5th International Symposium on Neuropsychiatry HIV

- - -

Barcelona, May 24-25th, 2012

Neuropsychological Screening 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

Cognitive Disorders *in HIV Infection*

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Cognitive Disorders *in HIV Infection*

HIV Specialization / Infectious Diseases

Cognitive Disorders *in HIV Infection*

Health Psychology

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Cognitive Disorders in HIV Infection

Psychiatry

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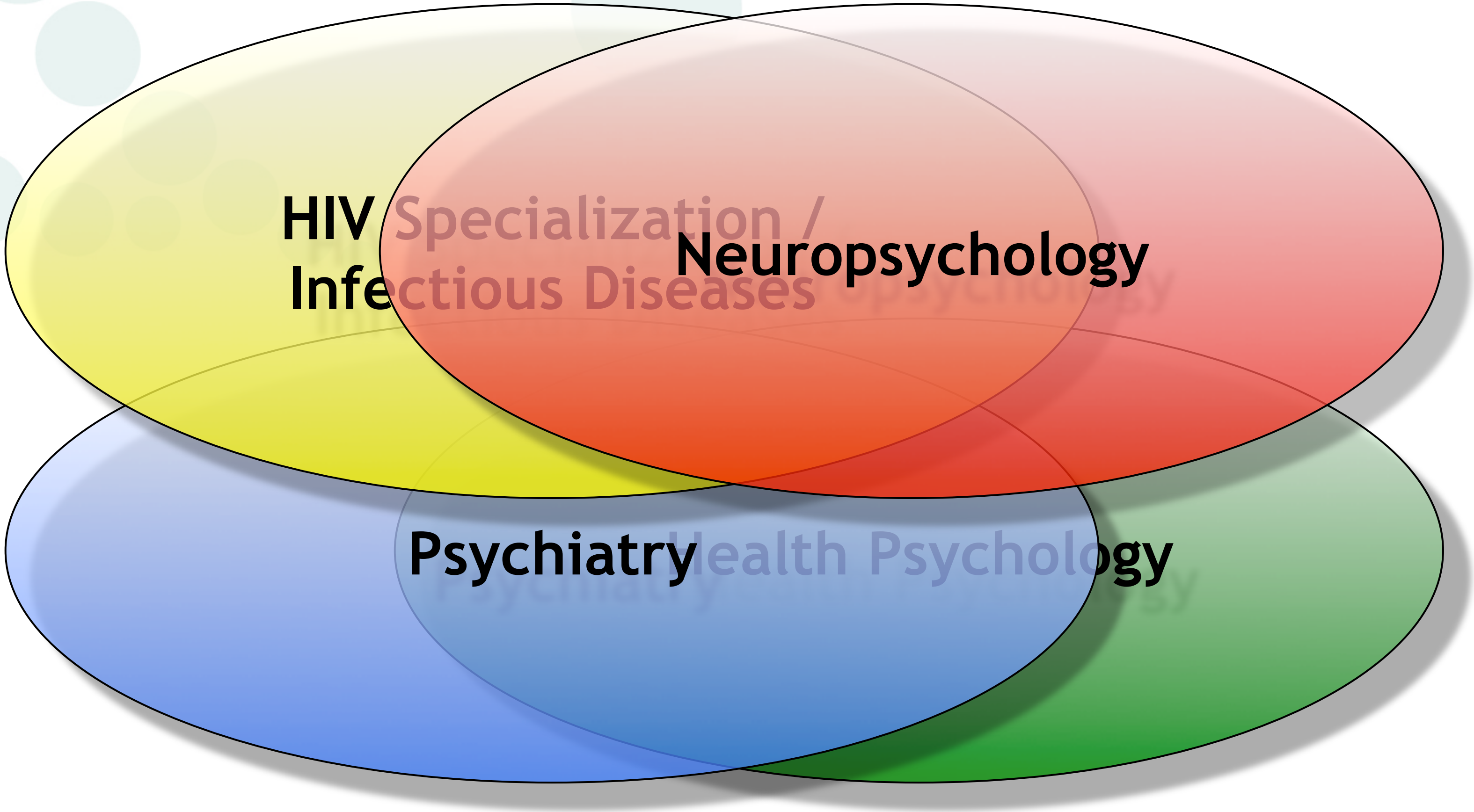
Cognitive Disorders *in HIV Infection*

Neuropsychology

***Cognitive Disorders** in HIV Infection*



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But... is the routine practice

in accordance

with

these new needs

in HIV Infection and its management??

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<u>*Clinical Practice*</u> *in HIV Infection*

- ☞ HIV Physicians
- ☞ Nurses
- ☞ **Health psychologists**
- ☞ **Psychiatrists**
- ☞ **Neuropsychologists!**

Why to Assess?

Which Tools?

Which Patients and When Monitoring?

Why to Assess?

Main Reasons

- ☑ *High incidence and prevalence*
- ☑ *Multiple risk factors associated*
- ☑ *Negative contributions*
- ☑ *Lack of treatment*
- ☑ *Complexity in clinical management!*

Prevalence of HIV-Associated NCI

HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy

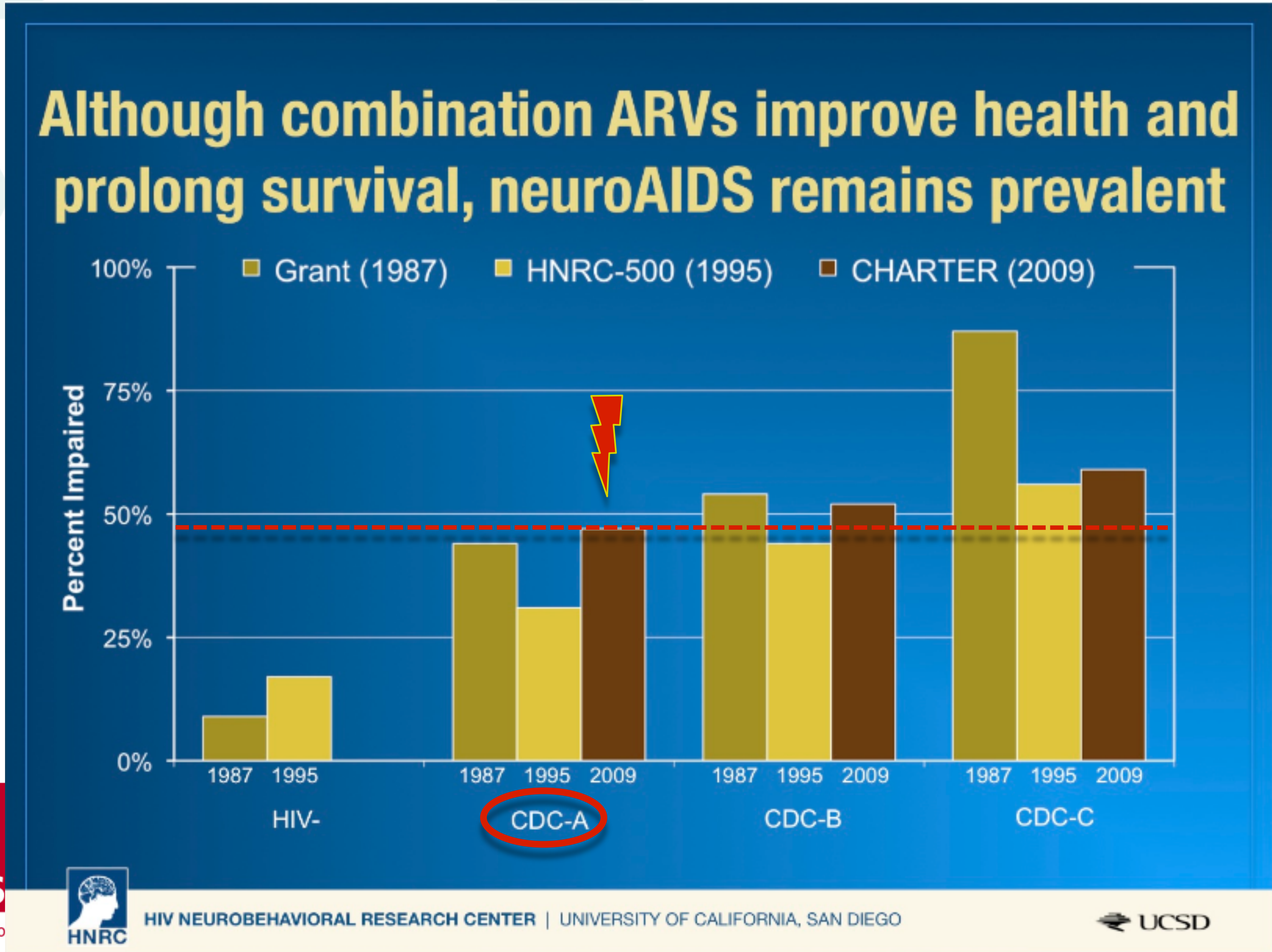
CHARTER Study

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

Prevalence of HIV-Associated NCI



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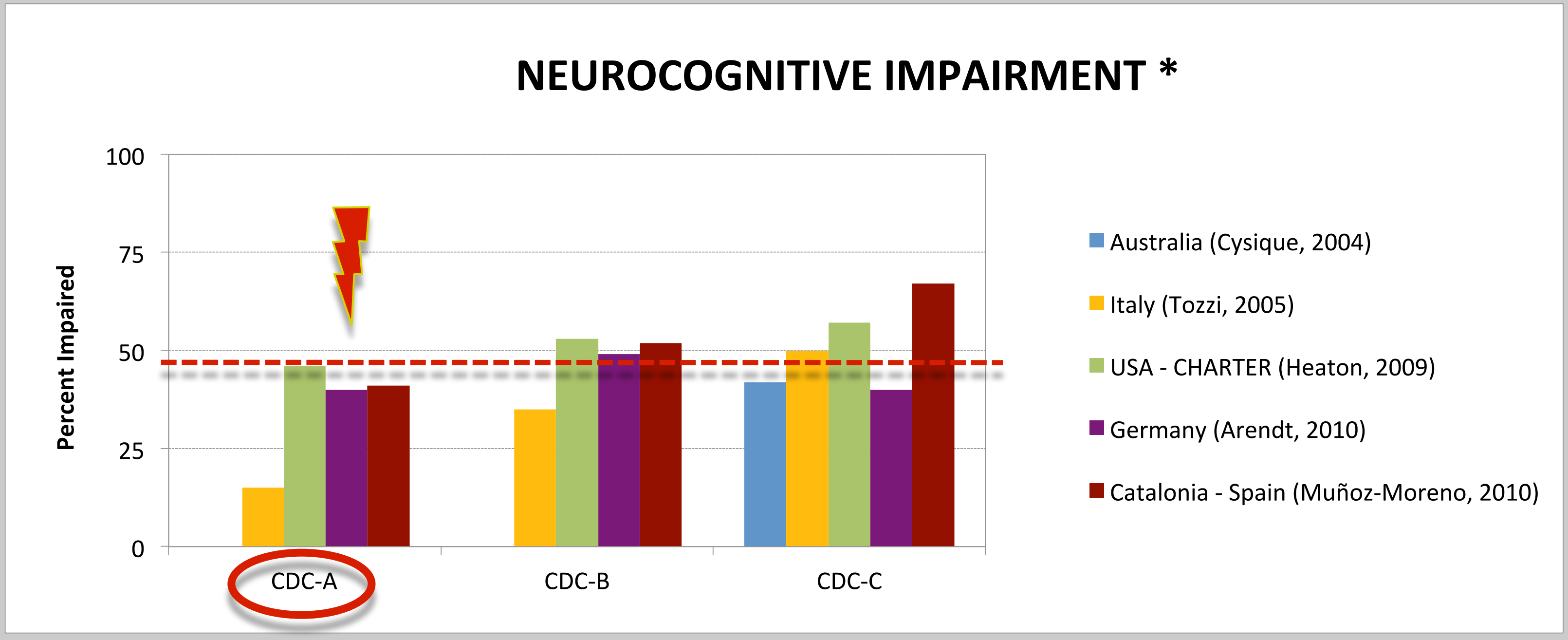
Confirming Data



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

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Leading to Negative Consequences...

Worse Quality of Life	Tozzi et al, 2003 Parsons et al, 2006
Interference on Daily Living Activities	Schifitto et al, 2001 Heaton et al, 2004 Gorman et al, 2009
Worse Adherence to Antiretroviral Treatment	Hinkin et al, 2004 Applebaum et al, 2009 Woods et al, 2009
More Frequent Virological Failure	Tozzi et al, 2005 Letendre et al, 2010
Predictor of Higher Death Rates	Ellis et al, 1997 Sevigny et al, 2007 Lescure et al, 2011

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	Smurzynski	Marra	Arendt	Garvey
Study	UCSD CIT	NIID	ALLRT	ACTG 736	Dusseldorf NeuroAIDS Cohort	Imperial College, UK
Sample Size	37	185	2,636	26	3,883	101
CPE: CSF VL	Lower VL	No CSF	No CSF	Lower VL	Lower VL	No CSF
Number of NP Tests	6	15	3	4	2	2
CPE: NP Tests	Better	Better	Better only by >3 drugs	Less Improvement	Better	No effects
Prospective	Yes	Yes	Yes	Yes	Yes	No
Controlled	No	No	No	No	No	No
Norms for NP Change	Yes	No	No	No	No	No

Cysique et al, Neurology 2009, 73(5):342-8; Tozzi et al, J Acquir Immune Defic Syndr 2009;52:56–63; Smurzynski et al, AIDS 2011;25:357-365; Marra et al, AIDS 2009, 23(11):1359-66; Arendt, et al. 18th CROI, Boston (MA, 2011. Poster #425; Garvey et al. 18th CROI, Boston (MA), 2011. Poster #393

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Antinori, 4th Meeting on HIV and CNS, Rome, 2011

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Antinori, 4th Meeting on HIV and CNS, Rome, 2011

Other ARV-Related 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, AIDS Res Hum Retroviruses, 2008

CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy

Ronald J. Ellis[a], Jayraan Badiee[a], Florin Vaida[a], Scott Letendre[a], Robert K. Heaton[a], David Clifford[b], Ann C. Collier[c], Benjamin Gelman[d], Justin McArthur[e], Susan Morgello[f], J. Allen McCutchan[a], Igor Grant[a], for the CHARTER Group

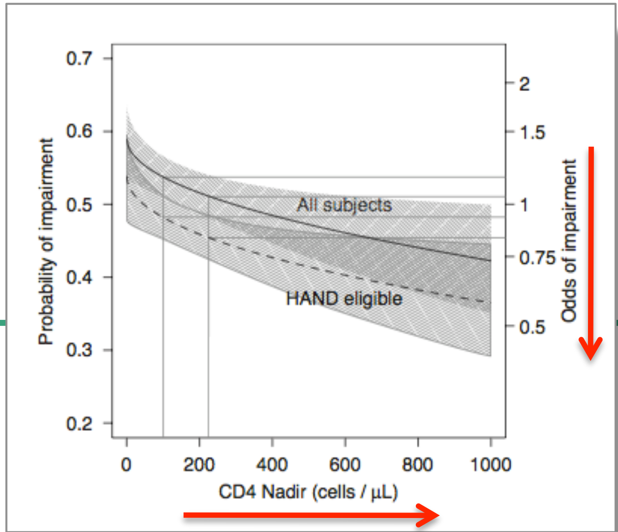
Ellis et al, AIDS, 2011

Other ARV-Related Approaches

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)	

Muñoz-Moreno et al, AIDS Res Hum Retroviruses, 2008



Ellis et al, AIDS, 2011

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Other ARV-Related Approaches

Journal of NeuroVirology, 00: 1-11, 2010
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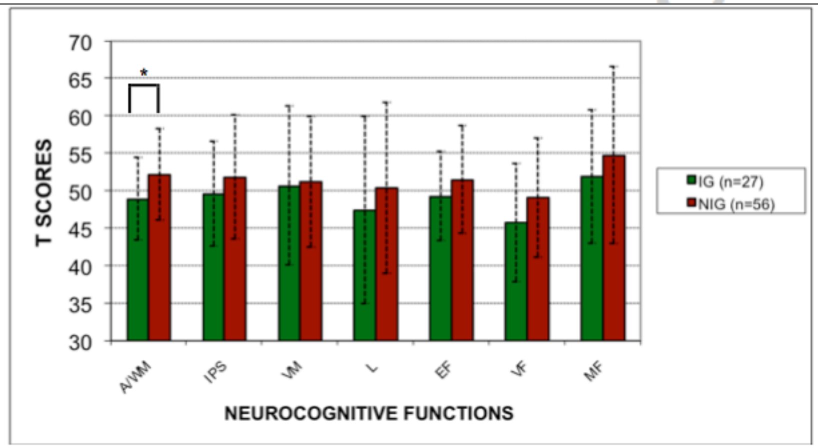
DOI: 10.3109/13550281003767710

informa
healthcare

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*



* : p<0.05.

Muñoz-Moreno et al, J Neurovirol, 2010

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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/mm^3 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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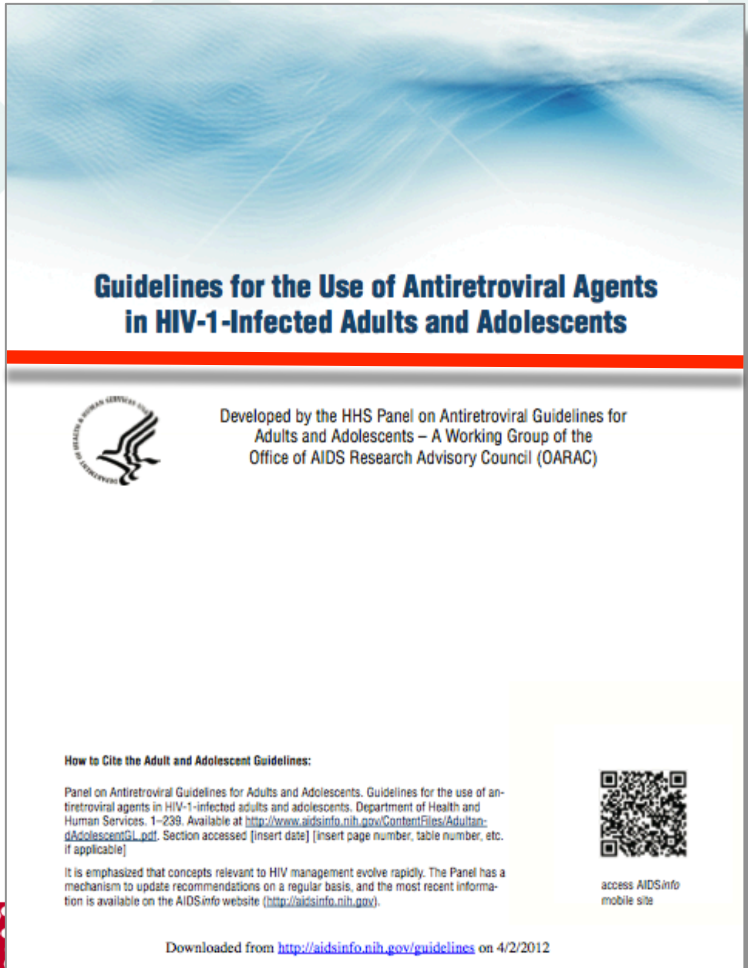
ARV Treatment Guidelines!


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

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access AIDS*info* mobile site

Downloaded from http://aidsinfo.nih.gov/guidelines on 4/2/2012

Neurological diseases

Although HIV RNA can be detected in the cerebrospinal fluid (CSF) of most untreated patients,[75-76] these patients usually do not present with overt symptoms of HIV-associated neurological disease.[77] In some patients CNS infection progresses to HIV encephalitis and can present as HIV-associated dementia (HAD).[78-80] This progression is usually in the context of more advanced untreated systemic HIV infection when severe CNS opportunistic infections (OIs) also cause high morbidity and mortality.[81]

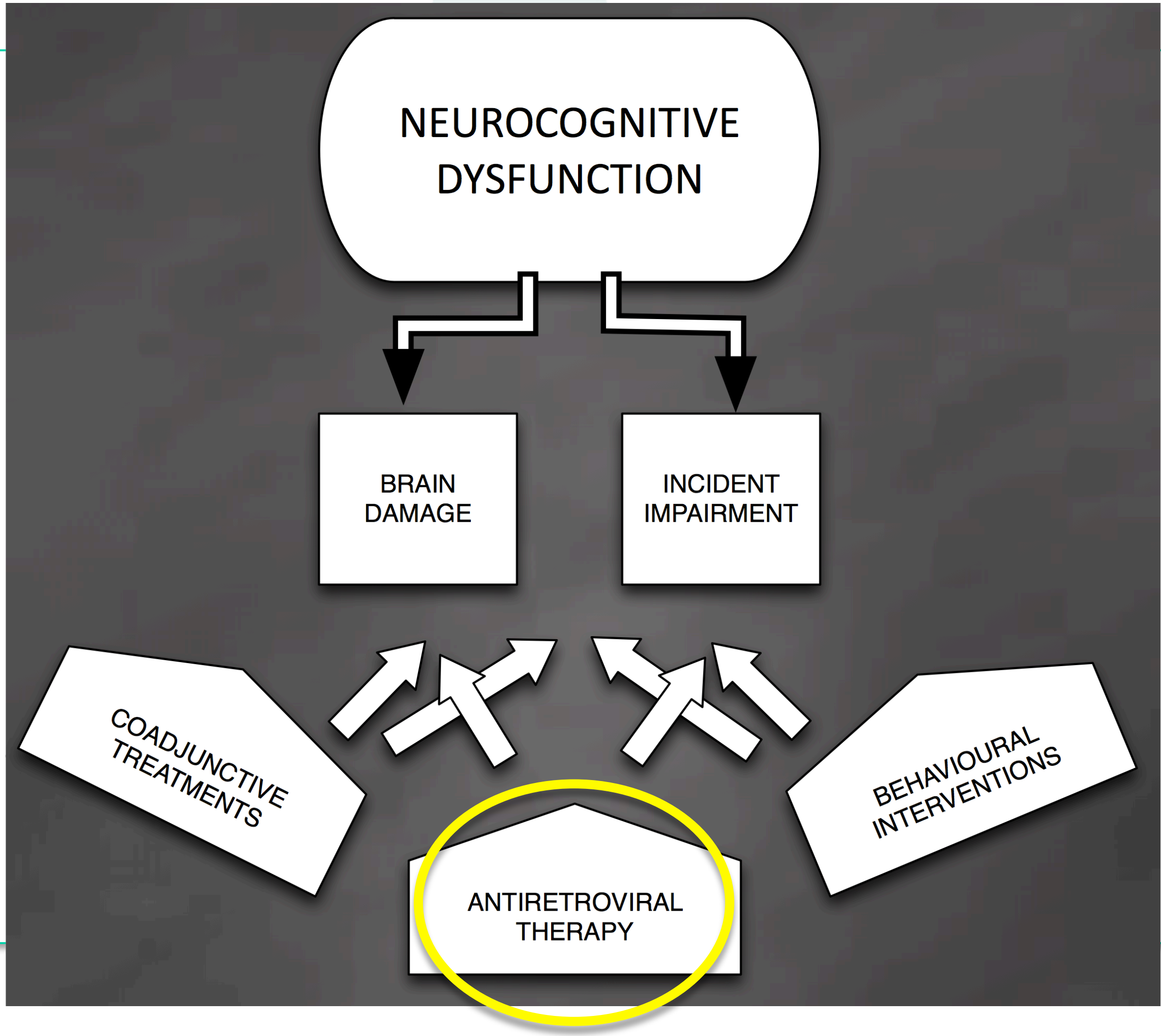
ART has had a profound impact on the nervous system complications of HIV infection. Effective viral suppression resulting from ART has dramatically reduced the incidence of HAD and severe CNS OIs.[82-84] Suppressive ART usually reduces CSF HIV RNA to undetectable levels.[85-86] Exceptional cases of symptomatic and asymptomatic CNS viral escape, in which HIV RNA is detectable in CSF despite viral suppression in plasma, have been documented.[87-88] This suggests that in some settings monitoring CSF HIV RNA may be useful.

Recent attention has turned to milder forms of CNS dysfunction, defined by impairment on formal neuropsychological testing.[80, 89] It is unclear whether this impairment is a consequence of injury sustained before treatment initiation or whether neurologic damage can continue or develop despite systemically effective ART.[90] The association of cognitive impairment with low nadir CD4 counts supports pretreatment injury and bolsters the argument that earlier initiation of ART may prevent subsequent brain dysfunction.[91-92]

The peripheral nervous system (PNS) also is a target in HIV infection, and several types of neuropathies have been identified.[93] Most common is HIV-associated polyneuropathy, a chronic, predominantly sensory and sometimes painful neuropathy. The impact of early treatment on this and other forms of neuropathy is not as clearly defined as on HAD.[94-95]

Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents (DHHS), March 2012:
http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

Therapeutical Approach



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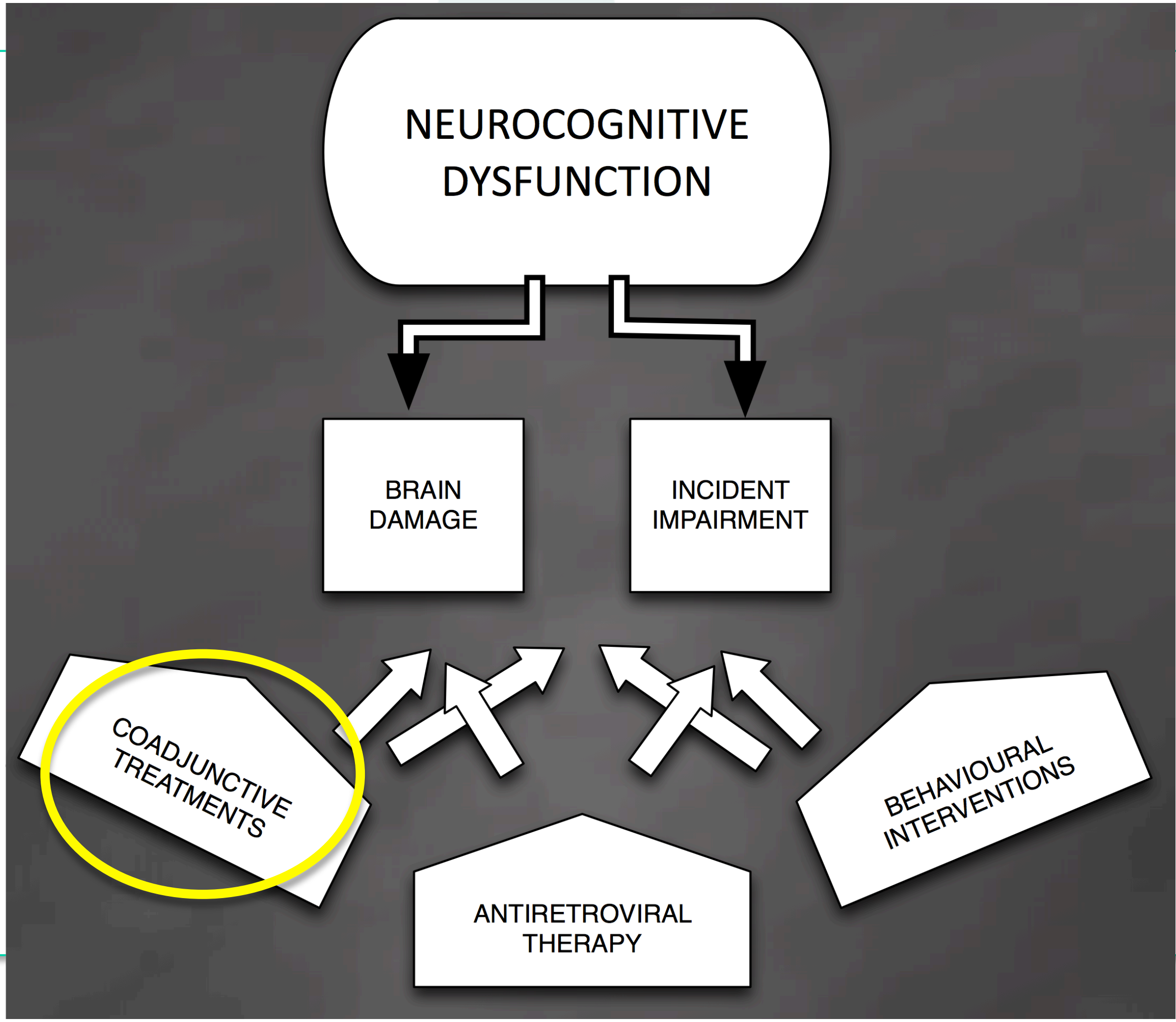
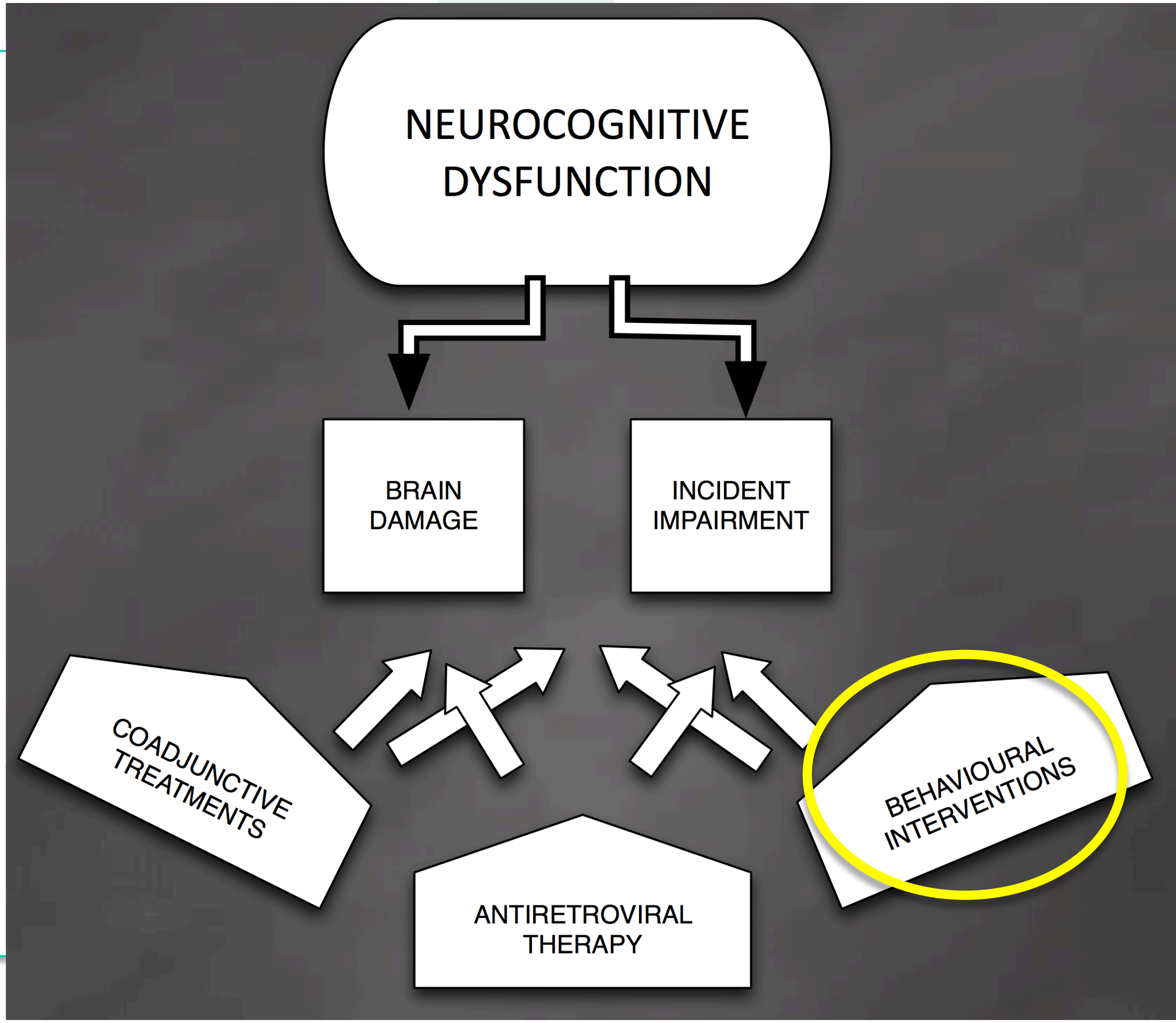
Therapeutical Approach



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

Why 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

International 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

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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

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HIV Infection - Literature

2010: Neurocognitive + HIV: 357 studies / 75 reviews

Neuropsychological + HIV: 1014 studies / 129 reviews

Cognitive + HIV: 1934 studies / 357 reviews

2011: Neurocognitive + HIV: 470 studies / 95 reviews

Neuropsychological + HIV: 1090 studies / 134 reviews

Cognitive + HIV: 2095 studies / 371 reviews

2012: Neurocognitive + HIV: 594 studies / 122 reviews

Neuropsychological + HIV: 1165 studies / 140 reviews

Cognitive + HIV: 2265 studies / 393 reviews

HIV Infection - Literature

2010:

Neurocognitive + HIV: 357 studies / 75 reviews

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237! - 151! - 331!

2011:

Neurocognitive + HIV: 470 studies / 95 reviews

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Cognitive + HIV: 2095 studies / 371 reviews

124! - 75! - 170!

2012:

Neurocognitive + HIV: 594 studies / 122 reviews

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- Different areas potentially assessed
- Variable tools

CONS:

- Availability / feasibility
- Duration of evaluations

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HIV-Associated Cognitive Profile

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

Attention / Working Memory
Information Processing Speed
Learning
Verbal Memory

Executive Functioning
Verbal Fluency
Motor Function

- Maybe has this changed??

Cortical hypothesis:

Brew, 2004
Valcour, 2006

Neuropsychological Testing

PROS:

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

CONS:

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

EXECUTIVE FUNCTIONS:
→ **- TMT-B: Trail Making Test - Part B**
→ **- WCST: Wisconsin Card Sorting Test**
→ **- Stroop's Test**

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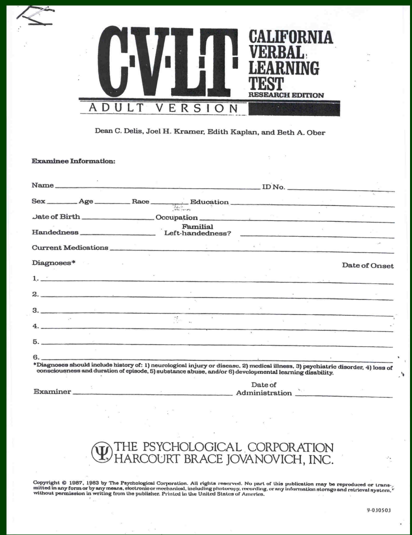
Motor Function

Grooved Pegboard Test

Matthews, 1964

Verbal Memory and Learning

California Verbal Learning Test - II



C·V·L·T CALIFORNIA VERBAL LEARNING TEST RESEARCH EDITION

ADULT VERSION

Dean C. Delis, Joel H. Kramer, Edith Kaplan, and Beth A. Ober

Examinee Information:

Name ______ ID No. ______

Sex ______ Age ______ Race ______ Education ______

Date of Birth ______ Occupation ______

Handedness ______ Familial Left-handedness? ______

Current Medications ______

Diagnoses* Date of Onset

1. ______
2. ______
3. ______
4. ______
5. ______
6. ______

*Diagnoses should include history of: 1) neurological injury or disease, 2) medical illness, 3) psychiatric disorder, 4) loss of consciousness and duration of episode, 5) substance abuse, and/or 6) developmental learning disability.

Examiner ______ Date of Administration ______

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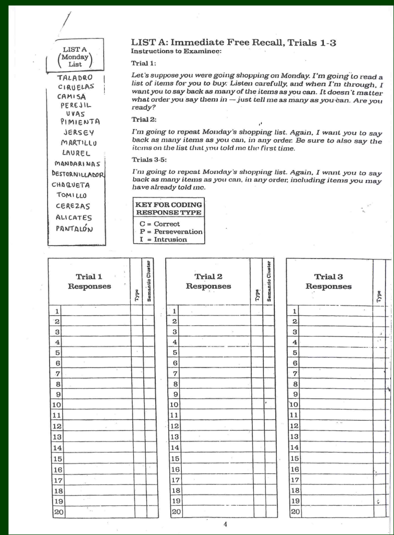


LIST A (Monday List)

TALADRO
CIRUELAS
CAMISA
PEREJIL
UVAS
PIMIENTA
JERSEY
MARTILLO
LAUREL
MANDARINAS
DESTORNILLADOR
CHAQUETA
TOMILLO
CEREZAS
ALICATES
PANTALÓN

LIST A: Immediate Free Recall, Trials 1-3

Instructions to Examinee:

Trial 1:

Let's suppose you were going shopping on Monday. I'm going to read a list of items for you to buy. Listen carefully, and when I'm through, I want you to say back as many of the items as you can. It doesn't matter what order you say them in — just tell me as many as you can. Are you ready?

Trial 2:

I'm going to repeat Monday's shopping list. Again, I want you to say back as many items as you can, in any order. Be sure to also say the items on the list that you told me the first time.

Trials 3-5:

I'm going to repeat Monday's shopping list. Again, I want you to say back as many items as you can, in any order, including items you may have already told me.

KEY FOR CODING RESPONSE TYPE
C = Correct
P = Perseveration
I = Intrusion

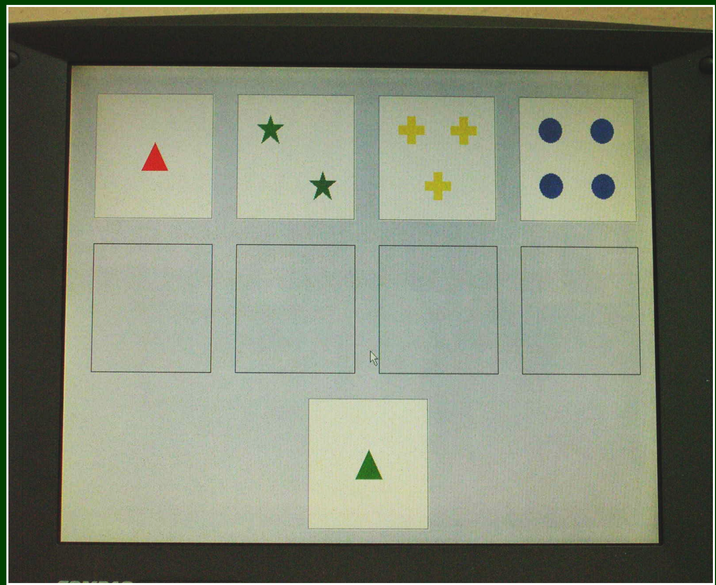
	Trial 1 Responses	Type	Semantic Cluster		Trial 2 Responses	Type	Semantic Cluster		Trial 3 Responses	Type
1				1				1		
2				2				2		
3				3				3		
4				4				4		
5				5				5		
6				6				6		
7				7				7		
8				8				8		
9				9				9		
10				10				10		
11				11				11		
12				12				12		
13				13				13		
14				14				14		
15				15				15		
16				16				16		
17				17				17		
18				18				18		
19				19				19		
20				20				20		

4

Delis, 2000

Executive Functioning

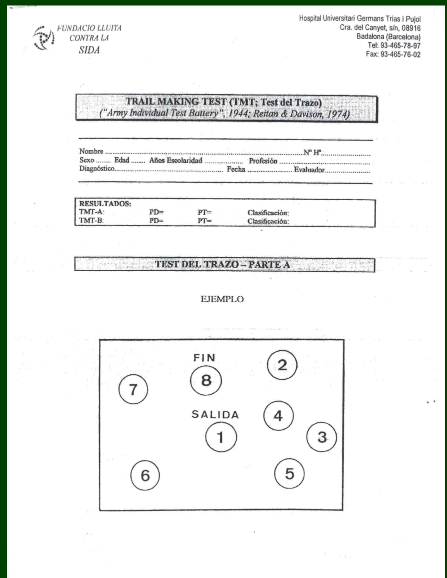
Wisconsin Card Sorting Test (WCST)



Kongs, 1993

Information Processing Speed

Trail Making Test - Part A (TMT-A)



FUNDACIO LLUITA CONTRA LA SIDA

Hospital Universitari Germans Trias i Pujol
Cra. del Canyet, s/n, 08916
Badalona (Barcelona)
Tel: 93-465-78-97
Fax: 93-465-76-02

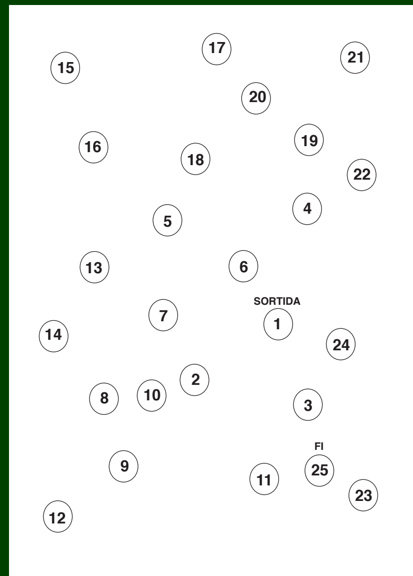
TRAIL MAKING TEST (TMT; Test del Trazo)
("Army Individual Test Battery", 1944; Reitan & Davison, 1974)

Nombre .... Nº Hª..................
Sexo .... Edad .... Años Escolaridad .... Profesión ....
Diagnóstico.................................... Fecha .... Evaluador....................

RESULTADOS:			
TMT-A:	PD=	PT=	Clasificación:
TMT-B:	PD=	PT=	Clasificación:

TEST DEL TRAZO – PARTE A

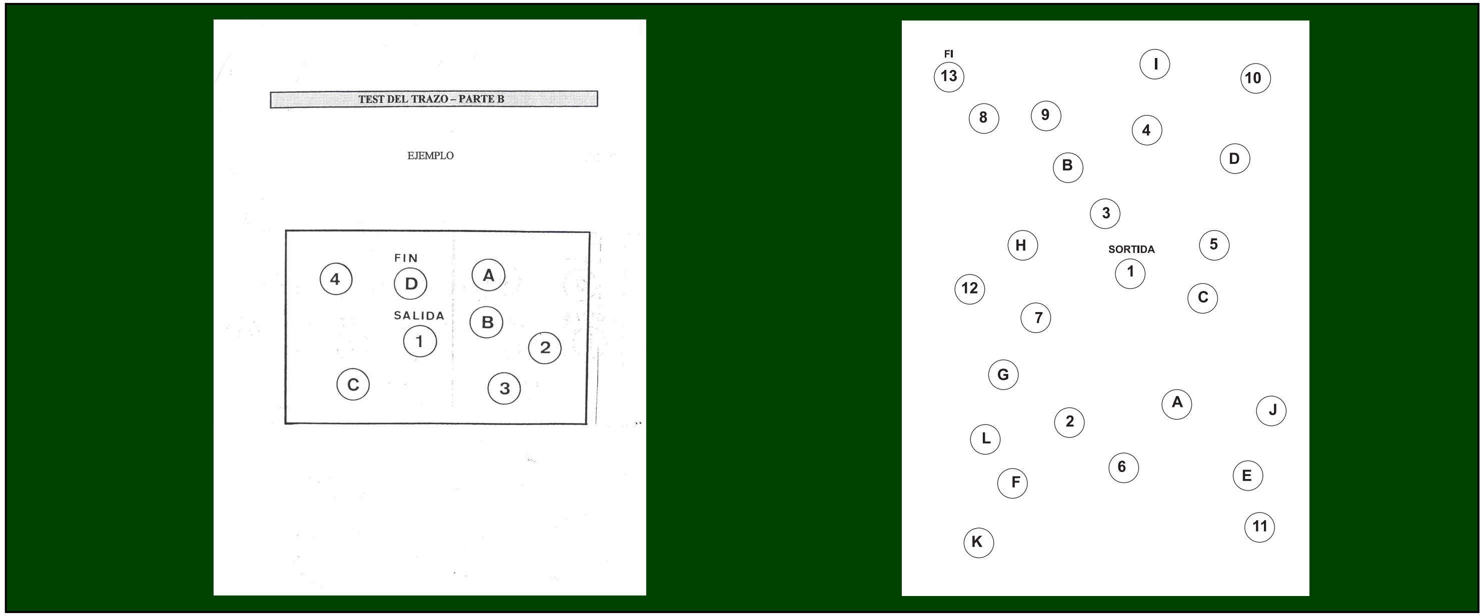
EJEMPLO



Reitan, 1974

Executive Functioning

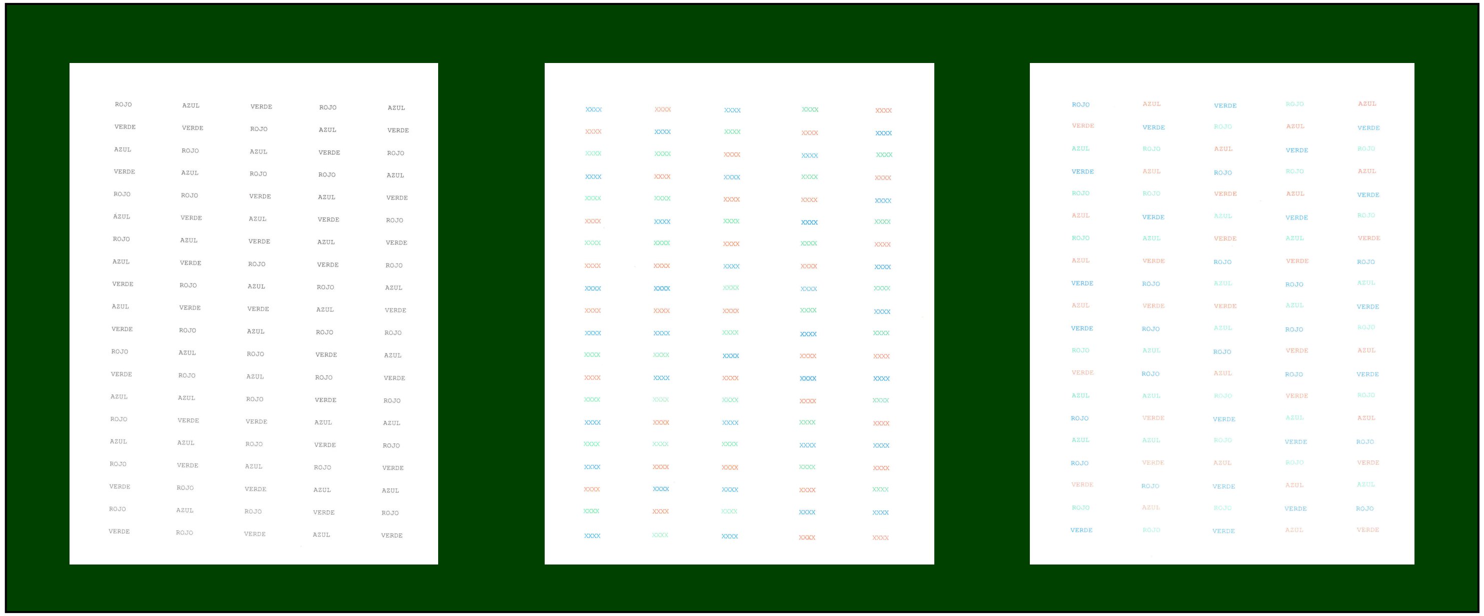
Trail Making Test - Part B (TMT-B)



Reitan, 1974

Executive Functioning

Stroop's Test



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Golden, 1978

Comprehensive Assessment

- Recommendations by Frascati Group,
in
Antinori et al, 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"
- Todos los días
- Muchas veces
- A veces
- Nunca

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

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

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

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

- 14 items
- 2 scales
- 1 total scale

Golden, 1978

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Depression Symptoms

Beck Depression Inventory (BDI)

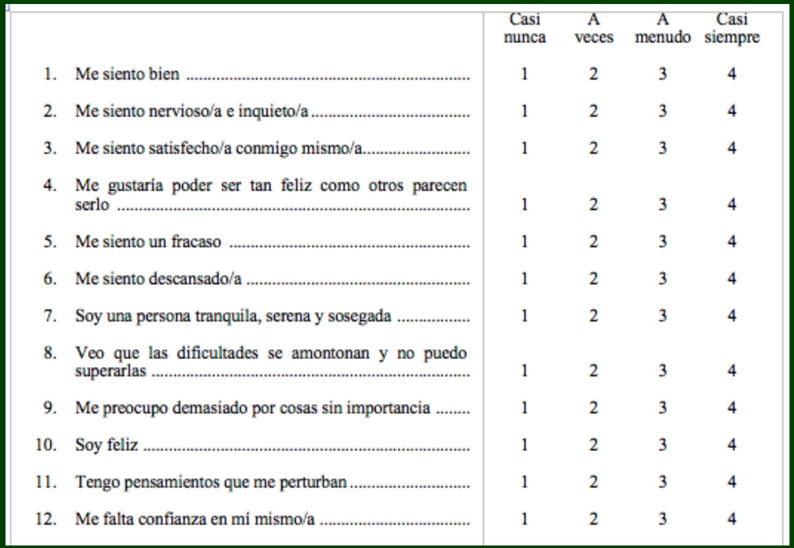
1	☐	a	No me siento triste
	☐	b	Me siento triste
	☐	c	Siempre me siento triste, no puedo evitarlo
	☐	d	Me siento tan triste o infeliz que no puedo soportarlo
2	☐	a	No me siento especialmente desanimado ante el futuro
	☐	b	Me siento desanimado ante el futuro
	☐	c	No hay nada que me haga ilusión
	☐	d	Veo 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

Anxiety Symptoms

State-Trait Anxiety Inventory (STAI)



	Casi nunca	A veces	A menudo	Casi siempre
1. Me siento bien	1	2	3	4
2. Me siento nervioso/a e inquieto/a	1	2	3	4
3. Me siento satisfecho/a conmigo mismo/a	1	2	3	4
4. Me gustaría poder ser tan feliz como otros parecen serlo	1	2	3	4
5. Me siento un fracaso	1	2	3	4
6. Me siento descansado/a	1	2	3	4
7. Soy una persona tranquila, serena y sosegada	1	2	3	4
8. Veo que las dificultades se amontonan y no puedo superarlas	1	2	3	4
9. Me preocupo demasiado por cosas sin importancia	1	2	3	4
10. Soy feliz	1	2	3	4
11. Tengo pensamientos que me perturban	1	2	3	4
12. Me falta confianza en mí mismo/a	1	2	3	4

- 20 items

- 1 scale

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Golden, 1978

Limitations in HIV Clinical Practice

PROS:

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

CONS:

- Availability / feasibility
- Duration of evaluations

Availability and Applicability

MAIN LIMITATIONS:

- *Need of a trained neuropsychologist*

- *Expertise and skills are relevant aspects in the application*

- *Multiple tools*

- *Manipulative tools, as well as variable instructions and correction processes*

- *Duration of assessments! (next section)*

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Limitations in HIV Clinical Practice

PROS:

- Strongly recommended
- Large experience in clinical neuropsychology
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- Variable tools

CONS:

- Availability / feasibility
- Duration of evaluations

Time Required for Neuropsychological Testing

- NIMH, 1990: 2 recommendations

Extended: 7-9 hours of duration

Brief: 1-2 hours of duration

- Nowadays…

Extended: 2-3 hours of duration

Brief: ?????

Journal of Clinical and Experimental Neuropsychology
1990, Vol. 12, No. 6, pp. 963-978

0168-8634/90/1206-0963$3.00
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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

Time Required for Neuropsychological Testing

- NIMH, 1990: 2 recommendations

Extended: 7-9 hours of duration

Brief: 1-2 hours of duration

☞ **Relevance of using Screening Tools!**

- Nowadays…

Extended: 2-3 hours of duration

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What Do We Know About Screening Tools?

Screening tools

Test	Reference	Duration	Pros	Cons
IHDS (International HIV Dementia Scale)	Sacktor et al, AIDS, 2005	5–10 min	- Quantitative score - Extensively used	- Designed for dementia - Limited specificity
PRMQ (Prospective and Retrospective Memory Questionnaire)	Woods et al, Neuropsychology, 2008	5–10 min	- Self-reported use - Brief duration	- Only 1 area covered - Insufficient evidence
CogState	Cysique et al, J Int Neuropsychol Soc, 2006	10–15 min	- 4 areas covered - Low practice effect	- Economical cost - Applicability (computerized)
MoCA (Montreal Cognitive Assessment)	Nasreddine et al, J Am Geriatr Soc, 2005	5–10 min	- 4 areas covered - Easy instructions	- Limited sensitivity - Insufficient evidence
HNRC Screening	Carey et al, Clin Neuropsychol, 2004	10–15 min	- High sensitivity/ specificity - Only 2 measures	- Scarce information provided - Applicability (pegboard)
BNCS (Brief NeuroCognitive Screen)	Ellis et al, J Neurovirol, 2005	5–10 min	- Extensively used - Experience on tests	- Scarce information provided - Limited sensitivity
NEU Screening	Muñoz-Moreno et al, unpublished (2012)	5–10 min	- High sensitivity/ specificity - Experience on tests	- Scarce information provided - Insufficient evidence

What Do We Know About Screening Tools?

1) International HIV Dementia Scale (IHDS)

- Advantages:
  - Easy instructions and paper use (3 items)
  - Quantitative score (cufoff ≤10 points)
  - Large and replicated validation (USA and Uganda)
- Disadvantages:
  - Specific for dementia (Davis et al, 2002; Smith et al, 2003; Bottiggi et al, 2007)
  - Insufficient specificity: 57% USA, 55% Uganda

International HIV Dementia Scale (IHDS)

Memory-Registration – Give four words to recall (dog, hat, bean, red) – 1 second to say each. Then ask the patient all four words after you have said them. Repeat words if the patient does not recall them all immediately. Tell the patient you will ask for recall of the words again a bit later.

1. Motor Speed: Have the patient tap the first two fingers of the non-dominant hand as widely and as quickly as possible.
   - 4 = 15 in 5 seconds
   - 3 = 11-14 in 5 seconds
   - 2 = 7-10 in 5 seconds
   - 1 = 3-6 in 5 seconds
   - 0 = 0-2 in 5 seconds

   ____

2. Psychomotor Speed: Have the patient perform the following movements with the non-dominant hand as quickly as possible: 1) Clench hand in fist on flat surface. 2) Put hand flat on surface with palm down. 3) Put hand perpendicular to flat surface on the side of the 5th digit. Demonstrate and have patient perform twice for practice.
   - 4 = 4 sequences in 10 seconds
   - 3 = 3 sequences in 10 seconds
   - 2 = 2 sequences in 10 seconds
   - 1 = 1 sequence in 10 seconds
   - 0 = unable to perform

   ____

3. Memory-Recall: Ask the patient to recall the four words. For words not recalled, prompt with a semantic clue as follows: animal (dog); piece of clothing (hat); vegetable (bean); color (red).
   - Give 1 point for each word spontaneously recalled.
   - Give 0.5 points for each correct answer after prompting
   - Maximum – 4 points.

   ____

Total International HIV Dementia Scale Score: This is the sum of the scores on items 1-3. The maximum possible score is 12 points. A patient with a score of ≤10 should be evaluated further for possible dementia.

Sacktor et al, AIDS, 2005

What Do We Know About Screening Tools?

2) Prospective and Retrospective Memory Questionnaire (PRMQ)

- Advantages:
  - Easy instructions and paper use (8 items)
  - Quantitative score (8–40 points)
  - Self reported by patient
  - Brief duration

The Prospective & Retrospective Memory Questionnaire (PRMQ)

This is a 16-item questionnaire by which individuals self-rate how often they make memory errors on a five-point scale. Scores can range between 16 (no memory errors) and 80 (multiple memory errors). The questionnaire can also be analyzed in sections relating to retrospective, prospective, self-cued, environmentally cued, and short- and long-term memory. It takes 10 min to complete, has high internal consistency, and normative population data exist.[31]

- Disadvantages:
  - 1 area covered (memory: prospective and retrospective)
  - Low validity due to self-reported assessment

Woods et al, Neuropsychology, 2008

What Do We Know About Screening Tools?

3) CogState

- Advantages:
  - 4 areas rapidly covered: attention, memory, executive functioning and motor function
  - Low practice effect (prospective trials)
  - Largely used in other diseases

CogState ClinicalTrials

www.cogstate.com

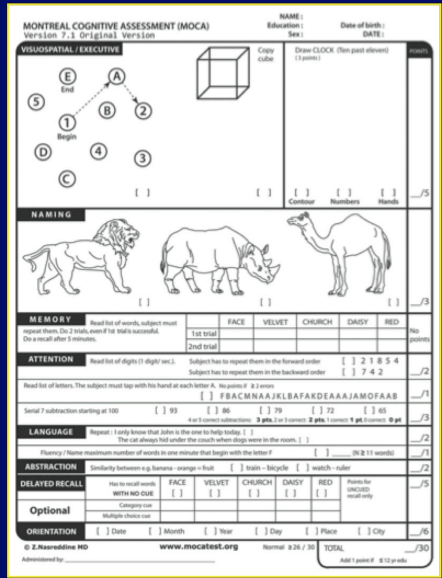
- Disadvantages:
  - Computer-based use (applicability)
  - Economical cost for copyright permission

Cysique et al, J Int Neuropsychol, 2006

What Do We Know About Screening Tools?

4) Montreal Cognitive Assessment (MoCA)

- Advantages:
  - 4 areas rapidly covered: attention, memory, executive functioning and verbal fluency
- Disadvantages:
  - Limited sensitivity: 59% (81% specificity) (Overton et al, CROI, 2011)
  - Scarce information provided



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — Copy cube — Draw CLOCK (Ten past eleven) (3 points) — POINTS

E End, A, 5, B, 2, 1 Begin, D, 4, 3, C

[ ] [ ] [ ] Contour [ ] Numbers [ ] Hands ___/5

NAMING [ ] [ ] [ ] ___/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED	
1st trial						No points
2nd trial						

ATTENTION Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 ___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] FBACMNAAJKLBAFAKDEAAAJAMOFAAB ___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** ___/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] ___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) ___/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler ___/2

DELAYED RECALL	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only	___/5
Optional	Category cue							
	Multiple choice cue							

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City ___/6

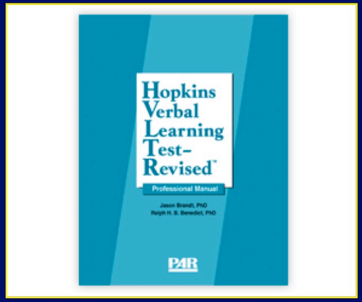
© Z.Nasreddine MD www.mocatest.org Normal ≥26 / 30 TOTAL ___/30
Administered by: ____________ Add 1 point if ≤ 12 yr edu

Nasreddine et al, J Am Geriatr Soc, 2005

What Do We Know About Screening Tools?

5) HIV Neurobehavioral Research Center Screening (HNRC)

- Advantages:
  - Only 2 measures to assess (learning and motor function)
  - Highly adequate sensitivity and specificity (78% and 85%)

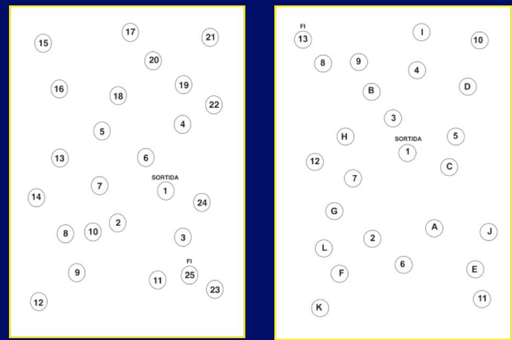


- Disadvantages:
  - Scarce information provided
  - Pegboard needed (applicability)

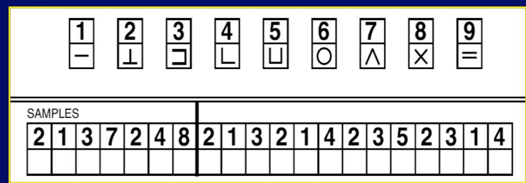
Carey et al, Clin Neuropsychol, 2004

What Do We Know About Screening Tools?

6) Brief NeuroCognitive Screen (BNCS)



- Advantages:
  - Widely used and extensive information provided in studies (Ellis et al, 2005; Robertson et al, 2007; Smurzynski et al, 2011)
  - Experience on tests (included in comprehensive batteries)



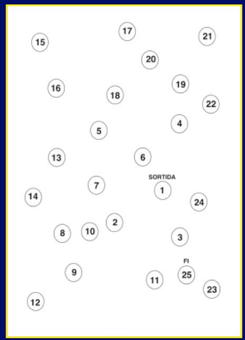
- Disadvantages:
  - Low sensitivity: 65% (72% specificity)
  - Scarce information provided

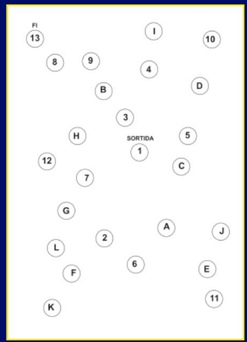
Ellis et al, J Neurovirol, 2005

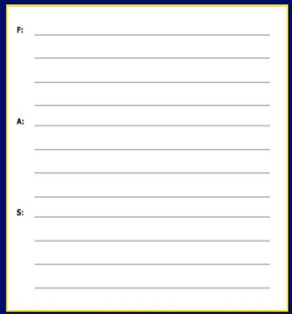
What Do We Know About Screening Tools?

7) NEU Screening

- Advantages:
  - Highly adequate sensitivity and specificity (74% and 81%)
  - Experience on tests (included in comprehensive batteries)
  - Recently proposed (Jan 2012)







- Disadvantages:
  - Scarce information provided
  - Not published yet

Muñoz-Moreno et al, unpublished (2012)

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 *

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**: Considering availability of lumbar puncture in clinical practice!*

Demographic Factors

Well identified:

☞ Older Age

☞ Education Level (*Cognitive Reserve!*)

☞ Employment!

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Self-Reported NC Complaints

FIGURE 1.

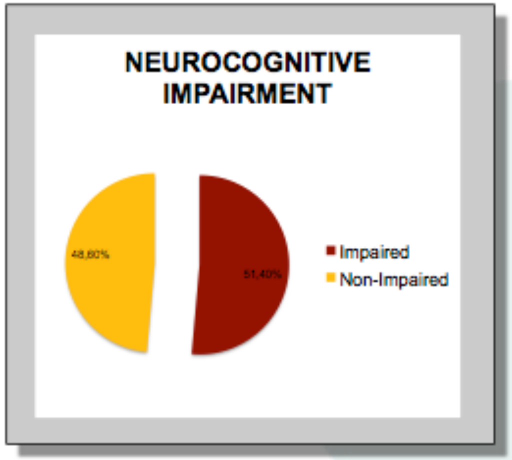
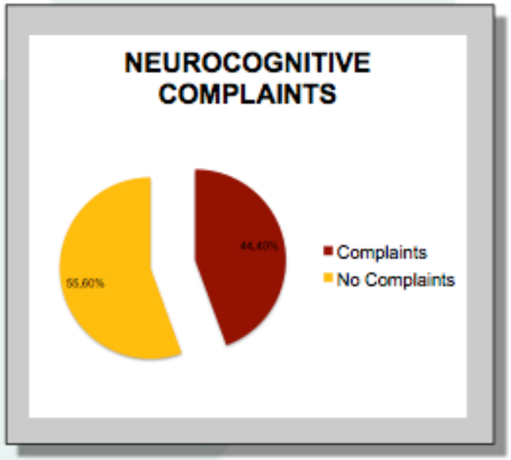


FIGURE 2.



Muñoz-Moreno et al, INS, Helsinki, 2009

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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!

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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

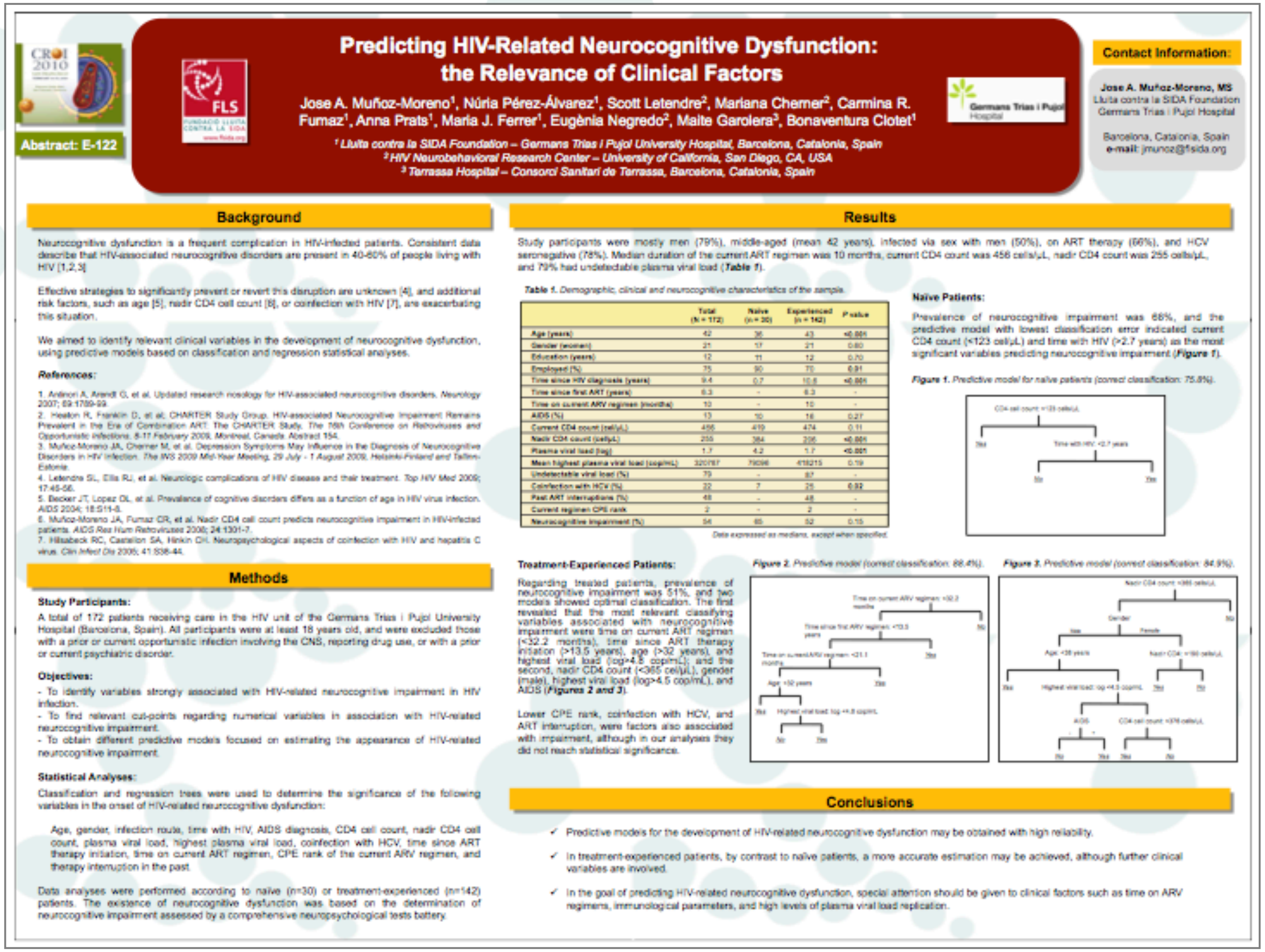
The final algorithm utilized age, current CD4 cell count, past central nervous system HIV-related diseases and current treatment duration and required approximately 3 min to complete, with a good overall prediction accuracy of 78% (against the gold standard; NP-impairment status derived from standard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

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

Similar Findings



Muñoz-Moreno et al, CROI, 2010

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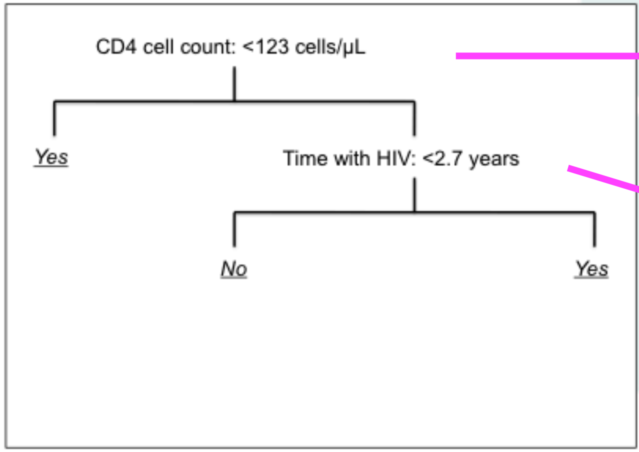
Clinical Factors As Predictors

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



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

- Time with HIV
(>2.7 years)

**: 75.8% of correct classification*

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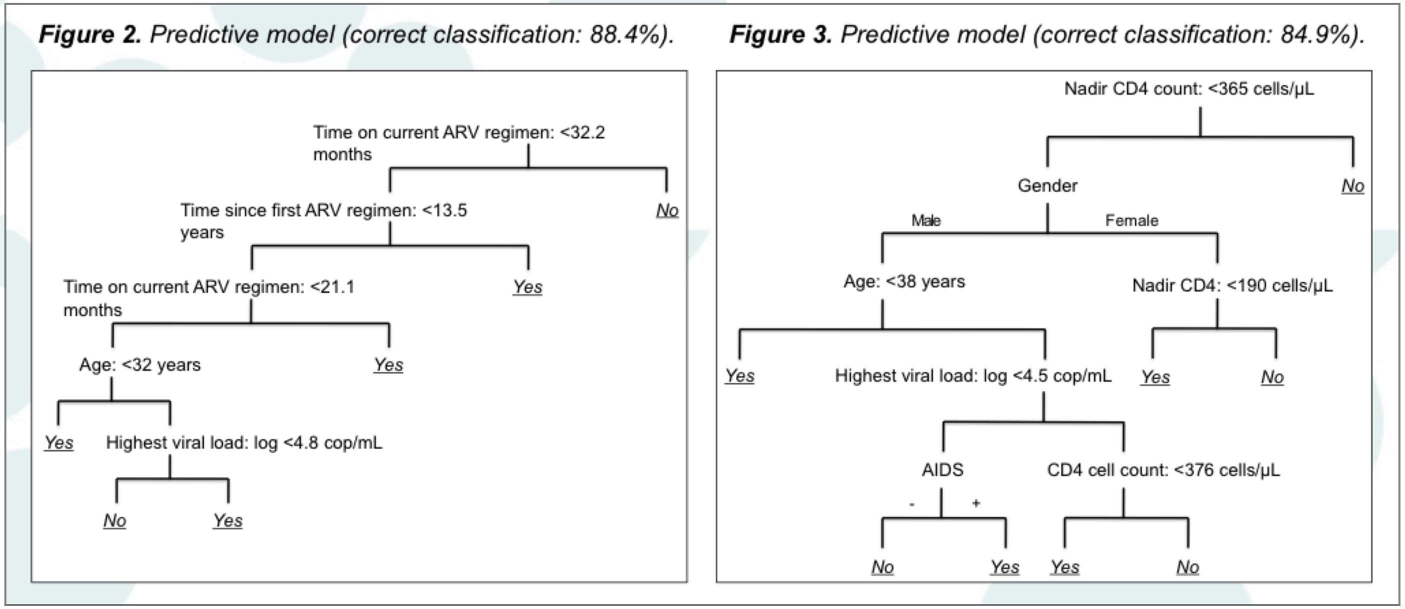
Clinical Factors As Predictors



- 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

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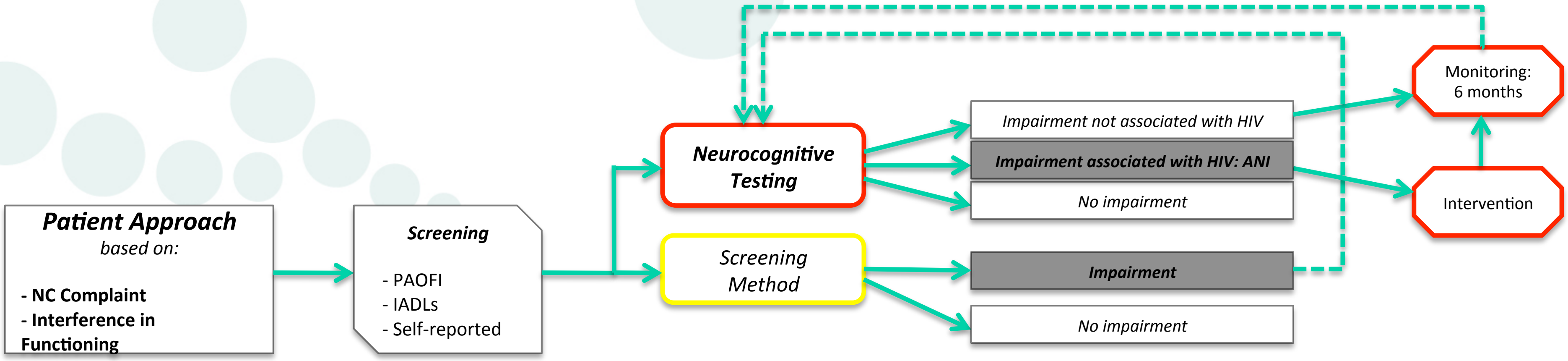

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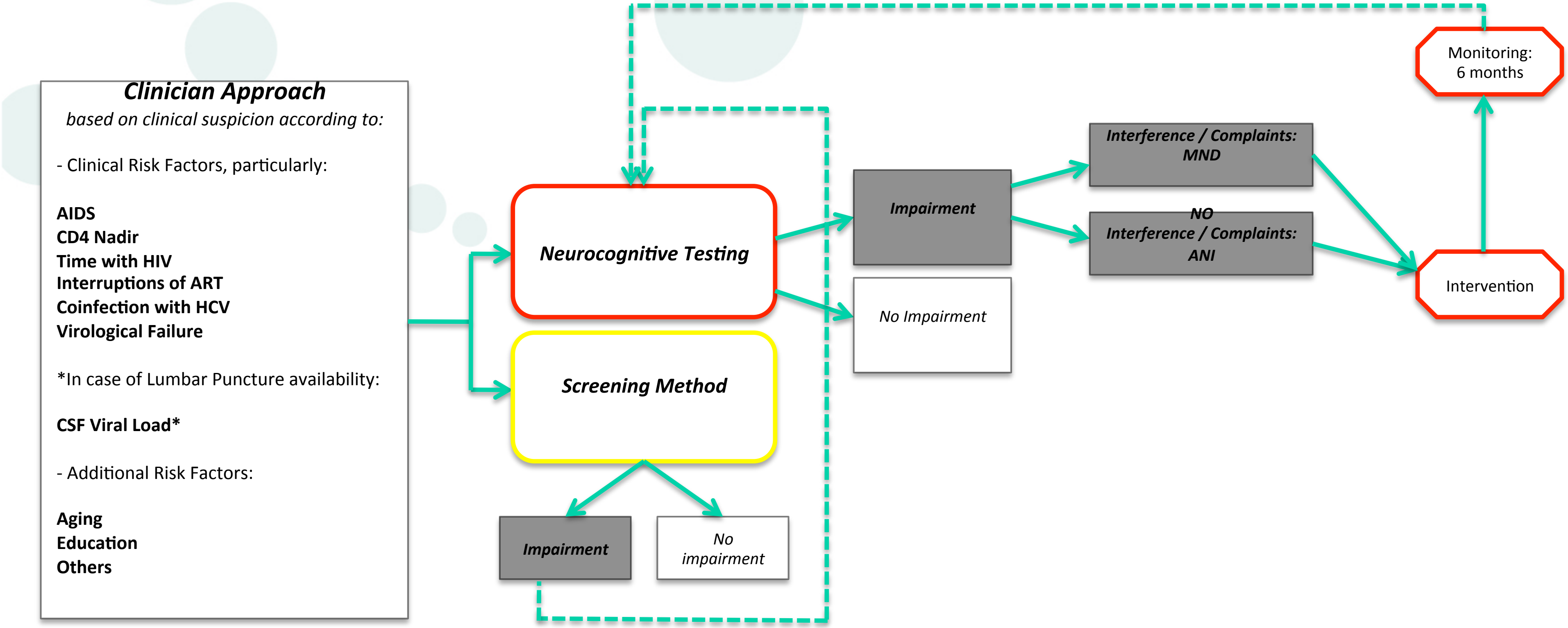

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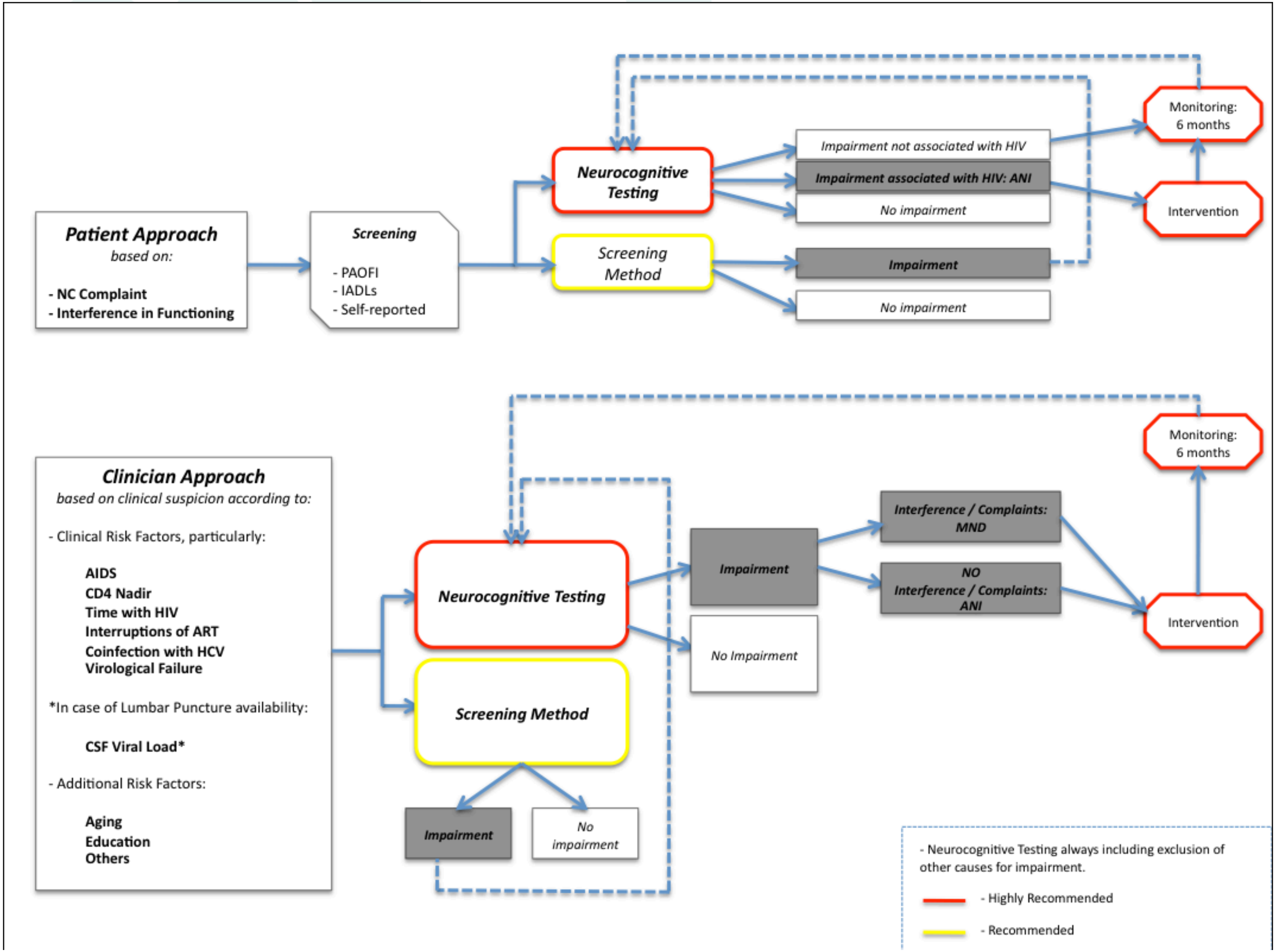
Patient Approach
based on:
- NC Complaint
- Interference in Functioning
Screening
- PAOFI
- IADLs
- Self-reported
Neurocognitive Testing
Screening Method
Impairment not associated with HIV
Impairment associated with HIV: ANI
No impairment
Impairment
No impairment
Monitoring: 6 months
Intervention
Clinician 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
Monitoring: 6 months
Intervention
- Neurocognitive Testing always including exclusion of other causes for impairment.
- Highly Recommended
- Recommended

Thanks

for your attention!

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