MRC Clinical Trials Unit

Smarter studies
Global impact
Better health

UCL

Neurocognitive impairment: Diagnosis

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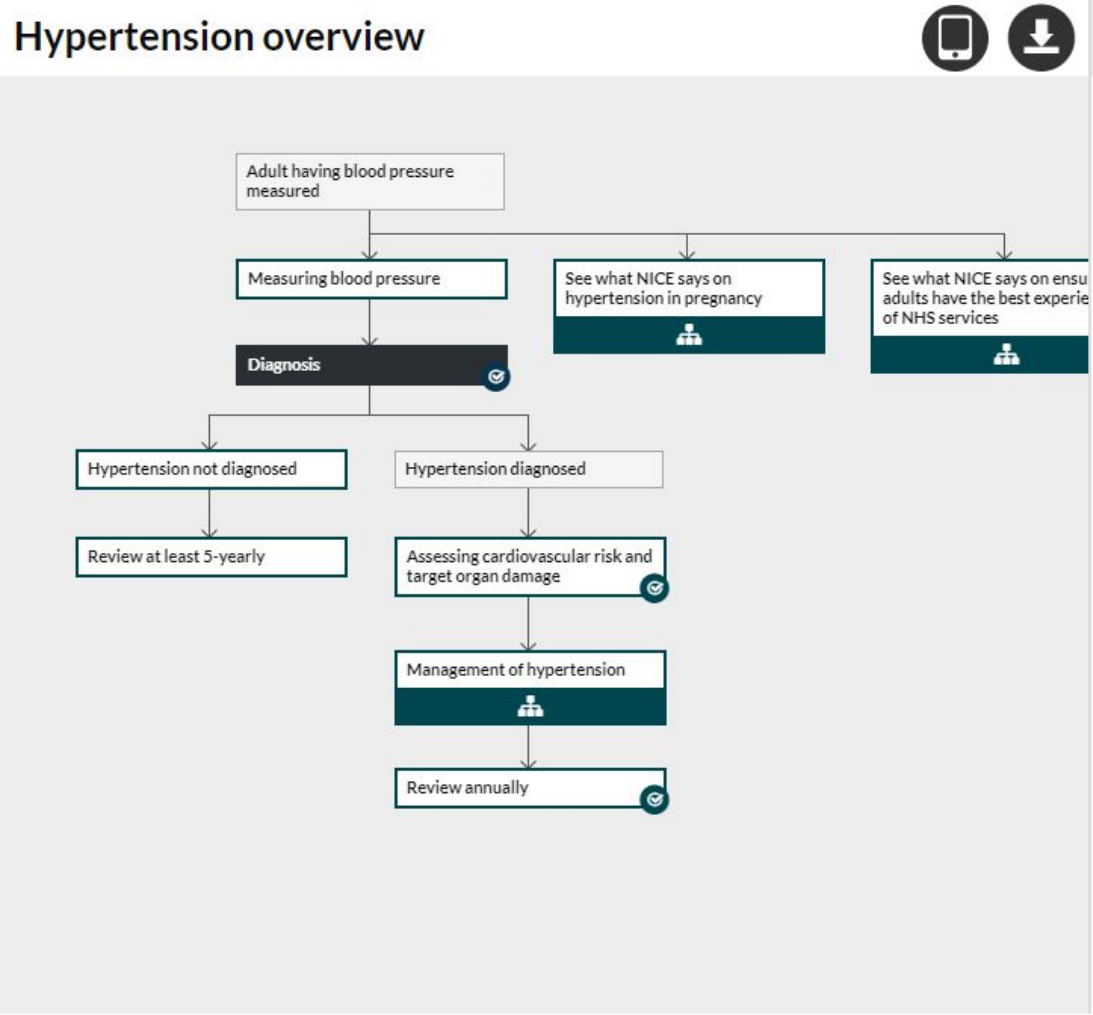
18th May 2018

Outline

- Diagnostic guidance
- Instead of guidance
- Challenges in diagnosing HIV-associated NCI
- What we do at my site (personal view)
- Other models
- What next?

What I would like to have…



Hypertension – everything NICE says in an interactive flowch

Diagnosis

If the clinic blood pressure is 140/90 mmHg or higher, offer ABPM to confi the diagnosis of hypertension.

If a person is unable to tolerate ABPM, HBPM is a suitable alternative to confirm the diagnosis of hypertension.

If the person has severe hypertension, consider starting antihypertensive drug treatment immediately, without waiting for the results of ABPM or HBF

While waiting for confirmation of a diagnosis of hypertension, carry out investigations for target organ damage (such as left ventricular hypertrophy, chronic kidney disease and hypertensive retinopathy) and a formal assessme of cardiovascular risk using a cardiovascular risk assessment tool (see assessi cardiovascular risk and target organ damage).

When using ABPM to confirm a diagnosis of hypertension, ensure that at leas two measurements per hour are taken during the person's usual waking hour (for example, between 08:00 and 22:00). Use the average value of at least 14 measurements taken during the person's usual waking hours to confirm a diagnosis of hypertension.

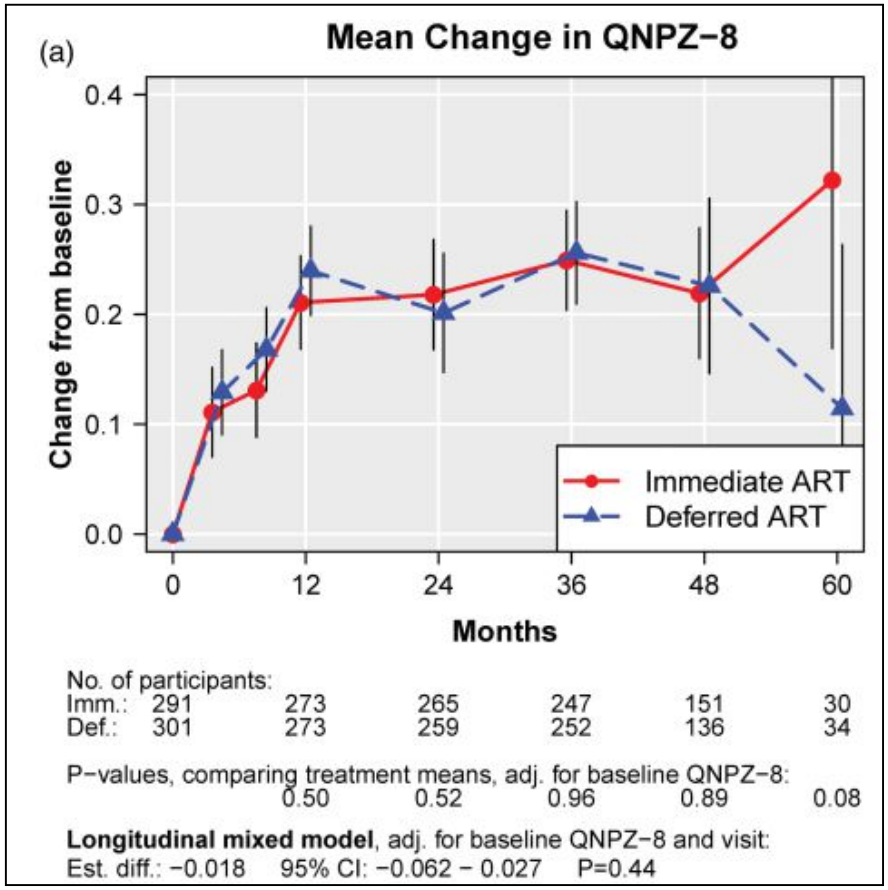
When using HBPM to confirm a diagnosis of hypertension, ensure that:

- for each blood pressure recording, two consecutive measurements are tal at least 1 minute apart and with the person seated **and**
- blood pressure is recorded twice daily, ideally in the morning and evening

- NICE (National Institute for Health Care Excellence) guidance

NICE accredited
www.nice.org.uk/accreditation

What we have…



Wright et al *AIDS* 2018; 32(8): 985-97

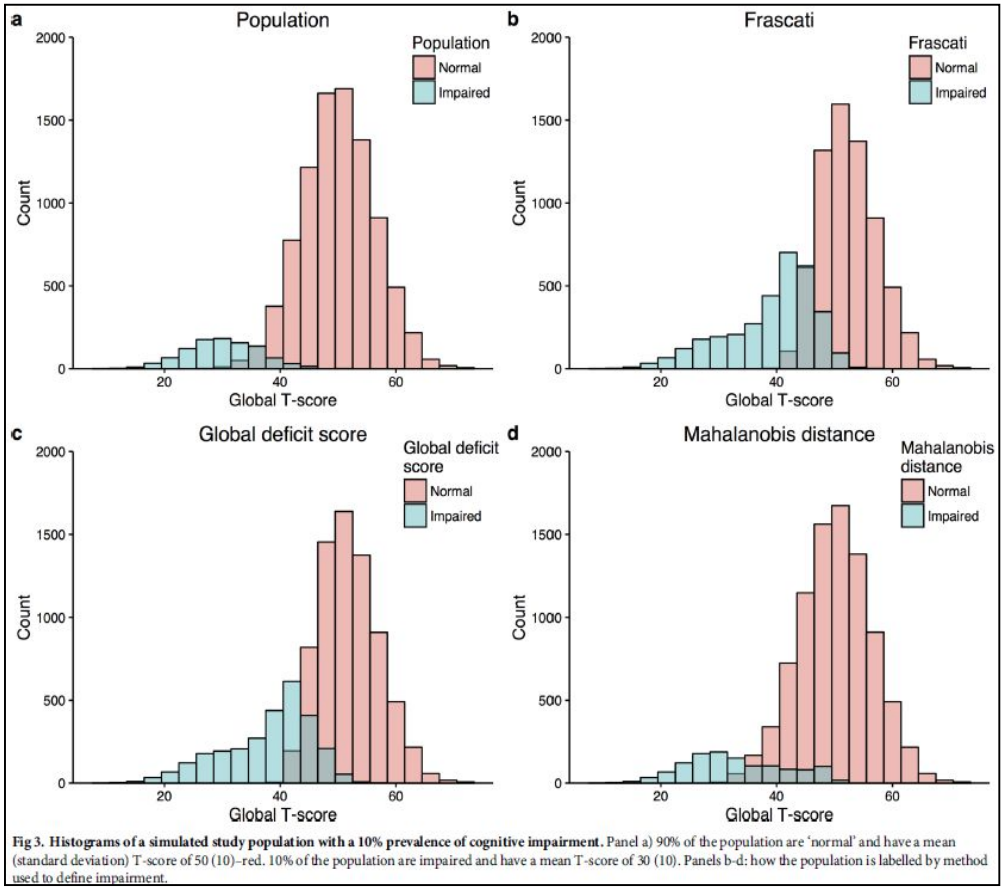


Fig 3. Histograms of a simulated study population with a 10% prevalence of cognitive impairment. Panel a) 90% of the population are 'normal' and have a mean (standard deviation) T-score of 50 (10)–red. 10% of the population are impaired and have a mean T-score of 30 (10). Panels b-d: how the population is labelled by method used to define impairment.

Underwood et al *PLoS One* 2018; 13(4): e0194760

- Data derived from RCTs and cohort studies informing medical labelling

Diagnosing dementia

Table 1: Diagnostic criteria for dementia

Type of dementia	Diagnostic criteria
Alzheimer's disease	Preferred criteria: NINCDS/ADRDA. Alternatives include ICD-10 and DSM-IV
Vascular dementia	Preferred criteria: NINDS-AIREN. Alternatives include ICD-10 and DSM-IV
Dementia with Lewy bodies	International Consensus criteria for dementia with Lewy bodies
Frontotemporal dementia	Lund-Manchester criteria, NINDS criteria for frontotemporal dementia

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; ICD-10, International Classification of Diseases, 10th revision; NINCDS/ADRDA, National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; NINDS–AIREN, Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences.

https://www.nice.org.uk/guidance/CG42/chapter/1-Guidance#diagnosis-and-assessment-of-dementia

But, what about milder cognitive impairment?

MCI diagnosis

- International Working Group on MCI criteria:
  - Cognitive decline (evidenced by self and/or Other)
  - Clinician report and impairment on objective cognitive tasks
  - Evidence of decline over time on objective tasks
  - Preserved basic activities of daily living (ADLs) (or minimal impairment in complex instrumental functions)
  - Does not meet DSM-IV, ICD-10 criteria for a dementia syndrome

Winblad et al. *J Intern Med* 2004;256(3):240-6

Neuroimaging markers

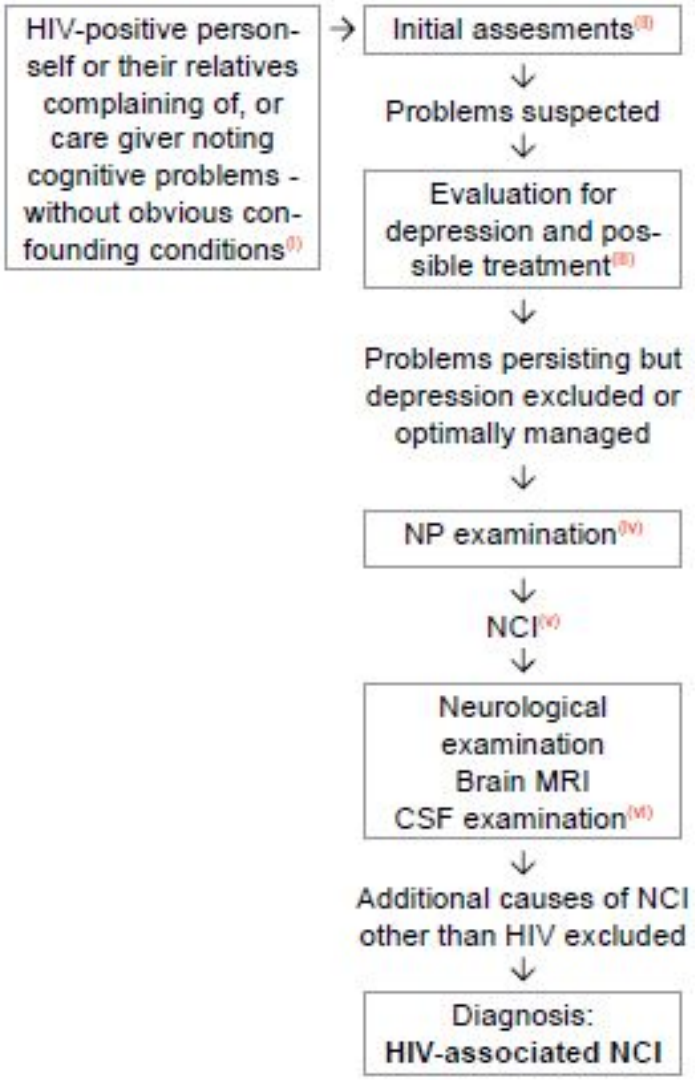
Table 1 Availability of evidence and panellists' decisions supporting the use of brain FDGPET in the diagnostic work-up of the main forms of mild cognitive impairment

PICO	Relative availability of evidence	Panellists' recommendations	Main reasons for final decision
1 – MCI due to AD	Fair	YES	A normal FDG-PET scan excludes neurodegeneration due to AD
2 – MCI due to FTLD	Lacking	YES	Typical hypometabolism pattern
3 – MCI due to DLB	Lacking	YES	Typical hypometabolism pattern

PICO, population, intervention, comparison, and outcome; MCI, Mild cognitive impairment; AD, Alzheimer disease; FTLD, fronto-temporal lobe degeneration; DLB, dementia with Lewy bodies

Arbizu et al. *Eur J Nucl Med Mol Imaging* 2018 [Epub ahead of print]

EACS algorithm for diagnosis and management of NCI



A diagnosis of exclusion

Based exclusively on neuropsychological testing

Multidisciplinary challenge

iv **NP examination** will have to include tests exploring the following cogniti- ve domains: fluency, executive functions, speed of information proces- sing, attention/working memory, verbal and visual learning, verbal and visual memory, motor skills plus assessment of daily functioning.

v **NCI** is defined by impairment in cognitive function on the above neuro- psychological test where performance is compared to age- and educa- tion-matched appropriate controls and is considered clinically significant.

vi **Neurological examination, brain MRI and CSF examination** are required to exclude other pathologies and to further characterise HIV- associated NCI by including assessment of CSF HIV-VL level and, where appropriate, evidence for genotypic drug resistance (GDR) in a paired CSF and plasma sample.

vii **CSF escape definition:**
either CSF HIV-VL detectable and plasma HIV-VL undetectable; or both CSF HIV-VL and plasma HIV-VL detectable, with CSF HIV-VL higher than plasma HIV-VL.

EACS algorithm for diagnosis and management of NCI

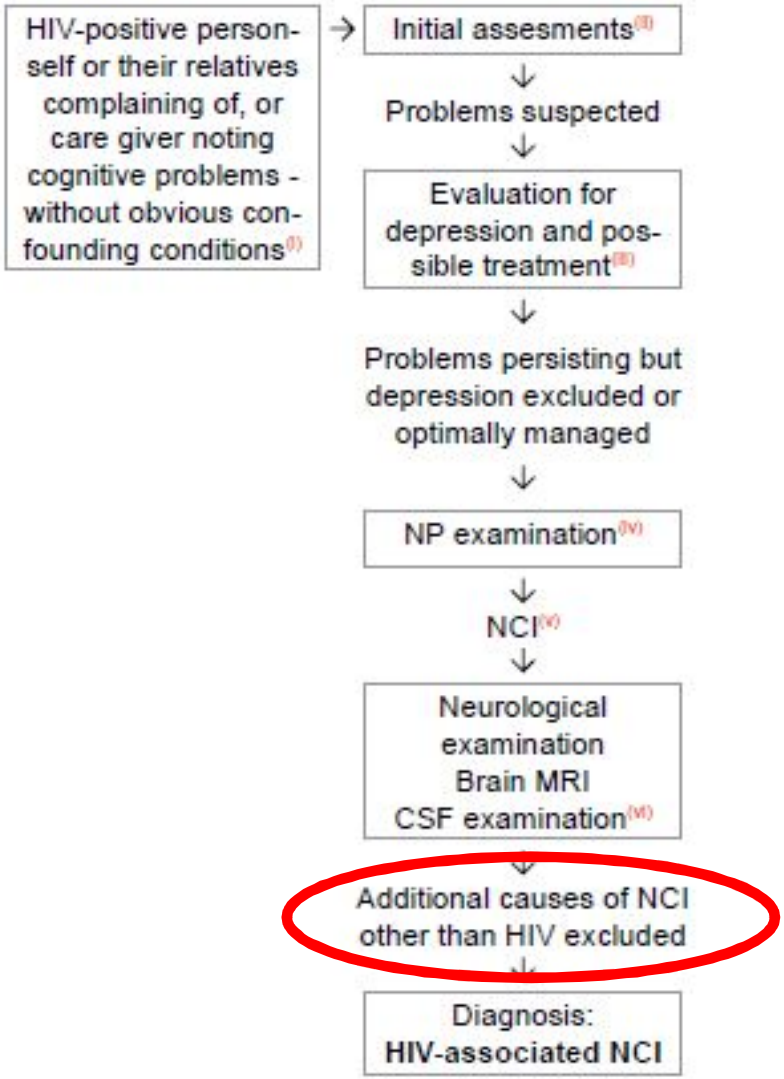


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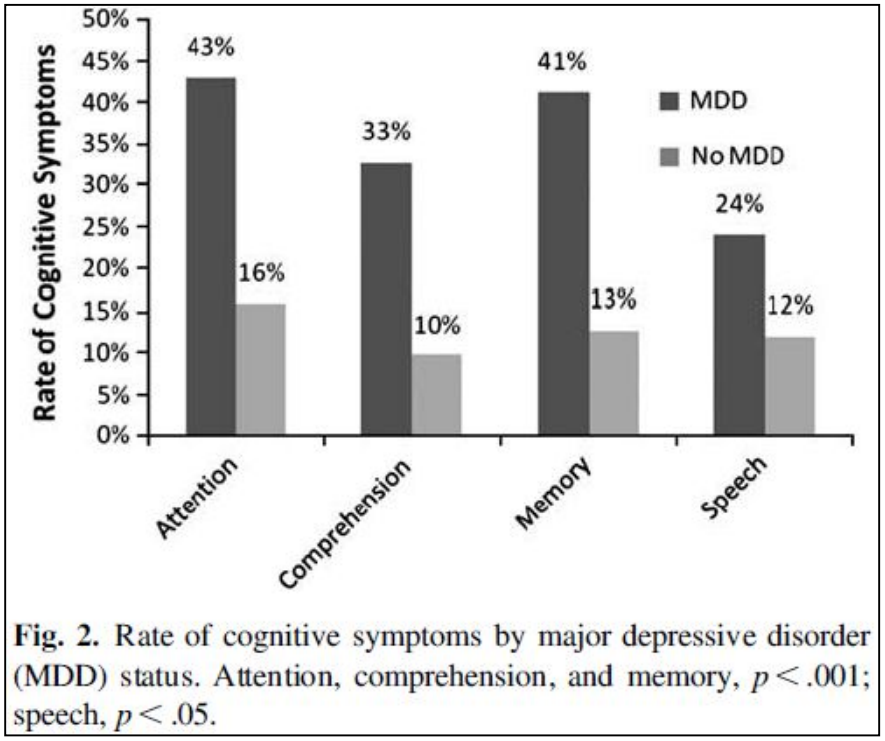
Fig. 2. Rate of cognitive symptoms by major Depressive disorder (MDD) status.
Attention, Comprehension, an memory, p<.001; speech, p<.05



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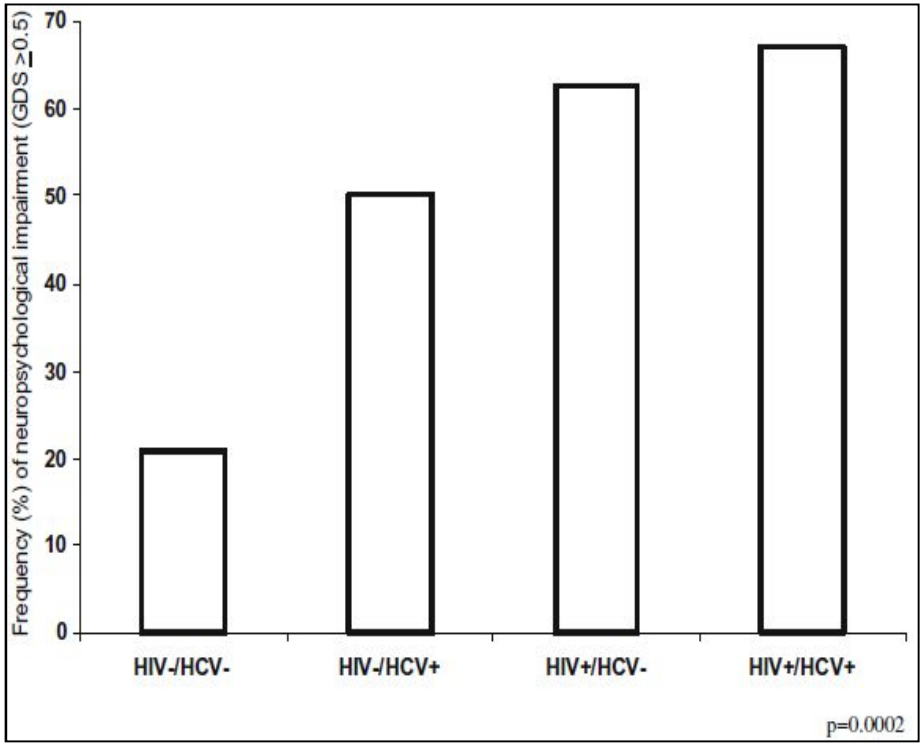
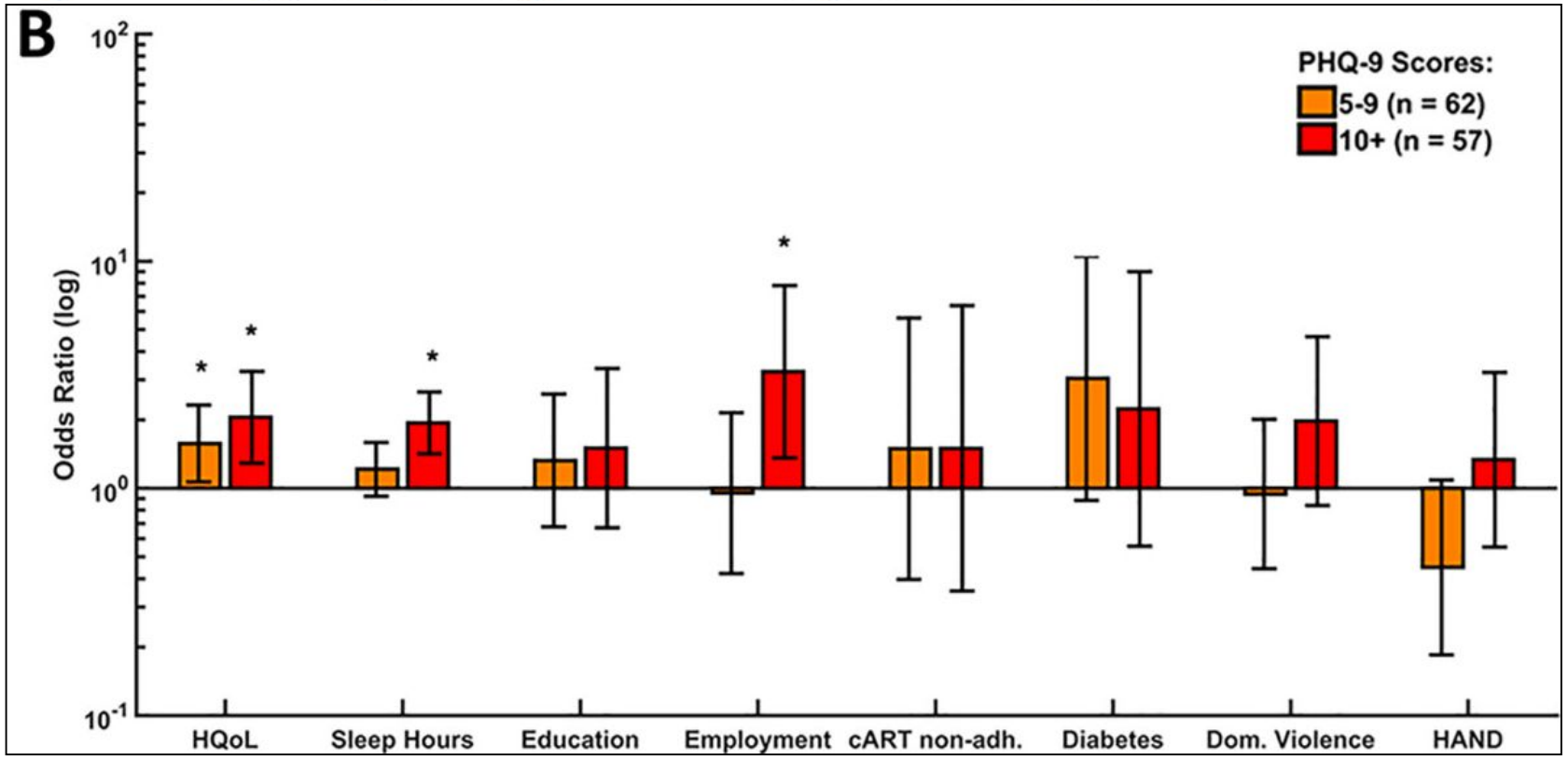
Fellows et al. *J Int Neuropsychol Soc* 2013; 19: 216-25

Fig. 1 Frequency of global neuropsychological impairment based on global deficit score (GDS) ≥0.5



De Almeida et al. *J Neurovirol* 2018 [Epub ahead of print]

Figure 1. Neuropsychological testing and multivariate analysis of depression predictors.



Depression was associated with specific clinical and demographic factors but not with sustained immunosuppression or neurocognitive impairment

Tymchuk et al. *Can J Psychiatry* 2018; 63(5): 329-36

Neuroimaging markers in HIV

Table 5. Association Between Imaging Measurements and Neurocognitive Impairment, Defined as a z-score <−1 in at Least Two Out of Seven Cognitive Domains: Logistic Regression Models[a]

	Overall Neurocognitive Impairment			Symptomatic Neurocognitive Impairment		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
White matter hyperintensities						
Lesion volume (log10)[a]	1.0	.9, 1.1	.857	1.1	1.0, 1.2	.266
Atrophy scores						
GCA	1.2	.6, 2.7	.580	**6.2**	**1.7, 22.3**	**.005**
TLA	1.3	.6, 2.7	.515	1.8	.8, 4.4	.173
Bicaudate index	1.1	.6, 2.2	.737	2.0	.9, 4.4	.100
Single voxel MRS						
NAA/Cho[a]	1.2	.6, 2.6	.590	1.9	.8, 4.5	.140
NAA/Cr[a]	1.7	.8, 3.4	.164	1.9	.9, 4.3	.116
mI/Cr[a]	1.0	.5, 1.8	.953	0.8	.4, 1.5	.454

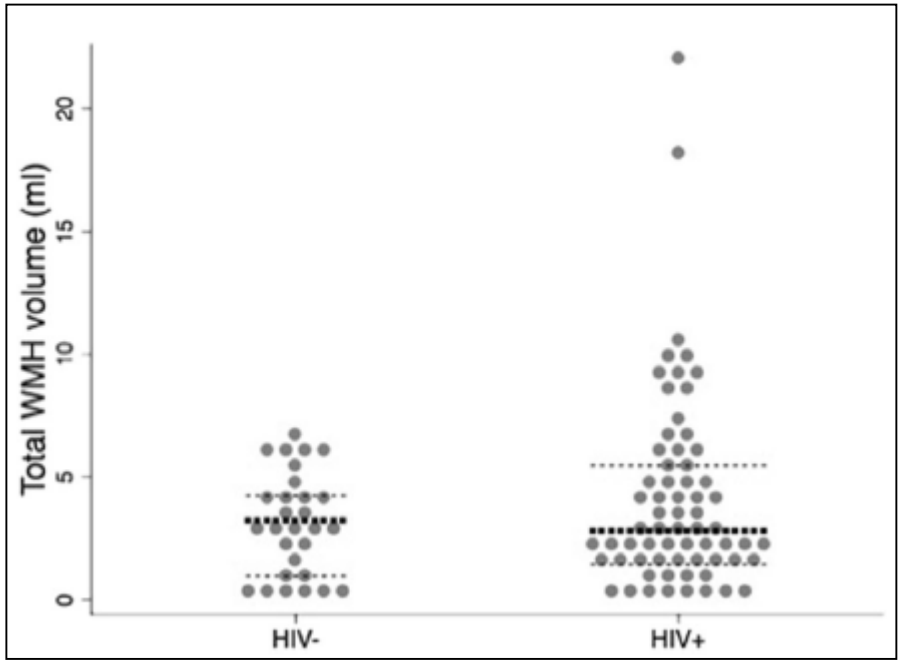
Bolded text indicates the significant result.

Abbreviations: CI, confidence interval; GCA, Global cortical atrophy score; mI/Cr, Myo-inositol to creatine ratio; MRS, magnetic resonance spectroscopy; NAA/Cho, N-acetyl aspartate to choline ratio; NAA/Cr, N-acetyl aspartate to creatine ratio; OR, odds ratio; TLA, Medial temporal lobe atrophy score.

[a] Adjusted for study arm allocation, age (per additional year), ethnicity (black vs other), education (per additional year on formal education) and nadir CD4 count (per 100c more).

Arenas-Pinto et al *CID* 2016; 63(2): 257-64

Fig. 1 WMH burden by HIV serostatus 15/65 cases (23%) of HIV+ participants had a total WMH volume >95th percentile of controls (*dark lines* median, *light lines* =25th/75th percentile)



Watson et al. et al *J Neurovirol* 2017; 23: 422-29

Diffuse white matter signal abnormalities

Table 2. Factors Associated With Human Immunodeficiency Virus Cerebrospinal Fluid Discordance (n = 163 Lumbar Punctures)

			Univariable Analysis		Multivariable Analysis	
	Discordant CSF/Plasma					
Characteristic	No (n = 139)	Yes (n = 24)	Unadjusted Odds Ratio (95% CI)	*P* Value[a]	Adjusted Odds Ratio (95% CI)	*P* Value[b]
Male sex: No. of LPs	98 (71)	17 (71)	1.0 (.4–2.6)	.97		
Male sex	90 (70)	11 (61)	0.7 (.2–1.9)	.43		
No. of LPs by age, y						
23–38	35 (25)	3 (13)	1	.16		
39–44	33 (24)	7 (29)	2.5 (.6–10.6)			
45–51	41 (30)	6 (25)	1.7 (.4–7.4)			
52–80	30 (22)	8 (33)	3.1 (.7–13.2)			
No. of LPs by presenting symptoms						
Acute neurology	42 (32)	6 (27)	1	.97		
Chronic symptoms of NCI	36 (28)	8 (36)	1.6 (.5–5.0)			
Subacute neurological complaint (n/N = 153/163)	53 (41)	8 (36)	1.1 (.3–3.3)			
Total No. of LPs						
1	116 (84)	16 (67)	1	.006	1	.04
2	20 (14)	4 (17)	1.5 (.4–4.8)		1.9 (.5–7.2)	
≥3	3 (2)	4 (17)	9.7 (1.8–50.7)		30.4 (2.1–446.0)	
Median plasma VL, $\log_{10}$ copies/mL (IQR)	1.7 (1.7–3.8)	2.1 (1.7–3.8)		.55[c]		
Median nadir CD4, cells/μL (IQR) (n/N = 122/163)	130 (40–250)	152 (50–260)		.76[c]		
No. of LPs by nadir CD4 category, cells/μL (n/N = 122/163)						
0–99	37 (36)	7 (37)				
100–199	30 (29)	5 (26)				
>200	36 (35)	7 (37)				
Median current CD4 count, cells/μL (IQR) (n/N = 159/163)	430 (180–620)	445 (330–770)				
On ART, No. of LPs (n/N = 156/163)	105 (79)	21 (91)				
No. of LPs by CPE category						
No ART	28 (21)	2 (09)	1	.66		
Low	37 (28)	11 (48)	4.2 (.8–21.3)			
Medium	46 (35)	5 (22)	1.5 (.3–8.5)			
High	22 (17)	5 (22)	3.2 (.5–18.8)			
Using medium CPE as baseline						
Off ART			0.8 (.2–4.0)			
Low			3.1 (.8–11.9)			
Medium			1 (base)			
High			1.9 (.4–8.9)			
Focal MRI white matter lesions, No. of LPs	36 (31)	6 (29)	0.9 (.3–2.5)	.80		
Diffuse white matter, No. of LPs						
Nil	79 (66)	10 (48)	1	.02	1	.007
Subtle	33 (28)	5 (24)	1.1 (.4–3.6)		1.4 (.4–5.4)	
Definite	8 (7)	6 (29)	5.6 (1.5–20.6)		10.3 (2.3–45.0)	

CSF discordance associated with DWMSA (aOR: 10.3; 95% CI: 2.3-45.0; p=0.007)

Kugathasan et al *CID* 2017; 64(8): 1059-65

NCAT clinic at MMC

- **Referral system:**
  - **From HIV clinic only**
- Multidisciplinary team clinic:
  - Clinical Psychology
  - Neurology
  - HIV
- Assessment:
  - Psychological
  - Medical
  - Imaging
  - Virology
- Outcome:
  - Recommendation

Initial assessment:

- Thyroid function
- Testosterone
- Glucose
- QRISK
- GAD-7
- PHQ-9
- Alcohol screen
- Drug inventory
- ADL

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Virtual clinic:

- To define plan of action
- Risk assessment
- Further assessment
- GP involvement (consider)

MDT meeting:

NCAT clinic appointment

NCAT clinic at MMC

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  - From HIV clinic only
- Multidisciplinary team clinic:
  - Clinical Psychology
  - Neurology
  - HIV
- **Assessment:**
  - **Psychological**
  - **Medical**
  - **Imaging**
  - **Virology**
- Outcome:
  - Recommendation

Neuropsychological assessment

- Cognition + mental health

Imaging:

- MRI scan (if appropriate)

Virology (LP):

- If appropriate and accepted

NCAT clinic at MMC

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  - From HIV clinic only
- Multidisciplinary team clinic:
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  - Neurology
  - HIV
- Assessment:
  - Psychological
  - Medical
  - Imaging
  - Virology
- **Outcome:**
  - **Recommendation**

Follow-up assessment

- Unlikely

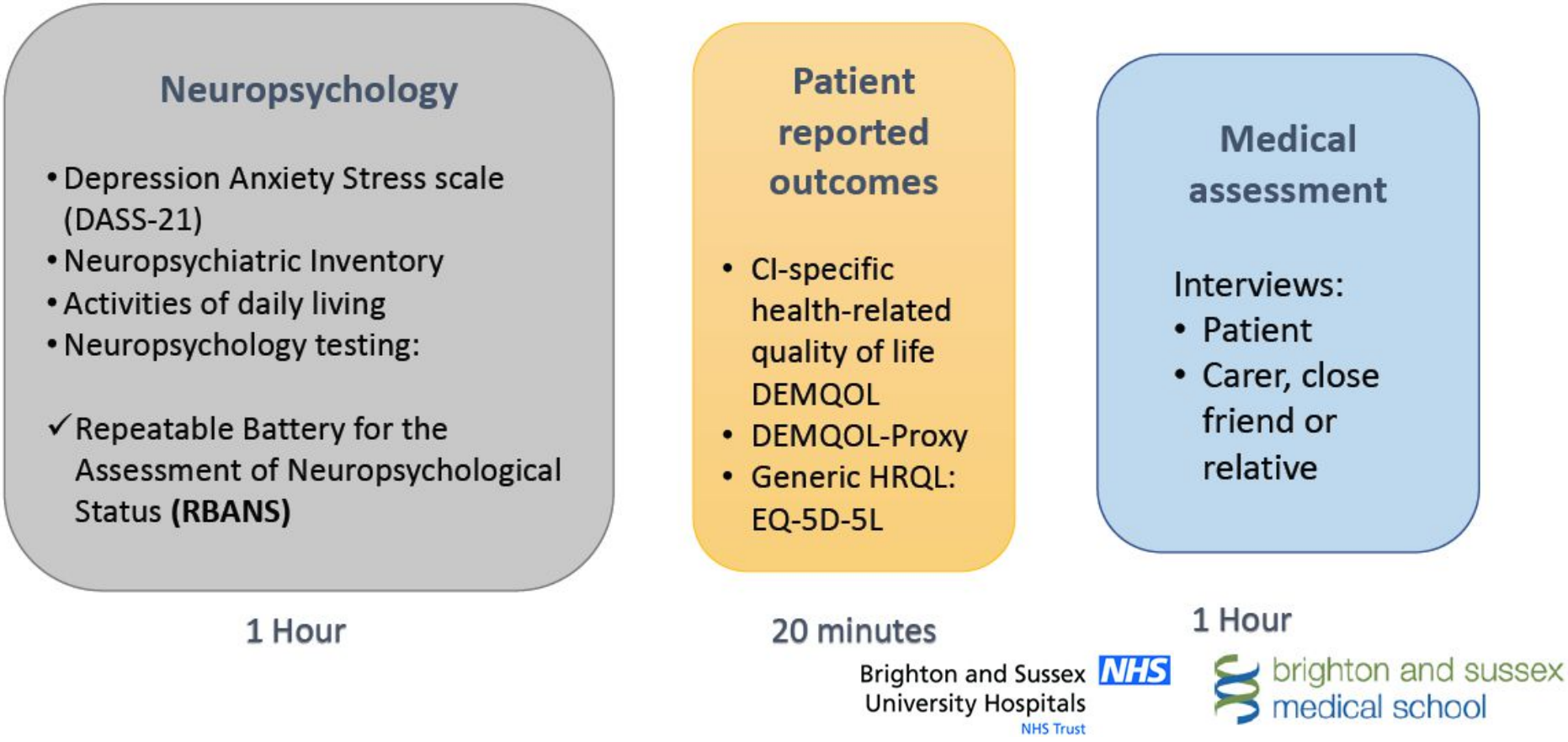
ART adjustment

- If escape proved

Management of comorbidities

- Often the case

"One stop" service for people with cognitive complains



Jaime Vera, Oral presentation. April 2018

Take home message

- Diagnosis is always a major challenge
- Pure cases of NCI are unusual
- Biomarkers are welcome but elusive
- Diagnostic criteria based on neuropsychological testing: the challenge is getting better at it.

- Many thanks to
  - Dr Jonathan Cratledge
  - Dr Lewis Haddow
  - Prof Nicholas Paton

  - And to you all for your attention!