Screening for Neurocognitive Impairment: a Practical Approach

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Screening tests for HAND: Views from an ID physicians

- Who is aware of the problem
- Who visits patients
- With little knolewdge in tests and related statistics

The AIDS dementia complex (ADC)

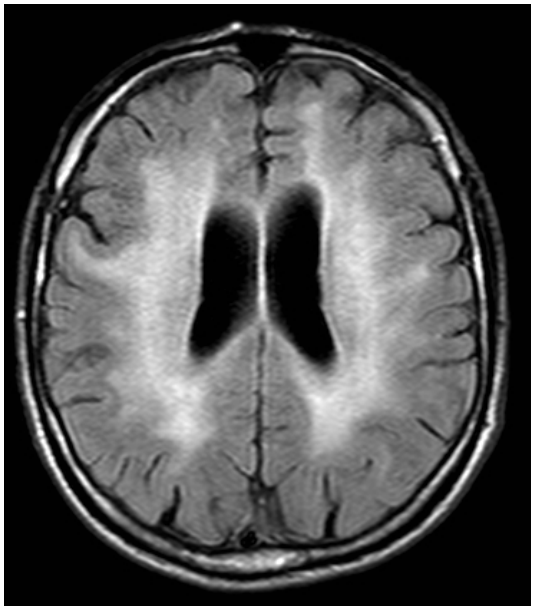
AAN definition criteria (1991)

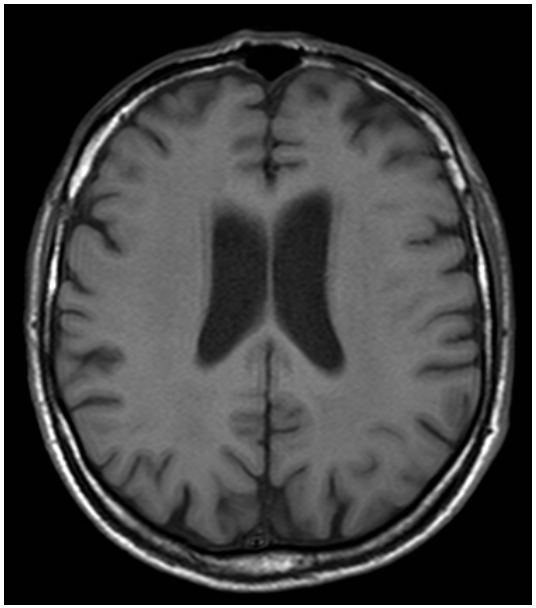
1. Acquired abnormality in at least two of the following cognitive abilities:
   - Attention/concentration
   - Speed of processing of information
   - Abstraction/reasoning
   - Visuospatial skills
   - Memory/learning
   - Speech/language

2. At least one of the following:
   - Acquired abnormality in motor function or performance
   - Decline in motivation or emotional control or change in social behavior

3. Absence of clouding of counsciousness

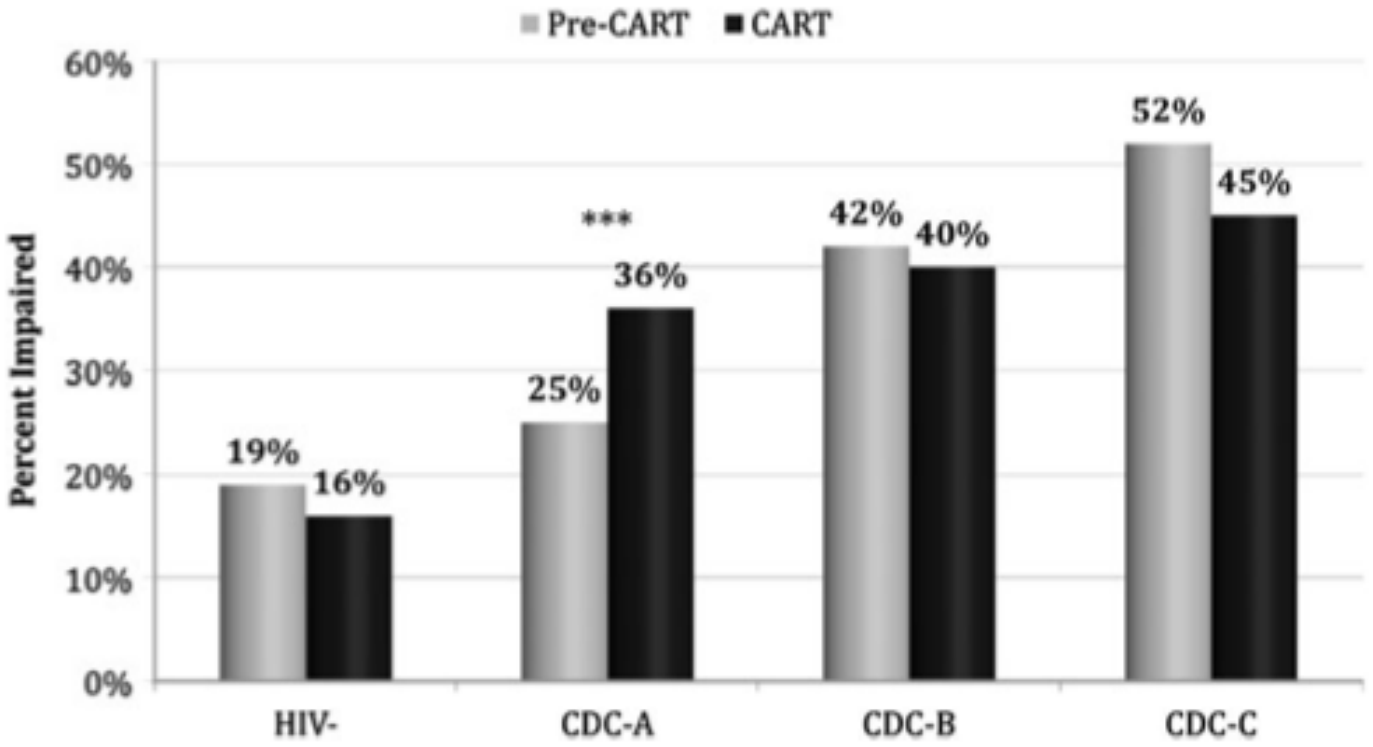
4. Absence of evidence of other etiology





Neurocognitive Impairment remains highly prevalent after the introduction of cART

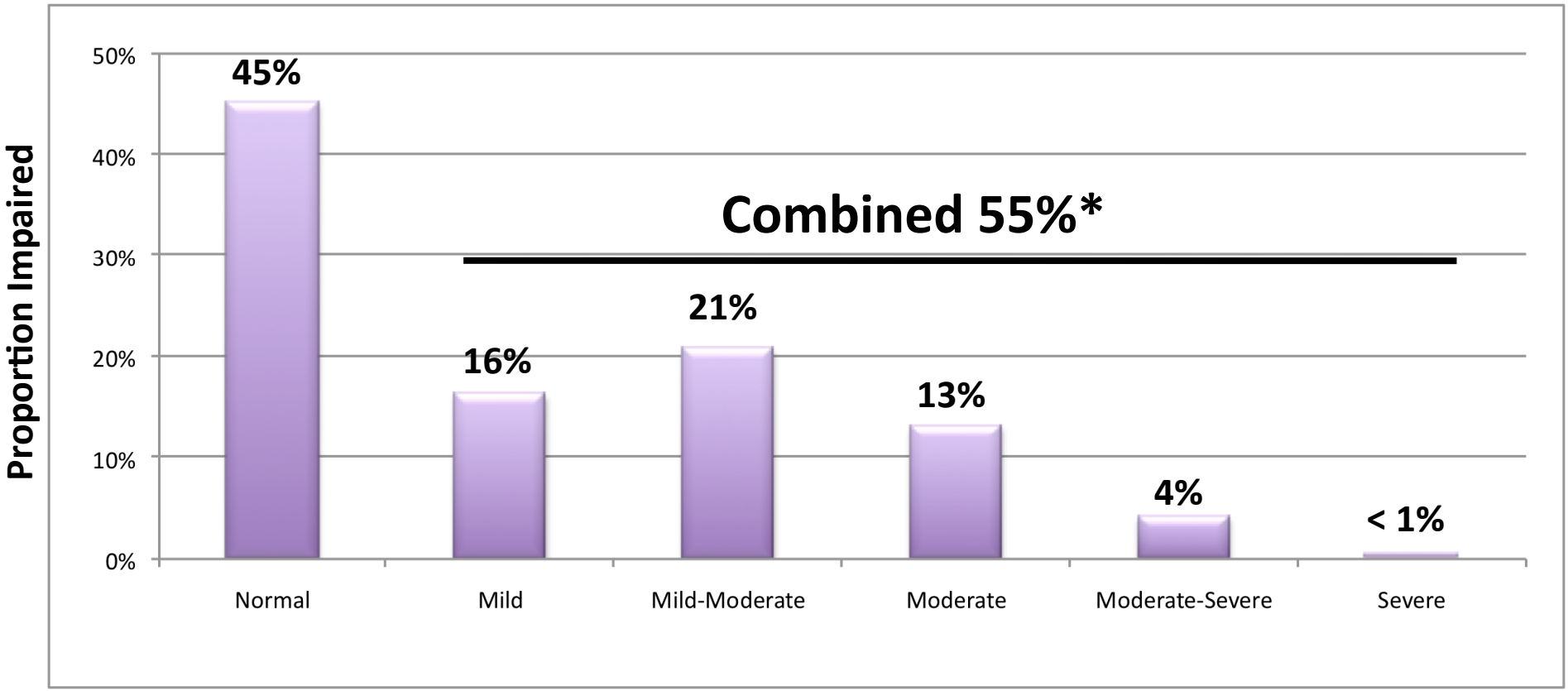
857 pre-cART; 937cART



Heaton R et al., JNV 2011

Epidemiology of NeuroAIDS

High Prevalence of Global Impairment in 2007



***41% after removing most confounded individuals**

CNS HIV AntiRetroviral Therapy Effects Research Project, Years 2003-2007

Definition of HIV-Associated Neurocognitive Disorders (HAND)

	Acquired Impairment in ≥2 Cognitive Abilities	Interferes with Daily Functioning
Asymptomatic Neurocognitive Impairment (ANI)	**YES**	**NO**
Mild Neurocognitive Disorder (MND)	**YES**	**MILD**
HIV-Associated Dementia (HAD)	**MARKED**	**MARKED**

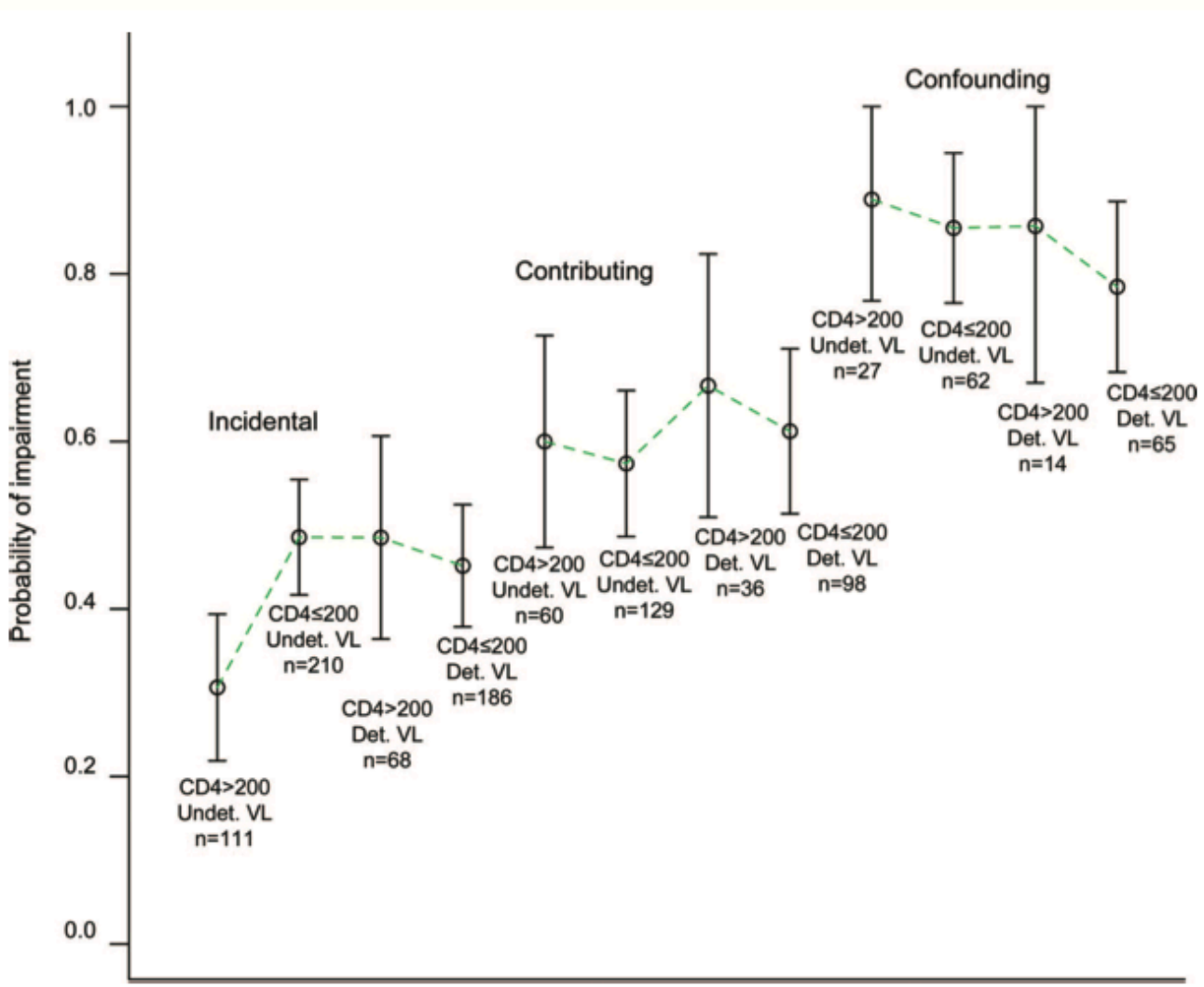
No Pre-Existing Cause, Delirium absent

Antinori A et al., Neurology 2007

What's behind NCI in treated patients?

- **HIV ?**
  - CSF escape
  - Low level replication (including below detection limit)
- **Other causes?**
  - Previously established irreversible tissue damage
  - Psychiatric disorders
  - Drugs, alcool
  - "Physiological" aging
  - Forms of age-related dementia (Alzheimer's and other neurodegenerative diseases)
  - Metabolic problems
  - Cerebro-vascular disease
  - HCV infection
  - Drug toxicity (ART, other drugs)

Presence of contributing and confounding conditions increase the probability of NCI in HIV infection



Heaton R et al., Neurology 2010

Should NCI patients require specific consideration ART-wise?

- If CSF HIV replication:

→ Optimize ART using “CNS effective” drugs

- If NOT (other causes?)

→ Best approach to be established

Is a screening test for HAND worthwhile in HIV patients?

- Will it affect patient outcome?
- Does a reliable screening test exist?

Desirable features for a screening test for HAND

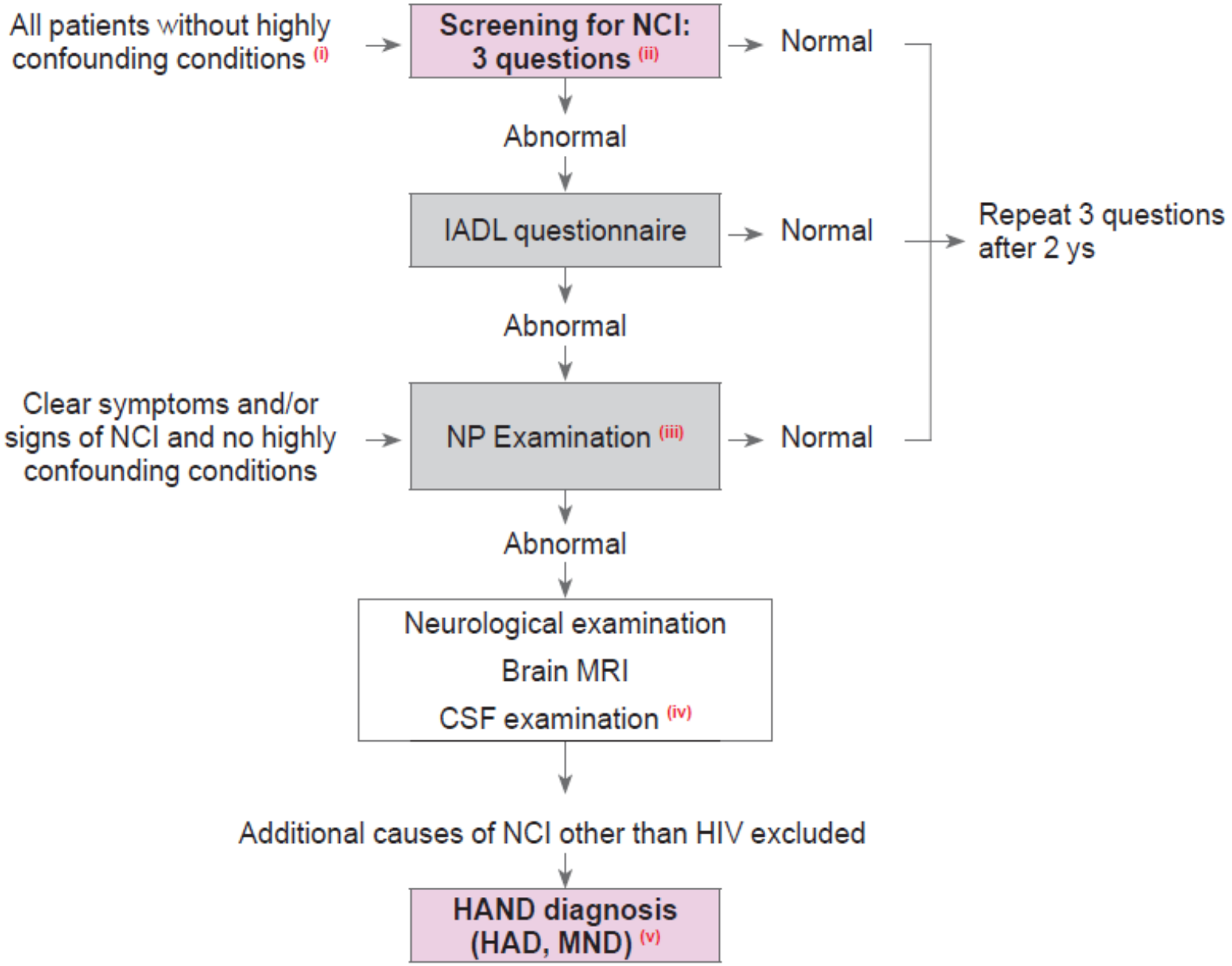
- Sensitive
- Standardized
- Administrable by non-specialized personnel
- Requiring little time

HAND screening approaches and duration

- Standardized questions 5 min
- International HIV dementia scale (IHDS) 5-10 min
- HIV dementia scale (HDS) 10-15 min
- Mini-mental status examination (MMSE) 10-15 min
- Montreal cognitive assessment (MOCA) 10-15 min
- Neupsychological tests variable
- Computerized tests variable

EACS Guidelines 2011

Algorithm for diagnosis and management of HIV-associated Neurocognitive Impairment (NCI)

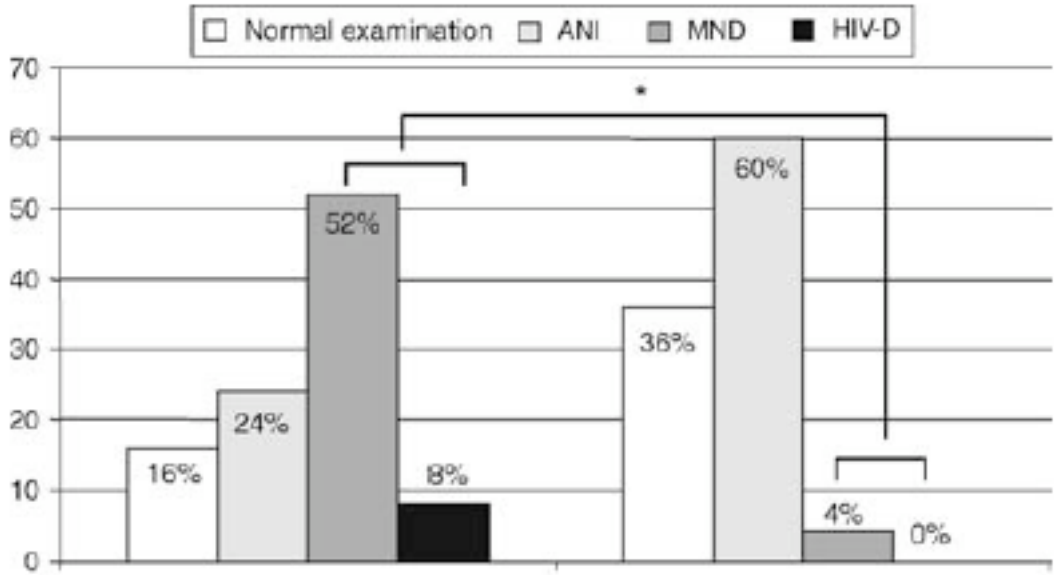


3 questions (*ref. Simioni et al., AIDS 2009*)

1. Do you experience frequent memory loss (e.g. do you forget the occurrence of special events even the more recent ones, appointments, etc.)?
2. Do you feel that you are slower when reasoning, planning activities, or solving problems?
3. Do you have difficulties paying attention (e.g. to a conversation, a book, or a movie)?

- For each question, patients can answer: a) never, b) hardly ever, or c) yes, definitely.
- Patients are considered to have an “abnormal” result when answering “yes, definitely” on at least one question.

Prevalence of HAND in 200 cART-treated suppressed patients



Complaining	
MND+HAD	**60%**
ANI	24%

Non-complaining	
MND+HAD	**4%**
ANI	60%

Estimated prevalence of HAND	69%
Estimated prevalence of MND+HAD	**19%**

From Simioni S. et al., AIDS 2009

INSTRUMENTAL ACTIVITIES OF DAILY LIVING SCALE (IADL)

A. Ability to use telephone

1. Operates telephone on own initiative; looks up and dials numbers, etc.	1
2. Dials a few well-known numbers	1
3. Answers telephone but does not dial	1
4. Does not use telephone at all	0

B. Shopping

1. Takes care of all shopping needs independently	1
2. Shops independently for small purchases	0
3. Needs to be accompanied on any shopping trip	0
4. Completely unable to shop	0

C. Food preparation

1. Plans, prepares, and serves adequate meals independently	1
2. Prepares adequate meals if supplied with ingredients	0
3. Heats and serves prepared meals, or prepares meals but does not maintain adequate diet	0
4. Needs to have meals prepared and served	0

D. Housekeeping

1. Maintains house alone or with occasional assistance (e.g., "heavy work domestic help")	1
2. Performs light daily tasks such as dishwashing, bed making	1
3. Performs light daily tasks but cannot maintain acceptable level of cleanliness	1
4. Needs help with all home maintenance tasks	1
5. Does not participate in any housekeeping tasks	0

E. Laundry

1. Does personal laundry completely	1
2. Launders small items; rinses stockings, etc.	1
3. All laundry must be done by others	0

F. Mode of transportation

1. Travels independently on public transportation or drives own car	1
2. Arranges own travel via taxi, but does not otherwise use public transportation	1
3. Travels on public transportation when assisted or accompanied by another	1
4. Travel limited to taxi or automobile with assistance of another	0
5. Does not travel at all	0

G. Responsibility for own medications

1. Is responsible for taking medication in correct dosages at correct time	1
2. Takes responsibility if medication is prepared in advance in separate dosages	0
3. Is not capable of dispensing own medication	0

H. Ability to handle finances

1. Manages financial matters independently (budgets, writes checks, pays rent and bills, goes to bank), collects and keeps track of income	1
2. Manages day-to-day purchases, but needs help with banking, major purchases, etc.	1
3. Incapable of handling money	0

Source: *Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9(3):179-186.*

ADDITIONAL QUESTIONS ON JOB PERFORMANCE

I. Unable to perform same aspects of previous job (not due to medical symptoms)	0
L. Reduced efficiency or productivity; or more errors or difficulties meeting expectations; or greater effort to perform the same activities	0

Scoring (TOTAL): If patient receives a score of 0 to at least two of the items above (A-L), then he/she is considered to be functional impaired

Source: *Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007 Oct 30;69(18):1789-99.*

The 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 N et al, AIDS 2005

Table 2. Characterization of varying cut-offs for HIV dementia on the International HIV Dementia Scale (IHDS).

Cut-off value	Sensitivity	Specificity
US cohort		
12.0	100%	0%
11.5	92%	22%
11.0	92%	31%
10.5	83%	52%
10.0	80%	57%
9.5	71%	79%
9.0	63%	88%
8.5	46%	95%
8.0	46%	100%
Uganda cohort		
12.0	100%	0%
11.5	100%	20%
11.0	96%	23%
10.5	88%	48%
10.0	80%	55%
9.5	64%	71%
9.0	60%	79%
8.5	40%	89%
8.0	36%	89%
7.5	20%	95%

IHDS sensitivity and specificity

Study	Pt Nr.	Pt origin	Sensitivity	Specificity
Sacktor 2005	66	USA	80%	57%
Sacktor 2005	81	Uganda	80%	55%
Sing 2008	20	South Africa	88%	50%
Skinner 2009	33	Canada	77%	65%
Joska 2011	96	South Africa	45%	79%

Abbreviated NP test battery (4 tests)

#	Test 1	Test 2	Test 3	Test 4	Time	Sens.	Spec.	PPV	NPV	OR
1	Stroop Color	HVLT-R Learn	PASAT	ACTF	18	86.5	87.1	61.5	96.4	43.2
2	Stroop Color	HVLT-R Learn	PASAT	Pegs-ND	19	83.8	83.2	54.4	95.6	25.6
3	Stroop Color	HVLT-R Learn	PASAT	Pegs-D	19	81.1	85.2	56.6	95.0	24.6
4	Stroop Color	BVMT-R Learn	PASAT	ACTF	18	73.0	92.9	71.1	93.5	35.3
5	TMT-A	HVLT-R Learn	PASAT	ACTF	18	81.6	84.0	55.4	94.9	23.2
6	Stroop Color	HVLT-R Learn	PASAT	Animal Flu	18	78.4	86.5	58.0	94.4	23.1
7	Stroop Color	Pegs-ND	PASAT	FAS	15	75.7	88.4	60.9	93.8	23.7
8	Stroop Color	Pegs-ND	PASAT	ACTF	11	75.7	87.7	59.6	93.8	22.3
9	SYM SRCH	HVLT-R Learn	PASAT	ACTF	20	73.7	88.5	60.9	93.2	21.5
10	DIG SYM	HVLT-R Learn	PASAT	ACTF	20	73.7	88.2	60.9	93.1	21.0

Abbreviated NP test battery (3 tests)

#	Test 1	Test 2	Test 3	Time	Sens.	Spec.	PPV	NPV	OR
1	Stroop Color	HVLT-R Learn	PASAT	16	86.5	75.5	45.7	95.9	19.7
2	TMT-A	HVLT-R Learn	PASAT	16	84.2	76.3	46.4	95.2	17.2
3	SYM SRCH	HVLT-R Learn	PASAT	18	78.9	79.5	48.4	93.9	14.5
4	Stroop Color	HVLT-R Learn	ACTF	13	78.4	80.0	47.5	94.1	14.5
5	Pegs-ND	BVMT-R Learn	PASAT	18	76.3	82.1	50.9	93.4	14.7
6	Pegs-D	HVLT-R Learn	PASAT	18	81.6	75.6	44.9	94.4	13.8
7	Stroop Color	HVLT-R Learn	Pegs-D	14	78.4	78.8	46.0	94.0	13.4
8	TMT-A	Pegs-ND	PASAT	9	76.3	80.1	48.3	93.3	13.0
9	Stroop Color	HVLT-R Learn	Animal Flu	13	75.7	80.6	47.5	93.5	12.9
10	Stroop Color	BVMT-R Learn	FAS	17	64.9	91.3	63.2	91.8	19.3

Moore DJ, CROI 2012

Abbreviated NP test battery (2 tests)

#	Test 1	Test 2	Time	Sens.	Spec.	PPV	NPV	OR
1	Stroop Color	HVLT-R Learn	11	73.0	83.1	50.0	93.0	13.3
2	Pegs-D	HVLT-R Learn	13	73.7	82.0	49.1	93.0	12.7
3	PASAT	BVMT-R Learn	15	63.2	89.7	60.0	90.9	15.0
4	PASAT	HVLT-R Learn	15	73.7	77.6	44.4	92.4	9.7
5	PASAT	Pegs-ND	8	71.1	79.5	45.8	91.9	9.5
6	Pegs-ND	HVLT-R Learn	13	71.1	77.6	42.9	91.9	8.5
7	Stroop Color	BVMT-R Learn	11	54.1	94.4	69.0	89.9	19.7
8	Stroop Color	Pegs-D	4	56.8	90.6	58.3	90.1	12.7
9	Stoop Incon	HVLT-R Learn	11	64.9	82.5	46.2	91.0	8.7
10	PASAT	Pegs-D	8	60.5	85.9	51.1	89.9	9.3

Moore DJ, CROI 2012

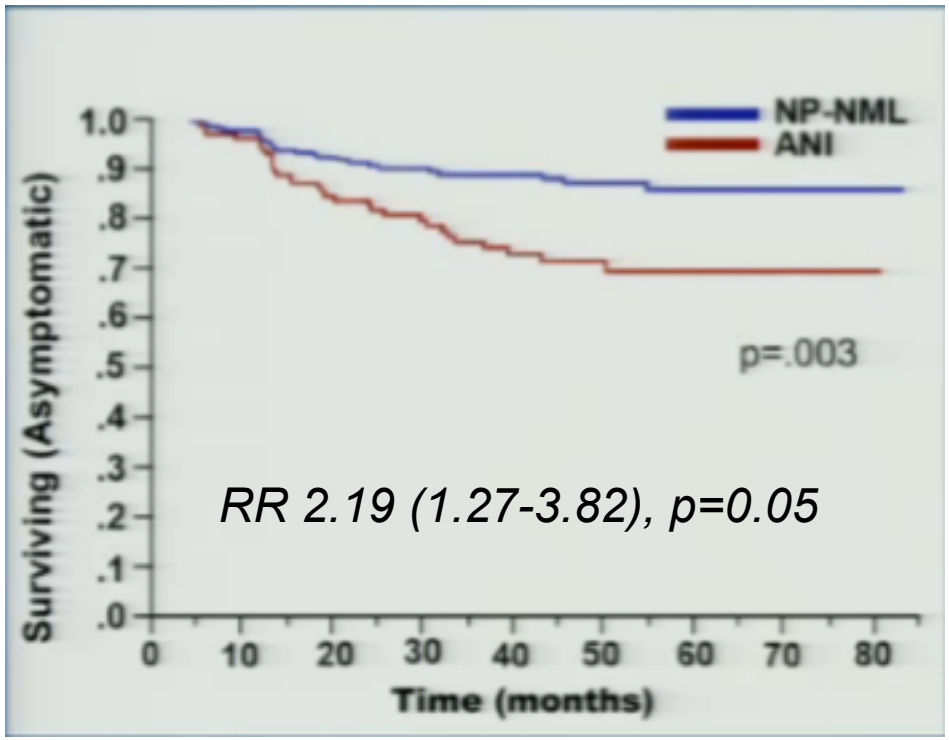
What about ANI (Asymptomatic Neurocognitive Impairment)?

- Clinical significance uncertain
- Not yet demonstration of progression to symptomatic forms

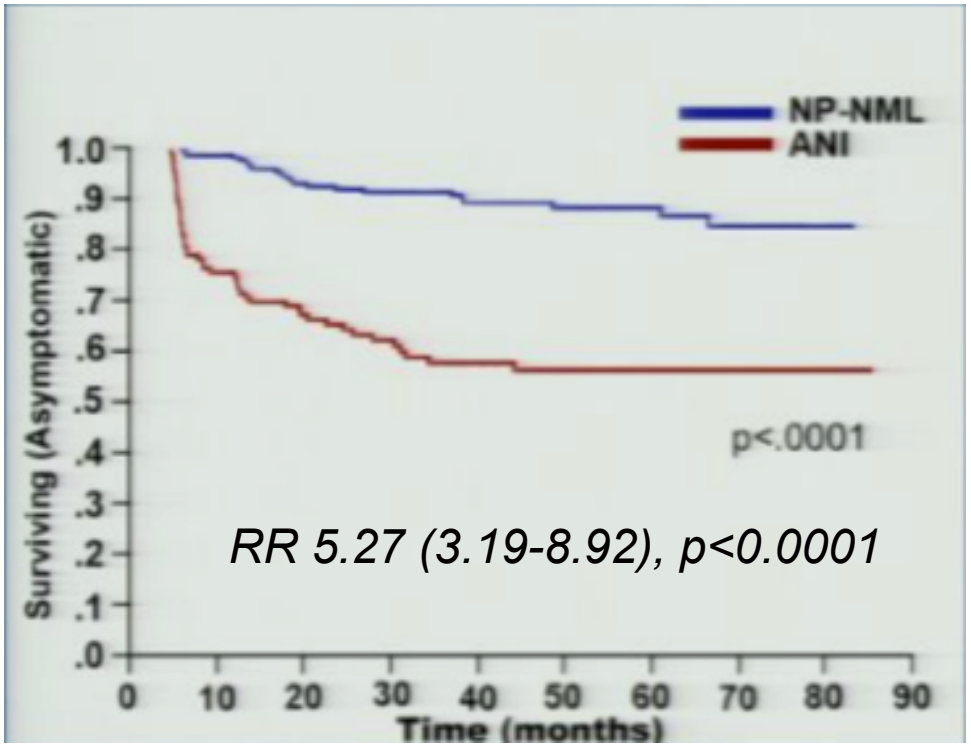
- HAND treatment not recommended according to EACS guidelines
- Clinical monitoring may help define evolution of ANI over time

ANI increases risk of symptomatic HAND (i.e., with functional impairment)

Self-reported functional impairment (PAOFI, ADL)



Performance-based functional impairment (MMT-R, WALPAR 3000)



ANI=121
NML=226
Median follow-up: 42.5 months

Grant I et al., CROI 2012

Baseline Comparison of ANI and NML: Background Characteristics

	NML (n=226)	ANI (n=121)	P-value
Age	43.0 (8.6)	44.8 (8.0)	
Education	12.9 (2.4)	13.5 (2.2)	.04
% Male	81.9%	81.8%	
% Caucasian	45.6%	46.3%	
% Lifetime Substance Dx	71.2%	69.4%	
% with Comorbidity	22.6%	44.6%	<.0001

Grant I et al., CROI 2012

Estimation of false positive diagnosis of HAND in a Kenyan population

Table 2. Comparison of HAND prevalence estimates by Frascati criteria in a Kenyan HIV-infected population across various criteria to define an abnormal cognitive domain, using Frascati criteria.*

		Criteria for an abnormal domain:		
		One abnormal test in domain	Abnormal average score across domain	Two abnormal tests in domain
Normal		**32% (70)** [25, 38]	**69% (152)** [63, 75]	**76% (169)** [71, 82]
Asymptomatic Neurocognitive Impairment	1. Two abnormal domains ≤1SD below mean 2. No functional decline	**52% (115)** [45, 59]	**20% (45)** [15, 26]	**14% (32)** [10, 19]
Mild Neurocognitive Disorder	1. Two abnormal domains ≤1SD below mean 2. Minor functional decline	**16% (35)** [11, 21]	**10% (23)** [6, 14]	**9% (19)** [5, 12]
HIV-Associated Dementia†	1. Two abnormal domains ≤2SD below mean 2. Major functional impairment	**0.5% (1)** [-0.4, 1]	**0.5% (1)** [-0.4, 1]	**0.5% (1)** [-0.4, 1]

Conclusions: Is a screening test for HAND worthwhile in HIV patients?

- Will it affect patient outcome?
  - It could, theoretically
  - But, practically, still to be demonstrated
- Does a reliable screening test exist?
  - Not at the moment