13th and 14th June 2014
Barcelona, Catalonia, Spain

When and How to Screen for Neurocognitive Impairment in Individuals with HIV Infection

Jose A. Muñoz-Moreno, Ph.D.

- - -

Lluita contra la SIDA Foundation
Germans Trias i Pujol University Hospital
Badalona, Barcelona
Catalonia, Spain

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1. Who to Screen?

2. When to Screen?

3. How to Screen?

1. Who to Screen?

- ✓ All patients, or at least those with risk factors.

2. When to Screen?

- ✓ Early in the follow-up, or when clinical interventions are applied.

3. How to Screen?

- ✓ Using one of the tools offered, chosen according to optimal characteristics.

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1. Why Should We Screen for Neurocognitive Impairment?

2. Which Patients Should Be Screened?

3. When Should We Screen Them?

4. Is There an Optimal Tool to Screen for HAND?

5. Other Recommendations to Consider?

1. Why Should We Screen for Neurocognitive Impairment?

Definition of Screening

Dictionary.com

screening

screen·ing [**skree**-ning] Show IPA

noun

1. the act or work of a person who screens, as in ascertaining the character and competence of applicants, employees, etc.
2. the showing of a motion picture: *There will be screenings at 6 p.m. and 8 p.m.*
3. **screenings,** (*used with a singular or plural verb*)
   a. undesirable material that has been separated from usable material by means of a screen or sieve: *screenings of imperfect grain.*
   b. extremely fine coal.
4. the meshed material used in screens for windows and doors.

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verb (used with object)

18. to shelter, protect, or conceal with or as if with a screen.
19. to select, reject, consider, or group (people, objects, ideas, etc.) by examining systematically: *Job applicants were screened by the personnel department.*
20. to provide with a screen or screens to exclude insects: *He screened the porch so they could enjoy sitting out on summer evenings.*
21. to sift or sort by passing through a screen.
22. to project (a motion picture, slide, etc.) on a screen.

Definition of Screening

WIKIPEDIA
The Free Encyclopedia

Screening

From Wikipedia, the free encyclopedia

Screening may refer to:

- Screening (economics), a strategy of combating adverse selection
- Screening (medicine), a strategy used in a population to identify an unrecognised disease in individuals without signs or symptoms
- Screening (printing), a process that represents lighter shades as tiny dots, rather than solid areas, of ink by passing ink through
- Baggage screening, a security measure
- Call screening, the process of evaluating the characteristics of a telephone call before deciding how or whether to answer it
- Film screening, the displaying of a motion picture or film
- Electric-field screening, the damping of electric fields caused by the presence of mobile charge carriers
- Mechanical screening, the practice of taking granulated ore material and separating it into multiple grades by particle size
- Screening (tactical), one military unit providing cover for another in terms of both physical presence and firepower
- Screening (process stage), process stage when cleaning paper pulp
- Electrostatic screening, a decease in shielding effort between the nucleus and last orbital due to electrons present between them
- Screening resumes, the process of sorting resumes to disqualify candidates using successively more detailed examinations of the resumes
- Smoke screening, blanketing an area with smoke to provide cover

Look up ***screening*** in Wiktionary, the free dictionary.

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Screening, in medicine, is a strategy used in a population to identify an unrecognized disease in individuals without signs or symptoms. This can include individuals with pre-symptomatic or unrecognized symptomatic disease. As such, screening tests are somewhat unique in that they are performed on persons apparently in good health.

Definition of Screening

AN ENCYCLOPÆDIA BRITANNICA COMPANY

Merriam-Webster

m-w.com

screen·ing *noun* \'skrē-niŋ\

: an event in which a movie is shown to an audience

: the act of doing a test on a person or a person's blood, urine, etc., to look for evidence of a disease, illegal drug, etc.

: the act of examining people or things in order to decide if they are suitable for a particular purpose

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Definition of Screening

Public Health England

UK Screening Portal

NSC

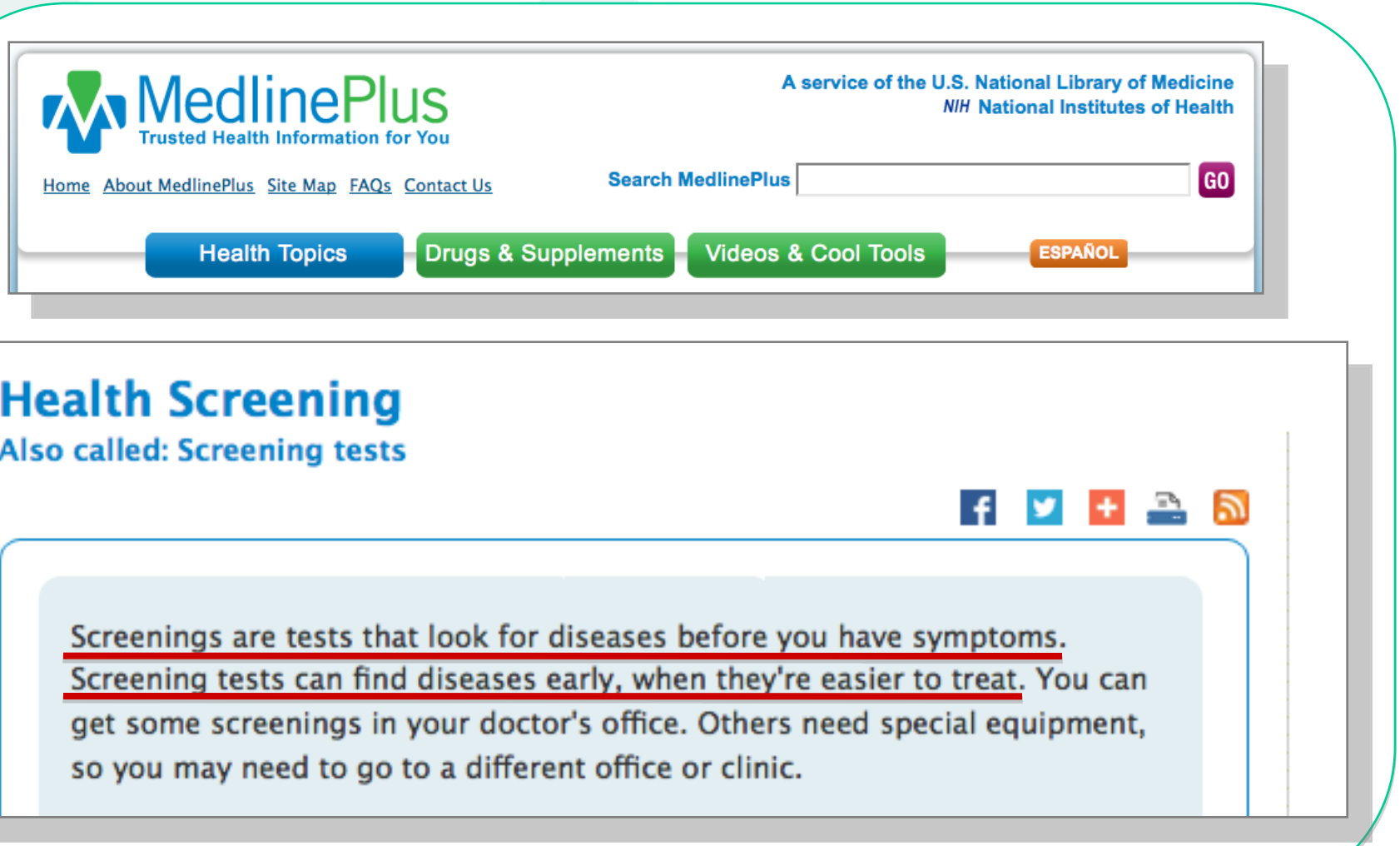
UK National Screening Committee

1. Definition

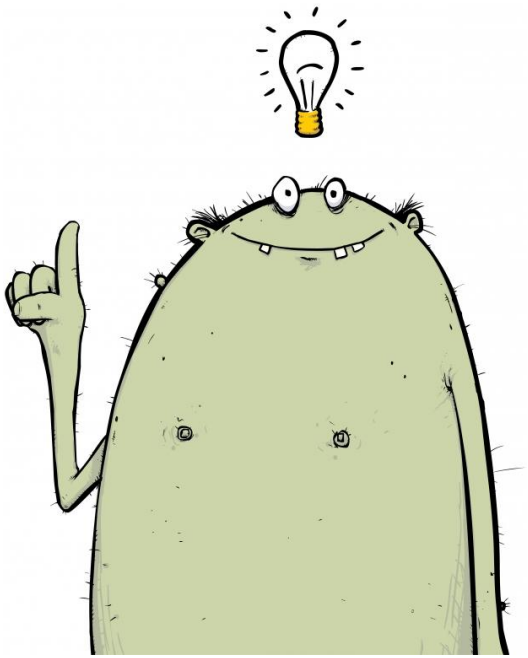
Screening is a process of identifying apparently healthy people who may be at increased risk of a disease or condition. They can then be offered information, further tests and appropriate treatment to reduce their risk and/or any complications arising from the disease or condition.

» Find definitions of screening-related words and terms in the UK NSC glossary

Definition of Screening



Conclusions



- *Systematic assessment.*
- *Identification of subjects without symptoms.*
- *Tests searching for evidence of disease.*
- *Identification of individuals at a high-risk condition.*
- *Tests that find diseases before they develop.*

Screening for NCI in HIV Infection

Screening for Cognitive Impairment in Human Immunodeficiency Virus

Victor Valcour,[1,2] Robert Paul,[3] Stephanie Chiao,[1] Lauren A. Wendelken,[1] and Bruce Miller[1]

[1]Memory and Aging Center, Department of Neurology, [2]Division of Geriatric Medicine, Department of Medicine, University of California–San Francisco; and [3]Department of Psychology, Division of Neuroscience, University of Missouri, St. Louis

HIV/AIDS • CID 2011:53 (15 October) • 837

SHOULD WE SCREEN FOR COGNITIVE IMPAIRMENT AND IF SO, HOW?

avoid psychoactive medications and illicit drugs may also be advantageous. In summary, it is likely that identifying impairment may impact treatments aimed at improving quality of life, but intervention trials are lacking and this effort must be considered within the context of competing priorities for primary care settings. Given the frequency of cognitive impairment in the HIV-positive population, screening is likely to identify far more truly impaired cases than false-positive cases.

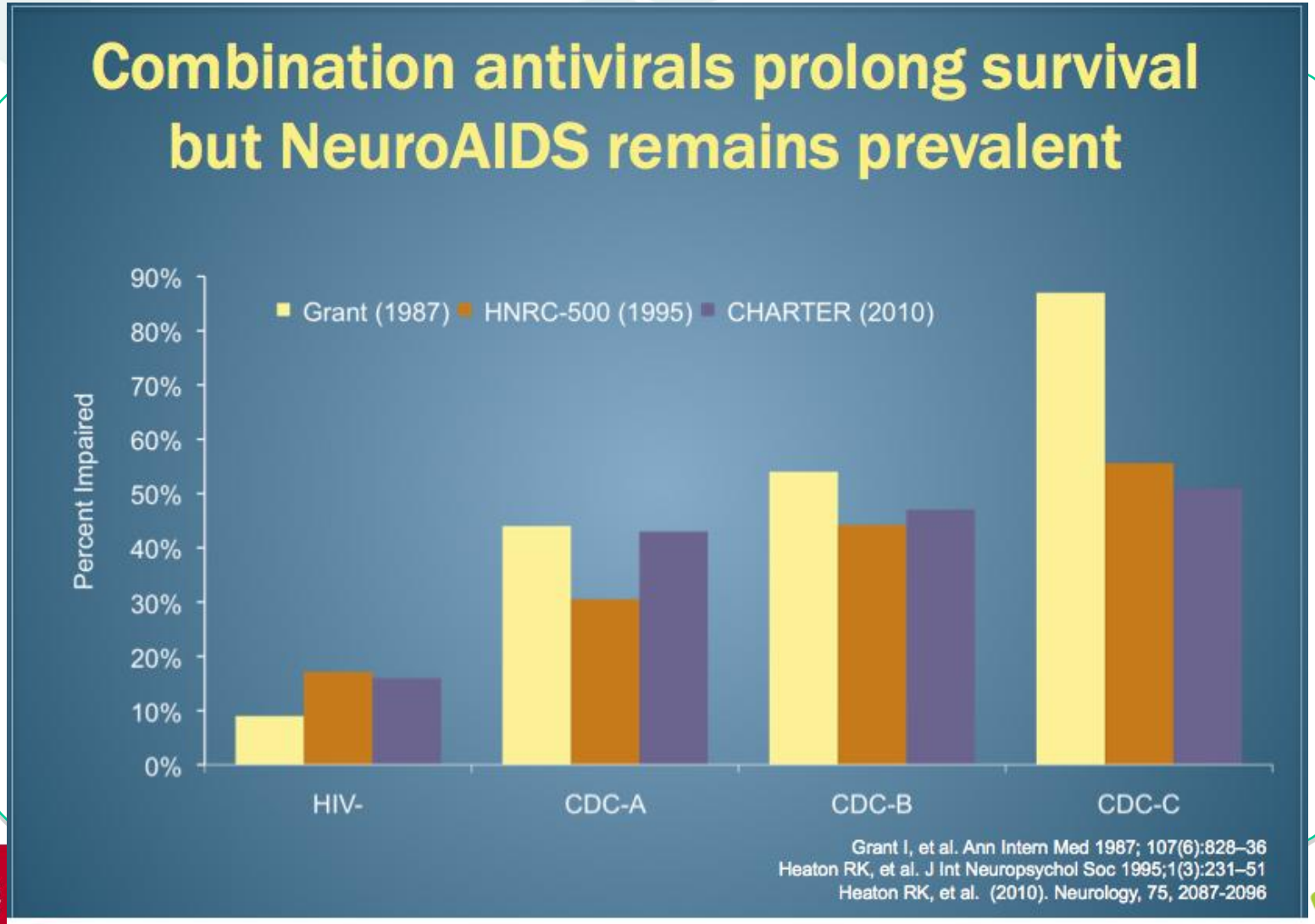
Overall, there are important considerations for early detection of cognitive impairment, particularly among older HIV-positive patients. Unlike the general healthy population, older HIV-positive patients are managing a complex medical condition that disrupts CNS integrity and cognitive function and may be life threatening if not adequately controlled through medical intervention. With HIV, treatment failure and broad antiretroviral medication resistance are potential outcomes of cognitive impairment. As such, unlike in the healthy older population, failure to identify cognitive deficits in the HIV-positive population may directly influence successful management of the disease. In balance, there are important clinical needs that can be addressed by research aimed at demonstrating whether improved detection results in improved outcomes.

Current Clinical Relevance of NCI?

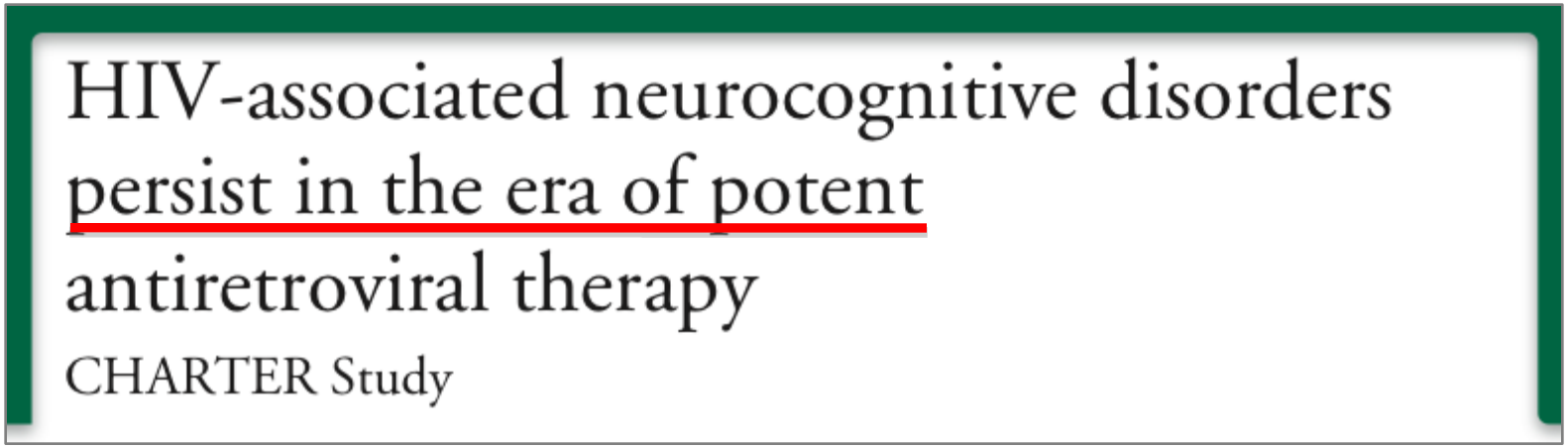
Current Clinical Relevance of NCI?

☞ *Highly frequent complication.*

Prevalence of NCI in HIV Infection



Prevalence of NCI in HIV Infection



HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy : CHARTER Study
R.K. Heaton, D.B. Clifford, D.R. Franklin, Jr., et al.
Neurology 2010;75;2087

Sacktor et al, 2003
Wojna et al, 2006
Arendt et al, 2007
Cysique et al, 2006
Tozzi et al, 2007
Robertson et al, 2007
Cohen et al, 2010
Harezlak et al, 2011
Heaton et al, 2011

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Prevalence of NCI in HIV Infection

OPEN ACCESS Freely available online

PLOS ONE

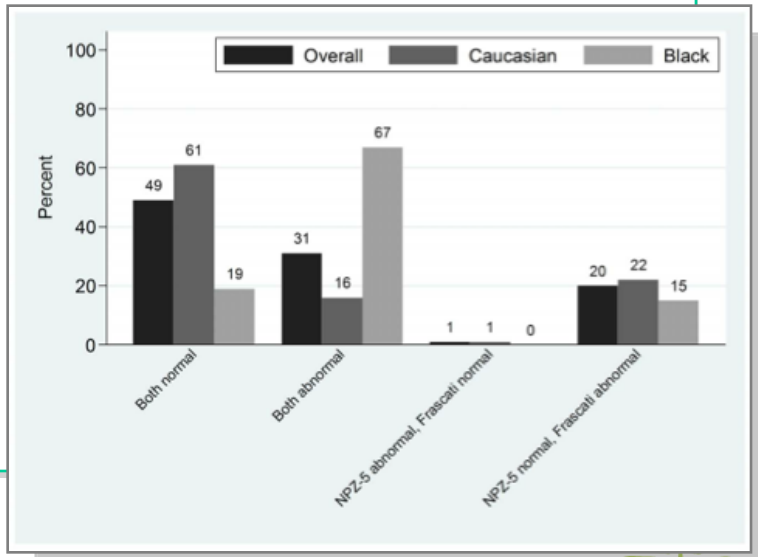
Neurocognitive Function in HIV Infected Patients on Antiretroviral Therapy

Alan Winston[1,2]*, Alejandro Arenas-Pinto[3,4], Wolfgang Stöhr[3], Martin Fisher[5], Chloe M. Orkin[6], Kazeem Aderogba[7], Andrew De Burgh-Thomas[8], Nigel O'Farrell[9], Charles J.N. Lacey[10], Clifford Leen[11,12], David Dunn[3], Nicholas I. Paton[3,13] for the PIVOT Trial Team[¶]

April 2013 | Volume 8 | Issue 4 | e61949

We hypothesise the differences in NC test results between the ethnicities observed in our study are due to differences in the characteristics of control datasets available for use for several reasons. Firstly, when utilising the demographically adjusted

substantially differ from a control population. Another seminal finding from our work for future clinical research, is the importance of recruiting well matched control populations to the HIV infected populations being studied, in order to aid the interpretation of study findings and in order to assess if findings are related to HIV-disease itself or the cohorts being studied.



Prevalence of NCI in HIV Infection

HIV-associated neurocognitive disorder in Australia: a case of a high-functioning and optimally treated cohort and implications for international neuroHIV research

Lucette A. Cysique, Robert K. Heaton, Jody Kamminga, Tammy Lane, Thomas M. Gates, Danielle M. Moore, Emma Hubner, Andrew Carr, Bruce J. Brew

Journal of NeuroVirology
June 2014, Volume 20, Issue 3, pp 258-268

Abstract

The Australian HIV-infected (HIV+) population is largely comprised of high-functioning men who have sex with men (MSM). Like other English-speaking countries, Australia mostly relies on US neuropsychological normative standards to detect and determine the prevalence of neurological disorders. Whether the US neuropsychological (NP) normative standards are appropriate in Australian HIV+ MSM has not been established. Ninety virally suppressed HIV+ and 49 HIV-uninfected (HIV−) men (respectively 86 and 85 % self-reported MSM; mean age 54 and 56 years, mean premorbid verbal IQ estimate 110 and 111) undertook standard NP testing. The raw neuropsychological data were transformed using the following: (1) US standards as uncorrected scaled scores and demographically corrected *T* scores (US norms); and (2) *z* scores (without demographic corrections) derived from Australian comparison group scaled scores (local norms). To determine HIV-associated neurocognitive disorder prevalence, we used a standard definition of impairment based upon a battery-wide summary score: the global deficit score (GDS). Impairment classification (GDS≥0.5) based on the local norms was best at discriminating between the two groups (HIV−=14.3 % vs. HIV+=53.3 %; $p<0.0001$). This definition was significantly associated with age. Impairment classification based on the US norms yielded much lower impairment rate regardless of the HIV status (HIV−=4.1 % vs. HIV+=14.7 %; $p=0.05$), but was associated with historical AIDS, and not age. Both types of summary scores were associated with reduced independence in activities of daily living ($p\leq0.03$). Accurate neuropsychological classifications of high (or low) functioning individuals may need country-specific norms that correct for performance-based (e.g., reading) estimates of premorbid cognition in addition to the traditional demographic factors.

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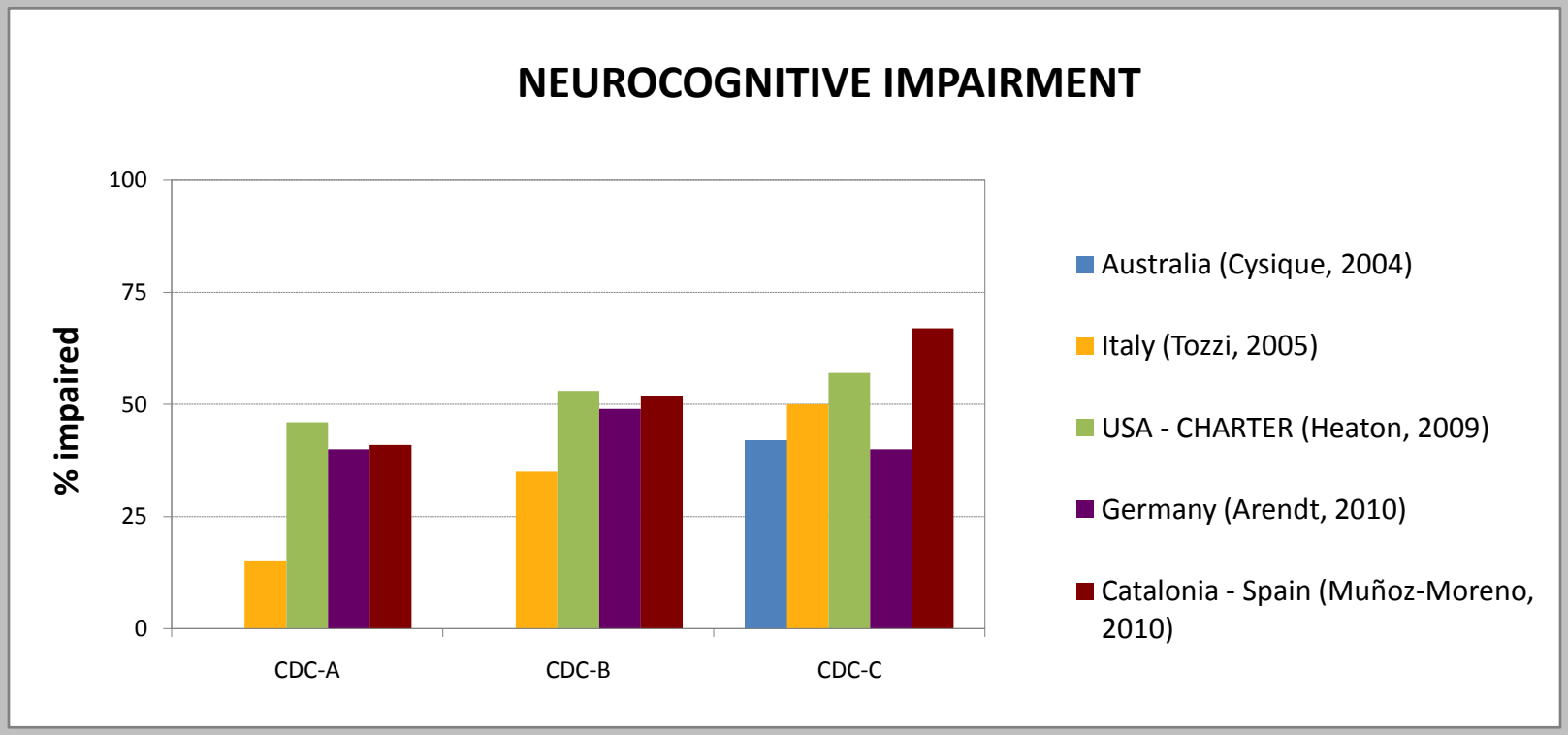
Prevalence of NCI in HIV Infection



Muñoz-Moreno et al, 10th ISNV, Milan, 2010

Current Clinical Relevance of NCI?

- *Highly frequent complication.*
- *Detrimental contributions.*

Impairment on Daily Functioning

Neurology. 2001 Feb 13;56(3):415-8.

Clinical trials in HIV-associated cognitive impairment: cognitive and functional outcomes.

Schifitto G[1], Kieburtz K, McDermott MP, McArthur J, Marder K, Sacktor N, Palumbo D, Selnes O, Stern Y, Epstein L, Albert S.

J Int Neuropsychol Soc. 2004 May;10(3):317-31.

The impact of HIV-associated neuropsychological impairment on everyday functioning.

Heaton RK[1], Marcotte TD, Mindt MR, Sadek J, Moore DJ, Bentley H, McCutchan JA, Reicks C, Grant I; HNRC Group.

Neuropsychol Rev. 2009 Jun;19(2):186-203. doi: 10.1007/s11065-009-9095-0. Epub 2009 May 27.

Functional consequences of HIV-associated neuropsychological impairment.

Gorman AA[1], Foley JM, Ettenhofer ML, Hinkin CH, van Gorp WG.

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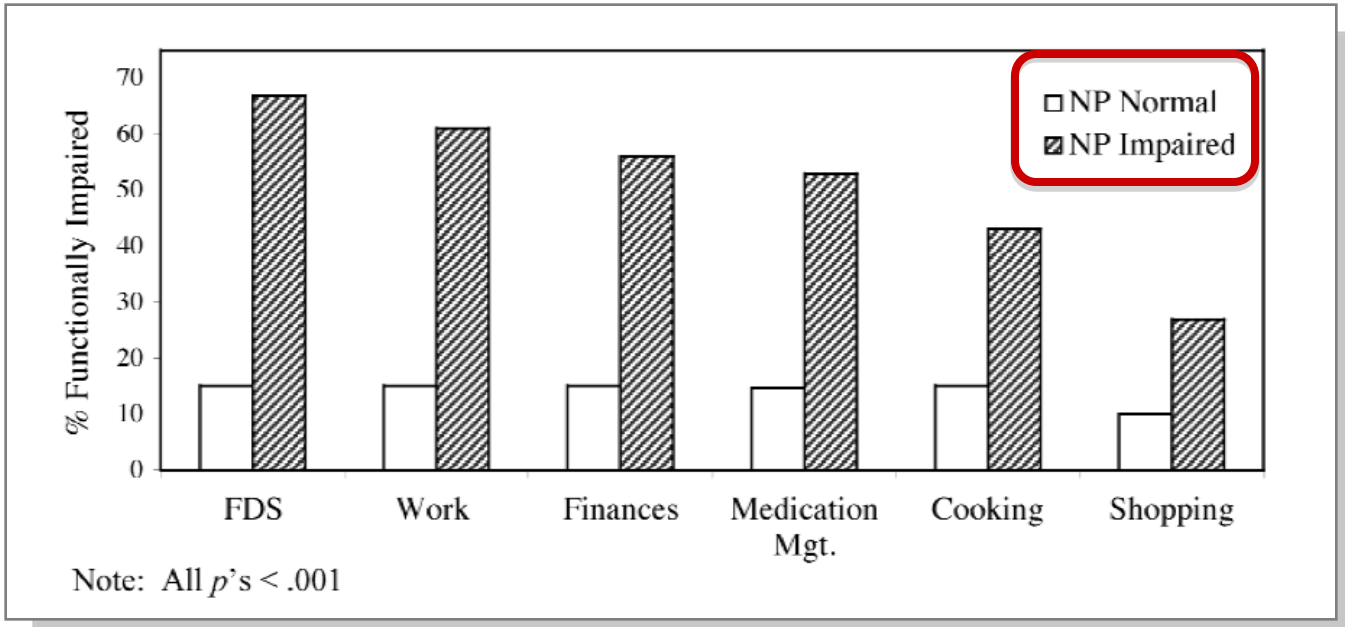

Impairment on Daily Functioning

J Clin Exp Neuropsychol. 2006 Jan;28(1):13-28.

Visual attention deficits are associated with driving accidents in cognitively-impaired HIV-infected individuals.

Marcotte TD[1], Lazzaretto D, Scott JC, Roberts E, Woods SP, Letendre S; HNRC Group.

Neuropsychology. 2011 Jul;25(4):511-9. doi: 10.1037/a0022491.

A neuropsychological investigation of multitasking in HIV infection: implications for everyday functioning.

Scott JC[1], Woods SP, Vigil O, Heaton RK, Schweinsburg BC, Ellis RJ, Grant I, Marcotte TD; San Diego HIV Neurobehavioral Research Center (HNRC) Group.

AIDS Care. 2011 Apr;23(4):435-43. doi: 10.1080/09540121.2010.507952.

Employment status is associated with both physical and mental health quality of life in people living with HIV.

Rueda S[1], Raboud J, Mustard C, Bayoumi A, Lavis JN, Rourke SB.

Rehabil Psychol. 2011 Feb;56(1):77-84. doi: 10.1037/a0022753.

Prospective memory deficits are associated with unemployment in persons living with HIV infection.

Woods SP[1], Weber E, Weisz BM, Twamley EW, Grant I; HIV Neurobehavioral Research Programs Group.

Impairment on Daily Functioning

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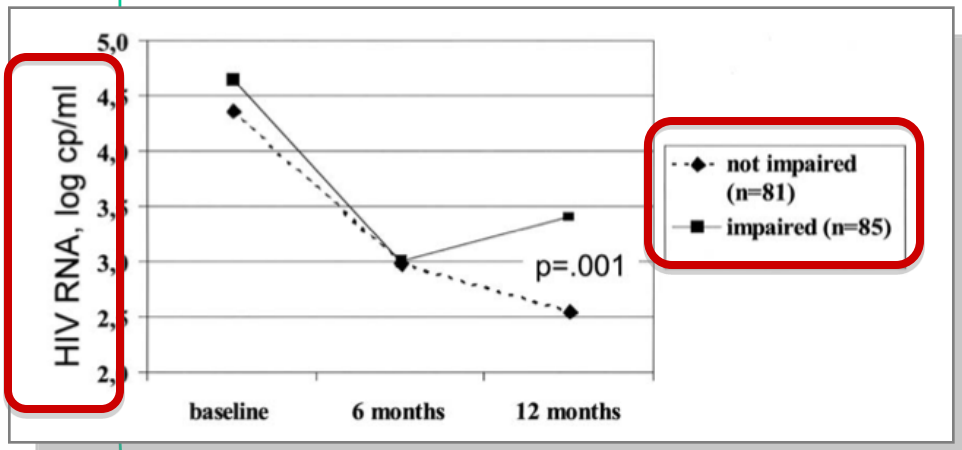
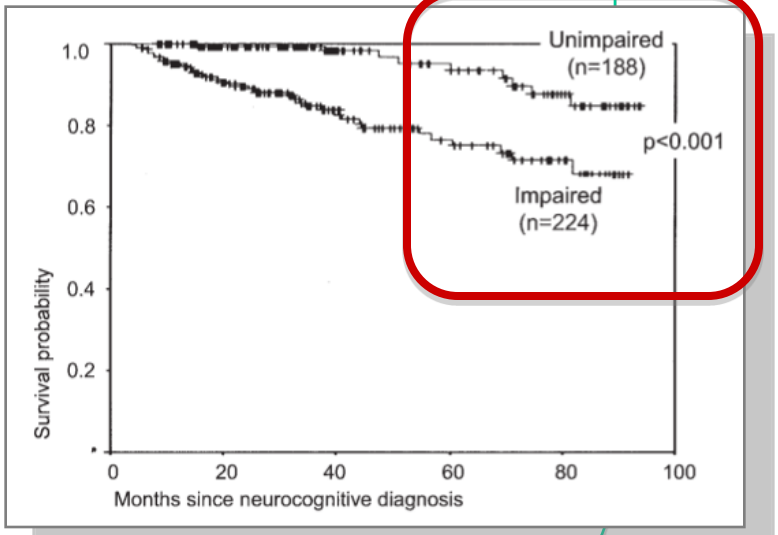
Clinical Implications: Virological Failure

AIDS Res Hum Retroviruses. 2005 Aug;21(8):706-13.

Neurocognitive impairment and survival in a cohort of HIV-infected patients treated with HAART.

Tozzi V[1], Balestra P, Serraino D, Bellagamba R, Corpolongo A, Piselli P, Lorenzini P, Visco-Comandini U, Vlassi C, Quartuccio ME, Giulianelli M, Noto P, Galgani S, Ippolito G, Antinori A, Narciso P.





Clinical Implications: Adherence to cART

J Acquir Immune Defic Syndr. 2002 Dec 15;31 Suppl 3:S132-5.

Neurocognitive aspects of medication adherence in HIV infection.

Selnes OA.

J Int Neuropsychol Soc. 2009 Jan;15(1):42-52. doi: 10.1017/S1355617708090012.

Timing is everything: antiretroviral nonadherence is associated with impairment in time-based prospective memory.

Woods SP[1], Dawson MS, Weber E, Gibson S, Grant I, Atkinson JH; HIV NEUROBEHAVIORAL RESEARCH CENTER GROUP.

J Acquir Immune Defic Syndr. 2013 Mar 1;62(3):282-92. doi: 10.1097/QAI.0b013e31827ed678.

Relationships among neurocognitive status, medication adherence measured by pharmacy refill records, and virologic suppression in HIV-infected persons.

Andrade AS[1], Deutsch R, A Celano S, Duarte NA, Marcotte TD, Umlauf A, Atkinson JH, McCutchan JA, Franklin D, Alexander TJ, McArthur JC, Marra C, Grant I, Collier AC.

Clinical Implications: Mortality

An Evaluation of Neurocognitive Status and Markers of Immune Activation as Predictors of Time to Death in Advanced HIV Infection

Jeffrey J. Sevigny, MD; Steven M. Albert, PhD; Michael P. McDermott, PhD; Giovanni Schifitto, MD; Justin C. McArthur, MBBS, MPH; Ned Sacktor, MD; Katherine Conant, MD; Ola A. Selnes, PhD; Yaakov Stern, PhD; Daniel R. McClernon, BS; Donna Palumbo, PhD; Karl Kieburtz, MD, MPH; Garrett Riggs, MD, PhD; Bruce Cohen, MD; Karen Marder, MD, MPH; Leon G. Epstein, MD

Sevigny et al, 2007

Conclusion: In patients with advanced HIV infection, HIV-associated dementia is an independent predictor of time to death.

Ellis et al, 1997 ***Dore et al, 2003*** ***Lescure et al, 2011***

Current Clinical Relevance of NCI?

- ☞ *Highly frequent complication.*
- ☞ *Detrimental contributions.*
- ☞ *Multiple risk factors.*

Risk Factors vs Protective Factors

Related to HOST		*Related to INFECTION*	
Demographic / Psychosocial	*Comorbidities*	*HIV*	*ART Therapy*
Age	**Cardiovascular**	**AIDS**	**Adherence**
Gender	**Drug Use**	**Nadir CD4+ Count**	**ART Interruptions**
Education	**HCV Coinfection**	**Viral Load**	**Neurotoxicity**
Unemployment	**Diabetes**	**HIV Clades**	**IRIS**
Risk Behaviours	**Vitamin B12**	**Tropism**	**...**
...	**...**	**...**	

Current Clinical Relevance of NCI?

- ☞ *Highly frequent complication.*
- ☞ *Detrimental contributions.*
- ☞ *Multiple risk factors.*
- ☞ *Absence of treatment.*
- ☞ *Complexity in the clinical management.*

2. Which Patients Should Be Screened?

Is Screening Required for All HIV-Infected Patients?

The MIND Exchange Group Recommendations

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

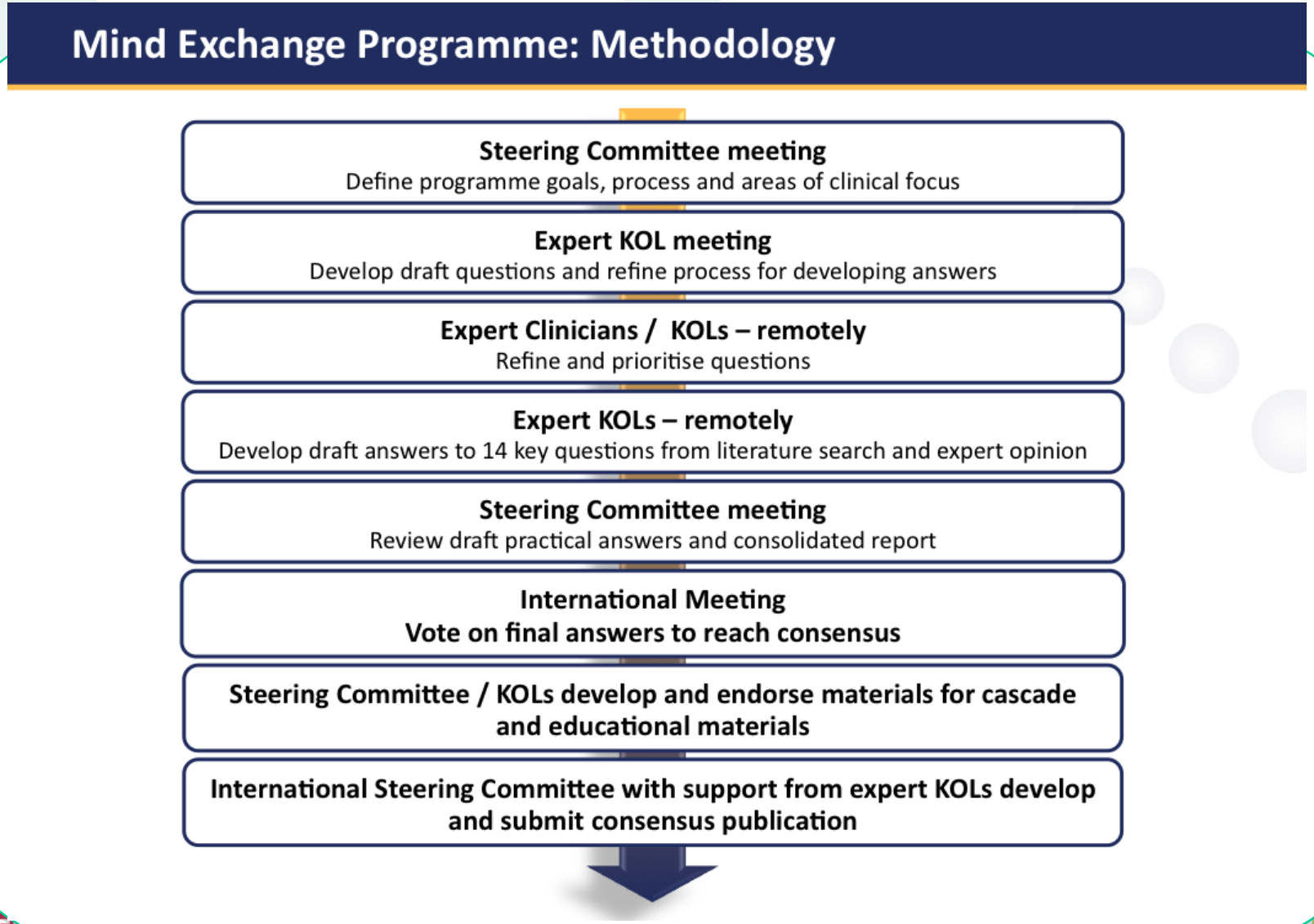
The Mind Exchange Working Group

HIV/AIDS • CID 2013:56 (1 April) • 1005

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

The MIND Exchange Group Recommendations



The MIND Exchange Group Recommendations

Mind Exchange Programme: Methodology

Steering Committee (5 members):

- Provided oversight and direction for the programme and the planned international meetings.

Expert KOL group (25 members):

- Generated comprehensive answers and recommendations for the prioritised questions in the management of HAND.

Expert clinician group (41 members):

- Supported with identification and prioritisation of the key unanswered questions in HAND management.

The MIND Exchange Group Recommendations

Mind Exchange Programme: Methodology

Austria
- Professor Christian Eggers

Australia
- Professor Bruce Brew
- Dr Lucette Cysique
- Professor Ian Everall

Canada
- Dr Adriana Carvalhal
- Dr Sean Rourke
- Dr Marie-Josée Brouillette

Colombia
- Dr Francisco Bernal-Cano

Czech Republic
- Professor Ladislav Machala

France
- Dr Jacques Gasnault
- Dr Yazdan Yazdanpannah

Germany
- Dr Ingo Husstedt
- Dr Mark Obermann

Italy
- Dr Paola Cinque

The Netherlands
- Professor Peter Portegies

Portugal
- Dr Silvia Ouakinin

Puerto Rico
- Professor Valerie Wojna

Romania
- Professor Adrian Streinu-Cercel

Spain
- Dr Daniel Podzamczer

Sweden
- Professor Magnus Gisslén

Turkey
- Professor Volkan Korten

United Kingdom
- Dr Simon Rackstraw
- Professor Lorraine Sherr
- Dr Alan Winston

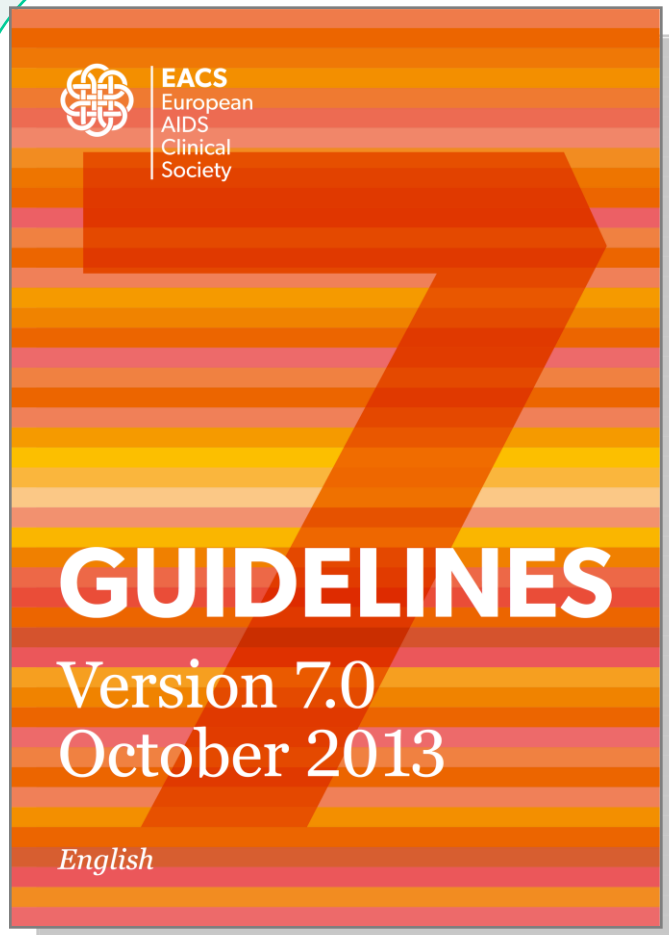
United States of America
- Professor Ronald Ellis

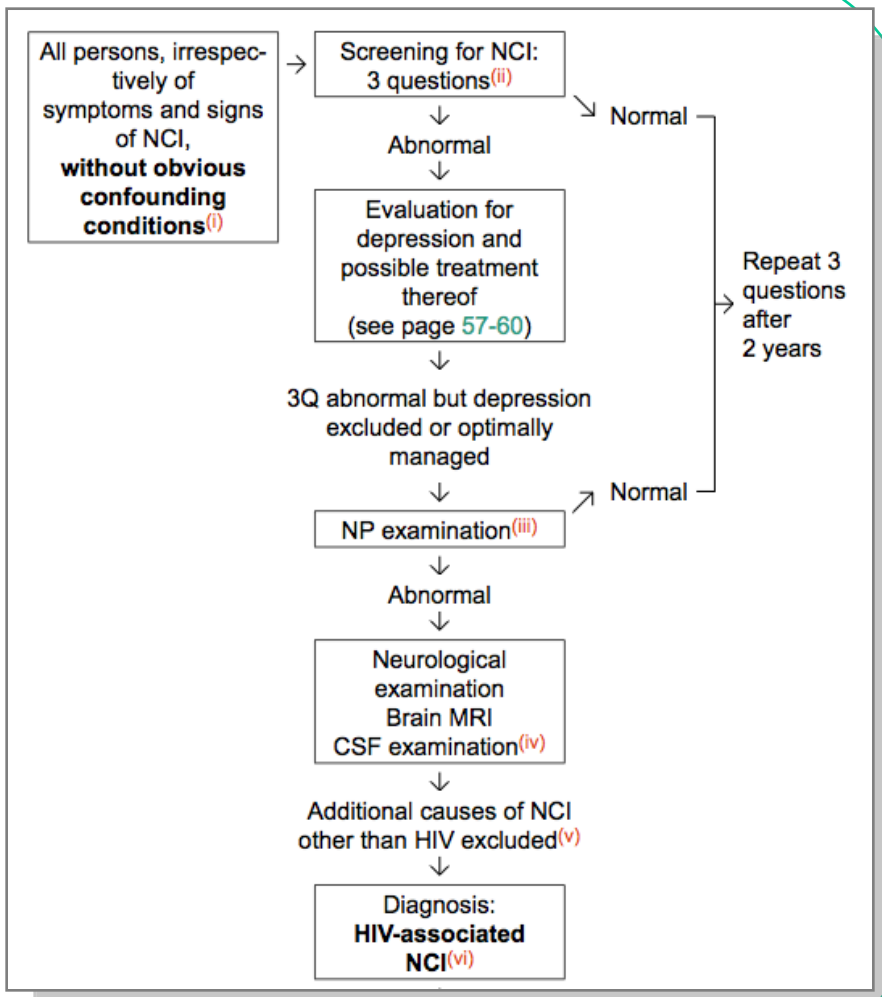
The MIND Exchange Group Recommendations

Final 14 Selected Key Questions

1	Which patients should be screened for HAND, and when? How often should patients be screened?
2	How can I identify patients at greatest risk of HAND? How, and to what extent, do different factors affect the risk of HAND?
3	Which tools should be used to screen for HAND?
4	How should I approach screening and differential diagnosis of HAND co-morbidities?
5	How can HAND be differentiated from neurodegenerative diseases in older patients?
6	How should NP testing be approached, in the diagnosis of HAND?
7	In addition to NP 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)? In which order, and at what stage, and in which patients should these assessments be performed?
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 I monitor 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 I consider in treated patients with persistent or worsening NCI and CSF viral load <50 copies/mL (non-detectable)? Should I still change the ARV when the virus is not detectable in the CSF?
12	What is the risk of ARV-related neurotoxicity, and how should this risk be managed? What should I do if I suspect ARV neurotoxicity?
13	When/how should I use pharmacological agents other than ARV in the management of HAND?
14	What can I do to prevent HAND?

The European AIDS Clinical Society (EACS) Guidelines





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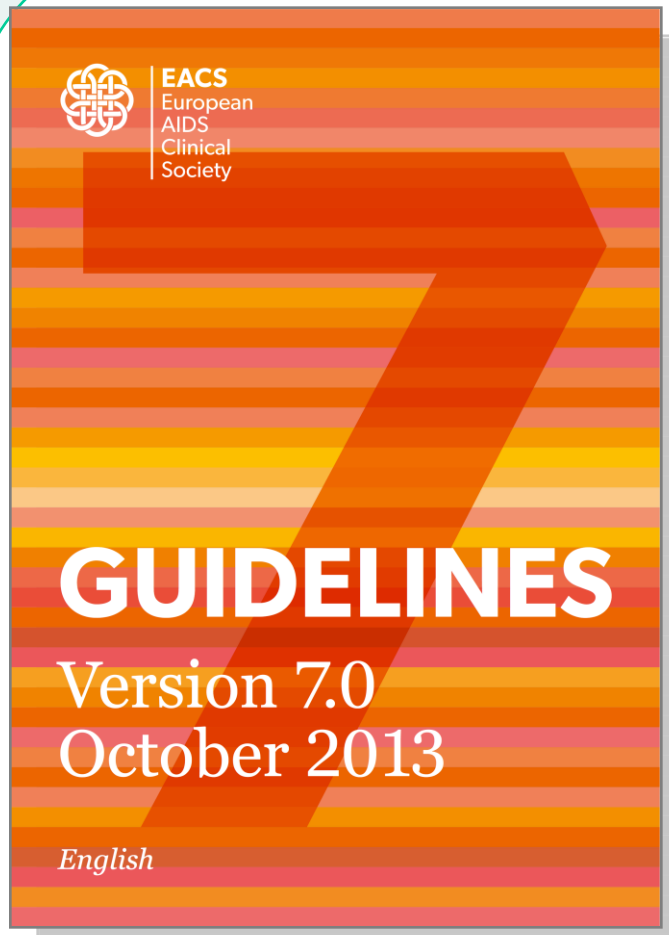
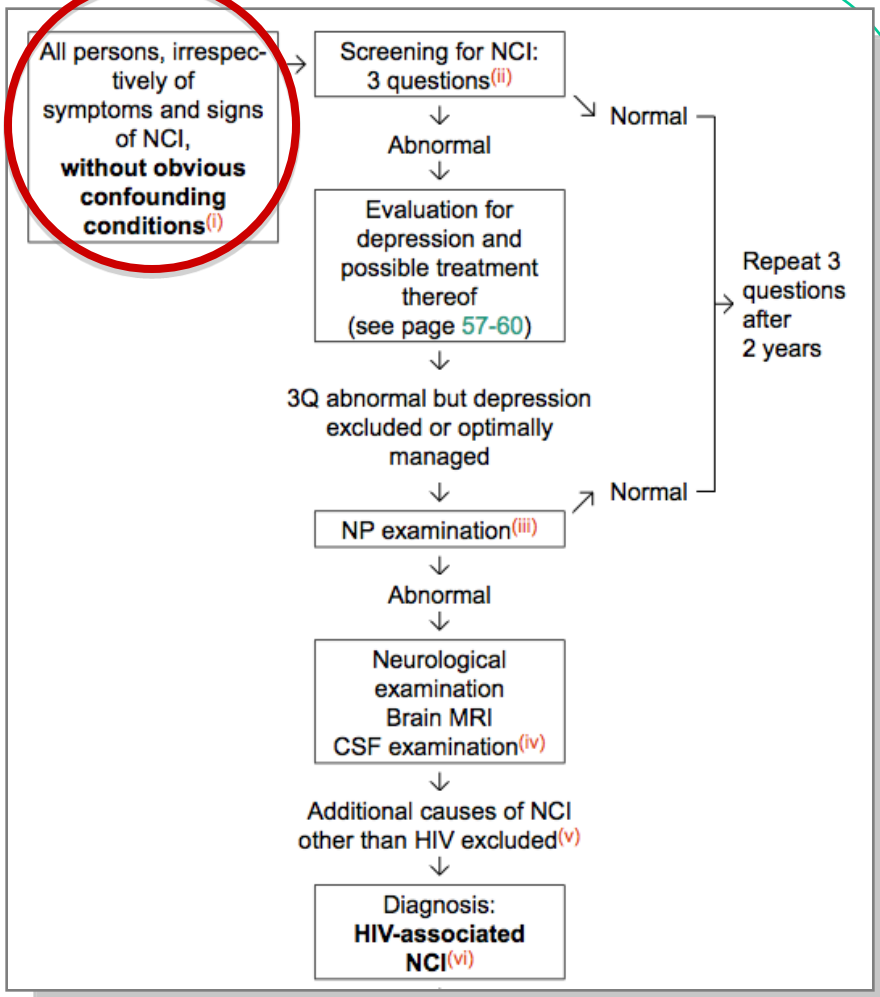
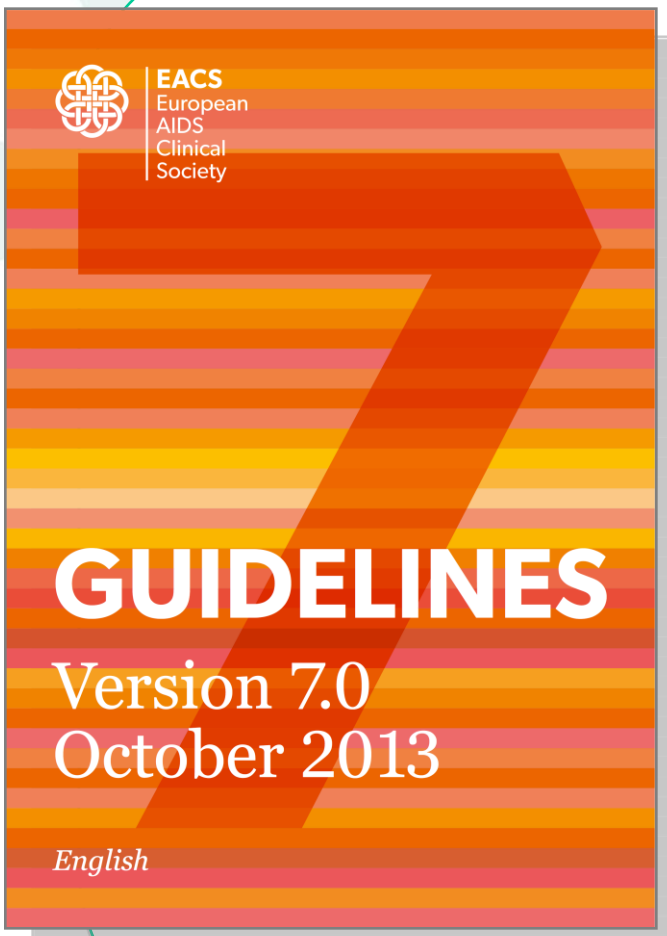
The European AIDS Clinical Society (EACS) Guidelines





The European AIDS Clinical Society (EACS) Guidelines

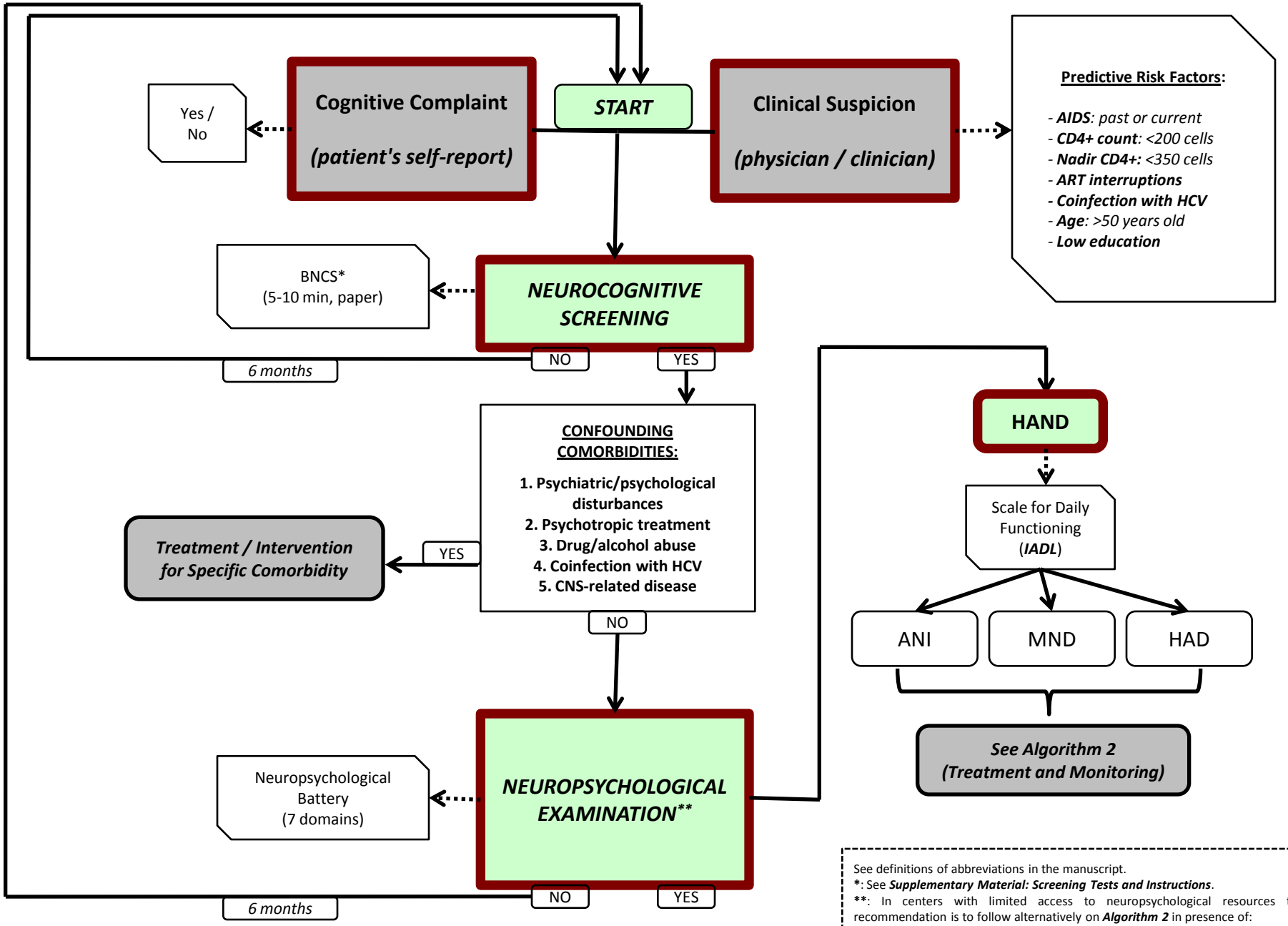


i Persons with obvious confounding conditions are not to be considered in this algorithm

Obvious confounding conditions include:

1. Severe psychiatric conditions
2. Abuse of psychotropic drugs
3. Alcohol abuse
4. Sequelae from previous CNS-OIs or other neurological diseases
5. Current CNS-OIs or other neurological diseases

ALGORITHM 1. Screening, assessment and diagnosis of HIV-Associated Neurocognitive Disorders (HAND).



See definitions of abbreviations in the manuscript.
*: See ***Supplementary Material: Screening Tests and Instructions***.
: In centers with limited access to neuropsychological resources the recommendation is to follow alternatively on ***Algorithm 2* in presence of:
1) Cognitive Complaint + 2) Clinical Suspicion + 3) Positive Sreening.

Controversy Regarding Asymptomatic Neurocognitive Impairment (ANI)

DEBATE Open Access

The definition of HIV-associated neurocognitive disorders: are we overestimating the real prevalence?

Magnus Gisslén[1*], Richard W Price[2] and Staffan Nilsson[3]

Gisslén *et al. BMC Infectious Diseases* 2011, **11**:356
http://www.biomedcentral.com/1471-2334/11/356

each domain, only one is required to fulfill this diagnostic criterion. Unfortunately, this definition necessitates that about 20% of the cognitively normal HIV-infected population is classified as suffering ANI. This liberal definition raises important ethical concerns and has as well diagnostic and therapeutic implications. Since neither its biological substrate, prognostic significance nor therapeutic implications are clearly established, we recommend that this diagnosis be modified or applied cautiously.

Controversy Regarding Asymptomatic Neurocognitive Impairment (ANI)

COMMENTARY Open Access

Asymptomatic neurocognitive disorders in patients infected by HIV: fact or fiction?

Carlo Torti[1*], Emanuele Focà[1], Bruno M Cesana[2] and Francois X Lescure[3]

Torti *et al. BMC Medicine* 2011, **9**:138
http://www.biomedcentral.com/1741-7015/9/138

their findings. Although a cautious approach would indicate a stricter follow-up of patients affected by this disorder, it is premature to consider it as a proper disease. Based on a review of the data in the current literature we conclude that it is urgent to conduct more studies to estimate the overall risk of progression of the asymptomatic neurocognitive impairment. Moreover, it is important to understand whether new biomarkers or neuroimaging tools can help to identify better the most at risk population.

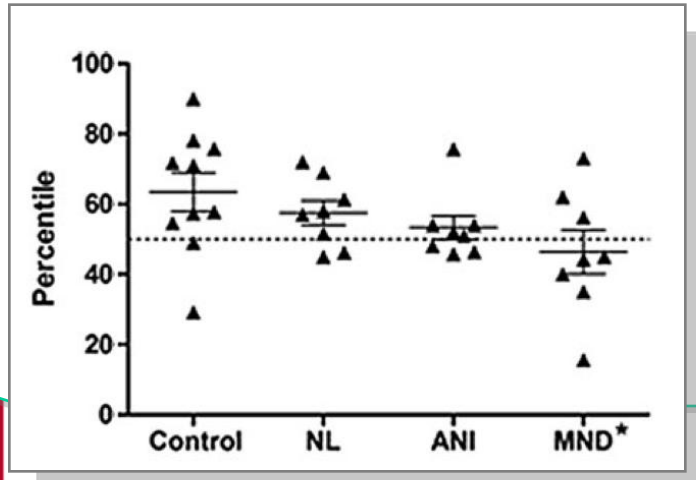
Controversy Regarding Asymptomatic Neurocognitive Impairment (ANI)

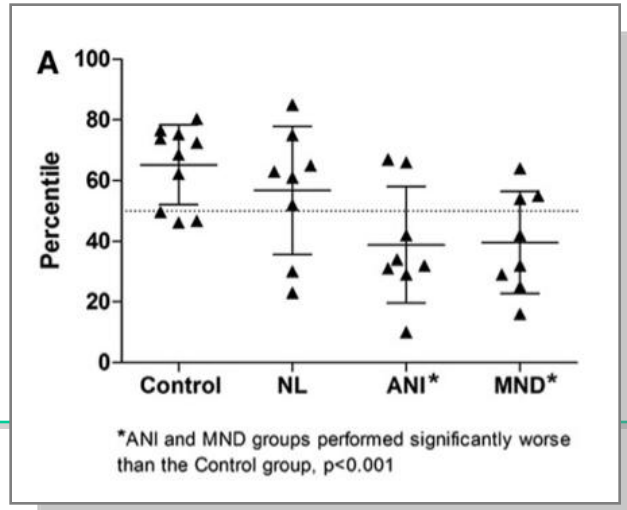
Deficits in Self-Awareness Impact the Diagnosis of Asymptomatic Neurocognitive Impairment in HIV

Stephanie Chiao,[1] Howard J. Rosen,[2] Krista Nicolas,[2] Lauren A. Wendelken,[2] Oscar Alcantar,[2] Katherine P. Rankin,[2] Bruce Miller,[2] and Victor Valcour[2,3]

AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 29, Number 6, 2013
© Mary Ann Liebert, Inc.
DOI: 10.1089/aid.2012.0229

of age and asked subjects to rate their performance relative to peers. We demonstrate that individuals with neuropsychological testing impairment often lack self-awareness of functional performance deficits. Specifically, ANI subjects rated functional performance similar to that of HIV-negative control subjects, despite noted deficits in objective measures of function. These findings have important implications for use of self-report of function in the diagnosis of HIV-associated neurocognitive disorders (HAND), likely underestimating symptomatic impairment.





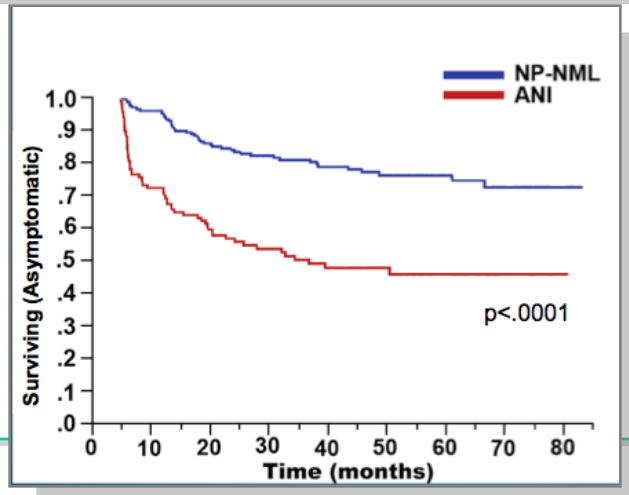
Controversy Regarding Asymptomatic Neurocognitive Impairment (ANI)

Neurology. 2014 May 9. [Epub ahead of print]

Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline.

Grant I[1], Franklin DR Jr, Deutsch R, Woods SP, Vaida F, Ellis RJ, Letendre SL, Marcotte TD, Atkinson JH, Collier AC, Marra CM, Clifford DB, Gelman BB, McArthur JC, Morgello S, Simpson DM, McCutchan JA, Abramson I, Gamst A, Fennema-Notestine C, Smith DM, Heaton RK; For the CHARTER Group.

CONCLUSIONS: This longitudinal study demonstrates that ANI conveys a 2-fold to 6-fold increase in **risk** for earlier development of **symptomatic** HAND, supporting the prognostic value of the ANI diagnosis in clinical settings. Identifying those at highest **risk** for **symptomatic decline** may offer an opportunity to modify treatment to delay progression.



NML (n=226)
ANI (n=121)

Adapted from Grant et al, 19th CROI, Seattle, 2012

Controversy Regarding Asymptomatic Neurocognitive Impairment (ANI)

NEJM Journal Watch

Neurocognitive Decline with HIV Infection

Richard T. Ellison III, MD reviewing Grant I et al. Neurology 2014 May 9. Albert SM and Martin EM. Neurology 2014 May 9.

Asymptomatic HIV-associated neurocognitive impairment is a risk factor for future symptomatic neurological decline.

COMMENT

These findings suggest that ANI is a notable risk factor for neurological decline in HIV-infected patients, and that a sizable proportion of HIV-infected patients will develop measurable decline. As noted by editorialists, it remains unclear whether these findings are applicable to other HIV populations, such as those with less-advanced disease or a lower prevalence of substance abuse.

3. When Should We Screen Them?

The MIND Exchange Group Recommendations

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

The Mind Exchange Working Group

HIV/AIDS • CID 2013:56 (1 April) • 1005

(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

The European AIDS Clinical Society (EACS) Guidelines

	Assessment	At HIV diagnosis	Prior to starting ART	Follow-up frequency	Comment
CO-MORBIDITIES					
Haematology	FBC	+	+	3-12 months	
	Haemoglobinopathies	+			Screen at risk persons
	G6PD	+			Screen at risk persons
Body composition	Body-mass index	+	+	Annual	
Cardiovascular disease	Risk assessment (Framingham score[iii])	+	+		Should be performed in all men > 40 years and women > 50 years without CVD
	ECG	+	+/-	Annual	Consider baseline ECG prior to starting ARVs associated with potential conduction problems
Hypertension	Blood pressure	+	+	Annual	
Lipids	TC, HDL-c, LDL-c, TG[iv]	+	+	Annual	Repeat in fasting state if used for medical intervention (i.e. ≥ 8h without caloric intake)

The European AIDS Clinical Society (EACS) Guidelines

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	ECG	+	+/-	Annual	Consider baseline ECG prior to starting ARVs associated with potential conduction problems
Hypertension	Blood pressure	+	+	Annual	
Lipids	TC, HDL-c, LDL-c, TG[iv]	+	+	Annual	Repeat in fasting state if used for medical intervention (i.e. ≥ 8h without caloric intake)
Neurocognitive impairment	Screening questionnaire	+	+	2 years	Screen all persons without highly confounding conditions. If abnormal or symptomatic, see algorithm page 61 for further assessment.

Studies Assessing Longitudinal Changes of NCI

Detecting change:
A comparison of three neuropsychological methods, using normal and clinical samples

Robert K. Heaton[a,*], Nancy Temkin[b], Sureyya Dikmen[b], Nanci Avitable[c], Michael J. Taylor[a], Thomas D. Marcotte[a], Igor Grant[a,d]

R.K. Heaton et al. / Archives of Clinical Neuropsychology 16 (2001) 75–91

The generalizability of neurocognitive test/retest data derived from a nonclinical sample for detecting change among two HIV+ cohorts

Andrew J. Levine[1], Charles H. Hinkin[2], Eric N. Miller[2,3], James T. Becker[4], Ola A. Selnes[5], and Bruce A. Cohen[6] for the Multicenter AIDS Cohort Study (MACS)

J Clin Exp Neuropsychol. 2007 August ; 29(6): 669–678.

Studies Assessing Longitudinal Changes of NCI

Dynamics of cognitive change in impaired HIV-positive patients initiating antiretroviral therapy

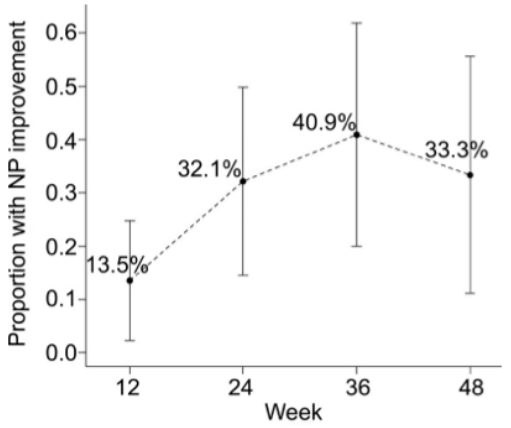
Neurology 73 August 4, 2009

L.A. Cysique, PhD
F. Vaida, PhD
S. Letendre, MD
S. Gibson, BS
M. Cherner, PhD
S.P. Woods, PsyD
J.A. McCutchan, MD
R.K. Heaton, PhD
R.J. Ellis, MD, PhD

Methods: Study participants included 37 HIV+ individuals with mild to moderate NP impairment who initiated CART and underwent NP testing at 12, 24, 36, and 48 weeks thereafter. NP change was assessed using a regression-based change score that was normed on a separate NP-stable group thereby controlling for regression toward the mean and practice effect. Mixed-effect regression models adjusting for loss to follow-up were used to evaluate the time course of cognitive change and its association with baseline and time-varying predictors.

Conclusion: Clinically meaningful neuropsychological improvement seemed to peak around 24–36 weeks after combination antiretroviral therapy initiation and was prolonged over the 1-year study period. This study also provides new evidence that benefit may be maximized by choosing antiretroviral medications that reach therapeutic concentrations in the CNS. ***Neurology*® 2009;73: 342–348**

Figure 1 Proportion of HIV+ individuals with neuropsychological improvement from baseline



Studies Assessing Longitudinal Changes of NCI

Normative data and validation of a regression based summary score for assessing meaningful neuropsychological change

Lucette A. Cysique[1,2], Donald Franklin, Jr[1], Ian Abramson[1], Ronald J. Ellis[1], Scott Letendre[1], Ann Collier[3], David Clifford[4], Benjamin Gelman[5], Justin McArthur[6], Susan Morgello[7], David Simpson[7], J. Allen McCutchan[1], Igor Grant[1], Robert K. Heaton[1], the CHARTER group, and the HNRC group

JOURNAL OF CLINICAL AND EXPERIMENTAL NEUROPSYCHOLOGY
2011, 33 (5), 505–522

NP measure	*T2*	*T3*	*T4*	*T5 +*
Letter Fluency	0.0	0.5	1.0	1.0
Animal Fluency	0.0	0.0	0.0	0.0
PASAT-50	0.5	1.0	1.0	1.0
WAIS–III L–N Sequencing	0.0	0.0	0.0	0.0
WAIS–III Digit Symbol	0.0	0.5	1.0	1.0
WAIS–III Symbol Search	0.5	1.0	1.0	1.0
Trail Making Test A	0.5	1.0	1.0	1.0
WCST-64 Perseverative Errors	1.0	2.0	2.0	2.0
Trail Making Test B	1.0	1.0	1.0	1.0
HVLT–R Total Learning	0.0	1.0	0.5	0.5
HVLT–R Delayed Recall	0.5	0.5	0.5	0.5
BVMT–R Total Learning	1.0	1.0	0.0	1.0
BVMT–R Delayed Recall	0.5	0.0	0.0	0.5
Grooved Pegboard DH	0.5	0.0	1.0	1.0
Grooved Pegboard NDH	0.0	0.5	0.5	1.0
Sum	6.0	10.0	10.5	12.5

	% decline		*% stable*		*% improve*		
Times	*HIV– reference sample*	*HIV+ reference sample*	*HIV– reference sample*	*HIV+ reference sample*	*HIV– reference sample*	*HIV+ reference sample*	*p*
Time 1 *pred* Time 2	4.65	3.23	90.70	93.55	4.65	3.23	.67
Time 2 *pred* Time 3	5.13	1.61	89.74	91.94	5.13	6.45	.29
Time 3 *pred* Time 4	4.30	2.56	91.40	96.15	4.30	1.28	.40
Time 4 *pred* Time 5	4.23	6.56	91.55	88.52	4.23	4.92	.81

Prior to the development of our norms, we have demonstrated, using two different statistical methods (the SRB method and mixed-effects regression analyses), that clinically stable HIV+ individuals perform similarly to HIV– individuals in terms of test–retest change despite a slightly higher impairment rate at baseline in the HIV+ sample. Our study confirms and extends our previous findings (Cysique et al., 2009) where we had found that clinically stable HIV+ individuals performed similarly to HIV– individuals over a one-year period. Here we

4. Is There an Optimal Tool to Screen for HAND?

What Is It Needed to Consider a Screening Tool an Optimal Screening Tool?

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☞ *Easy administration and correction?*

What Is It Needed to Consider a Screening Tool an Optimal Screening Tool?

- *Easy administration and correction?*
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- ☞ *Time for administration?*

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Available Screening Tools for NCI

Name	Reference	Duration	Pros	Cons
CogState®	*Cysique et al, J Int Neuropsych Soc, 2006*	10-15 min	- 4 areas covered - Low practice effect	- Economical cost - Feasibility (computerized)
CAMCI® (Computer Assessment of Mild Cogn. Impairm.)	*Becker et al, AIDS Patient Care and STDs, 2011*	20 min	- 4 areas covered - Low practice effect	- Economical cost - Feasibility (computerized)
HNRC Screening	*Carey et al, Clin Neuropsychol, 2004*	5-10 min	- Good accuracy (78%, 85%) - Only 2 measures	- Economical cost - Instrumental requirements (pegboard)
IHDS (International HIV Dementia Scale)	*Sacktor et al, AIDS, 2005*	5-10 min	- Quantitative score - Extensively used	- Designed for HAD - Limited accuracy
BNCS (Brief NeuroCognitive Screen)	*Ellis et al, J Neurovirol, 2005*	5-10 min	- Paper-based use - Extensively used	- Economical cost - Limited sensitivity (65%)
MoCA® (Montreal Cognitive Assessment)	*Koski et al, HIV Medicine, 2011*	5-10 min	- Quantitative score - 4 areas covered	- Designed for aging - Limited sensitivity (63%)
NEU Screen	*Muñoz-Moreno et al, JAIDS, 2013*	5-10 min	- Good accuracy (74%, 81%) - No copyright restrictions	- Limited to Spanish speakers - No formal validation

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The Hottest: Recent Works in the Field

The Hottest: Recent Works in the Field

Evaluation of brief screening tools for neurocognitive impairment in HIV/AIDS: a systematic review of the literature

Amy R. Zipursky[a,b], David Gogolishvili[a], Sergio Rueda[a,b], Jason Brunetta[c], Adriana Carvalhal[b,d], Jennifer A. Mccombe[e], M. John Gill[e], Anita Rachlis[b,f], Ron Rosenes[a], Gordon Arbess[b,d], Thomas Marcotte[g] and Sean B. Rourke[a,b,d]

AIDS 2013, **27**:2385–2401

- ☑ Systematic review especially focused on **brief screening tools** for HAND.
- ☑ 316 studies identified, 51 fulfilled inclusion criteria, and **31 evaluated** (39 tools).
- ☑ HDS and IHDS are accurate methods to screen for HAD, but limited detecting **mild impairment**.

The Hottest: Recent Works in the Field

OPEN ACCESS Freely available online

PLOS ONE

Identification of an Abbreviated Test Battery for Detection of HIV-Associated Neurocognitive Impairment in an Early-Managed HIV-Infected Cohort

David J. Moore[1]*, Mollie J. P. Roediger[2,3], Lynn E. Eberly[2,3], Kaitlin Blackstone[1], Braden Hale[3,4,5], Amy Weintrob[3,6], Anuradha Ganesan[3,7], Brian K. Agan[3], Scott L. Letendre[1], Nancy F. Crum-Cianflone[3,4,5]

November 2012 | Volume 7 | Issue 11 | e47310

- ☑ To investigate multiple test combinations (2 tests, 3 tests, 4 tests).
- ☑ Low prevalence of NCI in US military beneficiaries (**19%**).
- ☑ **2 tests** (Stroop + HVLT-R) sensitivity: **73%,** specificity**: 83%** (11 min).
- ☑ **3 tests** (Stroop + HVLT-R + PASAT) sensitivity: **86%,** specificity**: 75%** (16 min).
- ☑ **4 tests** (Stroop + HVLT-R + PASAT + AF) sensitivity**: 86%,** specificity**: 87%** (18 min).

The Hottest: Recent Works in the Field

Screening for Neurocognitive Impairment in HIV Individuals: The Utility of the Montreal Cognitive Assessment Test

Rodrigo Hasbun[1,*], Jairo Eraso[1], Sweeya Ramireddy[1], D' Arcy Wainwright[1], Lucrecia Salazar[1], Richard Grimes[1], Michele York[2], and Adriana Strutt[2]

Hasbun et al, J AIDS Clin Res, Dec 2012

- ☑ **ART-naïve patients** with an elevated frequency of NCI (75%).
- ☑ High proportion of **comorbidities**: active drug use, depression, unemployment, low education and other confounding factors.
- ☑ Sensitivity of **85%** and specificity of **40%** (score <26).

The Hottest: Recent Works in the Field

The Alzheimer Disease-8 and Montreal Cognitive Assessment as Screening Tools for Neurocognitive Impairment in HIV-Infected Persons

E. Turner Overton, MD[1], Tej Azad[2], Neva Parker[2], Debra Demarco-Shaw, RN[3], Judy Frain, RN[3], Teresa Spitz, RN[3], Elizabeth Westerhaus, MA[2], Robert Paul, PhD[4], David B. Clifford, MD[2], and Beau M. Ances, MD, PhD[2,5]

Overton et al, J Neurovirol, Feb 2013

- ☑ Alzheimer Disease-8, MoCA and Neuropsychological Testing in **200 HIV-infected patients**.
- ☑ NCI highly prevalent (**64%**).
- ☑ AD-8 sensitivity: 61%, specificity: 51% vs **MoCA sensitivity: 63%, specificity: 71%** (score ≤25).
- ☑ **MoCA sensitivity: 90%, specificity: 42%** (score ≤27).

The Hottest: Recent Works in the Field

Trail Making Test A Improves Performance Characteristics of the International HIV-Dementia Scale to Identify Symptomatic HAND

Thep Chalermchai, MD[1], Victor Valcour, MD[2,3], Pasiri Sithinamsuwan, MD[4], Suteeraporn Pinyakorn, MSc[5], David Clifford, MD[6], Robert H Paul, PhD[7], Somporn Tipsuk, RN[1], James L K Fletcher, BM, BCH[1], Victor DeGruttola, ScD[8], Silvia Ratto-Kim, PhD[10], Nicholas Hutchings[2], Cecilia Shikuma, MD[11], Jintanat Ananworanich, MD, PhD[1,5,9], and the SEARCH 007 and 011 study groups

Chalermchai et al, J Neurovirol, Apr 2013

- ☑ Study to seek an optimal cut-off for **IHDS** in Thailand (75 subjects).
- ☑ Only in **MND** and **HAD**.
- ☑ **IHDS** sensitivity**: 53%,** specificity**: 90%** (score ≤10).
- ☑ **IHDS + TMT-A** sensitivity**: 86%,** specificity**: 79%**.

The Hottest: Recent Works in the Field

A Brief and Feasible Paper-Based Method to Screen for Neurocognitive Impairment in HIV-Infected Patients: The NEU Screen

Jose A. Muñoz-Moreno, PhD,† Anna Prats, MS,*† Núria Pérez-Álvarez, MS,*‡ Carmina R. Fumaz, PhD,*† Maite Garolera, PhD,§‖ Eduardo Doval, PhD,† Eugènia Negredo, PhD,*† Maria J. Ferrer, MS,*† and Bonaventura Clotet, PhD,*†¶ for the NEU Study Group*

J Acquir Immune Defic Syndr • Volume 63, Number 5, August 15, 2013

- ☑ Multicenter study, **7 hospitals** in Catalonia (Spain), 106 HIV-infected patients with a wide range of comorbidities (55%).
- ☑ Restricted to **paper-based** tests and time duration of **≤10 minutes**.
- ☑ The NEU Screen consists of **3 scores** (TMT-A, TMT-B and COWAT) and presented a sensitivity of **74%** and specificity of **81%**.

Differences in North American and West European Study Populations When Detecting Neurocognitive Impairment in HIV Infection: A Comparison of Three Screening Methods

Jose A. Muñoz-Moreno[1,2], Anna Prats[1,2], Núria Pérez-Álvarez[1,3], Carmina R. Fumaz[1,2], Maria J. Ferrer[1,2], Eugènia Negredo[1,2], Montse Bernaus[4], Jordi Blanch[5], Elisabeth Deig[6], Lluís Force[7], Àngels Massabeu[8], Antònia Raich[9], Maite Garolera[10,11], Bonaventura Clotet[1,2,12] and the NEU Study Group

[1] Lluita contra la SIDA Foundation - Germans Trias i Pujol University Hospital (Badalona, Spain); [2] Autònoma de Barcelona University (Bellaterra, Spain); [3] Politècnica de Catalunya University (Barcelona, Spain); [4] Consorci Sanitari Parc Taulí (Sabadell, Spain); [5] Clínic i Provincial Hospital (Barcelona, Spain); [6] Fundació Asil - Granollers Hospital (Granollers, Spain); [7] Consorci Sanitari Mataró Hospital (Mataró, Spain); [8] Palamós Hospital (Palamós, Spain); [9] Althaia Xarxa Assistencial (Manresa, Spain); [10] Consorci Sanitari Terrassa Hospital (Terrassa, Spain); [11] Barcelona University (Barcelona, Spain)
[12] IrsiCaixa Foundation (Badalona, Spain)

11th International Symposium on NeuroVirology held jointly with 2012 Conference on HIV in the Nervous System, New York, New York

11th INTERNATIONAL SYMPOSIUM ON NEUROVIROLOGY (ISNV)

May 29 - June 2, New York City, NY

Abstract P155

Contact Information:

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Background

✓ Several screening methods for HIV-related neurocognitive impairment (NCI) have been proposed, although each of them present variable characteristics. Their differences mainly involve instrumental requirements, statistical properties and characteristics of the studies developed.

✓ We decided to compare 3 of these methods, all of they with similar properties, although validated in different study populations.

✓ Concretely, we compared 2 methods validated in the USA with the ***NEU screening***, a new tool offered in Europe for a rapid and feasible detection of NCI in people with HIV.

Methodology

Information about 3 screenings tools for NCI in HIV infection was contrasted. Specifically, the methods were the following:

1) A combination of 2 measures offered by the HIV Neurobehavioral Research Center (**HNRC**), by *Carey and cols, J Clin Exp Neuropsychol, 2004* (***Figure 1***).

Although the original report offered 2 pair combinations of scores as optimal, we decided to use only one according to the option showing highest sensitivity, considering this as a primary condition for an adequate screening method. Concretely, the combination used involved a total recall measure of the Hopkins Verbal Learning Test - revised (HVLT-R) and a motor measure for the non-dominant hand of the Grooved Pegboard Test (GPT). In our analyses, though, the specific total recall measure consisted of the equivalent score in the California Verbal Learning Test - 2nd version (CVLT-II), since that is the comparable test used regularly by our team for assessing verbal memory and learning.

2) The Brief NeuroCognitive Screen (**BNCS**), *by Ellis and cols, J Neurovirol, 2005* (***Figure 2***).

This method includes the parts A and B of the Trail Making Test (TMT-A and TMT-B) and the Digit Symbol task (DS) of the Weschler Adult Intelligence Scale, 3rd edition (WAIS-III).

3) The **NEU** screening (also presented in this conference, *Abstract P154*) (***Figure 3***).

This tool includes the parts A and B of the Trail Making Test (TMT-A and TMT-B) and the Controlled Oral Word Test (COWAT).

Comparisons were mainly structured according to (1) the design characteristics of the studies in which the 3 methods were offered; (2) assessment characteristics and other conditions concerning their use; and (3) relevant data on statistical properties. Considering both study and assessment characteristics the information used was based on the data offered in the original reports. With regard to statistical properties comparisons were also compared according to the information offered in the original reports, but additionally we compared their statistical performance in an European sample of 106 HIV-infected patients, which was the same sample used in the study presenting the NEU screening. Consequently, the sensitivity, specificity, predictive value and percentage of correct classification were calculated.

Figure 1. *Tests included in HNRC screening.*

Figure 2. *Tests included in BNCS.*

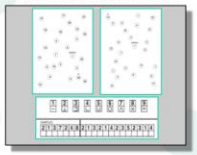

Figure 3. *Tests included in NEU screening.*

Results

The design characteristics of the studies in which the 3 methods were offered, were mostly similar. Study samples were basically comprised by middle -aged (HNRC: 41 [median years]; BNCS: 44; NEU: 44) Caucasian (63%; 60%; 93%) men (84%; 86%; 87%), with similar levels of education (13; 14; 12). The main difference in this regard was characterized by the regions in which the studies were developed: HNRC and BNCS in North America and NEU in West Europe (***Table 1***). Considering the assessment and use characteristics of these tools, most of properties were similar as well, except for the instrumental requirements. Although NEU allows to assess 3 neurocognitive areas through 3 different scores, HNRC covers 2 areas with 2 scores, and BNCS 2 areas with 3 scores. The approximate duration time for application is essentially the same (about 10 minutes), and a key difference is the instrumental use, since BNCS and NEU are based only on a paper use, and HNRC needs a pegboard for using one of the 2 scores (***Table 1***). With regard to the statistical properties, in the original studies sensitivity and specificity were the following: HNRC: 78%-85%; BNCS: 65%-72%; NEU: 74%-81%. However, when the American-population-based methods were replicated in our European sample of patients, the specificity increased in both of them, although the sensitivity decreased: BNCS: 66%-85%; HNRC: 47%-91% (***Table 2***).

Table 1. *Study and assessment characteristics of the 3 methods.*

	Main study characteristics				*Assessment characteristics*				
	Multicenter	Region	Race	N	# Areas	# Scores	Instrumental required	Paper-based use	Approximate duration
HNRC Screening	-	North America	Caucasian (63%)	190	2	2	Yes	-	10'
BNCS	Yes	North America	Caucasian (60%)	301	2	3	-	Yes	10'
NEU Screening	Yes	West Europe	Caucasian (93%)	106	3	3	-	Yes	10'

Table 2. *Statistical properties according to the original and the European samples.*

	Original studies				*European sample*			
	Sensitivity	Specificity	Predictive Positive Value	Correct classification	Sensitivity	Specificity	Predictive Positive Value	Correct classification
HNRC Screening	78%	85%	68%	-	47%	91%	82%	69%
BNCS	65%	72%	-	68%	66%	85%	80%	76%
NEU Screening	74%	81%	79%	78%	74%	81%	79%	78%

Information omitted was not reported by authors in the original studies.

Conclusions

✓ Brief tools proposed for the screening of NCI in HIV infection present similar characteristics, particularly in terms of the number of areas assessed and scores used, but also based on the approximate time of application.

✓ Nonetheless, the statistical properties shown by each of them may differ according to the populations studied, and mainly depending on country-based cultural discrepancies.

✓ Differently to methods validated in North America, the NEU screening appears to offer better properties in European HIV population, although this should be confirmed in larger cohorts.

Acknowledgements:

We would like to sincerely thank the collaboration offered by the rest of colleagues in the ***NEU Study Group****:*

- Lluita contra la SIDA Foundation (Barcelona, Catalonia, Spain):
Inma Nieto-Verdugo, Marian González-García, Jessica Toro and Albert Tuldrá

- Autònoma de Barcelona University (Barcelona, Catalonia, Spain):
Eduardo Doval

This work was partially supported by ***FIPSE*** *(Fundación para la Investigación y la Prevención del SIDA en España, grant 24673/07), the Spanish AIDS network* ***RIS*** *(Red Temática Cooperativa de Investigación en SIDA, RD06/0006), and a research grant from* ***ViiV Healthcare****.*

Comparison of 3 Screening Methods: HNRC, BNCS and NEU

	Main study characteristics			
	Multicenter	Region	Race	N
HNRC Screening	-	North America	Caucasian (63%)	190
BNCS	Yes	North America	Caucasian (60%)	301
NEU Screening	Yes	West Europe	Caucasian (93%)	106

	Assessment characteristics				
	# Areas	# Scores	Instrumental required	Paper-based use	Approximate duration
HNRC Screening	2	2	Yes	-	10'
BNCS	2	3	-	Yes	10'
NEU Screening	3	3	-	Yes	10'

	Original studies				*European sample*			
	Sensitivity	Specificity	Predictive Positive Value	Correct classification	Sensitivity	Specificity	Predictive Positive Value	Correct classification
HNRC Screening	*78%*	*85%*	*68%*	-	*47%*	*91%*	*82%*	*69%*
BNCS	*65%*	*72%*	-	*68%*	*66%*	*85%*	*80%*	*76%*
NEU Screening	*74%*	*81%*	*79%*	*78%*	*74%*	*81%*	*79%*	*78%*

Abstract # 480

CROI 2014
March 3 to March 6, 2014
Boston, Massachusetts

Accuracy of the NEU Screen Detecting Cognitive Impairment in Virologically Suppressed Patients with HIV Infection

Jose A. Muñoz-Moreno[1,2], Anna Prats[1,2], Núria Pérez-Álvarez[1,3], Carmina R. Fumaz[1,2], Maria J. Ferrer[1,2], Maite Garolera[4,5], Bonaventura Clotet[1,6,7]

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FUNDACIÓ LLUITA CONTRA LA SIDA
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BACKGROUND

- ✓ Several methods have been proposed to screen for neurocognitive impairment (NCI) in HIV infection, although none of them has achieved a clear consolidation for its use in the clinical practice[1].
- ✓ There is a disparity in terms of potential advantages of these tools, mainly according to the time for administration, instrumental requirements, and the accuracy to screen for impairment[2].
- ✓ The NEU Screen has been recently presented, a tool including 3 cognitive measures with a sensitivity of 74.5% and specificity of 81.8% detecting NCI in HIV population[3].
- ✓ This method is rapid to apply (≤10 minutes for administration), has no copyrights limitations, and is based on a pencil-and-paper use.
- ✓ In this work we aimed to study the accuracy of the NEU Screen detecting NCI in virologically suppressed patients with HIV, and also according to distinct patient profiles.

References:

[1] Valcour V, et al. Screening for cognitive impairment in human immunodeficiency virus. Clin Infect Dis 2011 Oct; 53 (8): 836-42.

[2] Mind Exchange Working Group. Assessment, diagnosis, and treatment of HIV-associated neurocognitive disorder: a consensus report of the mind exchange program. Clin Infect Dis. 2013 Apr;56(7):1004-17.

[3] Muñoz-Moreno et al. A brief and feasible paper-based method to screen for neurocognitive impairment in HIV-infected patients: the NEU screen. J Acquir Immune Defic Syndr. 2013 Aug 15;63(5):585-92.

METHODS

Study Population:
Data from 156 HIV-infected outpatients receiving care in he HIV Unit of the Germans Trias i Pujol University Hospital (Barcelona, Catalonia, Spain) were used for these analyses. They were selected because were ≥18 years old, had undetectable plasma viral load for ≥6 months prior the study assessments, and had not participated in the original study of the NEU proposal.

Study Variables:
Neurocognitive functioning was assessed by the application of a standard comprehensive battery of neuropsychological tests (15 measures, 7 domains). Demographic and clinical variables were also recorded. NCI was defined as performing ≥1 standard deviation below the normative mean in ≥2 cognitive areas. T scores were used for all comparisons and were based on available normative data.

Statistical Analyses:
NCI was considered as gold standard, and sensitivity and specificity tests were applied to study the accuracy of the NEU Screen. A proposal of an abbreviated battery also offered in the NEU Study was additionally tested (7 scores, 7 domains). Logistic regression was used to analyze variables linked to the correct classification. In this regard, we joined the sample of the NEU Study and the sample of the present work to investigate possible links more consistently. In order to study distinct patient profiles in which NCI could be more optimally identified, we also developed analyses in sub-groups of patients separated by representative demographic and clinical factors.

RESULTS

- Subjects were mostly men (81%), getting infected having sex with other men (47%), with a median (interquartile range) age of 43 (38;50) years, current CD4 count of 522 (380;718) cells/μL, and nadir CD4 count of 188 (80;285) cells/μL. The remaining demographic and clinical characteristics are displayed in ***Table 1***.

Table 1. *Characteristics of the study sample.*

	Study sample (N=156)
Age, years	43 (38 ; 50)
Gender, women (%)	29 (19)
Education, years	12 (8 ; 15)
Employed (%)	109 (70)
Homosexual infection route (%)	70 (47)
Time since HIV diagnosis, years	11 (6 ; 15)
Time since first antiretroviral treatment, years	8 (4 ; 11)
Time on current treatment, months	14 (51 ; 139)
Current CD4 cell count, cells/μL	522 (380 ; 718)
Nadir CD4 cell count, cells/μL	188 (80 ; 285)
Zenith plasma viral load, copies/mL	87500 (15750 ; 214000)
AIDS condition (%)	24 (16)
Coinfection with HCV (%)	31 (21)
Potential comorbidities for NCI (%)	42 (27)

Data expressed as medians (interquartile range) except when specified.

- NCI was present in 82 (52%) individuals, of whom 42 (54%) reported cognitive complaints. Rate of impairment was significantly related to time since HIV diagnosis (p=0.01).
- The sensitivity and specifity found for the NEU Screen were 73.1% and 74.3%, respectively, and positive predictive value (PPV) 75.9% and negative predictive value (NPV) 71.4%. When the NEU abbreviated battery was analyzed the sensitivity obtained was 97.5%, the specificity 100%, PPV 100%, and NPV 97.3% (***Table 2***).

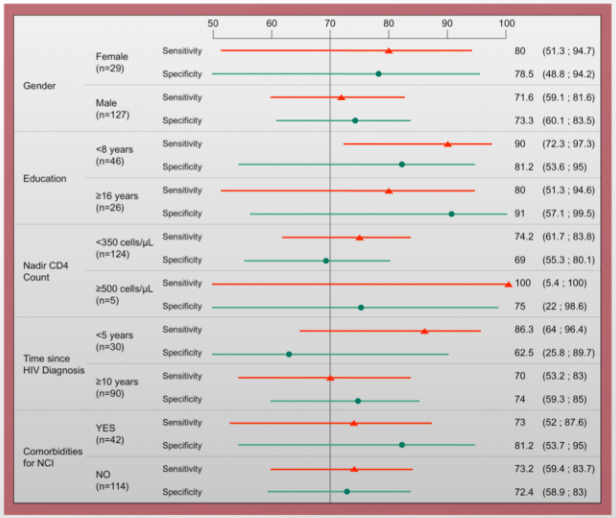
Table 2. *Accuracy of the NEU Screen and the NEU abbreviated battery.*

	Characteristics
NEU Screen	
Sensitivity	73.1 (62 ; 82)
Specificity	74.3 (62.6 ; 83.4)
PPV	75.9 (64.7 ; 84.5)
NPV	71.4 (59.8 ; 80.8)
NEU Abbreviated Battery	
Sensitivity	97.5 (90.6 ; 99.5)
Specificity	100 (93.8 ; 99.8)
PPV	100 (94.2 ; 99.8)
NPV	97.3 (89.9 ; 99.5)

Data expressed as values (95% CI).

- According to logistic regression models none of the demographic or clinical variables were significantly associated with the correct classification. When the NEU Study sample and the present were joined (262 subjects), analyses still did not find any factor in association.

Figure 1. *Accuracy of the NEU Screen according to representative variables.*



Data expressed as values (95% CI).

- When different sub-groups were compared in terms of representative demographic and clinical variables, the highest accuracies were observed in women (sensitivity: 80%, specificity: 78.5%); patients with <8 (90%, 81.2%) or ≥16 (80%, 91%) years of education; and <5 years since HIV diagnosis (86.3%, 62.5%), as shown in ***Figure 1***.

CONCLUSIONS

- ✓ The present work confirms fairly high sensitivity and specificity of the NEU Screen detecting NCI in virologically suppressed HIV-infected patients.
- ✓ This method includes 3 cognitive tests, has an expected time for administration of ≤10 minutes, and is based on a pencil-and-paper use.
- ✓ Demographic and clinical factors, such as gender, education level or immunological status, may play a relevant role in the accuracy of screening tools when detecting NCI in people with HIV.

ACKNOWLEDGEMENTS

FLS FUNDACIÓ LLUITA CONTRA LA SIDA · Germans Trias i Pujol Hospital · UAB Universitat Autònoma de Barcelona · UPC · CST Consorci Sanitari de Terrassa · IrsiCaixa · Universitat de Barcelona · UVIC UNIVERSITAT DE VIC

Optimal Moment to Screen

Q3 Which tools should be used to screen for HAND?

- **No single HAND screening tool** is suitable for use across all practice settings, and these scales can not assist in differentiating impairment related to HIV from that related to other conditions *(CEBM 1b; GOR B)*.
- The **HIV Dementia Scale (HDS) and The International HIV Dementia Scale (IHDS)** are the most widely used rapid screening tools for HAND.
- **Computerised screening tests** are available and can be considered where resources are available. The **CogState** *(CEBM 1b)*, **the CAMCI** *(CEBM 1b)* **and the CANTAB** *(CEBM 1b)* have undergone validation studies in HIV.
- With expertise of a neuropsychologist and suitable population norms, brief screening instruments consisting of a combination of **two neuropsychological tests** may be considered; these have shown good sensitivity, including milder forms of HAND *(CEBM 2b; GOR B)*.

Optimal Moment to Screen

Q3 Which tools should be used to screen for HAND?

- A **diagnosis of HAND** can only be made after conducting a complete **medical history, neurological examination and neuropsychological testing** *(CEBM 5; GOR D)*.
- **Several screening tools** are available. The choice depends on:

  a. Whether the **expertise** of a neuropsychologist is available.
  b. Whether the clinician wants to screen for **HAD or 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.

- Screening tools should not be used in **isolation of clinical factors**. Screening tests are not a substitute for detailed neuropsychological testing *(CEBM 2b; GOR B)*.

5. Other Recommendations to Consider?

Final Considerations

- *Other Relevant Variables to Consider.*

Additional Variables Recommended to Control

Updated research nosology for HIV-associated neurocognitive disorders

Neurology 69 October 30, 2007

A. Antinori, MD
G. Arendt, MD
J.T. Becker, PhD
B.J. Brew, MBBS, MD, FRACP
D.A. Byrd, PhD
M. Cherner, PhD
D.B. Clifford, MD
P. Cinque, MD, PhD
L.G. Epstein, MD
K. Goodkin, MD, PhD
M. Gisslen, MD, PhD
I. Grant, MD
R.K. Heaton, PhD
J. Joseph, PhD
K. Marder, MD, MPH
C.M. Marra, MD
J.C. McArthur, MBBS, MPH
M. Nunn, PhD
R.W. Price, MD
L. Pulliam, PhD
K.R. Robertson, PhD
N. Sacktor, MD
V. Valcour, MD
V.E. Wojna, MD

Additional Variables Recommended to Control

Q4 How should I approach screening and differential diagnosis of HAND co-morbidities?

- Numerous **co-morbidities can co-exist with HAND** and contribute to neurocognitive impairment in people with HIV. Broad guidance may be found in Antinori et al., 2007 *(CEBM 5; GOR D)*.

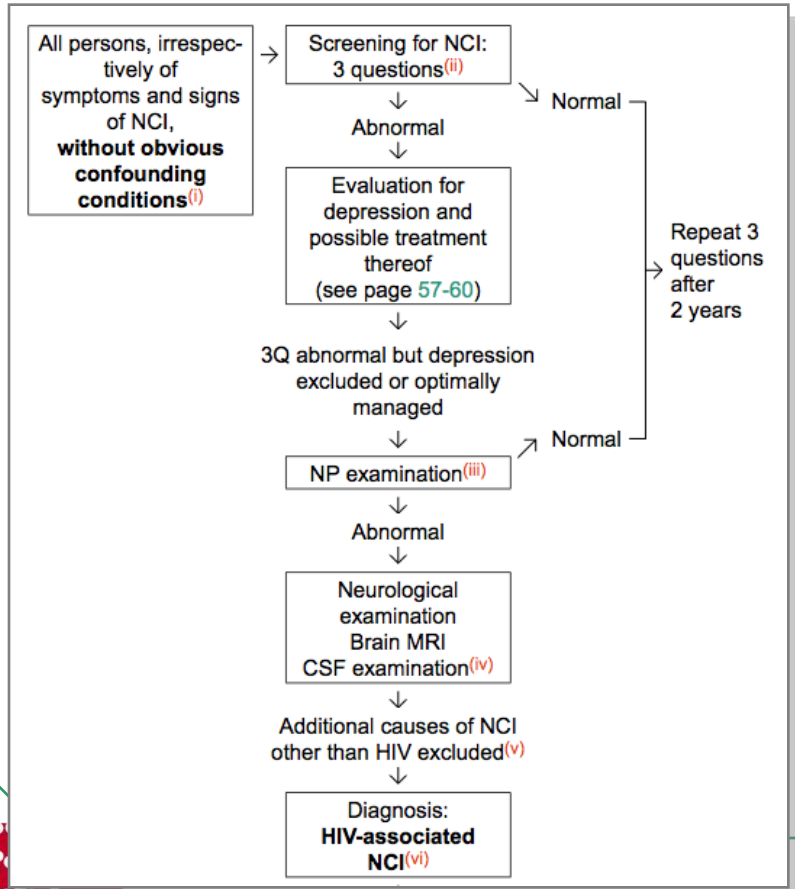
  a. **Psychiatric illnesses**, particularly major depressive disorder (MDD), anxiety and post traumatic stress disorder *(CEBM 1b; GOR A)*.
  b. **Prescription drugs** *(CEBM 2b; GOR C)*.
  c. **Syphilis, opportunistic infections (OI) and other HIV-related CNS disorders** *(CEBM 2b; GOR C)*.
  d. **Cerebrovascular disease and metabolic syndrome** *(CEBM 1b; GOR B)*.
  e. Other **chronic neurological disorders** *(CEBM 1b; GOR B)*.

Final Considerations

- *Other Relevant Variables to Consider.*
- *International Recommendations as a Help.*

International Recommendations

EACS, 2013



Mind Exchange, 2013

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?

Spanish Clinical Guidelines

Consensus Report on the Clinical Management of

HIV-Associated Neurocognitive Disorders (HAND)

GeSIDA Grupo de Estudio del SIDA-SEIMC

GOBIERNO DE ESPAÑA · MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

INDEX

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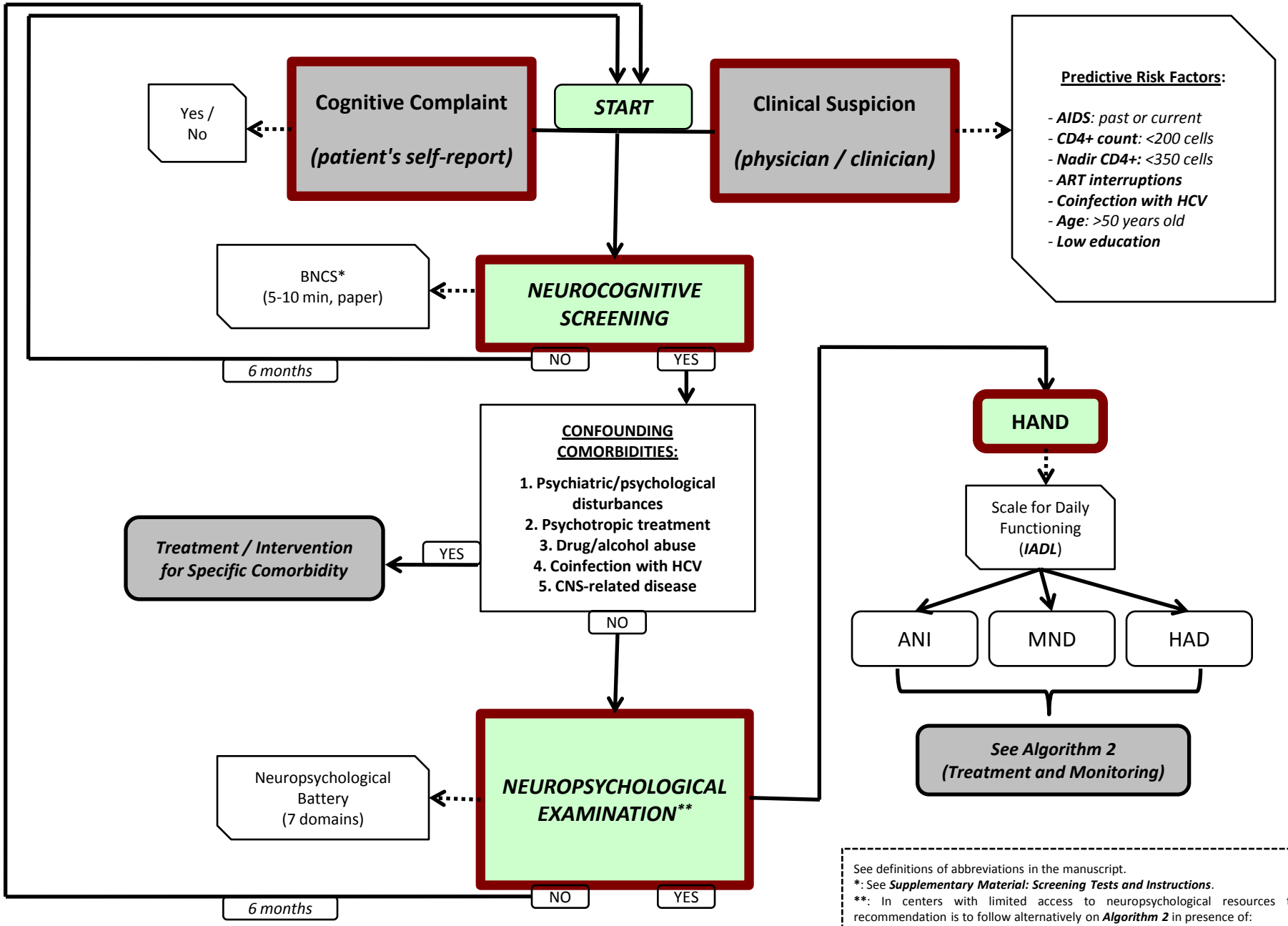
ALGORITHM 1. Screening, assessment and diagnosis of HIV-Associated Neurocognitive Disorders (HAND).



See definitions of abbreviations in the manuscript.
*: See ***Supplementary Material: Screening Tests and Instructions***.
: In centers with limited access to neuropsychological resources the recommendation is to follow alternatively on ***Algorithm 2* in presence of:
1) Cognitive Complaint + 2) Clinical Suspicion + 3) Positive Sreening.

Final Considerations

- *Other Relevant Variables to Consider.*
- *International Recommendations as a Help.*
- *Cost-Benefit Issues.*

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Key Cost-Benefit Aspects

Neuropsychiatric disorders in HIV infection: impact of diagnosis on economic costs of care

Helen Yeung[a], Hartmut B. Krentz[b,c], M. John Gill[c] and Christopher Power[d,e]

AIDS 2006, **20**:2005–2009

Objective: To investigate the added direct costs of medical care for patients with and without NPD.

Methods: Nine dimensions of patient-specific costs [as costs per patient per month (CPM)] were followed prospectively between 1997 and 2003 in a community-based HIV/AIDS clinic for HIV-1-seropositive patients with a diagnosis of NPD (n = 188) and without (n = 153). Patients with NPD were stratified into subgroups of cognitive impairment (CI), peripheral neuropathies (PN), or other neuropsychiatric disorders (OND).

Conclusions: Neuropsychiatric disorders in patients with HIV/AIDS increase medical costs both before and after diagnosis, primarily owing to the management of the neuropsychiatric illness. Cost analyses offer useful measures of evolving patient needs, and provide a basis for allocation of healthcare resources.

Key Cost-Benefit Aspects

OC5

IMPACT OF HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS ON HEALTH STATUS, QUALITY-ADJUSTED LIFE YEARS AND MEDICAL COSTS USING THE HEALTH UTILITIES INDEX: RESULTS FROM THE OHTN COHORT STUDY

S.B. Rourke[1,2,3], A. Rachlis[4], J. Gill[5], A. Carvalhal[2,3], J. McCombe[6], C. Kovacs[7], J. Brunetta[7], G. Arbess[2], A. Burchell[1,3], J. Raboud[8], R. Rosenes[1], R. Reinhard[1], T. Bekele[2], S. Choi[2,3], T. Marcotte[9] and the Centre for Brain Health in HIV/AIDS

Objectives: HIV-associated neurocognitive disorders (HAND) and -related medical comorbidities can significantly affect overall health status, health-related quality of life (HRQOL), and quality-adjusted life years (QALYs). The health economics of these conditions have not received much attention although recent work in Canada has shown a considerable incremental medical cost associated with HAND (Yeung et al, 2005). With increasing demand on health care resource allocation, it is important to understand the contributions of these conditions to health care services and costs. Our objective was to examine the contribution of HAND and medical comorbidities to health status, QALYs, and medical costs in people with HIV.

Conclusions: Our results indicate that the presence of HAND (specifically MND and HAD), and their associated medical co-morbidities, have a significant impact on HRQOL, QALYs, and health care costs. Effective clinical management of HAND and related medical co-morbidities could lead to significant benefits on QALYs gained and considerable potential savings in medical costs.

CONCLUSIONS

CONCLUSIONS

- ✓ *There are several relevant reasons to screen for NCI in HIV population, although currently there is a significant lack of studies assessing its benefits or possible impact.*

CONCLUSIONS

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- ✓ *Screening for NCI should be complemented with screening of other significant conditions, mainly emotional status and confounding comorbidities.*

Thanks for your attention!

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