ART Monitoring in the Netherlands

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HIV Monitoring Foundation
Moscow, 5 June 2007

STICHTING HIV MONITORING

Overview

- introduction
- what is monitored?
- procedures
- Oracle Clinical
- some results

Introduction

HIV Monitoring Foundation

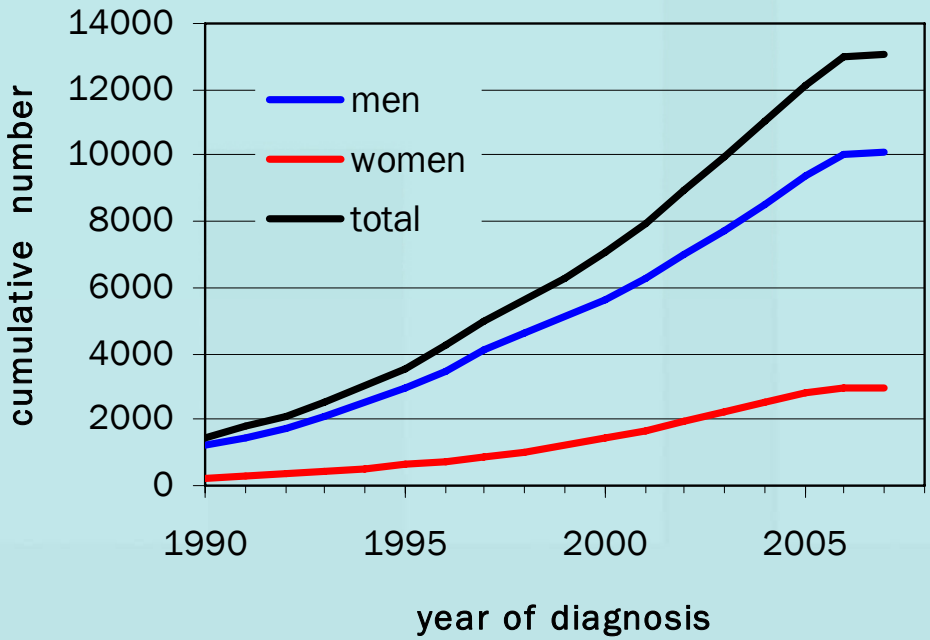
- founded on November 11, 2001
- appointed by Minister of Health as the executive organisation for registration and monitoring of HIV-infected patients followed in the Dutch treatment centres
- part of HIV care

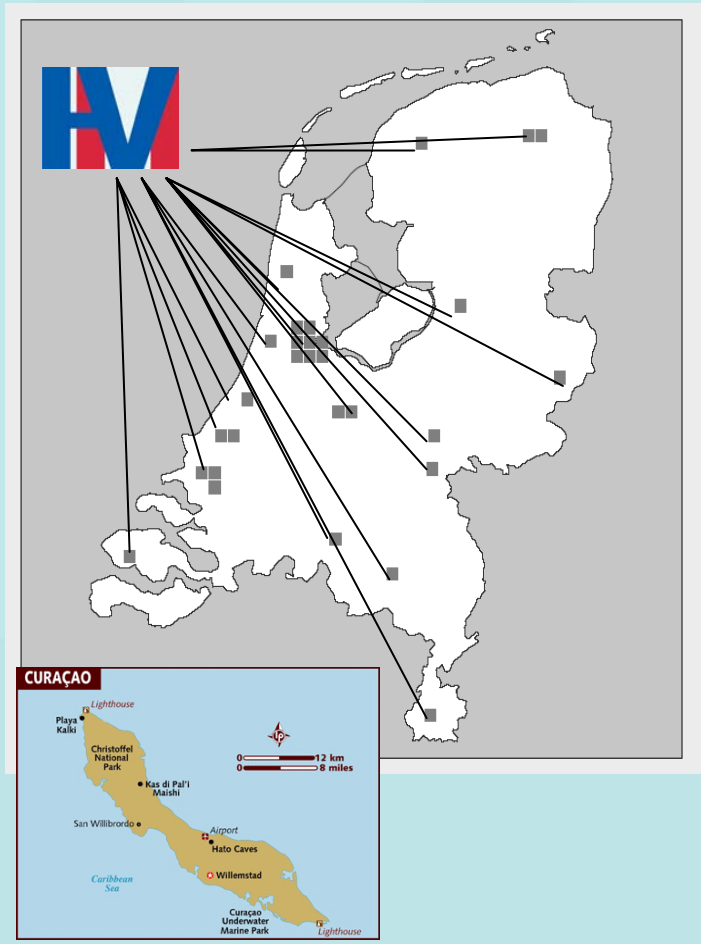
Activities

- collection and maintenance of anonymous data
- report to government and other organisations
- make data available for treating physicians
- provide data for scientific research

HIV Monitoring Foundation

April 2007: 13071 patients registered





Total number of HIV-infected persons in the Netherlands is estimated between 16000 and 24000.

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Items collected upon enrolment

Adults

Demographic data

- date of birth, gender, first and second nationality, country of birth, height

History of HIV infection

- date of the last negative and first positive HIV-1 and HIV-2 test
- patient diagnosed with a primary HIV infection? (yes, no, most likely)

HIV transmission

- most likely transmission route
- in case of sexual transmission: steady partner or multiple sexual contacts
- country of infection

HIV-infected children

Demographic data

- nationality and country of birth of patient's parents
- family data
- HIV status of patient's mother, father, brothers and sisters
- pregnancy duration, way of birth, weight at birth, Apgar scores, congenital defects, perinatal exposure to ARV therapy and co-medication, perinatal complications

Clinical data collected at every visit

Clinical examination

- weight, blood pressure, CDC events

HIV-related events (CDC)

Adverse events

- every event that results in a change of antiretroviral treatment
- some events are always recorded, e.g. cardiovascular events

Antiretroviral therapy

- start and stop date, dosage and units, route of admission, reason for stop and the status of medication at current visit (ongoing: yes or no)

Co-medication

- prophylaxis & treatment CDC events
- anti-epileptic agents
- anti-coagulant agents, platelet aggregation inhibitors
- anti-hypertensive agents, anti-arrhythmic agents
- lipid-lowering agents
- anti-diabetic agents, insulin and its derivatives
- anabolic steroids and appetite stimulants
- hepatitis B treatment; hepatitis C treatment
- medication that interacts with antiretroviral therapy

Data collected at every visit (Lab results)

HIV virology

RNA concentration, laboratory, sample date, viral load assay type, sample material, cut-off and undetectable (yes or no)

Immunology

T-cell count, laboratory and sample date for the following determinates: CD4 count, CD8 count, CD4 percentage, CD8 percentage, CD4/CD8 ratio

Other viral infections

laboratory, sample date for HBsAg, HBsAb, HBcAb, HBeAg, HBeAb, HBV-DNA,HCV-Ab, HCV-RNA, CMV-IgG, CMV-IgM

Participation in clinical trials

trial name, start and stop date

Chemistry

value, units, laboratory and sample date for glucose, amylase, ALAT/SGPT, ASAT/SGOT, alkaline phosphatase, gamma GT, lactate, triglycerides, cholesterol, cholesterol HDL

Haematology

value, units, laboratory and sample date for haemoglobin, leukocytes, thrombocytes

ART drug concentrations

patient material, laboratory, sample dates, time after drug intake, dosage and units of the medication

Other data and end of follow-up

Molecular epidemiology

- HIV subtype
- genotypic RT and protease sequence obtained at
  - HIV diagnosis
  - therapy failure

Pregnancy

End of follow-up

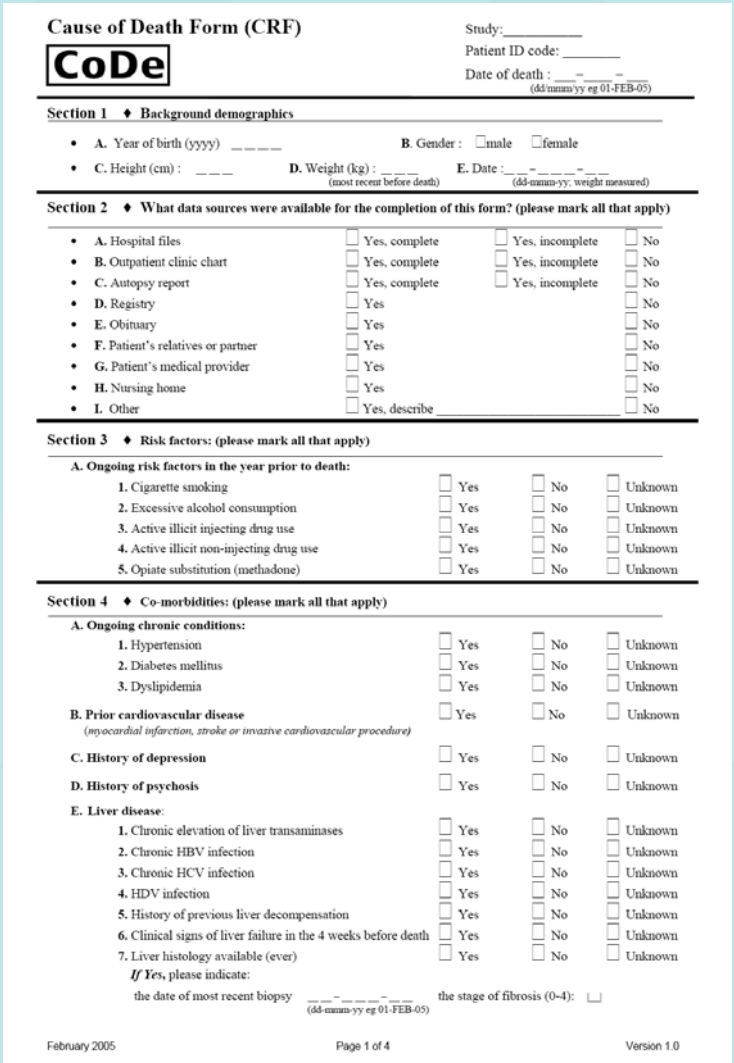
- death
- moved abroad
- lost to follow-up

Death

- date
- cause of death incl. clinical details
  - HIV-related
  - ARV-related
- suicide
- euthanasia
- post-mortem examination

since 2005 CoDe classification

CoDe classification



Cause of Death Form (CRF)

CoDe

Study:_____
Patient ID code: _____
Date of death : ___-___-___
(dd/mmm/yy eg 01-FEB-05)

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-mmm-yy; weight measured)

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 (ever)	☐ Yes	☐ No	☐ Unknown

If Yes, please indicate:
the date of most recent biopsy ___-___-___ (dd-mmm-yy eg 01-FEB-05) the stage of fibrosis (0-4): ☐

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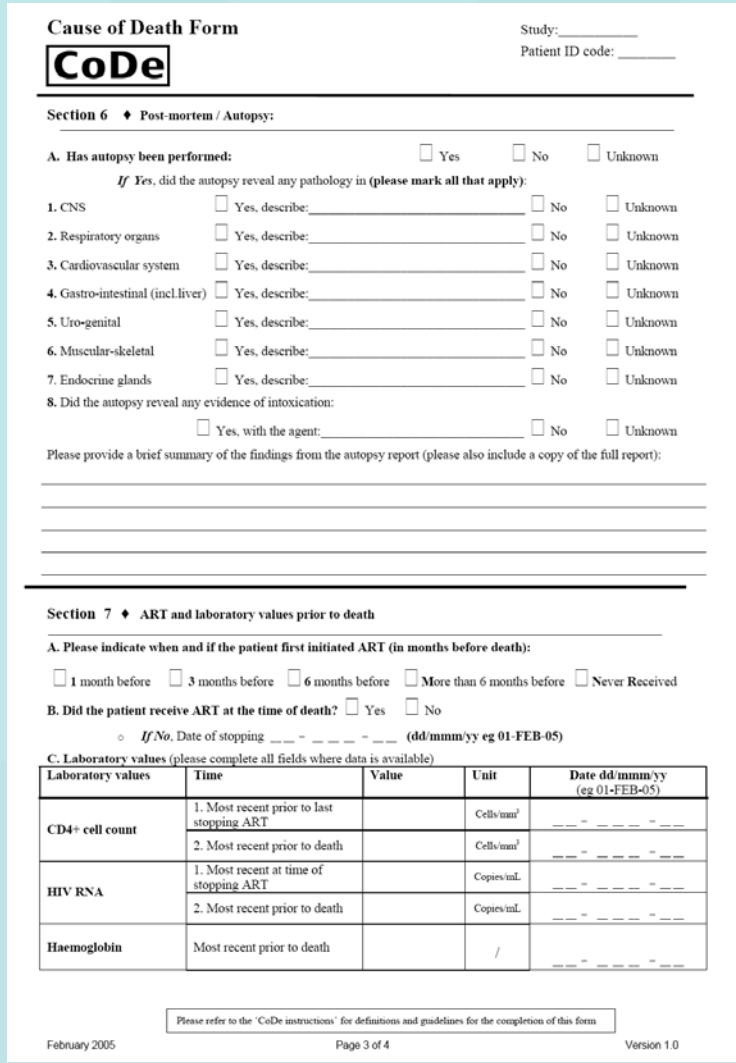

Cause of Death Form

CoDe

Study:_____
Patient ID code: _____

Section 6 ♦ Post-mortem / Autopsy:

A. Has autopsy been performed: ☐ Yes ☐ No ☐ Unknown

If Yes, did the autopsy reveal any pathology in **(please mark all that apply)**:

1. CNS	☐ Yes, describe:_____	☐ No	☐ Unknown
2. Respiratory organs	☐ Yes, describe:_____	☐ No	☐ Unknown
3. Cardiovascular system	☐ Yes, describe:_____	☐ No	☐ Unknown
4. Gastro-intestinal (incl.liver)	☐ Yes, describe:_____	☐ No	☐ Unknown
5. Uro-genital	☐ Yes, describe:_____	☐ No	☐ Unknown
6. Muscular-skeletal	☐ Yes, describe:_____	☐ No	☐ Unknown
7. Endocrine glands	☐ Yes, describe:_____	☐ No	☐ Unknown

8. Did the autopsy reveal any evidence of intoxication:
☐ Yes, with the agent:_____ ☐ No ☐ Unknown

Please provide a brief summary of the findings from the autopsy report (please also include a copy of the full report):

Section 7 ♦ ART and laboratory values prior to death

A. Please indicate when and if the patient first initiated ART (in months before death):

☐ **1** month before ☐ **3** months before ☐ **6** months before ☐ **M**ore than 6 months before ☐ **N**ever **R**eceived

B. Did the patient receive ART at the time of death? ☐ Yes ☐ No

- ***If No***, Date of stopping ___-___-___ **(dd/mmm/yy eg 01-FEB-05)**

C. Laboratory values (please complete all fields where data is available)

Laboratory values	Time	Value	Unit	Date dd/mmm/yy (eg 01-FEB-05)
CD4+ cell count	1. Most recent prior to last stopping ART		Cells/mm³	___-___-___
	2. Most recent prior to death		Cells/mm³	___-___-___
HIV RNA	1. Most recent at time of stopping ART		Copies/mL	___-___-___
	2. Most recent prior to death		Copies/mL	___-___-___
Haemoglobin	Most recent prior to death		/	___-___-___

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

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Already in the database

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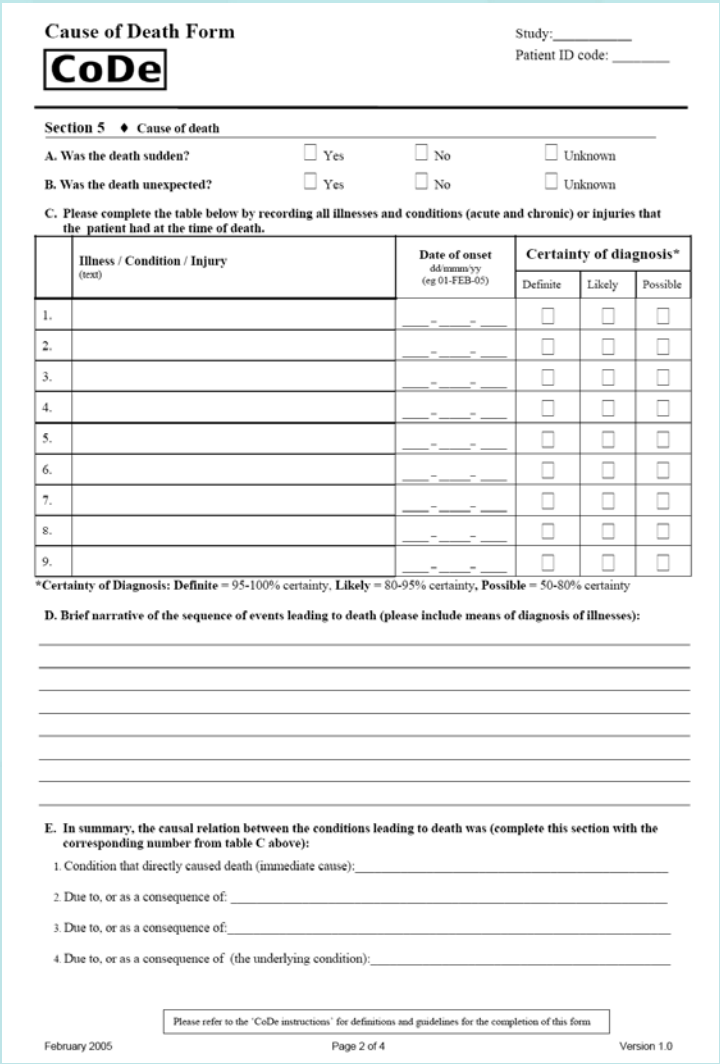
CoDe classification



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 (text)	Date of onset dd/mmm/yy (eg 01-FEB-05)	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 illnesses):

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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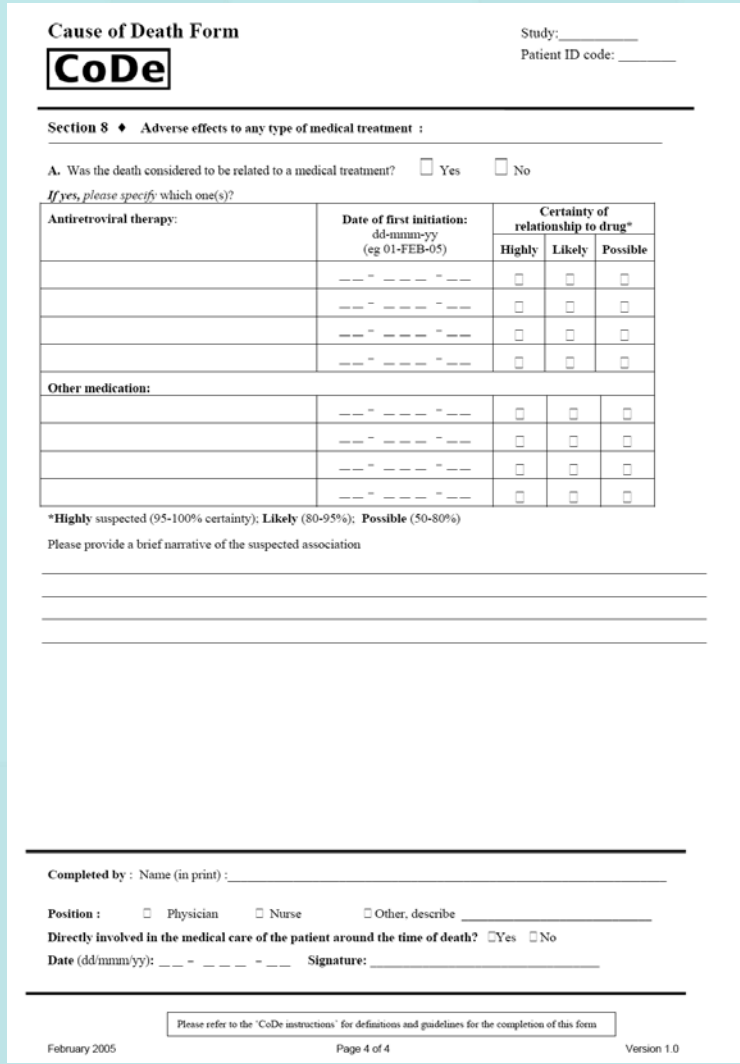

Cause of Death Form

CoDe

Study:_____
Patient ID code: _____

Section 8 ♦ Adverse effects to any type of medical treatment :

A. Was the death considered to be related to a medical treatment? ☐ Yes ☐ No

If yes, please specify which one(s)?

Antiretroviral therapy:	Date of first initiation: dd-mmm-yy (eg 01-FEB-05)	Certainty of relationship to drug*		
		Highly	Likely	Possible
	__-___-__	☐	☐	☐
	__-___-__	☐	☐	☐
	__-___-__	☐	☐	☐
	__-___-__	☐	☐	☐
Other medication:				
	__-___-__	☐	☐	☐
	__-___-__	☐	☐	☐
	__-___-__	☐	☐	☐
	__-___-__	☐	☐	☐

***Highly** suspected (95-100% certainty); **Likely** (80-95%); **Possible** (50-80%)

Please provide a brief narrative of the suspected association

Completed by : Name (in print) :_____

Position : ☐ Physician ☐ Nurse ☐ Other, describe _____

Directly involved in the medical care of the patient around the time of death? ☐Yes ☐No

Date (dd/mmm/yy): __-___-__ **Signature:** _____

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

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Separately collected data

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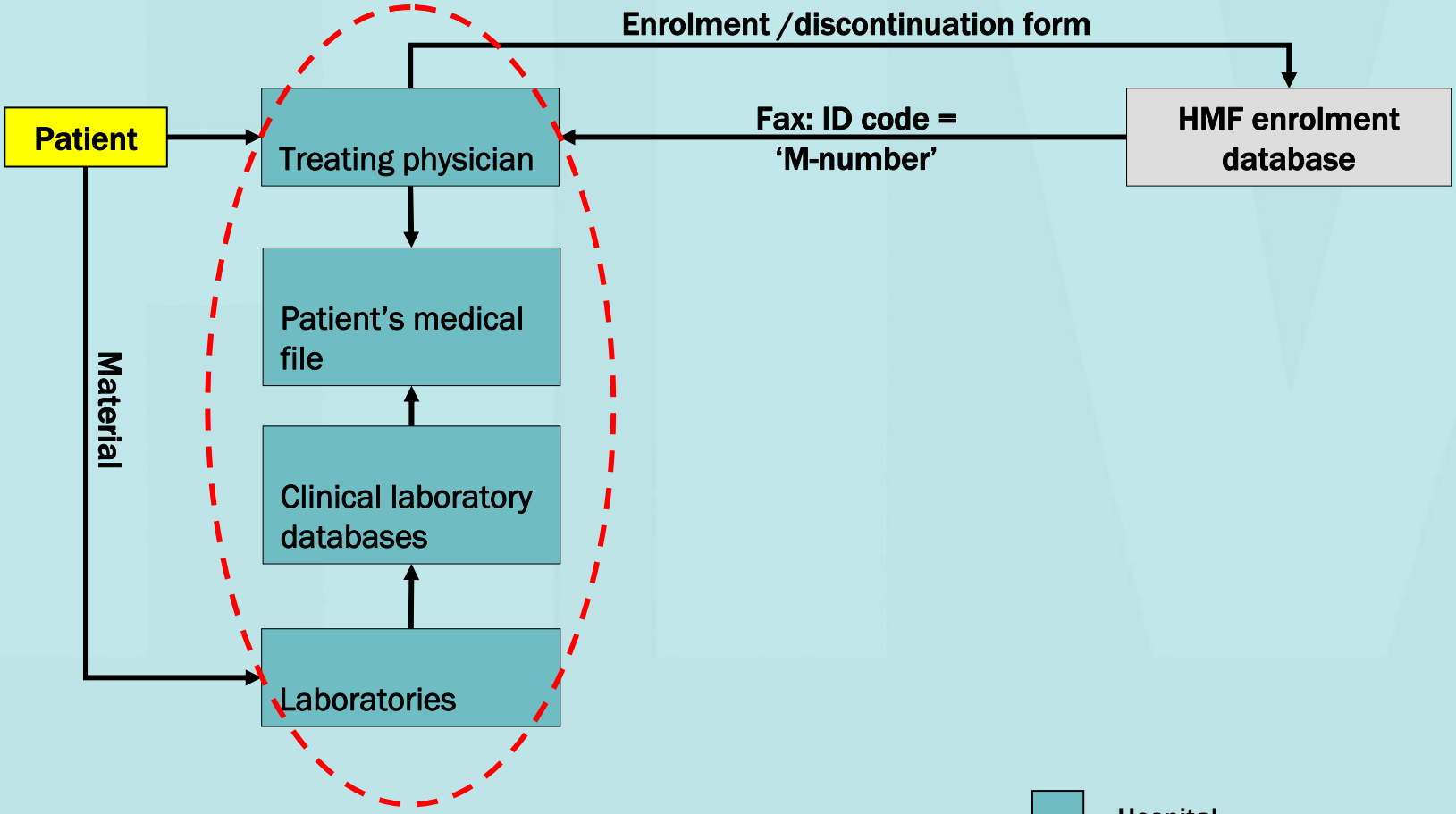
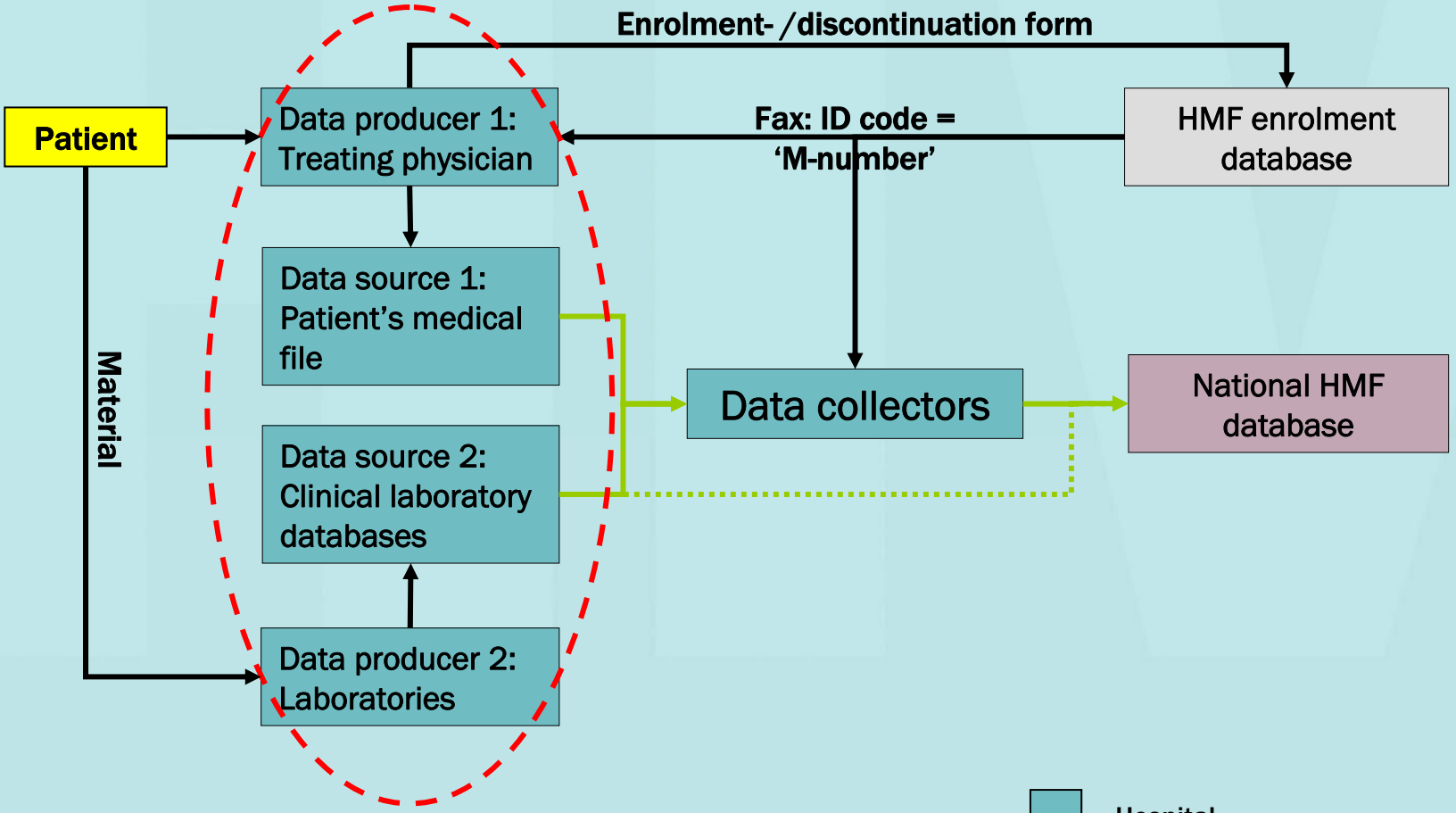
Procedures

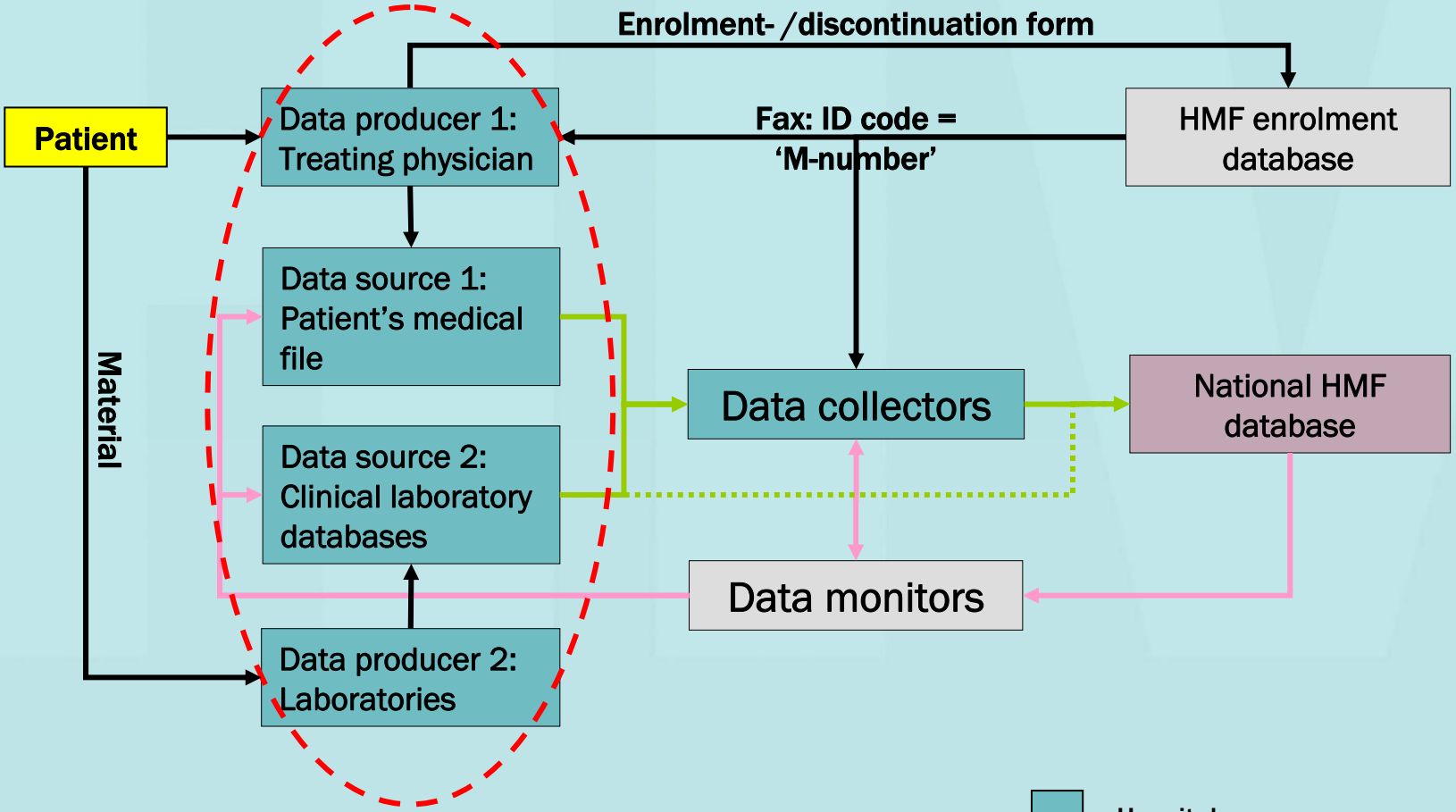


Routine patient care

Procedures


Enrolment- /discontinuation form
Patient
Data producer 1: Treating physician
Fax: ID code = 'M-number'
HMF enrolment database
Data source 1: Patient's medical file
Material
Data collectors
National HMF database
Data source 2: Clinical laboratory databases
Data producer 2: Laboratories
Routine patient care
= Hospital
= HMF
= AMC
= Data entry

Procedures



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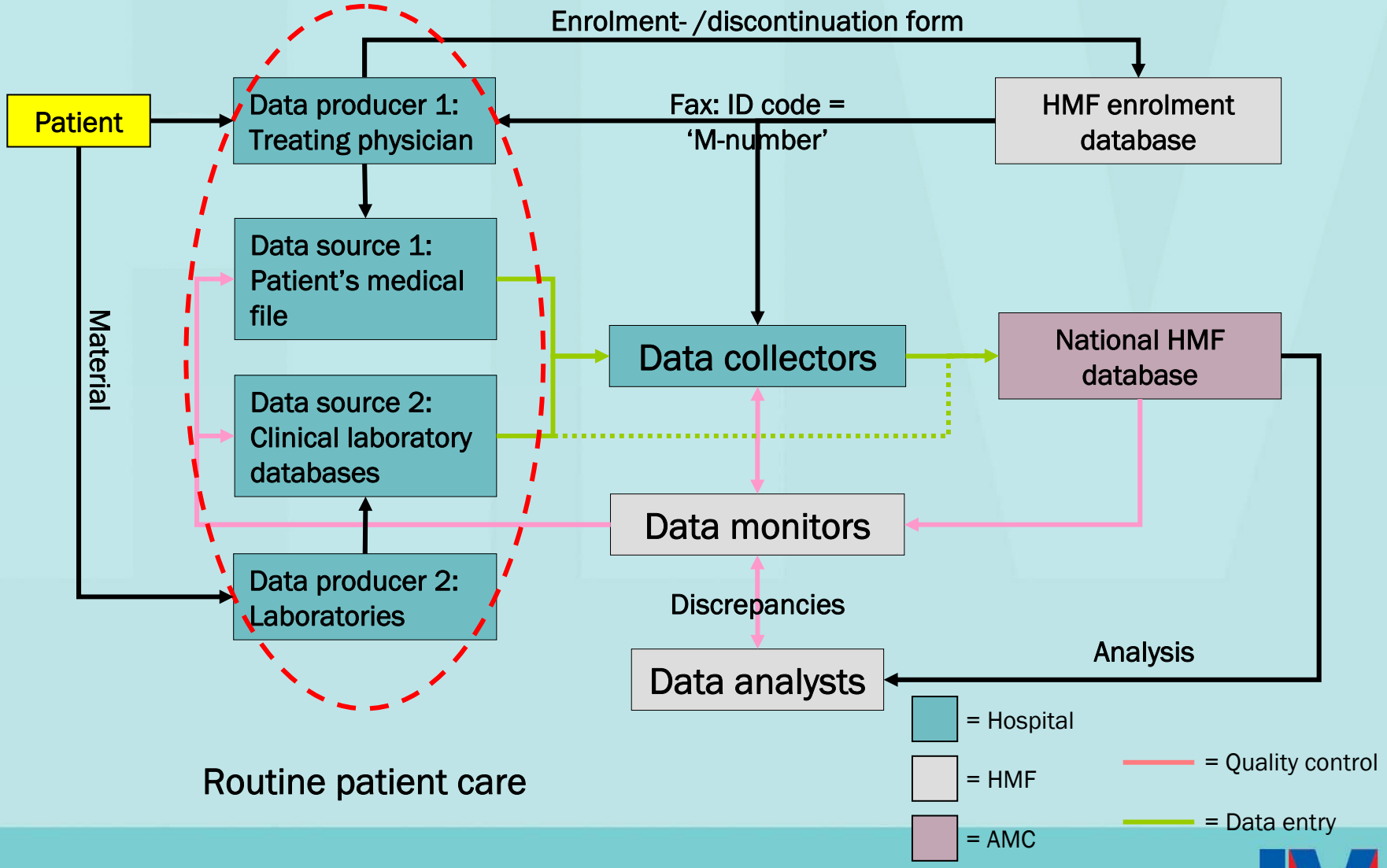
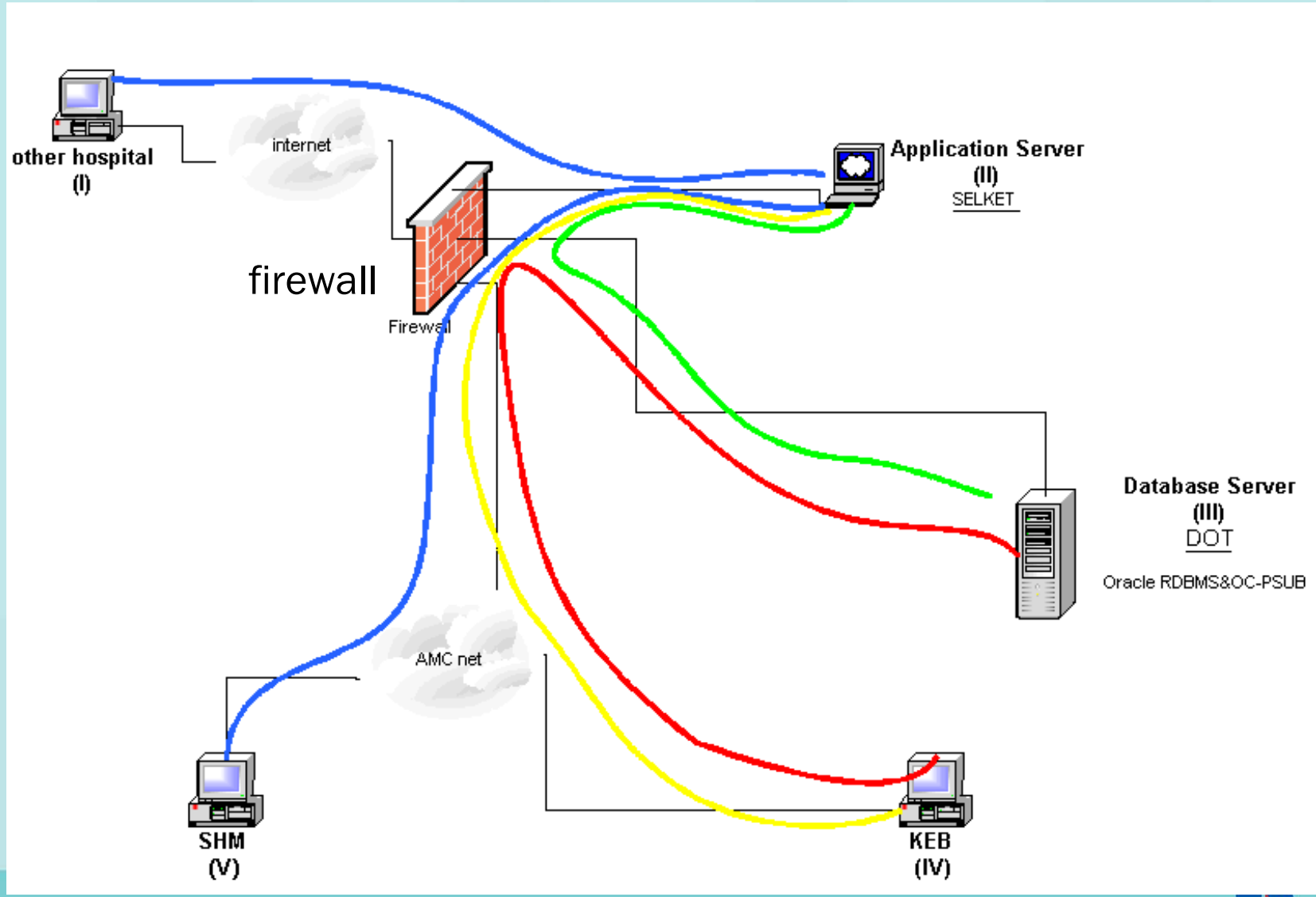
Procedures


Enrolment- /discontinuation form
Patient
Data producer 1: Treating physician
Fax: ID code = 'M-number'
HMF enrolment database
Material
Data source 1: Patient's medical file
Data collectors
National HMF database
Data source 2: Clinical laboratory databases
Data monitors
Data producer 2: Laboratories
Discrepancies
Analysis
Data analysts
Routine patient care
= Hospital
= HMF
= AMC
= Quality control
= Data entry

Technical structure of OC



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Technical structure

- Oracle application and the database each run on a separate server.
- servers are located behind the firewall of the Academic Medical Centre (AMC) in Amsterdam.
- users form inside and outside the AMC have access to the application but not to the database.
- only data managers and programmers have access to both the application and the database program.
- data are solely stored on the central database server.
- data is entered online, just need internet connection
- overnight the most up-to-date version is available

Oracle Clinical

Key Features

- integrated subsystems for
  - study design
  - study data definition
  - study conduct (data capture and validation)
  - analysis and reporting
  - laboratory reference ranges
- reuse of standardized Global Library objects (storage of definition of standard data elements, code lists, CRF data entry layouts, validation and derivation criteria and data extract specifications)
- distributed architecture with comprehensive replication of Global library, study design, data definitions, and study data
- models complex Case Report Forms
- integrated non-programmatic creation of data validations
- powerful built-in discrepancy management system providing total management of each discrepancy from creation through to resolution
- full audit trails on data definitions, patient data, and discrepancies
- flexible Batch Data Load
- integrated randomisation

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Oracle Clinical

Study Conduct and Data Validation

- GUI forms-based data entry
- “heads down” data entry
- multiple-pass data entry options
- unimpeded data entry through ‘enter what you see’ approach
- alternative data capture using data capture API option
- access to Oracle Clinical tables via a documented, stable interface
- online discrepancy review with hot links to view and update data
- extensive reports for tracking error resolution process
- integrated data validation procedures stored as database objects
- mass changes to correct systematic data errors

Access and Reporting

- Standard reports provided for immediate or scheduled execution
- Automatic creation of SAS extracts, data sets and pass-through views
- Powerful View Builder provides ability to build your own custom extract views

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Oracle Clinical

Other General Features

Web deployed Internet application

- configurable security
- extensive online documentation
- extensive context-sensitive online help
- HTML-based Extended Help
- links to customer defined HTML based Help

Client platforms:

- MS Windows NT 4.0, 98, 2000 or XP
- Netscape Communicator 4.5+
- Internet Explorer 5.5+

Server operating systems:

- HP-UX 11.0 (32 and 64 bit)
- Sun Solaris 2.7 and 2.8
- HP Tru64 UNIX 4.0g
- MS NT Server Version 4.0 with service pack 6a (Intel architecture only)

Oracle software for the mid-tier platform (MS NT 4.0 only):

- Oracle Developer Server 6i
- Oracle 9iAS Application Server with the Apache listener

Database server:

- Oracle RDBMS Version 8.1.7

Test version Live

- https://selket.amc.nl/shm/indext.htm
- Login
- Username: collamc02
- Password: collamc02
- Database: SHM
- Study: SHMINT
- Patient: specify one patient

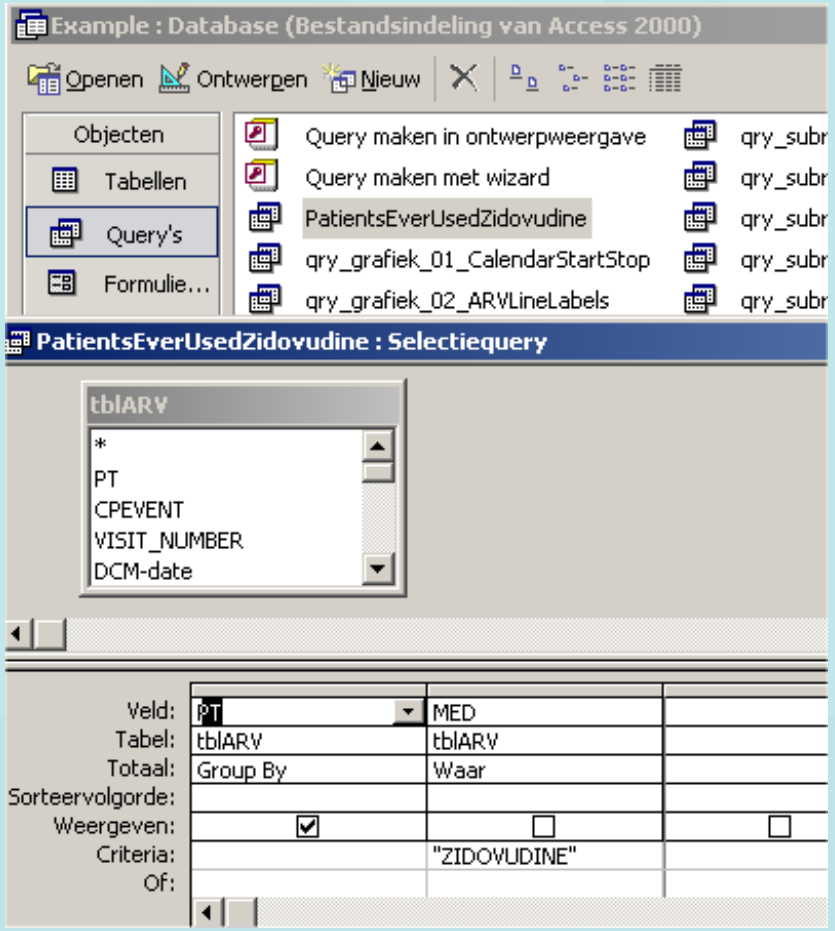
Data overviews in Access db

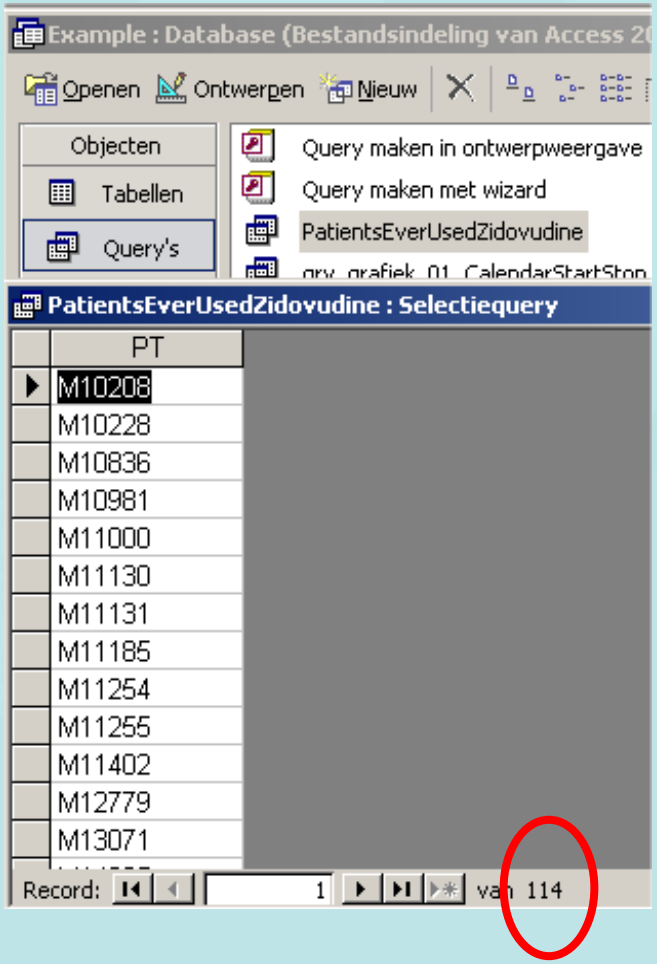
- total overview of one patient's data
- overview of one patient's data by subject (CDC events, co-medication, viral load, etc)
- graphic display of immunology, virology and antiretroviral therapy (ARVT)
- selections can be made by using queries

Analysis group uses

- SAS for analysis
- Splus to make patient graphical overviews

Patient selection by a query





114 patients have used Zidovudine

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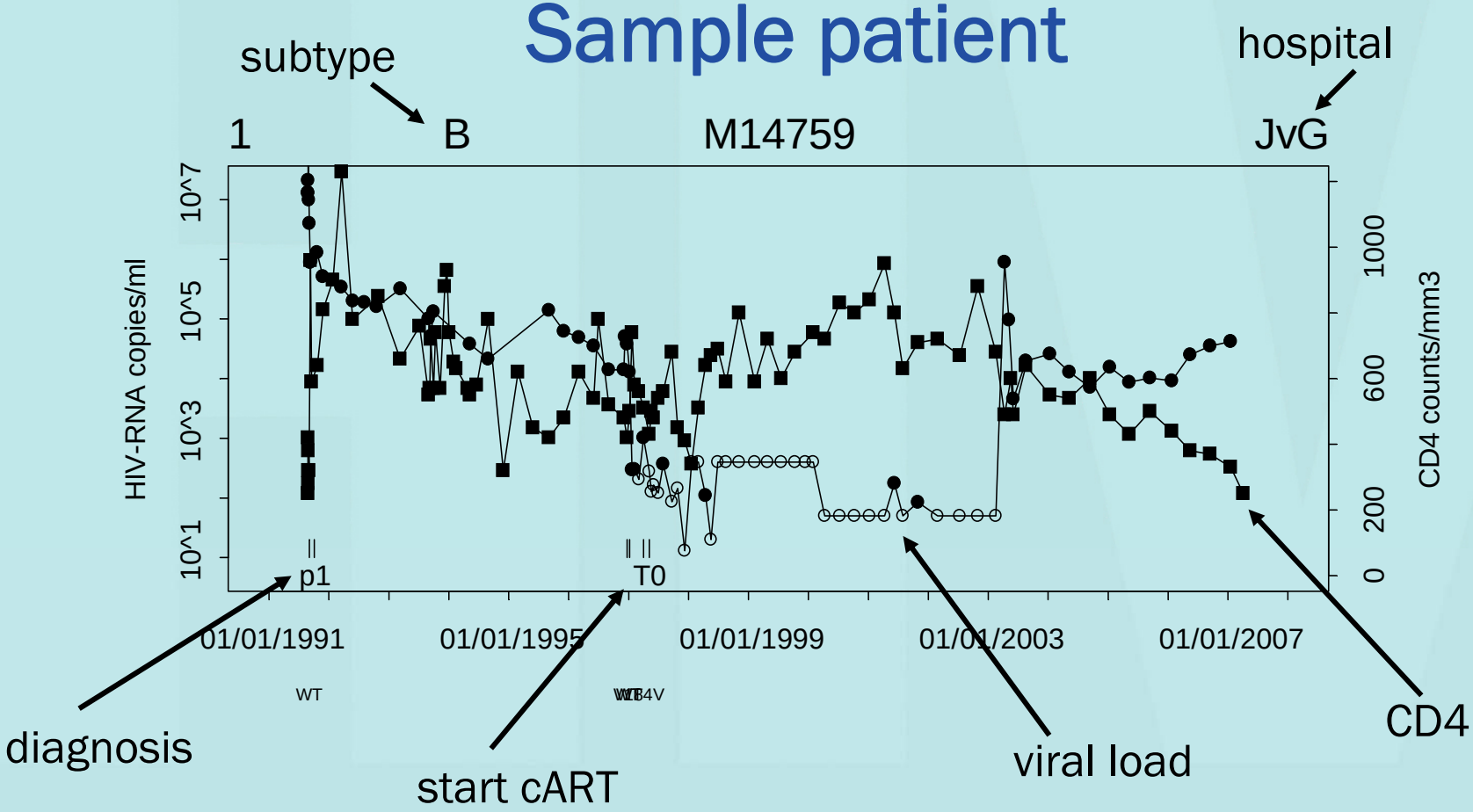
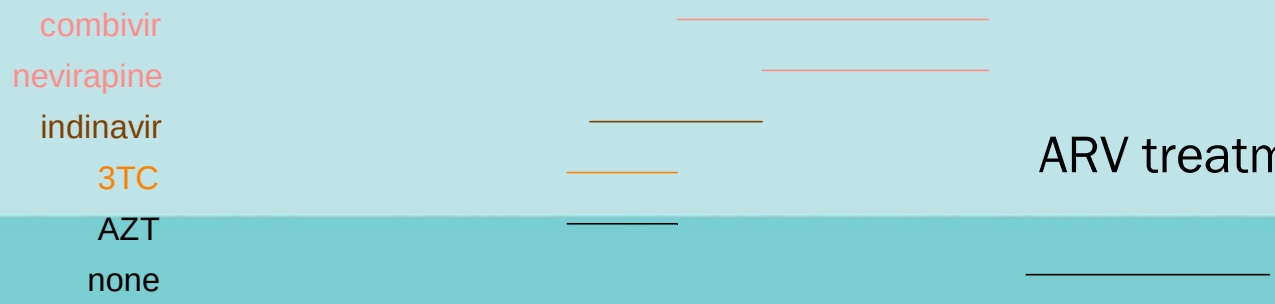
Recommendations

- treat monitoring of HIV as part of patient care
- involve HIV-treating physicians into the review process not only of data to be collected (defining data items), but also in the usage of data for reporting (ownership)
- involve well-trained personnel for data collection and data entry (and if possible local extraction) that is connected to HIV-treating physicians
- try to act as a national monitoring system, but try also to be as independent as possible from institutions
- clarify the aims of monitoring (treatment) of HIV-infected persons as transparent as possible: define the groups you're aiming at, including doctors and patients
- define security measures, IT systems etc. together with the IT staff and consider outsourcing
- connect yourself to a group that has gone through it already, preferably a group outside your own country to start with
- HMF is willing to share the Oracle database structure

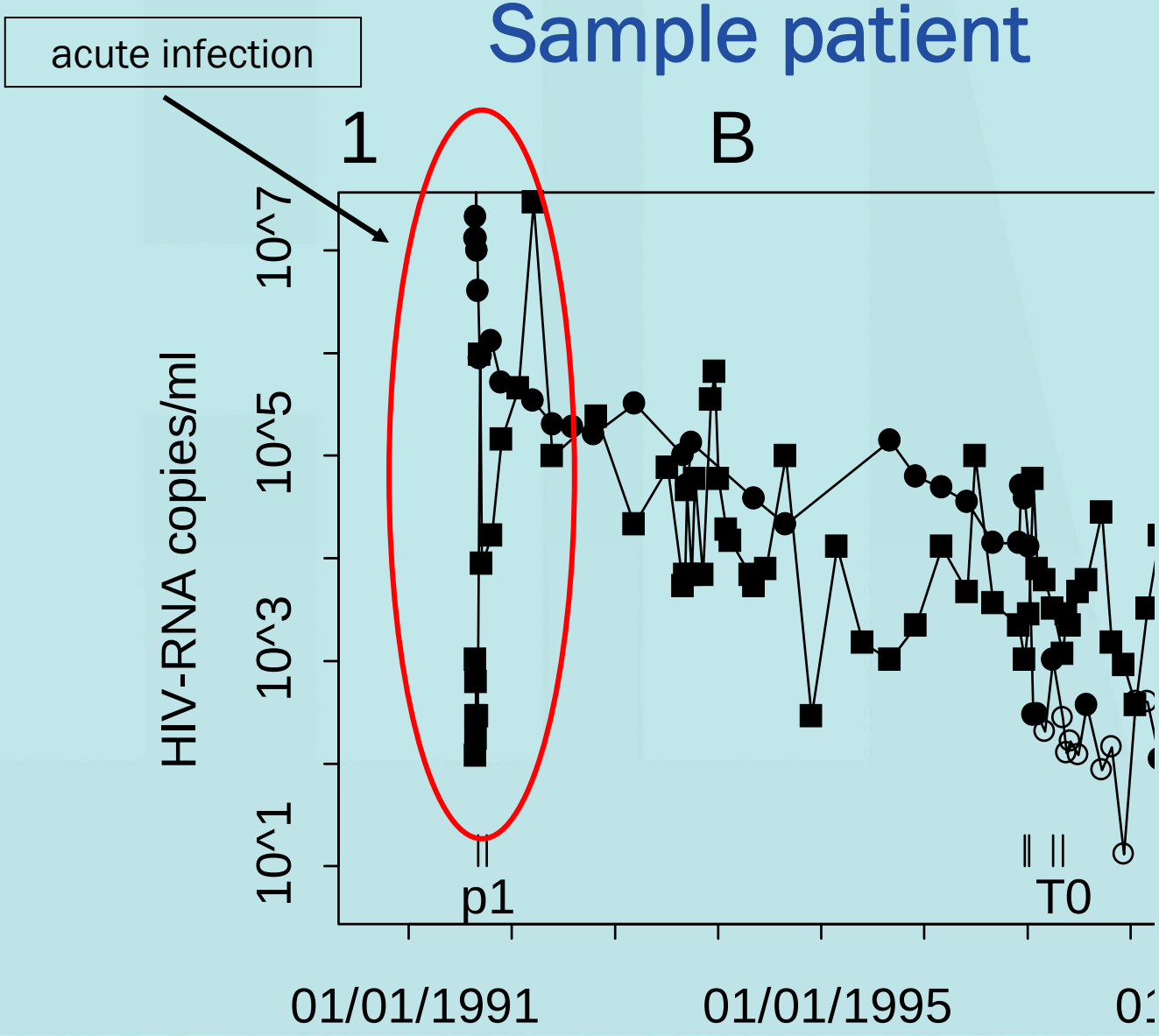
Some results

Sample patient

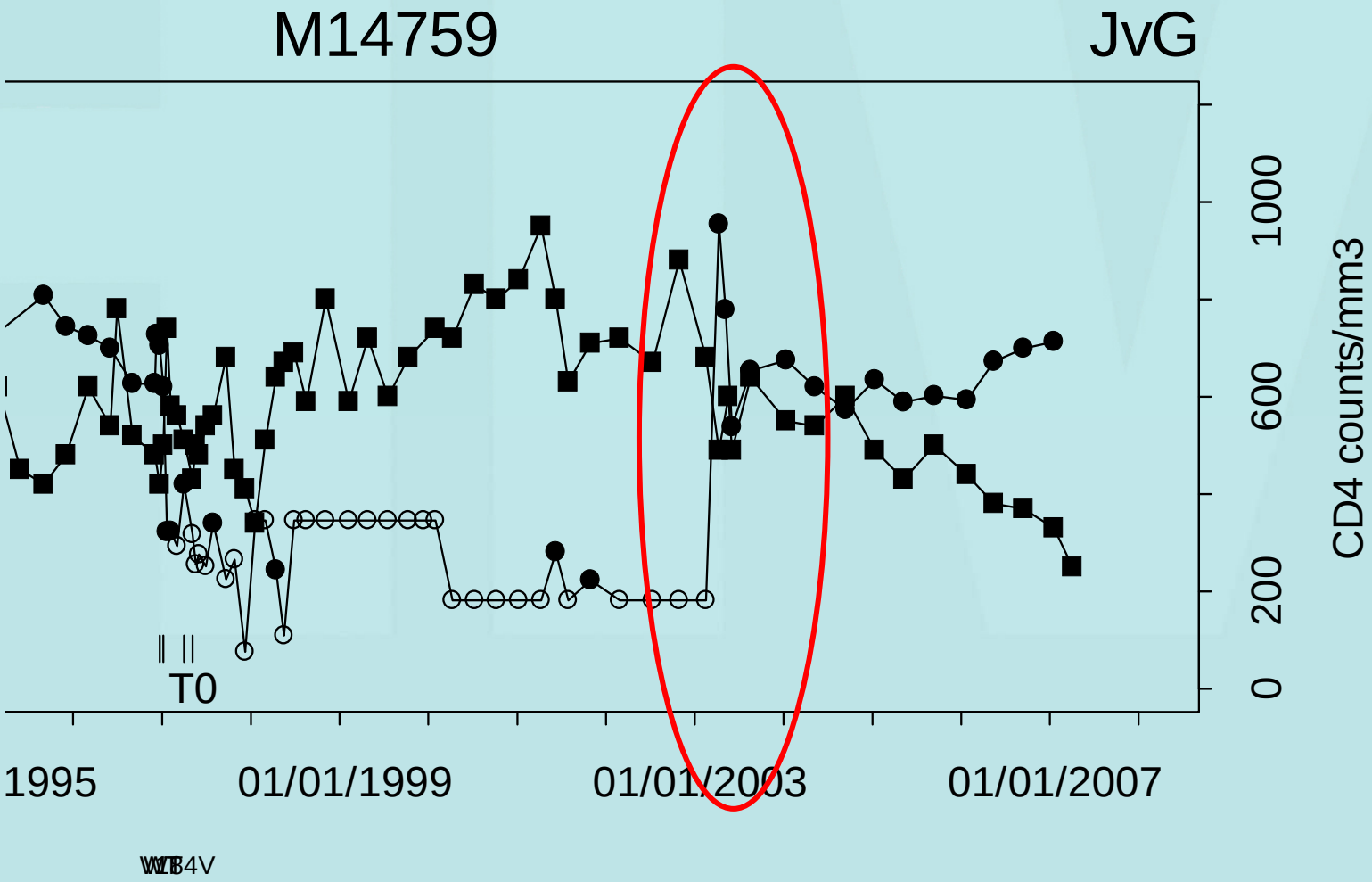




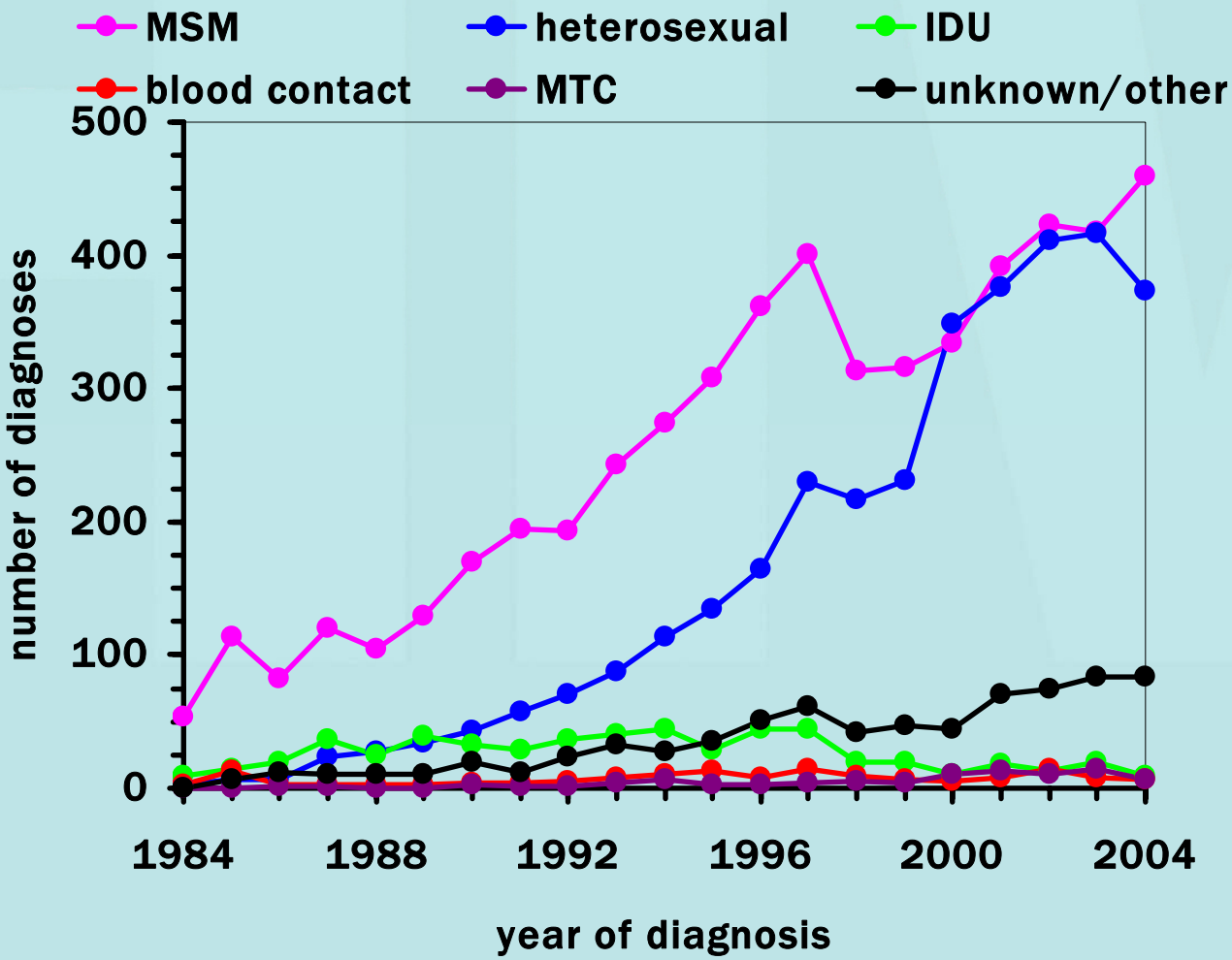
Sample patient



Sample patient



HIV transmission risk groups



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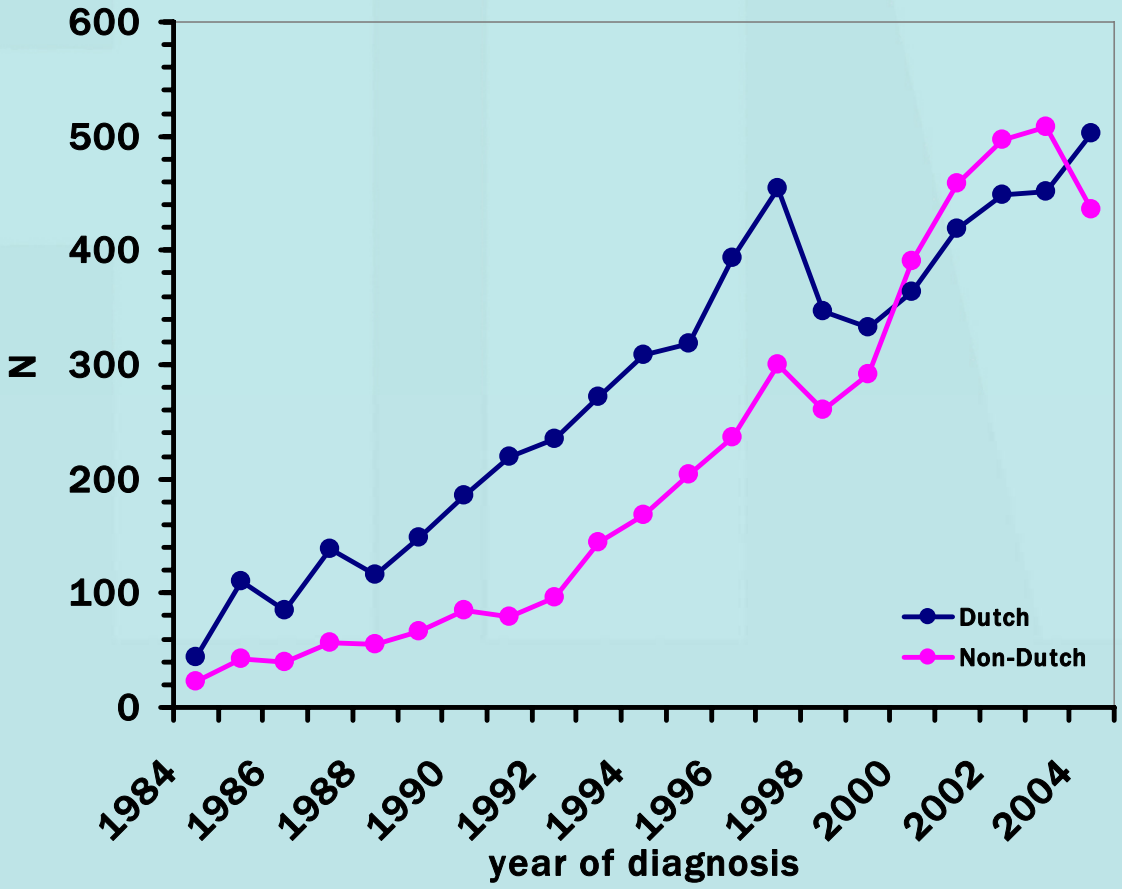
Region of origin



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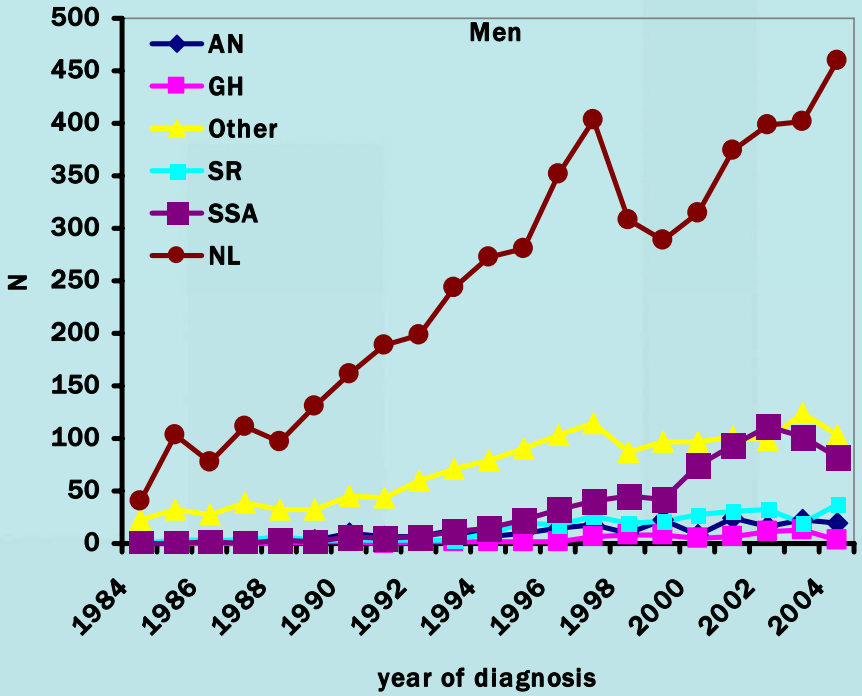
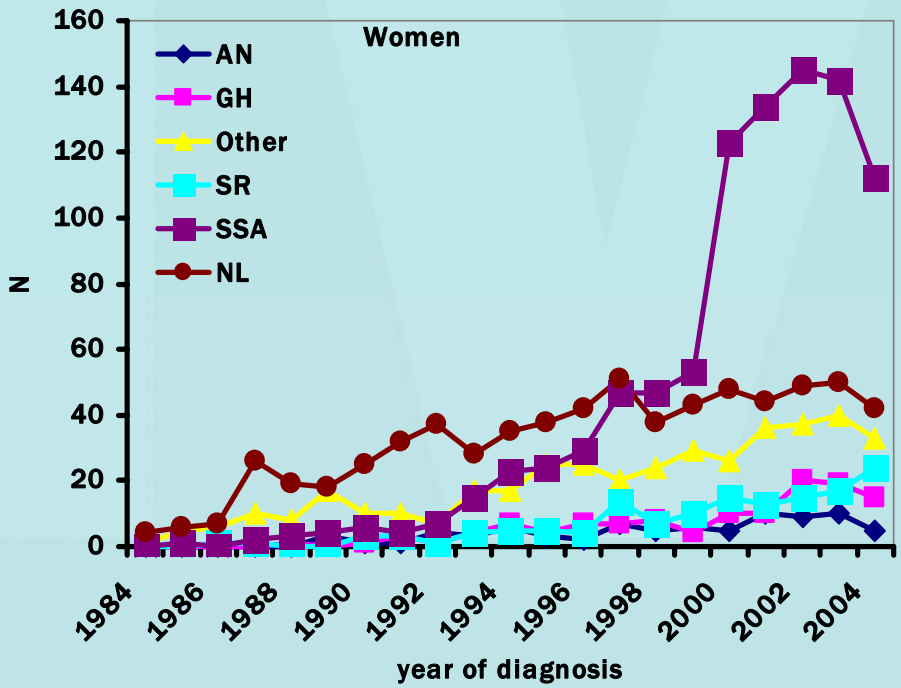
Men and women diagnosed with HIV





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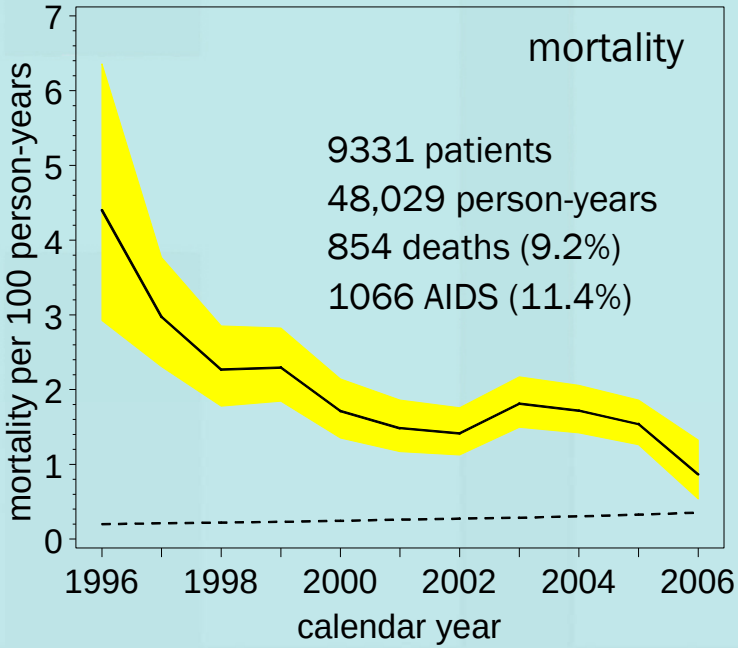
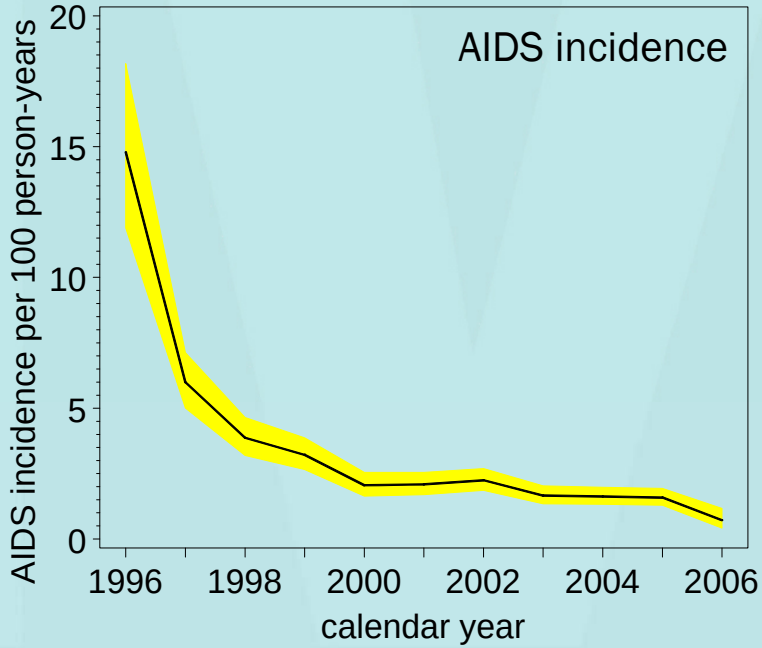
Death and AIDS after start of HAART





- No change in mortality when pre-treated patients were excluded.
- Mortality in the pre-treated population 2 times higher than in the therapy naïve population, but incidence of AIDS is similar.

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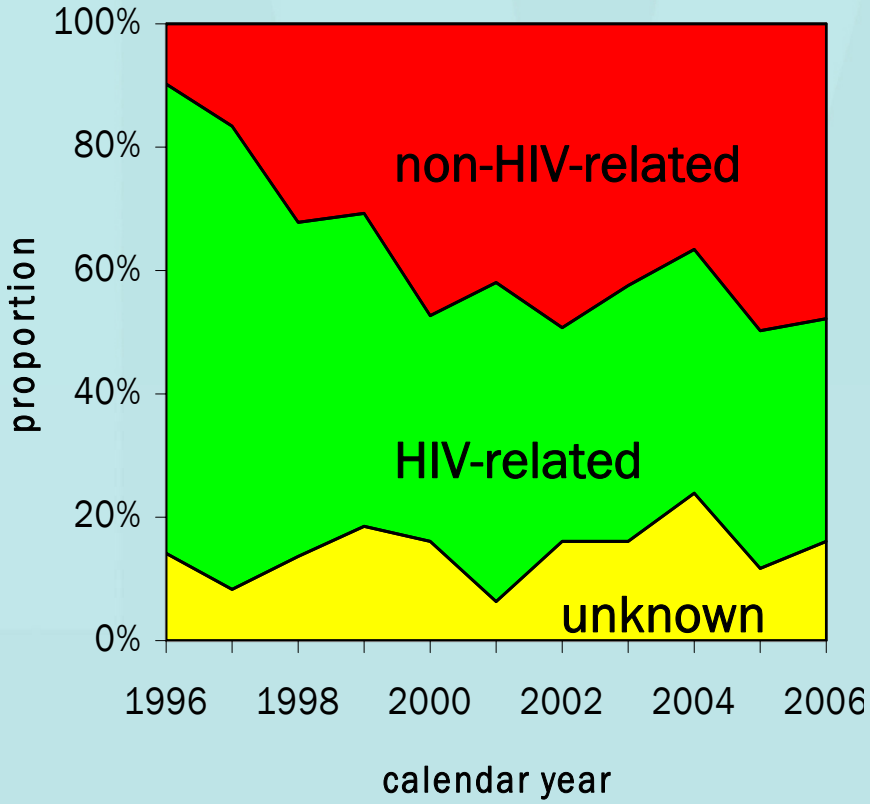
(non-)HIV-related mortality

- HIV-related mortality decreased since 1996:
  - 391 (39.7%) HIV-related cases of death
  - 226 (58%) in patients with AIDS diagnosis in the year before the start of HAART
- Causes of death in 2005:
  - 39% HIV-related
  - 50% non-HIV-related
  - 11% unknown



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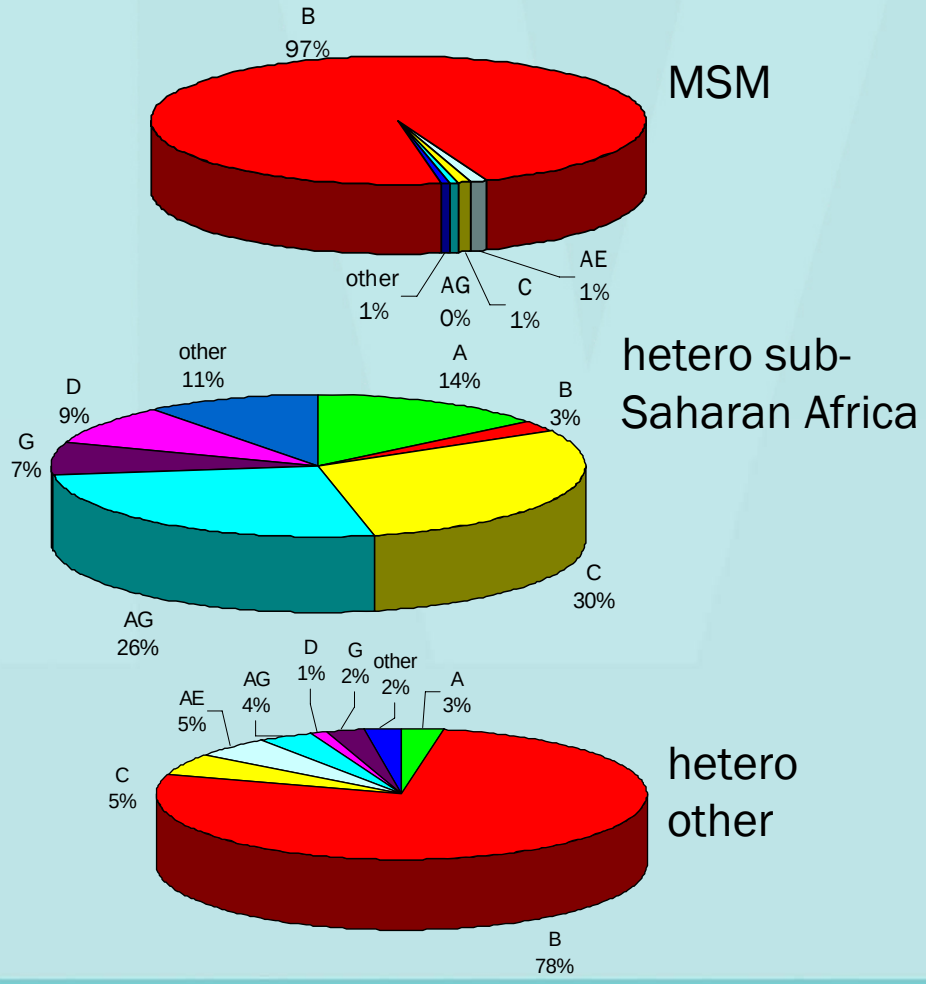
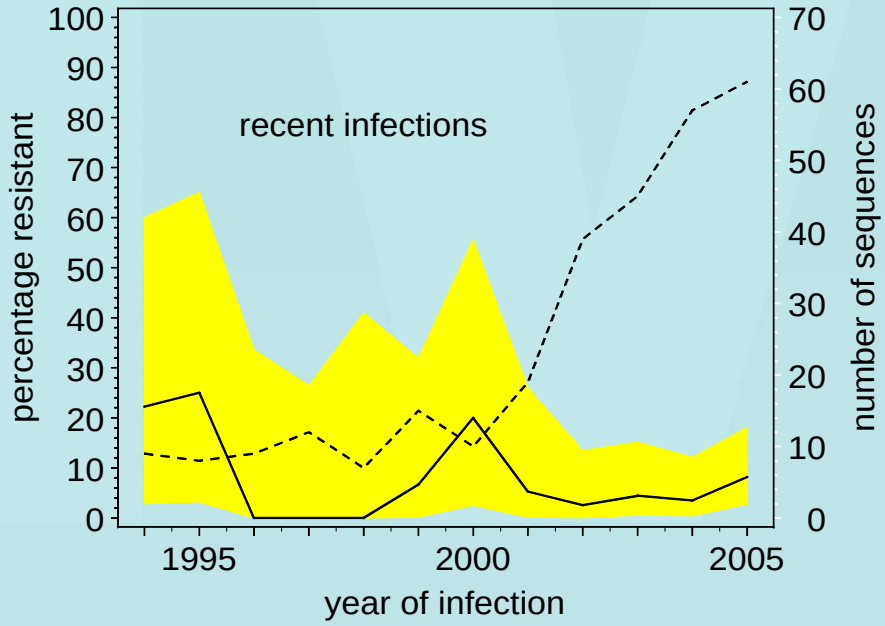
Molecular epidemiology

- HIV subtypes can be used to study the changes in the HIV epidemic.
- most MSM have subtype B, so infections predominantly take place within the group.
- distribution of subtypes within Africans agrees with that in the country of origin, so infections are mostly imported or occur within the own group.



Resistance in recently infected patients

- 18/298 (6.0%) had one or more mutations associated with resistance.
- After 2001, this percentage was 4.8% (10/207).
- 3 patients with “high-level” resistance; 1 of them resistance to all three drug classes.
- Transmission of resistant HIV virus is limited.



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