C.I.C.A.
COORDINAMENTO ITALIANO
CASE/ALLOGGIO HIV/AIDS

SEMINARIO NAZIONALE

ALLA RICERCA DEI
"PENSIERI PERDUTI"
disturbi neurocognitivi
nelle persone con hiv/aids

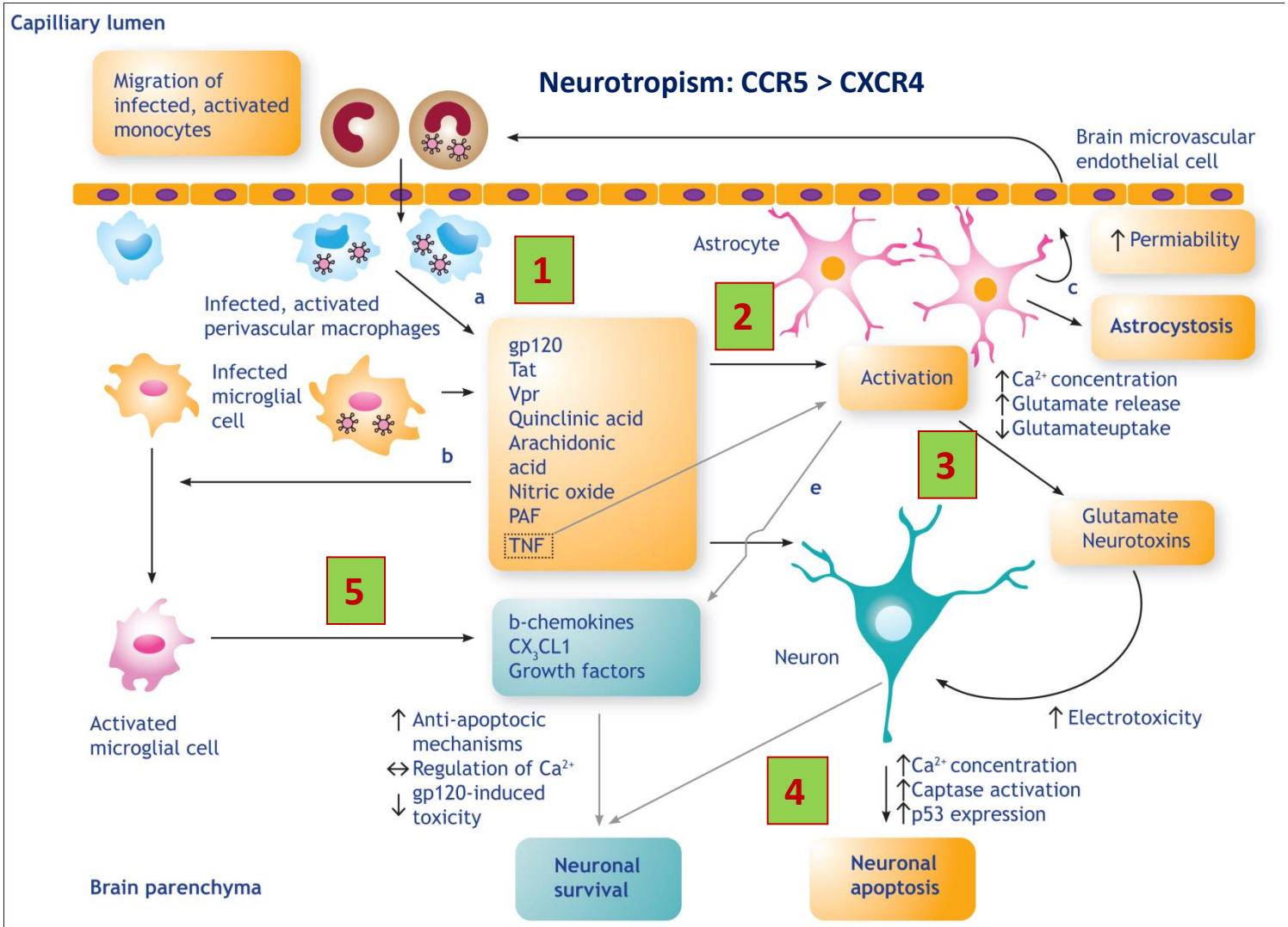
Disturbi neurocognitivi nelle persone con HIV/AIDS: di cosa stiamo parlando

Andrea Antinori

INMI L. Spallanzani IRCCS, Roma

PATOGENESI

HIV-associated neurocognitive disorders (HAND): physiopathological mechanisms



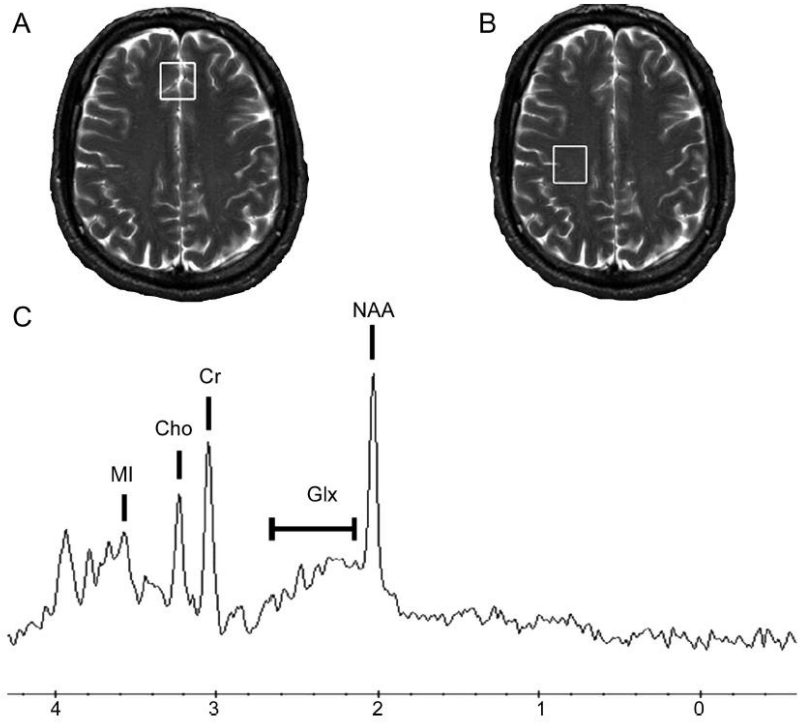
Autophagy*

➢Ubiquitin proteosome system
➢Immunoproteosome**

*Gougeon ML et al. Apoptosis 2009; 14: 501-508
**Nguyen TP et al. Am J Pathol 2010; 176: 893-902

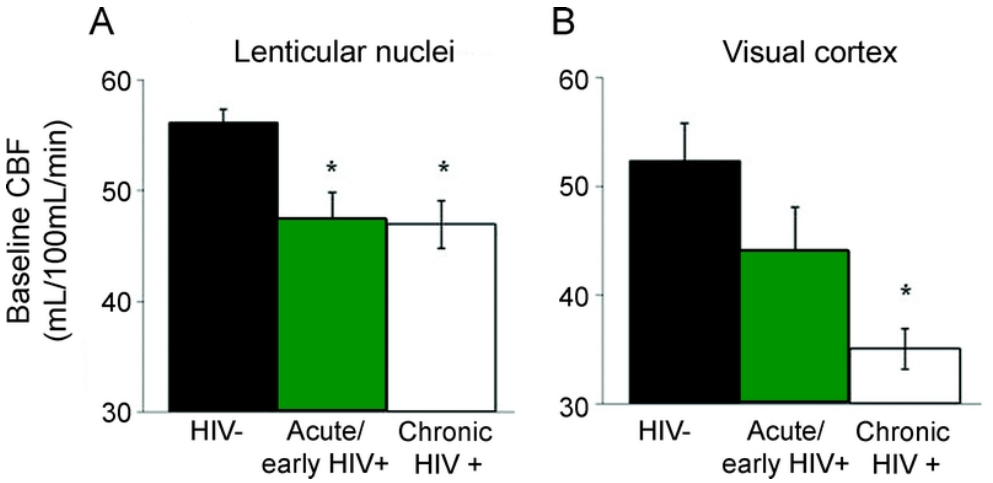
Adapted from Gonzalez-Scarano F et al. Nat Rev Immunol 2005;5:69-81

Brain injury occurs early in HIV infection



Lower NAA and Glx levels in the cortical gray matter suggests that HIV causes neuronal dysfunction soon after infection, within 60 days from an evolving WB

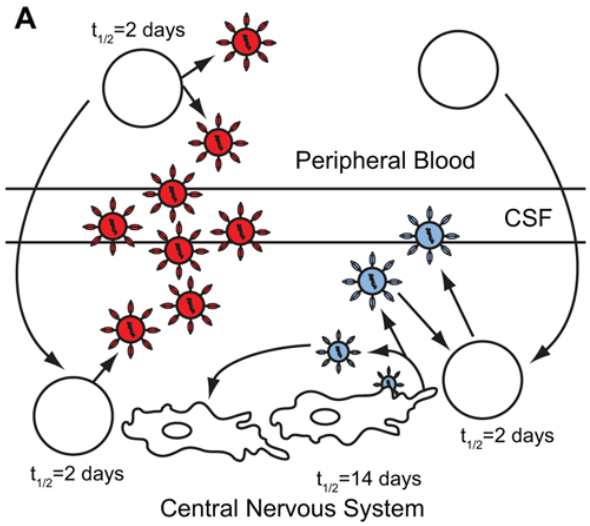
Lentz MR, et al. Neurology, 2009

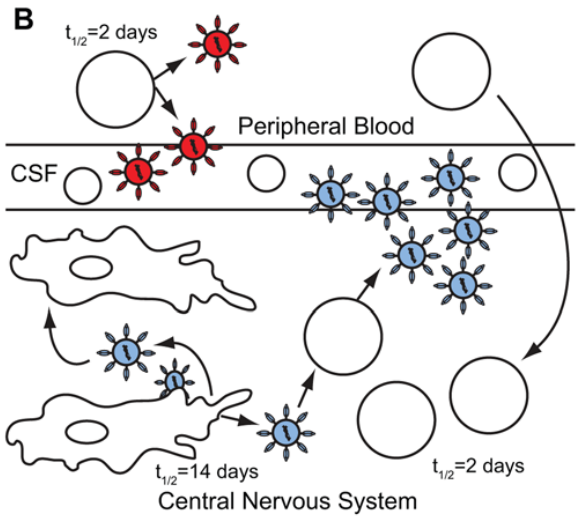


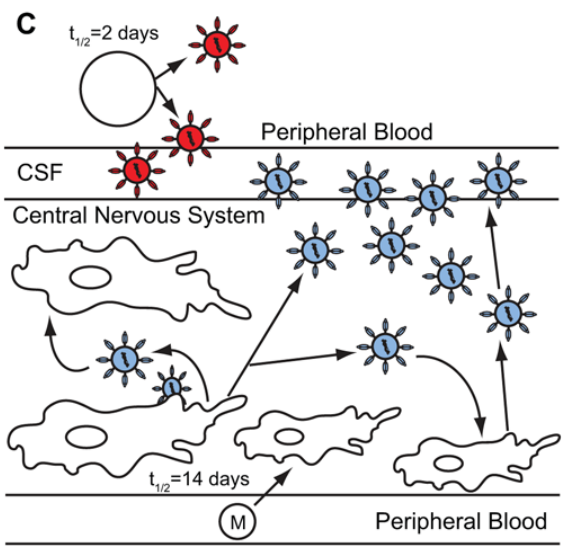
Resting cerebral blood flow (rCBF) reductions occur soon after seroconversion and possibly reflect neuronal or vascular injury among HIV+ individuals not yet expressing NPS impairment.

Ances BM, et al. Neurology, 2009

Model of HIV-1 infection in the central nervous system







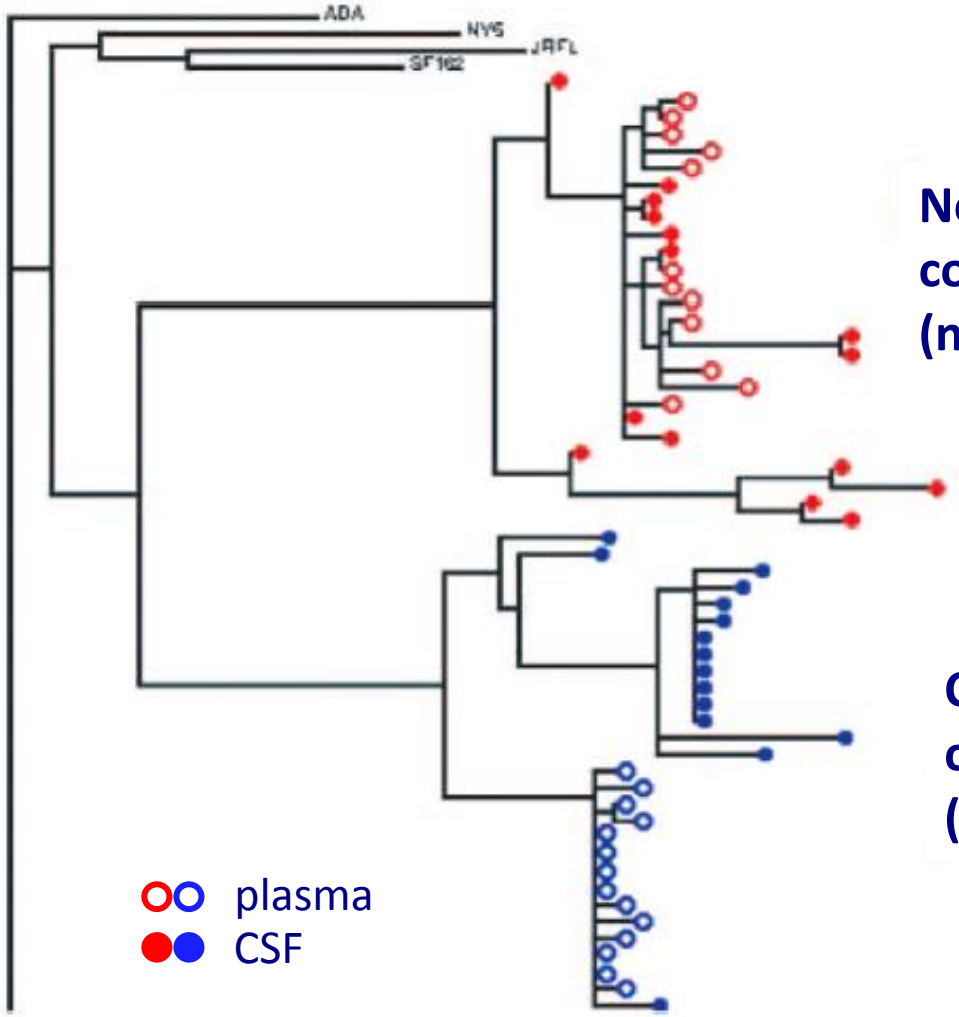
A. Asymptomatic subjects without detectable compartmentalized virus or CSF pleocytosis.

B. Asymptomatic and neurologically symptomatic subjects with compartmentalization, high CSF pleocytosis and rapid viral decay.

C. Neurologically symptomatic subjects with slow viral decay.

Schnell G, et al. PLoS Pathogens, 2009

Compartmentalization of HIV strains in CSF

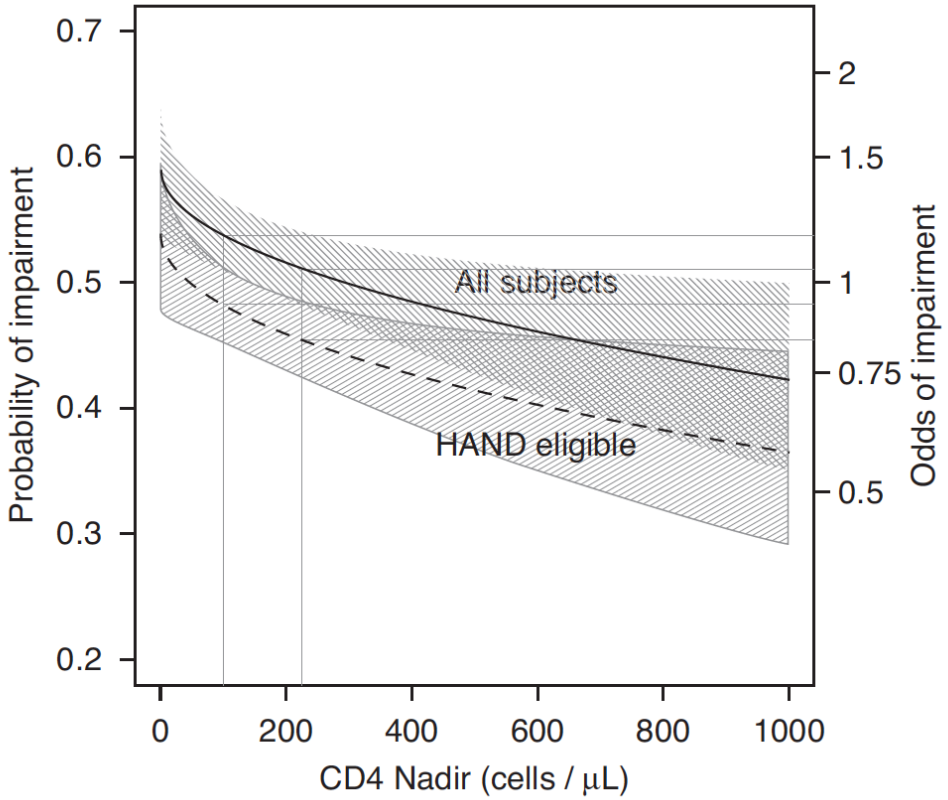


No CSF compartmentalization (neuroasymptomatic)

CSF compartmentalization (ADC)

Pillai SK et al., Brain 2007

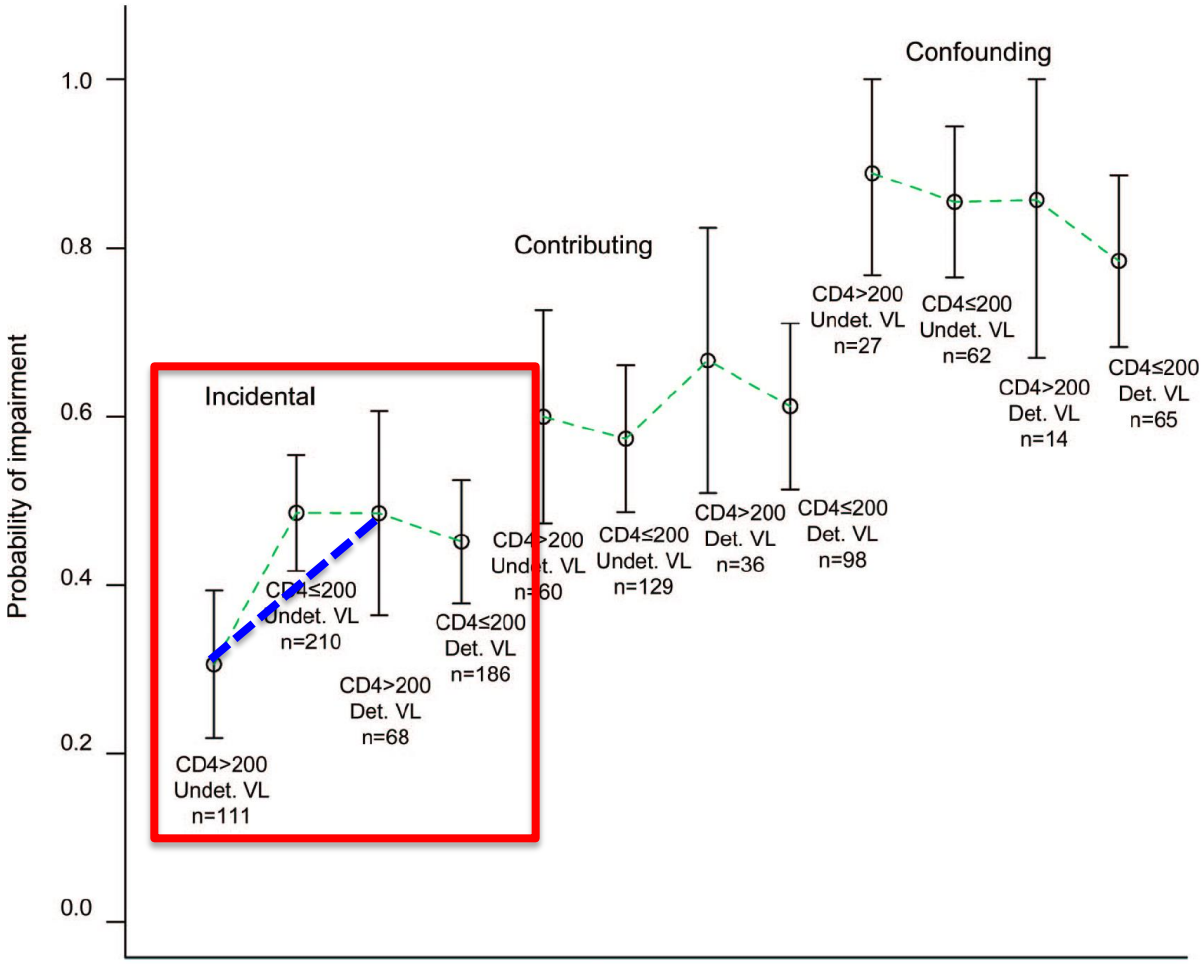
CD4 nadir is a predictor of HIV neurocognitive impairment



Ellis RJ, et al. AIDS, 2011

Across the range of values observed in the cohort, higher CD4 nadirs were associated with lower risk of neuropsychological impairment such that for every 5-unit increase in square-root CD4 nadir, the odds of neuropsychological impairment was reduced by 10%. This was true for all individuals (solid curve) as well as for HAND-eligible patients (those without major confounding neurocognitive comorbidities; dashed curve).

HIV-RNA in plasma is an independent predictor of NCI



Heaton RK, et al. Neurology, 2010

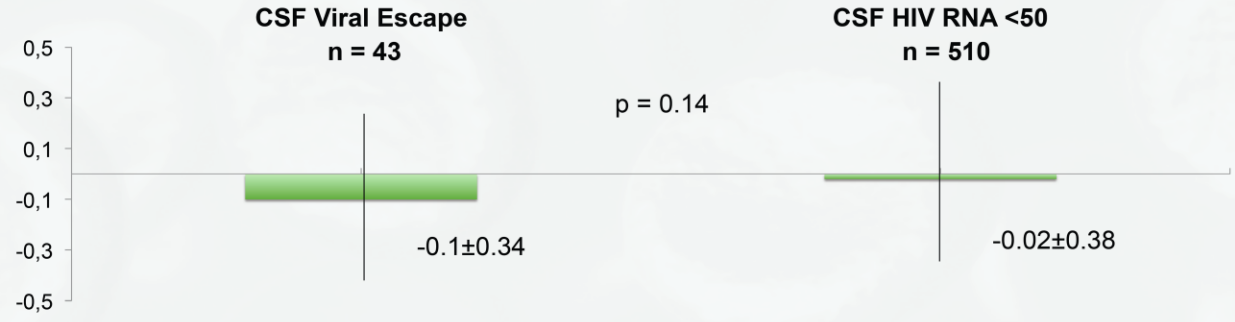
Incidence, Risk Factors and Neurocognitive impact of CSF Viral Escape

CSF Viral Escape (all types) = 37.4 cases per 1000 person-years
CSF Blips (single occurrence of CVE while suppressed in plasma) = 19.1 cases per 1000 person-years
Persistent CSF Viral Escape (≥2 consecutive CVE while suppressed in plasma) = 8.5 cases per 1000 person-years
CVE – LS (CVE next to a period of loss of HIV-suppression in plasma) = 9.8 cases per 1000 person-years,

MULTIVARIABLE MIXED MODEL RESULTS

	p Value	OR (95% CI)
Protease inhibitors based ART (yes, taking PI)	0.015	21.69 (1.8-261.9)
CSF Pleocytosis (yes, WBC >5 cells/ml)	<0.001	21.6 (6.66-69.93)
Level of plasma HIV RNA within 0-50 cop/mL (per +10 count)	0.032	1.32 (1.02-1.69)

NEUROCOGNITIVE EVOLUTION (by GDS change)



Perez-Valero I, et al. 20th CROI, Atlanta (GA), 2013; Poster #402.

Acute meningoencephalitis in chronic HIV infection: putative CNS escape of HIV replication

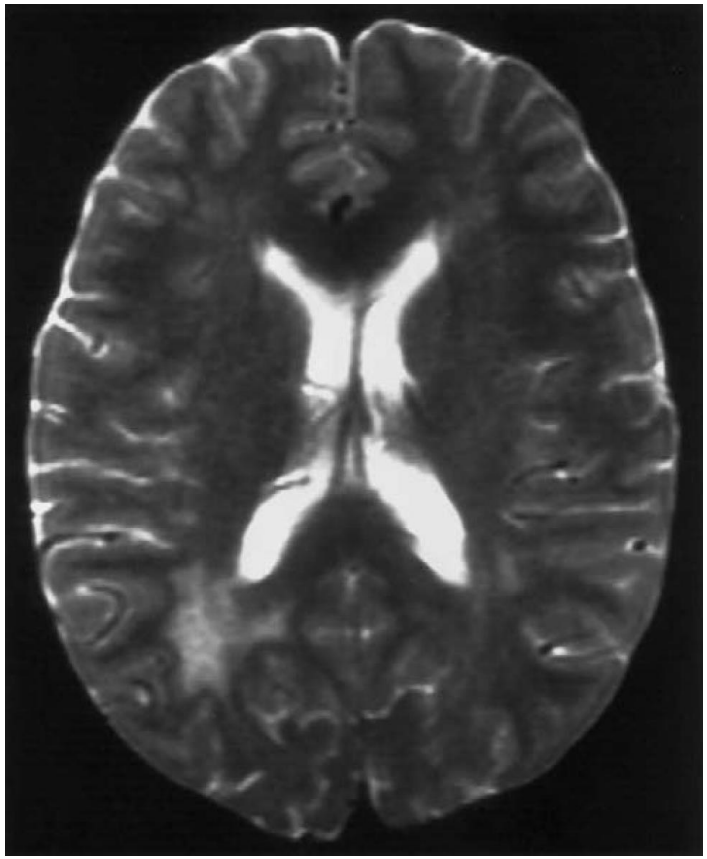


Table 1. Plasma and CSF HIV viral loads and CSF leukocytosis before and after change in or initiation of HAART.

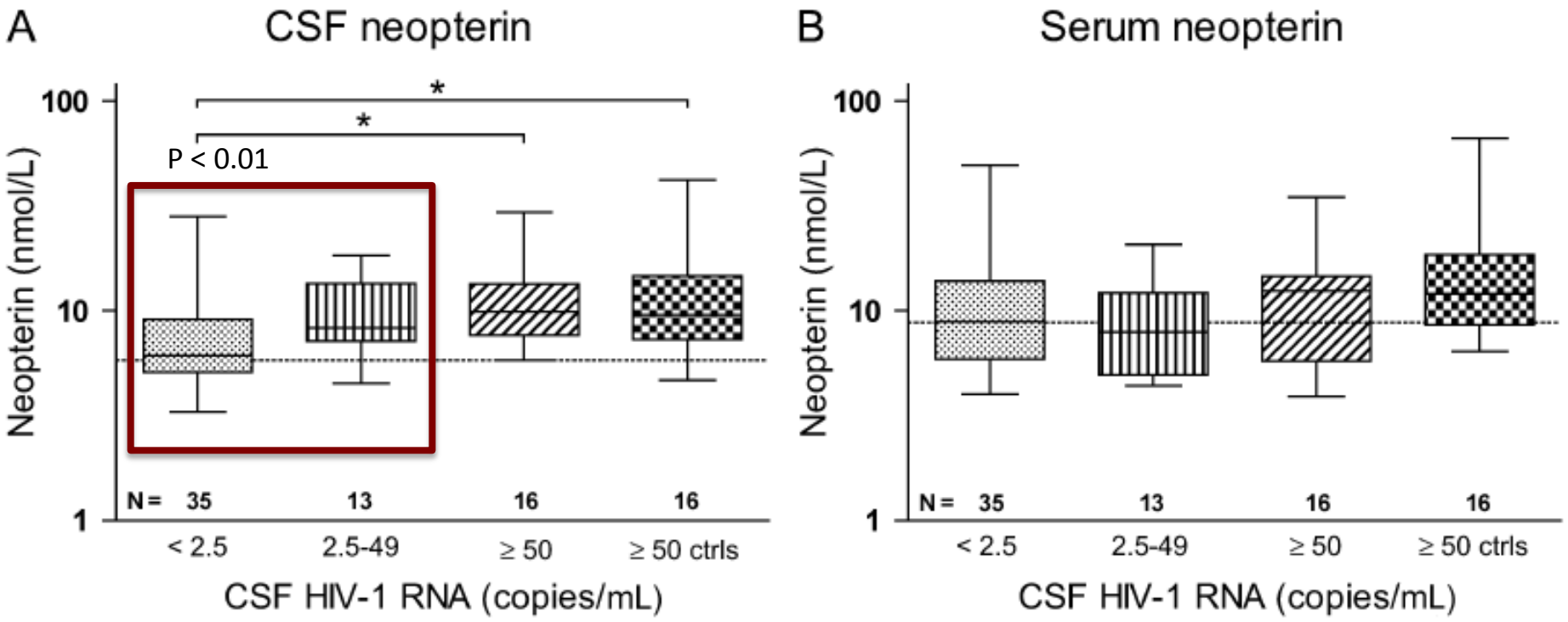
	Values within 1 month of presentation with acute neurologic symptoms			Values ⩽3 months after initiation of a new HAART regimen		
Patient	Plasma HIV RNA load, copies/mL	CSF HIV RNA load, copies/mL	CSF WBC count range, cells/mm^3	Plasma HIV RNA load, copies/mL	CSF HIV RNA load, copies/mL	CSF WBC count range, cells/mm^3
1	<445	7059	39–95	<115	<230	30
2	1637[a]	180,692	73–248	<21	<15	5
3	4872	11,227	2–17	<300	80	4

[a] The plasma HIV RNA measurement was obtained ~3 weeks before the CSF HIV RNA measurement.

Wendel KA & McArthur JC, Clin Infect Dis, 2003

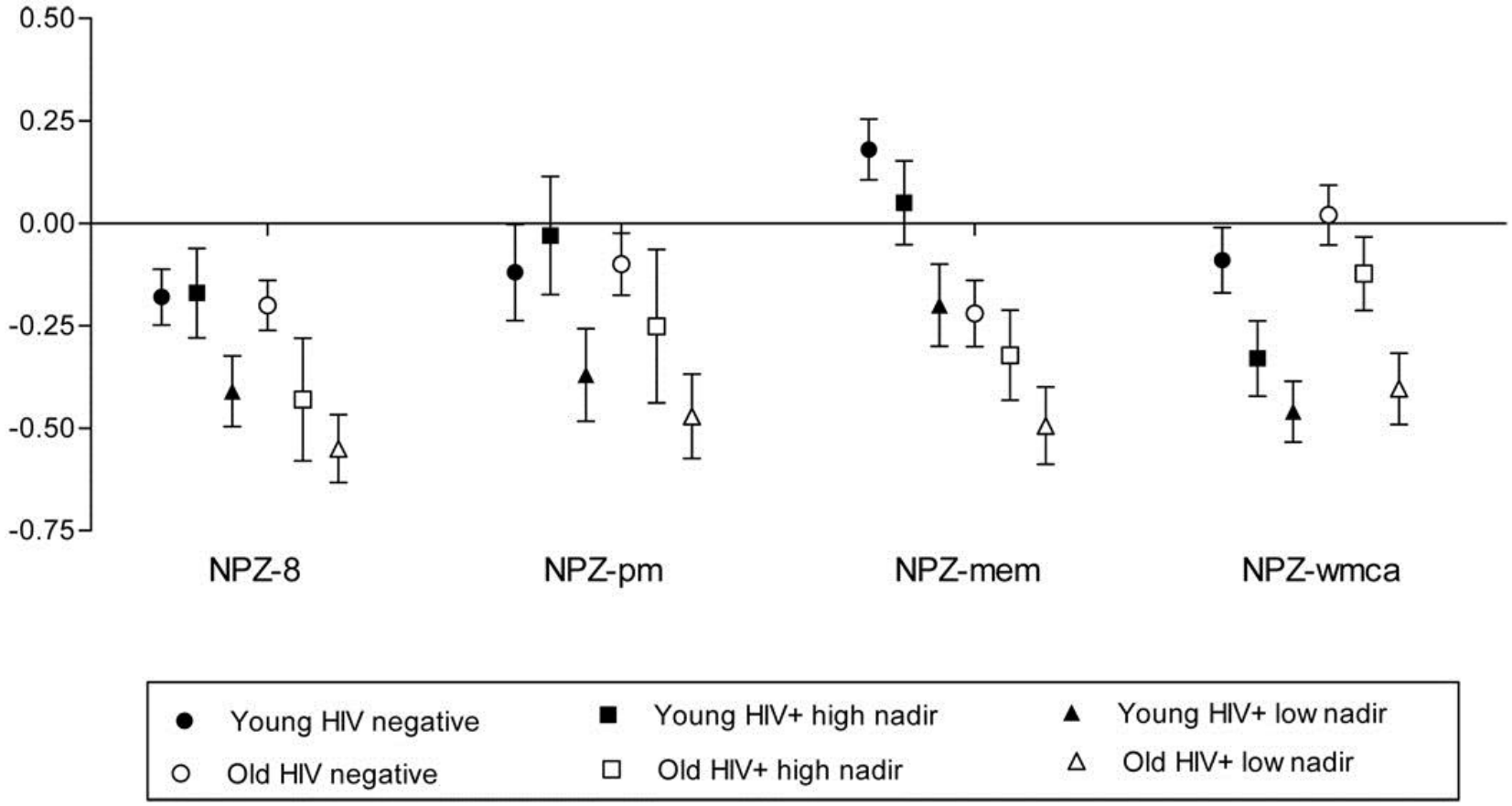
Neopterin and CSF HIV RNA

Subjects on HAART with plasma VL <50 copies/mL.
CSF-RNA measured by sensitive PCR



Yilmaz A et al. *J AIDS* 2008; 47: 168

Neuropsychological domain scores in HIV-negative and HIV subjects by age group



Valcour V, et al. J Int Neuropsychol Soc, 2011

Metabolic variables in HIV-associated neurocognitive disorder

Variable	Odds ratio	95% CI	*p* Value
AIDS	49.57	2.26, 1089	0.013
Diabetes	17.6	0.76, 409	0.07
BMI, kg/m^2	0.69	0.49, 0.98	0.038
Waist circumference, cm	1.34	1.13, 1.60	0.001
Triglycerides, mg/dL	0.32	0.09, 1.21	0.09

As in HIV-uninfected persons, central obesity, but not more generalized increases in body mass (BMI), was associated with a higher prevalence of NCI in HIV persons. Diabetes appeared to be associated with NCI only in older patients. Avoidance of antiretroviral drugs that induce central obesity might protect from or help to reverse neurocognitive impairment in HIVinfected persons.

	CHARTER cohort (n = 1,325)			Age ≥55 y (n = 118)		
	Diabetic (n = 115)	Nondiabetic (n = 1,210)	*p* Value[a]	Diabetic (n = 21)	Nondiabetic (n = 97)	*p* Value[a]
GDS ≥0.5, n (%)	44 (38.3)	418 (34.6)	0.43	11 (52.4)	29 (29.9)	0.05
Global rating, n (%)	55 (47.8)	563 (46.5)	0.79	13 (61.9)	43 (44.3)	0.14

McCutchan A, et al. Neurology, 2012

How can clinicians identify patients at greatest risk of HAND?

RISK FACTORS (I):

Disease factors

1. Low *nadir* CD4 (pre-cART); Low *current* CD4
2. High plasma HIV RNA; high CSF HIV RNA
3. Presence of past HIV-related CNS diseases
4. Longer HIV duration

Treatment factors

1. Low cART adherence
2. Episodes of cART interruption
3. Non-optimal ARV regimen (non-suppressed plasma viral load)
4. Low cART duration (related to treatment failure)

How can clinicians identify patients at greatest risk of HAND?

RISK FACTORS (II):

Co-morbidities

1. Positive HCV serostatus with high HCV RNA
2. History of acute cardiovascular event
3. Cardiovascular risk factors, such as:
   - Hyperlipidaemia
   - Elevated blood pressure
   - Chronic diabetes and diabetes type II
4. Presence of anaemia and thrombocytopenia

•Demographic factors (in decreasing order of priority)

1. Greater age
2. Low cognitive reserve, low level of educational achievement, some ethnicities and gender associated with lower socio-economic status in some countries lack of access to standard care and poverty.

How can clinicians identify patients at greatest risk of HAND?

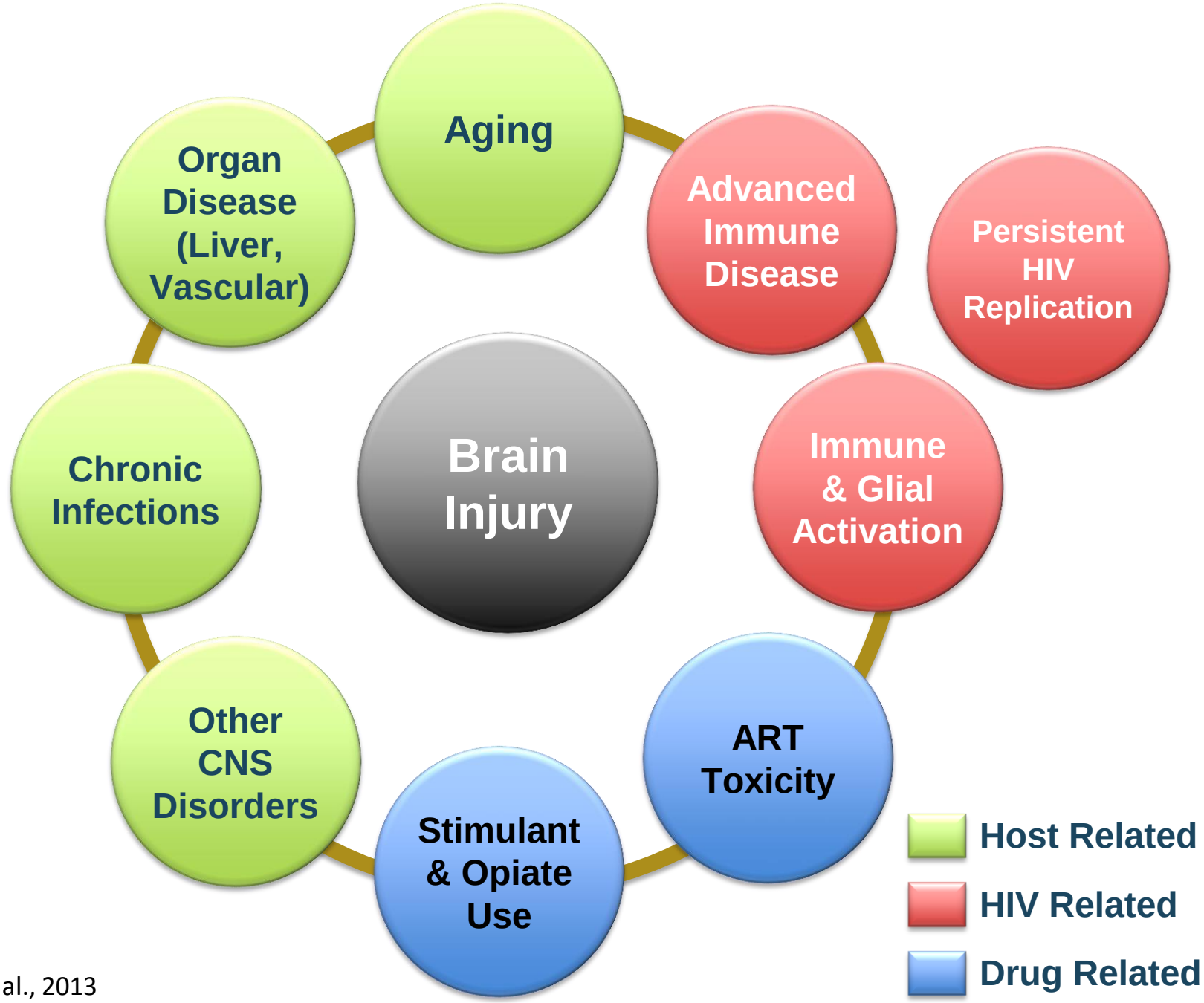
RISK FACTORS (III):

Other neurological and psychiatric factors (including potential confounds to diagnosis of HAND)

1. Neuropsychiatric disorders: previous or current major depressive disorder, generalised anxiety disorder, psychosis, and bipolar disorder.
2. History of traumatic brain injury.
3. History of chronic substance abuse (including alcohol, methamphetamines, cocaine, heroin, some prescription drugs, and heavy use of recreational drugs such as marijuana).

Complex cART factors

1. Lower central nervous system penetration efficiency (CPE)
2. Potential neurotoxicity



Letendre S, et al., 2013

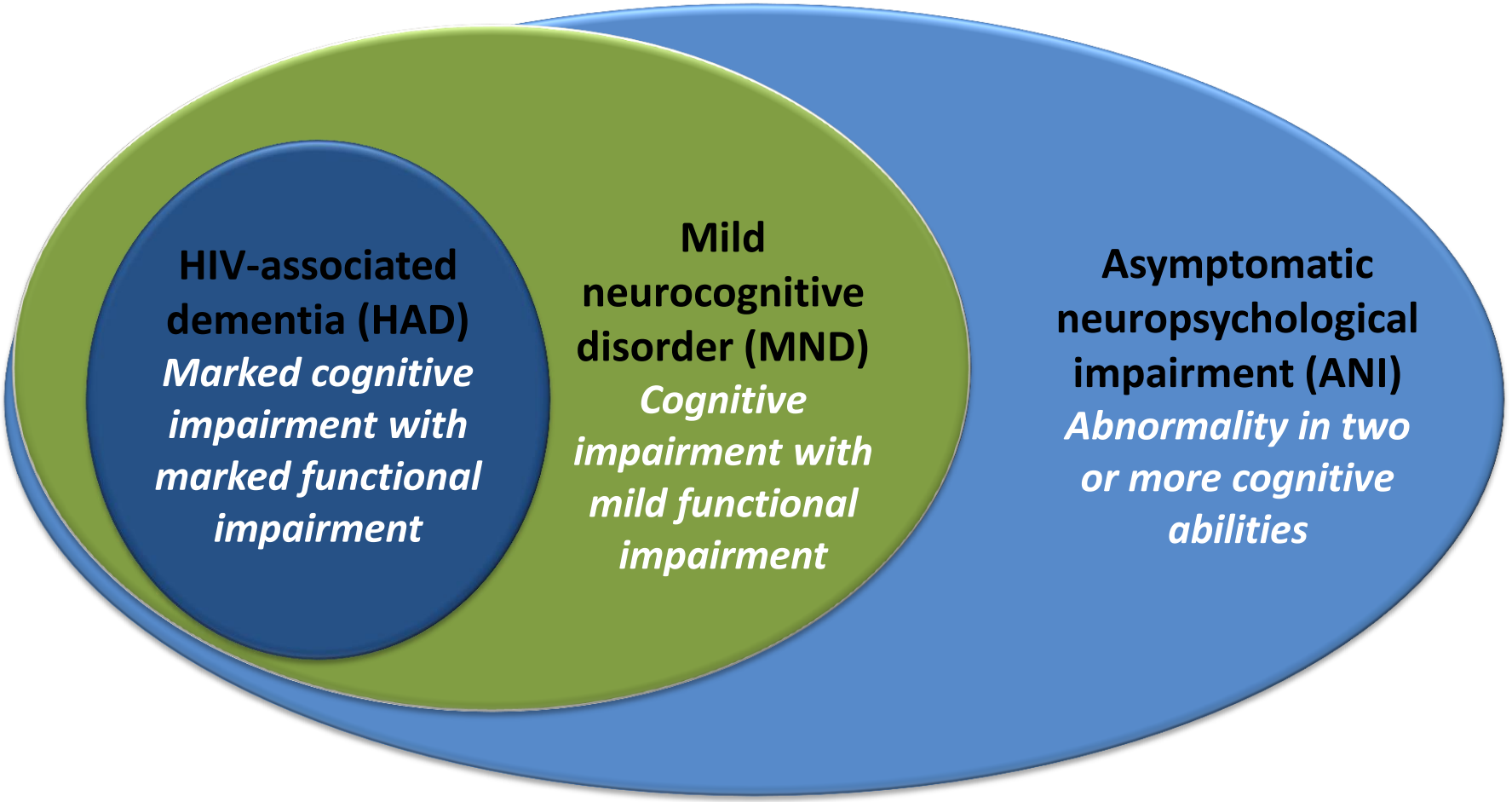
DEFINIZIONE E CLASSIFICAZIONE

Categories of HIV-associated Neurocognitive Disorders (HAND)

HIV-associated asymptomatic neurocognitive impairment (ANI)	• Impairment in ≥2 neurocognitive domains (attention; executive memory; speed of information processing, etc.) with ≥1 SD below the mean • The cognitive impairment does not interfere with daily functioning
HIV-associated mild neurocognitive disorder (MND)	• Similar to ANI, but with mild–moderate interference w/daily functioning
HIV-1-associated dementia (HAD)	• Impairment in ≥ 2 neurocognitive domain with ≥2 SD below the mean • Marked interference with daily functioning

adapted from: Antinori A, et al. Neurology 2007;69:1789-99

HAND: Frascati criteria



Antinori A et al. Neurology 2007;69:1789–99.

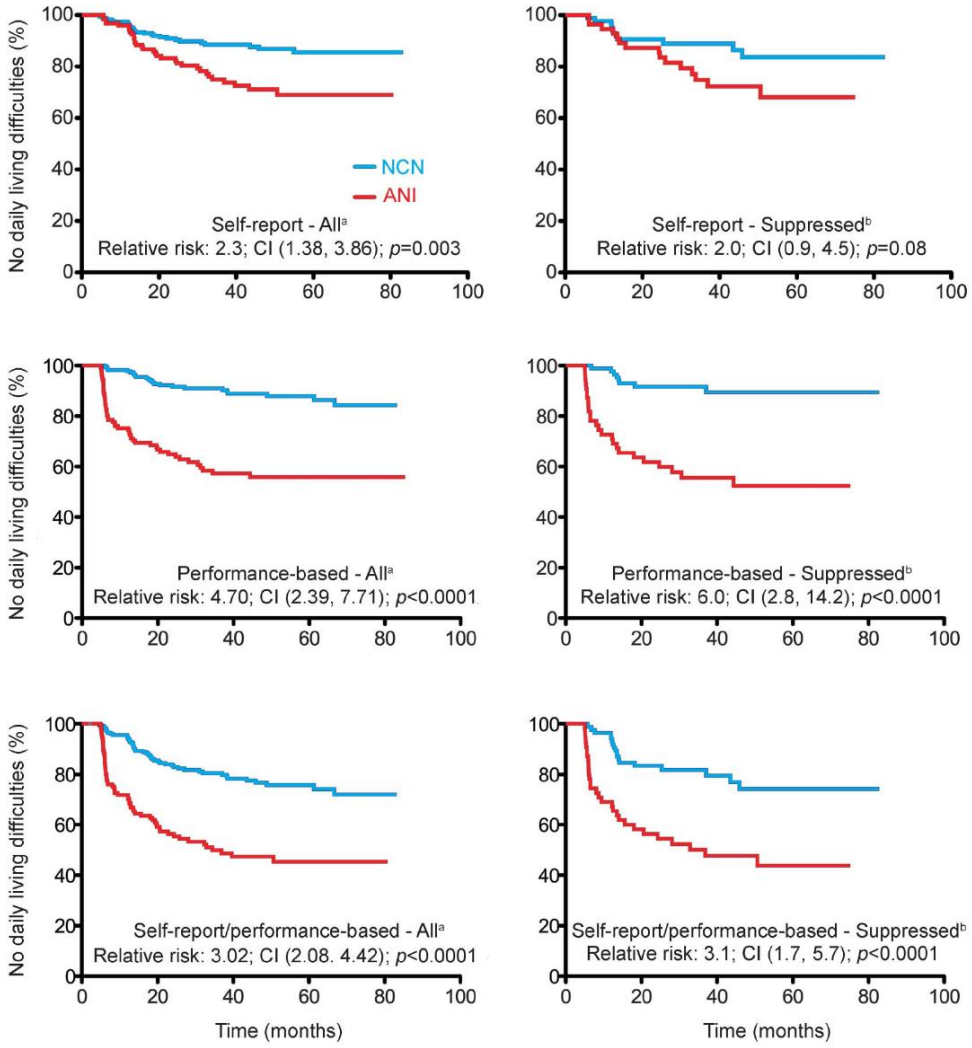
Clinical Definition of HIV-Associated Neurocognitive Disorders (HAND)

	Acquired Impairment in ≥ 2 Cognitive Abilities	Interferes* with Daily Functioning	No Current Severely Confounding Condition	No Pre-existing Cause	Delirium Absent
Asymptomatic Neurocognitive Impairment (ANI)	✔	No	✔	✔	✔
Mild Neurocognitive Disorder (MND)	✔	Mild	✔	✔	✔
HIV-Associated Dementia (HAD)	Marked	Marked	✔	✔	✔

*by performing Instrumental Activities of Daily Living (IADL)

Antinori et al, Neurology 2007, 69: 1789-99

ANI increases risk for earlier decline to symptomatic HAND even with viral suppression on cART



A total of 347 human participants from the CHARTER cohort were NCN (n=5,226) or had ANI (n=5,121) at baseline. Neurocognitive assessments occurred approximately every 6 months, with median (interquartile range) follow-up of 45.2 (28.7–63.7) months. Symptomatic decline was based on self-report (SR) or objective, performance-based (PB) problems in everyday functioning.

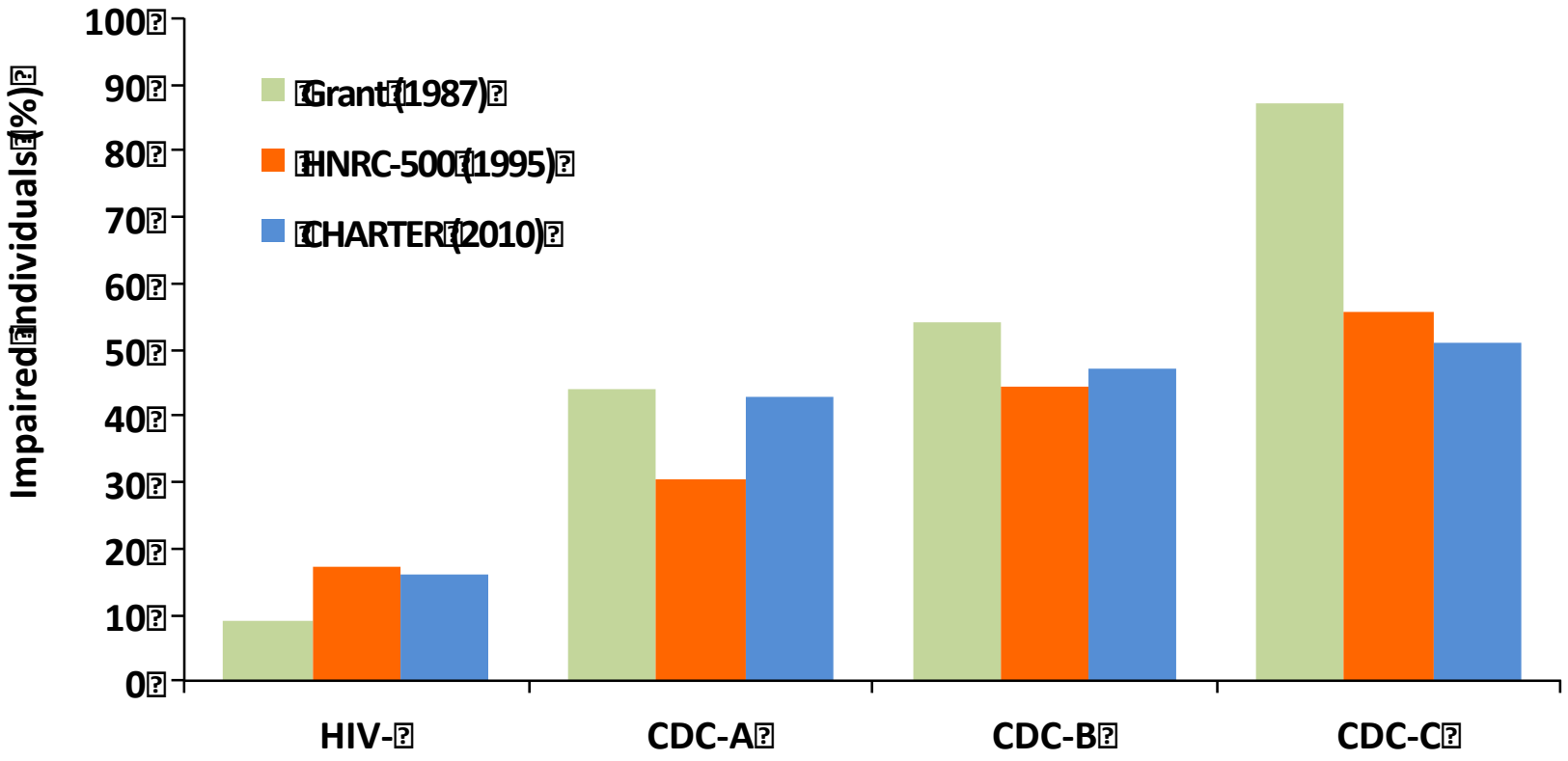
The ANI group had a shorter time to symptomatic HAND than the NCN after adjusting for baseline predictors: adjusted risk ratios for symptomatic HAND were 2.0 (95% CI 1.1–3.6; p=0.02) for SR, 5.8 (95% CI 3.2–10.7; p <0.0001) for PB, and 3.2 (95% CI 2.0–5.0; p <0.0001) for either SR or PB.

ANI conveys a 2-fold to 6-fold increase in risk for earlier development of symptomatic HAND, supporting the prognostic value of the ANI diagnosis in clinical settings.

Grant I, et al. Neurology, 2014

PREVALENZA

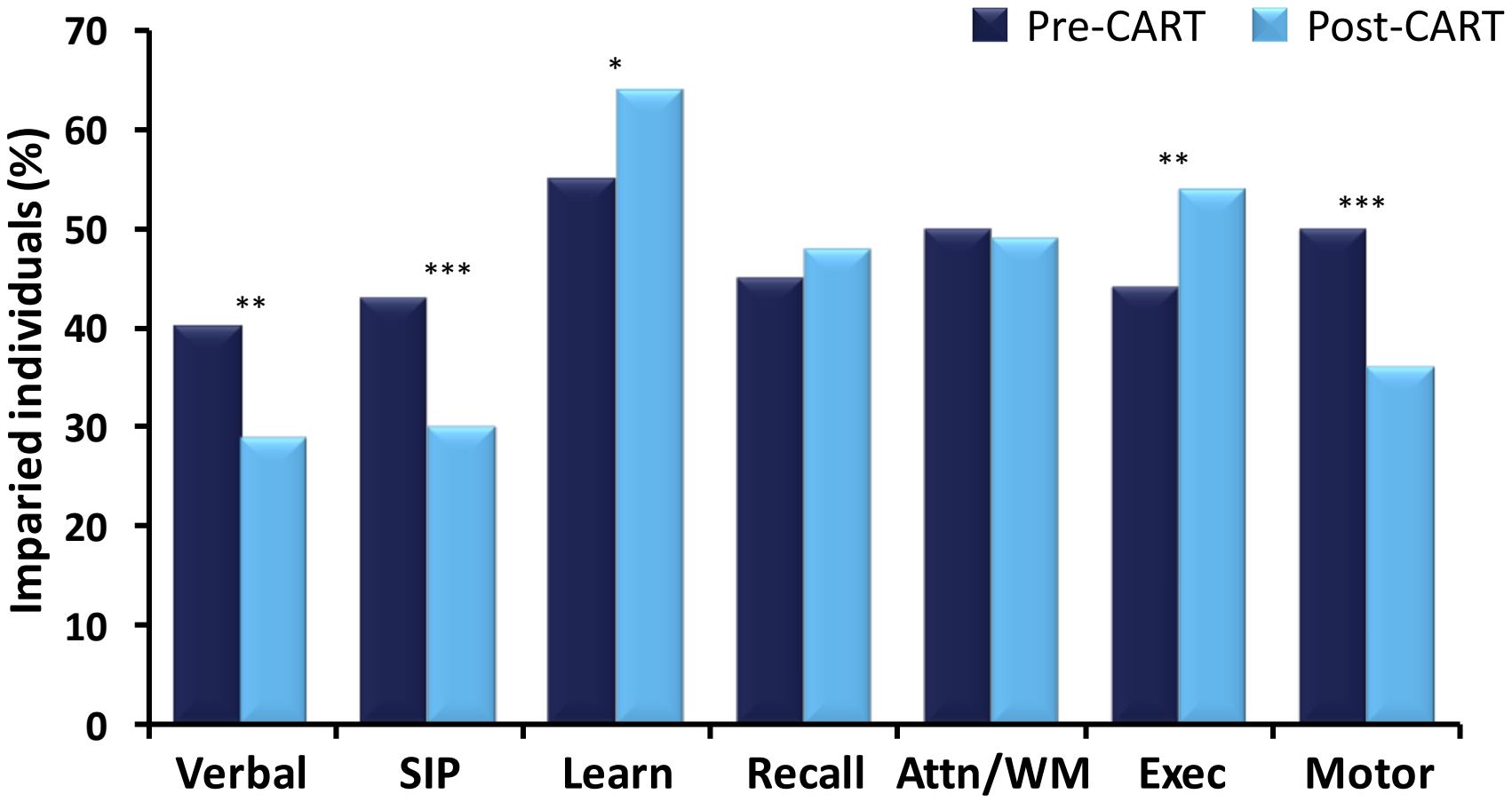
Despite ARV benefits on morbidity and mortality HAND remains prevalent



ARV, antiretroviral; CDC, Centers for Disease Control; HAND, HIV-associated neurocognitive disorders

Grant I, et al., *Ann Intern Med* 1987;107:828–36; Heaton RK., et al. *J Int Neuropsychol Soc* 1995;1:231–51; Heaton RK, et al., *Neurology* 2010;75:2087–2096.

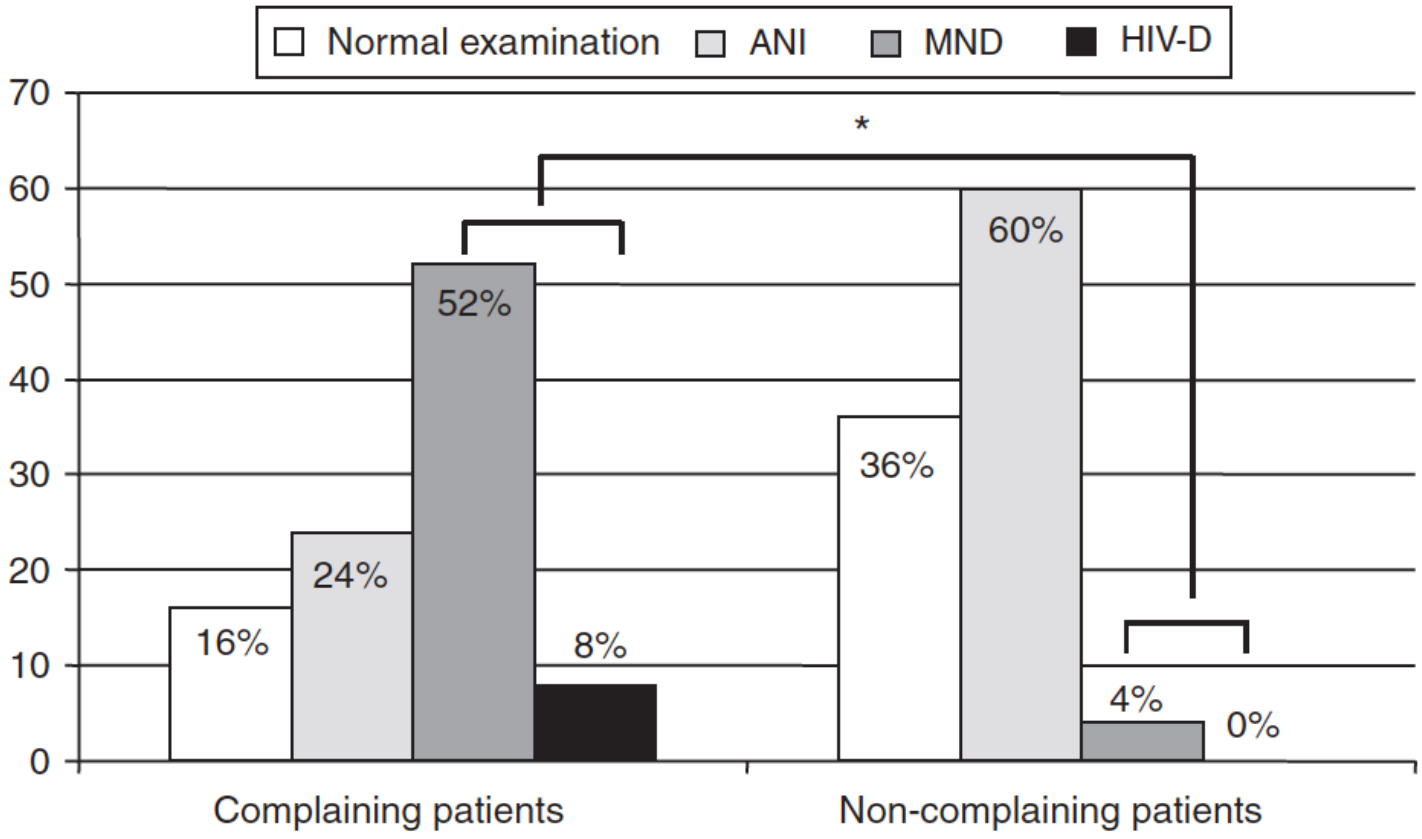
Neurocognitive impairment patterns pre- and post-CART



*p<0.05; **p<0.01; ***p<0.001

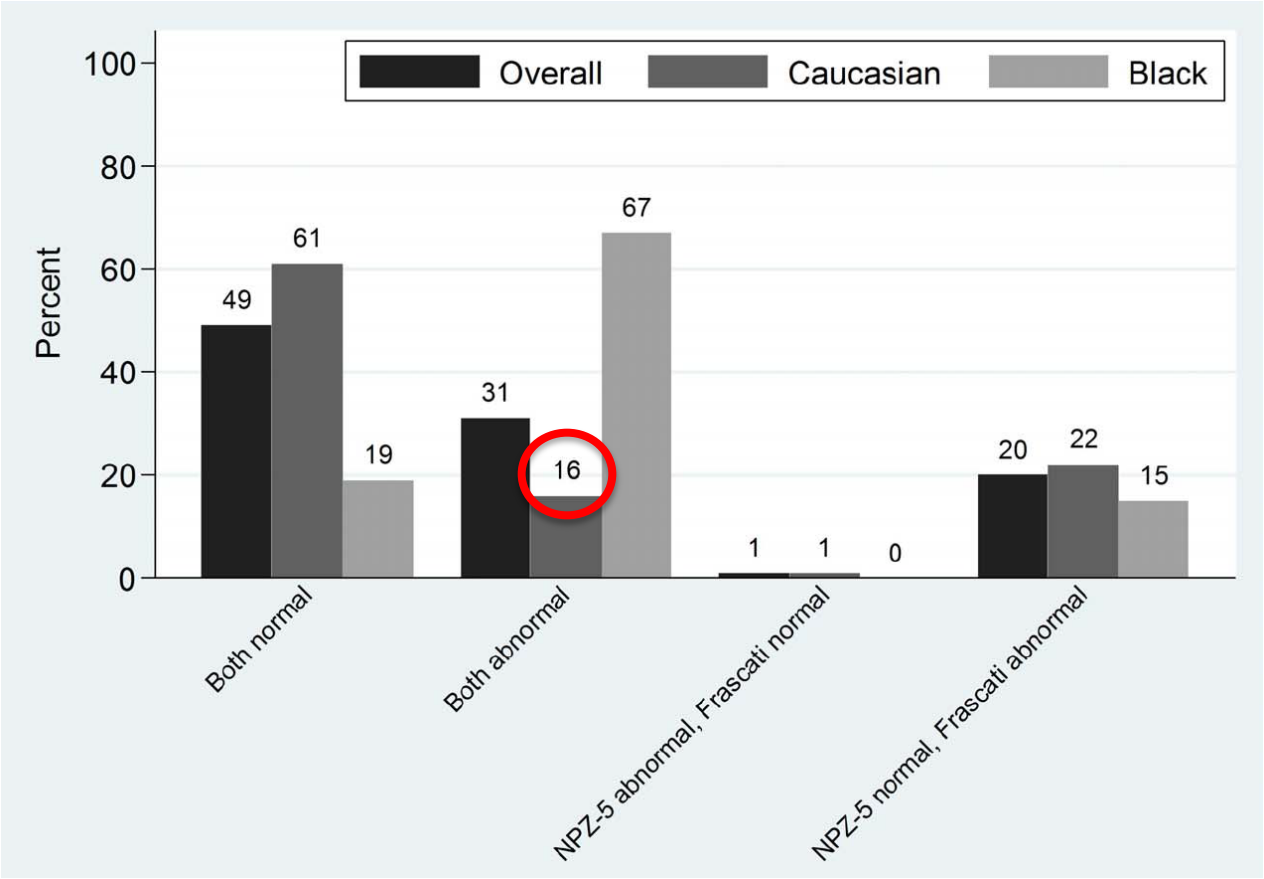
Heaton RK et al. *J Neurovirol* 2011;17:3–16.
Antinori A et al. *Neurology* 2007;69:1789–99.

Prevalence of HAND in patients with suppressed HIV viremia



Simioni S, et al. AIDS, 2010

Low rate of NCI in HIV-infected subjects with prolonged plasma viral load suppression



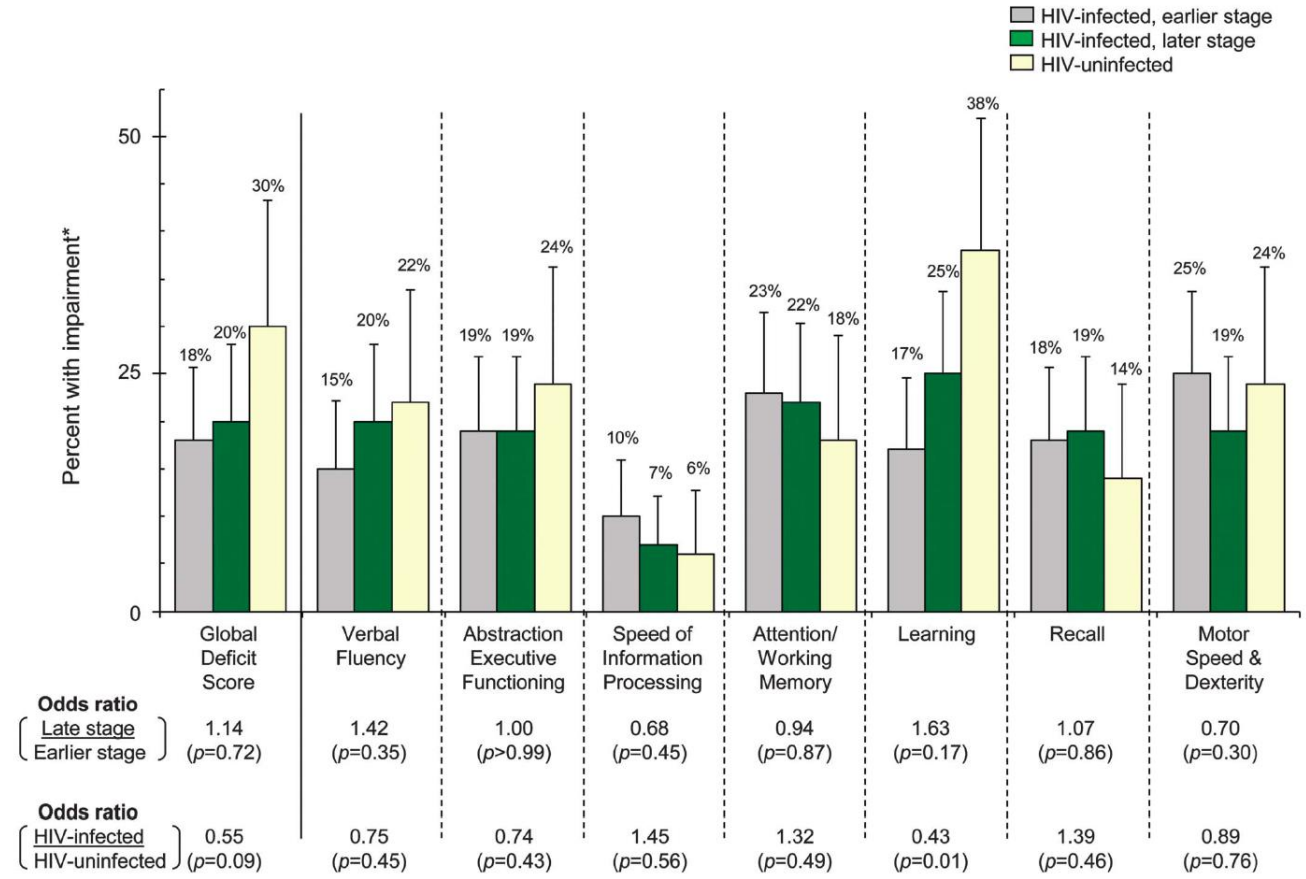
557 patients in PIVOT, (pVL <50 copies/mL in all) were included. Years undetectable pVL: 4 (SD 3).

In the multivariate analysis, only Black ethnicity was associated with poorer NPZ-5 scores (P=0.001).

Winston A, et al. PLoS One, 2013

Low prevalence of NCI in early diagnosed and managed HIV-infected persons

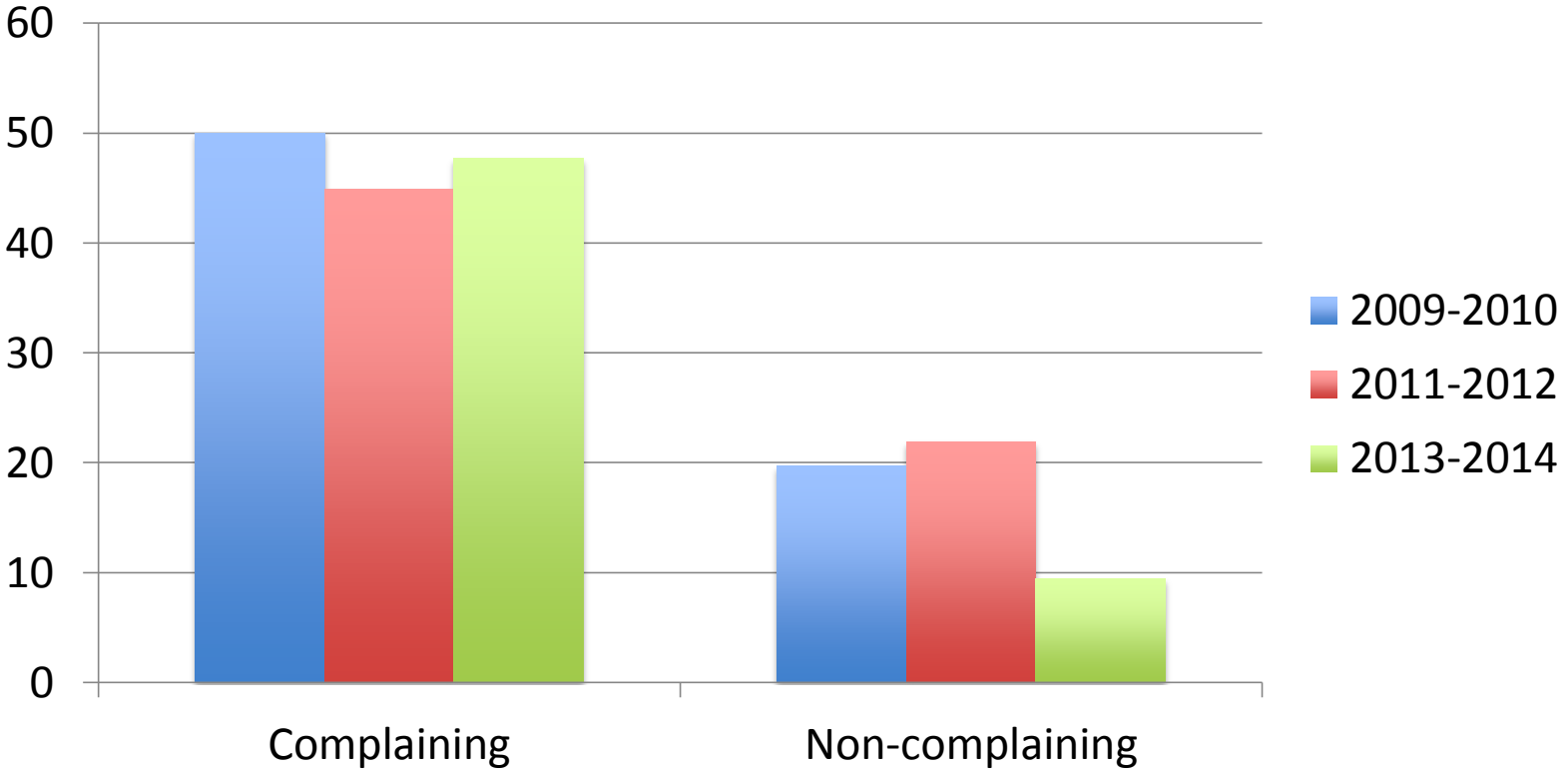
200 HIV-1 patients had a median age of 36 years, 91%were seroconverters (median window of 1.2 years), had a median duration of HIV of 5 years, had a CD4 nadir of 319, had current CD4 of 546 cells/mm3, and 64% were on highly active ARV therapy (initiated 1.3 years after diagnosis at a median CD4 of 333 cells/mm3).



Crum-Cianflone NF, et al. Neurology, 2013

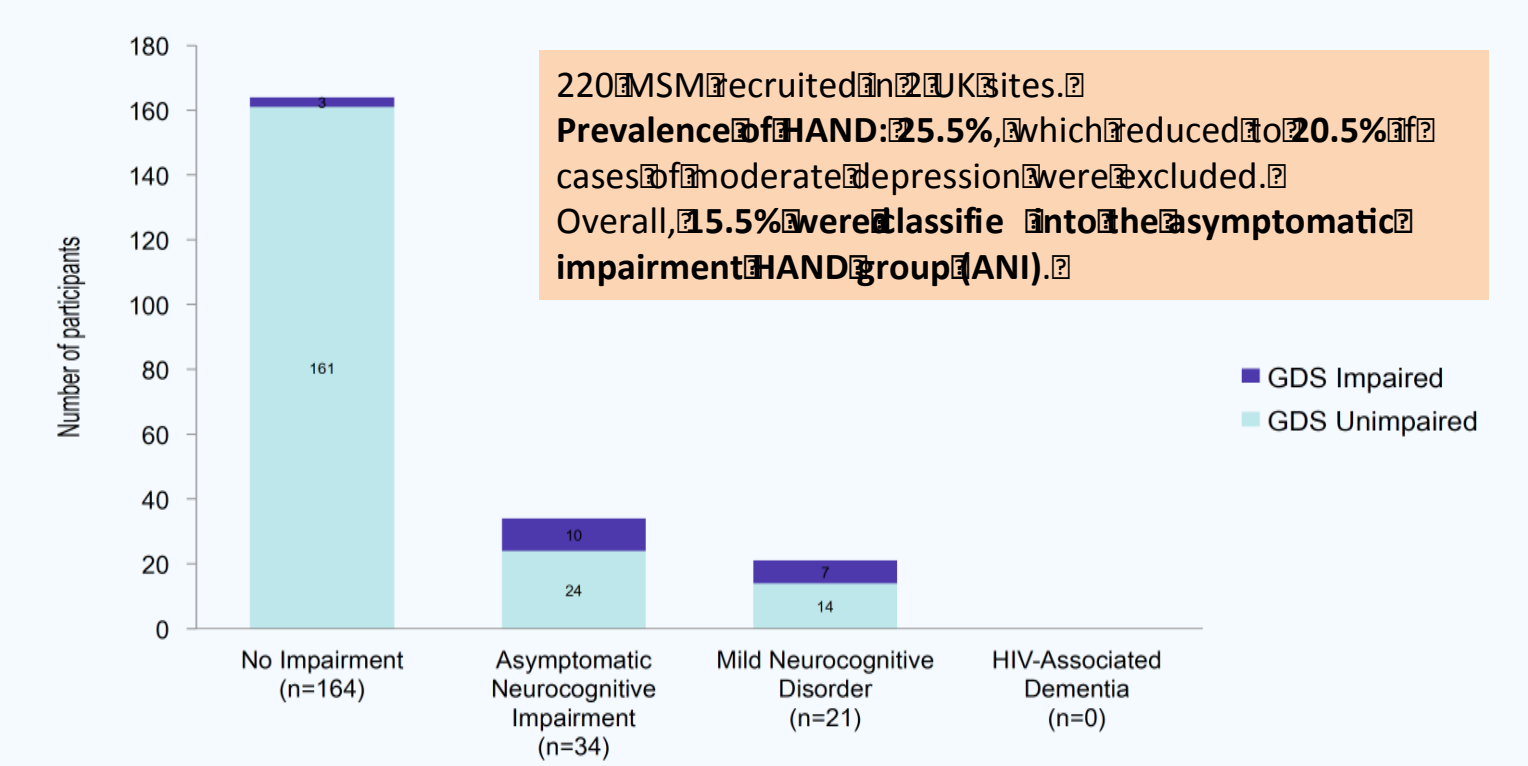
Prevalence of NCI in a recent ART-treated HIV population

569 consecutive HIV-infected cART-treated individuals from 2009 to 2014, contributing a total of 858 NPA tests, were included (male 82%; median age 48 years; MSMs 51%; HCV+ 15%; CD4 nadir >200 cell/ mm^3 61%; current CD4 >350 cell/mm^3 83%; HIV-RNA <40 c/mL 83%). At the time of NPA, 49% of patients were receiving a NNRTI-based, 32% a PIr-based, and 11% a NRTI-sparing regimen, for a median time of exposure to current regimen of 25 months (IQR 9-46). A cognitive complaint of memory loss, attention deficit or concentration difficulties was observed in 313 (36%) tested patients, whereas 545 (64%) were non-complaining.



Antinori A, et al. unpublished, 2014

Low prevalence of HAND in HIV+ unselected MSM population



220 MSM recruited in 21 UK sites.
Prevalence of HAND: 25.5%, which reduced to **20.5%** if cases of moderate depression were excluded.
Overall, **15.5% were classified into the asymptomatic impairment HAND group (ANI).**

The GDS algorithm classified 9.1% (95% CI: 5.9 to 13.6) as impaired, half of whom were categorised as ANI by the HAND rating system. 3.2% of those considered GDS impaired were in the MND category while 1.4% classified as GDS impaired were classed in the non-impaired group according to Frascati HAND criteria.
These defining shave implications for classifying HAND, and suggest that impairment in the MSM HIV+ve population may be overestimated.

McDonnell J, et al. 20th CROI, Atlanta (GA), 2013; Poster #453.

SCREENING E DIAGNOSI

Why is the screening of HAND relevant in the HIV-infected patient management?

- HIV-associated neurocognitive disorders (HAND) are **largely prevalent** even in ART-treated population with minimal comorbidities.
- Even if HAND may occur preferably in high-risk patients, according with known risk factors or predictors, **it could affect all HIV-infected population in all time points of natural history.**
- For practical purpose, **a comprehensive neuropsychological assessment is not feasible for screening.**
- Time needed to complete and lack of specific expertise in neurocognitive function assessment may be a barrier to a sensitive clinical diagnosis for HIV patient management.

Ideal characteristics of a screening test for HAND in clinical practice

- Having high sensitivity and high negative predictive value to predict changes of cognition.
- Having a predictive value to detect neurocognitive impairment even in patients with asymptomatic or mild disorders.
- To be simple, brief, easy to administer, with minimal training, by any health professional available in outpatients clinic.
- To be preferably free of language or cultural barriers.
- To be validated for using in HIV-infected population.
- To be not much expensive.

Practical issues for HAND screening application in HIV clinical setting

- To identify **targeted population**
  - All patients
  - Only selected targeted patients (with cognitive complaints, with mood changes, with known risk factors for HAND)
- To establish **optimal time point** for screening evaluation
  - At first observation in order to have baseline data
  - Periodically in all patients
  - At major change points (befor starting ART, at virological failure, before treatment change in switching, at time of occurring comorbidities, at time of declining adherence)
- To select an **optimal screening tool** according with benefits and limitations
  - Validated in HIV, sensitive for subcortical impairment, able to detect both symptomatic and asymptomatic impairment, easy to perform, time-saving, requiring less training, less costly

Screening for HAND: Mind Exchange Recommendations

Key Questions:

Which patients should be screened for HAND, and when?

- It is appropriate to assess neurocognitive functioning in **all patients with HIV** as there is limited rationale for screening only symptomatic patients or only those with recognized risk factors for HAND (e.g., nadir CD4+ T-cell counts below 200 cells/mm^3)
- Because the CNS is commonly one of the first targets of HIV infection, good practice suggests that a patient's neurocognitive profile **should be assessed early** (within 6 months of diagnosis, as soon as clinically appropriate) using a sensitive screening tool
- If possible, **screening should take place before the initiation of cART**, as this will establish accurate baseline data and allow for subsequent changes to be more accurately assessed

Screening for HAND: Mind Exchange Recommendations

Key Questions:

How often should patients be screened?

- Although there are insufficient data to establish the best time for follow-up assessments, the consensus group agreed that **screening for HAND should occur every 6–12 months in higher risk patients, or every 12–24 months in lower risk patients**.
- Several risk factors have been independently associated with an increased likelihood of HAND. The clinical significance of risk factors should be considered in light of the patien's full medical history.
- Screening should also be carried out immediately **if there is evidence of clinical deterioration or at the time of major changes in clinical status** (e.g. cART initiation or change, or diagnosis of mental health disorders).

Screening for HAND:

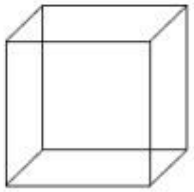
Which tools do you use to screen for HAND?

1. HIV Dementia Scale/International Dementia Scale (HDS/IHDS)
2. Montreal Assessment of Mild Cognitive Impairment (MoCA)
3. Computerised methods: Computer Assessment of Mild Cognitive Impairment (CAMCI) and Cogstate
4. Mini Mental Test
5. Self reporting
6. Other

HIV Dementia Scale - HDS

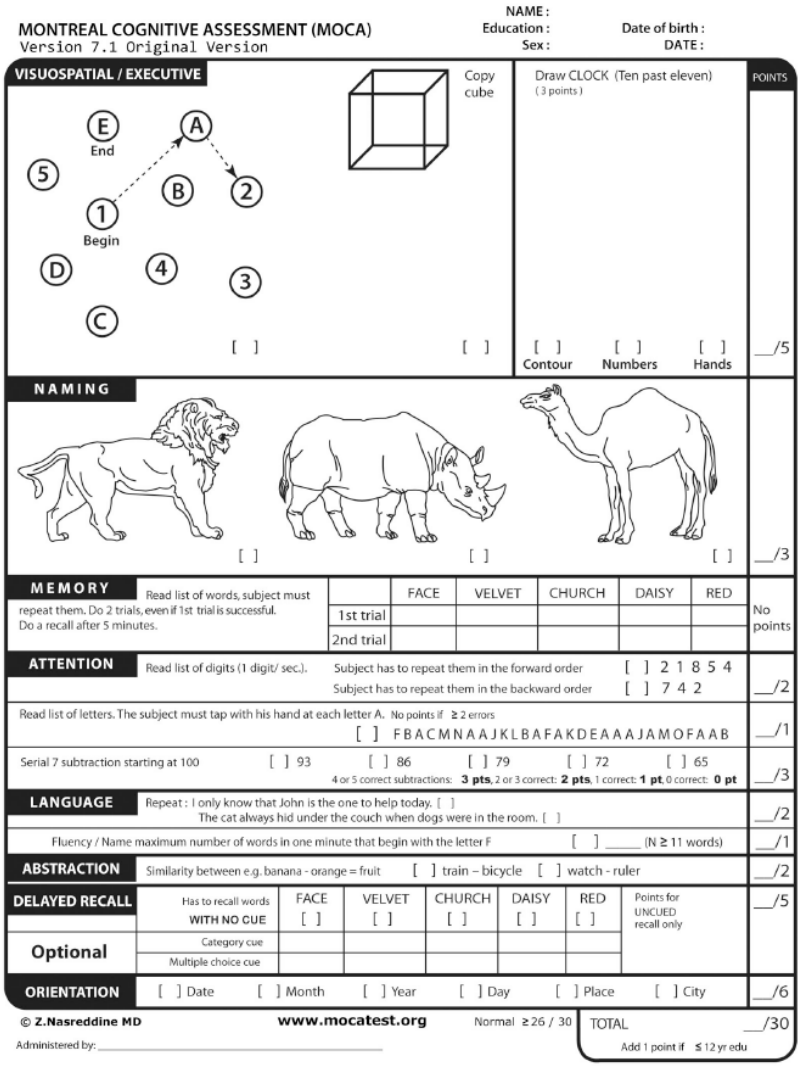
- Paper based (5min)
- Originally designed to identify patients with HIV-associated dementia for further neuropsychiatric testing
- Four domains assessed: memory, attention, psychomotor speed and construction
- A score of ≥10 out of a possible 16 is considered "unimpaired"

Maximum Score	Score	
		MEMORY - REGISTRATION Give four words to recall (dog, hat, green, peach) – 1 second to say each. Then ask the patient all 4 after you have said them.
4	( )	**ATTENTION** Anti-saccadic eye movements: 20 commands _____errors of 20 trials ≤3 errors = 4; 4 errors = 3; 5 errors = 2; 6 errors = 1; >6 errors = 0
6	( )	**PSYCHOMOTOR SPEED** Ask patient to write the alphabet in upper case letters horizontally across the page and record time. _____ in seconds. <21 sec = 6; 21.1 to 24 sec = 5; 24.1 to 27 sec = 4; 27.1 to 30 sec = 3; 30.1 to 33 sec = 2; 33.1 to 36 sec = 1; >36 sec = 0
4	( )	**MEMORY/RECALL** Ask for 4 words from Registration above. Give 1 point for each correct. For words not recalled, prompt with a "semantic" clue, as follows: animal (dog); piece of clothing (hat), color (green), fruit (peach). Give 1/2 point for each correct word after prompting.
2	( )	**CONSTRUCTION** Copy the cube below; record time:_____ seconds <25 sec = 2; 25 to 35 sec = 1; >35 sec = 0
TOTAL SCORE:	_____ /16	



Montreal Cognitive Assessment - MoCA

- Paper based, 30-item test (10min)
- Originally designed to screen geriatric patients at risk of early dementia for mild cognitive impairment
- Domains assessed: orientation, attention, language, executive functions, visuo-construction, and memory
- A score of ≥26 out of a possible 30 is considered “unimpaired”



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					
2nd trial					

No points

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 [ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B /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 /5

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
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. Add 1 point if ≤ 12 yr edu

Administered by:

The Cogstate

- Laptop based (10 mins)
- A score of ≥80 on any of the tasks is considered unimpaired
- Brief battery measures attention/vigilance, processing speed, working memory, and visual learning
- Can be used to detect change in cognitive function over very brief intervals (minutes), and longer intervals (weeks or months)

CogState

Zipursky *et al,* 2013. Systematic review evaluating brief screening tools of neurocognitive impairment in HIV/AIDS

- Meta-analysis of 31 studies (39 tools evaluated) regarding detection and differentiation between normal cognition and neurocognitive impairment and HAND in adult populations with HIV
- In detection of a range of cognitive impairment:
  - **The HIV Dementia Scale (HDS) showed poor pooled sensitivity (0.48)**
  - **The International HIV Dementia Scale (IHDS) showed moderate pooled sensitivity (0.62)**
  - **Five newer screening tools had relatively good sensitivities (>0.70); but none differentiated HAND conditions well enough to suggest broader use**
- Need for development of further tools to identify milder HAND conditions

Zipursky et al. *AIDS* 2013

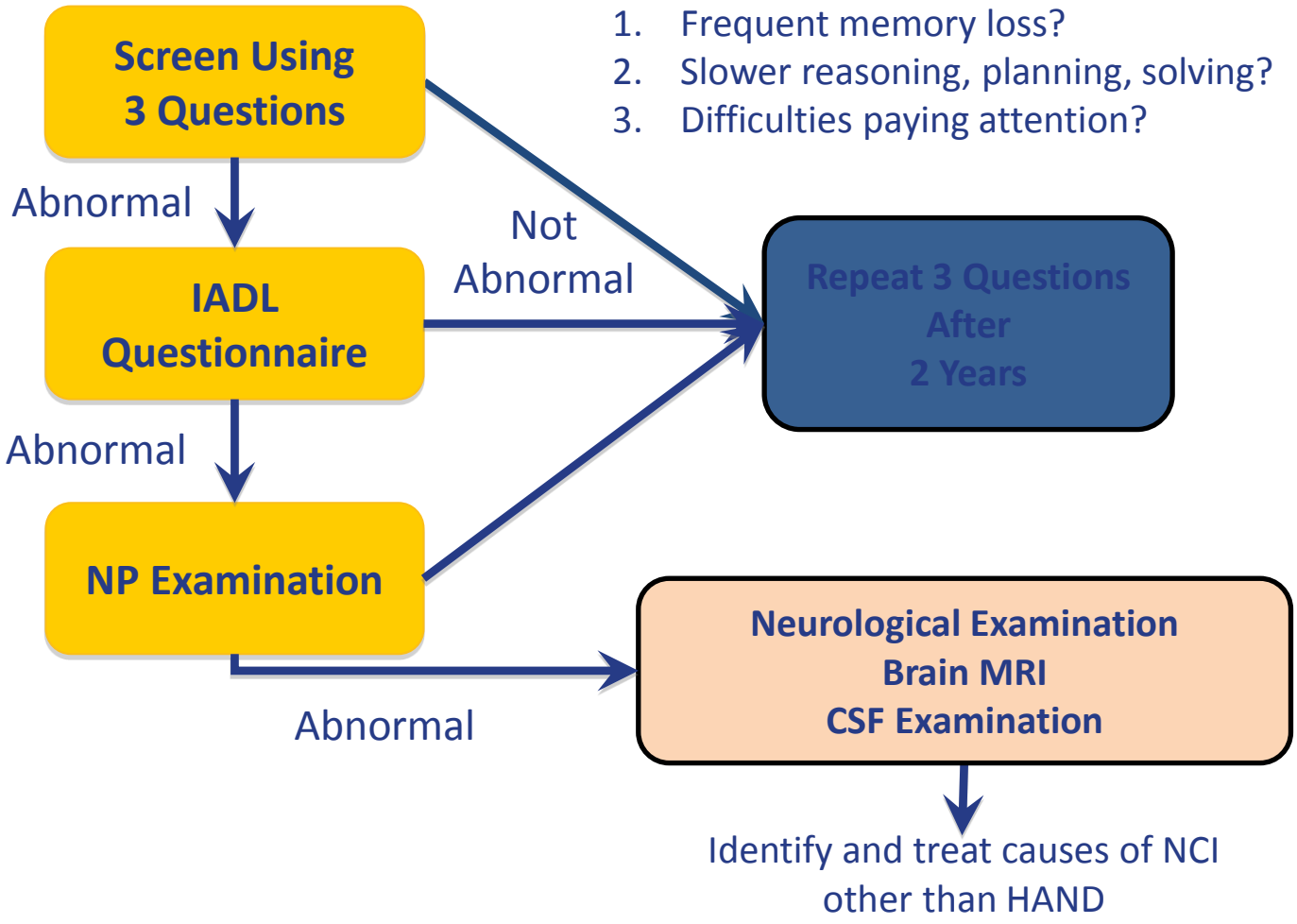
Screening for HAND: Considerations with Symptoms

Considerations/Issues

Symptoms and Subjective Reporting

- How useful is the reliance on cognitive complaints by patients, or the “subjective” ratings of cognitive status to diagnose HAND?
- How does depression relate to/interact with the cognitive complaints which occur in HAND?
- How might the presence and type of neuropsychological impairment impact on reporting of cognitive complaints?

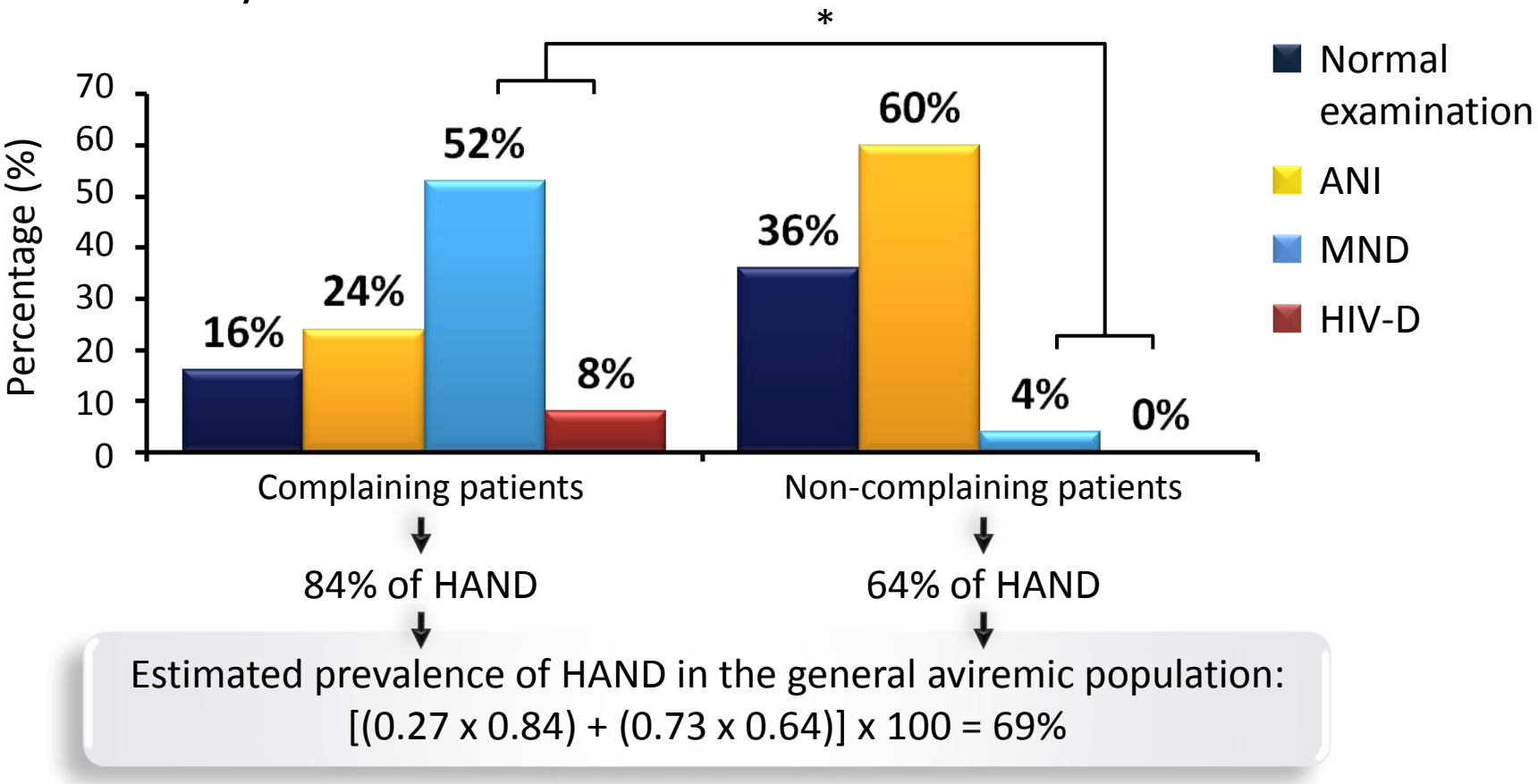
HAND Screening tests according with EACS Guidelines (2011)



European AIDS Clinical Society Guidelines, October 2011; Available at: http://www.europeanaidsclinicalsociety.org/ [last accessed 15 Nov 2011]

The role of patients in detecting neurocognitive impairment

- Patients may detect neurocognitive difficulties before they are noted by clinicians



ANI, Asymptomatic neurocognitive impairment; HAD, HIV-associated dementia; MND, HIV-associated mild neurocognitive disorder

Rourke SB *et al. J Clin Exp Neuropsychol* 1999;21:737–56.

Useful Available Tools for Screening for HIV-Associated Neurocognitive Disorder - I

Tool	Description	Benefits	Limitations
Grooved Pegboard Test [31]	Test of manipulative dexterity requiring complex visual-motor coordination		• Difficult to use in patients with severe peripheral neuropathy and/or extreme motor limitations • Requires equipment, although the cost is relatively low (US$100), and stopwatch • Must be scored and interpreted by a trained psychologist or neuropsychologist • Scoring and interpretation must be based on adequate normative data (ie, data appropriate to the individual being assessed)
Executive Interview [32]	Developed and validated in geriatric patients and patients with Alzheimer's disease as a brief assessment of frontal or executive neurocognitive function Has been shown to be a significant individual predictor of dementia in hospitalized patients with HIV	• Has good internal consistency • Correlates with other measures of executive neurocognitive function • Not affected by age or sex	• Less sensitive than HDS • Lower education was associated with an increased risk of incorrect classification of dementia • Accuracy in mild HAND has not been reliably shown
Cognitive functional status subscale of the (MOS-HIV) [33]	MOS-HIV is a widely used instrument to assess QoL in patients with HIV. Its neurocognitive functional status subscale measures functional status owing to neurocognitive impairment. Best use may be as a screening instrument to select those subjects whose self-reported neurocognitive functional status warrants formal NP test evaluation	• Sensitive to changes in NP test performance in early disease • Sensitive to neurocognitive behavior that involves neurocognitive or psychomotor speed	• No sensitivity to attention and only limited sensitivity to memory function • Accuracy in mild HAND has not been reliably shown

Abbreviations: HAD, HIV-associated dementia; HAND, HIV-associated neurocognitive disorder; HDS, HIV Dementia Scale; HIV, human immunodeficiency virus; IHDS, International HIV Dementia Scale; MOS-HIV, Medical Outcomes Study HIV Health Survey; NP, neuropsychological; QoL, quality of life.

The Mind Exchange Working Group, Clin Infect Dis, 2014

Useful Available Tools for Screening for HIV-Associated Neurocognitive Disorder - II

Tool	Description	Benefits	Limitations
HDS [24–28]	A validated brief screening tool designed primarily for use in outpatient clinics to identify dementia in people with HIV using NP tests of motor speed, concentration, and memory.	• Very fast to administer (3–5 min) • Very fast to score and interpret • Excellent specificity	• Modest sensitivity (80% when the score was 10 or less for a maximum of 16 points) leading to high rates of false negatives. High sensitivity for HAD. But HAD is relatively rare in successfully cART-treated patients • Requires a trained examiner to assess antisaccadic eye movement • Not sufficiently sensitive to detect mild HAND, particularly in highly educated individuals and in this case the use of demographically corrected norms or a cutoff of 14 points may be useful • Alphabet writing and cube-copying tests may be difficult for those with a non-Western educational background; the IHDS is more appropriate in these cases
IHDS [27, 29, 30]	A sensitive and rapid screening test for HIV dementia, which relies on assessment of motor speed and psychomotor speed It includes 3 subtests: timed finger-tapping; timed alternating hand sequence test; recall of 4 items at 2 min	• Very fast to administer and score. Can be conducted in 2–3 min and requires only a stopwatch • Demonstrated appropriate sensitivity and specificity for screening for dementia • Does not require a trained examiner • Does not require proficiency in English • Can be easily applied in different settings and cultures	• Limited ability to detect milder forms of HIV-associated neurocognitive impairment and distinguish between different stages of HIV dementia • Additional research is needed to determine appropriate cutoff values in different clinical and geographical settings • Additional research needed into the role of depression on performance and scoring
Total Recall measure of the Hopkins Verbal Learning Test–Revised [31]	Originally developed to detect dementia, it has been shown to measure neurocognitive impairment in HIV. In particular, it can be used to detect verbal learning and retrieval deficits	• Has 6 alternate forms reducing potential practice effects and enabling its use in follow-up and monitoring of neurocognitive changes over time • Easy and fast (4 min) to administer • Good test to assess patients with severe peripheral neuropathy and/or extreme motor limitations	• Must be administered by a trained examiner • Must be scored and interpreted by a trained psychologist or neuropsychologist • Scoring and interpretation must be based on adequate normative data (ie, data appropriate to the individual being assessed)

The Mind Exchange Working Group, Clin Infect Dis, 2014

Lessons Learned and Recommendations

- Cognitive screening instruments **vary in their ability to detect** the different forms of HAND.
- Most screening measures perform well in detecting HIV-Associated Dementia (HAD) but **poorly in the detection of Asymptomatic Neuropsychological Impairment (ANI) or Mild Neurocognitive Disorder (MND)**.
- HIV Dementia Scale[1] is best tool currently available to detect milder forms of HAND but recommend age and education corrections[2] to increase sensitivity.
- **Combination of two brief neuropsychological tests[3]** perform well in identifying HIV-associated cognitive impairment.
- Comprehensive neuropsychological testing is recommended as a standard of practice, at least in specialized HIV centres where resources are available.

1. Power et al., 1995; J AIDS and Human Retrovirology, 8(3): 273-8; 2. Morgan et al., 2008; J Clin Exp Neuropsychology, 30(1): 83-90; 3. Carey et al., 2004; Clin Neuropsychologist, 18(2): 234-48

Abbreviated Test Batteries for Detection of HIV-Associated Neurocognitive Impairment

Detection of HAND	Se (%)	Sp (%)	PPV (%)	NPV (%)	CCR (%)	Time (min)
Three questions	25.6	84.6	41.7	72.6	66.9	3
IHDS	61.5	80.2	57.1	82.9	74.6	4
MMSE	12.8	98.9	83.3	72.6	73.1	10
IHDS+Trial making (TM) A	79.5	72.5	55.4	89.2	74.6	10
IHDS+Trial making (TM) B	87.2	70.3	55.7	92.8	75.4	12
IHDS+Digit symbol (DS)	82.1	72.5	56.1	90.4	75.4	8
IHDS+Grooved pegboard (GP)	64.1	73.6	51.0	82.7	64.1	10
IHDS+GP+TM A	79.5	67.0	50.8	88.4	79.5	16
IHDS+GP+TM B	87.2	63.7	50.7	92.1	87.2	18

Rank	Tests	Administration Time (min)	Sensitivity (95% CI)[1]	Specificity (95% CI)[1]	PPV (95% CI)[1]	NPV (95% CI)[1]	OR (95% CI)
1	STRPCOL/HVLTR-LRN	11	73.0 (55.6–85.7)	83.1 (76.3–88.2)	50.0 (35.0–62.1)	93.0 (87.7–96.5)	13.3 (5.8–30.7)
2	HVLTR-LRN/PD	13	73.7 (56.7–86.1)	82.0 (75.0–87.1)	49.1 (35.4–61.7)	93.0 (87.5–96.4)	12.7 (5.6–29.1)
3	PASAT/BVMTR-LRN	15	63.2 (46.3–77.8)	89.7 (84.3–93.8)	60.0 (43.9–74.3)	90.9 (85.4–94.8)	15.0 (6.5–34.7)
4	PASAT/HVLTR-LRN	15	73.7 (56.8–86.2)	77.6 (70.4–83.3)	44.4 (31.7–56.5)	92.4 (86.6–96.2)	9.7 (4.3–21.9)
5	PASAT/PND	8	71.1 (54.3–84.2)	79.5 (72.6–85.4)	45.8 (32.8–58.8)	91.9 (86.0–95.6)	9.5 (4.3–21.2)
6	HVLTR-LRN/PND	13	71.1 (54.1–83.9)	77.6 (70.4–83.3)	42.9 (30.0–55.1)	91.9 (86.2–95.7)	8.5 (3.9–18.8)
7	STRPCOL/BVMTR-LRN	11	54.1 (37.1–69.7)	94.4 (89.7–97.4)	69.0 (50.0–84.2)	89.9 (84.5–93.9)	19.7 (7.8–50.2)
8	STRPCOL/PD	4	56.8 (40.0–71.8)	90.6 (85.2–94.4)	58.3 (40.7–73.7)	90.1 (84.5–94.0)	12.7 (5.5–29.4)
9	STRPINC/HVLTR-LRN	11	64.9 (47.2–79.3)	82.5 (75.4–87.6)	46.2 (31.8–59.6)	91.0 (85.4–95.0)	8.7 (4.0–19.1)
10	PASAT/WCST	20	60.0 (41.7–75.0)	86.9 (81.0–91.7)	51.2 (35.3–66.7)	90.5 (84.8–94.6)	10.0 (4.4–22.7)

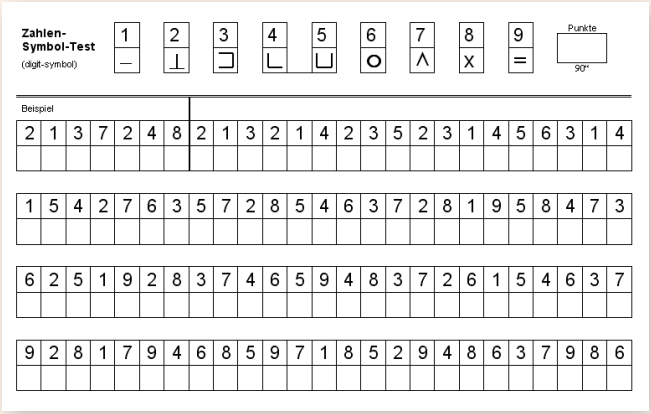
[1]95% bootstrap CI for Sensitivity, Specificity, PPV and NPV.

Abbreviations: BVMTR-LRN, Brief Visuospatial Memory Test-Revised (Learning Trials); CI, Confidence Interval; HVLTR-LRN, Hopkins Verbal Learning Test-Revised (Learning Trials); NPV, Negative Predictive Value; OR, Odds Ratio; PASAT, Paced Auditory Serial Addition Test; PD, Grooved Pegboard-Dominant hand; PND, Grooved Pegboard-non Dominant hand; PPV, Positive Predictive Value; STRPCOL, Stroop Color Test; STRPINC, Stroop Incongruent Test; WCST, Wisconsin Card Sorting Test (Total Errors).

Antinori A, et al. 20th CROI, Atlanta (GA), 2013; Poster #455; Moore DJ, et al. PLoS One, 2012

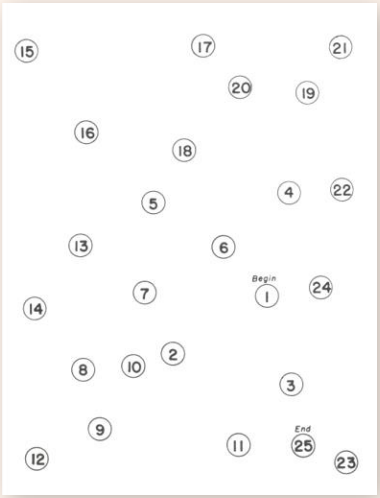
Neuropsychological tests

Digit-Symbol-Test [1]

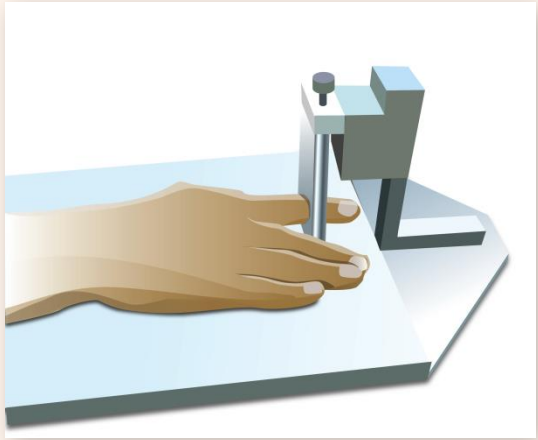


Grooved -Pegboard [2]

Trail-Making-Test 1+2 [3]



Fine Motor Movements [4]



1. Smith A., http://www.annarbor.co.uk/index.php?main_page=index&cPath=249_306 - last accessed November 2010.
2. http://www.si-instruments.com . 3. http://www.tbi-impact.org/cde/mod_templates/12_F_08_TMT.pdf 4. Arendt G . J Neurol 1990;237:362-8

Examples of NP tests that may be used to document impairments in ability domains

Fluency
- Controlled Oral Word Association Test (FAS) (1, 2)
- Thurstone Word Fluency Test (3)
- Category Fluency (4)
- Action Fluency (5)
- Design Fluency Tests (6, 7)

Executive Functions
- Stroop Color and Word Test (8)
- Trailmaking Test – Part B (3, 9)
- Color Trails –II (10)
- Wisconsin Card Sorting Test (11)
- Halstead Category Test (3, 9)
- Odd Man Out Test (12-14)
- Tower Tests (15-17)
- Delis-Kaplan Executive Function System (7)

Speed of Information Processing
- WAIS-III Digit Symbol Subtest (18)
- WAIS-III Symbol Search Subtest (18)
- Symbol Digit Modalities Test (19)
- Trailmaking Test – Part A (3, 9)
- Color Trails – I (10)
- Digit Vigilance Test (3, 20)
- Stroop Color Naming (8)
- Reaction Time Tests, e.g., California Computerized Assessment Battery (21)

Attention/Working Memory
- WAIS-III Digit Span Subtest (18)
- WAIS-III Letter-Number Sequencing Subtest (18)
- WMS-III Spatial Span Subtest (22)
- Paced Auditory Serial Addition Test (23)
- Digit Vigilance Test (error component) (3, 20)

Verbal and Visual Learning

Verbal:
- California Verbal Learning Test (Original and Revised; Total Learning) (24)
- Rey Auditory Verbal Learning Test (Total Learning) (25)
- Story Memory Test (Learning component) (3)
- Hopkins Verbal Learning Test- Revised (Total Learning) (26)
- Buschke Selective Reminding Test (27)
- WMS-III Logical Memory I (22)
- WMS-III Paired Associates I (22)

Visual:
- WMS-III Visual Reproduction-I (22)
- WMS-III Family Pictures-I (22)
- Brief Visuospatial Memory Test – Revised (Total Learning) (28)
- Figure Memory Test (Learning component) (3)
- Rey-Osterreith Complex Figure Test (Immediate Recall) (29, 30)

Verbal and Visual Memory
- Delayed recall scores of the 12 learning/memory tests listed above, with interpretation also guided by results on any normed, forgetting/savings scores and delayed recognition scores.

Motor Skills
- Grooved Pegboard Test (3, 31)
- Purdue Pegboard Test (32, 33)
- Arendt Central Motor Test Battery (34, 35)
- Finger Tapping Test (3)
- Timed Gait (36)

Antinori A, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology 2007; 69: 1789-99

How should neuropsychological testing be approached, in the diagnosis of HAND?

Full neuropsychological evaluation may be most appropriate in:

- Patients with neurocognitive impairment at screening, if the diagnosis of HAND is in doubt **(CEBM 5; GOR D)** (Antinori et al., 2007)
- Patients with cognitive deficits that impact everyday life **(CEBM 5; GOR D)** (Antinori et al., 2007)
- Patients with clinical progression of HAND **(CEBM 5; GOR D)** (Antinori et al., 2007)
- Patients at risk of HAND using a validated screening tool or evidence-supported risk factors **(CEBM 1b; GOR B)** (Cysique et al., 2010a)

Al-Khindi T *et al. J Int Neuropsychol Soc* 2011;17:956–69; Muñoz-Moreno JA *et al. AIDS Res Hum Retroviruses* 2008;24:1301–7; Ellis RJ *et al. Arch Neurol* 2002;59:923–8; Robertson KE *et al. AIDS* 2007;21:1915 – 21; Antinori A *et al*. *Neurology* 2007;69:1789–99; Cysique LA *et al. HIV Med* 2010;11:642–9.

How should neuropsychological testing be approached, in the diagnosis of HAND?

Comprehensive testing should:

- Test **at least 6 cognitive domains (CEBM 5; GOR D)** (Antinori et al., 2007)
  - Verbal; attention/working memory, executive function; learning, recall, speed of information processing, and motor skills
- **Use similar tests for ANI, MND and HAD diagnosis/assess independence in activities of daily living (CEBM 5; GOR D)** (Antinori et al., 2007; see also Al-Khindi et al., 2011; Cysique et al., 2010a; Muñoz-Moreno et al., 2008; Ellis et al., 2002; Heaton et al., 2010; Heaton et al., 2011; Robertson et al., 2007; Robertson et al. 2010; Vivithanaporn et al., 2010)
- Be sensitive and specific to HAND and other diagnoses in question (See standard reference book - Lezak et al., 2004).
- Be adaptive according to the abilities of the patient (See standard reference book - Lezak et al., 2004).
- **Ideally be administered by a neuropsychologist** (See standard reference book - Lezak et al., 2004).

How should neuropsychological testing be approached, in the diagnosis of HAND?

- Use **normative data** to correctly interpret quantitative test results (See standard reference books: Heaton et al., 2004b; Lezak et al., 2004; Strauss et al, 2006).
  - Select data to represent the demographic characteristics of a particular patient to as great an extent as possible
  - Effects of age, education, and gender must be considered. Also, consider ethnicity in some countries
  - Geographic characteristics (e.g., urban vs. rural) may also need to be considered
- In follow-up testing, use normative longitudinal data to adjust for the **impact of repeated testing (the 'learning or practice effect')** on test sensitivity **(CEBM 1c; GOR B)** (Heaton et al., 2001; Salthouse & Tucker-Drob, 2008).

Tests additional to NP assessment for diagnosis of HAND in patients with NCI

Test	Purpose
Thorough medical and neurological history	Will identify previous conditions associated with an acquired static encephalopathy (such as TBI, OIs)
Developmental history (academic performance, occupational attainment)	Will help to establish the premorbid level of neurocognitive functioning (CEBM 3b; GOR C) [42]
Assessment of past and active alcohol and substance abuse or dependence using DSM-IV	Acute intoxication or withdrawal or active substance abuse or dependence can interfere with reliable evaluation of neurocognitive status (CEBM 3a; GOR B) [43–45]. Poor performance on NP testing may be explained, at least in part, by extensive past history of alcohol or substances
Assessment of depression, anxiety, and posttraumatic stress disorder using a structured questionnaire (CEBM 5; GOR D)	To identify psychiatric conditions that may influence self-reported neurocognitive performance as well as performance on some neurocognitive tests
Neurological examination	To assess neurological signs (eg, asterixis, myoclonus, ocular motor signs, spasticity) that may suggest an etiology other than HIV infection (CEBM 5; GOR D)
Laboratory studies	To stage HIV infection (CD4 cell count and HIV RNA) and assess for comorbid infections (eg, neurosyphilis, hepatitis C) and metabolic and endocrine disorders (hypothyroidism and hypogonadism) (CEBM 5; GOR D)
CSF analysis	For OIs and other infections (CEBM 1; GOR A) [46–49] and in individuals with high CD4 T-cell count and undetectable plasma HIV RNA (to assess for detectable CSF HIV RNA) [50]; genotypic resistance testing in patients with detectable HIV RNA
MRI	To evaluate other conditions that may impact on neurocognitive impairment (eg, active opportunistic CNS disease, cerebral infarction or hemorrhage, subcortical [vascular] leukoencephalopathy, and inactive cerebral lesions related to prior CNS opportunistic disease; CEBM 2b; GOR C) [51, 52]. Magnetic resonance spectroscopy appears more sensitive than structural MRI in milder forms of HAND and shows different metabolite changes in HAND subtypes [53, 54]
Lawton & Brody's modified Activities of Daily Living scale and the Patient's Assessment of Own Functioning Inventory	Provides a formal assessment of functional impairment [22, 54, 55]

Abbreviations: CEBM, Centre for Evidence-Based Medicine; CNS, central nervous system; CSF, cerebrospinal fluid; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; GOR, grade of recommendation; HAND, HIV-associated neurocognitive disorder; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; NP, neuropsychological; OI, opportunistic infection; RNA, ribonucleic acid; TBI, traumatic brain injury.

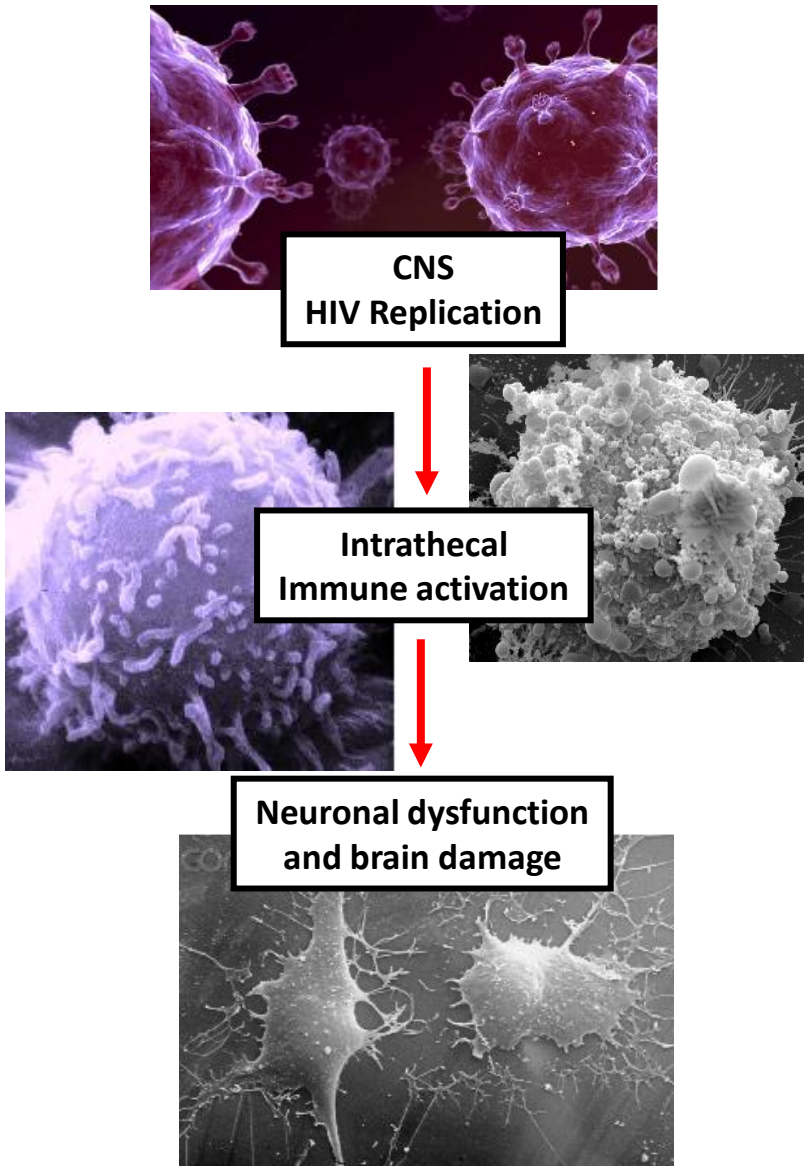
The Mind Exchange Working Group, Clin Infect Dis, 2014

HIV infection of the CNS and CSF biomarkers

Virological markers

Markers of immune activation

Markers of neuronal damage



What is the role of lumbar puncture/CSF analysis in the monitoring of HAND, and when should it be performed?

Role of lumbar puncture/CSF analysis in the *diagnosis* of HAND:

a) The role of lumbar puncture in diagnosis is in the **evaluation of HIV replication and HIV characterisation by genotypic testing**. Markers of immune activation and neuronal damage would need additional clinical validation to gain a role in the diagnostic work-up. **(CEBM 2a; GOR C)** (Hagberg *et al*. 2010; Mellgren *et al*. 2005; Canestri *et al*. 2010)

b) **CSF analysis should be performed in patients with neurological symptoms and/or signs**. **(CEBM 2a; GOR B)** (Portegies *et al*. 2004; CDC MMWR guidelines 2009)

c) Ideally, CSF analysis should be done at presentation of symptoms/signs. **(CEBM 2a; GOR C)** (Portegies *et al*. 2004; CDC MMWR guidelines 2009)

d) In untreated patients 'diagnostic' CSF analysis would be better performed before starting ART. **(CEBM 2b; GOR C)** (Mellgren *et al*. 2005)

e) Similarly, in treated patients 'diagnostic' CSF analysis would be better performed before changing ART. **(CEBM 2b; GOR C)** (Mellgren *et al*. 2005)

What is the role of lumbar puncture/CSF analysis in the monitoring of HAND, and when should it be performed?

Role and timing of lumbar puncture/CSF analysis in the *monitoring* of patients diagnosed with HAND:

a) Since almost all patients will show a reduction/clearance of HIV-RNA in CSF following cART, **there is no general indication to repeat CSF analysis** during the follow-up. **(CEBM 2b; GOR B)** (Mellgren et al., 2005)

b) Exceptions could be:

I. Patients who changed ART because of CSF escape (repeat after >12 weeks). **(CEBM 4; GOR C)** (Canestri et al., 2010)

II. Patients who do not improve neurologically (repeat after >12 weeks). **(CEBM 5; GOR D)**.

Linee Guida Italiane sull'utilizzo dei farmaci antiretrovirali e sulla gestione diagnostico-clinica delle persone con infezione da HIV-1

Ottobre 2011

Su mandato del *Ministro della Salute*

In collaborazione con

Ministero della Salute

Commissione Nazionale per la lotta contro l'AIDS
Consulta delle Associazioni per la lotta contro l'AIDS

e

SIMIT

1.**Screening neurocognitivo: strumenti**
a. Test delle 3 domande (vedi allegato); b. IDHS (vedi allegato); c. MMSE (vedi allegato)

2. Screening psichiatrico: strumenti
a. Anamnesi mirata per pregressi episodi psichiatrici o assunzione di farmaci psichiatrici; b. Patient Health Questionnaire Depression Scale (PHQ9)(vedi allegato); c. Generalized Anxiety Disorder (GAD) (vedi allegato).

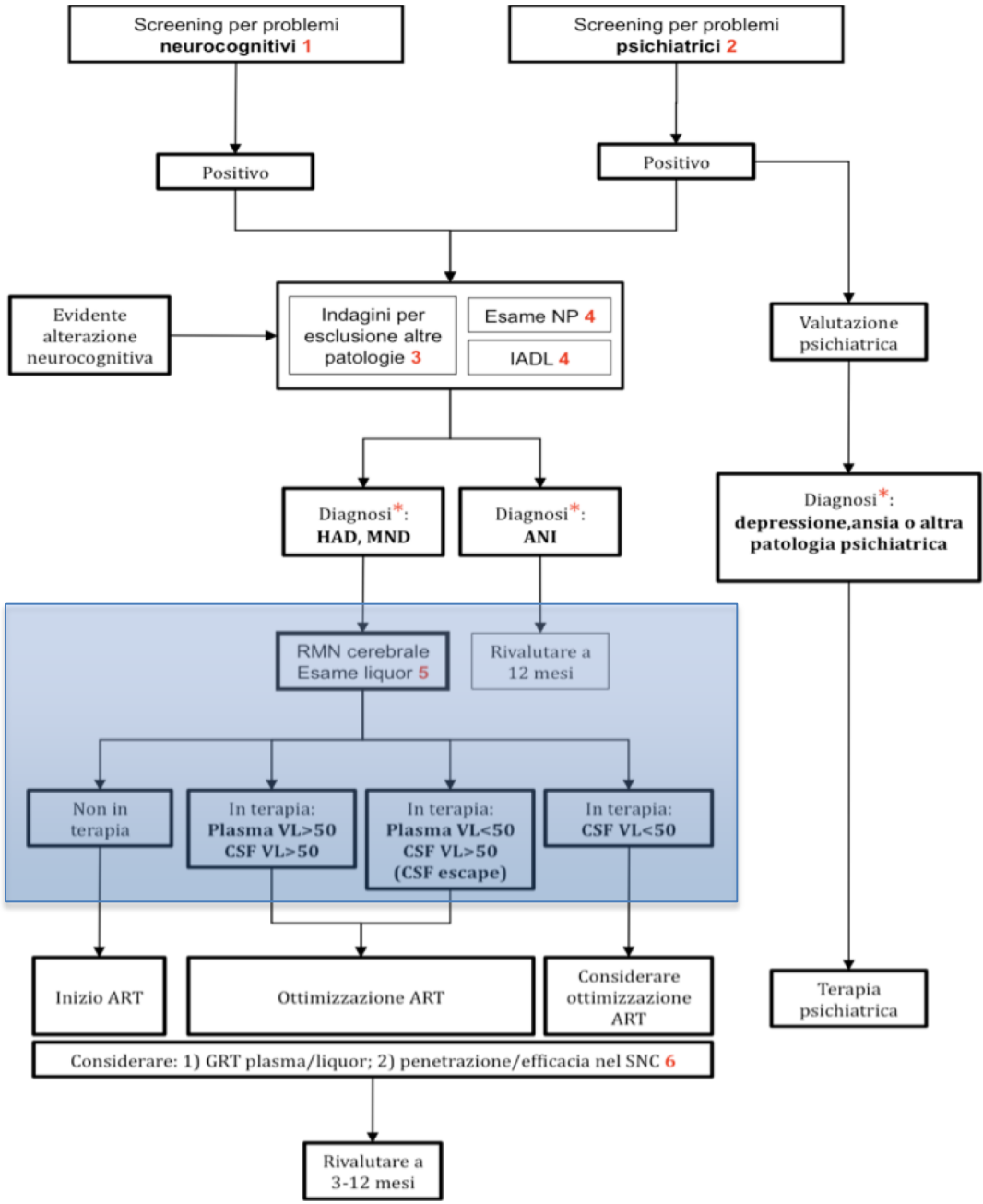
3. Indagini per altre patologie: strumenti
Anamnesi, esame obiettivo generale e neurologico, esami ematici, eventualmente RMN e puntura lombare. L'obiettivo è di escludere potenziali cause di deficit neuro cognitivo (abuso attuale o pregresso di stupefacenti, psicofarmaci o alcool, demenza cerebrovascolare, malattia di Alzheimer, infezioni o tumori del SNC attuali o pregresse, encefalopatia metabolica, cirrosi).

4. Test neuropsicologici (vedi allegato), IADL (vedi allegato)

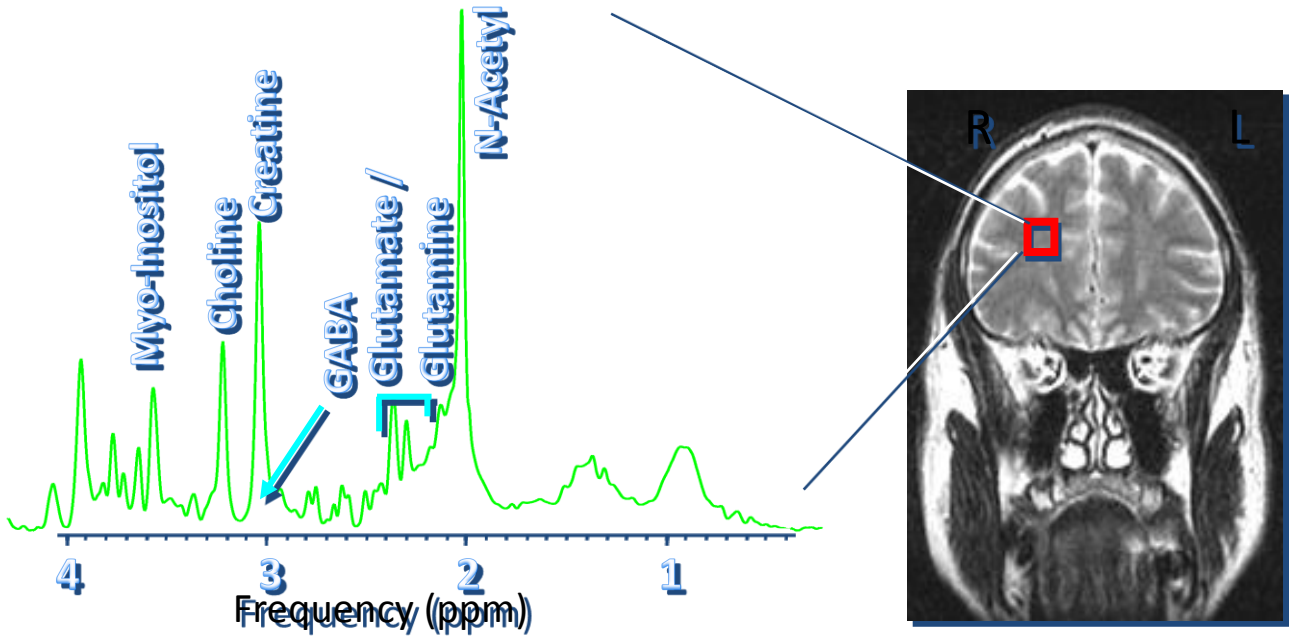
5. **RMN e puntura lombare**
Se non già affettuate per escludere altre patologie. A questo livello l'esame del liquor è indicato per studiare la presenza di HIV-RNA (contemporaneamente alla valutazione su plasma) e di farmacoresistenza. La puntura lombare è indicata nei pazienti con HAD e MND [AII] e da considerare anche nei pazienti con ANI e fattori di rischio per *CSF escape* o discordanza virologica con VL liquor >VL plasma (nadir CD4 < 200/µL; terapia antiretrovirale di lunga durata, storia di multi fallimento e/o multi resistenza e/o bassa aderenza alla terapia) [BII]. In caso di *CSF escape*, considerare le opzioni raccomandate nei pazienti con MND o HAD [BIII]

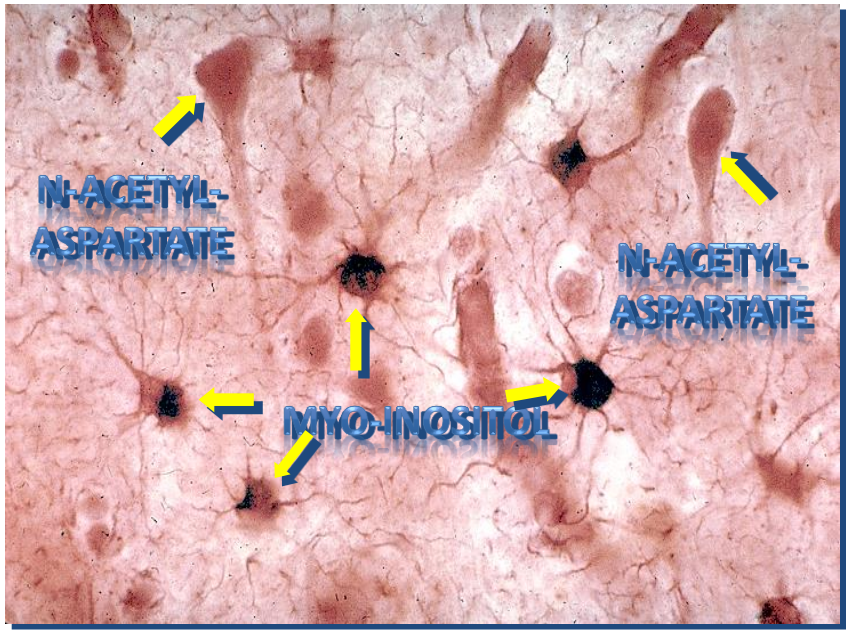
6**. Farmaci consigliati per elevata penetrazione/efficacia**.
Per la scelta di farmaci ad elevate penetrazione ed efficacia nel SNC si consiglia di utilizzare i farmaci aventi un punteggio di 4 o di 3 nel *Central nervous system Penetration Effectiveness* – CPE Score (*Letendre S et al*, CROI 2010) [vedi in seguito]

* Nel caso le indagini risultassero negative per disturbi cognitivi o psichiatrici, si raccomanda la rivalutazione a 6-12 mesi



Proton MR Spectroscopy (1H MRS)





Neuronal Marker: NAA, Glu+Gln:
Glial Marker: Myo-inositol

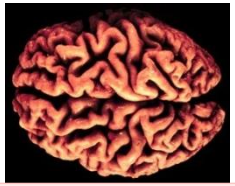
Total Creatine
Choline compounds

Differential diagnosis of new or worsening cognitive symptoms in people living with HIV

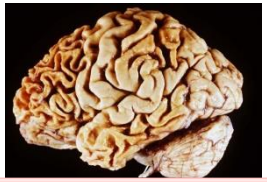
- Other neurodegenerative disorders
  - Alzheimer's disease
  - Vascular dementia
- Mood disorders
  - Major depression
- Drug toxicity
  - Stimulants
  - Antiretrovirals
- Sleep disorders
- New or undetected infections
  - Hepatitis C
  - Hepatitis B
    - Should be vaccinated
  - Systemic infections
    - Syphilis
    - Tuberculosis
  - Central nervous system opportunists
    - Cryptococcus
    - Toxoplasma
    - Epstein-Barr virus

Dementias in the differential diagnosis of HAND

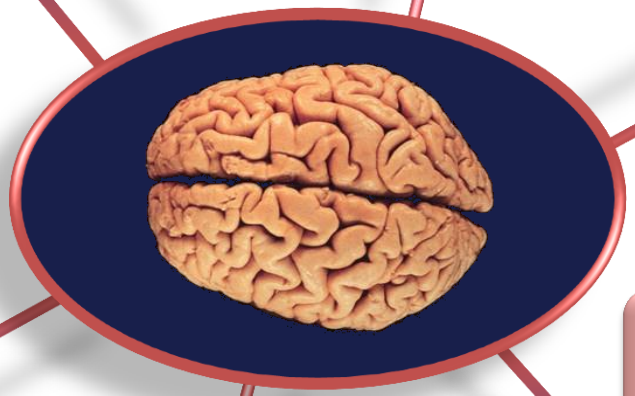
Infectious dementias
- **Viral**
- **Prion‘s disease**

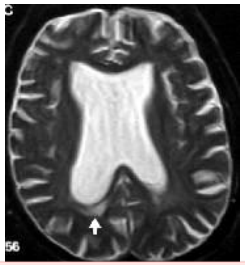


Alzheimer‘s-type



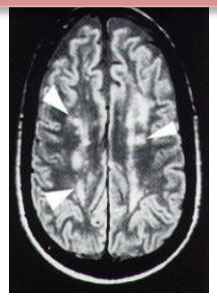
Pick‘s disease





Normal pressure hydrocephalus

Vascular dementia SAE
(Binswanger‘s disease)



"Focal" dementias
(progressive aphasia, semantic dementia)

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

Other conditions to consider in the differential diagnosis

- Psychiatric illnesses (particularly major depression, anxiety, and post-traumatic stress disorder) and substance abuse/dependence. **(CEBM 1b; GOR A)** (Owe-Larson et al., 2009)
- Prescription drugs
  - Drugs with anticholinergic properties and polypharmacy (particularly in older adults) **(CEBM 2b; GOR C)** (Carriere et al., 2009; Mulsant et al. , 2003; Ehrt et al., 2010)
- Infections other than HIV
  - Syphilis, opportunistic infections and other HIV-related CNS disorders **(CEBM 2b; GOR C)** (Monterro de Almeida et al., 2010; Clifford, 2009b)
  - HCV co-infection and associated liver disease may worsen HAND **(CEBM 2b, 5; GOR B)** (Cherner et al., 2005; Hinkin et al., 2008; Forton et al., 2005)

CEBM, University of Oxford Centre for Evidence-Based Medicine Hierarchies of Evidence scale; GOR, grade of recommendation

Becker JT *et al. Neurology* 2009;73:1292–9; Foley J *et al. Clin Neuropsychol* 2010;24:265–85; Wright EJ *et al. Neurology* 2010;75:864–73; Hinkin CH *et al. J Clin Epidemiol* 2001;54(Suppl 1):S44–52; Hinkin CH *et al. AIDS* 2004;18(Suppl 1):S19–25; Gonzalez R, Cherner M. *Int Rev Psychiatry* 2008;20:49–60; Lin K *et al. J Clin Exp Neuropsychol* 2011;33:326–34; Garg RK. *Postgrad Med J* 1999;75:387–90; Kellinghaus C *et al. Seizure* 2008;17:27–33; Esiri MM *et al. J Neurol Neurosurg Psychiatry* 1998;65:29–33; Vehmas A *et al. J Neuroimmunol* 2004;157:99–110; Xu J, Ikezu T. *J Neuroimmune Pharmacol* 2009;4:200–12; Brew BJ, Letendre SL. *Int Rev Psychiatry* 2008;20:73–88; Patrick L. *Altern Med Rev* 2000;5:39–51; Kalita J Misra UK. *J Neurol* 2008;255:353–9; Moffat SD *et al. J Clin Endocrinol Metab* 2002;87:5001–7; Quinlan P *et al. Dement Geriatr Cogn Disord* 2010;30:205–11; Owe-Larsson B *et al. Afr J Psychiatry (Johannesbg)* 2009;12:115–28; Carrière I *et al. Arch Intern Med* 2009;169:1317–24;
Mulsant BH *et al. Arch Gen Psychiatry* 2003;60:198–203; Clifford DB *et al. Neurology* 2009;73:309–14; Cherner M *et al. Neurology* 2005;64:1343–7;
Hinkin CH *et al. J Addict Dis* 2008;27:11–7; Forton DM *et al. AIDS* 2005;19(Suppl 3):S53–63.

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

- Cerebrovascular disease and metabolic syndrome, particularly in patients who have long-standing HIV disease **(CEBM 1b; GOR B)** (Becker et al., 2009; Foley et al., 2010a; Wright et al., 2010; Valcour et al., 2006b; Tebas, 2008; Nachega et al., 2009)
- Aging is a major co-morbidity that is associated with long-term of HIV disease, cART, and immune activation **(CEBM 1b; GOR B)** (Goodkin et al., 2001; Hinkin et al., 2001; Hinkin et al., 2004; Gonzalez and Cherner 2008; Wojna et al., 2010)
- Other chronic neurodegenerative disorders
  - Traumatic brain injury **(CEBM 1b; GOR B)** (Lin et al., 2011), seizures **(CEBM 2b; GOR B)** (Garg, 1999; Kellinghaus et al., 2008) and Alzheimer's disease **(CEBM 1b; GOR B)** (Esiri et al., 1998; Izycka-Swieszewska et al., 2000; Vehmas et al., 2004; Xu and Ikezu 2009)
- Vitamin or hormone deficiency **(CEBM 2b; GOR C)** (Agarwal et al., 2010)
  - Red cell folate **(CEBM 5; GOR D)** (Brew and Letendre, 2008), B12 (CEBM 2a; GOR B) (Patrick, 2000; Kalita & Misra, 2008), testosterone **(CEBM 1b; GOR B)** (Moffat et al., 2002) and thyroid function **(CEBM 2b; GOR C)** (Quinlan et al., 2010)

Becker JT et al. Neurology 2009;73:1292–9; Foley J et al. Clin Neuropsychol 2010;24:265–85; Wright EJ et al. Neurology 2010;75:864–73; Hinkin CH et al. J Clin Epidemiol 2001;54(Suppl 1):S44–52; Hinkin CH et al. AIDS 2004;18(Suppl 1):S19–25; Gonzalez R, Cherner M. Int Rev Psychiatry 2008;20:49–60; Lin K et al. J Clin Exp Neuropsychol 2011;33:326–34; Garg RK. Postgrad Med J 1999;75:387–90; Kellinghaus C et al. Seizure 2008;17:27–33; Esiri MM et al. J Neurol Neurosurg Psychiatry 1998;65:29–33; Vehmas A et al. J Neuroimmunol 2004;157:99–110; Xu J, Ikezu T. J Neuroimmune Pharmacol 2009;4:200–12; Brew BJ, Letendre SL. Int Rev Psychiatry 2008;20:73–88; Patrick L. Altern Med Rev 2000;5:39–51; Kalita J Misra UK. J Neurol 2008;255:353–9; Moffat SD et al. J Clin Endocrinol Metab 2002;87:5001–7; Quinlan P et al. Dement Geriatr Cogn Disord 2010;30:205–11; Owe-Larsson B et al. Afr J Psychiatry (Johannesbg) 2009;12:115–28; Carrière I et al. Arch Intern Med 2009;169:1317–24;
Mulsant BH et al. Arch Gen Psychiatry 2003;60:198–203; Clifford DB et al. Neurology 2009;73:309–14; Cherner M et al. Neurology 2005;64:1343–7;
Hinkin CH et al. J Addict Dis 2008;27:11–7; Forton DM et al. AIDS 2005;19(Suppl 3):S53–63. Cysique LA et al. HIV Med 2010;11:642–9.

Prevalence of depression in patients with HIV

- 20–30% of patients with HIV suffer from depression[1]
- Depression is more common in patients with the following characteristics:
  - Women[2]
  - Non-Caucasian ethnicity[3]
  - Progressed to AIDS[4]
  - Unemployed[3]
  - Have dependants who are minors[3]
  - Hepatitis C co-infection[5]

1. Coughlin SS. *Am J Epidemiol* 2013;177:126–130; 2. Nyirenda *et al. J Affect Disord* 2013; Epub ahead of print. doi: 10.1016/j.jad.2013.05.005;
3. Shacham E *et al. AIDS Patient Care STDs* 2009;23:949–55; *4.* Ramasubbu R *et al. Ann Clin Psychol* 2012;24:82–90;
6. New York State Department of Health. Depression and mania in patients with HIV/AIDS. New York (NY): New York State Department of Health; 2010. Available at: http://cdn.hivguidelines.org/wp-content/uploads/depression-and-mania-posted-10-19-2010.pdf. Last accessed July 2013.

Depression in patients with HIV

- Depression in patients with HIV is associated with[1,2]
  - Lower quality of life
  - Reduced adherence to ART
  - Poorer self-care
  - Worse treatment outcomes
  - Impairment in social and vocational functioning
  - Social isolation
  - High-risk behaviour and substance abuse

- Patients with HIV and depression may be less likely to receive HAART[3,4]

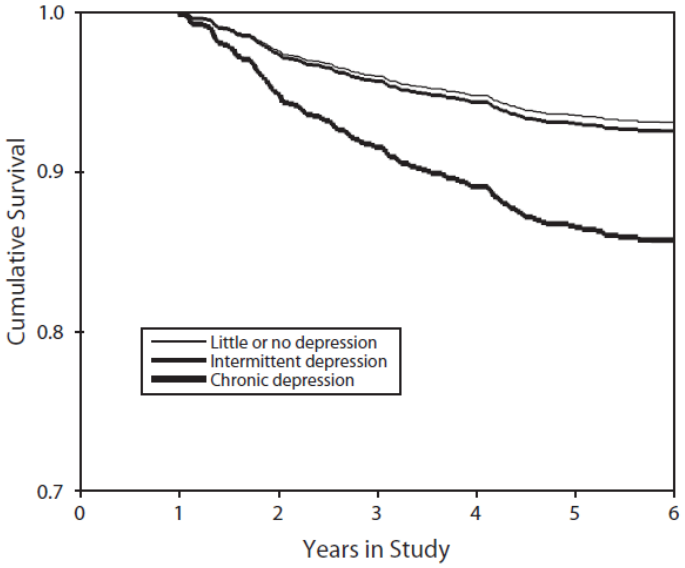
1. New York State Department of Health. Depression and mania in patients with HIV/AIDS. New York (NY): New York State Department of Health; 2010. Available at: http://cdn.hivguidelines.org/wp-content/uploads/depression-and-mania-posted-10-19-2010.pdf. Last accessed July 2013;
2. Relf MV *et al. J Assoc Nurses AIDS Care* 2013;24(1 Suppl):S15–28;
3. Tegger MK *et al. AIDS Patient Care STDS* 2008;22:233–43; 4. Bhatia R *et al. AIDS Behav* 2011;15:1161–70.

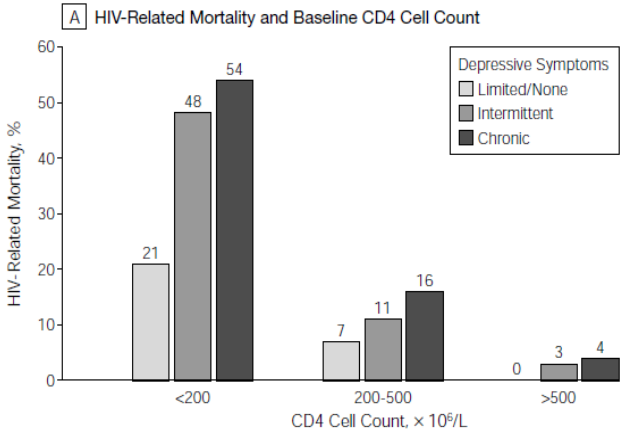
Patients with HIV and depression have lower treatment adherence

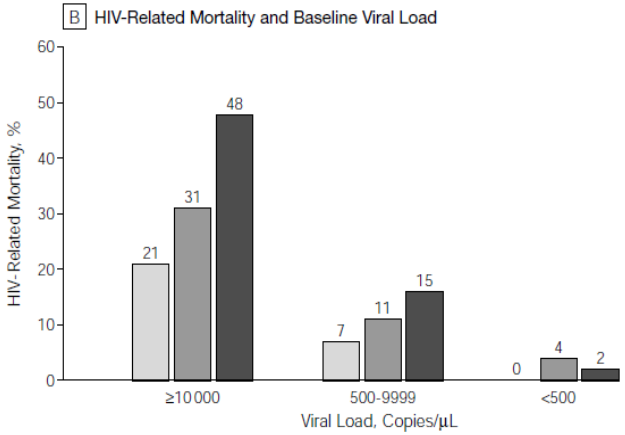
- Depression is negatively correlated with treatment adherence in patients with HIV[1]
  - Adherence decreases as the severity of depression increases[1]
  - Patients are more likely to discontinue treatment[2]
- Cognitive symptoms of depression are particularly correlated with non-adherence[1]
  - Fatigue is the only vegetative symptom associated with non-adherence
- Lower treatment adherence in patients with HIV and depression leads to an increased viral load[2]

1. Wagner GJ et al. Ann Behav Med 2011;42:352–60; 2. Carrico AW et al. J Acquir Immune Defic Syndr 2011;56:146–50.

Patients with HIV and depression have a higher mortality risk







Risk of mortality in patients with HIV and depression is independent of CD4+ count and viral load

Cook JA *et al. Am J Pub Health* 2004;94:1133–40.

Screening depression in patients with HIV

- Many screening techniques can be performed in ≤10 minutes[1]
  - Screening methods as short as two questions have been recommended[2]
  - Questionnaire length does not impact accuracy[3]

Screening instruments used for evaluating comorbid depression in patients with medical illness

Screening instrument	Method of administration	Administration time	Assessment
Hamilton Depression Rating Scale (HAM-D)	Clinician administrated	20 to 30 minutes	Severity of depression
Montgomery-Åsberg Depression Rating Scale (MADRS)	Clinician administrated	5 to 10 minutes	Severity of depression
Symptom Check List 90-Revision (SCL-90-R)	Self report	15 minutes	Screens depression/other psychiatric comorbidity
Brief Symptom Inventory (BSI) (Abbreviated SCL-90-R)	Self report	10 minutes	Screens depression/other psychiatric comorbidity
Illness Distress Scale (IDS)	Self report	5 to 10 minutes	Severity of physical and emotional distress
Psychological Distress Inventory (PDI)	Self report	5 minutes	Severity of distress
Carroll Depression Rating Scale (CDRS)	Self report	5 minutes	Severity of depression
Geriatric Depression Scale (GDS)	Self report	5 minutes	Severity of depression
Zung Depression Scale (Zung)	Self report	5 minutes	Severity of depression
Beck Depression Inventory for Primary Care (BDI-PC)	Self report	5 minutes	Severity of depression
Beck Depression Inventory–Fast Screen for Medical Patients (BDI-FS)	Self report	<5 minutes	Severity of depression
Depression in the Medically Ill scale (DMI-10)	Self report	5 minutes	Severity of depression
General Health Questionnaire (GHQ)	Self report	Dependent on the version	Severity of depression
Patient Health Questionnaire (PHQ-9)	Self report	<5 minutes	Presence of depression
Medical Outcomes Study Depression Questionnaire (MOS-DQ)	Self report	<5 minutes	Presence of depression
Hospital Anxiety and Depression Scale (HADS)	Self report	<5 minutes	Severity of depression
Centre for Epidemiological Studies Depression Scale (CES-D)	Self report	10 minutes	Severity of depression

Source: Reference 45.

1. Ramasubbu R *et al. Ann Clin Psychiatr* 2012;24:82–90;
2. New York State Department of Health. Depression and mania in patients with HIV/AIDS. New York (NY): New York State Department of Health; 2010. Available at: http://cdn.hivguidelines.org/wp-content/uploads/depression-and-mania-posted-10-19-2010.pdf. Last accessed July 2013;
3. Akena D *et al. BMC Psychiatry* 2012;12:187.

Neurocognitive impairment in patients with HIV and depression

- Depression-related neurocognitive impairment and HAND are independent[1]
- **Testing for HAND may be confounded by the presence of depression**
  - Evidence surrounding the impact of depression on neuropsychological functioning in patients with HIV is conflicting[2–4]
  - Because depression could manifest itself as cognitive impairment, it must be ruled out before diagnosing HAND[1]
  - However, depression is a risk factor for HAND[2]

1. Dubé B *et al. J Psychiatry Neurosci* 2005;30:237–46; 2. Cysique LA *et al. J Int Neuropsychol Soc* 2007;13:1–11;
3. Millikin CP *et al. J Clin Exp Neuropsychol* 2003;25:201–15; 4. Gibbie T *et al. HIV Med* 2006;7:112–21; 4..

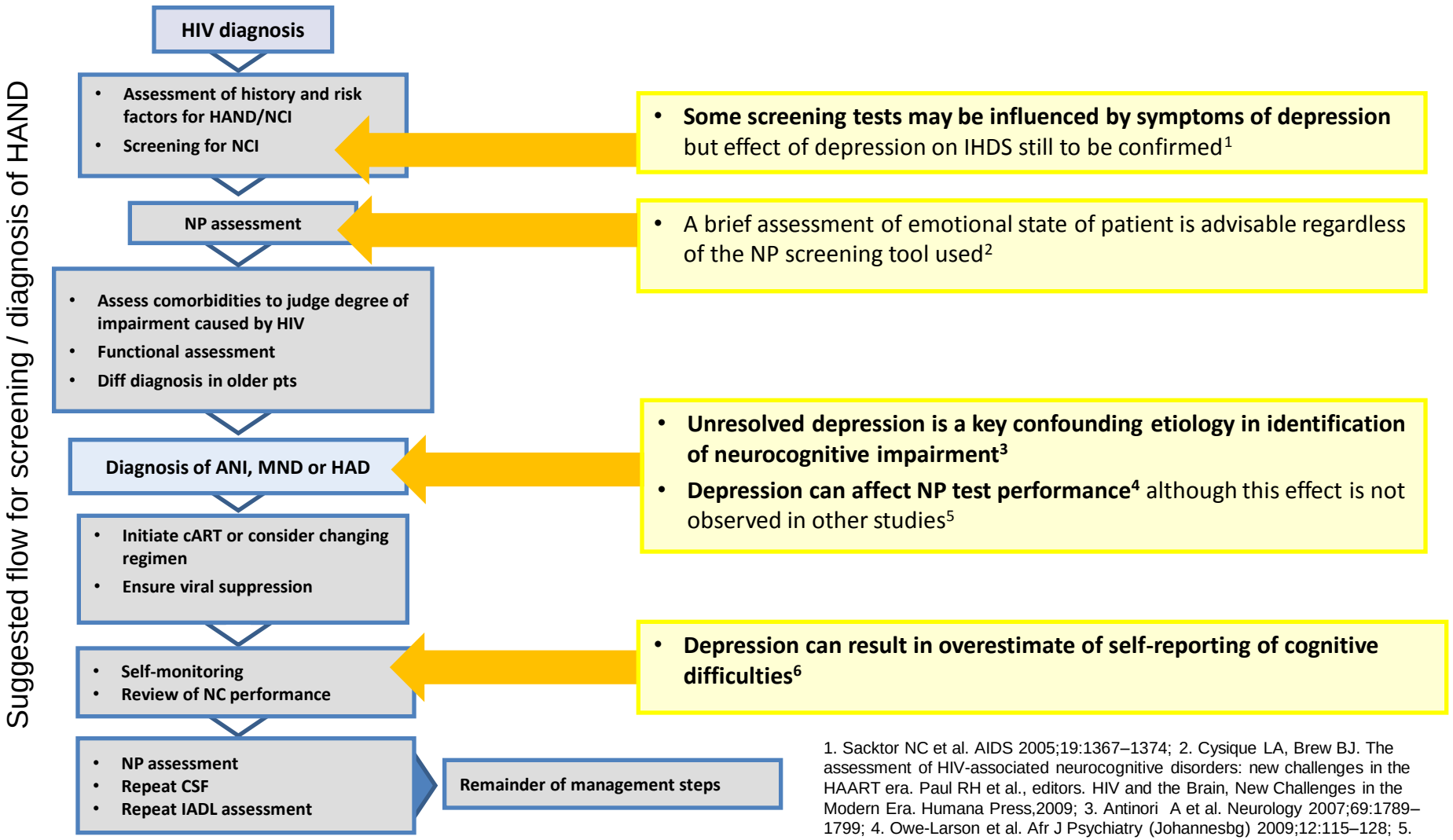
Depression as confounder to HIV-associated cognitive disorders

	Secondary Condition: compatible with HIV related neuro-cognitive disorder	**Contributing condition: HIV-related neurocognitive disorder**	**Confounding condition: unable to attribute abnormalities to direct effects of HIV**
Depression*	Depressed mood and/or major depressive disorder but without psychotic features, and no clinical indication of inadequate effort/motivation on cognitive testing (NP or MSE). Normal performance on ≥1 effort-demanding NP test (e.g., Trails B, WAIS-III Processing Speed or Letter-Number Sequencing, PASAT).	Major depressive disorder with psychotic features or some clinical evidence of fluctuating or suboptimal effort on cognitive testing. Nevertheless, impairment is present on non-speeded tests or on tests on which patient appeared to put forth good effort. Patient responds well to task demands with some examiner encouragement.	Major depressive disorder with psychotic features and/or persisting clinical evidence of suboptimal effort in the cognitive testing process. Patient does not respond well to examiner prompting or encouragement, OR Major depression with functional complaints but normal cognitive results and normal performance on any objective tests of functional abilities.

*Other classifying confounds for history of remote traumatic brain injury, history of developmental disability, history of alcohol or other substance use disorder, HIV-related CNS opportunistic disease, non-HIV-related neurologic condition, systemic disease, co-infection with HCV.

Antinori A., et al. Neurology 2007; 69: 1789-99

How can depression confound the diagnosis of HAND?



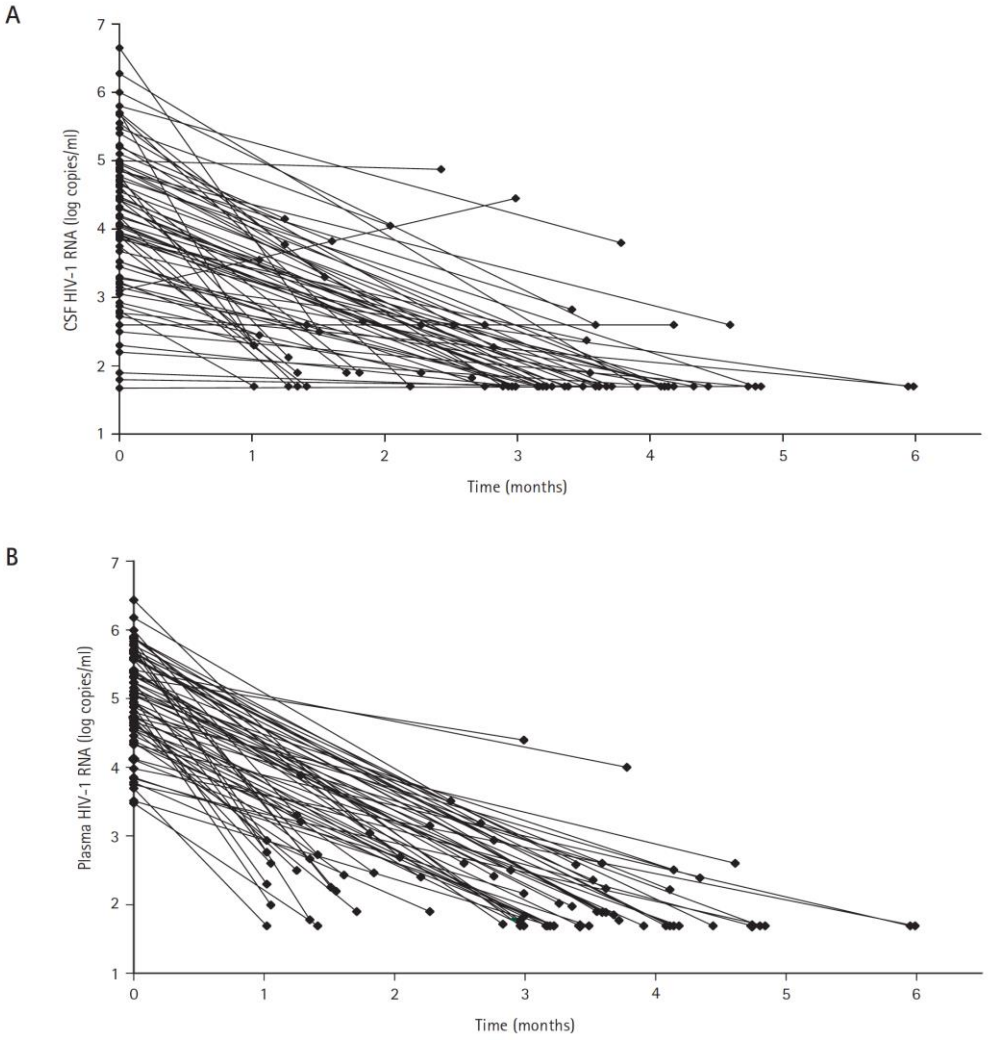
1. Sacktor NC et al. AIDS 2005;19:1367–1374; 2. Cysique LA, Brew BJ. The assessment of HIV-associated neurocognitive disorders: new challenges in the HAART era. Paul RH et al., editors. HIV and the Brain, New Challenges in the Modern Era. Humana Press,2009; 3. Antinori A et al. Neurology 2007;69:1789–1799; 4. Owe-Larson et al. Afr J Psychiatry (Johannesbg) 2009;12:115–128; 5. Cysique et al. J Int Neuropsychol Soc 2007;13:781–790; 6. Thames AD et al. J Clin Exp Neuropsychol 2011;33:200–209.

How frequently should patients with HAND be monitored?

- Frequency of monitoring can be influenced by
  - Whether the patient is on cART
  - Whether virological suppression has been achieved
  - How low the nadir CD4 count is
- Patients with HAD or MND commencing therapy should initially be monitored at 3 and 6 months, then 6 monthly until a response plateau is observed
  - Once a plateau is observed, monitoring should be performed annually
  - If no response is observed, other causes of impairment should be re-evaluated
    - In this case there is a possibility of immune reconstitution characterised by deterioration following an initial response
- Patients with ANI commencing therapy should initially be monitored at 6 months, and annually thereafter

TRATTAMENTO

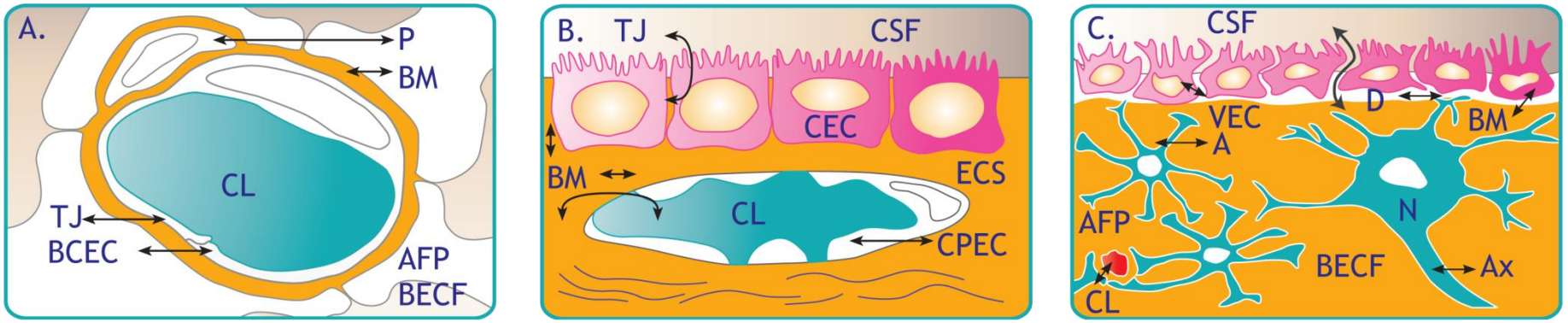
Most of ARV regimens that work systemically will also work in CNS (1997-2004)



74 antiretroviral-naive HIV-1-infected patients from five different centres in Germany, Italy, Sweden and the USA were included. 39% of the patients had a HIV-1-associated neurological disease and 53% of the patients had AIDS. HIV-1 RNA in CSF and plasma were quantified before and after approximately 3 months of treatment. At baseline, the median value of HIV-1 RNA in CSF was 4.12 log copies/ml (interquartile range (IQR): 3.28–4.85) and it decreased to <1.70 log copies/ml (IQR: <1.70–2.48; P<0.001) after in median 3 months of treatment. Seventy-six percent of the patients had HIV-1 RNA levels below the limits of detection in CSF and 45% in plasma.

Mellgren A, et al. Antiviral Ther, 2005

Blood-brain-barrier



A	astrocyte
AFP	astrocyte foot process
Ax	axon
BCEC	brain capillary endothelial cell
BECF	brain extracellular fluid
BM	basal membrane
CEC	capillary endothelial cell
CL	capillary lumen
CEC	capillary endothelial cell

CL	capillary lumen
CPEC	choroid plexus endothelial cell
CSF	cerebrospinal fluid
D	(neuronal) dendritus
ECS	extracellular space
N	neuron
P	pericyte
TJ	tight junction
VEC	ventricular endothelial cell

CPE score – Methods
Approach to classification

	Best evidence	Better evidence	Good evidence
	Pharmacodynamics	Pharmacokinetics	Characteristics
Effectiveness	Effectiveness in clinical studies	Concentrations exceed WT IC50	Consistent with effectiveness
Higher (1.0)	Independent (ZDV)	Consistent (LPV/r)	Subtantial penetration (NVP, ABV, IDV/r)
Intermediate (0.5)	Not clearly independent	Inconsistently (d4T)	Marginal penetration (ATV/r, EFV)
Lower (0)	Ineffective (SQV)	Rarely (ddI)	Poor penetration (ENF, NFV, TDF)

Letendre S, et al. Arch Neurol, 2008

2010 Revised CNS Penetration-Effectiveness Ranks

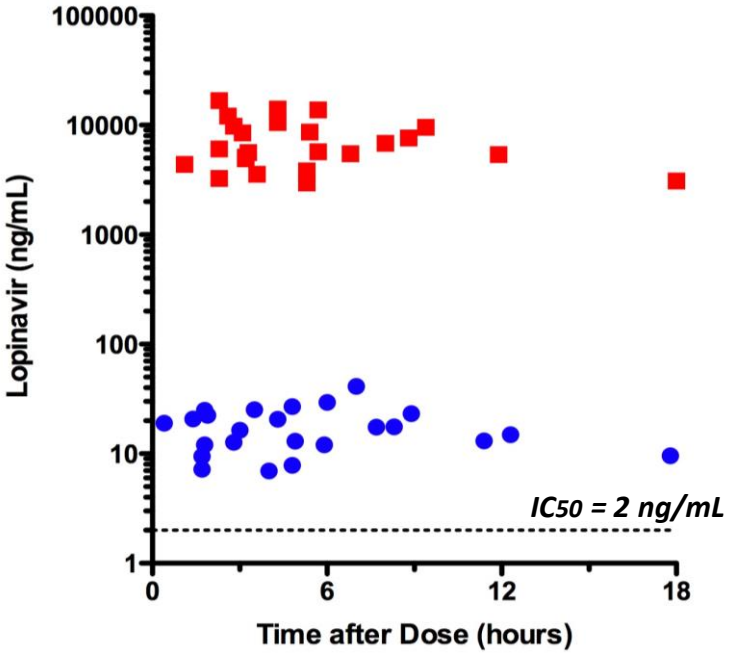
	4	3	2	1
NRTIs	Zidovudine	Abacavir	Lamivudine	Didanosine
		Emtricitabine	Stavudine	Tenofovir
				Zalcitabine
NNRTIs	Nevirapine	Delavirdine	Etravirine	
		Efavirenz		
PIs	Indinavir-r	Darunavir-r	Atazanavir	Nelfinavir
		Fosamprenavir-r	Atazanavir-r	Ritonavir
		Indinavir	Fosamprenavir	Saquinavir
		Lopinavir-r		Saquinavir-r
				Tipranavir-r
Entry Inhs		Maraviroc		Enfuvirtide
Integrase Inhs		Raltegravir		

Letendre et al, 17th CROI, 2010

Pharmacokinetics in CSF

PIs Differ in CSF Penetration

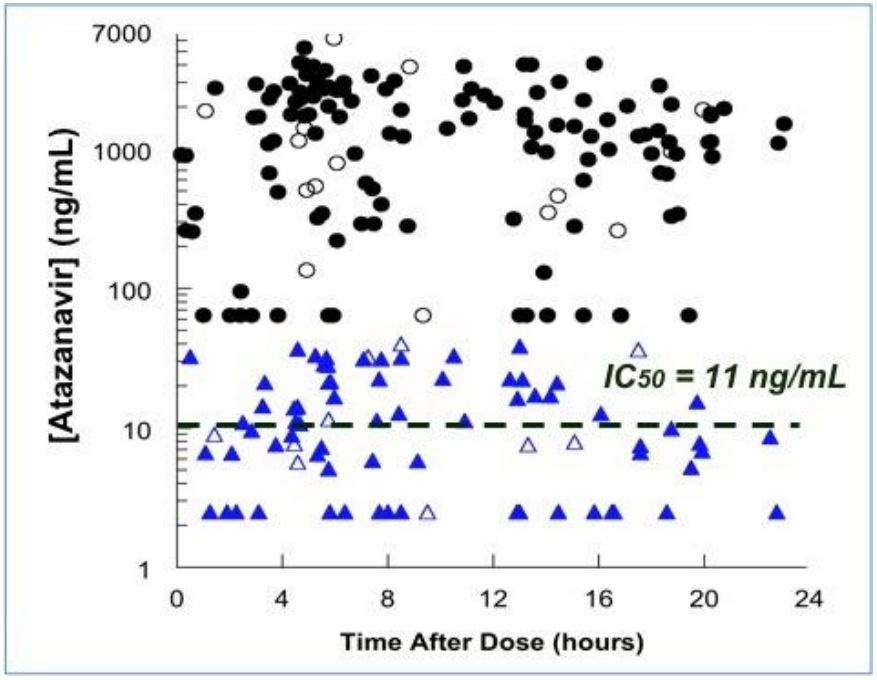
Lopinavir



Extent of CSF penetration was 0.23% of plasma concentrations

Capparelli et al, AIDS 2005; 19:949–952

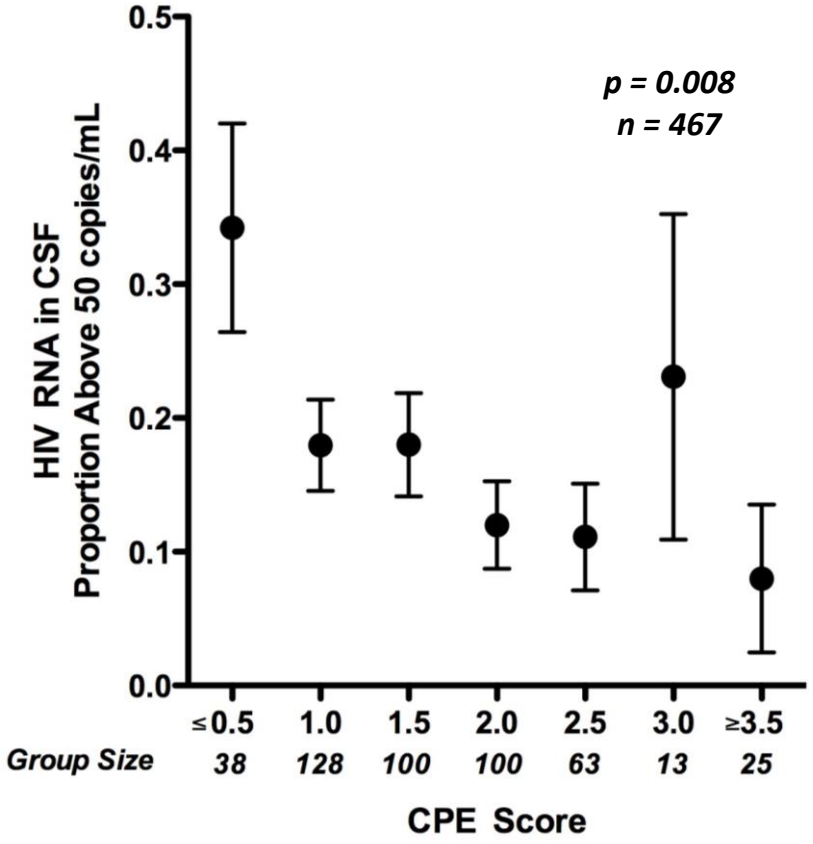
Atazanavir



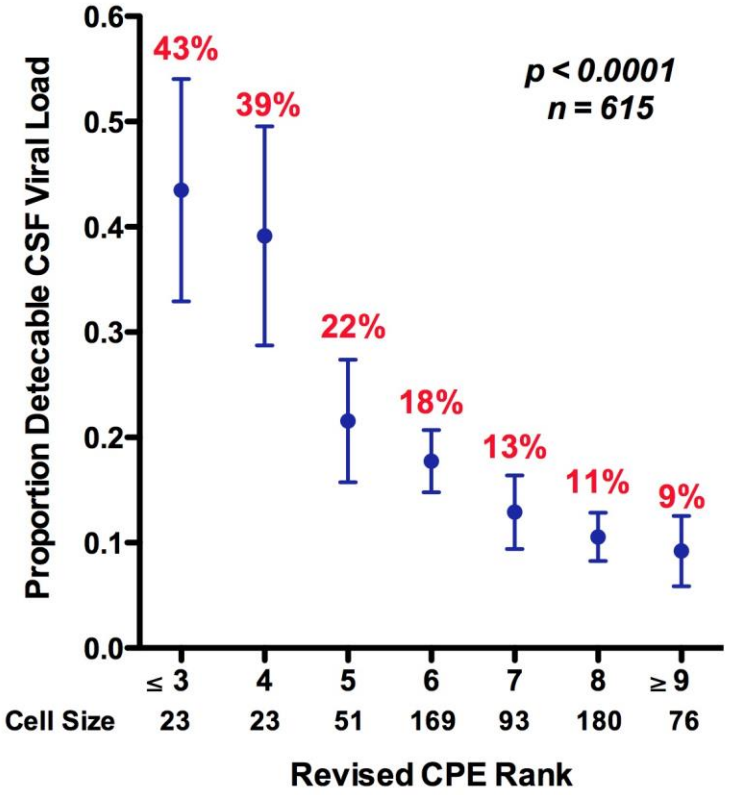
Extent of CSF penetration was 1% of plasma concentrations

Best et al, AIDS 2009; 23: 83-87

Validation of CNS Penetration-Effectiveness (CPE) Ranks by HIV RNA in CSF



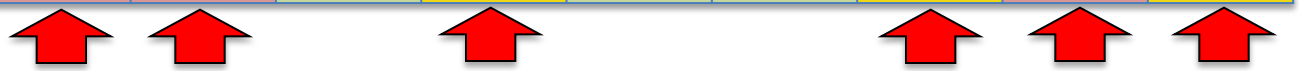
Original CPE Ranks
Cross-Sectional Visits



Revised CPE Ranks
Cross-Sectional Visits

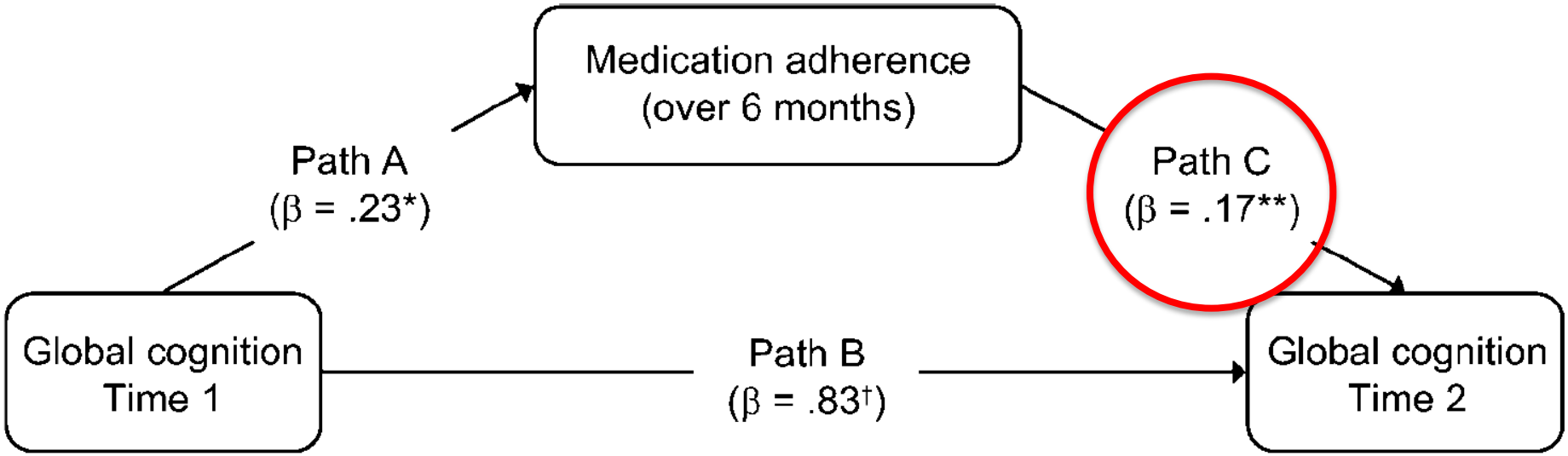
NPS findings supporting CSF penetration are not uniform

	Cysique	Tozzi	Smurzynski	Marra	Winston	Arendt	Garvey	Rourke	Ciccarelli	Robertson	Kahouadji	Ellis
Study	UCSD CIT	INMI	ALLRT	ACTG 736	ALTAIR	Dusseldorf NA Cohort	Imperial College, UK	OHTN Cohort Study	UCSC	ACTG 5199	INSERM	HNRP/UCSD
Sample Size	37	185	2,636	26	30	3,883	101	545	101	860	54	49
CPE: CSF VL	Lower VL	No CSF	No CSF	Lower VL	No CSF	Lower VL	No CSF	No CSF	No CSF	No CSF	No CSF	No effect
Number of NP Tests	6	15	3	4	CogState	2	2	4	18	6	4	14
CPE: NP Tests	**Better**	**Better**	**Better (only by >3 drugs)**	**Poorer**	**Poorer**	**Better**	**No effects**	**Better**	**Better**	**No effect**	**Poorer**	**No effect**
Prospective	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Controlled	No	No	No	No	Yes	No	No	No	No	Yes	No	Yes
Norms for NP Change	Yes	No	No	No	No	No	No	No	Yes	No	No	No



Cysique et al, Neurology 2009, 73(5):342-8; Tozzi et al, J Acquir Immune Defic Syndr 2009;52:56–63; Smurzynski et al, AIDS 2011;25:357-365; Marra et al, AIDS 2009, 23(11):1359-66; Winston A, et al. Clin Infect Dis 2010;50:920-929; Arendt, et al. 18th CROI, Boston (MA, 2011. Poster #425; Garvey et al. HIV Clin Trials, 2011;12(6):333-338; Rourke SB, et al. 6th IAS Conference on HIV Pathogenesis, Teatment and Prevention, Rome, 2011; Ciccarelli N, et al. Antiviral Ther, 2013; Roberston et al. Clin Infect Dis 2012;55(6):868–76; Kahouadji Y, et al. HIV Medicine 2012;14:311-315; Ellis et al. 20th CROI, Atlanta (GA), 2013; Abst#20.

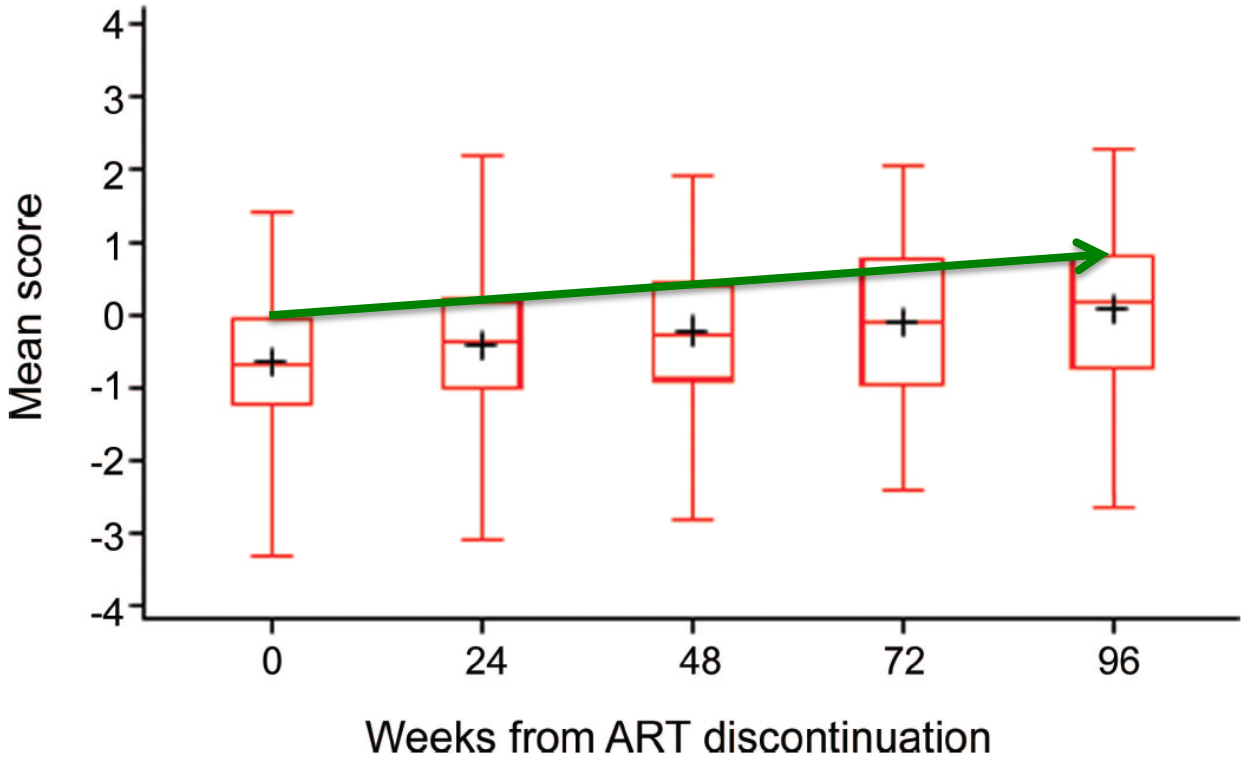
Reciprocal prediction of medication adherence and neurocognition in HIV/AIDS



Ettenhofer ML, et al. Neurology, 2010

Discontinuing cART is associated with an improvement in NP tests.

Which role for drug neurotoxicity?



Plot of mean neuropsychological summary score following treatment interruption

Robertson K, et al. Neurology, 2010

Hazard ratios for CPE score

HIV-CAUSAL Collaboration, 1998–2013

CPE score	Person-years	No. of events	Unadjusted hazard ratio	95% CI	Adjusted hazard ratio[a]	95% CI
HIV dementia						
Low	140,962	127	1.00	Reference	1.00	Reference
Medium	86,799	72	0.97	0.72, 1.30	1.01	0.73, 1.39
High	32,097	36	1.55	1.06, 2.26	1.74	1.15, 2.65
Opportunistic infections[b]						
Low	140,553	245	1.00	Reference	1.00	Reference
Medium	86,455	134	1.09	0.88, 1.34	0.99	0.80, 1.22
High	31,985	49	1.18	0.87, 1.62	1.08	0.77, 1.52
Toxoplasmosis						
Low	140,983	106	1.00	Reference	1.00	Reference
Medium	86,807	45	0.86	0.60, 1.22	0.80	0.56, 1.15
High	32,099	18	0.94	0.57, 1.57	0.90	0.50, 1.62
Cryptococcal meningitis						
Low	141,098	64	1.00	Reference	1.00	Reference
Medium	86,818	48	1.35	0.92, 1.98	1.08	0.73, 1.62
High	32,121	16	1.43	0.83, 2.48	1.13	0.61, 2.11
Progressive multifocal leukoencephalopathy						
Low	141,109	81	1.00	Reference	1.00	Reference
Medium	86,849	43	1.12	0.77, 1.64	1.08	0.73, 1.58
High	32,116	17	1.36	0.80, 2.33	1.32	0.71, 2.47

Caniglia EC, et al. Neurology, 2014

A total of 61,938 individuals were followed for a median of 37 months.

The hazard ratio (95% CI) for initiating a combined ARV therapy regimen with a high vs low CPE score was 1.74 (1.15, 2.65) for HIV dementia,

The respective hazard ratios (95% CI) for a medium vs low CPE score were 1.01 (0.73, 1.39).

Initiation of a combined antiretroviral therapy regimen with a high CPE score increases the risk of HIV dementia, but not of other neuroAIDS conditions.

CSF HIV risk score for assessing central nervous system activity in persons with HIV

Variable	Regression Coefficient	Odds Ratio	95% CI	*P* Value	Shrunken[b] Regression Coefficient β_i	Reference Value W_{ij} (Midpoint)	β_j $(W_{ij}\text{-}W_{iRef})$	Risk Score $(\beta_i \times [(W_{ij}\text{-}W_{iRef})]/B^c)$
CPE score	−0.266[d]	0.77	0.67, 0.88	<0.001	−0.249			
≥10						12 (W_{1Ref})	0	0
5–9						7	1.245	6
<5						4	1.992	9
Race								
White		1.00	Referent			0 (W_{2Ref})	0	0
Black	0.593	1.81	1.06, 3.09	0.02	0.556	1	0.556	3
Hispanic/other	0.875	2.39	1.16, 4.95	0.02	0.820	1	0.820	4
Current depression								
No		1.00	Referent			0 (W_{3Ref})	0	0
Yes	0.808	2.25	1.18, 4.28	0.01	0.757	1	0.757	4
HIV medication adherence, %								
≥95		1.00	Referent			97.5 (W_{4Ref})	0	0
85–94	0.584	1.79	0.67, 4.79	0.23	0.547	89.5	0.547	3
<85	0.599	1.82	0.90, 3.68	0.10	0.561	80.0	0.561	3
Log plasma RNA, copies/mL	1.584[d]	4.88	3.91, 6.09	<0.001	1.486			
<1.699						1.699 (W_{5Ref})	0	0
1.699–2.299						1.999	0.446	2
2.301–3.999						3.150	2.156	10
>4.0						5.627	3.928	18
Current cART, months	−0.011[d]	0.99	0.98, 1.00	0.07	−0.010			
≥36						75 (W_{6Ref})	0	0
25–35						30	0.450	2
13–24						18	0.570	3
7–12						9	0.660	3
≤6						3	0.720	4

CSF HIV Risk Score	Predicted Probability, %	95% CI
0	0.24	0.11, 0.53
5	0.75	0.40, 1.4
10	2.32	1.5, 3.7
15	7.0	5.1, 9.5
20	19.2	15.7, 23.2
25	42.9	34.6, 49.6
30	70.3	61.5, 77.9
35	88.2	81.2, 92.9
39	95.0	90.5, 97.4

The CSF HIV risk score ranges from 0 to 42 points, with a mean of 15.4 (standard deviation, 7.3) points. At risk scores greater than 25, the probability of detecting CSF HIV RNA was at least 42.9% (95% CI: 36.6, 49.6). For each 1-point increase, the odds of detecting CSF HIV RNA increased by 26% (odds ratio = 1.26, 95% CI: 1.21, 1.31; P < 0.01).

Hammond ER, et al. Am J Epidemiol, 2014

C.I.C.A.
COORDINAMENTO ITALIANO
CASE/ALLOGGIO HIV/AIDS

SEMINARIO NAZIONALE

ALLA RICERCA DEI "PENSIERI PERDUTI"

disturbi neurocognitivi
nelle persone con hiv/aids

28-30 ottobre 2014
CERTOSA 1515
AVIGLIANA TORINO

Grazie per l'attenzione!