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*Published in:*  
AIDS

*DOI:*  
[10.1097/00002030-199714000-00012](https://doi.org/10.1097/00002030-199714000-00012)

[Link to publication](#)

*Citation for published version (APA):*

Prins, M., Hernandez Aguado, I., Brettle, R. P., Robertson, J. R., Broers, B., Carre, N., ... van den Hoek, J. A. R. (1997). Pre-Aids mortality from natural causes associated with HIV disease progression: evidence from the European seroconverter study among injecting drug users. *AIDS*, 11, 1747-1756. DOI: 10.1097/00002030-199714000-00012

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# Pre-AIDS mortality from natural causes associated with HIV disease progression: evidence from the European Seroconverter Study among injecting drug users

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and Anneke van den Hoek

**Objectives:** To study differences in pre-AIDS mortality between European cohorts of injecting drug users (IDU) and to evaluate whether pre-AIDS mortality increased with time since HIV seroconversion and decreasing CD4 count.

**Methods:** The study population consisted of 664 IDU with documented intervals of HIV seroconversion from eight cohort studies. Differences in pre-AIDS mortality were studied between European sites; an evaluation of whether pre-AIDS mortality increased with time since HIV seroconversion and decreasing CD4 count was carried out using Poisson regression.

**Results:** One hundred and seven IDU died, of whom 57 did not have AIDS. Pre-AIDS causes of death were overdose/suicide (49%), natural causes such as bacterial infections/cirrhosis (40%), and unintentional injuries/unknown (11%). Considering pre-AIDS death and AIDS as competing risks, 14.7% were expected to have died without AIDS and 17.3% to have developed AIDS at 7 years from seroconversion. No statistically significant differences in pre-AIDS mortality were found between European regions, men and women, age categories and calendar time periods. Overall pre-AIDS mortality did not increase with time since seroconversion, but did increase with decreasing CD4 count. Evaluating cause-specific mortality, only pre-AIDS mortality from natural causes appeared to be associated with time since seroconversion as well as immunosuppression. For natural causes, the death rate per 100 person-years was 0.13 the first 2 years after seroconversion, 0.73 in years 2–4 [risk relative (RR) to years 0–2, 5.6], 1.83 in years 4–6 (RR, 14.0) and 1.54 for  $\geq 6$  years (RR, 11.7). This rate was 0 for a CD4 cell count  $\geq 500 \times 10^6/l$ , 1.06 for  $200\text{--}500 \times 10^6/l$  and 4.06 for  $< 200 \times 10^6/l$  (RR versus  $\geq 200 \times 10^6/l$ , 7.0). In multivariate analysis, both CD4 count and time since seroconversion appeared to be independently associated with death from natural causes; CD4 count appeared to be the strongest predictor (adjusted RR, 5.9).

**Conclusions:** A high pre-AIDS mortality rate was observed among IDU. No significant differences were observed across European sites. Pre-AIDS mortality from natural causes but not from overdose and suicide was associated with HIV disease progression.

*AIDS* 1997, 11:1747–1756

**Keywords:** Injecting drug users, pre-AIDS mortality, HIV disease progression

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Sponsorship: This research was supported by the Dutch AIDS Foundation (Stichting AIDS Fonds), as part of the Stimulation Programme on AIDS Research of the Dutch Programme Committee for AIDS Research (94.008) and by the grants of the original studies.

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Date of receipt: 21 March 1997; revised: 3 July 1997; accepted: 11 July 1997.

## Introduction

Because of their lifestyle, injecting drug users (IDU) are at increased risk of premature mortality compared with the general population [1–4]. In the last decade, death rates increased considerably for IDU in countries with a high HIV-1 prevalence amongst this group due to the impact of the AIDS epidemic [5–8].

An increase of non-AIDS deaths concomitant with the introduction of HIV epidemic was first noticed amongst IDU in New York City at the beginning of the 1980s [6,9]. Since then several studies have shown that deaths due to non-AIDS causes are higher among HIV-positive IDU than among HIV-negative IDU [2,4–6,10,11]. Among HIV-infected IDU, mortality before being diagnosed with AIDS (denoted as pre-AIDS mortality) has been found to increase with a decreasing CD4 cell count [10], indicating that not accounting for pre-AIDS mortality could overestimate the AIDS-free survival curve. To date, all studies have evaluated pre-AIDS mortality in seroprevalent cohorts. To our knowledge, neither the probability of dying for the complete course from HIV-1 seroconversion to AIDS has been described, nor has an evaluation of whether the risk of pre-AIDS mortality increases with time since HIV-1 seroconversion.

In the present study, data were merged from IDU with documented intervals of HIV seroconversion obtained from eight cohorts in various European cities. Differences in pre-AIDS mortality rates between these regions, in which drug use, drug policy and access to health care might differ, were studied. The relationship between pre-AIDS mortality and time since HIV-1 seroconversion as well as immunosuppression were also studied.

## Methods

### Study population

The HIV-1-positive study population comprised 664 IDU for whom the dates of the last negative and first positive HIV-1 test were known. An IDU was defined as a person who, since 1979, had injected drugs before HIV-1 seroconversion.

These IDU originated from eight ongoing prospective studies of HIV infection participating in the European Seroconverter Study: the Valencian HIV Seroconversion Study ( $n = 246$ ); the Edinburgh Drug Addiction Study and the Edinburgh City Hospital Cohort Study (total number of seroconverters of these two studies combined, 169); the Amsterdam Cohort Study among drug users ( $n = 99$ ); the Geneva HIV

Cohort Study ( $n = 60$ ); the French SEROCO Study ( $n = 38$ ); the Scottish National Collaborative HIV testing Study from Glasgow ( $n = 31$ ); and the Innsbruck AIDS Study ( $n = 21$ ). The study from Glasgow originally included Scotland-wide HIV-infected individuals, but in the present study predominantly included HIV-seroconverted IDU from Glasgow and surrounding regions because those followed in the Edinburgh cohorts were excluded from these Scotland-wide data.

The original studies started between 1982 and 1988. The design and methodology of each study have been described in detail elsewhere [12–19]. Briefly, participants underwent standardized clinical examination, blood testing and most of them completed questionnaires every 3–6 months. Lymphocyte subsets were determined by flow cytometry. Information on AIDS diagnosis and cause of death were obtained from review of medical records and/or through matching with local and national registers at each study location.

The total study population was composed of IDU who entered the study HIV-negative and seroconverted during follow-up (prospectively identified seroconverters, 351), and IDU who were HIV-infected at entry into the study but who had earlier blood samples available to determine the interval of seroconversion (retrospectively identified seroconverters, 313). For the latter, HIV-negative blood samples were mostly obtained for reasons unrelated to HIV disease progression, such as hepatitis B testing or knowledge of risk behaviour.

In this analysis, AIDS was defined by the 1987 criteria of the Centers for Disease Control and Prevention (CDC) [20]. The Glaswegian, French and Innsbruck data were combined because of the small number of seroconverters included in each cohort.

### Statistical analysis

The expected date of seroconversion was calculated for each IDU by the following procedure: first, the cumulative HIV-1 seroincidence was estimated over calendar time for each cohort separately applying methods for interval-censored data; second, using the cohort-specific seroincidence distribution, the expected date of seroconversion was calculated for each subject conditional upon the date of each subject's last HIV-negative and first HIV-positive test [21–23].

Product-limit estimates of the cumulative pre-AIDS mortality and the cumulative AIDS-free incidence following HIV seroconversion were calculated using a competing risk model based on influenced transition probabilities [24]. Kaplan–Meier estimates of the cumulative pre-AIDS mortality stratified by cohort were also calculated. In these calculations, as well as for the calculation of person-years at risk of pre-AIDS dying, subjects were considered at risk from the calculated date of seroconversion for prospectively identified

seroconverters through the date of pre-AIDS death, AIDS, loss to follow-up or censoring. For retrospectively identified seroconverters the date of study entry was taken as the first date since seroconversion at which they were included in the risk set (i.e., left-truncation). Depending on the closing date of each data file merged and taking into account reporting delay of registries, the date of censoring (i.e., cut-off date of the analysis) was ultimately 1 August 1995.

To evaluate differences in pre-AIDS mortality rates between the participating cohorts, and to examine the relationship of pre-AIDS mortality with time since HIV seroconversion and CD4 lymphocyte counts, incidence rates and relative risks (RR) with their corresponding 95% confidence intervals (CI) were calculated. To calculate incidence rates, pre-AIDS deaths were divided by person-years according to study site, time since seroconversion (< 2, 2–4, 4–6 and  $\geq 6$  years) and categories of CD4 lymphocyte counts ( $\geq 500$ , 200–500 and  $< 200 \times 10^6/l$ ). Evaluating site differences, the Edinburgh cohorts were chosen as the reference category because these relatively large cohorts became infected earlier than the other cohorts.

To evaluate the association between CD4 lymphocyte count and pre-AIDS mortality, the risk of pre-AIDS mortality was predicted from the CD4 count at the preceding visit. To limit misclassification of person-time due to temporal changes in this marker, observations were censored maximally 1 year after each visit with a CD4 count measurement.

Gender, age and calendar time were also evaluated as covariates of pre-AIDS mortality. Categories of age were defined by cut-off points at the 33rd and 67th percentile of the age at seroconversion for the total group (23 and 27 years, respectively). Calendar time was divided into the following three periods: < 1990, 1990–1991,  $\geq 1992$ . Both calendar time and age were treated as time-dependent covariates.

Poisson regression was used to test for significance and multivariate analyses [25]. Significance was determined by likelihood ratio tests. Apart from CD4 lymphocyte count, time since HIV seroconversion and site, all univariately associated covariates ( $P < 0.10$ ), were considered for entry in the multivariate models using a forward stepwise procedure. In multivariate analysis, we tested for interactions between covariates in the final models and considered the confounding effect of covariates. Covariates had been evaluated within each cohort before pooled analyses of the data were performed. Furthermore, bias due to the length of the seroconversion interval, and the interval between seroconversion and recruitment among retrospectively identified seroconverters were examined by repeating the analysis for subjects with a seroconversion interval

of less than 2 years and those recruited before or maximally 1 year after seroconversion. This did not change the main results substantially.

Finally, in addition to studying pre-AIDS deaths from any cause, we repeated our person-time methods separately for pre-AIDS deaths from natural causes (all deaths excluding deaths from overdose, suicide, unintentional injuries and unknown causes) and pre-AIDS deaths due to overdose or suicide. In these cause-specific analyses, subjects who died from causes other than causes of interest were censored at the date of death. The small number of pre-AIDS deaths ( $n = 6$ ) other than from natural causes, overdose and suicide precluded separate analysis.

## Results

Characteristics of the 664 IDU stratified by cohort are displayed in Table 1. The median follow-up time from HIV seroconversion until pre-AIDS death, AIDS, or the end of the study was 4.0 years [interquartile range (IQR), 2.1–6.9 years]. The 313 IDU (47.1%) for whom seroconversion was determined retrospectively had a median lag time between seroconversion and enrolment of 1.6 (IQR, 0.7–2.7) years. Median age at seroconversion ranged from 23.1 years for the Edinburgh cohorts to 29.7 years for the Amsterdam cohort, and median calendar year of seroconversion ranged from 1984 in Edinburgh to 1991 in the Valencian region. For all subjects, the median interval between the last negative and the first positive HIV test was 1.1 year; 296 IDU (44.6%) had seroconversion intervals of less than 1 year, 178 (26.8%) between 1 and 2 years, and 190 (28.6%) of 2 years or more. A total of 108 subjects died, of whom 57 died without AIDS and 50 with AIDS. For one subject who died, the occurrence of AIDS could not be ascertained. Of those not known to have developed AIDS or to have died, 28% of the total population had their last study visit more than 1 year before the cut-off date of the analysis.

### Causes of pre-AIDS death and CD4 counts preceding death

Causes of pre-AIDS deaths are listed in Table 2. Natural causes contributed to 23 pre-AIDS deaths (40.4%). Most of these deaths were attributable to bacterial infections, followed by cirrhosis/liver failure. Twenty-four deaths (42.1%) from overdose occurred and four deaths (7.0%) were attributed to suicide. The documented suicides were committed by electrocution ( $n = 1$ ), defenestration ( $n = 1$ ), overdose accompanied by a farewell letter ( $n = 1$ ), and by unknown methods ( $n = 1$ ). Remaining causes were accidents ( $n = 4$ ) and

**Table 1.** Characteristics of 664 injecting drug users (IDU) registered in the European Seroconverter Study, 1982–1995.

	n	Age (years) at seroconversion [median (IQR)]	Female [n (%)]	Seroconversion interval* (years) [median (IQR)]	Calendar year of seroconversion [median (IQR)]	n		
						AIDS	Pre-AIDS deaths	Post-AIDS deaths
Study site								
Valencia	246	24.7 (21.9–27.6)	65 (26.4)	1.1 (0.69–2.0)	91.8 (90.5–93.0)	11	8	5
Edinburgh	169	23.1 (20.4–27.9)	57 (33.7)	1.3 (0.52–2.4)	84.1 (83.9–86.0)	41	19	23
Amsterdam	99	29.7 (26.5–35.2)	45 (45.5)	0.77 (0.32–3.8)	88.5 (86.3–91.1)	13	14 <sup>‡</sup>	8 <sup>‡</sup>
Geneva	60	25.5 (23.0–29.0)	21 (35.0)	1.3 (0.60–3.2)	86.8 (85.3–89.2)	11	7	7
Other <sup>†</sup>	90	24.7 (22.3–28.0)	33 (36.7)	0.91 (0.35–1.6)	89.8 (88.8–92.0)	11	9	7
Total	664	25.2 (22.2–29.1)	221 (33.3)	1.1 (0.49–2.3)	89.8 (85.8–92.0)	87	57 <sup>‡</sup>	50 <sup>‡</sup>

\*Interval between the date of the last negative and the date of the first positive HIV test. <sup>†</sup>The French SEROCO Study (n = 38), the Scottish National Collaborative HIV testing Study (n = 31) and the Innsbruck AIDS Study (n = 21). <sup>‡</sup>For one subject from Amsterdam who died, neither cause of death nor development of AIDS could be ascertained; therefore, for the Amsterdam and total population, the total number of deaths are 23 and 108, respectively. IQR, Interquartile range.

violence (n = 1). Cause of death was unknown for one subject.

Among the 57 IDU who died without AIDS, 33 (57.9%) had a CD4 cell count in the year preceding pre-AIDS death. For these 33 subjects, the median lag-time between CD4 determination and pre-AIDS death was 2.9 months (IQR, 1.2–4.1) and the median CD4 cell count  $350 \times 10^6/l$  (IQR, 193–580).

### Cumulative pre-AIDS mortality

Considering pre-AIDS mortality and AIDS as competing risks, at 3 years from seroconversion, 5.8% of all IDU were expected to have died without AIDS and 4.3% were expected to have developed AIDS (Fig. 1). At 5 years since seroconversion these figures were 9.4 and 11.1%, and at 7 years 14.7 and 17.3%, respectively. As shown by the vertical distance between both lines (Fig. 1) at the 7-year timepoint, 68.1% of the population was still alive without AIDS. Median progression

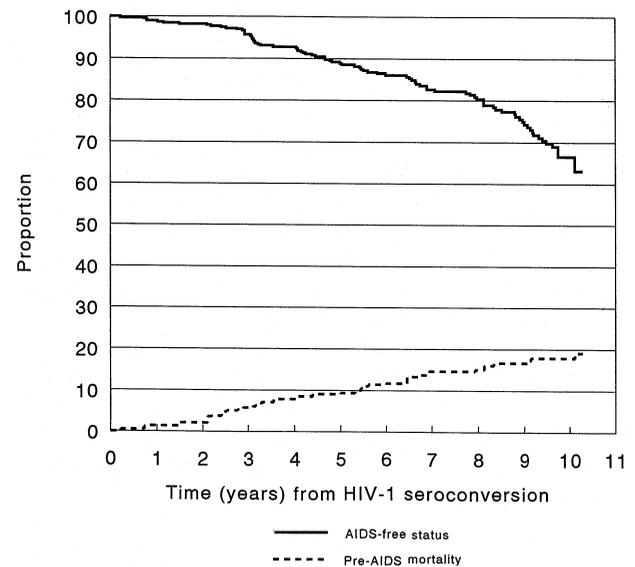
time to pre-AIDS mortality or AIDS was 9.72 years. Using this competing risk model to calculate the rate ratio of pre-AIDS dying compared with developing AIDS, this ratio appeared to decrease slightly with increasing time since seroconversion from 1.02 at 2 years to 0.79 at 10 years from seroconversion.

By Kaplan–Meier estimates, considering AIDS not as competing risk but as censoring moment, the probability of pre-AIDS dying within 7 years from seroconversion was 16.0% (95% CI, 12.2–20.8). On comparison, 19.0% (95% CI, 14.8–24.1) developed AIDS within that time period by Kaplan–Meier estimates. Fig. 2

**Table 2.** Causes of pre-AIDS death among 664 injecting drug users registered in the European Seroconverter Study, 1982–1995.

Cause of death	n (% among all pre-AIDS deaths)
Deaths from natural causes	23 (40.4)
Pneumonia	5 (8.8)
Endocarditis	2 (3.5)
Bacterial sepsis	1 (1.8)
Pneumococcal meningitis	1 (1.8)
Brain abscess	1 (1.8)
Brain haemorrhage	1 (1.8)
Cirrhosis/liver failure	7 (12.3)
Heart disease (not specified)	1 (1.8)
HIV-related (not specified)	1 (1.8)
Miscellaneous*	3 (5.3)
Overdose/suicide deaths	28 (49.1)
Overdose	24 (42.1)
Suicide	4 (7.0)
Other	6 (10.5)
Accidents	4 (7.0)
Homicide	1 (1.8)
Unknown	1 (1.8)
Total	57

\*Pneumonia and pulmonary tuberculosis (n = 1), pulmonary oedema and cirrhosis/liver failure (n = 1) and endocarditis and cirrhosis/liver failure (n = 1).



**Fig. 1.** Cumulative incidence of pre-AIDS mortality and AIDS-free status among 664 injecting drug users registered in the European Seroconverter Study, 1982–1995, estimated by product-limit methods for a competing risk model. The vertical distances between the both lines at a specified timepoint corresponds to the estimated percentage of those alive and without AIDS. Curves were truncated when fewer than 10 subjects remain at risk.

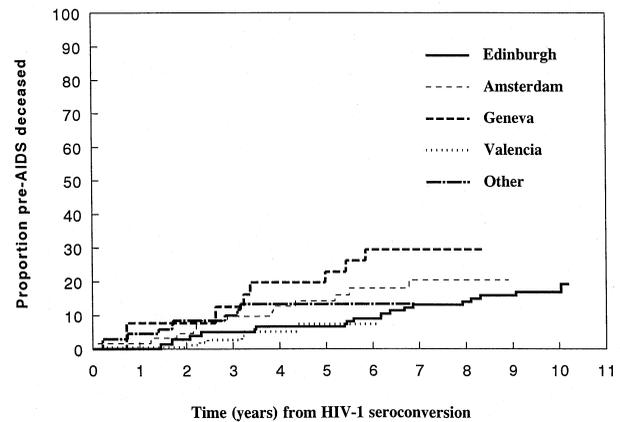
shows the Kaplan–Meier curves of pre-AIDS mortality for each cohort. Progression rates did not differ significantly across sites (likelihood ratio statistic by Cox proportional hazards analysis,  $P = 0.13$ ).

### Mortality rates and risk factors for pre-AIDS mortality

The total number of person-years at risk until pre-AIDS death, AIDS, loss to follow-up or censoring was 2454, resulting in a crude pre-AIDS mortality rate per 100 person-years of 2.32 (95% CI, 1.79–3.01) for all IDU. Table 3 shows the pre-AIDS mortality rates, crude RR and their 95% CI according to variables of interest.

#### Pre-AIDS mortality from all causes

In univariate analyses studying pre-AIDS deaths from all causes, an increasing trend in mortality with time since HIV seroconversion was not demonstrated, although pre-AIDS mortality rates more than 2 years after seroconversion were somewhat higher than in the first 2 years. Pre-AIDS mortality rates increased with a decreasing CD4 cell count ( $P = 0.088$ ). The risk of pre-AIDS mortality was about three times higher when CD4 counts fell below  $200 \times 10^6$  cells/l, relative to CD4 counts  $\geq 500 \times 10^6$  cells/l. Since the CD4 cell count might fall temporarily immediately after seroconversion and this might cause some misclassification, we also examined the relationship between CD4 lymphocyte count and pre-AIDS mortality excluding CD4 counts in the first year after seroconversion; RR became 1.44 (95% CI, 0.54–3.83) and 3.30 (95% CI, 1.20–9.08) for a CD4 cell count of 200–500 and  $< 200 \times 10^6$ /l, respectively ( $P = 0.053$ ). The death rate



**Fig. 2.** Kaplan–Meier estimates of the cumulative proportion deceased without being diagnosed with AIDS among 664 injecting drug users registered in the European Seroconverter Study, 1982–1995, grouped by study site. Curves were truncated when fewer than 10 subjects remain at risk.

of 1.96 per 100 person-years for time periods with missing CD4 cell counts was very close to the rate for a CD4 cell count  $\geq 500 \times 10^6$ /l. An explanation might be that 41% of the person-years with missing CD4 cell counts took place in the first 2 years following seroconversion when CD4 cell counts were relatively high.

The lowest pre-AIDS mortality rate was found in Valencia, and the highest in Geneva, but both differences did not reach statistical significance when compared with the Edinburgh cohorts. After adjustment for

**Table 3.** Number of pre-AIDS deaths, person-years at risk (PY), pre-AIDS death rate per 100 PY (rate) and crude relative risk (RR) according to selected characteristics, stratified by major categories of causes of death.

	Cause of death									
	All causes (n = 57)				Natural causes* (n = 23)			Overdose/suicide (n = 28)		
	n	PY	Rate	RR (95% CI)	n	Rate	RR (95% CI)	n	Rate	RR (95% CI)
Years since HIV-1 seroconversion										
< 2	13	762	1.71	1.0	1	0.13	1.0	9	1.18	1.0
2–4	20	682	2.93	1.72 (0.85–3.46)	5	0.73	5.59 (0.65–47.8)	13	1.91	1.61 (0.69–3.78)
4–6	10	491	2.04	1.19 (0.52–2.72)	9	1.83	14.00 (1.77–110.3)	0	0	0.50 (0.18–1.41) <sup>†</sup>
$\geq 6$	14	519	2.70	1.58 (0.74–3.36)	8	1.54	11.70 (1.47–93.9)	6	1.16	
CD4 lymphocyte count ( $\times 10^9$ /l)										
$\geq 500$	8	466	1.72	1.0	0	0	1.0 <sup>‡</sup>	5	1.07	1.0
200–500	15	568	2.64	1.54 (0.65–3.63)	6	1.06		8	1.41	1.31 (0.43–4.01)
< 200	10	197	5.07	2.96 (1.17–7.48)	8	4.06	6.99 (2.43–20.2) <sup>‡</sup>	2	1.01	0.95 (0.18–4.87)
Missing	24	1224	1.96	1.14 (0.51–2.54)	9	0.74	1.27 (0.45–3.56) <sup>‡</sup>	13	1.06	0.99 (0.35–2.77)
Study site										
Edinburgh	19	918	2.07	1.0	10	1.09	1.0	9	0.98	1.0
Amsterdam	14	445	3.14	1.52 (0.76–3.03)	5	1.12	1.03 (0.35–3.02)	6	1.35	1.38 (0.49–3.86)
Geneva	7	150	4.68	2.26 (0.95–5.38)	4	2.68	2.46 (0.77–7.83)	3	2.01	2.05 (0.55–7.56)
Valencia	8	634	1.26	0.61 (0.27–1.39)	3	0.47	0.43 (0.12–1.58)	3	0.47	0.48 (0.13–1.78)
Other <sup>§</sup>	9	307	2.93	1.42 (0.64–3.13)	1	0.33	0.30 (0.04–2.34)	7	2.28	2.32 (0.87–6.24)

\*All pre-AIDS deaths excluding deaths from overdose, suicide, unintentional injuries and unknown causes. Individual diseases are listed in Table 2. <sup>†</sup>Because no death occurred at 4–6 years from seroconversion, the categories 4–6 and  $\geq 6$  years were combined. <sup>‡</sup>Because no death occurred within the  $\geq 500 \times 10^9$ /l category, the categories  $\geq 500$  and  $200\text{--}500 \times 10^9$ /l were combined and taken as reference category. <sup>§</sup>The French SEROCO Study, the Scottish National Collaborative HIV testing Study and the Innsbruck AIDS Study.

time since seroconversion and CD4 lymphocyte count, the RR for Valencia increased to 0.68 (95% CI, 0.27–1.70) and the death rate for Geneva became significantly different from that in Edinburgh (RR, 2.55; 95% CI, 1.02–6.33). The RR for the Amsterdam cohort and the other cohorts combined did not change substantially after adjusting for duration of infection and CD4 cell count. Additional adjustment for gender and age had only a minor influence on the presented RR for the sites.

Pre-AIDS mortality from all causes was not significantly associated with gender, age and calendar period of follow-up: crude RR for women compared with men, 0.93 (95% CI, 0.53–1.61); RR for those aged 23–27 years, 1.00 (95% CI, 0.41–2.43), and for those aged > 27 years, 1.45 (95% CI, 0.64–3.26) compared with those aged <23 years; RR for 1990–1991, 1.25 (95% CI, 0.63–2.47) and for ≥ 1992, 1.37 (95% CI, 0.73–2.58) compared with <1990. CD4 count appeared to be the only variable independently associated with pre-AIDS death from all causes. None of the remaining covariates appeared to be confounders. CD4 log-transformed and treated as a continuous variable was found to be more predictive than absolute CD4 counts in categories.

#### Pre-AIDS mortality from natural causes

Both time since seroconversion and decreasing CD4 lymphocyte count were univariately significantly associated with death from natural causes ( $P = 0.003$  and  $0.001$ , respectively). The mortality rates were 0.13 the first 2 years, 0.73 in years 2–4 (RR, 5.59), 1.83 in years 4–6 (RR, 14.0) and 1.54 at 6 years or more after seroconversion (RR, 11.7; Table 3). RR of 6.99 was found for a CD4 cell count  $< 200 \times 10^6/l$ , relative to a CD4 count  $\geq 200 \times 10^6/l$ . Mortality from natural causes was also found to be significantly associated with older age ( $P = 0.020$ ). RR was 1.75 (95% CI, 0.20–15.7) and 5.36 (95% CI, 0.72–40.2) for subjects aged 23–27 years and older than 27 years, respectively, relative to subjects aged 22 years or less. No significant differences in pre-AIDS mortality from natural causes by gender and calendar period of follow-up could be demonstrated.

In multivariate analysis, both time since HIV seroconversion and CD4 cell count were independent predictors of pre-AIDS mortality from natural causes. Table 4 shows the results when age and site were added to the model. Compared with RR for age obtained in the univariate analysis, RR decreased to non-significant values. As was the case for overall pre-AIDS mortality, Geneva had the highest risk of pre-AIDS death from natural causes. This association did not reach statistical significance, which may have been due to small numbers. Compared with the results from the univariate analysis, RR for time since HIV seroconversion and

**Table 4.** Multivariate Poisson analyses predicting pre-AIDS mortality from natural causes\* and AIDS among 664 injecting drug users registered the European Seroconverter Study, 1982–1995.

	Adjusted RR (95% CI)	
	Pre-AIDS mortality from natural causes*	AIDS
Years since HIV-1 seroconversion		
< 2	1.0	1.0
2–4	5.10 (0.57–45.7)	2.97 (1.22–7.20)
4–6	11.07 (1.22–100.3)	3.47 (1.34–8.95)
≥ 6	6.86 (0.68–69.1)	4.16 (1.57–11.00)
CD4 lymphocyte count ( $\times 10^6/l$ )		
≥ 200	1.0	1.0
< 200	5.90 (1.98–17.6)	11.81 (6.39–21.8)
Missing	2.06 (0.69–6.17)	2.71 (1.42–5.17)
Study site		
Edinburgh	1.0	1.0
Amsterdam	1.33 (0.43–4.14)	0.94 (0.49–1.81)
Geneva	2.77 (0.82–9.40)	2.32 (1.16–4.67)
Valencia	1.38 (0.32–5.91)	1.20 (0.55–2.63)
Other <sup>†</sup>	0.61 (0.07–5.06)	1.72 (0.84–3.53)
Age (years)		
< 23	1.0	1.0
23–27	1.04 (0.11–9.72)	1.52 (0.51–4.55)
≥ 27	2.27 (0.27–18.8)	2.13 (0.73–6.25)

\*All pre-AIDS deaths excluding deaths from overdose, suicide, unintentional injuries and unknown causes (see Table 2 for individual diseases). <sup>†</sup>The French SEROCO Study, the Scottish National Collaborative HIV testing Study and the Innsbruck AIDS Study. RR, Relative risk; CI, confidence interval.

CD4 lymphocyte count decreased slightly towards 1. However, the risk still increased considerably with decreasing CD4 cell count and ongoing HIV infection, although the risk ≥ 6 years after seroconversion appeared to be smaller than in years 4–6. Log-transformed CD4 values appeared to be more predictive than categorized CD4 count. When replacing CD4 count in categories with log-transformed CD4 in the multivariate model, the elevated risks with ongoing time since seroconversion decreased. The effect was larger for more prolonged duration of infection, with a decrease of 53% for the category ≥ 6 years since HIV seroconversion.

#### Pre-AIDS mortality due to overdose and suicide

None of the variables studied, including time since seroconversion and CD4 lymphocyte count, were found to be significantly associated with pre-AIDS death from overdose or suicide. Regarding site differences, a relatively low rate of overdose and suicide deaths was found in the Valencia region and a high rate for both the Geneva cohort and the combined cohorts (Table 3). The latter was due to a very high overdose death rate in the Glasgow cohort.

In addition to parallel pre-AIDS mortality from natural causes with progression to AIDS, the person-time methods were carried out for progression from seroconversion to AIDS. The incidence rate was small in

the first 2 years following seroconversion (0.92 per 100 person-years) and rose rapidly thereafter (3.08, 4.28 and 7.32 per 100 person-years for years 2–4, 4–6,  $\geq 6$ , respectively;  $P < 0.001$ ). The risk of developing AIDS was strongly related to a decreasing CD4 lymphocyte count ( $P < 0.001$ ). The rate was 0.21 for a CD4 cell count  $\geq 500 \times 10^6/l$ , 2.47 for  $200\text{--}500 \times 10^6/l$  and 20.30 for  $< 200 \times 10^6/l$ . Table 4 shows the results when time since seroconversion, CD4 count, age and site were considered together in a multivariate model. It is clear from Table 4 that the results for pre-AIDS death from natural causes resembled the results for progression to AIDS, although the relationship between outcome and immunosuppression was somewhat stronger for AIDS than for mortality.

## Discussion

This study showed a high pre-AIDS mortality rate among IDU in various European sites, with no significant differences between them. A striking result of this study was that pre-AIDS death from natural causes was found to be related with ongoing time since HIV seroconversion and immunosuppression. The increase in these death rates by ongoing time since seroconversion and a decreasing CD4 count showed similarity with the rates observed for AIDS. As already postulated by researchers in New York City in 1988 [6,9], this strongly suggests that pre-AIDS death from natural causes is at least partially the result of HIV disease progression.

Our findings confirmed the results obtained in a recent study in the Amsterdam cohort of drug users [10]. In this previous study, which included seroprevalent subjects, crude RR for pre-AIDS mortality of 1.41 (95% CI, 0.43–4.57) and 2.66 (95% CI, 0.66–10.6) for CD4 count levels of  $200\text{--}500 \times 10^6$  cells/l and  $< 200 \times 10^6$  cells/l, respectively, relative to a CD4 count  $\geq 500 \times 10^6$  cells/l were found, but numbers were small. These risk ratios are very close to those for overall pre-AIDS mortality in our study. Since we studied a larger group, we were able to demonstrate a significant association. Furthermore, we could show that this association was even stronger for pre-AIDS deaths from natural causes. In contrast, the association does not hold for pre-AIDS deaths from overdose or suicide.

Because our study population consisted of subjects with well-estimated dates of HIV seroconversion, we were able to demonstrate that the risk of pre-AIDS mortality from natural causes also increased with ongoing time periods since seroconversion. Considering time since seroconversion and CD4 cell count together in a

model, immunosuppression was still found to be strongly associated with pre-AIDS death from natural causes. In contrast, after adjusting for log-transformed CD4 count the elevated risk for increasing time since seroconversion reduced markedly, especially with more prolonged duration of infection. This suggests that at later timepoints CD4 count is much more relevant than time since HIV seroconversion. This finding is in agreement with several studies showing that time from HIV infection to AIDS or death due to AIDS are largely explained by CD4 lymphocyte count and not or to a lesser extent by the duration of HIV infection [26–28].

Several studies found an increased overdose/suicide death rate among HIV-positive IDU compared with HIV-negative IDU [2–4,29,30], whereas one study did not [11]. It has been argued that the increased overdose death rate among HIV-positive IDU might be causally related to HIV infection by an increasing probability of lethal outcome from drug use among seropositive IDU compared with seronegative IDU [3]. Another explanation might be that the increased risk among HIV-positive IDU is the result of unrecognized HIV-related diseases [31]. In our study, we did not find any indication that the evaluated overdose and suicide death rate among HIV-positive IDU is a consequence from disease progression, since the rate did not increase with time since seroconversion nor with a decreasing CD4 count. The increased overdose mortality rate among HIV-positive IDU might be explained by a selection of population with a high-risk lifestyle or psychiatric comorbidity that has already resulted in HIV infection. Nonetheless, an association between overdose/suicide mortality and disease progression after AIDS diagnosis might exist, since we studied only pre-AIDS deaths.

We stress that drawing firm conclusions about geographic differences in pre-AIDS mortality among the general population of HIV-infected IDU is hazardous because we studied a selected group, namely cohort participants, and because numbers were small. We can only be certain that pre-AIDS mortality was common among all IDU cohorts studied and that there were no significant differences across these cohorts. The risk in the Geneva cohort tended to be increased for pre-AIDS mortality as well as for progression to AIDS. A possible explanation is that fast progressors were slightly over-represented in this clinic-based cohort in which almost all seroconversions were determined retrospectively. The relatively high overdose death rate amongst the Glasgow cohort might be related to the increase in drug-related deaths in Glasgow in the beginning of the 1990s, which was probably due to mixing heroin with benzodiazepines and alcohol [32,33]. It has been hypothesized that the tendency of a low overdose/suicide death rate in Spain might be explained by a better supportive social network in the Valencian region than

in the other regions, but data to test this hypothesis are lacking. In general, drug use, methadone provision and social and medical conditions vary in the different regions involved. For example, methadone has been available in Edinburgh since 1986 but is still very restricted in France; most IDU in Amsterdam do not live with their family in contrast to IDU in the Valencian region, for example. In other words, we cannot exclude the possibility that our results on site differences are confounded by factors that we did not take into account and that are often difficult to evaluate, such as drug use, psychopathology, poverty, methadone provision, social and medical care, study design-related factors (e.g., inclusion criteria, setting of follow-up), and completeness of mortality registers.

In this study, AIDS was defined using the 1987 CDC criteria [20]. In 1993, recurrent bacterial pneumonia, pulmonary tuberculosis and cervical neoplasia were added to the AIDS case definition in Europe [34]. Since diagnostic criteria (e.g., for recurrent pneumonia) are very strict, at most only for six (11%) of the 57 pre-AIDS deaths in this study, the cause of death might have satisfied this expanded definition. Of course, some subjects who died before AIDS might have met the criteria of the expanded definition some time before dying, regardless of the cause of death. In general, since pre-AIDS mortality and AIDS do not occur at random (i.e., both pre-AIDS mortality and AIDS are more likely when subjects are immunosuppressed), the introduction of the expanded definition should result in a decrease in pre-AIDS mortality rates. However, because diseases such as infective endocarditis are not defined as AIDS according to this expanded definition and because for example overdose is associated with the lifestyle of IDU, we would still expect to find a relatively high pre-AIDS death rate among this group when we apply the 1993 criteria. Furthermore, the recent introduction of early combination therapy (protease inhibitors and nucleoside combinations), which should be initiated before immunological damage has occurred, might delay the diagnosis of AIDS and also pre-AIDS death from natural causes. Consequently, the number of pre-AIDS death from other causes might increase because of longer exposure to a high-risk lifestyle.

Several limitations to our study should be noted. First, as mentioned previously, our results cannot be generalized, because we studied a restricted group of HIV-infected IDU. IDU not followed in cohort studies might have poorer access to health care resulting in a higher pre-AIDS mortality rate. In addition, other relevant characteristics might differ between cohort participants and non-participants. Second, the statistical power was not large in our study because of the relatively small number of pre-AIDS deaths. Therefore, causes of death were grouped together, although the

association between some cofactors and pre-AIDS mortality may not be uniform. By combining overdose and suicide deaths, misclassification is expected to be small because there were only four documented suicides, of which one was an overdose with farewell letter. Furthermore, it is not known whether the documented overdoses were accidental or suicidal. Regarding pre-AIDS death from natural causes, death rates due to bacterial infections have consistently been found to be elevated among HIV-positive IDU in comparison with HIV-negative IDU [4-6,11,29,30]. Studies evaluating cirrhosis/liver failure death rates do not give concordant results; some have found a higher rate in HIV-positive IDU than in HIV-negative IDU [2,4,29,30], but one did not [11]. Since seroprevalent groups were studied, these inconsistent results might be due to differential time since infection. When we calculated death rates by time since seroconversion and immunosuppression separately for deaths due to bacterial infections and deaths from cirrhosis/liver failure, in both cases increasing rates were observed over time and with a decreasing CD4 count (data not shown). Finally, although assignment of the cause of death represented the best judgement of the investigators at each site based on all available information, the source of information (clinical diagnosis, post-mortem results, death certificate) differed across and within sites. Hence, some misclassification might have been present, but we feel that it is very unlikely that this has seriously biased our results.

We found strong evidence that pre-AIDS mortality among IDU underestimates the burden of disease in this population. Implications are that in survival analysis to AIDS or death from AIDS, pre-AIDS deaths from natural causes should not be treated as random censoring events because this might result in substantially biased progression estimates. Pre-AIDS death from overdose and suicide does not violate the requirement for random censoring. Those applying back-calculation methods to estimate the HIV incidence from seroprevalence and AIDS surveillance data as well as those using models such as Markov models to estimate the AIDS incubation time should consider all-cause pre-AIDS mortality.

Although there are not many well-defined cohorts of IDU, further studies among large groups of HIV-seroconverted IDU are needed to confirm our results and to study the impact of the introduction of the expanded AIDS case definition on pre-AIDS mortality. Pre-AIDS mortality and its association with disease progression should also be studied amongst other populations with a relatively high likelihood of pre-AIDS death, such as HIV-infected haemophilia patients [35] and HIV-infected individuals in sub-Saharan African countries [36].

In practice, clinicians should be aware of the risk of premature death among HIV-infected IDU who do not yet have AIDS. IDU who have low CD4 counts are at increased risk for premature death from natural causes. For these HIV-infected IDU, clinical check-ups should be intensified in order to detect diseases earlier. Increased attention to bacterial infections is warranted. Both CD4 count and time since seroconversion may be useful for considering specific interventions (next to HIV therapy) directed at the prevention and early treatment of bacterial infections [e.g., vaccination and (prophylactic) antibiotics].

## Acknowledgements

The authors thank A.M. Richardson (Edinburgh), R.B. Gekus, L. Gerber, J.S. Bax, E.J.C. van Ameijden, H.J.A. van Haastrecht (Amsterdam), B. Hirschel, H. McArdle (Geneva), J. McMenamin (Glasgow) and the partners in the Valencian HIV Seroconversion Study (FIS 95/0228, 95/1688) for their contributions to this study. The authors also thank the laboratories collaborating with the original studies for determining lymphocyte subsets, the clinicians and health workers who contributed by collecting data, and the participants for their ongoing participation.

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