

Should antiretroviral therapy for HIV infection be tailored for intracerebral penetration?

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ABSTRACT

The continuous replication of HIV-1 in the central nervous system, in particular the brain, and its potential long-term deleterious effect is the focus of this review. Cognitive deficits are observed in a significant percentage of HIV-1-infected patients. That may occur despite successful peripheral suppression of the HIV-1 replication. Compartmentalisation of HIV-1 in the brain, genetic mutation of HIV-1, age, HCV coinfection and poor intracerebral penetration, as well as possibly a direct toxic effect of antiretroviral drugs, are factors that may account for potential creeping damage of the brain after many years of treatment. Patients with neurological symptoms or cognitive deficits may require another approach to the treatment of their HIV infection.

KEYWORDS

Antiretroviral drug, central nervous system, HIV, penetration

INTRODUCTION

The central nervous system (CNS) is a major target of HIV-1 infection and HIV-1-related diseases.^{1,2} Chronic HIV-1 infection of the CNS begins during primary infection and continues in nearly all untreated seropositive individuals. Late during the course of systemic infection, asymptomatic and seemingly benign CNS disease can progress to more severe disease. The clinical presentation is heterogeneous and can include a syndrome of cognitive, motor, and behavioural dysfunction formerly known as AIDS dementia complex (ADC), now called

HIV-associated dementia (HAD). Less serious stages are nowadays included in the collective term, HIV-associated neurocognitive disorders (HAND).³ In the late stages of immune suppression, the CNS is also vulnerable to opportunistic infections. This review will focus on the effects of HIV-1 infection on the CNS as well as the effects of combination antiretroviral therapy (ART) and its limitations with respect to the CNS. Consideration will be given to whether chronic infection in treated individuals has long-term neurological sequelae and, if so, whether they can be treated or even prevented.

OVERALL IMPACT OF ART ON AIDS-RELATED NEUROLOGICAL DISEASES

Combination ART has substantially influenced HIV-induced CNS disease. The incidence of all AIDS-related CNS diseases is now markedly reduced, at least in developed countries. This was well documented in the EuroSIDA cohort study, which showed a tenfold decrease in CNS diseases that paralleled a decrease in systemic AIDS-related complications after combination ART was introduced.⁴ HAD was the most common severe CNS disease before the introduction of ART, and showed the greatest reduction in incidence between 1994 and 2002.⁴

Zidovudine was the first antiretroviral drug with therapeutic benefit on the course of HAD. But since an early AIDS Clinical Trials Group (ACTG) study (protocol 005) showed this effect,⁵ few controlled treatment trials with other antiretroviral drugs have been performed. Although ART can clearly arrest HAD and reverse its neurological disability, the general magnitude of this

syndrome that markedly impacts ADLs. Neurocognitive impairment may persist despite successful treatment with antiretroviral therapy.^{42,43} Therefore combination ART for HIV-1 infection may incompletely treat the CNS.

Influence of ART on CSF HIV RNA

In general, HIV-1 in CSF responds very well to ART,⁴⁴⁻⁵¹ as HIV-1 RNA levels in plasma become undetectable, so do those in CSF in nearly all individuals. However, the relative rates of viral decay in the two compartments may differ in some, with HIV-1 RNA concentrations falling more slowly in CSF than in plasma. Slower decay has been noted in subjects with HAD and lower blood CD4 cell counts but without CSF pleocytosis.⁵⁰⁻⁵³ These observations can be interpreted as being consistent with a simple model of compartmentalised CSF HIV-1 infection, with the lag in viral response in CSF due to slow cell turnover and consequent prolonged virion production by brain macrophages, reduced trafficking of shorter-lived lymphocytes into the CSF from blood, and lower drug concentrations in the CNS. Drug penetration in the CNS largely depends on the physicochemical properties e.g. protein binding, molecule size, lipophilicity, or use of membrane transporters in the blood brain barrier such as P-glycoprotein. In addition drug penetration into the CNS also can be modified.⁵⁴⁻⁵⁶ Considerable differences exist between antiretroviral drugs with respect to penetration into the CNS. Letendre *et al.*⁵⁶ have proposed a simple scheme for grouping drugs by CSF penetration ability based on drug properties and clinical studies, rating them as 0 (lower penetration), 0.5 (intermediate penetration), or 1 (higher penetration). No drug concentrations in CSF have yet been published for newer antiretroviral drugs such as darunavir, etravirine, raltegravir, and maraviroc.

Although potentially useful as a guide for selecting treatment, several observations suggest that the model may not fully account for treatment effects in all settings. For example, it may not explain the overall effectiveness of a wide variety of drug regimens in the suppression of CSF HIV-1 RNA levels or why cases of high CSF virus levels in the presence of suppressed plasma virus levels are rare. The very rapid decay of HIV-1 in CSF is equivalent to that of plasma virus in some subjects, which may reflect increased permeability of the blood-brain barrier or high levels of pretreatment lymphocyte trafficking. Such inter-individual differences may reflect differences in genetic traits, such as expression of chemokine receptors and adhesion molecules, or in comorbidities, such as recreational drug use and HCV coinfection. Also it should be stressed that potency of the complete (usually three drug) regimen and to what extent concentrations exceed the IC₉₀ are more relevant than single drug concentrations in the CSF. This and the issues mentioned above are areas for ongoing and future research.

Table 1. Categorisation of antiretroviral drugs by estimated neuroeffectiveness (CNS penetration-effectiveness rank)

	Better	Intermediate	Worse
NRTIs	Abacavir	Emtricitabine	Didanosine
	Zidovudine	Lamivudine	Tenofovir
		Stavudine	Zalcitabine
NNRTIs	Delavirdine	Efavirenz	
	Nevirapine		
PIs	Amprenavir-r	Amprenavir	Nelfinavir
	Indinavir-r	Atazanavir	Ritonavir
	Lopinavir-r	Atazanavir-r	Saquinavir
		Indinavir	Saquinavir-r
			Tipranavir-r
Fusion inhibitors		Enfuvirtide	

-r = drugs boosted by ritonavir. Source: Dr S. Letendre.

CNS SIDE EFFECTS OF HAART

To date, the most widely recognised antiretroviral with CNS side effects is the non-nucleoside reverse transcriptase inhibitor efavirenz.⁵⁷ Vivid and dysphoric dreams, in particular during the first weeks of treatment, are commonly reported symptoms. Less than 10% discontinue treatment because of these symptoms. Prospective studies have not found a clear deleterious effect of efavirenz on longer term neuropsychological performance or on depressive scores,^{58,59} although the findings are not entirely consistent.⁶⁰ The mechanism of these symptoms is not well understood, although they seem to be linked with higher levels of drug exposure.^{61,62} So far, no conclusive data show that other antiretroviral drugs have a direct toxic effect on the brain. However, some animal and human data on a potential deleterious effect of NRTI on brain mitochondria and cellular metabolism do exist.⁶³ In addition there is some concern that drug-induced injury of mitochondria or changes in lipid metabolism, for example, may injure the brain, particularly in more vulnerable hosts (e.g., older individuals).

ANTIRETROVIRAL THERAPY AND NEUROCOGNITIVE PERFORMANCE

Would initiation of ART earlier in the course of HIV disease further reduce the risk of development of HAND? Hitherto, should treatment with neuroeffective antiretroviral drugs be recommended in all individuals at the time of treatment initiation?⁶⁴ These questions cannot yet be confidently answered. Many issues should be taken into account in the treatment of HIV disease: in the first

place potency, then toxicity, and also dosing simplicity. The literature on the effects of ART on neurocognitive performance is not entirely consistent. Case reports show improvement of symptoms of dementia that paralleled improvement of HIV RNA levels and the inflammatory markers in the CSF.^{67,68} Some research studies identified that more neuroeffective regimens were associated with greater improvement^{65,66} but others did not.^{69,70} Important methodological differences between these studies exist including the approach to testing, the method of estimating neuroeffectiveness, the types of regimens used, and the demographic and disease characteristics of the study population. Importantly, improvement in neurocognitive performance is a secondary effect of control of HIV replication, which is the primary effect of ART. Control of HIV in the CNS is a necessary but not necessarily sufficient condition for neurocognitive protection or improvement. For all these reasons, caution must be exercised in interpretation of these research findings. Additional clinical trials to address the question whether ART regimens should be optimised for neuroeffectiveness are not easily performed but at least one is underway.⁷¹ Another important question for future clinical trials to address is the use of adjuvant therapies to improve intracerebral penetration.⁷²⁻⁷⁵

Given these uncertainties, how should treatment be tailored to the nervous system now? This question cannot easily be answered. The existing data so far indicate that in neurologically asymptomatic patients – that is, in most of those who initiate therapy – the CNS likely warrants no special consideration. However, in patients who have HAND, a different approach could be advocated. In these patients treatment could be initiated with a regimen that penetrates well into the CSF and into the brain. The effect then could be monitored by measurement of HIV RNA and drug levels in CSF as well as repeated neuropsychological tests.

CONCLUSIONS

Although a number of important treatment issues have not yet been addressed, the advent of ART has had a profound impact on severe CNS disease as a complication of HIV-1 infection. This impact includes a marked reduction in the incidence of major CNS opportunistic infections and HAD, and effective treatment for patients presenting with new-onset HAND. With this success, attention has turned to other aspects of CNS HIV-1 infection and particularly to the question of the optimal management of milder, but still clinically relevant, HAND syndromes. CNS HIV-1 infection and the associated neuroinflammation may damage the brain during the long period before treatment is initiated and may even continue in the presence of effective

systemic viral suppression. Now that the most conspicuous and severe neurological complications of HIV-1 infection can be avoided in most cases, the effects of therapy on the remaining clinical syndromes of brain injury must be carefully considered and explored.

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