

## Editorial NeuroAIDS review

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### Introduction

NeuroAIDS is a disease that incorporates both infectious and degenerative pathophysiologic pathways. It has a known cause, has several animal models, and is under investigation and treatment using multiple avenues, *in vivo* and *in vitro* [1–7]. Select highlights from the spectrum of NeuroAIDS research predominantly related to human immunodeficiency virus-1 clade B (HIV-1B) are reviewed below.

### Clinical

#### Diagnosis, neurology, and neuroimaging

HIV-1 invades the central nervous system (CNS) early and can cause persistent infection and inflammation. Although early infection is typically asymptomatic,

cerebrospinal fluid (CSF) analysis and magnetic resonance spectroscopy (MRS) imaging can detect CNS abnormalities during this period [8–11].

Chronic HIV-1 infection can result in neurodegenerative disease, overall termed NeuroAIDS. The clinical expression of this process includes neurocognitive impairments such as decreased attention/concentration, psychomotor speed, memory, learning, information processing, and executive function. There is also motor slowing, incoordination, and tremor, that may progress to disabling weakness, spasticity, extrapyramidal movement disorders, and paraparesis [12,13]. In addition, there may be behavioral effects such as apathy and irritability. Psychomotor retardation (associated with damage to the frontal-striatal systems) also may occur [14,15]. The clinical severity of this process ranges from asymptomatic neurocognitive impairment (ANI), to a mild neurocognitive disorder (MND), to full-blown HIV-associated

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dementia (HAD) [16]. The clinical nosology applied to this process has evolved, from the original AIDS dementia complex (ADC) [13], to HIV-associated cognitive-motor complex (HIVCMC) [17], and most recently to HIV-associated neurocognitive disorders (HAND) [16].

HIV-associated neurocognitive disorders were first identified in individuals with advanced AIDS, who had for example opportunistic infections, high viral loads, and elevated markers of immune activation. The development of HAND is influenced by host and viral characteristics, comorbid factors, substance abuse, and antiretroviral therapy. Although older literature focuses on HAD, milder forms of HAND (MND, ANI) were recently reported to be common in highly active antiretroviral therapy (HAART)-treated individuals with partial immune reconstitution, higher CD4<sup>+</sup> cell counts, and suppressed viral loads. This is consistent with the decline in the incidence per 1000 person-years of HAD from 6.49 in 1997 to 0.66 in 2006 and associated with the introduction of HAART in 1996 [18]. More recently, HAND showed decreased association with immune activation and had a more diffuse range of neuropsychological deficits that may overlap with other brain diseases [18–21].

In-vivo studies of HAND have utilized neuroimaging techniques including MRS, functional MRI (fMRI), and morphometry. MRS measures brain biochemistry, fMRI measures changes in blood flow related to neural activity in the brain, and morphometry models quantitative changes in neuroanatomical structures. These techniques also have been used to detect changes in the brains of asymptomatic HIV-1-positive patients [10,14,22].

### Aging and neuropathology

In the US, the percentage of HIV-1-positive individuals, 50 years of age and older, increased from 19% to more than 25% between 2001 and 2005, primarily due to HAART-related increased survival. Seniors often present with advanced HIV-1 disease because an AIDS diagnosis was overlooked [18]. Aging adversely affects both cell-mediated and humoral immunity. Older HIV-1-positive persons tend to progress to AIDS and to die more rapidly, and increased age is a strong risk factor for HAND. Comorbid conditions, the cognitive changes that occur in 'normal' aging, and the increased risk for neurodegenerative diseases all present major difficulties in the assessment of neurocognitive impairment in older HIV-1-positive adults [23,24]. The diagnostic and neuropathological characteristics of some of these conditions and those of HAND are summarized in Table 1 [25–44].

Immune dysfunction, inflammation, and hyperlipidemia are features of HIV-1 infection (and its treatment) and are risk factors for Alzheimer's disease in the elderly. Likewise, increased amyloid has been reported in HIV-1-positive brain tissue (Fig. 1), possibly because HIV-1 Tat protein inhibits amyloid degradation. Moreover, Tat

production, HAART, and aging may also result in increased phosphorylation of tau protein in the hippocampus. Expression of alpha-synuclein is increased in the substantia nigra of some HIV-positive brains. In the setting of HIV-1, these findings of the accumulation of abnormal proteins may point to common pathways activated in multiple brain diseases, possibly by brain inflammation [45–50].

### Drug abuse

Drug abusers with HIV-1 infection have higher viral loads, increased immunosuppression, more severe cognitive impairment, and neuropathological changes. However, causality is difficult to ascertain because drug abusers (commonly poly-drug abusers) are often non-compliant with medications and ambiguous in self-report [51,52].

In-vitro studies show that opiates, cocaine, and methamphetamine potentiate HIV-1 replication and synergize with HIV-1 proteins to cause glial cell activation, neurotoxicity, and breakdown of the blood–brain barrier [53]. The opioid system has dichotomous effects on HIV-1 replication. Mu receptor stimulation increases HIV-1 infection via increased expression of chemokine receptors (CCR3, CCR5, and CXCR4), that are also co-receptors for HIV-1 [54], whereas kappa receptor activation decreases CCR5 expression [55]. Opiates activate HIV-1 replication in latently infected macrophages and cocaine increases HIV-1 replication in macrophages via production of IL-10 [56,57]. In addition, cocaine increases HIV-1 replication in astrocytes and in dendritic cells (by up-regulation of DC-SIGN) [58,59] and methamphetamine increases HIV-1 infection via dopamine receptor signaling leading to up-regulation of CCR5 [60]. Moreover, cocaine and methamphetamine may both accelerate the development of HAND through increased dopamine, macrophage infiltration, and HIV-1 replication [61].

Cocaine and methamphetamine enhance monocyte migration across the blood–brain barrier involving disruption of endothelial cell tight junctions. Cocaine increases adhesion molecule expression [53], whereas methamphetamine up-regulates inflammatory genes in endothelial cells [62]. Morphine alone does not alter the blood–brain barrier; however, in combination with HIV-1-Tat protein, it alters tight junction expression [63]. Morphine withdrawal and associated stress also damages the blood–brain barrier [64]. Morphine and cocaine separately are not toxic to striatal neurons, but they each substantially potentiate Tat neurotoxicity [65]. For example, in a Tat transgenic mouse model, morphine caused shortening of dendrites [66]. Cocaine potentiates Tat-mediated glial cell activation and oxidative stress [65,67]. In post-mortem human brains, selective degeneration of pyramidal neurons and interneurons in the neocortex and limbic system have been associated

**Table 1. Diagnosis (clinical and neuropathology).**

Clinical condition	Selected key clinical diagnosis/signs/symptoms	Selected key findings on pathological examination of post mortem brain	References
HAND	At this time, there is no single, agreed-upon, diagnostic biomarker of HIV-associated neurocognitive disorders (HAND). Rather, HAND remains a clinical diagnosis, made in those HIV-1-positive individuals who manifest cognitive decline and in whom other conditions can be excluded by clinical and laboratory tests, such as other CNS infections, metabolic diseases, and depression. This requires a holistic appreciation of the individual's virologic and immunologic status, other medications/recreational drugs, and comorbid diseases, as well as the neurological and neurocognitive examination. In general, HAND is not associated with a decreased or fluctuating level of consciousness, focal findings such as hemiparesis, hemianopsia, or aphasia, or systemic signs of meningismus or fever. The neurological examination may be normal, or show diffuse, symmetrical abnormalities in the pyramidal and extrapyramidal motor systems, hyper-reflexia, and frontal release signs. Similarly, key neurocognitive findings are nonlateralizing. Key findings include motor and psychomotor slowing, decreased attention and concentration, decreased executive function, information processing, learning and memory. In particular, working (short-term) memory is affected early on, and is consistent with a mixed encoding and retrieval profile. In contrast, the memory loss in Alzheimer's disease consists of rapid forgetting due to inability to process novel information.	The neuropathologic examination is in large part dictated by the clinical setting and by what is easily seen using tissue sections stained with hematoxylin and eosin (H&E). Unfortunately, many changes are not strictly associated with a particular clinical diagnosis, are nonspecific, and do not lead to a diagnosis. For example, the neuropathologic evaluation in the case of HIV-1-positive individuals with neurocognitive deficits, seeks to identify positive evidence of HIV-1 in the CNS as well as any conditions clinically expected or otherwise that may be causing or contributing to the deficits. However, particularly given the widespread use of antiretrovirals, the presence of HIV-1 in the brain at autopsy is neither necessary nor sufficient for the clinical diagnosis of any level of neurocognitive damage in HIV-1-infected patients.	[16,25,26]
Asymptomatic neurocognitive impairment (ANI)	Normal level of consciousness. Neurological examination is nonfocal. Subclinical neurocognitive impairment as diagnosed by neuropsychological testing (e.g. global rating <5), and no significant impairment of activities of daily living.	Usually minimal and nondiagnostic and/or related to treatment or comorbid conditions.	[16,25,26]
Minor neurocognitive disorder (MIND)	Normal level of consciousness. Neurological examination is nonfocal. Mild decline in cognition in addition to mild everyday functioning impairment and affects the more difficult activities of daily living.	Usually minimal and nondiagnostic and/or related to treatment or comorbid conditions.	[16,25,26]
HIV-associated dementia (HAD)	Normal level of consciousness. Neurological examination is nonfocal, or may demonstrate spasticity and/or extrapyramidal signs. Significant decline in cognition (e.g. global rating >7) along with major functional impairment, that affects routine activities of daily living.	In untreated or inadequately treated cases, findings may include multinucleated giant cells and/or immunoreactivity for HIV-1 antigens in the brain. These findings indicate the presence of HIV-1 in the brain but the correlation with HAD is not one-to-one and only nonspecific atrophy and gliosis may be seen, especially with ART exposure.	[16,25,26]
Other neurodegenerative conditions	Mild cognitive impairment	When MCI is 'amnesic', then it usually evolves into AD and would likely have some pathology. However, MCI is also used to describe 'nonamnesic' conditions, and would therefore be a potential precursor to non-AD conditions. Possibly, one might expect to detect the beginnings of neuropathological changes in patients with MCI of a nonamnesic nature as with amnesic changes. Indeed, neuropathological changes are variable in MCI ranging from no significant changes to changes seen in degenerative diseases including AD and diffuse Lewy body disease. Moreover, MRI scans of patients with MCI can detect progressive brain gray matter loss in some of these patients.	[27-30]

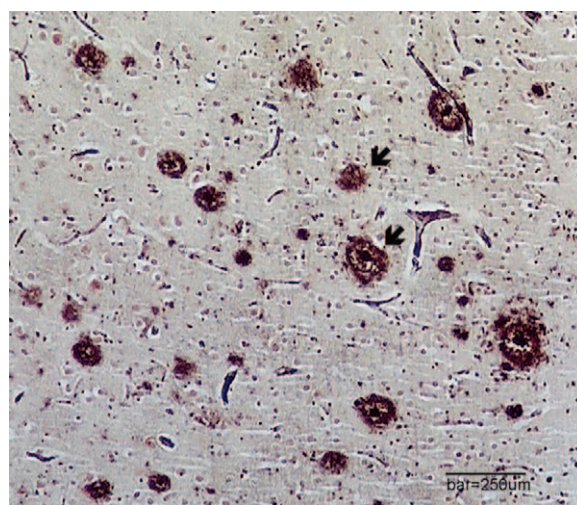
Table 1 (continued)

Clinical condition	Selected key clinical diagnosis/signs/symptoms	Selected key findings on pathological examination of post mortem brain	References
AD	Clinically pertinent in age-appropriate HIV-1-positive and those with genetic markers for familial AD. Presence of an early and significant episodic memory impairment that includes gradual and progressive change in memory function over more than 6 months; objective evidence (e.g. neuropsychological testing) of significantly impaired episodic memory functioning; the episodic memory impairment can be isolated or associated with other cognitive changes.	Cortical atrophy with relative sparing of primary sensory and motor cortices; amyloid plaques and neurofibrillary tangles.	[31]
Diffuse Lewy body (DLB) disease	Dementia denied as progressive cognitive decline sufficient to interfere with daily functioning. Memory deficits may not be prominent. In addition, two or more of the following for diagnosis of probable DLB, or one for diagnosis of possible DLB. Fluctuating cognition with pronounced variations in attention and alertness; recurrent visual hallucinations that are typically well formed and detailed; spontaneous features of Parkinsonism.	Alpha-synuclein positive Lewy bodies in the cerebral cortex and other areas of the brain.	[32]
Vascular dementia	Clinically pertinent in age-appropriate HIV-1-positive individuals that manifest focal clinical signs and symptoms, stepwise or fluctuating pattern, with historical, clinical or laboratory evidence of significant vascular disease, evidence of cerebrovascular disease or stroke on imaging. Dementia, as defined as a decline in cognitive functioning, including memory impairment and at least two other cognitive domains. A clear temporal relationship between vascular disease and dementia.	Loss of brain tissue due to infarction, often multifocal, intimal and medial thickening with and without atherosclerosis cerebral blood vessels.	[33,34]
Other CNS infections Neurosyphilis	Symptoms include cognitive deficits, meningitis, and stroke. Diagnosis confirmed by positive CSF VDRL, but some cases may require empiric treatment due to the low sensitivity of this test.	Chronic, plasma cell rich meningo-encephalitis; spirochetes identified by various methods.	[35,36]
CNS tuberculosis	Symptoms of chronic meningo-encephalitis, such as altered level of consciousness, cognitive impairment, headache, small vessel stroke. Diagnosis confirmed by CSF acid-fast bacterial culture or PCR.	Granulomas usually basal lepto-meningeal; acid-fast bacilli identified by culture or special stain.	[36]
Chronic fungal meningitides	Usually present as subacute meningitis or meningo-encephalitis with fever, malaise, headache, and impaired cognition. Diagnosis is confirmed by positive CSF India ink ( <i>Cryptococcus</i> ), fungal cultures, and/or serology. In some cases, diagnosis is made empirically, when there is documented extra-neural infection and no other cause for neurological symptoms.	Inflammatory infiltrate varies; identification of organism by culture or special stain.	[36,37]
CNS toxoplasmosis	Definitive diagnosis can be made by brain biopsy; probable diagnosis can be established in patients with encephalitis, enhancing brain lesions surrounded by edema on MRI or CT, positive IgG toxoplasma serology and clinical response to antitoxoplasma treatment.	Inflammation variable: identification of organism by routine examination or immunohistochemistry.	[37,38]
PML	Progressive focal neurologic deficits, such as aphasia, hemiparesis, hemianopsia, usually corresponding to space-occupying white matter lesions on MRI. Definitive diagnosis can be made in patients with symptomatic brain lesions by brain biopsy or positive CSF JCV PCR; however, the latter is relatively insensitive.	Demyelination with viral inclusions in oligodendroglia cells: may confirm with immunohistochemical stain for polyoma virus.	[38,39]
CMV encephalitis	Presenting CNS syndromes include cognitive impairment, delirium, cranial neuropathies, ataxia, myelitis, and polyradiculopathy. The demonstration of CMV by CSF PCR or in brain tissue in a patient with a compatible clinical syndrome establishes the diagnosis.	Various lesions, often ependymitis: identification of organism by characteristic inclusions or by immunohistochemistry.	[38,40]

**Table 1** (continued)

Clinical condition	Selected key clinical diagnosis/signs/symptoms	Selected key findings on pathological examination of post mortem brain	References
CNS tumor Primary CNS lymphoma	Symptoms (such as headache, personality changes, cognitive dysfunction, seizures or focal motor signs) are referable to one or more brain mass lesions, typically contrast enhancing; biopsy remains the standard of diagnosis. Most patients have very low (<50 cells/ $\mu$ l) CD4 <sup>+</sup> cell count. Detection of Epstein–Barr virus by CSF PCR is highly suggestive.	Identification of neoplastic lymphoid infiltrate, usually high-grade B cell, by immunohistochemistry and other methods.	[36,38]
Toxic-metabolic encephalopathies Hepatic failure	Fluctuating level of consciousness, disturbed sleep, personality changes, delirium; extrapyramidal signs in advanced cases; abnormal psychometric tests; slow EEG with triphasic waveforms; elevated serum ammonia.	May see Alzheimer type II gliosis.	[41,42]
Chronic hypoxemia	Symptoms of headache, disorientation, somnolence, diagnosed by low $pO_2$ , acidosis, and elevated $pCO_2$ .	Hypoxia/ischemia can accompany some toxic-metabolic conditions in which case there may be neuronal loss most frequently of vulnerable cells such as hippocampal pyramidal cells.	[43,44]
Depression	Complaints of memory loss are out of proportion to actual loss of function as measured by neuropsychological testing and/or activities of daily living. No associated neurological signs or abnormal imaging.	No identified pathological variable in HIV-1-positive.	[26]

This table shows selected key clinical diagnoses, signs, and symptoms in NeuroAIDS and potential neuropathological correlates (when they occur). Other comorbid and complicating neurodegenerative conditions, infections and toxic encephalopathies are mentioned as well: AD, Alzheimer’s disease; CMV, cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalography; IgG, immunoglobulin G; PML, progressive multifocal leukoencephalopathy; VDRL, venereal disease research laboratory.



**Fig. 1. Amyloid-containing plaques (arrows) in the frontal cortex of a demented 69-year-old HIV-1-positive woman.** Clinically, HIV-associated neurocognitive disorder was only one factor contributing to her dementia. At death, her brain contained numerous amyloid plaques and tau-neurofibrillary tangles (not shown), typical of AD (modified Bielschowsky silver stain, bar equals 250  $\mu$ m). AD, Alzheimer’s disease.

with cognitive alterations in methamphetamine and cocaine users [68]. Loss of calbindin and parvalbumin interneurons correlates with memory deficits in HIV-1-infected methamphetamine users [69].

**Treatment**

Goals for treatment of NeuroAIDS include suppressing HIV through optimizing HAART and treating associated psychiatric, neurological, and neuropsychological dysfunctions including mood disorders, substance abuse, and painful peripheral neuropathies. Whereas it is commonly accepted that antiretroviral therapy ameliorates HAND, there is debate about the best regimen for HAND. Moreover, whether brain and CSF penetration play a role in treatment efficacy is under investigation as well. One study reported that neuropsychological test scores improved after a HAART regimen with high penetration and another study indicated no improvement, irrespective of blood–brain barrier penetration [70,71]. Additional studies suggested antiretroviral drugs with better CSF penetration improved outcomes [72–76]. Such studies include brain assessment by examination of CSF when CNS proteins and metabolites can be found, as well as by direct imaging techniques including MRI [72,75].

Palliative and adjunctive therapy of HAND [palliative therapy ameliorates symptoms without affecting the disease and adjunctive therapy does not treat the known cause of HIV-1 by reducing viral replication, but treats the downstream effects (e.g. neurodegeneration)] may improve the patient’s ability to function. For example, since depression may be an important confounder in the

diagnosis of HAND and reduces quality of life, HIV-1-positive individuals should be screened for mood disorders, and these can be treated with antidepressants [3]. In addition, methylphenidate and other psychostimulants, often used for attention deficit disorders, may help to reduce apathy and improve psychomotor slowing in HAND. Several drugs were investigated as potential neuroprotective agents. In a phase II randomized controlled trial within the Adult AIDS Clinical Trials Group (ACTG), adults with mild to severe ADC, receiving stable antiretroviral therapy and memantine treatment, showed improvement of MRS parameters in the brain; however, there was no significant clinical improvement [77]. Likewise, a trial of selegiline, a monoamine oxidase (MAO)-B inhibitor with antioxidant and neurotrophic properties, passed safety assessment in phase II studies in cognitively impaired HIV-1-positive patients, but failed to demonstrate cognitive or functional improvement [78]. An anticonvulsant (and mood-stabilizing) drug, sodium valproate (VPA) inhibits the activity of the glycogen synthase kinase-3-beta (GSK-3 $\beta$ ) pathway [79]. Preliminary clinical studies using VPA suggested this drug might treat symptoms related to HAND by reversing HIV-1-induced damage to gray matter. Patients treated with VPA showed improved neuropsychological function compared to placebo; however, there were concerns related to toxicity, drug interactions, and lack of long-term benefit to reduce the size of the latent HIV-1 reservoir [80–82].

## Molecular

### Brain virus load

Comprehensive quantification of HIV-1 load in brain parenchyma can utilize at least three different types of measurements: proviral DNA, unspliced viral RNA, and multisplined viral RNA (HIV-1-multisplined RNA indicates viral replication; unspliced HIV-1 RNA indicates persistence with incomplete or dysfunctional replication). In brain virus load studies, several brain regions generally are sampled with the underlying hypothesis that increased brain HIV-1 viral load should be associated with premortem neurocognitive impairment such as HAND or HAD. However, this is not always the case and may be associated with several factors including variations in previous duration of infection, sampling across brain regions, irreparable neuronal damage, persistence of inflammation, as well as variations in HAART [83–88]. However, HAART probably reduces RNA viral load more effectively than proviral DNA load. Indeed, in some studies the circulating peripheral HIV proviral DNA load in macrophage/monocytes (CD14/CD16) was associated with HAD and minor cognitive motor disorder, independent of HIV RNA levels; the majority of these patients were treated with HAART [89–91]. Additional factors that may

require attention include HAART resistance mutations, the particular mutational profile of the peripheral and CSF viruses that may influence HIV-1 neurovirulence, epigenetic mechanisms, and micro-(mi-) RNA expression. Factors including elevated plasma lipo-polysaccharide (LPS) as well as co-infections including HCV may be important in groups such as injection drug and alcohol abusers [91–96].

### Brain virus evolution

In NeuroAIDS, HIV-1 evolution (HIV-1 evolution refers to the increased and wide phylogenetic and sequence diversity that occurs over time and place. The different groups of sequences are referred to as swarms or quasispecies. The term, HIV-1 evolution, is also used to typify their wide variations of sequence diversity and phylogenetically clustered groups in the human brain in NeuroAIDS [97–99]) is hypothesized to modulate HIV-1 neuroinvasiveness and subsequent pathogenesis, for example strains with increased neurovirulence may have specific changes in the Nef protein associated with neurodegeneration *in vitro* [100]. In corollary, HIV-1 evolution may occur separately in compartmentalized brain regions, CSF, blood, and spleen and this paradigm has stood the test of 12 years of research. Compartmentalization may also occur also at the cellular level in astrocytes, macrophages, and multinucleated giant cells. In addition, a feline model, using feline immunodeficiency virus (FIV) produced supporting evidence of this precept [97,98,101–107]. Overall, this paradigm has been demonstrated for several HIV-1 genes including Env, Pol, Gag, and Nef [108]. However, one phylogenetic study did not conform to the compartmentalization paradigm [109]. In such studies, the conclusions depend heavily on the reliability of the sequences analyzed. Moreover, maintaining criteria for sequence database veracity continues to be important but should be systematically applied [110–113].

### Genetics of susceptibility and progression

Genes associated with immune and neurobiological functioning may play a role in NeuroAIDS progression and susceptibility to HAND. Candidate gene studies have identified a number of polymorphisms that modify the function or expression of immunologic factors and neurotransmitters thought to be involved in HIV-1 infection and NeuroAIDS progression (Table 2) [114–128].

A deletion within the CCR5 gene, for example, confers resistance to HIV-1 infection and an early study found that a disproportionately small number of heterozygous carriers of this allele were detected among a sample of HAD patients [114,115]. Since those early studies, this and other polymorphisms within genes associated with immune functioning have been associated with risk for and progression to HAND [e.g. chemokine (C-C motif) receptor-2, chemokine (C-C motif) ligand-3, stromal

**Table 2. Genetics of susceptibility.**

Gene	Explanation	References
Chemokine (C-C motif) receptor-5 (CCR5)	A deletion in the CCR5 HIV-1 co-receptor gene, resulting in the CCR5-Δ32 allele, confers resistance to infection and slower disease progression. Some studies found an association of this polymorphism with lower risk for HAND, whereas other studies did not.	[114–118]
CCR2	A SNP in the CCR2 minor HIV-1 co-receptor gene, resulting in the CCR2-V64I allele, is associated with slower cognitive decline.	[119]
Apolipoprotein E (ApoE)	Some studies found a positive relationship between the ε4 allele and HAND, whereas other studies did not find an association between ε4 and HAND or encephalitis. Some studies suggested an age-modified association of older individuals who possess the ε4 allele with greater risk for HAND.	[24,117,120–124]
Macrophage inflammatory protein-1 alpha (MIP-1α, CCL3)	In one cross-sectional study, the minor allele resulting from SNP rs113071 was associated with a two-fold increased risk of HAND.	[125]
Stromal cell-derived factor-1 (SDF-1)	One study found that among a sample of primarily African American children, homozygosity for the SDF1-3'-A allele was associated with faster progression and decline in neurocognitive ability. A more recent study found no association between this allele and neurocognitive deficits in a sample of Chinese adults.	[116,117]
Monocyte chemoattractant protein-1 (MCP-1, CCL2)	One study reported homozygosity for the MCP-1-2578G allele to be associated with 50% reduction in risk for HIV-1 infection. However, once infected, the same genotype was associated with accelerated disease progression and a 4.5-fold increased risk of HAD. Another SNP resulting in the MCP-1–2518G allele was found to be marginally associated with CNS impairment in HIV-1-positive children, but not associated with cognitive deficits in adults.	[117,126,127]
Tumor necrosis factor-alpha (TNF-α)	Two studies found an association between the TNF-α 308A allele and HAD. However, no association was found between this SNP and postmortem signs of HIV-encephalitis in a separate study.	[120,121,128]
Mannose-binding lectin (protein C)-2 (MBL2)	Homozygosity for an MBL2 allele (termed O/O), resulting in essentially nonfunctional MBL2, was associated with faster cognitive decline over 12 months in an HIV-1-positive Chinese cohort.	[117]

CNS, central nervous system; HAND, HIV-associated neurocognitive disorder; SNP, single-nucleotide polymorphism.

cell-derived factor-1, monocyte chemo-attractant protein-1, and tumor necrosis factor-1 alpha (TNF-1α) [116,117,119–121,125,129–132], although few findings have been replicated. The ε4 allele of apolipoprotein E (ApoE), long implicated in the pathogenesis of Alzheimer's disease, has been examined as a risk factor for HAND, also with equivocal findings thus far [24,117,123,124,126,133]. Notably, in addition to a greater incidence of HAND among ApoE-4 carriers, Spector *et al.* [117] found the mannose-binding lectin (protein C)-2 O/O genotype to be associated with increased risk for progressive cognitive decline over 12 months among a Chinese cohort, whereas none of the aforementioned immunologic factors were associated with incidence of HAND or cognitive decline.

Dopaminergic pathway genes including dopamine transporter and catechol-O-methyltransferase (COMT) are also of interest in the neuropathogenesis of HAND, as dopamine pathway dysfunction appears to underlie many neurobehavioral deficits seen in HIV-1-infected indi-

viduals [24,134,135]. Recent studies have begun to examine the role of COMT polymorphisms in HAND, although much work remains to determine if genotype and HIV confer an additive or synergistic effect on neurocognitive functioning. The recent application of genome-wide association studies may reveal previously unknown factors involved in HIV-1-related neuropathogenesis. This method, which requires very large cohorts, previously has been successful in revealing novel genes associated with viral set point and HIV-1 progression [118].

### Host gene expression

HIV-1 infection activates macrophage/microglia and astrocytes, which produces several neurotoxins including pro-inflammatory cytokines including TNF-α, IL-1β, and interferon (IFN)-γ. These inflammatory mediators promote inflammatory signaling cascades in NeuroAIDS with a cumulative result of neuronal toxicity [49,136–138]. TNF-α levels increase in the CNS of patients with HAND and in-vitro exposure of macrophages and

microglia to gp120 or Tat induces TNF-1 $\alpha$  expression [139]. TNF-1 $\alpha$  up-regulates the expression of intercellular adhesion molecule-1 (ICAM-1), vascular endothelium adhesion molecule-1 (VCAM-1), and surface E-selectin on astrocytes and cerebral endothelial cells, with consequent transendothelial migration of activated macrophages from the periphery into the CNS. TNF-1 $\alpha$  up-regulates monocyte chemoattractant-1 and fractalkine expression [140,141], and neuronal expression of genes for calbindin, macrophage and astrocyte expression of macrophage inflammatory protein (MIP)-1 $\alpha$ , regulated on activation normal T cell expressed and secreted (RANTES), and MIP-1 $\beta$ . TNF- $\alpha$  also increases the release of glutamate by astrocytes and microglia [142], and decreases the uptake of neuro-toxic glutamate by macrophage/microglia [143]. These effects are mediated by over-stimulation of NMDA receptors, which results in excessive calcium influx and generation of nitric oxide and superoxide anions, which are neurotoxic [144]. In human neuron cultures, exposure to gp120 and Tat causes increased expression of sphingomyelin and ceramide that is likely mediated by TNF- $\alpha$  and IL-1 $\beta$ . In human astrocyte cultures, activation of indoleamine-2,3-dioxygenase (IDO) results in elevation of tryptophan catabolism and the production of neurotoxins including kynurenine due to Tat protein for HIV-1B and not C. The authors conclude from the latter experiment that the prevalence of HAD may correlate with epidemiological differences in HIV-1B vs. C [139,145–148]. Finally, microarray technology has been applied to NeuroAIDS to measure simultaneous expression of large numbers of genes including recently discovered micro-(mi)-RNAs, as reviewed in detail elsewhere (Table 3) [49,50,96,136, 138,140,141,145–154].

### Promising modes of therapeutic gene delivery

Few drugs treat NeuroAIDS effectively in part because of incomplete CNS penetration. However, noninvasive

intra-nasal delivery of therapeutic drugs to the CNS can bypass the blood–brain barrier via the olfactory nerve [155]. Novel CNS delivery systems can blunt induction of apoptosis by using recombinant SV40–derived vectors to deliver antioxidant enzymes [e.g. Cu/Zn-superoxide dismutase (SOD1) and glutathione peroxidase (GPx1)]. This protects cells from free radical-mediated gp120-induced apoptosis by detoxifying oxygen free radicals, and leads to a 10-fold reduction of neuronal apoptosis. Further testing in animal models and in clinical trials for treatment of HAND is now needed [156,157]. However, these protocols carry safety concerns because of the direct connection of olfactory nerves into the brain.

Transgene expression, another brain-targeted treatment, is improved with the systemic injection of the polyol sugar, mannitol. Mannitol, though not as well tolerated as originally thought, opens the blood–brain barrier transiently, with a concomitant increase in the number of brain cells exposed to experimental treatments. Thus, mannitol can be used for delivery of vectors (to produce transgenes) and the amyloid-beta homologue (Gd-DTPA-K6A $\beta$ 1–30) to image plaques [158–160].

Adenoviruses, lentiviruses, onco-retroviruses, and herpes simplex virus serve as transgene vectors, but often are associated with inflammation that reduces the effectiveness of the gene transfer. Adeno-associated virus (AAV) causes a mild immune response while it incorporates its genome in dividing and nondividing cells, and AAV-2 strains carry extensive gene loads with enhanced infectivity of neurons via axonal entry and retrograde transport [161]. AAV yields successful gene transfer in animal models of Alzheimer's disease, PD, and other CNS disorders [162], and in phase I trials for PD. However, the use of AAV is not without caveats as AAV-mediated gene transfer can induce tumors in animal models [163].

**Table 3. Gene expression in NeuroAIDS.**

Cells	Comments	References
Macrophage/microglia	HIV-1 infection of these cells causes up-regulation of the expression of: TNF- $\alpha$ , IFN- $\gamma$ , IL-1 $\beta$ , MCP-1, fractalkine, MIP-1a, and MIP-1b.	[49,136,138,140,141]
	GLUT5 and HCgp39	[155]
Cerebral endothelial cells	ICAM-1, VCAM-1, and surface E-selectin	[136,138]
	vWf	[155]
Astrocytes	ICAM-1, VCAM-1	[136]
	Up-regulation of interferon antiviral responses, intercellular contacts, cell adhesion and signaling	[136]
Neurons	Sphingomyelin and ceramide	[145–148]
Mixed glial cultures	IL-1 $\beta$ , TIMP-1, Caspase 9, S100A8 and 9, MMP12, IL-8, MCP1, MRC-1, and IL-6	[151]
Macrophage/monocytes	CCL2(MCP1), CCL7, CXCL5, TNFSF14, kinases, and phosphatases	[153]

A few select cytokines, chemokines, and other molecules involved in pathogenesis of NeuroAIDS are tabulated. The expression of these genes is up-regulated compared to normal tissue. In addition, many of these molecules are down-regulated; a complete list is extensive and beyond our scope here. Tumor necrosis factor-alpha (TNF- $\alpha$ ); interferon-gamma (IFN- $\gamma$ ); interleukin-1 $\beta$  (IL-1 $\beta$ ); monocyte chemoattractant-1 (MCP-1); macrophage inflammatory protein (MIP)-1a and MIP-1b; human cartilage glycoprotein 39 (HCgp39); intercellular adhesion molecule-1 (ICAM-1); vascular endothelium adhesion molecule-1 (VCAM-1); von Willebrand factor (vWf); human S100A8 (S100A8), matrix metalloproteinase-12 (MMP-12), interleukin-8 (IL-8); monocyte chemotactic protein 1 (MCP-1); mannose receptor, C type 1 (MRC-1); interleukin 6 (IL-6); chemokine C-C motif ligand 2 (CCL2); chemokine C-C motif ligand 7 (CCL7); matrix metalloproteinase-12 (MMP-12); chemokine C-X-C motif 5 (CXCL5), tumor necrosis factor ligand superfamily member 14 (TNFSF14).

**Table 4. Therapy that penetrates the blood–brain barrier.**

Therapeutic Intervention	Brief description	References
Viral modes of administration	Noninvasive intra-nasal delivery via the olfactory nerve	[155]
Recombinant SV40-derived vectors	Of antioxidant enzymes to blunt induction of apoptosis (e.g. Cu/Zn-superoxide dismutase (SOD1), glutathione peroxidase (GPx1)	[156,157]
Systemic mannitol-aided transgene expression	Open the blood–brain barrier transiently	[158–160]
Virus-mediated modes of administration	Virus-induced mild immune and inflammatory response that fosters incorporation of the viral genome in dividing and nondividing cells	[161–164]
Adenovirus AAV-2 strains	Via axonal entry and retrograde transport	[161,162]
Lentiviruses	With or without enhancement by mannitol and bradykinin	[164]

Lentiviruses have a long incubation period and delayed immunogenicity. They deliver a significant quantity of genetic material into the host cell's DNA, and can infect neighboring cells, without producing extracellular particles. The efficiency of their CNS uptake was enhanced with mannitol and the vasodilator, bradykinin. However, lentiviruses have distinct immune and biologic properties that need further investigation (Tables 4 and 5 and Fig. 2) [53,137,155–189].

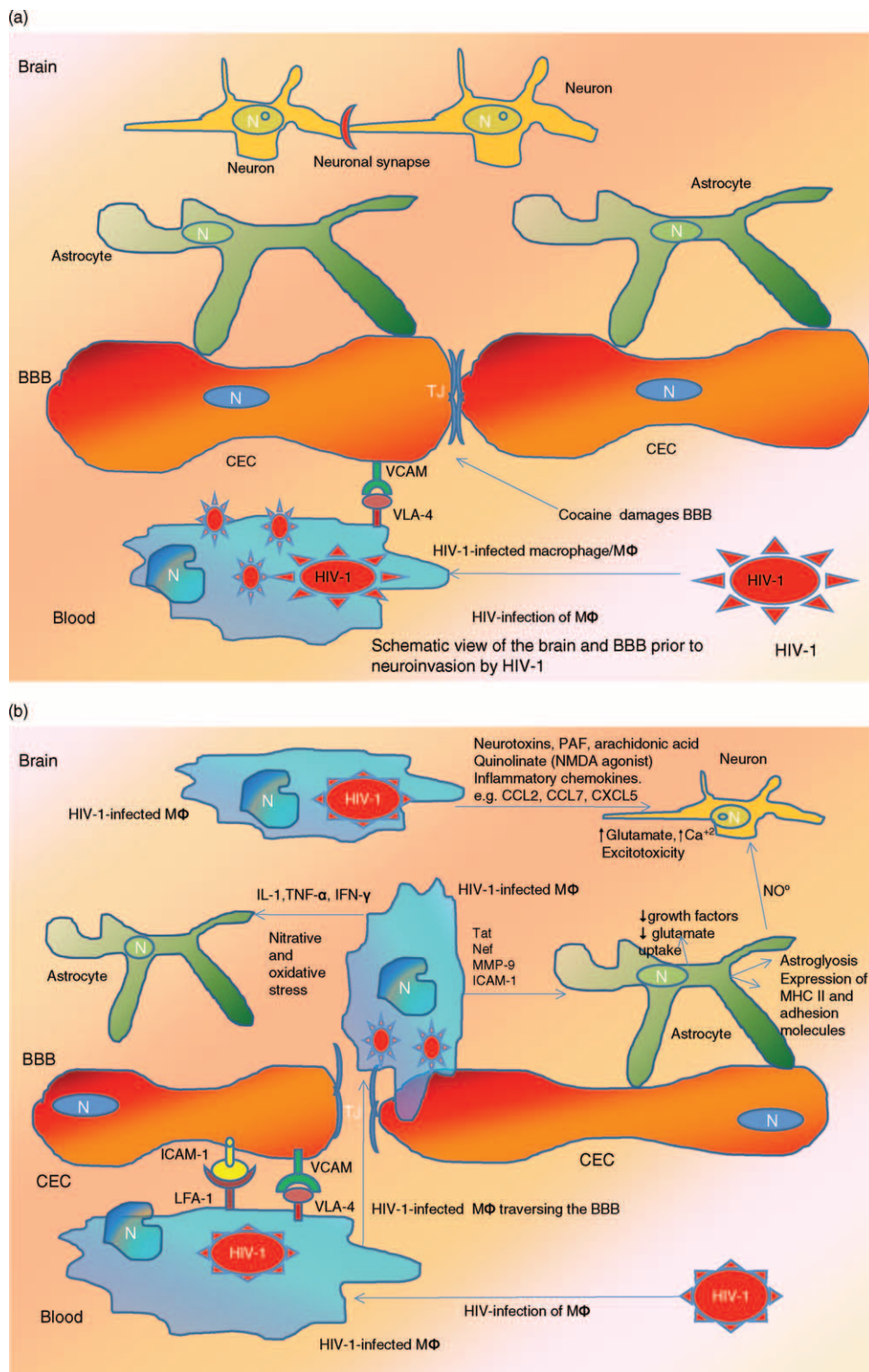
### Vaccines: classical and nonclassical

To produce a vaccine against NeuroAIDS, an effective HIV-1 vaccine must first be developed and the design and development of HIV-1 vaccines is still in progress [190]. The STEP HIV vaccine trial failure [STEP, an international HIV-1 vaccine clinical trial that commenced in 2004, is also known as the HVTN 502 or Merck V520-023 study, cosponsored by NIAID and Merck Corp. The trial tests three recombinant

**Table 5. Drugs that penetrate the BBB.**

Drug class	Drug	CPE 2010 rank	Transporter	References
Nucleoside/nucleotide reverse transcriptase inhibitors	Zidovudine	4	P-gp, BCRP, ENT, CNT, OAT	[167–170]
	Abacavir	3	P-gp	[167]
	Emtricitabine	3	MRP	[165,171]
	Didanosine	2	ENT, CNT	[172,173]
	Lamivudine	2	OCT, MRP	[170,174]
	Stavudine	2	CNT	[167,170]
	Tenofovir	1	MRP	[165,171]
	Zalcitabine	1	OAT, ENT, CNT	[170,173,174]
Nonnucleoside reverse transcriptase inhibitors	Nevirapine	4	P-gp, MRP	[165,171]
	Delavirdine	3	P-gp, MRP	[171]
	Efavirenz	3	P-gp, MRP	[171]
	Etravirine	2	Unknown	-
Protease inhibitors	Indinavir/ritonavir	4	P-gp	[167,175]
	Darunavir/ritonavir	3	MRP	[176,177]
	Fosamprenavir/ritonavir	3	P-gp	[178]
	Indinavir	3	P-gp	[175]
	Lopinavir/ritonavir	3	MRP	[179]
	Atazanavir	2	P-gp	[180]
	Atazanavir/ritonavir	2	P-gp	[180]
	Fosamprenavir	2	P-gp	[178]
	Nelfinavir	1	P-gp, BCRP	[175,181]
	Ritonavir	1	P-gp, BCRP	[181,182]
	Saquinavir	1	P-gp, MRP, BCRP	[175,179,181]
Saquinavir/ritonavir	1	P-gp, MRP, BCRP	[175,179,181]	
Tipranavir/ritonavir	1	P-gp	[183]	
CCR-5 inhibitor	Maraviroc	3	P-gp	[184]
Fusion inhibitor	Enfuvirtide	1	Unknown	[184]
Integrase inhibitor	Raltegravir	3	Unknown	[185]

This table shows the CNS-Penetration effectiveness (CPE) ranking of antiretrovirals. A higher number estimates better penetration in the CNS. Thus, 4 indicates highest penetration and 1 indicates lowest penetration. The initial CPE rank was based on physicochemical characteristics, CSF concentrations, and efficacy data [165]. However, recent cross-sectional data that included CSF vs. plasma viral load studies from the CHARTER Cohort led to a revised CPE ranking system. The new system reflects stronger associations with CSF viral load analysis by incorporating recent pharmacokinetic and pharmacodynamic data [166]. Drug transporters involved in each antiretroviral distribution at the BBB are mentioned. The transporters are ATP-binding cassette (ABC) superfamily including P-Glycoprotein (P-gp), Multidrug resistance associated protein (MRP) and breast cancer resistance protein (BCRP). Solute Carrier superfamily (SLC) includes organic anion-transporting polypeptide (OATP), organic anion transporter (OAT), and organic cation transporter (OCT). Nucleoside transporters such as equilibrative nucleoside transporter (ENT), concentrative nucleoside transporter (CNT). Unknown, transporter is not characterized. –, no information available. Roche discontinued manufacturing Hivid (ddC) due to availability of newer antiretrovirals (<http://www.nelm.nhs.uk/en/NeLM-Area/Other-Lib-Updates/SPC-Changes/501482/>, last accessed 7/6/2010).



**Fig. 2. Blood–brain barrier in NeuroAIDS.** (a) Blood–brain barrier (BBB) prior to infection. Normally, the human BBB, which is composed of interacting adjacent cerebral endothelial cells (CECs) and astrocytes, effectively separates the CNS from cellular and molecular components of the peripheral circulation and creates a unique reservoir environment for functioning neurons and astrocytes among other cells in the brain. Adjacent CECs contain tight junctions (TJs) that serve as the anatomic and functional barrier against harmful molecules from the blood stream. The process of transendothelial migration of HIV-1-infected monocytes involves interactions among adhesion molecules on CECs [e.g. vascular endothelial adhesion molecule (VCAM)] and their ligands on the activated leukocyte [very late antigen-4 (VLA-4)]. During the course of NeuroAIDS, HIV-1-infected macrophage/monocytes

adenovirus-5 (rAD5) vectors, each expressing an HIV-1 gene: *Ad5-gag*, *Ad5-pol* and *Ad5-Nef* (<http://www.hvtn.org/media/pr/step111307.html>) and this led to further intense debate related to the utility of the vaccine approach [191]. Some of the major concerns associated with the development of HIV/AIDS vaccines are viral diversity (viral mutation), HIV-1-host molecular mimicry (sequence level homology among viral and human genes), and HLA polymorphism among ethnic groups (including Black, Hispanic, Oriental, Pacific Islander, American Indian, Australian aboriginal, and Caucasian). The latest IMGT/HLA database (<http://www.ebi.ac.uk/imgt/hla/>) update (as of 3-06-2010) has 4447 HLA alleles displaying sequence polymorphisms among these ethnicities. Nevertheless, efforts are underway using a multifaceted strategy for vaccine development. Four priming injections of a recombinant canary pox vector (ALVAC-HIV) and two booster injections of gp120 subunit (AIDSVAX-B/E) in a community-based, randomized, multicenter, double-blind, placebo-controlled efficacy trial (NCT00223080) in Thailand, showed some encouraging results for future research in that there was a trend ( $P=0.08$ ) to prevent HIV-1 infection among vaccine recipients (efficacy 26.4%). However, the vaccine did not affect the degree of viremia or the CD4+ T-cell count in patients who later seroconverted [192]. Nonetheless, recent data from sequence to structure relationship studies [193–195] with corresponding immunological findings [196] to HIV-1 gp120 provide encouraging insights to continue use HIV-1 Env as a potential target for vaccine development.

A novel approach uses population-specific HLA sequences to design short HIV-1 oligopeptide-specific T-cell-based epitopes in the context of NeuroAIDS [197]. An HIV/AIDS oligopeptide vaccine consists of a cocktail of short synthetic antigenic oligopeptides (8–20 residues) [197,198]. These oligopeptides exhibit either CD8+ or CD4+ T-cell immunity by specifically binding to respective class I or class II HLA alleles (that is

illustrated in Fig. 3) [199]. The LANL/HIV database (<http://www.hiv.lanl.gov/content/immunology/index.html>) documents a range of HIV-1-specific oligopeptides exhibiting T-cell immunity, with known HLA specificity. Cocktails of these oligopeptides are administered in conjunction with incomplete Freund's adjuvant (water-in-oil emulsion) to stimulate specific T-cell response [197,198]. Moreover, short oligopeptides are more capable of entering the brain than larger envelope and other viral proteins and hence are promising vaccine paradigm candidates for HIV/AIDS and NeuroAIDS [197].

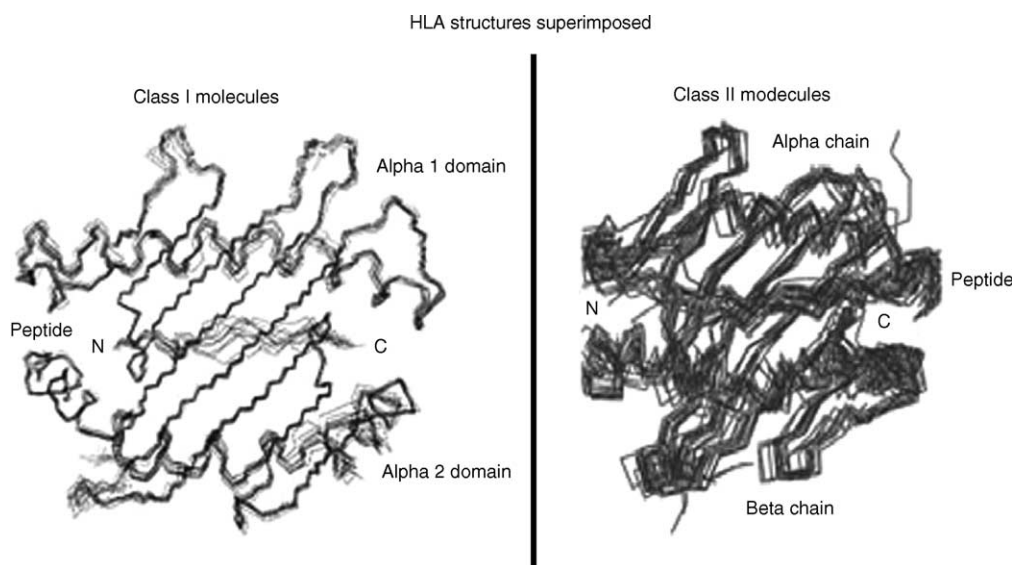
## Animal models

Several animal model systems have been developed to investigate HIV-1-induced CNS disease. Transgenic mice were utilized to generate strains expressing HIV-1-encoded neurotoxic proteins, including Tat, under the control of a doxycycline promoter, HIV-1 gp120 under control of the glial fibrillary acidic protein (GFAP) promoter (for expression in astrocytes), and gp160 under the control of neurofilament promoters (for expression in neurons), to investigate the role of these HIV-1 proteins in neuropathogenesis. Additional technologies exploited the severe combined immune deficient/human (SCID/hu) mouse system when SCID mice were inoculated intracranially with HIV-1-infected human monocytes. FIV (FIV is a cat lentivirus related to HIV-1) infection was also utilized as a model for HIV-1 infection and this FIV/cat system proved useful to investigate cognitive and behavioral deficits in an infection-based model [200–206].

Simian immunodeficiency virus (SIV) is also known to induce neuropathologic changes in infected macaques [207]; however, several approaches were developed to circumvent the relatively low incidence of neuropathogenic infection. Passage in microglial cell culture generated

### Fig. 2 (continued)

from the blood, traverse the TJs of the CECs and infiltrate the brain parenchyma. Once within this milieu, they differentiate into macrophage/microglia (MΦ). Drugs including cocaine and methamphetamine damage the BBB and further facilitate ingress of the HIV-1-infected monocytes into the brain. (b) BBB postinfection. Once within the brain parenchyma, HIV-1-infected MΦ secrete elevated levels of pro-inflammatory cytokines including interleukin-β (IL-β), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α), which in turn activate uninfected macrophage/microglia and adversely affect astrocytes. These pro-inflammatory cytokines also increase BBB permeability and induce further expression of adhesion molecules including VCAM and inter-cellular adhesion molecule (ICAM) by activated CECs, which in turn promote further ingress of HIV-1-infected monocytes into the CNS. In addition to cytokines, inflammatory chemokines contribute to brain inflammation [e.g. chemokine ligand 2 (CCL2); chemokine ligand 7 (CCL7); C-X-C motif chemokine 5 (CXCL5)]. Within the CNS, MΦs produce nitric oxide (NO) and promote oxidative injury that affects both astrocytes and CECs. HIV-1-infected MΦs also release HIV-1 Tat protein that induces expression of the adhesion molecules by CECs. Neuronal injury in the context of NeuroAIDS is also promoted by processes including the activation of the N-methyl-D-aspartate receptor (NMDAR)-coupled ion channels, which in turn leads to massive influx of Ca<sup>+2</sup> ions. This process then leads to activation of several enzymes including matrix metallo-proteinases, generation of free radicals, and release of glutamate, which cause neuronal apoptosis. Other inflammatory mediators such as platelet activating factor (PAF), arachidonate, and quinolinate (an NMDA agonist) also participate in neuronal injury. HIV-1 infection of astrocytes also leads to astroglyosis and inflammatory cascades. Reproduced with permission from [53,137,186–189].



**Fig. 3. HLA structures (class I and II) superimposed with peptides in complex form using a set of known HLA-peptide structures determined by X-ray crystallography.** The illustration shows structural features of superimposed multiple short peptides binding to HLA molecules, which is a prerequisite to stimulate T-cell immunity. HLA molecules are often polymorphic across ethnic groups and hence peptide binding specificity varies for each population. Reproduced with permission from [199].

a virus that replicates more efficiently within the CNS and results in increased incidence of neuropathological infection [208]. A multiviral combination (pathogenic and neurovirulent viruses together) yields a significant increase in the incidence of CNS disease in macaques. For example, co-inoculation of the SIV/DeltaB670 and SIV/17E-Fr precipitated neuropathogenic infection in pigtailed macaques [209]. Subsequently, a single virus system

induced neuropathogenic infection in greater than 90% of infected pigtailed macaques [210]. The latter two systems offer the desired high incidence of neuropathogenesis and disease pattern that are remarkably similar to NeuroAIDS. Depletion of CD8<sup>+</sup> T cells increased the incidence of CNS disease for more traditional SIV isolates (Table 6) [200–206,208–211]. These model systems help demonstrate pathogenic mechanisms in HIV-1-induced

**Table 6. Animal models.**

Animal model system	Advantage	Disadvantage	References
Mice Transgenic for gp120, gp160, or Tat	Can determine specific effects of individual proteins	Cannot study effects of virus replication	[200–202]
SCID mice injected intracerebrally with HIV-1-infected macrophages	Utilizes replication-competent virus infection	Direct injection into CNS required in absence of systemic infection	[203]
FIV infection of cats	Utilizes replication competent virus/host system, can be used for behavioral testing	Cellular tropism of FIV differs from that of HIV-1 so effects may be different	[204–206]
SIV-infected microglia in macaques	Virus infection in natural virus/host system, viral tropism skewed towards CNS	Complicated and tedious system to produce infected microglia	[208]
Combination of two SIV isolates for infection of macaques	Rapid, consistent development of AIDS and neurological dysfunction	Combination of viruses makes it difficult to ascertain the effects of specific viral genetics on neuropathogenesis	[209]
Single SIV isolate infection of macaques	High incidence (>90%) of neuropathogenesis	SIV, although an excellent model, still differs from HIV-1	[210]
SIV infection of macaques coupled with CD8 cell depletion	Rapid development of AIDS and neuropathogenic disease	Eliminates a key component of the immune response, which may have effects on other immune mediators such that pathogenesis may be altered as compared with natural infection	[211]

CNS, central nervous system; FIV, feline immunodeficiency virus; SCID, severe combined immune deficiency; SIV, simian immunodeficiency virus.

CNS disease. Continued improvements should enable a comprehensive understanding of HIV-1-induced neurological disease and the development of effective therapies.

## Conclusion

Since the earliest studies in NeuroAIDS, nearly 30 years ago, many different approaches and models for NeuroAIDS evolved. We conclude with key current issues dealt with in this review. CNS infection by HIV-1 can result in NeuroAIDS. The infection is chronic and subsequent neurodegeneration leads to several domains of neurocognitive impairment. NeuroAIDS is increased in older HIV-1+ adults and associated drug abuse exacerbates these impairments, synergizes with virus replication, and increases virus load and immunosuppression. In the brain, HIV-1 load and evolution affect these outcomes. However, HAART greatly reduces virus load by decreasing viral replication but has little effect on the viral reservoirs in the brain. Despite the use of HAART, milder forms of HAND are present in nearly 50% of HIV-1-positive adults. Thus palliative and adjunctive therapy are necessary to improve the patient's ability to function, although to date most clinical trials with such approaches have shown minimal or no efficacy. At the genetic level, immunologic, neurotransmitter host gene polymorphisms, and perturbed gene expression may influence NeuroAIDS progression and susceptibility; however, these tests currently lack the sensitivity and specificity for use in clinical practice for prediction of susceptibility of NeuroAIDS. Novel therapies that deliver genes into the CNS using AAV and other viruses as vectors may be a potential therapeutic approach to combat destructive processes such as apoptosis and inflammation thereby reducing brain damage in NeuroAIDS. Great dexterity is provided by animal models including transgenic mice, felines, and nonhuman primates to investigate all these aspects of viral infection and disease. These animal models also have great potential for the development of therapeutics for NeuroAIDS. Finally, HIV/AIDS therapeutic vaccines still require development for overall use and effectiveness let alone for the brain. The obstacles to vaccines include viral diversity, HIV-1-host molecular mimicry, and HLA polymorphism among ethnic groups. The use of oligopeptide vaccines is a step in a more effective direction. Directions of future studies that attack HIV/NeuroAIDS include greater sophistication in manipulation to target specific signaling and molecular processes. Specific developments in medications and vaccines that cross the blood-brain barrier are crucial as well.

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Authors and contributions: P.S. – introduction, brain virus load and evolution, Conclusion, editing manuscript, and corresponding author.

P.K. – vaccines, Figure 3.

R.K.F. – brain virus load.

D.C. – diagnosis, neurology, and neuroimaging; aging and neuropathology, Figure 1, Table 1.

F.C. – gene therapy, Table 4.

E.S. – diagnosis, neurology, and neuroimaging, Table 1.

A.J.L. – genetics, Table 2.

A.M. – gene expression, Figure 2, Table 3.

F.J.N. – animal models, Table 6.

C.S. – treatment, Table 5.

A.N. – drug abuse.

J.T.S. – treatment, Table 5.

In addition, all authors contributed to correcting and editing the text.

Raisa Avezova and Philippe Grisel, MD, PhD contributed to gene therapy.

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