

# HIV-associated cognitive impairment in The Netherlands

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# Overview

- Background information / historical overview on HAND
- Current research in The Netherlands focussing on HAND
  - AGE<sub>h</sub>IV Cohort Study
- Results
- COBRA collaboration

# Background information

Pre-cART era:

- One third of patients → severe cognitive and motor impairment
- Clinical syndrome characterized by Price and Navia in 1986 and termed AIDS Dementia Complex (ADC)
- ADC affected three areas of functioning:
  - 1) cognition (slowness, attention/memory deficits)
  - 2) motor function (slowness, loss of balance)
  - 3) behaviour (apathy, social withdrawal, mood changes)

# Background information

Post-cART era:

- cART very effectively inhibits viral replication
- ADC (or HIV Associated Dementia, HAD) became a rare complication of HIV infection
- Late presenters, poor adherence

**Problem solved?**

# Problem solved?

- Many patients still complain about slowness, memory deficits, problems in concentration, planning, multi-tasking
- Complaints seem to be rather mild

# Published results

Various research groups investigated this issue:

# Published results

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[J Neurovirol](#). 2004 Dec;10(6):350-7.

**Prevalence and pattern of neuropsychological impairment in human immunodeficiency virus-infected/acquired immunodeficiency syndrome (HIV/AIDS) patients across pre- and post-highly active antiretroviral therapy eras: a combined study of two cohorts.**

[Cysique LA](#)<sup>1</sup>, [Maruff P](#), [Brew BJ](#).

[Neurology](#). 2010 Dec 7;75(23):2087-96. doi: 10.1212/WNL.0b013e318200d727.

**HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study.**

[Heaton RK](#)<sup>1</sup>, [Clifford DB](#), [Franklin DR Jr](#), [Woods SP](#), [Ake C](#), [Vaida F](#), [Ellis RJ](#), [Letendre SL](#), [Marcotte TD](#), [Atkinson JH](#), [Rivera-Mindt M](#), [Vigil OR](#), [Taylor MJ](#), [Collier AC](#), [Marra CM](#), [Gelman BB](#), [McArthur JC](#), [Morgello S](#), [Simpson DM](#), [McCutchan JA](#), [Abramson I](#), [Gamst A](#), [Fennema-Notestine C](#), [Jernigan TL](#), [Wong J](#), [Grant I](#); CHARTER Group.

[AIDS](#). 2010 Jun 1;24(9):1243-50. doi: 10.1097/QAD.0b013e3283354a7b.

**Cognitive dysfunction in HIV patients despite long-standing suppression of viremia.**

[Simioni S](#)<sup>1</sup>, [Cavassini M](#), [Annoni JM](#), [Rimbault Abraham A](#), [Bourquin I](#), [Schiffer V](#), [Calmy A](#), [Chave JP](#), [Giacobini E](#), [Hirschel B](#), [Du Pasquier RA](#).

[AIDS](#). 2004 Jan 1;18 Suppl 1:S11-8.

**Prevalence of cognitive disorders differs as a function of age in HIV virus infection.**

[Becker JT](#)<sup>1</sup>, [Lopez OL](#), [Dew MA](#), [Aizenstein HJ](#).



# Published results

Publications summarized:

- HIV Associated Dementia: rare
- Milder forms of cognitive impairment: quite prevalent
- Prevalence of mild cognitive impairment: 15-60%

# Frascati criteria

- To classify this broadening clinical spectrum of cognitive impairment a new terminology/classification was developed

**Updated research nosology for HIV-associated neurocognitive disorders**

A. Antinori, G. Arendt, J. T. Becker, B. J. Brew, D. A. Byrd, M. Cherner, D. B. Clifford, P. Cinque, L. G. Epstein, K. Goodkin, M. Gisslen, I. Grant, R. K. Heaton, J. Joseph, K. Marder, C. M. Marra, J. C. McArthur, M. Nunn, R. W. Price, L. Pulliam, K. R. Robertson, N. Sacktor, V. Valcour and V. E. Wojna

*Neurology* 2007;69;1789-1799; originally published online Oct 3, 2007;

DOI: 10.1212/01.WNL.0000287431.88658.8b

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- As these criteria were developed during an expert meeting in Frascati, they are often referred to as the Frascati criteria

# Frascati criteria

## HAND

- HIV Associated Neurocognitive Disorder
- Umbrella definition comprising 3 subtypes



- 1) ANI = Asymptomatic Neurocognitive Impairment
  - No interference with daily activities
- 2) MND = Mild Neurocognitive Disorder
  - Mild interference with daily activities
- 3) HAD = HIV Associated Dementia
  - Severe interference with daily activities

# Many unanswered questions remain

- What is the optimal manner to diagnose HIV-associated cognitive impairment?
  - Are the Frascati criteria sufficient or probably oversensitive?
  - What is the clinical relevance of ANI?
- What is the “actual” prevalence of HIV-associated cognitive impairment?
- Most cohorts lack a comparable HIV-uninfected control group
  - What is the effect of HIV/ART?
  - What is the effect of lifestyle factors?

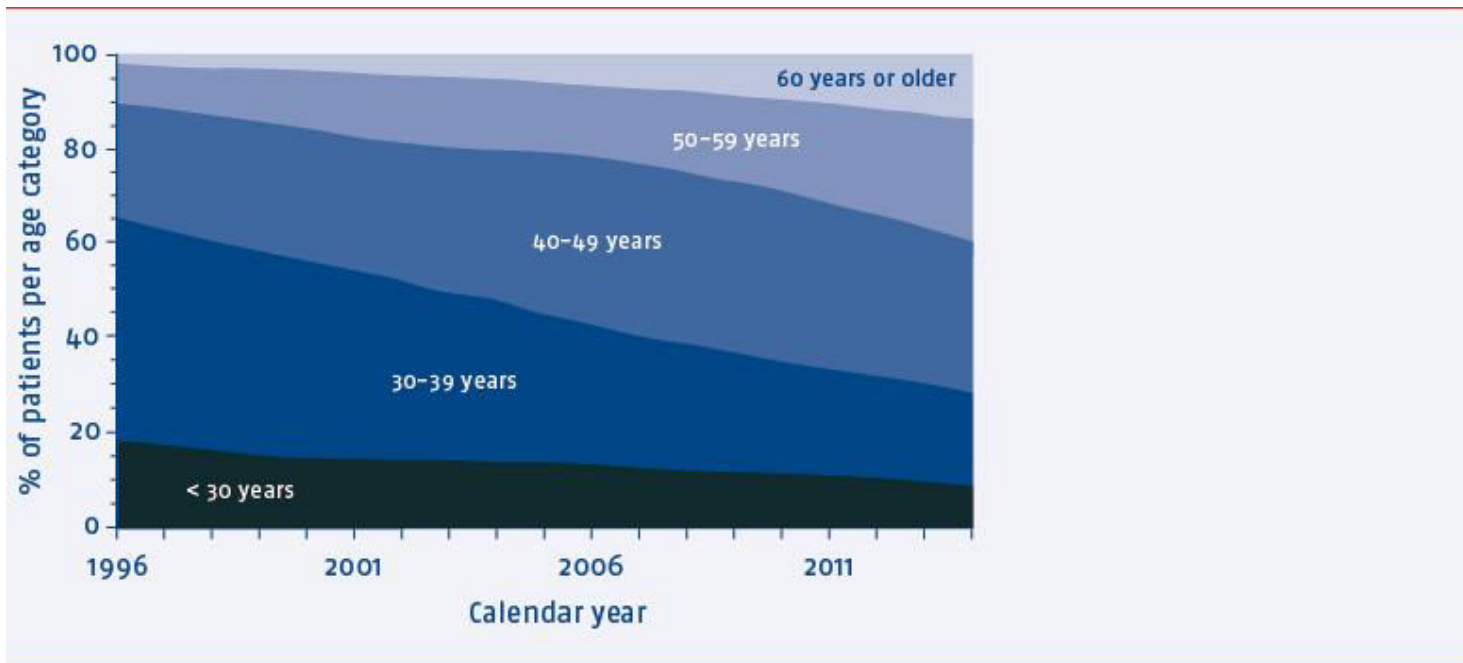
# HIV-associated cognitive impairment in The Netherlands

- Started cohort study focussing on HAND in 2011
- Nested substudy within the larger AGE<sub>h</sub>IV Cohort Study



# HIV infection in The Netherlands

- 18.000 HIV-infected individuals in care
- +/- 1.000 new diagnoses every year
- 40% of the HIV-infected population in care in Amsterdam
- 3.000 patients in care at the Academic Medical Center



# AGE<sub>h</sub>IV Cohort Study



- Prospective cohort study (enrolment started in 2010)
- Investigates prevalence, incidence and risk factors of ageing-associated comorbidities and organ dysfunction
  
- HIV-infected individuals (n=598)
  - HIV outpatient clinic at the Academic Medical Center (Amsterdam)
- HIV-uninfected individuals (n=550)
  - Sexual health clinic at the Municipal Health Services of Amsterdam
  - From the ongoing Amsterdam Cohort Studies (gay men cohort)



# AGE<sub>h</sub>IV Cohort Study



- Inclusion criteria:
  - $\geq 45$  years of age
  - Laboratory confirmed presence or absence of HIV-infection
- All participants undergo an extensive study visit every 2 years
  - Length, weight, hip/waist circumference
  - Blood pressure, ECG, arterial stiffness
  - Cognitive screening instruments (MMSE, HDS)
  - Frailty
  - Spirometry
  - Bone density (DXA scan)
  - Extensive laboratory measurements
  - Immunology analysis
  - Questionnaire (mood, quality of life, intoxications, work/income, etc)

# Cognitive nested substudy



- Inclusion criteria:
  - Male gender
  - Sustained suppression of HIV viremia on ART (plasma HIV-RNA <40 copies/mL  $\geq$  12 months)
- Exclusion criteria:
  - History of severe neurological disorder or traumatic brain injury
  - Current/past (HIV-associated) CNS infection or tumour
  - Current severe psychiatric disorder
  - Current IV drug use
  - Daily use of illicit drugs (except daily cannabis use)
  - Current excessive alcohol consumption (>48 units/week)
  - Insufficient command of the Dutch language
  - Mental retardation

# Study procedures (baseline and after 2 years)

- Full neuropsychological assessment (NPA)
  - Six cognitive domains (fluency, attention, information processing speed, executive function, memory, and motor function)
- Detailed neuroimaging
  - MRI, MR spectroscopy, DTI
- Lumbar puncture (CSF analysis)
  - Inflammation, viral replication, neuronal damage, ART
- Retinal analysis
  - CT measuring retinal structure and thinning

# Baseline characteristics

<i>Data presented as % or median (IQR)</i>	<b>HIV-positives (n=103)</b>	<b>HIV-negatives (n=74)</b>	<b>P-value</b>
Age (years)	52.8 (48.0-60.8)	53.3 (49.0-60.7)	0.65
Men having sex with men (MSM)	93.2%	90.4%	0.50
Dutch origin	86.4%	89.0%	0.60
Education (ISCED level)*	6 (5-6)	6 (5-6)	0.43
Premorbid intelligence (IQ)	102 (95-111)	103 (97-112)	0.29
Depressive symptoms (BDI score)#	4 (2-8)	3 (1-5)	0.09

\* Educational level was defined using the International Standard Classification of Education (ISCED) 2011.

# Depressive symptoms were assessed using the Beck Depression Inventory (BDI).

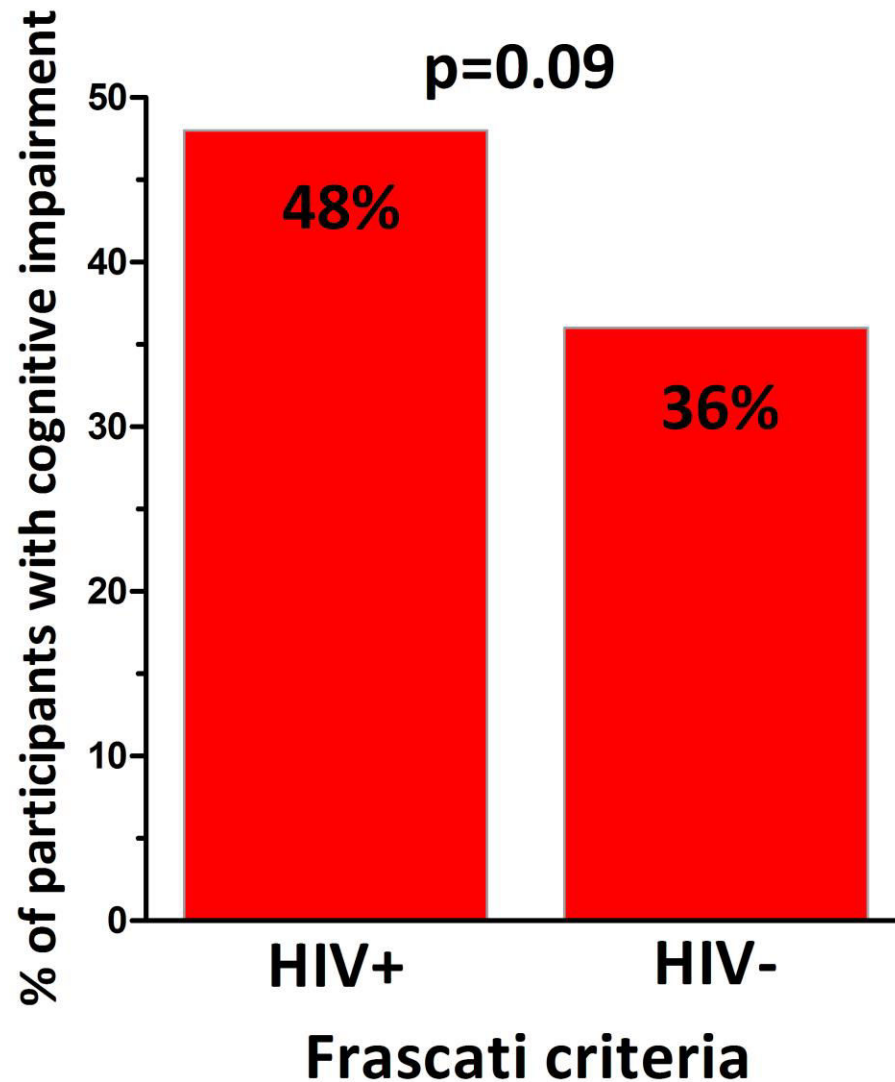
## HIV-related characteristics

<i>Data presented as % or median (IQR)</i>	<b>HIV-positives (n=103)</b>
Known duration of HIV-infection (years)	13.5 (7.4-17.1)
CD4 count at enrolment (cells/mm <sup>3</sup> )	625 (475-800)
Nadir CD4 count (cells/mm <sup>3</sup> )	170 (60-250)
Duration undetectable viral load (years)	8.3 (3.5-11.2)
Duration since start of first ART (years)	11.6 (4.9-14.9)
ART-naïve at start cART	79.6%
Prior AIDS	35.0%
HCV co-infection	0%

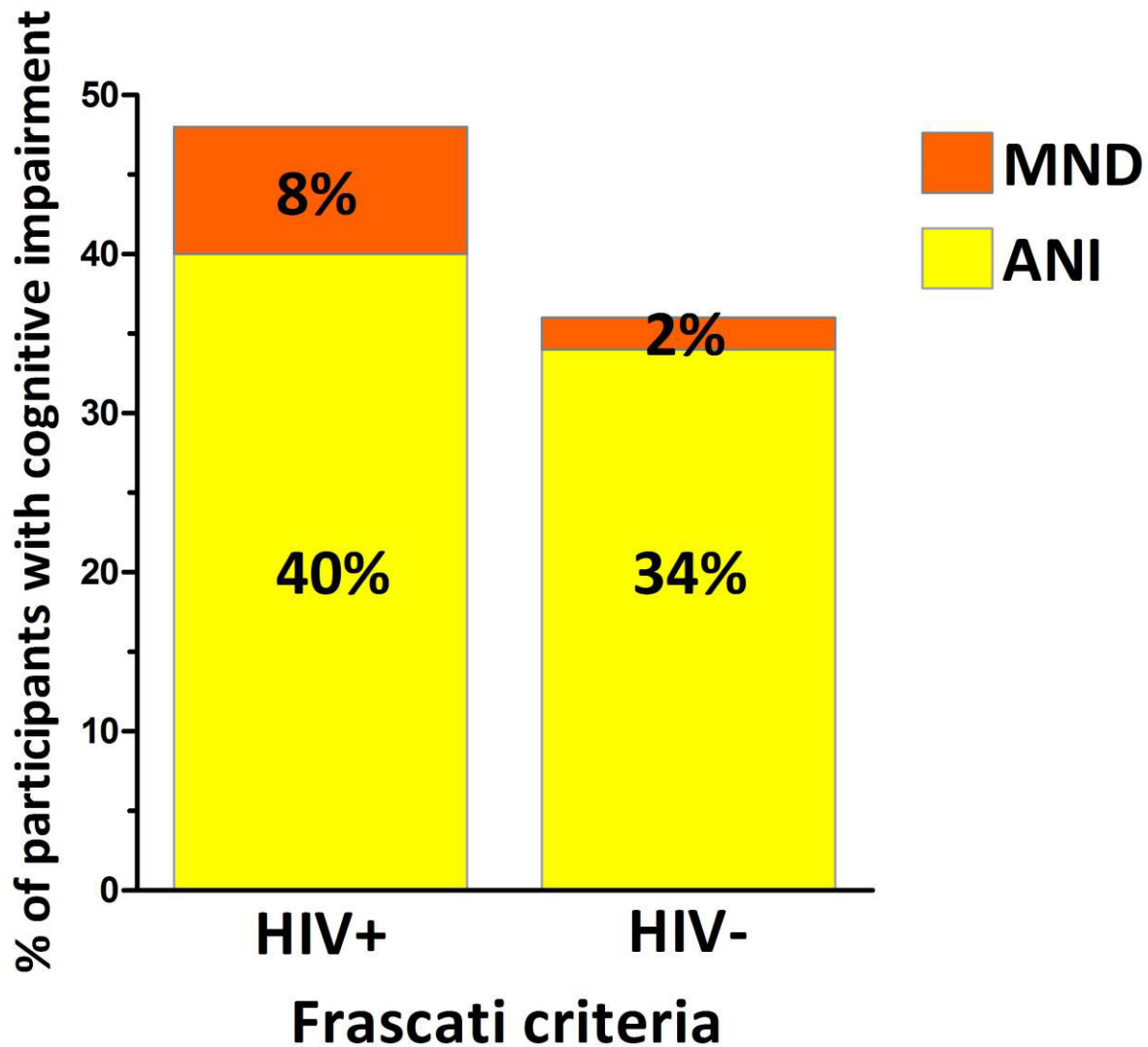
## Lifestyle-related characteristics

<i>Data presented as % or median (IQR)</i>	<b>HIV-positives (n=103)</b>	<b>HIV-negatives (n=74)</b>	<b>P- value</b>
Daily to monthly use of ecstasy	1.9%	12.3%	0.01
Daily to monthly use of cocaine	3.9%	4.1%	1.00
Daily to monthly use of cannabis	15.5%	15.1%	1.00
Alcohol intake (units per week)	6 (2-14)	5 (3-12)	0.86
Currently smoking	30.1%	19.2%	0.10

# Cognitive impairment by Frascati criteria



# Cognitive impairment by Frascati criteria





# Interpretation

- CI by Frascati criteria is highly prevalent among HIV-infected participants, but nearly equally so in HIV-uninfected participants
- High false-positive rate

# Shortcomings Frascati criteria

## Shortcoming no.1:

- Score  $<1$  SD below the normative mean is used for the diagnosis ANI/MND
- Normally distributed test scores, 16% of the normal population will perform 1 SD below the mean for a certain test
- Threshold for abnormality too low?

# Shortcomings Frascati criteria

Shortcoming no.2:

- Multiple tests are performed during the NPA
- Multiple tests → chances increase for an erroneously abnormal result (false positive result)
- Familywise error
  
- Frascati criteria do not dictate how to handle multiple testing (different interpretations by different studies)

# Multivariate normative comparison (MNC)

Novel mathematical method specifically designed to control false-positive rate while retaining sensitivity

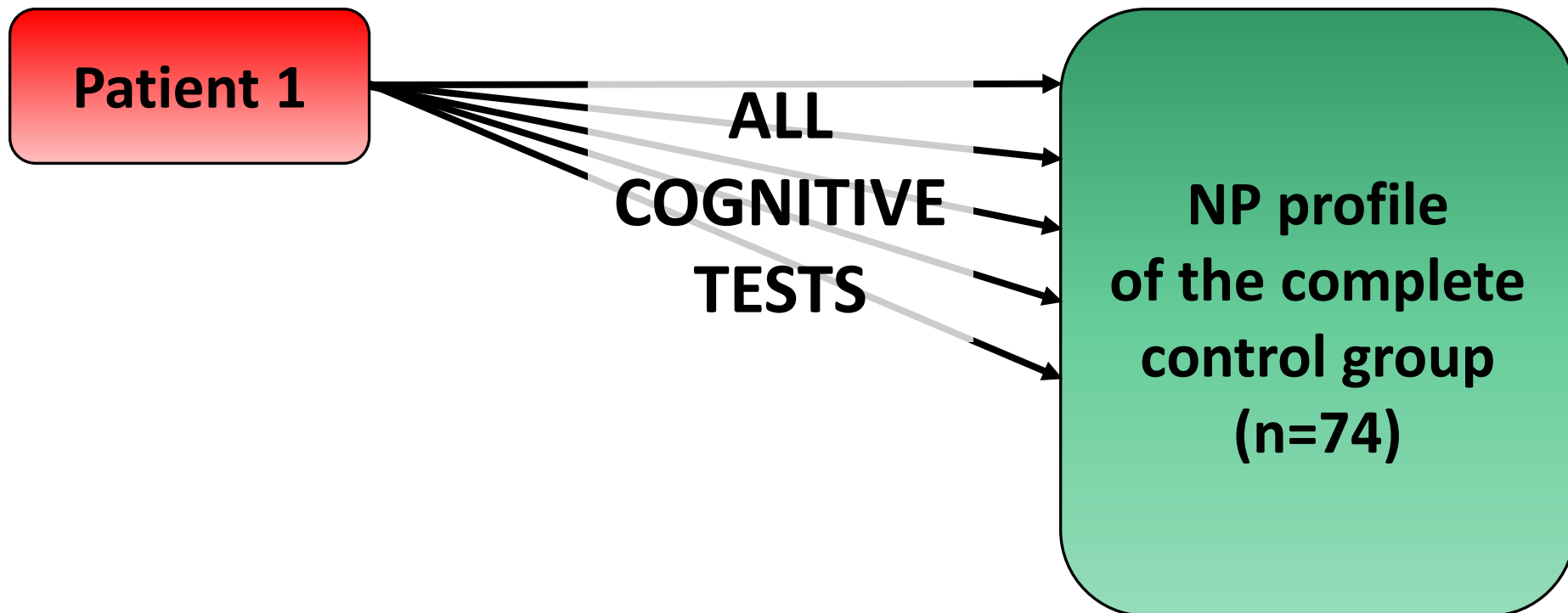
# Multivariate normative comparison (MNC)

Novel mathematical method specifically designed to control false-positive rate while retaining sensitivity

**NP profile  
of the complete  
control group  
(n=74)**

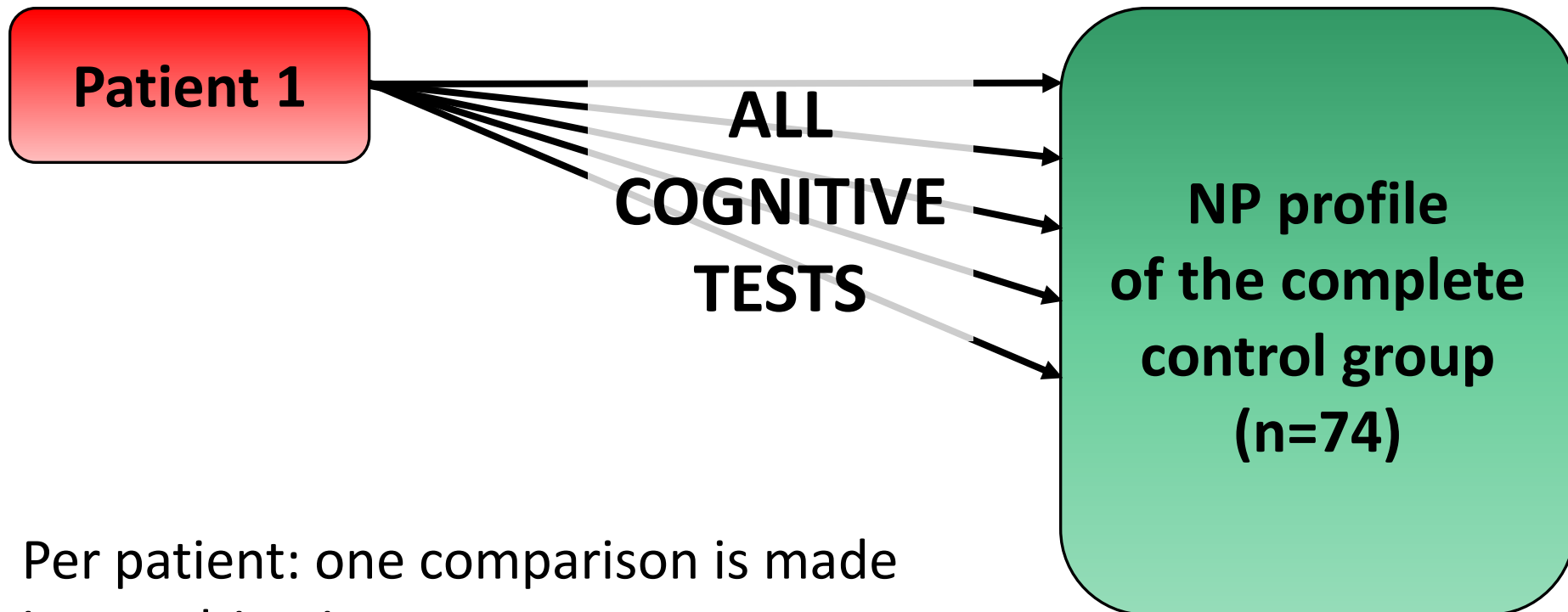
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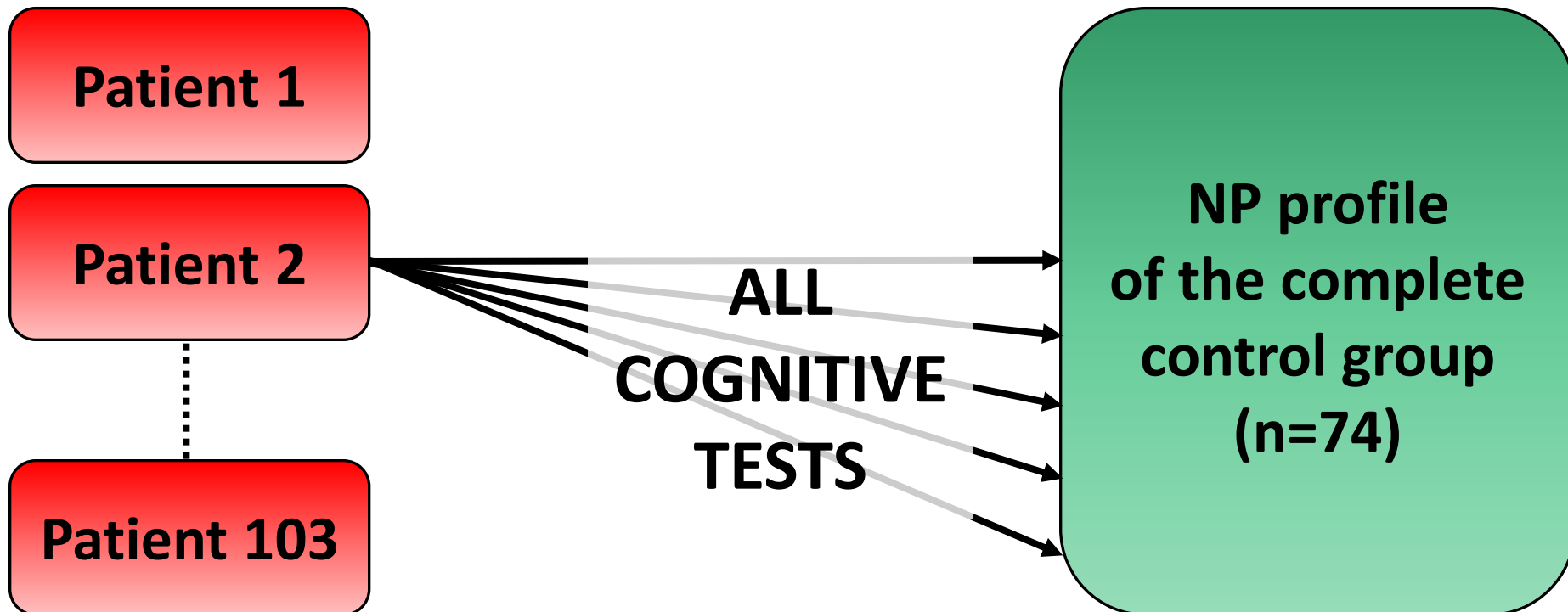
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Per patient: one comparison is made in a multivariate manner

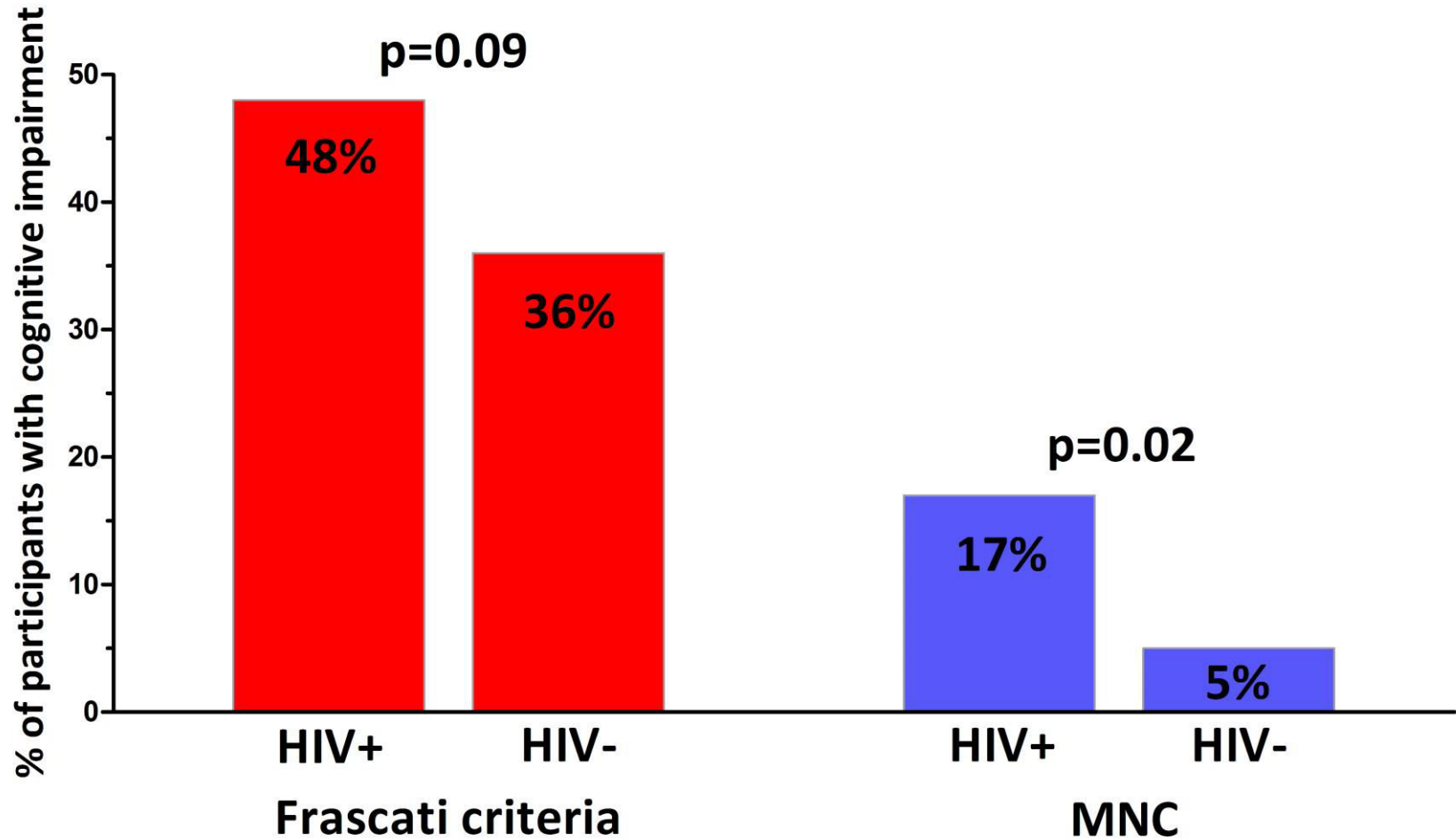
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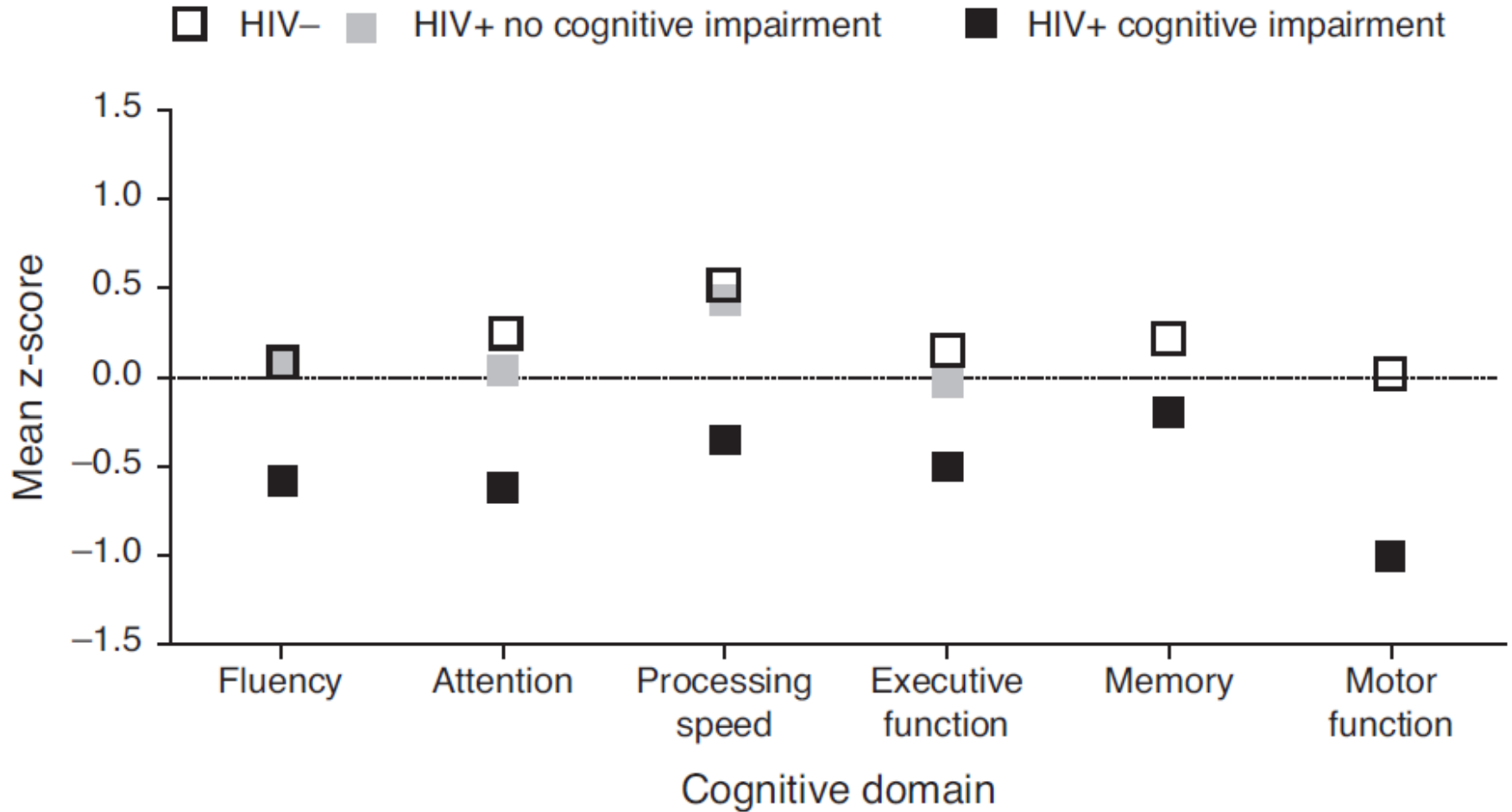




# Cognitive impairment by MNC



# Results of the different cognitive domains



# Interpretation

- MNC reduces the false-positive rate
- MNC is able to detect deviations in *patterns* from the norm
- Cognitive impairment seems mild, with subtle abnormalities across a broad range of cognitive domains

*Su T, Schouten J, Geurtsen GJ et al. AIDS 2015. Multivariate normative comparison, a novel method for more reliably detecting cognitive impairment in HIV infection*

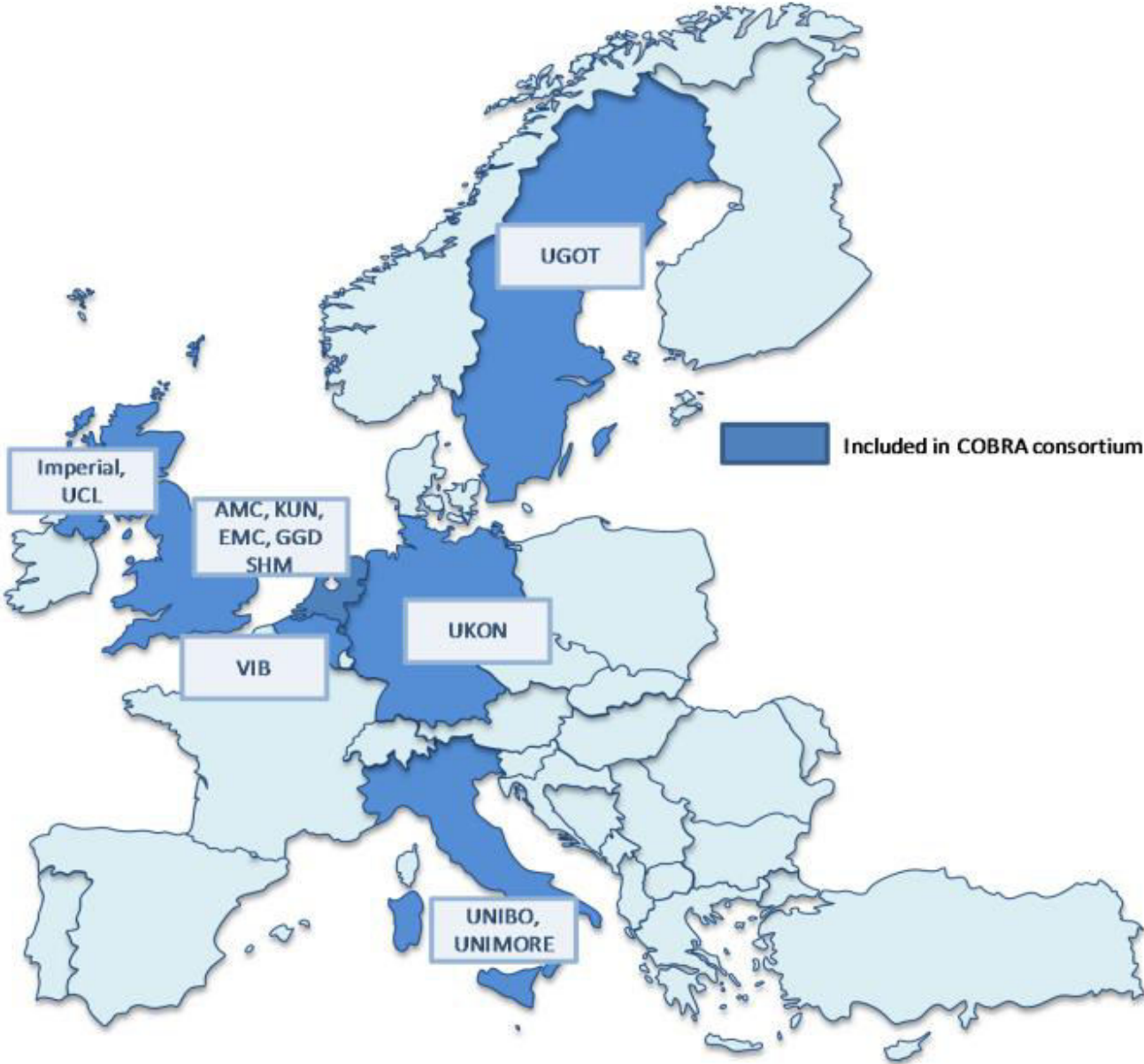
# COBRA collaboration



- During enrolment of the nested cognitive substudy a collaboration was started with various European partners
- Co-morbidity in relation to AIDS (COBRA)
- Focusses further on age-associated non-AIDS comorbidity
- Specifically on cognitive dysfunction / cerebral damage
- Funded by the EU FP7 Programme



# COBRA consortium



# COBRA study

## Clinical part:

- Two clinical cohorts (n=125 in A'dam / n=125 London)
- Recruited from AGE<sub>h</sub>IV Cohort and Poppy Study
- Detailed neuroimaging
- Neuropsychological assessment (cognitive function)



## Biomarkers:

- Biomarkers analysis (on plasma and cerebrospinal fluid)
- Use of most promising biomarkers of aging coming out of MARK-AGE

## Mouse models:

- Humanized immune system mouse model of HIV infection



# Age<sub>h</sub>IV Study Team



## Academic Medical Center

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## Amsterdam Institute of Global Health and Development

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Abbott

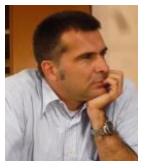
Janssen Pharmaceuticals

Merck & Co

Bristol Myers Squibb







# All our study participants



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