### Question 1. Which patients should be screened for HAND, and when? How often should patients be screened?

<table>
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<th>Who to screen:</th>
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<tr>
<td>1. It is recommended that cognitive functioning is assessed in all patients with HIV (Centre for Evidence Based Medicine level of evidence [CEBM] 5; grade of recommendation [GOR] D). Assessment can assist in treatment and management decisions, provide reassurance, and detect cognitive, behavioral, and mood changes before symptoms arise or are acknowledged (CEBM 2b) [1–4].</td>
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<td>2. There is no rationale for screening only symptomatic patients, and the positive predictive value of cognitive complaints for the presence of HAND in patients with HIV is unclear (CEBM 2b) [5–8].</td>
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<td>3. Similarly, as HIV almost always affects the central nervous system (CNS) during the natural history of the disease, there is no rationale for limiting screening of cognitive function impairment only to those with recognized risk factors for HAND (e.g., HIV ribonucleic acid (RNA) relapse). However, changes in HIV dynamics in the human body can predispose for the participation of opportunistic processes in cognitive deterioration (CEBM 2b; GOR C) [9].</td>
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When to screen:

1. The CNS is commonly one of the first targets of HIV infection, and it is recommended that the neurocognitive profile is assessed early in the disease using a sensitive screening tool (CEBM 5; GOR D)[4].

2. Good practice dictates that all patients with HIV should be screened for HAND within 6 months of diagnosis, as soon as clinically appropriate (CEBM 5; GOR D). This will establish accurate baseline data and allow for subsequent changes to be more accurately assessed.

3. Screening should take place before the initiation of combination antiretroviral therapy (cART) therapy, if possible (CEBM 5; GOR D).

4. There are insufficient data to establish the best time for HAND follow-up by either neuropsychological assessment or self-reporting of cognitive complaints, since different population factors can affect cognitive reserve during the natural history of the disease (CEBM 2b)[1].

5. However, it is good practice to screen for HAND every 6–12 months (in higher risk patients) or every 12–24 months (in lower risk patients) (CEBM 5; GOR D). At a minimum, this should include some questioning about cognitive symptoms (e.g., as in Simioni et al. 2010). Please see question 2 for information on risk factors for HAND.

6. If there is evidence of clinical deterioration, the patient should be re-screened straight away (CEBM 5; GOR D).

7. Screening should also take place at major change points (e.g., treatment introduction, treatment change, diagnosis of mental health problems or bereavement) (CEBM 3b; GOR C [10]).

8. We should be aware of practice effects in follow-up screening, although their impact
is currently unknown (CEBM 5; GOR D).

Question 2. How can clinicians identify patients at greater risk of HAND?

1. The presence of each risk factor listed below has been independently associated with an increased likelihood of HAND, but it is necessary to consider the full medical history in order to assess the clinical significance of any factor/s. The risk of HAND is increased if risk factors present in combination, occur with greater frequency, or re-occur, but there is still a lack of quantitative evidence on how they interact to increase the risk. Quantitative tools, which will assess the impact of a combination of the factors presented in these guidelines on the risk of developing or worsening of HAND, are in development. Therefore, clinical acumen remains an important part of the assessment.

2. All risk factors should ideally be assessed, although assessment of the disease and treatment factors should be the highest priority.

3. Any factors that can be modified (e.g., cardiovascular risk factors) may be targeted in a preventative strategy, to reduce further risk of neurocognitive decline.

Please refer to question 1 for guidance on the recommended frequency of screening in patients at differing risk of HAND.

RISK FACTORS SUPPORTED BY THE EVIDENCE AND THAT CAN BE READILY ASSESSED IN THE CLINIC:
Disease factors (all should be considered as part of good clinical practice)

- Low nadir CD4 (CEBM 1b; GOR B) [11–13]
- High plasma HIV RNA; high cerebrospinal fluid (CSF) HIV RNA (CEBM 2b; GOR B) [14,15]
- Low current CD4 (pre-combination ARV therapy (cART)) (CEBM 2b; GOR B) [13,16,17]
- Presence of past HIV-related CNS diseases (CEBM 1b; GOR B) [17]
- Longer HIV duration (CEBM 2b; GOR B) [18]

Treatment factors (all should be considered as part of good clinical practice)

- Low cART adherence (CEBM 1b; GOR B) [19]
- Episodes of cART interruption (CEBM 2a; GOR B) [20,21]
- Non-optimal ARV regimen (non-cART; in the context of non-suppressed plasma viral load) (CEBM 2a; GOR B) [20]
- Low cART duration (related to treatment failure) (CEBM 1b; GOR B) [17]

Co-morbidities

- Positive hepatitis C virus (HCV) serostatus with high HCV RNA (CEBM 1b; GOR B) [22]
- History of acute cardiovascular event (CEBM 1b; GOR B) [23]
- Cardiovascular risk factors, such as:
  - Hyperlipidemia (CEBM 1b; GOR B) [23]
- Elevated blood pressure (CEBM 1b; GOR B)[23]
- Chronic diabetes and diabetes type II (CEBM 2b; GOR B)[24,25]
  - Presence of anemia (CEBM 2b; GOR B) [26,27] and thrombocytopenia (CEBM 1b; GOR B)[28]

Demographic factors (in decreasing order of priority)

- Greater age (CEBM 1b; GOR B) [17,29–31]
- Low cognitive reserve (CEBM 2b; GOR B)[32], low level of educational achievement (CEBM 2b; GOR B)[33,34], some ethnicities (CEBM 2b; GOR B)[35] and gender associated with lower socio-economic status in some countries (CEBM 3a; GOR B)[36], lack of access to standard care, and poverty (CEBM 3b; GOR B)[37]

Other neurological and psychiatric factors (including potential confounds to diagnosis of HAND) *Please see also question 4*

- Neuropsychiatric disorders: previous or current major depressive disorder (MDD), generalized anxiety disorder, psychosis, and bipolar disorder (CEBM 2b; GOR B)[3,38,39]
- History of traumatic brain injury (CEBM 2b; GOR C)[40]
- History of chronic substance abuse (including alcohol, methamphetamines, cocaine, heroin, some prescription drugs, and heavy use of recreational drugs such as marijuana) (CEBM 2a; GOR B) [41–43]
Complex cART factors

- Lower CNS penetration efficiency (CPE) (CEBM 2a; GOR B)[44]
- Potential neurotoxicity (CEBM 3b; GOR C)[45] Please see also question 12

RISK FACTORS SUPPORTED BY THE EVIDENCE BUT WHICH CANNOT BE EASILY ASSESSED IN THE CLINIC:

Biomarkers

- High CSF neopterin (CEBM 2a; GOR B)[46,47]
- High plasma HIV DNA (CEBM 2b; GOR B)[48–50]
- High neurofilament light chain protein (CEBM 2a; GOR B)[46]
- High monocyte chemoattractant protein 1 (CEBM 2a; GOR B)[46]
- High serum osteopontin (CEBM 4; GOR C)[51,52]

**Question 3. Which tools should be used to screen for HAND?**

1. A diagnosis of HAND can only be made after a complete medical history, neurological examination, neuropsychological testing and (sometimes) neuroimaging are conducted (CEBM 5; GOR D)[53].

2. Several screening tools are available*. The choice of tool depends on:
   a. Whether the expertise of a neuropsychologist is available
   b. Whether the clinician wants to screen for HIV-associated dementia (HAD) or for the milder forms of HAND
   c. The cost associated with testing
d. The time available for testing
e. The characteristics of the population in which it will be used (CEBM 5; GOR D)

3. Cognitive screening tools should not be used in isolation of clinical factors. Clinical data (for example, from brief questioning**) and risk profiles (see question 2) should be used to increase suspicion for HAND. Screening tests are not a substitute for detailed neuropsychological testing (CEBM 1b; GOR B)[54,55].

4. No single HAND screening tool is suitable for use across all practice settings (CEBM 1b; GOR B) [56–58]. In addition, these scales cannot assist in differentiating impairment related to HIV from that related to other conditions.

5. The HIV Dementia Scale (HDS) and the International HIV Dementia Scale (IHDS) are the most widely used rapid screening tools for HAND:
   a. The HDS was initially developed to detect HAD, with a classical cut-off of 10 points or less (CEBM 1b; GOR B) [59]. Sensitivity to the milder forms of impairment is enhanced by modifying the cut-off score (CEBM 1b; GOR A) [60,61], including correction for demographic factors (CEBM 2b; GOR B) [62]. The HDS is free and takes less than 10 minutes to administer.
   b. The IHDS may be used in preference to the HDS in patients with a low level of literacy and numeracy (CEBM 1b; GOR B) [54]. An IHDS cut-off value of 9.5 maximized the sensitivity and specificity for HIV dementia at 71% and 79%, respectively (CEBM 1b) [54]. The IHDS is limited in its ability to detect milder forms of HAND (CEBM 1b) [54], although increasing the cut-off score again increases the sensitivity to milder impairment (CEBM 1b) [63]. The IHDS is free and takes a few minutes to administer.
   c. More research is needed to determine appropriate cut-off values of the HDS and IHDS in different clinical and geographical settings and the role that
symptoms of depression may have on IHDS performance and scoring (CEBM 1b) [54].

6. Computerized screening tests are available and can be considered where resources are available. The CogState (CEBM 1b) [64; 65] and the Computer Assessment of Mild Cognitive Impairment (CEBM 1b) [19] have undergone limited validation studies in HIV.

7. Where the expertise of a neuropsychologist is available and suitable population norms are available, brief screening instruments consisting of a combination of two neuropsychological tests may be considered; these have shown good sensitivity, including to the milder forms of HAND (CEBM 2b; GOR B) [66].

8. Repeated screening may be beneficial to detect changes in performance over time, although existing tools were designed for cross-sectional rather than longitudinal assessment. If a screening test is repeated over time, bear in mind that performance could improve as a result of the practice effect, rather than a true improvement in cognition. Ideally, alternative versions of the same test would be used for different administrations.

Note regarding levels of evidence: 1a grading in practical answer to question 3 from clinical decision rule (CDR) with 1b studies from different clinical centers; 1b grading from validating cohort study with good reference standards, or CDR tested within one clinical center.

*Including: the HDS [56,57,59, 60], the IHDS [54,56,67], the Total Recall measure of the Hopkins Verbal Learning Test [66], the Grooved Pegboard Test [66], the Mini Mental State Examination [59], the Executive Interview [68], the cognitive functional status subscale of the Medical Outcomes Study HIV Health Survey [69], the NeuroScreen (series of short tests including trail making test and digit symbol) [70], the Prospective
and Retrospective Memory Questionnaire [71], the Rey-Osterrieth Complex Figure Copy and Memory tests [72].

**For example, the 3-question screen validated by Simioni et al., 2010. [60]

1. Do you experience frequent memory loss (e.g., do you forget the occurrence of special events even the more recent ones, appointments, etc.)?
2. Do you feel that you are slower when reasoning, planning activities, or solving problems?
3. Do you have difficulties paying attention (e.g., to a conversation, a book, or a movie)?

For each question, patients can answer: a) never, b) hardly ever, or c) yes, definitely.

Patients are considered to have an ‘abnormal’ result when answering “yes, definitely” on at least one question.

**Question 4. Which co-morbidities should be considered in a patient with HAND?**

Please also see table 2 (in published article) that supports the practical answers to questions 2 and 4

1. Numerous co-morbidities can co-exist with HAND and contribute to neurocognitive impairment (NCI) in people with HIV. A co-morbidity may confound the accurate diagnosis of HAND, although this may be difficult to judge, or may compound the effect of the HIV virus. Broad guidance may be found in Antinori et al., 2007 (CEBM 5; GOR D) [53]. The following co-morbidities and risk factors for NCI in people with HIV should be considered (although this list is not exhaustive):
   a. Psychiatric illnesses (particularly MDD, anxiety, and post-traumatic stress
disorder), as well as illicit drug/alcohol abuse/dependence. These are common in patients with HIV, and can alter cognitive function and contribute to HAND (CEBM 1b; GOR A) [73]. MDD and drug/alcohol abuse/dependence also increase the risk of poor adherence to cART, worsening HAND (CEBM 1a, 2b; GOR B) [73–75].

b. Prescription drugs. Many prescription drugs, current and past, can adversely affect cognition. Drugs with anticholinergic properties, and combinations of CNS medications (particularly in older adults), are associated with an increased risk of cognitive decline (CEBM 2b; GOR C) [76–78].

c. Syphilis, opportunistic infections (OIs) and other HIV-related CNS disorders (CEBM 2b; GOR C) [79,80] Co-infection with HCV is common and may worsen HAND with an additive effect on cognitive impairment (CEBM 2b, 5; GOR B) [81–83].

d. Alzheimer's disease. HAND and Alzheimer's disease may co-exist in the aging person with HIV (CEBM 1b; GOR B) [84–87].

e. Cerebrovascular disease and metabolic syndrome. These are risk factors to consider in HIV-infected individuals, and particularly those with long-standing HIV disease (CEBM 1b; GOR B) [23, 25,88–91].

f. Aging. This is a major co-morbidity that is associated with additive effects of long-term exposure of the brain to HIV infection, cART effects and neuroinflammation, as well as the additive effect of co-morbidities such as MDD and drug/alcohol abuse/dependence (CEBM 1b; GOR B) [92–96].

g. Other chronic neurological disorders. These include traumatic brain injury (CEBM 1b; GOR B) [97] and seizures (CEBM 2b; GOR B) [98,99].

h. Vitamin or hormone deficiency (CEBM 2b; GOR C) [100]. Red cell folate (CEBM 5; GOR D) [101], B12 (CEBM 2a; GOR B) [102,103], testosterone
Question 5. How can HAND be differentiated from neurodegenerative diseases in older patients?

1. HAND can usually be differentiated from other neurodegenerative disorders (including Alzheimer’s disease, Parkinson’s disease and vascular cognitive impairment), most often by clinical findings. Where appropriate, assessment should include neuropsychological evaluation, blood tests, CSF analysis and imaging (CEBM 5; GOR D) [106].

2. The clinical features of HAND are those of a dominant sub-cortical type of cognitive impairment, with a common abnormality being psychomotor slowing (this abnormality is less prominent in HAND than in the past, but remains important), often in addition to impaired learning and executive function. There are no cortical features such as dysphasia, alexia, or agraphia (CEBM 2b) [107, 108].

3. Neuropsychological assessment is useful to determine whether the pattern of cognitive impairment is consistent with HAND. The finding of dominant psychomotor slowing is uncommon in most neurodegenerative diseases (CEBM 2b; GOR C) [107, 108].

4. In HAND, but not typically in neurodegenerative disorders, blood levels of B12, red cell folate levels and thyroid function are normal [106].

5. CSF testing, where available, can also be helpful. In HAND (but not typically in neurodegenerative diseases), in patients not on cART, there is an elevated CSF HIV viral load as well as markers of immune activation such as beta 2 microglobulin and...
neopterin (CEBM 2b; GOR B) [109–112]. Please see also questions 7 and 8.

6. Other CSF markers such as amyloid beta 1-42 and t-tau can be abnormal in both HAND and Alzheimer's disease and are therefore not helpful in differentiating the two diseases (CEBM 2b; GOR B) [113,114], although soluble amino-terminal ectodomain β-amyloid precursor protein holds promise (CEBM 2b; GOR B) [114].

7. Imaging may be helpful in addressing the possibility of disorders such as Creutzfeld–Jakob disease and normal pressure hydrocephalus. Spectroscopy of the basal ganglia may be useful, as it is abnormal in HAND and rarely in other degenerative disorders (CEBM 2b; GOR B) [115,116].

Question 6. How should neuropsychological testing be approached, in the diagnosis of HAND?

1. A full neuropsychological evaluation (where available and accessible) may be appropriate in the following groups of patients:
   a. Patients demonstrating NC1 at cognitive screening, if the diagnosis of HAND is in doubt (CEBM 5; GOR D) [53]. Please see also question 3.
   b. In patients where a differential diagnosis is in question (CEBM 5; GOR D) [53].
   c. Patients with cognitive deficits that impact on everyday life, including aspects of work, finance management, medication adherence, and simpler activities such as housework, cooking (CEBM 5; GOR D) [53].
   d. Patients with evidence of clinical progression of HAND or increasing cognitive complaints (CEBM 5; GOR D) [53].
   e. Patients identified as at risk of HAND using a validated, non-cognitive screening tool, and/or based on traditional risk factors for HAD, particularly if cognitive difficulties are also evident (CEBM 1b; GOR B) [17]. Please see also...
2. Comprehensive standard neuropsychological testing should be based on the following:
   a. A comprehensive test battery including at least 6 cognitive domains including verbal/language fluency; attention/working memory; abstraction/executive function; memory functions (learning and recall); speed of information processing; and motor skills (CEBM 5; GOR D) [53].
   b. Standard computerized-based neuropsychological tests may be used by clinical neuropsychologists, or they may prefer paper-and-pencil version of the same tests. The importance is again in the use of standard and validated instruments for detection of HAND. See standard reference book: Lezak et al., 2004 [117].
   c. Similar neuropsychological tests are recommended to be used for asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HAD diagnosis, although a step-down battery is often more appropriate in patients with severe impairment. A standard assessment of independence in activities of daily living is needed to differentiate ANI, MND and HAD (CEBM 5; GOR D) [11,13,17, 40,53,118–122].
3. The selection of a neuropsychological test battery is usually made by a neuropsychologist in order to be sensitive and specific to HAND and/or the differential diagnosis in question. In addition, the test battery will be adapted according to the sensory abilities of a patient, their reading and writing capacities, and their capacity to understand instructions of differing complexity. See standard reference book: Lezak et al., 2004 [117].
4. Standard neuropsychological testing should ideally be conducted by qualified neuropsychologists, psychometricians, and psychologists and follow national
regulation on the use of psychometric testing. Because tests are standardized (i.e., administration, scoring, and interpretation follow strict standard procedures) the variability between administrators is minimal if appropriate training has been received. See standard reference book: Lezak et al., 2004 [117].

5. The use of normative data (to adjust for demographic/sociodemographic factors) is essential for the correct interpretation of standard neuropsychological tests with quantitative outcomes. See standard reference books; Lezak et al., 2004; Heaton et al., 2004; Strauss et al., 2006 [117,123,124]. Note that the neuropsychologist will also use qualitative information (e.g., level of motivation, level of reading or writing proficiency, etc.) to contextualize the quantitative results.
   a. In developing and developed countries the effects of age, education, and gender (as well as ethnicity in some countries) must be considered. See standard reference books: Lezak et al., 2004; Strauss et al., 2006 [117,124].
   b. Geographic characteristics (such as coming from an urban versus rural environment) may need to be considered in addition to the traditional demographic factors in developing countries. See standard reference books: Lezak et al., 2004; Heaton et al., 2008; Strauss et al., 2006 [117,123,124].
   c. Normative data should be selected to best represent the demographic references for a particular participant. In some instances, local norms based on a smaller sample size are recommended over non-local norms based on large sample sizes. See standard reference book: Strauss et al., 2006 [124].

6. Before standard neuropsychological assessment, patients should be informed about the following:
   a. Purpose of the examination
   b. Nature of the examination
c. Use to which examination information will be put

d. Confidentiality

e. Procedure of feedback after the examination

f. The test procedures (a brief explanation)

Results are provided to patients in a standard format that includes clinical interpretation of the nature and severity of cognitive impairment (no raw scores are included). Results are passed on to relevant physicians. See standard reference book: Lezak et al., 2004 [117].

7. In follow-up testing, the use of normative longitudinal data is recommended to adjust for the impact of repeated testing (the 'learning or practice effect') on test sensitivity (CEBM 1c; GOR B) [125,126]. These data are usually provided with standard neuropsychological instrument manuals and are increasingly developed by researchers in specific areas of clinical research using a set battery of tests sensitive to a specific condition (e.g., in HIV infection see: Cysique et al., 2011) [44].

Further reading on this topic is recommended. The following has been specially designed for medical doctors: Holtz JL. Applied Clinical Neuropsychology: An Introduction. New York: Springer Publishing Company; 2011.

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<tr>
<th>Question 7. In addition to cognitive testing, which other assessments should be used in the diagnosis of HAND (e.g., psychiatric assessment, lumbar puncture/CSF analysis, imaging, exclusion of other pathologies)?</th>
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<tr>
<td>In addition to cognitive assessment, the following assessments should be used in the diagnosis of HAND in all HIV-infected individuals with suspected or demonstrated cognitive impairment. The overall objective of these other assessments is to identify co-</td>
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morbidities and enable a clinical judgment to be made about whether they contribute to cognitive impairment.

Please see the practical answer to question 4 for guidance on some of the specific co-morbidities that are particularly relevant in people with HIV

1. A thorough medical and neurological history will identify previous conditions associated with an acquired static encephalopathy, such as traumatic brain injury and past CNS OIs. A developmental history, including academic performance and achievement, as well as occupational attainment, will help to establish the premorbid level of neurocognitive functioning. Neuropsychological assessment typically includes structured approaches to gathering a good developmental history that are not routinely used in the medical clinic (CEBM 3b; GOR C)[40].

2. Patients with suspected neurocognitive decline should be evaluated for active substance abuse or dependence. Acute intoxication or withdrawal, or active substance abuse or dependence, can interfere with reliable evaluation of cognitive status. Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) criteria distinguish intermittent recreational use (which is of minor importance) from intoxication, abuse, and dependence (CEBM 3a; GOR B)[127–129].

3. When performing an assessment for psychiatric conditions that may influence self-reported cognitive performance such as depression, anxiety, and post-traumatic stress disorder, consider using a structured questionnaire where possible (CEBM 5; GOR D).

4. A thorough neurological examination by an appropriately trained clinician should be undertaken to evaluate for focal neurological signs, asterixis, myoclonus, ocular motor signs, spasticity, and other findings that may suggest an etiology of NCI other than HIV infection itself (CEBM 5; GOR D).
5. Laboratory studies should be done to stage HIV infection (CD4 cell count and HIV RNA) and assess for co-morbid infections, such as neurosyphilis, and for metabolic and endocrine disorders, such as hypothyroidism and hypogonadism (CEBM 5; GOR D).

6. CSF analysis for OIs and other infections should be considered if clinically appropriate (CEBM 1; GOR A) [58,130–132]. Please also see the practical answer to question 8.

7. Although many blood and CSF biomarkers have been studied in research investigations, none has consistently demonstrated sufficient discriminability to be used in the clinic as a diagnostic marker for HAND (CEBM 5; GOR D) (e.g., Lyons et al., 2011; Sun et al., 2010) [133, 134].

8. Magnetic resonance imaging (MRI) is useful in evaluating other conditions that may impact on NCI such as active opportunistic CNS disease, cerebral infarction or hemorrhage, and inactive cerebral lesions related to prior CNS opportunistic disease (CEBM 2b; GOR C) [135,136].
   a. The most common findings on structural MRI in individuals with HAND are atrophy and multifocal, small, subcortical T2 and FLAIR hyperintensities. These findings are not specific or pathognomonic (CEBM 5; GOR D).
   b. MRI where available is preferred to computed tomography (CEBM 5; GOR D).

9. A formal assessment of functional impairment using instruments such as Lawton & Brody’s modified Activities of Daily Living scale and the Patient’s Assessment of Own Functioning Inventory is desirable [1, 137,138]. When a formal assessment is not practical, a spouse, partner, or family member may be useful in providing complementary information on everyday functioning (CEBM 5; GOR D).
### Question 8. What is the role of lumbar puncture/CSF analysis in the management of HAND, and when should it be performed?

**1. Role of lumbar puncture/CSF analysis in the diagnosis of HAND:**

   a. The role of lumbar puncture in diagnosis is in the evaluation of HIV replication and HIV characterization by genotypic testing. Markers of immune activation and neuronal damage would need additional clinical validation to gain a role in the diagnostic work-up (CEBM 2a; GOR C) [47,139,140].

   b. CSF analysis should be performed in patients with neurological symptoms and/or signs (CEBM 2a; GOR B) [130,132].

   c. Ideally, CSF analysis should be done at presentation of symptoms/signs (CEBM 2a; GOR C) [130,132].

   d. In untreated patients ‘diagnostic’ CSF analysis would be better performed before starting cART (CEBM 2b; GOR C) [139].

   e. Similarly, in treated patients ‘diagnostic’ CSF analysis would be better performed before changing cART (CEBM 2b; GOR C) [139].

**2. Role and timing of lumbar puncture/CSF analysis in the monitoring of patients diagnosed with HAND:**

   a. Since almost all patients will show a reduction/clearance of HIV-RNA in CSF following cART, there is no general indication to repeat CSF analysis during the follow-up (CEBM 2b; GOR B) [139].

   b. Exceptions could be:

      i. Patients who changed cART because of CSF escape (repeat after >12 weeks), and do not experiment any neurological improvement after changing therapy (CEBM 4; GOR C) [140].

      ii. Patients who do not improve neurologically (repeat after >12 weeks)
Question 9. When, and how often, should neurocognitive performance be reviewed in patients who have been diagnosed with HAND?

1. There is a lack of rigorous large-scale data as to which tools are most appropriate and practical to use for monitoring (CEBM 5; GOR D).

2. The following are significant issues – the test/re-test reliability of tools, inter-rater reliability, and both practice and ceiling effects (CEBM 5; GOR D) (see e.g., Levine et al., 2007) [141].

3. Monitoring of patients who have not received cART:
   a. If patients have HAND they should be on cART (CEBM 2a; GOR C) [142].
   b. If for whatever reason a patient with HAND is not receiving cART, they should be reviewed clinically every few weeks, if at all practical (CEBM 3b; GOR C) [143,144].

4. Frequency of monitoring of patients who are receiving treatment (from the perspective of HAND, considering both efficacy and safety):
   a. Patients with symptomatic HAND (HAD and MND) commencing therapy should be monitored clinically, initially at 3 and 6 months, then 6 monthly until a plateau of response has been observed (CEBM 1b; GOR B) [145, 146], and thereafter annually. If there is clearly no response – and especially if there is deterioration at these early time points – other causes of impairment should be re-evaluated (CEBM 5; GOR D). Among these is the possibility of immune reconstitution syndrome characterized by deterioration following an initial response (CEBM 4; GOR C) [147, 148].
   b. Patients with ANI commencing therapy should be monitored initially at
5. Expected timescale for improvement:
   a. The earliest time point at which improvement would be expected is 1 month, although up to 9 months has also been observed (CEBM 1b; GOR B) [20, 150].
   b. Several studies observed improvement by 2 months (CEBM 1b) [151–154]. Earlier responses may be seen in those naive to cART (CEBM 1a and 1b) [152–154].

6. Criteria by which to determine the need for assessment, or the frequency of monitoring:
   a. The frequency of monitoring should be influenced by whether the patient is on cART, whether virological suppression has been achieved, how low the nadir CD4 count is, and the clinical status of the patient (CEBM 5; GOR D).

7. Role of the patient (particularly the asymptomatic patient) and patient education in detecting neurocognitive deterioration:
   a. Patients may detect neurocognitive difficulties before they are noted by clinicians. Consequently, those reporting cognitive difficulties should be evaluated fully (CEBM 1b; GOR B) [60]. However, self-report alone can either underestimate (as a result of impaired patient insight) or overestimate (as a result of anxiety and depression) true cognitive difficulties (CEBM 1b) [155].

**Question 10.** What is the natural history of ANI and MND, and how should this impact patient management?

1. Natural history of ANI or MND:
   a. There are no systematic published studies on the progression of ANI to MND, or of MND to HAD.
b. There are no systematic longitudinal studies that have examined the timeframe for progression with respect to ANI or MND.

c. There is some evidence that markers of progression of HIV disease (low CD4, acquired immunodeficiency syndrome (AIDS) diagnosis, high plasma viral load), neuropsychological status (worse processing speed), and MDD are associated with worsening of neuropsychological performance over time; however, none of these studies have involved a systematic classification of patients into normal, ANI, MND, or HAD categories in order to determine the factors associated with progression of disease [11,13,17, 40,118–122].

d. Most studies performed so far include both virologically suppressed subjects and patients with virologic failure, and it is not possible from existing data to conclude if patients with successful treatment (i.e., plasma viral load <50 copies/mL) are at risk of progression.

e. There are no systematic studies that address the extent to which cognitive deficit may be permanent or reversible.

2. Implications for choice of treatment:

a. cART given for about 1 year is associated with modest benefits in neuropsychological functioning, particularly in the areas of attention, processing speed, and executive performance. Limited or no benefit has been observed in language skills, memory, or visuospatial functioning with cART or HAART (CEBM 1a) [20,118,142,156,157].

b. The degree of improvement in cognitive functioning is strongly correlated with changes in CD4 cell counts (CEBM a) [13,40,122,158–160].

c. If neurocognitive complications are present, treatment with ARV agents that have higher CNS penetration has been associated with improved neurocognitive outcomes (CEBM 2b; GOR B) [20,146,156;161]. See Table 5
Numerous non-ARV therapy medications or neuromodulators have been studied to determine whether they have any therapeutic benefit to ameliorate cognitive impairments, but none have yet proven effective in controlled trials (CEBM 1b) [20,162–168]. Please see also question 13.

3. Assessment of impact of ARV-based therapy on Instrumental Activities of Daily Living (IADLs):
   a. Standardized instruments that utilize performance-based measures of everyday functioning and activities, or those that assess everyday performance using systematic self-report formats, are recommended to assess the impact of cART on IADLs. Each of the methods provides useful information with respect to IADLs (CEBM 2b; GOR B)[1,3,169–171].

**Question 11. What interventions should be considered in treated patients with persistent or worsening NCI and CSF viral load <50 copies/mL (non-detectable)?**

**Should the ARV therapy still be changed when the virus is not detectable in the CSF?**

1. In these circumstances, other causes of NCI, such as non-infectious types of dementia (including neurodegenerative diseases and vascular dementia), MDD, current drug use, and infections including HCV need to be considered as differential diagnoses. A clinician with expertise in this field should be consulted. Diagnostic measures may include brain MRI, lumbar puncture, and psychiatric evaluation (CEMB 5; GOR D). Please see also questions 4 and 7.

2. After ruling out alternative diagnoses, the possibility of HIV-related NCI must be considered. Two situations need to be differentiated: the case of detectable and
undetectable virus in the plasma.

a. If virus is detectable in the plasma (but not CSF), adapt the antiviral regimen according to resistance profiles and possibly the CPE score (CEBM 2b; GOR C) [172].

b. For the case of undetectable plasma (and CSF) virus, the same considerations apply, but the evidence is less strong (CEBM 2c; GOR C) [172]. Where available, an ultrasensitive version of HIV RNA detection, with a lower limit of detection of 2.5 copies/mL, may be performed on the CSF (this is currently only available in research settings). If virus is detectable by this method, modification of the antiviral regimen according to CPE score, and to CSF viral resistance profile (if facilities are available for genotypic assessment on low viral loads), appears to be a reasonable option. If the ultrasensitive assay for HIV RNA detection is not available, the possibility of CSF viral load >2.5 copies/mL should be considered, and again the regimen could be modified accordingly (CEBM 2b; GOR C) [173,174]. See Figure 2 for algorithm showing management of treated patients with persistent or worsening NCI and undetectable CSF viral load (<50 copies/mL). See Table 5 (in published article) for 2010 CPE rankings.

3. If NCI is continuing, refer to the recommendations provided in question 12 about potential ARV-related neurotoxicity.

a. There is conflicting evidence on the effects of treatment interruption in patients with suppression in both compartments. Therefore, this intervention should only be considered as a last resort for a short period of time and must be accompanied by close observation of neurocognitive and virological parameters (CEBM 2b; GOR C) [21,121,175]. However, treatment interruption is not recommended at present (CEBM 5; GOR D).

4. For tailoring an individual approach for a given patient with cognitive impairment
despite viral suppression in plasma and CSF, factors predicting progression of cognitive impairment should be considered. These include modifiable factors such as MDD, substance abuse, and cerebrovascular risk factors, and non-modifiable factors such as CD4 nadir, age, family history of dementia (CEBM 2b; GOR C) [12,176].

Question 12. What is the risk of ARV-related neurotoxicity? What should be done if ARV neurotoxicity is suspected?

1. Risk of ARV-related neurotoxicity:
   a. Evidence documenting adverse clinical neurocognitive effects of cART is limited. There is some in vitro evidence for neurotoxicity [177], but its relevance to the clinical situation is unclear.
   b. Evidence of neuropsychiatric side effects is greatest for efavirenz (a non-nucleoside reverse transcriptase inhibitor). However, these effects are prominent in the first few weeks of therapy and resolve spontaneously; any potential long-term side effects are unknown (CEBM 1b) [178–180].
   c. Interruption of cART is not currently recommended as it is likely to lead to a fall in CD4 count and increased risk of mortality (CEBM 1b; GOR B). However, evidence for the neurotoxicity of cART has come from some studies that suggest cognitive improvement following cessation of cART (CEBM 3b) [121].

2. Management of suspected neurotoxicity:
   a. If CNS side effects persist for more than 4 weeks, consider therapeutic drug monitoring followed by dose adjustment (CEBM 2b; GOR C) [181,182]. If symptoms persist, the agent could be switched to an alternative (CEBM 5;
**Question 13. When/how should pharmacological agents other than ARV agents be used in the management of HAND?**

In addition to cART, several drugs have been evaluated in clinical trials and cohort studies as potential adjuvant therapies for HAND. These include minocycline, memantine, selegiline, lithium, valproic acid, lexipafant, CPI 1189, peptide T, nimodipine, and psychostimulants.

1. Existing studies, designed primarily to assess tolerability and safety, have not yet provided evidence that they are effective (CEBM 1a)[184].

2. Most studies of adjunctive therapies conducted to date were not powered to detect change, and there is a need for clinical trials with adequate sample size and duration in order to determine the effectiveness of adjunctive therapies in the treatment of HAND.

3. Based on the lack of evidence, it is not possible to recommend the use of adjuvant therapies for routine clinical treatment of HAND, despite evidence of good safety and tolerability in most studies.

**Question 14. What can be done to prevent HAND?**

Potential strategies to prevent HAND:

1. There is a limited evidence base for the earlier introduction of ARV therapy in patients with HIV, for the prevention of HAND:
   a. Among individuals treated with modern ARV regimens, current CD4 does not
relate to likelihood of HAND, but nadir CD4 is a predictor even when current
CD4 is not low. This provides indirect support for the idea that initiation of ARV
therapy, before there is a serious immune suppression event, may be of
neurological benefit (CEBM 2b; GOR B) [40]. Recent studies even indicate
possible neurological benefits of treating patients at very early stages, such as
the acute HIV-infection stage (CEBM 2b; GOR B) [12].
b. We could consider that earlier treatment of patients at high risk of NCI, for
instance, aging people at the early stages of HIV infection, could be legitimate
(CEBM 5; GOR D). In others, current guidelines should be followed (CEBM 2b,
GOR C) [12].
c. However, in HIV-infected patients, the possibility of prolonged treatment-
related neurotoxic effects should also be considered and weighed against
benefits of earlier cART initiation (CEBM 2b; GOR C) [185].
d. Overall, the question of which CD4 level is optimal for initiation of cART to
prevent HAND, and in which specific patients earlier initiation is beneficial,
remains without a clear answer (CEBM 5).

2. Initiation of CNS-penetrating cART:
   a. There are no data on the use of CNS-penetrating cART for preventing HAND,
and there is, therefore, no evidence to support the initiation of therapy with
better CNS-penetrating regimens in neuro-normal patients, especially those at
greater risk of HAND, such as aging people or those co-infected with
hepatitis B or C (CEBM 5; GOR D).
b. In the treatment of NCI, several studies have assessed the effect on
neurocognitive function of cART regimens ranked according to their predicted
effectiveness (termed CPE ranking) in suppressing HIV replication within the
CNS. Generally, better neurocognitive performance has been observed in
patients receiving higher CPE cART (CEBM 2b) [186,187]. However, the evidence base is limited and some of the data are contradictory regarding the potential benefits of CPEcART (CEBM 2b) [188].

3. Lifestyle and other interventions:
   a. Some data are available to recommend lifestyle interventions in HIV-infected patients suffering from, or at risk of, HAND. Such interventions include cognitive neurorehabilitation and increasing physical activity. There should also be treatment of co-morbidities such as MDD and other depressive disorders, and alcohol or drug abuse (CEBM 2a and 2b; GOR C) [189–191].

4. Compliance interventions/counseling:
   a. Interventions aimed at improving or preserving executive functions could prevent progressive decline in neurocognitive abilities and enhance adherence (CEBM 3b; GOR C)[192,193].
   b. Specific rehabilitation on memory, assistance with technology, and health-education programs could help HIV/AIDS patients to attain better adherence and other lifestyle outcomes (CEBM 4; GOR C)[194].

5. Treatment of potential co-morbidities (e.g., HCV)
   a. Recent data support the premise that some medications used to treat psychiatric co-morbidities in HIV-infected individuals may also protect the brain from toxic by-products of HIV replication and neuroinflammation. Treating MDD in HIV/HCV co-infected patients may reduce the impact of fatigue on daily functioning, relieving the burden of dual infection complications, such as NCI (CEBM 3b; GOR C) [195].
   b. Direct and indirect data tend to show benefits in treating potential co-morbidities, such as HCV, cardiovascular risk factors, metabolic disorders, and MDD, to reduce NCI in HIV-infected patients (CEBM 2b and 5; GOR C)
However, the evidence is not strong and further prospective work is required. It should be noted that interferon-based treatments of HCV themselves have been associated with NCI (CEBM 3a) [197].

References


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