The importance of cohort collaborations for guiding clinical management of individuals with HIV infection

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- Why do we need cohort collaborations for HIV infection?
- An example of a successful cohort collaboration – The Antiretroviral Therapy Cohort Collaboration (ART-CC)
- What makes a cohort collaboration successful?
- The potential limitations of these collaborations and ways to deal with them

Cohort studies in HIV infection

Much of our knowledge about HIV infection has been obtained from cohort studies:

- Description of the natural history of infection
- Identification of the CD4 count and viral load as good surrogate markers of clinical progression
- Identification of co-factors (including older age and viral infections [CMV, HCV]) for progression
- Assessment of impact of highly active antiretroviral therapy on outcomes

The main limitations of cohort studies

However, despite the tremendous role played by cohort studies in HIV infection, their value is hampered by two main factors:

- Their size
- The representativeness of the cohort

(i) Cohort size

Even the largest cohorts may be insufficiently powered to study rare events

- Data Collection on Adverse Events of Antiretroviral Therapy (D:A:D) Study considers relationship between exposure to HAART and cardiovascular disease
- Around 30,000 person-years of follow-up required to detect a doubling in risk of cardiovascular disease (around 6,000 patients followed for 5 years)

Cohorts that were large enough in the pre-HAART era may now be too small to answer questions relating to clinical events

(i) Representativeness

Cohorts may be limited in terms of:

- Geographic location
- Site of care (urban/rural)
- Exposure group (IDU, haemophilia, homosexual)
- Treatment status (naïve, experienced)
- Other characteristics (seroconverters, patients receiving health care from single health care insurer)

Early cohort collaborations – the Multi-cohort Analysis Project (MAP)

- Collaboration between statisticians, clinicians and epidemiologists working on 5 HIV cohorts
  - Edinburgh City Hospital cohort, Italian Seroconversion cohort, Royal Free Hospital Haemophilia cohort, National Cancer Institute cohort, Toronto Sexual Contact Study cohort
- Two-week workshop in Cambridge, 1993
- Aim: to pool data from HIV seroconverter cohorts to perform a variety of analyses on the prognostic value of biological markers (CD4, CD8, IgA, β2M)
- 4 papers in *Statistics in Medicine* and 2 in *AIDS*

Early cohort collaborations – the CASCADE Study

- Concerted Action on SeroConversion to AIDS and Death in Europe
- Initiated in 1997 as a collaboration between the investigators of 22 seroconverter cohorts
- Currently a network of epidemiologists, statisticians, virologists and clinicians from 15 European countries, Australia and Canada
- Aims to study issues relating to entire course of infection that cannot be addressed in individual cohorts

The Antiretroviral Therapy (ART) Cohort Collaboration

Aim of collaboration:

To provide reliable estimates of the prognosis of antiretroviral-naïve individuals starting HAART for the first time

- In particular, to consider progression to a new AIDS event or death

ART
Cohort Collaboration

The Antiretroviral Therapy (ART) Cohort Collaboration

Inclusion criteria (patients)

- Aged >16 years
- Not previously received antiretroviral treatment
- Starting HAART containing ≥3 drugs
- CD4 count and HIV RNA level at baseline

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Inclusion criteria (cohorts)

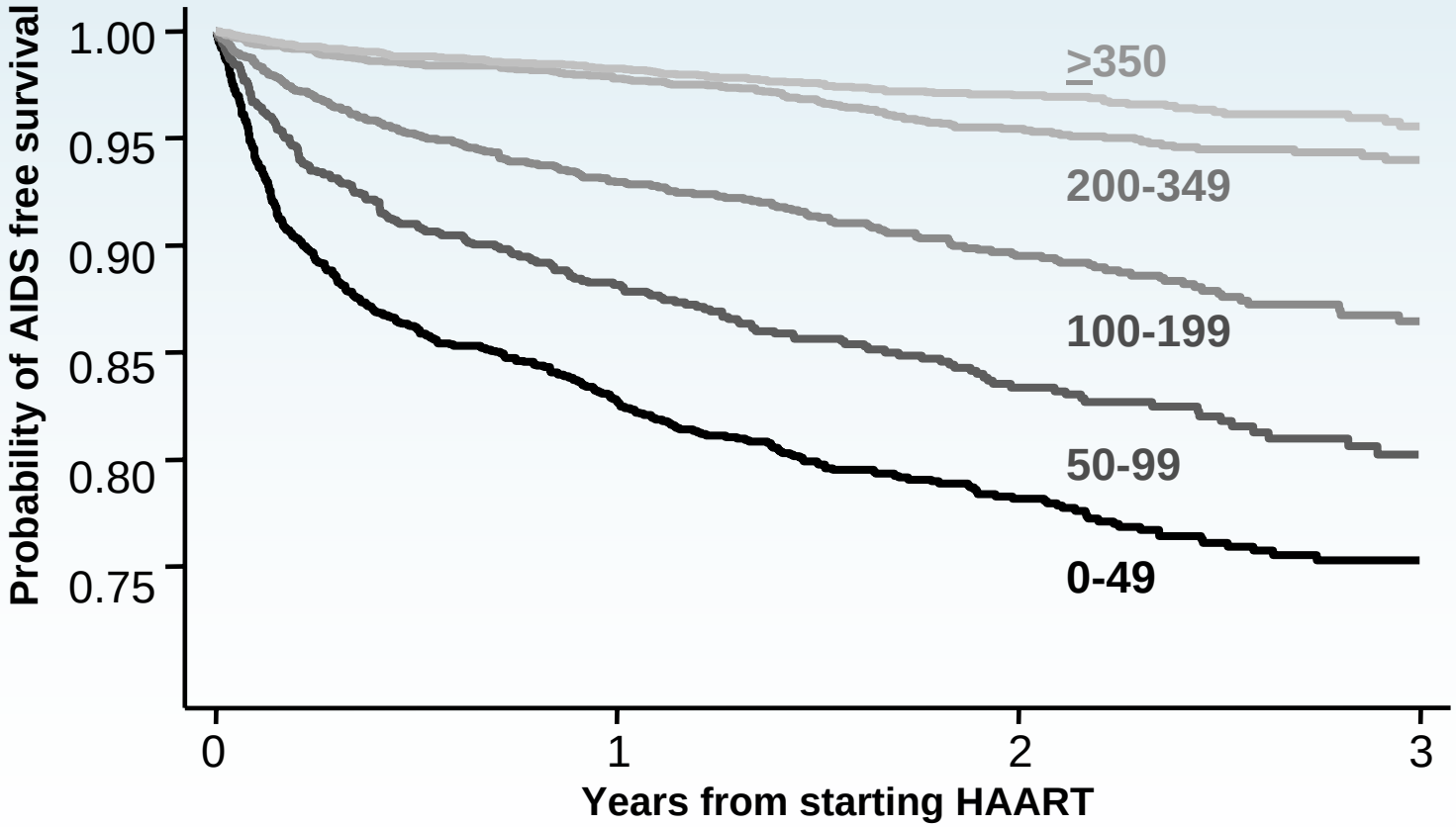
- Enrolled at least 100 such patients
- Median follow-up of at least 1 year
- Able to provide required data in a timely manner

The Antiretroviral Therapy (ART) Cohort Collaboration

Participating cohorts

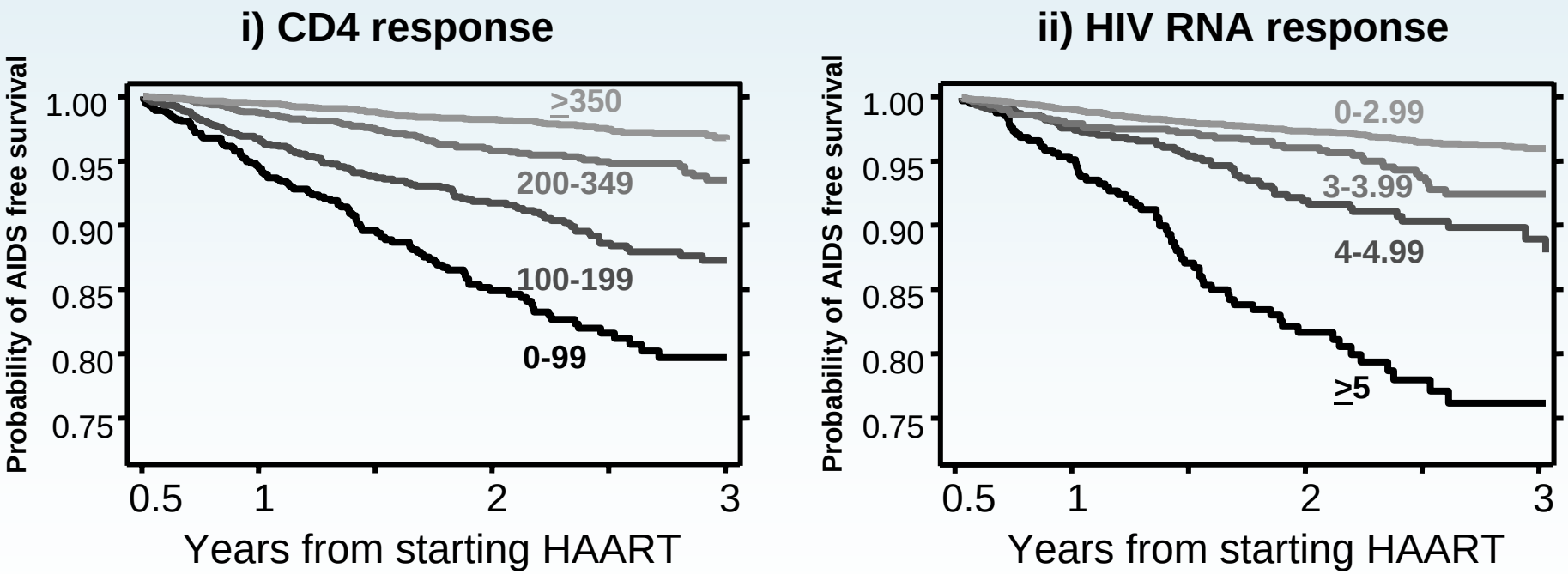
- French Hospital Database on HIV
- ICoNA, Italy
- Swiss HIV Cohort Study
- ATHENA, Netherlands
- EuroSIDA
- CHORUS, US
- Frankfurt HIV Cohort, Germany
- APROCO, France
- BC Centre for Excellence in HIV, Canada
- Royal Free Hospital Cohort, London
- South Alberta Clinic, Canada
- Köln/Bonn Cohort, Germany

Relationship between baseline CD4 count and progression to AIDS or death



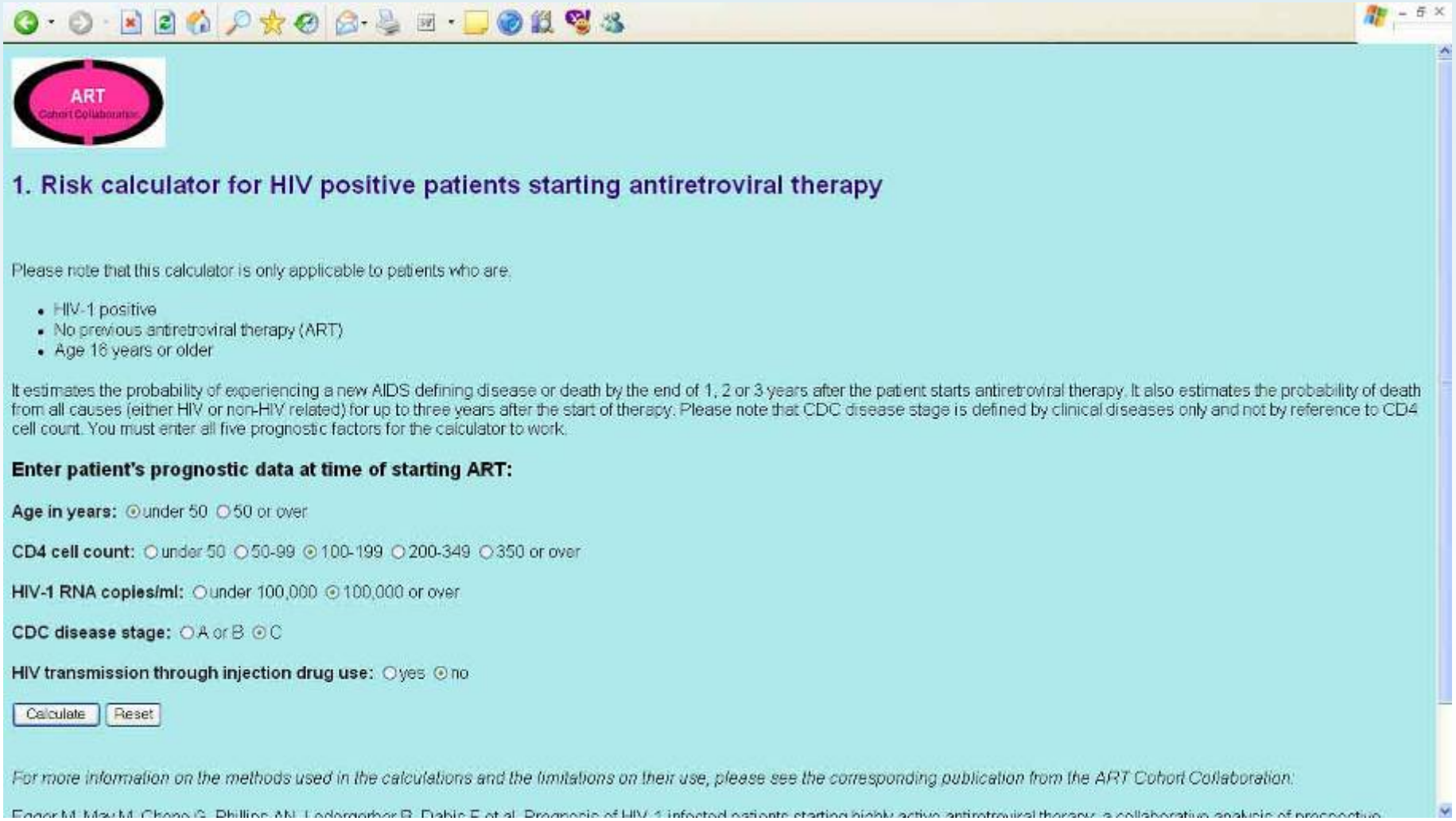
The ART Cohort Collaboration. Lancet (2002); **360**: 119-29.

AIDS-free survival stratified by CD4 count and HIV RNA at 6 months



The ART Cohort Collaboration. Lancet (2003); **362**: 679-86.

The ART Cohort Collaboration



ART
Cohort Collaboration

1. Risk calculator for HIV positive patients starting antiretroviral therapy

Please note that this calculator is only applicable to patients who are:

- HIV-1 positive
- No previous antiretroviral therapy (ART)
- Age 16 years or older

It estimates the probability of experiencing a new AIDS defining disease or death by the end of 1, 2 or 3 years after the patient starts antiretroviral therapy. It also estimates the probability of death from all causes (either HIV or non-HIV related) for up to three years after the start of therapy. Please note that CDC disease stage is defined by clinical diseases only and not by reference to CD4 cell count. You must enter all five prognostic factors for the calculator to work.

Enter patient's prognostic data at time of starting ART:

Age in years: ⊙under 50 ○50 or over

CD4 cell count: ○under 50 ○50-99 ⊙100-199 ○200-349 ○350 or over

HIV-1 RNA copies/ml: ○under 100,000 ⊙100,000 or over

CDC disease stage: ○A or B ⊙C

HIV transmission through injection drug use: ○yes ⊙no

Calculate Reset

For more information on the methods used in the calculations and the limitations on their use, please see the corresponding publication from the ART Cohort Collaboration:

Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F et al. Prognosis of HIV-1 infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective

The ART Cohort Collaboration

Patient data entered

Prognostic factor	Patient data
Age	less than 50 years old
CD4 cell count	100 to 199
HIV-1 RNA copies/ml	over 100,000
CDC disease stage	C
Transmission through injection drug use	no

Estimated probability of progression to new AIDS defining disease or death

Time from start of HAART	Predicted probability	95% Confidence interval
End of year 1	8.69%	7.25% to 10.41%
End of year 2	13.17%	11.12% to 15.56%
End of year 3	16.70%	14.10% to 19.72%

Estimated probability of death

Time from start of HAART	Predicted probability	95% Confidence interval
End of year 1	2.02%	1.41% to 2.90%
End of year 2	4.06%	2.99% to 5.50%
End of year 3	6.08%	4.47% to 8.24%

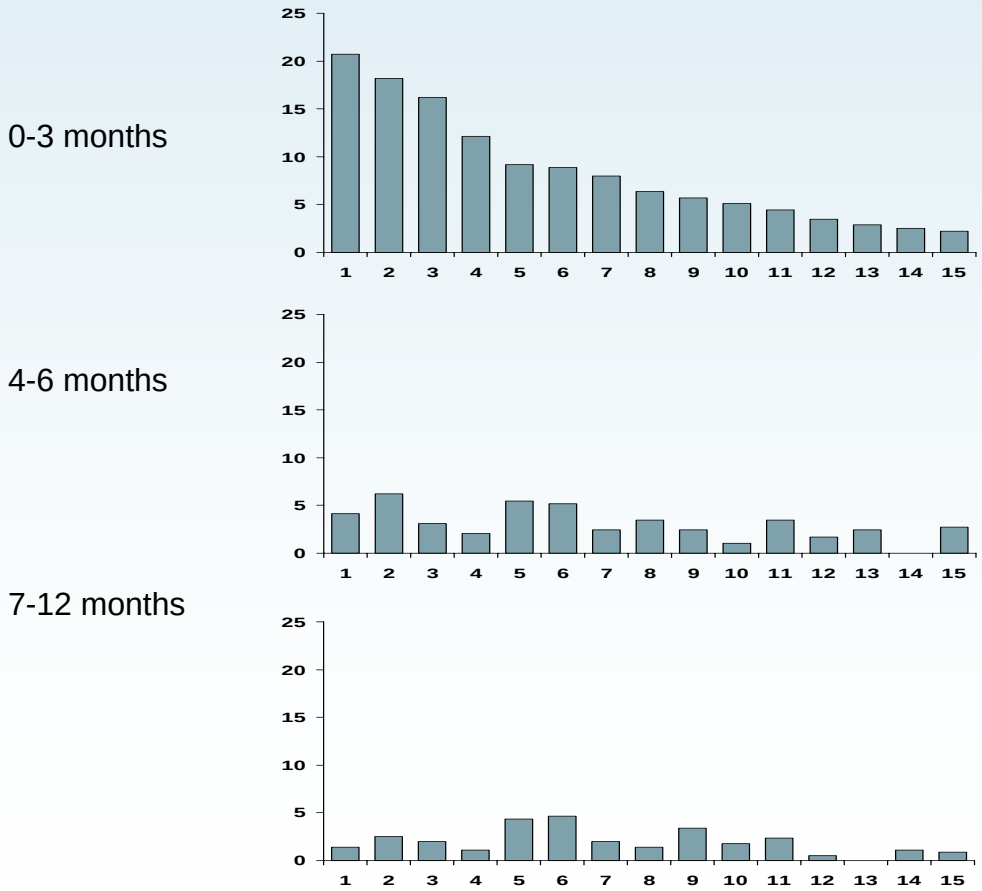
For more information on the methods used in the calculations and the limitations on their use, please see the corresponding publication from the ART Cohort Collaboration.

Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospect studies. Lancet 2002; 360:119-29 (pdf of paper here)

Clinical events in first year of HAART

Period after starting HAART

Incidence (per 1000 person-years)



1. *Mycobacterium avium* disease
2. Kaposis Sarcoma
3. Cytomegalovirus disease
4. *Pneumocystis carinii* pneumonia
5. Tuberculosis
6. Oesophageal candida
7. HIV-related encephalopathy
8. Toxoplasmosis of the brain
9. Non-Hodgkin's lymphoma
10. Herpes simplex disease
11. Wasting syndrome
12. Progressive multifocal leukoencephalopathy
13. Cryptococcosis
14. Cryptosporidiosis
15. Bacterial pneumonia

The ART Cohort Collaboration. Arch Int Med (2005); **165**: 416-423.

Factors associated with incidence of TB

		Relative rate (95% CI)	P-value
Duration of HAART (/year)		0.59 (0.39-0.89)	0.009
Risk group	Homosexual	1	
	IDU	2.98 (1.37-6.45)	
	Heterosexual	2.69 (1.41-5.12)	
	Other/not known	1.54 (0.55-4.35)	0.006
Year of HAART	≤1997	0.24 (0.11-0.56)	
	1998	0.36 (0.16-0.80)	
	1999	0.57 (0.26-1.21)	
	2000	0.81 (0.39-1.68)	
	≥2001	1	0.003
CD4 count (/100 cells/mm^3)	At HAART	0.89 (0.83-0.96)	0.009
	At 6 months	0.90 (0.81-0.99)	0.07
HIV RNA <400 copies/ml	At 6 months	2.21 (1.33-3.67)	0.003

The ART Cohort Collaboration. Clin Infect Dis (2005); **41**: 1772-82.

What makes a cohort collaboration successful?

- Should not compete (for funding or research outputs) with participating cohorts
- Questions to be addressed must not be possible to answer in participating cohorts
- Must recognise the effort that has gone into the creation of participating cohorts
- Collaborators should play a role in study management (through steering committee membership, etc.)

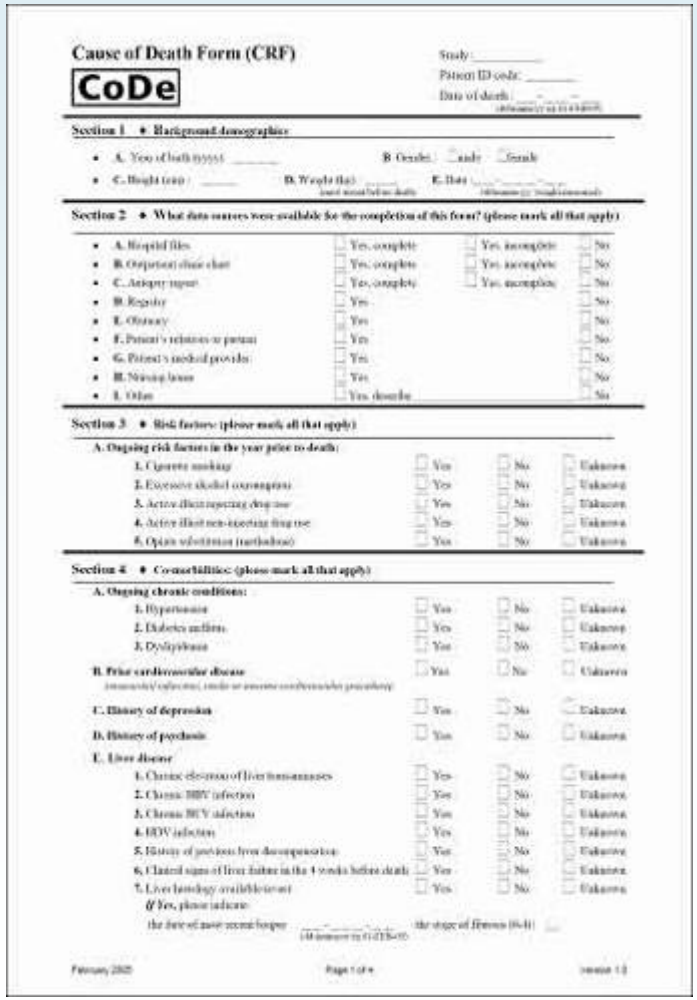
The problems with cohort collaborations
Data collection and transfer

- Cohorts are likely to use different methods to collect and store data
- Coding schemes may vary from cohort to cohort and will often be language-specific
- Data may be transferred in a variety of formats - although it is possible to convert most datasets into a common format, this is time-consuming
- Attempts to harmonise data collection and transfer methods may be helpful

‘Coding of Deaths in HIV’ (CoDe) Project

- No uniform classification system for causes of death in HIV patients
- Cohorts have either created their own or have used ICD 9/10 codes - ICD system is not well adapted to HIV infection
- CoDe project (www.cphiv.dk/CoDe) is a uniform coding system that can be applied to deaths in HIV-positive individuals
- Evolved from a meeting of investigators of large HIV cohort studies and randomised trials

CoDe CRF page 1 and 2



Cause of Death Form (CRF)

CoDe

Study: _____

Patient ID code: _____

Date of death: _____

Section 1 ♦ Background demographics

- A. Year of birth (yyyy): _____ B. Gender: ☐ male ☐ female
- C. Height (cm): _____ D. Weight (kg): _____ (most recent before death) E. Date: _____ (dd/mm/yyyy or yy if >10 years)

Section 2 ♦ What data sources were available for the completion of this form? (please mark all that apply)

A. Hospital files	☐ Yes, complete	☐ Yes, incomplete	☐ No
B. Outpatient clinic chart	☐ Yes, complete	☐ Yes, incomplete	☐ No
C. Autopsy report	☐ Yes, complete	☐ Yes, incomplete	☐ No
D. Registry	☐ Yes		☐ No
E. Obituary	☐ Yes		☐ No
F. Patient's relatives or partner	☐ Yes		☐ No
G. Patient's medical provider	☐ Yes		☐ No
H. Nursing home	☐ Yes		☐ No
I. Other	☐ Yes, describe: _____		☐ No

Section 3 ♦ Risk factors: (please mark all that apply)

A. Ongoing risk factors in the year prior to death:

1. Cigarette smoking	☐ Yes	☐ No	☐ Unknown
2. Excessive alcohol consumption	☐ Yes	☐ No	☐ Unknown
3. Active illicit injecting drug use	☐ Yes	☐ No	☐ Unknown
4. Active illicit non-injecting drug use	☐ Yes	☐ No	☐ Unknown
5. Opiate substitution (methadone)	☐ Yes	☐ No	☐ Unknown

Section 4 ♦ Co-morbidities: (please mark all that apply)

A. Ongoing chronic conditions:

1. Hypertension	☐ Yes	☐ No	☐ Unknown
2. Diabetes mellitus	☐ Yes	☐ No	☐ Unknown
3. Dyslipidemia	☐ Yes	☐ No	☐ Unknown
B. Prior cardiovascular disease (myocardial infarction, stroke or invasive cardiovascular procedure)	☐ Yes	☐ No	☐ Unknown
C. History of depression	☐ Yes	☐ No	☐ Unknown
D. History of psychosis	☐ Yes	☐ No	☐ Unknown
E. Liver disease			
1. Chronic elevation of liver transaminases	☐ Yes	☐ No	☐ Unknown
2. Chronic HBV infection	☐ Yes	☐ No	☐ Unknown
3. Chronic HCV infection	☐ Yes	☐ No	☐ Unknown
4. HDV infection	☐ Yes	☐ No	☐ Unknown
5. History of previous liver decompensation	☐ Yes	☐ No	☐ Unknown
6. Clinical signs of liver failure in the 4 weeks before death	☐ Yes	☐ No	☐ Unknown
7. Liver histology available/relevant	☐ Yes	☐ No	☐ Unknown

If Yes, please indicate:

the date of most recent biopsy: _____ (dd/mm/yyyy or yy if >10 years) the stage of fibrosis (0-4): ☐

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Cause of Death Form

CoDe

Study: _____

Patient ID code: _____

Section 5 ♦ Cause of death

A. Was the death sudden? ☐ Yes ☐ No ☐ Unknown

B. Was the death unexpected? ☐ Yes ☐ No ☐ Unknown

C. Please complete the table below by recording all illnesses and conditions (acute and chronic) or injuries that the patient had at the time of death.

	Illness / Condition / Injury	Date of onset (dd/mm/yyyy or yy if >10 years)	Certainty of diagnosis*		
			Definite	Likely	Possible
1.			☐	☐	☐
2.			☐	☐	☐
3.			☐	☐	☐
4.			☐	☐	☐
5.			☐	☐	☐
6.			☐	☐	☐
7.			☐	☐	☐
8.			☐	☐	☐
9.			☐	☐	☐

*Certainty of Diagnosis: Definite = 95–100% certainty, Likely = 80–95% certainty, Possible = 50–80% certainty

D. Brief narrative of the sequence of events leading to death (please include means of diagnosis of illness(s)):

_____

_____

_____

_____

_____

_____

_____

_____

E. In summary, the causal relation between the conditions leading to death was (complete this section with the corresponding number from table C above):

1. Condition that directly caused death (immediate cause): _____
2. Due to, or as a consequence of: _____
3. Due to, or as a consequence of: _____
4. Due to, or as a consequence of (the underlying condition): _____

Please refer to the CoDe instructions for definitions and guidelines for the completion of this form.

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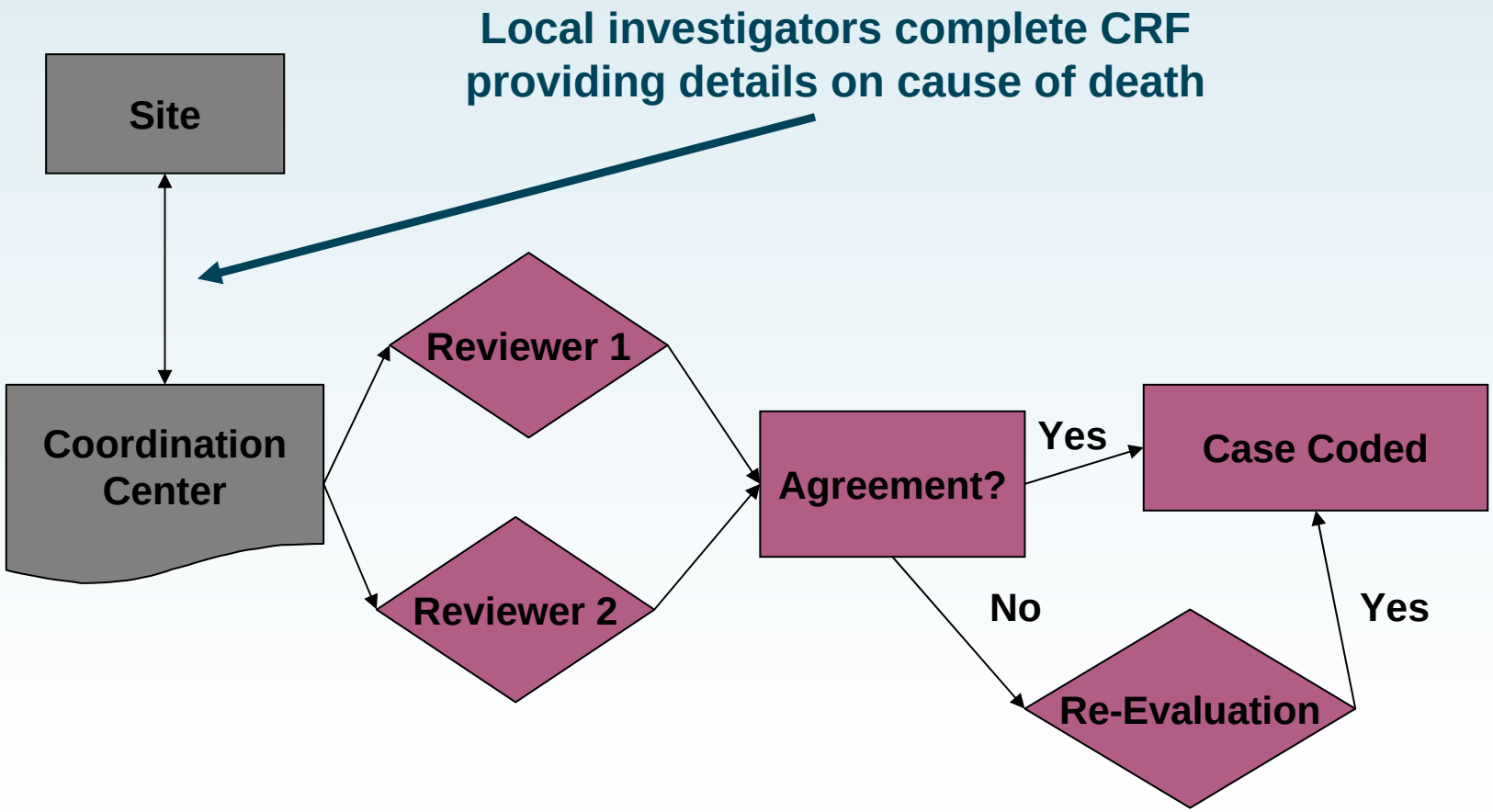
www.cphiv.dk/CoDe

CoDe Flow Diagram



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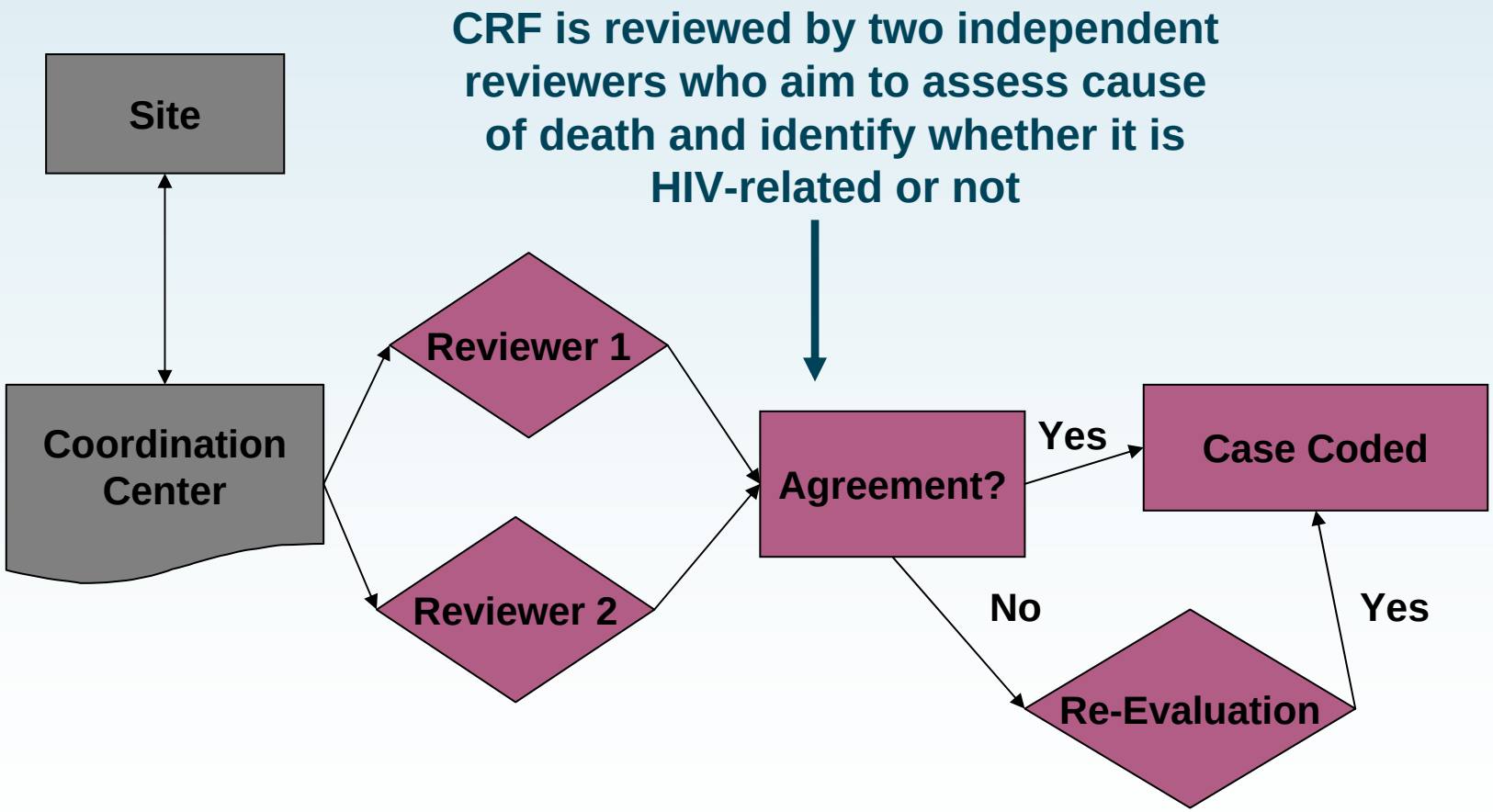
CoDe Flow Diagram



www.cphiv.dk/CoDe

Is the death immunodeficiency related?

YES - AIDS (CDC C) or Hodgkin's Lymphoma

NO - Cause(s) of death incompatible with immunodeficiency, e.g. patient dying in a plane crash

UNCLEAR - See table below

CD4 cell count before death	CD4 ≤ 50 cells/µL	CD4 = 50-199 cells/µL	CD4 ≥ 200 cells/µL
Sudden death	Possibly	Assumed not	Assumed not
Not sudden death	Likely	Possibly	Assumed not

www.cphiv.dk/CoDe

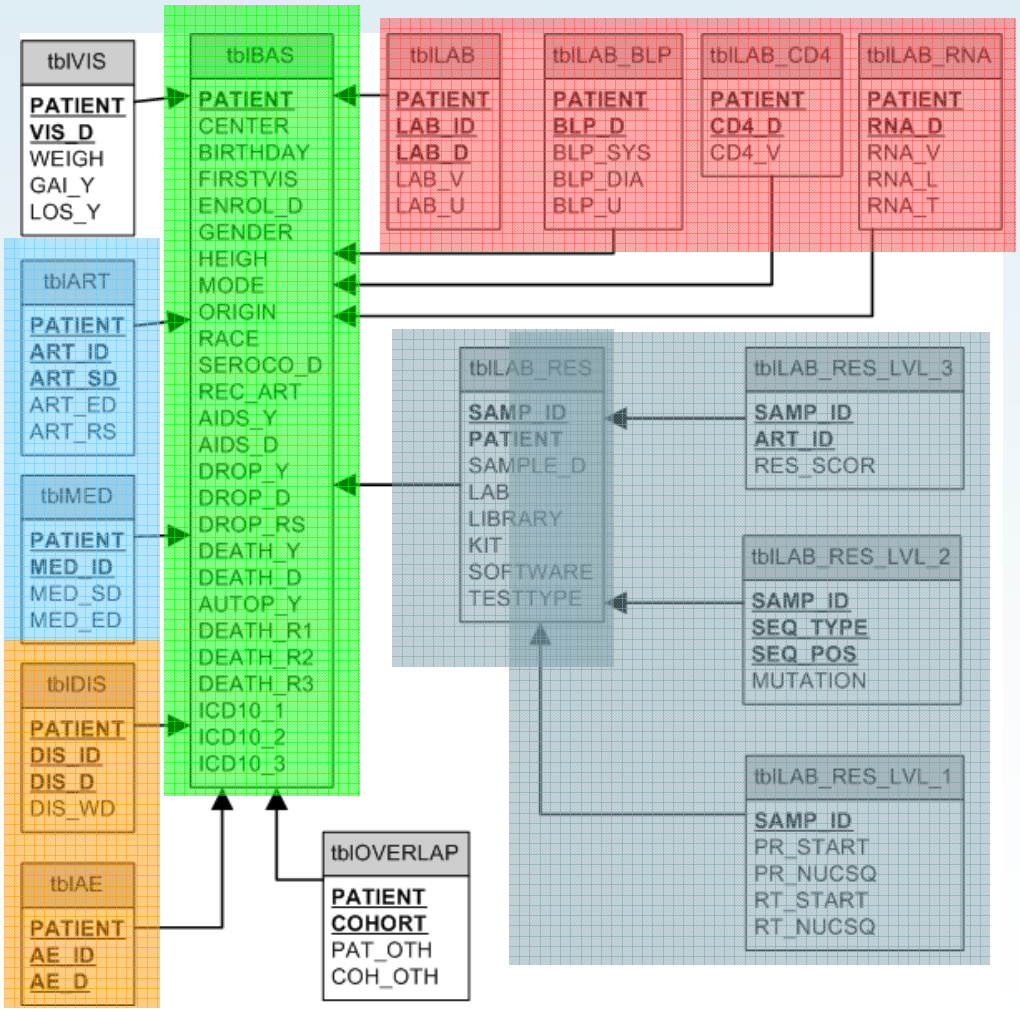
HIV Collaboration Data Exchange Protocol (HICDEP)

- Provides harmonised formats for data exchange between cohorts
- Provides guidance on possible data structure and formats for new cohorts
- Protocol, sample database and list of codes available electronically at www.cphiv.dk/HICDEP/tabid/60/Default.aspx

HICDEP – structure of database

Basic info
Lab + BP
Medication
Diseases/AE
Resistance

+ Visit info
+ Overlap



Conclusions

- Cohort collaborations have already provided valuable information that has been used to improve patient care
- However, cohort collaborations are dependent on the continued follow-up of participating cohorts – thus care should be taken to ensure that participation in a collaboration does not impact negatively on an individual cohort
- Where cohort collaborations are being initiated, a number of simple steps can be taken to simplify the data collection and transfer process

Acknowledgements

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ART Cohort Collaboration

Jonathan Sterne, Matthias Egger, Margaret May

Good luck to France….

Good luck to France….

But even better luck to England!