

# 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.**

Cognitive 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 Digit span (WAIS-R)
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].	Paced auditory serial addition test Letter-number sequencing (WAIS-III) Wisconsin card sorting test
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].	Trail making test B Stroop color-word Halstead category test California verbal learning 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].	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 Boston naming 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].	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
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].	Speech sound perception test 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  $^{99}\text{Tc}$ ) 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- $\alpha$
Monocyte Chemoattractant Protein-1 (MCP-1)/CCL2
Interferon- $\gamma$ inducible Protein-10 (IL-10)/CXCL10
Macrophage Inflammatory Protein- $\alpha$ (MIP1- $\alpha$ )/CCL3,
MIP1- $\beta$ /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
Soluble Amyloid Protein Precursor (sAPP) $\alpha/\beta$
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<sup>PC</sup>], 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 study 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, thiocetic 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. Thiocetic 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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