6th International Symposium

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www.neuropsychiatry-hiv.com

HIV Neuropsychiatry

Management of Neurocognitive Impairment in HIV Infection: Recommendations from the Recently Published Spanish Guidelines (GeSIDA 2013)

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GeSIDA / SPNS - November 2012

Documento de Consenso sobre el Manejo Clínico de los Trastornos Neurocognitivos Asociados a la Infección por el VIH.

Noviembre 2012

Grupo de expertos del Grupo de Estudio de Sida (GeSIDA) y de la Secretaría del Plan nacional sobre el Sida (SPNS)

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Consensus Report on the Clinical Management of

HIV-Associated Neurocognitive Disorders (HAND)

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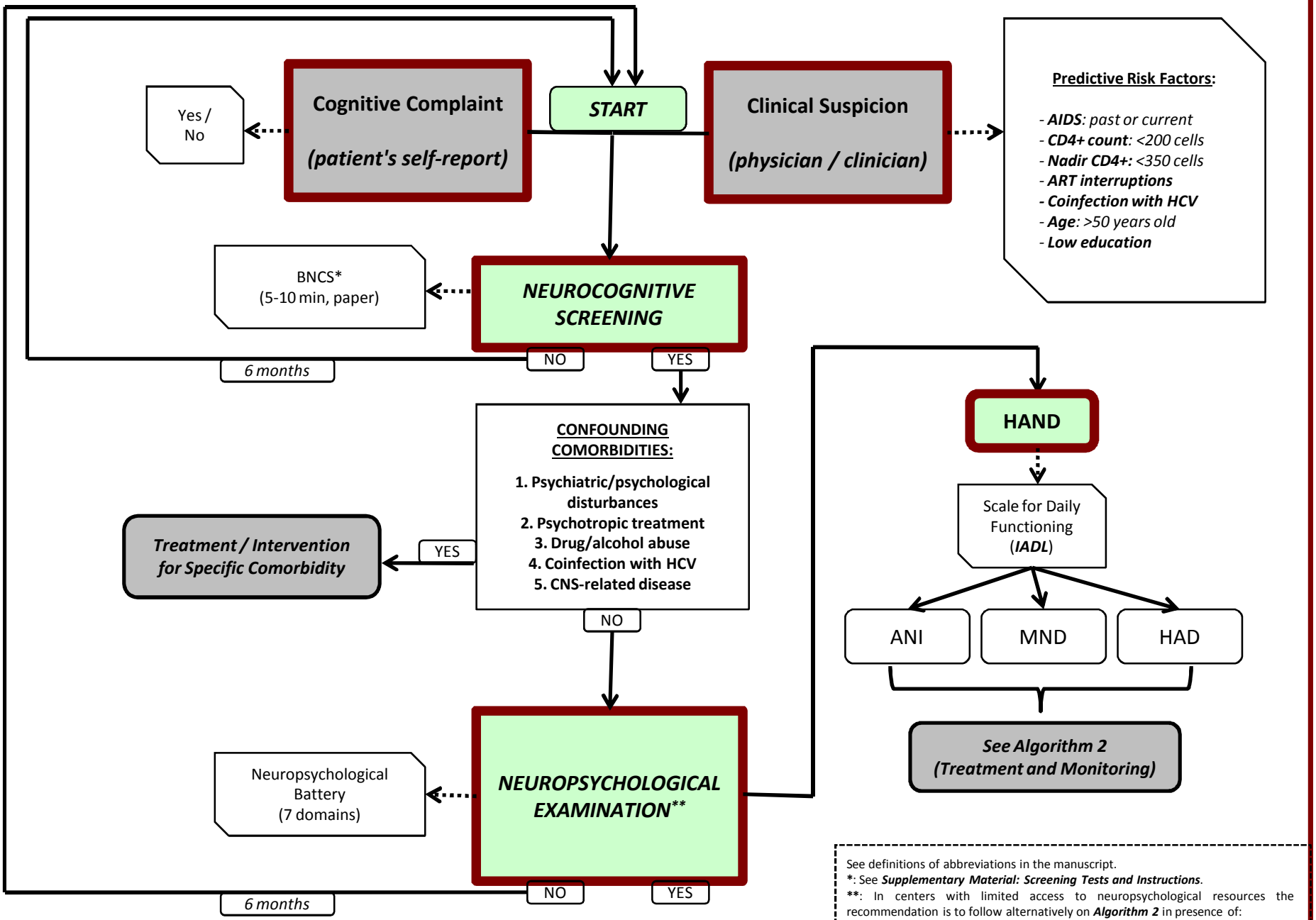
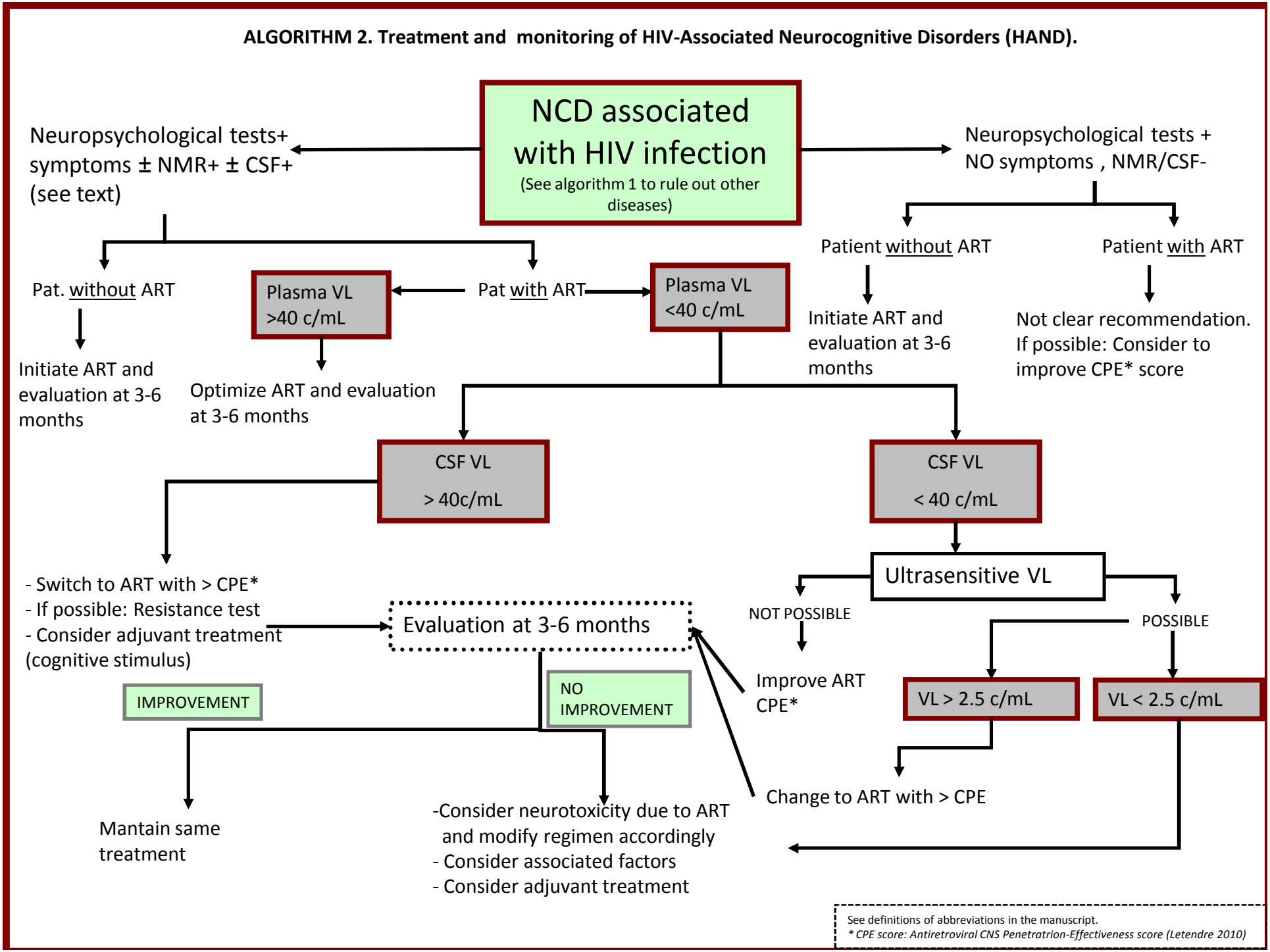
ALGORITHM 1. Screening, assessment and diagnosis of HIV-Associated Neurocognitive Disorders (HAND).



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.

ALGORITHM 2. Treatment and monitoring of HIV-Associated Neurocognitive Disorders (HAND).



CASE STUDY 1

Demographical Data

- ✓ *Gender*: Man
- ✓ *Age*: 52 years old
- ✓ *Marital status*: Single
- ✓ *Employment*: Administrative (office tasks)

- ✓ *Infection route*: HTS
- ✓ *HIV diagnosis*: 3 years, 5 months

- ✓ ***Cognitive complaints****: memory loss (difficultness for names recall) and verbal fluency (words hard to find).*

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Clinical Data

- ✓ *On CART*: **3TC+ABC+ATV** (CPE Score: 7)
- ✓ *Current ART regimen*: 1 month
- ✓ *First ART regimen*: 3 years, 5 months

- ✓ *CD4+ cell count*: **524** cells/µL
- ✓ *Nadir CD4+ count*: **161** cells/µL (3 years, 5 months)
- ✓ *Plasma VL*: **50** copies/mL
- ✓ *Highest plasma VL*: **30 000** cop/mL (3 years, 5 months)

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Neuropsychological Assessment

- ✓ *Education*: 14 years
- ✓ *Premorbid intelligence*: normal-superior
- ✓ *Emotional status*: mild depression and anxiety symptoms
- ✓ *Confounding comorbidities**: NO

**: coinfection with hepatitis C virus (HCV), current drug abuse, current psychiatric disorder, current psychopharmacological treatment, past/current CNS opportunistic infection, and past/ current CNS-related disease.*

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Neuropsychological Outcomes

- **Mild impairment in attention/working memory**.
- Normal scores in the rest of domains (*information processing speed, verbal memory, learning, motor function, verbal fluency and executive functioning*).

CONCLUSION: *The deficits found do not configure a pattern of clinical relevance.*

QUESTIONS

- *What is the clinical relevance of HIV-related cognitive complaints?*

Cognitive Complaints

- Frequency of HIV-related cognitive complaints in Spain:

N=268

Figure 1.

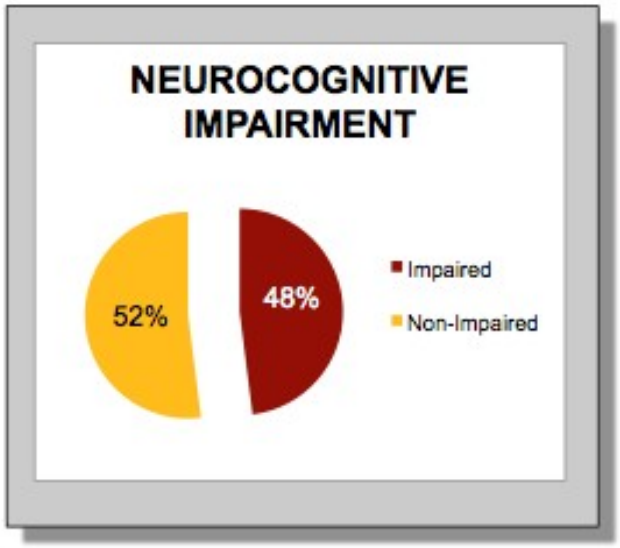
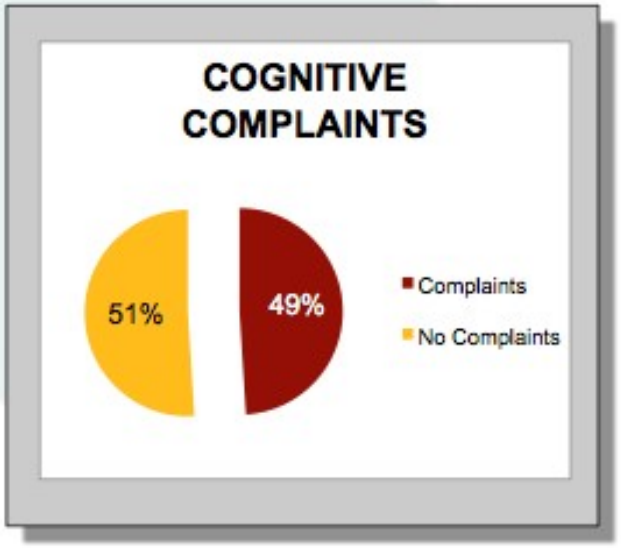


Figure 2.



Muñoz-Moreno et al, Helsinki, INS, 2009

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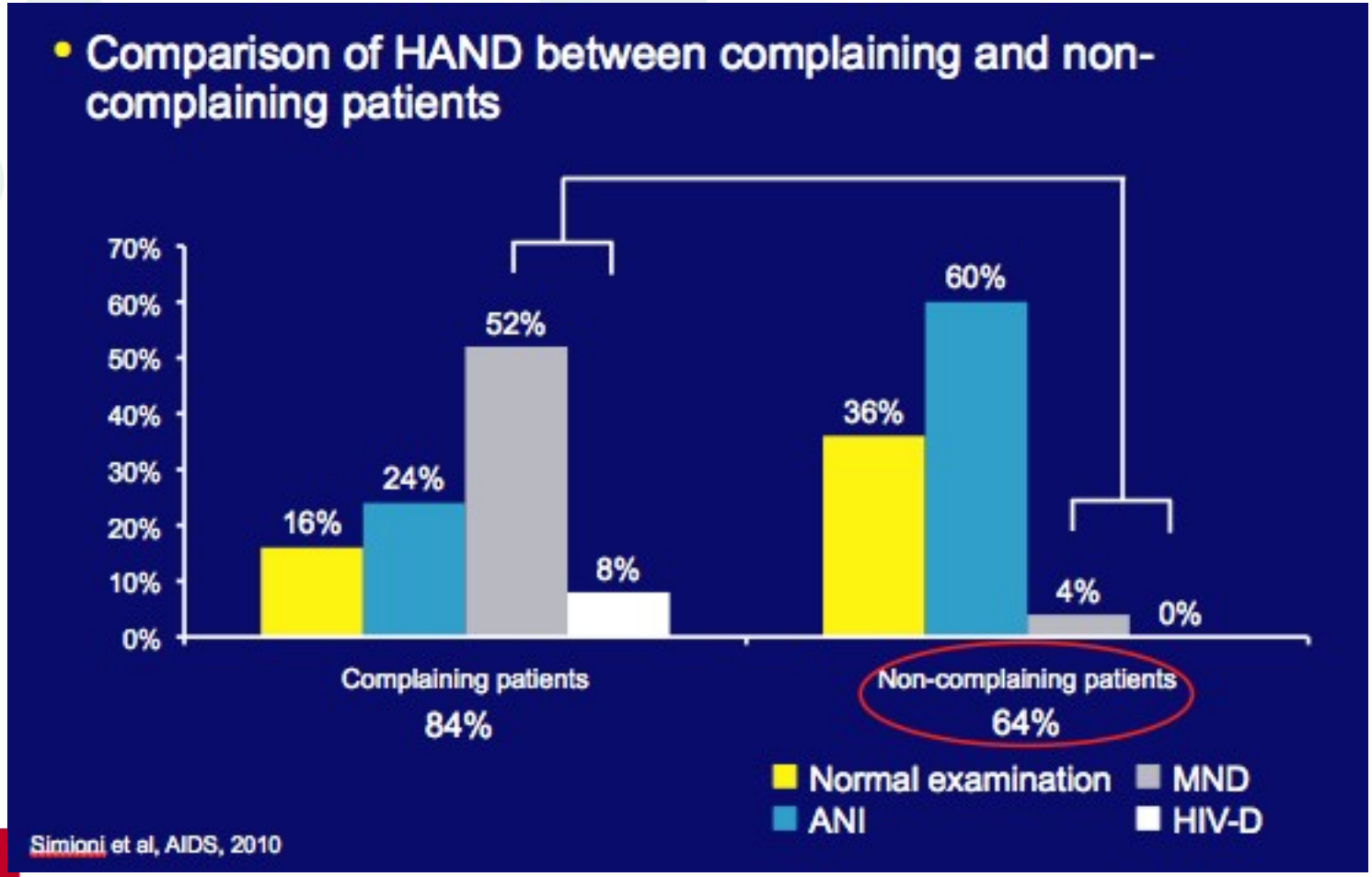
Cognitive Complaints



Simioni et al, AIDS, 2010

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Cognitive Complaints

- 3 Clinical Profiles:

- *1) Cognitive Complaints + HAND*
- *2 Cognitive Complaints + No HAND*
- *3) No Cognitive Complaints + HAND!!*

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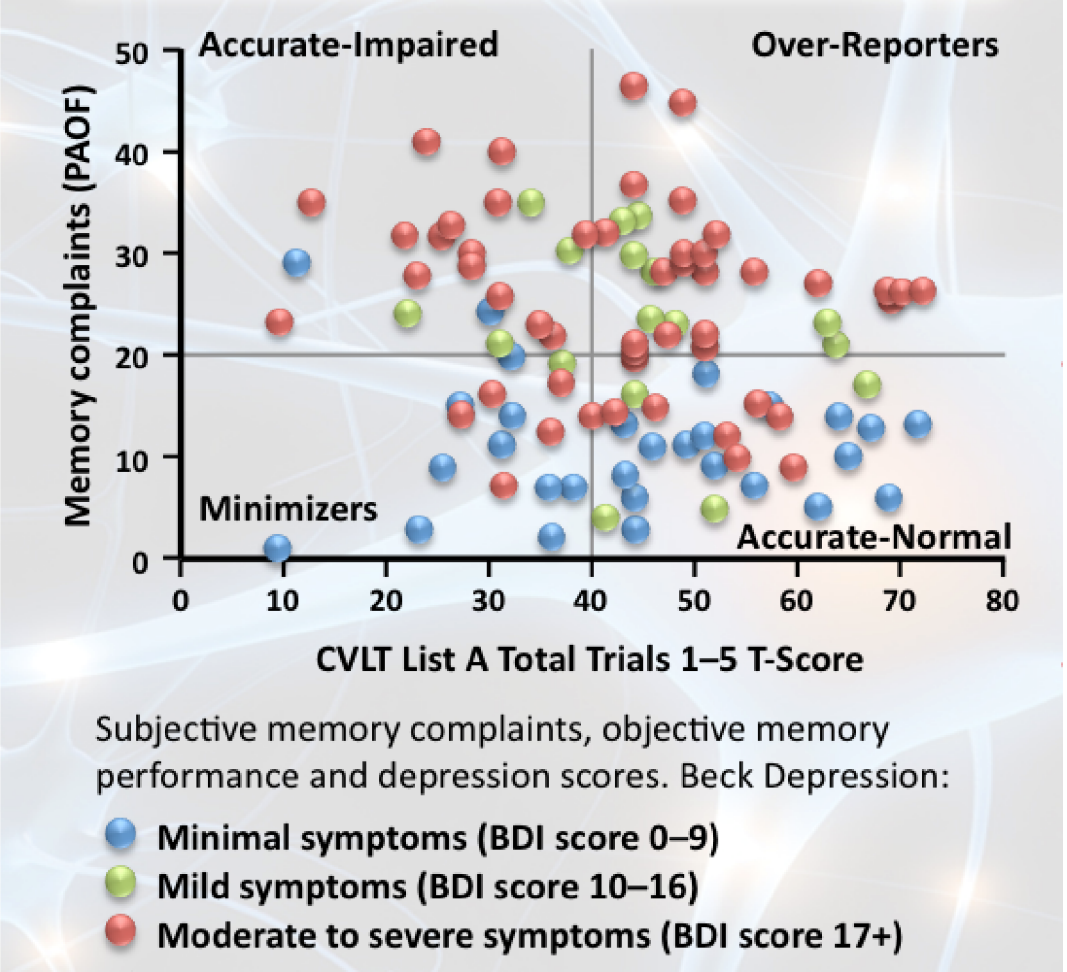
According to Emotional Status



- *2 "accurate" subtypes*
- *Over-reporters*
- *Minimizers*

Courtesy of Sean Rourke, Paris, Dec 2012

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QUESTIONS

- *What is the clinical relevance of HIV-related cognitive complaints?*

- *How can emotional disturbances be controlled?*

Emotional Screening

1) Hospital Anxiety and Depression Scale (HADS):

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

2) Beck Depression Inventory (BDI):

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

3) 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.*

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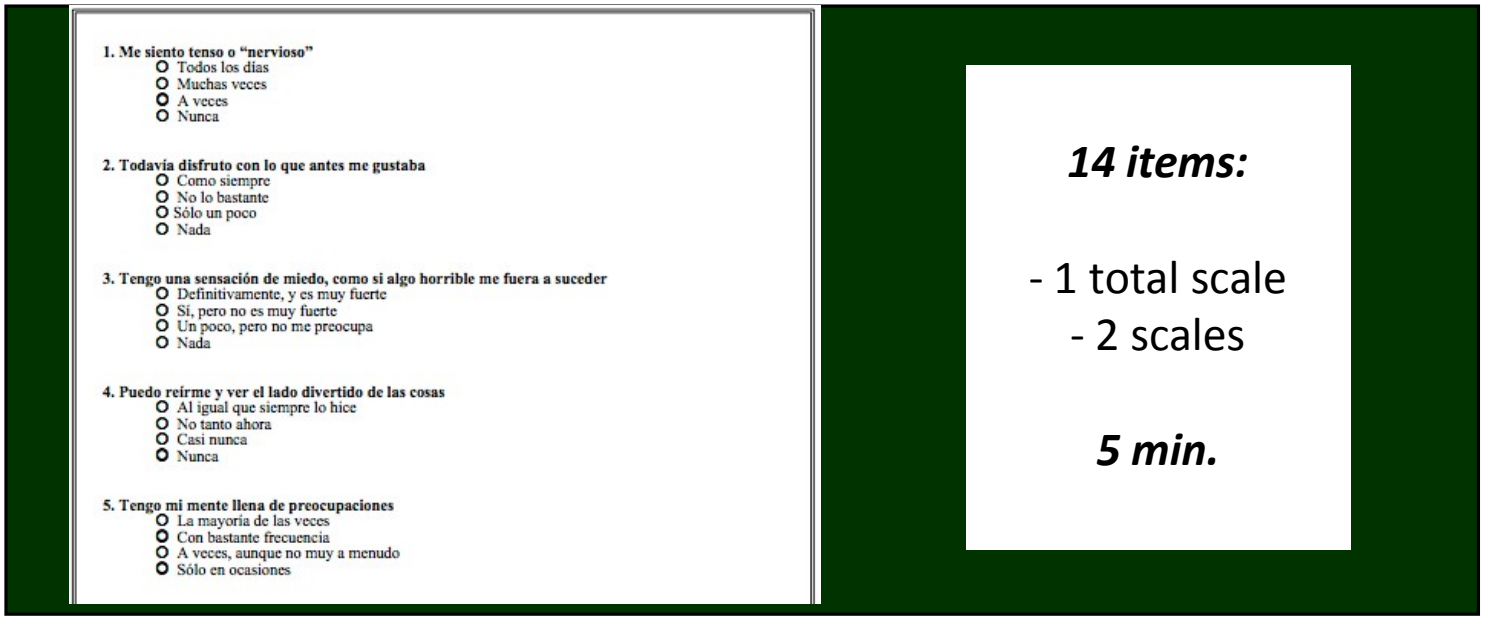
Depression and Anxiety Symptoms

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:

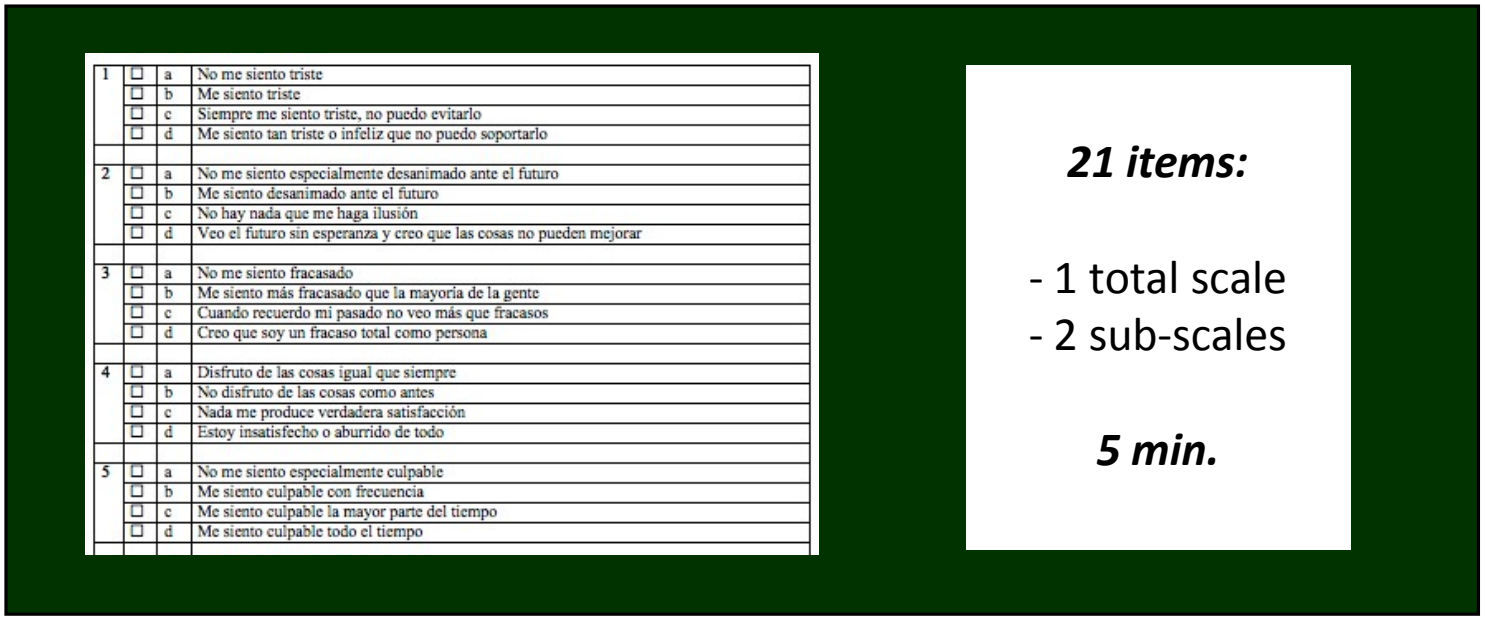
- 1 total scale
- 2 scales

5 min.

Zigmond, 1983

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 total scale
- 2 sub-scales

5 min.

Beck, 1979

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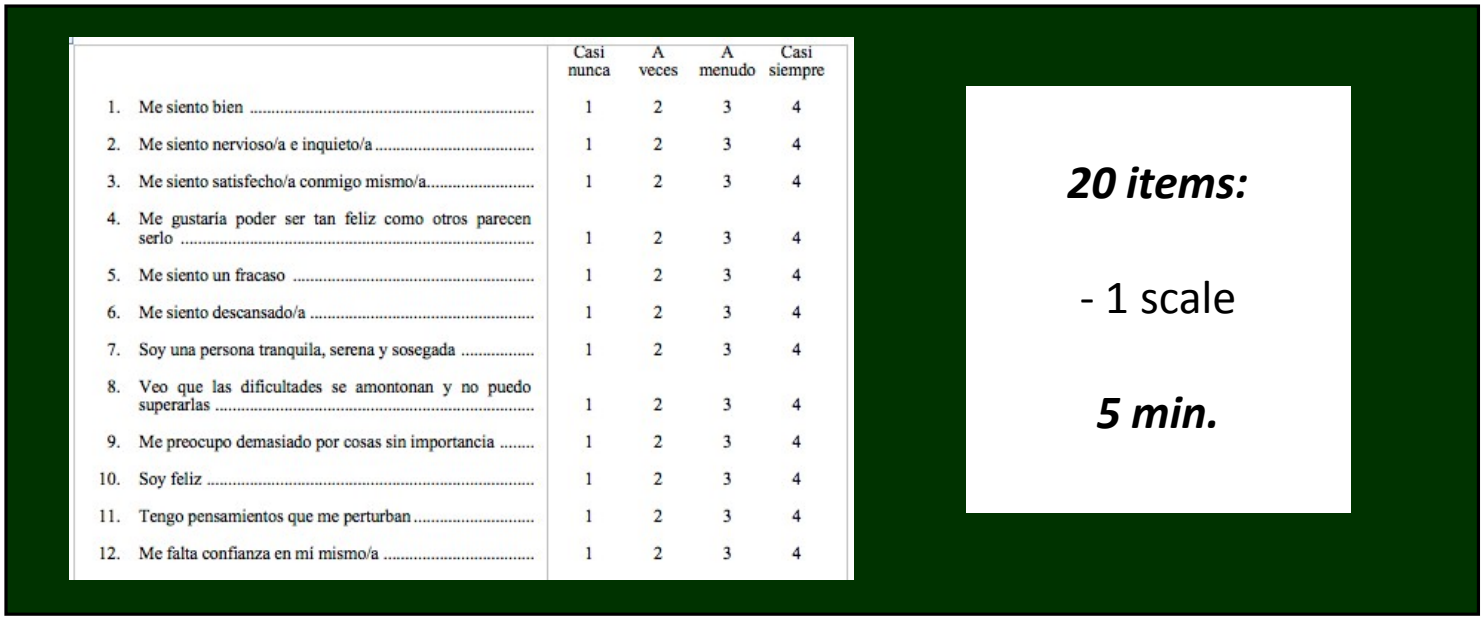
Anxiety Symptoms

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

5 min.

Spielberger, 1970

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QUESTIONS

- *What is the clinical relevance of HIV-related cognitive complaints?*
- *How can emotional disturbances be controlled?*
- *Could the impairment be detected by a neurocognitive screening tool?*

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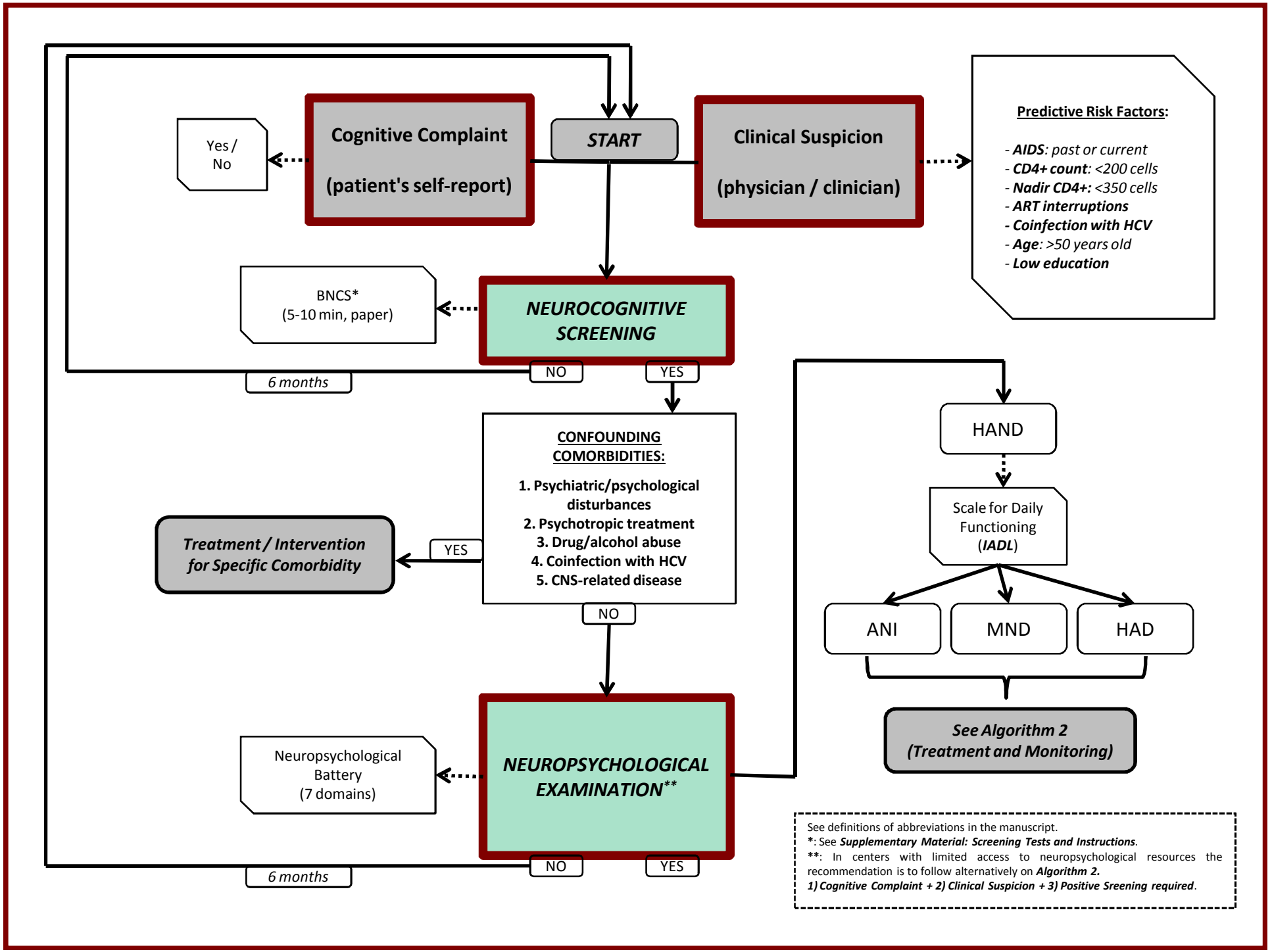
Yes / No
Cognitive Complaint (patient's self-report)
START
Clinical Suspicion (physician / clinician)
Predictive Risk Factors:
- AIDS: past or current
- CD4+ count: <200 cells
- Nadir CD4+: <350 cells
- ART interruptions
- Coinfection with HCV
- Age: >50 years old
- Low education
BNCS* (5-10 min, paper)
NEUROCOGNITIVE SCREENING
NO
YES
6 months
CONFOUNDING COMORBIDITIES:
1. Psychiatric/psychological disturbances
2. Psychotropic treatment
3. Drug/alcohol abuse
4. Coinfection with HCV
5. CNS-related disease
YES
Treatment / Intervention for Specific Comorbidity
NO
HAND
Scale for Daily Functioning (IADL)
ANI
MND
HAD
See Algorithm 2 (Treatment and Monitoring)
Neuropsychological Battery (7 domains)
NEUROPSYCHOLOGICAL EXAMINATION**
NO
YES
6 months
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.
1) Cognitive Complaint + 2) Clinical Suspicion + 3) Positive Sreening required.

Screening Tools

Screening Method	Reference	Duration	Pros	Cons
IHDS *(International HIV Dementia Scale)*	Sacktor et al, AIDS, 2005	5-10 min	- Quantitative score - Extensively used	- Designed for HAD - Limited sensitivity
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	- Copyright issues - Applicability (computerized)
MoCA *(Montreal Cognitive Assessment)*	Nasreddine et al, J Am Geriatr Soc, 2005	5-10 min	- 4 areas covered - Easy instructions	- Limited specificity - Better for HAD?
HNRC Screening	Carey et al, Clin Neuropsychol, 2004	5-10 min	- High sensitivity/specificity - Only 2 measures	- Copyright issues - Instrumental requirement (pegboard)
BNCS *(Brief NeuroCognitive Screen)*	Ellis et al, J Neurovirol, 2005	5-10 min	- Extensively used - Experience on tests	- Limited sensitivity for Spanish speakers
NEU Screen	Muñoz-Moreno et al, ISNV, New York, 2012	5-10 min	- High sensitivity/specificity - Experience on tests	- No experience on English speakers

Screening Tools

Screening Method	Reference	Duration	Pros	Cons
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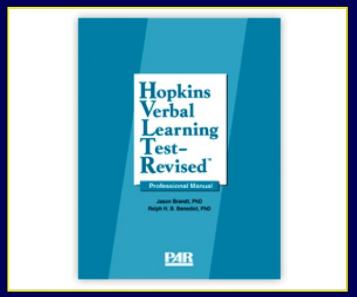
HRNC Screen (2004)

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)

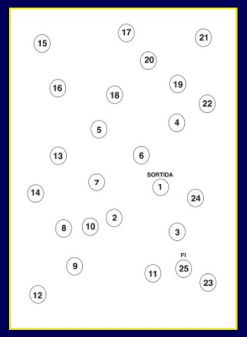


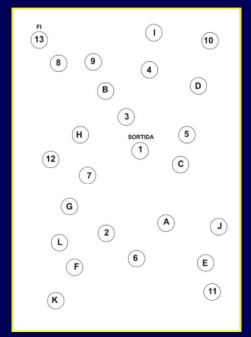
Carey et al, Clin Neuropsychol, 2004

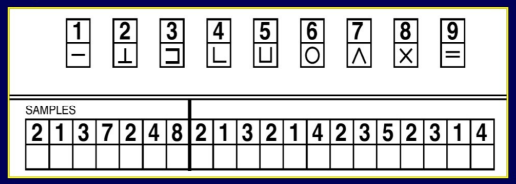
Brief NeuroCognitive Screen (BNCS) (2005)

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)







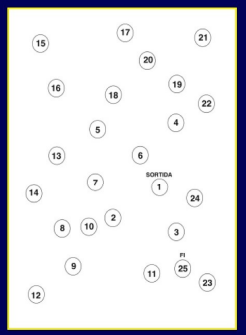
- Disadvantages:
  - Low sensitivity: 65% (72% specificity)
  - Scarce information provided

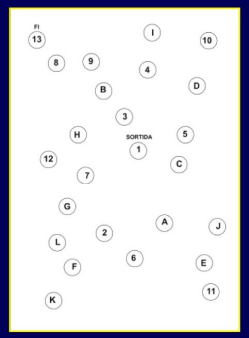
Ellis et al, J Neurovirol, 2005

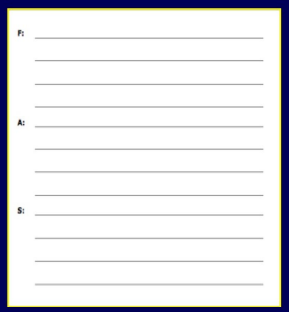
NEU Screen (2012)

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)

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] Autónoma de Barcelona University (Bellaterra, Spain); [3] Politècnica de Catalunya University (Barcelona, Spain); [4] Consorci Sanitari Parc Taulí (Sabadell, Spain); [5] Clinic 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 (ISNV)

May 29 - June 2, New York City, NY

Abstract P155

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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.*

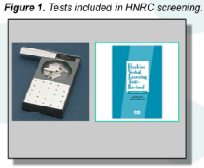


Figure 2. *Tests included in BNCS.*

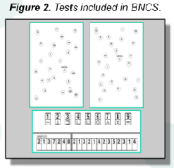
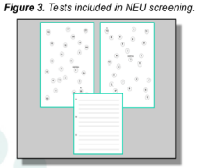


Figure 3. *Tests included in NEU screening.*



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, Marlen González-García, Jessica Toro and Albert Tuldrà

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

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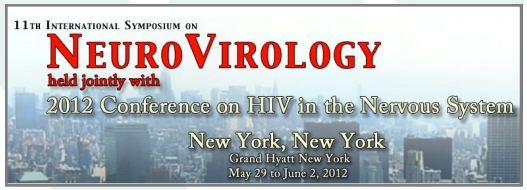

11th International Symposium on NeuroVirology
&
2012 Conference on HIV Infection in the Nervous System
- - -
New York, 29th May - 2nd June, 2012

Abstract P155

Oral Communication

Differences in North American and West European Study Populations When Detecting Neurocognitive Impairment in HIV Infection:

A Comparison of 3 Screening Methods

Muñoz-Moreno, JA[1,2]; Prats, A[1,2]; Pérez-Álvarez, N[1,3]; Fumaz, CR[1,2], Ferrer, MJ[1,2], Negredo, E[1,2]; Bernaus, M[4]; Blanch, J[5]; Deig, E[6]; Force, Ll[7]; Masabeu, A[8]; Raich, A[9]; Garolera, M[10,11]; Clotet, B[1,2,12]; *and the NEU Study Group*

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

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3 Screening Methods: HNRC vs BNCS vs 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			*68%*	-			*82%*	*69%*
BNCS			-	*68%*			*80%*	*76%*
NEU Screening	*74%*	*81%*	*79%*	*78%*			*79%*	*78%*

Screening Methods

- ***HRNC Screen*** *(Carey et al, 2004):*

  Negative *(0 / 2 scores)*

- ***BNCS*** *(Ellis et al, 2005):*

  Negative *(0 / 3 scores)*

- ***NEU Screen*** *(Muñoz-Moreno et al, 2012):*

  Negative *(0 / 3 scores)*

CASE STUDY 2

Demographical Data

- ✓ *Gender*: Man
- ✓ *Age*: 31 years old
- ✓ *Marital status*: Single
- ✓ *Employment*: Graphic designer

- ✓ *Infection route*: HMS
- ✓ *HIV diagnosis*: 14 years, 9 months

- ✓ ***Cognitive complaints****: difficultness for keeping information in mind (since 6 years ago, aprox).*

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Clinical Data

- ✓ *On CART*: **FTC/TDF+EFV** (CPE Score: 7)
- ✓ *Current ART regimen*: 5 months
- ✓ *First ART regimen*: 4 years, 11 months

- ✓ *CD4+ cell count*: **896** cells/µL
- ✓ *Nadir CD4+ count*: **123** cells/µL (5 years, 1 months)
- ✓ *Plasma VL*: **25** copies/mL
- ✓ *Highest plasma VL*: **45 000** cop/mL (9 years, 4 months)

Neuropsychological Assessment

- ✓ *Education*: 17 years
- ✓ *Premorbid intelligence*: normal
- ✓ *Emotional status*: normal
- ✓ *Confounding comorbidities**: NO

**: coinfection with hepatitis C virus (HCV), current drug abuse, current psychiatric disorder, current psychopharmacological treatment, past/current CNS opportunistic infection, and past/ current CNS-related disease.*

Neuropsychological Outcomes

- **Slowness in information processing speed.**
- **Mild impairment in executive functioning (cognitive flexibility).**

- Interference on daily living.

CONCLUSION: *The deficits found configure a fronto-subcortical pattern of affectation that is compatible with mild neurocognitive impairment associated with HIV (MND).*

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QUESTIONS

- *What is the clinical relevance of time with VIH?*

Time with HIV

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,

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

Cysique et al, HIV Medicine, 2010

Abstract: E-122

Predicting HIV-Related Neurocognitive Dysfunction: the Relevance of Clinical Factors

Jose A. Muñoz-Moreno[1], Núria Pérez-Álvarez[1], Scott Letendre[2], Mariana Cherner[2], Carmina R. Fumaz[1], Anna Prats[1], Maria J. Ferrer[1], Eugènia Negredo[2], Maite Garolera[3], Bonaventura Clotet[1]

[1] Lluita contra la SIDA Foundation – Germans Trias i Pujol University Hospital, Barcelona, Catalonia, Spain
[2] HIV Neurobehavioral Research Center – University of California, San Diego, CA, USA
[3] Terrassa Hospital – Consorci Sanitari de Terrassa, Barcelona, Catalonia, Spain

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Background

Neurocognitive dysfunction is a frequent complication in HIV-infected patients. Consistent data describe that HIV-associated neurocognitive disorders are present in 40-60% of people living with HIV [1,2,3]

Effective strategies to significantly prevent or revert this disruption are unknown [4], and additional risk factors, such as age [5], nadir CD4 cell count [6], or coinfection with HIV [7], are exacerbating this situation.

We aimed to identify relevant clinical variables in the development of neurocognitive dysfunction, using predictive models based on classification and regression statistical analyses.

References:

1. Antinori A, Arendt G, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology* 2007; 69:1789-99.
2. Heaton R, Franklin D, et al. CHARTER Study Group. HIV-associated Neurocognitive Impairment Remains Prevalent in the Era of Combination ART: The CHARTER Study. *The 16th Conference on Retroviruses and Opportunistic Infections. 8-11 February 2009, Montreal, Canada. Abstract 154.*
3. Muñoz-Moreno JA, Cherner M, et al. Depression Symptoms May Influence in the Diagnosis of Neurocognitive Disorders in HIV Infection. *The IWS 2009 Mid-Year Meeting, 29 July - 1 August 2009, Helsinki-Finland and Tallinn-Estonia.*
4. Letendre SL, Ellis RJ, et al. Neurologic complications of HIV disease and their treatment. *Top HIV Med* 2009; 17:45-56.
5. Becker JT, Lopez OL, et al. Prevalence of cognitive disorders differs as a function of age in HIV virus infection. *AIDS* 2004; 18:S11-8.
6. Muñoz-Moreno JA, Fumaz CR, et al. Nadir CD4 cell count predicts neurocognitive impairment in HIV-infected patients. *AIDS Res Hum Retroviruses* 2008; 24:1301-7.
7. Hillsabeck RC, Castellon SA, Hinkin CH. Neuropsychological aspects of coinfection with HIV and hepatitis C virus. *Clin Infect Dis* 2005; 41:S58-64.

Methods

Study Participants:

A total of 172 patients receiving care in the HIV unit of the Germans Trias i Pujol University Hospital (Barcelona, Spain). All participants were at least 18 years old, and were excluded those with a prior or current opportunistic infection involving the CNS, reporting drug use, or with a prior or current psychiatric disorder.

Objectives:

- To identify variables strongly associated with HIV-related neurocognitive impairment in HIV infection.
- To find relevant cut-points regarding numerical variables in association with HIV-related neurocognitive impairment.
- To obtain different predictive models focused on estimating the appearance of HIV-related neurocognitive impairment.

Statistical Analyses:

Classification and regression trees were used to determine the significance of the following variables in the onset of HIV-related neurocognitive dysfunction:

Age, gender, infection route, time with HIV, AIDS diagnosis, CD4 cell count, nadir CD4 cell count, plasma viral load, highest plasma viral load, coinfection with HCV, time since ART therapy initiation, time on current ART regimen, CPE rank of the current ARV regimen, and therapy interruption in the past.

Data analyses were performed according to naïve (n=30) or treatment-experienced (n=142) patients. The existence of neurocognitive dysfunction was based on the determination of neurocognitive impairment assessed by a comprehensive neuropsychological tests battery.

Results

Study participants were mostly men (78%), middle-aged (mean 42 years), infected via sex with men (50%), on ART therapy (66%), and HCV seronegative (78%). Median duration of the current ART regimen was 10 months, current CD4 count was 456 cells/µL, nadir CD4 count was 255 cells/µL, and 79% had undetectable plasma viral load (**Table 1**).

Table 1. *Demographic, clinical and neurocognitive characteristics of the sample.*

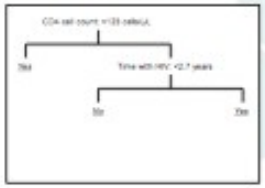
	Total (N = 172)	Naïve (n = 30)	Experienced (n = 142)	P naïve
Age (years)	42	36	43	<0.001
Gender (women)	21	17	21	0.60
Education (years)	12	11	12	0.70
Employed (%)	75	90	70	0.01
Time since HIV diagnosis (years)	9.4	0.7	10.8	<0.001
Time since first ART (years)	6.3	-	6.3	-
Time on current ARV regimen (months)	10	-	10	-
AIDS (%)	13	10	16	0.27
Current CD4 count (cell/µL)	456	419	474	0.11
Nadir CD4 count (cell/µL)	255	384	206	<0.001
Plasma viral load (log)	1.7	4.2	1.7	<0.001
Mean highest plasma viral load (copies/mL)	320187	78098	419215	0.19
Undetectable viral load (%)	79	-	87	-
Coinfection with HCV (%)	22	7	25	0.02
Past ART interruptions (%)	48	-	48	-
Current regimen CPE rank	2	-	2	-
Neurocognitive impairment (%)	54	60	52	0.15

Data expressed as medians, except when specified.

Naïve Patients:

Prevalence of neurocognitive impairment was 60%, and the predictive model with lowest classification error indicated current CD4 count (<123 cell/µL) and time with HIV (>2.7 years) as the most significant variables predicting neurocognitive impairment (**Figure 1**).

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



Treatment-Experienced Patients:

Regarding treated patients, prevalence of neurocognitive impairment was 51%, and two models showed optimal classification. The first revealed that the most relevant classifying variables associated with neurocognitive impairment were time on current ART regimen (<32.2 months), time since ART therapy initiation (>13.5 years), age (>32 years), and highest viral load (log>4.8 copies/mL); and the second, nadir CD4 count (<365 cell/µL), gender (male), highest viral load (log>4.5 cop/mL), and AIDS (**Figures 2 and 3**).

Lower CPE rank, coinfection with HCV, and ART interruption, were factors also associated with impairment, although in our analyses they did not reach statistical significance.

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

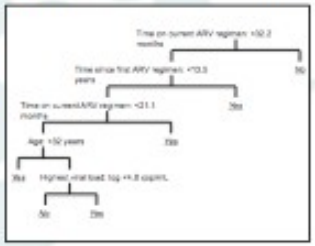
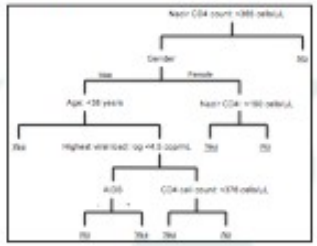


Figure 3. *Predictive model (correct classification: 84.9%).*



Conclusions

- ✓ Predictive models for the development of HIV-related neurocognitive dysfunction may be obtained with high reliability.
- ✓ In treatment-experienced patients, by contrast to naïve patients, a more accurate estimation may be achieved, although further clinical variables are involved.
- ✓ In the goal of predicting HIV-related neurocognitive dysfunction, special attention should be given to clinical factors such as time on ARV regimens, immunological parameters, and high levels of plasma viral load replication.

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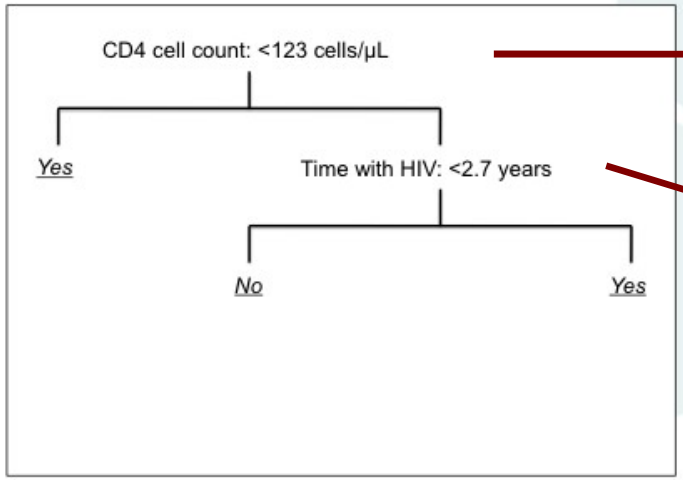
Muñoz-Moreno et al, CROI San Francisco, 2010, Abstract 416

Time with HIV

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*

Muñoz-Moreno et al, CROI San Francisco, 2010, Abstract 416

QUESTIONS

- *What is the clinical relevance of time with VIH?*

- *What is the clinical relevance of nadir CD4 cell count?*

Nadir CD4 Cell Count

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

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)	

Chi Square for linear trend:
p=0.046

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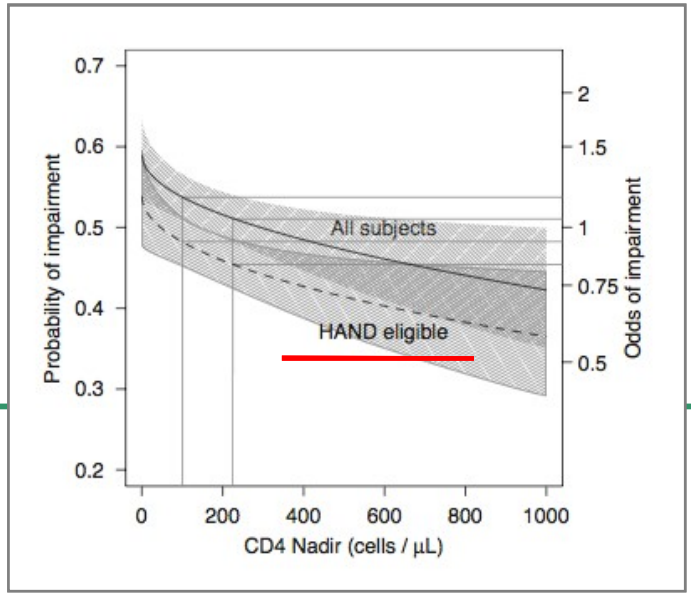
Nadir CD4 Cell Count

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



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QUESTIONS

- *What is the clinical relevance of time with VIH?*
- *What is the clinical relevance of nadir CD4 cell count?*
- *Could the impairment be detected by a neurocognitive screening tool?*

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Screening Methods

- ***HRNC Screen*** *(Carey et al, 2004):*

  Negative *(0 / 2 scores)*

- ***BNCS*** *(Ellis et al, 2005):*

  Positive *(1 / 3 scores)*

- ***NEU Screen*** *(Muñoz-Moreno et al, 2012):*

  Positive *(1 / 3 scores)*

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CASE STUDY 3

Demographical Data

- ✓ *Gender*: Man
- ✓ *Age*: 26 years old
- ✓ *Marital status*: Single
- ✓ *Employment*: Student

- ✓ *Infection route*: HMS
- ✓ *HIV diagnosis*: 4 months

- ✓ ***Cognitive complaints****: No perception of cognitive changes.*

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Clinical Data

- ✓ *Naïve patient*

- ✓ *CD4+ cell count*: **370** cells/µL
- ✓ *Nadir CD4+ count*: **370** cells/µL (current)
- ✓ *Plasma VL*: **67 000** copies/mL
- ✓ *Highest plasma VL*: **320 000** cop/mL (3 months)

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Neuropsychological Assessment

- ✓ *Education*: 15 years
- ✓ *Premorbid intelligence*: normal
- ✓ *Emotional status*: normal
- ✓ *Confounding comorbidities**: NO

**: coinfection with hepatitis C virus (HCV), current drug abuse, current psychiatric disorder, current psychopharmacological treatment, past/current CNS opportunistic infection, and past/ current CNS-related disease.*

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Neuropsychological Outcomes

- **Deficits in attention/working memory.**
- **Mild impairment in verbal fluency.**
- **Mild impairment in executive functioning (cognitive flexibility).**

- No interference of daily living functioning.

CONCLUSION: *The deficits found configure a fronto-subcortical pattern of affectation that is compatible with an asymptomatic neurocognitive impairment associated with HIV (ANI).*

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QUESTIONS

- *Should we intervene if there is no interference of daily functioning?*

HIV-Associated Neurocognitive Disorders (HAND)

	No Previous Cause	*No Confounding Comorbidities*	*Acquired Impairment: ≤1 SD, ≥2 Domains*	*Impaired Daily Functioning*
Asymptomatic Neurocognitive Impairment (ANI)	✓	✓	✓	No
Mild Neurocognitive Disorder (MND)	✓	✓	Mild	Yes
HIV-Associated Dementia (HAD)	✓	✓	Marked	Yes

Antinori et al, Neurology, 2007

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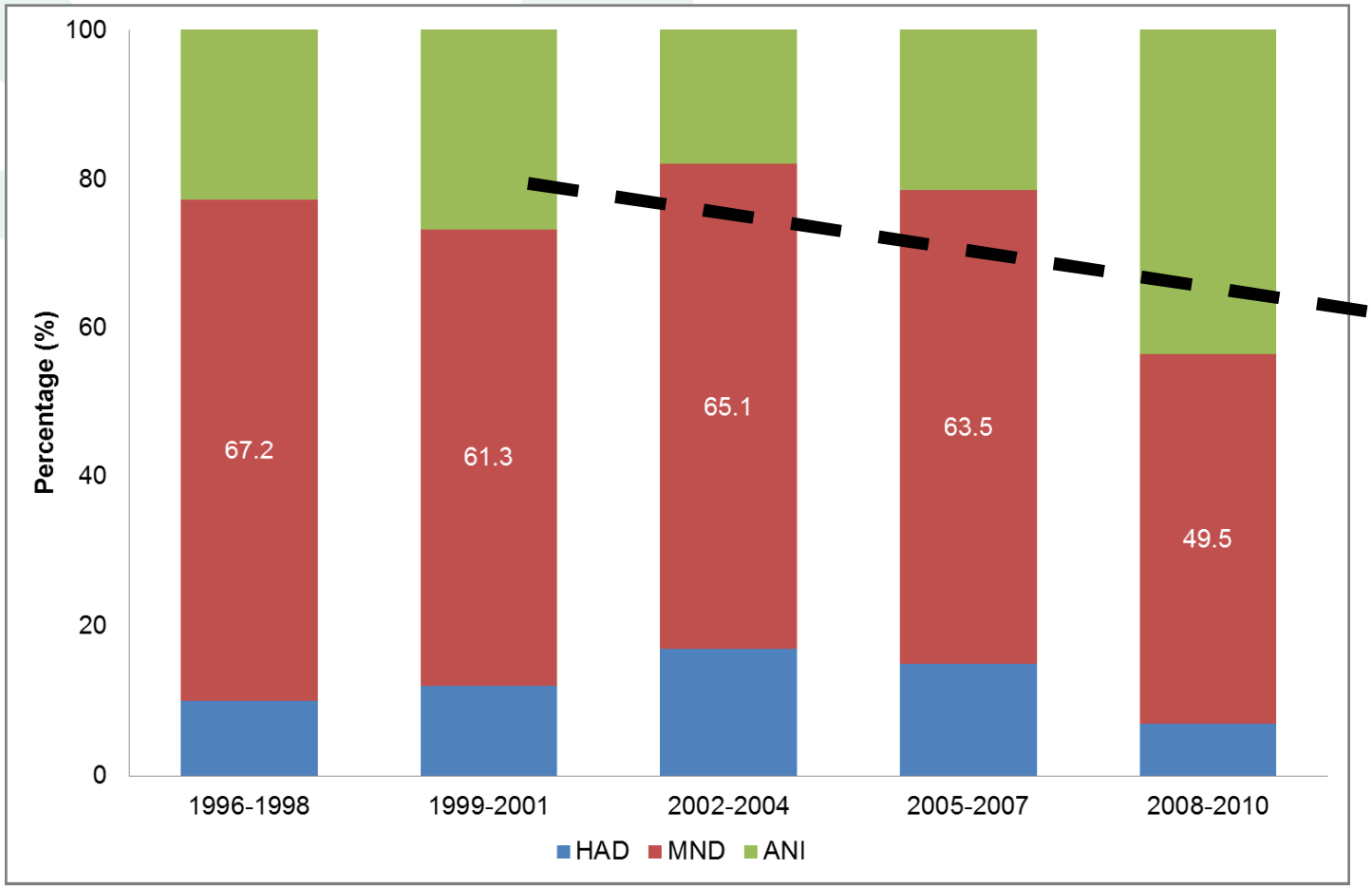
Asymptomatic Neurocognitive Disorder (ANI)



Tozzi et al, International CNS Meeting, Frascati, 2011

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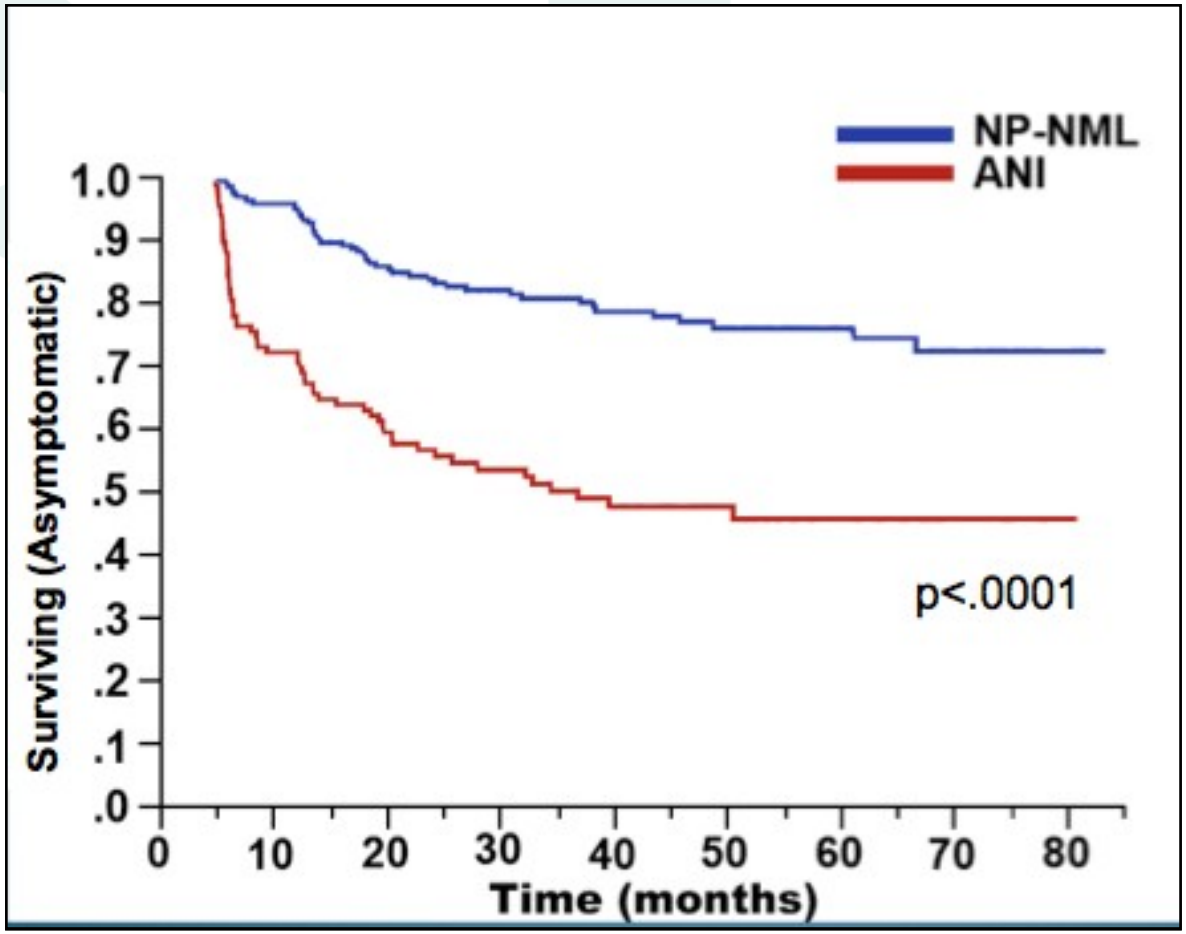
Asymptomatic Neurocognitive Disorder (ANI)



NML (n=226)

ANI (n=121)

Relative risk: 3.02

CI: 2.08, 4.42

Grant et al, CROI, Seattle, 2012

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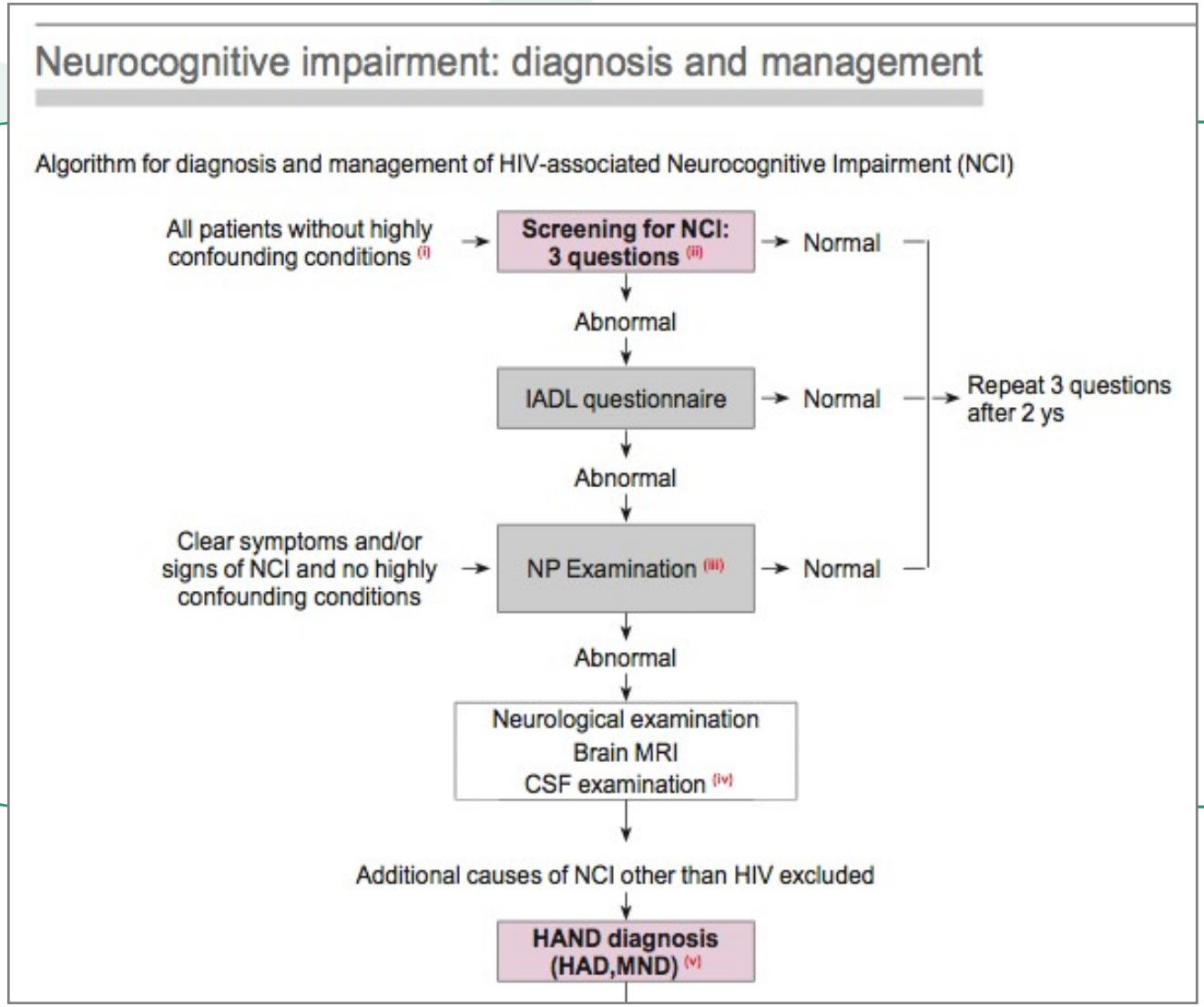
Asymptomatic Neurocognitive Disorder (ANI)

	No Decline (n=237)	Decline (n=110)	P-value
Background Factors			
Age	42.6 (8.7)	45.7 (7.4)	.002
Education	13.2 (2.3)	12.6 (2.2)	.007
% Male	86.9%	70.9%	.0003
% Lifetime Substance Dx	65.8%	80.9%	.004
% with Comorbidity	24.9%	41.8%	.001
Disease Factors			
% AIDS	54.4%	67.3%	.02
Nadir CD4	204 [56-378]	163 [55-277]	.03
% HCV+	18.1%	32.7%	.003

Grant et al, CROI, Seattle, 2012

EACS Guidelines - November 2012



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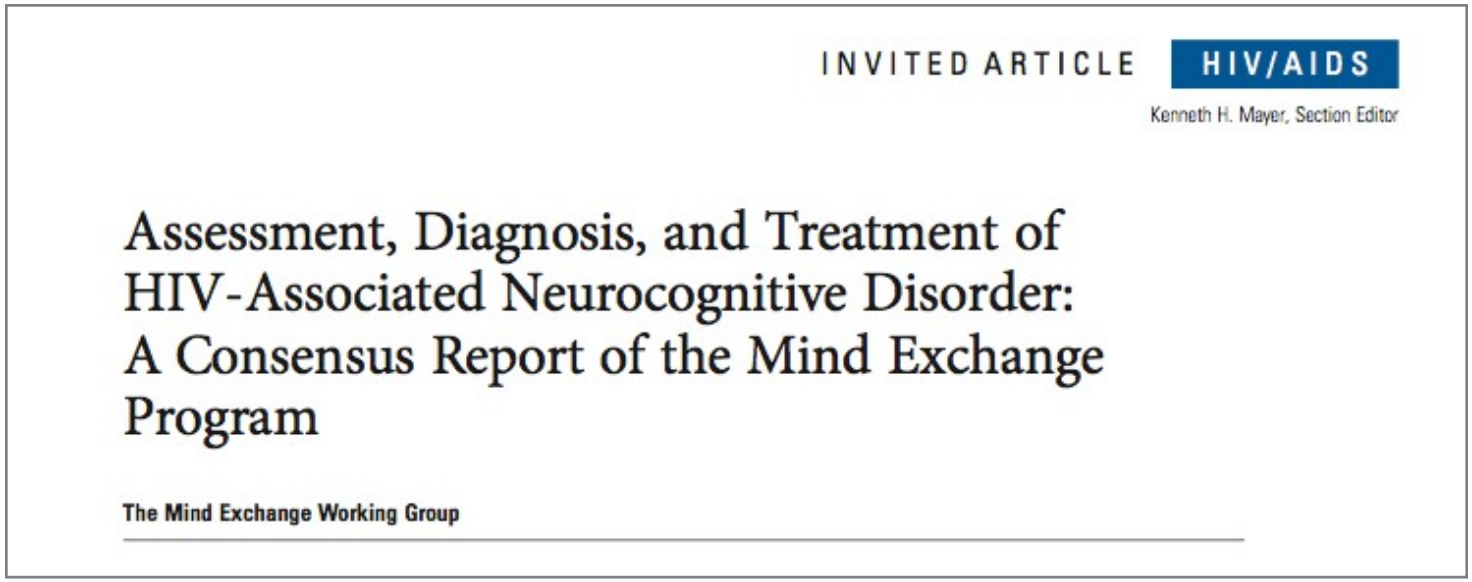
MIND Exchange Project: International Educational Program



INVITED ARTICLE HIV/AIDS

Kenneth H. Mayer, Section Editor

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

The Mind Exchange Working Group

The Mind Exchange Working Group, CID, 2013

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Selected questions (1)

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 factors such as the following affect the risk of HAND? : Aging, CD4 nadir; naive CD4 cells
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?

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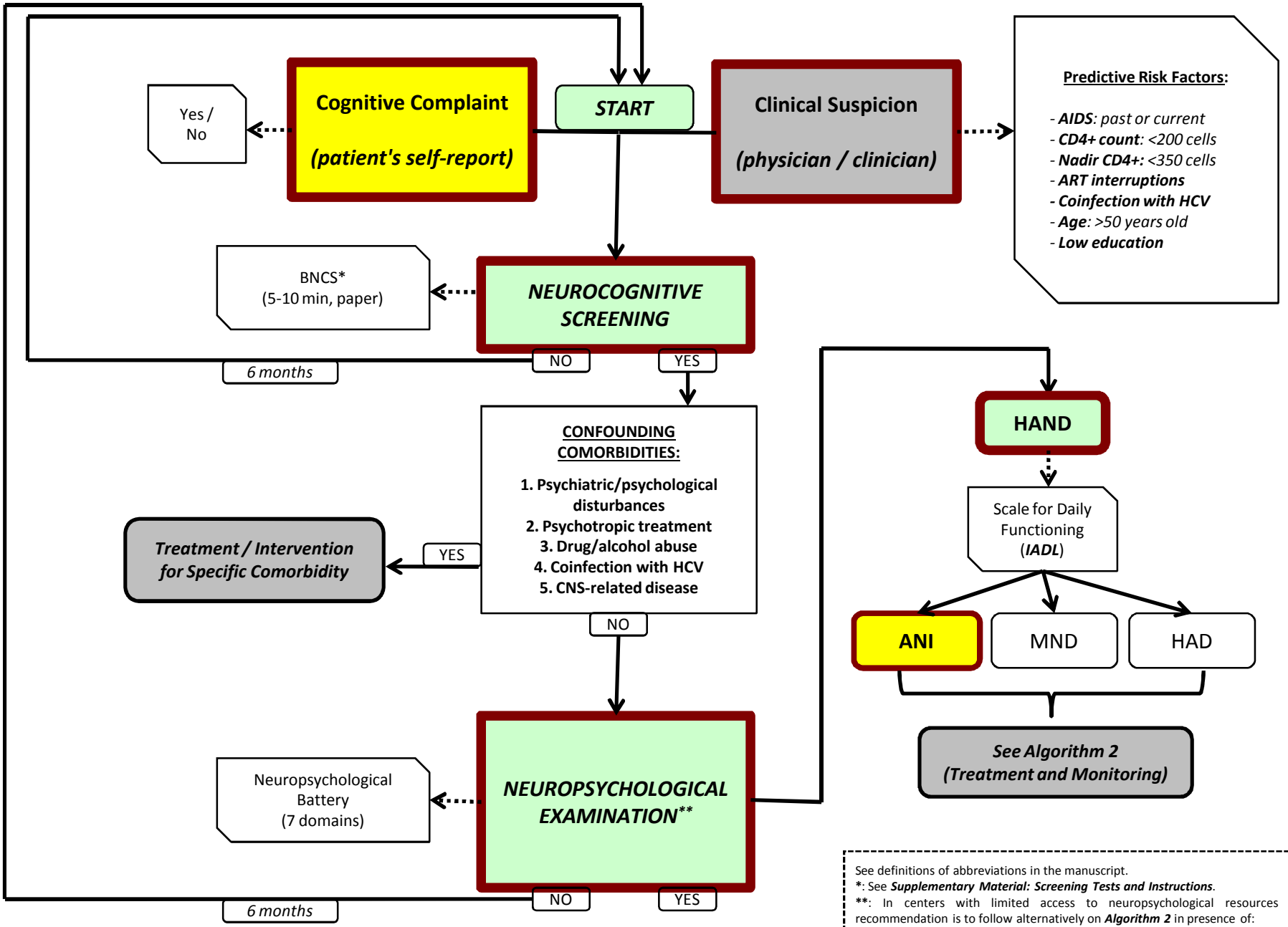
ALGORITHM 1. Screening, assessment and diagnosis of HIV-Associated Neurocognitive Disorders (HAND).



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.

QUESTIONS

- *Should we intervene if there is no interference of daily functioning?*

- *What is the clinical relevance of being a treatment-naïve patient?*

Treatment-Naïve Patients

Composite scores	All patients (n=94)	ARV-naïve patients (n=62)	ARV-experienced patients (n=32)	P
NPZ4 global score, mean (±SD)	-2.17 (±1.85)	-2.03 (±1.61)	-2.47 (±2.31)	0.377
NPZ8 global score, mean (±SD)	-1.79 (±1.25)	-1.73 (±1.24)	-1.96 (±1.29)	0.499

		Total (N=1160)	Unimpaired (N=702) (61%)	Impaired (N=458) (39%)	P
ART history at parent entry	Naïve	584 (50%)	350 (50%)	234 (51%)	0.68
	Experienced	576 (50%)	352 (50%)	224 (49%)	

Tozzi et al, JAIDS, 2007; Robertson et al, AIDS, 2007

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Treatment-Naïve Patients

- Prevalence of NCI in our cohort:

☞ *Naïve*: **45%**

☞ *Naïve + CD4 <500 cells/µL*: **58%**

☞ *Experienced + VL <50 cop/mL + No Comorbidities*: **41%**

QUESTIONS

- *Should we intervene if there is no interference of daily functioning?*
- *What is the clinical relevance of being a treatment-naïve patient?*
- *Could the impairment be detected by a neurocognitive screening tool?*

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Screening Methods

- ***HRNC Screen*** *(Carey et al, 2004):*

  Negative *(0 / 2 scores)*

- ***BNCS*** *(Ellis et al, 2005):*

  Negative *(0 / 3 scores)*

- ***NEU Screen*** *(Muñoz-Moreno et al, 2012):*

  Positive *(1 / 3 scores)*

Thanks for your participation!

Jose A. Muñoz-Moreno, Ph.D.

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