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Central Nervous System Antiretroviral High Penetration Therapy

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Abstract

The use of highly effective antiretroviral therapy penetration into the central nervous system has indicators for input that can eradicate the viral load in cerebrospinal fluid, thereby helping to prevent the virus compartmentalization in CNS and hence probably preventing perpetuation of these cognitive disorders associated with HIV virus. However, more studies are necessary in order to demonstrate the real pathophysiological mechanisms associated with these effects and to prove that the side effects associated with the use of these medications are harmless than the benefits achieved on the neurocognitive disorders.

Keywords: Central nervous system; HIV; Neurocognitive disorders; Antiretroviral therapy; CNS penetration-effectiveness

Introduction

Since 1996 Brazilian Ministry of Health is ensuring universal access to antiretroviral treatment for all those living with human immunodeficiency virus (HIV) that have formal indication to use it, according to current treatment recommendations. This broad access to treatment provided the emergence of a new scenario over the years. It was observed that the amount of patients with adequate viral load and CD4 control is increasingly, but they have showed incipient or even evident cognitive impairment/neurological after refinement with neuropsychological tests. Therefore, as HIV infection is a systemic disease, it is necessary, in addition to general physical examination, be particularly aware of the clinical signs suggesting neurological manifestations of the disease, through a good cognitive screening [1,2].

Antiretroviral therapy (ART) may result in a significant improvement at neurocognitive sphere in many individuals with neurocognitive disorders associated with HIV (HAND). However, this is highly variable among individuals, and besides, several cohort studies have shown that HAND may persist despite virological suppression and immune recovery with HAART. The explanation for persistent HAND could probably be an inadequate treatment of HIV infection at the central nervous system (CNS) due to the relative low penetration of many antiretroviral drugs through the blood-brain barrier [3-5].

Even with the development of a highly Active Antiretroviral Therapy (HAART), it was not considered possible blocking the progression of cognitive impairment above. The continued studies on the subject a few years ago demonstrate a significant evolution to understand the disease neuropathogenesis and the effects of drugs and their penetration on CNS, what has acquired a special meaning, since there is an expectation that we might be able to understand, interfere with the progress, and modify the cognitive deterioration process associated with the vírus, preventing neuronal attacks caused by HIV [6,7].

Thus, as a result, it was selected, among the HAART drugs available, those with a better penetration into the central nervous system, in order to prevent cognitive disorders (HAND) on asymptomatic patients and possibly prevent progressive deterioration on those already evident compromised ones [6,8].

As CNS penetration is limited, it is possible that sub therapeutic ART could be leading to the development of virus resistant into the central nervous system and thus wouldn´t revert neurological deficits already installed. Therefore, it is important to examine people who have serological viral suppression as the presence of the virus in the CNS. In this group, there is no opportunity to evaluate whether HAART regimens that lead to viral RNA serological suppression have different effects on CNS virus concentration, and further, its correlation with neurocognitive impairment [4,9,10].

The method used to classify antiretroviral therapy CNS penetration-effectiveness has a hierarchical approach, based on physicochemical properties, pharmacokinetic data, pharmacodynamics (characteristics considered in the construction of the category including molecular weight, lipophilicity, octanol partition coefficient - water constants dissociation and protein bound). The pharmacokinetic data are considered more influential than the physical characteristics to compare drug concentration in the central nervous system. The pharmacodynamic data are considered the most important. All the data were compiled and compared between the drugs, which were then classified into one of the three categories [4,7,11]:

- 0.0 (low: relatively poor estimated CNS penetration);

- 0.5 (mean: intermediate estimated CNS penetration);

- 1.0 (High: relatively good estimated CNS penetration);

The group of studies CHARTER built a table with CNS penetration-effectiveness score of antiretroviral drug combination regimens for HIV. There was a used CSF sample collected by lumbar puncture and performed in high sensitivity tests for drug concentrations as well as to determine HIV viral loads in the CSF. Scores greater than 7 were associated with lower viral loads statistical significance [12-14] (Figure 1) (Table 1).

To evaluate the establishment of initial HIV reservoirs, Spudich and colleagues evaluated whether the virus originally seen in CNS compartment is identical to that detected in peripheral blood at early acute HIV infection. Plasma samples and CSF with HIV RNA levels exceeding 10,000 copies/ml were paired blood and analyzed on the full

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Drug Class	CPE Score		
	1	0.5	0
Nucleoside Reverse Transcriptase Inhibitor (NRTI)	Abacavir Zidovudine	Emtricitabine Lamivudine Stavudine	Adefovir Zalcitabine Didanosine Tenofovir
Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)	Delavirdine Nevirapine	Ethvirenz	
Protease Inhibitor (PI)	Amprenavir-r Danmavir Fosamprenavir-r Lopinavir-r Indinavir-r	Amprenavir Atazanavir Atazanarir-r Fosamprenavir Indinavir	Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
Integrase Inhibitors		Elvitegravir Raltegravir	
Entry Inhibitors	Vicriviroc Maraviroc		Enfiwirfide T-I249

Table 1: CNS penetration- effectiveness score (CPE Score): Antiretroviral Therapy CNS penetration scoring system [6].

Drug Class	CPE Score 4	3	2	1
Nucleoside Reverse Transcriptase Inhibitors	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir Zalcitabine
Nonnucleoside Reverse Transcriptase Inhibitors	Nevirapine	Delavirdine Efavirenz	Etravirine	
Protease Inhibitors	Indinavir/r	Darunavir/r Fosamprenavir/r Indinavir Lopinavir/r	Atazanavir Atazanavir/r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir/r Tipranavir/r
Entry/Fusion Inhibitors		Maraviroc		Enfuvirtide
Integrase Strand Transfer Inhibitors		Raltegravir		

Figure 1: CNS penetration-effectiveness score (CPE Score): Antirretroviral therapy CNS penetration scoring system CNS [11].

sequencing of the viral genome. Phylogenetic analysis revealed highly similar sequences between the two compartments. In conclusion, these findings suggested that there isn´t a substantial selection for specific HIV subtypes, which is able to penetrate in CNS during the acute phase of infection [15].

Ferguson and co-workers evaluated that inflammatory response in acute HIV infection may result in establishing a reservoir of HIV in CNS. They used a monkey model to examine the effects of an HIV vaccine administered during primary infection. In animals that did not receive the immunization, white matter brain astrogliosis and microgliosis were observed 127 days after infection and progressed by 300 days post-infection. Animals that received a vaccine against HIV had lower RNA peak plasma during recent HIV infection. Therefore, it was found that treatment strategies aiming to protect CNS on HIV infection are also relevant to avoid local HIV reservoir on CNS [15].

A study conducted in San Diego - USA, Neurobehavioral Research Center on HIV [8], revealed that some patients with HAND showed cognitive improvement soon after the start of ART (13% at 12 weeks), and better along the following weeks (24, 36 and 48 weeks after the start, with improved rates of up to 41%). Furthermore, major improvement was noticed in subjects who had the lowest performance in initial evaluations. Despite minor improvement, it was noted good results in less committed participants on initial studies.

Continuous improvement were detected up to 1 year after changing therapy, supporting results from long-term observation groups, which demonstrate benefits of ART along three years and even in patients with immune reconstitution syndrome for a period greater than five years. This suggests that the window for the recovery of brain damage caused by HIV may be relatively long [8,15,16].

The neuropsychological improvement (NP) was associated with a reduction in HIV viral load plasma. Several mechanisms have been proposed in literature to explain the NP improvement. First, ART reduces HIV brain replication (as well as blood); as a result, the activated circulating monocytes are reduced, leading to a reduction of their migration to the brain. With a reduction of HIV and a reduction of monocyte activation, neurotoxins and neuroinflammation production is also reduced [5,11,16].

The CPE score (penetration effectiveness CNS) greater than 2, was another improvement NP predictor in multivariate analyzes. The beneficial effect of the drugs with good penetration into the cerebrospinal fluid (CSF) has been observed in several other longitudinal studies. This is a great non-negligible positive effect as a possible factor that will provide valuable information for future clinical trials. Best CNS penetration is likely to lead to a greater neurocognitive improvement as best suppresses viral replication in the CNS [16-20].

Conclusion

This study reveals that patients with HAND should be more accurately monitored in order to minimize the impact of HAND on productivity and quality of life. The therapy with good CNS penetration (CPE scores greater than 2) should be selected whenever possible based on treatment history and use of toxicity and drug resistance tests. Adherence is also a critical factor that determines improvement on cognitive functions and better performance in neurocognitive assessment tests [15-17].

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