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Role of the Immune System in HIV-associated Neuroinflammation and Neurocognitive Implications

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Abstract

Individuals living with HIV who are optimally treated with combination antiretroviral therapy (cART) can now lead an extended life. In spite of this remarkable survival benefit from viral suppression achieved by cART in peripheral blood, the rate of mild to moderate cognitive impairment remains high. A cognitive decline that includes impairments in attention, learning and executive function is accompanied by increased rates of mood disorders that together adversely impact the daily life of those with chronic HIV infection. The evidence is clear that cells in the brain are infected with HIV that has crossed the blood-brain barrier both as cell-free virus and within infected monocytes and T cells. Viral proteins that circulate in blood can induce brain endothelial cells to release cytokines, invoking another source of neuroinflammation. The difficulty of efficient delivery of cART to the central nervous system (CNS) contributes to elevated viral load in the CNS, resulting in a persistent HIV-associated neurocognitive disorders (HAND). The pathogenesis of HAND is multifaceted, and mounting evidence indicates that immune cells play a major role. HIV-infected monocytes and T cells not only infect brain resident cells upon migration into the CNS but also produce proinflammatory cytokines such as TNF and IL-1β, which in turn, further activate microglia and astrocytes. These activated brain resident cells, along with perivascular macrophages, are the main contributors to neuroinflammation in HIV infection and release neurotoxic factors such as excitatory amino acids and inflammatory mediators, resulting in neuronal dysfunction and death. Cytokines, which are elevated in the blood of patients with HIV infection, may also contribute to brain inflammation by entering the brain from the blood. Host factors such as aging and co-morbid conditions such as cytomegalovirus co-infection and vascular pathology are important factors that affect the HIV-host immune interactions in HAND pathogenesis. By these diverse mechanisms, HIV-1 induces a

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neuroinflammatory response that is likely to be a major contributor to the cognitive and behavior changes seen in HIV infection.

Keywords

blood brain barrier; cognition; HIV; inflammation; microglia; neuroAIDS; neuroinflammation; virus

1. Introduction

> "A 24-year-old unmarried woman presented with 9 months' history of abnormal behavior and depressed mood, 6 months' history of tremulousness of both hands, and history of urinary and bowel incontinence for 3 months. She stopped taking care of self and started showing disinterest and apathy toward day-to-day activities… impaired sustained attention and recent memory… Magnetic resonance imaging of the brain revealed diffuse cortical atrophy…The CSF analysis showed clear acellular fluid…in view of the relatively rapid onset of cognitive impairment with prominent motor symptoms, the patient was checked for HIV and was found to be positive… diagnosed with HIV-associated dementia. However, she died suddenly before we could initiate antiretroviral therapy.
>
> " (case report, Verma et al., 2013)

More than 30 years have passed since the epidemic presentation of opportunistic infections and other unusual diseases among previously healthy homosexual men in the U.S. It was later termed acquired immunodeficiency syndrome (AIDS) (see Fauci, 2008; Rosca et al., 2012 for a historical perspective). The causal link was made to a retrovirus called human immunodeficiency virus (HIV) (Barre-Sinoussi, 1983; Popovic et al., 1984). Over 25 million HIV-infected (HIV+) people have since died, and over 30 million people are currently living with HIV/AIDS worldwide, one million of whom are in the U.S. The total number of people living with HIV infection in the U.S. has increased in spite of stable numbers of new cases (Center for Disease Control HIV Statistics), which indicates improved survival attributable to effective therapy. As the population with chronic HIV infection grows, more attention must be given to the persistent symptoms that affect a high percentage of individuals living with HIV infection, including neurocognitive impairment (NCI).

It is now widely recognized that microbial infections of a non-CNS origin have an impact on the central nervous system (CNS) and that the immune system plays a major role that is both protective and pathogenic. Over the years, central and peripheral nervous system complications due to HIV infection have been called AIDS dementia complex, HIV encephalopathy, HIV-associated dementia (HAD), neuroAIDS and, more recently, HIV-associated neurocognitive disorders (HAND) (Antinori et al., 2007), reflecting its symptom presentation and severity through the development and evolution of antiretroviral treatments (ART). In this review the term HAND is used, especially, to describe mild and moderate forms of NCI that are observed more often than severe dementia ("HAD") among HIV+ individuals treated with combination antiretroviral therapy (cART). Before ART was available, over half of HIV-infected individuals suffered from HAD, a severe impairment

that includes motor dysfunction. Even being treated with the initial ART (monotherapy), up to 50% of HIV-infected individuals exhibited various degrees of NCI (Grant & Heaton, 1992). cART (or highly active ART, HAART) led to dramatically improved survival of HIV-infected patients and decreased prevalence of overt dementia. Meanwhile, the incidence of HIV-related mild cognitive impairment persists with a significant impact on mortality (Ellis et al., 1997) and quality of life (Heaton et al., 2010). In addition, increased postmortem findings of HIV encephalopathy in the cART era (Neuenburg et al., 2002) imply that prolonged survival leads to a higher number of HIV+ patients continuing to suffer from NCI during the course of their "chronic" disease. Despite great gains in knowledge, much work remains to clarify the cellular and molecular underpinnings of NCI among the HIV-infected, which will inform effective prevention and treatment strategies of HAND.

This review focuses on host immune responses to HIV and their impact on the CNS and neurocognitive function. First, clinical presentations of HAND are discussed. Current knowledge of the pathogenesis of HAND in humans, focusing on immune activation and neuroinflammation, is discussed as are animal and *in vitro* studies that reveal HIV viral and cellular processes. A particular emphasis is given to the mechanisms of HIV transport and immune cell migration across the blood brain barrier (BBB) as critical processes in HIV-induced CNS pathology. Common co-infections among HIV+ individuals such as cytomegalovirus (CMV) are discussed briefly for their documented psycho-neuro-cognitive impact and immune system implications, as they shed light on HIV-related neurocognitive pathology. Lastly, host factors such as aging are highlighted for future research, as growing evidence indicates the importance of HIV-host interactions in the pathogenesis of HAND. Acute infections of the CNS or opportunistic infections by other pathogenic microbes secondary to HIV infection are outside the scope of this review. The clinical manifestations of various CNS infections, including HIV, especially in the aging population, are reviewed elsewhere (see Ellis et al., 2014, chapter 18).

2. Clinical Features of HIV-related Neurocognitive Impairment

Cognitive, behavioral and motor impairments significantly affect daily living of individuals with advanced HAD: inability to complete complex tasks, delayed speech output, loss of initiative, impaired fine motor speeds and skills, unsteady gait, etc. (Ances & Ellis, 2007). However, these severe cases of HAD are becoming increasingly uncommon since the advent of highly effective cART (Joska et al., 2010). Meanwhile, it is troubling to many living with HIV infection and care providers that the rate of mild to moderate cognitive impairment remains high (over 50%) even among individuals who have achieved viral suppression as a result of optimal treatment (Heaton et al., 2011; Robertson et al., 2007). Indeed, the rates of HAND among individuals with mild HIV symptomatology (i.e., CDC stage A based on the previous classification) are higher in the cART era in comparison to those in the pre-cART era (Heaton et al., 2011).

Subtle presentations of mild to moderate HAND and little or gradual change over an extended period of time lead to difficulty in detection and monitoring of the symptoms, necessitating the need for comprehensive and sensitive, yet practical evaluation tools. Periodic administration of comprehensive neuropsychological (NP) tests with proper

normative corrections is useful in diagnosing and evaluating the progression of HAND (Cysique et al., 2011). Validation of truncated NP tests is also important for the cases in which a comprehensive NP test is unavailable. Complementary evaluations such as brain imaging and analyses of soluble markers in cerebrospinal fluid (CSF) can be potentially informative in characterizing HAND. The results of a comprehensive NP testing battery provide domain-specific (e.g., executive function, psychomotor, verbal learning, etc.) and overall neurocognitive performance evaluations that can be followed over time, enabling objective measurements of time-, disease progression- and treatment-dependent changes. Among different domains of NP function, deficits in motor speed, information processing speed and verbal fluency were more often observed before the cART era, whereas impaired learning and executive function are more frequently observed among the individuals treated with cART (Heaton et al., 2011). Both lifetime and current depression rates are greater in HIV+ compared to seronegative individuals, and among HIV+ individuals significantly higher rates of current depression are found in more advanced HIV disease (i.e., CDC-B and C stages) (Heaton et al., 2011). Moreover, HAND is associated with current depressive symptoms regardless of cART treatment status or types (Ances & Ellis, 2007). Thus, potential confounding conditions such as depression and substance abuse should be considered in interpretation of NP test results.

Mild to moderate cognitive impairment rarely progresses to dementia in HIV disease managed with cART, leading to the notion that the clinical course of HAND differs from that of typical neurodegenerative diseases such as Alzheimer's disease (Valcour et al., 2011). At the same time, some of the hallmark neuropathology of typical neurodegenerative diseases have been observed among HIV+ individuals, such as the β-amyloid plaques of Alzheimer's disease and the α-synuclein deposits of Parkinson's disease (Andras & Toborek, 2013; Esiri et al., 1998; Khanlou et al., 2009). Structural brain imaging of individuals with HIV and suspected NCI shows impact on deep grey matter structures and subcortical regions (Valcour et al., 2011) and cerebral atrophy with ventricular enlargement (Ances & Ellis, 2007). Others report neuropathological findings in cortical regions, especially in the cART era (Clifford & Ances, 2013; Heaton et al., 2011). Furthermore, some studies report brain imaging findings in association with neurobehavioral presentations: white matter changes were associated with presentation of apathy (Hoare et al., 2010). Older individuals with HAND exhibited less activation in the left frontal regions ("attention network") and poor performance during the cognitive tasks that required increased attention compared to HIV− and HIV+ individuals without NCI (Chang et al., 2008).

3. Pathogenesis of HAND

Pathogenesis of NCI in HIV infection is multi-faceted. HIV viral load in CSF is generally a better predictor/correlate of NCI than that in blood. For example, elevated viral load in CSF in spite of undetectable viral load in plasma, termed CSF viral escape, was linked to HAND symptoms, including attention deficit, memory complaints and impaired psychomotor speed (Khoury et al., 2013). However, the degrees of correlation between cognitive impairment and CSF viral load are not particularly robust, especially in the cART era, indicating that the pathophysiology of HAND involves more than just the immediate neurotoxicity of the virus.

In rare cases of HIV+ individuals who maintain low plasma levels of HIV-1 RNA in the absence of ART, termed elite controllers, both viral load (Dahl et al., 2013) and inflammatory marker levels in CSF are low (Probasco et al., 2010). The viral control ability of and little disease progression among elite controllers are, thus, in part attributed to strong virus-specific immune responses (Rosenberg et al., 1997; Pereyra et al., 2009) and low non-specific inflammatory responses. This further highlights the significance of the host's immune responses in HIV-related pathology, likely including HAND. Pathogenetic factors of NCI other than HIV virus elucidated to date include infected immune cells that have trafficked into the CNS, infected resident CNS cells such as microglia and astrocytes, and soluble neurotoxic factors, including inflammatory cytokines released by activated cells (infected and non-infected). In contrast to the extensive literature on the pathophysiology of HAND, few studies directly correlate specific neurocognitive outcomes with specific characteristics of HIV-induced CNS pathology.

3.1 CNS tropism by HIV

The role of HIV itself in CNS pathology is evident, given the prompt presentations of HAD in the beginning of the AIDS epidemic and high rates of neurological symptoms found before the cART era. The CNS is particularly vulnerable to invasion by the family of lentiviruses to which HIV belongs (Ances and Ellis, 2007; Valcour et al., 2011; Wiley et al., 1999). In comparison to HAD, the association of NCI, with its more inclusive list of signs and symptoms, with viral loads in CSF and plasma is less consistent (Cysique et al., 2009; Ellis et al., 1997b; Letendre et al., 2004; Nath et al., 2008). Successful viral suppression achieved through cART for the majority of treated HIV+ individuals has led to a markedly reduced prevalence of moderate to severe HIV-associated cognitive, behavioral and motor presentations. Together, these findings indicate that HIV is neurovirulent and neuropathogenic, leading to impaired neurocognitive function. Pathological evidence of brain invasion by HIV includes neuronal loss, synaptic and dendritic damage, astrogliosis, microgliosis and multinucleated giant cell formation (Budka et al., 1991; Everall et al., 1993).

Viral penetration of the blood brain barrier—The HIV virus does not have the capability to enter the CNS via retrograde nerve transmission, but depends on hematogenous spread to the CNS. HIV infection of the CNS is achieved through trafficking of cell-free virus and infected cells from peripheral blood into the brain (Figure 1). HIV interacts with the brain microvascular endothelial cells (BMVECs) in a number of ways (Table 1). Ultrastructural studies show cell-free HIV-1 crosses the BBB by transcytosis in vesicles (Dohgu et al., 2012). These vesicles are likely akin to the processes that underlie adsorptive endocytosis and are usually routed first to lysosomes and subsequently rerouted back to the luminal (blood-facing) surface. However, in some cases, vesicles are routed across to the abluminal (brain-facing) side by transcytotic mechanisms (Banks and Broadwell, 1994). Sialic acid and heparan residues are important to BBB transport of both HIV-1 and its binding protein gp120 (Banks et al., 2001; Bobardt et al., 2004). The binding of viral glycoproteins to cell surface glycoproteins, the hallmark of adsorptive endocytosis, is the general mechanism by which viruses invade cells (Marsh, 1984; Schweighardt and Atwood, 2001). The mannose-6 phosphate receptor, which is used by herpes varicella zoster virus to

enter cells (Hambleton, 2005), has recently been identified as being used by HIV to cross the BBB (Dohgu et al., 2012). In addition, *in vitro* studies strongly suggest that HIV-1 crosses between endothelial cells through disrupted tight junctions by the paracellular route (Fiala et al., 1997). Disruption of the BBB occurs in part from the HIV infection and loss of pericytes (Nakagawa et al., 2012), cells whose loss has been also implicated in BBB disruption in diabetes mellitus and Alzheimer's disease.

All of these processes are enhanced by the proinflammatory environment induced by HIV (Alonso et al., 1997). Specifically, inflammation increases the rate at which free virus and viral proteins cross the BBB (Banks et al., 1999; Dohgu and Banks, 2008). Pericytes of the BBB endothelium enhance the ability of HIV-1 free virus to cross the BBB, presumably mediated by the ability of pericytes to secrete cytokines (Dohgu and Banks, 2013). LPS-stimulation of cultured mouse brain endothelial cells *in vitro* resulted in IL-6 and GM-CSF secretion from the luminal side of the brain endothelial cells that increased uptake and transport of HIV-1; the LPS-induced uptake was blocked by antibodies against IL-6 and GM-CSF (Dohgu et al., 2011). Both IL-6 and GM-CSF acted through mitogen-activated protein kinase ERK 1/2 and p38 mitogen-activated protein kinase dependent pathways. Elevated circulating LPS levels in HIV+ individuals attributed to the increased microbial translocation from the gut (Brenchley et al., 2006) is one of the factors that contributes to chronic immune activation in HIV. Thus, LPS released into the blood stream secondary to HIV-1 induced gastroenteropathy may facilitate entry of HIV-1 into the brain by inducing the release of inflammatory mediators by brain endothelial cells.

Neurotoxicity of HIV proteins—The neurotoxic effects of many HIV-1 proteins (e.g., Gag, Pol, Env, Tat, Rev, Nef, Vpu, Vpr, Vif) are reported primarily in animal and cell culture studies. The viral envelope (Env) or surface glycoprotein (gp)120 targets and binds to the glycoproteins CD4, CXCR4, and CCR5 on helper T cells and monocytes, leading to viral internalization by these cells. These infected cells then cross the BBB. Once in the brain, HIV-infected monocyte/macrophages lead to infection of resident microglial cells and further activate microglia and astrocytes by shedding gp120 (Nottet, 1999). Studies of HIV gp120 transgenic mice show gp120 expression in astrocytes leads to dendritic damage, microgliosis and astrocytosis similar to that seen in neuropathological findings of HIV+ humans (Toggas et al., 1994). Other transgenic mouse studies show that circulating gp120 leads to increased BBB permeability (Cioni & Annunziata, 2002) and increased vascular adhesion molecule expression in brain blood vessels (Toneatto et al., 1999). Thus HIV and its proteins impact the brain and its vasculature through peripheral and CNS pathways. Furthermore, exposure to gp120 *in vitro* results in gliosis and neuronal dendritic damage in human primary forebrain tissue culture (Iskander et al., 2004) and apoptosis of human primary neurons (Jana & Pahan, 2004). The neuronal toxicity of gp120 is thought to be indirect, as gp120-induced neuronal injury was observed only in the presence of macrophages in mixed neuronal glial cell culture (Lipton, 1992). Thus, the effects of gp120 on neuronal viability or function are likely mediated by brain endothelial, macrophage, microglial and astrocytic activation, leading to release of neurotoxins such as inflammatory cytokines, glutamate and quinolinic acid (see Kaul, 2001, 2009 for review).

Although less well investigated, the other proteins of HIV also appear to be toxic to the CNS. A number of studies have reported that treatment of primary neuron cultures with HIV-1 regulatory protein transactivator of transcription (Tat) leads to neuronal dysfunction and injury, which is mediated by microRNA dysregulation (Chang et al., 2011; Eletto et al., 2008; Mukerjee et al., 2008). HIV and simian immunodeficiency virus (SIV) negative regulatory factor (Nef) leads to astrocyte and neural cell death directly and also indirectly via production of IP-10 (Marie et al., 2004). Functionally, Nef expressed in astrocytes results in impaired spatial and recognition memory in rats (Chompre et al., 2012). Post-mortem findings of HIV+ patients with HAD showed expression of Nef in hippocampal neurons (Torres-Munoz et al., 2001), consistent with this protein being involved in the memory impairment of those individuals.

Other HIV impacts on the blood-brain barrier—Another issue of CNS viral tropism with therapeutic implications is the difficulty of achieving complete viral suppression in the CNS; HIV-1 and its proteins act on the BBB to further reduce the entry of anti-viral drugs, maintaining the CNS as a potential reservoir for HIV (Hayashi et al., 2006; Ronaldson and Bendayan, 2006). Many antiviral drugs, including protease inhibitors (PIs; e.g., Ritonavir, Indinavir), a key component of cART, are substrates for brain-to-blood transporters such as P-glycoprotein (P-gp; Kim et al., 1998). Located on the luminal surface of brain endothelial cells, P-gp pumps substances out of the brain and blocks many types of drugs from entering the brain (Begley, 2004). HIV-1, through its induction of inflammatory processes, increases P-gp activity at the BBB (Hayashi et al., 2006). Thus, antiviral drugs are prevented from accumulating to therapeutic levels in the CNS. At the same time, PIs can lower P-gp activity in human thymocytes *ex vivo* and so likely increase intracellular retention of the drug (Haraguchi et al., 2011). It is also plausible that the pathogenesis caused by HIV and viral replication has diverse impacts on different target organs so that neurotoxicity and resulting cognitive outcomes of HIV and viral proteins may be pronounced indirectly, even at relatively low viral levels in the brain. Findings such as the persistence of high rates of mild to moderate HAND even among HIV+ individuals with long-term suppression of viremia (Simioni et al., 2010) support this notion. Given the immediate CNS tropism by HIV upon infection and its impact on neuropathology, better HAND preventive measures (e.g., earlier initiation of cART) and cART regimens with more effective CNS-penetrating drugs are in great need.

Recently, the CNS penetration effectiveness (CPE) ranking system has been applied to various ART drugs (Letendre et al., 2008). The CPE scores for single or combination ART drugs are calculated using the chemical (e.g., molecular weight, protein binding, etc.), CSF pharmacokinetic (e.g., CSF vs. blood concentrations of the drug) and CNS effectiveness (e.g., CSF viral load reduction, cognitive improvement) characteristics of the drugs (Letender et al., 2008; Smurzynski et al., 2011). Evidence indicates that cART regimens with greater CPE scores (e.g., lopinavir, efavirenz) are associated with lower HIV RNA levels in CSF and better performance on neuropsychological tests (Cusini et al., 2013; Marra et al., 2009; Smurzynski et al., 2011; Tozzi et al., 2009). However, the effects of cART regimens that are comprised of drugs with higher CPE scores on survival in patients with or without HAND remain to be determined (Lanoy et al., 2011; McManus et al., 2011).

3.2 CNS migration of immune cells

Some viruses such as HIV readily "seek refugee" in the CNS, which is anatomically and functionally aloof from the peripheral circulation and surveillance by the immune system. Meanwhile, findings increasingly indicate that immune surveillance of the CNS is a critical component in maintaining optimal brain functions and that disruption of immune cell entry into the brain leads to impaired learning and memory and behavioral abnormalities (Kipnis et al., 2008; Schwartz and Shechter, 2010). A recent review re-emphasizes that the choroid plexus is likely a major site through which the immune system (especially, CNS-specializing adaptive immune cells) performs constant maintenance of CNS health (Baruch & Schwartz, 2013). In the case of HIV infection, CNS pathology is not only inadequately controlled but also seemingly facilitated by the immune system. Indeed, CD4 nadir is predictive of HAND (Ellis et al., 2011; Marcotte et al., 2003). This "perfect storm" of immune dysfunction with CNS implications in HIV infection is achieved through a marked decline in adaptive immunity and surveillance via CD4 T cell depletion during viremia and infiltration of the brain by HIV-infected monocytes and T cells, sustaining neuroinflammation.

Blood-borne monocytes—Blood markers associated with monocyte activation, including sCD14 and LPS levels, are elevated in HIV+ individuals with NCI (Ancuta et al., 2008). Monocytes/macrophages are a predominant cell type that infiltrates the CNS in HIV infection. HIV-infected peripheral blood monocytes enter the CNS through the BBB and lead to neuronal death and functional loss that underlie HAD/HAND (Kereveur et al., 1999; Nottet, 1999; Persidsky et al., 1999). In post-mortem brain samples of HIV+ patients with NCI, increased numbers of blood-derived monocytes are found in the brain's perivascular spaces ("perivascular monocytes") (Fischer-Smith et al., 2001). HAD severity is correlated with the accumulation of macrophages in basal ganglia and frontal lobe sections (Glass et al., 1995). In an *in vitro* cellular model of the BBB, HIV-infected monocytes did not cross better than non-infected monocytes, but monocytes activated by LPS treatment and expressing higher levels of TNF-α, IL-6 and IL-10, did cross at a greater degree (Persidsky et al., 1997). Return of macrophages across the *in vitro* BBB back to the lumin (blood) was significantly reduced for those infected with HIV, suggestive that infected macrophages may have a longer residence time once in the CNS than do non-infected monocytes.(Westhorpe et al., 2009). These findings together indicate that cellular HIV infection is not likely an independent factor of monocyte transmigration into the CNS but a crucial step that leads to a cascade of neuroinflammation which then promotes neurotropism of monocytes. Once migrated, the increased residence-time of HIV-infected macrophages in the brain may also contribute to the establishment of HIV viral reservoirs in the CNS and also viral variants (Karris and Smith, 2011).

Some cellular surface markers found on activated monocytes, such as CD16, are implicated in the transmigration of HIV-infected monocytes into the brain. Whereas the majority of circulating monocytes express a high level of CD14 on their surface, about 10% of blood monocytes demonstrate an activated, highly proinflammatory phenotype characterized by expression of CD16 and lower levels of CD14 (Belge et al., 2002; Ziegler-Heitbrock, 2007, 2010). The proportion of circulating monocytes that are CD16+ is increased up to 40% among patients with HIV infection (Ellery and Crowe, 2005; Pulliam et al., 2004),

especially among those presenting with HAND symptoms (Fischer-Smith et al., 2001; Pulliam et al., 1997). CD16+ monocytes transmigrate across the *in vitro* BBB model preferentially in comparison to CD16 negative monocytes in response to exposure to CCL2 (Buckner et al., 2011; Williams et al., 2012). Further, CD16+ monocytes express higher levels of cell migration markers such as the chemokine receptors CXCR5 (Weber et al., 2000), CX3CR1 (Buckner et al., 2011) and integrin CD11b (Hong & Mills, 2008), indicating a high tissue migratory property. The clinical implications of CD16+ monocyte trafficking are not particularly specific to HIV infection and HAND, however, as they are expanded in chronic inflammatory conditions such as atherosclerosis (Heine et al., 2012) and also shown to demarginate more readily under physical stress (Hong and Mills, 2008; Dimitrov et al., 2012) among individuals without HIV infection.

Role of T cells—Growing evidence supports the role of T cells as a CNS-infiltrating cell population in HIV+ individuals with neurological symptoms, especially those receiving cART who are considered immunocompetent (Hornik et al., 2013). Studies of other inflammatory neurological diseases such as multiple sclerosis provide insight on the role of T cells in CNS pathology; for example, CNS-migrating T cells have been found to be memory cells that express high levels of chemokine receptors (CXCR3, CCR5) (Balashov et al., 1999; Guinti et al., 2003). The association between low CD4 count and increased severity of HAND symptoms (Ellis et al., 2011; Marcotte et al., 2003) may simply reflect the HIV disease severity factor in HAND but might also be indicating that CD4 T cells play a protective role against the advancement of HAND. Contradicting to this protective hypothesis (Aubert et al., 2011; Shan et al., 2012) are findings showing that T cells are major players in the development of HAND pathogenesis, especially among the individuals presenting with immune reconstitution symptoms (Antonellie et al., 2010; Gray et al., 2013; Miller et al., 2004). In HIV+ patients, expression of CCR5 and cellular adhesion molecule (CAM) VLA-4 is greater in CD8+ T cells from the CSF than CD8+ T cells from the periphery (Shacklett et al., 2004). We have recently found that CD4+ T cells from CSF also express significantly higher levels of CXCR3 and integrin CD49d compared to those in the peripheral blood and that % CXCR3+ CD4 T cells in CSF is associated with global NCI. This indicates that CNS-migrating T cells play a critical role in HAND (Hong et al., 2013).

Role of brain microvascular endothelial cells—Leukocyte migration through the BBB is mediated by a number of CAMs expressed on BMVECs, including selectins (P-, E-, and L-selectins), intracellular adhesion molecules (ICAMs), and vascular cell adhesion molecules (VCAMs). Leukocytes firmly adhere to endothelial CAMs by expressing Mac-1, lymphocyte function-associated antigens (LFA-1), and very late antigen (VLA-4). Increased brain endothelial cell expression of E-selectin, VCAM, and other binding proteins is critical for passage of HIV-infected immune cells across the BBB (Nottet et al., 1996, 1999). Elevated expression of VCAM-1, LFAs, and ICAM-1 on astrocytes was seen among AIDS patients (Kereveur et al., 1999; Seilhean et al., 1997). The HIV envelope protein gp120 can further increase immune cell trafficking by directly acting upon brain endothelial cells through a protein kinase C (PKC)-dependent pathway (Chaudhuri et al., 2008). HIV-1 also induces IL-6 expression through a signal transducer and activator of transcription 1 (STAT 1)-dependent pathway that, in turn, diminishes expression of BBB tight junction proteins.

These effects should result in facilitation of immune cell trafficking into the brain (Chaudhuri et al., 2008).

3.3 Immune activation and neuroinflammation

CNS infiltration by cell-free viruses and HIV-infected, highly activated monocytes/macrophages and T cells initiates a cascade of neuroinflammation, resulting in marked astrocytosis and microglial activation. Postmortem findings in brain from HIV+ individuals show signs of neuroinflammation (e.g., microglosis, microglial nodules, astrocytosis) even in the cART era (Everall et al., 2009; Kumar et al., 2007). Notably, the primary brain regions that are affected by inflammation are the hippocampus and entorhinal and temporal cortices, areas of the brain particularly associated with memory, during the cART era compared to neuroinflammation found in basal ganglia before the cART era (Anthony & Bell, 2008). In addition, persistent immune activation is recognized as a primary risk factor for neuropathological outcomes in chronic HIV infection. Evidence of cellular players and inflammatory mediators of neuroinflammation in HIV infection includes brain resident and CNS-migrating immune cells and the inflammatory molecules produced by them.

Brain resident cells—Microglia, which are the brain's resident phagocytes, contributing to innate immunity in the CNS, are key regulators of HIV-associated neuroinflammatory processes (see Garden, 2005 for review). As discussed in other sections of this review, brain resident cells become infected with HIV, as cell free virus and infected immune cells transmigrate into the CNS from peripheral blood; as these infected microglial cells achieve viral replication, they further spread the infection within the CNS (Bagasra et al., 1996). Studies with both human brain tissue and primary microglial cultures show that once infected, activated brain microglial cells cause neuronal damage and cognitive dysfunction by releasing neurotoxic agents (Giulian et al., 1990), including inflammatory cytokines such as TNF and IL-1β (Brabers and Nottet, 2006; Walsh et al., 2014; Wesselingh et al., 1997), glutamate (Huang et al., 2011) and quinolinic acid (Guillemin et al., 2005). *In vivo* studies with feline immunodeficiency virus infections show activation of inflammasome genes in microglia, cerebrocortical neuronal loss and neurological deficits (Walsh et al., 2014). Although chemokines and their receptors mediate recruitment of infected peripheral blood cells to the CNS, other chemokines produced by activated microglia, such as fractalkine and MIP-1α/β, may play a protective role (Meucci et al., 2000) and are associated with improved cognition (Letendre et al., 1999). This highlights the importance of the delicate balance between immunocompetence versus over-activation of microglia in maintaining neuronal health. Compared to HIV-infected microglia and perivascular macrophages that are active in HIV viral replication and inflammatory molecule production, astrocytes are thought to play a greater role in chemotaxis and activation of monocytes/macrophages rather than in active viral replication (Muratori et al., 2010). There also appears to be a CXCR4-mediated microglia-astrocyte signaling cascade, leading to the release of the neurotoxin glutamate (Bezzi et al., 2001).

Infiltrating T cells—As aforementioned, CNS-infiltrating monocytes are the primary blood-derived contributors to neuroinflammation in HIV. More recently, pronounced T cell migration into the CNS with findings of neuroinflammation and brain pathology (e.g., white

matter damage, demyelination) were found among individuals who are treated with cART; these individuals exhibit CD4+ T cell recovery and HIV viral suppression and are described as displaying HIV-related immune reconstitution inflammatory syndrome (IRIS) (Antonelli et al., 2010; Venkataramana et al., 2006). IRIS results from the ability of a recovering immune system to mount an intensified inflammatory response to preexisting infections or immune activators. CNS-manifestations of HIV-related IRIS appear to vary, including meningitis and multifocal leukoencephalopathy accompanied by cognitive impairment, with the findings of substantial CNS infiltration by T cells, especially CD8+ T cells in the brain parenchyma (Venkataramana et al., 2006). CNS-infiltrating memory T cells readily produce IFN-γ, contributing to neuroinflammation (Balashov et al., 1999; Guinti et al., 2003). There remains a paucity of studies that investigate functional and inflammatory profiles of CNS-migrating T cells in association with the degree or symptoms of HAND. We recently found that HAND, as measured using a global NP deficit score, was associated with high levels of intracellular IFN-γ expression in and low lytic activity of virus-specific CD8+ T cells found in CSF, myeloid inflammation and persistent HIV in CSF (Schrier et al., manuscript submitted).

Soluble inflammatory mediators in blood vs. CSF—Much effort has been devoted to investigating soluble factors in blood and CSF for discovery of reliable biomarkers of HAND pathogenesis. In addition to the aforementioned TNF, IL-1β and IFN-γ produced by activated monocytes/macrophages, microglia and T cells, HIV+ individuals presenting signs of dementia showed higher levels of chemokines such as MCP-1 and CXCL-10 in CSF (Mehla et al., 2012). Chemokine CXCL-10, also known as IP-10 (a ligand for CXCR3), in combination with HIV-1 is neurotoxic and leads to pro-inflammatory cytokine production (e.g., TNF, IFN-γ). Similarly, exposure to HIV-1 together with TNF and IFN-γ led to greater expression of CXCL-10 in primary human astrocyte cultures than those treated with HIV or cytokines only (Williams et al., 2009). Blood and CSF levels of soluble CD14, an indicator of monocyte activation, were greater in HIV+ individuals who exhibited global cognitive impairment with particular deficits in attention and learning domains (Kamat et al., 2012; Lyons et al., 2011), suggesting that sCD14 is potentially a promising marker of HAND.

IFNs are classically known for their anti-viral effects and are critical in viral control during the early phase of HIV infection. However, growing evidence indicates that chronic activation of type I IFN responses contributes to HIV-associated CNS dysfunction, especially among those with chronic HIV infection (see Pulliam, 2014; Cha et al., 2014 for review). CSF levels of IFN-α was greater in individuals presenting with HAD symptoms (Rho et al., 1995) and correlated with HIV RNA levels in CSF of HAD patients (Perrella et al., 2001). A weak association between blood levels of IFN-α and HAD symptoms suggests that the source of the detrimental CSF IFN-α are cells resident in the brain. Nonetheless, peripheral injection of neutralizing antibody for IFN-α resulted in better performance in reference and working memory tasks and in decreased microgliosis and dendritic loss in a mouse HIV encephalitis model (Sas et al., 2009). Meanwhile, a recent study re-emphasized the significance of the antiviral role of IFN-α by showing that blocking IFN-I receptors increased viral reservoir, T cell depletion and progression to AIDS in an SIV model (Sandler et al., 2014). Furthermore, activation of brain endothelial cells through their toll-like

receptor 3 (TLR3) induces release of endogenous IFNs which, in turn, appeared to suppress the ability of HIV to replicate in brain macrophages *in vitro* (Li et al., 2013). Thus, future research on therapeutic options to mitigate neuroinflammatory cytokine activities such as IFN-α for neuropsychiatric outcomes of HIV, should thoroughly consider such factors as blood and CSF viral load, cART regimen, HIV disease state/course, etc.

4. Other considerations in HAND pathogenesis and progression

4.1 Aging and immunosenescence

Chronological aging is a risk factor for a general decline of cognitive function in both healthy and diseased populations, and aging can be a synergistic factor in NCI in HIV+ individuals. More than half of the approximately 1.3 million HIV+ individuals in the U.S. will be more than 50 years old by 2015. This remarkable success of cART in controlling the virus and significantly extending the lifespan of HIV+ individuals is accompanied by a range of aging-related symptomotology, including increased risk for neurodegenerative diseases. What is more troubling is that aging-related complications appear to occur at a much younger age among HIV+ individuals, including the premature onset of cardiovascular disease, cerebrovascular diseases and NCI. The risk of HAD increased by 1.6 fold per decade of age in the pre-cART era, but in the cART era, risk for cognitive impairment was 3-fold greater in HIV+ individuals aged > 50 after adjusting for covariates (Valcour et al., 2004). Factors affecting brain dysfunction, especially in older HIV+ individuals, may include prolonged exposure to HIV and cART, age-dependent acceleration of HIV pathogenesis, interaction with other age-dependent neurological diseases and age-related changes in cART toxicity. The literature suggests a greater rate of NCI in older compared to younger HIV+ individuals, albeit the interaction between age and HIV is small. This may suggest that much of the effect of age on HAND is attributed to conditions co-morbid with aging, such as immune activation, metabolic disease, and vascular pathology (see Valcour et al., 2004, Wendelken & Valcour, 2012 for review). As discussed in earlier sections of this review, persistent inflammation, both peripheral and CNS, lies at the center of HAND pathogenesis, and accelerated immunological aging in HIV+ individuals due to chronic viral infection has been the topic of aging-related morbidity discussions (see Hunt, 2014 for review). The data also suggest a greater decline of naïve T cells with advancing age in HIV+ individuals, which contributes to immunosenescence (Appay et al., 2011). The independent effect of accelerated immunosenescence and chronic immune activation on HAND among aging HIV+ individuals is of great clinical significance and warrants systematic longitudinal research.

4.2 Vascular pathology

While many mechanisms might explain the interactive effects of age and HIV on the CNS, a likely candidate may involve emergent vascular pathology. Similarly to cardiovascular disease in HIV, age-related cerebrovascular diseases occur prematurely in HIV+ compared to HIV-seronegative individuals. For example, the number of hospitalizations for stroke are increased in HIV patients by an alarming 60%, in spite of a decreasing stroke occurrence in the general population (Ovbiagele & Nath, 2011). HIV and aging-related cerebrovascular dysfunction likely contribute to accelerated changes in BBB permeability, microvascular

disease, and also large vessel disease and stroke observed in older HIV+ individuals (Corral et al., 2009; Dobbs & Berger, 2009). Chronic immune activation with its induction of cerebrovascular inflammation is a promising mechanism, especially given the burgeoning literature of immune-activation-related vascular pathology and cardiovascular disease in HIV (Hsue et al., 2004). As with atherosclerotic lesions in the cardiovascular system, HIV-infected blood monocytes that infiltrate the brain and those that differentiate into activated perivascular macrophages may play a major role in CNS vascular pathology.

4.3 HIV co-infections with Cytomegalovirus or Hepatitis C: CNS implications

Neurocognitive symptoms in HIV+ individuals can be a result of HIV infection itself but can also result from opportunistic infections. Co-infection with the herpes virus, cytomegalovirus (CMV), is prevalent among HIV+ individuals; over 90% are CMV seropositive. Severe complications such as retinitis, leading to blindness, are caused by primary infection or reactivation of CMV among immunocompromised HIV+ patients or those experiencing IRIS. Meanwhile, latent CMV co-infection does not appear to have significant implications for the course of HIV disease among those receiving cART. However, growing evidence indicates a role for CMV in HAND among treated HIV+ individuals (Barrett et al., 2012; Letendre et al., 2012). CMV-associated CNS complications among those receiving cART differ from cognitive presentations of overt neurologic complications, including HIV-associated CMV encephalitis, which is seen among those with advanced-stage HIV disease (McCutchan, 1995). Proportions of CMV-responding T cells were considerably higher in blood of HIV+ than seronegative individuals (Naeger et al., 2010). Furthermore, CMV-specific CD8+ T cells have been detected in the CSF of HIV-infected individuals, although at lower frequency than that in blood (Shacklett et al., 2004). A large literature outside of the HIV field indicates an impact of CMV on the CNS and cognition (Cheeran et al., 2001; Tarter et al., 2013) and on CMV-derived persistent immune activation and immunosenescence (Pawelec et al., 2009). The relative contribution between latent CMV and HIV to HAND in an HIV+ population is difficult to determine, as the majority of HIV+ individuals are CMV-infected. Nevertheless, the critical role of CMV in HIV-related cognitive impairment via persistent immune activation warrants further investigation.

Chronic blood-borne viral infection with hepatitis-C virus (HCV) has also been a topic of investigation in HIV research. HCV is detected in the brain of HIV+ individuals post mortem (Letendre et al., 2007). HCV infection was associated with worse NP performance and greater NP impairment rates regardless of HIV status and with higher levels of HIV RNA, MCP-1, TNF, and sTNF RII in CSF of HIV+ individuals (Letendre et al., 2005). HCV-HIV co-infection is more detrimental to neurocognitive function, even when the viral load of HIV is suppressed (Laskus et al., 2005; Rempel et al., 2013). Co-infected individuals also exhibit greater monocytic type-1 IFN response genes (Rempel et al., 2013) and greater frequencies of activated CD4+ and CD8+ T cells (Feuth et al., 2013) compared to mono-infected individuals. One of the most frequent side effects of IFN therapy, which is widely used in treating HCV, is development or worsening of depression (Udina et al., 2012). Thus, CNS-related complications in chronic HCV disease may be attributed to both HCV and its treatment. Nonetheless, evidence suggests that persistent immune activation and

inflammation likely underlie the impact of HCV-HIV co-infection on the CNS and, in turn, on cognition and mood.

5. Future Directions and Therapeutic Implications

In spite of a significant decline in frank dementia in HIV infection, owing to successful viral suppression through greatly enhanced cART efficacy, prevalence of mild to moderate HAND persists and is even on the rise. With a considerably increased survival rate and extended life span for the HIV-infected, the number of individuals experiencing HAND symptoms is likely to continually increase. Meanwhile, HAND rarely progresses to dementia, which suggests that the pathophysiology of HAND differs from that of a typical neurodegenerative disease such as Alzheimer's disease. Also, imaging and autopsy studies show non-focal, diffuse neuropathological findings, which indicate the broad effects of the pathogenesis of HAND on the CNS. In spite of some evidence of HIV-induced neuronal injury in the hippocampus (Anthony & Bell, 2008; Torres-Munoz et al., 2001) and impaired memory functions found in the aforementioned animal models and clinical studies, the specific associations between neuropathological findings and clinical neurocognitive symptoms in HIV remain unclear.

There exists ample evidence that HIV infiltrates into the brain and replicates in brain resident cells other than neurons. Plasma and CSF viral loads and CSF leukocyte numbers appear to be associated among HIV+ viremic individuals and individuals undergoing ART treatment interruption, but this virus-immune relationship is inconsistent among individuals receiving cART. These suggest peripheral HIV infection readily affects the CNS, but peripheral viral suppression through cART often does not achieve suppression of CNS viral replication and immune cell infiltration. The best evidence points to a persistent neuroinflammation induced and maintained by virus, infiltrating immune cells, and brain resident cells, resulting in neurotoxic inflammatory mediator production and ultimately leading to neuronal damage and cognitive impairment in chronic HIV infection.

In developed countries, the clinical implications and therapeutic management of HIV-related diseases have become those of a chronic disease rather than of an acute, fatal condition. Hence, there is an increased need for long-term management strategies for chronic neurocognitive and psychological pathology in individuals living with HIV. Those mechanisms potentially shared by cardiovascular and cerebrovascular pathogenesis in aging HIV+ individuals especially warrant careful investigations. Growing evidence indicates that increasing cardiovascular pathology seen among HIV+ individuals is also in part mediated by persistent immune activation and inflammation (Hsue et al., 2006; Parrinello et al., 2012), which indicates shared pathogenesis factors affecting various end organs. The impact of chronic immune activation on vascular pathology presents a promising direction for future research: cerebrovascular pathogenesis and NCI among HIV+ individuals. Given the evidence of seemingly synergistic effects of co-infections such as CMV infection on HAND, early screening for prevalent co-infections with neurocognitive implications would be beneficial.

In spite of a high HAND rate, not all HIV+ individuals present/experience the symptoms of cognitive impairment. The cause of this inter-individual variability remains unanswered, although a burgeoning literature emphasizes the importance of viral and host genetic factors (Karris and Smith, 2011). In addition, growing evidence that immune activation and neuroinflammation are primary factors in HAND highlights the significance of the host's immune responses and host-virus interactions in HAND pathogenesis. Thus, future therapeutic strategies to mitigate HAND should carefully reflect on its multifactorial pathogenesis, including a personalized medicine approach with consideration for the genetic factors that drive the host immune and virus interactions. Various other host factors that may moderate HIV-1-induced neuroinflammatory responses, including behavioral factors, warrant further research.

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Research highlight

This review highlights the HIV-immune interactions, leading to neuroinflammatory responses, which are likely key in the pathogenesis of HIV-associated neurocognitive impairment.

Highlights

- HAND affects a high percentage of HIV+ individuals in spite of viral suppression.
- Host's immune responses, leading to neuroinflammation, appear crucial.
- CNS infiltration by HIV and immune cells through the BBB is a key process.
- Host factors such as age and CMV co-infection are important moderators of HAND.

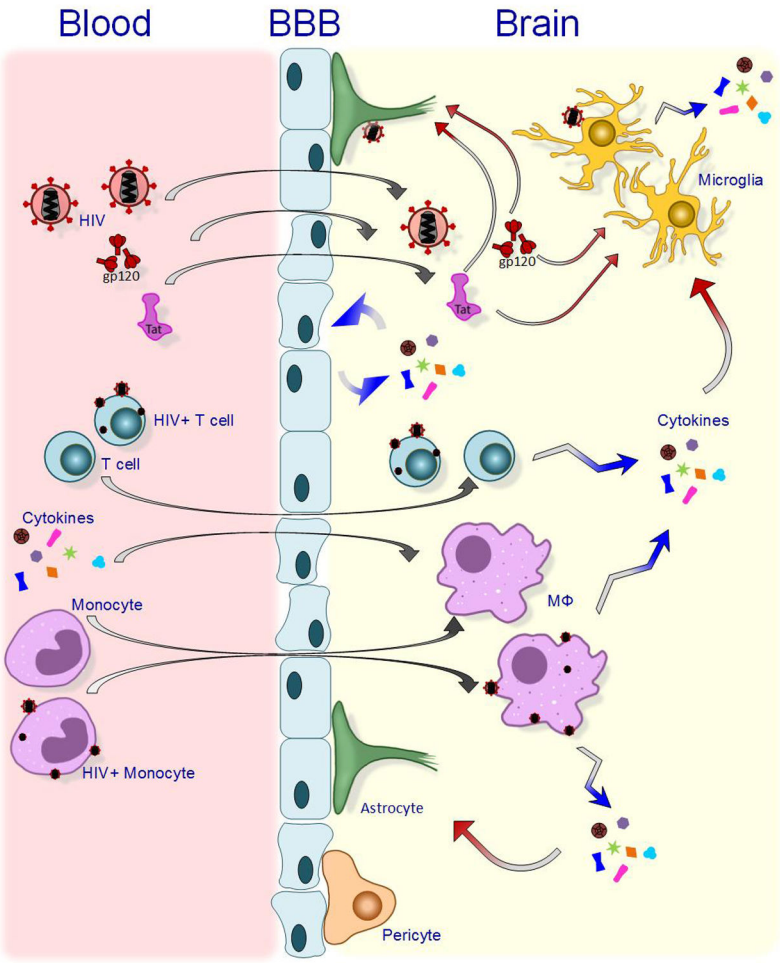

Figure 1.

Viral and cellular transmigration from peripheral blood to the brain in neuroinflammation of HIV disease. The evidence shows a number of ways by which HIV, viral products and infected or activated immune cells infiltrate the CNS through the blood-brain-barrier (BBB), as illustrated in this schematic. Firstly, HIV and its viral proteins (gp120, Tat) cross the BBB via transcytosis or paracellularly and infect microglia and astrocytes, which are then activated, releasing inflammatory cytokines. This cascade of events leads to neuronal death. Secondly, HIV-infected monocytes and T cells migrate to the brain, and macrophages and activated T cells lead to neuroinflammation by infecting microglia and astrocytes and by releasing inflammatory cytokines that further activate microglia and astrocytes. HIV-infected microglia are active in viral replication and inflammatory molecule production. Thirdly, inflammatory cytokines in blood are shown to cross the BBB. Fourth, luminal endothelial cells of the BBB also release cytokines that can further activate BBB endothelial cells and other cell types in the brain, which contributes to compromised BBB integrity and facilitates the infiltration of virus and immune cells. Lastly, evidence also shows the contribution of pericytes to BBB disruption and HIV transmigration.

Table 1

Interactions between the blood-brain-barrier (BBB) and HIV

Mechanisms involving the BBB in HIV Infection
Passage of HIV Cell-free Virus Across the BBB • Transcytotic (Mannose 6 Phosphate Receptor Dependent) • Paracellular (Tight Junction Dissolution)
Passage of HIV-1 Proteins (gp120, Tat) Across the BBB
Increased Immune Cell Trafficking Across the BBB • Activated & Infected T Cells • Activated & Infected Monocytes
Transport of Cytokines Across the BBB
Induction of Cytokine Release from Barrier Cells
Increased BBB Leakiness
Brain-to-blood Efflux of Antivirals • Protease Inhibitors by P-glycoprotein • AZT by Organic Ion Transporter
Altered BBB Transporter Expression and Function (e.g. P-glycoprotein)
Neurovascular Unit Effects