

14TH ANNUAL CONFERENCE
OF THE BRITISH HIV ASSOCIATION (BHIVA)



Ms Margaret May

University of Bristol

23-25 April 2008, Belfast Waterfront Hall, Northern Ireland, UK

HIV prognosis for those who start cART

Margaret May
Department of Social Medicine
University of Bristol, UK



Questions addressed:

- What is the prognosis of HIV+ patients starting cART at different levels of immunodeficiency and disease stage?
- What is the risk of mortality after an AIDS defining event occurs on treatment?
- What do treated HIV patients die from?
 - How are risk factors associated with different causes of death?
 - What are the competing risks of specific causes of mortality ?
- What is their excess mortality compared with the background population?
- What is their life expectancy?

Topics not covered

- Children
- ART experienced patients
- Drug regimens
- Laboratory markers other than CD4 and VL
- Co-morbidities
- Adverse events
- Drug toxicities
- Host genetics
- Viral subtype



Where the greatest burden of HIV disease is
(see ART-LINC papers)



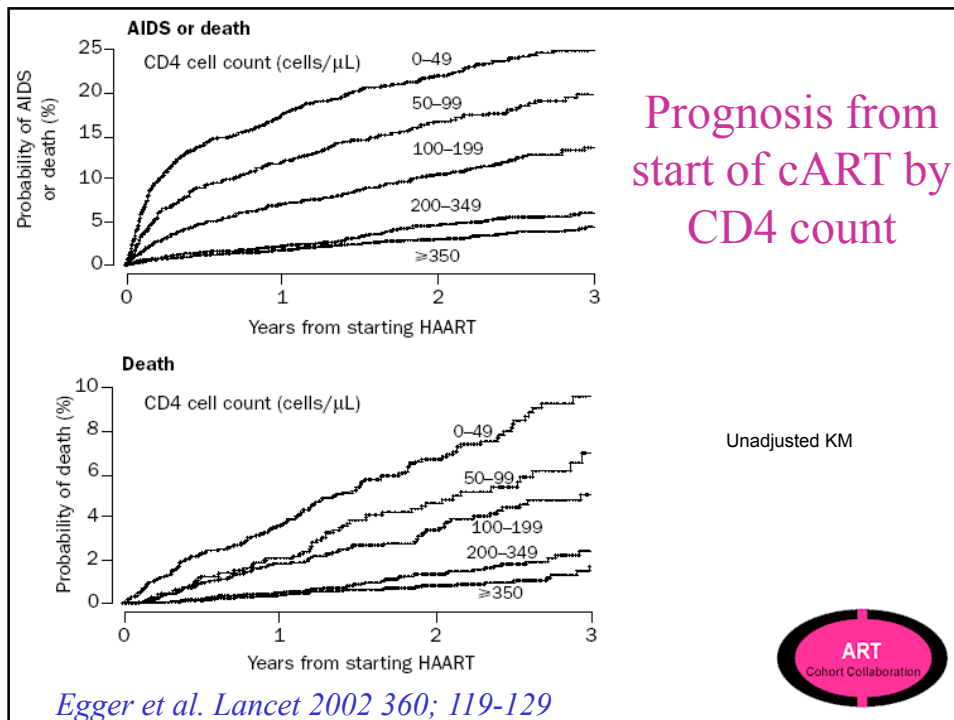
Background: ART-CC

- The Antiretroviral Therapy Cohort Collaboration (ART-CC)
 - Started by Matthias Egger in 2000 to model progression to clinical events
 - Originally 13 cohorts (now 17) from Europe, Canada and US contributed data on 12,574 ART-naïve patients starting triple therapy
- ART-CC prognostic model for patients starting ART published in the Lancet 2002
 - Further papers taking into account response to therapy, OIs, TB, trends over calendar time, longer follow up, drug regimen
- Recent work includes:
 - Comparing mortality with the background population (SMR and Life Expectancy)
 - Analysing competing risks of causes of mortality

ARTICLES

📌 Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies

*Matthias Egger, Margaret May, Geneviève Chêne, Andrew N Phillips, Bruno Ledergerber, François Dabis, Dominique Costagliola, Antonella D'Arminio Monforte, Frank de Wolf, Peter Reiss, Jens D Lundgren, Amy C Justice, Schlomo Staszewski, Catherine Lepout, Robert S Hogg, Caroline A Sabin, M John Gill, Bernd Salzberger, Jonathan A C Sterne, and the ART Cohort Collaboration**
Egger et al. Lancet 2002 360; 119-129



Prognosis from start of cART

Hazard ratios for baseline CD4 count (cells/ μ L)		
	AIDS or death	Death
<50	1 (ref)	1 (ref)
50-99	0.74 (0.62-0.89)	0.72 (0.53-0.99)
100-199	0.52 (0.44-0.63)	0.66 (0.49-0.90)
200-349	0.24 (0.20-0.30)	0.36 (0.25-0.51)
\geq 350	0.18 (0.14-0.22)	0.22 (0.15-0.34)


- Adjusted for age, sex, IDU, disease stage, and viral load
- Older age, IDU and prior AIDS also associated with progression
- VL only associated if >5 log copies
- Probability of progression at 3 years ranged from 3.4% to 50%

Egger et al. Lancet 2002;360:119-129

Prognosis up to 5 years after start of cART

- Updated analyses on 20,379 patients who started cART between 1995-2003
 - longer follow up and more recently recruited patients
- Results in terms of HR broadly similar to earlier analysis
- Probability of progression at 5 years ranged from 5.6% to 77%
depending on age, CD4, VL, clinical stage and IDU
- Risk calculator of probabilities of progression up to 5 years available www.art-cohort-collaboration.org

May et al. AIDS 2007;21:1185-1197



Risk calculator for HIV positive patients starting antiretroviral therapy

Home

Risk Calculator

Collaborating Cohorts

Members of the study groups

Steering Committee

Publications

Supplementary material

Investigator pages

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 each year up to 5 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 five 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: 16 to 29 30 to 39 40 to 49 50 or over

CD4 cell count: under 25 25-49 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

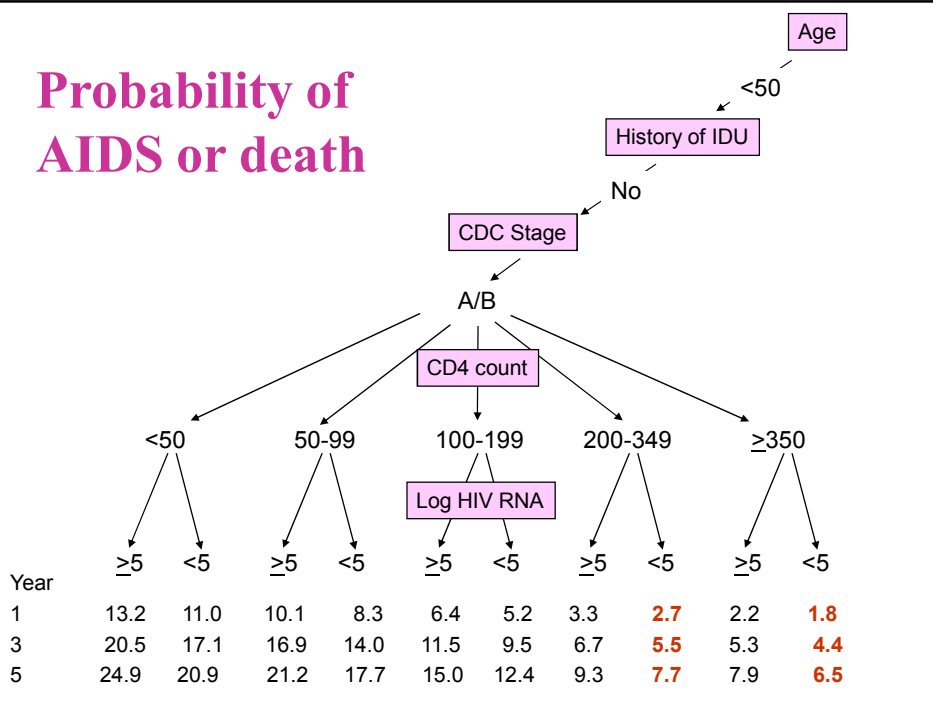
HIV transmission through injection drug use: yes no

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:

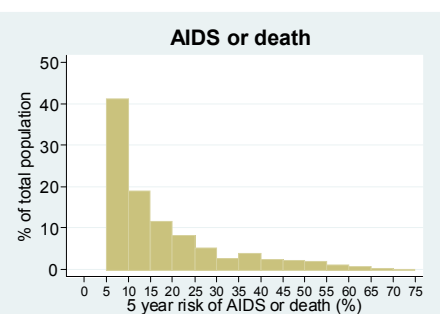
The ART Cohort Collaboration: Prognosis of HIV-1 infected patients up to five years after initiation of HAART: collaborative analysis of prospective studies [AIDS 2007, 21:1185-1197](http://AIDS.2007.21.1185-1197) Writing committee: Margaret May, Jonathan Sterne, Caroline Sabin, Dominique Costagliola, Amy Justice, Rodolphe Thiébaud, John Gill, Andrew Phillips, Peter Reiss, Robert Hogg, Bruno Ledergerber, Antonella D'Arminio Monforte, Norbert Schmeisser, Schlomo Staszewski and Matthias Egger

[Click here to return to main risk calculator page](#)

Probability of AIDS or death

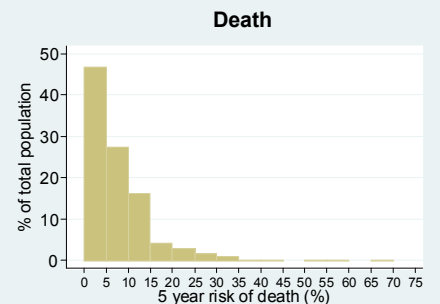


Population distribution of risk



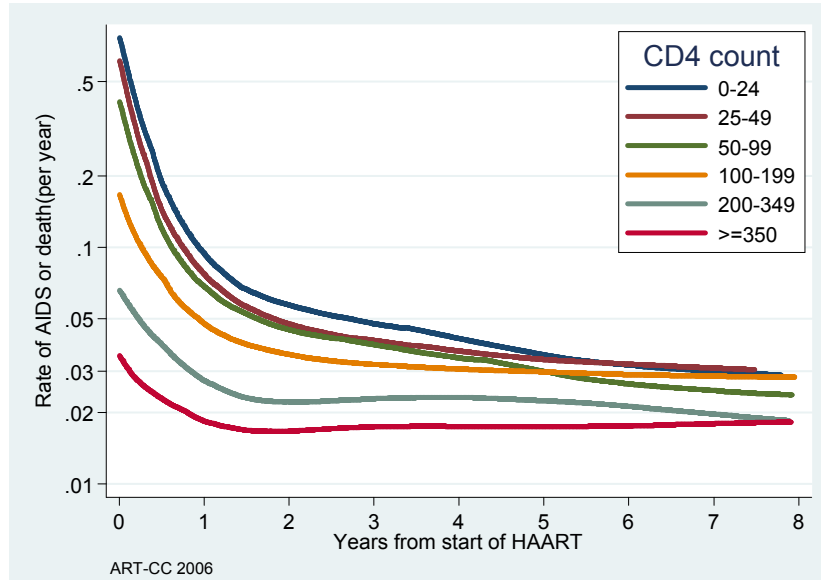
P(AIDS or death)	N(%)
<10%	7628 (41%)
10 – 29%	8101 (44%)
30 – 49%	2059 (11%)
>50%	669 (3.6%)

49% of patients started cART with either CD4<200 or a diagnosis of AIDS



P(Death)	N(%)
<10%	15080 (74%)
10 – 29%	5049 (25%)
30 – 49%	237 (1.2%)
>50%	13 (0.06%)

Rate of AIDS or death after starting cART

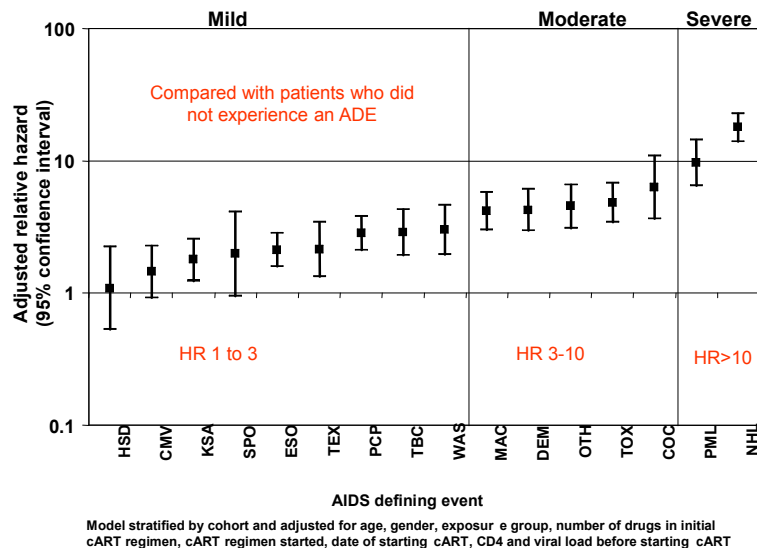


What is the risk of mortality after an AIDS defining event (ADE) occurs on treatment?

- AIDS syndrome defined in the 1980s for surveillance purposes
- used as a composite outcome
 - in clinical research
 - prognostic marker in routine clinical care
- Substantial variation in
 - median CD4 count at diagnosis of different ADEs
 - Relative hazard of death following diagnosis
- We identified 3 groups of ADEs based on prognosis after diagnosis:
 - severe ADEs => substantial increase in the risk of death
 - moderate ADEs
 - mild ADEs => relatively small influence on subsequent mortality.

Mocroft et al. ART-CC CROI 2007

Adjusted mortality hazard associated with each type of AIDS defining event



Mocroft et al. ART-CC CROI 2007

What do treated HIV patients die from?

ART-CC cause of death analyses

- cART has dramatically decreased mortality from HIV related infections and malignancies
- Concerns about mortality directly caused by cART
- New understanding on the wider pathologic aspects of HIV infection beyond the destruction of immunity
- Recognition that non-AIDS causes of death are becoming relatively more important
- Clear need for detailed and ongoing evaluation of the cause of death in patients on cART
- All deaths from 13 ART-CC cohorts with either ICD9 or ICD10 or free text coding were reviewed
 - Underlying cause of death was classified using CoDe protocol (www.cphiv.dk)

Tabulation of CoDe

Assigned CoDe	N	%
10. AIDS	192	10.2%
11. AIDS infection	371	19.6%
12. AIDS malignancy	236	12.5%
20. Infection	127	6.7%
30. Hepatitis	60	3.2%
40. Malignancy	190	10.0%
80. MI/IHD	51	2.7%
140. Liver failure	50	2.6%
160. Accident/violent	35	1.9%
190. Substance abuse	42	2.2%
240. Heart/vascular	56	3.0%
900. Other*	146	7.7%
920. Unknown	287	15.2%
TOTAL	1891	100%

Total no. patients = 39,207

* "Other" includes those coded "90 other" (N=8) plus any CoDe with N<30

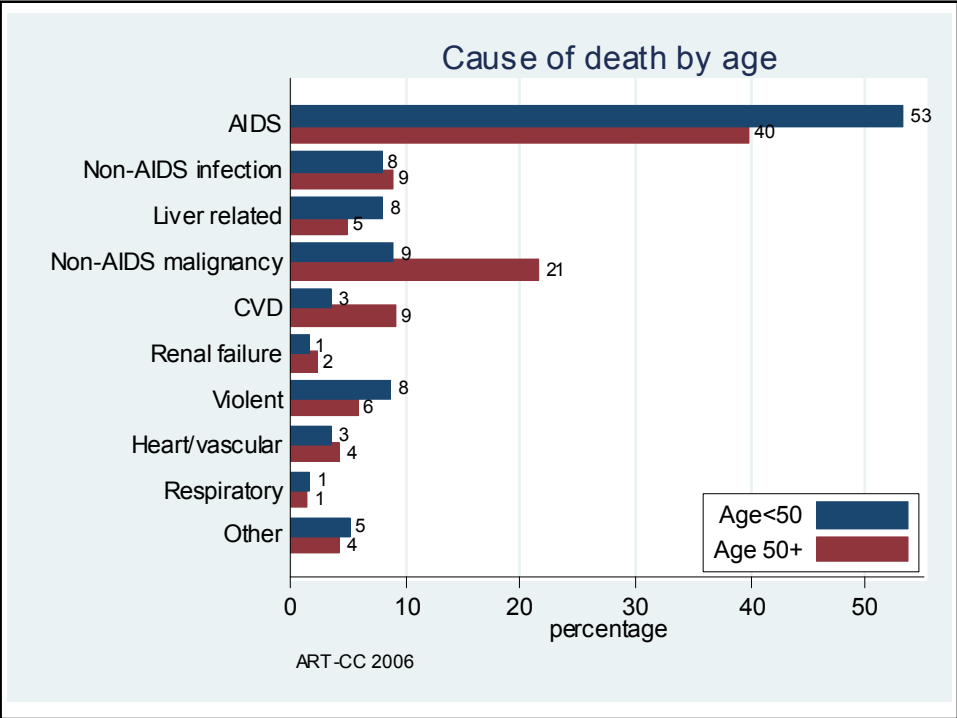
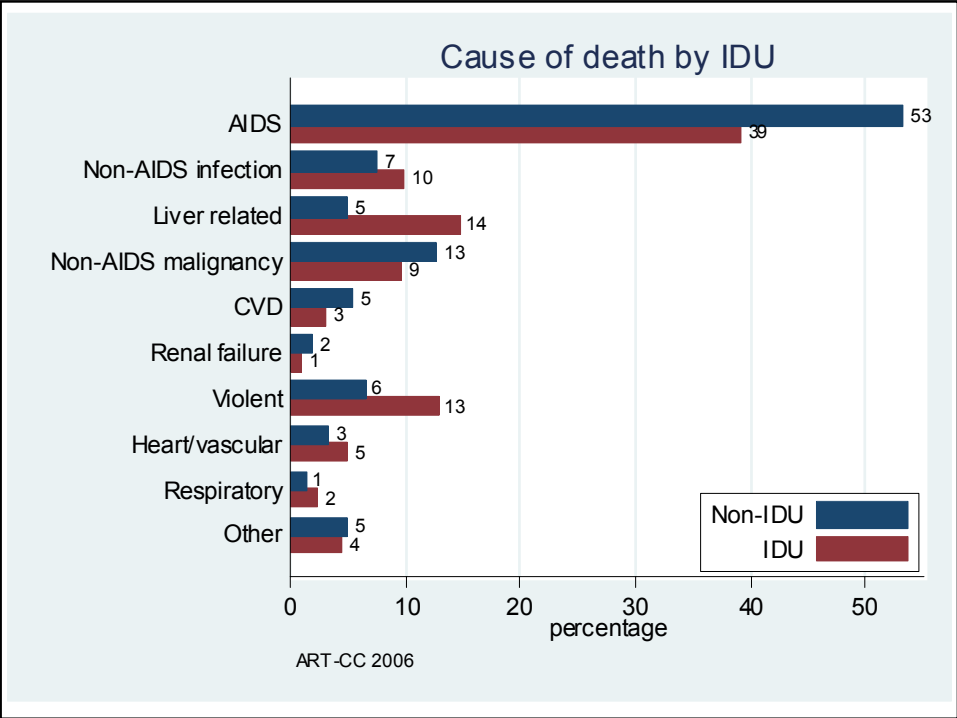
Gill et al. ART-CC 2008 unpublished

Tabulation of assigned CoDe

Assigned CoDe	N	%
10. AIDS	192	12.0%
11. AIDS infection	371	23.1%
12. AIDS malignancy	236	14.7%
20. Infection	127	7.9%
30. Hepatitis	60	3.7%
40. Malignancy	190	11.8%
80. MI/IHD	51	3.2%
140. Liver failure	50	3.1%
160. Accident/violent	35	2.2%
170. Suicide	48	3.0%
190. Substance abuse	42	2.6%
240. Heart/vascular	56	3.5%
900. Other*	146	9.1%
TOTAL	1604	100%

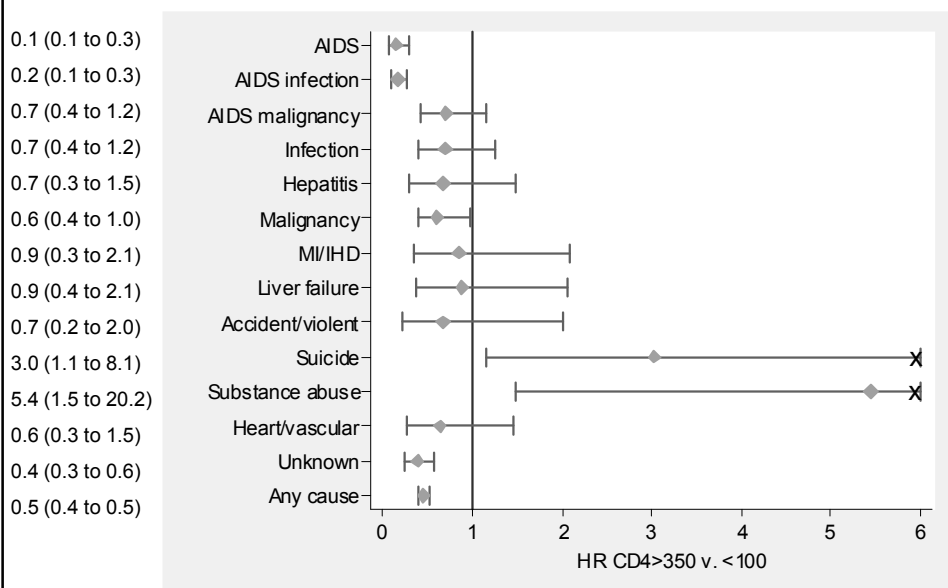
**50%
AIDS**

* "Other" includes those coded "90 other" (N=8) plus any CoDe with N<30

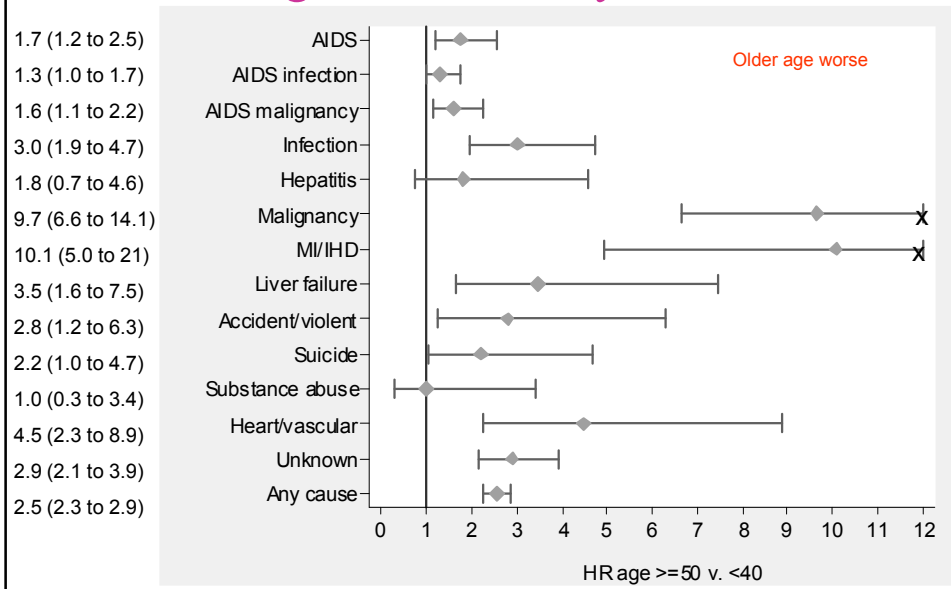


What are the risk factor associations with different causes of death?

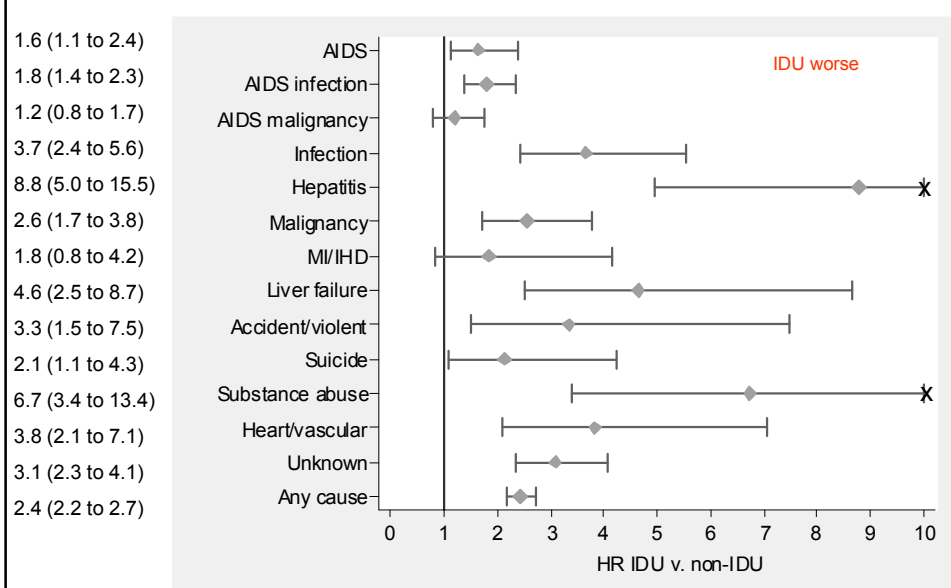
Cause specific hazard ratio (95% CI) for CD4 count at start of cART >350 v. <100



Cause specific hazard ratio (95% CI) age ≥ 50 v. <40 years

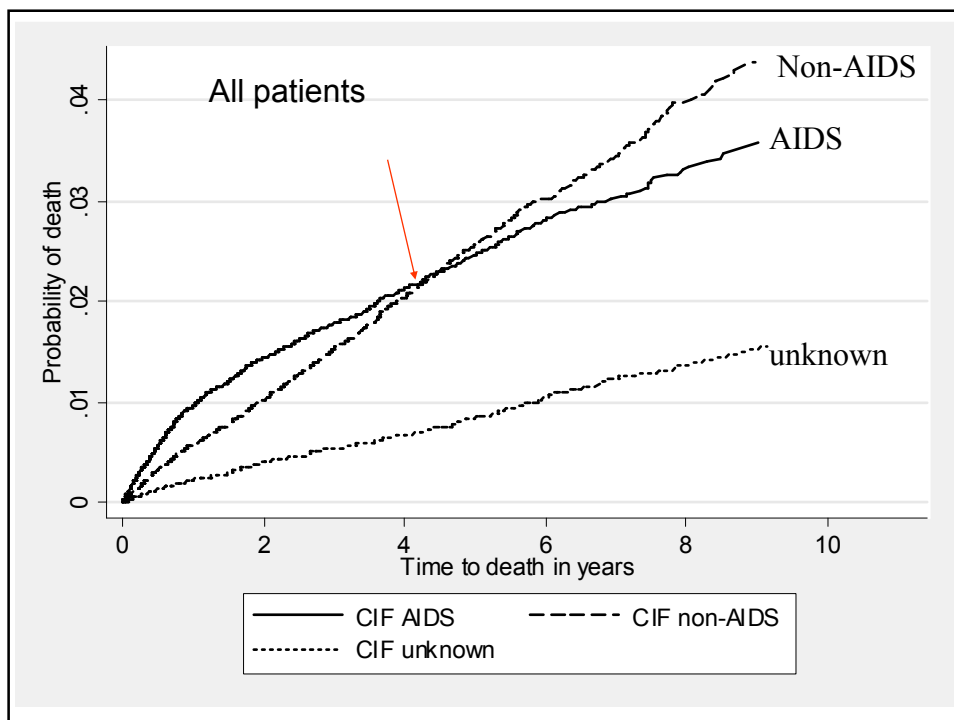


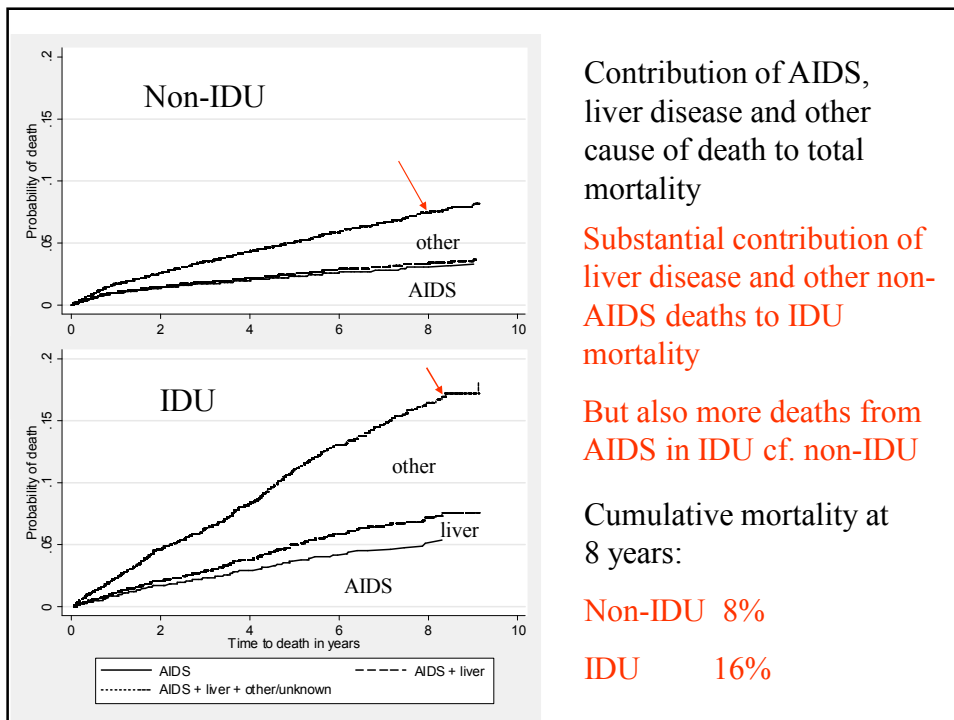
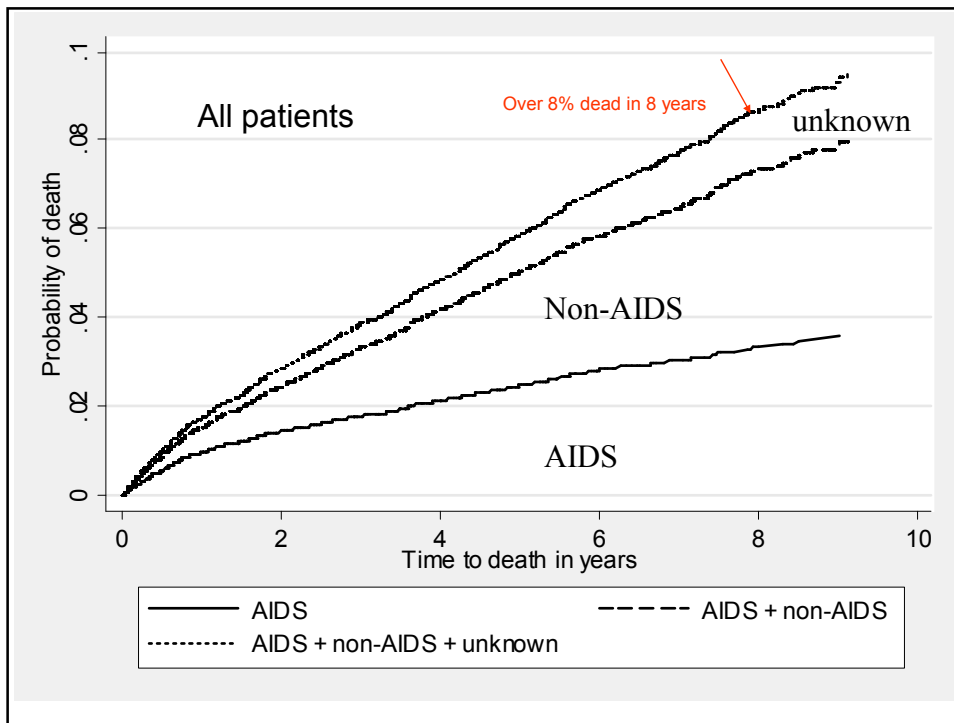
Cause specific hazard ratio (95% CI) IDU v. non-IDU



Estimated mortality taking into account competing risks

- Interested in cumulative mortality
 - partitioned into causes
 - for different risk groups
- Method: Model cause-specific cumulative incidence function (CIF)
 - similar to Kaplan-Meier (KM) estimate
 - takes into account competing risks of death
 - can model several causes at once
- Stacked CIFs partition total cumulative mortality into specific causes





Summary on causes of death

- IDU associated with higher all cause mortality
- IDU had increased risk of liver failure, hepatitis, CVD as well as substance use associated deaths
 - But also had a higher absolute risk of AIDS deaths
- Older age associated with non-AIDS malignancies and CVD
- Causes of death vary considerably according to characteristics at starting therapy
- Association with CD4 must be interpreted cautiously due to its use in assigning CoDe at low CD4 count
 - But association is with CD4 at start of cART and CoDe uses CD4 nearest to death

What is the mortality rate of HIV+ patients compared with the background population?

- In patients who survived 6 months...
- Lowest SMR 1.05 (0.82 to 1.35) in MSM
 - started cART free of AIDS, reached CD4 ≥ 350 and suppressed VL < 500 by 6 m
- Highest SMR 73.6 (46.4 to 116.9) in IDUs
 - with diagnosis of AIDS at initiation
 - failed to suppress viral replication < 500 and had CD4 < 50 at 6m

	<u>% with SMR < 2</u>	<u>% with SMR > 10</u>
MSM	46%	4%
Heterosexual contact	42%	14%
IDU	0%	47%

- Mortality of HIV-infected patients treated with cART continues to be higher than in the general population
- For many patients the excess mortality is moderate and comparable to patients with other chronic conditions

Zwahlen et al. ART-CC 2008 unpublished

What is the life expectancy of patients on cART?

- Abridged life tables constructed to estimate LE stratified by CD4 count and IDU
- Comparison of 3 time periods
- Expectation of life at age 20 is reported
 - Average no. years remaining to be lived by those starting cART at age 20
- For comparison, in the US, LE at age 20 was 58.4 years in 2003

	Crude death rate	Life expectancy (years)			
		All	IDU	CD4 <100	CD4 ≥350
1996 - 99	50.2	22.7	14.8	12.3	33.5
2000 - 02	34.1	26.8	20.1	20.1	35.0
2002 - 06	34.3	28.7	19.8	19.8	35.8

The average LE of those who start cART at age 20 is approximately half that of the general population

Hogg et al. ART-CC 2008 unpublished

Conclusions

- Prognosis depends critically on the CD4 count at start of treatment
 - Also on AIDS diagnosis, age, IDU and to a lesser extent viral load
- Not all AIDS events are equal: prognosis after an AIDS event during treatment depends on whether it is a serious event (eg NHL, not HSD)
 - Implications for design of RCT endpoints
 - Need more research on serious events (COHERE project on NHL)
- 50% of deaths in treated patients are attributed to AIDS
 - Cause of death varies by patient characteristics
 - IDU: absolute risk very high; liver disease/suicide/substance abuse frequent
 - Older age: increased proportion of non-AIDS defining malignancy/CVD
- For many patients the excess mortality is moderate and comparable to patients with other chronic conditions
- Life expectancy at age 20 for those starting cART is approximately half of that of general population, but has improved since the early era of cART
- To improve prognosis, patients need to be diagnosed and treated earlier in the course of HIV infection

Contributing Cohorts

Alabama: UAB 1917 Clinic Cohort, University of Alabama at Birmingham, USA

Aquitaine: Bordeaux University Hospital and four other public hospitals in the Aquitaine region, France

ATHENA: (AIDS Therapy Evaluation project Netherlands): 23 HIV treatment centres including 25 hospitals in The Netherlands

BCCfE: British Columbia Centre for Excellence in HIV/AIDS

CHORUS: 4 clinics in the United States (Nashville, New York, San Francisco and Los Angeles)

EUROSIDA: 82 hospitals in 29 European countries and Argentina

Frankfurt: Klinikum der JW Goethe-Universität Frankfurt

FHDH (French Hospital Database on HIV): National cohort study based on 69 hospitals in France

ICONA (Italian Cohort of Antiretroviral-Naive Patients): cohort of treatment-naïve patients based in 65 clinics in Italy

Köln/Bonn: Departments of Internal Medicine at University of Cologne and Bonn, Germany

PISCIS: Proyecto para la Informatización del Seguimiento Clínico-epidemiológico de la Infección por HIV y SIDA. Catalonia and Balearic islands, Spain. 10 regional hospitals in Barcelona, Majorca and Girona.

Royal Free: Ian Charleson Centre at the Royal Free Hospital London, UK

South Alberta: Southern Alberta Clinic, Canada

Swiss: Swiss HIV Cohort Study (7 centres in Switzerland)

VACS: observational cohort study of HIV-positive and matched HIV-negative veterans based on the Veterans Health Administration, USA

Vancouver: St. Paul's Hospital in Vancouver, Canada

Washington: University of Washington Harborview Medical Center, USA



Sources of funding

UK Medical Research Council (MRC) and GlaxoSmithKline(GSK)

Agence Nationale de Recherches sur le Sida (ANRS), Institut National de la Santé et de la Recherche Médicale (INSERM), French, Italian, Swiss Ministries of Health, Dutch Stichting HIV Monitoring, European Commission, British Columbia and Alberta Governments, Michael Smith Foundation for Health Research, Canadian Institutes of Health Research, GlaxoSmithKline, Roche, Boehringer-Ingelheim, St. Paul's Hospital Foundation, UAB Center for AIDS Research, CFAR Network of Integrated, Clinical Sciences (C-NICS), NA-ACCORD, NIH, FIPSE

Acknowledgements: ART-CC Steering committee

Jordi Casabona (PISCIS), Geneviève Chêne (Aquitaine), Dominique Costagliola (FHDH), François Dabis (Aquitaine), Antonella D'Arminio Monforte (ICONA), Frank de Wolf (ATHENA), Matthias Egger (SHCS), Gerd Fatkenheuer (Köln/Bonn), John Gill (South Alberta Clinic), Robert Hogg (BCCfE-HIV), Amy Justice (VACS), Mari Kitahata (Washington), Bruno Ledergerber (SHCS), Amanda Mocroft (EuroSIDA), Andrew Phillips (EuroSIDA), Peter Reiss (ATHENA), Michael Saag (Alabama), Caroline Sabin (Royal Free), Schlomo Staszewski (Frankfurt), Ian Weller.

Coordinating Team: Matthias Egger, Ross Harris, Jonathan Sterne (Principal Investigator)





14TH ANNUAL CONFERENCE
OF THE
BRITISH HIV ASSOCIATION (BHIVA)

23-25 April 2008, Belfast Waterfront Hall, Northern Ireland, UK