

## **APPENDIX D – Training material**

D:A:D

# D:A:D Study Teaching Material

“Data Collection of Adverse events of anti-HIV Drugs”  
(D:A:D) study

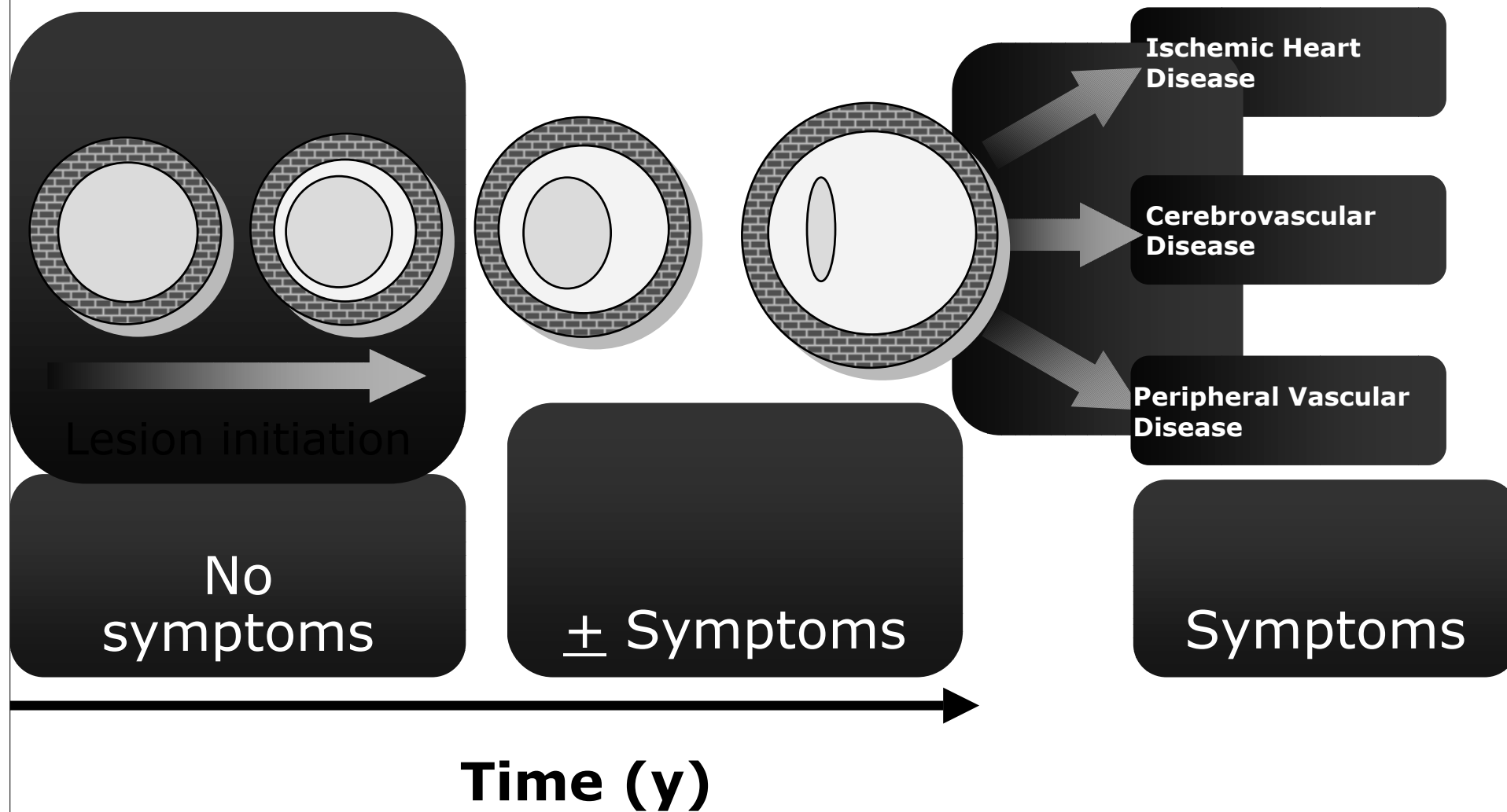
D:A:D

## Background

- Combination ART (CART) is associated with dyslipidaemia, insulin resistance, abnormal body fat distribution
- The D:A:D Study, initiated in 1999 as part of EMEA initiative, aims to assess whether exposure to CART is associated with an increased risk of myocardial infarction (MI)
  - Definition of CART: NNRTI and/or PI in combination with NRTI

D:A:D

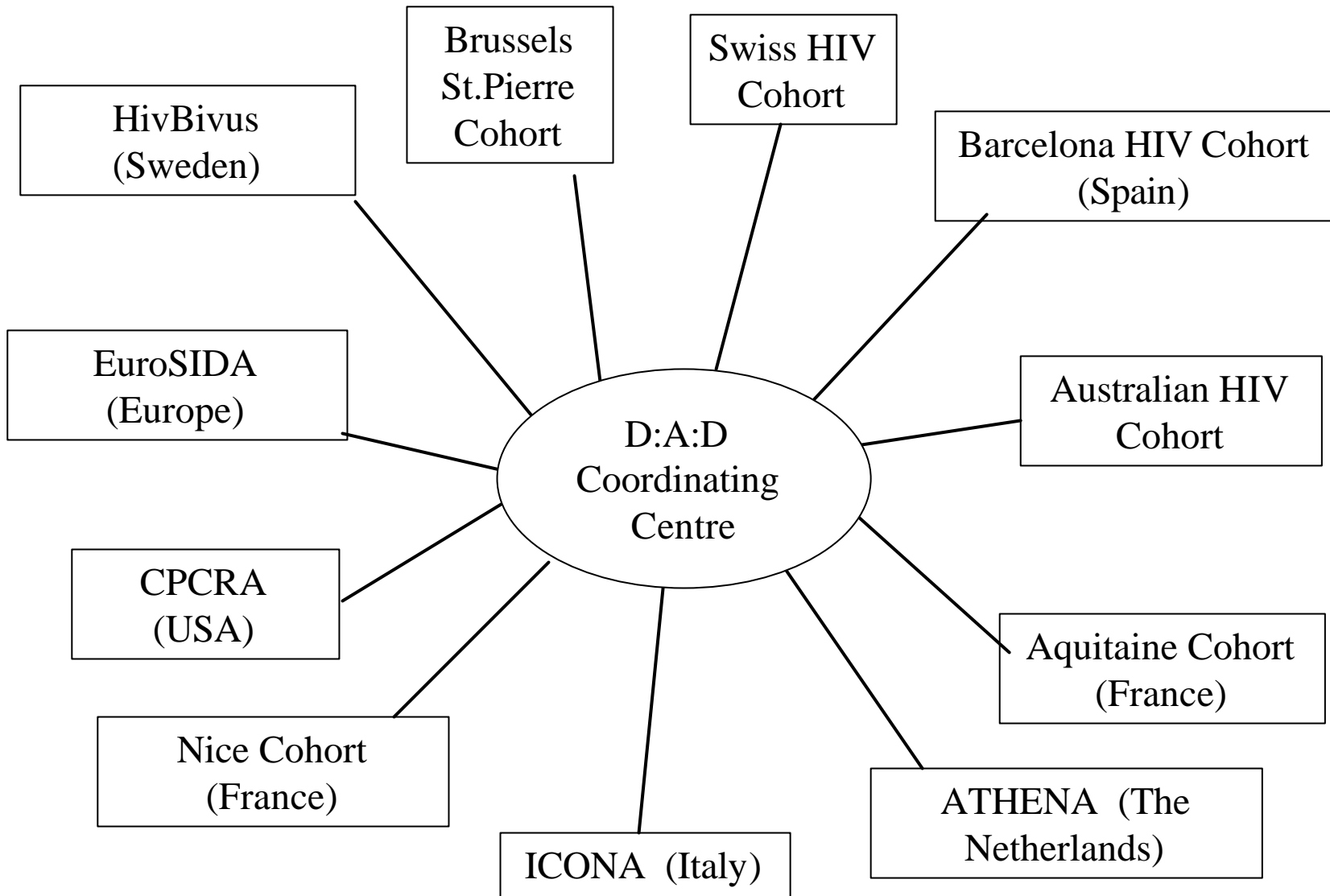
## Schematic Time Course of Human Atherogenesis



D:A:D

## Methods

- Prospective, multinational cohort study  
11 cohorts from Europe, Australia and USA
  - All patients under follow-up included – regardless of ART-status (n=23,468)
    - Included from 12/1999-4/2001
- DAD Cohort II (n=12,000) included 5/2001-2/2004
- Information collected: HIV-related and ART, risk and occurrence of CVD and diabetes mellitus



N=35,000+

D:A:D

D:A:D

## D:A:D events

### Primary:

- Myocardial Infarction (MI)

### Other Endpoints:

- Stroke
- Invasive Cardiovascular procedures
- Diabetes
- Death (all causes – now CoDe)
- All events are reported 'real time' to the DAD Study Coordinating Office at CHIP
- Reimbursement of 200 US\$ per form
- Event reporting forms at: [www.cphiv.dk](http://www.cphiv.dk)

D:A:D

## CoDe – Coding Causes of Death

The goal of the CoDe Project is to develop a uniform coding system that can be applied universally to studies of individuals with HIV infection, including:

- a detailed data collection
- a centralised review process

The data collection on causes of death in D:A:D has changed to implement CoDe

Protocol, forms and instructions are available at:  
[www.cphiv.dk/CoDe](http://www.cphiv.dk/CoDe)

D:A:D

## Definition of MI

- Definition as applied in the WHO MONICA study
- Diagnosis based on information on:
  - Cardiac pain, cardiac enzymes, troponine, ECG changes, autopsy findings
- Categories:
  - Fatal and non-fatal (survival 28 days)
  - Definite, possible or unclassifiable

D:A:D

**D:A:D**

*Example of completed event checking chart*

**Event Checking Chart  
Cases of MI**

XX Hospital (999), EuroSIDA

Name of centre and cohort \_\_\_\_\_

Patient ID code: \_\_\_\_\_ Gender: MALE

Year of birth (yyyy): 1949 Date of event (dd/mm/yy): 01/06/00

1. Number of available ECG's, copies of which are included.

Total (aim 3-6) 5 Prior to MI (aim 1-2) 0 From time of MI (aim 1-2) 3 After MI (aim 1-2) 2

Are all ECG's marked with:  pt ID-code,  date & time,  ecg-velocity?

2. Serological markers.

Register sequence of and/or peak-values of measurements performed within 72 hours of the event. (For iso-enzymes: peak-value of CK-MB and the corresponding value of CK, peak-value of LDH-1 and the corresponding value of LDH-2).

CK unit U/L (20-110)	CK-MB / unit U/L (2-23)	Troponin T/ unit	Troponin I/ unit ng/ml (0.01-0.07)	LDH-1 / unit LDH U/L (200-480)	LDH-2 / unit U/L (200-480)	Other serology marker- which? unit ng/L	Time from MI / hours
505	55		0.520	484		430	H 5
4160	467			1445			H 10
2225	289		17.36	1673			H 19
668 174	94			1566 960		18	H 43 H 91

3. Narrative description of the event/ Summary of symptoms.

Duration of symptoms (> 20 min.?): yes, ≈ 5 h

Quality of symptoms, summary:  
retrosternal pain not totally cured by TNT, left arm

Typical     Atypical     Incomplete     Missing

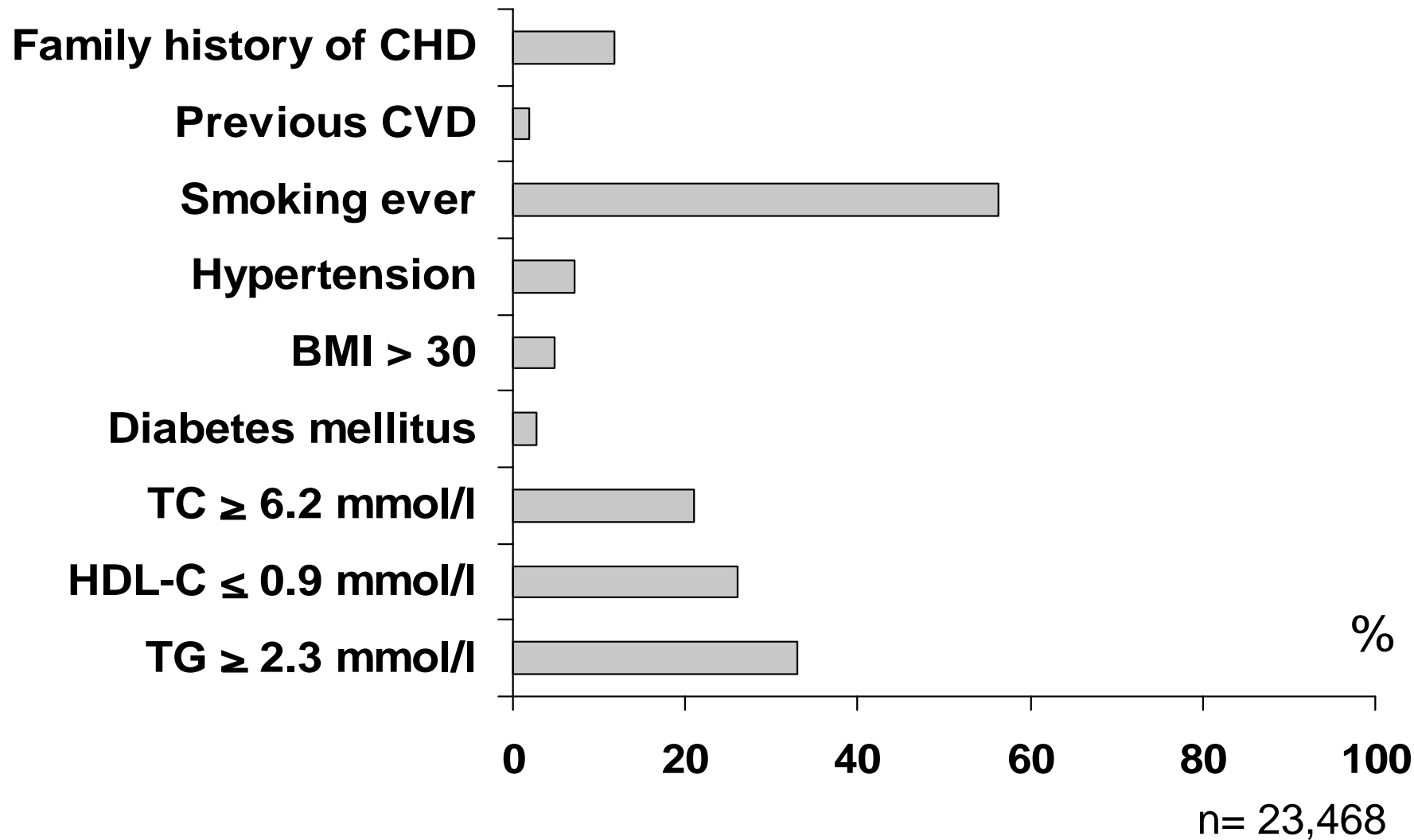
All available information regarding this event has been collected.  
\_\_\_\_\_  
( dd/mm/yyyy )

# Baseline demographics (DAD Cohort I)

- 23,441 participants
- Median age: 39 (IQR 34 – 45)
- 24% female
- 45% men-sex-men, 20% injecting drug users
- 26% prior AIDS
- Median CD4 count: 418 (IQR: 255 - 612)
- Proportion with undetectable HIV-RNA: 55%

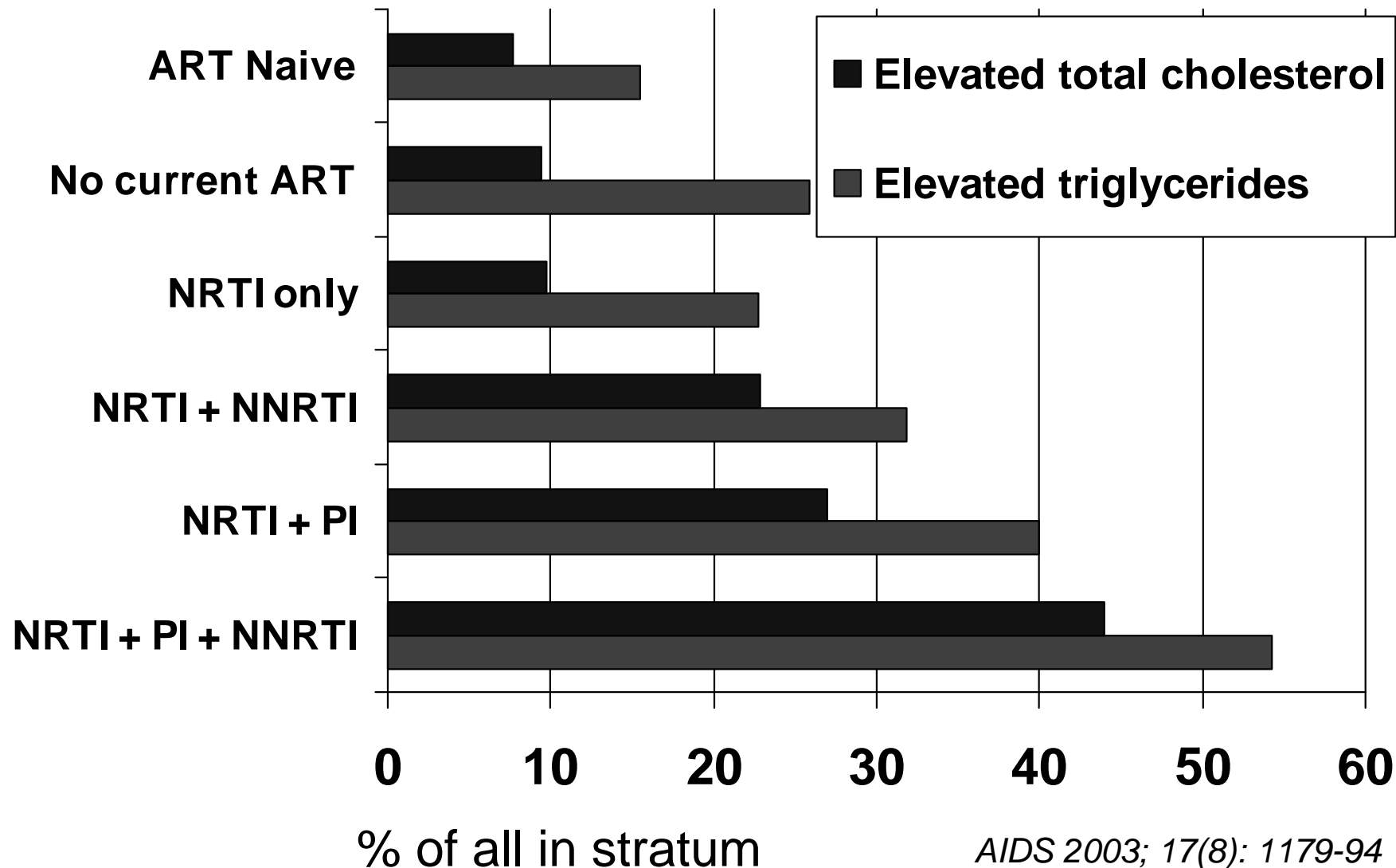
D:A:D

## Baseline Risk Factors for CVD



D:A:D

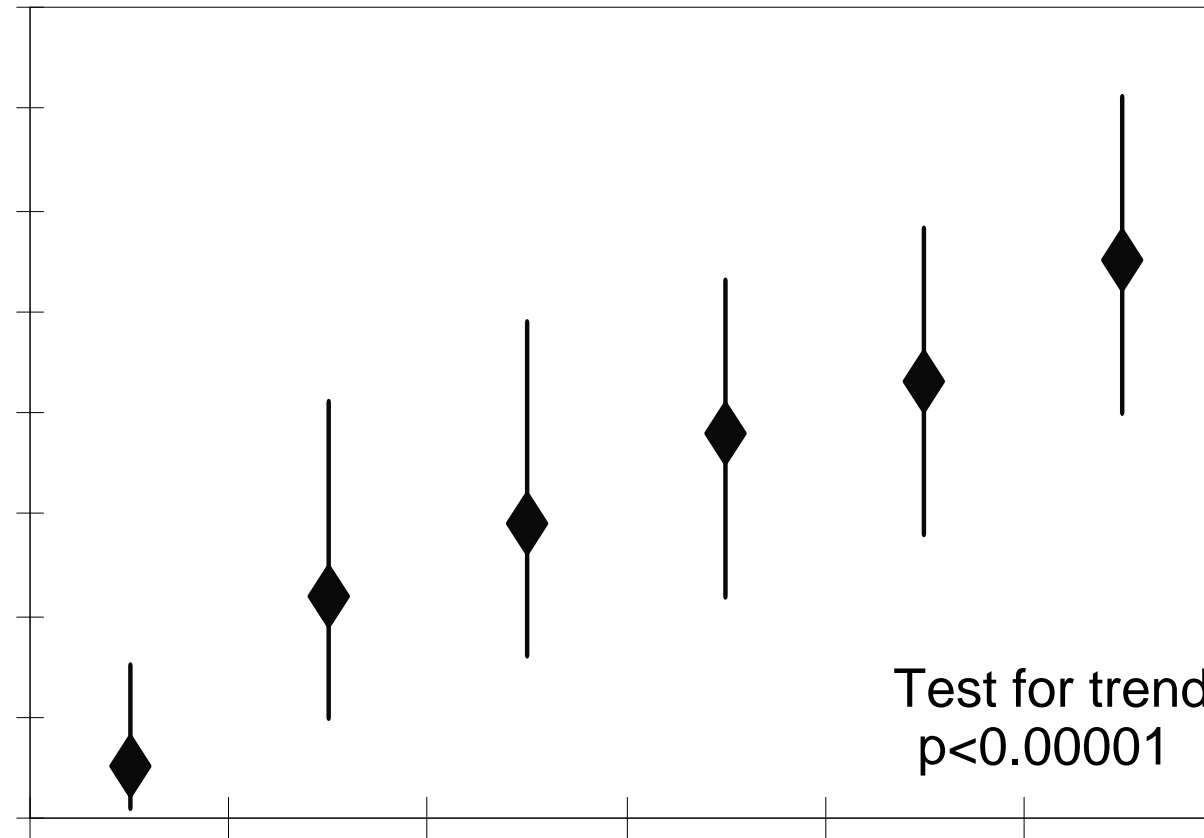
# Lipid elevation and ART status at baseline



D:A:D

# MI by CART exposure

**MIs per  
1,000 PY  
(95% CI)**



Years on CART	None	<1	1-2	2-3	3-4	>4	Total
No. MIs	3	9	14	22	31	47	126
No. PY	5,714	4,140	4,801	5,847	7,220	8,477	36,199

*N. Engl. J. Med. 2003;349(21); 1993-2003*

D:A:D

## Summary

- CART was independently associated with a 26% increased risk of MI per year of exposure
- Traditional risk factors independently associated with risk of MI:
  - Age, gender, smoking, previous CVD
- Other risk factors:
  - Total cholesterol, triglycerides, diabetes mellitus

D:A:D

## Perspective

- Absolute risk of MI overall remains low (3.5 per 1,000 PY) and should be balanced against the known beneficial effects of CART
- Individuals already at high risk of CVD and on CART need special attention with regards to reducing modifiable risk factors
- Further follow-up required to:
  - monitor incidence trend over time – linear?
  - identify factors explaining the association
  - distinguish associations with ART drug classes
- The D:A:D study continues at least until 2006

# THE STUDY COORDINATING OFFICE

## Copenhagen HIV Programme (CHIP)

**Principle investigator:** Jens D. Lundgren, MD, DMSc  
**Study coordinator:** Nina Friis-Møller, MD  
**Data manager:** Allen Sawitz

**Study documents and newsletters available at:**  
**[www.cphiv.dk](http://www.cphiv.dk)**

Contact e-mail: [dad@cphiv.dk](mailto:dad@cphiv.dk)

Phone: +45 36 32 30 15

Fax: +45 36 47 33 40

D:A:D