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$_h$IV Cohort Study

• Results

• COBRA collaboration
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:
Various research groups investigated this issue:


Cysique LA¹, Maruff P, Brew BJ.


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


**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 S¹, Cavassini M, Annoni JM, Rimbault Abraham A, Bourquin I, Schiffer V, Calmy A, Chave JP, Giacobini E, Hirschel B, Du Pasquier RA.


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

Becker JT¹, 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.
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
Neurology 2007;69;1789-1799; originally published online Oct 3, 2007;
DOI: 10.1212/01.WNL.0000287431.88658.8b

• 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_hIV 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\textsubscript{h}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_{h}IV Cohort Study

• Inclusion criteria:
  o ≥ 45 years of age
  o Laboratory confirmed presence or absence of HIV-infection

• All participants undergo an extensive study visit every 2 years
  o Length, weight, hip/waist circumference
  o Blood pressure, ECG, arterial stiffness
  o Cognitive screening instruments (MMSE, HDS)
  o Frailty
  o Spirometry
  o Bone density (DXA scan)
  o Extensive laboratory measurements
  o Immunology analysis
  o Questionnaire (mood, quality of life, intoxications, work/income, etc)
Cognitive nested substudy

• Inclusion criteria:
  o Male gender
  o Sustained suppression of HIV viremia on ART (plasma HIV-RNA <40 copies/mL ≥ 12 months)

• Exclusion criteria:
  o History of severe neurological disorder or traumatic brain injury
  o Current/past (HIV-associated) CNS infection or tumour
  o Current severe psychiatric disorder
  o Current IV drug use
  o Daily use of illicit drugs (except daily cannabis use)
  o Current excessive alcohol consumption (>48 units/week)
  o Insufficient command of the Dutch language
  o Mental retardation
Study procedures (baseline and after 2 years)

• Full neuropsychological assessment (NPA)
  o Six cognitive domains (fluency, attention, information processing speed, executive function, memory, and motor function)

• Detailed neuroimaging
  o MRI, MR spectroscopy, DTI

• Lumbar puncture (CSF analysis)
  o Inflammation, viral replication, neuronal damage, ART

• Retinal analysis
  o CT measuring retinal structure and thinning
## Baseline characteristics

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

* 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

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

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

![Graph showing cognitive impairment percentages](image)

- **HIV+** subgroup: 48%
- **HIV-** subgroup: 36%

**p = 0.09**
Cognitive impairment by Frascati criteria

- HIV+: 8% MND, 40% ANI
- HIV-: 2% MND, 34% ANI
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)
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)
- ALL COGNITIVE TESTS
- Patient 1
Multivariate normative comparison (MNC)

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

Per patient: one comparison is made in a multivariate manner

Patient 1

ALL COGNITIVE TESTS

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

Patient 1

Patient 2

Patient 103

ALL COGNITIVE TESTS
Cognitive impairment by MNC

![Chart showing the percentage of participants with cognitive impairment by HIV status and MNC criteria.]

- **HIV+ with Frascati criteria**: 48%
- **HIV+ with MNC**: 17%
- **HIV- with Frascati criteria**: 36%
- **HIV- with MNC**: 5%

**Statistical significance**:
- **Frascati criteria**: p=0.09
- **MNC**: p=0.02
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

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

Included in COBRA consortium:
- Imperial, UCL
- AMC, KUN, EMC, GGD SHM
- VIB
- UKON
- UNIBO, UNIMORE
COBRA study

Clinical part:
• Two clinical cohorts (n=125 in A’dam / n=125 London)
• Recruited from AGEnhIV 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_hIV Study Team

### Academic Medical Center
- P. Reiss (PI)
- F.W. Wit
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- J. Schouten
- K. Kooij
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- S. Moll
- A. van Roosmalen
- G.R. Visser

### HIV Monitoring Foundation
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- S. Zaheri
- Y.M. Ruijs
- L. Gras
- A. Kesselring

### Amsterdam Institute of Global Health and Development
- M. Heidenrijk
- R. Meester
- F. Janssen

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- ViiV Healthcare
- Abbott
- Janssen Pharmaceuticals
- Merck & Co
- Bristol Myers Squibb
All our study participants

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cohort study

ZonMw

Aids Fonds

GILEAD

ViiV

Bristol-Myers Squibb

Janssen

MERCK