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REVIEW ARTICLE

Central Nervous System Penetration of Antiretroviral Drugs: Pharmacokinetic, Pharmacodynamic and Pharmacogenomic Considerations

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Abstract The prevalence of HIV-associated neurocognitive disorder (HAND) is increasing despite the widespread use of combination antiretroviral therapy (ART). Initial reports suggest that the use of antiretrovirals with good central nervous system (CNS) penetration leads to better neurocognitive outcomes, but this has not yet been confirmed in a large cohort study or randomised controlled trial. There is emerging evidence that high CNS concentrations of some antiretrovirals are potentially neurotoxic and may be associated with the development of HAND. Antiretroviral CNS exposure is ideally determined by determining the ratio of cerebrospinal fluid (CSF):plasma area under the curve of unbound drug, but usually only total drug concentrations are measured and the ratio of CSF:plasma drug concentration is done at a single time point, which can result in misclassifying CNS penetration ability. Efavirenz was previously thought to have poor CNS penetration, measured by the CSF:plasma ratio (0.87 %), but when unbound concentrations were measured it was found to have good CNS penetration (85 %). Indinavir and efavirenz are the only antiretroviral drugs for which CNS area under the concentration–time curves using unbound plasma and CSF concentrations has been calculated. Patient data to support the contribution of blood–brain barrier transporter polymorphisms to CNS antiretroviral concentrations are currently limited and lack power to detect true associations. Correlations between CNS antiretroviral exposure and effect is multifaceted, and to accurately predict CNS effects there is a need to develop a sophisticated intra-brain pharmacokinetic–pharmacodynamic–pharmacogenetic model that includes transporters as well as the influence of HIV.

Key Points

There are limited antiretroviral pharmacokinetic studies that adequately estimate CNS exposure calculating area under the concentration–time curve using total and unbound cerebrospinal fluid antiretroviral concentrations.

Data on the clinical relevance and extent of the contribution of polymorphisms in genes encoding for blood–brain transporters to CNS antiretroviral exposure are limited due to the small number of studies and lack of power.

Current understanding and categorizing of antiretroviral CNS penetration has not translated into better clinical outcomes and there is a need to develop a sophisticated intra-brain pharmacokinetic–pharmacodynamic–pharmacogenetic model that includes transporters as well as the influence of HIV.

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1 Introduction

The overall prevalence of all forms of HIV-associated neurocognitive disorders (HANDs) is increasing despite the widespread use of combination antiretroviral therapy (ART) [1]. While the incidence of severe disorders, such as HIV-dementia (HIV-D), has significantly reduced, milder forms of HAND are on the rise. This disease burden is, in large part, being driven by the longer life expectancy of treated individuals and the associated neurocognitive impairment due to cardiovascular disease and related degenerative diseases of aging [2]. HAND is associated with a range of functional impairments that can affect employment, driving and medication adherence [1, 3]. Proposed mechanisms of the development or progression of HAND in people receiving ART include persistent neurodegeneration and neurotoxicity from antiretroviral drugs [4]. In vitro data suggest that antiretroviral drugs cause neurotoxicity at therapeutic doses [5, 6]. Better central nervous system (CNS)-penetrating antiretroviral drugs were initially associated with better neurocognitive outcomes, but large cohort data suggest an associated increased risk of developing dementia [7, 8].

The association between viral replication and cerebrospinal fluid (CSF) antiretroviral concentrations has been the subject of intensive investigation. Physiochemical properties of the drug (size, lipophilicity, plasma protein binding, active transport into the CNS and metabolism in the CNS) can predict CNS drug exposure to some extent but pharmacokinetic studies are required for confirmation [9]. Pharmacokinetic studies of CNS penetration of drugs are usually done by sampling CSF, which is in close contact with brain extracellular fluid [10]. There are caveats when making inferences about CNS drug exposure using CSF drug concentrations [11, 12]. First, CSF acts as a slowly equilibrating compartment relative to plasma with reduced and delayed concentration peaks and an overall flatter profile shape of the area under the concentration–time curves (AUCs) [13]. CSF:plasma drug ratios, which are often used as a measure of CNS exposure, will therefore vary depending on the time of sampling. Estimation of CSF and plasma AUCs followed by calculating the ratio of exposure is a more robust method of estimating CNS drug penetration [11]; however, CSF AUC estimation is hampered by the difficulty in obtaining multiple CSF samples. Second, measuring total drug concentrations rather than unbound concentrations gives misleading information about CNS exposure as only unbound drug is able to act at the receptor site [14]. Efavirenz CSF penetration was thought to be limited based on total efavirenz concentrations, but efavirenz CSF penetration is excellent, with similar plasma and CSF unbound concentrations [14]. Third, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) are both highly protein bound, with NNRTIs predominantly binding to α1-acid glycoprotein, while PIs bind to albumin [14, 15]. Antiretroviral entry into the CNS is therefore governed largely by multiple influx and efflux drug transporters at the blood–brain barrier and the blood–CSF barrier [16–19]. Drug exchange between blood, CSF and brain extracellular fluid does not occur freely, and drug concentration measurements made in any one of these compartments may not accurately reflect events in the other compartments [10, 20]. Fourth, genetic polymorphisms in relevant metabolizing enzymes and transporters at the different blood–brain interfaces may influence drug disposition and response [21, 22]. Last, HIV disease compromises the blood–brain barrier integrity which will influence drug exposure [23]. Healthy volunteer data may therefore not reflect drug exposure seen in HIV-infected patients.

A recent review in *Clinical Pharmacokinetics* discussed the pharmacokinetics and pharmacodynamics of antiretrovirals in the CNS [24]. We critically reviewed the pharmacokinetic data of antiretroviral drug exposure in the CNS with the focus on the quality of the CSF pharmacokinetic studies according to the different antiretroviral drug classes, which included a focus on total and unbound concentration analysis. We identified variables that influence CNS exposure, including the potential role of genetic polymorphisms on drug transporters and their influence on CNS antiretroviral exposure. Finally, we explored links between antiretroviral CNS pharmacokinetics and clinical outcomes.

1.1 Study Selection

We conducted a systematic search in the PubMed database from inception until 1 January 2015. Two reviewers (ED and JJ) independently identified studies that reported on the measurement of CSF antiretroviral concentrations in HIV-infected patients. Discrepancies between the two reviewers were mediated by a third reviewer (GM). We evaluated the quality of the data using the following criteria: a priori sample size calculation, CSF and plasma antiretroviral bound and unbound drug analysis, and estimation of CSF and plasma antiretroviral exposure using AUC. We evaluated pharmacodynamic or clinical outcomes if any were reported, and excluded studies that evaluated antiretroviral drug exposure in animal models.

1.2 Search Strategy

We conducted multiple searches on human antiretroviral pharmacokinetic studies in HIV-infected patients which

measured drug concentrations in the CSF. For *search 1* we used the following Medical Subject Heading (MeSH) terms: Search (HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tiab] OR hiv-1*[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab] OR human immunedeficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*[tiab]) AND (deficiency virus[tiab])) OR acquired immunodeficiency syndrome[tiab] OR acquired immunedeficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*[tiab]) AND (deficiency syndrome[tiab])) OR "sexually transmitted diseases, Viral"[MeSH:NoExp]). For *search 2* we used the following MeSH terms: Search (antiretroviral therapy, highly active[MeSH] OR anti-retroviral agents[MeSH] OR antiviral agents[MeSH:NoExp] OR ((anti[tiab]) AND (hiv[tiab])) OR antiretroviral*[tiab] OR ((anti[tiab]) AND (retroviral*[tiab])) OR HAART[tiab] OR ((anti[tiab]) AND (acquired immunodeficiency[tiab])) OR ((anti[tiab]) AND (acquired immuno-deficiency[tiab])) OR ((anti[tiab]) AND (acquired immune-deficiency[tiab])) OR ((anti[tiab]) AND (acquired immun*[tiab]) AND (deficiency [tiab])). For *search 3* we used the following MeSH terms: Search (central nervous system[mh] OR central nervous system*[tiab] OR cerebrospinal fluid[mh] OR cerebrospinal fluid*[tiab]). For *search 4* we used the following MeSH terms: Search (pharmacokinetics[mh] OR pharmacokinetics[tiab] OR transport*[tiab] OR penetra*[tiab] OR blood-brain barrier[mh] OR blood-brain barrier*[tiab]). We combined searches 1 and 2 and further refined the search by performing searches 3 and 4. The search strategy identified 505 articles that studied the CSF exposure of 18 different antiretroviral drugs. A meta-analysis was not possible due to study methodology heterogeneity. We opted to discuss each antiretroviral drug class critically, and conducted an additional search focused on human genetic polymorphisms and the association with CSF antiretroviral exposure.

2 Pharmacokinetics and Pharmacodynamics

Various pharmacodynamic markers for HIV CNS are used [25]. CSF inhibitory concentrations are frequently used in antiretroviral pharmacokinetic studies. Recently, CSF 95 % inhibitory quotients (IQ_{95}) were proposed as an improved marker, with high CSF IQ_{95} being associated with better CSF viral suppression and a lower prevalence of CSF escape [26]. IQ_{95} is the ratio between the CSF concentration and the 95 % inhibitory concentration (IC_{95}), and a ratio of more than 1 is considered adequate exposure. The relationship between IQ_{95} and the potential for neurotoxicity has not been investigated. Clinical neurocognitive endpoints and the relationship with antiretroviral pharmacokinetics has been best described by the CNS penetration-effectiveness (CPE) score hypothesis studies. The updated CPE score places antiretroviral drugs into four categories according to physiochemical drug properties, measured CSF drug concentrations, and efficacy as determined by CSF viral suppression and neurocognitive improvement [27]. Antiretrovirals with lower CPE scores are associated with higher CSF viral loads [8]. Antiretrovirals with higher CPE scores penetrate the CNS better and are thought to be more appropriate for patients with HIV-associated neurocognitive symptoms. In uncontrolled observational studies, higher CNS-penetrating antiretrovirals were associated with better CSF viral load suppression, while others also showed an association with improved neurocognitive outcomes compared with lower penetrating antiretrovirals [8, 28–30]. In a large cohort of nearly 62,000 patients followed-up for a median of 37 months, patients receiving drugs with a high CPE score were found to be at increased risk of developing dementia, with a hazard ratio of 1.74 (95 % confidence interval 1.15–2.65), compared with patients receiving ART with a lower CPE score [7]. Antiretroviral-mediated increase in the deposition of β-amyloid, as well as neurotoxicity, were cited as some of the reasons for the findings [6, 31]; however, this finding should be further studied as the association may have been confounded by the majority of patients switching from their original ART regimen, and initiation with a high CPE regimen may have been informed by patients presenting with neurocognitive symptoms. The association between higher CPE scores and better neurocognitive outcomes was not demonstrated in a recent randomised controlled trial, but the trial was underpowered and stopped early due to low accrual [32]. Current understanding and categorizing of antiretroviral CNS penetration has not translated into better clinical outcomes. In the following sections, we will review the pharmacokinetic data on which CNS penetration inferences are based on, and highlight the gaps in our knowledge.

2.1 Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

The nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) have good CNS penetration, with the exception of tenofovir (see Table 1). Exposure of NRTIs in the CSF exceeds the in vitro inhibitory concentration to suppress 50 % viral replication (IC_{50}), but no unbound data are available (see Table 2). However, CSF sampling measures extracellular drug concentrations and NRTIs require intracellular phosphorylation to be pharmacologically active,

Table 1 Nucleoside and nucleotide reverse transcriptase inhibitors' central nervous system pharmacokinetic data

Reported CSF penetration in relation to plasma exposure	CSF exposure	Plasma exposure	Methodology sample (CSF–plasma)	References
Abacavir				
Range of 150–600 mg 12-hourly				
Total concentration CSF/plasma AUC ratio: 36 ± 5 %[b] (95 % CI 28–46)	Total concentration: 128 (37–384) ng/ml[a]	Total concentration: 139 ng/ml (<40 to 1130) ng/ml[a]	POPPK estimates of paired CSF–plasma total concentrations of 70 CSF and 64 plasma samples taken at various time points during the dosing interval	[83]
Range of 600–1800 mg daily				
Total concentration CSF/plasma AUC ratio: 35 (31–44) %[a]	Total AUC_{∞}: 5.14 (2.01–13.13) μg·h/ml[c]	Total AUC_{∞}: 12.81 (8.66–18.96) μg·h/ml[c]	Analysis of seven paired CSF–plasma total concentrations taken during the first 6 h of dosing from three patients who received a single dose	[36]
Total concentration CSF/plasma ratio: 42 (80–173) %[a]	Total concentration: 0.14 (0.09–0.19) μg/ml[a]	Total AUC_{∞}: 0.74 (0.66–0.84) μg·h/ml[c] to 0.92 (0.83–1.02) μg·h/ml, depending on the dose	Analysis of nine mid-dose paired CSF–plasma total concentrations taken 1.5 h post-dosing	[37]
Lamivudine				
Range of 8–20 mg/kg daily				
Total concentration CSF/plasma ratio: 6 (4–8) %[e]	Total concentration: range 94–328 ng/l	Not stated	Analysis of six paired CSF–plasma total concentrations taken at 2 h post-dosing from six patients	[84]
Range of 0.5–10 mg/kg/daily				
Total concentration CSF/plasma ratio: 12 (0–46) %[a]	Total concentration: 0.07 (undetectable–0.12) μM[a] to 0.99 (0.32–2.23) μM[a]	Total AUC_{oral}: 2.84 (1.04) μM·h[c] to 61.8 (35.8) μM·h[c], depending on the dose	Analysis of 68 paired CSF–plasma total concentrations taken at 2–4 h post-dosing from 44 children	[85]
150 mg 12-hourly				
Total concentration CSF/plasma ratio: median range 6–30 % (interpreted from a graph)	Total concentration: range 0.29–0.35 μmol/l	Total concentration: median range 400–960 ng/ml (interpreted from a graph)	Analysis of 22 paired CSF–plasma total concentrations taken at 2–8 h post-dosing from 22 patients	[86]
Total concentration CSF/plasma ratio: 15.1 (1.3)[c] (range 12.4–17.5) %	Total AUC_{12}: 3346 (219) nM·h[c] (range 2768–3740) nM·h	Total AUC_{12}: 22,216 (580)[c] (range 21,307–23,787) nM·h	Analysis of ultra-intensive paired CSF–plasma total concentrations taken twice over 48 h from four patients	[81]
Total concentration CSF/plasma ratio: 22.9 (0–49) %[e]	Not reported	Not reported	Analysis of 55 paired CSF–plasma total concentrations	[49]
Stavudine				
Total concentration CSF/plasma ratio: 38.9 (3.9)[c] (range 34.1–50.4) %	Total AUC_{12}: 1814 (414) nM·h[c] (range 1034–2938) nM·h	Total AUC_{12}: 4524 (622)[c] (range 3035–5825) nM·h	Analysis of ultra-intensive paired CSF–plasma total concentrations taken twice over 48 h from four patients	[81]
Total concentration CSF/plasma ratio: median range 20–85 % (interpreted from a graph)	Total concentration: range 0.20–0.27 μmol/l	Total concentration: median range 100–280 ng/ml (interpreted from a graph)	Analysis of 17 paired CSF–plasma total concentrations taken at 2–8 h post-dosing from 17 patients	[86]

Table 1 continued

Reported CSF penetration in relation to plasma exposure	CSF exposure	Plasma exposure	Methodology sample (CSF–plasma)	References
Total concentration CSF/plasma ratio: 40 (6) %[c]	Total concentration: 62.09 (12.88) ng/ml[c]	TotalAUC_{∞}: 2116 (346.52) ng·h/ml[c]	Analysis of four paired CSF–plasma total concentrations taken at 4–5 h post-dosing from four patients	[87]
Total concentration CSF/plasma ratio: 20.4 (0.0–20.4)[a]	Not reported	Not reported	Analysis of 31 paired CSF–plasma total concentrations.	[49]
Tenofovir				
Total concentration CSF/plasma ratio: 5.7 (3.0–10.0)[c] (range 0.4–84) %	Total concentration: 5.5 (2.7–11.3)[b] (range <0.9–38.5) ng/ml	Total concentration: 95.5 (46.9–153.2)[b] (range <0.9–859.7) ng/ml	Analysis of 77 paired CSF-plasma total concentrations taken at a mean of 11 h post-dosing	[38]
Zidovudine				
200 mg 8-hourly				
Total concentration CSF/plasma ratio: median range 15–120 % (interpreted from a graph)	Total concentration: range 0.12–0.17 μmol/l	Total concentration: median range 40–340 ng/ml (interpreted from a graph)	Analysis of 11 paired CSF–plasma total concentrations taken at 2–8 h post-dosing from 11 patients	[86]
Total concentration CSF/plasma ratio: 78 (6–320) %[a]	Total concentration: 93 (23–170) ng/ml[a]	Total concentration: 118 (13–740) ng/ml[a]	Analysis of 23 paired CSF–plasma total concentrations taken at 2–8 h post-dosing from 23 patients	[88]
Total concentration 3-amino-3-deoxythymidine: 10 (18–23) %[a]	Total 3-amino-3-deoxythymidine: 1.7 (0.75–4.8) ng/ml[a]	Total concentration 3-amino-3-deoxythymidine: 2.5 (0.77–6.6) ng/ml[a]		
Single dose of 2.5 mg/kg intravenously				
Total concentration CSF/plasma ratio: 75 ± 26 %[c]	Total AUC_{∞}: 358 ± 200 μmol·min/l	Total AUC_6: 448 ± 213 μmol·min/l	Analysis of six paired CSF–plasma total concentrations taken up to 6 h post-dosing from six patients	[34]

AUC area under the concentration–time curve, AUC_{oral} AUC for the oral dose, AUC_6 AUC from time zero to 6 h, AUC_{12} AUC from time zero to 12 h, AUC_{∞} AUC from time zero to infinity, *CI* confidence interval, *CSF* cerebrospinal fluid, *POPPK* population pharmacokinetic

[a] Median (range)

[b] Median (interquartile range)

[c] Mean (standard deviation)

[d] Geometric means (95 % CI)

[e] Mean (range)

Table 2 Nucleoside and nucleotide reverse transcriptase inhibitors' central nervous system pharmacodynamic data

Drug	In vitro efficacy in CSF	Efficacy data	References
Abacavir	IC_{50} 0.07 μg/ml	POPPK model predicted that CSF troughs would exceed the IC_{50} for 85 % of the dose interval	[83]
		CSF C_{max} exceeded the IC_{50} by 8–20 times	[36, 37]
Lamivudine	IC_{50} (not specified)	Total CSF concentrations exceed the IC_{50}	[86]
Stavudine	IC_{50} 0.009–4.1 μmol/l	Total CSF concentrations exceed the IC_{50}	[86]
	IC_{50} 52 ng/ml	Total CSF concentrations exceed the IC_{50}	[87]
Tenofovir	IC_{50} 11.5 ng/ml	Total CSF concentrations did not exceed the IC_{50} in 77 % (59/77) of patients	[38]
Zidovudine	IC_{50} 0.002–2.400 μmol/l	Total CSF concentrations exceed the IC_{50}	[86]
	IC_{50} (not specified)	Total CSF trough concentrations exceed the IC_{50} by twofold	[34]

C_{max} maximum concentration, *CSF* cerebrospinal fluid, *IC_{50}* 50 % inhibitory concentration, *POPPK* population pharmacokinetic

limiting efficacy conclusions from total or unbound NRTI concentrations [33]. Zidovudine penetrates the CNS well, with total intravenous CNS exposure of 75 % of that in plasma [34, 35]. Approximately 35 % of total abacavir plasma concentrations penetrate the CSF [36, 37]. Lamivudine, stavudine and tenofovir CSF AUCs have not been described (see Table 1). Only 5 % of tenofovir penetrates the CSF, most likely via active transport, therefore CSF concentrations are well below the in vitro IC_{50} to suppress viral replication for most patients [38].

2.2 Non-Nucleoside Reverse Transcriptase Inhibitors

Efavirenz is more than 99.5 % protein bound, with low total efavirenz cerebrospinal exposure of less than 1 % of that of plasma; however, unbound efavirenz concentrations reach equilibrium between the two compartments (see Table 3) [14, 39]. The equilibrium between unbound concentrations in CSF and plasma is in contrast to the PIs and suggests that unbound efavirenz easily penetrates the CNS and is not actively cleared from the CNS. Efavirenz is predominantly metabolized by cytochrome P450 (CYP) 2B6 into several metabolites, of which 8-hydroxy efavirenz is the main metabolite [40, 41]. Other metabolites include 7-hydroxy efavirenz and 8,14 hydroxy efavirenz [40]. Efavirenz metabolites do not seem to inhibit viral replication but may play a role in its adverse event profile, which predominantly involves the CNS [5, 14, 40, 42]. 8-hydroxy efavirenz has been hypothesized to be implicated in neurotoxicity [5]. Extensive metabolisers may generate more 8-hydroxy efavirenz and be predisposed to develop more neurotoxicity [43]. CSF 8-hydroxy efavirenz has in fact been associated with an increase in patient neurocognitive symptoms [44]; however, no association was found between 8-hydroxy efavirenz and CYP2B6 genotype or efavirenz plasma concentration in a small study of patients of mostly Asian origin [44]. The investigators postulated that 8-hydroxy efavirenz gets trapped in the CNS. Plasma 8-hydroxy efavirenz or CNS-metabolised 8-hydroxy efavirenz may undergo glucoronidation and be unable to cross the blood–brain barrier [44]. Total and unbound efavirenz exposure in the CSF is significantly higher than the IC_{50} required to suppress viral replication (see Table 4) [14, 39, 40, 45, 46]. Efavirenz has the highest IQ_{95} of the NNRTIs [26].

Limited CSF penetration data exist for nevirapine but its drug properties may allow for good CSF penetration [47–49]. Nevirapine is the least protein bound NNRTI (60 % protein binding) and has a low molecular weight of 266.6 g/mol. The effect of CSF penetration on viral suppression has not been studied.

Etravirine is extensively protein bound (96–99.9 %) in CSF and in plasma [50]. Total etravirine concentrations in the CSF are 1–4 % of total plasma etravirine concentrations, but less than 2 % of CSF total etravirine concentration is unbound [50, 51]. The unbound etravirine concentration is well below the in vitro IC_{50} to suppress viral replication but does not seem to affect its in vivo CSF viral activity (see Table 4) [50, 51]. Nguyen et al. [50] postulated that adequate intracellular etravirine rather than unbound extracellular etravirine is required for viral suppression.

2.3 Protease Inhibitors

The PIs have a molecular weight above 500 Da and are more than 90 % plasma protein bound, with the exception of indinavir, which is less than 60 % protein bound in plasma [13, 52]. The low protein binding of indinavir translates into higher total drug concentrations in the CSF than with other PIs. Only 6 % of indinavir in the CSF is bound to proteins [13, 52]. Unbound PI concentrations in the CSF do not reach equilibrium, even at steady-state [13, 52, 53]. The lack of equilibrium is likely explained by

Table 3 Non-nucleoside reverse transcriptase inhibitors' central nervous system pharmacokinetic data

Reported CSF penetration in relation to plasma exposure	CSF exposure	Plasma exposure	Methodology sample (CSF–plasma)	References
Efavirenz				
Total concentration plasma/CSF ratio: 134 (116–198) %	Total concentration: 18.8 (9.34–22.74) ng/ml[b]	Total concentration: 2170 (1684–3953) ng/ml[b]	Analysis of 13 mid-dose paired CSF–plasma unbound and total concentrations	[14]
Unbound concentration plasma/CSF ratio: 120 (97–212) % (plasma/CSF ratio calculated, not CSF/plasma ratio)	Unbound concentration: 4.1 (2.2–4.8) ng/ml[b]	Unbound concentration: 4.8 (3.7–6.7) ng/ml[b]		
Total concentration CSF/plasma ratio: 0.5 (0.26–0.76)[b] or 0.5 %	Total concentration: 13.9 (4.1–21.2) ng/ml[b]	Total concentration: 2145 (1384–4423) ng/ml[b]	POPPK estimates of 80 mid-dose paired CSF–plasma total concentrations	[45]
POPPK estimate total concentration CSF penetration: 0.48 (0.47–0.49) % with AUC_{CSF} less than 1 % of AUC_{plasma}				
Total concentration efavirenz CSF/plasma ratio: 0.88 %	Total concentration efavirenz: 19 (7–24) ng/ml[b]	Total concentration efavirenz: 2170 (1896–2520) ng/ml[b]	Analysis of 13 mid-dose paired CSF–plasma unbound and total concentrations	[5, 40]
Total concentration 8-hydroxy efavirenz CSF/plasma ratio: 1.07 % (not reported, but calculated by authors)	Total concentration 8-hydroxy efavirenz: 3.37 (2.58–6.54) ng/ml[b] Total concentration 7-hydroxy efavirenz: undetectable Total concentration 8,14-hydroxy efavirenz: detectable in $n = 2/13$: 0.375 ng/ml and 0.444 ng/ml Unbound concentration 8-, 7- and 8,14-hydroxy efavirenz: undetectable	Total concentration 8-hydroxy efavirenz: 314.5 (206–362.3) ng/ml[b] Total concentration 7-hydroxy efavirenz: 8.84 (6.21–12.48) ng/ml[b] Total concentration 8,14-hydroxy efavirenz: 5.63 (4.58–6.16) ng/ml[b] Unbound concentration 8-, 7- and 8,14-hydroxy efavirenz: Undetectable		
Total concentration CSF/plasma AUC_{24} ratio: 0.44 (0.03–0.9) %[a] Unbound concentration CSF/plasma ratio (estimated): 88 %	Total AUC_{24}: 0.38 mg·h/l Total concentration efavirenz: 16.3 (7.3–22.3) ng/ml[a] Unbound concentration (estimated): 16.3 ng/ml	Total AUC_{24}: 86.28 mg·h/l Total concentration efavirenz: 3718 (2439–4952) ng/ml[b] Unbound concentration (estimated): 18.6 ng/ml	POPPK estimates of paired CSF–plasma total concentrations over 24 h dosing interval in one patient	[39]
Total concentration efavirenz CSF/plasma ratio: 1.07 %	Total concentration efavirenz: 10 (7.0–14.0) ng/ml[a]	Total concentration efavirenz: 936 (382–1116) ng/ml[a]	Analysis of 18 mid-dose paired CSF–plasma total concentrations	[46]
Nevirapine				
Total concentration CSF/plasma ratio: *ABCB1*-3435 C/T or T/T genotype: 62 % *ABCB*1-3435 C/C genotype: 43 %	Reported per CYP2B6 genotype	Reported per CYP2B6 genotype	Analysis of 14 paired CSF–plasma total concentrations taken around t_{max} in 11 paediatric patients	[48]
Total concentration CSF/plasma ratio: 62.6 (41–77) %[a]	Not reported	Not reported	Analysis of 16 paired CSF-plasma total concentrations.	[49]
Not calculated	Total concentration: 932 (219–1837) ng/ml[a]	Total AUC_{24}: 109,120 (52,284–190,324) ng·h/ml	Analysis of plasma and CSF total concentrations in 15 patients over a 2-year period	[47]

Table 3 continued

Reported CSF penetration in relation to plasma exposure	CSF exposure	Plasma exposure	Methodology sample (CSF–plasma)	References
Etravirine				
Total concentration CSF/plasma ratio: 1 (0.5–3) %	Total concentration: 7.24 (3.59–17.9) ng/ml[a]	Total concentration: 611.5 (148–991) ng/ml[a]	Analysis of 12 trough paired CSF–plasma total concentrations	[51]
Total concentration CSF/ unbound plasma (estimated): 1206 %		Estimated unbound concentration: 0.1 % of total (not shown)		
Total concentration CSF/plasma ratio: 4.3 (1.1–14.1)[a]; (3–5.9)[b] %	Total concentration: 9.5 (2.0–38.9)[a]; (6.4–26.4) ng/ml[b]	Total concentration: 215.2 (64–869.5)[a]; (154.1–70.4) ng/ml[b]	Analysis of 17 mid-dose paired CSF–plasma unbound and total concentrations taken over the dosing interval	[50]
Total concentration CSF/unbound plasma ratio: 101 (18–710)[a]; (76–160)[b] %	Unbound concentration: 0.13 (0.03–0.76)[a]; (0.08–0.27) ng/ml[b]	Unbound concentration: 6.2 (1.3–47.8)[a]; (4.9–34.7) ng/ml[b]		

AUC area under the concentration–time curve, AUC_{CSF} AUC of efavirenz cerebrospinal fluid concentrations, AUC_{plasma} AUC of efavirenz plasma concentrations, AUC_{24} AUC from time zero to 24 h, *CSF* cerebrospinal fluid, *CYP* cytochrome P450, *POPPK* population pharmacokinetic, t_{max} time to maximum concentration,

[a] Median (range)

[b] Median (interquartile range)

active removal of the PIs from the CSF by efflux pumps such as p-glycoprotein [13, 52].

Indinavir CSF exposure has been very well characterized, although it is no longer routinely used [54]. Table 5 summarizes the pharmacokinetic data of indinavir exposure at different dosing regimens. In vitro data suggest that unboosted indinavir reaches sufficient concentrations to inhibit wild-type virus in the majority of patients (see Table 6) [13, 55–57]. Ritonavir boosting to increase CSF concentrations specifically has been studied using indinavir [52]. Ritonavir increased plasma but not CSF unbound indinavir exposure [52]. Ritonavir has a minimal effect on p-glycoprotein at the blood–brain barrier level as low unbound concentrations reach the CNS in comparison to the gut and liver [52, 58]

Atazanavir, which has 86 % protein binding, is the PI that has the second highest proportion of unbound drug in the CSF [59]. Ritonavir added to atazanavir increases plasma total atazanavir concentrations by more than double, while CSF concentrations only increase slightly (see Table 5) [59]. The modelled estimate of total atazanavir penetration boosted with ritonavir in the CSF is 0.74 % of plasma concentrations [59]. CSF atazanavir failed to achieve concentrations above the in vitro IC_{50} in many patients (see Table 6). Unboosted atazanavir has the lowest IQ_{95} of the PIs [26]. Additional ritonavir increases the IQ_{95} of atazanavir similar to that of boosted lopinavir [26].

Nelfinavir manufacturing has been discontinued and no longer available as a treatment option. It is highly protein bound (99.7 ± 0.10 %) and reaches undetectable CSF concentrations, mostly when measured [57, 60–63]. Total nelfinavir CSF exposure in relation to plasma has not been adequately quantified despite sensitive methodology and instrumentation (see Table 5) [63, 64]. CSF nelfinavir concentrations are in the range of in vitro inhibitory concentrations of wild-type virus (see Table 6) [63, 64].

When boosted with ritonavir, lopinavir reaches therapeutic concentrations in plasma. Lopinavir is 97–99 % protein bound, with less than 0.5 % of total lopinavir concentrations reaching the CSF (see Table 5) [46, 60, 61, 65, 66]. Lopinavir total CSF concentrations exceed in vitro concentrations required to inhibit wild-type virus [46, 65, 66]. Data on lopinavir AUC exposure and CSF unbound concentrations are lacking.

Darunavir is only 6.5 % unbound in plasma and 97.2 % in CSF [53]. At the darunavir/ritonavir dose of 600/100 mg, total darunavir CSF concentrations are approximately 1 % of total plasma concentrations (see Table 5) [53, 67, 68]. Unbound darunavir CSF concentrations are significantly higher at 8.5 % of unbound plasma concentrations [53]. Darunavir has adequate CSF exposure (see Table 6) and the highest IQ_{95} of all the evaluated antiretrovirals [26].

Table 4 Non-nucleoside reverse transcriptase inhibitors' central nervous system pharmacodynamic data

Drug	In vitro efficacy in CSF	Efficacy data	References
Efavirenz	IC_{50} 0.51 ng/ml	CSF unbound above the wild-type in vitro IC_{50} in lymphocytes of 0.51 ng/ml, and CSF total concentrations exceeded the wild-type IC_{50} in lymphocytes of 0.51 ng/ml by a ratio of 26 (8–41)[a]	[14, 45]
		CSF total concentrations exceeded the IC_{50} in 14/18 (78 %) patients	[46]
	IC_{50} 0.36 ng/ml	CSF total concentration above the IC_{50}. Metabolites (8-, 7- and 8,14-OH) considered to be minimally effective at inhibiting viral replication. CSF concentrations below the IC_{50} for 8-OH efavirenz (42.25 ng/ml), 7-OH efavirenz (44.68 ng/ml) and 8,14-OH efavirenz (2238.4 ng/ml)	[40]
	IC_{50} 1.3 ng/ml	CSF total concentration exceeded the wild-type IC_{50} in lymphocytes in a protein-free medium of 1.3 ng/ml by 12-fold	[39]
Etravirine	IC_{50} range of 0.39–2.4 ng/ml	CSF total concentrations exceeded the IC_{50} range	[51]
	IC_{50} of 0.9 ng/ml	CSF total concentrations exceeded the vitro unbound IC_{50} for wild-type HIV-1 of 0.9 ng/ml, but unbound CSF concentrations were all below the IC_{50}	[50]

CSF cerebrospinal fluid, *IC_{50}* 50 % inhibitory concentration

[a] Interquartile range

The unbound plasma fraction of saquinavir is less than 1 % [69, 70]. CSF unbound concentrations are mostly unmeasurable, and when measured the unbound saquinavir CSF:plasma ratio is less than 1 % [69]. CSF concentrations are below the in vitro concentrations required to inhibit wild-type virus (see Table 6) [63, 69, 71].

2.4 Other Antiretroviral Drugs

The CSF concentrations of the fusion inhibitor enfuvirtide are not quantifiable due to negligible CSF penetration [72]. Although no unbound AUC penetration data are available, total CSF and plasma paired samples indicate that the entry inhibitor maraviroc and the integrase inhibitor raltegravir enter the CSF. Maraviroc achieves total CSF concentrations in excess of threefold the effective concentration to inhibit viral replication of 0.57 ng/ml [73]. In seven paired total CSF and plasma concentrations the median and range of plasma and CSF concentrations were 94.9 (21.4–478) and 3.63 (1.83–12.2) ng/ml, respectively, giving a median CSF/plasma ratio of 3 % (1–10) [73]. Raltegravir total CSF concentrations are approximately 6.0 % that of plasma, and exceed the concentration required to inhibit 50 % of viral replication in all patients but fail to exceed the IC_{95} in at least half of the patients (see Tables 7, 8) [74, 75].

3 Pharmacogenetic Data

A spectrum of transporters, classified into ATP-binding cassette (ABC) or solute-carrier (SLC) transporters, exist to facilitate or prevent the movement of molecules across the blood–CNS interface. Transport of ART out of the CNS is mediated by p-glycoprotein (also known as MDR-1 or ABCB1), the multidrug resistance-associated proteins (or MRPs, also known as ABCC) and breast cancer resistance protein (BCRP, also known as ABCG2) [17, 76, 77]. Limited data are available on the SLC superfamily at the blood–brain barrier, but they also seem to play an important role in the efflux of molecules [78]. Although CYP1B1 has been detected at the human blood–brain barrier, CYP3A4, CYP2C9 and CYP2D6 have not, and the impact of the enzymatic barrier on cerebral disposition of ART is probably negligible [18]. Genetic polymorphisms in ART blood–brain barrier transporters may therefore contribute to the difference in CNS ART exposure [19, 79]. Patient data to support the contribution of blood–brain barrier transporter polymorphisms to CNS antiretroviral concentrations are currently limited (see Table 9) and plagued by the lack of power to detect true associations [80].

4 Discussion and Conclusion

We reviewed the CNS pharmacokinetic, pharmacodynamic and pharmacogenetic data of ART. The movement of drug molecules into the CNS is complex, and extrapolation of CNS drug exposure from CSF drug concentrations oversimplifies the pharmacokinetics of CNS ART; however, CSF is the most accessible CNS matrix [10]. The majority of published ART CNS penetration studies measured CNS penetration by using single paired CSF–plasma

Table 5 Protease inhibitors' central nervous system pharmacokinetic data

Reported CSF penetration in relation to plasma exposure	CSF exposure	Plasma exposure	Methodology sample (CSF–plasma)	References
Indinavir				
800 mg 8-hourly without ritonavir				
Not stated	Total concentration: 223 (200)[c] (range 80–660) nmol/l	Total concentration: 2086 (3400)[c] (range 70–10,300) nmol/l	Analysis of 32 paired CSF–plasma total concentrations at various time points during the dosing interval from 25 patients	[89]
Total concentration CSF/plasma AUC_8 ratio: 6.5 (1.0)[c] (range 4.9–8.0) %	Total AUC_8: 1720 (538)[c] (range 886–2256) nmol·h/l	Total AUC_8: 26,939 (8908)[c] (range 11,845–38,930) nmol·h/l	Analysis of 80 paired CSF–plasma unbound and total concentrations over 8 h dosing interval from eight patients	[13]
Unbound concentration CSF/plasma AUC_8 ratio: 14.7 (2.6)[c] (range 10.3–17.7) %	Unbound AUC_8: 1616 (493)[c] (range 861–2172) nmol·h/l	Unbound AUC_8: 11,218 (3780)[c] (range 5165–16,974) nmol·h/l		
Total concentration CSF/plasma ratio: 6 (95 % CI 5–9) %	Total concentration: 145 (43–480) nM[a]	Total concentration: 1491 (40–11,670) nM[a]	POPPK analysis of 22 paired CSF–plasma total concentrations at various time points during the dosing interval from 22 patients	[56]
Total concentration CSF/plasma ratio: 1.7 (0.2–5.1) %[d]	Total concentration: 0.11 (0.032–0.25) μmol/l[d]	Total concentration: mean 10.28 μmol/l	Analysis of 19 paired CSF–plasma total concentrations at various time points during the dosing interval from 19 patients	[90]
Total concentration CSF/plasma ratio: median 14 %	Total concentration: 86 (13)[c]; median 81 ng/ml	Total concentration: 485 (137)[c]; median 283 ng/ml	Analysis of 16 paired CSF–plasma total concentrations at various time points during the dosing interval from 16 patients	[60]
Total concentration CSF/plasma ratio: 17 (10–49) %[b]	Total concentration: 73 (52–92) ng/ml[b]	Total concentration: 357 (155–914) ng/ml[b]	Analysis of 28 paired CSF–plasma total concentrations at various time points during the dosing interval from 14 patients	[61]
800 mg 8-hourly with 100 mg ritonavir 12-hourly				
Not stated	Total concentration: 104 (68–207) ng/ml[b] with ritonavir: 100 mg ritonavir dosed with 800 mg indinavir 8- or 12-hourly	Total AUC_8: 29,035 (25,559–30,496) ng·h/ml[b] Total AUC_{24}: 87,105 (76,677–91,488) ng·h/ml[b]	Analysis of four paired CSF–plasma total concentrations taken 1 h after dosing from four patients	[55]
800 mg 12-hourly with 100 mg ritonavir 12-hourly				
Not stated	Total concentration: 104 (68–207) ng/ml[b] with ritonavir: 100 mg ritonavir dosed with 800 mg indinavir 8- or 12-hourly	Total AUC_{12}: 30,121 (24,352–38,438) ng·h/ml[b] Total AUC_{24}: 60,242 (48,704–76,876) ng·h/ml[b]	Analysis of four paired CSF–plasma total concentrations taken 1 h after dosing from four patients	[55]
Total concentration CSF/plasma ratio: 9.9 (3.3)[c] (range 7.4–16.6) %	Total AUC_{12}: 6606 (2481)[c] (range 3903–11,385) nmol·h/l	Total AUC_{12}: 68,913 (23,302)[c] (range 50,404–117,049) nmol·h/l	Analysis of 63 paired CSF–plasma unbound and total concentrations over 8 h dosing interval taken from seven patients	[52]
Unbound concentration CSF/plasma ratio: 17.5 (6.4)[c] (range 12.8–31.4) %	Unbound AUC_{12}: 6502 (2397)[c] (range 3903–11,043) nmol·h/l	Unbound AUC_{12}: 38,829 (15,124)[c] (range (26,614–71,283) nmol·h/l		
1000 mg 8-hourly without ritonavir				

Table 5 continued

Reported CSF penetration in relation to plasma exposure	CSF exposure	Plasma exposure	Methodology sample (CSF–plasma)	References
Not stated	Total concentration: 39 (27–54) ng/ml[b] without ritonavir Total concentration: 104 (68–207) ng/ml[b] with ritonavir: 100 mg ritonavir dosed with 800 mg indinavir 8- or 12-hourly	Total AUC_8: 16,474 (13,624–19,481) ng·h/ml[b] Total AUC_{24}: 49,422 (40,873–58,442) ng·h/ml[b]	Analysis of 11 paired CSF–plasma total concentrations taken 1 h after dosing taken from 11 patients	[55]
Not stated	Total concentration: median 71 ng/ml	Not stated	Analysis of 17 paired CSF–plasma total concentrations at various time points during the dosing interval from 11 patients	[57]
Atazanavir				
400 mg daily				
Total concentration CSF/plasma ratio: 1.12 (0.5–13.9) %[a]	Total concentration: 7.9 (<5 to 40) ng/ml[a]	Total concentration: 523 (<128 to 6200) ng/ml[a]	Analysis of nine paired CSF–plasma total concentrations at various time points during the dosing interval	[59]
300 mg daily with ritonavir				
Total concentration CSF/plasma ratio: 0.74 %	Total concentration: 10.3 (<5 to 38) ng/ml[a]	Total concentration: 1278 (<128 to 5295) ng/ml[a]	POPPK analysis of 62 paired CSF–plasma total concentrations at various time points during the dosing interval	[59]
400 mg daily and 300 mg daily with ritonavir				
Not stated	Total concentration: 14.5 (1.9–17.5) ng/ml[b] Extrapolated C_{min} 7.3 (1.9–10.4) ng/ml[b]	Total concentration: 700 (470–964) ng/ml[b] Extrapolated C_{min} 265 (177–447) ng/ml[b]	Analysis of 12 paired CSF–plasma total concentrations at a median post-dose sampling interval of 15.5 h	[46]
Total concentration CSF/plasma ratio: 0.9 (0.8)[c] (range 0.1–2.7) %	Total concentration: 8.3 (0.6–40) ng/ml[a]	Total concentration: 1250 (205–3555) ng/ml[a]	Analysis of 22 paired CSF–plasma total concentrations at various time points during the dosing interval from 22 patients	[91]
Nelfinavir				
Not stated	Total concentration: <2.0 (<2.0 to 23.0) nM[a] (detectable in 9 of 15 samples)	Total concentration: 4.1 (<0.13 to 10.6) μM[a] Unbound concentration: 10.0 (<2.0 to 31.0) nM[a]	Analysis of 15 paired CSF–plasma unbound and total concentrations at different intervals from eight patients	[63]
Not stated	Total concentration: 9 (6–29) nM[a] (detectable in 16 of 18 samples and quantifiable in 8 of 18 samples)	Not stated	Analysis of 18 paired CSF–plasma unbound and total concentrations at various time points during the dosing interval from 18 patients	[64]
Lopinavir				
Total concentration CSF/plasma ratio: 0.225 (0.194–0.324) %[b]	Total concentration: 11,200 (6760–16,400) pg/ml[b]	Total AUC_{12}: 71.3 (48.4–87.6) μg·h/ml[b]	Analysis of ten paired CSF–plasma total trough concentrations from ten patients	[66]

Table 5 continued

Reported CSF penetration in relation to plasma exposure	CSF exposure	Plasma exposure	Methodology sample (CSF–plasma)	References
Total concentration CSF/plasma ratio: 0.23 (0.12–0.75) %[b]	Total concentration: 17.0 (12.1–22.7) μg/l[b]	Total concentration: 5889 (4805–9620) μg/l[b]	Analysis of 31 paired CSF–plasma total concentrations at a median post-dose sampling interval of 4.3 h from 26 patients	[65]
Not calculable	Undetectable	Total concentration: 5463 (720) ng/ml[c]	Analysis of 16 paired CSF–plasma total trough concentrations from 16 patients	[60]
Not stated	Total concentration: 23 (17.5–40)[b] ng/ml Extrapolated C_{min}18.4 (10.5–29.3)[b] ng/ml	Total concentration: 5435 (4049–7816) ng/ml[b] Extrapolated C_{min} 3566 (2579–5388) ng/ml[b]	Analysis of 42 paired CSF–plasma total concentrations at a median post-dose sampling interval of 6 h	[46]
Not calculable	Undetectable	Total concentration C_{min}: 5863 (3505–7453) ng/ml[b]	Analysis of 12 paired CSF–plasma total trough concentrations from 12 patients	[61]
Darunavir				
800 mg and 100 mg ritonavir daily				
Total concentration CSF/plasma ratio: 0.32 (0.25–0.44) %[b]	Total concentration: 10.7 (6.7–23) ng/ml[b]	Not separately reported	Analysis of nine paired CSF–plasma total trough concentrations	[68]
600 mg and 100 mg ritonavir 12-hourly				
Total concentration CSF/plasma ratio: 0.9 (0.60–1.53) %[b]	Total concentration: 38.2 (30.2–52.3) ng/ml[b]	Not separately reported	Analysis of 14 paired CSF–plasma total trough concentrations	[68]
Total concentration CSF/plasma ratio: 1.4 (0.9–1.8)[b] (range 0.3–2.6) % Unbound concentration CSF/plasma ratio: 8.5 (6.2–12.7)[b] (range 2.9–412.4) %	Total concentration: 55.8 (39.5–79.1)[b] (range 19.4–159.6) ng/ml Unbound concentration: 50.2 (35.0–72.6)[b] (range 0–143.8) ng/ml	Total concentration: 4094 (2993–6411)[b] (range 104–11,298) ng/ml Unbound concentration: 538 (369–968)[b] (range 1–2206) ng/ml	Analysis of 29 paired CSF–plasma unbound and total concentrations at various time points during the dosing interval from 16 patients	[53]
Total concentration CSF/plasma ratio: 0.9 (0.3–1.8) %[b]	Total concentration: 34.2 (15.9–212) ng/ml[b]	Total concentration: 3930 (1800–12,900) ng/ml[a]	Analysis of 14 paired CSF–plasma total concentrations at various time points during the dosing interval from eight patients	[67]
Saquinavir				
Dosing regimen not stated				
Total concentration CSF/plasma ratio: 0.1 and 0.2 %, respectively	Total concentration: measured in 2/11 participants: 0.3 and 1.6 ng/ml, respectively	Not stated	Analysis of 11 paired CSF-plasma total concentrations at 6–8 h post-dosing from 11 patients	[71]
Not stated	Total concentration: <2.5 (<2.5 to 9.0) nM[a] (detectable in 7 of 15 samples)	Total concentration: 300 (<80 to 6600) nM[a] Unbound concentration: <2.5 (<2.5 to 96.0) nM[a]	Analysis of 15 paired CSF–plasma unbound and total concentrations at different intervals from eight patients	[63]
400 mg with 400 mg ritonavir 12-hourly				
Unbound concentration CSF/plasma ratio: 0.16 ± 0.09 %[c]	Unbound concentration: 0.40 ± 0.30 ng/ml[c] (detectable in 5 of 12 samples)	Unbound concentration: 6.8 ± 9.5 ng/ml[c]	Analysis of 12 mid-dose paired CSF–plasma unbound and total concentrations	[69]

Table 5 continued

Reported CSF penetration in relation to plasma exposure	CSF exposure	Plasma exposure	Methodology sample (CSF–plasma)	References
600 mg with food 8-hourly				
Not calculable	Undetectable	Total concentration: 167 ng/ml	Analysis of five mid-dose paired CSF–plasma total concentrations	[70]
600 mg with ritonavir 12-hourly				
0.3 %	6.5 ng/ml	Total concentration: 1094 ng/ml	Analysis of four mid-dose paired CSF–plasma total concentrations	[70]
Calculated in $n = 1$	Detectable in $n = 1$			

AUC area under the concentration–time curve, *AUC8* AUC from time zero to 8 h, *AUC12* AUC from time zero to 12 h, *AUC24* AUC from time zero to 24 h, C_{min} minimum concentration during dosing interval, *CI* confidence interval, *CSF* cerebrospinal fluid, *POPPK* population pharmacokinetic

[a] Median (range)

[b] Median (interquartile range)

[c] Mean (standard deviation)

[d] Mean (range)

concentration points to determine exposure. AUC accurately estimates exposure, which can only be determined by using multiple paired CSF–plasma concentrations in a patient or by combining samples from multiple patients using a population pharmacokinetic approach. Indinavir and efavirenz CNS penetration was characterized by measuring unbound plasma and CSF concentrations to calculate AUCs. The importance of measuring total and unbound drug concentrations is illustrated by efavirenz, where the CSF total concentration is a tiny fraction of plasma total concentration, while unbound concentrations in the two compartments are similar [14]. The unbound concentration of indinavir in the CSF is double that of the total concentration in the CSF [81]. Accurate inferences of ART CNS penetration without unbound AUC data in plasma and CSF compartments are limited.

Future studies should measure total and unbound antiretroviral concentrations and aim to calculate AUCs as a measure of exposure. High CPE score ART CNS exposure is a risk factor for HIV-D, suggesting that a therapeutic window does indeed exist for ART in the CNS where concentrations at the higher and lower spectrum lead to ART toxicity or viral replication, respectively [7, 27]. Laboratory evidence suggests that antiretrovirals are directly neurotoxic [5, 6]. Neurons challenged for a week with different concentrations of antiretrovirals, including therapeutic concentrations, underwent structural loss, as quantified using microtubule-associated protein-2 [6]. Neurotoxicity was most pronounced with abacavir, atazanavir, efavirenz, etravirine and nevirapine. Of particular interest is the inactive metabolite of efavirenz (8-hydroxy efavirenz), which was tenfold more toxic than efavirenz in rat neuronal cultures and has been associated with more CNS symptoms in patients [5, 44]. Future studies should quantify ART CNS therapeutic ranges not only to determine which antiretroviral drugs penetrate the CNS adequately to suppress viral replication but also which antiretroviral drugs penetrate the CNS to such an extent that they contribute to neurotoxicity. The impact of genetic polymorphisms in drug transport across membranes (including the blood–brain barrier) is well established for many drugs, including ART [21, 22, 82]. However, data on the clinical relevance and extent of the contribution of polymorphisms in genes encoding for blood–brain transporters to CNS antiretroviral exposure are limited due to the small number of studies and the lack of power. The invasiveness of lumbar punctures limits the sample size of CSF exposure studies. Correlations between CNS antiretrovira lexposure and effect is multifaceted. To accurately predict CNS effects there is a need to develop a sophisticated intra-brain pharmacokinetic–pharmacodynamic–pharmacogenetic model that includes transporters as well as the influence of HIV.

Table 6 Protease inhibitors' central nervous system pharmacodynamic data

Drug	In vitro efficacy in CSF	Efficacy data	References
Indinavir	IC_{95} 30–60 ng/ml MEC 40 ng/ml	Total CSF concentrations exceeded IC_{95} and MEC when indinavir is dosed with ritonavir. Without ritonavir, patients may have CSF total concentrations below IC_{95} and MEC	[55]
	IC_{95} 25–100 nmol/l	Unbound CSF concentrations exceeded the IC_{95} for 85 % of the dosing interval in seven of eight participants with a C_{min} 122 (51)[a] (range 49–204 nmol/l)	[13]
		Median total CSF concentration exceeded the IC_{95}	[89]
		Unbound CSF concentrations exceeded the IC_{95} for 100 % of the dosing interval in all participants with a C_{min} 280 (131)[a] (range 149–527 nmol/l)	[52]
		All total CSF concentrations exceeded 25 nmol/l, while only 54 % (12/22) of patients exceeded 100 nM	[56]
	IC_{95} 18–70 ng/ml	Median total CSF concentration exceeded IC_{95}	[57]
Atazanavir	IC_{50} 1 ng/ml	Total CSF concentrations were near the IC_{50} in 16 % (11/67) of samples	[59]
		Total CSF concentrations were below the IC_{50} in 17 % (2/12) of samples	[46]
		Total CSF concentrations were considered to be above the IC_{50} in general	[91]
Nelfinavir	IC_{50} (not specified)	Detectable CSF concentrations were in the range of IC_{50} for wild-type virus	[63]
	IC_{95} 0.35–10 nM	Unbound nelfinavir in CSF in the concentration range of the IC_{95} in some of the CSF samples (8/18)	[64]
Lopinavir	IC_{50} 1.9 μg/l (3.0 nmol/)	Total CSF concentrations exceeded IC_{50} for wild-type replication by a median (IQR) 5.9-fold (3.9–8.6)	[66]
		Total CSF concentrations exceeded IC_{50} for wild-type replication by a median (IQR) 5.3-fold (3.8–7.2)	[65]
		Extrapolated trough concentrations above IC_{50} for 98 % (41/42) of CSF samples	[46]
	CSF HIV-1 RNA levels	HIV-1 RNA levels detectable in 3 of 10 patients (median 350 copies/ml)	[60]
		HIV-1 RNA levels detectable in 3 of 12 patients (median 350 copies/ml)	[61]
Darunavir	IC_{50} 2.75 ng/ml	None of the patients receiving darunavir/ritonavir 600/100 mg 12-hourly compared with 12 % receiving 800/100 mg daily were below the IC_{50}	[68]
	IC_{50} 1.78 ng/ml IC_{90} 2.43 ng/ml	All unbound CSF concentrations exceeded the IC_{50} and IC_{90} wild-type HIV-1 by a median of 28.1-fold and 20.6-fold, respectively	[53]
	IC_{50} 12–55 ng/ml	Total CSF concentrations were in the range of, or exceeded, the IC_{50}	[67]
Saquinavir	IC_{50} 42–55 ng/ml	Detectable CSF concentrations were below the IC_{50} for wild-type virus	[63, 69, 71]

C_{min} minimum concentration during dosing interval, *CSF* cerebrospinal fluid, *IC_{95}* 95 % inhibitory concentration, *IC_{50}* 50 % inhibitory concentration, *IC_{90}* 90 % inhibitory concentration, *IQR* interquartile range, *MEC* minimal effective concentration,

[a] Mean (standard deviation)

Table 7 Integrase inhibitors' central nervous system pharmacokinetic data

Reported CSF penetration in relation to plasma exposure	CSF exposure	Plasma exposure	Methodology sample (CSF–plasma)	References
Raltegravir				
400 mg 12-hourly				
CSF/plasma total concentration ratio: 3 (1–61) %[a]	Total concentration: 18.4 (<2.0 to 126) ng/ml[a]	Total concentration: 448 (37–5180) ng/ml[a]	Analysis of 25 paired CSF–plasma total concentrations taken at 1.2–14 h post-dosing from 16 patients	[74]
CSF/plasma total concentration ratio: 5.8 (2.1–17.8)[c] (range 1–53.5) %	Total concentration: 14.5 (9.3–26.1)[c] (range 6.0–94.2) ng/ml	Total concentration: 260.9 (72–640.4)[c] (range 17.8–4870) ng/ml	Analysis of 22 paired CSF–plasma total concentrations taken at 6.1 ± 4.2 h[b] post-dosing from 18 patients	[92]
Plasma AUC_{12}/CSF_{4h} total concentration ratio: 6.0 ± 2.6 %[b]	Total concentration: 30.1 (17.0 50.4) ng/ml[c]	Total AUC_{12}: 6.55 (3.48–13.0) h·mg/ml[c]	Analysis of 40 paired CSF–plasma total concentrations taken at 4 h post-dosing from 40 participants	[80]

Table 7 continued

Reported CSF penetration in relation to plasma exposure	CSF exposure	Plasma exposure	Methodology sample (CSF–plasma)	References
CSF/plasma total concentration ratio: 20.6 (3.8–36.3)[c] (range 0.5–133) %	Total concentration: 31.0 (21–56) ng/ml[c]	Total concentration: 165 (83–552) ng/ml[c]	Analysis of 41 paired CSF–plasma total concentrations taken at 2–15 h post-dosing from 41 participants	[25]

AUC area under the concentration–time curve, AUC_{12} AUC from time zero to 12 h, *CSF* cerebrospinal fluid, CSF_{4h} cerebrospinal fluid concentration at 4 hours

[a] Median (range)

[b] Mean (standard deviation)

[c] Median (interquartile range)

Table 8 Integrase inhibitors' central nervous system pharmacodynamic data

Drug	In vitro efficacy in CSF	Efficacy data	References
Raltegravir	IC_{95} 9–15 ng/ml	Total CSF concentrations exceed the IC_{95} in half of the patients (13/25)	[74]
	IC_{50} 3.2 ng/ml IC_{95} 9–15 ng/ml	Total CSF concentrations exceed the IC_{50} by a median of 4.5-fold, and little less than half of the patients (10/21) exceeded the IC_{95}	[92]
		Total CSF concentrations exceeded the IC_{50} in all patients, and 28.6 % (10/35) exceeded the IC_{95}	[25]

CSF cerebrospinal fluid, IC_{50} 50 % inhibitory concentration, IC_{95} 95 % inhibitory concentration,

Table 9 Pharmacogenetic associations with central nervous system antiretroviral exposure

Drug	Genetic associations explored	Findings	References
Nevirapine	*ABCB1* 3435 C>T *CYP2B6*-G516T	ABCB1-C3435T C/T or T/T genotypes ($n = 9$) associated with higher nevirapine CSF/plasma ratios compared with ABCB1-C3435T C/C genotype ($n = 5$); $p = 0.01$. No significant difference was observed when the ratios were compared with the CYP2B6-G516T genotype ($p = 1.00$)	[48]
Darunavir	*ABCB1* 3435 C>T *ABCB1* 1236 C>T *ABCB1* 2677 G>T *ABCC2* −24 G>A ***SLCO1A2* 38 A>G** *SLCO1A2* 516 A>C	AA compared with AG genotype-carrying patients showed a trend towards higher CSF concentrations and plasma/CSF ratios: 32 (22–72) ng/ml[a] vs. 29.8 (139–36.4) ng/ml[a] ($p = 0.13$) and 0.78 (0.78–1.88) %[a] vs. 0.56 (0.35–0.96) %[a] ($p = 0.13$), respectively	[68]
Nelfinavir	*ABCB1* 3435 C>T *ABCB1* 2677 G>A/T	CC 3435 genotype occurred more frequently in patients with undetectable CSF viral loads (6/7 compared with 6/12), but the finding was not statistically significant	[64]
Raltegravir	*ABCB1* 3435 C>T	No significant association between ABCB1 3435 C>T and the CSF/plasma AUC or concentration	[80]
	ABCB1 3435 C>T *ABCB1* 1236 C>T *ABCB1* 2677 G>A/T *SLCO1A2* 38 A>G *SLCO1A2* 516 A>C *ABCC2* 24 G>A *SLC22A6* 453 G>A $HNF4_{\alpha}$ 613 C>G	No significance between selected SNPs and CSF/plasma ratios	[25]

Bolded text denotes an association

AUC area under the concentration–time curve, *CSF* cerebrospinal fluid, *CYP* cytochrome P450, *SNPs* single nucleotide polymorphisms

[a] Median (interquartile range)

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