The advent of combination antiretroviral treatment has had a profound impact on CNS HIV infection and its clinical complications, but neurological impairment still occurs in patients on systemically effective combination therapy, and in some patients it may be important to consider antiretroviral drug entry and effects within the CNS. There are now data on the CNS exposure for most antiretroviral drugs. This review focuses on the CNS pharmacokinetics and pharmacodynamics of antiretroviral drugs in humans, and also discusses controversies in this field.

Keywords: cerebrospinal fluid, antiretroviral drugs, pharmacokinetics, pharmacodynamics

Introduction

Shortly after the first cases of AIDS were described in 1981, it became clear that the causative agent, later identified as HIV, was a virus that not only was destructive to the immune system, but also had the ability to enter and damage the CNS.1,2 Prior to the introduction of combination antiretroviral therapy (cART), HIV-associated dementia (HAD) and its underlying substrate of HIV encephalitis (HIVE) was a common complication of HIV infection.3,4 Fortunately, this severe HIV-related disease is now rare in patients well maintained on cART.5,6 Less severe (but still important) neurological impairment is prevalent, ranging in some studies to occurring in as many as 70% of treated patients.7–12

The preventative and therapeutic effects of cART on HIV-related brain disease likely result from a combination of systemic and local effects of therapy. In the periphery, antiretroviral treatment maintains host defences, reduces immune activation and limits the continuous reseeding of the brain.13 In addition to these indirect effects, antiretroviral drugs also can have a direct suppressive effect on HIV propagation within the CNS. This local inhibition may be critical in some patients and requires that therapeutic levels of drugs reach infected cells within the CNS.14

Pharmacokinetic issues

The CNS and its barriers

The CNS is surrounded by the blood–brain barrier (BBB) and the blood–cerebrospinal fluid (CSF) barrier (BCB).15 These barriers prevent most molecules from entering the CNS, thereby maintaining a stable brain environment. The BBB differs from other capillaries in the body in a number of ways. It is formed by endothelial cells that are fused together with tight junctions. These cells lack intercellular pores, have a paucity of pinocytosis and possess a large mitochondrial content to fuel the transport pumps active in barrier function. The endothelial cells and pericytes are enclosed by a basement membrane and almost completely surrounded by astrocyte foot processes. The BCB is composed of the choroid plexuses and the arachnoid membrane. The choroid plexus actively regulates the formation of CSF. There are tight junctions in the BCB as well, between the epithelial cells in the choroid plexus, but these do not form a continuous barrier similar to that of the BBB. Lastly, there is exchange between the CSF and the brain extracellular fluid. The CSF is separated from the extracellular fluid of the brain by loosely linked ependymal cells of the ventricles, and diffusion of molecules can occur in both directions and further exchange can occur via perivascular spaces and the CSF.16

Antiviral drug characteristics related to CNS entry and exclusion

Several general drug characteristics determine entry into the CNS through these barriers, including molecular weight, plasma protein binding, lipophilicity and whether or not they are substrates for active transport systems.

Protein binding is both an important determinant of drug penetration into the CNS and a factor in interpreting drug measurements in the blood and CSF. There are both general differences between drugs and interindividual variation in the fraction of bound drug in plasma that can affect a drug’s availability and measurement. Highly protein-bound drugs will have lower unbound concentrations relative to the total drug measured; since only the unbound proportion of a drug can diffuse across the BBB, the concentration gradient of the free drug is lower and, in effect, less drug is available to enter into the CNS. The CSF contains much less protein than plasma and it is usually...
assumed that the unbound fraction of a drug that passes across the BBB is all largely unbound in the CSF, although this has not been extensively tested. The protease inhibitors (PIs) darunavir and indinavir have been shown to be much less bound to proteins in CSF than in plasma. Lipophilicity is also an important determinant of drug diffusion across the BBB. In general, lipid-soluble drugs readily diffuse into the CNS. This property is often predicted by the oil/water partition coefficient for neutral compounds. The optimal oil/water partition coefficient is ~100. Drugs with very low partition coefficients will not diffuse across the BBB because they are not lipid soluble. Drugs with very high partition coefficients (>1000) will also have lower diffusion capacity, because it is difficult for highly lipophilic drugs to diffuse from the lipid layer into the brain extracellular fluid. For acids and bases, lipid solubility is further determined by their degree of ionization, which is pH dependent.

Drugs that are metabolized by the cytochrome P450 3A isozyme also tend to be substrates for P-glycoprotein (P-gp), although this association is not entirely consistent. P-gp is a potent and important system for excluding ‘unwanted’ molecules and is particularly important for PIs, CCR5 inhibitors and integrase inhibitors (HIV integrase inhibitors). Additional host characteristics that can influence CNS drug concentrations include the degree of local inflammation, which is pH dependent.

In order to thoroughly estimate CNS drug exposure, it would be desirable to sample tissue or biological fluids from different parts of the CNS. For obvious reasons, this is difficult in living subjects, although such studies have been performed on animals. As an alternative, clinical studies have used antiretroviral drug concentrations in the CSF as a measure of CNS drug exposure, although it remains uncertain how accurately CSF concentrations reflect brain parenchymal drug exposure. As an example, the nucleoside reverse transcriptase inhibitors (NRTIs) zidovudine and stavudine achieve CSF concentrations in the same range, but animal models show better uptake into brain tissue for zidovudine. Additionally, drug concentrations in brain tissue are not uniform; they vary with the distance from the CSF interface and the vascularity of brain regions, e.g. between white and grey matter. Since much of the burden of infection is focused in the perivascular areas, this may or not be important in the delivery of drugs to infected cells.

**Relationship between CSF drug concentrations and inhibitory drug concentrations**

In theory, to effectively suppress HIV replication it is necessary to maintain inhibitory concentrations (ICs) of the drug over the entire therapeutic interval. This requires that the minimum drug concentration exceeds the IC. The IC is a theoretical concentration that has been calculated based on in vitro findings using strains susceptible to the drug. In this way, one can determine the concentration of the drug necessary to inhibit 50% (IC50), 90% (IC90) or 95% (IC95) of viral replication. In each of these cases, while much or most of the viral replication can be inhibited, inhibition may still be incomplete. For example, by definition, at the exact IC95, 5% residual viral replication remains and it is important that drug levels exceed this value. But it is not clear how much this should be. Is 2-fold enough, or should it be 10-fold or 100-fold? In patients this likely also depends on the overall drug regimen, which may allow effects that are both temporally and functionally additive or synergistic. This consideration may become increasingly important in treating CNS infection with new types of treatment regimens, e.g. NRTI-sparing regimens such as monotherapy with a ritonavir-boosted PI. While this regimen might be enough to suppress systemic infection, reduced drug concentrations inside the CNS may be too low to inhibit local viral replication, leading to CSF escape and an increased risk of developing neurological complications and resistance in the long run. For patients on effective cART, where several drugs suppress the virus, it may be enough if the CSF concentrations are in the range of or slightly exceed the IC.

The IC of an antiretroviral drug can vary considerably, depending on the methods used to determine it, which can include various tests (measuring different markers of HIV replication, cell types (T cells, monocyte cell lines or primary human cells), types of infection (acute, chronic or latent) and viral strains (wild-type, modestly resistant or highly resistant). When the IC is corrected by the drug binding to plasma proteins, it provides an additional measure, the effective concentration (EC), which should provide a better estimate of in vivo effectiveness. This correction can occur in several ways, with very different results.

The addition of 50% human serum to an IC assay attenuates the antiviral activity of that drug. This is most pronounced for highly protein-bound drugs, such as the PIs, where the IC50 values can increase up to 26-fold. The IC50 with 50% human serum most likely overestimates the IC50 for the CSF compartment, but the protein-free IC50 may underestimate these values, at least to some extent. Given the large variability in published IC values, one should be cautious when comparing CSF drug levels with IC values.
**Extracellular drug concentrations and drug action**

A further consideration in relating drug concentrations to in vivo effectiveness relates to their concentrations at the site of action. For enfuvirtide and maraviroc this is outside the cells, and the relationship of the free drug concentration is relatively straightforward. However, the NRTIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs), IIs and PIs exert their effect intracellularly, and the extracellular drug concentrations do not always correlate with intracellular concentrations and activity. This intracellular effect may vary with the nucleotide pool, the requirement for NRTI phosphorylation by cellular kinases to become active and other factors.\(^3^0\) For the NNRTIs efavirenz and nevirapine, drug appears to accumulate intracellularly (this effect is more pronounced for efavirenz) without clear correlation to plasma drug concentrations.\(^3^1,3^2\) In contrast, plasma concentrations of IIs and PIs appear to better correlate with intracellular levels.\(^3^3,3^4\)

**Effect of drugs on different cell types**

In the periphery, up to 99% of the plasma viraeemia is sustained by short-lived CD4\(^+\) T cells.\(^3^5\) In the CNS, the vast majority of productively infected cells are macrophages and microglia.\(^3^6\) There is some evidence that antiretroviral drugs have different effects in CD4\(^+\) T cells and macrophages. In vitro, NRTIs exhibit greater activity against HIV in macrophages than in replicating cells such as activated lymphocytes.\(^3^7\) The NNRTIs and PIs are equally active in macrophages and lymphocytes.\(^3^8\)

**CSF penetration of current antiretroviral drugs**

This section briefly summarizes the available pharmacokinetic and pharmacodynamic data on the antiretroviral drugs currently in use.

**NRTIs**

In general, the NRTIs are small compounds with a low binding to plasma proteins, characteristics that favour diffusion across the BBB (Table 1). On the other hand, they tend to be more hydrophilic than other drug classes. While it would be optimal to analyse the intracellular concentrations of the active triphosphate metabolites in different cell types in vivo, this requires difficult and complex techniques, particularly in relation to the CNS, and is not practical in the clinical setting. The NRTIs have been demonstrated to be transported back into blood from the CNS by a carrier-mediated efflux mechanism that can be inhibited by probenicid.\(^3^9\)

**Abacavir**

Abacavir has been shown to penetrate well into the CSF. Three studies with different dosing schedules have analysed CSF abacavir concentrations.\(^4^0–4^2\) In the largest study a majority of the 54 patients received abacavir 300 mg twice daily as part of cART.\(^5^2\) The median CSF abacavir concentration was 128 ng/mL (range 37–384 ng/mL). According to population pharmacokinetic modelling, the predicted CSF trough concentrations exceeded the IC\(_{50}\) for abacavir (70 ng/mL) for 85% of the dose interval. The CSF/plasma abacavir ratio is approximated to be

**Table 1. Drug characteristics for reverse transcriptase inhibitors**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Molecular weight (Da)</th>
<th>Protein binding (%)</th>
<th>Lipid solubility</th>
<th>Protein-free IC(_{50}) (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside reverse transcriptase inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>abacavir</td>
<td>286</td>
<td>50</td>
<td>low</td>
<td>457.6</td>
</tr>
<tr>
<td>didanosine</td>
<td>236</td>
<td>&lt;5</td>
<td>low</td>
<td>1180.0</td>
</tr>
<tr>
<td>emtricitabine</td>
<td>247</td>
<td>&lt;4</td>
<td>low</td>
<td>70.0</td>
</tr>
<tr>
<td>lamivudine</td>
<td>229</td>
<td>16–36</td>
<td>low</td>
<td>549.6</td>
</tr>
<tr>
<td>stavudine</td>
<td>224</td>
<td>negligible</td>
<td>low</td>
<td>112.0</td>
</tr>
<tr>
<td>tenofovir</td>
<td>288</td>
<td>&lt;7</td>
<td>low</td>
<td>201.6</td>
</tr>
<tr>
<td>zidovudine</td>
<td>267</td>
<td>34–38</td>
<td>low</td>
<td>5.3</td>
</tr>
<tr>
<td>Non-nucleoside reverse transcriptase inhibitors</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>efavirenz</td>
<td>316</td>
<td>99.5–99.8</td>
<td>high</td>
<td>1.3</td>
</tr>
<tr>
<td>nevirapine</td>
<td>266</td>
<td>60</td>
<td>intermediate</td>
<td>32.0</td>
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<tr>
<td>etravirine</td>
<td>435</td>
<td>99.9</td>
<td>high</td>
<td>0.9</td>
</tr>
</tbody>
</table>

The IC\(_{50}\) values for the reverse transcriptase inhibitors are from two independent publications.\(^2^6,2^7\) In both studies the PhenoSense\(^\text{®}\) HIV assay (Monogram Biosciences) was used to determine IC\(_{50}\) values.

31%–44%.\(^4^0,4^2\) Despite its good penetration into the CNS, there are no studies to demonstrate a virological or clinical effect in the CNS. Adding high-dose abacavir for HAD patients on stable cART did not improve performance scores or reduce CSF HIV RNA levels more than placebo.\(^4^3\)

**Didanosine**

Didanosine differs from other NRTIs in not having any of the regular bases, but instead has hypoxanthine attached to the sugar ring. In two studies, CSF levels of didanosine were undetectable and in one study with four patients it was detectable at low concentrations.\(^4^4,4^5\) Without detectable drug levels, antiviral effect cannot be expected and it has been found that monotherapy with didanosine did not reduce the CSF viral load.\(^4^6\)

**Emtricitabine**

Emtricitabine is structurally very similar to lamivudine and has achieved common use. In 21 paired CSF and plasma samples, the median CSF emtricitabine concentration was 109 ng/mL (range 39–386 ng/mL) and the median CSF/plasma ratio was 43%.\(^4^7\) Most of the CSF samples were above the median IC\(_{50}\) (70 ng/mL) and the authors concluded that emtricitabine may inhibit HIV replication in the CSF.

**Lamivudine**

Lamivudine has been one of the most used NRTIs for many years. In a study assessing the reduction of the CSF viral load in patients treated with lamivudine (150 mg twice daily) plus either zidovudine (200 mg three times daily) or stavudine (40 mg twice daily), the CSF concentrations of lamivudine (range 66–80 ng/mL) were all above the IC\(_{50}\).\(^4^8\) In 52 CSF samples from 22 HIV-infected patients, the median CSF lamivudine level was 95 ng/mL (range 12–263 ng/mL) and the median CSF/plasma ratio was 12%.\(^4^9\)
Stavudine
Owing to its side effects (mainly mitochondrial toxicity), stavudine use has declined drastically. CSF concentrations of stavudine have been determined in a number of studies in adults receiving a single oral dose or in patients receiving long-term treatment with stavudine.54–57 Patients on chronic treatment with stavudine had higher CSF concentrations than the volunteers receiving one dose, with concentrations ranging from 0.0 to 109.9 ng/mL. The mean CSF concentration (51.6 ng/mL) exceeded the mean EC50.51 A model-based analysis has estimated the steady-state ratio of AUCs of CSF and plasma concentrations of stavudine to be 0.27, and the mean residence time of drug in the CSF to be 7 h.52

Tenofovir
Tenofovir has become one of the NRTIs recommended for first-line treatment regimens. In a large, as yet unpublished study (117 HIV-infected patients),53 the median CSF tenofovir concentration was 5.0 ng/mL [interquartile range (IQR) 2.2–8.2 ng/mL] and the median CSF/plasma ratio was 4%. None of the CSF samples had concentrations exceeding the median IC50 for wild-type virus (201 ng/mL). What is interesting is that many of the plasma tenofovir concentrations did not exceed the IC50 either. This illustrates the difficulty in finding the ‘correct’ IC value.

Zidovudine
The CSF pharmacokinetics of zidovudine, the first registered anti-HIV drug, has been extensively studied in adults and children.54–57 In the largest study, with 39 patients, the CSF zidovudine levels ranged from 14 to 283 ng/mL.54 Not only has zidovudine been demonstrated to reach therapeutic CSF concentrations in all of these studies, but it has also been shown to decrease CSF HIV RNA levels and to improve neurocognitive dysfunction, caused by HAD, when used as a single agent.3,46,58–60 Diffusion of zidovudine into CSF is ≏20-fold higher than for didanosine, most likely because of its much higher lipophilicity.19 Because of side effects, zidovudine use has markedly decreased in the developed world. Whether the resultant theoretical decline in CNS efficacy will impact neurological disease is not yet certain.

NNRTIs
The NNRTIs are a small heterogeneous group of antiretroviral drugs with varying degrees of plasma protein binding and lipophilicity (Table 1).

Efavirenz
The first published study of the CNS penetration of efavirenz (10 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%.53 In another study, efavirenz was undetectable in 11 patients.64 There is, however, no information about the lower limit of detection or quantification in the latter study. Recently, a larger study with 80 CSF samples reported a median CSF efavirenz concentration of 13.9 ng/mL (IQR 4.1–21.2 ng/mL). All but two samples were above the IC50 (0.51 ng/mL).62

Table 2. Drug characteristics for protease inhibitors, integrase inhibitors and entry inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Molecular weight (Da)</th>
<th>Protein binding (%)</th>
<th>Lipid solubility</th>
<th>Protein-free IC50 (ng/mL)</th>
</tr>
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<tr>
<td>Protease inhibitors</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>amprenavir</td>
<td>506</td>
<td>90</td>
<td>intermediate</td>
<td>5.3</td>
</tr>
<tr>
<td>atazanavir</td>
<td>705</td>
<td>86</td>
<td>intermediate</td>
<td>1.7</td>
</tr>
<tr>
<td>darunavir</td>
<td>548</td>
<td>95</td>
<td>high</td>
<td>0.4</td>
</tr>
<tr>
<td>fosamprenavir</td>
<td>586</td>
<td>90</td>
<td>intermediate</td>
<td>5.3</td>
</tr>
<tr>
<td>indinavir</td>
<td>712</td>
<td>60</td>
<td>intermediate</td>
<td>4.3</td>
</tr>
<tr>
<td>lopinavir</td>
<td>629</td>
<td>97–99</td>
<td>not found</td>
<td>3.1</td>
</tr>
<tr>
<td>nelfinavir</td>
<td>664</td>
<td>&gt;98</td>
<td>high</td>
<td>11.0</td>
</tr>
<tr>
<td>ritonavir</td>
<td>721</td>
<td>98–99</td>
<td>not found</td>
<td>not found</td>
</tr>
<tr>
<td>saquinavir</td>
<td>671</td>
<td>98</td>
<td>intermediate</td>
<td>3.6</td>
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<tr>
<td>tipranavir</td>
<td>603</td>
<td>&gt;99.9</td>
<td>high</td>
<td>53.0</td>
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<td>Integrase inhibitors</td>
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<tr>
<td>raltegravir</td>
<td>594</td>
<td>83</td>
<td>low</td>
<td>3.6</td>
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<tr>
<td>Entry inhibitors</td>
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<tr>
<td>maraviroc</td>
<td>514</td>
<td>76</td>
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<td>—a</td>
</tr>
<tr>
<td>enfuvirtide</td>
<td>4492</td>
<td>92</td>
<td>not found</td>
<td>—a</td>
</tr>
</tbody>
</table>

The IC50 values were retrieved from two independent publications, both using the PhenoSense® HIV assay (Monogram Biosciences).36,27

The active efflux pump that restricts the entry of large (>500 Da), lipophilic agents into the blood from the gut and into the brain.

References
from the blood (Table 2). The CSF concentrations of ritonavir-boosted atazanavir, darunavir and lopinavir in relation to the protein-free IC₅₀ are presented in Figure 1.

**Ritonavir**

Nowadays, ritonavir is used exclusively to boost other PIs rather than as a direct therapeutic agent. It increases the plasma AUCs, half-lives and trough concentrations of other PIs by inhibiting the cytochrome P450 3A isozyme. It is also an inhibitor of P-gp, and thus can enhance CSF levels of other drugs both by increasing plasma concentrations and more directly by inhibiting efflux. The CSF levels of ritonavir, when used as part of a double-PI regimen (400 mg twice daily), were measurable in 11 of 11 CSF samples, with CSF concentrations ranging from 1.9 to 23 ng/mL. The median CSF/plasma ratio was 0.2%. These CSF ritonavir levels did not exceed the protein-free IC₅₀ of ritonavir (42–55 ng/mL) used in this study. The low dose of ritonavir used when boosting (usually 100–200 mg/day) leads to even lower CSF concentrations.

**Amprenavir and fosamprenavir**

After oral administration, fosamprenavir is rapidly and almost completely hydrolysed to amprenavir before reaching the systemic circulation. After a single dose of 630 mg of amprenavir, CSF samples were collected from five healthy males. Only one sample had quantifiable CSF amprenavir levels. In another, plasma (11 ng/mL) and 24% were close to the IC₅₀ determined without human proteins (1.0 ng/mL). The authors concluded that these CSF levels of amprenavir might not protect against HIV replication in the CSF. To evaluate the effect of monotherapy with amprenavir/ritonavir on cART, lumbar punctures were performed on 20 patients who had received this regimen as maintenance therapy for 24 weeks. Plasma HIV RNA levels were <50 copies/mL in all patients, but three patients had elevated CSF viral loads (160–6500 copies/mL), indicating a high incidence of CSF escape.

**Darunavir**

Darunavir is the most recently licensed PI. In 14 samples from eight experienced HIV-infected patients receiving 600 mg/100 mg of darunavir/ritonavir twice daily plus optimized background therapy, the median CSF darunavir concentration was 34.2 ng/mL (range 15.9–212 ng/mL). All CSF samples had darunavir levels above the lower range of the IC₅₀ in the presence of 50% human serum (12 ng/mL). Since darunavir is only 6.8% bound to proteins in the CSF, an IC₅₀ adjusted for the CSF compartment would probably be lower than the IC₅₀ used in this study. Darunavir/ritonavir is currently being investigated as a possible candidate for monotherapy. The aim of the MONOI-ANRS study was to evaluate monotherapy with darunavir/ritonavir as a maintenance strategy for patients on suppressive cART. Among the 112 participants randomized to receive darunavir/ritonavir twice daily, two developed neurological symptoms compared with none among the 113 patients randomized to continue with cART. In these two patients the CSF demonstrated elevated HIV RNA levels, 330 and 580 copies/mL, respectively, whereas plasma HIV RNA levels were suppressed. The addition of two NRTIs led to improvements in symptoms and reductions of the CSF viral load.

**Indinavir**

Indinavir is only rarely used nowadays because of its dosing frequency and renal toxicity, but it is the PI with the most favourable characteristics for passage through the BBB. It is also the only PI that achieves therapeutic concentrations in CSF without ritonavir-boosting (dosing 800 mg three times daily). Concentrations are even higher in the presence of ritonavir, with a mean CSF indinavir minimum concentration of 203 ng/mL. Here, the CSF concentrations were compared with the IC₉₅ (18–71 ng/mL) and all the CSF samples were above the upper limit of this range throughout the entire dosing interval. The unbound proportion of indinavir in the CSF has been demonstrated to be 98.6%.
Lopinavir
Lopinavir has been detected and quantified in three studies with 15, 31 and 10 paired CSF and plasma samples, respectively.\textsuperscript{73,74,75} The results were similar; the median CSF concentrations were 17.6 ng/mL (IQR 15.1–30.2 ng/mL), 17.0 ng/mL (IQR 12.1–22.7 ng/mL) and 11.2 ng/mL (IQR 6.7–16.4 ng/mL). The CSF/plasma lopinavir ratio was \(\sim 0.2\%\) in all three studies. All the CSF samples were above the median IC\textsubscript{50} (1.9 ng/mL) for wild-type virus. Monotherapy trials with lopinavir/ritonavir have been conducted, but in contrast to darunavir/ ritonavir monotherapy it appears inferior to standard cART in suppressing virus in blood.\textsuperscript{74} Treatment with lopinavir/ritonavir as a single agent has been shown to reduce the CSF HIV RNA levels,\textsuperscript{75,76} but a recent study with patients on effective cART randomized to lopinavir/ritonavir monotherapy (\(n=29\)) or continued treatment (\(n=31\)) had to be terminated prematurely because the high rate of failures in the monotherapy arm.\textsuperscript{24} In the continued treatment arm, 13 patients switched to monotherapy after 48 weeks of therapy. In total, four of six patients with plasma failure developed neurological symptoms. All were on monotherapy. In five of the failing patients, lumbar punctures were performed. All had elevated CSF HIV RNA levels (3.1–5.1 \(\log_{10}\) copies/mL). In addition, 8 patients among 25 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 the CSF. Only four of the eight subjects reached the predefined CSF-failing criterion (\(>2.6 \log_{10}\) copies/mL) and only one out of these four patients had undetectable plasma HIV RNA.

Nelfinavir
The CSF concentrations of nelfinavir were similar in two published studies.\textsuperscript{77,78} Nelfinavir was quantifiable in 9/15 samples and 8/18 samples, respectively. Some of the concentrations were in the range of the IC\textsubscript{50}, but most of them were below it. When used as a single agent for 17 days (in three patients), nelfinavir failed to suppress the CSF viral load.\textsuperscript{75}

Saquinavir
Several studies have consistently shown that saquinavir is undetectable in CSF and when used as monotherapy it does not reduce the CSF viral load.\textsuperscript{67,77,79,80} Higher plasma concentrations of saquinavir are achieved when it is boosted with ritonavir, but even with this boosting the CSF concentrations of saquinavir have been shown to be low.\textsuperscript{67}

Tipranavir
There are no published data on the CSF concentrations of tipranavir, but from its molecular properties it is not expected to reach therapeutic levels in the CSF.

Fusion inhibitors
Enfuvirtide
Enfuvirtide is a synthetic 36 amino acid oligopeptide.\textsuperscript{85} Its chemical structure suggests that enfuvirtide would not reach effective drug concentrations in the brain (Table 2). Indeed, CSF concentrations of enfuvirtide were below the lower limit of quantification (25 ng/mL) in 18 out of 18 CSF samples.\textsuperscript{56} In plasma, enfuvirtide concentrations were \(>100\)-fold higher. A recent report very elegantly demonstrated the selection of enfuvirtide-resistant virus in CSF, causing subsequent loss of viral suppression in plasma.\textsuperscript{67} The CSF concentration of enfuvirtide in this patient was 55 ng/mL.

Chemokine receptor blockers
Maraviroc
Maraviroc is the only licensed CCR5 coreceptor antagonist for the treatment of HIV-1 infection, and like the PIs and raltegravir it has been shown to be a substrate for P-gp.\textsuperscript{88} In two different studies, maraviroc was detectable in all seven CSF samples with a median concentration of 3.6 ng/mL (range 1.8–12.2 ng/mL) and in 11 out of 12 CSF samples with a median concentration of 2.6 ng/mL (range \(<0.5–7.2\) ng/mL).\textsuperscript{89,90} Median CSF/plasma ratios were 3\% and 2.2\%, respectively. All CSF samples were \(\geq 3\)-fold above the median EC\textsubscript{50} for maraviroc (0.57 ng/mL).\textsuperscript{91}

Aggregate drug effects: CNS penetration effectiveness score
The CNS penetration effectiveness (CPE) score has been proposed as a method for estimating the combined CNS effectiveness of ART regimens.\textsuperscript{92} 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).\textsuperscript{93} This ranking is based on a drug’s chemical properties (molecular weight, protein binding, lipophilicity and charge at physiological pH), pharmacokinetic data (mainly CSF concentrations compared with inhibitory concentrations for wild-type HIV-1) and, when available and most importantly, pharmacodynamic data (effectiveness in the CNS in clinical studies).\textsuperscript{92} The total CPE rank for a
regimen can be calculated by summing the individual penetration scores for each antiretroviral drug in the regimen. The CPE rank has been shown to correlate with improvements in cognitive performance and with CSF viral loads in some studies, while other studies have found no correlation with neurocognitive improvement, detectable CSF viral loads or level of intrathecal immune activation. This suggests that using a simple categorical scale may not be sufficient in judging CNS efficacy and that a degree of caution in implementing the CPE ranking system in routine clinical practice is indicated. Other limitations are that the amount of data for some drugs is very limited and that they do not take into account possible genotypic resistance, but as more information is gathered the CPE ranking system will probably develop further.

**Methods of evaluating CNS drug effects (pharmacodynamics)**

Pharmacodynamic data are only available for a few drugs, since the determination of the effect of a single drug on the CNS HIV infection requires observations during monotherapy, which has only been done with a small number of drugs. Indeed, if the issue of CNS effects proves to be important, it might be very useful to include CSF measurements during the initial phase of drug development, as a brief period of monotherapy exists in Phase 1 studies.

**CSF HIV RNA responses**

Both neurologically asymptomatic and neurologically impaired HIV-infected patients initiating cART usually show a marked decrease of CSF HIV RNA levels after starting therapy, although the relative rates of viral decay in the CSF and blood may differ between these two groups of patients. Slower decay of HIV RNA levels in CSF than in blood has been noted in subjects with HAD and lower blood CD4+ cell counts but without CSF pleocytosis. Even in patients failing therapy systematically, ART is often more effective in CSF than in blood, but this is not always the case. A recent study showed that 10% of patients on effective standard cART had CSF viral load >50 copies/mL despite having <50 copies/mL in blood. A reduction of CSF HIV RNA levels after initiation of treatment with a single drug has only been studied for some antiretroviral drugs.

**Changes in clinical neurological function or neurocognitive performance**

As for major opportunistic infections, the widespread use of cART has markedly reduced the incidence of HAD. Nowadays, patients presenting with severe cognitive/motor decline similar to that encountered before cART are uncommon and confined almost exclusively to late-presenting untreated patients or those failing treatment because of drug resistance or non-adherence. In the past few years, more attention has been paid to milder forms of neurocognitive impairments: asymptomatic neurocognitive impairment and mild neurocognitive disorder. Neuropsychological studies from different parts of the world report this kind of abnormality in 15%–68% of patients. The prevalence may, however, be overestimated because of very sensitive definitions of neurocognitive dysfunction. Several studies have demonstrated improvements in cognitive functioning after the introduction of cART, although some studies describe only incomplete recovery, stabilization of symptoms or even further deterioration. An association between the use of so-called neuroactive drugs largely based on the CPE score discussed above and good neurocognitive performance has been reported.

**Character of CNS infection bearing on antiretroviral treatment**

**Non-compartmentalized and compartmentalized infection**

HIV can be detected within the CSF of virtually all those infected, beginning with the primary infection, continuing throughout the course of neurologically asymptomatic infection to those developing HAD. In untreated individuals, CSF HIV RNA levels are generally 10-fold lower than plasma levels, but the difference between the viral loads in the two fluids varies widely. During early untreated infection, HIV populations in CSF and blood may be identical (non-compartmentalized infection), but subsequently during chronic infection the populations diverge (compartmentalized infection). The greatest divergence is seen in patients with HAD/HIVE. This CSF viral heterogeneity appears to be important in treating and evaluating the antiviral therapy of CNS infection. Non-compartmentalized infection appears to derive chiefly from trafficking CD4+ T cells and responds rapidly to treatment, in parallel with blood decay. While this may also be the case with some compartmentalized infection, in others the response is slower and suggests a different cell source, likely macrophages in the brain.

**Modes of drug effect**

Given the variable sources of CSF virus, antiretroviral drugs can have an effect in several ways. Theoretically, non-compartmentalized infection may not rely heavily on CNS penetration, since it will decay as the blood source is cleared. In contrast, compartmentalized infection may require good CNS penetration and activity, since the cell source remains behind the barriers to drug entry. This direct effect is probably more important in patients with advanced disease and/or HAD. When one considers the influence of CNS penetration on the CSF viral load, it may be that this relates to only one component of CSF virus while for another component this is less important. Routine CSF HIV RNA measurements, of course, do not allow this distinction. Systemic therapy might also contribute to a reduction in CNS infection by less direct mechanisms, including through an effect on immune activation with reduced cell and viral traffic. In most patients these mechanisms seem to be effective in suppressing infection, even when regimens do not achieve theoretically desirable levels of one or more of the components. The mentioned recent reports of symptomatic and asymptomatic viral escape and observations of persistent low-level immune activation may indicate that CNS treatment, including treatment of this compartmentalized CNS sort, may be needed in the long run.
Conclusions

The interest in HIV-related neurological complications has shifted since the 1980s. In the beginning, when many patients developed HAD and other neurological complications, this was a prominent issue. With the gradual introduction of antiretroviral drugs and the following increase in survival and dramatic reduction of all AIDS-defining conditions, including HAD, attention on the CNS impact of treatment diminished. Lately, interest in this issue has again increased with the prospect that an appreciable number of HIV-infected individuals will develop cognitive impairment despite effective treatment. The number is uncertain and may also depend on the time that treatment is started. Moreover, not all cognitive impairment may be attributable to HIV infection, since many patients have other risks (e.g., drug abuse) and may be susceptible to the premature effects of cardiovascular disease and other conditions related to ageing.

The use of antiretroviral drugs with good CNS penetration (zidovudine, lopinavir/ritonavir and indinavir) has declined markedly, and the use of drugs with less favourable characteristics for entry into the CNS (tenofovir and atazanavir/ritonavir) has increased. We do not know the long-term effects of many of these new drugs and drug combinations on the CNS HIV infection. Will we now experience more cases of CSF escape with antiretroviral regimens that are less effective in the CNS?

Recommendations

The most recent HIV treatment guidelines (version 6-0) of the European AIDS Clinical Society131 and the Swedish Reference Group for Antiviral Therapy132 contain a section on the diagnosis and management of neurocognitive impairment in HIV-infected individuals, but most other current treatment guidelines have no special considerations regarding the CNS.133,134 Below, we will try to outline how we regard the issue of treating the CNS HIV infection in some special circumstances.

Neurologically asymptomatic subjects/normal neuropsychological evaluation

In neurologically asymptomatic patients—i.e. most of those who initiate therapy—it is likely that the CNS warrants no special consideration and cART can be initiated or continued as now recommended by guidelines.

Subjects who present with new or progressive neurological symptoms and signs consistent with HAD

Untreated patients who present with new or worsening neurological symptoms and signs consistent with HAD should be further investigated with neuroimaging (magnetic resonance imaging), if available, and CSF evaluation. The determination of viral markers (HIV RNA), inflammatory markers (neopterin, β2-microglobulin or MCP-1) and markers of neurological damage (neurofilament light-chain protein or t-tau) can be of considerable assistance in the diagnostic process, both to rule out other causes of neurological abnormalities and to document a role for HIV. Plasma resistance testing should be performed as recommended by the treatment guidelines. The basis for treatment recommendations in these patients is not clear, but they should preferably initiate a regimen that penetrates well into the CSF/CNS. A triple-drug regimen consisting of two NRTIs + one ritonavir-boosted PI is most likely sufficient, and one suggestion is a combination of lamivudine and zidovudine, plus darunavir/ritonavir or lopinavir/ritonavir. While zidovudine is not now recommended as first-line therapy, it is one of the most studied drugs regarding CSF pharmacodynamics. Zidovudine might subsequently be replaced by tenofovir or abacavir after a period of time to reduce toxicity and ease adherence. In some cases, the addition of nevirapine to a PI-based regimen can be considered. Nevirapine also has good CNS penetration, but has a low genetic barrier to resistance and might therefore not be suitable for patients with neurocognitive impairment with possible adherence problems, when used instead of a PI.

For patients already on therapy who present with new neurological symptoms and signs, we recommend the same evaluation as for patients without treatment to exclude alternative diagnoses and evaluate a possible role for HIV and CNS escape. Importantly, this includes CSF analysis as outlined above. If possible, this should include resistance testing on CSF virus, and a change in therapy should take into account both the CSF virus susceptibility and try to include at least two drugs that either have known CNS activity or reach therapeutic levels in CSF, similar to the regimen suggested above. To evaluate the treatment effect, a new lumbar puncture after 3–4 months is recommended for analysis of the CSF viral load and markers of inflammation and neurological damage.

Subjects with abnormalities on neuropsychological testing, without clear evidence of progression

Neuroimaging and CSF evaluation might assist in choosing an ART regimen for a naive patient with abnormalities on neuropsychological testing who is about to start treatment. If there is no evidence of HIV encephalitis or alternative causes of impairment, and CSF HIV RNA levels are low (less than the plasma viral load), therapy could most likely be chosen as for neurologically asymptomatic patients. If CSF HIV RNA is greater than the plasma viral load, treatment with a focus on the CNS (as for subjects who present with new or progressive neurological symptoms and signs consistent with HAD) can be considered. Subjects already on cART with CSF HIV RNA <50 copies/mL can continue with the same regimen if imaging does not reveal any signs of HIV encephalitis. If, however, the patient has HIV RNA >50 copies/mL in plasma and/or CSF, therapy should be adjusted with consideration of the virus susceptibility and, if relevant, CNS penetration.

Subjects with CSF escape

Some patients, with or without neurological symptoms, present with so-called CSF escape (most often defined as CSF HIV RNA >50 copies/mL and plasma HIV RNA <50 copies/mL).96,130 In symptomatic patients, switching treatment to a more ‘neuro-effective’ one has been shown to improve symptoms and to reduce the CSF viral load in individual cases, and appears to be prudent.130 CSF escape in neuro-asymptomatic patients has been discovered in the context of studies. The meaning of these asymptomatic increases in CSF HIV RNA are not yet clear, nor is their natural history—are they equivalent
to plasma blips or do they signify indolent encephalitis with eventual neurodegenerative consequences? Additionally, CSF escape can be secondary to another neuroinflammatory condition and is not an unusual finding in patients who have other conditions, such as CNS opportunistic infections, e.g. herpes zoster, neurosyphilis and Lyme disease.\textsuperscript{135,136} In these patients, the increase in CSF viral load is transient and probably does not need special antiretroviral consideration. However, patients with CSF escape and no other CNS diseases need to be longitudinally followed and, if high CSF HIV RNA levels are present, further investigations and change of therapy can be considered as for treated patients with neurocognitive symptoms.

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Transparency declarations

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References


The document contains a list of references and abstracts related to HIV and its treatments, focusing on the penetration of antiretroviral drugs into the central nervous system (CNS). The references are cited in the text, providing evidence for the effectiveness of certain drugs in the CNS compared to their plasma concentrations.

For example, one reference mentions the use of nevirapine in plasma and its association with improved virological response. Another reference discusses the pharmacokinetics of amprenavir and its stability in brain entry with combination ritonavir and saquinavir.

The references also highlight the importance of understanding drug transporters and their role in CNS penetration, such as P-glycoprotein, which limits oral absorption and brain entry of HIV-1 protease inhibitors. The use of combination therapies, like ritonavir with or without nucleoside analogues, is discussed in the context of improving CNS drug levels.

Overall, the text provides a comprehensive overview of the challenges and advancements in the treatment of HIV, particularly focusing on optimizing drug delivery to the CNS through the use of appropriate combination therapies and understanding the role of drug transporters.


