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REVIEW

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.

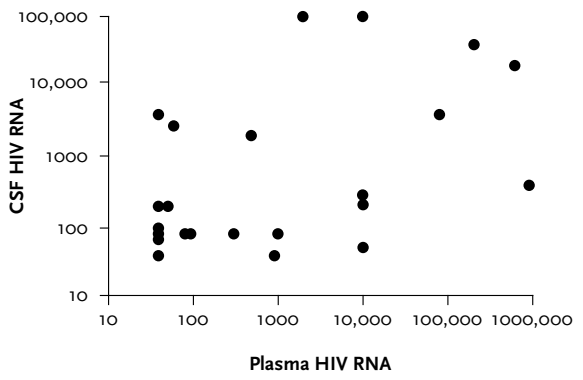
OVERALL IMPACT OF ART ON AIDS-RELATED NEUROLOGICAL DISEASES

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

effect is variable and not precisely defined. Low CD4 counts were an important risk factor for HAD in the era before combination ART, and continue to be so in the modern treatment era, also for the development of HAND.[6] Additional risk factors for new or progressive HAND in the modern treatment era include incomplete immune recovery, rapid immune recovery with immune recovery inflammatory syndrome (IRIS),[7] hepatitis C virus (HCV) coinfection,[8-10] and advancing age.[11] The aggregate experience that ART primarily ameliorates HAND, however, appears to be compelling, and indicates that neurological dysfunction can be reversed.[11-14]

Figure 1. *Plasma and CSF HIV RNA concentrations in 31 HIV-1 seropositive patients*



Plasma and CSF samples were taken at the same day with a maximal time span of one hour.
Source: Radboud University Medical Center, Department of General Internal Medicine, Nijmegen, the Netherlands.

CHRONIC CNS HIV-1 INFECTION: VIROLOGICAL AND BIOCHEMICAL ASPECTS AND ITS CLINICAL IMPACT

In the absence of treatment, HIV replication in cells of the nervous system is a nearly constant component of HIV-1 infection and has been characterised most clearly by studies analysing cerebrospinal fluid (CSF). During life, it is not possible to measure HIV replication in the brain. Therefore, HIV RNA levels in the CSF together with markers of inflammation and neuropsychological tests are considered to give guidance on the degree of brain damage during the course of HIV-1 infection.[15-17]

HIV-1 RNA can be detected in the CSF of nearly all those with infection, from the period of initial viraemia through the course of neurologically asymptomatic infection and in those developing HAND.[15-18] A number of studies have shown that HIV-1 RNA in CSF is nearly ubiquitous but variable in its magnitude and in its relation to HIV-1 RNA level in blood.[15-21] Generally, in untreated individuals, CSF HIV-1 RNA levels are approximately tenfold lower than plasma HIV-1 RNA levels, but the difference between viral concentrations in the two fluids varies considerably with levels in CSF exceeding those in blood in some individuals. An example of the relationship between HIV RNA levels in CSF and blood is shown in *figure 1*. In general, HIV RNA levels in CSF correlate with those in blood although this correlation weakens in those who have advanced HIV disease or who have HAND.[18] In addition to quantitative differences between CSF and blood, viral populations that are found in the nervous system can also diverge qualitatively from those in blood. Genetic compartmentalisation of HIV-1 has been demonstrated by several studies.[22-27] During acute infection, HIV-1 populations in CSF and blood are probably monophyletic, but then, during chronic infection, the populations expand and diverge, with the greatest divergence in patients who have HAND. Functional compartmentalisation has also been shown with respect to drug resistance, use of entry receptors, and cell tropism. Differences in drug susceptibility between CSF and blood HIV-1 populations have also been reported.[28-31] Although viral replication in CSF in the presence of sub-therapeutic drug concentrations might enhance the selection of resistance mutations, few studies have carefully compared drug concentrations in CSF with the development of drug resistance.[32] Recent findings on the adaptations of HIV-1 to neural cells[33-35] have advanced our understanding of HIV-1 neuroadaptation and neurovirulence but additional work is needed to understand, for instance, the clinical implications of these and other findings.

CSF analysis also indicates that HIV-1 infection is associated with chronic immune activation in the nervous system (neuroinflammation, as indicated by frequent, although usually mild, CSF pleocytosis and elevated levels of several soluble immunological markers[19,36-38] e.g. neopterin, β-2-microglobulin, quinolinic acid, and CCL2/MCP-1. The persistence of HIV-1 and the associated neuroinflammation raise the important question of whether chronic asymptomatic infection is accompanied by ongoing, low-grade brain injury despite the lack of overt symptoms and signs. If this chronic inflammatory[37] state leads to brain injury, will survivors develop neurological impairment years later despite otherwise effective therapy? Several studies have reported neurocognitive impairment in HIV-infected patients, typically with a detrimental impact on activities of daily living (ADLs).[1,4-43] Indeed, diminished group performance has led to the inclusion of the designation 'HIV-associated asymptomatic neurological impairment' (ANI) as a diagnosis subsumed in the HAND classification approach.[3] The other diagnoses that comprise HAND are 'mild neurocognitive disorder', a milder symptomatic syndrome that clearly impacts ADLs, and 'HIV-associated dementia', a more severe, symptomatic

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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