HIV-1 infection and cognitive impairment in the cART-era: a review

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With the introduction of combination antiretroviral therapy (cART) AIDS dementia complex (ADC) or HIV-associated dementia (HAD), as it was termed later, largely disappeared in clinical practice. However, in the past few years, patients, long-term infected and treated, including those with systemically well-controlled infection, started to complain about milder memory problems and slowness, difficulties in concentration, planning, and multitasking.

Neuropsychological studies have confirmed that cognitive impairment occurs in a substantial (15–50%) proportion of patients.

Among HIV-1-infected patients cognitive impairment was and is one of the most feared complications of HIV-1-infection. In addition, neurocognitive impairment may affect adherence to treatment and ultimately result in increased morbidity for systemic disease.

So what may be going on in the CNS after so many years of apparently controlled HIV-1-infection is an urgent and important challenge in the field of HIV-medicine.

In this review we summarize the key currently available data. We describe the clinical neurological and neuropsychological findings, the preferred diagnostic approach with new imaging techniques and CSF-analysis. We try to integrate data on pathogenesis and finally discuss possible therapeutic interventions.

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Introduction

Within years after the start of the epidemic it became clear that many HIV-1-infected patients developed severe progressive cognitive and motor impairment in the final months of their illness. This clinical syndrome was characterized clinically and neuropathologically by Price and Navia in 1986 and termed AIDS dementia complex

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(ADC) [1,2]. ADC causes symptoms in three areas: cognition, motor function and behavior. Cognitive impairment predominantly consists of mental slowing and attention/memory deficits. Motor symptoms comprise slowness and loss of balance; behavioural changes are characterized by apathy, social withdrawal and mood disturbances.

Many studies confirmed the hypothesis that HIV-1 itself was causing dysfunction and damage in the central nervous system (CNS). Shortly after the primary infection HIV-1 enters the brain in mononuclear cells, and settles in perivascular macrophages and microglial cells. Replication of HIV-1 in these cells leads to immune-activation and the production of viral and inflammatory proteins that eventually leads to cognitive decline and motor dysfunction in a subset of patients.

With the introduction of combination antiretroviral therapy (cART), ADC or HIV-associated dementia (HAD), as it was termed later, largely disappeared in clinical practice. Many clinical, pathological, and cerebrospinal fluid (CSF) studies showed that antiretroviral drugs inhibit local virus-replication in the brain and in doing so limit local damage. Even severely impaired patients could improve after the initiation of treatment. Some drugs likely did better than others, but in general most combinations prevented the development of HAD. HAD became a rare complication, occurring occasionally in late-presenting as yet untreated patients, in patients on treatment but with poor adherence, or in patients in whom systemic and CNS-infection had an unparalleled course.

However, in the past few years, patients, long-term infected and treated, including those with systemically well-controlled infection, started to complain about milder memory problems and slowness, difficulties in concentration, planning, and multitasking.

In recent years a new terminology has been developed to classify a broadening clinical spectrum of neurocognitive impairment, including milder abnormalities (Table 1) [3]. Neuropsychological studies have confirmed that cognitive impairment occurs in a substantial (15−50%) proportion of patients [4,5]. It has, however, to be noted that there is a current discussion about the prevalence of neurocognitive dysfunction, which might be overestimated because of very sensitive criteria when applying the new terminology. In addition, compared to the first decade of the epidemic, a shift has occurred in certain demographic variables and risk factors, e.g. increased age, lower transmission among drug users, which might affect the proportion of patients with cognitive impairment.

Among HIV-1-infected patients cognitive impairment was and is one of the most feared complications of HIV-1-infection. In addition, neurocognitive impairment may affect adherence to treatment and ultimately result in increased morbidity for systemic disease [6]. So what may be going on in the CNS after so many years of apparently controlled HIV-1-infection is an urgent and important challenge in the field of HIV-medicine.

In this review we summarize the key currently available data. We describe the clinical neurological and neuropsychological findings, the preferred diagnostic approach with new imaging techniques and CSF-analysis. We try to integrate data on pathogenesis and finally discuss possible therapeutic interventions. In doing so it will become clear that there remains a broad research agenda in this field for the years ahead.

Neuropsychology

The neuropsychological profile of post-cART HIV-associated neurocognitive disorders (HAND) and its similarity to the pre-cART subcortical profile is a subject of debate. In recent years abnormalities of greater or lesser extent have been demonstrated in many different cognitive domains, resulting in an expanding phenotype of HAND and a broadening neuropsychological profile [5,7,8]. Despite this heterogeneity the strongest impaired cognitive domains in HAND still fit the subcortical profile with the core deficits being: mental slowness, attention/memory deficits and impaired executive functioning [8].

Table 1. Terminology.

HAND	HIV Associated Neurocognitive Disease	Umbrella definition comprising ANI, MND and HAD
ANI	Asymptomatic Neurocognitive Impairment	Cognitive impairment (at least 1 standard deviation below the mean), involving at least two cognitive domains. The cognitive impairment does not interfere with everyday functioning.
MND	Mild Neurocognitive Disorder	Cognitive impairment (at least 1 standard deviation below the mean), involving at least two cognitive domains. The cognitive impairment produces at least mild interference in daily functioning.
HAD	HIV Associated Dementia	Marked cognitive impairment (at least 2 standard deviation below the mean), involving at least two cognitive domains. The cognitive impairment produces marked interference with day-to-day functioning.
ADC	AIDS Dementia Complex	Former term of HAD
MCMD	Minor Cognitive Motor Disorder	Former term of ANI and MND combined

The following cognitive domains are recommended to be surveyed if HAND is suspected (as these are most commonly associated with HAND) [3]: speed of information processing, attention/working memory, executive functioning, memory, verbal/language, sensory-perceptual and motor skills (Table 2).

Neuropsychological testing

Many different tests are available to evaluate each of these cognitive domains (Table 2) and most of the large HIV cohort studies have developed their own neuropsychological test battery.

As these test batteries are usually extensive and time-consuming, there is a need for a rapid screening tool for neurocognitive deficits. The Mini Mental State Examination (MMSE) is the most well-known cognitive bedside test but has a limited usefulness for the detection of HAND as it mainly detects cortical (as in Alzheimer's disease) instead of subcortical dysfunction [9].

The HIV Dementia Scale (HDS) tests four cognitive domains (verbal memory recall, psychomotor speed, visual construction and response inhibition) and has originally been designed to detect HAD [10]. The usefulness of the HDS for detecting milder cognitive deficits is under investigation [4,11].

The HDS requires a certain amount of literacy and language comprehension, which limits the usefulness of this test. For this reason, the International HIV Dementia Scale has been developed (IHDS), testing three cognitive domains (psychomotor speed, motor speed and verbal memory recall) [12]. The usefulness of the IHDS for detecting milder cognitive deficits is still under investigation.

Standardized and regularly administered symptom questionnaires likely also have a role in clinical screening.

Of note, these screening tests are no substitute for performing a complete neuropsychological evaluation which remains required for the diagnosis of HAND.

Neuroimaging

Many studies during the course of the HIV-epidemic have proven neuroimaging to be both an essential diagnostic tool in clinical HIV-neurology and useful in enlarging insight in the pathogenesis of HIV-infection of the CNS.

Computed tomography (CT) and magnetic resonance imaging (MRI)

Cerebral atrophy and white matter abnormalities are the two most common findings in HAD in early imaging studies. While atrophy can be disclosed by both CT and MRI, the latter is largely superior for the identification and characterization of white matter abnormalities. Atrophy is seen most often in the basal ganglia (especially the caudate nucleus) and frontal white matter although cortical regions have also been reported to be atrophic [1,13]. Atrophy has been associated with advanced disease stage and (to a lesser extent) with cognitive dysfunction in early studies [13,14]. Post-cART studies demonstrate stronger correlations between atrophy and cognitive dysfunction [13,15,16]. Whereas one pre-cART prospective study reports cerebral atrophy to be progressive [14], no increase of atrophy has been described in a 7-year follow-up study in post-cART years (likely indicating a beneficial effect of cART) [17].

MRI in HAD frequently reveals patchy or diffuse, usually symmetrical, periventricular white matter abnormalities [18]. Small white matter abnormalities however have been found in non-demented HIV-patients as well and even in HIV-negative non-demented controls. Therefore, earlier MRI-studies report a controversial relationship between cognition and white matter abnormalities and consider the latter to be non-specific [13,19,20]. Later MRI-studies though using advanced and more sensitive MRI-techniques do demonstrate a relationship between white matter abnormalities and cognition. MRI white matter abnormalities also correspond to a histopathological diagnosis of HIV-encephalitis [21].

Several more advanced MRI-techniques are hereby discussed in detail:

Magnetic resonance spectroscopy (MRS)

MRS measures metabolite concentrations in different brain regions. MRS-studies (pre and post-cART) in patients with cognitive dysfunction have demonstrated reduced levels of N-acetyl aspartate (NAA), a marker for neuronal integrity, and increased levels of the glial activation markers myoinositol (MI) and choline (CHO). Glial activation (MI/CHO increase) indicates an inflammatory process and precedes neuronal loss (NAA decrease). Abnormalities are found mainly in the frontal white matter and basal ganglia [13,22–25]. The abnormal metabolite profile is reported to improve with cART [26–28]. MRS has proven to be more sensitive for early cognitive impairment than SPECT or MRI [29,30].

Diffusion tensor imaging (DTI)

DTI, used in HIV-research since 2001 [31], is an MRI-technique that measures water diffusion in tissues and enables to visualize distribution and orientation of white matter tracts. This technique is especially useful in demonstrating subtle white matter abnormalities. DTI-studies in HIV-patients report white matter abnormalities diffusely in the brain and more specific in the frontal white matter and corpus callosum, despite cART. Abnormalities are correlated strongly with cognitive

Table 2. Frequently used tests to examine different cognitive domains.

Cogntitive domain	Cognitive domain and HAND	Tests
Speed of information processing	Slowing of mental processes continues to be one of the most frequent cognitive abnormalities in HIV-1 infection [4,8]. As mental speed facilitates most if not all cognitive and motor processes, slowness is by some authors even regarded as the key deficit which in turn leads to defects in other cognitive domains [144].	Trail making test A
		Stroop color-word
		Symbol digit modalities test
		Digit symbol (WAIS/WAIS-R)
		Simple reaction time
		Choice reaction time
Attention/working memory	Attention and working memory are two closely related cognitive functions with the working memory (the ability to create a memory for temporary processing and storage of information) being highly dependent on attentional function. As a result of this close functional relationship, attentional deficits frequently occur simultaneously with working memory deficits [8,145,146].	Digit span (WAIS-R)
		Paced auditory serial addition test
		Letter-number sequencing (WAIS-III)
Executive functioning	Many different aspects of executive dysfunction (such as reasoning, planning, complex problem solving and set shifting between tasks and strategies) are reported in HAND [8,145].	Wisconsin card sorting test
		Trail making test B
		Stroop color-word
		Halstead category test
Memory	The episodic memory (storing personally experienced episodes and events) is one of the various components of the memory as a whole. The episodic memory is divided in a retrospective (experienced events in the past) and a prospective part (the ability to execute a future intention or ''remembering to remember''), the latter requiring intact executive functions as well (e.g. planning and set shifting). In HAND especially the prospective episodic memory and learning of new information are reported to be impaired [8,147].	California verbal learning test
		Hopkins verbal learning test
		Brief visuospatial memory test
		Rey-Osterrieth complex figure
		Visual reproduction WMS
		Logical memory WMS
		Story learning Halstead-Reitan battery
		Rey auditory verbal learning test
		Memory for intentions screening test
Verbal/language	The most frequently identified language defect in HAND is fluency impairment, although this may be the result of other cognitive impairments such as slowness or executive dysfunction [8,145].	Boston naming test
		Category fluency (animals)
		Letter fluency
		Action/verbal fluency
Sensory-perceptual	The interpretation and integration of visual, auditory or sensory stimuli takes place in this cognitive domain. Abnormalities in this predominantly cortical domain are less frequently observed in HAND.	Tactile form recognition right and left
		Speech sound perception test
Motor skills	Severe motor abnormalities (e.g. chorea, myoclonus, dyskinesia, dystonia) were seen frequently in the pre-cART era and formed one of the three cardinal symptoms in HAD. Although severe deficits are rare in the post-cART era, more milder impairments (slowing, incoordination) are still prevalent in HAND [8,145,148].	Finger tapping dom/nondom hand
		Grooved pegboard dom/nondom hand
		Grip strength
		Timed gait
		Unified Parkinson's disease rating scale

Note: Computerized testing (such as CogState or CalCap) is another possibility to evaluate different cognitive domains [149,150].

deficits [13,26,32–34], but the sensitivity for early changes is controversial.

Functional MRI (fMRI)

fMRI measures neuronal activity during specific neuropsychological tasks (which are performed while in the scanner). This technique is used in HIV-research since 1998 [35] and most studies demonstrate increased neuronal activation in cognitively impaired patients, which is regarded as a compensatory mechanism resulting from decreased cerebral efficiency [13,26,36]. fMRI abnormalities correlate strongly with increased glial markers (MI/CHO) in frontal white matter and basal ganglia, indicating a subcortical inflammatory process [37].

Perfusion MRI (pMRI)

pMRI measures cerebral blood flow and volume and is used in HIV-research since 2000 [38]. Most studies report decreased cerebral blood flow or volume in cognitively unimpaired and especially impaired patients [13,26,39].

Magnetization transfer imaging (MTI)

MTI has appeared useful for the detection of damage in normal appearing white matter (on regular MRI), having the potential to visualize subtle abnormalities. It has been proven useful in neurodegenerative diseases such as multiple sclerosis [13]. MTI is used in HIV-research since 1997 [40] and has demonstrated white matter abnormalities diffusely in different brain regions, correlating with cognitive impairment [41].

Nuclear medicine techniques: single photon emission computed tomography (SPECT) and positron emission tomography (PET)

SPECT measures the uptake of radiotracers (usually 99Tc) in the brain, which reflects the cerebral blood flow. Early SPECT-studies show cortical and subcortical areas of hypoperfusion. Although the correlation with cognitive function is controversial [13,22,26,42], these changes in perfusion seem to precede abnormalities found with CT or MRI [26]. In later SPECT-studies similar findings of reduced blood flow are reported. Remarkable is the report of increased cerebral blood flow among patients with severe cognitive deficits, which is thought to reflect active inflammation [26,43].

PET measures (glucose)metabolism in different brain regions. Early PET-studies showed hypometabolism in the basal ganglia, which was relatively specific for HAD [13,22,26]. Later studies revealed a characteristic time course with hypermetabolism in early neurocognitive disease developing into hypometabolism during advanced disease [13,26,44].

In conclusion, as white matter abnormalities have in many studies been related to cognitive impairment, promising techniques are those visualizing white matter in detail, such as DTI.

CSF-markers

Many potential CSF-markers have been studied in HIV-1-infected patients for management of CNS HIV-infection – including diagnosis, prediction, assessment of disease activity and response to treatments – and provide insight into underlying pathogenic mechanisms.

CSF-markers can practically be classified into virological, host response and CNS tissue damage markers (Table 3). However, no single marker has so far proved to be reliable for practical purposes. The mechanisms leading from HIV-1-infection of the CNS to tissue dysfunction and neurocognitive impairment are not straightforward and abnormal levels of CSF-markers are often also present in patients with asymptomatic HIV-1 infection or other CNS pathological conditions. Nonetheless, the use of several CSF-markers in combination could be useful to recognize HIV-related neurocognitive dysfunction, including milder forms (MND and ANI), both in untreated and treated patients.

In the absence of treatment, CSF HIV-1-RNA levels usually remain stable in neurologically asymptomatic patients

Table 3. Potentially useful CSF-markers of HIV-1 CNS infection [151].

- Virological Markers
  - HIV-1 RNA
  - Env/pol sequence analysis for compartmentalization
- Host Response Markers
  - Markers of Inflammation
    - White Blood Cells
    - Cytokines and Chemokines
      - Tumor Necrosis Factor-α
      - Monocyte Chemotactic Protein-1 (MCP-1)/CCL2
      - Interferon-γ inducible Protein-10 (IL-10)/CXCL10
      - Macrophage Inflammatory Protein-α (MIP1-α)/CCL3, MIP1-β/CCL4, RANTES/CCL5
      - Fractalkine / CX3CL1
    - Neopterin
    - Beta-2 Microglobulin
  - Proteases
    - Matrix Metalloproteases
    - Urokinase Plasminogen Activator (uPA) and soluble receptor (sUPAr)
  - Neurotoxic Host Factors
    - Quinolinic Acid and Tryptophan
    - Glutamate
    - Nitric Oxide (NO)
  - Markers of Apoptosis
  - Fas and Fas-Ligand
- Markers of CNS Damage
  - Neuronal Markers
    - Neurofilament Protein Light Chain (NFL)
    - Tau Protein
    - Solubile Amyloid Protein Precursor (sAPP) α/β
    - 14-3-3 Protein

over several years [45], but tend to increase with clinical disease progression. Levels are highest in patients with HAD or HIV-encephalitis [46,47], irrespective of plasma viremia, supporting the view that, in these conditions, CSF-virus is mainly derived from productive infection of macrophages and microglial cells within the CNS. Infection of these cells leads to the release of soluble factors which can be measured in CSF.

Among these factors, the chemokine CCL2 (or monocyte chemotactic protein-1, MCP-1), and neopterin, a product of the guanosine triphosphate metabolism, both produced by activated macrophages and other mononuclear phagocytes, have been well-characterized for their potential to serve as disease marker. In HIV-1-positive, neurologically asymptomatic patients, CSF CCL2 levels are similar to or slightly higher than those found in HIV-negative controls [48], whereas levels of neopterin are already abnormally elevated [47]. Significantly higher CSF levels of both CCL2 and neopterin are found in patients with HAD and HIV-encephalitis [47,49]. CSF concentrations of both markers correlate with CSF HIV-1-RNA levels, but less with their respective levels in plasma, strongly arguing for intrathecal origin [47,49,50].

Among markers of tissue damage, NFL, the light chain of neurofilament, a major structural component of axons, appears one of the most promising [51]. The highest levels are found in patients with HAD or opportunistic CNS-infections. However, concentrations can also be increased in neurologically asymptomatic patients with advanced systemic disease stage, suggesting subclinical axonal injury already at this stage.

Untreated patients initiating cART show a decrease of all these markers within weeks after starting therapy in both asymptomatic and neurologically impaired patients.

Different dynamics of HIV-1-RNA decay is observed between CSF and plasma: either parallel or slower in CSF [52–55], reflecting the principal source of virus-replication (systemic vs. intrathecal) [52]. CCL2, neopterin and NFL levels decrease upon treatment – more markedly in HAD patients, with higher baseline concentrations - in parallel with CSF HIV-1-RNA [47,56] [personal observation[PC]], suggesting that, by reducing viral replication in the brain, treatment interferes locally with the inflammatory process and consequent tissue damage.

In patients on cART with sustained systemic HIV-1-RNA suppression to undetectable levels, the relationship between CSF HIV-1-RNA and neurological status doesn't seem to be maintained [57], with low or undetectable CSF HIV-1-RNA levels frequently observed in neurologically impaired patients on cART [58]. Indeed, suppression of CSF replication is observed not only in patients showing full systemic responses, but also in a large proportion of patients failing to respond systemically [59] and it seems to be maintained for years, also when ultrasensitive methods, i.e., with limit of detection of <2–2.5 copies/mL, are used [60,61]. The opposite scenario, CSF "escape" in patients with suppressed plasma replication occurs in approximately 10% [62], and may disclose an active brain process and be associated with neurological symptoms and cognitive impairment [63]. CSF-markers of macrophage-activation may remain abnormally elevated in treated patients with suppressed replication in both CSF and plasma [64,65].

One of the current challenges is to understand the principal cause of this persistent intrathecal immune-activation, whether it is ongoing low-grade viral replication in brain tissue, rather than systemic immune-activation, chronically established tissue damage or presence of other CNS conditions.

Historically, CSF-markers of HIV-induced neurocognitive impairment were studied to differentiate HAD from opportunistic infections. However, current differential diagnosis involves many novel potential causes of cognitive impairment, such as aging, with its physiological changes and associated pathological conditions, primarily Alzheimer's disease [66–68], HCV co-infection [69], metabolic complications [70] and possible toxicity of treatments [71]. In this new scenario it is essential that CSF-markers can recognise whether HIV-1-replication and consequent immune-activation is the main cause of neurocognitive impairment, in order to optimize management.

Other CSF-markers, in addition to those described, appear promising both for patient management and pathogenesis studies (Table 3), including the soluble urokinase plasminogen activator receptor (suPAR), a novel marker of immune-activation [72]; the tau protein and the soluble forms of the amyloid precursor protein (sAPP alpha and beta), all markers of tissue damage [68]. In addition, the use of new, high-throughput technologies, such as proteomics and metabolomics, may enable to search for known or unknown molecules, possibly present at abnormal concentrations in the CSF of patients with HAND [73,74].

Neuropathology

Two specific neuropathological conditions that result from HIV-1-infection of the brain were defined in 1991: HIV-encephalitis (HIVE) and HIV-leukoencephalopathy (HIVL) [75]. The hallmark of HIVE and HIVL is the presence of multinucleated giant cells (MGCs) that are formed by fusion of infected and activated macrophages. Other features of HIVE and HIVL are activated macrophages and microglial cells, the latter sometimes forming microglial noduli (MGN), reactive astrogliosis and white matter pallor [75,76]. HIVE and HIVL are overlapping entities but in HIVL white matter damage is the dominating feature. In most HIV-1-infected brains the virus itself is detected in various regions [77], though preferentially in the basal ganglia, hippocampus, white matter and frontal cortex [75–77]. Further and probably resultant neuropathologic findings include injury and loss of dendrites, synapses and neurons, resulting macroscopically in brain atrophy [76,78,79].

To define the neuropathological substrate of cognitive impairment, efforts were made to correlate cognitive functioning with these neuropathological abnormalities. In pre-cART studies, the strongest correlations were demonstrated between cognitive dysfunction and increased expression of brain tissue markers of macrophage/microglial activation and between cognitive dysfunction and signs of neurodegeneration. Abnormalities such as HIV viral load, HIVE and HIVL were only loosely correlated with cognitive impairment [78–86]. The pathological correlate of HAND in the cART-era has not been defined, however, high-level macrophage/microglial-activation, similar to that observed in pre-cART studies, is also observed in cART-treated patients [87].

Brain tissue viral load is significantly lower among cART-treated patients with HIVE [88]. Otherwise, post-cART autopsy studies (although sparse and probably subjected to post-mortem exam selection bias) still report an HIVE incidence of 11–30% [84,89,90]. Compared with a pre-cART incidence of 10–54% this is only a moderate decrease, if any at all. So called minimal non-specific abnormalities are even reported more frequently in post-cART studies, but their significance remains to be clarified [84,89,91]. In two large post-cART cohort autopsy studies the CNS remains the second most frequently affected organ [89,92]. These observations are remarkable, considering that other neuropathologic abnormalities such as opportunistic infections and malignancies within the CNS have decreased significantly since the introduction of cART.

Pathogenesis

The pathogenic mechanisms behind CNS dysfunction in HIV-1-infection remain to a certain extent unclear. There are discrepancies between the distribution and number of HIV-1-infected cells and the severity of the clinical course and brain tissue pathology which support other mechanisms than direct viral cytotoxicity as a cause of CNS damage.

HIV-1 enters the CNS early following infection [93,94], primarily by means of monocytes and lymphocytes infected before trafficking across the blood-brain barrier (BBB). After entry, a chronic productive HIV-1-infection of macrophages and microglial cells is established. Normally, microglial cells express CD4-antigen at low levels, but they are likely to up-regulate the expression during cellular activation [95]. Besides CD4, macrophages and microglia also express CCR5 on their surface.

The CNS-infection leads to a chronic intrathecal immune-activation that is present during the entire infectious course [96] and while viral products may have direct toxic effects against neurons or astrocytes, the primary mechanism of neuronal damage is likely a result of the inflammatory process initiated by HIV-1-infected cells [97]. Macrophages and microglia act as both the major targets for HIV-1-replication and a source of neurotoxins [98]. Secreted cellular products such as cytokines, quinolinic and arachidonic acids and nitric oxide can have neurotoxic effects, and chemokines and pro-inflammatory cytokines promote further cell-activation and recruitment of additional macrophages and T-cells, thereby amplifying HIV-1-induced neurotoxicity [99].

Astrocytes can be infected (and perhaps even more extensively than previously thought [100]) by HIV-1, but the infection is generally non-productive with restricted viral gene expression [101]. However, astrocytes may indirectly contribute to the neuropathogenesis by activation and/or dysfunction leading to increased cytokine production, reduced uptake of neurotoxins and impairment of the BBB [102]. Dysfunction of the BBB may be the priming event in the pathogenesis of HAD [103]; increased BBB-permeability is a consistent finding in HAD [104] but also commonly found in early HIV-disease where it correlates to the degree of intrathecal immune-activation [105].

Neurons are not infected, but neuronal loss and decreased synaptic and dendritic density are, together with microglial and astrocyte proliferation and activation, commonly found and closely associated with HAD [106].

HIV-1-related neurodegeneration is also linked to intrathecal immune-activation [51] and signs of axonal disruption forecast the development of HAD [107]. Some reports suggest a similarity between pathogenesis of HIV-1 brain injury and Alzheimer's disease (AD), because of the deposition of amyloid plaques and precursor proteins in both conditions. However, the plaques observed in AD are typically intraneuronal, whereas these are both intra- and extra-neuronal in HIV-1 infection [108]. Patients with HAD have abnormal CSF-biomarkers of amyloid and tau metabolism [109] (like in AD), but the pattern differs from AD [68]. These differences imply separate underlying pathogenetic pathways of brain injury in HIV-

1-associated neurodegeneration and AD. Chronic immune-activation has an essential part in HIV-1 neuropathogenesis and it is commenced and driven by the CNS viral infection.

cART often has a dramatic beneficial effect on neurological and neurocognitive dysfunction in subjects with HAD supporting that a substantial share of symptoms relates to active, reversible toxic processes [110]. However, symptoms are not always totally reversed and persistent intrathecal immune-activation [65] and detectable CSF viral load [59] [Edén, in press] also after several years of otherwise effective treatment indicate an ongoing active process within the brain as well during successful antiretroviral therapy.

Compelling evidence from several studies demonstrate that HIV-1-infection in the CNS is compartmentalized from the systemic infection, although to varying degrees at different stages of the infection [111–113]. It is important not to overlook the CNS when discussing HIV-1 persistence and eradication strategies, as the brain may act as a sanctuary for latent or slowly replicating virus.

The consequences of the chronic, low-grade, CNS immune-activation have not yet been elucidated although concerns have been raised about an increased risk of HAND and/or other neurocognitive complaints, such as AD and vascular dementia, in the aging HIV-1-infected population.

Risk factors and comorbidities

Several risk factors and associated physiological and pathological conditions have been identified in patients with cognitive impairment – listed in Table 4. In particular, the consistent association with low nadir CD4 cell count suggests that previous CNS damage might be relevant in the pathogenesis of HAND [114]. On the other hand, both physiological aging and several current pathological conditions may themselves be associated with cognitive, neurological or psychiatric dysfunction and thus contribute to a various extent to sustain the picture of neurocognitive impairment. Practically, the presence of any of these conditions may confound the diagnosis of HAND.

In addition, individuals may also genetically be more susceptible to develop cognitive problems. For example, the E4 isoform of apolipoprotein E (APOE) has been linked, especially in the elderly, to an increased risk of HAD [115], and polymorphisms of CCL2 and its receptor CCR2 seem associated with neuropsychological abnormalities [116]. Finally, viral (genetic) factors might also affect neurotoxicity; the influence of viral subtypes on cognitive functioning is under investigation but not yet elucidated [117–119].

Interventions

cART

Zidovudine (the first approved antiretroviral drug for HIV) has been proven to have beneficial effects on cognitive functioning [120,121]. After the introduction of cART in 1996 many studies have reported additional improvements on cognitive functioning [122–128]. Some patients however only stabilize or show incomplete recovery on cART [124,127] and a small proportion of patients even deteriorates cognitively despite cART [128].

cART and the CNS

cART entry into the CNS is hampered by the BBB. Drugs easily passing the BBB and affecting (macrophages in) the CNS are so called neuroactive drugs.

Several studies have shown an association between the use of neuroactive drugs (defined in different ways) and good neurocognitive performance [123,129]. To better define and quantify CNS-effectiveness, a CNS penetration effectiveness (CPE) score, based on individual drug ranking, was more recently proposed [130–132]. Each individual antiretroviral drug has been given a score between 1 and 4; summing up the individual scores results in the CPE-score, with higher scores indicating more CNS-effectiveness. Regimens with higher CPE-scores have been correlated with neuropsychological improvement [128,133]. Reversely, a low CPE-ranking is associated with an 88% increase in the odds of detectable

Table 4. Risk factors and conditions/comorbidities associated with neurocognitive impairment in HIV-1-infection.

Risk factors	Conditions/Comorbidities
CD4 nadir [114]	HCV co-infection [152–155]
Aging [156,157]	Substance or alcohol abuse [152,158]
Microbial translocation [152,159]	Cardiovascular disease and metabolic disorder [152,160,161]
Anaemia [162]	Depression and other psychiatric conditions [163]
Thrombocytopenia [164]	Alzheimer's Disease and other neurodegenerative CNS diseases
Host genetic factors [115,116]	
Viral genetic factors [117]	

CSF viral load [130]. One contrasting smaller study reports less neurocognitive improvement in patients with high CPE-rankings [134].

Though efforts have been made to develop this tool to optimize treatment, there are limitations of the CPE-score and it is not yet validated for clinical use. The most important limitation is the amount of data available for each drug; inevitably, only some have been classified based on clinical information; others have been classified based only on pharmacokinetic or chemical features. Secondly, other factors may be of importance for the efficacy of cART in the CNS, such as genotypic resistance [63]. Furthermore, since it was first reported, several adjustments have been made to the CPE-scoring system, resulting in renewed versions. The CPE-scoring system will probably evolve further in the coming years, and large prospective studies will be required to establish the full value of this approach for clinical management.

Adverse effects of cART

Direct evidence for cART-related neurotoxicity is sparse [135]. Some nucleoside reverse transcriptase inhibitors are known (as is HIV-1-infection itself) to cause mitochondrial dysfunction in peripheral tissues (liver, heart, muscles) [135]. Whether or not neuronal damage as a result of mitochondrial dysfunction occurs is unknown. One MRS-study reports a decrease in NAA (a marker for neuronal integrity) in patients using didanosine and/or stavudine [136], indicating neuronal damage possibly as a result of mitochondrial dysfunction. In addition, in vitro research showed protease inhibitors to cause proteasome dysfunction resulting in intracellular accumulation of toxic proteins, possibly causing cell damage [137].

The non-nucleoside reverse transcriptase inhibitor efavirenz frequently causes neuropsychiatric side effects such as bad dreams, sleep disorders, dizziness, and anxiety. These effects usually subside after the first few weeks of therapy, but may persist in a minority of cases [138]. However, a negative effect of efavirenz on cognitive functioning in both short and long term has not been demonstrated [139].

Structured treatment interruptions (STIs) lead to viral rebound, deteriorating immune-function and worsening CSF-markers [140] and subsequently to increased incidence of opportunistic infections and death. However, the effect of STIs on cognitive function is controversial, which is interesting in the context of cART-neurotoxicity. One study investigating treatment interruptions reported cognitive stability for 6 months, despite worsening immunosuppression and viral rebound [141]. Another study investigating patients with high pre-entry and nadir CD4 who discontinued cART reported a modest neuropsychological improvement following interruption [71]. These results could support a degree of cART-neurotoxicity.

In the long term, as nadir CD4 has been recognized as a risk factor for developing HAND, STIs (resulting in decreasing CD4-counts) nevertheless might cause cognitive decline. Of note, intermittent antiretroviral therapy has clearly been associated with a higher risk of mortality from non-AIDS morbidity and mortality than continuous cART [142].

Adjunctive agents

Several non-cART agents have been investigated in vitro, in animal models and in humans (Table 5). However, so far the results of these trials are disappointing (as is the case in trials for other neurodegenerative diseases). None of them have offered a substantial solution in treating cognitive disorders in HIV-1 [135,143].

Discussion

Do we see new cognitive problems in HIV-1-infected individuals?

Yes, studies from different parts of the world, including large cohorts, report abnormal scores on neuropsychological assessments in 15–50% of patients.

Neuropsychological test batteries differ between studies and there is discussion on what is an abnormal test result. Patients with cognitive complaints show worse test results than those without.

What is the character of the abnormalities found?

The abnormalities found on neuropsychological assessments are milder than in full-blown HAD. In essence the core abnormality is slowness; patients do poor on all tests with a time-factor in it. The longer-term course of these cognitive impairments however is not known yet.

Which diagnostic tests are useful in the clinical setting?

Neuropsychological assessment, CSF-examination and MRI of the brain are important tools and accessible in many clinical settings. Neuropsychological examination will more reliably reveal the presence and character of neurocognitive disturbances. Virological, host response and CNS tissue damage CSF-markers may be helpful to diagnose CNS immune-activation and HIV-RNA load in particular reflects more directly to what extent the process is HIV-driven. DTI, providing detailed information of the integrity of the white matter, may become an important marker in the future.

What is going on in the brain?

Chronic immune-activation, HIV-driven or caused by other conditions such as aging (or a combination), might be the mechanism behind the cognitive problems we see

Table 5. Adjunctive agents.

Psychostimulants	HIV-infection of the CNS causes hypoactivation of the dopaminergic system [165]. Psychostimulants are known to stimulate the dopaminergic system and have thus been investigated in patients with HIV-related cognitive impairment. Methylphenidate and dextroamphetamine have shown to improve cognitive function though this effect seems short-lived and may be a result of relieving depressive symptoms [166,167]. As these agents are known to cause dependence, it might not be appropriate to prescribe these agents to patients with a history or a risk of substance abuse.
Selegiline	Selegiline is a MAO-B inhibitor and speculated to reduce oxidative stress and to have neuroprotective properties. Though two small studies report selegiline to improve cognitive functioning [168,169], three larger studies report no significant effect [170,171].
Valproic acid	VPA is supposed to have neuroprotective properties by inhibiting neuronal loss, stimulating neurogenesis and reducing neurotoxicity of HIV-infected macrophages [172]. On the other hand has VPA shown to induce microglial apoptosis and activate HIV replication in microglial cells [173,174]. One small study demonstrated a trend toward cognitive improvement and a significant improvement in MRS brain metabolite profile [175]. A negative effect of VPA on cognitive functioning though has been reported in HIV-patients using VPA for a longer period of time and in higher dosages [176].
Lexipafant	Lexipafant supposedly inhibits platelet-activating factor (PAF), which is an inflammatory mediator contributing to neuronal injury. A randomized trial reports merely a trend towards cognitive improvement [177].
Calcium channel blocker	Preventing excitotoxicity using a calcium channel blocker has been investigated in HAND, showing only a trend towards neurocognitive improvement [178].
Memantine	Memantine, an NMDA antagonist, supposedly has neuroprotective properties [179,180], but two trials have shown no significant cognitive improvement [181,182].
Minocycline	Minocycline is a broad-spectrum antibiotic and a member of the tetracycline family. Aside from antimicrobial properties it is supposed to have the ability to inhibit microglial activation and HIV replication and to exhibit antioxidative and neuroprotective properties [183–186]. A trial in humans is being conducted but not yet published.
Lithium	Lithium is used for depression and bipolar disorder and is supposed to have neuroprotective properties [187]. One small studie reports cognitive improvement (though this effect may also be the result of improving depressive symptoms), another small study solely reports improvements on neuroimaging [188,189].
Antioxidants	Inflammation results in free radicals leading to oxidative stress and cell damage. Antioxidants, inhibiting this oxidative stress, have been investigated and are still under investigation in treating HAND. Examples are CPI-1189, OPC-14117, thioctic acid and nutritional components such as vitamin C and E, green tea derived EGCG and curcumin [190–195]. The few agents that have been studied on humans have not shown convincing improvements on neurocognitive functioning. Thioctic acid has even shown a negative effect on cognition [169].
Serotonin reuptake inhibitor	In a cohort study serotonin reuptake inhibitors (in particular sertraline, citalopram and trazodone) are associated with lower CSF viral load and better neurocognitive performance, but this effect may also be the result of improving depressive symptoms [196].
Nanoparticles	Nanoparticles or nanocarriers may increase the penetration of antiretroviral drugs through the BBB and facilitate drug transport into the brain. Subsequently they may increase the bioavailability of ART in the brain. The use of nanotechnology for the treatment of HIV and the CNS is yet to be further investigated [197,198].

today. But many uncertainties remain. The clinical course of the cognitive impairment is unknown; it might be the result of a process that has been going on for years or there could be a subacute deterioration in which viral control in the CNS is suddenly lost. We do not know whether this will in the end happen in all HIV-infected individuals or in a subset of patients at risk. We may have missed an ongoing CNS replication in systemically well-controlled patients. We still do not know how to manage patients with low-level detectable HIV-1-RNA in the CSF. CSF, MRI and neuropathological studies have provided information about the localization, the character and the magnitude of the pathology that is present in cognitive impairment though this information is fragmented and so far unable to elucidate and interconnect all aspects related to cognitive impairment.

The HIV-neurology research agenda

In the coming years the clinical course of these impairments should be followed closely in large cohorts of patients. Risk factors and conditions other than HIV that could lead to neurocognitive dysfunction need to be defined more accurately.

More CSF-parameters need to be assessed and new MRI-techniques will hopefully provide us with more information on the white matter pathology, blood flow and vascular changes. For all antiretroviral drugs, CNS/CSF-penetration studies should be performed, as well as clinical trials comparing different antiretroviral regimens. Promising adjunctive treatments should also selectively be studied. These efforts are essential to understand what is going on in the brain in longstanding HIV-1-infection and to prevent dysfunction and provide optimal management and cure.

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References

1. Navia BA, Jordan BD, Price RW. **The AIDS dementia complex: I. Clinical features.** *Ann Neurol* 1986; **19**:517–524.
2. Navia BA, Cho ES, Petito CK, Price RW. **The AIDS dementia complex: II. Neuropathology.** *Ann Neurol* 1986; **19**:525–535.
3. Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, *et al*. **Updated research nosology for HIV-associated neurocognitive disorders.** *Neurology* 2007; **69**:1789–1799.
4. Simioni S, Cavassini M, Annoni JM, Rimbault Abraham A, Bourquin I, Schiffer V, *et al.* **Cognitive dysfunction in HIV patients despite long-standing suppression of viremia.** *Aids* 2009.
5. Cysique LA, Maruff P, Brew BJ. **Prevalence and pattern of neuropsychological impairment in human immunodeficiency virus-infected/acquired immunodeficiency syndrome (HIV/AIDS) patients across pre- and post-highly active antiretroviral therapy eras: a combined study of two cohorts.** *J Neurovirol* 2004; **10**:350–357.
6. Hinkin CH, Castellon SA, Durvasula RS, Hardy DJ, Lam MN, Mason KI, *et al*. **Medication adherence among HIV+ adults: effects of cognitive dysfunction and regimen complexity.** *Neurology* 2002; **59**:1944–1950.
7. Cysique LA, Maruff P, Brew BJ. **The neuropsychological profile of symptomatic AIDS and ADC patients in the pre-HAART era: a meta-analysis.** *J Int Neuropsychol Soc* 2006; **12**:368–382.
8. Woods SP, Moore DJ, Weber E, Grant I. **Cognitive neuropsychology of HIV-associated neurocognitive disorders.** *Neuropsychol Rev* 2009; **19**:152–168.
9. Skinner S, Adewale AJ, DeBlock L, Gill MJ, Power C. **Neurocognitive screening tools in HIV/AIDS: comparative performance among patients exposed to antiretroviral therapy.** *HIV Med* 2009; **10**:246–252.
10. Power C, Selnes OA, Grim JA, McArthur JC. **HIV Dementia Scale: a rapid screening test.** *J Acquir Immune Defic Syndr Hum Retrovirol* 1995; **8**:273–278.
11. Bottiggi KA, Chang JJ, Schmitt FA, Avison MJ, Mootoor Y, Nath A, Berger JR. **The HIV Dementia Scale: predictive power in mild dementia and HAART.** *J Neurol Sci* 2007; **260**:11–15.
12. Sacktor NC, Wong M, Nakasujja N, Skolasky RL, Selnes OA, Musisi S, *et al*. **The International HIV Dementia Scale: a new rapid screening test for HIV dementia.** *Aids* 2005; **19**:1367–1374.
13. Tate DF. **Neuroimaging among HIV-infected patients: current knowledge and future directions.** In: *HIV and the brain*. Edited by Paul RH; 2009. pp. 75–107.
14. Stout JC, Ellis RJ, Jernigan TL, Archibald SL, Abramson I, Wolfson T, *et al*. **Progressive cerebral volume loss in human immunodeficiency virus infection: a longitudinal volumetric magnetic resonance imaging study. HIV Neurobehavioral Research Center Group.** *Arch Neurol* 1998; **55**:161–168.
15. Patel SH, Kolson DL, Glosser G, Matozzo I, Ge Y, Babb JS, *et al*. **Correlation between percentage of brain parenchymal volume and neurocognitive performance in HIV-infected patients.** *AJNR Am J Neuroradiol* 2002; **23**:543–549.
16. Chiang MC, Dutton RA, Hayashi KM, Lopez OL, Aizenstein HJ, Toga AW, *et al*. **3D pattern of brain atrophy in HIV/AIDS visualized using tensor-based morphometry.** *Neuroimage* 2007; **34**:44–60.
17. Samuelsson K, Pirskanen-Matell R, Bremmer S, Hindmarsh T, Nilsson BY, Persson HE. **The nervous system in early HIV infection: a prospective study through 7 years.** *Eur J Neurol* 2006; **13**:283–291.
18. Dal Pan GJ, McArthur JH, Aylward E, Selnes OA, Nance-Sproson TE, Kumar AJ, *et al*. **Patterns of cerebral atrophy in HIV-1-infected individuals: results of a quantitative MRI analysis.** *Neurology* 1992; **42**:2125–2130.
19. McArthur JC, Kumar AJ, Johnson DW, Selnes OA, Becker JT, Herman C, *et al*. **Incidental white matter hyperintensities on magnetic resonance imaging in HIV-1 infection. Multicenter AIDS Cohort Study.** *J Acquir Immune Defic Syndr* 1990; **3**:252–259.
20. Paul R, Cohen R, Navia B, Tashima K. **Relationships between cognition and structural neuroimaging findings in adults with human immunodeficiency virus type-1.** *Neurosci Biobehav Rev* 2002; **26**:353–359.
21. Archibald SL, Masliah E, Fennema-Notestine C, Marcotte TD, Ellis RJ, McCutchan JA, *et al*. **Correlation of in vivo neuroimaging abnormalities with postmortem human immunodeficiency virus encephalitis and dendritic loss.** *Arch Neurol* 2004; **61**:369–376.
22. Brew BJ. **AIDS dementia complex.** In: *Handbook of clinical neurology*. Edited by Portegies P; 2007. pp. 79–91.
23. Chang L, Ernst T, Leonido-Yee M, Walot I, Singer E. **Cerebral metabolite abnormalities correlate with clinical severity of HIV-1 cognitive motor complex.** *Neurology* 1999; **52**:100–108.
24. Mohamed MA, Lentz MR, Lee V, Halpern EF, Sacktor N, Selnes O, *et al*. **Factor analysis of proton MR spectroscopic imaging data in HIV infection: metabolite-derived factors help identify infection and dementia.** *Radiology* 2010; **254**:577–586.
25. Sacktor N, Skolasky RL, Ernst T, Mao X, Selnes O, Pomper MG, *et al*. **A multicenter study of two magnetic resonance spectroscopy techniques in individuals with HIV dementia.** *J Magn Reson Imaging* 2005; **21**:325–333.
26. Tucker KA, Robertson KR, Lin W, Smith JK, An H, Chen Y, *et al*. **Neuroimaging in human immunodeficiency virus infection.** *J Neuroimmunol* 2004; **157**:153–162.
27. Stankoff B, Tourbah A, Suarez S, Turell E, Stievenart JL, Payan C, *et al*. **Clinical and spectroscopic improvement in HIV-associated cognitive impairment.** *Neurology* 2001; **56**:112–115.
28. Chang L, Ernst T, Leonido-Yee M, Witt M, Speck O, Walot I, Miller EN. **Highly active antiretroviral therapy reverses brain metabolite abnormalities in mild HIV dementia.** *Neurology* 1999; **53**:782–789.
29. Ernst T, Itti E, Itti L, Chang L. **Changes in cerebral metabolism are detected prior to perfusion changes in early HIV-CMC: A coregistered (1)H MRS and SPECT study.** *J Magn Reson*

Imaging 2000; **12**:859–865.

30. Paul RH, Ernst T, Brickman AM, Yiannoutsos CT, Tate DF, Cohen RA, Navia BA. **Relative sensitivity of magnetic resonance spectroscopy and quantitative magnetic resonance imaging to cognitive function among nondemented individuals infected with HIV.** *J Int Neuropsychol Soc* 2008; **14**:725–733.
31. Pomara N, Crandall DT, Choi SJ, Johnson G, Lim KO. **White matter abnormalities in HIV-1 infection: a diffusion tensor imaging study.** *Psychiatry Res* 2001; **106**:15–24.
32. Ragin AB, Wu Y, Storey P, Cohen BA, Edelman RR, Epstein LG. **Diffusion tensor imaging of subcortical brain injury in patients infected with human immunodeficiency virus.** *J Neurovirol* 2005; **11**:292–298.
33. Gongvatana A, Schweinsburg BC, Taylor MJ, Theilmann RJ, Letendre SL, Alhassoon OM, *et al*. **White matter tract injury and cognitive impairment in human immunodeficiency virus-infected individuals.** *J Neurovirol* 2009; **15**:187–195.
34. Chen Y, An H, Zhu H, Stone T, Smith JK, Hall C, *et al*. **White matter abnormalities revealed by diffusion tensor imaging in non-demented and demented HIV+ patients.** *Neuroimage* 2009; **47**:1154–1162.
35. Tracey I, Hamberg LM, Guimaraes AR, Hunter G, Chang I, Navia BA, Gonzalez RG. **Increased cerebral blood volume in HIV-positive patients detected by functional MRI.** *Neurology* 1998; **50**:1821–1826.
36. Ernst T, Yakupov R, Nakama H, Crocket G, Cole M, Watters M, *et al*. **Declined neural efficiency in cognitively stable human immunodeficiency virus patients.** *Ann Neurol* 2009; **65**:316–325.
37. Ernst T, Chang L, Arnold S. **Increased glial metabolites predict increased working memory network activation in HIV brain injury.** *Neuroimage* 2003; **19**:1686–1693.
38. Chang L, Ernst T, Leonido-Yee M, Speck O. **Perfusion MRI detects rCBF abnormalities in early stages of HIV-cognitive motor complex.** *Neurology* 2000; **54**:389–396.
39. Ances BM, Sisti D, Vaida F, Liang CL, Leontiev O, Perthen JE, *et al*. **Resting cerebral blood flow: a potential biomarker of the effects of HIV in the brain.** *Neurology* 2009; **73**:702–708.
40. Dousset V, Armand JP, Lacoste D, Mieze S, Letenneur L, Dartigues JF, Caill JM. **Magnetization transfer study of HIV encephalitis and progressive multifocal leukoencephalopathy. Groupe d'Epidemiologie Clinique du SIDA en Aquitaine.** *AJNR Am J Neuroradiol* 1997; **18**:895–901.
41. Wu Y, Storey P, Carrillo A, Saglamer C, Cohen BA, Epstein LG, *et al*. **Whole brain and localized magnetization transfer measurements are associated with cognitive impairment in patients infected with human immunodeficiency virus.** *AJNR Am J Neuroradiol* 2008; **29**:140–145.
42. Sacktor N, Van Heertum RL, Dooneief G, Gorman J, Khandji A, Marder K, *et al*. **A comparison of cerebral SPECT abnormalities in HIV-positive homosexual men with and without cognitive impairment.** *Arch Neurol* 1995; **52**:1170–1173.
43. Christensson B, Ljungberg B, Ryding E, Svenson G, Rosen I. **SPECT with 99mTc-HMPAO in subjects with HIV infection: cognitive dysfunction correlates with high uptake.** *Scand J Infect Dis* 1999; **31**:349–354.
44. von Giesen HJ, Antke C, Hefter H, Wenserski F, Seitz RJ, Arendt G. **Potential time course of human immunodeficiency virus type 1-associated minor motor deficits: electrophysiologic and positron emission tomography findings.** *Arch Neurol* 2000; **57**:1601–1607.
45. Ellis RJ, Childers ME, Zimmerman JD, Frost SD, Deutsch R, McCutchan JA. **Human immunodeficiency virus-1 RNA levels in cerebrospinal fluid exhibit a set point in clinically stable patients not receiving antiretroviral therapy.** *J Infect Dis* 2003; **187**:1818–1821.
46. Cinque P, Vago L, Ceresa D, Mainini F, Terreni MR, Vagani A, *et al*. **Cerebrospinal fluid HIV-1 RNA levels: correlation with HIV encephalitis.** *Aids* 1998; **12**:389–394.
47. Hagberg L, Cinque P, Gisslen M, Brew BJ, Spudich S, Bestetti A, *et al*. **Cerebrospinal fluid neopterin: an informative biomarker of central nervous system immune activation in HIV-1 infection.** *AIDS Res Ther* 2010; **7**:15.
48. Enting RH, Foudraine NA, Lange JM, Jurriaans S, van der Poll T, Weverling GJ, Portegies P. **Cerebrospinal fluid beta2-microglobulin, monocyte chemotactic protein-1, and soluble tumour necrosis factor alpha receptors before and after treatment with lamivudine plus zidovudine or stavudine.** *J Neuroimmunol* 2000; **102**:216–221.
49. Cinque P, Vago L, Mengozzi M, Torri V, Ceresa D, Vicenzi E, *et al*. **Elevated cerebrospinal fluid levels of monocyte chemotactic protein-1 correlate with HIV-1 encephalitis and local viral replication.** *Aids* 1998; **12**:1327–1332.
50. Kelder W, McArthur JC, Nance-Sproson T, McClernon D, Griffin DE. **Beta-chemokines MCP-1 and RANTES are selectively increased in cerebrospinal fluid of patients with human immunodeficiency virus-associated dementia.** *Ann Neurol* 1998; **44**:831–835.
51. Abdulle S, Mellgren A, Brew BJ, Cinque P, Hagberg L, Price RW, *et al*. **CSF neurofilament protein (NFL) – a marker of active HIV-related neurodegeneration.** *J Neurol* 2007; **254**:1026–1032.
52. Staprans S, Marlowe N, Glidden D, Novakovic-Agopian T, Grant RM, Heyes M, *et al*. **Time course of cerebrospinal fluid responses to antiretroviral therapy: evidence for variable compartmentalization of infection.** *Aids* 1999; **13**:1051–1061.
53. Ellis RJ, Gamst AC, Capparelli E, Spector SA, Hsia K, Wolfson T, *et al*. **Cerebrospinal fluid HIV RNA originates from both local CNS and systemic sources.** *Neurology* 2000; **54**:927–936.
54. Cinque P, Presi S, Bestetti A, Pierotti C, Racca S, Boeri E, *et al*. **Effect of genotypic resistance on the virological response to highly active antiretroviral therapy in cerebrospinal fluid.** *AIDS Res Hum Retroviruses* 2001; **17**:377–383.
55. Eggers C, Hertogs K, Sturenburg HJ, van Lunzen J, Stellbrink HJ. **Delayed central nervous system virus suppression during highly active antiretroviral therapy is associated with HIV encephalopathy, but not with viral drug resistance or poor central nervous system drug penetration.** *Aids* 2003; **17**:1897–1906.
56. Mellgren A, Price RW, Hagberg L, Rosengren L, Brew BJ, Gisslen M. **Antiretroviral treatment reduces increased CSF neurofilament protein (NFL) in HIV-1 infection.** *Neurology* 2007; **69**:1536–1541.
57. Sevigny JJ, Albert SM, McDermott MP, McArthur JC, Sacktor N, Conant K, *et al*. **Evaluation of HIV RNA and markers of immune activation as predictors of HIV-associated dementia.** *Neurology* 2004; **63**:2084–2090.
58. Cysique LA, Brew BJ, Halman M, Catalan J, Sacktor N, Price RW, *et al*. **Undetectable cerebrospinal fluid HIV RNA and beta-2 microglobulin do not indicate inactive AIDS dementia complex in highly active antiretroviral therapy-treated patients.** *J Acquir Immune Defic Syndr* 2005; **39**:426–429.
59. Spudich S, Lollo N, Liegler T, Deeks SG, Price RW. **Treatment benefit on cerebrospinal fluid HIV-1 levels in the setting of systemic virological suppression and failure.** *J Infect Dis* 2006; **194**:1686–1696.
60. Yilmaz A, Svennerholm B, Hagberg L, Gisslen M. **Cerebrospinal fluid viral loads reach less than 2 copies/ml in HIV-1-infected patients with effective antiretroviral therapy.** *Antivir Ther* 2006; **11**:833–837.
61. Probasco JC, Deeks SG, Lee E, Hoh R, Hunt PW, Liegler T, *et al*. **Cerebrospinal fluid in HIV-1 systemic viral controllers: absence of HIV-1 RNA and intrathecal inflammation.** *Aids* 2010; **24**:1001–1005.
62. Eden A FD, Hagberg L, Nilsson S, Spudich S, Svennerholm B, Price RW, Gisslen M. **Ten percent of HIV-1 infected subjects on suppressive antiretroviral treatment have viral escape in cerebrospinal fluid.** *J Infect Dis* 2010 in press.
63. Canestri A, Lescure FX, Jaureguiberry S, Moulignier A, Amiel C, Marcelin AG, *et al*. **Discordance between cerebral spinal fluid and plasma HIV replication in patients with neurological symptoms who are receiving suppressive antiretroviral therapy.** *Clin Infect Dis* 2010; **50**:773–778.
64. Gisolf EH, van Praag RM, Jurriaans S, Portegies P, Goudsmit J, Danner SA, *et al*. **Increasing cerebrospinal fluid chemokine concentrations despite undetectable cerebrospinal fluid HIV RNA in HIV-1-infected patients receiving antiretroviral therapy.** *J Acquir Immune Defic Syndr* 2000; **25**:426–433.
65. Eden A, Price RW, Spudich S, Fuchs D, Hagberg L, Gisslen M. **Immune activation of the central nervous system is still present after >4 years of effective highly active antiretroviral therapy.** *J Infect Dis* 2007; **196**:1779–1783.

66. Conde JR, Streit WJ. **Microglia in the aging brain.** *J Neuropathol Exp Neurol* 2006; **65**:199–203.
67. Gonzalez-Scarano F, Baltuch G. **Microglia as mediators of inflammatory and degenerative diseases.** *Annu Rev Neurosci* 1999; **22**:219–240.
68. Gisslen M, Krut J, Andreasson U, Blennow K, Cinque P, Brew BJ, *et al*. **Amyloid and tau cerebrospinal fluid biomarkers in HIV infection.** *BMC Neurol* 2009; **9**:63.
69. Wilkinson J, Radkowski M, Laskus T. **Hepatitis C virus neuroinvasion: identification of infected cells.** *J Virol* 2009; **83**:1312–1319.
70. Wright EJ, Grund B, Robertson K, Brew BJ, Roediger M, Bain MP, *et al*. **Cardiovascular risk factors associated with lower baseline cognitive performance in HIV-positive persons.** *Neurology* 2010.
71. Robertson KR, Su Z, Margolis DM, Krambrink A, Havlir DV, Evans S, Skiest DJ. **Neurocognitive effects of treatment interruption in stable HIV-positive patients in an observational cohort.** *Neurology* 2010; **74**:1260–1266.
72. Cinque P, Nebuloni M, Santovito ML, Price RW, Gisslen M, Hagberg L, *et al*. **The urokinase receptor is overexpressed in the AIDS dementia complex and other neurological manifestations.** *Ann Neurol* 2004; **55**:687–694.
73. Laspiur JP, Anderson ER, Ciborowski P, Wojna V, Rozek W, Duan F, *et al*. **CSF proteomic fingerprints for HIV-associated cognitive impairment.** *J Neuroimmunol* 2007; **192**:157–170.
74. Wikoff WR, Pendyala G, Siuzdak G, Fox HS. **Metabolomic analysis of the cerebrospinal fluid reveals changes in phospholipase expression in the CNS of SIV-infected macaques.** *J Clin Invest* 2008; **118**:2661–2669.
75. Budka H. **Neuropathology of human immunodeficiency virus infection.** *Brain Pathol* 1991; **1**:163–175.
76. Bell JE. **An update on the neuropathology of HIV in the HAART era.** *Histopathology* 2004; **45**:549–559.
77. Wiley CA, Soontornniyomkij V, Radhakrishnan L, Masliah E, Mellors J, Hermann SA, *et al*. **Distribution of brain HIV load in AIDS.** *Brain Pathol* 1998; **8**:277–284.
78. Everall IP, Heaton RK, Marcotte TD, Ellis RJ, McCutchan JA, Atkinson JH, *et al*. **Cortical synaptic density is reduced in mild to moderate human immunodeficiency virus neurocognitive disorder. HNRC Group. HIV Neurobehavioral Research Center.** *Brain Pathol* 1999; **9**:209–217.
79. Moore DJ, Masliah E, Rippeth JD, Gonzalez R, Carey CL, Cherner M, *et al*. **Cortical and subcortical neurodegeneration is associated with HIV neurocognitive impairment.** *Aids* 2006; **20**:879–887.
80. Cherner M, Masliah E, Ellis RJ, Marcotte TD, Moore DJ, Grant I, Heaton RK. **Neurocognitive dysfunction predicts postmortem findings of HIV encephalitis.** *Neurology* 2002; **59**:1563–1567.
81. Johnson RT, Glass JD, McArthur JC, Chesebro BW. **Quantitation of human immunodeficiency virus in brains of demented and nondemented patients with acquired immunodeficiency syndrome.** *Ann Neurol* 1996; **39**:392–395.
82. Ances BM, Ellis RJ. **Dementia and neurocognitive disorders due to HIV-1 infection.** *Semin Neurol* 2007; **27**:86–92.
83. Brew BJ, Rosenblum M, Cronin K, Price RW. **AIDS dementia complex and HIV-1 brain infection: clinical-virological correlations.** *Ann Neurol* 1995; **38**:563–570.
84. Everall I, Vaida F, Khanlou N, Lazzaretto D, Achim C, Letendre S, *et al*. **Cliniconeuropathologic correlates of human immunodeficiency virus in the era of antiretroviral therapy.** *J Neurovirol* 2009; **15**:360–370.
85. Kumar AM, Borodowsky I, Fernandez B, Gonzalez L, Kumar M. **Human immunodeficiency virus type 1 RNA Levels in different regions of human brain: quantification using real-time reverse transcriptase-polymerase chain reaction.** *J Neurovirol* 2007; **13**:210–224.
86. Glass JD, Fedor H, Wesselingh SL, McArthur JC. **Immunocytochemical quantitation of human immunodeficiency virus in the brain: correlations with dementia.** *Ann Neurol* 1995; **38**:755–762.
87. Anthony IC, Ramage SN, Carnie FW, Simmonds P, Bell JE. **Influence of HAART on HIV-related CNS disease and neuroinflammation.** *J Neuropathol Exp Neurol* 2005; **64**:529–536.
88. Langford D, Marquie-Beck J, de Almeida S, Lazzaretto D, Letendre S, Grant I, *et al*. **Relationship of antiretroviral treatment to postmortem brain tissue viral load in human immunodeficiency virus-infected patients.** *J Neurovirol* 2006; **12**:100–107.
89. Jellinger KA, Setinek U, Drlicek M, Bohm G, Steurer A, Lintner F. **Neuropathology and general autopsy findings in AIDS during the last 15 years.** *Acta Neuropathol* 2000; **100**:213–220.
90. Vago L, Bonetto S, Nebuloni M, Duca P, Carsana L, Zerbi P, D'Arminio-Monforte A. **Pathological findings in the central nervous system of AIDS patients on assumed antiretroviral therapeutic regimens: retrospective study of 1597 autopsies.** *Aids* 2002; **16**:1925–1928.
91. Gray F, Chretien F, Vallat-Decouvelaere AV, Scaravilli F. **The changing pattern of HIV neuropathology in the HAART era.** *J Neuropathol Exp Neurol* 2003; **62**:429–440.
92. Masliah E, DeTeresa RM, Mallory ME, Hansen LA. **Changes in pathological findings at autopsy in AIDS cases for the last 15 years.** *Aids* 2000; **14**:69–74.
93. Davis LE, Hjelle BL, Miller VE, Palmer DL, Llewellyn AL, Merlin TL, *et al*. **Early viral brain invasion in iatrogenic human immunodeficiency virus infection.** *Neurology* 1992; **42**:1736–1739.
94. Schacker T, Collier AC, Hughes J, Shea T, Corey L. **Clinical and epidemiologic features of primary HIV infection.** *Ann Intern Med* 1996; **125**:257–264.
95. Perry VH, Gordon S. **Modulation of CD4 antigen on macrophages and microglia in rat brain.** *J Exp Med* 1987; **166**:1138–1143.
96. Gisslen M, Fuchs D, Svennerholm B, Hagberg L. **Cerebrospinal fluid viral load, intrathecal immunoactivation, and cerebrospinal fluid monocytic cell count in HIV-1 infection.** *J Acquir Immune Defic Syndr* 1999; **21**:271–276.
97. Price RW, Brew B, Sidtis J, Rosenblum M, Scheck AC, Cleary P. **The brain in AIDS: central nervous system HIV-1 infection and AIDS dementia complex.** *Science* 1988; **239**:586–592.
98. Kim WK, Avarez X, Williams K. **The role of monocytes and perivascular macrophages in HIV and SIV neuropathogenesis: information from non-human primate models.** *Neurotox Res* 2005; **8**:107–115.
99. Gonzalez-Scarano F, Martin-Garcia J. **The neuropathogenesis of AIDS.** *Nat Rev Immunol* 2005; **5**:69–81.
100. Churchill MJ, Wesselingh SL, Cowley D, Pardo CA, McArthur JC, Brew BJ, Gorry PR. **Extensive astrocyte infection is prominent in human immunodeficiency virus-associated dementia.** *Ann Neurol* 2009; **66**:253–258.
101. Gorry PR, Ong C, Thorpe J, Bannwarth S, Thompson KA, Gatignol A, *et al*. **Astrocyte infection by HIV-1: mechanisms of restricted virus replication, and role in the pathogenesis of HIV-1-associated dementia.** *Curr HIV Res* 2003; **1**:463–473.
102. Minagar A, Shapshak P, Fujimura R, Ownby R, Heyes M, Eisdorfer C. **The role of macrophage/microglia and astrocytes in the pathogenesis of three neurologic disorders: HIV-associated dementia, Alzheimer disease, and multiple sclerosis.** *J Neurol Sci* 2002; **202**:13–23.
103. Power C, Kong PA, Crawford TO, Wesselingh S, Glass JD, McArthur JC, Trapp BD. **Cerebral white matter changes in acquired immunodeficiency syndrome dementia: alterations of the blood-brain barrier.** *Ann Neurol* 1993; **34**:339–350.
104. McArthur JC, Nance-Sproson TE, Griffin DE, Hoover D, Selnes OA, Miller EN, *et al*. **The diagnostic utility of elevation in cerebrospinal fluid beta 2-microglobulin in HIV-1 dementia. Multicenter AIDS Cohort Study.** *Neurology* 1992; **42**:1707–1712.
105. Andersson LM, Hagberg L, Fuchs D, Svennerholm B, Gisslen M. **Increased blood-brain barrier permeability in neuro-asymptomatic HIV-1-infected individuals–correlation with cerebrospinal fluid HIV-1 RNA and neopterin levels.** *J Neurovirol* 2001; **7**:542–547.
106. Kaul M, Lipton SA. **Mechanisms of neuroimmunity and neurodegeneration associated with HIV-1 infection and AIDS.** *J Neuroimmune Pharmacol* 2006; **1**:138–151.
107. Gisslen M, Hagberg L, Brew BJ, Cinque P, Price RW, Rosengren L. **Elevated cerebrospinal fluid neurofilament light protein concentrations predict the development of AIDS dementia complex.** *J Infect Dis* 2007; **195**:1774–1778.
108. Green DA, Masliah E, Vinters HV, Beizai P, Moore DJ, Achim CL. **Brain deposition of beta-amyloid is a common pathologic feature in HIV positive patients.** *Aids* 2005; **19**:407–411.

109. Clifford DB, Fagan AM, Holtzman DM, Morris JC, Teshome M, Shah AR, Kauwe JS. **CSF biomarkers of Alzheimer disease in HIV-associated neurologic disease.** *Neurology* 2009; **73**:1982–1987.
110. Price RW, Spudich S. **Antiretroviral therapy and central nervous system HIV type 1 infection.** *J Infect Dis* 2008; **197 (Suppl 3)**:S294–S306.
111. Harrington PR, Schnell G, Letendre SL, Ritola K, Robertson K, Hall C, *et al*. **Cross-sectional characterization of HIV-1 env compartmentalization in cerebrospinal fluid over the full disease course.** *AIDS* 2009; **23**:907–915.
112. Schnell G, Spudich S, Harrington P, Price RW, Swanstrom R. **Compartmentalized human immunodeficiency virus type 1 originates from long-lived cells in some subjects with HIV-1-associated dementia.** *PLoS Pathog* 2009; **5**:e1000395.
113. Dunfee RL, Thomas ER, Gorry PR, Wang J, Taylor J, Kunstman K, *et al*. **The HIV Env variant N283 enhances macrophage tropism and is associated with brain infection and dementia.** *Proc Natl Acad Sci U S A* 2006; **103**:15160–15165.
114. Valcour V, Yee P, Williams AE, Shiramizu B, Watters M, Selnes O, *et al*. **Lowest ever CD4 lymphocyte count (CD4 nadir) as a predictor of current cognitive and neurological status in human immunodeficiency virus type 1 infection–The Hawaii Aging with HIV Cohort.** *J Neurovirol* 2006; **12**:387–391.
115. Valcour V, Shikuma C, Shiramizu B, Watters M, Poff P, Selnes OA, *et al*. **Age, apolipoprotein E4, and the risk of HIV dementia: the Hawaii Aging with HIV Cohort.** *J Neuroimmunol* 2004; **157**:197–202.
116. Singh KK, Ellis RJ, Marquie-Beck J, Letendre S, Heaton RK, Grant I, Spector SA. **CCR2 polymorphisms affect neuropsychological impairment in HIV-1-infected adults.** *J Neuroimmunol* 2004; **157**:185–192.
117. Mishra M, Vetrivel S, Siddappa NB, Ranga U, Seth P. **Clade-specific differences in neurotoxicity of human immunodeficiency virus-1 B and C Tat of human neurons: significance of dicysteine C30C31 motif.** *Ann Neurol* 2008; **63**:366–376.
118. Sacktor N, Nakasujja N, Skolasky RL, Rezapour M, Robertson K, Musisi S, *et al*. **HIV subtype D is associated with dementia, compared with subtype A, in immunosuppressed individuals at risk of cognitive impairment in Kampala, Uganda.** *Clin Infect Dis* 2009; **49**:780–786.
119. Boivin MJ, Ruel TD, Boal HE, Bangirana P, Cao H, Eller LA, *et al*. **HIV-subtype A is associated with poorer neuropsychological performance compared with subtype D in antiretroviral therapy-naive Ugandan children.** *Aids* 2010; **24**:1163–1170.
120. Sidtis JJ, Gatsonis C, Price RW, Singer EJ, Collier AC, Richman DD, *et al*. **Zidovudine treatment of the AIDS dementia complex: results of a placebo-controlled trial. AIDS Clinical Trials Group.** *Ann Neurol* 1993; **33**:343–349.
121. Portegies P, de Gans J, Lange JM, Derix MM, Speelman H, Bakker M, *et al*. **Declining incidence of AIDS dementia complex after introduction of zidovudine treatment.** *Bmj* 1989; **299**:819–821.
122. Tozzi V, Balestra P, Galgani S, Narciso P, Ferri F, Sebastiani G, *et al*. **Positive and sustained effects of highly active antiretroviral therapy on HIV-1-associated neurocognitive impairment.** *Aids* 1999; **13**:1889–1897.
123. Cysique LA, Maruff P, Brew BJ. **Variable benefit in neuropsychological function in HIV-infected HAART-treated patients.** *Neurology* 2006; **66**:1447–1450.
124. Tozzi V, Balestra P, Bellagamba R, Corpolongo A, Salvatori MF, Visco-Comandini U, *et al*. **Persistence of neuropsychologic deficits despite long-term highly active antiretroviral therapy in patients with HIV-related neurocognitive impairment: prevalence and risk factors.** *J Acquir Immune Defic Syndr* 2007; **45**:174–182.
125. Robertson KR, Robertson WT, Ford S, Watson D, Fiscus S, Harp AG, Hall CD. **Highly active antiretroviral therapy improves neurocognitive functioning.** *J Acquir Immune Defic Syndr* 2004; **36**:562–566.
126. Marra CM, Lockhart D, Zunt JR, Perrin M, Coombs RW, Collier AC. **Changes in CSF and plasma HIV-1 RNA and cognition after starting potent antiretroviral therapy.** *Neurology* 2003; **60**:1388–1390.
127. McCutchan JA, Wu JW, Robertson K, Koletar SL, Ellis RJ, Cohn S, *et al*. **HIV suppression by HAART preserves cognitive function in advanced, immune-reconstituted AIDS patients.** *Aids* 2007; **21**:1109–1117.
128. Cysique LA, Vaida F, Letendre S, Gibson S, Cherner M, Woods SP, *et al*. **Dynamics of cognitive change in impaired HIV-positive patients initiating antiretroviral therapy.** *Neurology* 2009; **73**:342–348.
129. Letendre SL, McCutchan JA, Childers ME, Woods SP, Lazzaretto D, Heaton RK, *et al*. **Enhancing antiretroviral therapy for human immunodeficiency virus cognitive disorders.** *Ann Neurol* 2004; **56**:416–423.
130. Letendre S, Marquie-Beck J, Capparelli E, Best B, Clifford D, Collier AC, *et al*. **Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system.** *Arch Neurol* 2008; **65**:65–70.
131. Letendre S, Ellis R, Deutsch R, Clifford D, Marra C, McCutchan A, *et al*. *Correlates of Time-to-Loss-of-Viral-Response in CSF and Plasma in the CHARTER Cohort*. In: *CROI, paper #430*. San Francisco; 2010.
132. Letendre SL, Ellis RJ, Ances BM, McCutchan JA. **Neurologic complications of HIV disease and their treatment.** *Top HIV Med* 2010; **18**:45–55.
133. Tozzi V, Balestra P, Salvatori MF, Vlassi C, Liuzzi G, Giancola ML, *et al*. **Changes in cognition during antiretroviral therapy: comparison of 2 different ranking systems to measure antiretroviral drug efficacy on HIV-associated neurocognitive disorders.** *J Acquir Immune Defic Syndr* 2009; **52**:56–63.
134. Marra CM, Zhao Y, Clifford DB, Letendre S, Evans S, Henry K, *et al*. **Impact of combination antiretroviral therapy on cerebrospinal fluid HIV RNA and neurocognitive performance.** *Aids* 2009; **23**:1359–1366.
135. Cysique LA, Brew BJ. **Neuropsychological functioning and antiretroviral treatment in HIV/AIDS: a review.** *Neuropsychol Rev* 2009; **19**:169–185.
136. Schweinsburg BC, Taylor MJ, Alhassoon OM, Gonzalez R, Brown GG, Ellis RJ, *et al*. **Brain mitochondrial injury in human immunodeficiency virus-seropositive (HIV+) individuals taking nucleoside reverse transcriptase inhibitors.** *J Neurovirol* 2005; **11**:356–364.
137. Piccinini M, Rinaudo MT, Anselmino A, Buccinna B, Ramondetti C, Dematteis A, *et al*. **The HIV protease inhibitors nelfinavir and saquinavir, but not a variety of HIV reverse transcriptase inhibitors, adversely affect human proteasome function.** *Antivir Ther* 2005; **10**:215–223.
138. Rihs TA, Begley K, Smith DE, Sarangapany J, Callaghan A, Kelly M, *et al*. **Efavirenz and chronic neuropsychiatric symptoms: a cross-sectional case control study.** *HIV Med* 2006; **7**:544–548.
139. Clifford DB, Evans S, Yang Y, Acosta EP, Ribaudo H, Gulick RM. **Long-term impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals (ACTG 5097s).** *HIV Clin Trials* 2009; **10**:343–355.
140. Gisslen M, Rosengren L, Hagberg L, Deeks SG, Price RW. **Cerebrospinal fluid signs of neuronal damage after antiretroviral treatment interruption in HIV-1 infection.** *AIDS Res Ther* 2005; **2**:6.
141. Childers ME, Woods SP, Letendre S, McCutchan JA, Rosario D, Grant I, *et al*. **Cognitive functioning during highly active antiretroviral therapy interruption in human immunodeficiency virus type 1 infection.** *J Neurovirol* 2008; 1–8.
142. El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, *et al*. **CD4+ count-guided interruption of antiretroviral treatment.** *N Engl J Med* 2006; **355**:2283–2296.
143. McArthur JC, Steiner J, Sacktor N, Nath A. **Human immunodeficiency virus-associated neurocognitive disorders: Mind the gap.** *Ann Neurol* 2010; **67**:699–714.
144. Hardy DJ, Hinkin CH. **Reaction time performance in adults with HIV/AIDS.** *J Clin Exp Neuropsychol* 2002; **24**:912–929.
145. Dawes S, Suarez P, Casey CY, Cherner M, Marcotte TD, Letendre S, *et al*. **Variable patterns of neuropsychological performance in HIV-1 infection.** *J Clin Exp Neuropsychol* 2008; **30**:613–626.
146. Levine AJ, Hardy DJ, Barclay TR, Reinhard MJ, Cole MM, Hinkin CH. **Elements of attention in HIV-infected adults: evaluation of an existing model.** *J Clin Exp Neuropsychol* 2008; **30**:53–62.
147. Carey CL, Woods SP, Rippeth JD, Heaton RK, Grant I. **Prospective memory in HIV-1 infection.** *J Clin Exp Neuropsychol* 2006; **28**:536–548.

148. Robertson KR, Parsons TD, Sidtis JJ, Hanlon Inman T, Robertson WT, Hall CD, Price RW. **Timed Gait test: normative data for the assessment of the AIDS dementia complex.** *J Clin Exp Neuropsychol* 2006; **28**:1053–1064.
149. Gonzalez R, Heaton RK, Moore DJ, Letendre S, Ellis RJ, Wolfson T, *et al*. **Computerized reaction time battery versus a traditional neuropsychological battery: detecting HIV-related impairments.** *J Int Neuropsychol Soc* 2003; **9**:64–71.
150. Maruff P, Thomas E, Cysique L, Brew B, Collie A, Snyder P, Pietrzak RH. **Validity of the CogState brief battery: relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex.** *Arch Clin Neuropsychol* 2009; **24**:165–178.
151. Cinque P, Brew BJ, Gisslen M, Hagberg L, Price RW. **Cerebrospinal fluid markers in central nervous system HIV infection and AIDS dementia complex.** *Handb Clin Neurol* 2007; **85**:261–300.
152. Jayadev S, Garden GA. **Host and viral factors influencing the pathogenesis of HIV-associated neurocognitive disorders.** *J Neuroimmune Pharmacol* 2009; **4**:175–189.
153. Tozzi V, Balestra P, Lorenzini P, Bellagamba R, Galgani S, Corpolongo A, *et al*. **Prevalence and risk factors for human immunodeficiency virus-associated neurocognitive impairment, 1996 to 2002: results from an urban observational cohort.** *J Neurovirol* 2005; **11**:265–273.
154. Parsons TD, Tucker KA, Hall CD, Robertson WT, Eron JJ, Fried MW, Robertson KR. **Neurocognitive functioning and HAART in HIV and hepatitis C virus co-infection.** *Aids* 2006; **20**:1591–1595.
155. Hinkin CH, Castellon SA, Levine AJ, Barclay TR, Singer EJ. **Neurocognition in individuals co-infected with HIV and hepatitis C.** *J Addict Dis* 2008; **27**:11–17.
156. Kirk JB, Goetz MB. **Human immunodeficiency virus in an aging population, a complication of success.** *J Am Geriatr Soc* 2009; **57**:2129–2138.
157. Valcour V, Shikuma C, Shiramizu B, Watters M, Poff P, Selnes O, *et al*. **Higher frequency of dementia in older HIV-1 individuals: the Hawaii Aging with HIV-1 Cohort.** *Neurology* 2004; **63**:822–827.
158. Rippeth JD, Heaton RK, Carey CL, Marcotte TD, Moore DJ, Gonzalez R, *et al*. **Methamphetamine dependence increases risk of neuropsychological impairment in HIV infected persons.** *J Int Neuropsychol Soc* 2004; **10**:1–14.
159. Ancuta P, Kamat A, Kunstman KJ, Kim EY, Autissier P, Wurcel A, *et al*. **Microbial translocation is associated with increased monocyte activation and dementia in AIDS patients.** *PLoS One* 2008; **3**:e2516.
160. Valcour VG, Sacktor NC, Paul RH, Watters MR, Selnes OA, Shiramizu BT, *et al*. **Insulin resistance is associated with cognition among HIV-1-infected patients: the Hawaii Aging With HIV cohort.** *J Acquir Immune Defic Syndr* 2006; **43**:405–410.
161. Foley J, Ettenhofer M, Wright MJ, Siddiqi I, Choi M, Thames AD, *et al*. **Neurocognitive functioning in HIV-1 infection: effects of cerebrovascular risk factors and age.** *Clin Neuropsychol* 2010; **24**:265–285.
162. McArthur JC, Hoover DR, Bacellar H, Miller EN, Cohen BA, Becker JT, *et al*. **Dementia in AIDS patients: incidence and risk factors. Multicenter AIDS Cohort Study.** *Neurology* 1993; **43**:2245–2252.
163. Carter SL, Rourke SB, Murji S, Shore D, Rourke BP. **Cognitive complaints, depression, medical symptoms, and their association with neuropsychological functioning in HIV infection: a structural equation model analysis.** *Neuropsychology* 2003; **17**:410–419.
164. Wachtman LM, Skolasky RL, Tarwater PM, Esposito D, Schifitto G, Marder K, *et al*. **Platelet decline: an avenue for investigation into the pathogenesis of human immunodeficiency virus -associated dementia.** *Arch Neurol* 2007; **64**:1264–1272.
165. Kumar AM, Fernandez J, Singer EJ, Commins D, Waldrop-Valverde D, Ownby RL, Kumar M. **Human immunodeficiency virus type 1 in the central nervous system leads to decreased dopamine in different regions of postmortem human brains.** *J Neurovirol* 2009; 1–18.
166. Angrist B, d'Hollosy M, Sanfilipo M, Satriano J, Diamond G, Simberkoff M, Weinreb H. **Central nervous system stimulants as symptomatic treatments for AIDS-related neuropsychiatric impairment.** *J Clin Psychopharmacol* 1992; **12**:268–272.
167. Hinkin CH, Castellon SA, Hardy DJ, Farinpour R, Newton T, Singer E. **Methylphenidate improves HIV-1-associated cognitive slowing.** *J Neuropsychiatry Clin Neurosci* 2001; **13**:248–254.
168. Sacktor N, Schifitto G, McDermott MP, Marder K, McArthur JC, Kieburtz K. **Transdermal selegiline in HIV-associated cognitive impairment: pilot, placebo-controlled study.** *Neurology* 2000; **54**:233–235.
169. DanaConsortium. **A randomized, double-blind, placebo-controlled trial of deprenyl and thioctic acid in human immunodeficiency virus-associated cognitive impairment. Dana Consortium on the Therapy of HIV Dementia and Related Cognitive Disorders.** *Neurology* 1998; **50**:645–651.
170. Schifitto G, Yiannoutsos CT, Ernst T, Navia BA, Nath A, Sacktor N, *et al*. **Selegiline and oxidative stress in HIV-associated cognitive impairment.** *Neurology* 2009; **73**:1975–1981.
171. Evans SR, Yeh TM, Sacktor N, Clifford DB, Simpson D, Miller EN, *et al*. **Selegiline transdermal system (STS) for HIV-associated cognitive impairment: open-label report of ACTG 5090.** *HIV Clin Trials* 2007; **8**:437–446.
172. Dou H, Birusingh K, Faraci J, Gorantla S, Poluektova LY, Maggirwar SB, *et al*. **Neuroprotective activities of sodium valproate in a murine model of human immunodeficiency virus-1 encephalitis.** *J Neurosci* 2003; **23**:9162–9170.
173. Dragunow M, Greenwood JM, Cameron RE, Narayan PJ, O'Carroll SJ, Pearson AG, Gibbons HM. **Valproic acid induces caspase 3-mediated apoptosis in microglial cells.** *Neuroscience* 2006; **140**:1149–1156.
174. Robinson B, Turchan J, Anderson C, Chauhan A, Nath A. **Modulation of human immunodeficiency virus infection by anticonvulsant drugs.** *J Neurovirol* 2006; **12**:1–4.
175. Schifitto G, Peterson DR, Zhong J, Ni H, Cruttenden K, Gaugh M, *et al*. **Valproic acid adjunctive therapy for HIV-associated cognitive impairment: a first report.** *Neurology* 2006; **66**:919–921.
176. Cysique LA, Maruff P, Brew BJ. **Valproic acid is associated with cognitive decline in HIV-infected individuals: a clinical observational study.** *BMC Neurol* 2006; **6**:42.
177. Schifitto G, Sacktor N, Marder K, McDermott MP, McArthur JC, Kieburtz K, *et al*. **Randomized trial of the platelet-activating factor antagonist lexipafant in HIV-associated cognitive impairment. Neurological AIDS Research Consortium.** *Neurology* 1999; **53**:391–396.
178. Navia BA, Dafni U, Simpson D, Tucker T, Singer E, McArthur JC, *et al*. **A phase I/II trial of nimodipine for HIV-related neurologic complications.** *Neurology* 1998; **51**:221–228.
179. Anderson ER, Gendelman HE, Xiong H. **Memantine protects hippocampal neuronal function in murine human immunodeficiency virus type 1 encephalitis.** *J Neurosci* 2004; **24**:7194–7198.
180. Nath A, Haughey NJ, Jones M, Anderson C, Bell JE, Geiger JD. **Synergistic neurotoxicity by human immunodeficiency virus proteins Tat and gp120: protection by memantine.** *Ann Neurol* 2000; **47**:186–194.
181. Zhao Y, Navia BA, Marra CM, Singer EJ, Chang L, Berger J, *et al*. **Memantine for AIDS dementia complex: open-label report of ACTG 301.** *HIV Clin Trials* 2010; **11**:59–67.
182. Schifitto G, Navia BA, Yiannoutsos CT, Marra CM, Chang L, Ernst T, *et al*. **Memantine and HIV-associated cognitive impairment: a neuropsychological and proton magnetic resonance spectroscopy study.** *Aids* 2007; **21**:1877–1886.
183. Zink MC, Uhrlaub J, DeWitt J, Voelker T, Bullock B, Mankowski J, *et al*. **Neuroprotective and anti-human immunodeficiency virus activity of minocycline.** *Jama* 2005; **293**:2003–2011.
184. Si Q, Cosenza M, Kim MO, Zhao ML, Brownlee M, Goldstein H, Lee S. **A novel action of minocycline: inhibition of human immunodeficiency virus type 1 infection in microglia.** *J Neurovirol* 2004; **10**:284–292.
185. Kraus RL, Pasieczny R, Lariosa-Willingham K, Turner MS, Jiang A, Trauger JW. **Antioxidant properties of minocycline: neuroprotection in an oxidative stress assay and direct radical-scavenging activity.** *J Neurochem* 2005; **94**:819–827.
186. Szeto GL, Brice AK, Yang HC, Barber SA, Siliciano RF, Clements JE. **Minocycline attenuates HIV infection and reactivation by suppressing cellular activation in human CD4+ T**

cells. *J Infect Dis* 2010; **201**:1132–1140.

187. Everall IP, Bell C, Mallory M, Langford D, Adame A, Rockestein E, Masliah E. **Lithium ameliorates HIV-gp120-mediated neurotoxicity.** *Mol Cell Neurosci* 2002; **21**:493–501.
188. Letendre SL, Woods SP, Ellis RJ, Atkinson JH, Masliah E, van den Brande G, *et al*. **Lithium improves HIV-associated neurocognitive impairment.** *Aids* 2006; **20**:1885–1888.
189. Schifitto G, Zhong J, Gill D, Peterson DR, Gaugh MD, Zhu T, *et al*. **Lithium therapy for human immunodeficiency virus type 1-associated neurocognitive impairment.** *J Neurovirol* 2009; **15**:176–186.
190. Clifford DB, McArthur JC, Schifitto G, Kieburtz K, McDermott MP, Letendre S, *et al*. **A randomized clinical trial of CPI-1189 for HIV-associated cognitive-motor impairment.** *Neurology* 2002; **59**:1568–1573.
191. Allard JP, Aghdassi E, Chau J, Tam C, Kovacs CM, Salit IE, Walmsley SL. **Effects of vitamin E and C supplementation on oxidative stress and viral load in HIV-infected subjects.** *Aids* 1998; **12**:1653–1659.
192. Rrapo E, Zhu Y, Tian J, Hou H, Smith A, Fernandez F, *et al*. **Green Tea-EGCG reduces GFAP associated neuronal loss in HIV-1 Tat transgenic mice.** *Am J Transl Res* 2009; **1**:72–79.
193. Nance CL, Siwak EB, Shearer WT. **Preclinical development of the green tea catechin, epigallocatechin gallate, as an HIV-1 therapy.** *J Allergy Clin Immunol* 2009; **123**:459–465.
194. Giunta B, Obregon D, Hou H, Zeng J, Sun N, Nikolic V, *et al*. **EGCG mitigates neurotoxicity mediated by HIV-1 proteins gp120 and Tat in the presence of IFN-gamma: role of JAK/STAT1 signaling and implications for HIV-associated dementia..** *Brain Res* 2006; **1123**:216–225.
195. DanaConsortium. **Safety and tolerability of the antioxidant OPC-14117 in HIV-associated cognitive impairment. The Dana Consortium on the Therapy of HIV Dementia and Related Cognitive Disorders.** *Neurology* 1997; **49**:142–146.
196. Letendre SL, Marquie-Beck J, Ellis RJ, Woods SP, Best B, Clifford DB, *et al*. **The role of cohort studies in drug development: clinical evidence of antiviral activity of serotonin reuptake inhibitors and HMG-CoA reductase inhibitors in the central nervous system.** *J Neuroimmune Pharmacol* 2007; **2**:120–127.
197. Wong HL, Chattopadhyay N, Wu XY, Bendayan R. **Nanotechnology applications for improved delivery of antiretroviral drugs to the brain.** *Adv Drug Deliv Rev* 2010; **62**:503–517.
198. Mahajan SD, Roy I, Xu G, Yong KT, Ding H, Aalinkeel R, *et al*. **Enhancing the delivery of anti retroviral drug ‘‘Saquinavir’’ across the blood brain barrier using nanoparticles.** *Curr HIV Res* 2010; **8**:396–404.