Review

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HIV associated neurocognitive disorders

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With the development of new antiretroviral therapies, there has been significant developments in the understanding of the neuropathogenesis of HIV-associated brain disease and the effects of these drugs in the CNS. This fact originated a substantial improvement in the survival of patients and influenced the course of cognitive impairment associated with HIV infection. This review intends to be an update on the epidemiological, etiopathogenic, clinical and therapeutic aspects related to neurodeterioration. A key challenge for the clinician working in this area is to diagnose, as early as possible, the cognitive deficits ocuring in the primary stages of the disease, to determine the prognosis (according to clinical, laboratory and neuropsychological findings) and establish a therapeutic approach. So the neuropsychological assessment should be included in the routine evaluation of these patients. This would have an important impact on their quality of life and improve, the antiretroviral therapy compliance.

Key Words:
HIV/AIDS, Neuropsychological functioning, Cognition, Cognitive impairment, Psychiatry, Psychology

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Trastornos neurocognitivos asociados con la infección por el VIH

Con el desarrollo de las nuevas terapias antirretrovirales, se han producido importantes avances en el conocimiento de la neuropatogenia de la encefalopatía asociada con la infección por el VIH y de los efectos que estos fármacos tienen en SNC. Los nuevos tratamientos antirretrovirales, además, han dado lugar a una mejora sustancial en la supervivencia de los pacientes seropositivos para el VIH y han influido de forma decisiva en el curso del deterioro cognitivo asociado con la infección por el VIH. Esta revisión pretende ser una actualización de los aspectos epidemiológicos, etiopatogénicos, clínicos y terapéuticos relacionados con el deterioro neurocognitivo. Un reto de enorme importancia para los médicos y neuropsicólogos que trabajan con estos pacientes es del de diagnosticar lo antes posible los déficits cognitivos que se observan en la primeras fases de la infección con el fin de establecer el pronóstico de acuerdo con los resultados de las pruebas neuropsicológica y de laboratorio e instituir la estrategia terapéutica más adecuada. Por esta razón, la evaluación neuropsicológica debe incluirse en la práctica clínica diaria con estos pacientes. Esto contribuirá a mejorar su calidad de vida y el cumplimiento terapéutico del tratamiento antirretroviral.

Palabras clave:
VIH/SIDA, Función neuropsicológica, Cognición, Deterioro cognitivo, Psiquiatría, Psicología

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INTRODUCTION

The human immunodeficiency virus (HIV) is a neurotropic virus, which attacks the central nervous system (CNS) at an early stage, and which causes many of those infected to develop symptoms of a neurological and psychological nature.[1] The involvement and consequent disruption of the neurocognitive system have been recognized in infected patients since the year in which the acquired immunodeficiency syndrome (AIDS) was first described as a clinical entity.[2]

The existence of neurocognitive deterioration as directly linked to HIV – especially in the clinically asymptomatic phase of the disease – was somewhat controversial until 1987,[3] with the first global study of neurocognitive disturbances associated with HIV[4] having been published in 1995. Its results showed cognitive damage in all stages of the disease (i.e. clinically asymptomatic, symptomatic and AIDS), which compromised multiple cognitive domains. As with many other medical, surgical and psychiatric

pathologies, these findings revealed a universe of cognitive deficits, whose expression was greater or lesser, but which nevertheless had an impact on the lives of most of the infected patients.

In the time before Highly Active Antiretroviral Therapy (HAART), it was not considered possible to block the progression of the aforementioned deficits, but in the past few years a significant evolution in the knowledge of the neuropathogenesis of the brain disease linked to HIV and of the effects of those drugs and their penetration on the CNS,[5] altered that paradigm. For this reason, the clinical study of this pathology has acquired a much greater relevance, in the expectation that we will be able to understand, interfere in and modify the deterioration process.

So, when we approach the theme of neurocognition in HIV positive patients, we may encounter two realities: patients with access to "anti-dementia" drugs, and those who, not having that access, will suffer the consequences of neuronal attacks by HIV with more or less obvious signs of deterioration.

Cognition should be understood as a functional whole, including various capacities or functions, which allow an individual to adapt to everyday life challenges. For its study the cognitive neuropsychologist uses theoretical models of cognitive psychology and cognitive neurosciences to test hypotheses related to the neuronal processes, mechanisms and systems underlying the HIV Associated Neurocognitive Disorders (HAND).[3]

Epidemiology

The incidence and prevalence of HAND are difficult to determine, not only due to the variety of criteria used in its definition, but also due to the multitude of instruments used for its quantification. Before the introduction of HAART, deterioration increased and followed a progressive course throughout the various stages of the disease. The rates of global deterioration were around 35% in asymptomatic patients, 44% in those with moderate symptomology, and 55% in patients with AIDS.[3]

Meanwhile, Grant[6] using the nomenclature recently revised by Frascati's group[7] with new diagnostic criteria from the 2007 consensus, found 25% prevalence rates for Asymptomatic Neurocognitive Incapacity (ANI), 15% for Mild Neurocognitive Disorder (MND), and 10% for HIV Associated Dementia (HAD), with half of the sample group showing no neuropsychological changes (Figure 1).

The CHARTER (CNS HIV Antiretroviral Therapy Effects Research) study, which evaluated, over a five-year period, the changes in presentation of neurological disturbances within the context of HAART, showed similar results in relation to global deterioration, but different ones for diagnosis (2% for dementia, 29% for MND and 21% for ANI), reflecting the influence of new therapies, and also noting that in 25% of patients with deficits, documented by neuropsychological batteries, no symptoms of cognitive damage whatsoever had been reported, either by the patients themselves or by their families.[8]

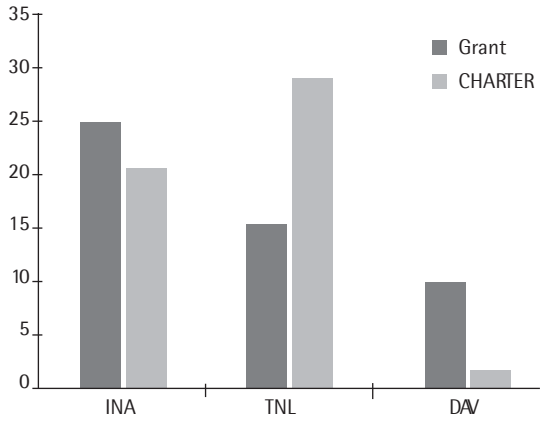

Figure 1 Estimated prevalence of HAND

COGNITIVE DOMAINS

The characteristics of HAND, mainly due to its diffuse nature, present significant challenges translating specific neurobiological mechanisms of HIV into cognitive neuropsychology quantification.

Due to the aforementioned diffuse nature of the disorder, HIV infection offers a limited conceptual model for the development of hypotheses on the role of specific cerebral systems in cognition: something which would be better evidenced in focal or restricted lesions[2]. Although these constraints make the clinical diagnosis, the specific therapeutic approach and the investigation of the different cognitive domains involved difficult, the authors have succeeded in describing, discriminating and individualizing some patterns of impact and damage.

In a classic study from 1995[4] – which was carried out previously to HAART and which therefore offered "cleaner" results – there were eight main domains affected by HIV in seropositive individuals (Figure 2).

More recently, the HIV Neurobehavioral Research Center (HNRC) of the University of California established seven

nuclear neurocognitive domains in their evaluation of patients, exposing the subcortical predominance of HIV impact on the CNS[9]: *speed of information processing*; *attention/working memory*; *executive function*; *learning*; *memory; verbal fluency and motor speed and dexterity.*

DIAGNOSTIC CRITERIA AND CLINICAL MANIFESTATIONS

Although when we refer to the neuropsychological symptoms associated with HIV infection we cover a broad spectrum of psychiatric and neurological manifestations, there are, nevertheless, three consensually systematized clinical conditions[7]: *Asymptomatic Neurocognitive Incapacity*, *Mild Neurocognitive Disorder* and *HIV Associated Dementia* (in contrast to the previous classification, which did not distinguish between the first two, designating them as *Minor Cognitive Motor Disorder* (MCMD).[10] As many features of neurodeterioration can be reversible, this nosological description should be understood in a spectral and dimensional sense, as a *continuum* of gravity that can evolve in both ways (Table 1).

Changes in cognitive-behavioral functioning may extend from a subjective sensation of psychomotor slowing and vague mnesic difficulties, to serious dementia, with mutism and gross neurological signs.[11] Although any cognitive ability may be compromised in HAND, some patterns are more common than others. Memory disorders, especially learning and the acquisition of new information tend to be prominent, as well as bradyphrenia, attention problems and disorders of the executive functions. If language is affected, it tends to be more evident in terms of fluency, with slow word generation, than in the difficulty or incapacity to name objects. As would be expected, the most marked and profound impairments are observed in more advanced stages of the disease, with language deterioration, visual-spatial difficulties, emotional indifference and the movement and behavior dysfunction, predominating. A major impact on the domains of attention, executive function, memory and motor function,[12] tends to interfere excessively with daily social and occupational functioning.[13]

ETIOPATHOGENESIS

HIV is known to cause an acute devastation of the immune system, but its effect on the CNS is much less understood. The virus invades it at an early stage of the infection, probably before the development of cellular or humoral immune response,[14] and causes – progressively – neurotoxicity, neurodegeneration, inflammatory responses (encephalitis) and cognitive deficits. This damage may be primary, due to the presence of the virus, or secondary, as a consequence of the immunosuppression associated with the development of opportunistic infections and neoplasms of the CNS, such as progressive multifocal leukoencephalopathy (PML), cryptococcosis, toxoplasmosis and lymphomas.[15]

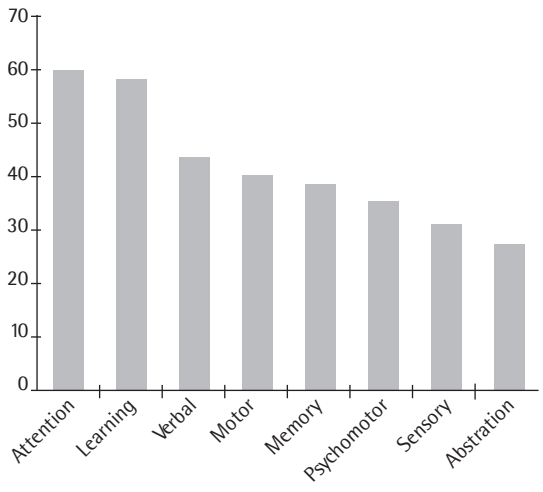

Figure 2 | Estimated prevalence by domain (Heaton et *al.*, 1995)

The virus infected cells rapidly propagate the primary infection. Despite the absence of symptoms in most cases, the brain may serve as an immunological sanctuary for the replication of the virus, on the one hand due to the blood-brain barrier which hinders the penetration of antiretroviral drugs and, on the other hand, to the perivascular macrophages, which serve as sequestration sites for the virus in the CNS.[16]

It is believed that the damage is predominantly subcortical since the usual symptoms, depict alterations in the cognitive functions supposedly carried out by the thalamus and the basal ganglia. Even so, there is evidence that the cortex is also affected, particularly by the deregulation of the broad neural networks, which depend on the integrity of the striate-frontal paths (mainly, the frontotemporal and frontoparietal systems) and not on isolated systems.[17]

In theory, all the cell types of the CNS can be infected by the virus, as long as they possess receptors and/or co-receptors (CCRS and CXCR4) that enable the virus's entry into the cell, but macrophages and microglia are the most commonly infected cell types.[17]

There is no convincing evidence that the viral infection directly impacts the neurons, and it is believed that the most

Table 1 | **Diagnostic criteria of HAND (Antinori *et al.*, 2007)**

HIV associated asymptomatic neurocognitive impairment (ANI)*

1. Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1.0 SD below the mean for age-education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills.
2. The cognitive impairment does not interfere with everyday functioning.
3. The cognitive impairment does not meet criteria for delirium or dementia.
4. There is no evidence of another pre-existing cause for the ANI.[1]

HIV associated mild neurocognitive disorder (MND)[2]

1. Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1.0 SD below the mean for age-education appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills.
2. Typically, this would correspond to an MSK scale stage of 0.5 to 1.0.
3. The cognitive impairment produces at least mild interference in daily functioning (at least one of the following):
   a. Self-report of reduced mental acuity, inefficiency in work, homemaking, or social functioning.
   b. Observation by knowledgeable others that the individual has undergone at least mild decline in mental acuity with resultant inefficiency in work, homemaking, or social functioning.
4. The cognitive impairment does not meet criteria for delirium or dementia.
5. There is no evidence of another pre-existing cause for the MND.[3]

HIV associated dementia (HAD)[4]

1. Marked acquired impairment in cognitive functioning, involving at least two ability domains; typically the impairment is in multiple domains, especially in learning of new information, slowed information processing, and defective attention/concentration. The cognitive impairment must be ascertained by neuropsychological testing with at least two domains 2 SD or greater than demographically corrected means. (Note that where neuropsychological testing is not available, standard neurological evaluation and simple bedside testing may be used, but this should be done as indicated in algorithm; see below.)
2. Typically, this would correspond to an MSK scale stage of 2.0 or greater.
3. The cognitive impairment produces marked interference with day-to-day functioning (work, home life, social activities).
4. The pattern of cognitive impairment does not meet criteria for delirium (e.g. clouding of consciousness is not a prominent feature); or, if delirium is present, criteria for dementia need to have been met on a prior examination when delirium was not present.
5. There is no evidence of another, pre-existing cause for the dementia (e.g. other CNS infection, CNS neoplasm, cerebrovascular disease, pre-existing neurologic disease, or severe substance abuse compatible with CNS disorder).[5]

* If there is a prior diagnosis of ANI, but currently the individual does not meet criteria, the diagnosis of ANI in remission can be made.

[1] If the individual with suspected ANI also satisfies criteria for a major depressive episode or substance dependence, the diagnosis of ANI should be deferred to a subsequent examination conducted at a time when the major depression has remitted or at least 1 month after cessation of substance use.

[2] If there is a prior diagnosis of MND, but currently the individual does not meet criteria, the diagnosis of MND in remission can be made.

[3] If the individual with suspected MND also satisfies criteria for a severe episode of major depression with significant functional limitations of psychotic features or substance dependence, the diagnosis of MND should be deferred to a subsequent examination conducted at a time when the major depression has remitted or at least 1 month after cessation of substance use.

[4] If there is a prior diagnosis of HAD, but currently the individual does not meet criteria, the diagnosis of HAD in remission can be made.

[5] If the individual with suspected HAD also satisfies criteria for a severe episode of major depression with significant functional limitations or psychotic features, or substance dependence, the diagnosis of HAD should be deferred to a subsequent examination conducted at a time when the major depression has remitted or at least 1 month has elapsed following cessation of substance use. Note that the consensus was that even when major depression and HAD occurred together, there is little evidence that pseudodementia exists and the cognitive deficits do not generally improve with treatment of depression.

probable reason for gliosis and neuronal loss is the increased regulation of proinflammatory cytokines, resulting in neuronal damage mainly in the frontal cortex. However, synaptic and dendritic alterations are correlated with the degree of cognitive performance – even in cases of light or moderate disorders[18] – being evident in about 50% of patients, and assuming the form of neuronal apoptosis and/or synapto-dendritic lesion,[19] although these (unlike neuronal apoptosis) are potentially reversible through an effective therapy.

Several neuroimaging techniques have been used for the *in vivo* observation of HIV neuropathology. The most relevant findings[20] show cerebral atrophy (probably from neuronal loss and demyelination), ventricular widening (a combination of central and cortical atrophy), focal high signal intensity in the white and gray subcortical matter, confluent areas of hypersignal and areas of solitary hypersignal, volume loss in the caudate nucleus and focal metabolic disorders of the basal ganglia, thalamus and temporal lobes in all stages of the disease. On the other hand, a consistent reduction has been noted in the neural marker N-acetyl aspartate (NAA) in the basal ganglia, and an increase in the glial marker myo-inositol (MI) and in the choline (Cho)/creatine (Cr) ratio, related with advanced dementia,[21] indicating possible neuronal lesion and significant reduction in regional cerebral blood flow in the frontal, lateral and medial parietal lobes, as well as in the posterior parietal white matter.

Autopsy studies of dementia patients show characteristic alterations of white matter and demyelination, microglial nodules, giant multinucleated cells, and perivascular infiltrate. The neocortex is involved in this pathology to a smaller degree, but can also present giant cells, infiltration of microphages and microglial cells, and reactive astrocytosis.[22] An elevated level of the nitric oxide synthase (iNOS) enzyme has been confirmed in the microphages and microglia in patients with dementia from HIV.[23, 24]

BIOLOGICAL MARKERS

A considerable amount of biological markers have been proposed in recent years as an aid to diagnosis and predictor of the presence and severity of HAND. However, with exception for CD4 count and viral load, no other biological markers have been proved useful for routine application.[25, 26]

With the advent of cART, differential diagnosis with other pathologies (hypertension, metabolic syndrome, vascular disease, other viral infections or malignancies) has gained increasing importance. Providing greater longevity, state of the art therapies, invite us to look at biological markers, factors of discrimination and to classify the degree of CNS involvement by HIV.[27]

Recent data supports different clinical phenotypes of HAND, including an inactive form, in which there is no permanent brain damage, either at the clinical or subclinical level.[28] The ability to identify the asymptomatic disease in real time through a marker, rather than through a series of tests over a period of weeks is clearly desirable. The evaluation of the response to HAART, preventing the inappropriate prescribing of new drugs and the increased risk of toxicity,[29-31] becomes an important investigation issue.

RISK FACTORS, COMORBIDITY AND DIFFERENTIAL DIAGNOSIS

The most important risk factors for cognitive deterioration appear to be age, the stage of the disease and the viral load.[32] In addition to these, some have identified other factors,[33] such as low educational level, low CD4 count and homo/bisexual and heterosexual behaviors. Sevigny and colleagues[34] proposed the resistance to medication, co-infection with hepatitis C (HCV), female gender and cognitive reserve as important predictors of the degree of deterioration in seropositive patients.

Cognitive impairment is associated with numerous medical conditions beyond infectious diseases, such as respiratory, cardiovascular, renal, gastrointestinal, autoimmune, endocrinal, nutritional and metabolic diseases, and exposure to toxins, surgical procedures (mainly cardiovascular), radiotherapy and chemotherapy, as well as to pharmacological iatrogenic action, in addition to anesthetics, antiretroviral medications and psychoactive drugs.[35]

Around 60%-70% of HIV-infected patients have one or more psychiatric pathologies previous to infection, above all depression, with high prevalence rates in the order of 50%, which in themselves can compromise cognitive.[36]

The abuse of and/or dependency on alcohol,[37] cannabis[38] and cocaine[39], co-infection with hepatitis C,[40] and delirium,[41] are also aspects to consider for differential diagnosis, in comorbidity or in double diagnosed cases.

Finally, with the advent of HAART, the mortality rates in patients with HIV decreased drastically, resulting in an increase of elderly people who live with the infection. Meanwhile, the impact of normal aging on the disease is controversial, since there are many risk factors that accompany it, such as cardiovascular disease, arterial hypertension and metabolic disorders.[42]

Table 2 | **Biomarkers of HIV-Related CNS Disease**

Effector Cells
- Lymphocytes (CD4 Cell Count, β-2-Microglobulin)
- Monocytes (CD14+/CD69+ Monocytes, Soluble CD14 - sCD14, Neopterin, Quinolinic Acid)
- Astrocytes (S-100β, Glial Fibrillary Acid Protein - GFAP)

Modulators
- Interleukins (IL-1 e IL-6).
- TNF Superfamily Proteins (TNFα)
- Interferons and Interferon-Inducible Proteins
- Chemokines

Other Modulators
- Transforming Growth Factor (TGF)-β
- Urokinase Plasminogen Activator Receptor (uPAR)

Toxins
- Viral Toxins (HIV RNA, HIV DNA, HIV-Encoded Proteins)
- Host Toxins (Arachidonic Acid Metabolites and Prostaglandins, Nitric Oxide, Platelet Activating Factor)

Target Cell
- Neuron (Neurofilament-Light - NFL, Tau).
- Endothelial Cells/Blood–Brain Barrier (Albumin, Immunoglobulin G and Total Protein, Serum Vascular Endothelial Growth Factor - VEGF, Intercellular Adhesion Molecules - gp 120, tat, Matrix Metalloproteinases - MMP-2,7 and 9)

Genetic Factors
- MCP-1, CCR2, APO-E4

Others
- B12, Red-Cell Folate, Thyroid Function, Vitamin E, Sphingomyelin and Ceramide.

COURSE AND PROGNOSIS

Longitudinal studies have been carried out towards evaluating course and neuropsychologial stability throughout the infection.[43] Instability in the diagnosis of HAND, has been noted with symptom regression in 7.5%-29% of patients and 19% fluctuating between evaluations from normality to various degrees of deterioration.[44] The CHARTER group found, over the course of a five years study that 29% of participants showed a decline in cognitive functioning, 47% remained stable and 17% demonstrated substantial improvements.[8]

So, it becomes unclear whether we are dealing with clear diagnostic entities (ANI, MND and HAD) or with a *continuum* of gravity,[45] some authors[46] even suggest that cognitive deterioration stabilizes at around 64 months of evolution, thus interrupting the progressive and one-directional decline which was supposed to happen.

It equally remains to be determined whether or not this transition reflects biological changes produced by HAART.[42] On the other hand, HAND, especially in its acute form, is associated with a rise in mortality and lower survival rates in AIDS patients, even in the era of HAART.[47]

The prognosis of HAND is variable and difficult to determine, but has considerably improved with the introduction of antiretroviral drugs. It depends mainly on the morbidity of the disease, on the number of hospitalizations, on quality of life. Even in the era of HAART, a serious cognitive compromise is associated with high rates of mortality.[48] This relationship is particularly strong in the case of HAD, even taking into account therapeutic compliance, disease progression (CD4) and demographic factors.[47] However, the change in life expectancy offered by the new therapies, increasing the time of infection and the prevalence of this disease in the elderly are the most important variables in the evolution and prognosis of cognitive disturbances in these patients.[49, 50]

These issues call for a front line the cognitive evaluation when faced with diagnostic and therapeutic decisions. With the use of neuropsychological instruments, we will be hopefully able to develop a stable insight for the course of deterioration, understanding the cognitive deficits which may remit (fully or partially), thus decisively influencing the prognosis and improving the patients' quality of life.

TREATMENT AND PREVENTION

There are no effective treatments for the neurological deficits associated with HIV, being the antiretroviral therapy introduced in 1996 the fundamental treatment for HAND. The majority of studies show the positive effect of cART,

Table 3 | **CNS penetration-effectiveness rank of cART (Letendre *et al*, 2008)**

	Good Evidence	Better Evidence	Best Evidence
	Drug characteristics	Pharmacokinetics	Pharmacodynamics
Estimated Neuro-Effectiveness	Consistent with	Concentrations exceed the wild-type IC50	Effectiveness in clinical Studies
Higher (1)	Substantial penetration	Consistently	Independent
Intermediate (0.5)	Marginal penetration	Inconsistently	Not clearly independent
Lower (0)	Poor penetration	Rarely	Ineffective

with very significant remission in mild and moderate deterioration, but that does not translate equally in all cognitive domains.[51] This is probably due to their diverse pharmacological properties, distribution in the CNS, concentration in cerebrospinal fluid (CSF), ability to reduce viral load or even their results treating HAND.[52]

Research results are, however, clear on the fact that antiretroviral drugs with better penetration of the CNS promote an improvement of attention, visual-spatial abilities and psychomotor speed, although memory and some executive deficits remain unaltered.[11] Acute reduction in viral load as measured in the CSF, with a resulting global clinical improvement, is the best anti-dementia strategy today, and one which mitigates the neurocognitive deterioration. Thus being the case, satisfactory therapeutic adhesion to the drugs – which have proven their efficiency in improving cognitive functions – becomes crucial. In this context, Letendre and colleagues have proposed an attempt at classifying the efficiency of penetration by HAART (Table 3).

The authors attributed a score to each drug in view of the CNS penetrating effectiveness (CPE) based upon the confluence of their physical, pharmacokinetic and pharmacodynamic properties: the drug may have a low (0), medium (0.5) or high CPE score,[52] despite no reliable assays to monitor the efficacy of the drugs tested.

Taking into account this methodology, the Nucleoside reverse transcriptase inhibitors (*Abacavir*, *Zidovudine*), Non-nucleoside reverse transcriptase inhibitors (*Delavirdine*, *Nevirapine*) and Protease inhibitors (*Amprenavir-r*, *Indinavir-r*, *Lopinavir-r*, *Darunavir*), seem to be the most effective neuroCART (cART regimens with superior CNS penetration) in treating and preventing HAND until now.[52]

Recent research has focused on interfering role with the inflammatory cascade, oxidative stress, neurotoxin release, viral replication reduction and apoptotic effects, as well as providing neuroprotection,[53] and the outcomes showed no significant or potentially iatrogenic effects.

However, while recently cART and neuroCART have been associated with the worsening of neurocognitive performance,[54] an early pharmacological strategy, with cART regimens in patients with high CPE scores and containing more than three drugs,[55] immune modulators and psychostimulants, seems likely to be the most appropriate treatment and prevention strategy of cognitive impairment.

Apart from **antiretroviral therapy,** many other substances have been tested as adjunctive therapy for HIV neurocognitive impairment, such as selegiline, memantine, minocycline, niphedipine, lexipafant, proinflammatory cytokines, Substance P, neurotrophic (NGF, FGF and BDNF) and anti-inflammatory factors (IL4 and IL10), methylphenidate and dextroamphetamine, valproic acid and lithium, in addition to coadjuvant nutritional therapy, such as Vitamin E and selenium in the daily diet, with modest therapeutic results.[53]

The psychiatric follow-up of patients with HAND or at risk of developing it, is in our view imperative, not only by the direct symptoms which they suffer, but especially due to the high comorbidity observed. Depression is the most prevalent comorbid psychiatric condition associated with HIV infection, but the contribution of neuropsychiatric impairment in HIV infection has yet to be clearly defined.[56] However, it is important to understand the treatment of affective disorders impact in cognitive function in these patients. Many studies have found considerable benefits in the use of psychoactive drugs[57] either for controlling that clinical condition, or because of the overlapping benefits with HAART, especially with antidepressants such as, selective serotonin reuptake inhibitors (SSRIs), psychostimulants and mood stabilizers, mainly lithium carbonate.[58]

Although the literature is unanimous on the advantages of cognitive rehabilitation in brain lesions, investigation is sparse on its application in patients with HAND, although some investigations,[59] using diverse techniques, have obtained encouraging results.

A cognitive remediation used frequently in patients with brain injury is based on the plasticity of the CNS, to stimulation and training. The main remediation strategies are the restoration and recovery, compensation and replacement, mixed strategies, group work and family. Nowadays, there are techniques and tasks, covering all cognitive domains, allowing a more specific treatment. The results vary with the form of onset of the deficit, the severity of injuries, their location, the premorbid level, age, handedness, gender and socioeconomic status.[60]

With disease stabilization, obtained by the new pharmacological therapies, more and more importance is given to the quality of life of HIV infected patients. This concerns not only biomedical decisions, but all the aspects of daily life (professional or social), which must be addressed. As we have previously seen, the diagnostic stability of HAND has made decision-making even more confusing, but from the moment we think more about the reversibility of deterioration, and less about irreversible syndromes of dementia, the ethical questions may easily become less uncertain and complex.[61]

Finally, therapeutic strategies and its results depend heavily on disease status (CDC 1993 Classification), mostly time of infection and age of the patients. Increased life expectancy in these patients, raises new challenges regarding the most prevalent comorbidity (medical, neurological and psychiatric), iatrogenic factors and the increasing cross effects of drugs, but also in the differential diagnosis with normal aging and all consequences arising from here.

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