Published in final edited form as:

Curr Opin Neurol. 2009 June ; 22(3): 315–320. doi:10.1097/WCO.0b013e328329cf3c.

HIV-1 associated dementia:

update on pathological mechanisms and therapeutic approaches

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Abstract

Purpose of review—Infection with HIV-1 can induce dementia despite successful administration of life-prolonging highly active antiretroviral therapy. This review will discuss recent progress toward a better understanding of the pathogenesis and an improved design of therapies for HIV-associated neurocognitive disorders.

Recent findings—Highly active antiretroviral therapy prolongs the lives of HIV patients, but the incidence of HIV-associated dementia as an AIDS-defining illness has increased and the brain is now recognized as a viral sanctuary that requires additional therapeutic effort. The neuropathology of HIV infection also has changed due to improved therapy, and while more similarities with other neurodegenerative diseases are being reported, predictive biomarkers remain elusive. However, improvements of in-vivo imaging technology and progress in uncovering the molecular mechanisms of HIV disease keep providing new insights. As such it appears that a prolonged activation of the immune system by HIV eventually leads to AIDS, and several lines of evidence indicate that simultaneously neurotoxic processes and impairment of neurogenesis both contribute to the development of HIV-associated neurocognitive disorders.

Summary—The improved understanding of the interaction between HIV and its human host provides hope that adjunctive therapies to antiretroviral treatment can be developed for HIV-associated neurocognitive disorders.

Keywords

dementia; HIV/AIDS; neurogenesis; neurotoxicity; therapy

Introduction

HIV-1 infection can induce neurocognitive complications that have recently been categorized as HIV-associated neurocognitive disorders (HANDs) [1•]. HAND defines three categories of disorders according to standardized measures of dysfunction: asymptomatic neurocognitive impairment, mild neurocognitive disorder (MND) and HIV-associated dementia (HAD). Although this classification scheme should improve the future assessment of the overall clinical situation for HIV disease of the central nervous system (CNS), new developments in the fields of biomarkers, imaging and the understanding at the cellular and molecular level of virus-host interactions are both underway and urgently needed to devise future improved treatments for HAND.

Neurocognitive sequelae and neuropathology of HIV infection and AIDS

HAD represents the most severe manifestation of HAND [1•] and occurred at the beginning of the AIDS epidemic primarily in patients with advanced HIV disease and low CD4 cell counts [2]. The advent of combination antiretroviral therapy (cART)/highly active antiretroviral therapy (HAART) in the mid-1990s was a major advance in the treatment of HIV infection that often prevented or at least delayed the progression to AIDS and at first also reduced the incidence of HAD. However, the incidence of dementia as an AIDS-defining illness has increased in recent years as HIV patients live longer, and HAD remains a significant independent risk factor for death due to AIDS [3,4•]. There is accumulating evidence that in the HAART era the less fulminant form of neurocognitive impairment, previously termed minor cognitive/motor disorder (MCMD), now MND, is more prevalent than clear dementia, but the observations over more than 10 years also indicate that HAART fails to provide complete protection from the development of HAD [1•,3,4•,5•,6•]. Although this failure of HAART to prevent deterioration or enable restoration of cognitive function has been largely ascribed to the limited penetration of many antiretroviral drugs into the CNS, it also needs to be considered that HAART, in particular in the long term, poses a potential toxicological problem that may affect neurocognitive performance on its own [4•,7•].

In any case, the neuropathology of HIV infection and AIDS has also shifted since the introduction of HAART [5•,6•,8•]. Since the beginning of the AIDS epidemic, neuroinflammation has been found to be common in HIV patients and was generally termed encephalitis (HIVE), represented by activated microglia, infiltrating peripheral macrophages (MΦ), often HIV-infected multinucleated giant cells and pronounced astrogliosis. Furthermore, neuroinflammation usually increased with the progression of infected individuals from the latent, asymptomatic stage of the disease to AIDS and HAD. In fact, activated microglia and infiltrating MΦ together with the reduced synaptic and dendritic density and frank neuronal loss are the best neuropathological correlates of HAD since the pre-HAART era [9,10]. Therefore, not surprisingly, inflammation has also been considered a pathologic mechanism. Although improved treatment may have been expected to reduce neuroinflammation, autopsy cases of HIV-related death collected since the introduction of HAART have rather suggested the opposite [8•]. The extent of microglial activation seemed comparable with that in fully developed, earlier AIDS cases, but the predominant sites of neuroinflammation appeared to have changed. While pre-HAART cases showed strong involvement of basal ganglia, post-HAART specimens indicated pronounced inflammation in the hippocampus and adjacent parts of entorhinal and temporal cortex [8•]. Moreover, HAART apparently limited or prevented lymphocyte infiltration, except in occasional, distinct events, now called immune reconstitution inflammatory syndrome (IRIS), where massive lymphocytosis, extensive demyelination and white matter damage occurred [5•,8•].

HIV-associated dementia, neurodegenerative diseases and aging

Neuropathological, neuropsychological and in-vivo imaging studies have generated evidence of persistent HIV-associated neurodegenerative processes and HAND despite successful HAART. The same studies also suggested commonalities between the development of HAND/HAD and other neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, for which aging is a major risk factor [6•,11,12•,13•]. Shared features of HAND and aging include alterations in domains of neuropsychology, physiology and immunology, whereas commonalities of HAND and neurodegenerative diseases are found in biomarkers and the localization of certain neuropathological signs, including inflammation, impaired protein degradation pathways and oxidative and nitrosative stress [6•]. Normal aging and HIV-infection and HAND share the deterioration of cognitive abilities and working memory, functional disturbance of the proteasome-ubiquitin complex and autophagy and increased

expression of inflammation markers [6•,14•]. Amyloid plaques (A β) similar to those in Alzheimer's disease, ubiquitinated deposits characteristic of frontotemporal dementia and Lewy bodies in Parkinson's disease have also been observed in brains of HIV patients [6•, 11,12•]. Furthermore, increased α -synuclein, another hallmark of Parkinson's disease, in substantia nigra and A β deposits were recently reported in HIV infection in older patients but not age-matched healthy individuals [12•]. A recent diffusion tensor imaging study that assessed mean diffusion as a measure of neuroinflammation reported that HIV patients showed over 1 year in time more than the normal aging-related increase of mean diffusion. Moreover, increases in mean diffusion correlated with the global cognitive deficit score [13•].

Altogether, it seems that a lasting and even a well controlled HIV infection may accelerate aging and facilitate the development of neurodegenerative diseases before the manifestation of HAD [6•,11,12•]. Of note, comorbidities, such as infection with hepatitis B or C virus, or drug abuse may contribute in the latter two cases [6•,8•,15].

Potential biomarkers for the development of HIV-associated dementia

Reliable biomarkers for the development of HAD remain elusive. Findings in the pre-HAART era suggested that CD4⁺ cell count and viral load in plasma and cerebrospinal fluid (CSF) correlated with severity of cognitive impairment. Viral load in CSF was considered to predict the development of HAD. In addition, several indicators of inflammation and immune activation as well as excitotoxins in CSF appeared to correlate with neurocognitive deterioration, such as tumor necrosis factor (TNF)- α , monocyte chemoattractant protein (MCP)-1/CCL2, β 2-microglobulin and quinolinic acid. However, HAART can suppress viral load in plasma and CSF, sometimes below the detection limit, improve or restore CD4⁺ cell count and largely reduce the amount of proinflammatory and immune activation factors in CSF [4••]. Although HAD is associated with failed antiretroviral therapy and neuroinflammation, an undetectable viral load does not exclude cognitive decline [4••,5•,8•].

However, efforts continue to identify reliable predictive indicators of HAD. One recent study found that reduced CSF levels of leptin, an important hormonal regulator of energy homeostasis, are associated with impaired learning and memory function in HIV patients [16].

Interestingly, another recent study [17•] found that in HIV patients and in a simian immunodeficiency virus (SIV) model, increased osteopontin in plasma but not CSF correlated with HAD. In the SIV model, increased plasma osteopontin preceded the development of neurological and systemic symptoms of disease. In addition, a separate but related study found that the expression of CD44v6, the osteopontin receptor, is upregulated on blood monocytes only before the development of SIV encephalitis (SIVE) [18•].

A recent metabolomic analysis of CSF based on advanced technology and methodology to determine and analyze molecular mass indicated that heightened levels of distinct fatty acids and lysophospholipids correlated with increased protein expression of phospholipase A2 isoenzyme (PLPA2) and encephalitis in the CNS of SIV-infected rhesus macaques [19].

Given the current lack of predictive biochemical markers and early physical diagnostic parameters for HAD, continuing improvements of in-vivo imaging techniques hold some hope to change the situation. A recent study in the SIV macaque model used a relatively novel approach, factor analysis, to evaluate magnetic resonance spectroscopy (MRS) data, and detected two metabolite patterns of which one correlated with SIV/AIDS and the other with severity of SIVE [20•]. The confirmation of the predictive value of the reported pattern in the human system remains to be seen. However, another recent MRS study found reduced glutamate, the major excitatory neurotransmitter, in frontal lobe white matter of HIV-positive

patients independently of HAART, suggesting a potential early indicator for neurocognitive impairment to come [21]. A third investigation used blood oxygen level-dependent functional magnetic resonance imaging (BOLD fMRI), and found that patients with HAART of low CNS penetration effectiveness (CPE) score show significantly higher response amplitude (increased oxidative stress and associated metabolic demands) than patients with high CPE cART and seronegative controls [22].

Possible pathogenic mechanisms underlying HIV-associated dementia

Recent studies by numerous groups have expanded our understanding of how both host and viral factors may contribute to HAD.

Host factors

Several lines of evidence strongly suggest that HIV-1 associated neurodegeneration and possibly HAD occurs via two major mechanisms. The first and the longest recognized is neurotoxicity as a consequence of either direct exposure to HIV-1 and its fragments or indirect injury through neurotoxins released by infected or immune-stimulated, inflammatory microglia and MΦ in the brain [23]. The second strike of HIV at the brain constitutes the impairment of neurogenesis [24,25•]. At the molecular level, both mechanisms are critically dependent on the HIV coreceptors CCR5 and CXCR4 as well as the stress-related p38 mitogen activated protein kinase (p38 MAPK) [25•,26,27].

However, both proposed pathogenic mechanisms of HAD likely occur side by side with other host-virus interactions. A recent study potentially important for the understanding of all aspects of HIV disease strongly suggests that the pathogenic or nonpathogenic course of HIV/SIV infection may be determined by the reaction of plasmacytoid dendritic cells to the virus, namely the time and amount of interferon (IFN)-α production [28••]. The signaling of Toll-like receptors (TLR)-7 and TLR-9 and in particular the extent of downstream activation of interferon-regulatory factor (IRF)-7 controls how much IFN-α is being produced. Although IFNs are important for an antiviral immune response, the lasting production of IFN-α in HIV/SIV infection seems to cause an erroneous and exhaustive immune activation leading eventually to immune suppression and progression to SIV/AIDS [28••].

Besides immune suppression, the extensive production of IFN-α may be of direct detrimental consequence to the brain, as IFN-α production in HIV-infected CNS correlates with neurocognitive impairment [29]. In this context it seems of interest to consider the obviously contrasting effect of IFN-β, which induces a dominant-negative form of the transcription factor CCAAT-enhancer-binding protein (CEBP)-β and suppression of SIV in MΦ [30], and triggers in MΦ and microglia the expression of β-chemokines MIP-1α, MIP-1β and RANTES, which are natural ligands of the HIV coreceptor CCR5 and inhibit HIV-1 infection and disease progression [31,32].

The contribution of MΦ to the development of HAD remains an important field of research. In normal brain perivascular MΦ, but not resident microglia, are CD163⁺. However, in both HIVE and SIVE, CD163⁺/CD16⁺ MΦ are found in the brain parenchyma and seem to constitute the primary productively infected cell population [33•]. The elevated number of CD163⁺/CD16⁺ monocytes/MΦ may reflect an alteration of mononuclear cell homeostasis in the periphery and are associated with increased viral burden and decline of CD4⁺ T cells. In SIV infection increased viral burden is associated with development of encephalitis and suggests that the CD163⁺/CD16⁺ monocyte/MΦ subset may be important in HIV/SIV CNS disease [33•].

Other recent studies also point toward the importance of the brain-MΦ interaction in HIV infection. Namely, nerve growth factor (NGF) was found to promote the attraction of monocytes by SDF-1/CXCL12 while decreasing HIV-1 replication in those attracted and infected cells [34]. Neurokinin-1 receptor (NK1R), the major ligand of which is the neuropeptide substance P, affects CCR5 in MΦ and NK1R antagonists inhibit HIV infectivity [35].

In the periphery, HIV-1 infection affects the intestinal tract and can cause leakage of bacteria into the blood stream. Such microbial translocation is reflected by elevated lipopolysaccharide (LPS) plasma levels, which is associated with increased monocyte activation and dementia in HIV-infected/AIDS patients [36•]. Moreover, another study suggests that HIV infection increases the vulnerability of the blood-brain barrier in response to LPS and facilitates transmigration of peripheral monocytes/MΦ [37]. These findings further support the important role of monocyte/MΦ and TLRs in HAD and are in line with another recent report that HIV-1 (or its envelope protein gp120) induces expression of TLRs (including the LPS-recognizing TLR-4) in the brain in association with neurodegeneration [38•].

Microglia and MΦ are besides memory CD4⁺T lymphocytes suspected of constituting cellular reservoirs of HIV-1 and thus of playing a potentially crucial role in viral persistence and the eventual progression to HAD [39•].

The potential role of lymphocytes in HAD has been controversial for a long time, but over the years it has been recognized that CD8⁺ lymphocytes play in general an important role not only in the control of CNS infections but also in the preservation of cognitive function. In fact, CD8⁺ T cells could potentially control intrathecal HIV replication [40], and regulatory T cells (T reg) might control myeloid cells and protect cognitive function by inducing in MΦ a cytoprotective M2 phenotype [41•].

Although neurons are usually not productively infected with HIV, they are exposed to viral gene products and virus-induced neurotoxins of microglia and MΦ. A recent study suggests the possibility that the expression of APO-BEC3G in neurons may limit HIV-1 expression in these cells [42]. However, cellular processes that potentially contribute to neuronal demise are stress in the endoplasmic reticulum, reflected by increased expression of BiP and ATF-6 in HIV-positive cerebral cortex [43], and disturbance of neuronal autophagy in HAD [14•].

Viral factors

The two gene products of HIV-1 that have been most intensely studied over the years in the context of HAD besides the intact virus itself are the structural envelope protein gp120 and the regulatory protein ‘transactivator of transcription’, Tat [27]. Recent studies have revealed new potential neurotoxic mechanisms mostly for the latter factor. One study links for the first time Tat to dysregulation of neuronal microRNAs (miR), including miR-128, the upregulation of which inhibits expression of the presynaptic protein SNAP25 [44•]. Tat may in this way compromise synaptic function. Another report describes a Tat-induced pathway to neurite retraction that requires p73, p53 and the Bcl family protein Bax [45]. Finally, a third new possible pathway to neuronal injury seems to involve activation of neuronal ryanodine receptors by Tat, which induces unfolded protein response and mitochondrial hyperpolarization [46].

Therapeutic approaches

As discussed before, HAART maintains a significant effect on the incidence of HAD but cannot prevent the progression of neurocognitive impairment [4•,5•,6•]. To date, at least 22 clinical trials have addressed the treatment for neurological complications of HIV infection including

HAD (often termed ‘AIDS dementia’; <http://clinicaltrials.gov>). Of those trials, 16 have been completed, three are active but no longer recruiting, and three are still recruiting. Unfortunately, so far none of the trials revealed a treatment option that prevents or reverses neurocognitive impairment or HAD. However, a recent investigation used the CPE rank to evaluate whether penetration of a cART/HAART regimen into the CNS was associated with lower CSF viral load and concluded that lower brain penetration of antiretroviral drugs allowed for continued HIV replication in the CNS and consequently higher CSF HIV viral loads and relatively worse cognitive performance [7•]. Thus, devising treatment regimens with the highest possible CPE rank may further reduce the risk for HIV patients of eventually developing HAD, and a clinical trial of CNS-targeted HAART (CIT2) is planned (<http://clinicaltrials.gov>).

The monoamine oxidase (MAO)-B inhibitor selegiline, administered using the selegiline transdermal system (STS), was one of the recently tested antioxidative drugs for the treatment of HIV-associated cognitive impairment [47]. Again, there was no significant benefit found for neurocognitive performance, but this and other previous trials indicated that periods longer than 6 months for treatment and evaluation may be required to achieve significant improvements.

Besides HAART and antioxidants, psychiatric medications, such as serotonin reuptake inhibitors (SRI; citalopram, paroxetine), lithium and valproic acid [both glucagon synthase kinase (GSK)-3 β inhibitors] have been tested as adjunct treatments of HAND and found to have limited beneficial effect [48].

Minocycline, a tetracycline-type antibiotic, has been shown to suppress SIVE via a mechanism that involves inhibition of apoptosis-signal-regulating kinase (ASK)1 and reduction of active p38 MAPK and JNK [49], and is one of the drugs being tested for clinical use.

Maraviroc, the first CCR5 inhibitor approved for treatment, unfortunately shows poor distribution to the CNS but some enrichment in gut-associated lymphocytic tissue (GALT). However, given the previously discussed finding that a compromised bacteria or endotoxin-leaking gut may promote the development of HAD [36•], protection of the GALT could indirectly contribute to the treatment or prevention of HAD [50].

Additional potential therapeutic options for HAD are being explored, including erythropoietin (EPO), insulin-like growth factor, neurotrophins, antibiotics, inhibitors of p38 MAPK, and blockers of Ca²⁺ ion channels, and are awaiting further evaluation [5•,51].

Conclusion

HAD still occurs in the era of HAART, though its onset appears to be delayed and severity reduced, while HIV patients live longer with the infection. Long-term HIV infection may facilitate the development of other neurodegenerative diseases and accelerate aging processes. The pathogenic mechanisms underlying HAD involve neurotoxicity and impaired neurogenesis and seem to heavily depend on the overall condition of the immune system. Although immune suppression and lack of lymphocytes apparently favor cognitive impairment, infected and activated macrophages and microglia seem to be a major factor promoting the development of HAD. Since HAART does apparently not suffice to prevent or reverse HAD, adjunctive and alternative therapies are being explored.

Acknowledgments

M. Kaul is supported by NIH grant R01 NS050621. During the time period reviewed here many more publications on HIV-associated dementia occurred than those explicitly discussed in this article. The author apologizes to all those colleagues whose contribution could not be mentioned due to space limitations.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 329).

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