

# Survival After the First AIDS Defining Illness and Causes of Death Before and After the advent of cART.

Results from the French Hospital Database on HIV. <http://www.ccde.fr/>

Sophie Grabar<sup>1,2</sup>, Emilie LANOY<sup>1</sup>, Clotilde ALLAVENA<sup>3</sup>, Murielle MARY-KRAUSE<sup>1</sup>, Christian RABAUD<sup>4</sup>, Michelle BENTATA<sup>5</sup>, Patricia FISCHER<sup>6</sup>, Aba MAHAMAT<sup>7</sup>, Chrystel CHESNEL<sup>8</sup>, Dominique Costagliola<sup>\*1</sup>

<sup>1</sup> Inserm U720, Paris; <sup>2</sup> Hôpital Cochin, Université Paris V, Paris; <sup>3</sup> CHU Hôtel-Dieu, Nantes; <sup>4</sup> CHU de Nancy, Vandoeuvre; <sup>5</sup> Hôpital Avicenne, Bobigny; <sup>6</sup> Hôpital Henri Mondor, Créteil; <sup>7</sup> Hôpital de Cayenne, Cayenne; <sup>8</sup> CHRU Strasbourg, Strasbourg, France.

Dr S. Grabar  
Hôpital Cochin  
Service de Biostatistique et informatique médicale  
27 Rue du Fg St Jacques  
75 679 Paris CEDEX 14, France  
E-mail: sophie.grabar@univ-paris5.fr



## ABSTRACT

**Background:** Many studies have reported the dramatic decline in the risk of death since the introduction of potent combined antiretroviral therapy (cART) but only few have evaluated whether the risk reduction was similar for each specific initial AIDS-defining illness (ADI) and for AIDS-defining and non-AIDS defining causes (ADC) of death.

**Methods:** From the French Hospital Database on HIV, we studied the survival after the first ADI in 3 calendar periods: pre-cART period (1993-1995), early cART period (1998-2000) and late cART period (2001-2003). Hazards of deaths between the 3 periods were estimated by Cox models adjusting for age, CD4, transmission group, and initiation of a mono, dual or cART therapy, as well as used of prophylaxis. Deaths from all causes, from ADC and from non-ADC were considered as specific endpoints. Risk of deaths accounting for competing risks were estimated at 3 years.

**Results:** 8027 patients presented an initial ADI in the pre-cART period (29986 PY, person-years), 3504 (14095 PY) and 2936 (6601 PY) respectively in the early and late cART periods. In the pre-cART period, the three most frequent initial ADI were PCP (15.6%), oesoph. candidiasis (14.3%) and Kaposi's sarcoma (13.9%). It was tuberculosis (22.7%), PCP (19.1%) and oesoph. candidiasis (16.2%) in the late cART period. Hazard of death was significantly reduced in the cART period as compared with the pre-cART period (HR=0.27; CI<sub>95%</sub> 0.24-0.30). Maximal decline was observed after a diagnosis of cryptosporidiosis (89%), KS (85%), CMV (83%), PCP (81%), whereas minimal decline was observed after PML (54%), lymphoma (58%), MAC (58%). Between the two cART periods, hazard of death was still decreasing globally (HR=0.87, CI<sub>95%</sub> 0.77-0.98) although statistical significance was not reached for any specific ADI. The risk of death from an ADC following an AIDS diagnosis was 5-fold reduced between the pre-cART period and the late cART periods (39% versus 8%) whereas the risk of death from a non-ADC was only 2-fold reduced (17% versus 9%).

**Conclusion:** The pattern of presentation of the initial ADI has changed over time. Tuberculosis is now the most frequent presenting ADI in France. A lengthening of survival concerned all the ADI, however, it was more pronounced for some diseases than for others. Benefit of cART was large on ADC of death but also concerned non-ADC to a smaller extent. In the cART period, the absolute risks of death from ADC and non-ADC cause of deaths are now similar.

## BACKGROUND

- Many studies have reported the dramatic decline in the risk of death since the introduction of potent antiretroviral therapy but only few have evaluated whether the risk reduction was similar after each specific initial AIDS-defining event.

## OBJECTIVES

- To study the impact of combined antiretroviral therapy (cART) on the first AIDS defining illness (ADI) and on survival after each individual ADI.
- To describe the initial ADI in 3 periods characterized by different treatment availability: pre-cART period (1993-1995) and early cART (1998-2000) and late cART (2001-2003) period.
- Trends in AIDS-defining causes (ADC) and non-ADC of deaths.

## PATIENTS

### Source: The FHDH database

- French Hospital Database on HIV (FHDH) Set-up in 1989. 62 hospitals.

- Inclusion criteria:
  - confirmed HIV-1 or HIV-2 infection
  - to be followed in an hospital
  - to have signed an informed consent

- Data are collected prospectively by trained research assistants from medical records on standardised f/up form (DMI2 software).

- >45 000 patients were followed in 2003
- 102 777 patients included by mid 2005

### Patients selection:

- HIV-infected patients from FHDH with a first ADI diagnosed in either:
  - pre-cART period (1993-1995): 8 027 patients, 29 986 PY
  - early cART period (1998-2000): 3 504 patients, 14095 PY
  - late cART period (2001-2003): 2936 patients, 6 601 PY

### Statistical methods:

- Multivariate analyzes:
  - Time to death since a first ADI
  - Event: separate analysis considered:
    - death from all causes
      - Kaplan Meier curves
      - Cox proportional hazards models adjusted for period adjusted for sex, age at AIDS onset, CD4 cell count, region of follow-up, region of origin, HIV exposure category, ART monotherapy, dual therapy or cART, and prophylaxis.
    - Analyzes were performed separately according to each first ADI.
  - AIDS-defining causes (ADC) and non ADC of death
    - AIDS CDC 1993 definition
    - modelled using competing risk of deaths

## RESULTS (1)

- By comparison with the pre-cART period, patients diagnosed with AIDS in the cART periods were more often heterosexual, less often homosexual and more often migrants from sub Saharan Africa (18.4% vs 2.7%). They tended to have higher CD4 cell counts at AIDS diagnosis (median 82 vs 45/mm<sup>3</sup>) and were more likely to be diagnosed with AIDS at enrolment in the FHDH database. (Table 1)

### First AIDS-defining illnesses

- The pattern of the first ADI has changed over time.
- The most frequent ADI were PCP (15.6%), esophageal candidiasis (14.3%) and KS (13.9%) in the pre-cART period, PCP (19.9%) tuberculosis (18.2%) and esophageal candidiasis (16.2%) in the early cART period, and tuberculosis (22.7%), PCP (19.1%), and esophageal candidiasis (16.2%) in the late cART period. (Figure 1)
- The median CD4 cell count at AIDS onset increased significantly across the 3 periods for all individual ADI, except for PCP (36/mm<sup>3</sup> and 33/mm<sup>3</sup> in the pre-cART and late cART periods) and cryptococcosis.

Table 1: Characteristics of patients diagnosed with first ADI.

	Pre cART period 1993-1995 (8027 pts)	Early cART period 1998-2000 (3504 pts)	Late cART period 2001-2003 (2936 pts)	p
<b>Men</b>	6496 (80.9)	2607 (74.4)	2 109 (71.8)	<10 <sup>-4</sup>
<b>HIV transmission group</b>				
Homosexual men	3488 (43.5)	1078 (30.8)	787 (26.8)	
IV drug users	2078 (25.9)	636 (18.2)	412 (14.0)	
Heterosexuals	1789 (22.3)	1431 (40.8)	1435 (48.9)	
Others	672 (8.3)	359 (10.2)	302 (10.3)	<10 <sup>-4</sup>
<b>Region of follow-up</b>				
Paris and suburbs	3762 (46.9)	1674 (47.8)	1529 (52.1)	<10 <sup>-4</sup>
Age at AIDS onset median (IQR)	35.3 (31.1-42.3)	38.2 (33.5-44.7)	39.8 (78.5)	<10 <sup>-4</sup>
<b>CD4 cell count at AIDS onset median (IQR)</b>	41 (13-123)	80 (25-210)	79 (26-210)	<10 <sup>-4</sup>
<b>Patients with CD4 &lt;200/mm<sup>3</sup> at AIDS n(%)</b>	6154 (76.7)	2404 (68.6)	2050 (69.8)	<10 <sup>-4</sup>
<b>Last known ARV treatment before AIDS onset</b>				
No treatment	3961 (49.3)	1908 (54.5)	1525 (51.9)	
Nucleoside monotherapy	3377 (42.1)	48 (1.4)	24 (0.8)	
Dual nucleoside therapy	681 (8.5)	292 (8.3)	131 (4.5)	
cART*	8 (0.1)	1256 (35.8)	1256 (42.8)	<10 <sup>-4</sup>
<b>Prophylaxis at AIDS diagnosis</b>				
Never prophylaxis	2682 (33.4)	661 (18.9)	564 (19.2)	
Never prophylaxis	693 (8.6)	547 (15.6)	465 (15.8)	
Prior prophylaxis but none at AIDS onset	4652 (58.0)	2296 (65.5)	1907 (65.0)	<10 <sup>-4</sup>
<b>AIDS at enrollment in FHDH</b>	2068 (25.8)	1363 (38.9)	1105 (37.6)	<10 <sup>-4</sup>
<b>AIDS or CD4 &lt;200/mm<sup>3</sup> at enrollment in FHDH More than one AIDS-defining illness at AIDS onset</b>	3620 (45.1)	1875 (53.5)	1568 (53.4)	<10 <sup>-4</sup>
	994 (12.4)	440 (12.5)	390 (13.3)	0.10
<b>Known sub-Saharan origin</b>	214 (2.7)	405 (11.6)	539 (18.4)	<10 <sup>-4</sup>

Figure 1: Relative frequency of each initial ADI

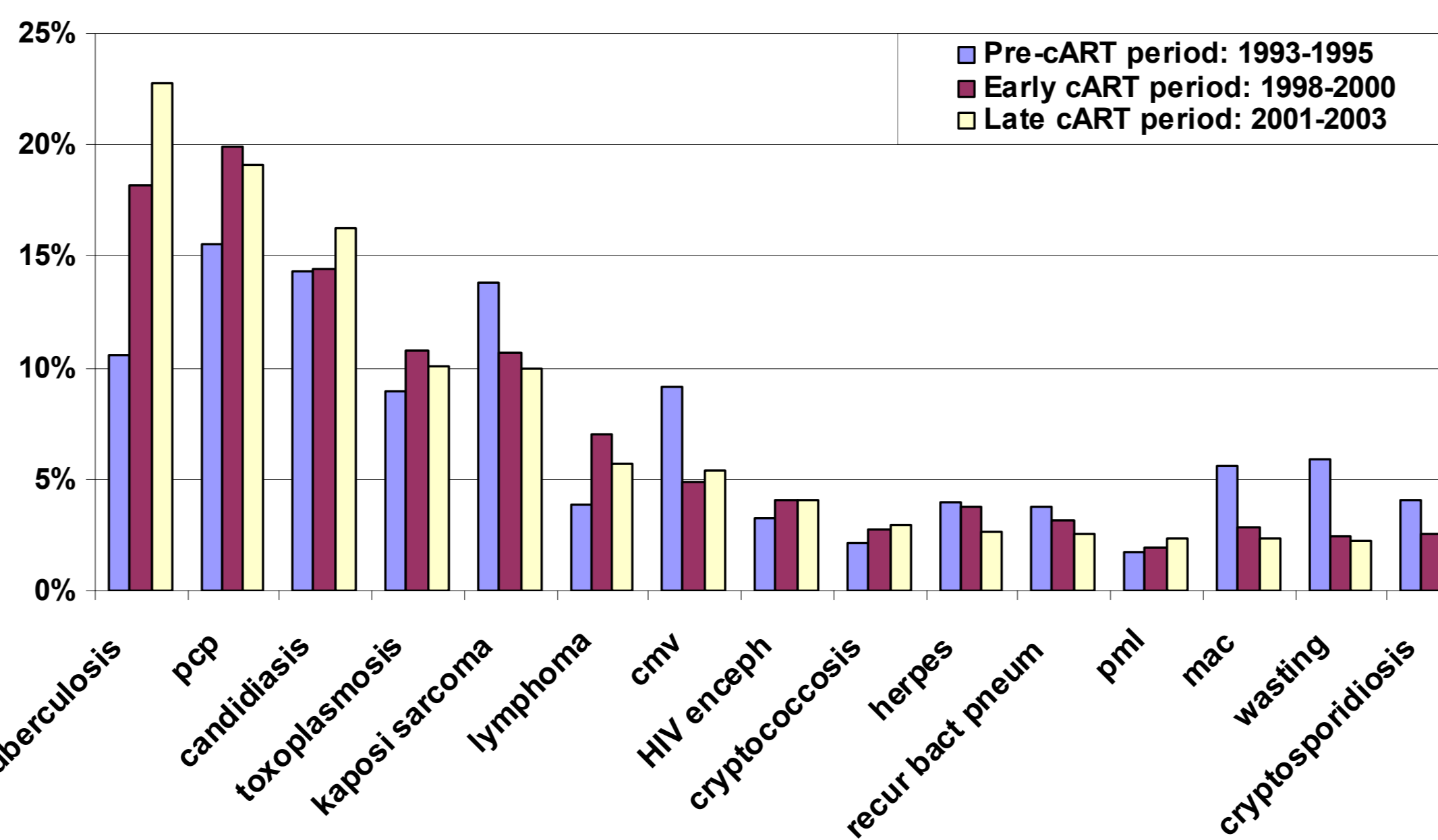


Figure 2: Adjusted hazards of death according to the initial AIDS-defining illness between the cART periods (2001-2003 and 1998-2000) and the pre-cART period (1993-1995).

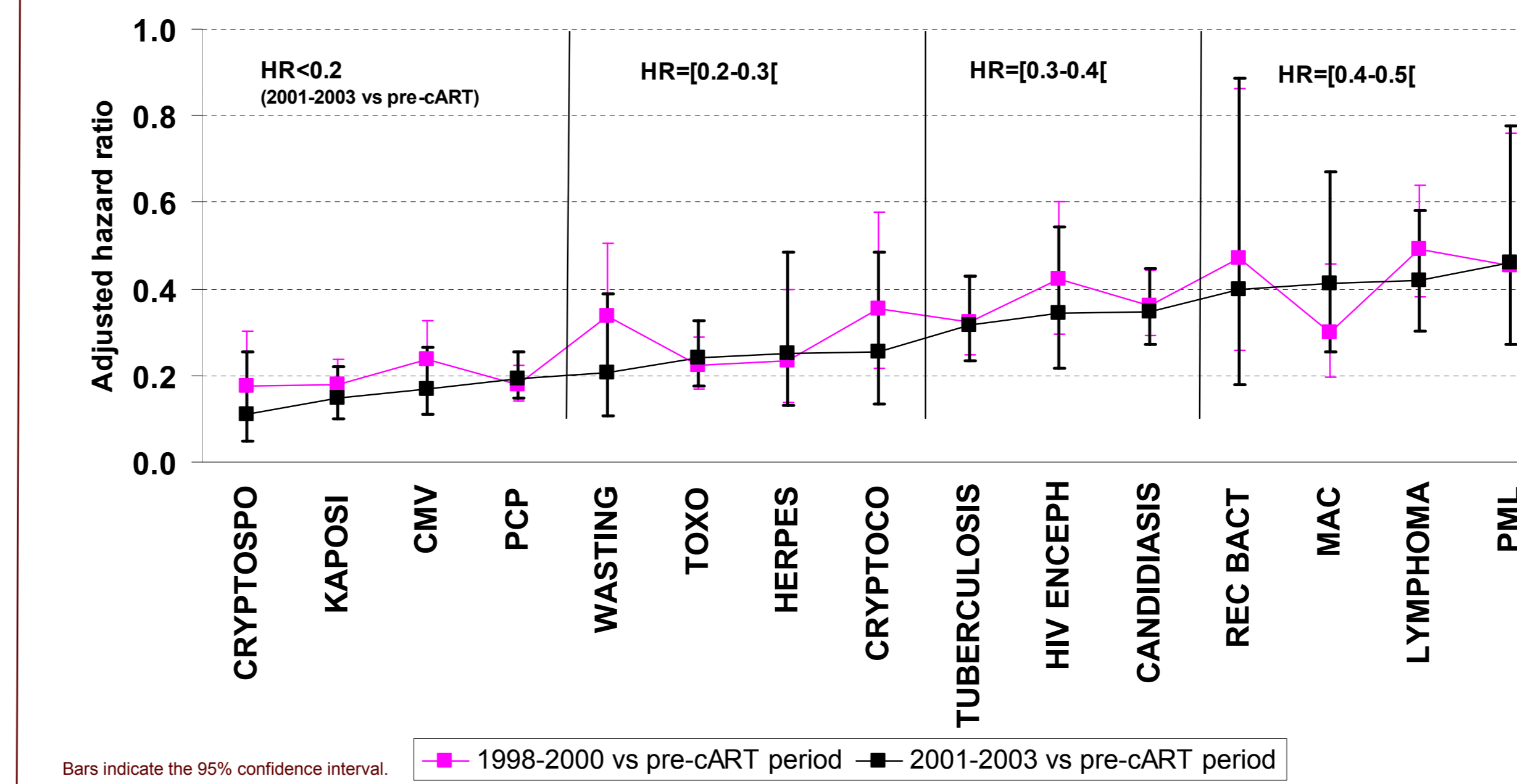
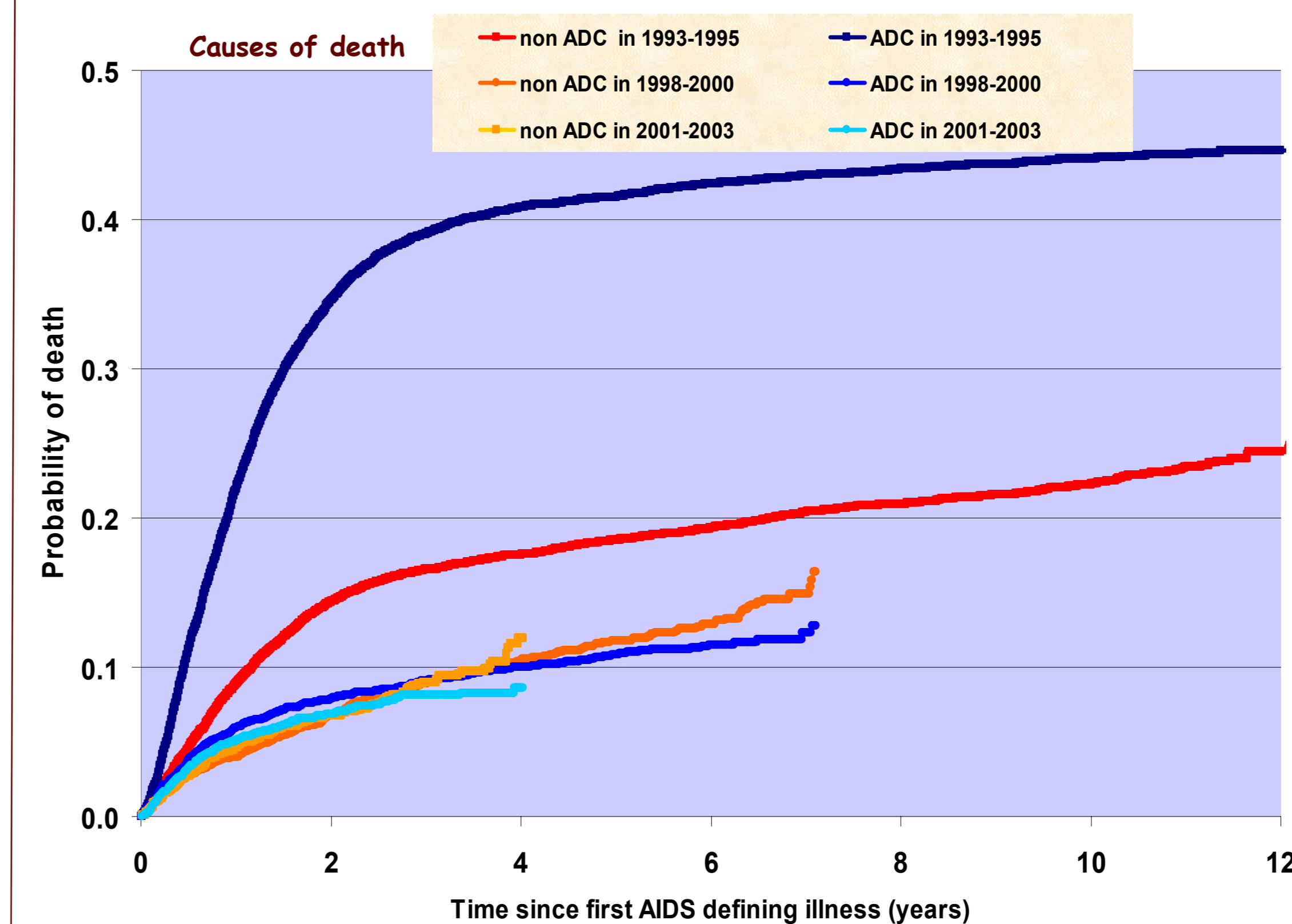


Figure 3: Cumulative incidence of death after the first AIDS-defining illness, according to the cause of death: a competing risk analysis.



## RESULTS (2)

### Survival according to the first AIDS-defining illness

- The gap between the best and worst survival rates after diagnosis of the different first ADI tended to become smaller with time.
- The 3-year survival estimates ranged from
  - 26% to 71% (for PML and recurrent bacterial pneumonia, respectively) in the pre-cART period,
  - 63% to 90% (for MAC and KS) in the late cART period.

### Risk and Causes of death

- Hazard of death was significantly reduced in the cART period as compared with the pre-cART period (HR=0.27; CI<sub>95%</sub> 0.24-0.30).
- Between the two cART periods, hazard of death was still decreasing (HR=0.87, CI<sub>95%</sub> 0.77-0.98) although statistical significance was not reached for any specific ADI.
- Figure 3 shows the cumulative incidence of death in the three periods, after taking competing risks into account, the cumulative 3-year incidence of death for ADC and for other causes are summarized in Table 2.

Table 2: cumulative 3-year incidence of death for ADC and for other causes

Risk of deaths at 3 years from	Pre-cART period	Late cART period
<b>Aids-defining cause</b>	39% (38-40)	8% (7-9)
<b>Non Aids defining cause</b>	17% (16-17)	9% (8-10)

## CONCLUSIONS

- The pattern of initial ADI has changed over the time.
  - Tuberculosis is now the most frequent initial ADI.
  - Survival with AIDS increased markedly, regardless of initial ADI.
  - Smallest increases were observed for PML, lymphoma, MAC and recurrent bacterial infection.
  - The risk of death from ADC and non-ADC are now similar
  - cART has had a major impact on ADC of death and also to a lesser extent on other causes.
- => This suggests that in future it would be interesting to identify and study clinical conditions not included in 1993 CDC definition of AIDS, but nonetheless associated with HIV immunodeficiency.