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REVIEW ARTICLE

CSF Penetration by Antiretroviral Drugs

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Abstract Severe HIV-associated neurocognitive disorders (HAND), such as HIV-associated dementia, and opportunistic CNS infections are now rare complications of HIV infection due to comprehensive highly active antiretroviral therapy (HAART). By contrast, mild to moderate neurocognitive disorders remain prevalent, despite good viral control in peripheral compartments. HIV infection seems to provoke chronic CNS injury that may evade systemic HAART. Penetration of antiretroviral drugs across the blood–brain barrier might be crucial for the treatment of HAND. This review identifies and evaluates the available clinical evidence on CSF penetration properties of antiretroviral drugs, addressing methodological issues and discussing the clinical relevance of drug concentration assessment. Although a substantial number of studies examined CSF concentrations of antiretroviral drugs, there is a need for adequate, well designed trials to provide more valid drug distribution profiles. Neuropsychological benefits and neurotoxicity of potentially CNS-active drugs require further investigation before penetration characteristics will regularly influence therapeutic strategies and outcome.

1 Introduction

HIV-associated neurocognitive disorders (HAND) remain a challenge for the treatment of HIV infection. After the virus has penetrated the CNS in early stages of infection, both infected lymphocytes crossing the blood–brain barrier (BBB) and resident macrophages and microglia sustain HIV replication in the CNS [1], leading to neuronal damage and HAND [2]. As a result of highly active antiretroviral therapy (HAART), the incidence of HIV-associated dementia (HAD) and HIV-associated CNS opportunistic infections has declined, but mild to moderate neurocognitive impairment remains prevalent [3–6]. HAART can improve and often reverse neurocognitive dysfunction and suppress the viral burden in the CSF, a suggested surrogate marker for CNS infection [7, 8]. Benefits of therapy, however, vary from individual to individual. Even with suppression of HIV-RNA in the CSF to undetectable levels, milder forms of neurocognitive dysfunction may persist [9, 10] and markers of intrathecal immunoactivation regularly remain elevated [11–13]. While the viral load in the systemic compartment rapidly falls below the detection limit after the initiation of HAART, the antiviral response is often delayed in the CSF relative to the blood [14]. All these observations suggest that HAART is not as effective in the CNS as it is in peripheral compartments, raising the concern of insufficient penetration of antiretroviral drugs (ARVs) across the BBB. The ability of ARVs to reach therapeutic concentrations within the CNS is crucial in the face of the high-replication rates of CNS infection, as occurs in HAD [1], and might also reduce ongoing low-grade viral replication [15–17], possibly preventing the genetic compartmentalization of HIV infection, the development of a drug-resistant virus and irreversible damage within the CNS.

The CHARTER (CNS HIV Antiretroviral Therapy Effects Research) study group has devised a ranking scheme in order to quantify and compare the effectiveness of ARVs in the CNS. A revised version of this system was

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proposed in 2010 (see Table 1) [18]. On the basis of information from the literature on measured CSF concentrations, physiochemical drug characteristics and effectiveness in the CNS (reflected by suppression of CSF viral load and improved neurocognitive performance), the ranking system divides drugs into four categories according to penetration estimates. Individual ranking scores of the drugs included in a therapeutic regimen are summed up in the CNS penetration-effectiveness (CPE) rank [15, 18]. Altogether, the application of this ranking system has been successful. Higher CPE scores, consistent with higher penetration estimates, are associated with lower HIV-RNA levels in the CSF [15, 17, 19]. There has also been an association between higher CPE scores and neurocognitive improvement in HAND-affected patients [16, 19–21] and perinatally HIV-infected children [22], though results have not always been consistent [17].

Although at present the role of CNS penetration by ARVs for the treatment of various forms of HAND is controversial, the extent to which components of HAART can be detected in the CNS is of strong interest for two reasons. First, to provide extensive information for prospective trials to further investigate this question. Secondly, the fact that HIV is a neurotropic virus that penetrates the CNS early in the course of disease implies that the CNS must be one of the target sites for therapy. Healthcare providers who treat neurological manifestations of HIV infection should be aware of basic pharmacological properties of HAART components. The aim of this systematic review is to synthesize and evaluate the available clinical data on the penetration of ARVs into the CSF. The findings are discussed in the context of their clinical implications.

1.1 Transport of Drugs Across the Blood–Brain Barrier

Passive transport across the BBB is influenced by the chemical and physical properties of a drug. The main contributing factors are ionization, molecular weight, lipophilicity and protein binding. High molecular weight can potentially impair passive drug transport across biological membranes. In this context, the molecular weight of some components of HAART, for example of many protease inhibitors (PIs), might be critical [23]. In contrast, lipophilic properties enhance passive drug diffusion, being generally directly proportional to the transport rate of a drug across lipid membranes. However, highly lipophilic drugs may be 'trapped' inside the membrane, complicating partition into the opposite extracellular compartment [23, 24]. Furthermore, the affinity to plasma proteins limits penetration, as the passage of drugs across the BBB is restricted to the unbound fraction [25].

In addition to passive drug diffusion and facilitated transport, a variety of active transporters carry anti-HIV drugs across the BBB and the blood–CSF barrier. Transport occurs in both directions and is affected by interaction, inhibition and induction by concomitant drugs [26]. Among a number of potential and more or less characterized transporters localized at the barriers to the CNS, the efflux transporter P-glycoprotein (P-gp) from the family of multidrug resistance-associated proteins (MRPs) was investigated most extensively. Expressed on the luminal surface of brain capillary endothelium and in the choroid plexus' epithelial cells [27], P-gp limits delivery of several ARVs to the CNS by active efflux, representing an efficient component of the BBB [23, 25].

Table 1 Revised CNS penetration-effectiveness (CPE) ranking (reprinted with permission from IAS–USA. Letendre et al. [18]. Updates available at: http://www.iasusa.org)

Antiretroviral drug class[a]	4	3	2	1
NRTI	Zidovudine	Abacavir	Didanosine	Tenofovir
		Emtricitabine	Lamivudine	Zalcitabine
			Stavudine	
NNRTI	Nevirapine	Delavirdine	Etravirine	
		Efavirenz		
PI	Indinavir/ritonavir	Darunavir/ritonavir	Atazanavir	Nelfinavir
		Fosamprenavir/ritonavir	Atazanavir/ritonavir	Ritonavir
		Indinavir	Fosamprenavir	Saquinavir
		Lopinavir/ritonavir		Saquinavir/ritonavir
				Tipranavir/ritonavir
Entry/fusion inhibitors		Maraviroc		Enfuvirtide
Integrase strand transfer inhibitors		Raltegravir		

NNRTI non-nucleoside reverse transcriptase inhibitor, *NRTI* nucleoside reverse transcriptase inhibitor, *PI* protease inhibitor

[a] Larger numbers reflect estimates of better penetration or effectiveness in the CNS

1.2 Methods of Literature Review

We performed a systematic search for studies assessing drug concentrations of commonly used anti-HIV drugs in the CSF, which are zidovudine (AZT), stavudine (d4T), lamivudine (3TC), abacavir sulfate (ABC), tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), nevirapine (NVP), efavirenz (EFV), etravirine (ETV), saquinavir (SQV), ritonavir (RTV), indinavir (IDV), nelfinavir (NFV), amprenavir (APV), lopinavir (LPV), atazanavir (ATV), fosamprenavir (FPV), darunavir (DRV), enfuvirtide (T-20), maraviroc (MVC) and raltegravir (RAL). PubMed was searched from 1980 to June 2012 for relevant studies. The following combinations of keywords were used: ('highly active antiretroviral therapy' OR HAART OR cART) AND (CSF OR 'cerebrospinal fluid'); [drug name] AND (CSF OR 'cerebrospinal fluid'); [drug name] AND (CNS OR 'central nervous system' OR brain). Additionally, reference lists of review articles were hand searched. Abstract data from the Conferences on Retroviruses and Opportunistic Infections (CROI) from 1997 to 2012 were searched. Reports on clinical studies were included when they provided concentration values of one or more of the above-mentioned ARVs in the CSF. Case reports and clinical trials considering less than four CSF samples per dose were excluded. Preliminary data from conference abstracts were included only if one or less published studies were available for a drug. Reports in languages other than English, French or German were excluded. From eligible reports, relevant information was extracted, including study design, study size, drug regimen, CSF post-dose sampling time, CSF drug concentrations, CSF-to-plasma concentration ratio, estimated antiviral activity in the CSF, neurological status of study subjects and neurological outcome measures.

2 Results

2405 records were identified through searching of PubMed. Sixty-six published studies met the eligibility criteria. Additionally, two unpublished conference abstracts were included in the review. The characteristics of eligible clinical studies are listed in Table 2, sorted by drug class and date of publication.

By now, CSF drug concentrations are available for all of the commonly used ARVs. Due to largely heterogeneous study designs and subject characteristics, we did not perform a quantitative meta-analysis in this review. Clinical data on CSF penetration of ARVs derive largely from observational trials with small study sizes. Generally, ARVs show limited penetration of the BBB, reflected by CSF-to-plasma concentrations ratios below 100 % in all studies included in this review. Still, drugs differ importantly in their ability to accumulate in the CSF.

2.1 Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) such as zidovudine were the first drugs found to be effective against HIV-associated CNS disease. In vitro, NRTIs show remarkable activity against HIV replication in macrophages, the principal target cells for HIV in the CNS [96]. Clinical studies have demonstrated notable CSF penetration for zidovudine, stavudine, lamivudine, abacavir and emtricitabine (Table 2). In contrast, CSF concentrations of tenofovir have been relatively low with a median CSF-to-plasma concentration ratio of about 5 % [51, 52].

The degree of binding to plasma proteins is generally low for NRTIs, ranging from 0.7 % for tenofovir to 50 % for abacavir, and should not substantially affect the amount of drug available to be distributed into the CNS. Abacavir has the most marked lipophilic properties and the highest affinity to plasma proteins among this class of ARVs. About 50 % of systemic abacavir is bound to plasma proteins and thus not available for transport into the CNS; substantial lipophilicity, however, enhances its ability to cross cell membranes and to penetrate into body tissues, including the brain [97]. Indeed, measured CSF concentrations of abacavir suggest considerable penetration (see Table 2).

CSF-to-plasma concentration ratios of zidovudine, stavudine, lamivudine, abacavir and emtricitabine increase over time after dosing [32–34, 43, 44, 48, 50, 98]. Accumulation and elimination kinetics of these drugs are slower in the central compartment than in plasma, reflected by delayed peak concentrations and extended drug exposure in the CSF. Therefore, most of the values presented in Table 2 are influenced by the time span between drug intake and CSF sampling.

CSF concentrations of zidovudine, stavudine, lamivudine, abacavir and emtricitabine exceeded the 50 % inhibitory concentration (IC_{50}), a measure of antiviral drug potency, in all studies evaluating this relationship and largely throughout the respective dosing interval. In contrast, tenofovir concentrations in the CSF exceeded IC_{50} in only a minority of samples [52]. In view of the remarkable efficacy of tenofovir in macrophages in vitro, it would be a promising agent for CNS HIV infection [96], activity in the CNS, however, seems to be limited by poor penetration [51, 52].

The exact entry route of NRTIs into the CNS is not clear. As CSF and plasma concentrations were not strongly associated with one another, processes other than simple passive diffusion are likely to play a role in the penetration

Table 2 CSF penetration by antiretroviral drugs

Reference	Study design	Regimen (no. of study subjects with CSF measure)	CSF post-dose sampling time (h)	CSF concentrations (ng/mL)	CSF : plasma ratio (%)	CSF concentrations compared to antiviral potency	Neurological status	Neurological outcome measures (additional drugs)
Zidovudine								
[28, 29]	Paediatric, phase I–II dose escalation trial	0.5 (3), 0.9 (8), 1.4 (7) or 1.8 (3) mg/kg/h IV infusion	Measure at steady-state	168 ± 86 (0.9 mg/kg/h); 200 ± 83 (1.4 mg/kg/h); [mean ± SD]	24 ± 9 (mean ± SD) [$n = 21$]	Not stated	Neurological deficit, encephalopathy, or both in 62 %; no opportunistic infections	Significant NP improvement in 8 patients with and 5 patients without encephalopathy after 6 months of therapy
[30]	Prospective, pilot study	100 mg PO every 4 h (6)	4 (day 7)	109 ± 59 (29–176) [mean ± SD (range)]	98 ± 54 (24–156) [mean ± SD (range)]	Exceed IC_{50} at the end of the dosing interval	No opportunistic infections	Not stated
[31]	Phase II, double-blind, randomized, placebo-controlled trial	250 mg PO (9) or 0.5 mg/kg IV (9) or 2.5 mg/kg IV (10) every 4 h	0.25–4 (every 2 weeks for the first 12 weeks)	115 (59–190) at 250 mg PO; 67 (<27–99) at 0.5 mg/kg IV; 155 (118–195) at 2.5 mg/kg IV; [mean (range)]	Not stated	Exceed IC_{90} in 0 % at 0.5 mg/kg IV, 63 % at 250 mg PO and 100 % at 2.5 mg/kg IV	Neurologically asymptomatic	4 out of 28 subjects have positive HIV culture in CSF during the 12-week period
[32]	Prospective, randomized trial	100 or 250 mg PO every 4 h (29)	1.5–2 (median, week 8)	41 (15–73) at ≤15 mg/kg/d; 84 (31–198) at >15 mg/kg/d; [median (range)]	8.8–120 (CSF : serum ratio)	Not stated	No opportunistic infections; 64 % report neurological symptoms, 47 % have abnormal neurological examination	Significant neurological improvement in 61.5 % after 8 weeks of therapy
[33]	Prospective, observational study	200–1250 mg/d PO in divided doses (39)	1–8	74 (14–283) [median (range)] [$n = 50$]	60 (4–262) [median (range)] [$n = 50$]	Exceed IC_{50} during 8-h dosing interval	Not stated	Not stated
[34]	Prospective, open-label study	2.5 mg/kg IV infusion over 1 h (6)	Before and after infusion, 1, 2, 3, 4, 5 and 6 h post-infusion	$AUC_{0–6}$ (μg·h/mL) = 1145 ± 722 (mean ± SD)	57 ± 23 (mean $AUC_{0–6}$ ratio ± SD)	Exceed IC_{50} during 12-h dosing interval	Not stated	Not stated
[35]	Retrospective study	100–400 mg PO (23)	2–8	93 (23–170) [median (range)]	78 (6–320) [median (range)]	Not stated	Not stated	Not stated
[36]	Substudy of an open, randomized, controlled trial	200 mg PO every 8 h (10)	2–4, 4–6 and 6–8 (weeks 0 and 12)	32–45	13–125 (means estimated from graph)	Largely exceed IC_{50}	Neurologically asymptomatic	CSF HIV-RNA BLD in all subjects after 12 weeks (3TC)
[37]	Prospective study	300 mg PO every 12 h (8)	1 (week 8)	38 (18–66) [median (range)]	Not stated	Not stated	Not stated	Not stated

Table 2 continued

Reference	Study design	Regimen (no. of study subjects with CSF measure)	CSF post-dose sampling time (h)	CSF concentrations (ng/mL)	CSF : plasma ratio (%)	CSF concentrations compared to antiviral potency	Neurological status	Neurological outcome measures (additional drugs)
[38]	Prospective, observational study	Dose not stated (18)	1–12 (after a median of 55 days)	Not stated	2 (0–674) [median (range)]	Not stated	78 % neurologically impaired	Not stated
Stavudine								
[39]	Paediatric phase I–II dose escalation trial	0.25–2.0 mg/kg/d PO in 2 divided doses (7)	2–3 (week 12)	16–53 at 1 mg/kg/d ($n = 4$)	16–97	Not stated	No opportunistic infections	Not stated
[40]	Open, randomized study	40 mg PO as single dose (12)	0.75–1.25, 2–3 or 4–5	63 ± 13 (mean ± SD) at 4–5 h post-dose ($n = 4$)	40 ± 6 (mean ± SD) at 4–5 h post-dose ($n = 4$)	Not stated	Healthy study subjects	Not stated
[36]	Substudy of an open, randomized, controlled trial	40 mg PO every 12 h (12)	2–4, 4–6 and 6–8 (weeks 0 and 12)	45–61	19–88 (means estimated from graph)	Largely exceed IC_{50}	Neurologically asymptomatic	CSF HIV-RNA BLD in all subjects after 12 weeks (3TC)
[41]	Paediatric, prospective study	1.8 mg/kg/d (mean) in 2 divided doses (4)	2.5–7.5 (week 12)	130–170	19–127	Not stated	Not stated	Not stated
[42]	Multi-centre, open-label, randomized, controlled trial	40 mg every 12 h (8)	Not stated (week 12)	213 (81–367) [median (range)]	43.6 (estimate)	Not stated	Neurological complications in 1 patient	Declining viral load in CSF within 48 weeks (RTV + SQV), independent benefit of d4T
[43]	Prospective study	40 mg PO every 12 h (4)	Sampling over 48 h at 6 mL/h	$AUC_{0\text{-}12}$ (ng·h/mL) = 406 ± 93 (232–659) [mean ± SD (range)]	38.9 ± 7.8 (mean $AUC_{0\text{-}12}$ ratio ± SD)	Not stated	Neurologically asymptomatic	Not stated
[37]	Prospective study	40 mg PO every 12 h (6)	1 (week 8)	71 (20–91) [median (range)]	Not stated	Not stated	Not stated	Not stated
[44]	Prospective, observational study	40 mg PO every 12 h (21)	2, 4, 6 and 8 (steady-state)	AUC (ng·h/ml) = 581 ± 20 (mean ± SD)	31.7 (mean AUC ratio)	Exceed IC_{50} during 8-h dosing interval	No CNS mass lesions	Not stated
[38]	Prospective, observational study	Dose not stated (31)	1–12 (after a median of 55 days)	Not stated	20.4 (0–20.4) [median (range)]	Not stated	78 % neurologically impaired	Not stated
Lamivudine								
[45]	Phase I–II dose escalation trial	8–20 mg/kg/d PO in 2 divided doses (6)	2	94–328	6 (4–8) [mean (range)]	Not stated	Karnofsky performance score at least 70; no peripheral neuropathy	Not stated

Table 2 continued

Reference	Study design	Regimen (no. of study subjects with CSF measure)	CSF post-dose sampling time (h)	CSF concentrations (ng/mL)	CSF : plasma ratio (%)	CSF concentrations compared to antiviral potency	Neurological status	Neurological outcome measures (additional drugs)
[46, 47]	Paediatric phase I–II dose escalation trial	1–20 mg/kg/d PO every 12 h (44), non steady-state	2–4 (day 4 and week 12)	15–273	11 (0–46) [median (range)]	Not stated	No AIDS, no opportunistic infections, no HIV encephalitis	No significant improvement in NP testing within 24 weeks
[36]	Substudy of an open, randomized, controlled trial	150 mg PO every 12 h (22)	2–4, 4–6 and 6–8 (weeks 0 and 12)	66–80	6–38 (means estimated from graph)	Largely exceed IC_{50}	Neurologically asymptomatic	CSF HIV-RNA BLD in all subjects after 12 weeks (d4T or AZT)
[43]	Prospective study	150 mg PO every 12 h (4)	Sampling over 48 h at 6 mL/h	$AUC_{0\text{-}12}$ (ng·h/mL) = 767 ± 50 (635–858) [mean ± SD (range)]	15.1 ± 1.3 (mean $AUC_{0\text{-}12}$ ratio ± SD)	Not stated	Neurologically asymptomatic	Not stated
[37]	Prospective study	150 mg PO every 12 h (11)	1 (week 8)	46 (36–87) [median (range)]	Not stated	Not stated	Not stated	Not stated
[38]	Prospective, observational study	Dose not stated (55)	1–12 (after a median of 55 days)	Not stated	22.9 (0–490) [median (range)]	Not stated	78 % neurologically impaired	Not stated
Abacavir								
[48]	Phase I mass balance study	600 mg PO (3), single dose	0, 0.5, 1, 1.5, 2.5, 4, and 6	AUC_{∞} (ng·h/mL) = 5140 (mean)	35 (31–44) [mean AUC_{∞} ratio (range)]	Exceed IC_{50}	No clinical significant neurological abnormalities	Not stated
[49]	Phase II dose escalation trial	200 mg PO every 8 h (6)	1.5 (week 4)	140 (90–190) [mean (range)]	42 (8–173) [mean (range)]	Exceed IC_{50}	Not stated	Not stated
[37]	Prospective study	300 mg PO every 12 h (12)	1 (week 8)	75 (18–147) [median (range)]	Not stated	Not stated	Not stated	Not stated
[50]	Population pharmacokinetic analysis	300 mg PO every 12 h (51), steady-state	Not standardized; multiple samples in several patients	128 (37–384) [median (range)]	36 ± 5 (mean AUC ratio ± SD)	Exceed IC_{50} for 85 % of the dose interval	No opportunistic infections	Not stated
[38]	Prospective, observational study	Dose not stated (4)	1–12 (after a median of 55 days)	Not stated	3.9 (0–236) [median (range)]	Not stated	78 % neurologically impaired	Not stated
Tenofovir								
[51]	Prospective pilot study	300 mg PO once daily (21)	15 (13.8–19.4) [median (range)]	6 (<2–8) [median (range)]	5 (0–13) [median (range)]	Not stated	29 % neurocognitive disorders	Not stated

Table 2 continued

Reference	Study design	Regimen (no. of study subjects with CSF measure)	CSF post-dose sampling time (h)	CSF concentrations (ng/mL)	CSF : plasma ratio (%)	CSF concentrations compared to antiviral potency	Neurological status	Neurological outcome measures (additional drugs)
[52]	Prospective, multi-centre, observational study (CHARTER)	300 mg PO once daily (77)	11 ± 7.8 (mean ± SD) [after a median of 8.5 months]	5.5 (2.7–11.3) [median (IQR)]	5.7 (3–10) [median (IQR)] ($n = 38$)	33 % exceed IC_{50}; CSF/IC_{50} ratio = 0.48 (0.24–0.98)	CHARTER cohort	CSF HIV-RNA BLD in 80 % after a median of 8.5 months (additional ARVs)
Emtricitabine								
[53] Preliminary data	Prospective, multi-centre, observational study (CHARTER)	"Standard dose" (21)	Not standardized; 11 ± 8 (mean ± SD)	109 (39–386) [median (range)]	43 (7–202) [median (range)]	CSF/wild-type IC_{50} ratio = 1.6 (1.2–2.8) [median (IQR)]	CHARTER cohort	Not stated
[51]	Prospective pilot study	200 mg PO once daily (21)	15 (13.8–19.4) [median (range)]	68 (2.5–98) [median (range)]	26 (5–41) [median (range)]	Not stated	29 % neurocognitive disorders	Not stated
Nevirapine								
[37]	Prospective study	200 mg PO every 12 h (15)	1 (week 8)	932 (219–1837) [median (range), $n = 9$]	Not stated	Not stated	Not stated	Not stated
[38]	Prospective, observational study	Dose not stated (16)	1–12 (after a median of 55 days)	Not stated	62.6 (41–77) [median (range)]	Not stated	78 % neurologically impaired	Not stated
[54]	Retrospective, paediatric study	NVP 120 mg/m^2 PO every 12 h (11)	3–5 (after >24 weeks)	Not stated	43–62 ($n = 14$)	Not stated	Known or suspected HIV encephalopathy	Not stated
Efavirenz								
[55]	Prospective, observational study	600 mg PO once daily (9)	9–21.7 (week 15–38)	11 (2–19) [mean (range)]	0.61 (0.26–0.99) [mean (range)]	Mean exceeds IC_{95} by 10-fold	Asymptomatic	CSF HIV-RNA BLD in all subjects after a median of 26 weeks (additional ARVs)
[38]	Prospective, observational study	Dose not stated (11)	1–12 (after a median of 55 days)	BLD	Not stated	Not stated	78 % neurologically impaired	Not stated
[56]	Prospective, observational study (CHARTER)	600 mg PO once daily (80)	12.5 ± 5.4 (mean ± SD)	13.9 (0.2–51.8) [median (range)]	0.5 (0.03–2.75) [median (range)] [$n = 69$]	Median exceeds IC_{50} by 26-fold, with two CSF concentrations below IC_{50}	CHARTER cohort	CSF HIV-RNA BLD in 85 % after ≥2 weeks (additional ARVs)

Table 2 continued

Reference	Study design	Regimen (no. of study subjects with CSF measure)	CSF post-dose sampling time (h)	CSF concentrations (ng/mL)	CSF : plasma ratio (%)	CSF concentrations compared to antiviral potency	Neurological status	Neurological outcome measures (additional drugs)
Etravirine								
[57] Preliminary data	Prospective, observational study (CHARTER)	Dose not stated (9)	4.9 (2.6–5.5) [median (IQR)] (after a median of 8.3 months)	9.5 (6.4–26.4) [median (IQR)]	4.3 (3–5.9) [median (IQR)]	Exceed the IC_{50} in all samples by a median of 13.6-fold	CHARTER cohort	CSF HIV-RNA BLD in 100 % after a median of 8.3 months (additional ARVs)
[58]	Prospective, observational study	400 mg PO once daily or 200 mg PO every 12 h (12)	12.5 (3–16) [median (range)] (after a median of 34 weeks)	7.24 (3.59–17.9) [median (range)]	1 (0.5–3) [median (range)]	Exceed IC_{50} in all cases	Asymptomatic	CSF HIV-RNA BLD in 92 % after ≥4 weeks (additional ARVs)
Saquinavir and ritonavir								
[59]	Substudy of a multi-centre, randomized, open-label dose escalation trial	SQV 400–600 mg PO every 8 or 12 h with RTV 400–600 mg PO every 8 or 12 h (12)	Not standardized (week 48)	SQV: BLD RTV: 12–21 ($n = 5$)	Not stated	Not stated	Asymptomatic	CSF HIV-RNA BLD in 93 % after 48 weeks (SQV + RTV)
[60]	Prospective, cross-sectional study	SQV 600 mg PO every 8 or 12 h (9) with or without RTV (dose not stated)	5 (after >3 months)	SQV: 6.5 ($n = 1$); <2 ($n = 8$)	SQV: 0.3 ($n = 1$)	Not stated	Not stated	CSF HIV-RNA BLD in 44 % after ≥3 months (additional ARVs)
[61]	Prospective, cross-sectional study	SQV and RTV PO, dose not stated (11)	6–8	SQV: 0.3 and 1.6 ($n = 2$); <0.2 ($n = 9$) RTV: 1.9–23 ($n = 11$)	SQV: 0.1–0.2 ($n = 2$) RTV: 0.2 (0.1–0.5) [median (range)]	Means below IC_{50}	Neurologically asymptomatic	Median CSF HIV-RNA level 80 copies/mL after >12 months
[62]	Prospective, dose escalation trial	SQV and RTV 400 mg every 12 h (12); with and without concomitant ketoconazole	4–5	Without ketoconazole: SQV: 0.29 ± 0.3 ($n = 5$) RTV: 2.4 ± 1.9 ($n = 12$) With ketoconazole: SQV: 1.1 ± 1.3 ($n = 5$) RTV: 6.6 ± 13.8 ($n = 12$) [mean ± SD]	Without ketoconazole: SQV: 6 ± 9 ($n = 4$) RTV: 9 ± 15 ($n = 12$) With ketoconazole: SQV: 35 ± 61 ($n = 4$) RTV: 26 ± 84 ($n = 12$) [mean ± SD]	Means below IC_{50} with and without ketoconazole	Not stated	Not stated

Table 2 continued

Reference	Study design	Regimen (no. of study subjects with CSF measure)	CSF post-dose sampling time (h)	CSF concentrations (ng/mL)	CSF : plasma ratio (%)	CSF concentrations compared to antiviral potency	Neurological status	Neurological outcome measures (additional drugs)
[42]	Multi-centre, open-label, randomized, controlled trial	SQV and RTV 400 mg PO every 12 h (22)	Not stated (week 12)	SQV: 2.5–14.7 ($n = 2$); <2.5 ($n = 20$) RTV: 25–57 ($n = 3$); <25 ($n = 19$)	Not stated	Not stated	Neurological complications in 1 patient	Declining viral load in CSF within 48 weeks (d4T); independent benefit of d4T
[63]	Prospective, open pilot study	SQV 1200 mg PO every 12 h (8)	0.25–13.25 (weeks 12 and 48)	SQV: 1.7–6.0 ($n = 7$); <1.7 ($n = 8$)	Not stated	Below IC_{50}	86 % neurologically asymptomatic	Persisting low-grade immunoactivation (NFV + NRTIs)
Ritonavir								
[64]	Prospective, observational study	DRV/RTV 800/100 mg PO once daily or 600/100 mg PO every 12 h (38)	2–28	0.26 (0.0–0.6) [median (range)]	0.09 (0–0.21) [median (range)]	Not stated	68.3 % neurologically asymptomatic	CSF viral load detectable in 58 % (additional ARVs)
Indinavir								
[65]	Retrospective, observational study	Dose not stated (13)	Not standardized	141 ± 25 (55–405) [mean ± SD (range)]	16.1 (estimate)	Not stated	Not stated	Not stated
[66]	Prospective, observational study	800 mg PO every 8 h (25)	Not standardized (month 3–18)	137 ± 123 (0.049–405) [mean ± SD (range)] [$n = 32$]	10.7 (estimate) [$n = 32$]	Exceed IC_{95}	Neurologically asymptomatic	Less signs of inflammation in CSF in IDV-treated group than in reference group; CSF HIV-RNA BLD in 80 % after a median of 12 months (2 NRTIs)
[41]	Paediatric, prospective study	500 mg/m^2 every 8 h (4)	2.5–7.5 (week 12)	150–980	3–94	Not stated	Not stated	Not stated
[67]	Prospective, observational study	800 mg PO every 8 h (22)	Not standardized	89 (26–295) [median (range)]	16 (0.4–228) [median (range)]; 6 (median AUC ratio)	All samples exceed clinical IC_{95}	No opportunistic infections	CSF HIV-RNA BLD in 68 % (1–2 NRTIs)
[68]	Prospective study	800–1000 mg PO every 8 h (12) or RTV-boosted 800 mg PO every 8–12 h (7)	1 (weeks 8, 24, 48 and 72)	Without RTV added: 39 (27–54) [median IQR)] RTV-boosted: 104 (68–207) [median (IQR)]	Not stated	Around IC_{95} without RTV; exceed IC_{95} with RTV	Not stated	CSF HIV-RNA BLD in all patients after 48 weeks (3 NRTIs + NVP)

Table 2 continued

Reference	Study design	Regimen (no. of study subjects with CSF measure)	CSF post-dose sampling time (h)	CSF concentrations (ng/mL)	CSF : plasma ratio (%)	CSF concentrations compared to antiviral potency	Neurological status	Neurological outcome measures (additional drugs)
[69]	Substudy of a prospective, pharmacological trial (ACTG-343)	800 mg PO every 8 h (19)	0.5–3.3 (mean 1.4) (week 24)	68 (20–153) [mean (range)]	1.7 (0.2–5.1) [mean (range)]	Exceed IC_{95}	No peripheral neuropathy	Not stated
[70]	Prospective, observational study	800 mg PO every 8 h (8)	0, 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 (after >6 months)	AUC_{0-8} (ng·h/mL) = 1056 ± 330 (mean ± SD)	Total: 6.5 ± 1.0 (mean AUC ratio ± SD) Free: 14.7 ± 2.6 (mean AUC ratio ± SD)	Exceed IC_{95} during 85 % of dosing interval in all but one patient	Asymptomatic	Not stated
[71]	Prospective study	800 mg PO every 8 h (11)	5–7.5 (week 48)	90 (50–170) [median (range)]	36 (estimate)	Exceed IC_{95}	Neurologically asymptomatic	CSF HIV-RNA BLD in all patients after 48 weeks (2 NRTIs)
[72]	Prospective study	RTV-boosted 800 mg PO every 12 h (7)	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 (week 3)	AUC_{0-8} (ng·h/mL) = 4055 ± 1523 (mean ± SD)	Total: 9.9 ± 3.3 (mean AUC ratio ± SD) Free: 17.5 ± 6.4 (mean AUC ratio ± SD)	Exceed IC_{95} in all samples	Not stated	Not stated
[73]	Prospective, observational study	Dose not stated (25)	Not stated (weeks 4 and 8)	Week 4 (n = 8): 77 (5–205) [median (range)] Week 8 (n = 11): 167 (35–405) [median (range)]	Week 4: 35.9 (estimate) Week 8: 9.2 (estimate)	Not stated	Nonfocal neurological examination	NP improvement at 4 weeks (AZT or IDV compared to treatment with other NRTIs)
[74]	Prospective study	1000 mg PO every 8 h (13)	0.25–8.25 (months 2 and 6)	71 (median)	Not stated	Approximate the upper IC_{95} limit	No opportunistic infections	CSF HIV-RNA BLD after 6 months; reduction in meningeal inflammation (NVP + NRTIs)
[75]	Prospective, observational study	800 mg PO every 8 h (14)	7–8 (after >6 months)	73 (52–92) [median (IQR)]	17 (10–49) [median (IQR)]	Exceed IC_{95}	Not stated	CSF HIV-RNA BLD in all subjects after ≥6 months (2 NRTIs)
[76]	Prospective, observational study	RTV-boosted 400 mg PO every 12 h (4)	10 (week 2)	39 (21–86) [median (range)]	Not stated	Exceed IC_{50}	Not stated	CSF HIV-RNA BLD in all patients at week 4 (LPV + RTV + NRTIs)
[38]	Prospective, observational study	Dose not stated (18)	1–12 (after a median of 55 days)	Not stated	11.1 (0–47) [median (range)]	Not stated	78 % neurologically impaired	Not stated

Table 2 continued

Reference	Study design	Regimen (no. of study subjects with CSF measure)	CSF post-dose sampling time (h)	CSF concentrations (ng/mL)	CSF : plasma ratio (%)	CSF concentrations compared to antiviral potency	Neurological status	Neurological outcome measures (additional drugs)
Nelfinavir								
[77]	Prospective, observational study	750–1000 mg PO every 8 h (6)	0.48–10.3 (3 days to 12 months after initiation of therapy)	BLD (<25)	Not stated	Below IC_{95}	66 % have AIDS dementia complex	Decline of CSF viral load in 83 % after 4 weeks (2–3 NRTIs)
[43]	Prospective study	750 mg PO every 8 h (4)	Continuous sampling for 48 h at 6 mL/h	BLD (<0.1)	Not stated	Not stated	Neurologically asymptomatic	Not stated
[74]	Prospective study	200 mg PO every 12 h (13)	0.25–8.25 (months 2 and 6)	BLD	Not stated	Not stated	No opportunistic infections	CSF HIV-RNA BLD after 6 months; reduction in meningeal inflammation (IDV + NVP + NRTIs)
[75]	Prospective, observational study	1250 mg PO every 12 h (13)	12	BLD (<20)	Not stated	Not stated	Not stated	CSF HIV-RNA BLD in 85 % after ≥6 months (2 NRTIs)
[38]	Prospective, observational study	Dose not stated (9)	1–12 (after a median of 55 days)	Not stated	BLD	Not stated	78 % neurologically impaired	Not stated
[63]	Prospective, open pilot study	1250 mg PO every 12 h (8)	0.25–13.25 (weeks 12 and 48)	1–13 ($n = 9$); <1 ($n = 6$)	<0.04 (estimate)	In the range of IC_{50} in most cases	86 % neurologically asymptomatic	Persisting low-grade immunoactivation (SQV + NRTIs)
[78]	Prospective, observational study	Dose not stated (19)	4–12	5 (3–17) [median (range)]	Not stated	Many samples exceed IC_{95}, adjusted for CSF protein binding	No HIV-associated neurological impairment	CSF HIV-RNA BLD in 63 % after ≥18 months (2 NRTIs)
Lopinavir								
[75]	Prospective, observational study	LPV/RTV 400/100 mg PO every 12 h (12)	7–8 (after >6 months)	BLD	Not stated	Not stated	Not stated	CSF HIV-RNA BLD in 75 % after ≥6 months (2 NRTIs)
[76]	Prospective, observational study	LPV/RTV 400/100 mg PO every 12 h (5)	10 (weeks 2 and 4)	After 2 weeks, without concomitant IDV: <10 ($n = 5$) After 4 weeks, with concomitant IDV: 27–29 ($n = 2$); <10 ($n = 2$)	Not stated	Not stated	Not stated	CSF HIV-RNA BLD in all patients at week 4 (IDV + RTV + NRTIs)
[79]	Prospective, observational study	LPV/RTV, dose not stated (13)	11 (2–12) [median (range)] (after a median of 3 and 12 months)	26.5 ± 19.8 (mean ± SD) [$n = 15$]	0.5 ($n = 15$)	Might exceed IC_{95} when adjusted for CSF protein binding	1 patient neurologically symptomatic	CSF HIV-RNA BLD and suppression of CSF immunoactivation after a median of 12 months (additional ARVs)

Table 2 continued

Reference	Study design	Regimen (no. of study subjects with CSF measure)	CSF post-dose sampling time (h)	CSF concentrations (ng/mL)	CSF : plasma ratio (%)	CSF concentrations compared to antiviral potency	Neurological status	Neurological outcome measures (additional drugs)
[80]	Prospective, observational study	LPV/RTV 400/100 mg PO every 12 h (26)	4.3 (2.5–6.0) [median (IQR)] (after a median of 88 days)	16.75 ± 8.6 (mean ± SD) [$n = 31$]	0.29 ± 0.15 (mean ± SD) [$n = 31$]	Exceed IC_{50} by a median of 5.3-fold	Not stated	Not stated
[81]	Prospective, open-label, observational study	LPV/RTV 400/100 mg PO every 12 h (10)	9.9 (9.7–10.2) [median (IQR)]	11.2 (6.8–16.4) [median (IQR)]	0.23 (0.19–0.32) [median (IQR)]	Exceed IC_{50} by a median of 5.9-fold	Not stated	Not stated
[82]	Phase I pharmacokinetic study	LPV/RTV 400/100 mg PO every 12 h (12)	4 or 6 (day 15)	After 4 h: 75.1 (45.0) After 6 h: 76.8 (30.8) [mean (SD)]	0.85 (0.32–1.83) [mean (range)]	Not stated	Neurologically asymptomatic	CSF HIV-RNA BLD in 83 % (TDF, FTC and MVC)
Atazanavir								
[83]	Prospective study	ATV/RTV 300–400/100 mg PO every 12 h (22)	12 (2–26) [median (range)] (day 1 and week 24)	8.3 (0.6–40) [median (range)]	0.9 ± 0.8 (0.1–2.7) [mean ± SD (range)]	Slightly above IC_{50}	No active opportunistic infections	CSF HIV-RNA BLD in 95 % after 24 weeks (ATV/RTV monotherapy)
[84]	Prospective, observational study	ATV 300–400 mg with or without RTV 100 mg PO every 24 h (117)	0.5–27 (after a median of 6.6 months)	With RTV: 10.3 (<5–38) [n = 62] Without RTV: 7.9 (<5–40) [$n = 9$]; [median (IQR)]	With RTV: 0.9 (0.2–3.4) [$n = 62$] Without RTV: 1.1 (0.5–13.9) [$n = 9$]; [median (IQR)]	Might exceed IC_{50} in some samples	Not stated	CSF HIV-RNA BLD in 70 % after a median of 6.6 months (additional ARVs)
Amprenavir/ fosamprenavir								
[85]	Phase I mass balance study	APV 630 mg PO (6), single dose	1, 2, 4 and 6 (day 1)	BLD (<10) in all but 1 sample	Not stated	Not stated	Healthy study subjects	Not stated
[86]	Prospective, multi-centre pilot study	FPV/RTV 700/100 mg PO every 12 h (10)	Not stated (week 24)	28.1 (6.39–83.6) [median (range)]	Not stated	Exceed IC_{50} in all subjects	Not stated	CSF HIV-RNA BLD in all samples after 24 weeks (FPV/RTV monotherapy)
[87]	Prospective, observational study	FPV/RTV 700/100 mg PO every 12 h or 1400/200 mg PO once daily or FPV 1400 mg PO every 12 h without RTV (75)	7.2 ± 5.2 (median ± SD) (after a median of 9.5 months)	With RTV: 26.1 (16.9–45.8) Without RTV: 23.4 (10.7–41.5) [median (IQR)]	1.2 (0.8–1.8) [median (IQR)]	Exceed IC_{50} in 97 % of samples with detectable APV by a median of 4.4-fold	Not stated	CSF HIV-RNA BLD in 88 % of samples (additional ARVs)

Table 2 continued

Reference	Study design	Regimen (no. of study subjects with CSF measure)	CSF post-dose sampling time (h)	CSF concentrations (ng/mL)	CSF : plasma ratio (%)	CSF concentrations compared to antiviral potency	Neurological status	Neurological outcome measures (additional drugs)
Darunavir								
[88]	Prospective, observational study	DRV/RTV 600/100 mg PO every 12 h (8)	Not stated (after a median of 12.5 weeks)	34.2 (15.9–212) [median (range)] [$n = 14$]	0.9 (0.3–1.8) [median (range)] [$n = 14$]	In the range or above IC_{50}	Neurological complications in 25 %	CSF HIV-RNA BLD in 79 % after a median of 12 weeks (additional ARVs)
[64]	Prospective, observational study	DRV/RTV 800/100 mg PO once daily or 600/100 mg PO every 12 h (38)	2–28	30 (14.4–39) [median (IQR)]; CSF trough concentrations significant lower in subjects receiving once-daily dosing	0.6 (0.38–1.03) [median (IQR)]	Exceed median IC_{50} in 88.4 %	68.3 % neurologically asymptomatic	CSF HIV-RNA detectable in 58 % (additional ARVs)
Enfuvirtide								
[89]	Prospective, observational study	Dose not stated (4)	Not standardized	<25 in all samples ($n = 18$)	Not stated	Not stated	Not stated	Not stated
Maraviroc								
[90]	Prospective pilot study	Variable dosage (7)	10.5 (3.0–44.0) [median (range)] after 25–29 days	3.63 (1.83–12.2) [median (range)]	3 (1–10) [median (range)]	Exceed mean EC_{90} by 3-fold	Neurologically asymptomatic	CSF HIV-RNA BLD in 71 % after 25–29 days (additional ARVs)
[91]	Prospective, observational study	150–600 mg PO every 12 h (6)	Not stated	102 (35–173) [median (range), $n = 4$], <10 in 2 samples	29	Exceed IC_{90} in 4 samples	Neurologically impaired	Decline of viral load, improvement of the clinical status (additional ARVs)
[92]	Prospective, observational study	150–600 mg PO every 12 h (12)	Approximately 12 (after a median of 13.5 weeks)	2.59 (<0.5–7.22) [median (range)]	2.2 (0.4–17) [median (range)]	Exceed EC_{90} in 92 %	Asymptomatic	CSF HIV-RNA BLD in 75 % after ≥4 weeks (nucleoside-sparing regimens in 92 %)
[82]	Phase I pharmacokinetic study	150 mg PO every 12 h (12)	4 or 6 (day 15)	After 4 h ($n = 6$): 7.54 (1.26) After 6 h ($n = 6$): 5.10 (1.21) [mean (SD)]	Overall: 1.01 (0.57–1.61) After 4 h: 0.93 (0.57–1.27) After 6 h: 1.09 (0.71–1.61) [(mean (range)]	Exceed IC_{90} in all subjects	Neurologically asymptomatic	CSF HIV-RNA BLD in 83 % (TDF, FTC and LPV/RTV)
[93]	Prospective, observational study (CHARTER)	150 mg or 300 mg PO every 12 h (7)	Not stated (after a median of 2.1 months)	2.4 (1.5–4.0) [median (IQR)]	2.8 (median)	Exceed IC_{50} in all samples by a median of 9.2-fold	CHARTER cohort	CSF HIV-RNA BLD in all samples after a median of 2.1 months (additional ARVs)

Table 2 continued

Reference	Study design	Regimen (no. of study subjects with CSF measure)	CSF post-dose sampling time (h)	CSF concentrations (ng/mL)	CSF : plasma ratio (%)	CSF concentrations compared to antiviral potency	Neurological status	Neurological outcome measures (additional drugs)
Raltegravir								
[94]	Prospective, observational study	400 mg PO every 12 h (16)	7.8 (1.2–14) [median (range)]	18.4 (2.0–126) [median (range), $n = 24$]	3 (1–61) [median (range), $n = 24$] 3 (AUC estimate, $n = 24$)	In the range or above IC_{95} in more than half of the cases	Not stated	Not stated
[95]	Prospective, observational study	400 mg PO every 12 h (18)	6.1 ± 4.2 (mean ± SD) after a median of 4.2 months	14.5 (9.3–26.1) [median (IQR)]	5.8 (2.1–17.8) [median (IQR)]	Exceed IC_{50} in all individuals by a median of 4.5-fold	No opportunistic infections, no moderate to severe cognitive impairment	CSF HIV-RNA BLD in 95 % of samples after a median of 4.2 months (additional ARVs)

3TC lamivudine, *ACTG* AIDS Clinical Trials Group, *ARVs* antiretroviral drugs, *ATV* atazanavir, *AUC* area under the concentration-time curve, *AZT* zidovudine, *BLD* below limit of detection, *CHARTER* CNS HIV Antiretroviral Therapy Effects Research, *d4T* stavudine, EC_{90} 90% effective concentration to inhibit viral replication, *FTC* emtricitabine, *DRV* darunavir, *FPV* fosamprenavir, $IC_{50} = 50$ % inhibitory concentration, IC_{95} 95 % inhibitory concentration, *IDV* indinavir, *IQR* interquartile range, *IV* intravenously, *LPV* lopinavir, *MVC* maraviroc, *NFV* nelfinavir, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *NRTI* nucleoside reverse transcriptase inhibitor, *NP* neuropsychological, *NVP* nevirapine, *PI* protease inhibitor, *PO* orally, *RTV* ritonavir, *SD* standard deviation, *SQV* saquinavir, *TDF* tenofovir

of tenofovir into the CSF [52]. Several unspecific organic anion and cation transporters may contribute to brain uptake and efflux of NRTIs [26, 99].

2.2 Non-Nucleoside Reverse Transcriptase Inhibitors

Penetration of nevirapine into the CSF is generally good, likely due to the lipophilic properties of that drug [37, 38, 54]. Concentration values, however, have not been related to parameters of antiviral potency. In concordance with clinical results, Gibbs et al. [100] found the degree of accumulation in the brain to be greater for nevirapine than for zidovudine, stavudine, abacavir, lamivudine, ritonavir, amprenavir and tenofovir in a guinea pig brain perfusion model. Unlike nevirapine, CSF penetration of efavirenz has been reported to be less than 1 % of concomitant plasma concentrations [55, 56], though this cannot be taken to indicate pharmacological ineffectiveness or viral escape in the central compartment. The estimated unbound concentrations of efavirenz in the CSF approximate the free plasma fraction and exceed the 95 % inhibitory concentration (IC_{95}) [55]. In addition, there is indirect evidence indicating that efavirenz does achieve relevant concentrations within the CNS, as this drug has widely recognized CNS adverse effects [101, 102]. Median CSF-to-plasma concentration ratios of etravirine have also been relatively low (1–4 %), but exceeded the IC_{50} [57, 58]. Extensive binding of etravirine to proteins, as observed in the blood (99.9 %), is not to be expected in the CSF, so that a contribution to viral control in the CNS is quite possible.

2.3 Protease Inhibitors

PIs have several physical and chemical characteristics that potentially impede passive diffusion into the central compartment [23]. A common property of this drug class is its extensive binding affinity to plasma proteins. Protein-bound fractions in the plasma range from 60 % for indinavir, 86 % for atazanavir and 90 % for fosamprenavir to more than 98 % for saquinavir, lopinavir, ritonavir and nelfinavir. Therefore, just a small fraction of the drug in the plasma is free to cross membranes. Molecular weights of PIs are high and might additionally limit penetration. PIs are highly lipophilic, a property generally favourable for passive transport, but penetration might be limited by 'membrane trapping' [23]. Lastly, P-gp-mediated efflux from the brain back to blood was demonstrated for PIs [103, 104].

Saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir and atazanavir have been detected in the CSF in a number of studies (see Table 2); for darunavir, two published studies were available [64, 88]. CSF concentrations of most PIs have been lower than expected from the estimated free plasma fraction, suggesting the influence of active transporters at the BBB and/or at the blood–CSF barrier. Indinavir, lopinavir, amprenavir and darunavir regularly exceeded inhibitory concentrations in the CSF, whereas saquinavir and ritonavir are not expected to achieve sufficient CSF concentrations.

A considerable number of studies investigated indinavir delivery to the CSF and found CSF-to-plasma ratios to be relatively high compared with other PIs. This high rate of permeation into the CSF can mainly be attributed to the only moderate affinity of indinavir to plasma proteins. Still, active retrograde transport of indinavir across the BBB is considered to limit accumulation in the CNS [66, 70]. Indinavir CSF-to-plasma ratios increase considerably within the dosing interval, reflecting delayed drug delivery from the plasma to the CSF. The CSF is supposed to act as a slowly equilibrating compartment, leading to stable concentrations and a longer elimination half-life of indinavir in the CSF relative to the systemic compartment [66, 69, 70, 72]. Lopinavir has demonstrated similar pharmacokinetic characteristics [81]. Under co-administration of ritonavir, CSF concentrations of indinavir increase more than 2-fold, paralleling minimum indinavir concentrations in plasma [72]. Ritonavir is a potent inhibitor of cytochrome P450 (CYP) 3A, thereby delaying systemic metabolism of indinavir and increasing the amount of drug available for transfer to the CNS [23, 68, 72]. CSF concentrations of other PIs might be similarly affected by co-administration of ritonavir [84, 87]. Other types of interaction between PIs have been detected, for example indinavir is suggested to exert an added inhibitory effect on lopinavir metabolism that might result in increased delivery of lopinavir to the CSF [76].

Although indinavir is predicted to exhibit better CSF penetration than other PIs, lower CSF-to-plasma ratios do not automatically mean reduced efficacy in the CNS. Limited penetration can be balanced by the potency of some PIs [105]. Compared with indinavir, the fraction of lopinavir penetrating into the CSF has been smaller, but closer in agreement with the reported free fraction in plasma [80]. Furthermore, CSF concentrations of lopinavir have been stable and still in the range of IC_{50} at the end of a 12-h dosing interval [81].

The interpretation of PI measurements in the CSF should account for the binding of drugs to CSF proteins. As a result of low protein levels in the CSF in unimpaired individuals, the estimated protein-bound fraction of drugs is generally lower in the CSF than in plasma, a fact that complicates the interpretation of CSF-to-plasma ratios of drugs with high affinity to proteins, such as PIs. The protein-bound fraction of indinavir in the CSF presumably ranges from 0 to 3 % and might be negligible [72]. In contrast, estimates for CSF protein binding of nelfinavir

and lopinavir are relatively high (60–90 %), but still much lower than in plasma [78, 79]. Consequently, the CSF-adjusted IC_{95} of nelfinavir might be several times lower than in the plasma [78]. Under that condition, nelfinavir might contribute to inhibiting viral replication in the CNS, although absolute CSF concentrations have been low [78].

2.4 Other Antiretroviral Drugs

Enfuvirtide, an HIV fusion inhibitor, has not been detected in the CSF and might not contribute to viral suppression in the CNS [89]. A substantial fraction of the entry inhibitor maraviroc, in contrast, appears to reach the CSF, leading to concentrations beyond the mean 90 % effective concentration to inhibit viral replication (EC_{90}) [90]. The low molecular weight of the drug and the relatively low plasma protein binding of about 76 % probably facilitate penetration to HIV sanctuary sites [91, 106]. Like PIs, maraviroc is a substrate of P-gp, a fact that might explain CSF concentrations being several-fold lower than the estimated free plasma fraction [92, 93]. Co-administration of ritonavir has been associated with higher CSF concentrations of maraviroc, presumably due to inhibition of maraviroc metabolism, thereby increasing systemic maraviroc exposure, leading to enhanced delivery to the CSF [90]. Very importantly, HIV strains infecting macrophages and microglia in the brain are predominantly C-C chemokine receptor type 5 (CCR5) tropic [107, 108], which is a precondition for virological efficacy of maraviroc.

Raltegravir, an inhibitor of HIV integrase, is also a suggested substrate for P-gp-mediated transport from the brain back into the systemic circulation. In a study by Yilmaz et al. [94] median CSF raltegravir concentrations have been nearly 4-fold lower than unbound drug concentrations in the plasma, exceeding the upper limit of the IC_{95} range in about half of the patients. Croteau et al. [95] found absolute CSF raltegravir concentrations comparable to these previous results, but drew different conclusions. Referencing IC_{50}, which is lower than IC_{95}, CSF concentrations are reported to exceed the concentration required to inhibit wild-type HIV in vitro in all individuals, suggesting that raltegravir is likely to contribute to the suppression of viral replication in the CNS.

3 Discussion

3.1 Considerations for the Assessment of CSF Penetration

Results from drug concentration assessment in the CSF are characterized by substantial intra- and inter-individual variability. Various factors might contribute to the variation among individuals and across clinical studies. In this context, baseline subject characteristics like dosing schedules, stage of disease, drug adherence and background HAART regimens deserve consideration. Some of these variables can be controlled by means of a comprehensive study design. Calculation and presentation of CSF-to-plasma ratios in addition to absolute CSF drug concentrations will address differential drug intake and systemic drug metabolism. Even so, this parameter has its limitations. On the one hand, CSF-to-plasma ratios are usually based on total drug concentrations and do not take protein-bound fractions into account. This is of particular concern for drugs with high affinity to plasma proteins such as most PIs. On the other hand, the ratios tend to change over time within the dosing interval. The ratio between the area under the concentration-time curve (AUC) in CSF and plasma might be a more accurate indicator for drug penetration than CSF-to-plasma ratios from samples obtained at single time points [50, 69, 70]. Ideally, intensive CSF sampling and simultaneous plasma sampling over the entire dosing interval or population-based pharmacokinetic modelling would provide information about the concentration time profile and address host genetic variability in CSF pharmacokinetics [109, 110]. For practical reasons, however, most studies included in this survey have simply assessed drug concentrations as a function of time. Of note, study subjects mostly received chronic oral dosing. CSF concentrations of ARVs can be significantly higher and are usually much more stable after long-term oral therapy than after a single dose [44], alleviating the problem of time dependency in drug measurement. Multiple dosing should therefore precede the assessment of CSF drug concentrations, particularly when drugs are known to accumulate in the CNS.

While absolute drug concentrations and CSF-to-plasma ratios provide pharmacokinetic information, antiviral drug potency parameters account for intracellular metabolism of drugs and allow estimation of antiviral effectiveness. Most of the reviewed studies compared the respective CSF drug concentrations with IC_{50} or IC_{95} in vitro. Assessment of the antiviral potency of a drug in vitro results in a concentration-effect curve that tends to be linear between 20 % and 80 % of maximum effect [111], therefore IC_{50} is generally less variable than IC_{95}. IC_{50} is usually referenced in clinical resistance testing reports assessing the fold change in susceptibility of test virus as compared with wild-type virus. As long as the exact drug concentrations required to inhibit HIV strains in the central compartment are not defined, there are no recommendations on which of these reference standards to use in the context of CSF drug assessment. The majority of the studies included in our survey have referenced IC_{50}.

Inhibitory concentrations have some limitations. First, reference inhibitory concentrations show marked variability depending on laboratory methods, viral strains and on whether they are derived from lymphocyte cell lines or from macrophages and monocytes. Compared with lymphocytes, in vitro inhibitory concentrations in macrophages are lower for NRTIs, similar for non-nucleotide reverse transcriptase inhibitors (NNRTIs) and higher for PIs [96]. Moreover, the IC_{50} is normally assessed in incubation media approximating conditions in the blood and thus containing more proteins than the CSF. Assessment of the IC_{50} in the presence of CSF would be desirable, but is not routinely performed due to methodological problems. Compared to standard in vitro conditions, the fraction of unbound, active drug is expected to be higher in the CSF, presumably leading to a lower IC_{50} in that compartment.

Importantly, in cells chronically infected by HIV, such as persistently infected macrophages in the CNS, the proviral DNA is firmly integrated within the host cell genome, and virus replication occurs independently of reverse transcriptase. Therefore, all reverse transcriptase inhibitors seem to be ineffective in these cells [96]. The inclusion of PIs in the therapeutic regimen allows for targeting of that cellular reservoir of HIV, however, the activity of PIs in chronically infected macrophages is several-fold lower than in lymphocytes [112]. As a consequence, even with PI concentrations in the CSF exceeding referenced in vitro inhibitory concentrations, CNS-standing-infected macrophages might escape from therapy.

Lastly, the effect of blood–CNS barrier disruption on ARV CNS penetration deserves consideration. Viral proteins and host inflammatory mediators affect the integrity of the BBB in the course of CNS-HIV infection, reflected by elevated CSF-to-plasma albumin ratios as a sign of abnormal BBB permeability soon after initial exposure [113]. and breakdown of tight junctions in patients with HIV encephalitis [114]. BBB disruption has been correlated with the severity of neurocognitive impairment [115], whereas in the majority of neurologically asymptomatic HIV-infected individuals, the BBB has been intact [116, 117]. These findings suggest that the delivery of ARVs to the CNS might be facilitated in patients with advanced HAND. Indeed, CSF concentrations of maraviroc have been higher in patients with neurological impairment than in neurologically asymptomatic individuals [82, 90, 91]. The CSF-to-plasma-to-albumin ratio mostly has not yet been associated with ARV concentrations in the CSF [33, 34, 66, 70, 72, 90], although evidence is not consistent [51, 94]. Penetration values derived from studies with neurologically asymptomatic subjects should not simply be extrapolated to patients with severe HAND until the effects of HIV infection on the BBB are better understood.

3.2 CSF as a Surrogate for CNS Drug Exposure

An important issue concerning CNS drug availability is the relevant sampling site. Clinical studies are generally bound to measure drug concentrations in the CSF as a surrogate for CNS drug exposure. Conversely, animal experiments can precisely quantify drug concentrations within the CNS and occasionally also point to the mechanisms and routes of drug entry. Providing information about drug concentrations in both the brain and the CSF, studies in animals have investigated the extent to which drug concentrations correlate in both compartments. Various experimental sampling and drug measurement techniques have been developed and were discussed in detail [118–120]. Table 3 presents reports on animal studies providing CSF-to-plasma or brain-to-plasma ratios of selected drugs with high penetration estimates, namely zidovudine, stavudine, abacavir, nevirapine, indinavir and maraviroc. Animal experiments have shown that drug concentrations in the CSF regularly differ from those in the brain. For example, brain-to-plasma ratios of saquinavir and nelfinavir have been found to be several-fold higher than CSF-to-plasma ratios in rodents and in non-human primates, respectively [140, 141]. Conversely, studies on animals consistently reported zidovudine and stavudine concentrations to be higher in the CSF than in brain samples, suggesting efflux mechanisms localized at the BBB [127, 131, 133, 142–144]. On one hand, brain levels are of direct interest: they indicate whether the BBB penetration is sufficient to inhibit the replication of virus residing in the brain. On the other hand, drug accumulation in the ventricular CSF itself could target infected perivascular and meningeal macrophages [24, 145]. In a comprehensive review, Shen et al. [25] assessed the applicability of CSF sampling for the assessment of CNS drug delivery in animals, concluding that CSF penetration studies remain a practical option for the assessment of drug availability in the CNS. Still, studies have to account for inherent physiochemical properties of drugs, such as lipophilicity, which determine the relationship between CSF and CNS concentrations [25]. However, in clinical studies CSF sampling is the most important way to get an idea of drug concentrations in the CNS. Comparative assessment of drug delivery in animal brain tissue and in human CSF might elucidate distribution kinetics and effective drug concentrations in the mammalian brain.

3.3 Widespread Neuropsychological Impairment Despite Highly Active Antiretroviral Therapy

Inadequate antiviral activity of ARVs in the CNS as a result of poor penetration is only one of several hypotheses that might explain persisting low-grade HIV replication in

Table 3 Animal studies assessing brain tissue and CSF penetration of antiretroviral drugs

Reference	Species	Method	CSF : plasma ratio (%)	Brain : plasma ratio (%)
Zidovudine				
[99]	Monkey	CSF samples (AUC)	16–25 [$n = 3$]	Not stated
[121]	Rabbit	CSF samples (AUC)	Without probenecid: 5.2 ± 2.3 (mean ± SD) [$n = 3$]; with probenecid: 6.8 ± 2.2 (mean ± SD) [$n = 3$]	Not stated
[122]	Rabbit	CSF samples (steady-state)	Without probenecid: 19.2 ± 0.3 (mean ± SD) [$n = 3$]; with probenecid: 29.9 ± 3.9 (mean ± SD) [$n = 3$]	Not stated
[123]	Mouse	Brain samples (AUC)	Not stated	4.5 ($n = 42$)
[124]	Rabbit	Microdialysis (AUC)	18 (15–19) [mean (range)] [$n = 6$]	9 (5–9) [mean (range)] [$n = 6$]
[125]	Dog	CSF samples (steady-state)	15 ± 5 (mean ± SD) [$n = 4$]	21 ± 5 (mean ± SD) [$n = 4$]
[126]	Rat	Microdialysis (AUC)	Not stated	18.6 [$n = 5$]
[127]	Rabbit	Microdialysis (AUC)	16.7 ± 4.5–4.8 (mean ± SD) [$n = 12$]	8.0 ± 1.9–2.0 (mean ± SD) [$n = 12$]
[128]	Monkey	CSF samples (steady-state)	22.4 ± 9.4 (mean ± SD) [$n = 4$]	Not stated
[129]	Rabbit	Microdialysis (steady-state)	27 ± 9 (mean ± SD)	18 ± 6 (mean ± SD)
[130]	Monkey	CSF samples (steady-state)	20 ± 8 (mean ± SD) [$n = 14$]	Not stated
[131]	Rat	CSF samples (steady-state)	25 ± 14 (mean ± SD) [$n = 5$]	Not stated
[132]	Rabbit	Microdialysis (steady-state)	28.8 ± 5.9 (mean ± SD) [$n = 5$]	19.4 ± 4.7 (mean ± SD) [$n = 5$]
[133]	Rat	Microdialysis (steady-state)	25 ± 8 (mean ± SD) [$n = 4$]	15 ± 4 (mean ± SD) [$n = 4$]
[134]	Dog	CSF samples (AUC)	32 [$n = 5$]	Not stated
[135]	Monkey	Microdialysis (AUC and steady-state) and CSF samples (steady-state)	CSF samples (steady-state): 17 ± 2 (mean ± SD) [$n = 5$]; microdialysis (AUC): 28 ± 6 [$n = 4$]	Microdialysis (steady-state): 13 ± 6 (mean ± SD) [$n = 5$]
Stavudine				
[133]	Rat	Microdialysis (steady-state)	50 ± 9 (mean ± SD) [$n = 7$]	34 ± 4 (mean ± SD) [$n = 7$]
[136]	Guinea pig	In situ brain perfusion	After 20 min: 1.13 ± 0.14 (mean ± SD)	After 20 min: 1.10 ± 0.09 (mean ± SD)
[137]	Rat	Microdialysis (AUC)	63 ± 7.7 (mean ± SD) [$n = 7$]	62 ± 11–17 (mean ± SD) [$n = 7$]
Abacavir				
[138]	Guinea pig	In situ brain perfusion	After 2.5 min: 0.6 ± 0.3; after 30 min: 12.6 ± 2.3 (mean ± SD)	After 2.5 min: 3.0 ± 1.3; after 30 min: 21.6 ± 5.1 (mean ± SD)
Nevirapine				
[100]	Guinea pig	In situ brain perfusion	After 30 min: 31.7 ± 6.0 (mean ± SD)	After 30 min: 45.6–59.4 ± 7.4–9.4 (mean ± SD)
Indinavir				
[139]	Rat	Brain samples (steady-state)	Not stated	18 ($n = 5$)
Maraviroc				
[106]	Rat	CSF samples (steady-state), brain samples after bolus injection	Approximately 5 ($n = 4$)	After 1 h: 25 ($n = 1$)

AUC area under the concentration-time curve, *SD* standard deviation

the CNS and persisting high prevalence of mild to moderate HAND under HAART. Other mutually non-exclusive explanations have been reviewed recently [146]. For example, in times of prolonged survival of HIV-infected individuals, age-associated disorders and complications of substance abuse gain more importance and might mimic,

aggravate and interact with HIV-related neurobehavioural disorders, thereby posing challenges to diagnosis of HAND [5]. Evidence, however, did not confirm neither a significant interactive HIV and age effect on cognitive function in an early 2000 cohort [147] nor an association between substance abuse and neurocognitive disorders in the CHARTER cohort [148]. Another focus of interest is the role of sustained intrathecal immune activation in HAND pathogenesis. HAART does not appreciably suppress CNS inflammatory markers despite systemically effective treatment and undetectable CSF HIV-RNA, suggesting continuous brain damage by host mediators of inflammation and subsequent neurocognitive impairment [11, 13, 149]. Lastly, there are increasing concerns of whether ARVs may have CNS toxic effects that are related to continuing high rates of HAND. In a cohort study, discontinuation of HAART in patients under good peripheral virological control unexpectedly resulted in significant improvement in neurocognitive function over 96 weeks off therapy [150]. A potential explanation is HAART-induced neurotoxicity, however, in the absence of a control group, practice effects that might have resulted in better neuropsychological test performance cannot be ruled out, and there might have been patient selection bias. Increasing the CNS penetration of ARVs might increase the likelihood of drug-related toxicity in the brain, but so far the mechanisms that might lead to toxic neuronal damage by ARVs remain hypothetical. More longitudinal studies will be necessary to answer these questions [148].

A risk of poor CNS penetration might arise from the selection of HIV strains with resistance patterns different from those of plasma HIV strains, consistent with genetic compartmentalization of virus within the CNS. Indeed, in a substantial proportion of subjects, HIV strains in the CNS have genotypically diverged from strains in the blood [151]. Levels of compartmentalization have been highest in patients with chronic infection or HAD [152] or after long-time therapy [38]. At present, however, it is not absolutely clear whether discordant HIV drug resistance between both compartments is related to insufficient CNS exposure to ARVs.

While targeting HAART to the CNS, therapeutic strategies should ensure efficacy in the systemic compartment at the same time. Low nadir CD4+ cell counts in the blood have been a robust predictor of neurocognitive impairment in both the pre-HAART and the HAART eras, suggesting that CNS impairment that is at least partially irreversible begins during early severe immune suppression [148]. Consequently, early treatment initiation aimed at preventing systemic immunosuppression might reduce the risk of HAND irrespective of the regimen's penetration effectiveness.

3.4 CNS-Active Drugs and Clinical Outcome

The pool of randomized controlled trials assessing the neuropsychological outcome under therapy with CNS-penetrating drugs is growing. In the pre-HAART era, study designs included single drug regimens based on NRTIs, providing evidence for CNS efficacy of single drugs. Since the introduction of PIs, NRTI monotherapy is expected to be inferior to combination therapy, so that patients in clinical studies are now predominantly being treated with multiple drugs. That might allow for the evaluation of the respective multidrug regimen, but the applicability for single drugs remains vague. As an alternative to standard HAART, i.e. combination triple therapy, ritonavir-boosted PI monotherapy has recently been considered for patients with intolerance to NRTIs or for treatment simplification. According to current recommendations, only patients under stable virological control and without any history of failure on prior PI-based therapy are eligible for PI monotherapy [153]. The poor availability of PIs in the CSF, however, gives rise to concerns over residual HIV replication in the CNS under nucleoside-sparing therapy. Large randomized cohort studies comparing standard triple HAART with lopinavir or darunavir monotherapy did not find nervous system adverse events to be more frequent in the monotherapy group after up to 96 weeks [154, 155]. Another study established neurological adverse events in only a small proportion of patients (2 %) under darunavir monotherapy, consistent with an elevated CSF viral load in these subjects [156]. Neuropsychological functioning, as assessed using a questionnaire, did not differ between patients randomized to darunavir monotherapy or to combination triple therapy [157]. Contrary to these findings, another study reported more patients experiencing therapeutic failure in the systemic compartment under lopinavir monotherapy ($n = 29$) than under triple HAART, consistent with both CSF HIV-RNA levels in the detectable range and neurological symptoms in most failing patients [158]. Moreover, 32 % of non-failing monotherapy patients had detectable HIV-RNA in the CSF at follow-up. Reintroduction of triple therapy in patients with therapeutic failure has been followed by improvement of neurological symptoms [156] and by decrease of the CSF viral load [105, 158]. The impact of PI monotherapy on virus levels in the CSF deserves further investigation.

Several studies addressed the question as to whether HAART including drugs that are more efficient in the CNS (neuroHAART) may be associated with better neurocognitive functioning. Evidence on this topic has recently been reviewed, providing qualitative and quantitative analysis [159]. Four longitudinal studies met the minimum quality criteria for inclusion in the meta-analysis, and all of them found a positive effect of neuroHAART (defined according

to the CPE ranking in most studies) on neurocognitive functioning [159]. Despite the overall success of the CPE score as a tool for clinical practice, further validation will be necessary and some questions remain open. A large retrospective study confirmed survival benefit in patients with neurological AIDS-defining conditions to be associated with a CPE score of $\geq$ 1.5 in the early HAART era; however, the association was not maintained in the later HAART era, perhaps as a result of more powerful HAART regimens [160]. Critics see limitations of the CPE score in the insufficient reflection of pharmacodynamic aspects, genotypic resistance and drug-drug interactions [110, 161]. Furthermore, the question of whether the early initiation of HAART with targeted neuroactive drugs in neurologically asymptomatic patients can prevent HAND has not yet been resolved.

As the level of evidence on CNS effectiveness is increasing, estimates on CSF penetration are beginning to impact decisions about the therapy of HAND. According to the 2011 treatment guidelines by the European AIDS Clinical Society (EACS), inclusion of potentially CNS-active drugs should be considered in all patients with diagnosed HAND and is explicitly recommended in HAND-affected patients with a CSF viral load of >50 cells/mL in the absence of viremia [153]

4 Conclusion

Treatment of HAND requires viral load control both in the systemic and in the CNS compartments. While suppression of viral load is frequently obtained in the blood plasma as a result of potent HAART, drug penetration into the CNS is the focus of interest. The ability of ARVs to penetrate the BBB is believed to influence the extent of neurocognitive improvement and the decay of viral load in the CSF. Drug concentrations in the CSF are indicative for concentrations in the CNS and they can be assessed in the clinical context. Still, evidence on CSF distribution is sparse for several antiretroviral substances, including drugs introduced more recently, and is based on observational studies rather than on controlled clinical trials.

In the light of ongoing HAND and of the potential benefit of CNS-active drugs, clinical CSF penetration studies that respect relevant study design issues will be required. Early preclinical drug development should include assessment of CNS drug delivery in animals. CSF penetration studies and validated neuropsychological testing in a subgroup of patients in the course of new drug applications will lead to a better understanding of drug potency in the brain. Ultimately, large clinical cohort studies will be critical to provide guidelines for a well directed selection of HAART for patients with HAND.

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