Prevalence and clinical management of the neurocognitive disorders in the HIV-infected population

Daniel Podzamczer, MD, PhD

Hospital Universitari Bellvitge, Barcelona, Spain

Background

Since the introduction of highly active antiretroviral therapy (ART) the incidence of HIV-associated dementia has declined substantially, however the prevalence of neurocognitive impairment (NCI) is increasing.

Clinical and epidemiological data and further medical training in this field are needed to understand better how to manage HIV-infected patients with NCI.

Regarding epidemiological data, the primary objective of CRANIum study was to describe and compare the prevalence of a positive screen (PS) for NCI in an HIV-infected population on ART-experienced versus ART-naïve patients in 15 countries in Western Europe and Canada.

For CME, the Mind Exchange Program (MEP) was performed by sixty-six experts from 30 countries between February/2011 and January/2012. MEP resulted in a final set of 14 questions identified as of critical clinical importance to be addressed by comprehensive literature search on PubMed and Cochrane Library.

The Prevalence of a Positive Screen for Neurocognitive Impairment (NCI) in HIV-1 Infected Patients Across Western Europe and Canada - The CRANIum Study

Study Design

Cross-sectional, epidemiologic study

<u>Inclusion criteria:</u>

- HIV-1 infected patients aged ≥ 18 years, attending a routine medical follow-up visit

- ARV-naïve pts or who received ART for < 4 weeks more that 6 months ago

- ARV-experienced pts, stable bPI or NNRTI based regimen for at least 9 months

<u>Exclusion criteria:</u>

- Current/active CNS opportunistic infections or CNS malignancies.

- Previous stroke or history of transient ischemic attacks, or neuromuscular disease that could affect a patient's ability to perform the screening tests.

- Illegal substance use or alcohol abuse in the previous 3 months.

Questionnaires completed during routine medical assessment

HADS – Anxiety and depressive scale[1]

BNCS – Brief Neuro-Cognitive Screen[2]

MOS-HIV – Medical Outcome Study – HIV Health Survey[3]

Trailmaking A y B y Digit Symbol

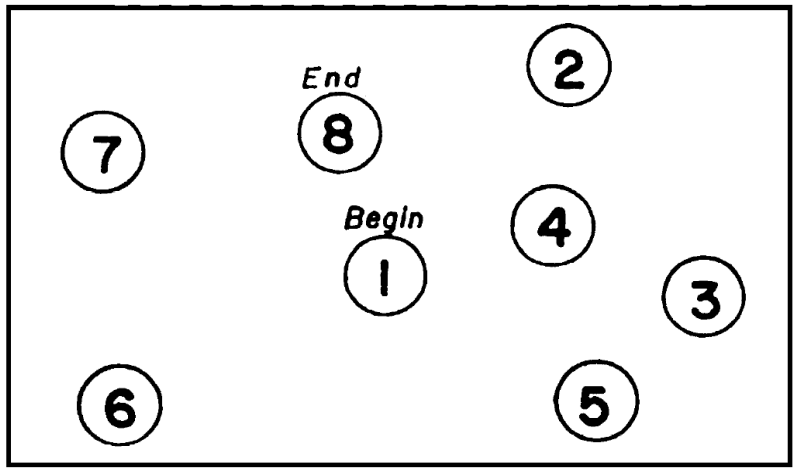
<u>Primary objective:</u>

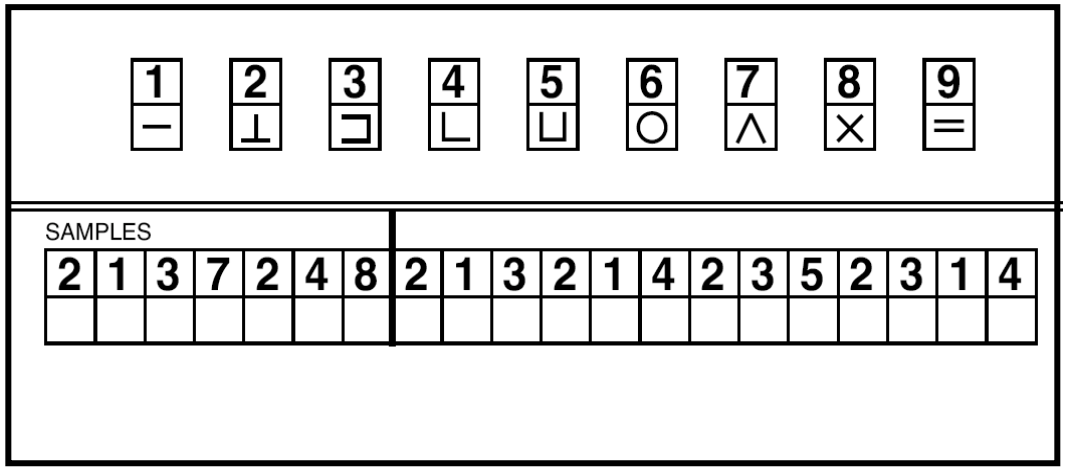
To describe and compare the prevalence of a positive screen for neurocognitive impairment and depression/anxiety in an HIV-1 infected population on Highly Active Antiretroviral Therapy (HAART) versus HAART-naive patients

Robertson K, et al. XIX International AIDS Conference 2012. Washington DC, USA.

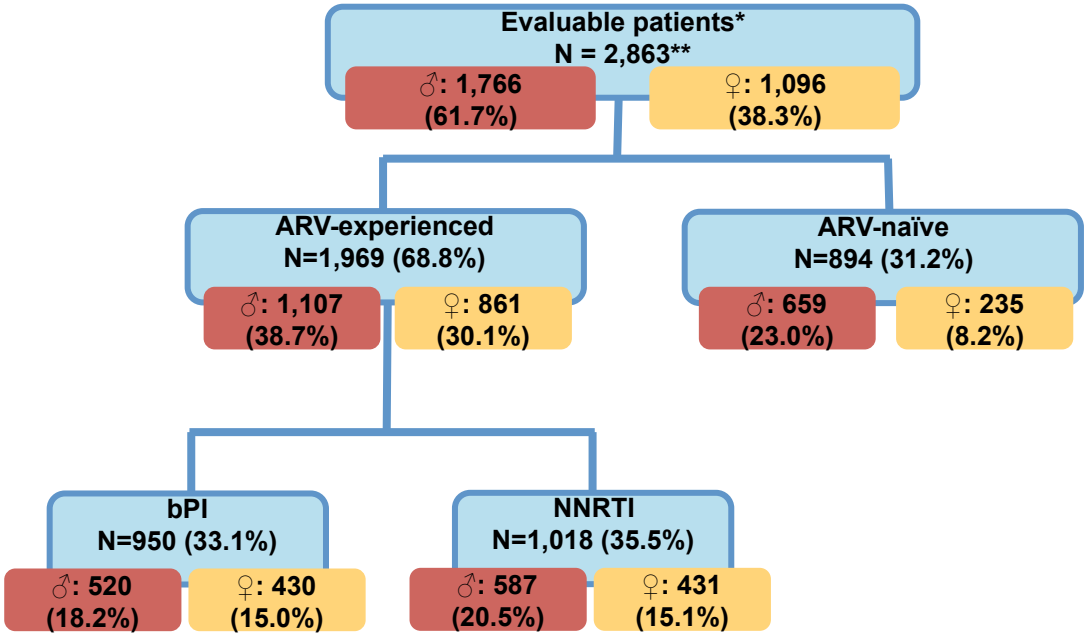
Screening Tools

- Brief Neuro-cognitive Screen (BNCS)
  - To be administered by study nurse or physician
    - Trail making part A
    - Trail making part B
    - Digit-symbol





Subject disposition



Country	Percentage of patients included
Austria	2.5
Belgium	2.0
Canada	4.3
France	16.6
Germany	10.7
Greece	5.2
Ireland	3.4
Israel	2.5
Italy	3.4
Norway	1.4
Portugal	2.9
Spain	28.7
Sweden	2.0
Switzerland	3.1
UK	11.4

Questionnaires completed:

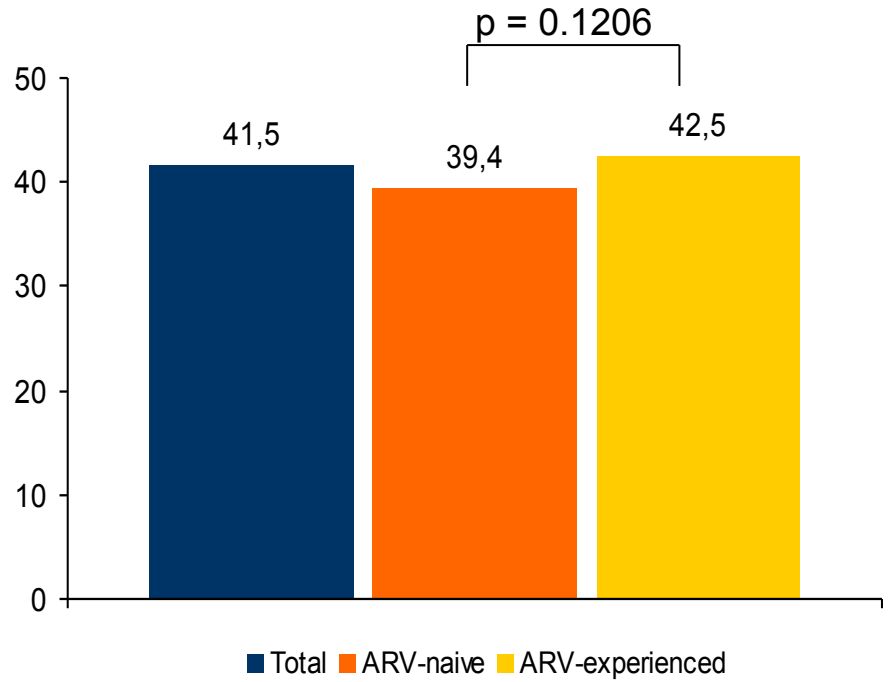
	All subjects	Male	Female
TMA completed- N (%)	2,852 (99.6)	1,759 (99.6)	1,093 (99.7)
TMB completed - N (%)	2,848 (99.4)	1,758 (99.5)	1,090 (99.4)
DS completed - N (%)	2,810 (98.1)	1,766 (100.0)	1,096 (100.0)
MOS-HIV completed N (%)	1,839 (64.3%)	1,162 (65.8%)	677 (61.8%)

* Total patients enrolled = 2,884

** Gender missing for one patient

Robertson K, et al. XIX International AIDS Conference 2012. Washington DC, USA.

Results – Positive Screen for NCI*



***PS for NCI= 1 SD in two tests or 2 SD in one test**

No statistical differences were found in the percentage of patients with a positive screening for NCI between the study groups when the overall population was analyzed.

There were no differences observed in the mean Mental Health Summary Score, however Physical Health Summary mean scores were significantly higher in the ART-naïve group (all subjects: 51.77; ARV-naïve: 53.81; and ARV-experienced: 50.95; $p<0.0001$).

Robertson K, et al. XIX International AIDS Conference 2012. Washington DC, USA.

Results: Average T-scores

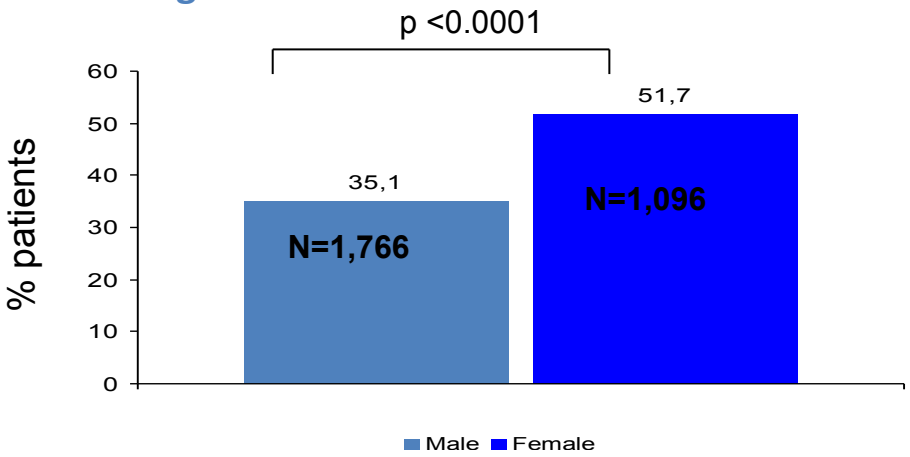
	All subjects	ART-naïve	ART-experienced	p value
Normal	1,865 (65,2%)	617 (69.0%)	1,248 (63.4%)	
Mild	505 (17.6%)	154 (17.2%)	351 (17.8%)	
Mild to moderate	253 (8.8%)	65 (7.3%)	188 (9.5%)	
Moderate	153 (5.3%)	39 (4.4%)	114 (5.8%)	0.0097
Moderate to severe	70 (2.4%)	18 (2.0%)	52 (2.6%)	
Severe	16 (0.6%)	1 (0.1%)	16 (0.8%)	

Robertson K, et al. XIX International AIDS Conference 2012. Washington DC, USA.

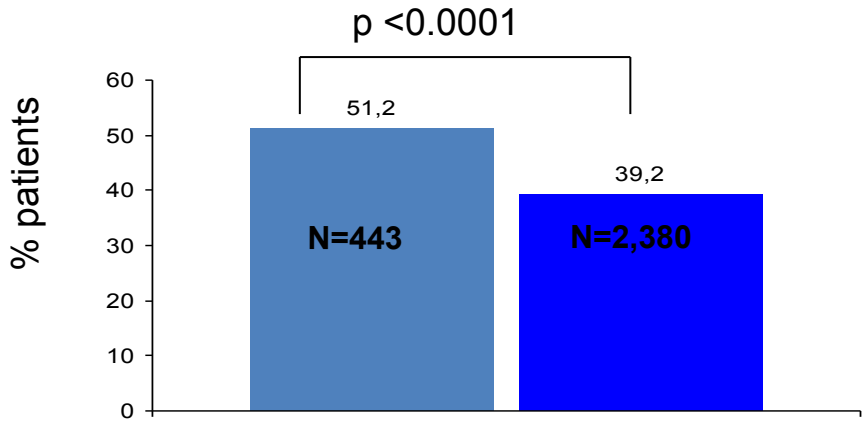
Positive screen for NCI

Additional Subgroup Analysis

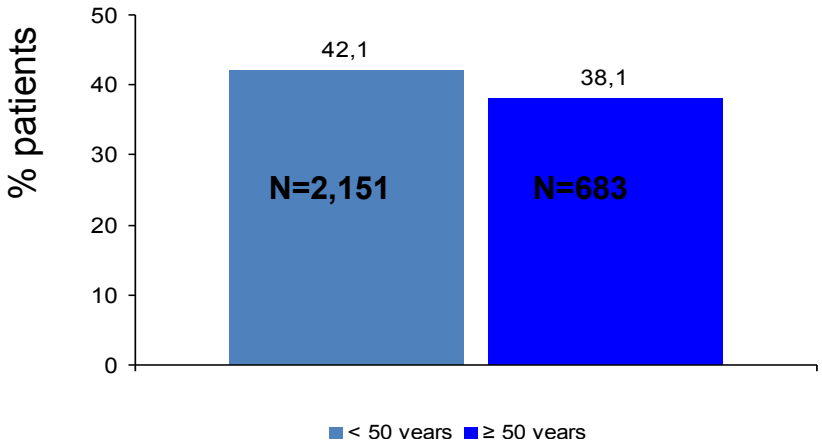
Per gender



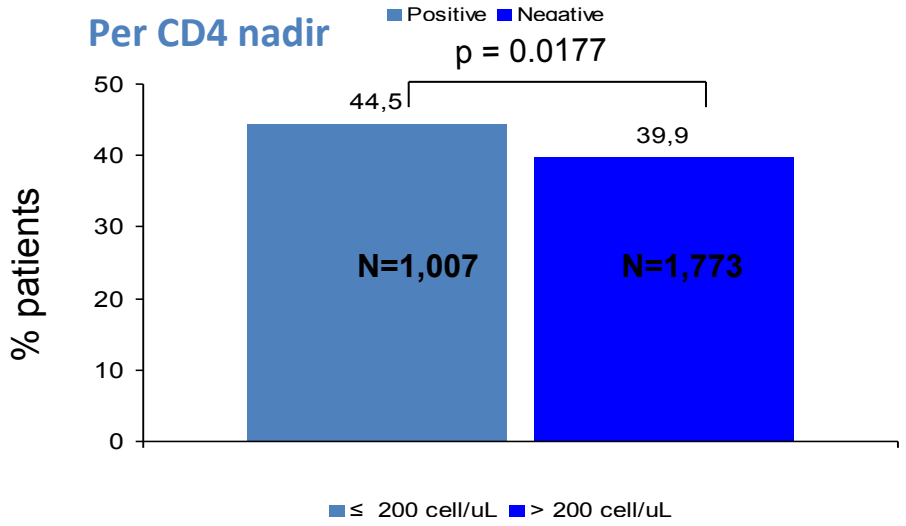
Per HADS-D screen



Per age group



Per CD4 nadir

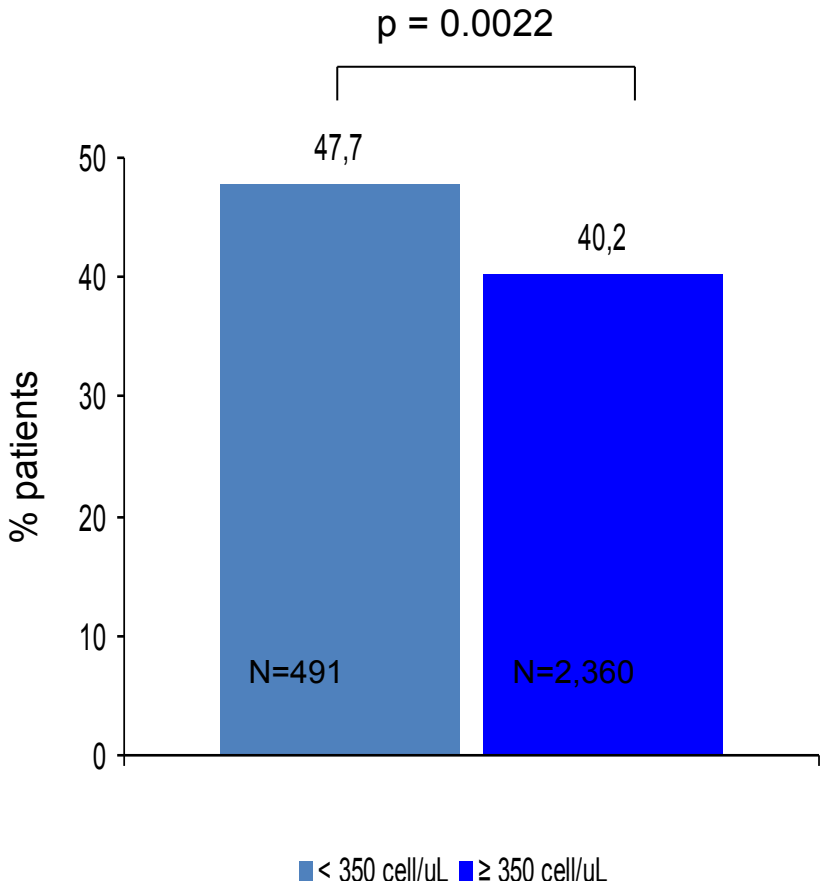


Robertson K, et al. XIX International AIDS Conference 2012. Washington DC, USA.

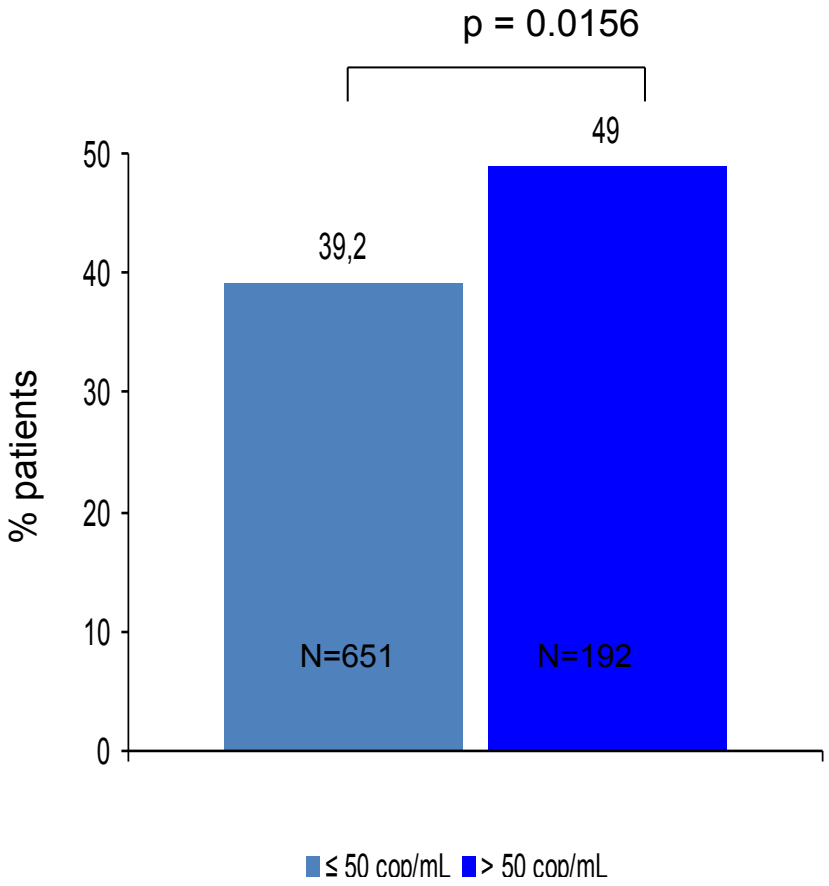
Positive screen for NCI

Additional Subgroup Analysis

Per most recent CD4 count

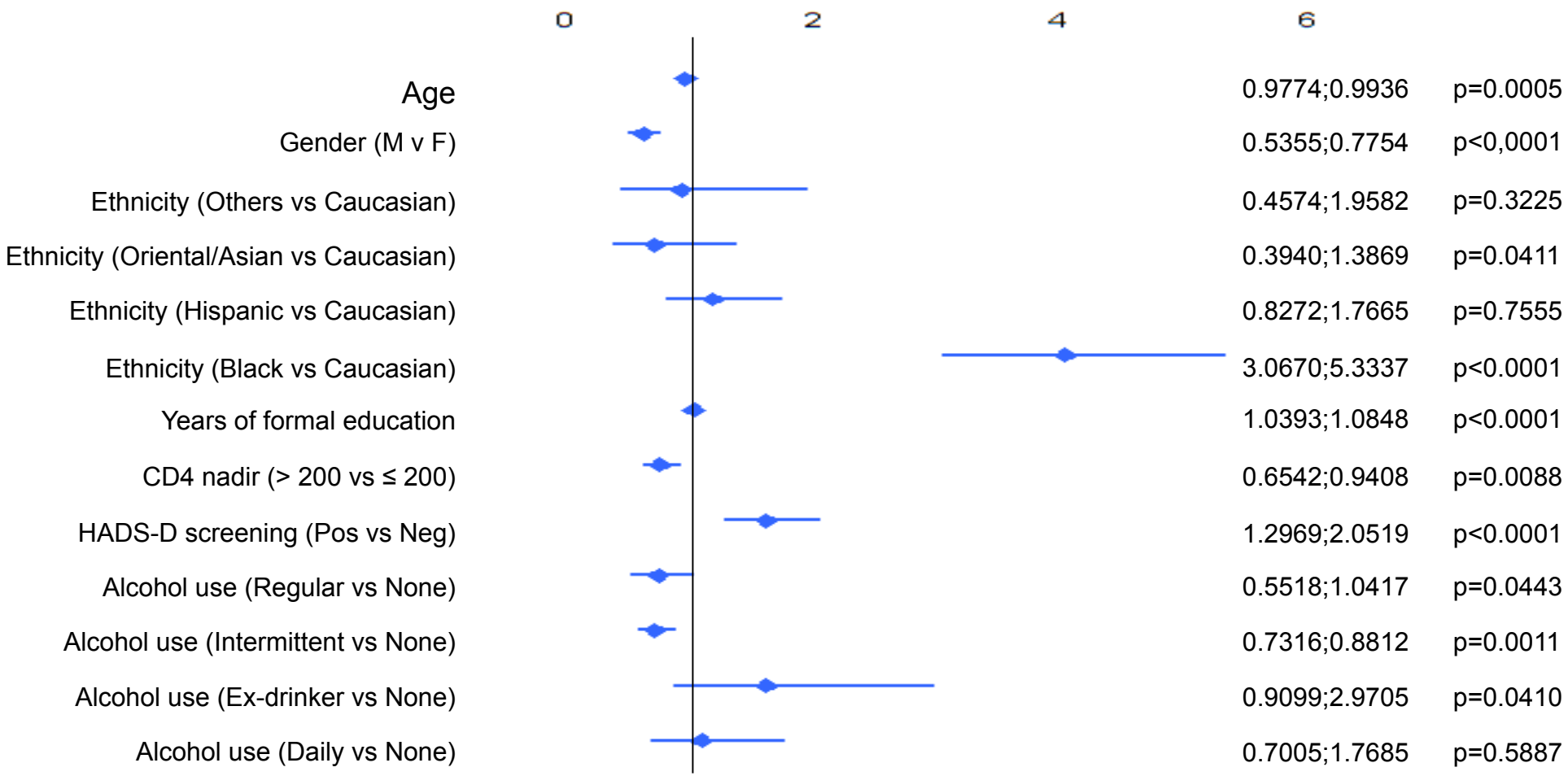


Per viral load for patients on HAART



Robertson K, et al. XIX International AIDS Conference 2012. Washington DC, USA.

Multivariate analysis: Association between demographic and disease characteristics and a positive screen for NCI



Limitations

- CRANIum was a **cross-sectional**, epidemiology study **without prospective follow-up data**. As such, interpretation of the predictive associations between risk factors and outcomes remain difficult **and do not demonstrate causality.**

- The **BNCS battery** includes tests that **evaluate only three cognitive domains** (Speed of information processing, Attention/working memory and Executive functioning). Although these tests have been found to be sensitive in detecting HIV-related NC changes, this brief battery **is used as a screening tool only** and is **not validated for independent diagnosis of NCI.**

- The **normative data used for interpretation of the BNCS** results are based on gender, age, education and ethnicity adjusted norms but **do not account for potential variation across countries** in this study, and this **might account for at least some of the differences** seen between men and women in our results.

Conclusions

- Overall, 41.5% of patients in the CRANIum study had a positive screen for NCI, consistent with prevalence rates previously reported in HIV-positive patients.

- There were no statistically differences found between the percentage of naïve and HAART-experienced patients with a positive screen for NCI (39.4% vs 42.5%, respectively; p=0.1206).

- When assessing level of cognitive impairment by average T-score, a higher proportion of HAART-naïve patients were categorized as having normal cognitive function compared with HAART-experienced patients. For both groups, the majority of patients with any degree of NCI fell within the mild impairment category.

- For HAART-experienced patients, a lower percentage of patients with a current viral load ≤50 copies/mL had a positive screen for NCI compared with patients with detectable plasma HIV-RNA.

Robertson K, et al. XIX International AIDS Conference 2012. Washington DC, USA.

CRANIum: Acknowledgements

•**The CRANIum study was sponsored by Abbott Laboratories**

•**The authors express their gratitude to:**

•**- The patients and their families for their participation and support during the study**

•**- The Abbott CRANIum Study Team and the clinical research personnel who worked on this study**

•**- The CRANIum investigators and their teams:**

•**Austria:** Dr. Vetter, Dr. Geit, Dr. Prammer, Dr. Kapper. **Belgium:** Dr. Vandekerckhove, Prof. Moutschen, Prof. Vandercam. **Canada:** Dra. Loutfy, Dr. DeWet, Dr. Baril, Dr. Trottier, Dra. Walmsley, Dr.Gill. **France:** Dr. Barbuat, Dr. Bouchaud, Dr. De Truchis, Dr. Djerad, Dr. Gasnault, Dr. Gilquin, Dr. Hocqueloux, Dr. Hoen, Dra. Khuong, Dr. Lafeuillade, Dr. Le Moal, Dra. Leclercq, Dr. Molina, Dr. Patey, Dr. Pellegrin, Dr. Rogeaux, Dr. Rouger, Dra. Salmon, Dr. Treilhou. **Germany:** Dr. Rockstroh, Dr. Schewe, Dr. Mayr, Dr. Pauli, Dr. Baumgarten, Dr. Lutz, Dr. Jäger, Dr. Knechten, Dr. Cordes. **Greece:** Dr. Gargalianos, Dr. Lazanas, Dra. Sabatakou, Dr. Katsabas, Dr. Skoutelis, Dr. Ploumidis. **Ireland:** Prof. Bergin, Dr. McNamara. **Israel:** Dr. Pollak, Dr. Zeev, Dr. Maayan, Dr. Levy, Dr. Riesenberg. **Italy:** Dr. Antinori, Dr. Carosi, Dra. Mussini, Dr. Galli, Dr. Lazzarin, Dr. Parruti, Dr. Rizzardini, Dr. Viale. **Norway:** Dr. Leiva, Dr. Ringstad. **Portugal:** Dr. Serrão, Dr. Vera, Dr. Mansinho. **Spain:** Dr. Hernández-Quero, Dr. de Dios Colmenero, Dr. Terrón, Dr. Rodríguez-Baño, Dr. Lozano, Dr. de Zárraga, Dr. Llunch, Dr. Florez, Dra. Martínez, Dr. Rodriguez, Dra. Sepúlveda, Dr. Elizaga, Dr. Bahamonde, Dra. Garcínuño, Dr. Podzamczer, Dr. Mallolas, Dr. Clotet, Dr. Domingo, Dr. Pedrol, Dr. Knobel, Dra. Ornella , Dr. Force, Dr. Barros, Dr. Martín, Dr. Arribas, Dr. Casado, Dr. Cuadrado, Dra. Oltra, Dr. Roca, Dr. Ortega, Dr. Fernández, Dr. Rodríguez, Dr. Morano, Dr. Canet, Dr. García-Henarejos, Dr. Cano, Dr. Goenaga, Dra. Muñoz, Dra. Goicoechea. **Sweden:** Prof. Nilsson Schönnesson, Dra. Schlaug, Dr. Flamholc, Dr. Bonnedahl, Dr. Briheim. **Switzerland:** Dr. Zimmerli, Prof. Vernazza, Dr. Cavassini. **UK:** Dr. Gompels, Prof. Lee, Dr. Price, Dr. Leen, Dr. Nelson, Prof. Johnson, Dr. Kulasegaram, Dr. Hay.

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

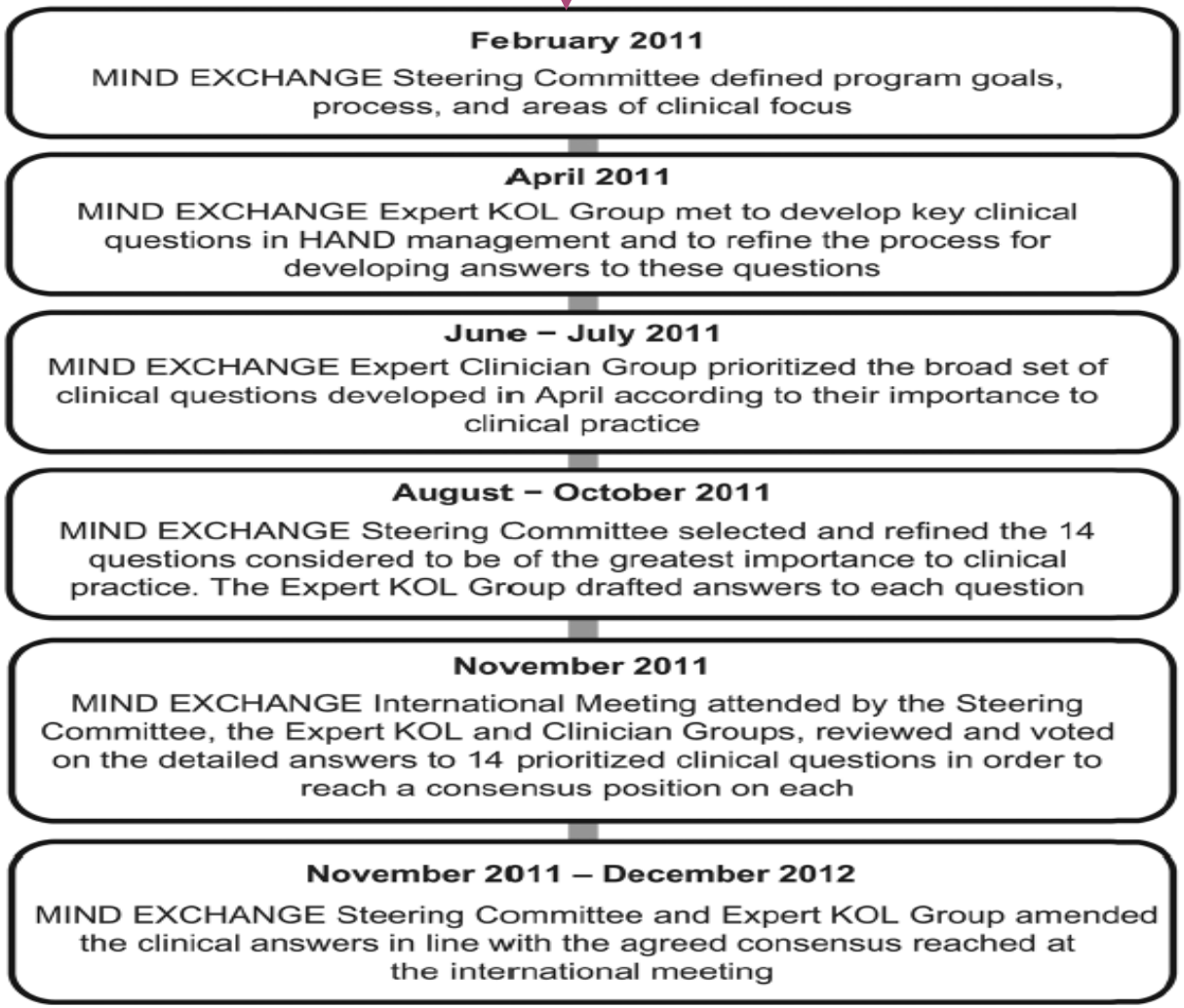
Methods

- Sixty-six specialists from 30 countries.
- The program was overeseen by a steering **commitee of 5 experts** (2 infectous disease specialist, a neurologist, a neuropsychiatrist and a clinical psychologist).
- A broad **list of clinical question across 5 topics**: Screening, diagnosis, monitoring, tretament, inversion treatment/ interventions, and prevention of HAND, was generated.
- This process resulted in a final set of **14 questions** identified. 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.
- 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.**

Letendre S, et al. CID 2013;56(7): 1004-17.

Oreview of the Mind Exchange Program

The program comprised several stages



Letendre S, et al. CID 2013;56(7): 1004-17.

Fourteen Key Clinical Question 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?

Letendre S, et al. CID 2013;56(7): 1004-17.

MIND EXCHANGE PROGRAM

- To assess neurocognitive functioning in all HIV pts (early and if possible before ART initiation)
- Screening every 6-12 m in higher-risk and 24 m in lower-risk pts
- To consider risk factors (independently assoc with HAND)
- To choose between the many brief screen tests according to clinical expertise, availability, etc
- Complete NP battery (at least 5 dom) to confirm HAND
- Comorbidities and their contribution to NCI (older pts and AD)
- Imaging and CSF analysis help to diagnose HAND

Screening for HAND

Evidence-supported risk factors	Risk Factor/Comorbidity for HAND and/or Non-HIV-Related NCI	Can Assist Identification of Patients: With Current HAND	Can Assist Identification of Patients: At Risk of Developing HAND in Future	Can Assist Identification of Patients: At Risk of Non-HIV-Related NCI	CEBM Levels (See Question Details for References)
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

Several **risk factors** have been independently associated with an increased likelihood of HAND:

1. Readily assesiable in clinic:
   - **Disease factors**
   - **Treatment factors**
   - **Comorbidities**
   - **Demographic factors**
   - **Neurological and psychiatric factors**
2. Difficult to assess in clinic:
   - **Biomarkers**

Letendre S, et al. CID 2013;56(7): 1004-17.

Useful Available Tools for Screening for HIV-Associated Neurocognitive Disorder

- HDS
- IHDS
- Total Recall measure of the Hopkins Verbal Learning Test–Revised
- Grooved Pegboard Test
- Executive Interview
- Cognitive functional status subscale of the (MOS-HIV)

  *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

  - Developmental history (academic performance, occupational attainment)
  - Assessment of past and active alcohol and substance abuse or dependence using DSM-IV
  - Assessment of depression, anxiety, and posttraumatic stress disorder using a structured questionnaire
  - Neurological examination
  - Laboratory studies
  - CSF analysis
  - Thorough medical and neurological history
  - MRI
  - Lawton & Brody's modified Activities of Daily Living scale and the Patient's Assessment of Own Functioning Inventory

Letendre S, et al. CID 2013;56(7): 1004-17.

Recommendations for Monitoring Patients With HIV-Associated Neurocognitive Disorder

Patients with HAND not on cART

→ Periodically reassessed, perhaps as frequently as monthly if practical

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 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.
- There may be a bidirectional relationship between cognition and cARTmedicationadherence, with poor adherence being associated with poor virologic response; therefore, specific interventions to optimize cART adherence should be employed

Patients with ANI commencing therapy

→ Monitored initially at 6 months and annually thereafter

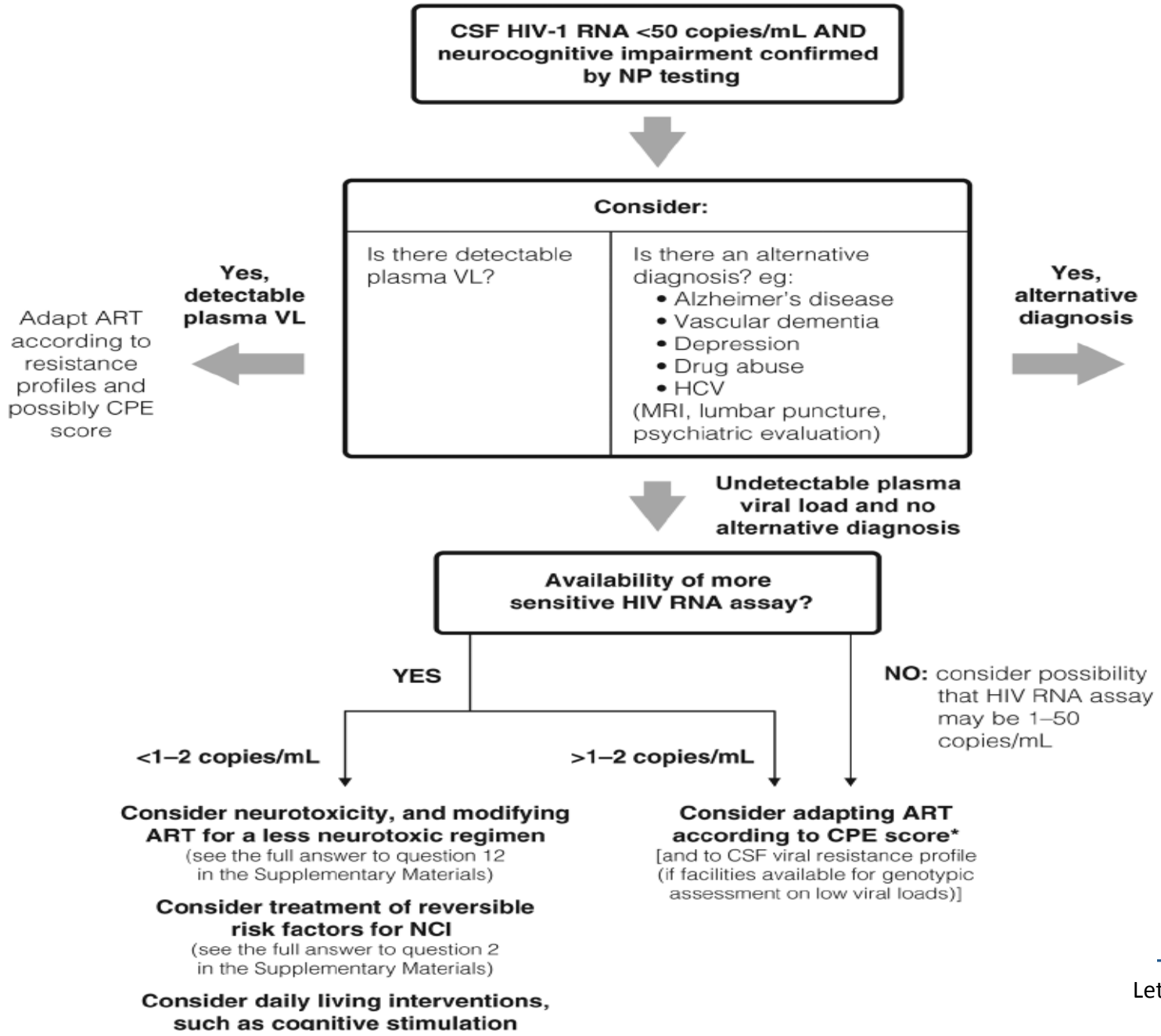
Letendre S, et al. CID 2013;56(7): 1004-17.

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		

*In alphabetic order

Letendre S, et al. CID 2013;56(7): 1004-17.



Algorithm showing management of treated patients with persistent or worsening neurocognitive impairment and undetectable cerebrospinal fluid human immunodeficiency virus RNA (<50 copies/mL)

Letendre S, et al. CID 2013;56(7): 1004-17.

Limitations

1. 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

2. 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.

3. 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

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.

Letendre S, et al. CID 2013;56(7): 1004-17.

HIV/AIDS INVITED ARTICLE

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

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