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The burden of HIV-associated neurocognitive disorder (HAND) in post-HAART era: a multidisciplinary review of the literature

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Abstract. – OBJECTIVE: The purpose of the present multidisciplinary review is to give an updated insight into the most recent findings regarding the pathophysiology, diagnosis and therapeutics of HIV-associated neurocognitive disorder (HAND).

MATERIALS AND METHODS: We performed a comprehensive search, through electronic databases (Pubmed – MEDLINE) and search engines (Google Scholar), of peer-reviewed publications (articles and reviews) and conferences proceedings on HAND pathophysiology, diagnosis, and therapy, from 1999 to 2016.

RESULTS: It seems to be increasingly clear that neurodegeneration in HIV-1 affected patients is a multi-faceted disease involving numerous factors, from chronic inflammation to central nervous system (CNS) compartmentalization of HIV. Diagnosis of HAND may benefit from both laboratory analysis and advanced specific neuroimaging techniques. As regards HAND therapy, modified HAART combinations and simplification strategies have been tested, while novel exciting frontiers seem to involve the use of nanoparticles with the ability to cross the Blood-Brain Barrier (BBB).

CONCLUSIONS: Albeit highly active antiretroviral therapy (HAART) allowed a major decrease in morbidity and mortality for AIDS patients, CNS involvement still represents a challenge in HIV patients even today, affecting up to 50% of patients with access to combination antiretroviral therapy (cART). Future studies will have to focus on CNS compartmentalization, drugs' ability to penetrate and suppress viral replication in this compartment, and on new approaches to reduce HIV-associated neuroinflammation.

Key Words:
HIV, Combination antiretroviral therapy (cART), AIDS, AIDS dementia, HIV-associated neurocognitive disorders (HAND), Cognitive impairment.

Introduction

Since the debut of highly active antiretroviral therapy (HAART), human immunodeficiency virus (HIV) disease has modified its course from being an acute and highly lethal disease to a treatable chronic illness, even in marginalized populations[1], leading to a new constellation of problems, generally referred to as "non-AIDS morbidity"[2]. Hence, as time went by, medical attention has shifted from the acute and mostly infectious complications[3] to long-term and possibly age-related ones, such as bone and renal affection, cardiovascular disease, non-AIDS (acquired immune deficiency syndrome) defining cancers and central nervous system disorders[4-30].

As most of the chronic diseases affecting the general population, even in HIV affected patients

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the pathogenesis of these affections is multi-faceted[31]: direct HIV replication, chronic inflammation, treatment-related adverse events, immunodeficiency, immunosenescence (the aging of the immune system), frailty.

Central nervous system (CNS) involvement in HIV patients is a quite common phenomenon, affecting up to 50% of patients with access to combination antiretroviral therapy (cART)[32]. With changes in memory, concentration, attention and motor skills, HAND (HIV-associated neurocognitive disorders) consists of a series of disabling neurological conditions, which affect specifically HIV-individuals and may vary between three main degree of severity (Frascati criteria)[33]: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HIV-associated dementia (HAD). According to this classification, ANI, which appears to be the most common form of HAND with approximately 70% of cases[32], differs from both MND and HAD due to the lack of symptoms or apparently any deficit which may affect daily functions. Nevertheless, recent studies raised the doubt if screening tests for HAND, especially for ANI, might be misleading, possibly heading to false-positive or even false-negative diagnosis[34]. The Consensus Report of the Mind Exchange Program[35] claimed that screening tests usually underestimate the real incidence of HAND and that there is no "perfect tool" suitable for use across all practice settings. However, while finding the most accurate test for HAND screening still remains a challenge, it appears to be appropriate collecting neurocognitive screening test anyway from all HIV patients, possibly before cART initiation[35]. Diagnosis of HAND should be made only after a comprehensive evaluation and exclusion of other potential causes[36]. In fact, neurocognitive impairment may occur in HIV patients not only related to the course of the disease, but also due to HAART effects, substance abuse, co-infections, cerebrovascular disease and other age-associated degenerative diseases of the CNS: these last two, in particular, have been more and more diagnosed in the last 10 years due to the remarkably increasing proportion of aged HIV-infected individuals optimally treated with cART, which reached a prolonged life expectancy to over age 50.

The purpose of this review was to summarize current knowledge about HAND, focusing on novel findings regarding pathophysiology and therapeutics of this disease.

Pathophysiology of HAND

While there is an ongoing debate to assess the pathophysiology of HAND, it is increasingly clear that neurodegeneration in HIV-1 affected patients is a multi-faceted disease.

HIV-associated chronic inflammation clearly seems to be one of the main factors, which contribute to the onset and maintenance of neurocognitive impairment in HIV-affected patients[36-41]. In fact, while a great number of HIV patients are not affected by any cognitive dysfunction or, at least, succeed in reversing them with appropriate cART[42], on the other hand, in another good portion of them, a residual disease often persists. Among other effects, mostly due to the activation of several signaling pathways and chemokines/cytokines release[38], chronic inflammation appears fundamental in reducing the degree of resistance of the blood-brain barrier (BBB), thus increasing the rate at which free virus and viral proteins cross it[43]. Through the activation of these signal pathways, HIV also ends in stimulating a process called excitotoxicity, by means of which an inappropriate amount of an excitatory neurotransmitter is released from the cells, hence evoking changes in cells polarization and ions levels, consequently activating enzymes which lead to neuronal damage and synaptic disruption[38].

Since HIV cannot infect directly neuronal cells, different models for explaining the neurodegeneration in HAND have been conceived (which are not necessarily exclusive)[44-46], two of which share the common denominator of initial perivascular macrophages and microglia HIV infection[38]. The first (direct) model consists in neuronal damage elicited by the direct contact between viral proteins (such as Tat, gp120 or Nef), released from infected monocytes, and neuronal cells[44,45]. According to the second (indirect) model instead, HIV proteins, released from infected cells, generate an inflammation mechanism, which then leads to neuronal death[44,45]. Neuronal damage in virally suppressed HIV-1 infected patients has also been recently confirmed by Eden et al[47], showing a correlation between mild HAND and CSF neopterin, a biomarker of macrophage and microglial activation in CNS. Nevertheless, to date, there is still debate on whether monocytes/macrophages may also represent an HIV latency site such as memory T cells[46], and more data will have to be gathered in order to clarify this possibility.

Microbial translocation, ascertainable through detection of lipopolysaccharide (LPS) levels in

plasma, has been described as another possible mechanism at the heart of CNS inflammation and HAND, due to its induction of persistent macrophages and T-cells activation and leading to a chronic inflammatory state[48-50].

As we said before, nowadays the process of *aging* is becoming more and more the pivot of the interest focused on HIV patients. A general decline in cognitive functions is a quite natural and inevitable process when a healthy or diseased individual, ages. In addition to this, there might be some comorbidities, such as cerebrovascular disease, Alzheimer or Parkinson's disease, which can participate to the onset of HAND in an older patient[51,52]. Finally, there is the direct contribute from HIV. It is now well accepted, in fact, that the aging brain appears to be more susceptible to neuronal injury related to HIV infection[51-55].

Furthermore, data from literature[56-59] showed that HIV disease had been independently associated to an earlier occurrence of frailty, which is defined as a clinical syndrome characterized by a low capacity of resistance to stressors, leading to a general decline of the human body involving multiple systems, and causing vulnerability to external stimula[60].

In spite of the dramatic reduction in the incidence of HAD since the introduction of cART[42], which proved its effectiveness against HIV even in the CNS, there is ongoing debate as to whether the potential neurotoxicity of ART had to be taken into consideration among all factors contributing to HAND[61,62]. According to Underwood et al[61], there are two main potential mechanisms of antiretroviral CNS neurotoxicity. A first indirect model of toxicity of ART on CNS is explained through vascular mechanisms, which may lead to a premature aging of the brain[61,63]. A second model put into play direct mitochondrial toxicity, showing evidence of depletion in mitochondrial DNA (mtDNA) in some cortical areas, with a corresponding increase of oxidative DNA damage[61]. In this last study, cytochrome-c oxidase (COX) was considered a marker of mitochondrial oxidative function: COX deficiency in muscle fibers exposed to nucleoside and nucleotide reverse transcript inhibitors (RTIs) was registered, but it appeared to consist in a clonal expansion of pre-existing, age-related, mtDNA mutations, thus leading to the conclusion that NRTIs might contribute to worsen a prior condition to neuronal damage[61]. The concept of mitochondrial dysfunction has also been strengthened by a more recent work by Samuels et al[64], which established a connection between mtDNA content in blood cells and the presence of cognitive impairment.

Finally, novel findings concentrated the attention on CNS compartmentalization of HIV, which appears to take place mostly before cART initiation[65,66] and leads towards the transformation of the CNS in a potential reservoir for HIV. Several viral escape mechanisms seem to contribute to this event (infection of long-lived memory CD4+ T cells, naïve CD4+ T cells, T follicular helper cells, macrophages and microglia)[66,67], and whether other cell types and tissues might be involved, such as gut-associated lymphoid tissue (GALT), γδ T cells[68], astrocytes[69] or oligodendrocytes[70], is still an open question. Recently, it has been shown that the presence of IFNγ expressing CD8+ T-cells, the absence of cytolytic CD8+ T-cells, high myeloid activation, and failure of ART to suppress HIV replication in CSF, they all contribute to increase the risk of HAND[71]. Furthermore, monocyte activation within the CNS compartment is directly associated with neuronal injury at all stages of HAND[72]. Finally, the presence of drug resistance mutations in CSF and blood might also play a role in CNS compartmentalization[73], but more prospective and specifically designed studies will be needed in order to clarify how HIV mutations might contribute to the so-called "CSF escape". Figure 1 gives a schematic representation of the multifactorial pathogenesis of HAND.

Diagnosis of HAND

We previously mentioned that the diagnosis of HAND should be made only after a comprehensive evaluation and exclusion of other potential causes[36].

After gathering a detailed medical and neurological history, assessing eventual alcohol and substance abuse, collecting informations about eventual comorbidities or co-infections[74] and evaluating patient's psychiatric conditions, neurocognitive impairment has to be recognized through clinical symptoms and signs: impaired attention, memory loss, deficit in motor skills or in performing activities of daily living, dementia. The clinical scenario has to be assessed with appropriate screening methods[35,36]: by means of neuropsychological performance (NP) testing and self-reported assessment of every day activities, patient symptoms may be classified in ANI, MND or HAD according to Frascati criteria[33].

Nowadays, neuroimaging techniques may be performed to achieve a more accurate differential diagnosis of HAND from other neurodegenera-

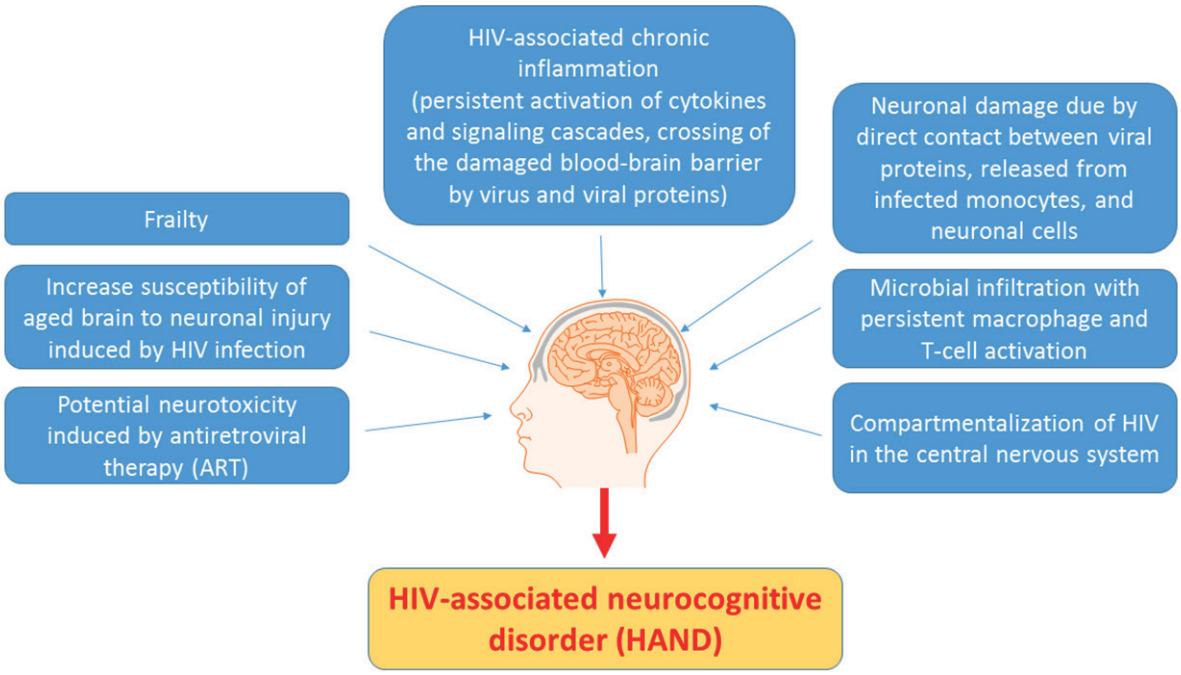

Figure 1. Schematic representation of the multifactorial pathogenesis of HIV-associated neurocognitive disorder (HAND). Refer to the main text for major details.

tive diseases especially in older patients, or from secondary causes of cognitive disorders, in order to adopt appropriate treatments. The term "neuroimaging" includes both morphological and structural assessments provided by radiological techniques, such as CT, MRI, Functional MRI and MR spectroscopy, as well as metabolic, functional and biochemical nuclear medicine methods, such as Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT) and the hybrid imaging PET/CT and SPECT/CT.

Although there is no specific tracer for HAND evaluation, the ability of nuclear medicine methods to assess the "*in vivo*" metabolic, functional and ultrastructural biochemical abnormalities provides valuable and safe support for clinicians, who also benefit from the quantitative analysis in both initial diagnosis and follow-up[75]. The two techniques, PET and SPECT, are able to identify metabolic and functional damage in an early stage, before neuronal death, both in the original areas of lesion appearance and in the remote sites of the efferent synapses[76]; these procedures also allow the follow-up of disease progression[76].

The PET imaging with ^{18}Fluorodeoxyglucose (FDG) is widely used to evaluate the metabolic activity of various pathological cells and tissues, such as neoplastic diseases, including brain metastases[77]. Moreover, neuron uptake of ^{18}FDG has been used in the differential diagnosis of a large number of neurodegenerative disorders, such as cognitive impairments, Parkinson's disease, and in the differential diagnosis of various cognitive disorders in HIV-affected patients. In Neuro-HIV, some specific metabolic patterns have been described, at PET ^{18}FDG evaluation, as able to improve diagnostic classification, with respect to the primary neurodegenerative forms. For instance, a low ^{18}FDG uptake due to an hypometabolism in cortical areas, associated to a high uptake in subcortical regions, especially in basal ganglia (that could be considered as abnormalities in connectivity between the different regions), could be classified as a typical pattern of HIV infection with AIDS[78,79]. Moreover, an irregularly reduced metabolism in cortical and subcortical areas is typical in even more advanced chronic states, evidencing the progression of functional damage[80]. An interesting ^{18}FDG PET study, regarding asymptomatic patients on HAART with HAND, showing a reduced metabolism of different degrees in the frontal regions, with normal MRI results has been reported[81]. These latter data have been confirmed in another study, underlying the earliest nuanced metabolic changes that occur in asymptomatic HIV+ patients on HAART therapy[82], which seems not always effective in pre-

venting HAND. Furthermore, some drugs included in HAART regimens are highly neurotoxic, thus possibly contributing to neuroinflammation and to subsequent HAND development (Figure 2 shows a typical PET pattern in a patient with HAND). To date, only few PET studies evaluating neuroinflammation in patients with HAND have been performed, some of which used ^{11}C PK1195 as a tracer[83,84]. The binding of ^{11}C PK1195 to the translocator protein, which is a mitochondrial receptor upregulated in activated microglia, seems to be significantly higher in HIV patients with HAND compared to those with no cognitive disorders[83,84]. This tracer could represent an interesting tool in HAND evaluation, but further studies with more cases and longer follow-up will be necessary to confirm its usefulness.

SPECT procedures, which are the most widely diffuse techniques in nuclear medicine, evaluate the *"in vivo"* specific functional state of the nerve and the specific cellular characteristics, such as enzyme activities, synthesis and/or receptor expression. These procedures have the potential to support cognitive impairment differential diagnosis and follow up in early disease. The uptake variations of lipophilic tracers, such as ^{99}mTc HM-PAO (hexamethyl-propilenamina-oxime) and ^{99}mTc ECD (ethyl-cysteine dimer),

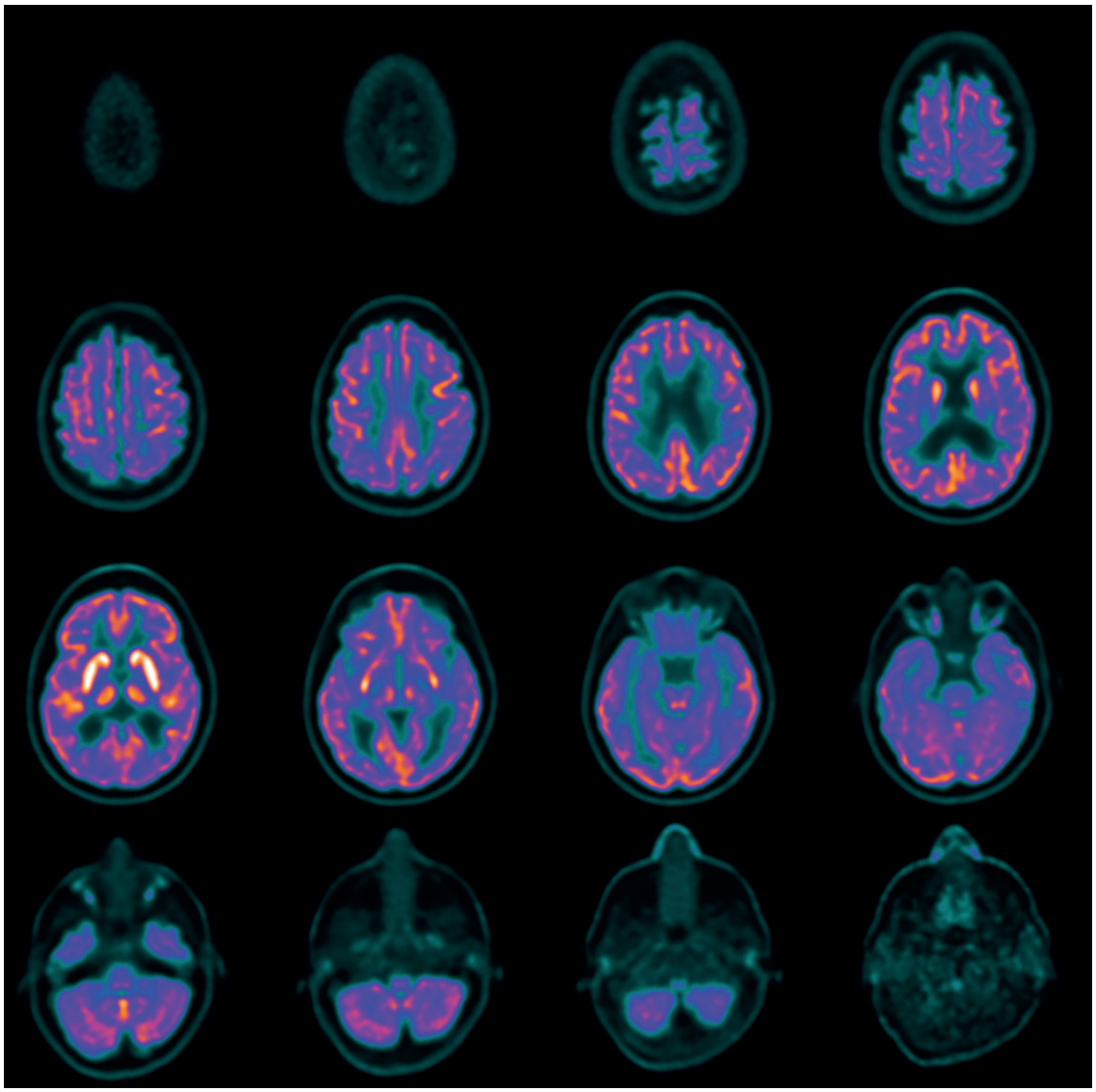

Figure 2. Typical 18FDG-PET pattern of HIV infection with HIV-associated neurocognitive disorder (HAND): global irregular 18FDG hypometabolism in cortical areas associated to a high tracer uptake in subcortical regions, especially in basal ganglia.

directly reflect the variations in regional cerebral perfusion, although different studies have demonstrated the existence of a close link between metabolism and perfusion parameters, allowing to consider the areas of impaired perfusion (at ^{99}mTc HM-PAO SPECT) as areas of altered metabolism. Thus, ^{99}mTc HM-PAO brain SPECT can give informations on pathological changes of the bio-molecular structure of nerve cells and on the physiopathology of the CNS[85]. Some typical cerebral perfusion abnormalities at ^{99}mTc HM-PAO SPECT were observed in all major types of cognitive disorders and dementias[86-88], but no evidence is available on the employment of this procedure in HAND cases.

In addition to the already existing radiopharmaceuticals for regional perfusion cerebral studies, new radiotracers have been introduced for biomolecular SPECT imaging in cognitive disorders evaluation. The qualitative and quantitative analyses of the presynaptic cellular dopaminergic receptor expression (DaT) in basal ganglia with ^{123}I Ioflupane SPECT, including statistical methods[89], could represent a useful tool in HAND diagnosis in the near future, since a dopaminergic dysfunction was observed in HIV patients with dementia[90]. This finding, in advanced stages of HIV infection, could be considered as dopaminergic system deterioration due to the neurotoxicity and to the neuroinflammation itself. On the other hand, during the early stages of the infection, the uptake of ^{123}I Ioflupane might be apparently normal because of the incretion of DaT expression caused by the neurotoxicity, and the tracer uptake would tend to decrease only with disease progression[91].

As regards laboratory analysis, CSF researches are often performed on HIV-1 infected patients to reveal neuronal damage[47] and also to rule out non-HIV neurological conditions[35]. Neuronal damage can be measured through neurofilament light protein (NFL) levels in CSF, while detection of CSF neopterin may be used as a biomarker of macrophage and microglial activation in CNS[47]. Moreover, a recent study showed a powerful correlation between CSF interferon alpha (IFNα) levels and CSF NFL, validating the relationship with neurocognitive impairment in ambulatory HIV-infected individuals[92].

Additional laboratory diagnostic tools may also result handful. As we already said, LPS may be found in the plasma of HIV-1 affected patients as a result of a gastroenteropathy-related bacterial translocation[48-50]. Also, plasma biomarkers of monocyte/macrophage activation, such as plasma soluble CD14 (sCD14) and soluble CD163 (sCD163), have been found to represent potential predictors of HAND progression and therapeutic responses, correlating inversely with global neurocognitive capacity, attention and learning scores[93,94].

Furthermore, several investigations corroborated the important role of HIV proteins in neuroinflammation. Viral protein Tat, for example, is implicated in neurodegeneration: a positive correlation between this viral protein levels and cognitive impairment in HAND has been showed[95], together with the implication of Tat interference with the trafficking of cyclin-dependent kinase 5 (CDK5, a kinase involved in cell migration, angiogenesis, neurogenesis and synaptic plasticity) between the nucleus and cytoplasm, leading to an hyper-activation of this kinase and eventually to neuronal death[96]. Another HIV-1 accessory viral protein (viral protein R: Vpr) recently raised the attention for its potential involvement in HAND pathogenesis, as well as an eventual biomarker of neuronal damage: Dampier et al[97] demonstrated the association between neuropsychological impairment in HIV-1 infected patients and the presence of specific amino-acid changes in peripheral blood-derived Vpr sequences. Specifically, some of them (N41 and A55) showed a direct relationship with poor results in neuropsychological assessment test scores, while some others (amino acids I37 and S41) resulted connected to lower deficit scores[97]. Viral proteins studies had already been performed in the past, and a correlation between these proteins and inflammation in HAND came into light. For example, envelope protein gp120/gp41 seems to be able to activate chemokine receptors (CXCR4 or CCR5) on neurons, as well as down-regulating glutamate uptake by astrocytes causing excitotoxicity[98,99]. Recent reports showed that the gp120 protein induces neuroinflammation, mitochondrial damage and energy metabolism impairment[100,101], as well as some neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) that cause parkinsonism in animal models of Parkinson's disease[102-104].

Moreover, HIV protein Nef also appears to have a role in neuronal apoptosis and in triggering the release of pro-inflammatory factors such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6) or macrophage inflammatory protein 1 (MIP-1)[105,106].

In conclusion, we can assume that multiple methods should be used, from neuropsychological performance evaluation, through neuroimaging, to cerebrospinal fluid and plasma analysis, in order to reach a more detailed knowledge of CNS changes during HIV infection and to be able to differentiate between HAND and other CNS disorders.

Therapeutics for HAND

The overarching idea for HAND therapy is to achieve permanent elimination of HIV from CNS reservoirs, while decreasing neuroinflammation, thus preventing or, at least, ameliorating cognitive impairment in HIV-1 affected patients. Even though the use of cART has been widely recognized as pivotal in preventing and partially containing the evolution of HAND[42], there is still the need to identify a realistic shelter for HIV patients from neurocognitive disorders related to the CNS viral infection.

In response to this need, different therapeutic approaches have been proposed. Particularly, large clinical trials conducted by means of AIDS clinical trials group (ACTG) sharpened the anti-inflammatory role of Minocycline (a second-generation tetracycline antibiotic), the anti-oxidant effect of Selegiline (a monoamine oxidase type B inhibitor) and the anti-excitotoxicity potentiality of Memantine (N-methyl-D-aspartate glutamate receptor (NMDAR) blocker)[38].

Chemokine receptor CCR5 has been implicated in participation to CNS inflammation and, specifically, as a co-receptor that mediates HIV entry[107]. For this reason, CCR5 antagonists such as Maraviroc, initially conceived as viral entry-inhibitors, are now being tested also in other inflammatory disorders that are unrelated to HIV infection, due to evidences, which proved their anti-inflammatory and anti-leukocyte trafficking role[108]. Furthermore, evidences showed that CCR5 might also have a role in maintaining HIV infection of the CNS, thus contributing to the CNS compartmentalization[108].

To date, there are also different ongoing studies assessing eventual modification in neurocognitive impairment in virally suppressed patients undergoing to simplification strategies for ART or receiving non-ART medications as adjunctive therapy[109]: switching to dual therapy regimens proved to be safe after one year of follow-up, the antidepressant medication paroxetine seems to represent an advantage at neuropsychological tests, while no benefits were registered from patients taking lithium as adjunctive therapy[110].

Finally, novel exciting frontiers of HAND therapy may consist in the increasing efficacy of HAART delivery and bioavailability by means of nanoparticles with the ability to cross the BBB without affecting its integrity. Nanocarriers such as natural and synthetic polymeric nanoparticles, dendrimers, liposomes, and various drug conjugates have been taken into consideration[110]. Over all, magnetic nanoparticles (MNPs) seem to possess the best potentialities, due to the externally applied magnetic force, which fastens MNPs-drug delivery to the target site (CNS)[111].

Conclusions

Albeit HAART allowed a major decrease in morbidity and mortality for AIDS patients, HIV-associated neurocognitive disorders still remain a burden, which should stimulate the search of novel and more effective therapeutic approaches.

Future studies will have to focus on CNS compartmentalization, drugs' ability to penetrate and suppress viral replication in this compartment, and on new approaches to reduce HIV-associated neuroinflammation.

Statement of Interests

Authors' declaration of personal interests: The authors declare that they had no financial interests or commercial associations during the course of this study.

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