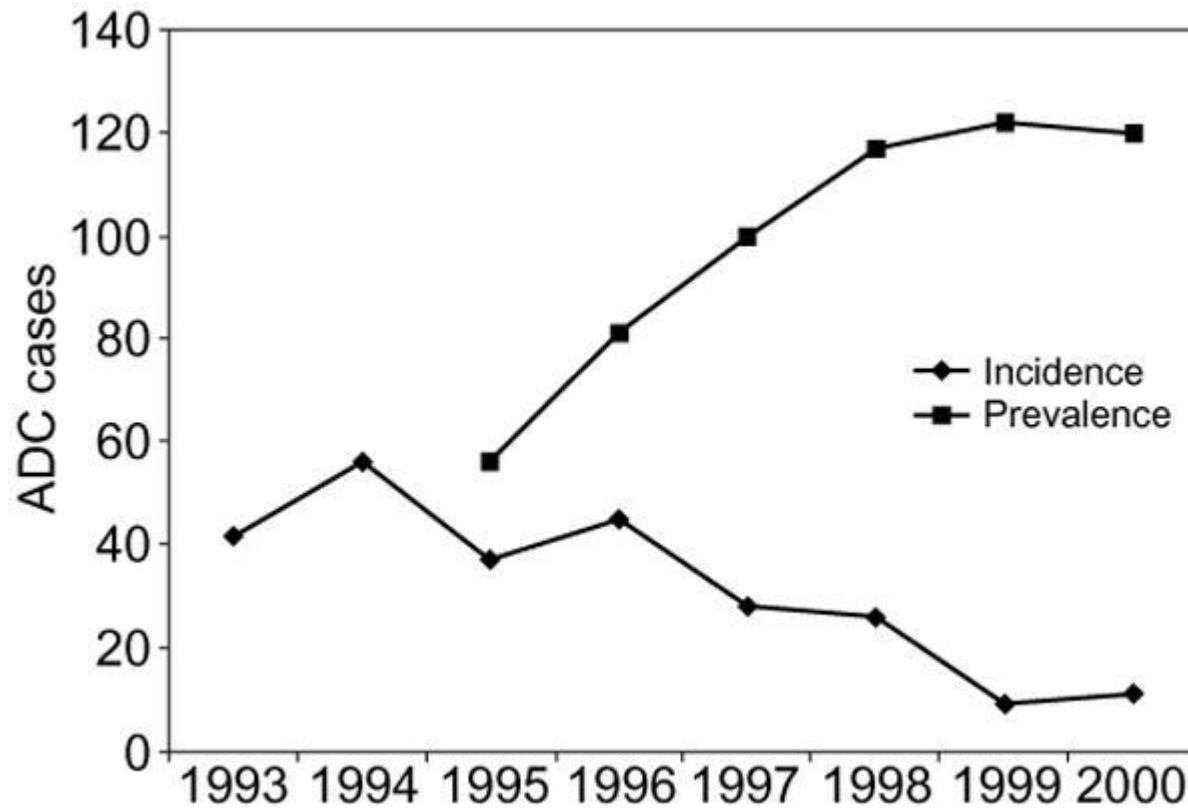


Asymptomatic NCI: Illusion or reality

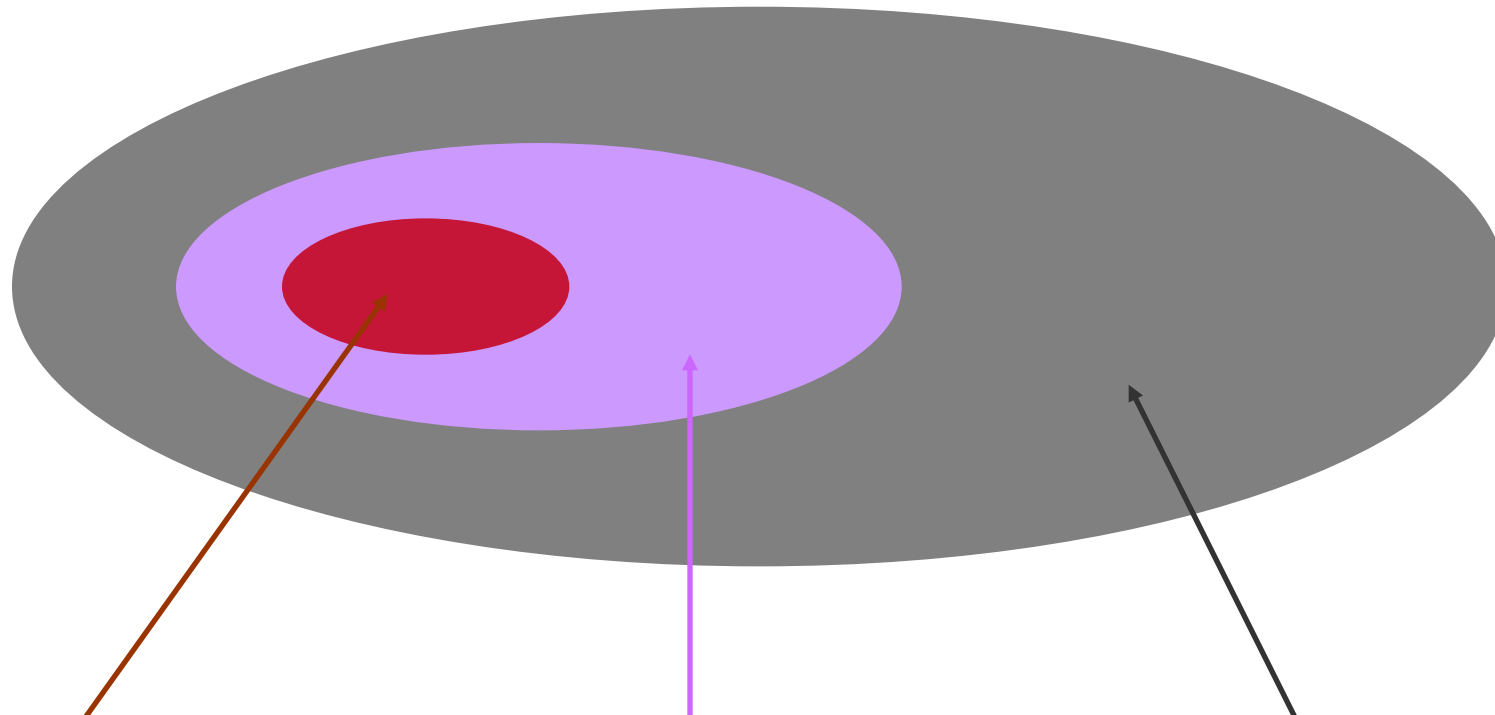
Alan Winston, St. Mary's Hospital, London
May 2012

HIV associated dementia in cART era



HAND – Frascati classification

Neurology 2007;69;1789-1799



HAD

- *Marked interference with daily life*

Symptomatic NCI

- *impairment >1 SD in 2 or more domains **
- ***does interfere with daily life***

Asymptomatic NCI

- *impairment >1 SD in 2 or more domains **
- *does not interfere with daily life*

* The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills

Asymptomatic NCI: Illusion or reality?

Are we ready for ANI?

1

2

3

4

5

6

7

Asymptomatic NCI: Illusion or reality?

Are we ready for ANI?

1 Do we know the true prevalence of ANI?

2

3

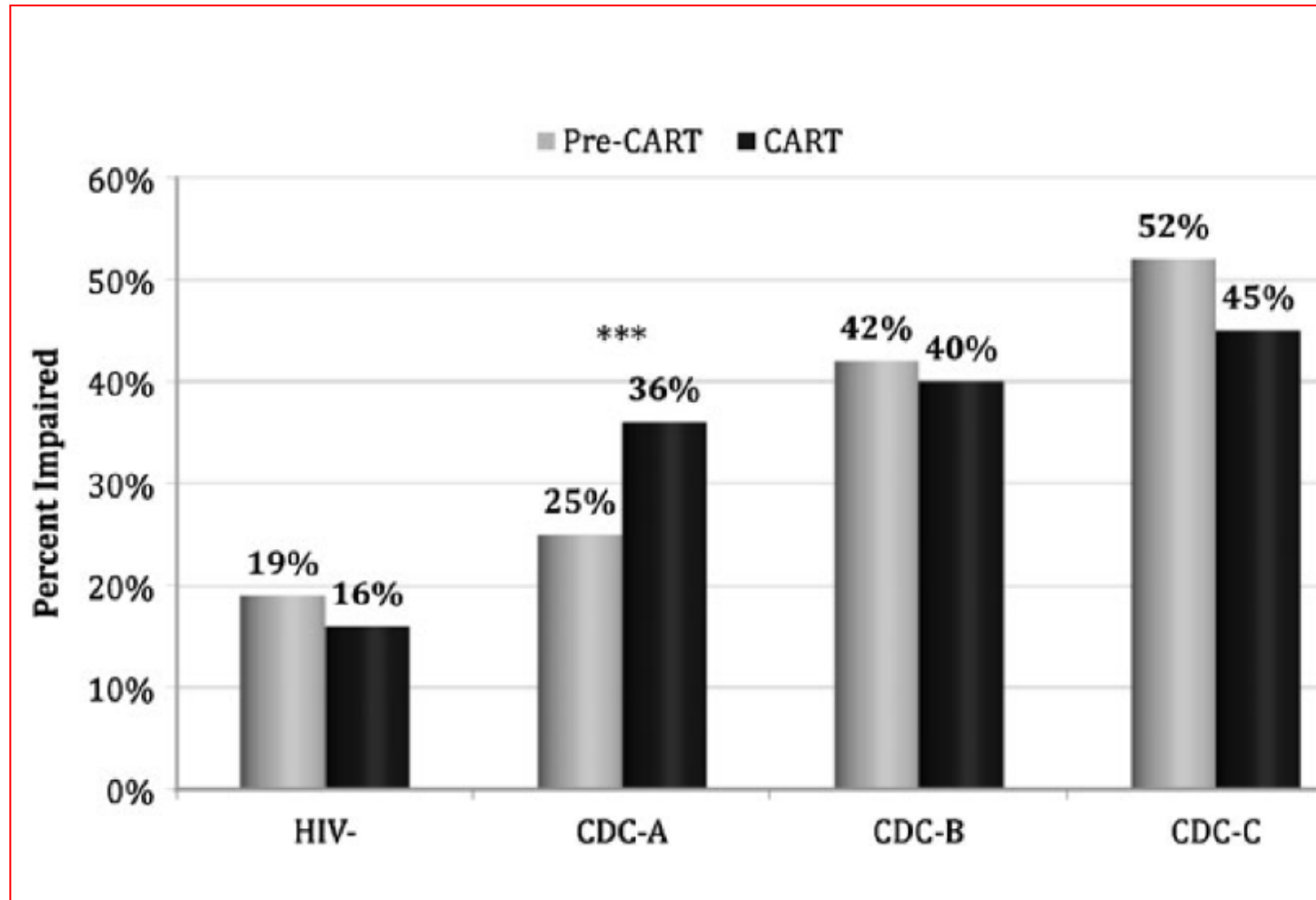
4

5

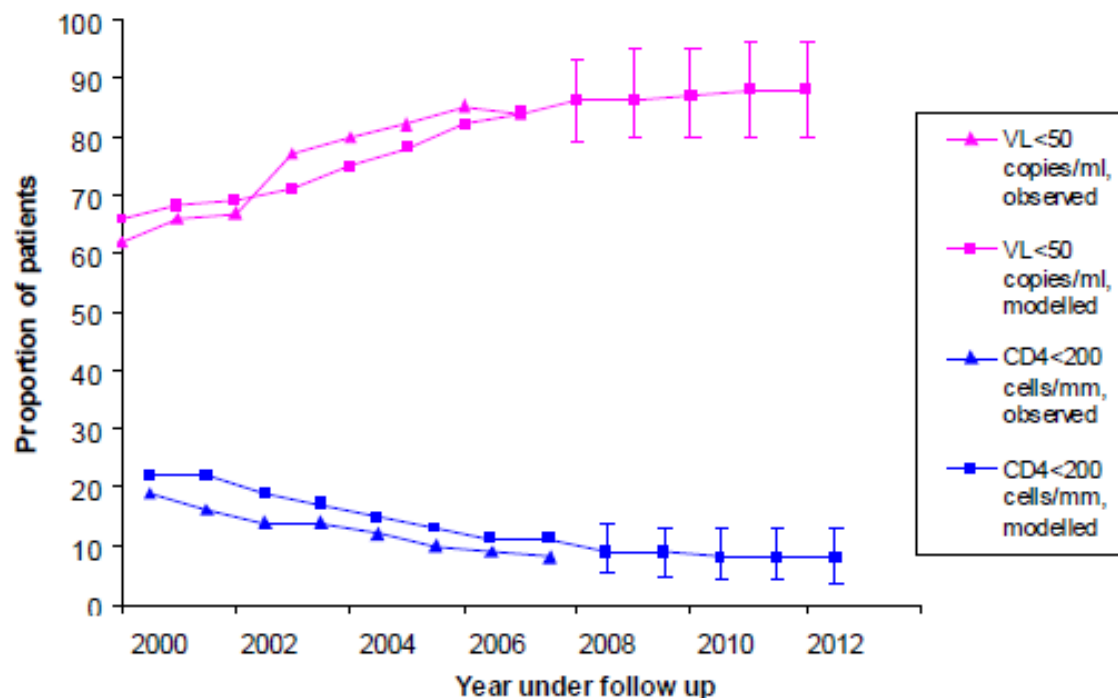
6

7

Prevalence of Cognitive Impairment



Trends in HIV Viral load UK CHIC 2000-2006



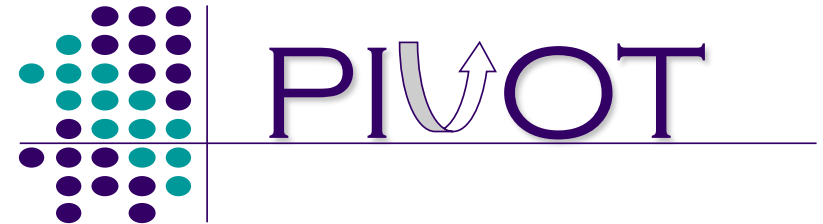
St. Mary's cohort:

- HIV infected subjects on effective cART
- Neuroasymptomatic
- Utilising CogState
- Overall rate of NCI in cohort = 19/101 (19%)

NC testing results from PIVOT

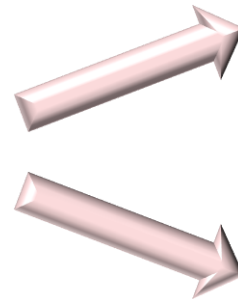
Protease Inhibitor monotherapy Versus Ongoing Triple-therapy in the long term management of HIV infection

- *multicentre study across UK*
- *over 40 sites*
- *open label, randomised study*



Eligible subjects:

- ***Receiving combination ART for at least 24 weeks with a regimen comprising 2 NRTIs and either an NNRTI or a PI***
- ***Plasma VL <50 copies/mL at screening and for at least 24 weeks prior to screening***
- ***CD4+ count >100 cells/uL at screening.***



Protease inhibitor monotherapy

Ongoing triple therapy

Study ongoing; fully recruited as of Autumn 2010
Total number recruited 587

NC testing results from PIVOT - methods

- *Neurocognitive testing undertaken prospectively in all subjects*
- *5 domains assessed*
- *Baseline test results available for this analysis*
- *Raw scores for each test were transformed to z-scores using normative data (age matched all tests and education matched CTT)*

| Domain | Test | Standard normative data | Adjusted normative data |
|--------------------|--|-------------------------------|--------------------------------------|
| Attention | Colour Trails Test 1 | n=1528, 70% Caucasian, [1] | n=182, inc. African American, [1] |
| Executive function | Colour Trails Test 2 | as above | as above |
| Verbal learning | Hopkins Verbal Learning Test (HVLTL), learning | n=1179, [2] | n=246, 42% African American, [4] |
| Verbal memory | Hopkins Verbal Learning Test (HVLTL), recall | as above | as above |
| Fine motor | Grooved Pegboard | [3] | - |

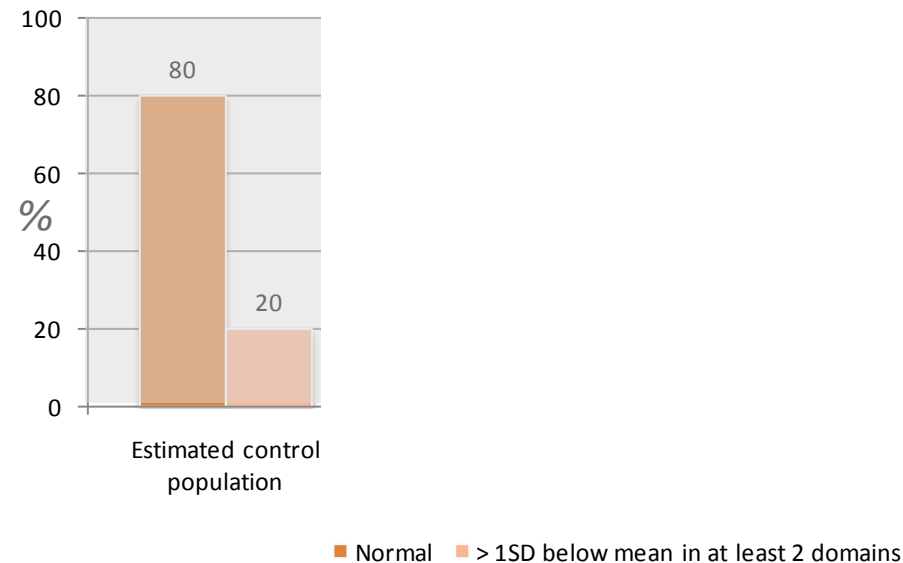
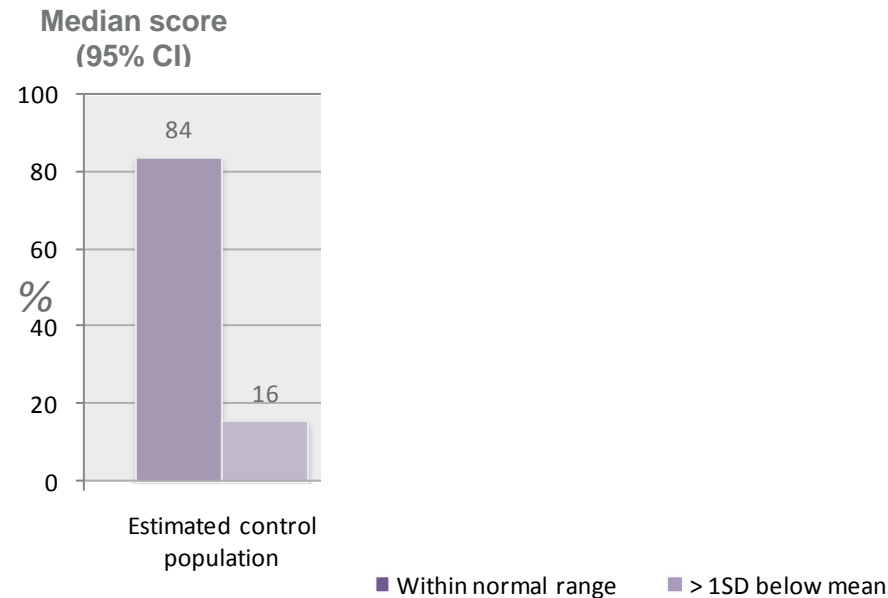
- References: 1. D'Elia LF et al. *Color Trails Test*. 1996 Odessa, FL: PAR
2. Brandt J and Benedict RHB. *Hopkins Verbal Learning test-Revised*. 2001 Odessa, FL:PAR
3. Trites R. *Neuropsychological test manual*. Ottawa, Ontario 1997
4. *Journal of Clinical and Experimental Neuropsychology*, Volume 33, Issue 7, 2011)

NC testing results from PIVOT – results

*Standard
normative data*

*Global scores
(NPZ-5)
N=560*

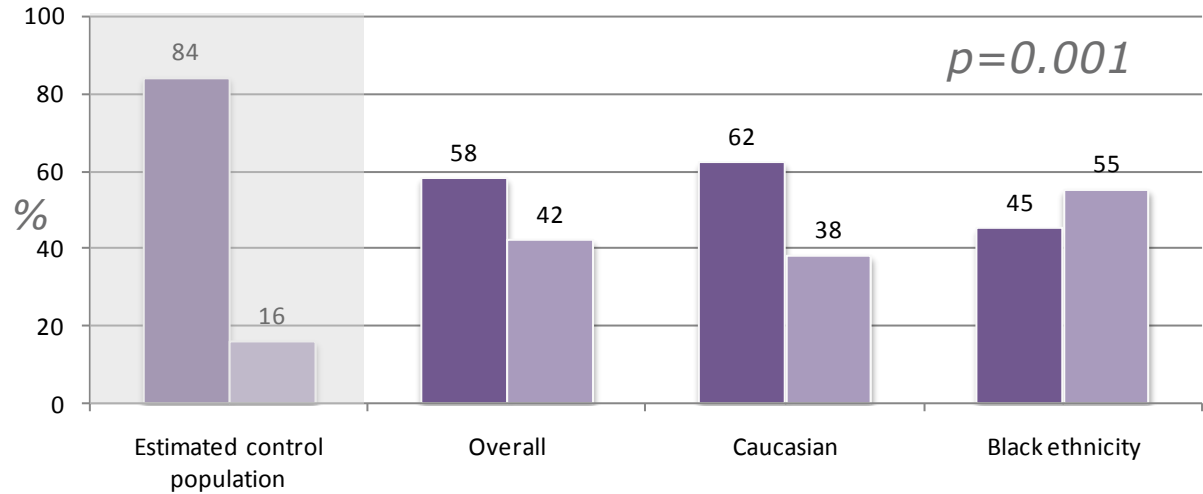
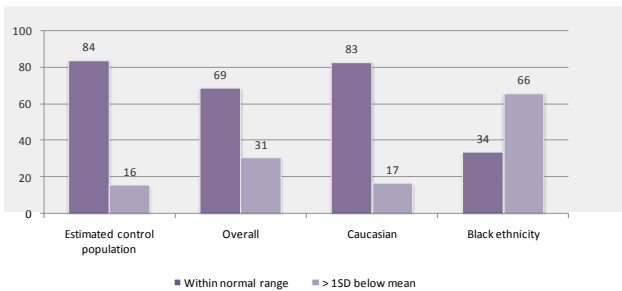
*Categorical Score
(Frascati)
N=560*



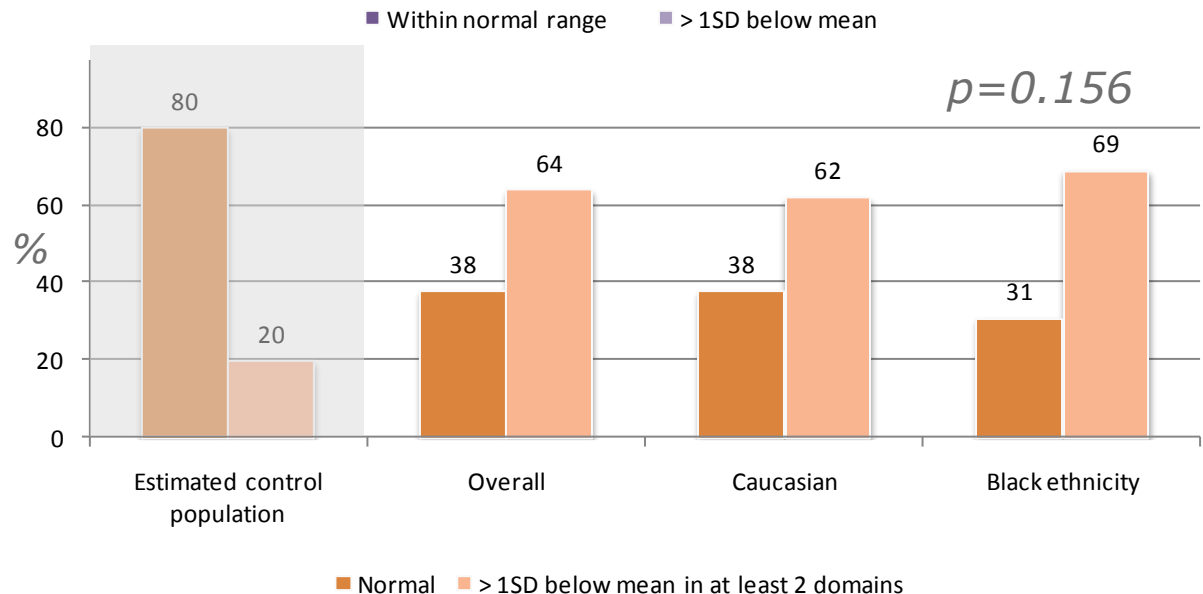
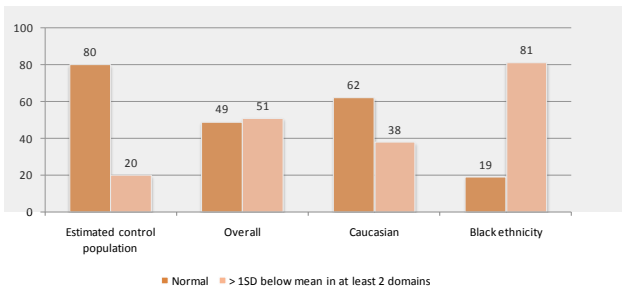
NC testing results from PIVOT – adjusted control data

Adjusted normative data

Global scores (NPZ-5)



Categorical Score (Frascati)



Asymptomatic NCI: Illusion or reality?

Are we ready for ANI?

| | | |
|---|--|----|
| 1 | Do we know the true prevalence of ANI? | No |
| 2 | | |
| 3 | | |
| 4 | | |
| 5 | | |
| 6 | | |
| 7 | | |

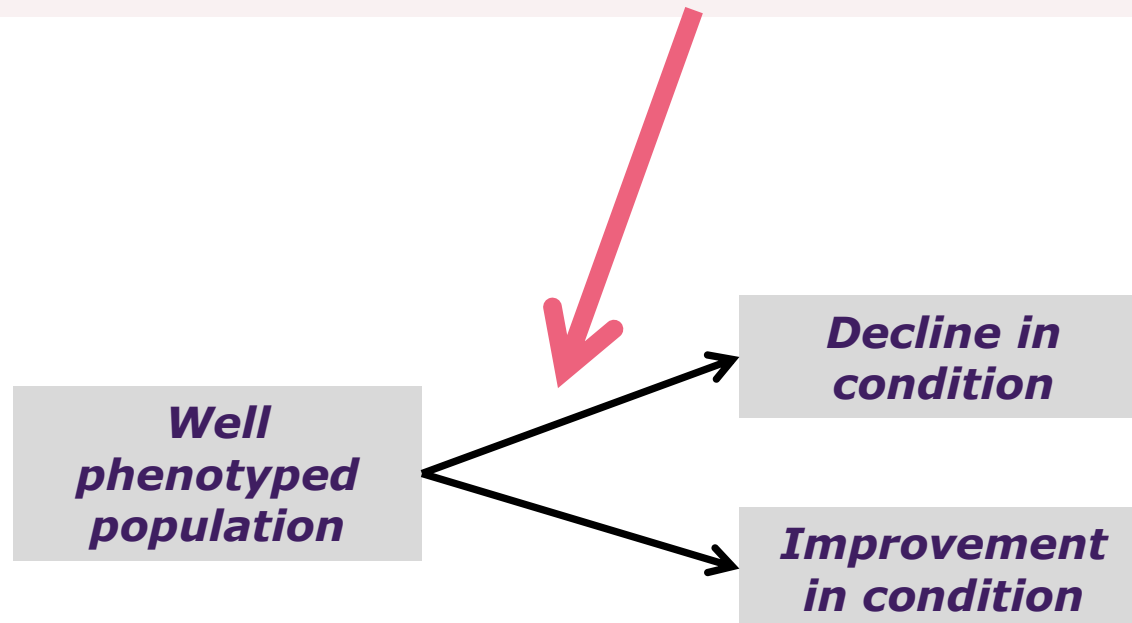
Asymptomatic NCI: Illusion or reality?

Are we ready for ANI?

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| 4 | | |
| 5 | | |
| 6 | | |
| 7 | | |

Overestimating prevalence of ANI

| Not a problem | Problematic |
|---|--|
| Better to overestimate than underestimate | Create unnecessary anxiety |
| Increase monitoring of subjects | Null hypothesis <ul style="list-style-type: none">• Natural history• Interventional studies |



Asymptomatic NCI: Illusion or reality?

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Asymptomatic NCI: Illusion or reality?

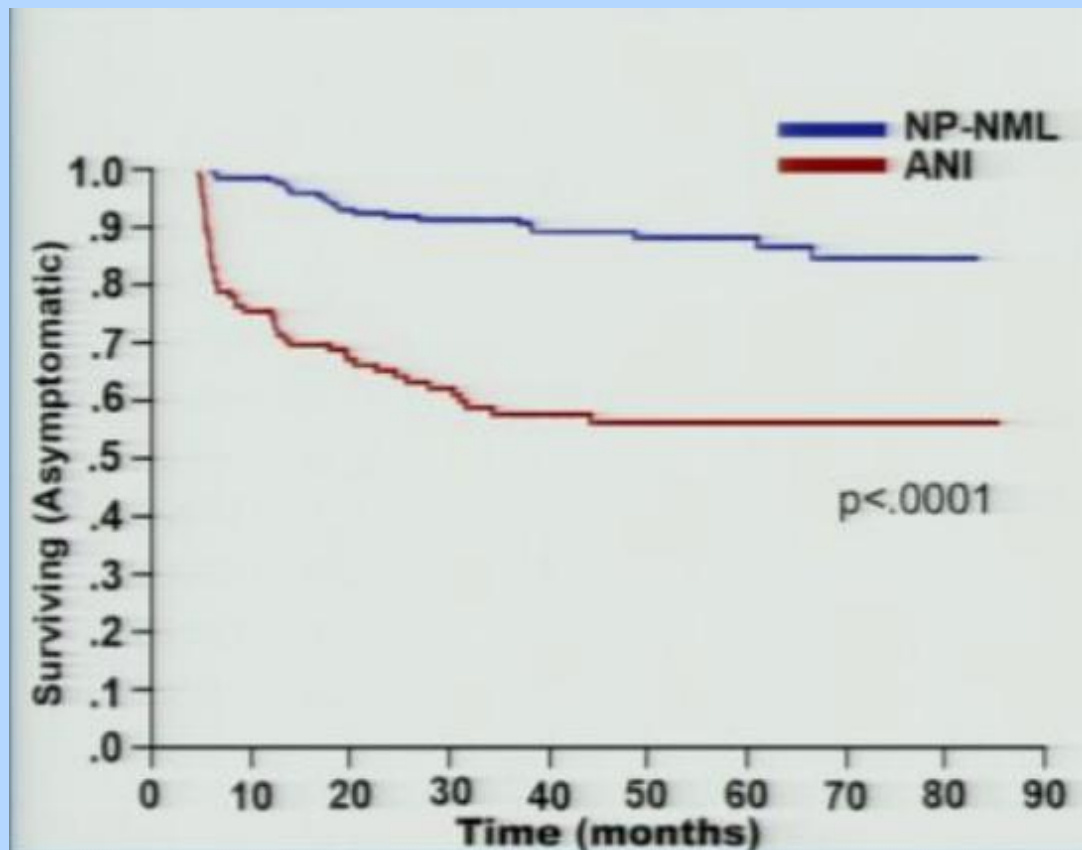
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| 5 | | |
| 6 | | |
| 7 | | |

Natural history of ANI

ANI Increases risk for symptomatic HAND:

- Performance based functional impairment



Relative risk:

- 4.70
- (CI 2.93 to 7.71)

Natural history of ANI

| Background Factors | No decline (n=237) | Decline (n=110) | P-value |
|-------------------------|-----------------------|--------------------|---------|
| Age | 42.6 (8.7) | 45.7 (7.4) | 0.002 |
| Education | 13.2 (2.3) | 12.6 (2.2) | 0.007 |
| % Male | 86.9% | 70.9% | 0.0003 |
| % lifetime substance Dx | 65.6% | 80.9% | 0.004 |
| % comorbidities | 24.9% | 41.8% | 0.001 |
| % AIDS | 54.4% | 67.3% | 0.02 |
| Nadir CD4 | 204 | 163 | 0.03 |
| % HCV +ve | 18.1% | 32.7% | 0.003 |

Ethnicity, on/off ART, current CD4, and estimated duration of HIV infection were non-significant

Asymptomatic NCI: Illusion or reality?

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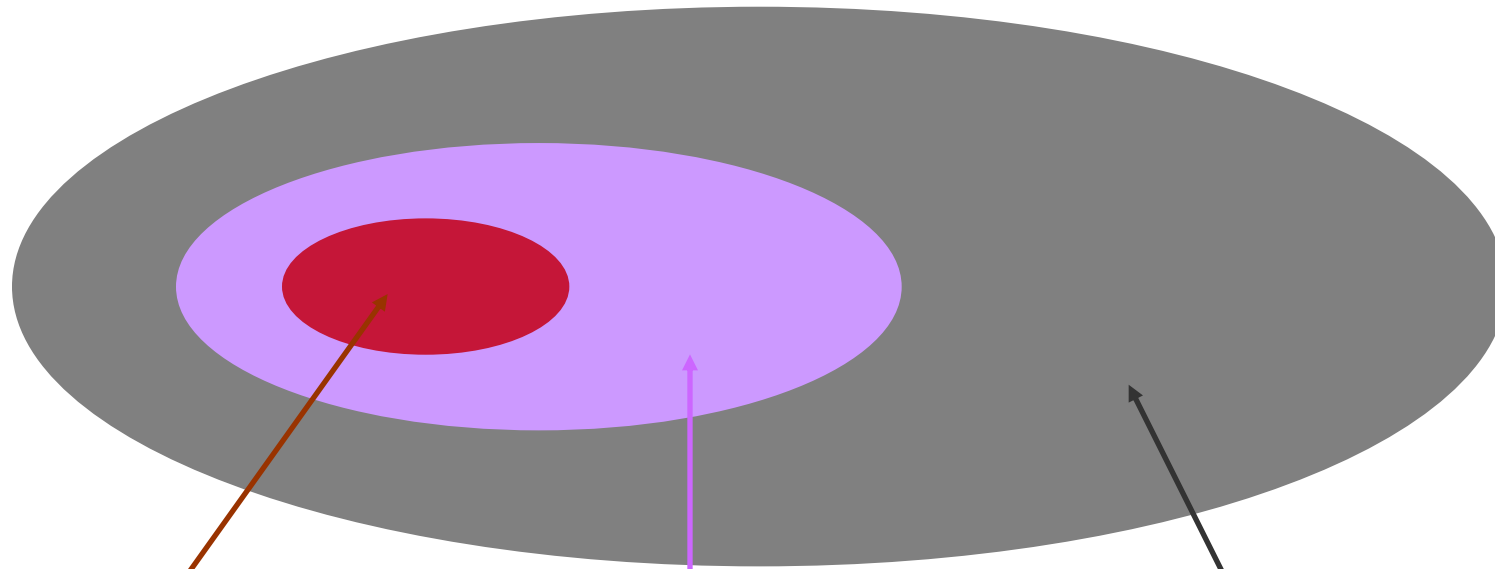
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HAND – Frascati classification

Neurology 2007;69;1789-1799



HAD

- *Marked interference with daily life*

Symptomatic NCI

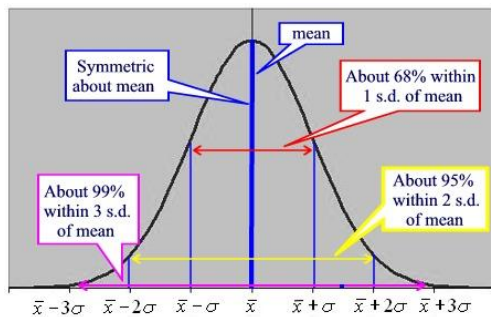
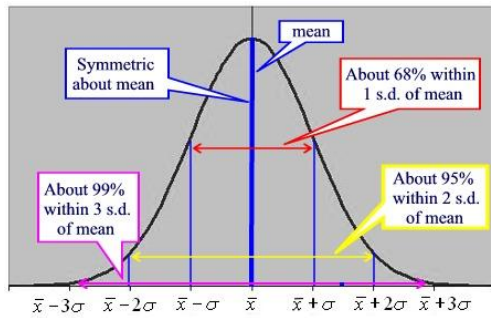
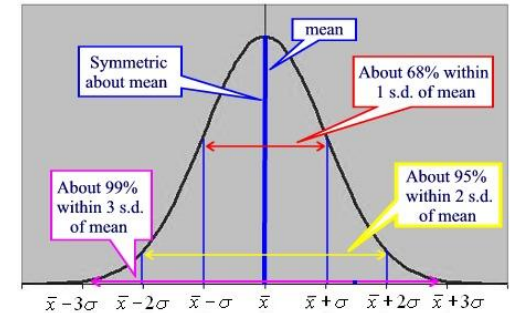
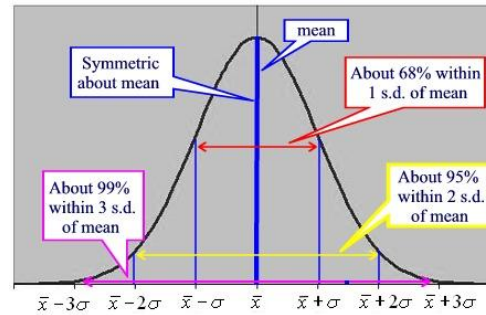
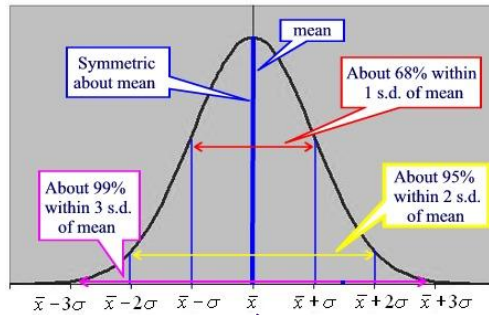
- *impairment >1 SD in 2 or more domains **
- *does interfere with daily life*

Asymptomatic NCI

- *impairment >1 SD in 2 or more domains **
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*** The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills**

Definition of NCI

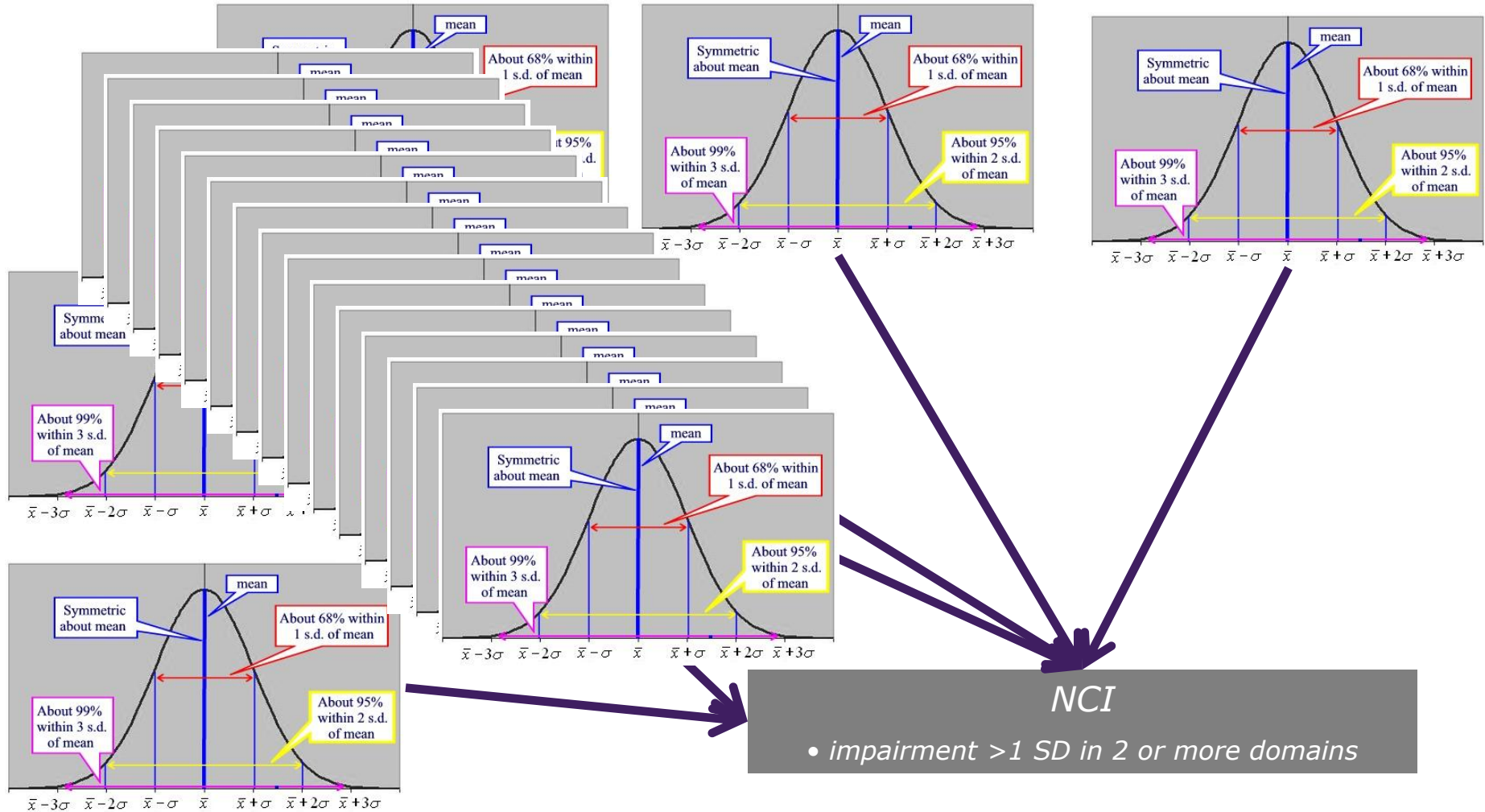


NCI

- *impairment >1 SD in 2 or more domains*

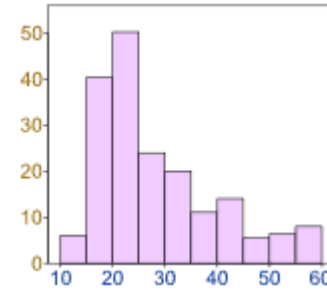
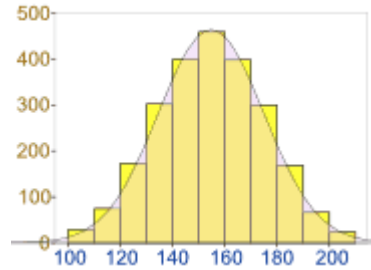
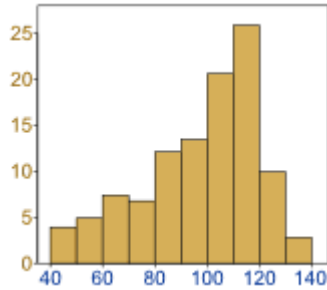
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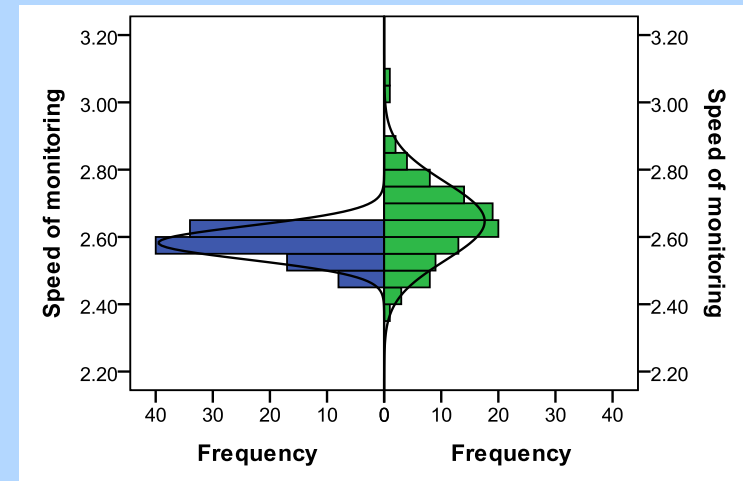
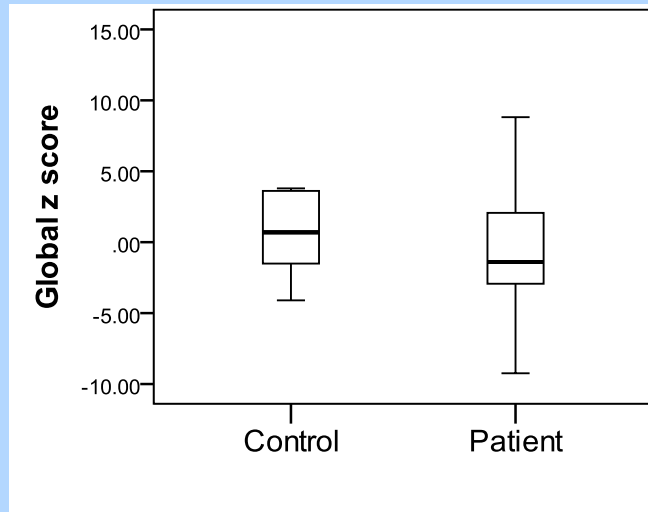


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Definition of NCI



What happens if the data are skewed?



St. Mary's cohort

Asymptomatic NCI: Illusion or reality?

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| 7 | | |

WHO screening criteria

| WHO Screening criteria | | |
|------------------------|---|--|
| 1 | important health problem | |
| 2 | accepted treatment for recognized disease | |
| 3 | facilities for diagnosis and treatment | |
| 4 | suitable latent and symptomatic stage | |
| 5 | suitable test or examination | |
| 6 | test acceptable to population | |
| 7 | natural history of condition understood | |
| 8 | agreed on policy on whom to treat | |
| 9 | cost of finding economically balanced with overall health | |
| 10 | case finding should be continuous process | |

WHO screening criteria

| WHO Screening criteria | | |
|------------------------|---|----------------|
| 1 | important health problem | yes |
| 2 | accepted treatment for recognized disease | no |
| 3 | facilities for diagnosis and treatment | not always |
| 4 | suitable latent and symptomatic stage | yes |
| 5 | suitable test or examination | not always |
| 6 | test acceptable to population | unknown |
| 7 | natural history of condition understood | not completely |
| 8 | agreed on policy on whom to treat | no |
| 9 | cost of finding economically balanced with overall health | no |
| 10 | case finding should be continuous process | difficult |

2 of 10 criteria met

Asymptomatic NCI: Illusion or reality?

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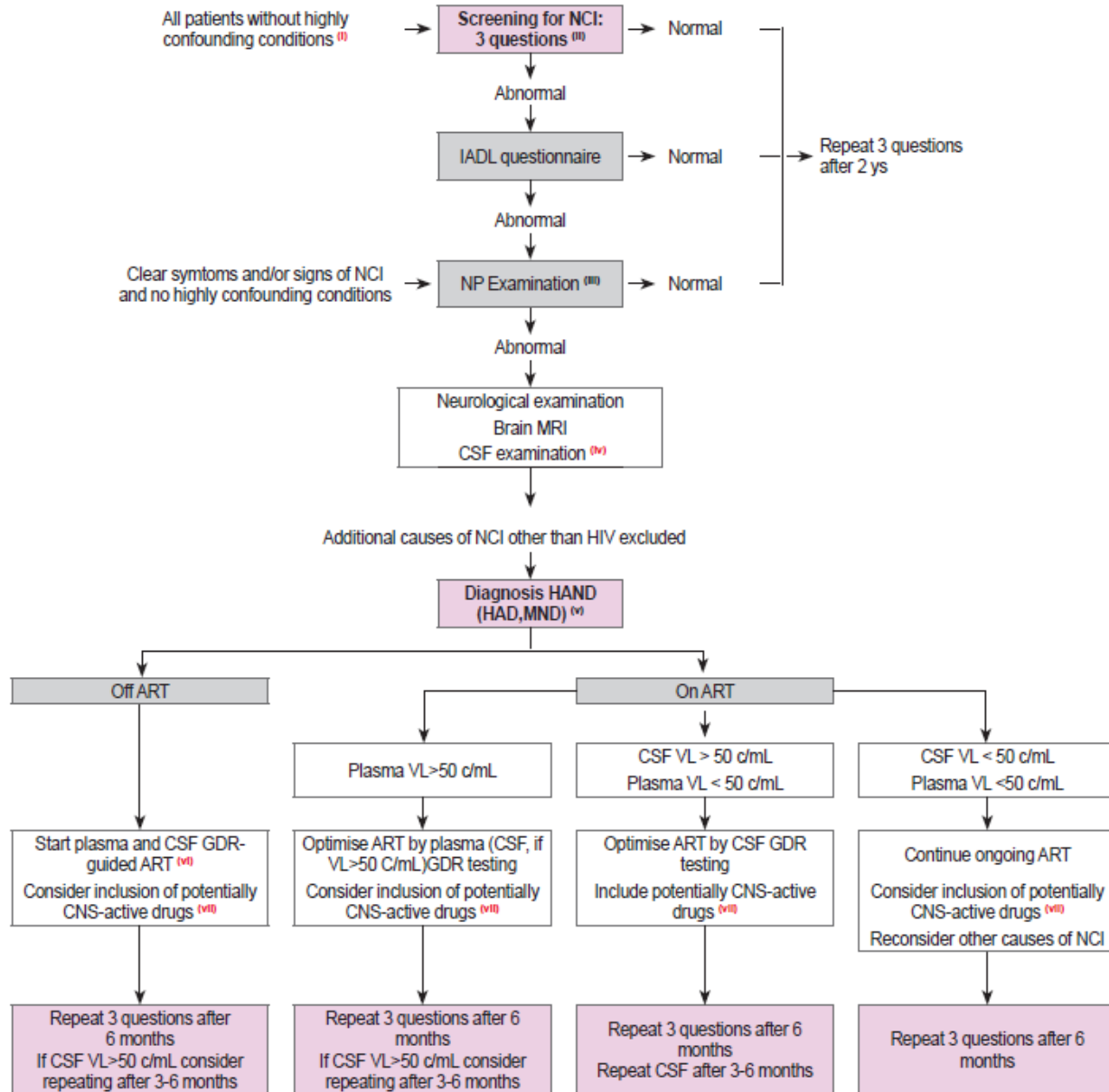
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Neurocognitive impairment: diagnosis and management

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



Asymptomatic NCI: Illusion or reality?

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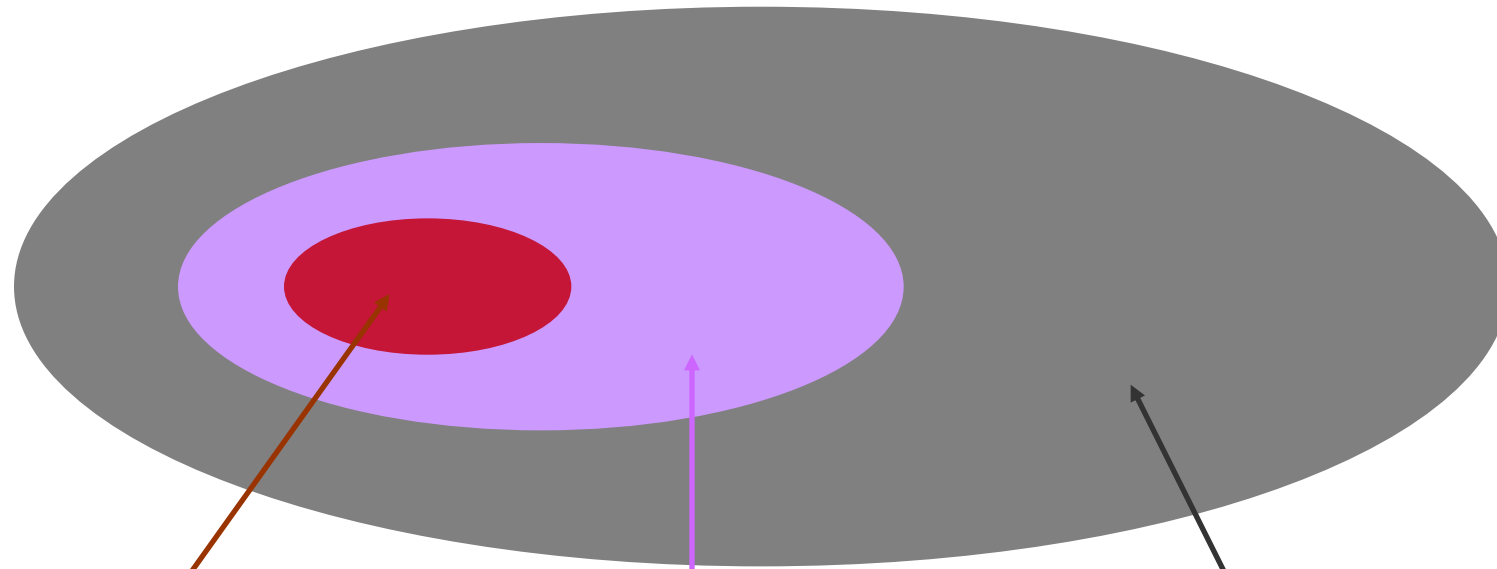
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| 7 | Do the Frascati Criteria recommend their use in general clinical practice? | |

HAND – Frascati classification

Neurology 2007;69;1789-1799



HAD

- *Marked interference with daily life*

Symptomatic NCI

- *impairment >1 SD in 2 or more domains **
- *does interfere with daily life*

Asymptomatic NCI

- *impairment >1 SD in 2 or more domains **
- *does not interfere with daily life*

'it is recommended that these be regarded as research criteria that will require further study before they are definitively adopted into clinical practice'

Asymptomatic NCI: Illusion or reality?

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The future

POPPY: 'Pharmacokinetic and Clinical Observations in People over Fifty'



Table 2: Recruitment targets at each site

| Centre | Patients seen in 2008/09 | | Recruitment targets | | | Total |
|--|--------------------------|-------------|---------------------|-------------|--------------|-------------|
| | <50 years | >50 years | HIV positive | | HIV negative | |
| | | | < 50 years | > 50 years | > 50 years | |
| St. Mary's Hospital | 1406 | 317 | 60 | 120 | 60 | 240 |
| King's College Hospital | 1264 | 207 | 40 | 80 | 40 | 160 |
| Chelsea & Westminster Hospital | 3146 | 902 | 190 | 380 | 190 | 760 |
| Homerton Hospital | 445 | 73 | 15 | 30 | 15 | 60 |
| Mortimer Market Centre | 2246 | 468 | 90 | 180 | 90 | 360 |
| Brighton and Sussex Hospital | 1159 | 386 | 80 | 160 | 80 | 320 |
| Mater Misericordiae University Hospital Dublin | 536 | 65 | 25 | 50* | 25 | 100 |
| Total | 10202 | 2418 | 500 | 1000 | 500 | 2000 |



Similar numbers to POPPY in Netherlands

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Thank you