4th International Symposium on

Psychiatry

HIV

Psiquiatría VIH

Barcelona, May 5th and 6th 2011

Neurocognitive Testing in HIV Infection:

How to Implement this Assessment in the Clinical Practice?

Jose A. Muñoz-Moreno

- - -

Lluita contra la SIDA Foundation

Germans Trias i Pujol University Hospital

- - -

Barcelona, Catalonia, Spain

Why to Assess?

Which Tools?

Which Patients and When Monitoring?

Why to Assess?

Main Reasons

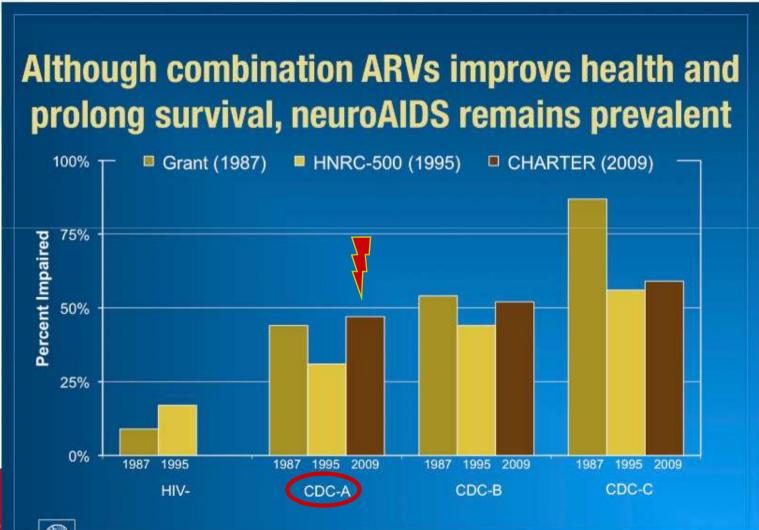☑ High and Unexpected Incidence and Prevalence

☑ Associated with Several Negative Consequences

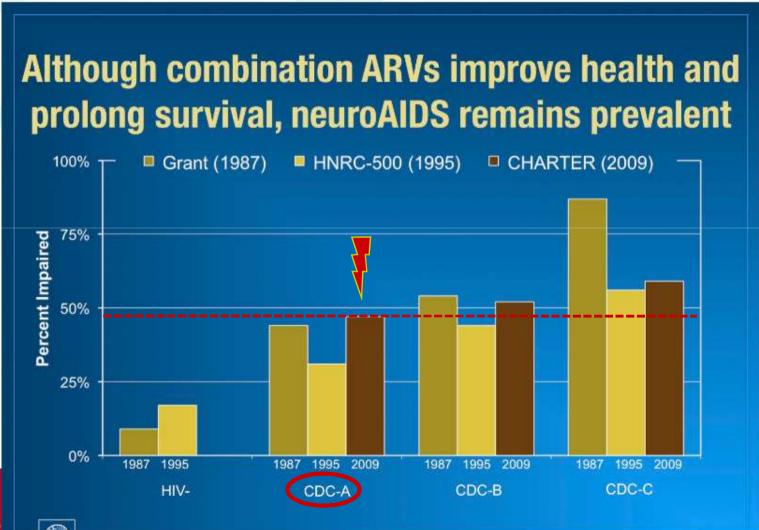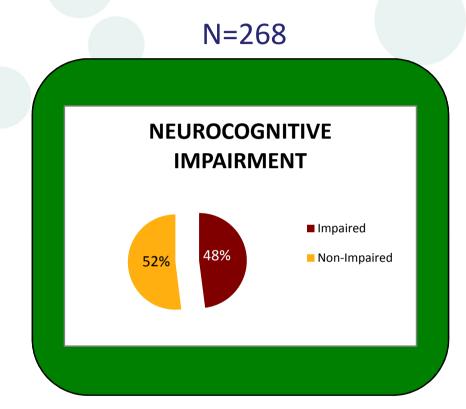☑ Significant Lack of Effective Treatments!

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Prevalence of HIV-Associated NCI

Although combination ARVs improve health and prolong survival, neuroAIDS remains prevalent

Legend: Grant (1987) ■ HNRC-500 (1995) ■ CHARTER (2009)

Y-axis: Percent Impaired (100%, 75%, 50%, 25%, 0%)

X-axis groups: HIV- (1987, 1995), CDC-A (1987, 1995, 2009), CDC-B (1987, 1995, 2009), CDC-C (1987, 1995, 2009)

HIV NEUROBEHAVIORAL RESEARCH CENTER | UNIVERSITY OF CALIFORNIA, SAN DIEGO

HNRC   UCSD

FLS   www.flsida.o

Prevalence of HIV-Associated NCI

And in Spain??

N=268

N=142

NEUROCOGNITIVE IMPAIRMENT

- Impaired
- Non-Impaired

52% 48%

100%

75%

50%

25%

0%

48,93%

56,25%

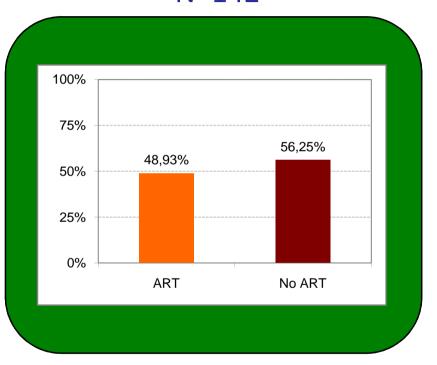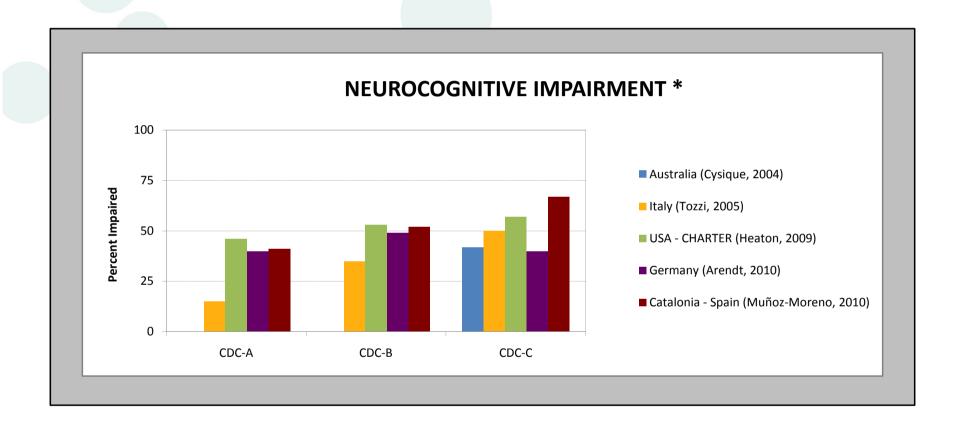ART   No ART

Muñoz-Moreno et al, 10th International Symposium on Neurovirology, Milan, 2010

Muñoz-Moreno et al, Mid-Year INS, Helsinki, 2009

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Confirming Data

NEUROCOGNITIVE IMPAIRMENT *

Legend:
- Australia (Cysique, 2004)
- Italy (Tozzi, 2005)
- USA - CHARTER (Heaton, 2009)
- Germany (Arendt, 2010)
- Catalonia - Spain (Muñoz-Moreno, 2010)

Muñoz-Moreno et al, 10th International Symposium on Neurovirology, Milan, 2010

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Confirming Data

NEUROCOGNITIVE IMPAIRMENT *

Percent Impaired

- Australia (Cysique, 2004)
- Italy (Tozzi, 2005)
- USA – CHARTER (Heaton, 2009)
- Germany (Arendt, 2010)
- Catalonia – Spain (Muñoz-Moreno, 2010)

CDC-A   CDC-B   CDC-C

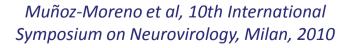*Muñoz-Moreno et al, 10th International Symposium on Neurovirology, Milan, 2010*
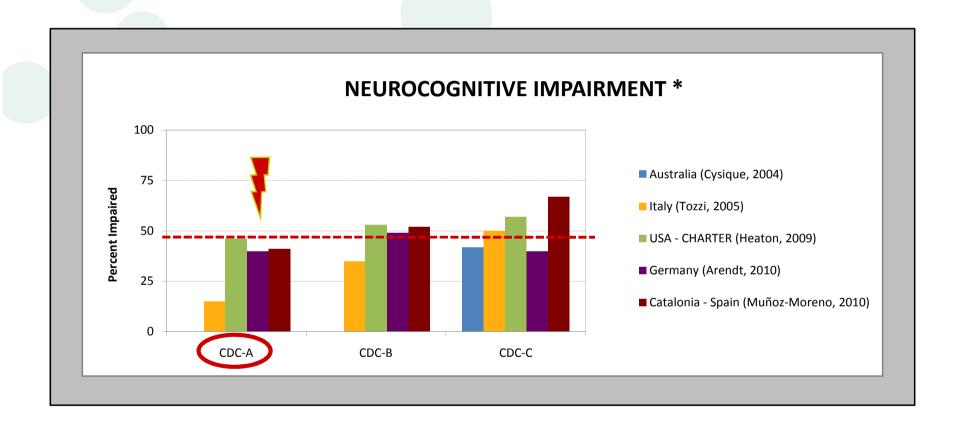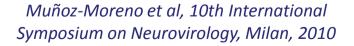
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Leading to Negative Consequences...

☞ Worse Quality of Life

Tozzi, 2003

☞ Interference on Daily Living Activities

Heaton, 2004

☞ Worse Adherence to Antiretroviral Treatment

Woods, 2009

☞ More Frequent Virological Failure

Tozzi, 2003

☞ Predictor of Higher Death Rates

Sevigny, 2007

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Interventions

NEUROACTIVE ARV DRUGS

NON-NEUROACTIVE ARV DRUGS

Letendre et al, Enhancing ART for HIV Cogntive Disorders, Ann Neurol, 2004

Giancola et al, Neuroactive ART Drugs Do Not Influence NC Performance, JAIDS, 2006

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Insufficient Although Growing Evidence...

	Cysique	Tozzi	Ellis	Marra
Study	*UCSD CIT*	*NIID*	*ALLRT*	*ACTG 736*
Sample Size	*37*	*185*	*2,636*	*26*
Prospective	Yes	Yes	Yes	Yes
Controlled	*No*	*No*	*No*	*No*
Number of NP Tests	6	15	3	4
CPE: CSF VL	***Lower VL***	*No CSF*	*No CSF*	***Lower VL***
CPE: NP Tests	***Better***	***Better***	***Better***	***Worse***
Used Norms for NP Change	**Yes**	No	No	No

Cysique et al, Neurology 2009, 73(5):342-8; Tozzi et al, J Acquir Immune Defic Syndr 2009;52:56–63; Ellis et al, Annual Meeting American Neurological Association 2009; Marra et al, AIDS 2009, 23(11):1359-66

*: Courtesy of Dr. Letendre

Other ARV Approaches

Nadir CD4 Cell Count Predicts Neurocognitive Impairment in HIV-Infected Patients

Jose A. Muñoz-Moreno,[1,2] Carmina R. Fumaz,[1,2] Maria J. Ferrer,[1,2] Anna Prats,[1,2] Eugènia Negredo,[1,2] Maite Garolera,[3] Núria Pérez-Álvarez,[1,4] José Moltó,[1,2] Guadalupe Gómez,[4] and Bonaventura Clotet[1,2,5]

Muñoz-Moreno, et al, 2008

TABLE 2. NEUROCOGNITIVE IMPAIRMENT BY NADIR CD4 CELL COUNT CUTOFF			
	No. of patients	% of impaired patients (n)	p value
Nadir CD4 cutoff 200 cells/ml			
Nadir ≤200	26	73.1 (19)	0.12
Nadir >200	38	52.6 (20)	
Nadir CD4 cutoff 250 cells/ml			
Nadir ≤250	33	66.7 (22)	0.31
Nadir >250	30	53.3 (16)	
Nadir CD4 cutoff 300 cells/ml			
Nadir ≤300	36	63.9 (23)	0.59
Nadir >300	23	56.5 (13)	
Nadir CD4 cutoff 350 cells/ml			
Nadir ≤350	35	57.1 (20)	0.76
Nadir >350	16	62.5 (10)	

Other ARV Approaches

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Poster # 429   Ronald J. Ellis | 220 Dickinson St., Suite B, MC 8231 | San Diego, CA 92103 | Phone: 619-543-5079 | Fax: 619-543-4744 | roellis@ucsd.edu

Higher CD4 Nadir is Associated with Reduced Rates of HIV-Associated Neurocognitive Disorders in the CHARTER Study:
Potential Implications for Early Treatment Initiation

Ronald J. Ellis, M.D., Ph.D.[1], Robert K. Heaton, Ph.D.[1], Scott Letendre, M.D.[1], Jayraan Badiee, M.P.H.[1], Jose A. Muñoz-Moreno, M.S.[1], Florin Vaida, Ph.D.[1], David B. Clifford, M.D.[2], Benjamin B. Gelman, M.D., Ph.D.[3],
David M. Simpson, M.D.[4], Igor Grant, M.D.[1], for the CHARTER Group
[1]University of California, San Diego; [2]Washington University, St. Louis; [3]University of Texas Medical Branch, Galveston; [4]Mount Sinai School of Medicine

CHARTER

CNS HIV ANTI-RETROVIRAL THERAPY EFFECTS RESEARCH

Muñoz-Moreno,
et al, 2008

Ellis, CROI, 2010

TABLE 2.   NEUROCOGNITIVE IMPAIRMENT BY NADIR CD4 CELL COUNT CUTOFF

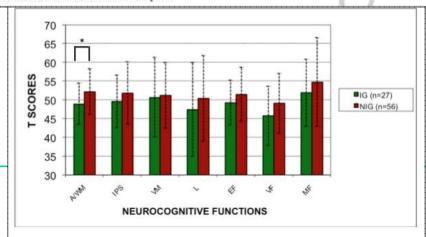|	No. of patients	% of impaired patients (n)	p value
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Other ARV Approaches

Interruptions of antiretroviral therapy in human immunodeficiency virus infection: are they detrimental to neurocognitive functioning?

Jose A. Muñoz-Moreno,[1,2] Carmina R. Fumaz,[1,2] Anna Prats,[1,2] Maria J. Ferrer,[1,2] Eugènia Negredo,[1,2] Núria Pérez-Álvarez,[1,3] José Moltó,[1,2] Guadalupe Gómez,[3] Maite Garolera,[4] and Bonaventura Clotet[1,2,5]

[1]Lluita contra la SIDA Foundation, Germans Trias i Pujol University Hospital, Badalona, Barcelona, Catalonia, Spain; [2]Autònoma de Barcelona University, Barcelona, Catalonia, Spain; [3]Politècnica de Catalunya University, Barcelona, Catalonia, Spain; [4]Consorci Sanitari de Terrassa Hospital, Terrassa, Barcelona, Catalonia, Spain; and [5]IrsiCaixa Foundation, Badalona, Barcelona, Catalonia, Spain

Muñoz-Moreno, et al, 2010

ARV Treatment Guidelines!

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

December 1, 2009

Developed by the DHHS Panel on
Antiretroviral Guidelines for Adults
and Adolescents – A Working Group of the
Office of AIDS Research Advisory Council (OARAC)

How to Cite the Adult and Adolescent Guidelines:
Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009; 1-161. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed (insert date) [insert page number, table number, etc. if applicable]

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the AIDS*info* Web site (http://aidsinfo.nih.gov).

Neurocognitive decline

Early in the HIV epidemic, HIV was identified in brain tissue [57] and assumed to be the cause of AIDS dementia complex [58]. The improvement of AIDS dementia complex symptoms with the use of antiretroviral therapy supported this assumption [59-60]. The CASCADE observational cohort reported a dramatic decline in the incidence of HIV-associated dementia from 6.49 per 1,000 person-years (before 1997) to 0.66 per 1,000 person-years (2003–2006), after the widespread use of potent antiretroviral therapy [61]. In this cohort, having a current CD4 count >350 cells/mm³ was associated with the lowest risk of developing HIV-associated dementia. HIV infection has also been associated with a number of less severe neurologic complications, including changes in neuropsychological ability, speed of processing, and everyday functioning [62]. Such syndromes also were predicted by a lower pretherapy CD4 nadir and/or by CD4 count while on therapy [63-64]. Additional clinical data are needed to determine the relative roles of ongoing HIV replication and potential neurotoxicity of antiretroviral agents in the development of neurocognitive dysfunction. Whether early initiation of therapy will prevent HIV-associated neurocognitive dysfunction remains unclear. However, the neurological complications that may accompany uncontrolled HIV replication and CD4 depletion suggest a potential benefit of earlier initiation of antiretroviral therapy **(CIII)**.

64. Munoz-Moreno JA, Fumaz CR, Ferrer MJ, et al. Nadir CD4 cell count predicts neurocognitive impairment in HIV-infected patients. *AIDS Res Hum Retroviruses*. 2008;24(10):1301-1307.
65. The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study group. Response to combination antiretroviral therapy: variation by age. *AIDS*. 2008;22(12):1463-1473.
66. Nogueras M, Navarro G, Anton E, et al. Epidemiological and clinical features, response to HAART, and survival in HIV-infected patients diagnosed at the age of 50 or more. *BMC Infect Dis*. 2006;6:159.
67. Bosch RJ, Bennett K, Collier AC, et al. Pretreatment factors associated with 3-year (144-week) virologic and immunologic responses to potent antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2007;44(3):268-277.
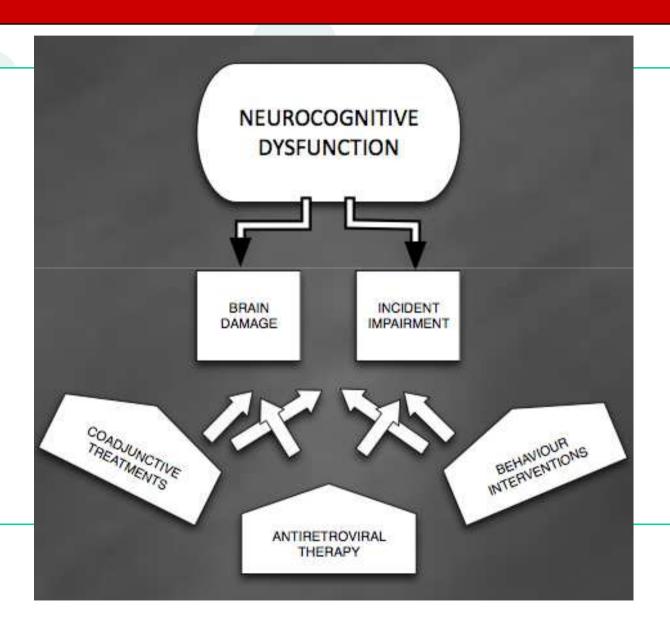
Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents (DHHS). December 2009:
http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

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Therapeutical Approach

Which Tools?

Comprehensive Batteries of Neuropsychological Tests

Table 5. Ability domains recommended for HIV-related neuropsychological assessment and examples of most common neuropsychological tests

Ability Domain / Tests

Premorbid Intelligence
- Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) Vocabulary Test [16]
- National Adult Reading Test (NART) Full IQ Scale (FIQS) [17]

Attention/Working Memory
- California Computerized Assessment Package (CalCAP) [18]
- Paced Auditory Serial Addition Task (PASAT) [19]
- WAIS-III Digits Test [16]
- WAIS-III Letter-Numbers Test [16]
- Continuous Performance Tests - Second Edition (CPT-II) [20]

Information Processing Speed
- Trail Making Tests (TMT) - Part A [21]
- Symbol Digit Modalities Test (SDMT) [22]
- CalCAP [18]

Motor Function
- Grooved Pegboard Test (GPT) [23]
- Electronic Tapping Test (ETT) [24]

Learning/Memory
- California Verbal Learning Test - Second Edition (CVLT-II) [25]
- Rey Auditory Verbal Learning Test [26]
- Wechsler Memory Scale - Revised (WMS-R) [27]

Visual Memory
- Rey Complex Figure Test [28]
- Modified Visual Reproduction Test [29]
- WMS-R [27]

Visuoconstruction
- Rey Complex Figure Test [28]
- WAIS-III Block Design Test [16]

Executive Functions
- Stroop Test [30]
- TMT - Part B [21]
- Wisconsin Card Sorting Test (WCST) [31]
- Category Test [21]

Verbal Fluency
- Controllled Oral Word Association (COWAT) [32]
- Animals Test [33]
- Boston Naming Test [34]

Emotional Status (Depression, Anxiety)
- Beck Depression Inventory - Second Edition (BDI-II) [35]
- State-Trait Anxiety Inventory (STAI) [36]
- Hamilton Depression Scale (HDS) [37]
- Hospital Anxiety Depression Scale (HADS) [38]
- Depression Anxiety Stress Scale (DASS) [39]

NEUROCOGNITIVE AND MOTOR DISORDERS IN HIV INFECTION. ASSESSMENT AND INTERVENTIONS

Jose A. Muñoz-Moreno•

Lluita contra la SIDA Foundation - HIV Unit, Germans Trias i Pujol University Hospital, Ctra. de Canyet, S/N 08916, Badalona, Barcelona, Catalonia, Spain.

Muñoz-Moreno JA, in Research Focus on Cognitive Disorders, NY, 2007

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Neurocognitive Areas and Tests

PROCESSING INFORMATION SPEED: → **- TMT-A: Trail Making Test - Part A**

MOTOR FUNCTION: → **- GPT: Grooved Pegboard Test**

VERBAL MEMORY: → **- CVLT-II: California Verbal Learning Test - II**

LEARNING:

- TMT-B: Trail Making Test - Part B

- WCST: Wisconsin Card Sorting Test

EXECUTIVE FUNCTIONS:

- Stroop's Test

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Motor Function

Grooved Pegboard Test

Matthews, 1964

Verbal Memory and Learning

California Verbal Learning Test - II
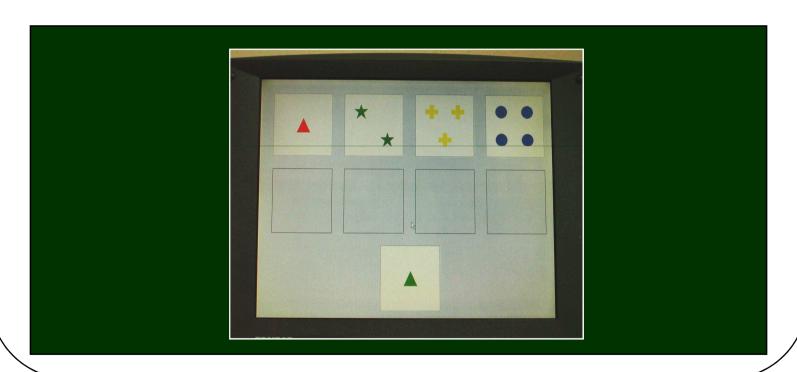
Delis, 2000

Executive Functioning

Wisconsin Card Sorting Test (WCST)

Kongs, 1993

Information Processing Speed
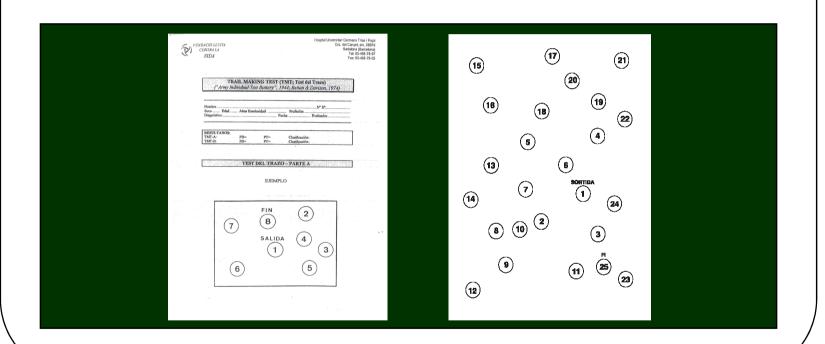
Trail Making Test - Part A (TMT-A)

Reitan, 1974
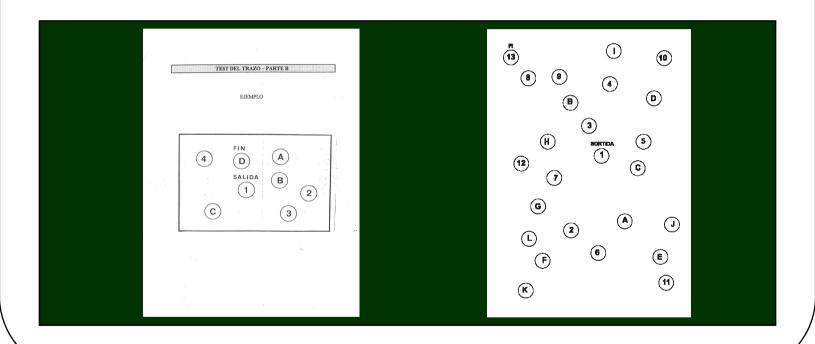
Executive Functioning

Trail Making Test - Part B (TMT-B)

Reitan, 1974
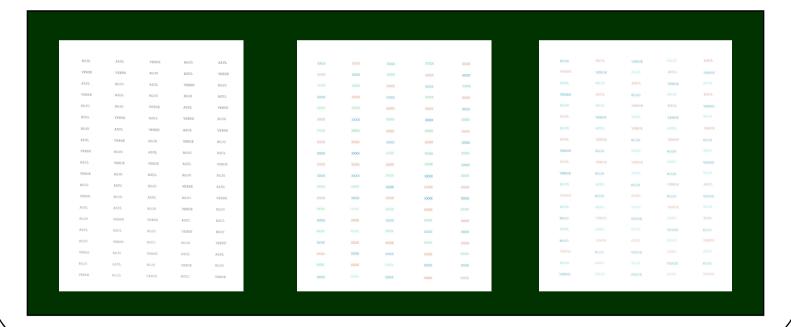
Executive Functioning

Stroop's Test

Golden, 1978

Requirements for Comprehensive NC Testing

- Recommendations by <u>Frascati Group</u>,
in
Antinori et al, Neurology, 2007:

1) Assessment of 7 recommended areas

2) Evaluation and control of demographic, clinical and emotional variables

3) Exclusion of conditions associated with NCI, currently or in past (confouding comorbidities!)

Confounding Factors

Neurology, 2007:

Table 1. Criteria for clinical diagnosis of central nervous system disorders in HIV-infected adults and adolescents

Table 2. HAND Criteria

Table 3. Examples of Tests

Table 4. Guidelines for classifying confounds to HIV-associated neurocognitive disorders

Confounding Factors

"Evidence of another etiology, including active CNS opportunistic infection or malignancy, psychiatric disorders (e.g., depressive disorder), active alcohol or substance use, or acute or chronic substance withdrawal, must be sought from history, physical and psychiatric examination, and appropriate laboratory and radiologic investigation (e.g., lumbar puncture, neuroimaging). If another potential etiology (e.g., major depression) is present, it is not the cause of the above cognitive, motor, or behavioral symptoms and signs."

Mainly:

- Drug abuse
- CNS opportunistic infections
- Psychatric or emotional disorders

Depression and Anxiety Symptoms

- Hospital Anxiety and Depression Scale (HADS):

Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983; 67: 361-370.

- Beck Depression Inventory (BDI):

Beck AT, Rush AJ, Shaw BF, and Emery G: *Cognitive Therapy of Depression*. Guilford Press, New York, 1979.

- State-Trait Anxiety Inventory (STAI):

Spielberger CD, Gorsuch RL, and Lushene RE: *Manual for the State-Trait Anxiety Inventory*. Consulting Psychologists Press, Palo Alto, CA, 1970.

Depression Symptoms

Hospital Anxiety and Depression Scale (HADS)

1. Me siento tenso o "nervioso"
   - O Todos los días
   - O Muchas veces
   - O A veces
   - O Nunca

2. Todavía disfruto con lo que antes me gustaba
   - O Como siempre
   - O No lo bastante
   - O Sólo un poco
   - O Nada

3. Tengo una sensación de miedo, como si algo horrible me fuera a suceder
   - O Definitivamente, y es muy fuerte
   - O Sí, pero no es muy fuerte
   - O Un poco, pero no me preocupa
   - O Nada

4. Puedo reírme y ver el lado divertido de las cosas
   - O Al igual que siempre lo hice
   - O No tanto ahora
   - O Casi nunca
   - O Nunca

5. Tengo mi mente llena de preocupaciones
   - O La mayoría de las veces
   - O Con bastante frecuencia
   - O A veces, aunque no muy a menudo
   - O Sólo en ocasiones

- 14 items
- 2 scales
- 1 total scale

Golden, 1978

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Depression Symptoms

Beck Depression Inventory (BDI)

1	☐	a	No me siento triste
	☐	b	Me siento triste
	☐	c	Siempre me siento triste, no puedo evitarlo
	☐	d	Me siento tan triste o infeliz que no puedo soportarlo
2	☐	a	No me siento especialmente desanimado ante el futuro
	☐	b	Me siento desanimado ante el futuro
	☐	c	No hay nada que me haga ilusión
	☐	d	Veo el futuro sin esperanza y creo que las cosas no pueden mejorar
3	☐	a	No me siento fracasado
	☐	b	Me siento más fracasado que la mayoría de la gente
	☐	c	Cuando recuerdo mi pasado no veo más que fracasos
	☐	d	Creo que soy un fracaso total como persona
4	☐	a	Disfruto de las cosas igual que siempre
	☐	b	No disfruto de las cosas como antes
	☐	c	Nada me produce verdadera satisfacción
	☐	d	Estoy insatisfecho o aburrido de todo
5	☐	a	No me siento especialmente culpable
	☐	b	Me siento culpable con frecuencia
	☐	c	Me siento culpable la mayor parte del tiempo
	☐	d	Me siento culpable todo el tiempo

- 21 items
- 1 scale
- 2 sub-scales

Golden, 1978

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Anxiety Symptoms

State-Trait Anxiety Inventory (STAI)

- 20 items

- 1 scale

Golden, 1978

Why Neurocognitive Testing??

PROS:

- Strongly recommended
- Large experience in clinical neuropsychology
- Experience in HIV infection
- Different areas potentially assessed
- Variable tools

CONS:

- Availability / feasibility
- Duration of evaluations

Neuropsychological Testing

PROS:

- Strongly recommended
- Large experience in clinical neuropsychology
- Experience in HIV infection
- Different areas potentially assessed
- Variable tools

CONS:

- Availability / feasibility
- Duration of evaluations

Recommendations

- National Institute of Mental Health, 1990

- American Tasks Force, 1991

- UNAIDS, 1997

- Antinori, 2007

- Significant number of reviews and studies recommending

Assessment of Aids-Related Cognitive Changes: Recommendations of the NIMH Workshop on Neuropsychological Assessment Approaches*

Janssen RS, Cornblath DR, Epstein LG, Foa RP, McArthur JC, Price RW, et al. **Nomenclature and research case definitions for neurological manifestations of human immunodeficiency virus type-1 (HIV-1) infection. Report of a Working Group of the American Academy of Neurology AIDS Task Force.** Neurology 1991; **41**:778–785.

UNAIDS Expert Consultation on Cognitive and Neuropsychological impairment in Early HIV infection

Updated research nosology for HIV-associated neurocognitive disorders

Neuropsychological Testing

PROS:

- Strongly recommended
- Large experience in clinical neuropsychology
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Clinical Neuropsychology

In multiple diseases regardless of HIV infection!

Pattern of neurocognitive alteration in...:

Multiple Sclerosis
Schizophrenia
Aging
Alzheimer's Disease
Parkinson's Disease
ETC, ETC...

Neuropsychological Testing

PROS:

- Strongly recommended
- Large experience in clinical neuropsychology
- Experience in HIV infection
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HIV Infection

PubMed:

Early publications: 1985-1987 (Grant et al, 1987)

"Evidence for early central nervous system involvement in the acquired immunodeficiency syndrome (AIDS) and other human immunodeficiency virus (HIV) infections. Studies with neuropsychologic testing and magnetic resonance imaging".

Currently: Neurocognitive + HIV: 357 studies / 75 reviews

Neuropsychological + HIV: 1014 studies / 129 reviews

Cognitive + HIV: 1934 studies / 357 reviews

Neuropsychological Testing

PROS:

- Strongly recommended
- Large experience in clinical neuropsychology
- Experience in HIV infection
- **Different areas potentially assessed**
- Variable tools

CONS:

- Availability / feasibility
- Duration of evaluations

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HIV-Associated Neurocognitive Profile

- Fronto-subcortical pattern, with altered areas well defined:

Attention / Working Memory   **Executive Functioning**
Information Processing Speed   **Verbal Fluency**
Learning   **Motor Function**
Verbal Memory

- Maybe currently is this changing??

Cortical hypothesis:

Brew, 2004
Valcour, 2006

Neuropsychological Testing

PROS:

- Strongly recommended
- Large experience in clinical neuropsychology
- Experience in HIV infection
- Different areas potentially assessed
- Variable tools

CONS:

- Availability / feasibility
- Duration of evaluations

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HAND Diagnosis:
HIV-Associated Neurocognitive Disorders

Updated research nosology for HIV-associated neurocognitive disorders

Antinori et al, Neurology, 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

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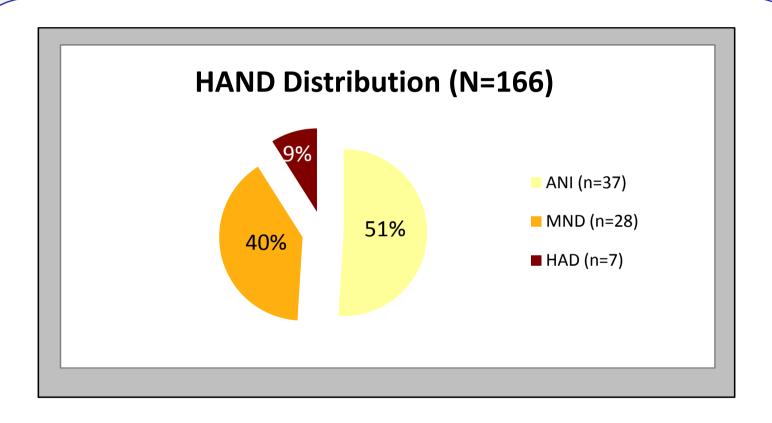
Diagnosis Establishment

	No Prior Cause	No Delirium	Acquired Impairment in ≥ 2 Functions	Daily Functioning Inerference / NC Complaint
1. Asymptomatic NC Impairment (ANI)	☑	☑	☑	No
2. Mild NC Disorder (MND)	☑	☑	☑	Mild
3. HIV-Associated Dementia (HAD)	☑	☑	Marked	Marked

HAND Distribution

HAND Distribution (N=166)

- ANI (n=37) — 51%
- MND (n=28) — 40%
- HAD (n=7) — 9%

Muñoz-Moreno et al, 10th International Symposium on Neurovirology, Milan, 2010

Neuropsychological Testing

PROS:

- Strongly recommended
- Large experience in clinical neuropsychology
- Experience in HIV infection
- Different areas potentially assessed
- Variable tools

CONS:

- Availability / feasibility
- Duration of evaluations

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Availability and Feasibility

MAIN LIMITATIONS:

- Need of a trained neuropsychologist

- Expertise and skills are relevant aspects in the application

- Multiple and variable instructions / correction processes

- Manipulative tools

- Duration of assessments (*next section*)

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Neuropsychological Testing

PROS:

- Strongly recommended
- Large experience in clinical neuropsychology
- Experience in HIV infection
- Different areas potentially assessed
- Variable tools

CONS:

- Availability / feasibility
- Duration of evaluations

Multiple Tools

NIMH, 1990: 2 recommendations

Extended: 7-9 hours of duration
Brief: 1-2 hours of duration

Nowadays...

Extended: 2-3 hours of duration
☞ Relevant need of screening tools!

SPECIAL PRESENTATION

Assessment of Aids-Related Cognitive Changes:
Recommendations of the NIMH Workshop on
Neuropsychological Assessment Approaches*

Nelson Butters, Igor Grant, James Haxby, Lewis L. Judd, Alex Martin,
Jay McClelland, Willo Pequegnat, Daniel Schacter, and Ellen Stover

ABSTRACT

This article presents an extended (7-9 hours) and a brief (1-2 hours) battery designed to evaluate early cognitive changes associated with seropositive, asymptomatic persons. The battery was recommended by an NIMH Workgroup which was guided by 10 principles in its development. The domains assessed by the battery are: (1) Indicators of Premorbid Intelligence; (2) Attention; (3) Speed of Processing; (4) Memory; (5) Abstraction; (6) Language; (7) Visuoperception; (8) Constructional Abilities; (9) Motor Abilities; and (10) Psychiatric Assessment. Although the battery assesses a wide range of psychological functioning, specific emphasis has been placed on divided and sustained attention as well as speed of processing and retrieval from working and long-term memory. Descriptions of both the traditional clinical tests and tasks used in cognitive psychology are provided. Although the Workgroup strongly recommends the use of the extended battery in order to

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What Do We Know About Screening Tools?

Test	Reference	Duration	Pros	Cons
HIV Dementia Scale (HDS)	*Power et al, JAIDS, 1995 **	10-15 min	- Instructions - Quantitative score	- Validated for dementia - Low sensitivity
HNRC Screening	*Carey et al, Clin Neuropsychol, 2004 **	10-15 min	- Duration	- Feasibility (pegboard) - Scarce information
CogState	*Cysique et al*, J Int Neuropsychol Soc , 2006 *	10-15 min	- Instructions - Statistical validation	- Feasibility? - Economical cost?
Brief Neurocognitive Screen	*Robertson et al, AIDS, 2007 **	10 min	- Duration - Feasibility (in paper)	- Scarce information
NEU Questionnaire	*Muñoz-Moreno et al (in development) **	25-30 min	- Instructions - Feasibility (in paper) - Statistical validation	*- Duration?* *- Statistical sensitivity?*

What Do We Know About Screening Tools?

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Brief Quantitative Instrument in Development

- NEU Instrument (Muñoz-Moreno, et al):

- Brief (25-30 minutes)

- Assessing 7 areas

- Not only a screening tool: quantitative outcomes

(adapted to HAND diagnosis)

- Printable

- Easy instructions and correction

Page 1

PRESENTACIÓN:

A continuación le presentamos el **Test NEU**, un instrumento que evalúa el funcionamiento neurocognitivo de personas infectadas con el VIH. Está compuesto por diferentes pruebas, las cuales evalúan 7 funciones neurocognitivas.

Por favor, siga atentamente las instrucciones que se detallan a continuación hasta llegar al final del documento.

DATOS DEL PACIENTE:

INICIALES:	FECHA:
ID:	

DATOS DEL EVALUADOR:

NOMBRE:	CARGO:
CENTRO:	

1

Page 2

1. PRUEBA DE MEMORIA Y APRENDIZAJE:

1º. Ensayo 1: "A continuación le leeré unas palabras. Cuando acabe me gustaría que me repitiera tantas palabras como le sea posible, teniendo en cuenta que el orden no importa".

2º. Antes de los ensayos 2, 3, 4 y 5: "Ahora le volveré a repetir las mismas palabras. Por favor, cuando acabe dígame tantas como le sea posible, teniendo en cuenta que ha de volver a decirme todas las que pueda, a pesar de que se las haya dicho antes, y sin importar el orden".

LISTA A	ENSAYO1	ENSAYO2	ENSAYO3	ENSAYO4	ENSAYO5
CAMIÓN					
ESPINACA					
JIRAFA					
ESTANTERÍA					
CEBOLLA					
MOTO					
CAMA					
CEBRA					
TREN					
SILLA					
AJO					
VACA					
ESCRITORIO					
BARCO					
ARDILLA					
COL					TOTAL
CORRECTAS					
Perseveraciones					
Intrusiones					

3º. "Ahora le leeré una lista de palabras totalmente diferente. Cuando acabe deberá decirme todas aquellas palabras que pueda sin tener en cuenta el orden".

LISTA B	ENSAYO 1
VIOLÍN	
PEPINO	
ELEFANTE	
ARMARIO	
NABO	
GUITARRA	
SÓTANO	
OVEJA	
CLARINETE	
GARAJE	
MAÍZ	
CONEJO	
PATIO	
SAXOFÓN	
TIGRE	
RÁBANO	
CORRECTAS	

2

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4º. Ahora se trata de hacer lo mismo que acaba de hacer, diciendo el color de la tinta, sin tener en cuenta lo que está escrito, lo más rápidamente que pueda". **45 segundos.**

ROJO	AZUL	VERDE	ROJO	AZUL
VERDE	VERDE	ROJO	AZUL	VERDE
AZUL	ROJO	AZUL	VERDE	ROJO
VERDE	AZUL	ROJO	ROJO	AZUL
ROJO	ROJO	VERDE	AZUL	VERDE
AZUL	VERDE	AZUL	VERDE	ROJO
ROJO	AZUL	VERDE	AZUL	VERDE
AZUL	VERDE	ROJO	VERDE	ROJO
VERDE	ROJO	AZUL	ROJO	AZUL
AZUL	VERDE	VERDE	AZUL	VERDE
VERDE	ROJO	AZUL	ROJO	VERDE
ROJO	AZUL	ROJO	VERDE	AZUL
VERDE	ROJO	AZUL	ROJO	VERDE
AZUL	AZUL	ROJO	VERDE	ROJO
ROJO	VERDE	VERDE	AZUL	AZUL
AZUL	AZUL	ROJO	VERDE	ROJO
ROJO	VERDE	AZUL	ROJO	VERDE
VERDE	ROJO	VERDE	AZUL	AZUL
ROJO	AZUL	ROJO	VERDE	ROJO
VERDE	ROJO	VERDE	AZUL	VERDE

11

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2. PRUEBA DE ATENCIÓN Y MEMORIA DE TRABAJO:

1º. "Ahora le leeré una secuencia de números. Cuando acabe, por favor, ¿me la podría repetir?"

	ORDEN DIRECTO Intento/Elemento		Punt. Intento			Punt. Elemento		
2	1	1-7	0	1	0	1	2	
	2	6-3	0	1				
3	1	5-8-2	0	1	0	1	2	
S	2	6-9-4	0	1				
P	4	1	6-4-3-9	0	1	0	1	2
	2	7-2-8-6	0	1				
A	5	1	4-2-7-3-1	0	1	0	1	2
N	2	7-5-8-3-6	0	1				
	6	1	6-1-9-7-4-3	0	1	0	1	2
	2	3-9-2-4-8-7	0	1				
	7	1	5-9-1-7-4-2-8	0	1	0	1	2
	2	4-1-7-9-3-8-6	0	1				
	8	1	5-8-1-9-2-6-4-7	0	1	0	1	2
	2	3-8-2-9-5-1-7-4	0	1				
	9	1	2-7-5-8-6-2-5-8-4	0	1	0	1	2
	2	7-1-3-9-4-2-5-6-8	0	1				
		TOTAL:						

2º. "Ahora volveré a leerle secuencias de números. Cuando acabe me las deberá repetir, pero en orden inverso (comenzando por el final hasta llegar al principio)".

	ORDEN INVERSO Intento/Elemento		Punt. Intento			Punt. Elemento		
2	1	2-4	0	1	0	1	2	
	2	5-7	0	1				
3	1	6-2-9	0	1	0	1	2	
S	2	4-1-5	0	1				
P	4	1	3-2-7-9	0	1	0	1	2
	2	4-9-6-8	0	1				
A	5	1	1-5-2-8-6	0	1	0	1	2
N	2	6-1-8-4-3	0	1				
	6	1	5-3-9-4-1-8	0	1	0	1	2
	2	7-2-4-8-5-6	0	1				
	7	1	8-1-2-9-3-6-5	0	1	0	1	2
	2	4-7-3-9-1-2-8	0	1				
	8	1	9-4-3-7-6-2-5-8	0	1	0	1	2
	2	7-2-8-1-9-6-5-3	0	1				
		TOTAL:						

4

Page 7

3º. "Ahora debajo puede ver un conjunto de números. Su tarea consiste en unirlos con una línea lo más rápidamente posible, teniendo en cuenta que no puede levantar el lápiz del papel".

EJEMPLO:

PRUEBA:

7

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6. PRUEBA DE FLUENCIA VERBAL:

1º. "Ahora le voy a decir una letra y usted deberá decir todas aquellas palabras que se le ocurran que empiecen con esa misma letra. En este caso NO podrá decir nombres propios (por ejemplo, nombres de personas o ciudades), ni tampoco derivados (aumentativos, diminutivos, ...)".
1 minuto por letra.

F:
_____

A:
_____

S:
_____

2º. "Ahora deberá decirme todos los animales que se le ocurran. Hasta que yo le diga basta".
1 minuto.

ANIMALES:
_____

¡Muchas gracias por su colaboración!

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Which Patients and When Monitoring?

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Characteristics of Patients: Which Predictors?

According to biomarkers?

According to clinical factors?

According to demographic variables?

According to emotional variables?

According to subjective complaints?

Clinical Factors

☞ High number of clinical factors are associated

Some of most representative:

☞ **AIDS**

☞ **CD4 Nadir**

☞ **Time with HIV**

☞ **Interruptions of ART**

☞ **Coinfection with HCV**

☞ **Virological Failure (in Plasma)**

☞ **CSF Viral Load** *

: Considering availability of lumbar puncture in clinical practice!

New Potential Risk Factors

Tozzi et al, Journal of Neurovirology, 2005

To assess prevalence and risk factors for human immunodeficiency virus (HIV)-related neurocognitive impairment (NCI), the authors performed a 7-year survey in the period 1996 to 2002. A total of 432 patients were examined. HIV-related NCI was diagnosed in 238 patients (55.1%), meeting the HIV dementia (HIV-D) criteria in 45 (10.4%). The prevalence of both NCI and HIV-D did not change significantly during the study period. Compared with patients without NCI, patients with NCI were older (40.4 versus 38.2 years; $P = .003$), had a higher prevalence of positive HCV serology (61.1% versus 38.9%; $P = .003$), and a lower nadir CD4 cell count (156 versus 222 cells/μl; $P < .001$). Compared with patients seen during 1996 to 1999, patients with NCI seen during 2000 to 2002 were older (40.7 versus 38.8 years; $P = .004$), had a less advanced disease stage (previous acquired immunodeficiency syndrome [AIDS] 28.8% versus 65.7%; $P < .001$) and a higher nadir CD4 count (174 versus 132 cells/μl; $P = .026$). This study showed an unchanged prevalence of both HIV-related NCI and HIV-D in the period 1996 to 2002. The authors found evidences for new additional potential risk factors for HIV-related NCI (older age, lower nadir CD4 count, positive hepatitis C virus [HCV] serology), and for a change of risk factors for NCI in the late highly active antiretroviral therapy (HAART) era (older age, less advanced disease, higher nadir CD4 count). *Journal of NeuroVirology* (2005) **11**, 265–273.

Demographic Factors

Well identified:

☞ **Older Age**

☞ **Education Level (*Cognitive Reserve!*)**
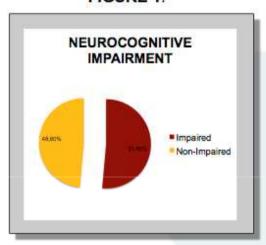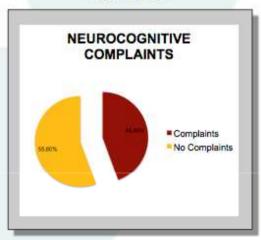
☞ **Employment!**

Self-Reported NC Complaints

Muñoz-Moreno et al, INS, Helsinki, 2009
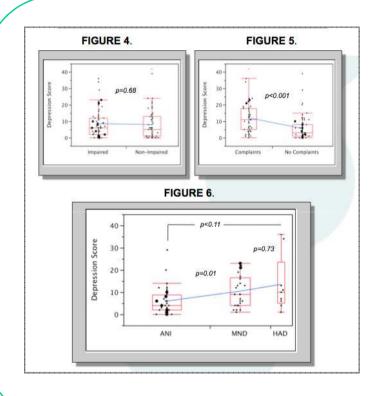
Self-Reported NC Complaints

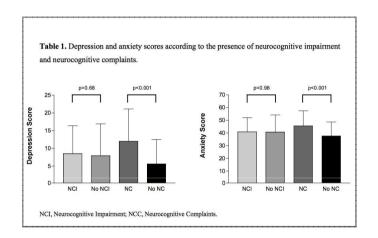**3 patients' patterns according to
presence or not of NC complaints:**

☞ 1) NC Complaint + Neurocognitive Impairment

☞ 2) NC Complaint + No Neurocognitive Impairment

☞ 3) No NC Complaint + Neurocognitive Impairment!

Self-Reported NC Complaints

FIGURE 4.

FIGURE 5.

FIGURE 6.

Table 1. Depression and anxiety scores according to the presence of neurocognitive impairment and neurocognitive complaints.

NCI, Neurocognitive Impairment; NCC, Neurocognitive Complaints.

Unpublished Data

And When Monitoring?

A screening algorithm for HIV-associated neurocognitive disorders

LA Cysique,[1] JM Murray,[2,3] M Dunbar,[2] V Jeyakumar[2] and BJ Brew[4]

Results

The final algorithm utilized age, current CD4 cell count, past central nervous system HIV-related diseases and current treatment duration and required approximately 3 min to complete, with a good overall prediction accuracy of 78% (against the gold standard; NP-impairment status derived from standard NP testing) and a good specificity of 70%.

Conclusion

This noncognitive-based algorithm should prove useful to identify HIV-infected patients with advanced disease at high risk of HAND who require more formal assessment. We propose staged guidelines, using the algorithm, for improved HAND therapeutic management. Future larger, international studies are planned to test the predictive effect of nadir CD4 cell count, hepatitis C virus infection, gender, ethnicity and HIV viral clade. We recommend the use of this first version for HIV-infected Caucasian men with advanced disease.

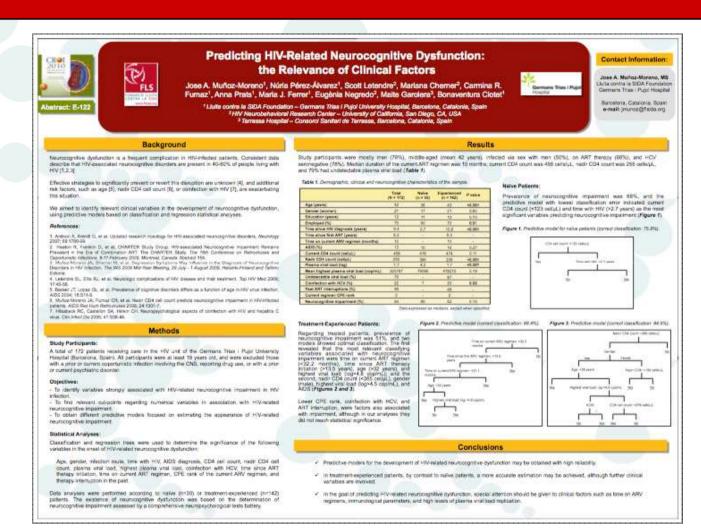$$NP\ impairment:\quad 0.351 \times age - 0.005 \times CD4 - 0.681 \times \log_{10} HIV\ RNA - 0.225 \times HIV\ duration + 3.356 \times CNS\ disease - 0.098 \times CART\ duration - 9.8748 \geq 0.$$
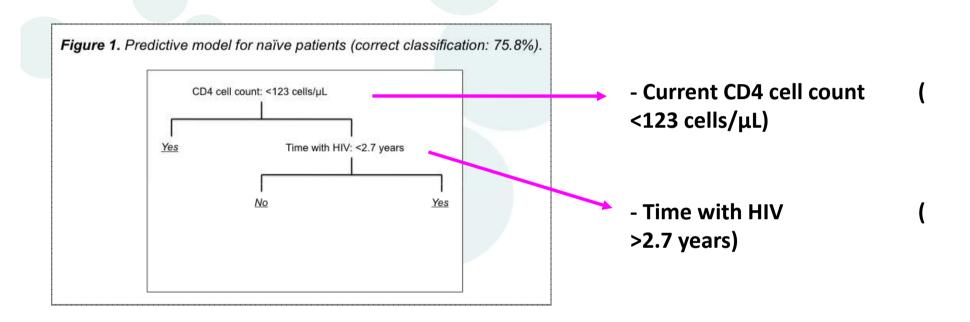
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Similar Findings

Muñoz-Moreno et al, CROI, 2010

Clinical Factors As Predictors

Figure 1. Predictive model for naïve patients (correct classification: 75.8%).

CD4 cell count: <123 cells/μL

Yes

Time with HIV: <2.7 years

No   Yes

- **Current CD4 cell count** (
<123 cells/μL)

- **Time with HIV** (
>2.7 years)
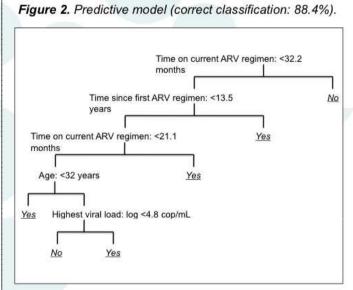
*: 75.8% of correct classification

Clinical Factors As Predictors

Figure 2. Predictive model (correct classification: 88.4%).

Figure 3. Predictive model (correct classification: 84.9%).

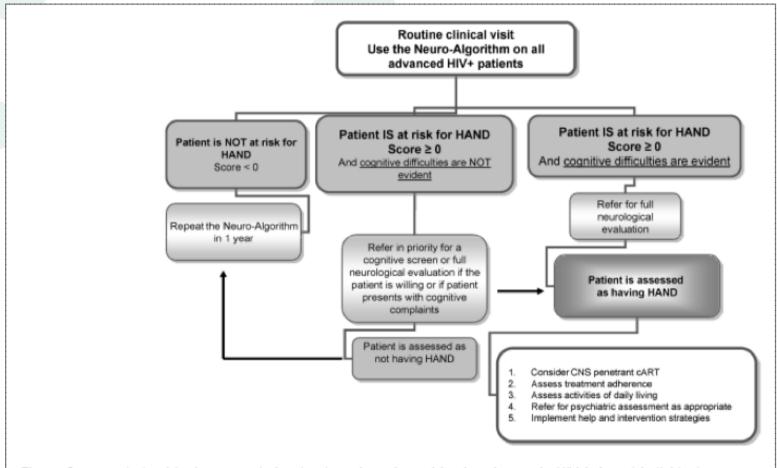- Nadir CD4 cell count   (
<365 cells/µL)

- Time on current regimen
          (>32.2 months)

- Highest viral load
          (>4.5 cop/mL)

*: 88.4% and 84.9%
of correct classification
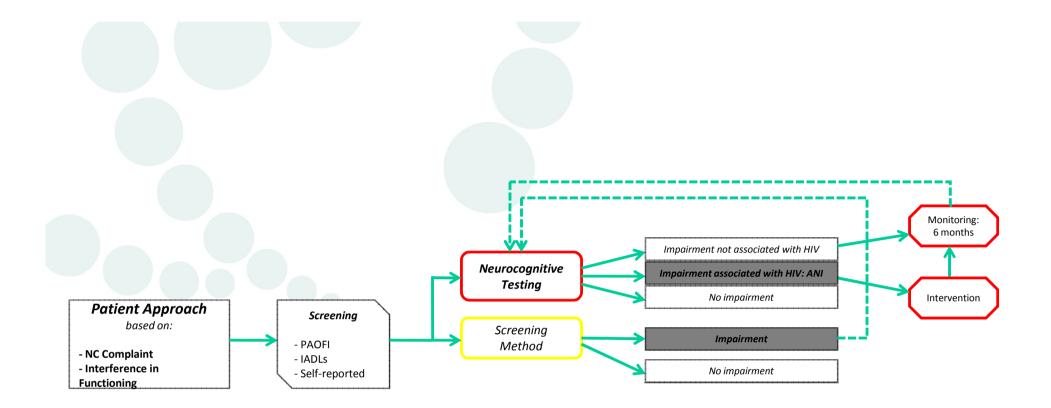
Algorithm Proposed - Cysique

Fig. 1 Suggested algorithmic approach for the detection of cognitive impairment in HIV-infected individuals.

Patient Approach
based on:

- **NC Complaint**
- **Interference in Functioning**

Screening

- PAOFI
- IADLs
- Self-reported

Neurocognitive Testing

Screening Method

Impairment not associated with HIV

Impairment associated with HIV: ANI

No impairment

Impairment

No impairment

Monitoring: 6 months

Intervention

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Clinician Approach

based on clinical suspicion according to:

- Clinical Risk Factors, particularly:

AIDS
CD4 Nadir
Time with HIV
Interruptions of ART
Coinfection with HCV
Virological Failure

*In case of Lumbar Puncture availability:

CSF Viral Load*

- Additional Risk Factors:

Aging
Education
Others

Neurocognitive Testing

Screening Method

Impairment

No Impairment

Impairment

No impairment

Interference / Complaints: MND

NO Interference / Complaints: ANI

Intervention

Monitoring: 6 months
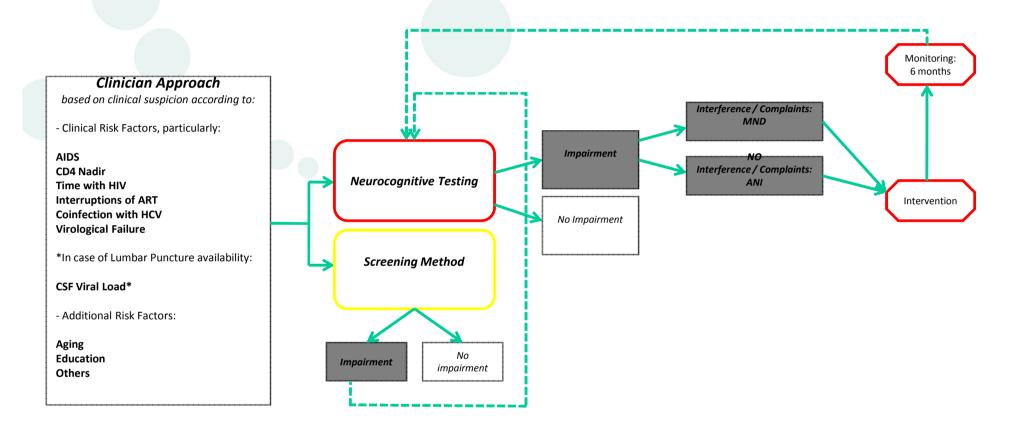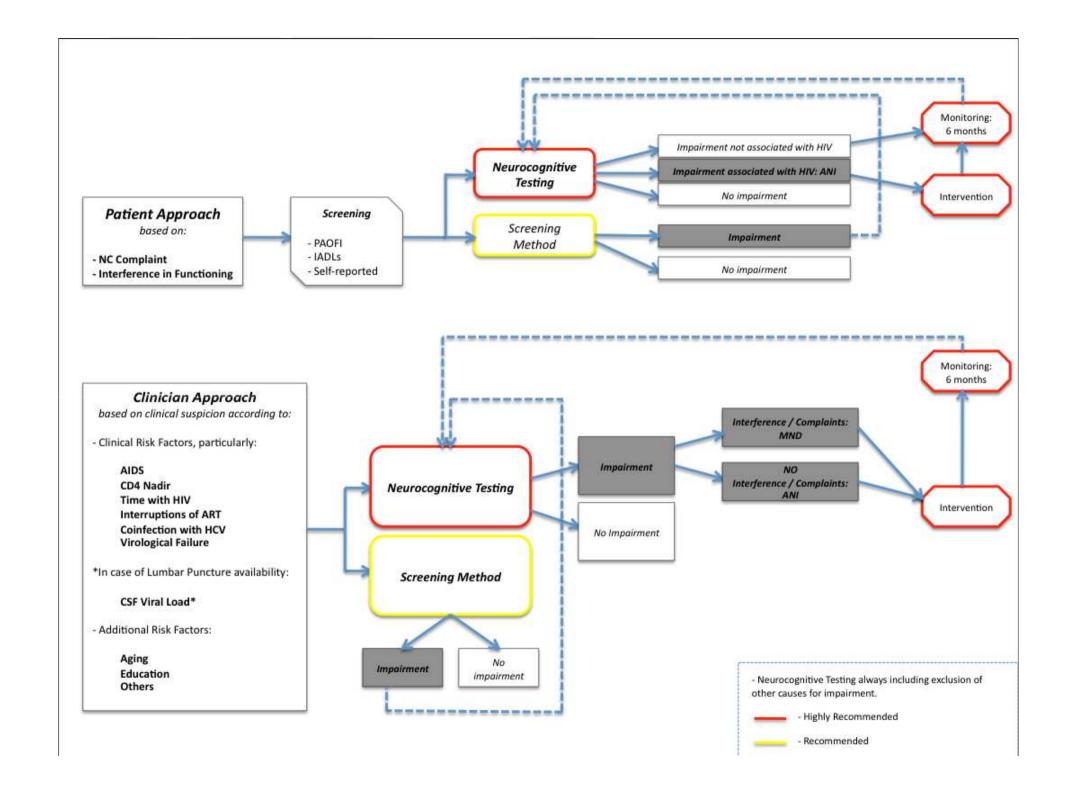
Announcement of Training in Neuropsychological Skills (Barcelona, Spain, July 2011)

Workshop on

Neuropsychological and Neuropsychiatric

Aspects in HIV Infection

- - -

July 7th - 8th, 2011

- <u>Location</u>: Germans Trias i Pujol University Hospital (Barcelona, Spain)

- <u>Duration</u>: 2 days (15 hours)

- <u>Programme</u>: Particularly focused on CNS disturbances and HAND

A: *Preliminary Concepts and Clinical Relevance*

B: *Interventions and Clinical Management*

- - -

C: *Neurocognitive Testing*

(Practical Approach)

Information and contact e-mail: info.fls.germanstrias@gencat.cat

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Many Thanks!

Jose A. Muñoz-Moreno

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