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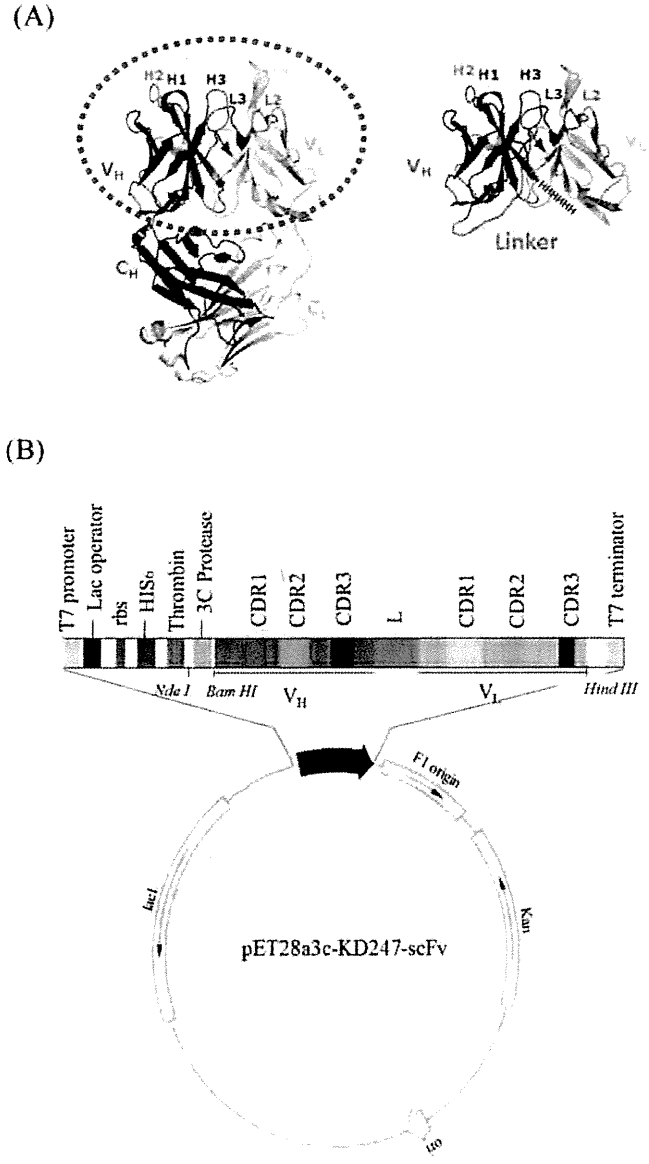

Figure 1.

Schematic diagram of pET28a3c-KD247-scFv. (A) The crystal structure of KD-247 F_{ab} (1.5 Å resolution, PDB: 3NTC) is shown with the complementarity determining regions (CDRs) highlighted in different colors. [Red: CDR 1 heavy chain (H1); Orange: CDR 2 heavy chain (H2); Purple: CDR 3 heavy chain (H3); Yellow: CDR 1 light chain (L1); Green: CDR 2 light chain (L2); Dark blue: CDR3 light chain (L3)]. The expected structure of KD-247 scFv was illustrated as a model. Figures were generated using PyMOL (8). (B) The variable domains of the heavy chain (V_H) and light chain (V_L) of KD-247 are connected with a peptide linker (L) to form the scFv. The twenty amino acid long peptide linker consists of four repeats of Glycine-Glycine-Glycine-Glycine-Serine, $(GGGGS)_4$. The scFv construct was subcloned at the N-terminal 6X Histidine tag (HIS_6) of the pET28a3c vector.

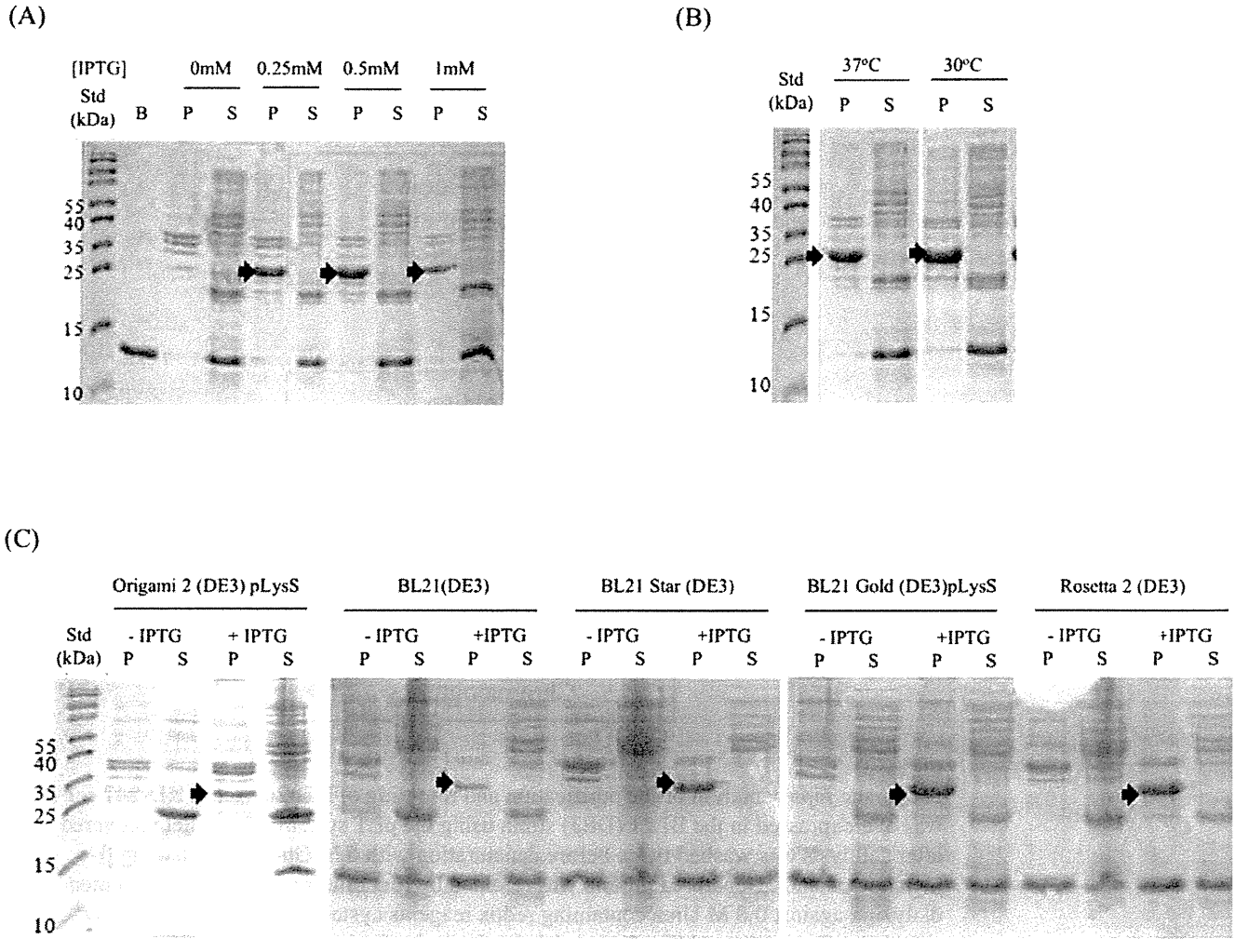

Figure 2.

SDS-PAGE showing the optimization of KD-247 scFv overexpression in *E. coli*. (A) Overexpression of KD-247 scFv in Origami 2 (DE3) pLysS at various IPTG concentrations (0.25 mM, 0.5 mM, and 1 mM) were examined. (B) KD-247 scFv expression was induced at 37 °C or 30 °C. (C) Overexpression of KD-247 scFv in various *E. coli* strains was compared. As shown by the arrows, KD-247 scFv was expressed as inclusion bodies in *E. coli*. [Std: Protein standards; P: Pellet; S: Supernatant; B: Lysis Buffer]

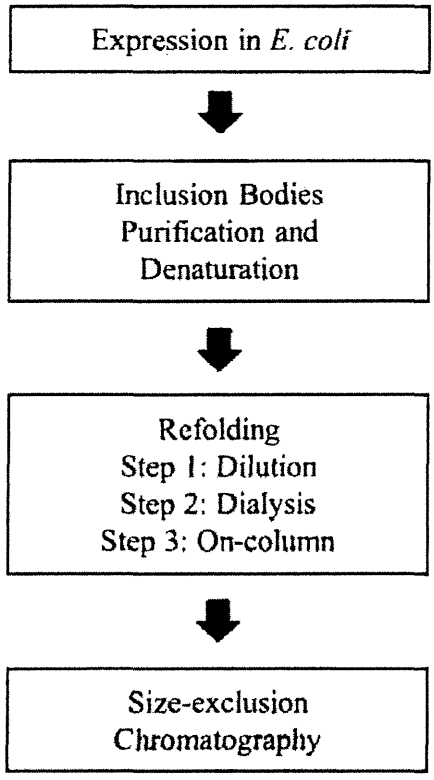

Figure 3.
Schematic representation of the purification and refolding of KD-247 scFv. KD-247 scFv was overexpressed in the BL21 (DE3) strain using the pET system. The pellet recovered after cell lysis was washed twice before denaturation with 6 M Gu-HCl containing β-mercaptoethanol. Denatured protein was refolded by first diluting in 6 M Urea and then dialyzing against 0.8 M Urea containing redox reagents cysteine and cystine. Partially refolded scFv was immobilized on a nickel column for further purification to remove residual urea. KD-247 scFv contains HIS_6 tag at the N-terminus, which enables nickel-affinity purification. scFvs eluted from the column were subjected to size-exclusion chromatography to obtain monomeric scFv.

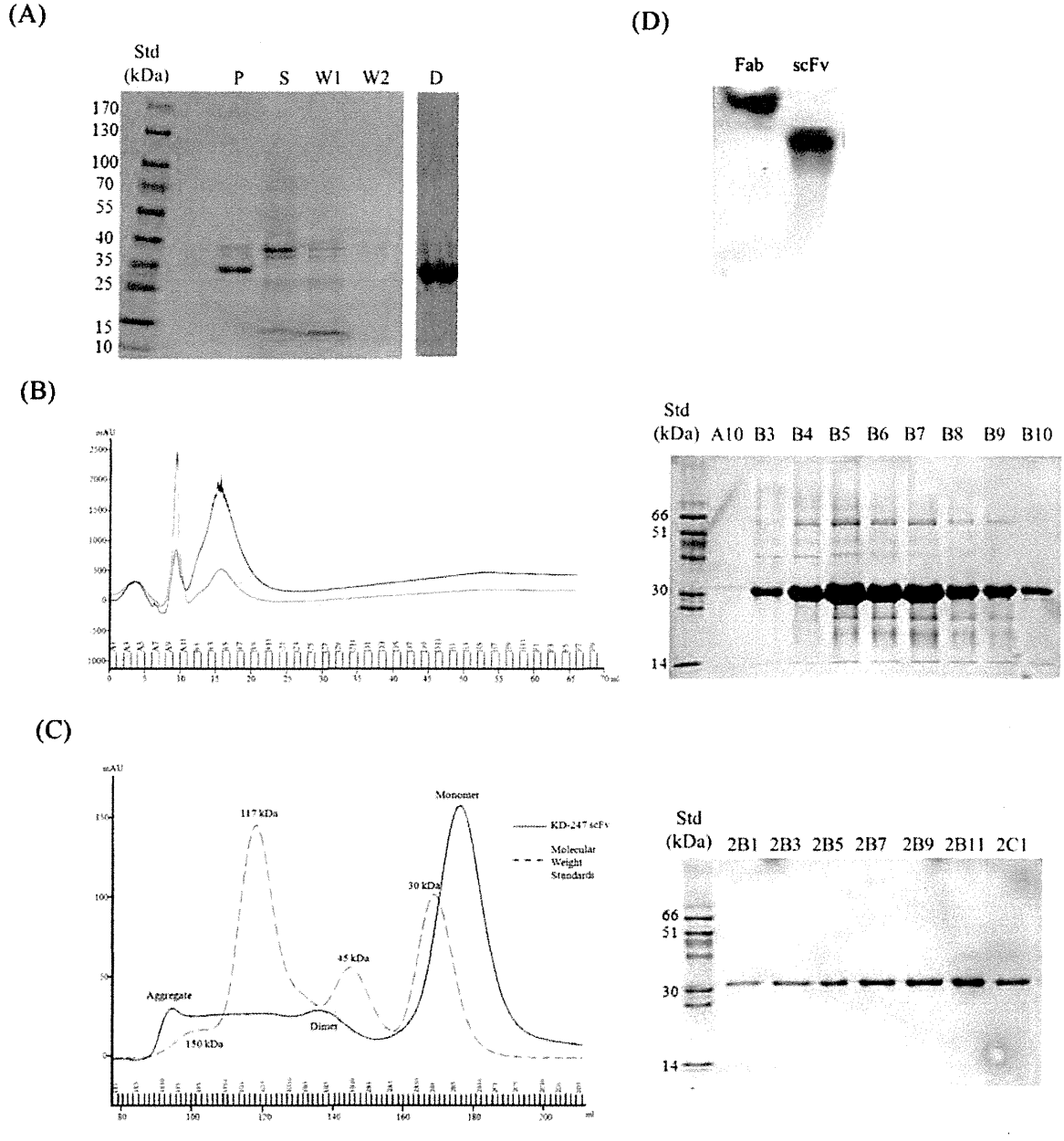

Figure 4.

Purification of KD-247 scFv from inclusion bodies. (A) SDS-PAGE showed proteins collected at various steps of purification. [P: pellet of lysed cells; S: supernatant of lysed cells; W1: supernatant after washing pellet with Wash Buffer A; W2: supernatant after washing pellet with Wash Buffer B; D: denatured scFv (diluted in 50 mM Tris-HCl pH 8.2, 150 mM NaCl)]. (B) Chromatogram showing the elution of scFvs from the nickel column. Blue line represents absorbance at 280 nm, red line represents absorbance at 254 nm. Elution fractions collected were analyzed by SDS-PAGE. (C) Size-exclusion chromatogram of KD-247 scFv in various refolded forms (blue solid line) compared to molecular weight standards (brown dashed line). Eluted scFvs in the monomeric fractions were analyzed by SDS-PAGE. (D) Native-PAGE of KD-247 F_{ab} compared to the monomeric KD-247 scFv recovered after concentration.

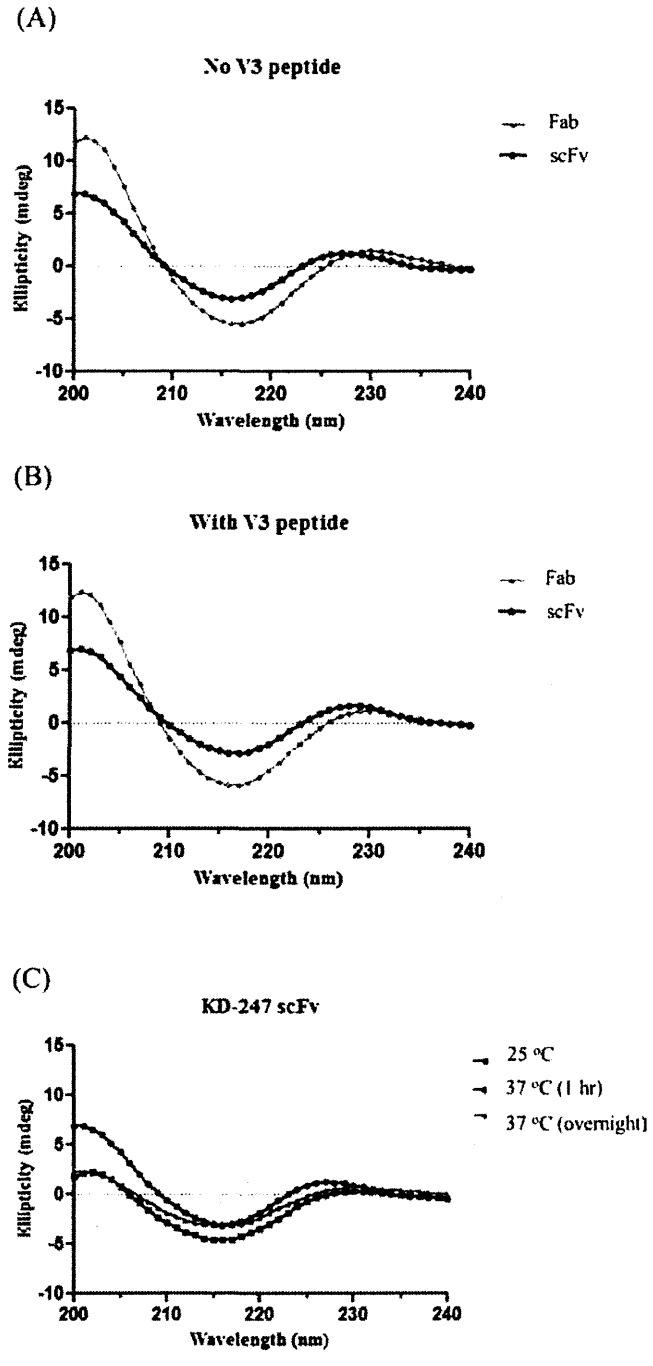

Figure 5.

Far-UV circular dichroism (CD) spectra to evaluate secondary structures. The refolded KD-247 scFv (black) was compared to KD-247 F_{ab} (grey) in the absence of V3 peptide (A) and in the presence of V3 peptide (B). (C) CD of the refolded scFv at 25 °C (black), after 1 hour incubation at 37 °C (blue) and after overnight incubation at 37 °C (red).

Table 1

Buffers for KD-247 scFv Purification

Lysis Buffer	50 mM Tris-HCl pH 8.2, 150 mM NaCl, 1 mM EDTA, 0.1% Triton X-100, 1 mM PMSF, 100 μg/ml lysozyme
Wash Buffer A	50 mM Tris-HCl pH 8.2, 150 mM NaCl, 3% Triton X-100, 1M Gu-HCl
Wash Buffer B	50 mM Tris-HCl pH 8.2, 150 mM NaCl
Denaturing Buffer	50 mM Tris-HCl pH 8.2, 150 mM NaCl, 6 M Gu-HCl, 10 mM β-mercaptoethanol
Refolding Buffer A	6 M Urea, 50 mM Tris-HCl pH 8.2, 150 mM NaCl
Refolding Buffer B	0.8 M Urea, 50 mM Tris-HCl pH 8.2, 150 mM NaCl, 2 mM Cysteine, 0.4 mM Cystine
Refolding Buffer C	50 mM Tris-HCl pH 8.2, 150 mM NaCl
Elution Buffer	50 mM Tris-HCl pH 8.2, 150 mM NaCl, 500 mM Imidazole

Table 2

50% neutralizing activity (IC_{50}) of KD-247 scFv by TZM-bl cell assay

	Clade B HIV-1 Env		Clade C HIV-1 Env
	BaL	**JR-FL**	**ZM53M.PB12**
Maraviroc	0.001 μM	0.003 μM	0.003 μM
KD-247 Fab	0.1 μM	0.5 μM	> 5 μM
KD-247 scFv	0.2 μM	0.6 μM	> 5 μM

Kenneth H. Mayer, Section Editor

Assessment, Diagnosis, and Treatment of HIV-Associated Neurocognitive Disorder: A Consensus Report of the Mind Exchange Program

The Mind Exchange Working Group

Many practical clinical questions regarding the management of human immunodeficiency virus (HIV)–associated neurocognitive disorder (HAND) remain unanswered. We sought to identify and develop practical answers to key clinical questions in HAND management. Sixty-six specialists from 30 countries provided input into the program, which was overseen by a steering committee. Fourteen questions were rated as being of greatest clinical importance. Answers were drafted by an expert group based on a comprehensive literature review. Sixty-three experts convened to determine consensus and level of evidence for the answers. Consensus was reached on all answers. For instance, good practice suggests that all HIV patients should be screened for HAND early in disease using standardized tools. Follow-up frequency depends on whether HAND is already present or whether clinical data suggest risk for developing HAND. Worsening neurocognitive impairment may trigger consideration of antiretroviral modification when other causes have been excluded. The Mind Exchange program provides practical guidance in the diagnosis, monitoring, and treatment of HAND.

Keywords. AIDS dementia complex; HIV-associated dementia (HAD); HIV-associated neurocognitive disorder (HAND); HIV encephalopathy; neurocognitive impairment.

Despite advances in the treatment of human immunodeficiency virus (HIV) [1], the central nervous system (CNS) is still often affected by this disease. Impairment of cognition caused by HIV disease is known as HIV-associated neurocognitive disorder (HAND) [2]. Importantly, compared with unaffected populations, HAND, even in its mild form, is associated with lower medication adherence [3], less ability to perform the most complex daily tasks [4–7], worse quality of life [8], difficulty obtaining employment, and shorter survival [8]. Athough the incidence of the most severe form of HAND—HIV-associated dementia (HAD)—has declined in the era of combination antiretroviral therapy (cART) [9], the incidence and prevalence of milder forms (asymptomatic neurocognitive impairment [ANI] and mild neurocognitive disorder [MND]) have remained stable or perhaps even increased [10]. In addition, as cART-treated patients survive into older age, there could be a rise in HAND due to interactive effects of chronic immune activation and aging on the CNS [11].

Gaps remain in translating emerging neuro-HIV research findings into clinical practice [12]. To address this problem, the Mind Exchange program was established with the goal to provide guidance of direct relevance to daily clinical practice. In this communication we describe the process of expert consensus development and specific recommendations on HAND diagnosis and management, based on the best available evidence.

Received 29 June 2012; accepted 13 November 2012; electronically published 21 November 2012.

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Clinical Infectious Diseases 2013;56(7):1004–17

DOI: 10.1093/cid/cis975

METHODS

Sixty-six specialists from a range of disciplines (including HIV clinicians, neurologists, neuropsychologists, clinical psychologists, and psychiatrists who care for and have experience with HIV patients) from 30 countries provided input into the Mind Exchange program, which took place between February 2011 and January 2012. The program was overseen by a steering committee of 5 experts, including 2 infectious disease specialists (from Italy and the United States), a neurologist (from Germany), a neuropsychiatrist (from the United States), and a clinical psychologist (from Spain).

The program comprised several stages (Figure 1). A broad list of clinical questions across the 5 topics (screening, diagnosis, monitoring, treatment/interventions, and prevention of HAND) was generated by a core group of international experts in a face-to-face meeting. A total of 83 questions were identified and included in a questionnaire for prioritization by the core expert group and a wider group of HIV clinicians; the questionnaire was circulated and returned by email, with 65 individuals from 30 countries responding. This process resulted in a final set of 14 questions identified as of critical clinical importance to be addressed during the remainder of the program.

A comprehensive literature search of PubMed and the Cochrane Library was performed for each of the 14 questions by a research or clinical fellow, or a member of the core expert group, using question-specific search strings and predefined limits (no time limit was specified). Abstracts from key international conferences were also searched.

For each question, a draft practical answer was generated by 2 or 3 members of the core expert group based on the findings of the literature review and their clinical opinion. Answers were reviewed by the steering committee and refined by the expert group. Following this, an international meeting with the steering committee, core expert group, and broader HIV clinician group was held to discuss and further refine the draft answers. These 63 participants from 30 countries voted on

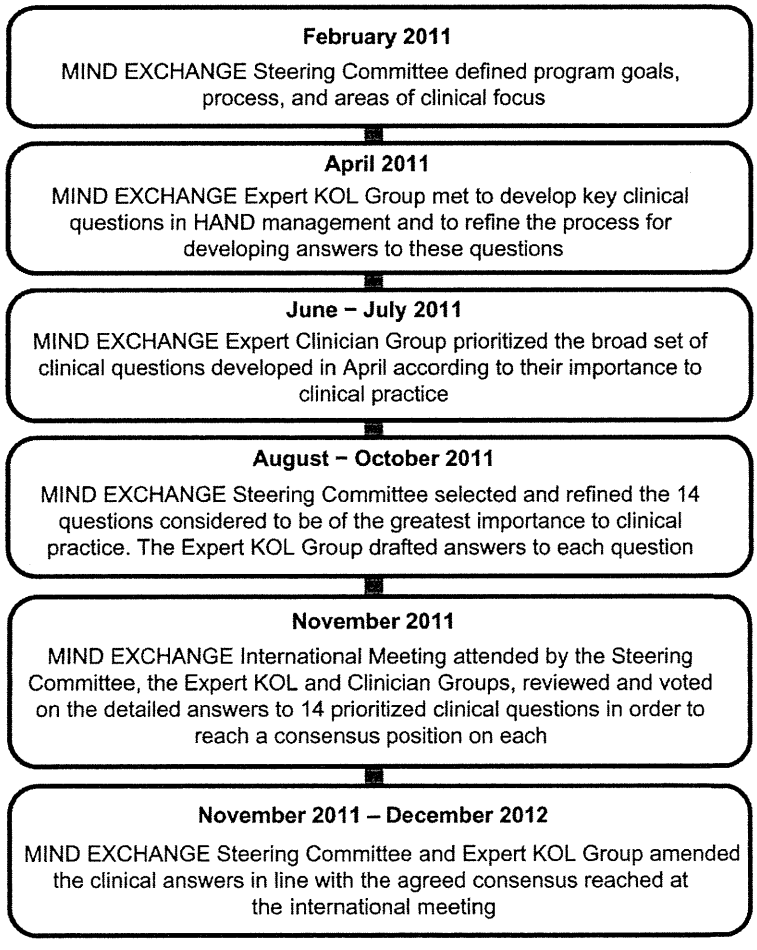

Figure 1. Overview of the Mind Exchange program. Abbreviation: KOL, key opinion leader.

their level of agreement with each draft answer using a scale of 1–9 (where 1 = strong disagreement and 9 = strong agreement). Consensus was defined as at least 75% of participants scoring within the 7–9 range. If <75% of participants scored within this range, the answer was debated and revised, followed by a second vote. Similar voting methodology has been employed in development of other consensus-based guidelines in the United Kingdom [13, 14].

The core expert group then further refined the answers to improve clarity and to reduce their length for this document. No substantive changes in the content or meaning of the answers were made. A level of evidence and grade of recommendation was assigned to each statement in the final answers, in accordance with the Oxford Centre for Evidence-Based Medicine (CEBM) 2009 criteria [15]. This system covers all study types and is appropriate for assigning levels of evidence across the broad range of clinical questions.

RESULTS

The 14 key questions are presented in Table 1. Agreement was achieved on the draft answers to all 14 questions at the international meeting. Here we present a summary of the major points of the guidance derived from each of the answers to the 14 questions.

Screening for HAND

It is appropriate to assess neurocognitive functioning in all patients with HIV (CEBM 5; grade of recommendation [GOR] D) as there is limited rationale for screening only symptomatic patients (CEBM 2b) [16–19] or only those with recognized risk factors for HAND (eg, nadir $CD4^+$ T-cell counts <200 cells/μL) (CEBM 2b; GOR C) [20]. Furthermore, because the CNS is commonly one of the first targets of HIV infection, good practice suggests that a patient's neurocognitive profile should be assessed early (within 6 months of diagnosis, as soon as clinically appropriate) using a sensitive screening tool (CEBM 5; GOR D) [21]. If possible, screening should take place before the initiation of cART (CEBM 5; GOR D), as this will establish accurate baseline data and allow for subsequent changes to be more accurately assessed.

Although there are insufficient data to establish the best time for follow-up assessments (CEBM 2b) [22], the consensus group agreed that screening for HAND should occur every 6–12 months in higher-risk patients or every 12–24 months in lower-risk patients (CEBM 5; GOR D). Several risk factors (Table 2) have been independently associated with an increased likelihood of HAND. The clinical significance of risk factors should be considered in light of the patient's full medical history. Screening should also be carried out immediately if there is evidence of clinical deterioration (CEBM 5, GOR D) or at the time of major changes in clinical status (eg, cART initiation or change or diagnosis of mental health disorders; CEBM 3b; GOR C) [23].

Table 1. Fourteen Key Clinical Questions That Were Identified and Addressed During the International Program

1	Which patients should be screened for HAND, and when? How often should patients be screened?
2	How can physicians identify patients at greater risk of HAND?
3	Which tools should be used to screen for HAND?
4	Which comorbidities should be considered in a patient with HAND?
5	How can HAND be differentiated from neurodegenerative diseases in older patients?
6	How should neuropsychological testing be approached in the diagnosis of HAND?
7	In addition to cognitive testing, which other assessments should be used in the diagnosis of HAND (eg, psychiatric assessment, lumbar puncture/CSF analysis, imaging, exclusion of other pathologies)?
8	What is the role of lumbar puncture/CSF analysis in the management of HAND, and when should it be performed?
9	When, and how often, should neurocognitive performance be reviewed in patients who have been diagnosed with HAND?
10	What is the natural history of ANI and MND, and how should this impact patient management?
11	What interventions should be considered in treated patients with persistent or worsening NCI and CSF viral load <50 copies/mL (nondetectable)? Should the ARV still be changed when the virus is not detectable in the CSF?
12	What is the risk of ARV-related neurotoxicity? What should be done if ARV neurotoxicity is suspected?
13	When/how should pharmacological agents other than ARV be used in the management of HAND?
14	What can be done to prevent HAND?

Abbreviations: ANI, asymptomatic neurocognitive impairment; ARV, antiretroviral; CSF, cerebrospinal fluid; HAND, human immunodeficiency virus–associated neurocognitive disorder; MND, mild neurocognitive disorder; NCI, neurocognitive impairment.

Many brief screening approaches have been proposed for the detection of neurocognitive disorders; the benefits and limitations of those tools for which there is substantial literature on their use in HAND are presented in Table 3. In addition to paper-based tools, some computerized tools are also available for screening (eg, CogState [34]; CANTAB reaction time [35]). No single tool is suitable for use across all practice settings, and the choice of a HAND screening tool depends on a number of considerations, including the availability of a clinician suitably trained to administer and interpret each tool; whether the clinician wants to screen for HAD only or for the milder forms of HAND; the financial and time cost of testing; and the characteristics of the population in which the tool will be used (CEBM 5; GOR D). Neurocognitive screening tools

Table 2. Comorbidities and Risk Factors Important to the Identification and Differential Diagnosis of HIV-Associated Neurocognitive Disorder

Evidence-supported risk factors	Risk Factor/Comorbidity for HAND and/or Non-HIV-Related NCI	Can Assist Identification of Patients			CEBM Levels (See Question Details for References)
		With Current HAND	At Risk of Developing HAND in Future	At Risk of Non-HIV-Related NCI	
Readily assesiable in clinic					
Disease factors	Low nadir $CD4^+$ T-cell count	X	X		CEBM 1b
	High plasma HIV RNA; high CSF HIV RNA	X	X		CEBM 2b
	Low current CD4 (pre-cART)	X	X		CEBM 2b
	Presence of past HIV-related CNS diseases	X	X		CEBM 1b
	Longer HIV duration	X	X		CEBM 2b
Treatment factors	Low cART adherence	X	X		CEBM 1b
	Episodes of cART interruption	X	X		CEBM 2a
	Nonoptimal cART regimen	X	X		CEBM 2a
	Short cART duration (related to treatment failure)	X	X		CEBM 1b
Comorbidities	Positive HCV serostatus with high HCV RNA	X	X	X	CEBM 1b
	History of acute CV event			X	CEBM 1b
	CV risk factors (hyperlipidemia, elevated blood pressure, chronic diabetes, and diabetes type II)			X	CEBM 1/2b
	Anemia and thrombocytopenia	X	X	X	CEBM 1/2b
Demographic factors	Older age	X	X	X	CEBM 1b
	Low level of educational achievement	X	X	X	CEBM 2b
	Ethnicity	X	X	X	CEBM 2b
	Sex (female, as associated with lower socioeconomic status in some countries)	X	X	X	CEBM 3a
	Lack of access to standard care; poverty	X	X	X	CEBM 3b
Other neurological and psychiatric factors	Neuropsychiatric disorders, eg, MDD, anxiety, PTSD, psychosis, bipolar disorder (current or history of)	X	X	X	CEBM 2b
	Illicit drug/alcohol abuse/dependence (current or history of)	X	X	X	CEBM 2a
	Syphilis or systemic infection	X	X	X	CEBM 2b
	Alzheimer's disease			X	Use APA (in press)
	Cerebrovascular disease			X	Use APA (in press)
	Traumatic brain injury and seizure	X	X	X	CEBM 2b
	Vitamin or hormone deficiency			X	Use APA (in press)
	Prior HCV coinfection[a]			X	CEBM 2b
Complex cART factors	Lower CPE	X	X		CEBM 2a
	cART neurotoxicity			X	CEBM 3b
Difficult to assess in clinic					
Biomarkers	Abnormal CSF neopterin	X			CEBM 2a
	Abnormal plasma HIV DNA	X			CEBM 2b
	Abnormal NFL	X			CEBM 2a
	Abnormal MCP–1	X			CEBM 2a
	Abnormal serum osteopontin	X			CEBM 4

Abbreviations: APA, American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders* (in press; see www.dsm5.org); ARV, antiretroviral; cART, combined antiretroviral therapy; CEBM, Centre for Evidence-Based Medicine; CNS, central nervous system; CPE, central nervous system penetration efficiency; CSF, cerebrospinal fluid; CV, cardiovascular; DNA, deoxyribonucleic acid; HAND, HIV-associated neurocognitive disorder; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MCP-1, monocyte chemoattractant protein-1; MDD, major depressive disorder; NCI, neurocognitive impairment; pts, patients; NFL, neurofilament light chain protein; PTSD, posttraumatic stress disorder; RNA, ribonucleic acid.

[a] Evidence of previous HCV infection (ie, in HCV-infected patients with no active HCV RNA, and without liver cirrhosis or failure) should also be considered a risk factor for non-HIV-related NCI [2]. For full referencing of this table please see the Supplementary Data.

Table 3. Useful Available Tools for Screening for HIV-Associated Neurocognitive Disorder

Tool	Description	Benefits	Limitations
HDS [24–28]	A validated brief screening tool designed primarily for use in outpatient clinics to identify dementia in people with HIV using NP tests of motor speed, concentration, and memory.	• Very fast to administer (3–5 min) • Very fast to score and interpret • Excellent specificity	• Modest sensitivity (80% when the score was 10 or less for a maximum of 16 points) leading to high rates of false negatives. High sensitivity for HAD. But HAD is relatively rare in successfully cART-treated patients • Requires a trained examiner to assess antisaccadic eye movement • Not sufficiently sensitive to detect mild HAND, particularly in highly educated individuals and in this case the use of demographically corrected norms or a cutoff of 14 points may be useful • Alphabet writing and cube-copying tests may be difficult for those with a non-Western educational background; the IHDS is more appropriate in these cases
IHDS [27, 29, 30]	A sensitive and rapid screening test for HIV dementia, which relies on assessment of motor speed and psychomotor speed It includes 3 subtests: timed finger-tapping; timed alternating hand sequence test; recall of 4 items at 2 min	• Very fast to administer and score. Can be conducted in 2–3 min and requires only a stopwatch • Demonstrated appropriate sensitivity and specificity for screening for dementia • Does not require a trained examiner • Does not require proficiency in English • Can be easily applied in different settings and cultures	• Limited ability to detect milder forms of HIV-associated neurocognitive impairment and distinguish between different stages of HIV dementia • Additional research is needed to determine appropriate cutoff values in different clinical and geographical settings • Additional research needed into the role of depression on performance and scoring
Total Recall measure of the Hopkins Verbal Learning Test–Revised [31]	Originally developed to detect dementia, it has been shown to measure neurocognitive impairment in HIV. In particular, it can be used to detect verbal learning and retrieval deficits	• Has 6 alternate forms reducing potential practice effects and enabling its use in follow-up and monitoring of neurocognitive changes over time • Easy and fast (4 min) to administer • Good test to assess patients with severe peripheral neuropathy and/or extreme motor limitations	• Must be administered by a trained examiner • Must be scored and interpreted by a trained psychologist or neuropsychologist • Scoring and interpretation must be based on adequate normative data (ie, data appropriate to the individual being assessed)
Grooved Pegboard Test [31]	Test of manipulative dexterity requiring complex visual-motor coordination		• Difficult to use in patients with severe peripheral neuropathy and/or extreme motor limitations • Requires equipment, although the cost is relatively low (US$100), and stopwatch • Must be scored and interpreted by a trained psychologist or neuropsychologist • Scoring and interpretation must be based on adequate normative data (ie, data appropriate to the individual being assessed)
Executive Interview [32]	Developed and validated in geriatric patients and patients with Alzheimer's disease as a brief assessment of frontal or executive neurocognitive function Has been shown to be a significant individual predictor of dementia in hospitalized patients with HIV	• Has good internal consistency • Correlates with other measures of executive neurocognitive function • Not affected by age or sex	• Less sensitive than HDS • Lower education was associated with an increased risk of incorrect classification of dementia • Accuracy in mild HAND has not been reliably shown

Table 3 continued.

Tool	Description	Benefits	Limitations
Cognitive functional status subscale of the (MOS-HIV) [33]	MOS-HIV is a widely used instrument to assess QoL in patients with HIV. Its neurocognitive functional status subscale measures functional status owing to neurocognitive impairment. Best use may be as a screening instrument to select those subjects whose self-reported neurocognitive functional status warrants formal NP test evaluation	• Sensitive to changes in NP test performance in early disease • Sensitive to neurocognitive behavior that involves neurocognitive or psychomotor speed	• No sensitivity to attention and only limited sensitivity to memory function • Accuracy in mild HAND has not been reliably shown

Abbreviations: HAD, HIV-associated dementia; HAND, HIV-associated neurocognitive disorder; HDS, HIV Dementia Scale; HIV, human immunodeficiency virus; IHDS, International HIV Dementia Scale; MOS-HIV, Medical Outcomes Study HIV Health Survey; NP, neuropsychological; QoL, quality of life.

should not be used in isolation from clinical information (eg, from brief questioning [see full answer to question 3 in the Supplementary Data] [24]) and risk profiles, which can be used to increase suspicion for HAND. Screening tests typically underestimate the true prevalence of HAND because they lack sensitivity to milder forms of the condition.

Neurocognitive/Neuropsychological Assessment (as Part of HAND Diagnostic Procedure)

A comprehensive neuropsychological (NP) evaluation is the accepted standard for the evaluation of HAND according to published criteria [2]. Because NP resources are limited in many clinical settings, a presumptive clinical diagnosis of HAND could be based on symptom questionnaires, screening tools, functional assessments, and limited NP testing. Patients with particular characteristics could then be targeted for full NP assessments: patients demonstrating neurocognitive impairment (NCI) at neurocognitive screening, if the differential diagnosis of HAND is in doubt (CEBM 5; GOR D) [2]; when the HAND diagnosis is uncertain (CEBM 5; GOR D) [2]; in patients who have evidence of impaired everyday functioning (CEBM 5; GOR D) [2]; in patients with evidence of clinical progression of HAND or increasing neurocognitive complaints (not associated with depression; CEBM 5; GOR D) [2]; and in patients identified as at risk of HAND based on traditional risk factors for HAD (eg, nadir $CD4^+$ T-cell count below approximately 200 cells/μL), particularly if neurocognitive difficulties are also evident (CEBM 1b; GOR B) [36].

Comprehensive NP testing should include a test battery of at least 5 neurocognitive domains (including verbal/language, attention/working memory, abstraction/executive function, learning/recall, speed of information processing, and motor skills [CEBM 5; GOR D]) [2] using standard and validated instruments for detection of HAND administered and interpreted by appropriately trained professionals [37]. Furthermore, tests should be performed at times when the patient is not experiencing excessive fatigue or severely depressed mood, and when the general medical status is stable (ie, without other active systemic diseases). The NP tests selected for use should ideally have been validated in the language and culture of the patient. The use of appropriate normative data from a healthy community population is recommended for the correct interpretation of standard NP tests with quantitative outcomes [37–39]. Furthermore, 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) [40, 41].

Differential Diagnosis of HAND

Various conditions (comorbidities) may either suggest a non-HIV cause for NCI, or their presence may compound HIV's effect on the CNS. To identify comorbidities and make a judgment as to whether or not they contribute to NCI, a number of assessments (in addition to neurocognitive assessments already described) should be used in HIV-infected individuals with suspected or demonstrated NCI (Table 4). In addition, in older patients, it is important to differentiate HAND from neurodegenerative disorders. Here both pattern and course of progression of NP impairment, and in certain instances, ancillary diagnostic information such as brain imaging, cerebrospinal fluid (CSF) studies, and blood tests can be helpful (Table 4). For example, in the older person with well-controlled HIV, the differential diagnosis of Alzheimer's disease may be suggested by progressive cognitive impairment with prominent difficulties in learning new information, rapid forgetting, and language problems (eg, deficits in naming and comprehension, which are not prominent in HAND), in the context of apolipoprotein e4 polymorphism (CEBM 2b; GOR B) [56–59].

CSF analysis should be performed in patients with neurological symptoms or signs (CEBM 2a; GOR B), preferably at presentation (CEBM 2a; GOR C) [46, 47], and should be preceded by imaging (to avoid lumbar puncture–associated risk).

Table 4. Tests Additional to Neuropsychological Assessment That Should Be Used in the Diagnosis of HIV-Associated Neurocognitive Disorder in HIV-Infected Patients With Suspected or Demonstrated Neurocognitive Impairment

Test	Purpose
Thorough medical and neurological history	Will identify previous conditions associated with an acquired static encephalopathy (such as TBI, OIs)
Developmental history (academic performance, occupational attainment)	Will help to establish the premorbid level of neurocognitive functioning (CEBM 3b; GOR C) [42]
Assessment of past and active alcohol and substance abuse or dependence using DSM-IV	Acute intoxication or withdrawal or active substance abuse or dependence can interfere with reliable evaluation of neurocognitive status (CEBM 3a; GOR B) [43–45]. Poor performance on NP testing may be explained, at least in part, by extensive past history of alcohol or substances
Assessment of depression, anxiety, and posttraumatic stress disorder using a structured questionnaire (CEBM 5; GOR D)	To identify psychiatric conditions that may influence self-reported neurocognitive performance as well as performance on some neurocognitive tests
Neurological examination	To assess neurological signs (eg, asterixis, myoclonus, ocular motor signs, spasticity) that may suggest an etiology other than HIV infection (CEBM 5; GOR D)
Laboratory studies	To stage HIV infection (CD4 cell count and HIV RNA) and assess for comorbid infections (eg, neurosyphilis, hepatitis C) and metabolic and endocrine disorders (hypothyroidism and hypogonadism) (CEBM 5; GOR D)
CSF analysis	For OIs and other infections (CEBM 1; GOR A) [46–49] and in individuals with high CD4 T-cell count and undetectable plasma HIV RNA (to assess for detectable CSF HIV RNA) [50]; genotypic resistance testing in patients with detectable HIV RNA
MRI	To evaluate other conditions that may impact on neurocognitive impairment (eg, active opportunistic CNS disease, cerebral infarction or hemorrhage, subcortical [vascular] leukoencephalopathy, and inactive cerebral lesions related to prior CNS opportunistic disease; CEBM 2b; GOR C) [51, 52]. Magnetic resonance spectroscopy appears more sensitive than structural MRI in milder forms of HAND and shows different metabolite changes in HAND subtypes [53, 54]
Lawton & Brody's modified Activities of Daily Living scale and the Patient's Assessment of Own Functioning Inventory	Provides a formal assessment of functional impairment [22, 54, 55]

Abbreviations: CEBM, Centre for Evidence-Based Medicine; CNS, central nervous system; CSF, cerebrospinal fluid; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; GOR, grade of recommendation; HAND, HIV-associated neurocognitive disorder; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; NP, neuropsychological; OI, opportunistic infection; RNA, ribonucleic acid; TBI, traumatic brain injury.

In these patients, CSF analysis should be performed to exclude non-HIV neurological conditions (eg, CNS-opportunistic infections and other infections; CEBM 2b; GOR C) [46–49, 60].

Monitoring HAND

In the absence of data from large-scale outcome studies of HAND (CEBM 5; GOR D), experts recommend that the frequency of neurocognitive monitoring should be increased in patients who (1) demonstrate clinical worsening of HIV disease; (2) have a history of low nadir CD4 (eg, <200 cells/μL), which is associated with worse neurocognitive outcomes; (3) are not receiving ART; (4) do not achieve virologic suppression despite cART; and (5) develop new or worsened neurologic symptoms or signs (CEBM 5; GOR D). Clinically stable patients can be reviewed less often (approximately every 2 years). Patients may detect neurocognitive difficulties before they are noted by clinicians. Consequently, those reporting neurocognitive difficulties should be evaluated fully (CEBM 1b; GOR B) [24]. However, self-report alone can either underestimate (as a result of impaired patient insight) or overestimate (as a result of comorbid anxiety and depression) true neurocognitive difficulties (CEBM 1b) [61]. Therefore, the consideration of both the clinical history and the personal complaints is needed to best determine time to follow-up.

Recommendations for monitoring patients are presented in Table 5. For patients commencing cART, the earliest time point at which improvement is expected is 1 month, with several studies showing improvement by 2 months [67, 68], and some by as much as 9 months (CEBM 1b) [64, 69]. Earlier responses may be seen in patients who are naive to cART (CEBM 1a and 1b) [68, 70, 71].

Most patients who attain virologic suppression in blood will also do so in CSF. Thus, there is no general indication to repeat CSF analysis following cART initiation (CEBM 2b; GOR B) [60]. CSF analysis may be repeated after at least 12 weeks in patients with undetectable plasma HIV RNA who do

Table 5. Recommendations for Monitoring Patients With HIV-Associated Neurocognitive Disorder

Patient Type	Monitoring Recommendation
Patients with HAND not on cART	• Periodically reassessed, perhaps as frequently as monthly if practical (CEBM 3b; GOR C) [62, 63]
Patients with HAD or MND commencing cART	• Monitored clinically, initially at months 3 and 6, then semiannually until a plateau of response has been observed (CEBM 1b; GOR B) [64, 65], and annually thereafter • If there is no clinical response or if there is deterioration at early time points, other causes of impairment should be considered (CEBM 5; GOR D) • There may be a bidirectional relationship between cognition and cART medication adherence, with poor adherence being associated with poor virologic response; therefore, specific interventions to optimize cART adherence should be employed [110]
Patients with ANI commencing therapy	• Monitored initially at 6 months and annually thereafter (CEBM 1b; GOR B) [65, 66]

Abbreviations: ANI, asymptomatic neurocognitive impairment; cART, combination antiretroviral therapy; CEBM, Centre for Evidence-Based Medicine; GOR, grade of recommendation; HAD, HIV-associated dementia; HAND, HIV-associated neurocognitive disorder; HIV, human immunodeficiency virus; MND, mild neurocognitive disorder.

not improve neurologically (CEBM 5; GOR D), and in those who changed cART because of CSF viral escape (CEBM 4; GOR C) [72].

Treatment and Prevention

There are no systematic published studies on the progression of ANI to MND, or of MND to HAD. There is some evidence that markers of progression of HIV disease (low $CD4^+$ T-cell count, AIDS diagnosis, high plasma HIV RNA), NP status (worse processing speed), and major depressive disorder may be associated with worsening of NP performance over time. It is not possible from existing data to conclude whether patients with successful treatment (ie, plasma HIV RNA <50 copies/mL) are at risk of progression and there are no systematic studies addressing the extent to which neurocognitive deficit may be permanent or reversible.

Data show that cART for approximately 1 year is associated with modest benefits in NP functioning, particularly attention, processing speed, and executive performance (CEBM 1a) [73–77]. The degree of improvement correlates with changes in $CD4^+$ T-cell counts (CEBM 1a) [42, 78–82]. Treatment with antiretrovirals that have greater distribution into the CNS

Table 6. Central Nervous System Penetration-Effectiveness Ranking 2010

CNS Penetration-Effectiveness Ranking	4	3	2	1
NRTIs	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir
NNRTIs	Nevirapine	Delavirdine Efavirenz	Etravirine	
PIs	Indinavir/r	Darunavir/r Fosamprenavir/r Indinavir Lopinavir/r	Atazanavir Atazanavir/r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir/r Tipranavir/r
Entry/fusion inhibitors		Maraviroc		Enfuvirtide
Integrase inhibitors		Raltegravir		

Abbreviations: CNS, central nervous system; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Source: Letendre et al [83, 84].

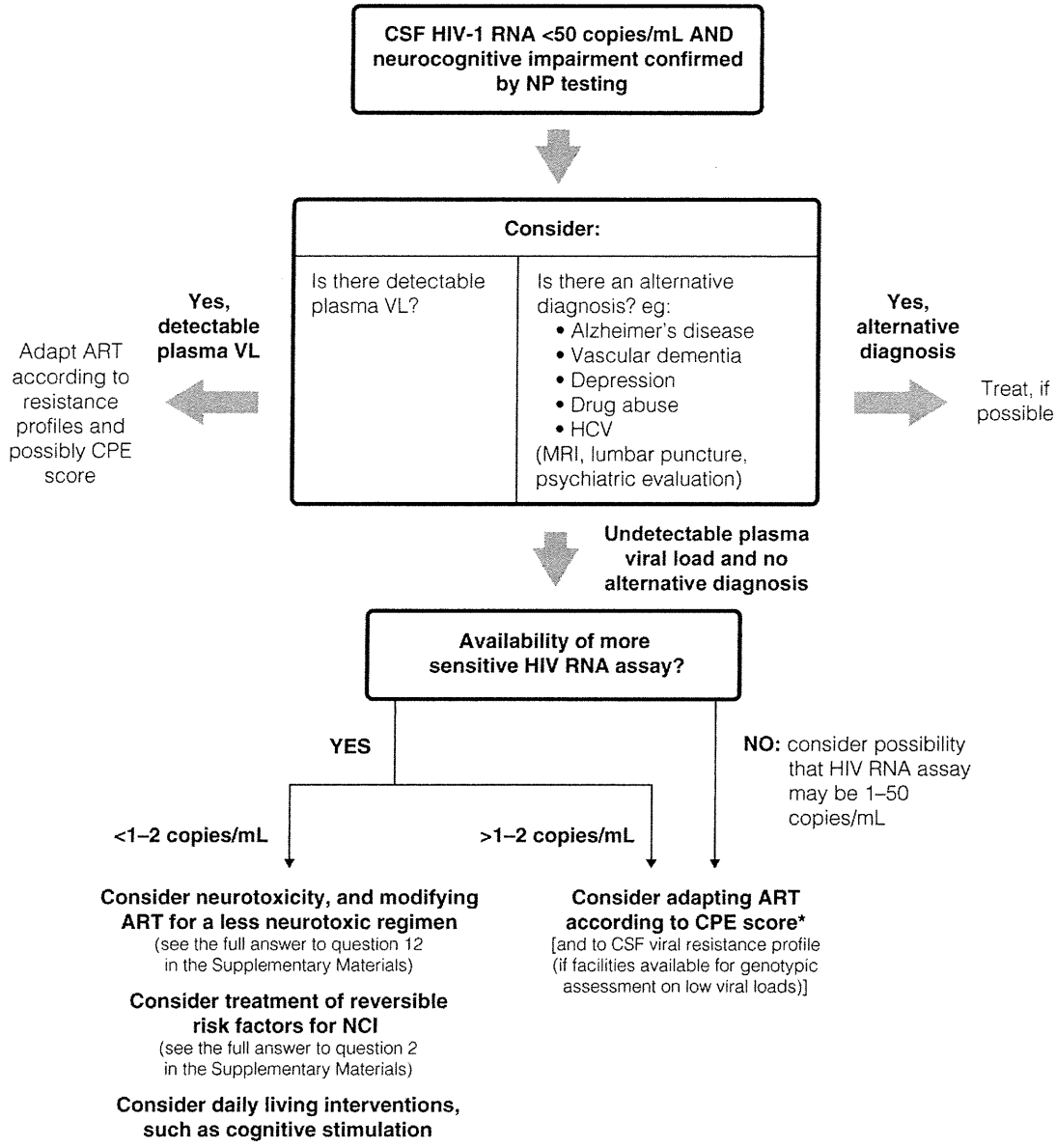

Figure 2. Algorithm showing management of treated patients with persistent or worsening neurocognitive impairment and undetectable cerebrospinal fluid human immunodeficiency virus RNA (<50 copies/mL). Abbreviations: ART, antiretroviral therapy; CPE, central nervous system penetration effectiveness; CSF, cerebrospinal fluid; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; NCI, neurocognitive impairment; NP, neuropsychological; RNA, ribonucleic acid; VL, viral load.

(CNS penetration) has been associated with better neurocognitive outcomes in some trials (CEBM 2b; GOR B); however, results are not consistent and randomized trials with large sample sizes are needed to corroborate these findings (Table 6) [64, 74, 76, 85]. Thus, the benefits of changing cART to improve CNS penetration for individuals whose infection is already well controlled are unproven.

In patients with persistent or worsening NCI and CSF HIV RNA <50 copies/mL, other possible causes of NCI must be considered (CEMB 5; GOR D). After ruling out alternative diagnoses, HAND should be considered. If HIV RNA is detectable in the plasma, we suggest first obtaining confirmation that the patient is adherent to their cART, as neurocognitive difficulties can interfere with adherence and, second, adapting the regimen according to resistance profiles and possibly the CNS penetration-effectiveness (CPE) score if appropriate (CEBM 2b; GOR C) [86]. If HIV RNA is undetectable in the plasma and CSF, we recommend that a more sensitive HIV

RNA assay with a lower limit of detection of 1–2.5 copies/mL be performed on the CSF (currently available only in research settings). If HIV RNA is detectable using a more sensitive assay, modification of the cART regimen according to CPE score (when appropriate) and to CSF viral resistance profile (if possible) may be an option. If the more sensitive HIV RNA assay is not available, the clinician may suspect the possibility of low-level CSF HIV RNA >2.5 copies/mL and consider regimen modification (CEBM 2b; GOR C) (Figure 2) [87, 88].

If treated patients have persistent NCI despite effective cART, the possibility of cART neurotoxicity must be considered. Evidence in the literature for antiretroviral neurotoxicity causing persistent NCI during stable cART is limited because it has not been systematically studied. Although some findings suggest neurocognitive improvement following cessation of cART (CEBM 3b) [89, 90], other reports question that evidence [91]. The use of treatment interruption is not recommended since its benefits do not outweigh its risks (CEBM 1b; GOR B) [92–94]. Evidence for the development of neuropsychiatric symptoms (eg, sleep disturbance, dizziness, anxiety, depression) is greatest for efavirenz; however, these effects typically occur early in therapy and in many cases resolve spontaneously [95, 96]. If cART neurotoxicity is suspected, and CNS side effects persist for >4 weeks, consider therapeutic drug monitoring followed by dose adjustment if indicated (CEBM 2b; GOR C) [97, 98]. If symptoms continue to persist, consider switching to an alternative treatment (CEBM 5; GOR D) [99].

In addition to cART, several drugs (including minocycline, memantine, selegiline, lithium, valproic acid, lexipafant, CPI 1189, peptide T, nimodipine, and psychostimulants) have been evaluated as potential therapies for HAND. Although there is evidence of good safety and tolerability in most studies, effectiveness has not been established (CEBM 1a) [100]. No therapy other than cART is currently recommended for routine treatment of HAND in the clinic.

Direct and indirect data tend to show benefits in treating potential comorbidities, such as hepatitis C virus, cardiovascular risk factors, metabolic disorders, major depressive disorder, and anxiety disorders, to reduce the severity of NCI in HIV-infected patients (CEBM 2b; and 5; GOR C) [101, 102].

There is a limited evidence base for the earlier introduction of cART for the prevention of HAND (CEBM 2b; GOR B) [103]. In general, current treatment guidelines should be followed (CEBM 2b; GOR C) [103]. Earlier treatment of patients at high risk of NCI, for instance, older people, could be considered (CEBM 5; GOR D). There are no data on the use of CNS-penetrating cART for preventing (as opposed to treating) HAND; therefore, there is no evidence to support the initiation of therapy with better CNS-penetrating regimens in neurologically normal patients, or in those at greater risk of HAND (CEBM 5; GOR D).

DISCUSSION

We have summarized the key points of the Mind Exchange program, a consensus-based, evidence-driven process to develop and consolidate practical guidance for the screening, diagnosis, monitoring, treatment, and prevention of HAND. The Mind Exchange program included an academically rigorous process, supported by a large number of leading HIV physicians, representing a broad range of clinical opinion from diverse geographic regions and a variety of clinical practices, with the intent to provide insightful, up-to-date, and evidence-based guidance to the HIV medical community. The program was designed to complement rather than duplicate existing guidance in HIV treatment guidelines.

This program does have several limitations. First, although literature searches were based on carefully constructed, formalized keyword strings, the review of the literature does not meet strict criteria for a systematic review. Nonetheless, the searches were thorough, well documented, and carried out in 2 databases and relevant HIV congresses, thus providing a broad database with which to address each of the 14 questions. Second, to provide the most clinically useful guidance within a manageable timeframe, the program did not set out to address all aspects of HAND management, but rather addressed the questions prioritized as most important to clinical practice. Despite this restriction, the answers provided do give a good spread of guidance across the range of HAND management. Finally, the guidance does not take into account differing resource settings, and it may not be possible for all physicians to apply all aspects of the guidance within their practice.

The consensus process has also highlighted areas of HAND diagnosis and management where further research and guidance is needed. For example, although good practice suggests that all patients with HIV should be screened for HAND as early as possible in their disease using a sensitive screening tool, some of the most widely available screening tools have limitations, particularly in their ability to detect milder forms of NCI. Other testing requires involvement of a specialist, especially for scoring and interpretation. In brief, there is no standard and validated, easy-to-perform test to screen for minor neurocognitive disorders applicable in all HIV-infected patients. The HIV Dementia Scale with a modified cutoff of 14 points (as opposed to the classical cutoff of 10 points) is useful in identifying those persons with HAD, but this scale and others are still limited in their ability to detect (and differentiate from other diagnoses) ANI and MND.

There are no data on the role of preventive measures for HAND and there are only emerging data on the progression of milder forms of impairment and the clinical significance of asymptomatic impairment. There are no data regarding the appropriate short monitoring tools for reviewing

neurocognitive performance in patients who have been diagnosed with HAND; while access to full NP assessment is appropriate in some patient groups, it remains an option that is not widely affordable. Short and validated monitoring tools for HAND are urgently needed. Last, data from large randomized trials are needed to confirm the potential association of the CNS penetration of cART with improved neurocognitive performance, while issues of potential long-term neurotoxicity demand investigation.

The clinical importance of HAND is receiving increasing attention as patients are surviving longer and neurocognitive health has become an issue of importance in the HIV and general community. Both HIV and non-HIV forms of NCI are diagnosed much earlier than they were in the past [104]. Despite this, some have questioned the benefit of early diagnoses when there is no proven treatment. But in the context of HIV infection, which is likely to be a chronic disease lasting decades in most patients, we have highlighted that there are already better treatment practices and that early diagnosis is a crucial step in identifying patients at risk, as well as patients in need of more frequent monitoring or specific interventions, including medication adherence checks.

Our program has attempted to address the fact that among many HIV clinicians, the knowledge of practical procedures to deal with HAND is limited. This highlights the need for further education and training on the importance of HAND and its clinical implications, particularly around raising awareness of the link between HAND and cART nonadherence, improving understanding of ANI, increasing the understanding and implementation of the neurocognitive diagnosis of HAND, and initiating effective management of HAND once it has been identified.

In conclusion, the Mind Exchange program complements existing guidelines, providing practical guidance in the diagnosis, ongoing monitoring, and treatment of HAND, which is of direct relevance to daily practice.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. Writing assistance was provided by Sue Cheer, Lucid, United Kingdom, who received funding assistance from Abbott. Abbott was not involved in development or review of this manuscript. The authors maintained complete control over the content of this paper. We also thank the following research and clinical fellows who helped perform the literature searches: Chad Bousman, David Croteau, Alicia Gonzalez, Allyson Ion, Thomas Marcotte, Ignacio Perez-Valero, Dr Tiroboschi, Xavier de la Tribonniére, and Joyce M. Velez.

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Author contributions. S. L., J. M.-M., G. A., and I. G. contributed significantly to the writing and reviewing of this manuscript. In addition, the manuscript was extensively reviewed by B. B., L. C., V. W., J. G., A. W., C. E., F. B.-C., M.-J. B., P. C., R. E., V. K., S. R., I. H., P. P. C., Y. Y., and A. C.

Financial support. Abbott Laboratories provided funding for this 18-month academically rigorous program, but had no involvement in the development, review, or shaping of the recommended guidance. The Steering Committee has been assisted by Lucid, a specialist UK-based medical communication company that was funded by Abbott Laboratories, in the organization of program events and the editorial process for the final program report. Lucid similarly played no part in affecting the nature of the guidance.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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