British HIV Association
BHIVA

Dr Alan Winston

Imperial College Healthcare NHS Trust, London

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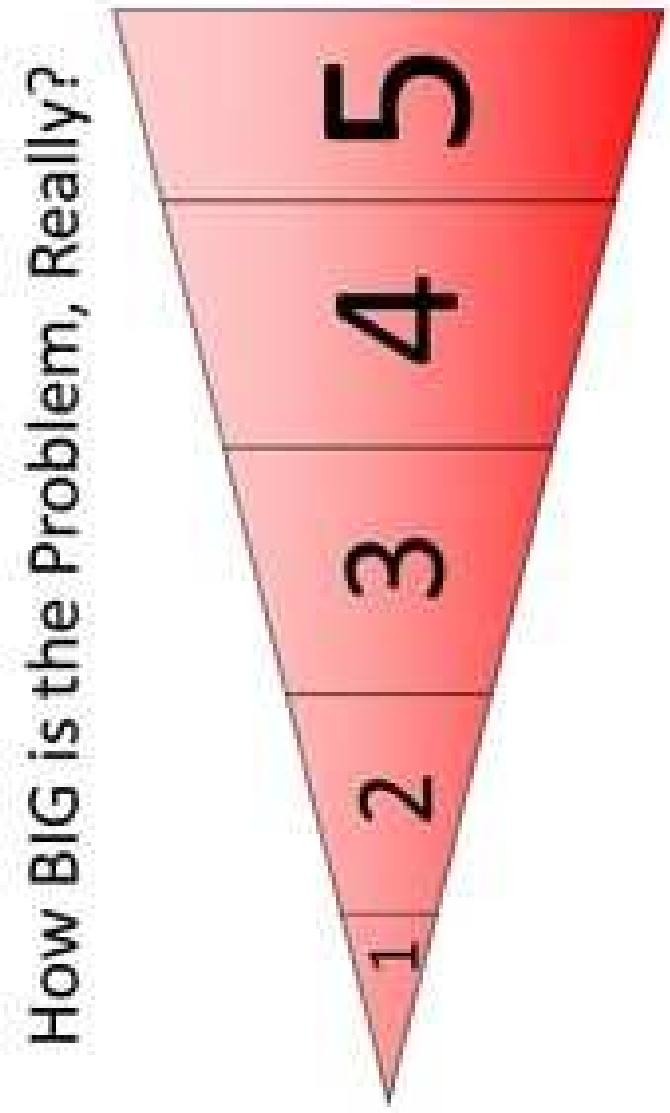
COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Dr Alan Winston	has received honoraria or research grants from or been a consultant or investigator in clinical trials sponsored by Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen-Cilag, Roche, Pfizer and ViiV Healthcare
Date	**October 2014**

Imperial College London

Managing cognitive impairment in the clinic.

Alan Winston
St. Mary's Hospital, London
10th October 2014

How big is this problem?



Question 1 : How big is this problem?

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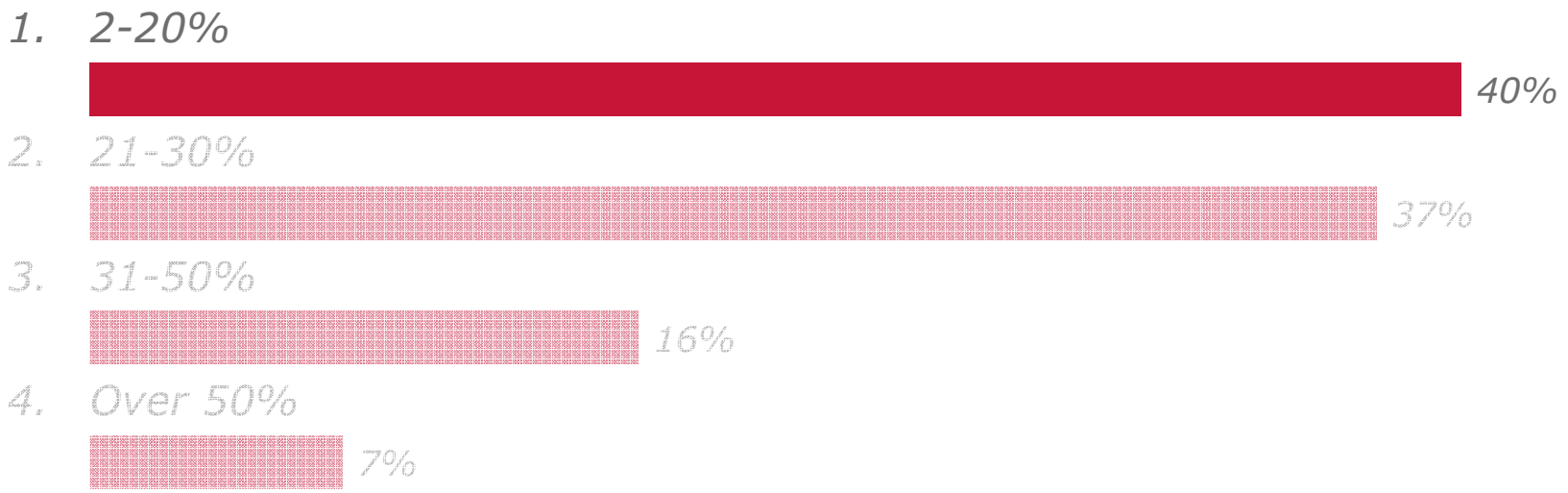
How common is symptomatic HIV-associated cognitive impairment in otherwise effectively treated individuals?



Cognitive impairment

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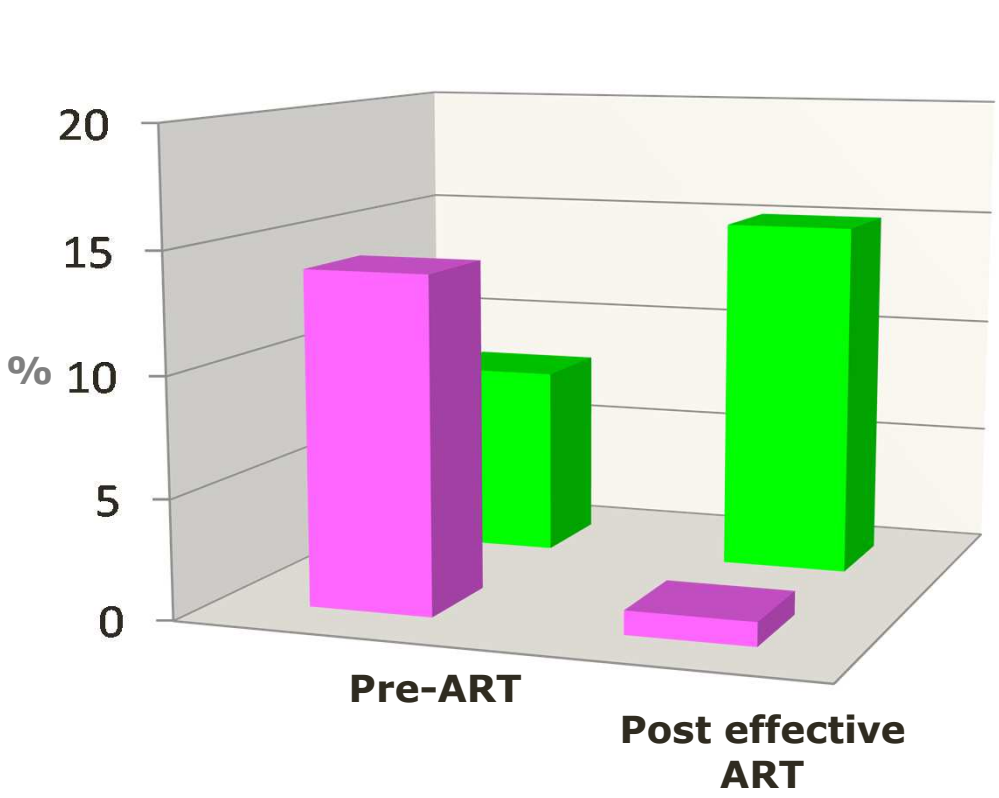
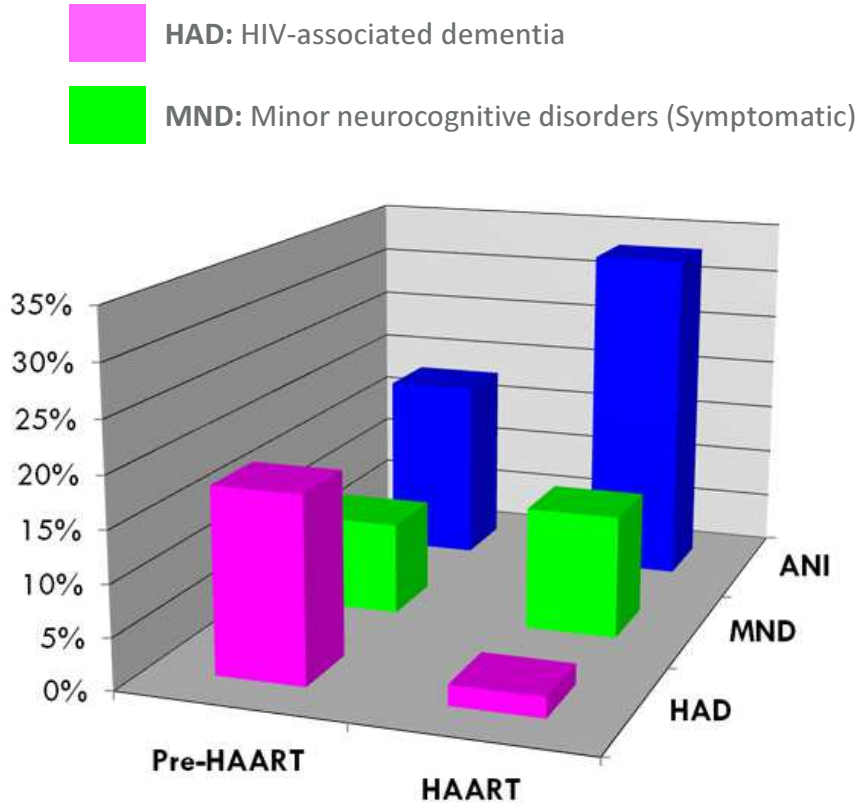
Prevalence of HIV-associated cognitive impairment:





Clinical implications of HIV-associated cognitive impairment:

- Social: Employment, undertake ADL
- Disease: loss of effective control of HIV

Natural history of asymptomatic NCI

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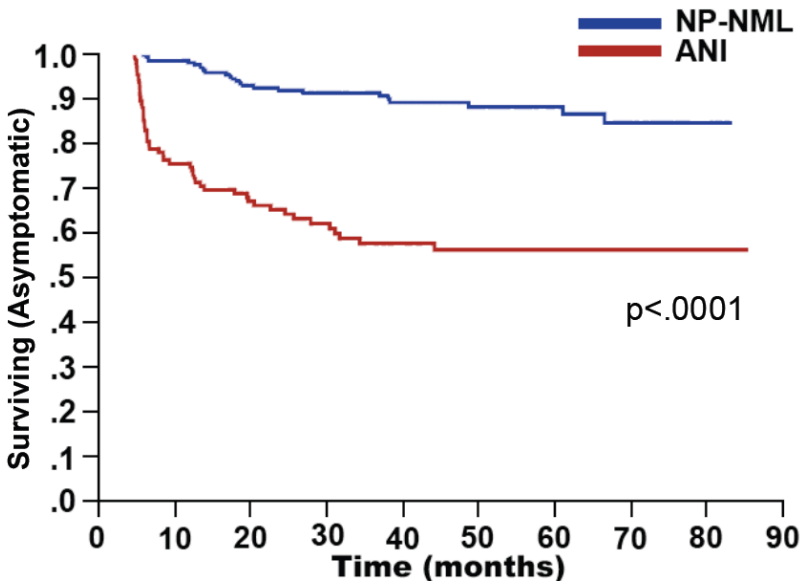

Background Factors	No decline (n=237)	Decline (n=110)	P-value
Age	42.6 (8.7)	45.7 (7.4)	0.002
Education	13.2 (2.3)	12.6 (2.2)	0.007
% Male	86.9%	70.9%	0.0003
% lifetime substance Dx	65.6%	80.9%	0.004
% comorbidities	24.9%	41.8%	0.001
% AIDS	54.4%	67.3%	0.02
Nadir CD4	204	163	0.03
% HCV +ve	18.1%	32.7%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

Relative risk of progressing

- **4.70 (CI: 2.93–7.71)**

Neurology. 2014 Jun 10;82(23):2055-62

Question 2 : Who should we look for it in?

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Which groups of PLWH should be screened for cognitive impairment?

1. *Everyone*

51%

2. *Only those with symptoms*

35%

3. *Only those healthcare professionals are worried about*

15%

Guideline recommendations

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EACS 2012 Guidelines:

'All persons, irrespective of symptoms and signs of NCI without confounding conditions'

Repeat screening every 2 years

BHIVA 2013 Standards of Care:

'PLWH should be screened for the presence of symptoms of …… and cognitive difficulties within the first 3 months of receiving an HIV diagnosis'

'Such screening should be repeated on an annual basis ……'

Initial screening tools

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EACS 2012 Guidelines:

Screen with 3 questions:

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

For each question, answers could be: a) never, b) hardly ever, or c) yes, definitely.

Results are considered “abnormal” when answering “yes, definitely” on at least one question.

BHIVA 2013 Standards of Care:

‘ Screening may vary from documented responses to specific screening questions, ……. all of which should be empirically validated for use in HIV or with other chronic health conditions’

Our experience

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Can the EACS guidelines for neurocognitive testing be practically implemented into a UK clinical setting?

Poster BHIVA 2012

Assessment	Number (%) positive	Number (% total) remaining screening
Total number		58 (100%)
Confounding conditions	24 (41%)	34 (59%)
Three screening questions	5 (15%)	

Neuropsychological testing

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Key investigation:
- Characterising cognitive impairment
- Subjects with symptoms of cognitive impairment or positive screening tests

Essential to rationalise use:
- Excluded depression first
- Excluded confounding conditions first
  - Psychiatric conditions, use psychotropic drugs and alcohol abuse, sequalae from previous or current CNS-OI or neurological diseases

Essential to interpret the results in correct clinical context:
- Consider the control population
- Discuss results with the neuropsychologist

In cases where cognitive impairment suggested:
- Further investigations to exclude confounding conditions
  - MRI brain
  - CSF examination (also assess viral suppression)

Phenotype of dementias

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	Cortical	Sub-cortical
Type of dementia	Alzheimers, fronto-temporal dementia	HIV-dementia, Parkinsons, Huntingtons
Main area(s) of damage	Cerebral cortex	Basal ganglia, thalamus
Language problems / aphasia	Common, early	No
Memory problems	Common, early	Rare
Personality / frontal changes	No	Common (typically emotional / irritable / personality change)
Executive / higher function decisions	Yes	Yes
Attention / motivation problems	No	Common, early

Is the phenotype changing?

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The effects of age and HIV infection on neuropsychological performance were analysed on the basis of HIV serostatus and age (<60 vs ≥60)

	HIV Negative		HIV+ Positive		Effects (*F* Values)		
	Younger, n = 22	Older, n = 17	Younger, n = 122	Older, n = 31			
Test	Mean ± Standard Deviation				HIV	Aging	HIV by Aging
Rey Auditory Verbal Learning Test							
Immediate recall	43.0 ± 6.9	37.4 ± 8.1	39.0 ± 8.4	33.6 ± 8.9	5.21[a]	13.64[b]	0.07
Delayed recal	9.1 ± 2.6	7.2 ± 2.3	7.9 ± 2.6	6.6 ± 3.0	3.00	9.44[b]	0.33
Digit Span							
Forward	6.0 ± 1.0	5.1 ± 1.0	5.6 ± 1.1	5.3 ± 0.9	0.04	9.10[b]	2.82
Backward	4.9 ± 1.1	3.7 ± 1.2	4.2 ± 1.3	3.9 ± 0.9	1.51	10.41[b]	2.84
Spatia Span							
Forward	5.6 ± 0.9	4.8 ± 0.7	4.8 ± 0.9	4.5 ± 0.9	9.78[b]	9.35[b]	2.05
Backward	4.4 ± 1.2	3.3 ± 0.5	3.9 ± 1.1	3.5 ± 0.8	0.44	17.05[b]	3.08
Rey complex figr e copy	33.2 ± 2.4	30.6 ± 3.8	32.2 ± 3.4	29.2 ± 5.0	3.18	15.70[b]	0.09
Rey complex figr e delayed recall	16.0 ± 5.6	13.1 ± 5.8	13.9 ± 5.8	9.2 ± 6.1	6.79[b]	11.28[b]	0.60
Stroop Test							
Errors	0.9 ± 1.1	1.9 ± 3.2	1.2 ± 1.8	2.1 ± 2.6	0.51	6.21[b]	0.02
Time	18.5 ± 7.7	32.7 ± 14.7	17.4 ± 8.5	29.1 ± 14.4	1.41	42.25[b]	0.35
Trial-Making Test Part B							
Time	102.7 ± 26.2	182.4 ± 70.8	135.9 ± 48.8	187.4 ± 70.1	2.38	29.71[b]	2.57
Errors	0.5 ± 0.9	1.3 ± 1.0	0.8 ± 1.1	1.4 ± 1.3	0.76	10.00[b]	0.09
Drawings	5.1 ± 1.7	4.9 ± 1.5	4.8 ± 1.7	3.8 ± 2.3	3.77	3.23	1.40
Raven matricese	32.1 ± 3.42	27.00 ± 4.9	29.3 ± 4.8	27.2 ± 5.5	1.88	14.89[b]	2.46
Letter fluncy	39.6 ± 9.0	32.7 ± 10.9	34.9 ± 11.5	29.7 ± 14.7	3.03	7.34[b]	0.15
Wechsler Adult Intelligence Scale Digit Symbol	9.4 ± 2.0	9.3 ± 2.8	8.6 ± 2.5	8.9 ± 2.3	3.02	7.34[b]	0.15
Doublerbarrage	0.98 ± 0.23	0.98 ± 0.02	0.96 ± 0.04	0.90 ± 0.19	8.43[b]	3.59	3.83
Reactio tirna t ask score	657.8 ± 162.1	779.4 ± 258.1	777.3 ± 184.2	883.7 ± 199.6	3.05	15.10[b]	1.38
Total number of pathological scores	1.3 ± 0.9	2.7 ± 2.2	2.6 ± 2.6	3.5 ± 2.5	5.73[a]	7.13[b]	0.66

[a] $P < .05$; [b] .01.

Cognitive performance in older HIV+ participants was not distinct from younger HIV+ participants

Ciccarelli N et al. *J Am Geriatr Soc* 2012;60:2048–2055

Question 3: clinical scenario

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A 45 year old man naïve to ART:

CD4 count 530 cells/uL
HIV RNA 8000 copies/mL
Complaining difficulty concentrating at work
MRI brain normal and excluded confounding conditions
Formal NP testing reports impaired testing results

What do you do?:

1. *Monitor closely with NP testing yearly*

13%

2. *Commence ART*

44%

3. *Commence ART including AZT*

6%

4. *Commence ART with a high CPE score*

36%

Management cognitive impairment

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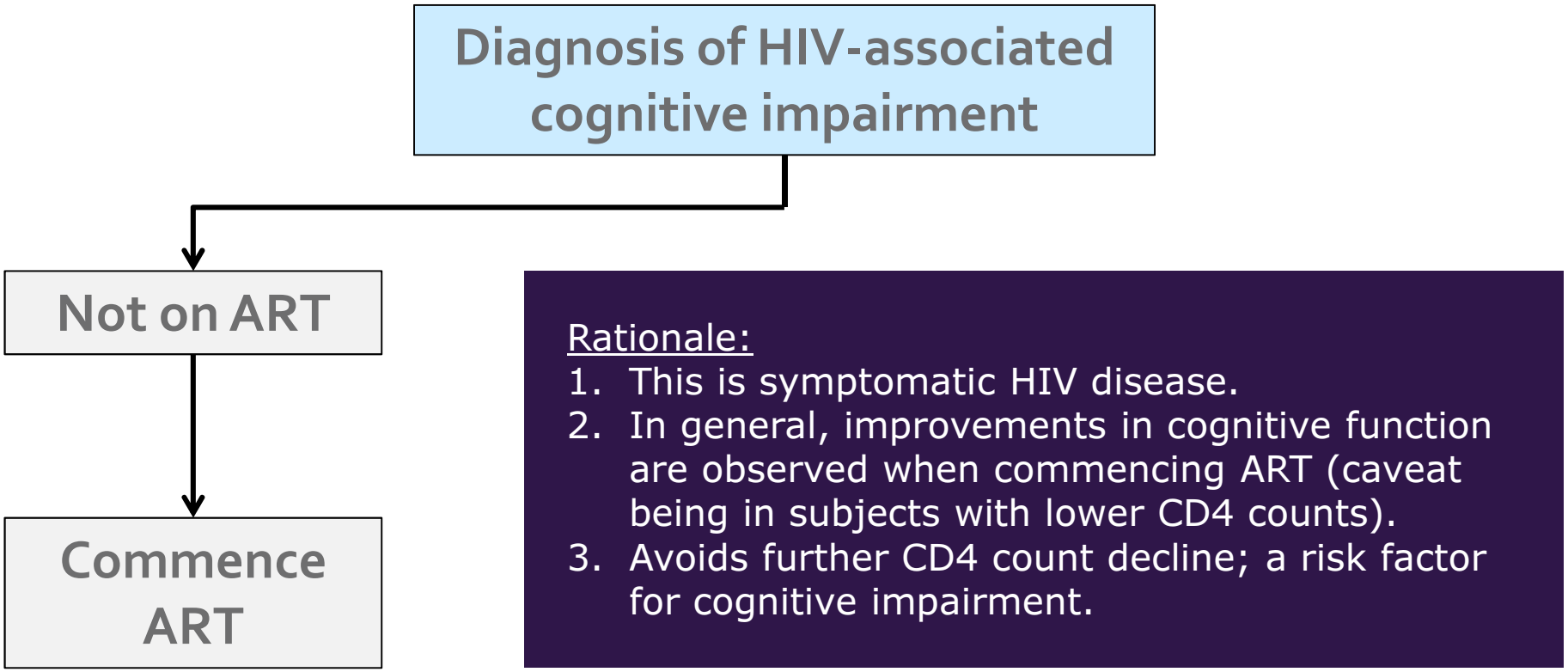

Nadir CD4

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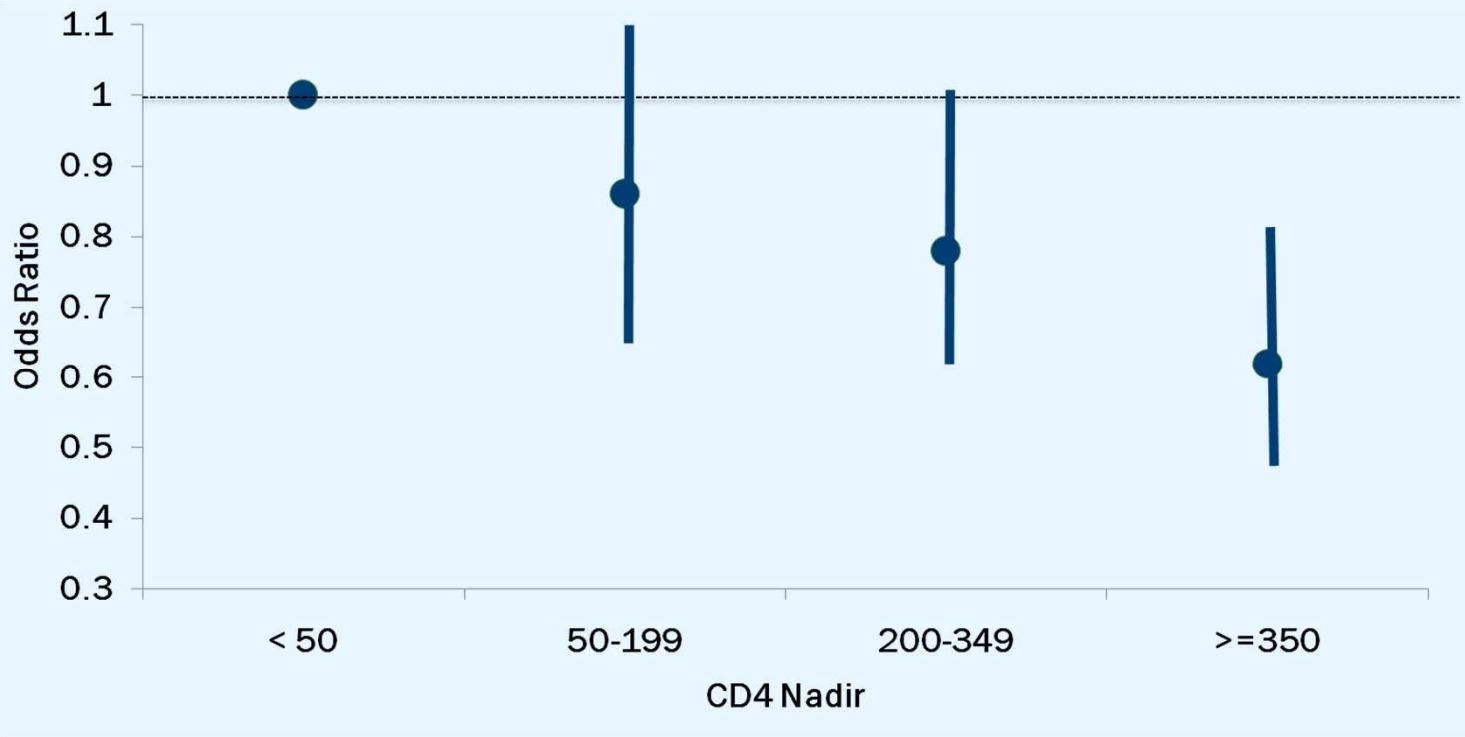
Odds Ratios for Cognitive Impairment According to CD4 Nadir Strata (All Subjects)

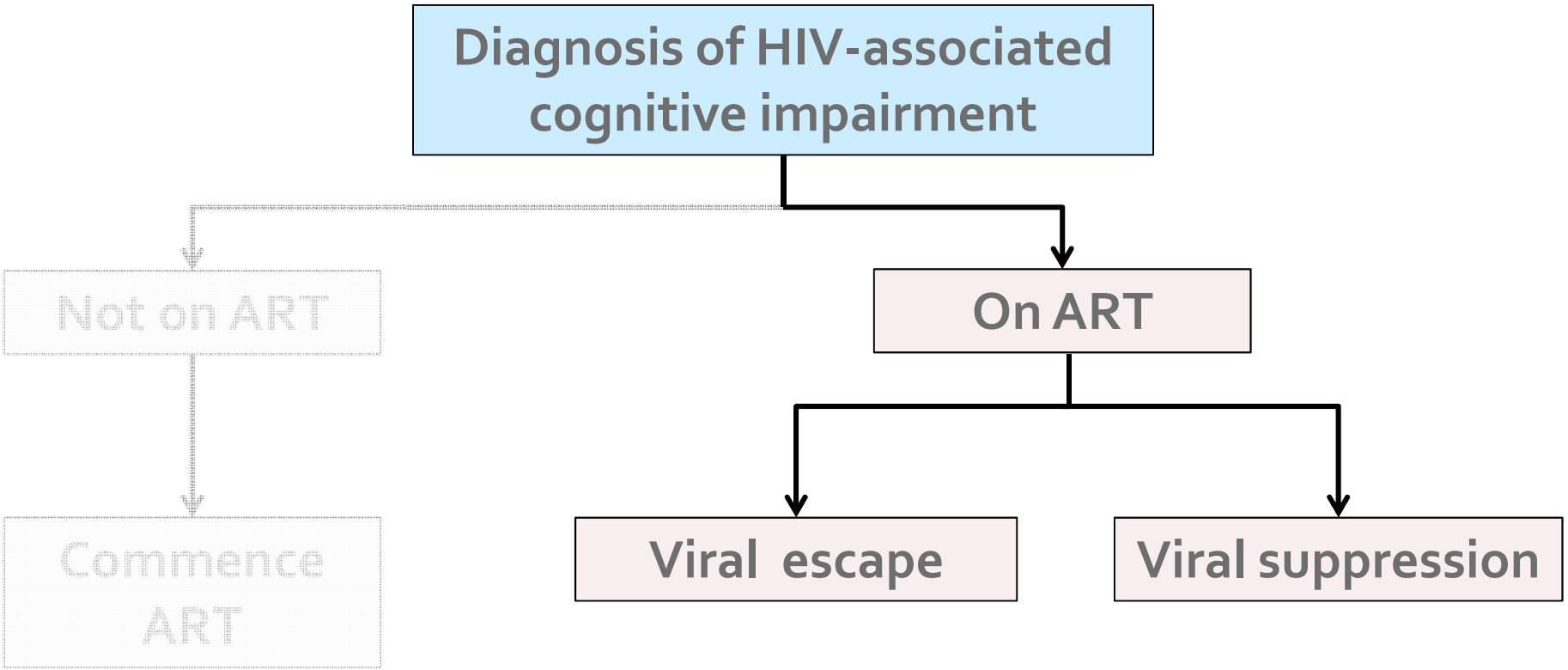


Neurology sub-study

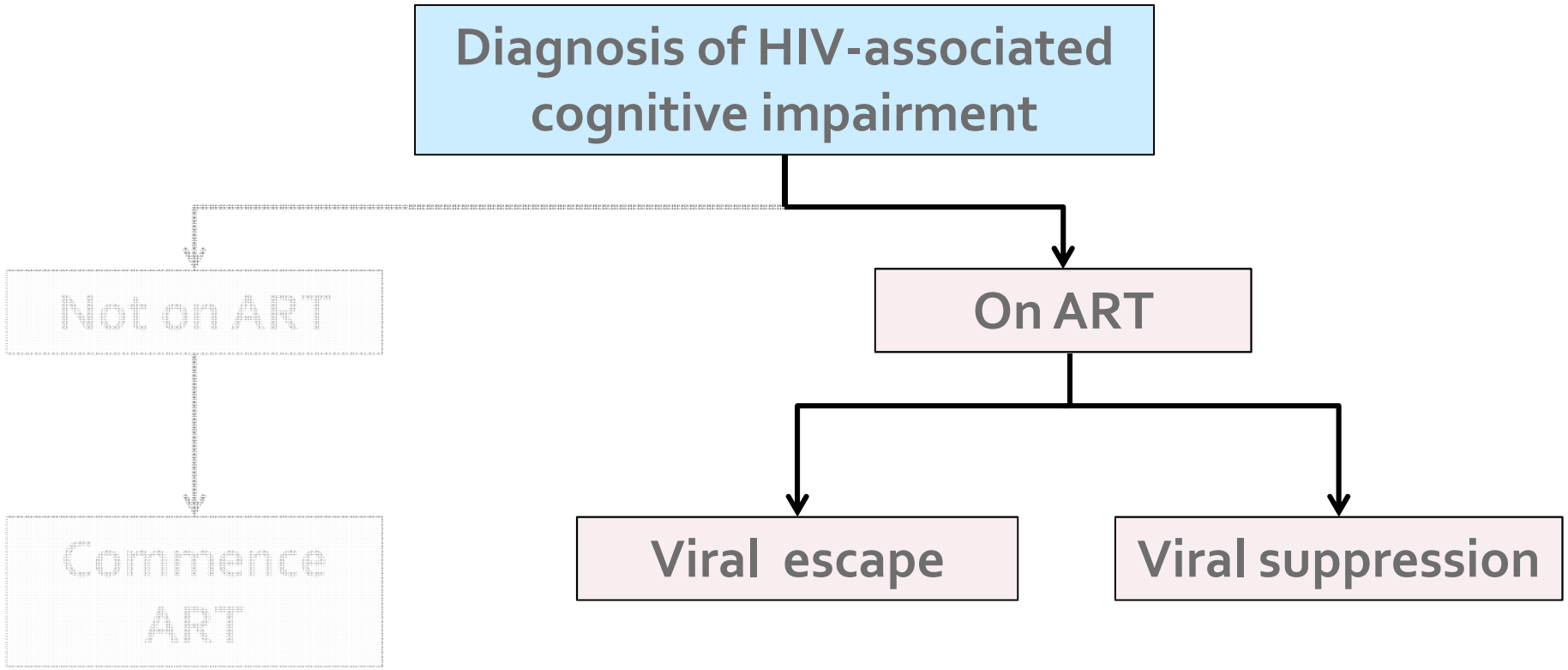
START

AIDS. 2011 Sep 10;25(14):1747-51

Management cognitive impairment



Management cognitive impairment



Viral escape

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Definition

- Lack of plasma virological suppression
- Lack of CSF virological suppression
  - Generally considered CSF HIV RNA 1log greater than plasma HIV RNA

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How common is this?

Asymptomatic subjects:

- 10-15% of subjects with suppressed plasma viraemia [1,2]
- 10% in those not on ART
- Higher rates if ultrasensitive assays used [3]
- Associated with markers of inflammation

Symptomatic subjects:

- Reported 20-100% subjects (depending on symptoms)
- Canestri syndrome [4]
- Resistance mutations well described in CSF when not apparent in the plasma compartment / resistance associated with lower plasma HIV RNA [5]

1. J Infect Dis. 2010 Dec 15;202(12):1819-25,
2. J Infect. 2012 Sep;65(3):239-45.
3. AIDS. 2014 Jul 14.
4 Clin Infect Dis. 2010 Mar 1;50(5):773-8
5 AIDS. 2010 Sep 24;24(15):2412-4.

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Management

- Optimise ART guided on current and historical plasma and CSF resistance testing

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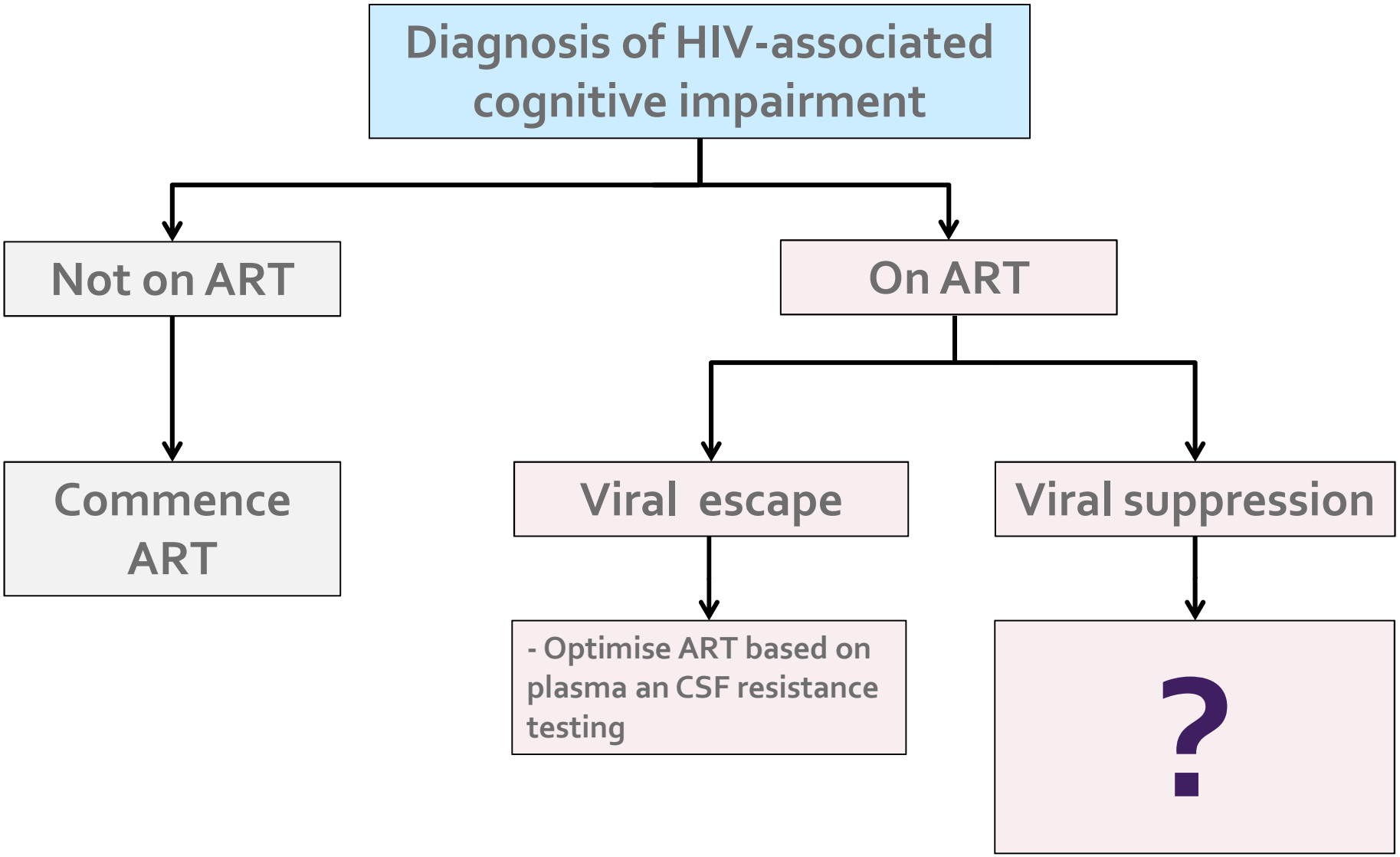

Management cognitive impairment

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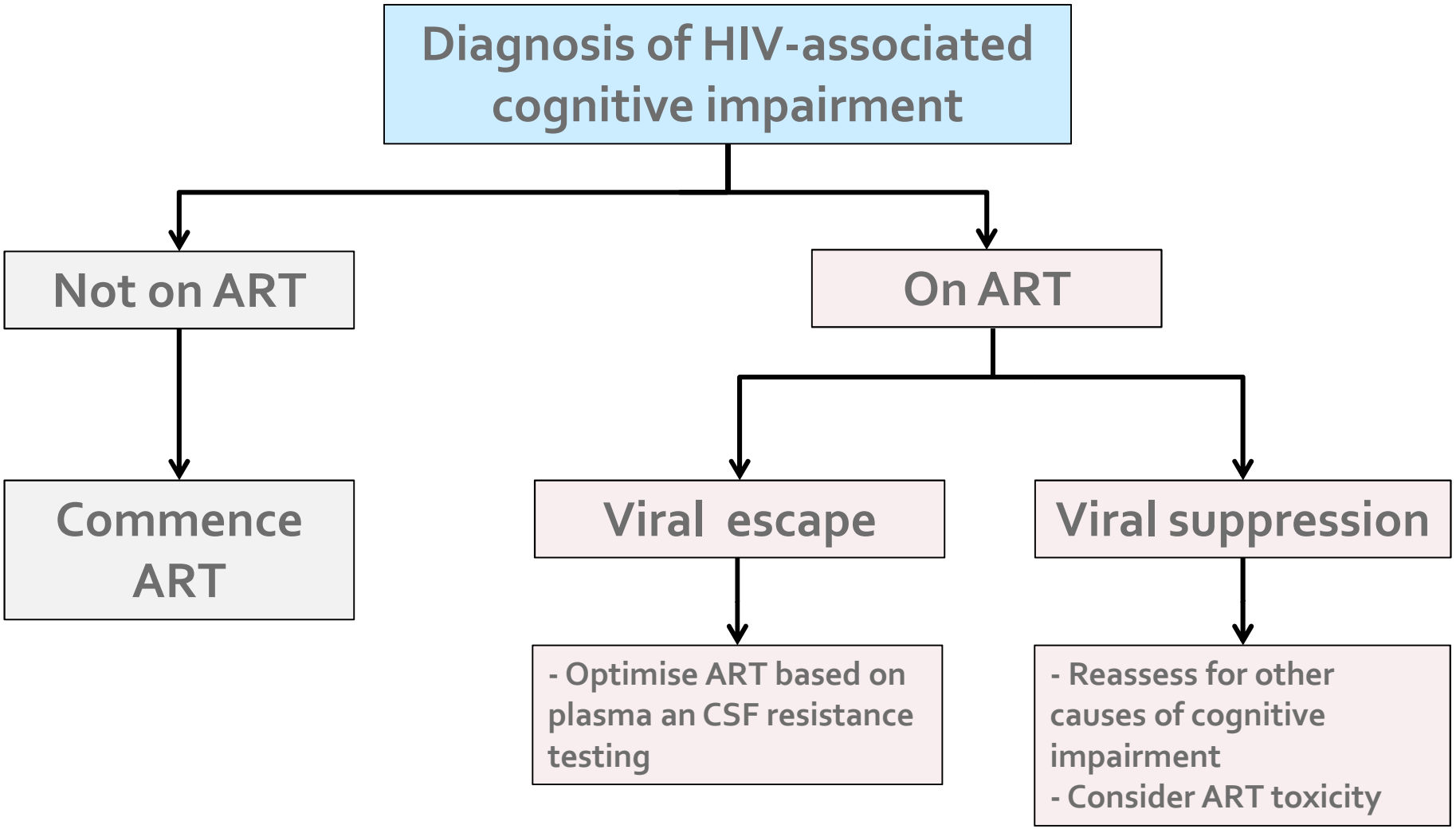

Cardiovascular risk factors

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SMART neurology substudy

- 292 patients
  - median CD4 536 cells/mm^3
  - 88% viral load <400 copies/mL
  - 92% on ARVs
- CVD and risk factors associated with poorer cognitive performance

Pathogenesis

- Underlying cerebral vascular disease
- Increased inflammatory responses

Factors	Population%	NCI	QNPZ-5	Z scores GPB
Age (per 10 years)		NS	NS	NS
Gender (female vs male)	41.7	NS	*P*=0.05 −0.21	NS
Race/ethnicity (black vs other)	19.7	*P*=0.08 2.25	*P*<0.001 −0.48	NS
Prior AIDS	20.7	*P*=0.08 0.41	*P*=0.05 0.24	–
Hepatitis B	2.1	–	*P*=0.05 −0.66	*P*=0.03 −1.05
Prior CVD	3.5	*P*=0.01 6.17	*P*=0.02 −0.65	*P*=0.06 −0.71
Blood pressure-lowering drugs	11.0	–	*P*=0.03 −0.37	–
Total cholesterol (per 10 mg/mL)		*P*=0.06 1.08	*P*=0.02 −0.03	–
HDL (per 10 mg/mL)		–	–	*P*=0.03 −0.11
Depression (CES-D ≥16)	23.8	–	*P*=0.07 −0.21	–

Wright EJ, et al. Neurology 2010;75:864–73

PET imaging – PK11195

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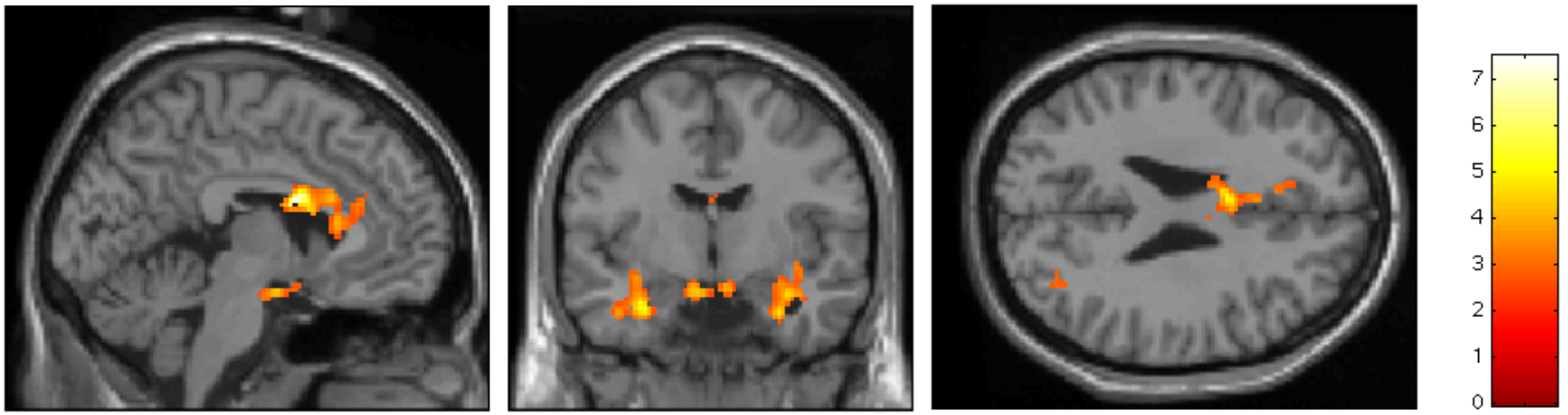
Subjects:
- HIV infected on cART
- Truly neuroasymptomatic

Increase binding PK11195 neuroasymptomatic HIV infection compared to HIV uninfected controls (n=7, 9)

		MNI coordinates			
Location of cluster	**Z-score**	**x**	**y**	**z**	**P-value**
L corpus callosum	4.61	-4	4	22	**0.001**
R anterior cingulate	3.28	6	12	10	**0.001**
R temporal lobe	5.60	26	0	-32	**0.001**
Posterior corpus callosum/ L posterior cingulate	3.90	-4	-56	2	**0.008**
L temporal lobe	3.83	-40	-2	-28	**0.026**
L frontal lobe	3.82	-12	4	-16	**0.038**



Garvey et al, AIDS. 2013 Jul 24

Efavirenz and cognitive function

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146 patients
129 (88.4%) were on cART
69 (47%) were classified as cognitively impaired
- 35.6% asymptomatic
- 11.6% mild neurocognitive impairment

Variable		β	OR	95% CI	P-value	β	OR	95% CI	P-value
		Univariate				Multivariate			
Gender	(male versus female)	0.25	0.78	(0.41–1.51)	0.466				
Age	per 10 years	0.26	0.77	(0.58–1.03)	0.078	0.19	0.83	(0.60–1.16)	0.296
Education	per year	0.12	0.89	(0.81–0.97)	**0.012**	0.16	0.85	(0.77–0.94)	**0.002**
Non-Italian born	versus Italian born	1.1	3.01	(1.09–8.35)	**0.034**	1.24	3.46	(1.09–10.99)	**0.035**
IVDU		0.13	1.14	(0.46–2.82)	0.78				
HCV		0.3	0.74	(0.33–1.69)	0.479				
Time since HIV diagnosis	per year	0.02	0.98	(0.93–1.03)	0.355				
AIDS defining illness		0.29	1.34	(0.64–2.81)	0.441				
CD4 nadir	per 100 cells	0.13	0.88	(0.69–1.12)	0.294				
Time on cART	per one year increase	0.02	1.02	(0.94–1.11)	0.639				
Efavirenz use		1.26	3.53	(1.37–9.08)	**0.009**	1.39	4	(1.43–11.20)	**0.008**
CPE rank	>7	0.45	1.43	(0.68–3.00)	0.346				
HIV RNA	per log increase	0.19	0.83	(0.58–1.19)	0.312				
HIV RNA < 50 copies/mL		0.64	1.9	(0.86–4.21)	0.114				
CD4 cell count	per 100 cell increase	0.05	0.96	(0.86–1.07)	0.42				

Neurology. 2011 Apr 19;76(16):1403-9

Interventional studies

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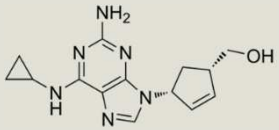
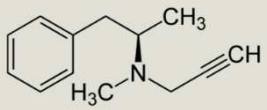
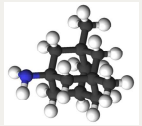
What not to do

Cognitive impairment Intervention	Mechanism of action	Outcome
Abacavir 	Antiretroviral intensification	**Failed** PLoS Clin Trials. 2007 Mar 30;2(3)
Lithium 	Reduce virus-induced neurodegeneration	**Failed** J Neurovirol. 2009;15(2):176-86
Selegeline 	Decrease oxidative stress	**Failed** Neurology. 2009; 8;73(23):1975-81
Memantine 	N-Methyl-D-aspartate (NMDA) receptor antagonist	**Failed** AIDS 2007, 21:1877–1886

ART intensification

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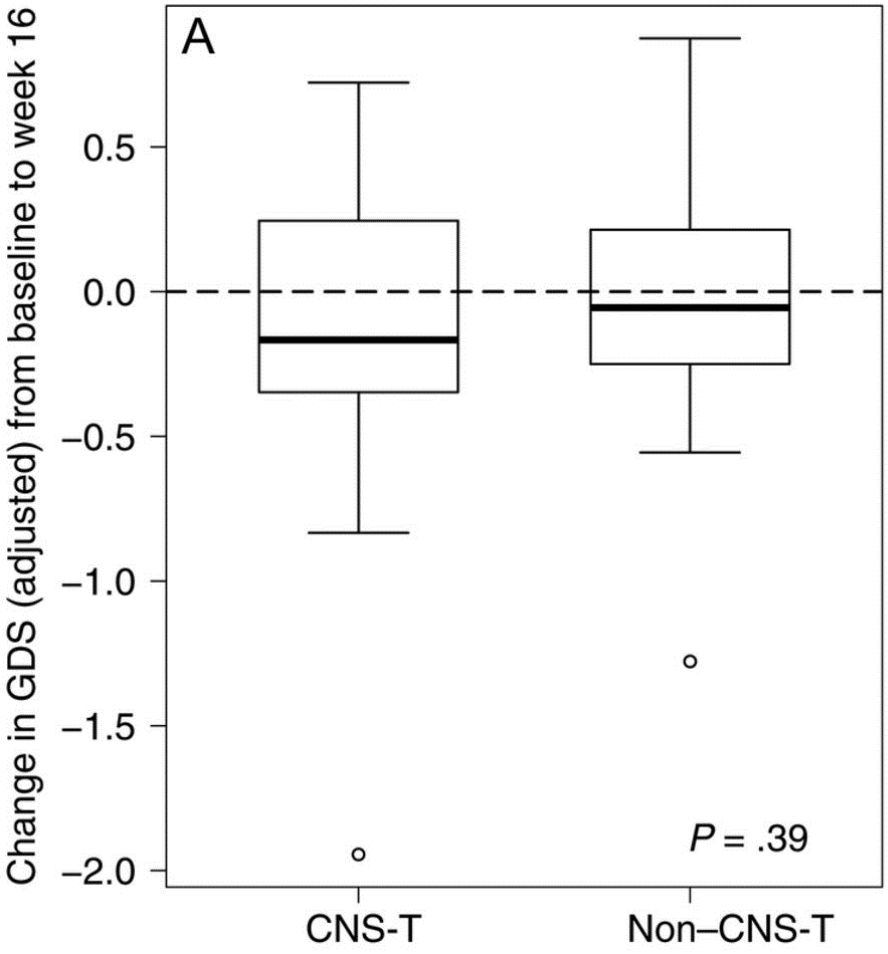

	CNS-T (n=26)	Non-CNS-T (n=23)	P-value
Plasma VL <50 (week 16)	54%	82%	0.065
CSF VL <50 (week 16)	68%	87%	0.17

What not to do

Clin Infect Dis. 2014 Jan 14

CPE score and outcome

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Hazard ratios for CPE score, HIV-CAUSAL Collaboration, 1998-2013

Event	CPE Score	Person-Years	Events	Unadjusted HR	95% CI	Adjusted HR	95% CI
HIV dementia							
	Low	128,302	115	1.00	(reference)	1.00	(reference)
	Medium	74,338	63	0.98	(0.71, 1.34)	1.04	(0.74, 1.47)
	High	31,137	32	1.41	(0.95, 2.10)	1.57	(1.01, 2.44)
Opportunistic Infections *							
	Low	127,904	221	1.00	(reference)	1.00	(reference)
	Medium	74,027	109	1.07	(0.85, 1.35)	0.97	(0.76, 1.24)
	High	31,035	45	1.13	(0.81, 1.56)	0.98	(0.69, 1.39)
Toxoplasmosis							
	Low	128,299	94	1.00	(reference)	1.00	(reference)
	Medium	74,347	34	0.84	(0.57, 1.25)	0.81	(0.53, 1.23)
	High	31,126	17	0.92	(0.54, 1.55)	0.85	(0.47, 1.52)
Cryptococcal meningitis							
	Low	128,385	61	1.00	(reference)	1.00	(reference)
	Medium	74,333	41	1.27	(0.85, 1.90)	0.97	(0.62, 1.50)
	High	31,153	15	1.34	(0.76, 2.37)	1.01	(0.56, 1.83)
Progressive multifocal leukoncephalopathy							
	Low	128,413	72	1.00	(reference)	1.00	(reference)
	Medium	74,358	36	1.16	(0.77, 1.74)	1.09	(0.71, 1.69)
	High	31,156	15	1.28	(0.72, 2.27)	1.16	(0.63, 2.15)

Neurology. 2014 Jul 8;83(2):134-41

Management cognitive impairment

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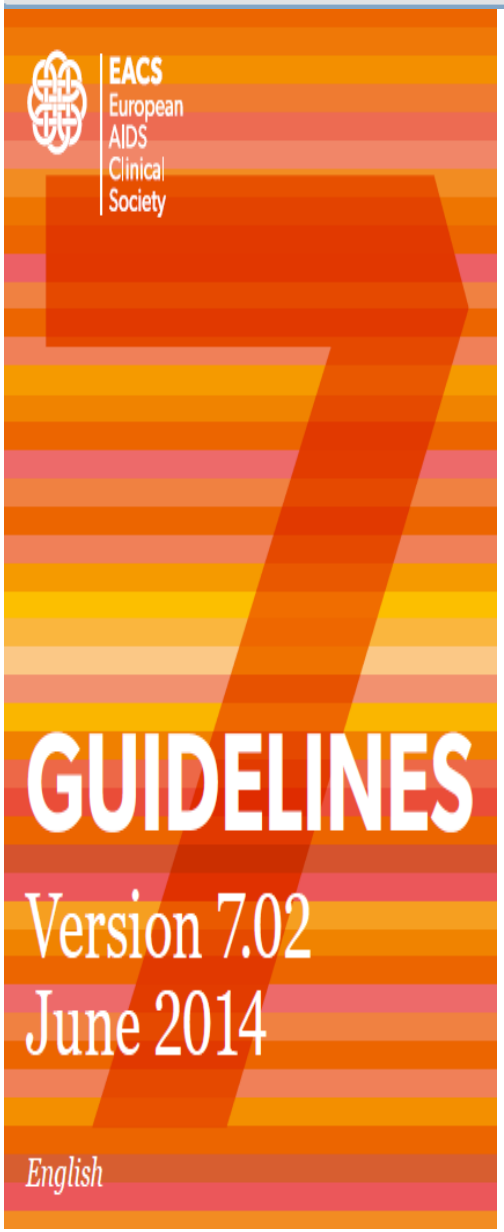

Diagnosis: **HIV-associated NCI**[vi]

- Off ART
  - Start ART (refer to general guidelines) Consider inclusion of potentially CNS-active drugs[ix]
- On ART
  - CSF viral escape[vii]
    - Optimise ART by CSF and plasma GDR testing[viii] Include potentially CNS-active drugs[ix]
    - Repeat CSF examination and other evaluations after ≥ 4 weeks
  - Other situations[viii]
    - Continue or switch ART (refer to general guidelines) Reconsider other causes of NCI

Thank you

- Paola Cinque, Milan, Italy
- Renaud du Pasquier, Lausanne, Switzerland

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Questions: