

Screening Tests for HIV associated Neurocognitive Disorders (HAND)



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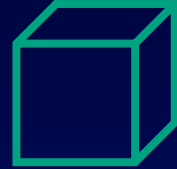
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Identifying HIV+ individuals at risk for HIV dementia

- **Screening tests are essential for directing limited resources for the diagnosis of dementia.**
- **Brief instruments have been developed for Alzheimer's (MMSE).**
- **MMSE designed to screen for a cortical dementia (Alzheimer's) which has a different cognitive profile from HAND (subcortical- more impaired psychomotor, motor performance, less impaired recognition memory)**

HIV Dementia Scale

Power et al JAIDS 1995

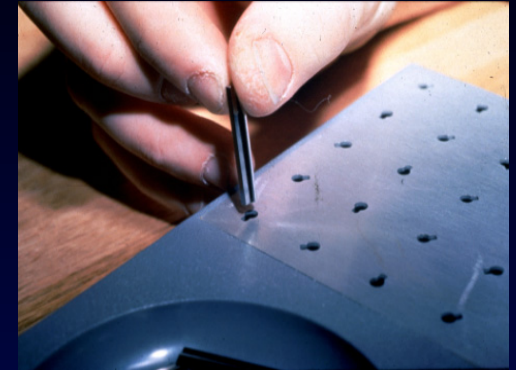
- **Memory-Registration** Give four words to recall (dog, hat, green, peach) – 1 second to say each. Then ask the patient all 4 after you have said them.) 4 (___)
 - **Attention† Anti-saccadic eye movements:** 20 (twenty) commands. ___ errors of 20 trials.
less than or equal to 3 errors = 4; 4 errors = 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 (use back of this form) and record time: ___ seconds.
less than or equal to 21 sec = 6; 21.1 – 24 sec = 5; 24.1 – 27 sec = 4; 27.1 – 30 sec = 3; 30.1 – 33 sec = 2; 33.1 – 36 sec = 1; > 36 sec = 0) 4 (___)
 - **Timed Construction:** Copy the cube below; record time: ___ seconds.
(< 25 sec = 2; 25 – 35 sec = 1; > 35 sec = 0)
- 
- **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 after prompting. 2 (___)

A score of less than 10 points is an indication of possible HIV dementia

HIV Dementia Scale (HDS)

Power et al JAIDS 1995;273-278

- **Sensitivity: 80%, Specificity: 91%**
- **Efficiency for diagnosing HIV dementia:
HDS 84%, Grooved Pegboard 85%, MMSE 72%**
- **In S Africa study (Ganaseen, J Neurological Sciences 2008; 62-64)
HDS identifies 17% HIV+ individuals with HAND (vs 2% for MMSE)**
- **HDS not as accurate for detecting HIV dementia in HAART treated patients as full neuropsychological test battery (NPZ8), (Bottiggi , J Neurological Sciences 2007)**
- **The HDS includes subtests (antisaccadic-error test, alphabet writing, cube-copying,) that are difficult to administer by non-neurologists or difficult for individuals with a non-Western educational background.**



International HIV Dementia Scale

(Sacktor et al. AIDS 2005 19:1367-1374)

Memory-Registration – Give four words to recall (dog, hat, bean, red) (in Luganda: kopo, engatto, doodo, myufo)– 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.

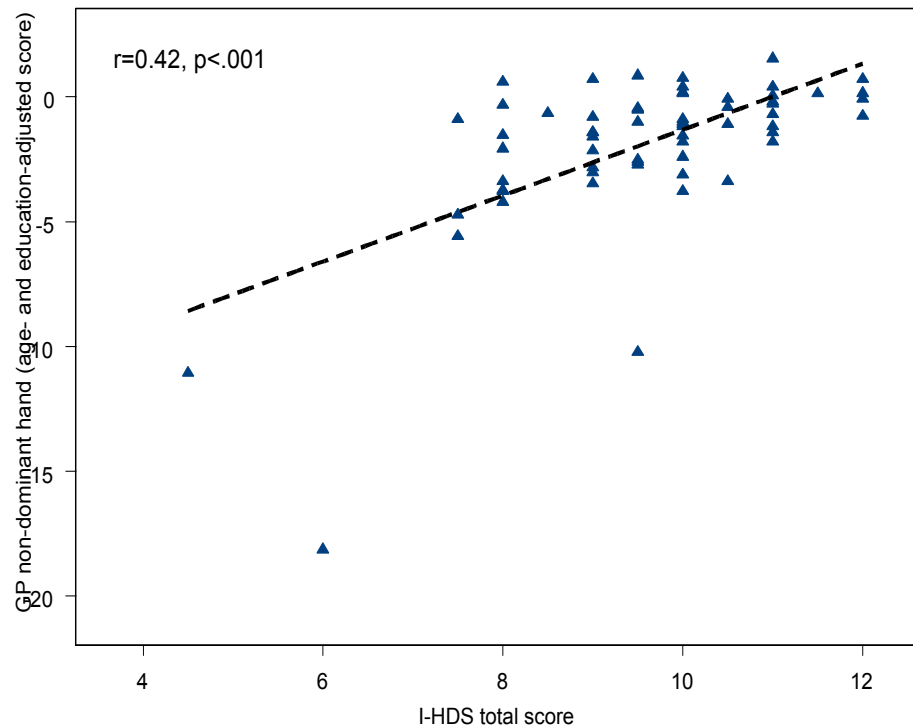
Total International HIV Dementia Scale Score

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.

IHDS and MSK Dementia Severity Rating- US Pilot Study (n=66)

	No Dementia		Dementia		
	No Impairment	Equivocal/ Subclinical	Mild	Moderate	Severe
MSK score	0	0.5	1	2	3
	n=5	n=36	n=15	n=9	n=1
Age-years [mean (SD)]	43.4	43.7 (6.6)	47.1 (5.8)	43.9 (8.2)	48.9
Education-years [mean (SD)]	13.8 (2.9)	13.1 (2.6)	12.8 (1.7)	11.8 (1.9)	13.0
Race (%non-white)	100%	92%	93%	89%	100%
Gender (%male)	80%	83%	67%	67%	0%
CD4 count [mean (SD)]	262 (181)	186 (166)	146 (120)	167 (194)	817
IHDS score [mean (SD)]	10.6 (1.3)	10.6 (1.1)	9.3 (1.4)	8.6 (1.8)	7.0
GP Nondom z score [mean (SD)]	0.35 (0.5)	-1.1 (1.2)	-2.2 (2.8)	-3.8 (3.1)	-18.1

Correlation of IHDS and Grooved Pegboard Non-dominant Hand (GP Nondom) Test Performance



- Performance on the IHDS correlated with performance on the GP nondom test ($r = 0.42$, $p < 0.001$).

Academic Alliance Dementia Cohort Study: Methods



- 81 HIV+ individuals received detailed demographic, neuropsychological, neurological and functional assessments.
- HIV+ individuals with active CNS infections were excluded.
- 100 HIV- individuals were also evaluated to establish age and education matched controls for the 6 neuropsychological tests.

Uganda Neuropsychological Test Battery



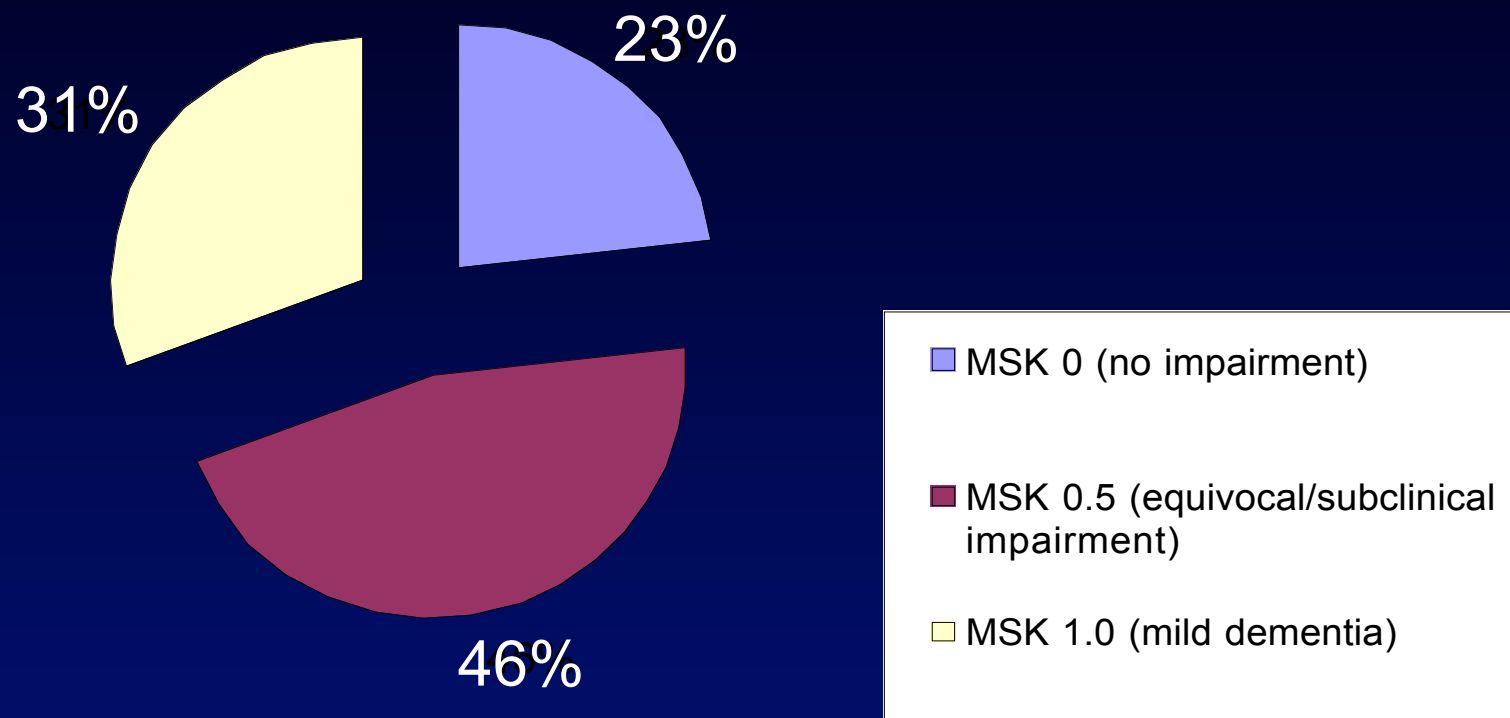
- **Motor Speed – Grooved Pegboard, Timed Gait**
- **Memory – WHO-UCLA Auditory Verbal Learning Test**
- **Attention/Executive – Digit Span – Forward and Backward, Color Trails 2**
- **Psychomotor speed – Symbol-Digit, Color Trails 1**

Demographics of HIV+ and HIV- Patients

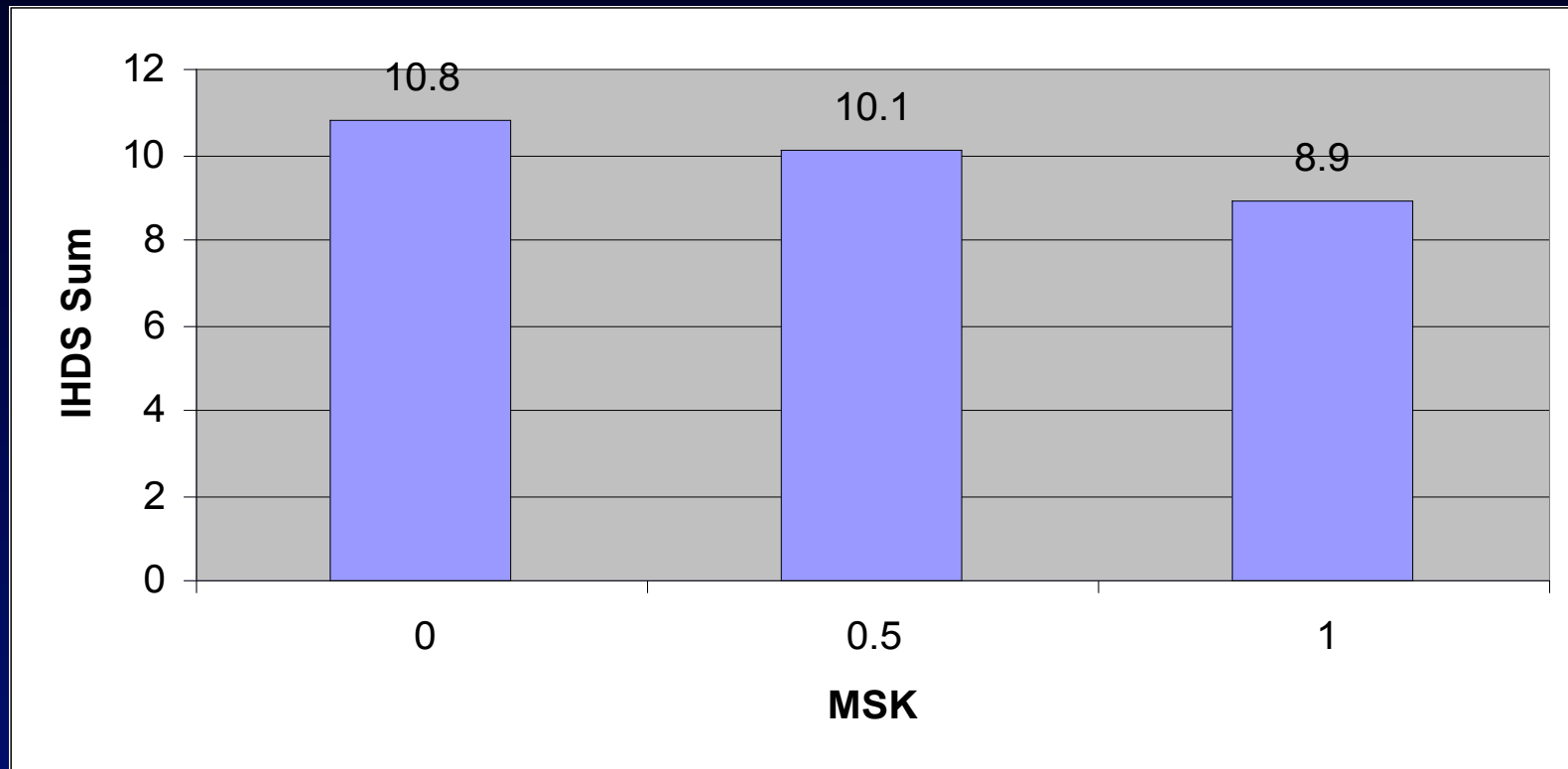
	HIV+ N=81	HIV- N=100
Age (years)-mean*	37.0	31.4
Education(years)- mean	8.7	9.7
Karnofsky-mean*	74.8	97.4
Male-percent*	31%	47%
CD4-mean	217	---

* P < 0.05

Frequency of Dementia in Academic Alliance Cohort

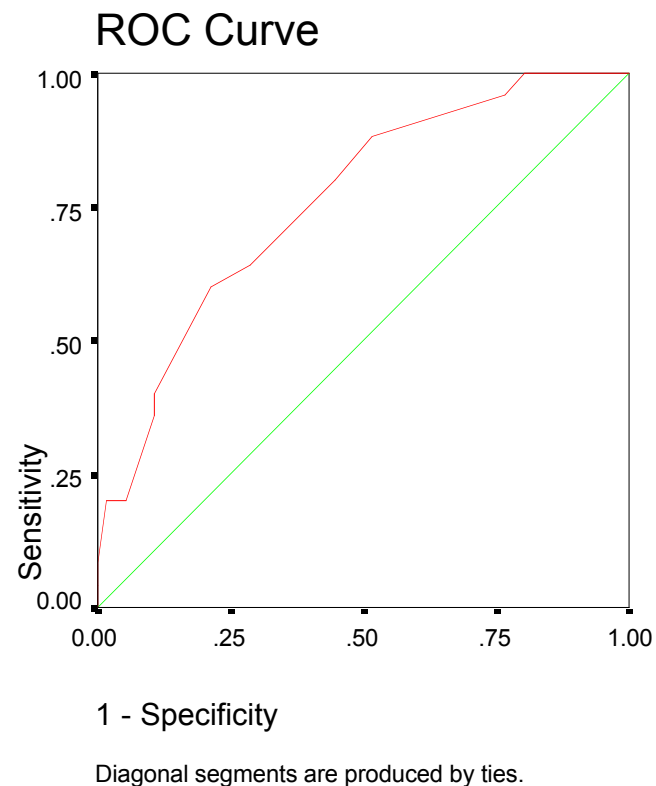


IHDS vs. MSK Rating



IHDS Sensitivity and Specificity in the Academic Alliance Cohort

- For HIV dementia, the sensitivity of the IHDS was 80% and specificity was 55%. (using a cutoff of ≤ 10 .)



Clinical Risk Factors Stratified by MSK Stage

	MSK GROUP			P value
	0	0.5	1	
Age, years	33.3	36.8	39.9	0.06
Education, years	12.3	7.9	7.2	<0.001
Male	36.8%	33.3%	20.8%	0.46
CD4 – mean	198.9	266.7	141.0	0.09
Syphilis	42.1%	40.5%	40.0%	0.99
Hypertension	10.5%	5.4%	12.0%	0.63
Seizure	0%	8.1%	0%	0.17
Neuropathy	31.6%	30.6%	29.2%	0.99
WHO Status 4	36.8%	13.5%	28.0%	0.14
Memory complaints – subjective	47.4%	50.0%	84.0%	0.01
Concentration complaints - subjective	31.6%	38.9%	45.8%	0.64
Karnofsky score – mean	78.4	75.4	71.2	0.12
Depression (CES-D ≥ 16)	72.2%	63.8%	60.0%	0.71
IHDS – total	10.8	10.1	8.9	<0.001

- Low education, subjective memory complaints, and impaired performance on the IHDS screening test (and trends for advanced age and low CD4 count) were associated with risk of HIV dementia.

Use of IHDS in Africa and India

- **Cameroon-** (Njamnshi, J AIDS, 2008, 393-397)- IHDS is useful tool for HAND in HIV+ adults, (HIV+ (n=204)- IHDS \leq 10, 21%; HIV- (n=204) IHDS \leq 10, 2.5%
- **S Africa-** (Singh, Afr. J Psychiatry, 2008, 282-286), HIV+ (n=20) with low CD4 counts, IHDS \leq 10 Sensitivity 88%, Specificity 50%
- **S Africa-** (Joska, AIDS Patient Care STDS, 2011, 95-101), HIV+ (n=96), HIV+ pts had greater impairment on IHDS than HIV- controls, confirmed with detailed NP battery, IHDS \leq 10, Sensitivity 45%, Specificity 79%
- **India-** (Riedel, J Neurovirol, 2006, 34-38), HIV+ (n=48), IHDS < 10 35%, HIV- (n=48), IHDS < 10 15%, P< 0.005

Factors Impacting Utility of IHDS

- **Education**- (Waldrop-Valverde, J Neurovirol 2010, 264-267), HIV+ and HIV- (n=295) with early stage infection in India; education not HIV status associated with IHDS performance
- **Stage of infection**- Clifford, J Neurovirol, 2007, 67-72, HIV+ (n=73), mean CD4 260, mean IHDS 10.4, HIV- (n=73), mean IHDS 10.7,- no difference in either IHDS or any NP test; community based, less severe immunosuppression
 - (Lopardo, J AIDS 2009, 488-492), HIV+ patients with preserved immunity in Argentina performed well on IHDS, HIV+ (n=260), IHDS mean 10.9
- **Hepatitis C co-infection**- (Garvey, CROI 2011 Poster #393), HIV+ asymptomatic pts on HAART in UK, poor performance associated with hepatitis C co-infection, P = 0.01
- **Stage of HAND impairment**

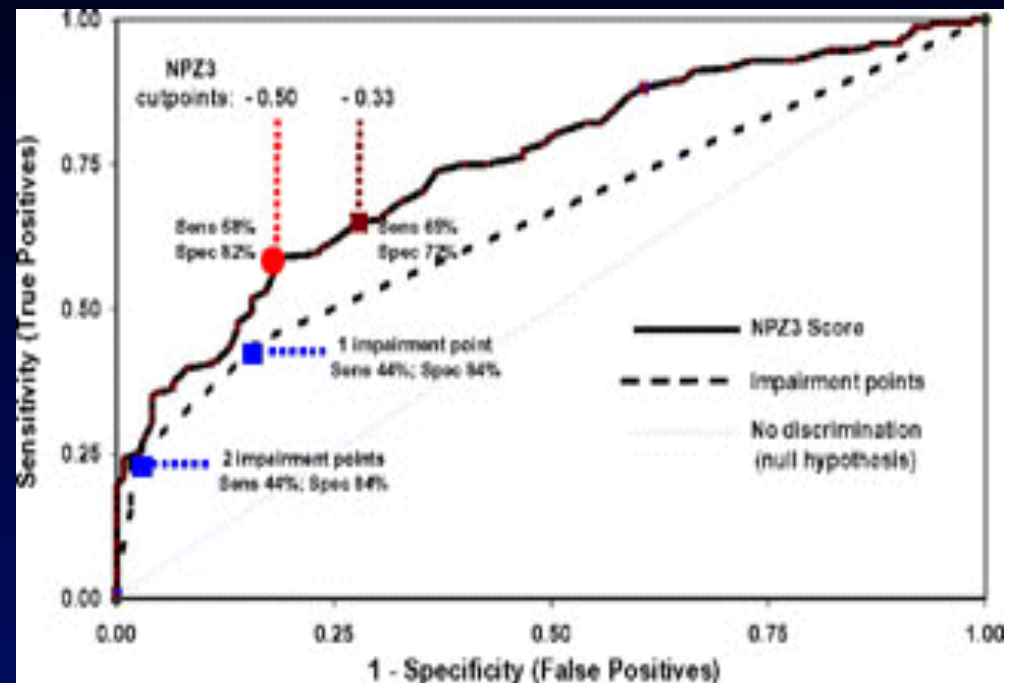
Additional Screening Tests for HAND (Overton, CROI 2011 Poster #401)

- **Montreal Cognitive Assessment (MOCA); 30 item screen for mild cognitive impairment, threshold ≤ 25 , HIV+ (n=119), HAND sensitivity 59%, specificity 81%**
- **AD-8: 8 item interview comparing current and previous functioning due to cognitive impairment, HAND sensitivity 62%, specificity 63%**
- **Both MOCA and AD-8 correlated with formal NP battery (NPZ-8), $p < 0.005$ for both**
- **Sensitivities lower than desired for screening tool**

Brief NeuroCognitive Screen (BNCS)

Ellis et al., J. Neurovirol 2005; 503-511

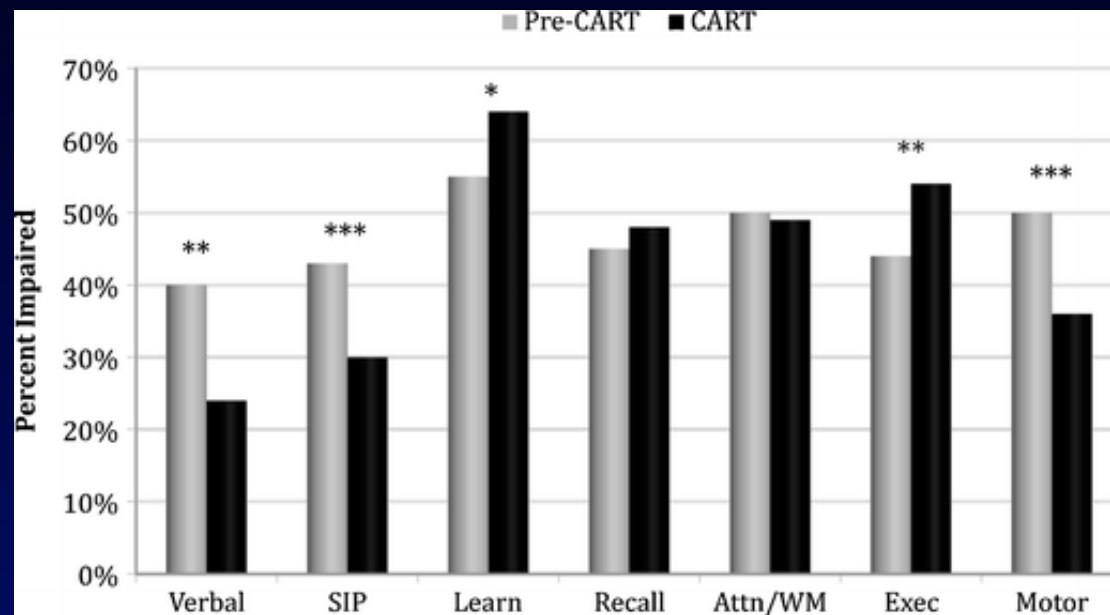
- WAIS-R Digit Symbol test, Trailmaking test (parts A and B)
- 15 minutes to administer
- Validated in NARC study of 301 HIV+ subjects (mean Z score of 3 tests)
- NPZ 3 cut-point -0.33; Sensitivity 65%, Specificity 72%, Correct Classification rate 68%
- Hopkins Verbal Learning test total score to assess memory in addition to psychomotor speed added to ACTG studies, e.g., ALLRT



HAND Screening Test Challenges

- **Severity of impairment:** tests developed for dementia, not HAND
- **Sensitivity:** cognitive domains affected by HIV-variable
- **Specificity:** cognitive impairment with HIV similar to impairment in confounding conditions, e.g., vascular disease, hepatitis C, etc.
- **Reliability:** screening tests need to be performed in same manner
- **Validity:** is cognitive profile of HAND changing with time, e.g., is profile of MND different from dementia, ? Greater age-related effects, more cortical deficits?

NP Domain impairment in pre-CART and CART era (Heaton et al J Neurovirology 2010)



HIV+ samples with NCI. *SIP* speed of information processing, *Learn* learning efficiency, *Recall* delayed recall, *Attn/WM* attention/working memory, *Exec* executive function; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Summary

- **Screening tools can identify individuals at high risk for HIV dementia**
- **Instruments need to be performed in standardized manner**
- **Screening test results need to be validated with gold standard of neuropsychological testing with functional assessments and co-morbid condition evaluations**
- **Norms for screening tests for HIV dementia need to be improved in HAART treated patients, in older patients, and in resource limited countries (ACTG 5170)**
- **Screening tests for mild forms of cognitive impairment (ANI and MND and dementia) need to be developed.**

Collaborators

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I never heard of an old man forgetting where he had buried his money. Old people remember what interests them.

Marcus Tullius Cicero 1st century BC