

# HIV Encephalopathy – Now and Then

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## 1. Introduction

HIV can cause a wide range of neurocognitive complications recently grouped under the name of HAND (HIV associated neurocognitive disorders). Depending on the degree of the impairment, there are three categories, progressing in disabilities from asymptomatic neurocognitive impairment (ANI) to HIV associated mild neurocognitive impairment (MND) and to HIV associated dementia (HAD)[1].

The introduction of HAART (highly active antiretroviral therapy) has led to a marked decrease in the incidence of HAND. But also the spectrum of HAND has changed in the HAART era; it seemed that minor cognitive impairment slightly increased. HAND consists of a triad of cognitive, behavioral and motor dysfunctions. With the exception of dementia, the symptoms are generally mild but can impact the quality of life and treatment adherence.

Diagnosis of HAND is based on a combination of careful history and neurological examination, neuropsychological testing, neuroimaging (especially magnetic resonance: MRI) and cerebrospinal fluid (CSF) analyses. The last two have a crucial role in differentiating from other etiologies. The differential diagnosis is quite broad in HIV patient with neurological impairment including HIV- related causes and also metabolic disturbances, substance abuse and psychiatric disorders.

Initiation of HAART with a good CNS penetration is the most effective mean of treating cognitive impairment.[2]

## 2. Epidemiology

HIV-encephalitis (HIVE) is the most frequent neurologic disorder of the brain in HIV-1 infection and is the principal cause of HAND. Neurocognitive impairments in overall HIV population appear to be nearly 50% [1], varying considerably by the region, due to the tests used for detection, HIV infection stage and comorbidities, virus subtype and treatment schedules.

The large majority of HIV-associated neurocognitive disorders (HAND) are asymptomatic (ANI) or mild (MND), but around 5% are severe, representing an AIDS-related illness: HIV-associated dementia (HAD). [3,4]

Paradoxically, HAART introduction didn't decrease the occurrence of HAND, but there was a shift from severe to moderate and mild forms [5]. Causes of continuing high rates of HAND despite HAART, have multiple possible explanations:

- the presence of irreversible brain injury prior to initiating ART;
- the possible neurotoxicity of some antiretroviral drugs;
- the persistence of minimal HIV replication in CNS and
- the effect of chronic immune activation, condition that lead to metabolic disorders and vascular degeneration, inclusive of CNS tissue.[6]

Risk factors for developing HAND included

- host factors: low educational status, older age, genetic predisposition, metabolic disorders, coinfection with hepatitis C virus and iv drug abuse.
- viral factors: virus subtype (subtypes B, C and D more related to HAND than subtype A; subtype F also associated with high prevalence of HAND) [1,7]
- relation host-virus: AIDS stage and presence of chronic immune activation - measured by different serum markers such as TNF-alpha and monocyte chemo-attractant protein 1 (MCP-1), hsCRP, IL6 and soluble CD14 - which leads to metabolic disorders and accelerated senescence; low nadir of CD4 T cell counts [8, 9]; HIV-DNA load in circulant macrophages and higher CSF viral load compared to serum viral load.[10,11]

Although HIV penetrates CNS early (during the acute HIV infection), the onset of HAND is delayed for years, superposing with moderate and advanced immune-suppression stages [12, 5]. It emerges gradually, in weeks or months.

There are no conclusive data regarding the HAND outcome: there is a variable degree of reversibility for ANI and MND, unlike typical neurodegenerative syndromes and MND doesn't progress necessarily to HAD.[1]. Although it is considered to be a treatable condition, HAND is associated with a shortened survival [13].

### 3. Pathogenesis of HIV encephalitis

HIV-encephalitis (HIVE) represents the mainly HAND substrate.

HIV enters the central nervous system early during the infection [12,5], transported by CD4 T lymphocytes and monocytes, that cross the blood-brain barrier (BBB). The infected monocytes become perivascular macrophages in nervous tissue. Then, HIV infects local macrophages (microglia). Perivascular macrophages and microglia fused together, forming multinucleated giant cells (MGCs). MGCs replicate the virus (serving as HIV-reservoir) and express neurotoxic molecules: viral (gp-120 and tat protein) and cellular [14]. These neurotoxins have at least two properties:

- they activate astrocytes, which in turn release cytokines and increase BBB permeability, promoting migration of more HIV-infected cells from blood to brain.
- they damage the neurons, with demyelination and neuronal loss.

Therefore, the picture of local histopathology in HIVE shows inflammatory changes and neuronal destructions: perivascular macrophages accumulation, reactive gliosis with microglial nodules and MGCs formation and focal neuronal necrosis with demyelination and neuroatrophy [15,1].

Macroscopically, in HIVE, there is global white matter pallor, a reduction in nervous substance thickness, especially in deep grey matter structures and in subcortical frontal white matter. Mostly affected are basal ganglia (especially caudate nucleus), corpus callosum and hippocampus, which correlate well with clinical cognitive and behavioral syndromes – but in a lesser extent with motor manifestations [1]

HIV proved to damage the neurons directly, via viral neurotoxins and indirectly, via immunologic pathways. The lasts consist in local changes (already mentioned cellular neurotoxins and BBB deterioration) and systemic changes, which means chronic immune activation.

The chronic immune activation can be done by any persistent infectious or noninfectious inflammation. The repercussion is an accelerated immune-mediated global vascular senescence (endothelial dysfunction with subsequent atherosclerosis) which has as consequences many metabolic disorders[16], including neuro-degeneration (subclinical atherosclerotic disease of the brain vessels)

In HIV infection, chronic immune activation takes place even in HIV-treated patients, with a good control of the plasma viral load, but with a poor control of viral sanctuary (reservoirs). It is demonstrated that despite plasma level suppression, HIV could continue to replicate in brain tissues with a rate of 3-10% [1]. This replication (as low as 2 copies/ml) is capable to maintain a persistent immune activation [8] with its consequences. The HIV presence/persistence in the brain in the HAART era has a series of explanations:

- incomplete suppression: the virus can not be totally suppressed in the brain tissues because of the poor penetration of antiretrovirals through BBB, thus too low drug's concentrations achieve there allowing the development of different HIV (resistant) cvasispecies in CNS. [8].
- viral afflux from peripheral reservoirs: there could exists a permanent traffic of the mononuclear infected cells (with pro-viral DNA: HIV-DNA) from peripheral reservoirs (bone marrow) to the brain. Even in patients with undetectable plasma viral load, we can find HIV-DNA in circulating monocytes, with the same viral signature as in the bone marrow and in the deep brain structures.

Other factors that may contribute to neurocognitive disorders in HIV patients with HIVE in HAART era are:

- the medication per se (antiretrovirals or miscellanea), which can have neurotoxic effects
- aging - there is an accelerated neuro-degeneration in older HIV subjects, which has similarities with neurodegenerative syndromes, with abnormal accumulation of beta-amyloid apolipoproteinE4, tau protein and synuclein[1,5]
- hepatitis C virus coinfection: both viruses invade SNC and cause synergic neurotoxic effects.
- iv drug abuse contribute to neuro-degeneration

A particular situation in HIV treated patients is IRIS (immune reconstitution syndrome). A severe HIVE development can be observed in patients receiving HAART, with a low basal CD4 T lymphocytes count and high initial HIV-RNA level, despite the good suppression obtained under treatment. Histo-pathologically numerous CD8-positive lymphocytes were found close to the neurons, in the perivascular areas and in the parenchyma. This condition

may be interpreted as an immune reconstitution phenomenon directed against HIV itself [17], leading to an extensive white matter destruction, with vacuolar leucoencephalopathy [12]

The neuro-injury in HIVE can be paraclinically appreciated by:

- biochemical and molecular analysis of plasma and CSF: uncontrolled viral replication increases the HAND risk; discordances in viral loads, with higher CSF load represent a particular risk; the presence of high levels of neopterin and beta-microglobulin in CSF (neuro-degeneration and macrophage/microglial activation markers) even in the absence of a CSF viral replication correspond to neuronal impairment; the low number of CD4 T lymphocytes in peripheral blood increases the risk of HAND (especially at CD4 below 200/mm<sup>3</sup>)[3]; presence of the chronic immune activation markers in peripheral blood is also a predictive factor for HAND, measured by hsCRP, soluble CD14, D-dimers, IL6, TNF-alpha and MCP-1; high level of HIV DNA in peripheral monocytes correlates well with HAND.
- histological, biochemical and molecular analysis of the nervous parenchima: there is reported HIV presence in brain tissue more frequently than in CSF [18,1-16], suggesting that CSF levels may underestimate HIV replication in brain tissue.
- imaging-based methods which can appreciate the nervous tissue injuries in HIVE

At present, the main goal of treatment is the effective suppression of the HIV from reservoirs, that can disrupt the vicious circle of chronic immune activation and reverse (partially) HIVE.

#### **4. HIV-associated neurocognitive disorders – Nomenclature and staging**

In 1991 the American Academy of Neurology AIDS Task Force developed a consensus nomenclature and case definition for HIV associated dementia (HAD) complex. Several terms are still used interchangeably, including AIDS dementia complex, HIV encephalopathy, HIV subacute encephalitis, and HAD. The severity of dementia in the consensus nomenclature (mild, moderate, and severe) reflects functional deficits that affect the activities of daily living.(19)

A milder form of cognitive impairment, HIV-1-associated minor cognitive/motor disorder (MCMD), was also introduced in 1996; however, it was not determined whether this represented an intermediate step in the progression to dementia. Subsequent research has shown that MCMD is a risk factor for HAD [20].

Since the introduction of HAART in 1996, the incidence of moderate or severe dementia fell from about 7% in 1989 to only 1% in 2000, and the severity of neurological disease appears to have been attenuated (21). Despite this remarkable effect on incidence rates, the prevalence of HIV Associated Neurocognitive Disorders (HAND) continues at very high rates. In response to the changes, in 2007 the National Institutes of Health created a working group to critically review the adequacy and utility of current definitions and diagnostic criteria (22). The report provides a new nosology (Table 1) which distinguishes among patients with subclinical dysfunctions categorized as suffering asymptomatic neurocognitive impairments (ANI), patients with greater cognitive decline that have mild adverse effects on daily living activities categorized as HIV-associated mild neurocognitive disorder (MND) and patients with significant functional impairment who can be categorized as having HIV - associated dementia (HAD). An algorithm is proposed to assist in standardized diagnostic classification of HAND. The clinical algorithms give guidelines

for decision making regarding: (1) cognitive impairment, (2) functional decline, (3) factoring in comorbidities, and alternative approaches when full neurodiagnostic assessment capabilities are not available (22).

<i>HIV-associated asymptomatic neurocognitive impairment (ANI)</i>
Acquired impairment in two or more cognitive domains, with evidence of performance >1.0 SD below the mean for age- and education-appropriate norms on standardized neuropsychological tests
Cognitive impairment does not interfere with everyday functioning
Cognitive impairment does not meet the criteria for delirium or dementia
No evidence of another preexisting cause for the ANI
If prior ANI existed, but no longer does, a diagnosis of ANI in remission is made
Diagnosis deferred for patients with major depression or substance abuse on examination
<i>HIV-associated mild neurocognitive disorder (MND)</i>
Acquired impairment in two or more cognitive domains, with evidence of performance >1.0 SD below the mean for age- and education-appropriate norms on standardized neuropsychological tests
Typically, impairment staging corresponds to an MSK scale stage of 0.5 to 1
The cognitive impairment produces at least mild interference in daily functioning (at least one of the following): (a) self-report of reduced mental acuity, inefficiency in work, homemaking, or social functioning; (b) observation by knowledgeable others that the individual had undergone at least mild decline in mental acuity with resultant inefficiency in work, homemaking, or social functioning
The cognitive impairment does not meet the criteria for delirium or dementia
No evidence of another preexisting cause for the MND
Remission and comorbid psychiatric disturbance criteria similar to that for ANI
<i>HIV-associated dementia (HAD)</i>
Marked acquired impairment in at least two cognitive domains. Typically impairments involve multiple domains, especially in learning of new information, slowed information processing, and defective attention/concentration
The impairments must be >2 SD below average on neuropsychological testing
Correspond to an MSK scale stage of 2.0 or greater
The cognitive impairment markedly interferes with daily functioning
The impairments do not meet the criteria for delirium
No evidence of another preexisting cause for dementia, such as CNS infection, neoplasm, etc., or severe substance abuse compatible with CNS disorder
Remission and comorbid psychiatric disturbance criteria similar to that for ANI and MND.
However, if dementia persists after one month on remission of major depression, a reassessment should be conducted to reassess for dementia

Table 1. Nosology of HIV-associated neurocognitive impairment (22).

## 5. Clinical manifestations

Neurocognitive impairment in people with HIV is characterized by a triad of cognitive, psychological, and motor dysfunctions. Symptoms may include any combination of the following: distractibility, poor concentration or attention, memory problems on short-term or long-term, impaired problem-solving or calculation ability, reduced ability to plan ahead, difficulty learning new things, problems with speech and language comprehension, abnormal visual perception, psychomotor slowness, poor balance, clumsiness, changes in mood (e.g., apathy, depression), social withdrawal, altered behaviour.

Specific neurological manifestations depend on which parts of the brain are affected. Impairment can range from so mild that it is not apparent without specialized testing, to so severe that it prevents independent living.

**HIV-associated dementia (HAD)** is diagnosed when there is evidence of marked declines in function in at least two separate cognitive domains, along with evidence of functional deterioration affecting activities of daily living (ADL) and self care. By definition, there must be evidence of significant declines from premorbid abilities.

The early described cases of HAD presented clinical features different from “classic” dementias such as Alzheimer’s disease and other cortical degenerative diseases (23). HAD is considered a “subcortical” type of dementia”, the neuropsychological profile involving : executive functions (ability of planning, decision-making, mental flexibility), concentration and complex attention ( sustained attention, divided attention, selective attention, processing speed), verbal memory, learning and memory recall (24,25). Cortical dementia is more likely to involve memory loss, language comprehension, visual- spatial dysfunction and deficient conceptual abilities. Most patients with HAD do not present primary amnesic disturbances. Impairments of memory and learning are different from those seen in Alzheimer’s disease: usually is retained the ability to store new memory but the efficiency for learning is diminished and the recognition memory is better preserved than recall memory, suggesting that the hippocampus is less affected.

Some patients with HAD may experience severe memory impairments or cortical symptoms that are virtually impossible to distinguish from Alzheimer’s disease and related dementia. The cognitive domains most commonly affected are those of attention and executive functions (23, 26, 27). Impaired reaction time and reduced processing speed determining cognitive slowing reflects the effects of HIV on subcortical white and the basal ganglia, most notably the caudate nucleus (the caudate has been shown to be particularly vulnerable to HIV) (28, 29,30). Primary language functions are not very affected in HAD, severe aphasia being rare present but verbal fluency is frequently impaired as an expression of executive dysfunction (31).

Patients with HAD frequently show impaired motor abilities even when other cognitive functions are relatively intact (26). They can present: psychomotor slowing, poor coordination, tremors, impaired fine motor skills (egg, handwriting, buttoning etc). The presence of motor problems along with other cognitive problems is one of the key factors that distinguished AIDS-dementia from Alzheimer’s disease and related dementias (32).

Behavioral changes include irritability, apathy, reduced social contact, decreased libido, and altered sleeping patterns. Mild to moderate depressive symptoms may precede the onset of

HAD (33); however, significant depression may confound the diagnosis of HAD and needs to be considered along with HAD since depressive symptoms can be ameliorated with both pharmacological and nonpharmacological intervention.

Patients with mild to moderate cognitive impairment often have a normal neurological exam. Early neurological findings include abnormal pursuit and saccadic eye movements and reduced rapid alternating and sequential hand movements. Later, patients develop gait abnormalities, hyperreflexia (ankle reflexes may be normal or reduced if HIV-associated neuropathy coexists) and postural instability. As HAD progresses, ataxia, tremor, hypertonia, and frontal release signs appear.

### **5.1 Milder neurocognitive disorders (ANI or MCD)**

For milder forms of HAND, difficulties in concentration, attention, and memory may be present while the neurologic examination is unremarkable (34). Affected individuals are easily distracted, make errors in tasks regularly conducted, lose their train of thought, complain of increased fatigue due to effort to organize, plan and making decision, require repeated prompting. Activities of daily living may take longer and become more laborious. Overall the clinical manifestations are similar to those of HAD but of lesser severity.

## **6. Diagnostic workup**

### **6.1 Biomarkers of HIV- Related Central Nervous System Disease**

**CSF analysis** is critical in ruling out alternative etiologies. Tests useful for differential diagnosis include: opening pressure, culture (particularly fungal and mycobacterium), cell count, protein, cryptococcal antigen, VDRL for neurosyphilis and polymerase chain reaction testing for toxoplasma, cytomegalovirus, Epstein Barr virus, John Cunningham virus, and herpes virus.

The CSF profile of patients with HAND is often indistinguishable from HIV-infected individuals without cognitive impairment. The nonspecific abnormalities may include mild elevated total protein and mild mononuclear pleocytosis. Almost all patients with HAD have elevated protein levels. A CSF leucocytosis greater than 50 cell/ $\mu$ L is unlikely to be due to HIV alone, especially when the CD4 is below 200 cell/ $\mu$ L (35). A polymorphonuclear pleocytosis is unlikely with HAD and raised the possibility of bacterial meningitis or cytomegalovirus ventriculitis (36).

Many biomarkers have been described but the discovery of reliable diagnostic markers has been elusive (37). These biomarkers can be divided into those related to pathogenesis and those reflecting the state of relevant cells. Recent studies have shown that both markers of immune activation (neopterin and beta-2 microglobulin) and neuronal destruction (neurofilament light chain) are elevated in HAD (38).

**$\beta$ -2-microglobulin** (light chain of the HLA I expressed on the surface of all nucleated cells with the exception of neurons) presents elevated concentrations in CSF in both inflammatory and lymphoproliferative conditions (39). CSF  $\beta$ -2-microglobulin correlates well with the severity of HAD and the levels decrease with successful treatment of HIV (39).

**Neopterin** (a product of guanosine triphosphate metabolism, mainly produced by activated monocytes, macrophages, and microglia) presents high CSF concentrations in patients with opportunistic CNS infections as well as HAD. The CSF concentrations correlate with HAD severity and decrease with antiretroviral therapy (40). In one study after 2 years of virologic suppression, only 55% had normal CSF neopterin levels (41).

**Neurofilament-Light** (a major structural element of large myelinated neurons) presents CSF levels significantly but nonspecifically raised in HAD and rise with HAART interruption (42, 43). It seems that levels fall to normal in the majority of patients initiated on HAART (44).

### **HIV RNA**

Plasma HIV RNA levels are not specific or sensitive to HAND. In HAART-treated patients, an undetectable plasma RNA level seems to occur more often in HAD for reasons that are unclear (45).

CSF HIV RNA is also nonspecific, with elevated levels in HAD, asymptomatic patients and those with opportunistic infections (45,46,47). Prior to HAART, higher CSF HIV RNA correlated with lower neuropsychological scores in subjects with more advanced disease (48). HAD can occur in the absence of an elevated HIV RNA in CSF (49, 50,51). Possible explanations for this situation are: residual deficits despite HAART (49); the presence of confounding conditions like hepatitis C or substance abuse or autonomous immune activation in response to the initial HIV infection (50).

## **6.2 Neuroimaging**

HAD is a diagnostic of exclusion. Computed tomography (CT) and magnetic resonance imaging (MRI) studies of the brain can support a diagnosis of HIV encephalopathy (HIVE) and rule out HIV-associated opportunistic infections or neoplasm.

**CT scan** reveals diffuse cortical atrophy, ventricular enlargement, and hypodensities in white matter in later stages. Basal ganglia calcifications are seen in adults but are more common in children. Usually computer tomography investigations offer normal results in ANI and MND.

**MRI:** When the infection becomes clinically symptomatic, the most common MRI findings are general atrophy in both cortical and subcortical regions of the brain (52). More specifically, these regions include frontal white matter and basal ganglia (53,54), with modifications in this area becoming more prominent in most advanced HAND stages. Caudate nucleus atrophy is a common finding (54,55,56). Another common imaging finding, although not a defining MRI feature of HIVE, is the presence of T2-weighted hyperintense images in white matter of the CNS (white matter signal abnormalities WMSA) (52,57,58). These lesions without mass effect can be solitary, diffuse unilateral or large bilateral, and are located predominantly in the periventricular white matter and centrum semiovale. These usually do not enhance after iv contrast administration and are better revealed on FLAIR MR sequences. WMSA corresponding loci of demyelization and vacuolation was shown to be related to HIV infection (dendrite pruning) (59) but also to vascular risk factors among older HIV infected patients (60). MRI findings are often but not always associated with performance on cognitive tests and are not always correlated with immunological function (CD4) or disease activity (viral load). Structural changes are sensitive to later stage of HAND but do not characterize very well the asymptomatic or the milder stages of the HIVE.

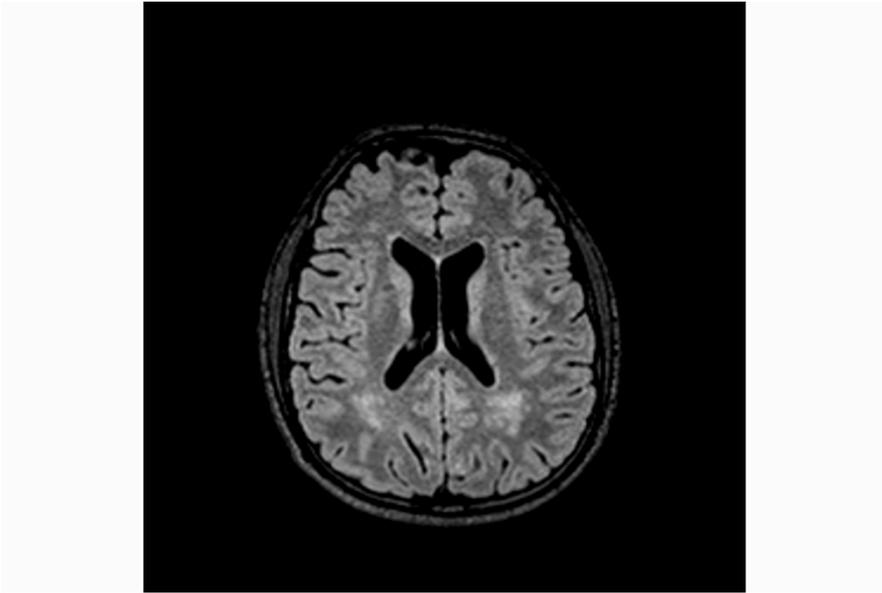


Fig. 1. HIV. MRI (T2-w FLAIR) transversal section: symmetric high signals in subcortical profound white matter and in periventricular areas (INBI Matei Bals collection, courtesy of Dr. M. Mardarescu)



Fig. 2. HIV. MRI (T2-w) transversal section: symmetric high signals in periventricular subcortical white matter, predominantly in parietal posterior areas (INBI Matei Bals collection, courtesy of Dr. M. Mardarescu)

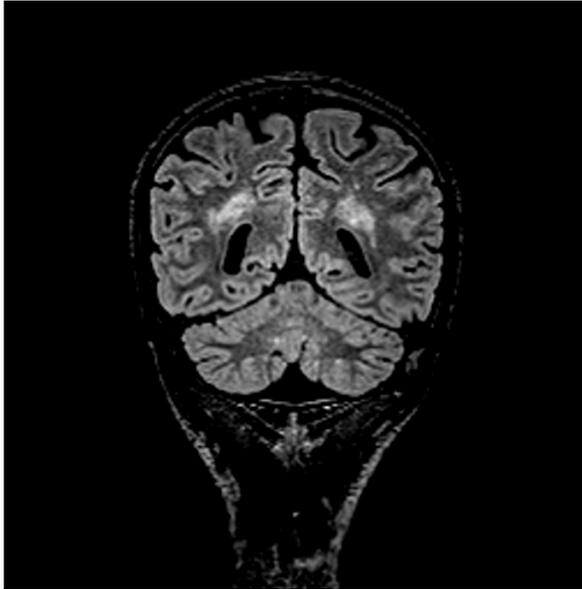


Fig. 3. HIVE. MRI (T2-w FLAIR) coronal section: symmetric high signals in periventricular white matter, predominantly in parietal posterior areas (INBI Matei Bals collection, courtesy of Dr. R. Draghicioiu)

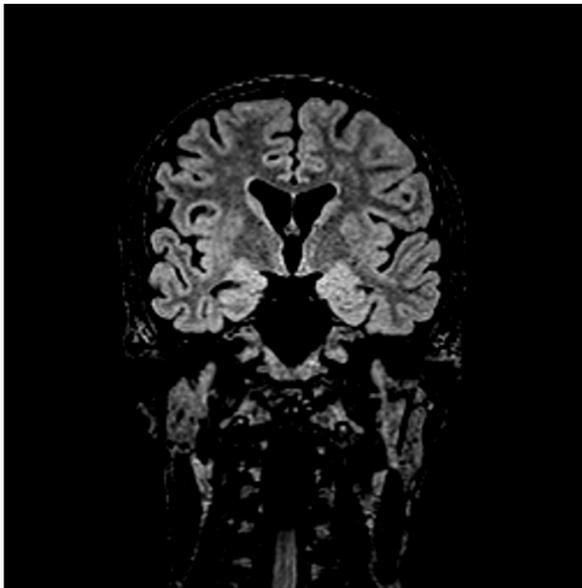


Fig. 4. HIVE. MRI (T2-w FLAIR) coronal section: mild ventriculomegaly with periventricular linear hypersignal and high signals in subcortical white matter (INBI Matei Bals collection, courtesy of Dr. R. Draghicioiu)

**Proton Magnetic Resonance Spectroscopy (MRS)** is a functional imaging technique that allows measuring a specific set of brain metabolites concentrations noninvasively. The most commonly reported neurochemical spectra in the examination of HIV + patients are: *N*-acetyl aspartate (NAA) -a marker of neuronal integrity, myo-inositol (mI) a glial cell marker, Choline (Cho) a marker of cell turnover and creatine (Cr) a marker of energy metabolism. Choline is useful in examining the white matter abnormalities and the creatine spectra is often used as a reference peak because the Cr signal is relatively constant across subjects. Functional MRI studies are not yet widely available, but they may be useful in examining HIV associated CNS abnormalities before neurocognitive disorders can be detected by clinical or neuropsychological evaluation. (61). Altered metabolic function in HIV infected persons appears early in the course of disease progression and is demonstrable by an elevation in Cho, mI and occasionally Cr in frontal areas and in the basal ganglia even in the asymptomatic stages (62,63,64). Elevations of these metabolites are interpreted to be a marker of inflammation and of glial activation and astroglyosis. In more advanced stages of the disease has been observed a decrease of NAA, especially in the frontal and subcortical areas of the brain, signaling neuronal injury (65, 66,67). The decreased NA/Cr ratio is more important in younger persons, suggesting that in older individuals, the metabolic changes seen may be a combination of age and HIV infection. There are equivocal evidences of metabolites improvement in HAART-treated patients but this issue requires further studies.

**Diffusion Magnetic Resonance Imaging (DTI)** is a relatively new MRI technique that produces images of biological tissues weighted with the local microstructural characteristics of water diffusion, which is capable of showing connections between brain regions. Researchers have focused on two primary metrics: the mean diffusivity (MD) and fractional anisotropy (FA). Several studies suggest that DTI is sensitive in revealing subtle white-matter abnormalities in the HIV+ cohort. General reductions in FA and increases in MD are apparent in multiple white-matter regions, especially in the frontal white matter and the corpus callosum, as compared to healthy controls but continued research in this field must be done (68,69,70,71).

**Single-photon emission computed tomography (SPECT)** may reveal abnormalities in cerebral blood flow in frontal, temporal, and parietal areas of the brain, the severity of which was shown to be associated with severity of cognitive symptoms (72,73,74).

**PET imaging:** Several studies demonstrated hypermetabolism of glucose in the basal ganglia, thalamus, temporal and parietal lobes (75,76,77) early in the disease even in the asymptomatic stage (75). In more advanced stages of the disease it was observed a hypometabolism for cortical and subcortical gray matter (78). The use of a new PET ligand [11C]-PK11195 might provide a window into active areas of inflammatory processes in HIV infection. PET scanning may also be useful to exclude CNS lymphoma, which shows increased uptake, whereas the lesions of HAND do not.

There are several other MRI imaging modalities that have been used to examine HIV-associated CNS effects: perfusion MRI, magnetization transfer imaging, and postcontrast enhancement imaging but the studies available are limited.

### 6.3 Neuropsychological testing

The diagnosis of HAND implies exclusion of other causes of cognitive impairment by neurological examination and neuroimaging evaluations. Neuropsychological assessment is important to quantify and determine the specific pattern of the cognitive abnormality, to classify the severity of the deficits (to detect mild, early cognitive abnormalities) and to long term follow up.

The assessment needs to be comprehensive enough to assess abilities of attention, working memory, delayed recall, learning, verbal fluency, speed of information processing, abstraction/problem solving and motor functions. It is important to use demographically-corrected norms even for these screening tools (79).

#### **European AIDS Clinical Society recommended screening for neurocognitive impairment.**

Any HIV-infected person complaining of disturbances in his/her memory (comprehension, clarity or speed) should be evaluated extensively, including neurological examination, neuropsychological assessment, cerebrospinal exam and imaging of the brain.

Patients without such symptoms that should be targeted for screening:

- uncontrolled HIV infection (detectable plasma HIV RNA)
- use of antiretroviral agents with limited CNS penetration
- low CD4 nadir (<200 cells/mm<sup>3</sup>)
- ongoing depression

Screening tool

- International HIV Dementia Scale (IHDS)

Assessment Methods:

S Letendre and co proposed a multi-step assessment of a HIV infected person susceptible for neurocognitive impairment consisting in:

*Symptom Questionnaire*: The Medical Outcomes Study HIV (MOS-HIV) Health Survey (table 2), The Patient's Assessment of Own Functioning Inventory PAOFI

*Screening Tests*: International HIV Dementia Scale, HIV Dementia Scale, Montreal Cognitive Assessment

*Brief Neuropsychological Testing*: ALLRT Brief Neurocognitive Screen, Grooved Pegboard, Action Fluency, Computerized Testing

*Comprehensive Neuropsychological Testing*: At least 5 cognitive abilities; At least 2 tests per ability

The most widely accepted neuropsychiatric screening techniques is the International HIV Dementia Scale (IHDS), although this scale is not enough sensitive for the assessment of early cognitive impairment. The scale consists of 4 subsets that target memory (e.g., recall, registration), psychomotor speed, constructional ability, and concentration.

A patient with a negative screening test may require more in-depth neuropsychological testing (80).

How much time during the past 4 weeks.....	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
Did you have difficulty reasoning and solving problems, e.g. making plans, making decisions, learning new things?	1	2	3	4	5	6
Did you forget things that happened recently, e.g., where you put things, appointments?	1	2	3	4	5	6
Did you have trouble keeping your attention on any activity for long?	1	2	3	4	5	6
Did you have difficulty doing activities involving concentration and thinking?	1	2	3	4	5	6

Knippels, et al. AIDS.2002; 16: 259-267

Table 2. MOS – HIV Cognitive Functional Status Scale

### **International HIV Dementia Scale (IHDS)**

**Memory-Registration:** Give four words to recall (dog, hat, bean, red) – 1 second to say each. Then ask the patient all four words after you have said them.

Repeat words if the patient does not recall them all immediately. Tell the patient you will ask for recall of the words again a bit later.

#### **1. Motor speed.**

Have the patient tap the first two fingers of the non-dominant hand as widely and as quickly as possible.

4 = 15 in 5 seconds

3 = 11-14 in 5 seconds

2 = 7-10 in 5 seconds

1 = 3-6 in 5 seconds

0 = 0-2 in 5 seconds

#### **2. Psychomotor speed.**

Have the patient perform the following movements with the non-dominant hand as quickly as possible:

- Clench hand in fist on flat surface.
- Put hand flat on surface with palm down.
- Put hand perpendicular to flat surface on the side of the 5th digit.
- Demonstrate and have patient perform twice for practice.

4 = 4 sequences in 10 seconds

3 = 3 sequences in 10 seconds

2 = 2 sequences in 10 seconds

1 = 1 sequence in 10 seconds

0 = unable to perform

#### **3. Memory-recall.**

Ask the patient to recall the four words. For words not recalled, prompt with a semantic clue as follows: animal (dog); piece of clothing (hat); vegetable (bean); color (red).

Give 1 point for each word spontaneously recalled. Give 0.5 points for each correct answer after prompting. Maximum – 4 points.

**Total International HIV Dementia Scale Score:** This is the sum of the scores on items 1-3. The maximum possible score is 12 points.

A patient with a score of  $\leq 10$  should be evaluated further for possible dementia.

Sacktor NC; Wong M; Nakasujja N; Skolasky RL; Selnes OA; Musisi S; Robertson K; McArthur JC; Ronald A; Katabira E. AIDS 2005;19(13):1367-74.

In advancing disease, tests that explore the following abilities may be helpful:

- Motor ability : Finger Tapping Test, Grooved Pegboard Test
- Concentration: Continuous Performance Test, Trail Making Test A and B
- Processing :Trail Making Test A and B, Choice Reaction Time
- Memory/learning : Weschler Memory Scale, California Verbal Learning Test
- Abstraction: Wisconsin Card-Sorting Test
- Speech/language: Boston Naming Test, Verbal Fluency Test

In addition to the neuropsychological tests, it is also recommended to briefly assess the level of depressive complaints using a validated psychiatric scale. The assessment should be complemented by an examination of activities of daily living (81) as this assessment serves to ascertain the presence of dementia versus milder stages of HAND (22,82).

Assessment of substance use history is of particular importance. The type of drugs, length of use, mode of use, and dosage should be recorded as they help to interpret the current level of neurocognitive abilities.

A brief assessment of medication adherence is recommended because it has been shown to be associated with severity of cognitive impairment in HIV-infection (83).

## 7. Differential diagnosis

Due to similar symptoms and signs, the differential diagnosis of HIV encephalopathy includes opportunistic infections as well as neoplastic etiology and encephalopathy due to reversible causes. We should also take into consideration HAART neurotoxicity and IRIS.

### 7.1 Opportunistic infections

**Progressive multifocal leucoencephalopathy (PML)** is the most common infiltrative brain lesion observed in patients with AIDS and is caused by a reactivation of the dormant JC virus, a DNA polyomavirus. The incidence of PML has not decreased after HAART introduction, being around 1-10% of AIDS patients.(84,85). The viral tropism for oligodendrocytes results in a progressive demyelinating disease and the symptoms depends on the afflicted areas. The common complaints are limb weakness (50% of cases), disturbance of speech, cognitive abnormalities(25 %), gait disorder (30%), seizures (10%) and visual impairments. The definitive diagnosis of PML is made by brain biopsy but due to its invasive character and occasional morbidity, it was replaced by newer techniques such as PCR for JC virus in the CSF and radiologic imaging.

PCR assays for the detection of JC virus DNA in the CSF are highly sensitive and specific (86) and could be used as a prognostic tool because it was observed that higher levels of JC in the CSF were correlated with lower survival rates. (87,88).

MRI is the modality of choice due to its higher sensitivity of lesion detection and superior contrast resolution compared to CT. Commonly, both PML and HIV encephalopathy displays nonenhancing lesions in the subcortical white matter, with little or no mass effect and hyperintense on T2-weighted and FLAIR magnetic resonance(89). But PML lesions are usually hypointense on T1-weighted images and become more hypointense as the disease

progresses (89). Typical imaging findings are patchy areas, often bilateral and asymmetric, located predominantly just below the cortical ribbon, involving the arcuate (U) fibers and sometimes seen in brainstem and cerebellum (90).

Magnetization transfer (MT) imaging is a new type of MR imaging which appears to be much more sensitive than standard MRI for the demyelinating process seen in PML. The signal used in MT imaging alter the magnetization of the tissue - bound protons which in turn causes a decrease in the signal coming from the free protons, producing a change in signal intensity on the MR image. The result is expressed as the change in signal intensity compared to normal MR image and is called magnetization transfer ratio (MTR). Studies (91,92) revealed that MTR in PML lesion is markedly reduced (22% to 26%) while in HIV encephalopathy has only mild reductions (38% to 40%), indicating that MT imaging could distinguish between them. Proton MR spectroscopy is another novel method which provides measurements of several neuromarkers, reflecting the neuronal viability. Only one study (93) compared the spectral changes in HIV encephalopathy with those in PML and found that the last one had a more profound decrease in NAA.

Although CNS tuberculosis and neurosyphilis are not opportunistic infections per se, they are discussed in this chapter due to their protean manifestations.

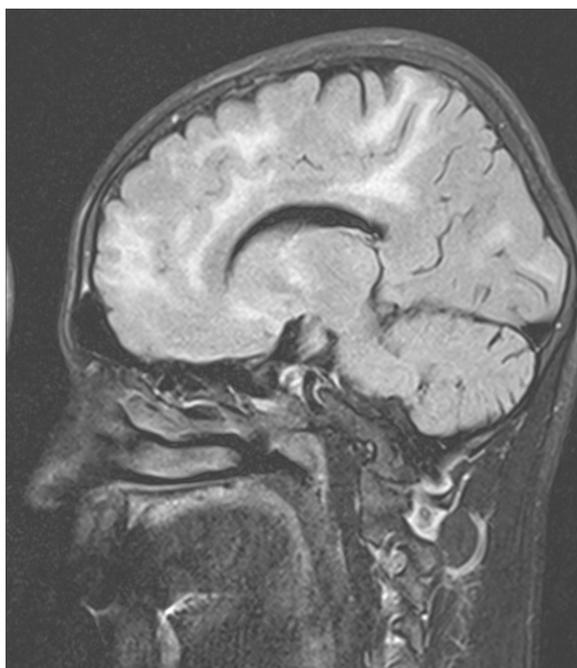


Fig. 5. PML: MRI (T2w FLAIR), sagittal section: diffuse high signal changes in the subcortical white matter of the frontal, parietal and occipital lobes, suggesting U-fibres involvement, with no mass effect (INBI Matei Bals collection, courtesy of dr R. Ungurianu)

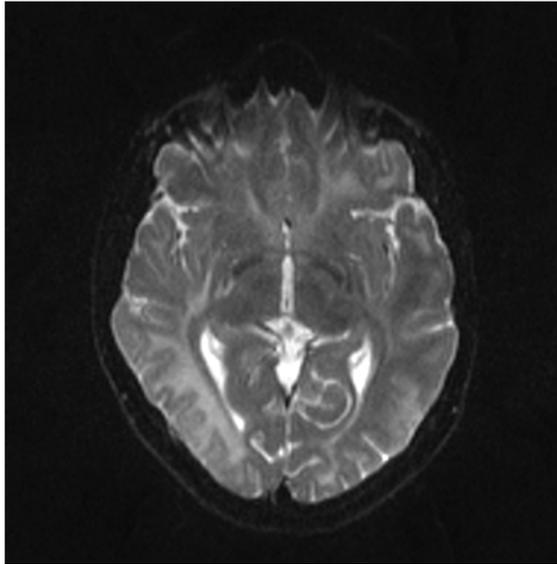


Fig. 6. PML: MRI (T2-w), transversal section: bilateral asymmetrical (predominantly on the right side) hyperintense signals in the subcortical white matter, just below the cortical ribbon (suggesting U-fibers involvement), without mass effect (INBI Matei Bals collection, courtesy of dr R. Ungurianu)

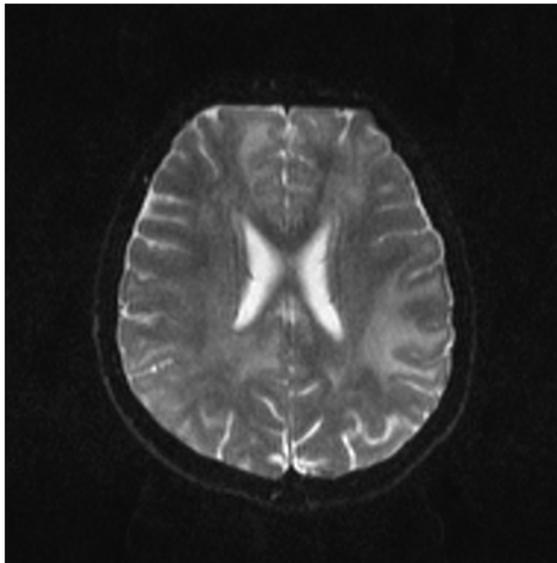


Fig. 7. PML: MRI transversal section (T2-w): bilateral asymmetrical, predominantly on left side, hyperintense signals in the subcortical white matter, just below the cortical ribbon (suggesting U-fibers involvement); no displacement of nervous substance, normal ventricles (INBI Matei Bals collection, courtesy of dr. R. Ungurianu)

**Tuberculosis** involves CNS in several ways including meningitis, cerebral abscess, tuberculoma and stroke due to vasospasm and thrombosis.

Besides typical presentations as meningitic syndrome, cases with atypical features are possible. Patients may present with a slowly progressive dementia characterized by personality changes, memory deficits and social withdrawal. Less common there is an encephalitic course manifested by seizures, stupor and coma.(94 )

The diagnosis relies on CSF analysis which typically reveals low glycorahia, elevated protein and a lymphocytic pleocytosis. Although CSF culture for acid fast bacilli is the gold standard for diagnosis, it takes 6-8 weeks to obtain a result and the sensitivity is low. PCR testing of the CSF is a rapid method for the detection of *M.tuberculosis* but the sensitivity is only 60% [95]

Because CNS and pulmonary TB could have simultaneous onset, a chest radiograph may provide supportive evidence.

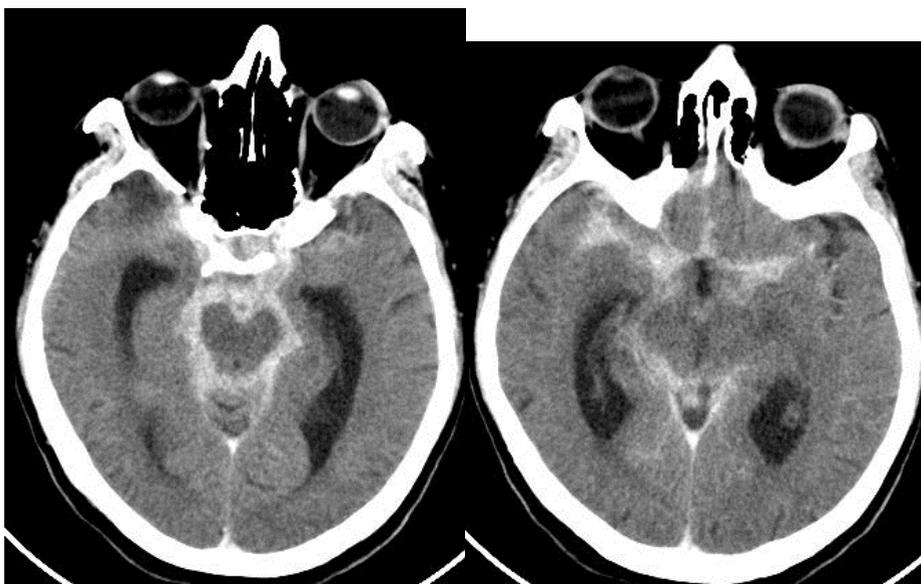


Fig. 8. Tuberculous meningo-encephalitis. CT (with contrast medium): Important enhancement in the basal cistern and meninges, in posterior and middle fossa, (cisterna magna, cisterna pontis, cisterna ambiens and suprachiasmatic cistern) with mild enlargement of the ventricles. Moderate cerebral edema – poor delineation between white matter and grey matter, with blurred appearance of cerebral sulcus (INBI Matei Bals collection, courtesy of dr V Molagic)

Neuroradiology plays an important role in diagnosis and the appearances take different forms:

- **intraparenchymal tuberculomas** appears as multiple lesions less than 1 cm that predominate at the gray-white matter interface and periventricular region; the lesions

have little mass effect or edema (96).CT demonstrates the lesion poorly but shows the presence of basilar arachnoiditis, cerebral edema, infarction and the presence and course of hydrocephalus. On MRI , the aspect correlates with the evolutive phase: on T1W images the lesions are isointense to gray matter and may have a hyperintense rim; on T2W there is a hyperintensity and nodular enhancement for non-caseating granulomas. The lesions become hypointense on T2 with rim enhancement while caseation occurs. Healed tuberculomas may calcify or may progress to areas of encephalomalacia (97)

- **tuberculous abscesses** are larger in size compared to tuberculomas, presenting as solitary loculated masses with mass effect and oedema; the ring enhancement is usually thin and uniform. They appear as hypodense lesion on CT and of high T2 signal on MRI.(98)
- **tuberculous meningitis** - basilar meningitis is the most frequent form and is seen as leptomeningeal thickening and enhancement involving the basal cisterns, prepontine and ambient cisterns and suprasellar areas.(99). Hydrocephalus is a common finding and its association with basilar meningitis on CT and compatible clinical features is strongly suggestive of tuberculous meningitis.( 100,101)



Fig. 9. Tuberculous meningo-encephalitis. CT (with contrast medium): Low-attenuating focal ischemic lesion in the fronto-parietal deep white matter in the proximity of right lateral ventricle (result from possible associated vasculitis) (INBI Matei Bals collection, courtesy of dr G Coltan)

**CMV encephalitis-** CMV reactivation in HIV patients emerges below a 50 CD4 T cells/mm<sup>3</sup> level (as opportunistic infection) and can lead to ocular manifestations (retinitis, vitritis), neurological (encephalitis), pulmonary (pneumonitis), digestive apparatus involvement (esophageal ulcers and colitis); hepato-splenomegaly, lymph nodes enlargement and fever. The diagnosis presumes a positive serology (IgG positive; rarely IgM positive).

Serial fundoscopies are indicated when a HIV patient with a poor immunological status complains about visual problems – showing a typical “cheese and ketchup” aspect of CMV retinitis. CMV viremia and blood pp65 antigen are positive. CMV PCR and pp65 antigen from CSF positive strengthen the diagnosis. Neuroimaging of CMV infection shows encephalitis (diffuse white matter impairment) and ventriculitis (ependymal enhancement).

CMV IRIS could be very harmful, with subsequent lost of sight and emphasizing of neurological signs.

**Cerebral toxoplasmosis** is an opportunistic parasitic infection in HIV infected patients, the most important neurological OI (opportunistic infections) in HAART era and it is due especially to a reactivation of a latent infection with *Toxoplasma gondii*. It appears below a level of 100 CD4 T cell/mm<sup>3</sup> with acute or subacute focal neurological deficits: paresis, sensory loss, aphasia; headache and a low degree of fever could be present; a chorioretinitis could accompany the neurological signs.

The serology must be positive (IgG antibodies) for proving reactivation. A negative result makes toxoplasmosis unlikely. Very rare, IgM antibodies are present and demonstrate acute illness.

The imaging exams are mandatory. MRI shows ring-enhancing mass(es) hyperintense lesions on T2W1/FLAIR, DWI; predilection for haemorrhages; decreased MR perfusion. There are solitary but typical multiple lesions.

CSF analysis may be contributory if PCR for toxoplasma is positive. A negative result never rules out the diagnostic.

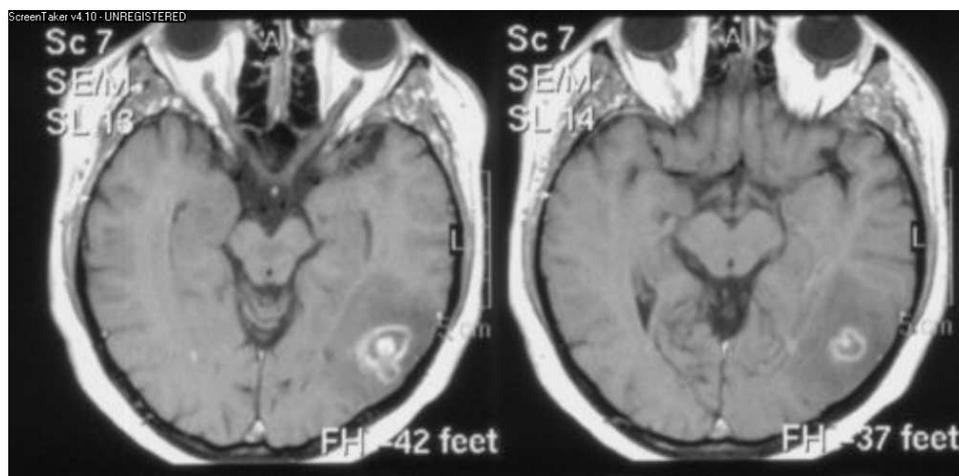


Fig. 10. Cerebral toxoplasmosis. MRI (T1-w with contrast medium) transversal sections: nodular lesion with annular peripheral enhancement (hypersignal) and surrounding edema (hyposignal); could produces mass effect (INBI Matei Bals collection)

A brain stereotactic biopsy can also be useful, especially when there is no clinical improvement in the first week of empirical antitoxoplasma treatment.

The fundoscopy is a necessary exam, especially for diagnose the association of a toxoplasmal chorioretinitis.

Toxoplasmosis IRIS is very uncommon.

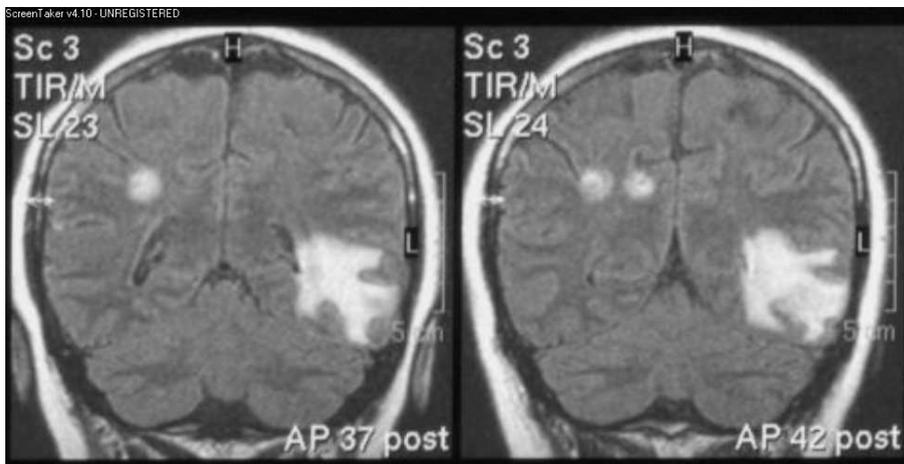


Fig. 11. Cerebral toxoplasmosis. MRI (T2-w FLAIR) coronal sections: several lesions, some nodular and one irregular with hypersignal – same patient as above (INBI Matei Bals collection)

**Cryptococcosis** is an opportunistic yeast infection with *Cryptococcus neoformans*, appearing lately during the HIV infection, below 100/mm<sup>3</sup> CD4 lymphocytes. It is an AIDS-defining illness. The CNS involvement is the most frequent manifestation (meningoencephalitis, rare cryptococcoma), but it could be accompanied by pulmonary symptoms (dry cough and chest pain) and skin lesions (moluscum-like appearance). Patients complain mainly of headaches and confusion, progressing in days, then gait impairment and cranial nerves signs due to the high CSF pressure; fever and meningeal signs could be absent. The lumbar puncture sets the diagnosis by highlighting the fungus: direct visualization by native preparation or with India ink stain, presence of *Cryptococcus* antigen, CSF culture positive; CSF has usually high pressure, low number of cells and mild raising in protein level. Relatively frequent the blood cultures are positive. Blood *Cryptococcus* antigen is positive (titer >1/8).

**Imaging:** The main manifestation, as a granulomatous meningitis has most often normal aspect on imaging exams, but a head CT scan or MRI are mandatory when there are even minimal neurological signs. There are some characteristic features in cryptococcal SNC infection: multiple T2 hyperintense small areas in basal ganglia, simetric nonenhancing cystic lesions - "gelatinous" pseudocysts within periventricular spaces, dilated Virchow-Robin spaces, mild ventricular dilatation with nodular meningeal enhancement; vasculitis and infarctions. Cryptococcomas are very rare and appear as isolated or multiple solid ring enhancing masses preferentially in choroid plexus.

In the course of IRIS, clinical signs are often atypical and characterized by extensive abscesses[8]

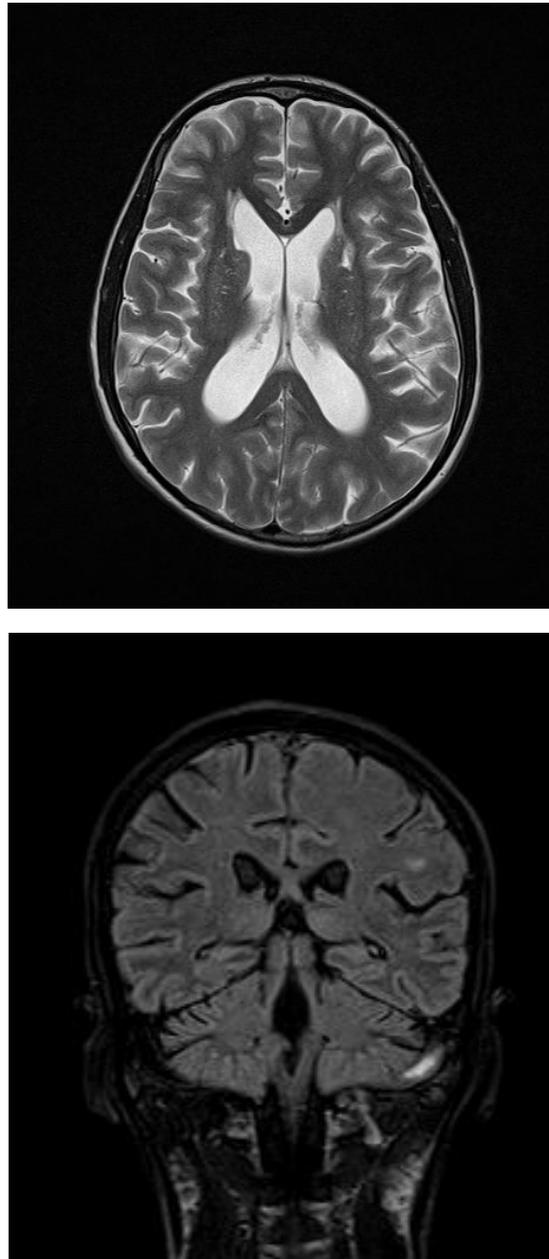


Fig. 12. Cryptococcal meningitis (A) MRI (T2-w), transversal section: dilated Virchow-Robin spaces and mild ventricular dilatations; (B) MRI (T2-FLAIR), coronal section: hyperintense nodule and mild ventricular enlargement (INBI Matei Bals collection)

## 7.2 Neurosyphilis

Defines the infection of the CNS by *Treponema pallidum* (T.pallidum) Because T. pallidum and HIV have the same route of transmission and different forms of neurosyphilis could have similar clinical features with HIV encephalopathy, it is worthwiling mentioning. Neurosyphilis can be classified into early forms (asymptomatic, symptomatic meningitis, meningovascular syphilis) and late forms (general paresis and tabes dorsalis).

The early forms affect the meninges, CSF and vasculature while the late forms affect the brain and spinal cord.(102).Consequently, the clinical features for symptomatic meningitis consist in headache, nausea, vomiting and stiff neck associated with visual impairment ; for meningovascular syphilis the typical presentation is similar to an ischemic stroke with an acute or chronic onset in a young person. General paresis is a progressive dementia with deficits in memory and judgment and less often with psychiatric symptoms (depression, mania, psychosis ). Tabes dorsalis is characterized by ataxia and attacks of severe pain.

There are described atypical forms of neurosyphilis, which mimic herpes encephalitis; the clinical presentation is dominated by cognitive changes with acute onset.(103)

Serologic tests are represented by non treponemal tests - Venereal Disease Research Laboratory (VDRL) and Rapid Plasma Reagin ( RPR ) test and treponemal test-fluorescent treponemal antibody absorption ( FTA-ABS ) or T.pallidum agglutination assay ( TPPA ). Usually, these tests are reactive in all patients with early neurosyphilis. However, non treponemal tests could be nonreactive in late forms of neurosyphilis. In this situation, if the clinical suspicion is high, a treponemal test should be done; in case of a nonreactive test, there is no indication for further evaluation. If the test is reactive, a lumbar puncture should be performed.

CSF examination is required for the diagnosis and should be done in every patient with compatible neurologic or ocular disease with known/unknown history of syphilis. CSF analysis reveals a lymphocytic pleocytosis (usually below 100 cells /microL), an elevated protein level and a reactive CSF VDRL, or a combination of these abnormalities. CSF VDRL is sensitive for the diagnosis but not specific. Therefore, in case of a negative CSF VDRL, a CSF-FTA-ABS should be performed.(104,105)

Neuroimaging shows different modifications for each stage;

- symptomatic meningitis -diffuse meningeal enhancement as well as enhancement of the CSF, cranial nerves and spinal root;-cerebral gummas appears as circumscribed masses with surrounding edema, located adjacent to the meninges and which extend into the cortex. On MRI , they are hypointense to isointense on T1W and hyperintense on T2W.
- meningovascular syphilis- single or multiple areas of infarction
- general paresis-cerebral atrophy
- atypical form (herpes encephalitis like)- on MRI the lesions have high signal on T2 and fluid attenuated-inversion recovery (FLAIR) and are unilateral or bilateral in medial temporal areas (103)

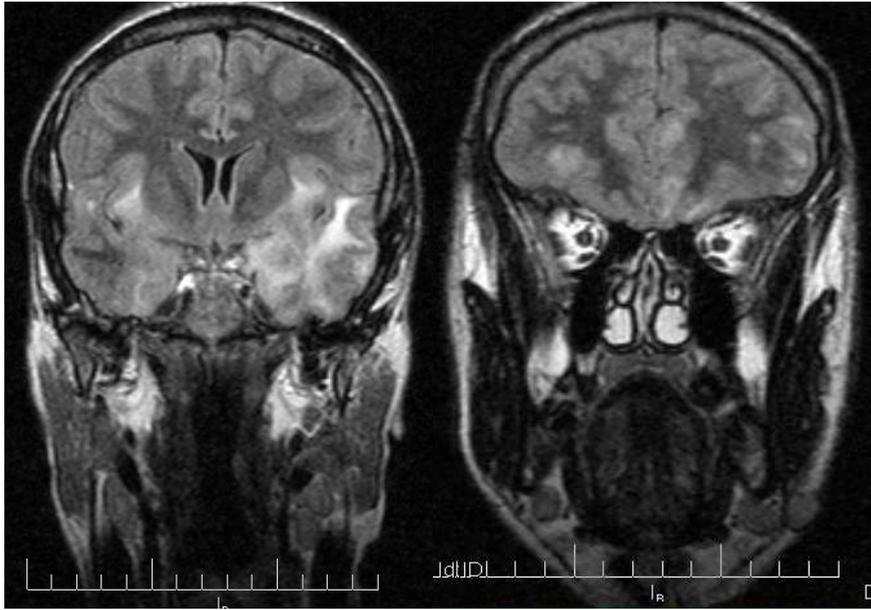


Fig. 13. Neurosyphilis. MRI (T2-w FLAIR) coronal section: bilateral diffuse hyperintensity signal in frontal and temporal areas, involving the subcortical white matter (Floreasca Emergency Clinical Hospital courtesy of dr C Predescu)

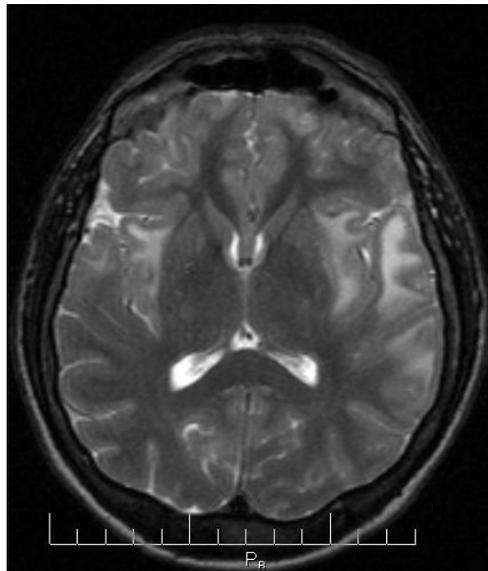


Fig. 14. Neurosyphilis MRI (T2-w) transversal section: bilateral hypointensity of the globus pallidus and putamen; disseminated temporal and insular high-signal lesions with subcortical topography (Floreasca Emergency Clinical Hospital, courtesy of dr C Predescu)

### 7.3 HAART neurotoxicity

There is a wide spectrum of CNS complications in patients with HIV, ranging from psychiatric syndromes to seizures and cognitive impairment. In some cases, these neuropsychiatric complications could be related with the antiretroviral drugs, especially for those which penetrate the CNS. For the clinician, it is important to distinguish between symptoms related to CNS complications of HIV infection and side effects of HAART.

The antiretrovirals most frequent associated with neuropsychiatric complications are nucleoside reverse transcriptase inhibitor ( NRTI ) and non nucleoside reverse transcriptase inhibitor ( NNRTI ).

#### NRTI

Zidovudine penetrate well the blood-brain barrier and therefore is a part of HAART regimens indicated for HAD. Moreover, Zidovudine has been found effective, at high doses, in slowing the progression of HAD . However, it was observed that up to 5% of patients who took Zidovudine for 1 year presented insomnia, agitation and confusion.(106)

In the past, there were some reports of psychiatric symptoms such as mania and depression, associated with Zidovudine treatment. If the treatment was discontinued, the manic symptoms disappeared.(107). In recent years, fewer psychiatric problems were reported, partly because nowadays Zidovudine is used in lower doses (600mg/day) compared to those used in pre HAART era (2000mg/day).

Other side effects reported were seizures, particularly in cases of overdose (108,109)

#### NNRTI

From this class of antiretrovirals, Efavirenz was the most frequent associated with CNS side effects including dizziness, headache, confusion, agitation, impaired concentration, amnesia,depersonalization, insomnia, hallucinations, abnormal or vivid dreams. These symptoms usually appear within the first month of treatment and decrease or even disappear spontaneously within 2 months.

Psychiatric adverse events associated with Efavirenz are less frequent than neurological ones, consisting in anxiety, depression and suicidal ideation.(110,111)

One of few studies investigating the neurotoxicity of Efavirenz on cognitive function showed that the treatment was associated with a higher risk of neurocognitive impairment, particularly on tasks requiring a higher attentional and executive load.(112)

Clinicians should carefully watch for changes in behavior, cognition and mood in HIV patients treated with Efavirenz and should advise their patients regarding CNS effects of therapy.

### 7.4 Neoplastic etiology

Primary CNS lymphoma ( PCNSL ) is the second most common cause of intracranial mass after toxoplasmosis. There are many possible presenting symptoms depending on the location and extent of the tumor. In general, half of the patients present with focal neurological deficits ( seizures, aphasia, hemiparesis and localized weakness ) and the other

half present with non focal symptoms such as lethargy, headache, memory loss, altered mental status and personality changes. (113)

Neuroimaging plays a crucial role in the positive and differential diagnosis and MRI is more sensitive than CT.

MRI- typically, PCNSL lesions are solitary but in 50% of the cases multiple lesions could be seen; they are hypointense on both T1W and T2W imaging and the enhancement pattern is variable (homogeneous, heterogeneous or ring-like). PCNSL lesions can be located in the periventricular white matter, basal ganglia, corpus callosum and thalami. The most common location within the cerebral white matter is the frontal lobe followed by temporal, parietal and occipital lobes. Uncommon locations such as brain stem, cranial nerves, pineal gland and cavernous sinus are also encountered in AIDS patients. An important imaging characteristic which helps to differentiate PCNSL from toxoplasmosis is the tendency of extension toward the ependymal surface of the ventricular system.(98). PCNSL lesions often measure from 2 to 6 cm, have mass effect and are surrounded by perilesional edema.

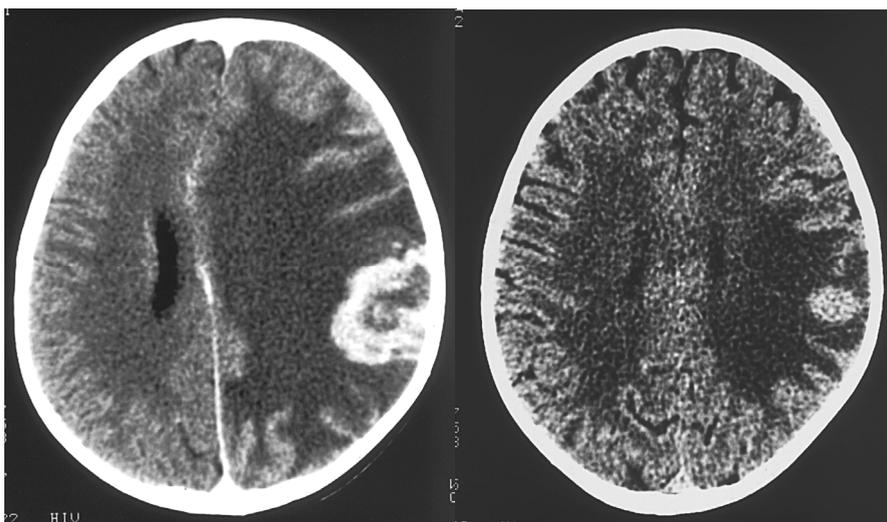


Fig. 15. Cerebral lymphoma: CT (with contrast medium), transverse section: solitary hyperintense lesion with annular enhancement and important perilesional edema with mass effect (A) at the diagnostic time and (B) after 4 months of treatment: important reduction of the lesion and remission of the mass effect (INBI Matei Bals and Fundeni Institute collections, courtesy of dr M Lazar)

Thallium 201 ( $^{201}\text{Tl}$ ) SPECT (single -photon emission CT) could be an important diagnostic tool. PCNSL lesions typically show increased uptake of  $^{201}\text{Tl}$  on SPECT imaging, in contrast to infectious and inflammatory lesions. This differentiating pattern of uptake becomes more evident on delayed scans (at 3-4h).

PET (positron emission tomography ) is useful for differential diagnosis because PNCSL lesions are more metabolically active than infectious lesions and take up F 18 fludeoxyglucose (FDG) during PET. Moreover, metabolic uptake in PNCSL lesions may not be affected by prior corticosteroid use.(114)

PCR detection of EBV DNA in CSF is limited by the risk of cerebral herniation in case of raised intracranial pressure.

### **7.5 Reversible encephalopathies**

Complaints of cognitive impairment could be related to the coexistence of other medical conditions or substance abuse. Therefore, we should check for thyroid dysfunctions, anemia due to vitamin B12 deficiency, liver cirrhosis (portal encephalopathy), renal failure (uremia), infections (sepsis), intoxications ( alcoholism, recreational drugs).

### **7.6 Immune reconstitution inflammatory syndrome (IRIS)**

A paradoxical clinical deterioration can occur in HIV patients shortly after HAART initiation and is due to an abrupt increase in immune surveillance which leads to pathologic inflammatory reactions. IRIS can be clinically expressed as an worsening of manifestations of underlying (known ) infection or an unmasking of a subclinical infection. Currently, there are no tested guidelines for the prevention or diagnosis of IRIS .Apart from clinical deterioration strictly related to HAART initiation, the diagnosis is suggested by a significant decrease in HIV RNA viral load and a rise in CD4 count.(17).

IRIS may actually worsen PML initially but a clinical improvement is possible in time. On neuroimaging there is a contrast enhancement atypical for non inflammatory PML lesions.(115,116)

## **8. Treatment**

HAART- consists of multiple antiretroviral drugs from different classes which stop HIV replication by acting in several key points of its life cycle. Besides suppression of viral replication, HAART reduces the appearance of resistance and restores immune function, increasing the CD4 count.

ADJUVANT THERAPIES- consist of several small molecules which have been identified to possess anti-inflammatory and neuroprotective properties.

The introduction of HAART since 1996 has led to major improvements in medical morbidity and life expectancy in HIV patients. The prevalence of opportunistic infections markedly decreased and the progression to AIDS was prevented or at least delayed. There were also registered significant improvement in neurological outcomes with a marked decrease in the incidence of HAD.(117,118)

Pre-HAART era prevalence estimates were approximately 16% in AIDS cases (119), whereas more recent estimates are less than 5%.(3)

However, HAART alone cannot eradicate HAND. Moreover, studies of HAND in treated patients showed high persisting rates of mild-to-moderate neurocognitive impairment (120),

suggesting that etiology of HAND could be multifactorial. Possible explanations for these observations are residual viral suppression in the CNS due to poor local penetration of some antiretroviral drugs, presence of drug-resistant viral strain and poor drug adherence. Other factors implicated are not HIV related and consist of possible neurotoxicity of antiretrovirals and coexisting illnesses such as cerebrovascular disease.( 3)

Current recommendations on initiating or changing HAART are based on peripheral parameters such as CD4 count and plasma viral load and not on the status of infection in CNS.

Although the optimal treatment for HAND has not been established, several studies have shown that antiretrovirals with good CNS penetration might positively affect cognition. Better penetration in the CNS, estimated by CPE score (CNS penetration effectiveness) is associated with a lower CSF viral load. (2,120). Based upon concentrations in CSF, drug properties and the results of clinical studies, each antiretroviral is assigned with a CPE score, ranging from 1 (low penetration) to 2 -3 (intermediate) and 4 (best penetration/effectiveness).

CPE score 1: Tenofovir, Zalcitabine, Nelfinavir, Ritonavir, Saquinavir/Ritonavir, Saquinavir, Tipranavir/Ritonavir, Enfuvirtide

CPE score 2: Didanosine, Lamivudine, Stavudine, Etravirine, Atazanavir/Ritonavir, Atazanavir, Fosamprenavir;

CPE score 3: Abacavir, Emtricitabine, Delavirdine, Efavirenz, Indinavir, Darunavir/Ritonavir, Fosamprenavir/Ritonavir, Lopinavir/Ritonavir, Maraviroc, Raltegravir

CPE score 4: Zidovudine, Nevirapine, Indinavir/Ritonavir

CPE rank is then calculated by adding up the scores for each antiretroviral drug in the regimen, according to CHARTER group score revised in 2010. (120)

In contrast, there are studies that failed to identify an association between a high CPE score and a better cognitive outcome. (112,121)

These controversial findings require further evaluation.

For the moment, EACS guidelines (version 5-4) recommend that, for patients who are not on treatment, the clinician should consider initiation an antiretroviral regimen in which at least 2 drugs penetrate CNS. Also for this category of patients, the risk for antiretroviral resistance should be considered ( if prior virological failure exists ).If the patient is already on treatment, changing the existing regimen with drugs which have better CNS penetration might be a solution. Whenever it is possible, genotyping of plasma and CSF HIV RNA should be done before changing the therapy.

Regarding adjuvant therapies, exploratory trials have focused on probable mechanisms of neurologic pathology. One study tested minocycline, which may have anti-inflammatory, antioxidant and antiapoptotic effects(122). Sellegiline was another tested compound due to its ability to block apoptotic cell death in chronic HIV brain infection.(123)

## 9. Conclusion

Despite HAART, cognitive impairment in HIV remains common. There are still unanswered questions regarding optimal timing and HAART regimen composition. Careful attention is needed to the treatment of cerebrovascular risk factors and co-morbidities.

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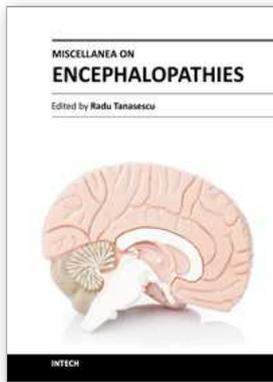
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