the challenges posed by the restrictions of the BBB (see figure 1). While the disruption of the barrier function or bypassing the BBB can enhance drug delivery to the CNS, these procedures are frequently invasive and may not be feasible. On the other hand, modifications of the ARVds or their linkage to other molecules or nanoparticles can result in increased delivery into the brain. Several of such approaches have proven their efficacy in animal models; however, comprehensive clinical studies are needed to determine their applicability to HIV treatment.

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List abbreviation

ANI	Asymptomatic neurocognitive impairment
ARVd	Anti-retroviral drug
BBB	Blood brain barrier
BMEC	Brain microvascular endothelial cells
CNS	Central nervous system
CPE	CNS penetrating efficiency
CPP	Cell penetrating peptide
FUS	Focused ultra-sound
HAART	Highly active anti-retroviral therapy
HAD	HIV associated dementia
HAND	HIV associated neurocognitive disorder
IC	Inhibitory concentration
JAMs	Junctional adhesion molecules
LRP-1	Lipoprotein receptor-related protein-1
MENC	novel electro-magnetic carrier
MMPs	Matrix metalloproteases
MNC	Magnetic nanocarrier
MND	Mild neurocognitive disorder
NNRTI	non-nucleoside reserve transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor

PI	Protease inhibitor

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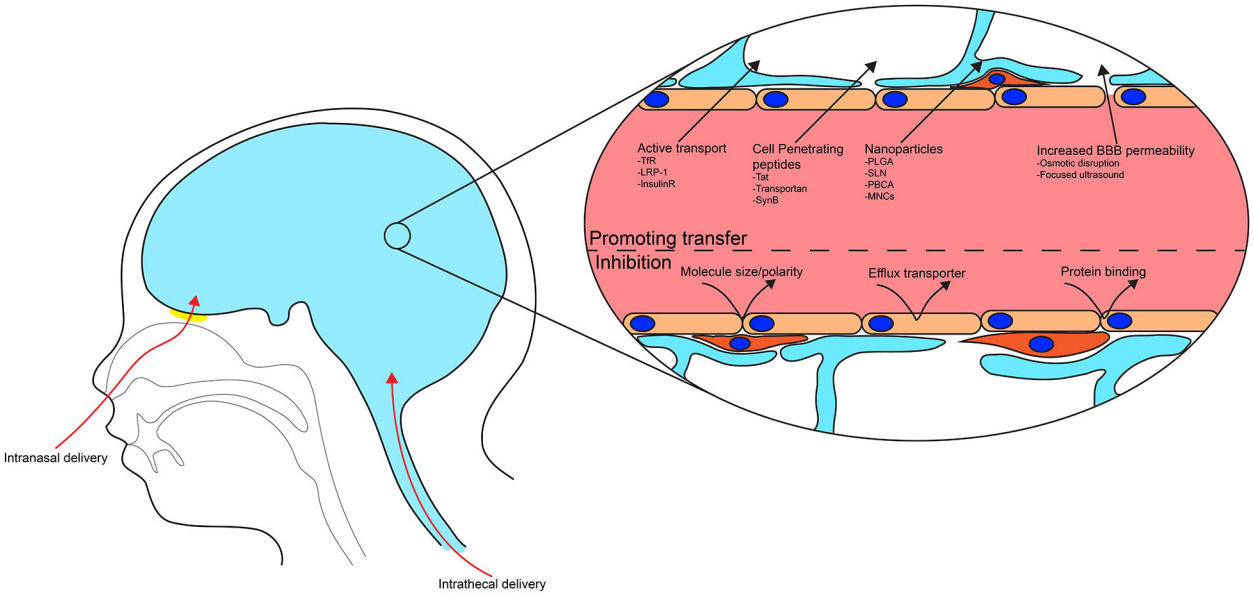

Figure 1: Delivery across the blood brain barrier.

The ability of a drug to reach the CNS is highly dependent on its properties. Molecule size, polarity, and protein binding are factors restricting the passage. Furthermore, a high affinity for efflux transporters will contribute to removing drugs from the CNS. To overcome these obstacles, several mechanisms are targeted, including bypassing BBB, inhibition of efflux transporters, nanotechnology, the use of cell penetrating peptides, and taking advantages from active transporters present at the BBB.

Table 1:

CNS penetrating efficiency (CPE) of anti-retroviral drugs used in HIV treatment.

CNS penetrating efficiency (CPE)					
Drug Class	**4**	**3**	**2**	**1**	**Non-classified**
Nucleoside Reverse Transcriptase Inhibitors	Zidovudine	Abacavir Emtricitabine	Didanosine Stavudine Lamivudine	Tenofovir Zalcitabine	
Nonnucleoside Reverse Transcriptase Inhibitors	Nevirapine	Delavirdine Efavirenz	Etravirine		Rilpivirine: CSF/Plasma ratio 1.2–1.6% but above IC_{50}
Protease Inhibitors	Indinavir/r	Darunavir/r Fosamprenavir/r Indinavir Lopinavir/r	Atazanavir Atazanavir/r Fosamprenavir/r	Nelfinavir Ritonavir Saquinavir Saquinavir/r Tipranavir/r	
Entry/Fusion Inhibitors	Vicriviroc	Maraviroc		Enfuvirtide	
Integrase Inhibitors		Raltegravir			Dolutrgravir: CSF/Plasma ratio 0.467–0.546% but above IC_{50} Elvitegravir: No data (clinical study underway UCSD, Letendre S.)

Table 2.

Summary of strategies to overcome BBB restrictions for CNS delivery

Physical	Direct delivery to the CNS	Intrathecal injection
		Intracerebral injection
	Targeted delivery	Intranasal delivery
	BBB disruption	Osmotic disruption
		Mannitol
		Polydixytol
		Focused ultrasound
Efflux transporter inhibition	Inhibition	P-glycoprotein
		Verapramil
		Cyclosporin A
		Valspodar
		Elacridar
		MRP
		Sulfinpyrazone
		Probenecid
		BCRP
		Fumitremorgin C
Drug coating/modification	Allosteric inhibition	Ritonavir
	Therapeutic making	Immunoliposome
	Receptor mediated transport	Transferin receptor
		Insulin receptor
		Lipoprotein receptor
	Cell penetrating peptide	Antennapeptide
		Tat
		Transportan
		Penatratin
		Angiopep
		SynB1/3
	Nanoparticles	Nanotube
		Liposome
		Solid lipid nanoparticles
		Nanospheres
		Nanocapsule
		Dendrimers
		Polymeric mycells
		Magnetic nanocarriers