

HIV and Non-HIV-related Deaths and Their Relationship to Immunodeficiency: The D:A:D Study

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BACKGROUND

Deaths in people with HIV infection are often classified according to whether they are thought to be “HIV-related” or not. We studied whether deaths generally thought to be unrelated to HIV were more likely to occur in people with a low CD4 count.

METHODS

D:A:D is a prospective study of 23,441 patients from 11 existing cohorts in Europe, Australia, and the USA. Detailed information on deaths occurring between the initiation of D:A:D in 2000 and February 2004 was collected.

Causes of death were coded centrally in to the following categories according to the *underlying* cause of death:

- HIV/AIDS
- Invasive bacterial infection
- Malignancy, non-AIDS, non-hepatitis
- Chronic viral hepatitis
- Liver failure (other)
- Myocardial infarction, definite or possible
- Stroke
- Other cardiovascular disease
- Other heart disease
- Complications to diabetes mellitus
- Pancreatitis
- Lactic acidosis
- Renal failure
- Drug overdose
- Suicide
- Euthanasia
- Other, specific
- Unknown

For the purpose of these analyses, the following groupings were applied:

HIV/AIDS-related:

- HIV/AIDS
- Invasive bacterial infection
- Euthanasia

Liver-related:

- Chronic viral hepatitis
- Liver failure (other)

Malignancy-related:

- Malignancy, non-AIDS, non-hepatitis

Heart-related:

- Myocardial infarction, definite or possible
- Other cardiovascular disease
- Other heart disease

Relative rates of factors associated with death were calculated using Poisson regression, adjusted for HIV RNA, age, cohort, race and smoking status.

Table 1

Total and Selected Causes of Death

	No. deaths	Rate (/100 pyrs)
All	1248	1.62
HIV/AIDS related	457	0.59
Liver-related	174	0.23
Heart-related	111	0.14
Malignancy (non-AIDS)	100	0.13

Figure 1

Causes of death in DAD 2000-2003 percentage/ Year

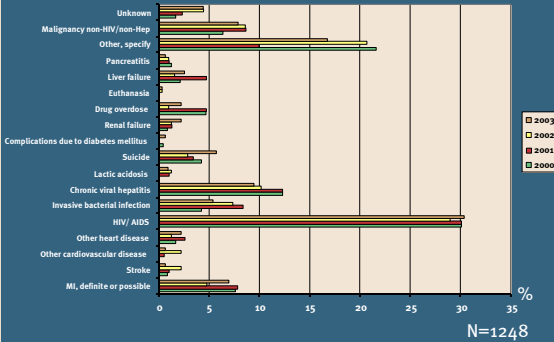


Table 2

HIV / AIDS-Related Deaths

CD4 count	Number	PY	Rate (95% CI) per 1000 PY	Rate ratio* (95% CI)
<50	210	1657	126.7 (109.6-143.9)	96.4 (61.6-150.7)
50-	55	1711	32.1 (23.7-40.6)	28.5 (17.6-46.0)
100-	83	6044	13.7 (10.8-16.7)	13.6 (8.7-21.2)
200-	47	15421	3.1 (2.2-3.9)	3.4 (2.1-5.4)
350-	29	17578	1.7 (1.1-2.3)	1.9 (1.2-3.3)
500-	28	34370	0.8 (0.5-1.1)	1.00

*Adjusted for HIV RNA, age, cohort, race and smoking status

Table 3

Liver-related Deaths

CD4 count	Number	PY	Rate (95% CI) per 1000 PY	Rate ratio* (95% CI)
<50	21	1657	12.7 (7.3-18.1)	26.6 (12.9-54.7)
50-	19	1711	11.1 (6.1-16.1)	22.2 (11.2-44.3)
100-	44	6044	7.3 (5.1-9.4)	13.5 (7.5-24.3)
200-	50	15421	3.2 (2.3-4.1)	6.5 (3.7-11.4)
350-	21	17578	1.2 (0.7-1.7)	2.5 (1.3-4.7)
500-	17	34370	0.5 (0.3-0.8)	1.00

*Adjusted for HIV RNA, age, cohort, race and smoking status

Table 4

Malignancy-related Deaths

CD4 count	Number	PY	Rate (95% CI) per 1000 PY	Rate ratio* (95% CI)
<50	9	1657	5.4 (2.5-10.3)	23.5 (9.4-58.7)
50-	9	1711	5.3 (2.4-10.0)	15.4 (6.6-36.2)
100-	33	6044	5.5 (3.6-7.3)	11.4 (6.1-21.4)
200-	26	15421	1.7 (1.0-2.3)	3.7 (1.9-6.9)
350-	8	17578	0.5 (0.2-0.9)	1.0 (0.4-2.4)
500-	15	34370	0.4 (0.2-0.7)	1.00

*Adjusted for HIV RNA, age, cohort, race and smoking status

Table 5

Heart-related Deaths

CD4 count	Number	PY	Rate (95% CI) per 1000 PY	Rate ratio* (95% CI)
<50	6	1657	3.6 (1.3-7.9)	3.1 (1.2-8.2)
50-	5	1711	2.9 (0.9-6.8)	2.1 (0.8-5.5)
100-	17	6044	2.8 (1.6-4.5)	1.9 (1.1-3.5)
200-	28	15421	1.8 (1.1-2.5)	1.3 (0.8-2.2)
350-	17	17578	1.0 (0.6-1.6)	0.8 (0.4-1.4)
500-	37	34370	1.1 (0.7-1.4)	1.00

*Adjusted for HIV RNA, age, cohort, race and smoking status

RESULTS

- Over a study period of 76,893 person-years of follow-up (PY), 1248 (5.3%) patients died.
- The incidence of deaths was 1.6/100 PY.
- 82% had used ART prior to enrolment for a median of 2.8 years.
- The leading cause of death was AIDS (30%), followed by liver-related deaths (14%, of which 79% were associated with chronic viral hepatitis), deaths from heart disease (including cardiovascular disease, 9%), and deaths from non-AIDS malignancies (8%) (Table 1).
- The proportion of deaths from these causes remained stable over time (Figure 1).
- HIV/AIDS-related death was, as expected, strongly associated with the latest CD4 cell count (Table 2).
- However, other causes of death were also associated with immunofunction (Tables 3-5; Figure 2).
- Liver-related deaths (relative rate 26.6 [12.9 to 54.7], p < 0.0001; Table 3) and deaths from non-AIDS malignancies (23.5 [9.4 to 58.7], p < 0.0001; Table 4) were similarly strongly associated with latest CD4 count. The relationship between the CD4 cell count and death from heart disease was less strong but remained significant (3.1 [1.2 to 8.2], p = 0.02; Table 5).
- The trends persisted after considering the associations between death from each cause and the CD4 count measured 3 and 6 months prior to death (illustrated for liver-related deaths in Figure 3; this figure also include a sensitivity analyses excluding 17 patients who had HIV/AIDS as a contributory cause of death ('liver_sens')).

CONCLUSIONS

- Deaths from causes generally thought to be non-HIV-related are more likely to occur in persons with lower rather than higher CD4 counts.
- Although residual confounding cannot be ruled out, low CD4 cell numbers seem to contribute to a proportion of such deaths, implying that immunodeficiency may be relevant to their pathogenesis.
- It appears that deaths occurring in persons with a very low CD4 count can only be categorized as non-HIV-related if there is clear evidence that the patient's immunodeficiency did not contribute to the death.

These findings were part of the basis for creating a new system for coding causes of death, including an assessment of immunodeficiency relatedness, the CoDe project (web: www.cphiv.dk/CoDe)

Figure 2

RR of Death according to Immunofunction and Specific Cause

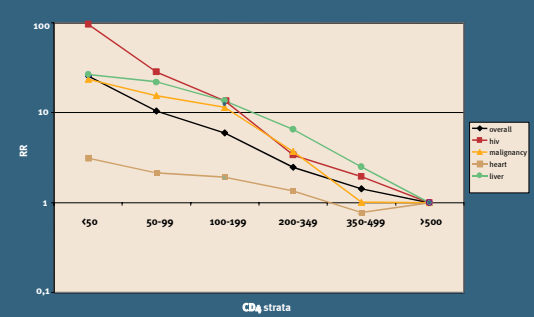
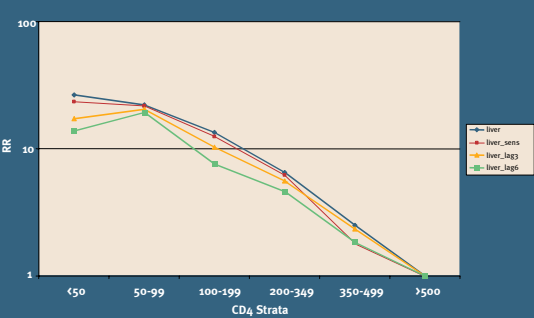


Figure 3

RR of Liver related Death According to Immunofunction and Lag-time



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