

All-cause mortality in treated HIV-infected adults with CD4 \geq 500/mm³ compared with the general population: evidence from a large European observational cohort collaboration[†]

The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord[‡]

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Background Using data from a large European collaborative study, we aimed to identify the circumstances in which treated HIV-infected individuals will experience similar mortality rates to those of the general population.

Methods Adults were eligible if they initiated combination anti-retroviral treatment (cART) between 1998 and 2008 and had one prior CD4 measurement within 6 months. Standardized mortality ratios (SMRs) and excess mortality rates compared with the general population were estimated using Poisson regression. Periods of follow-up were classified according to the current CD4 count.

- Results** Of the 80 642 individuals, 70% were men, 16% were injecting drug users (IDUs), the median age was 37 years, median CD4 count $225/\text{mm}^3$ at cART initiation and median follow-up was 3.5 years. The overall mortality rate was 1.2/100 person-years (PY) (men: 1.3, women: 0.9), 4.2 times as high as that in the general population (SMR for men: 3.8, for women: 7.4). Among 35 316 individuals with a CD4 count $\geq 500/\text{mm}^3$, the mortality rate was 0.37/100 PY (SMR 1.5); mortality rates were similar to those of the general population in non-IDU men [SMR 0.9, 95% confidence interval (95% CI) 0.7–1.3] and, after 3 years, in women (SMR 1.1, 95% CI 0.7–1.7). Mortality rates in IDUs remained elevated, though a trend to decrease with longer durations with high CD4 count was seen. A prior AIDS diagnosis was associated with higher mortality.
- Conclusions** Mortality patterns in most non-IDU HIV-infected individuals with high CD4 counts on cART are similar to those in the general population. The persistent role of a prior AIDS diagnosis underlines the importance of early diagnosis of HIV infection.
- Keywords** HIV infection, CD4 lymphocyte count, mortality, anti-retroviral therapy, highly active

Introduction

Immune restoration occurs in most HIV-infected patients treated with combination anti-retroviral therapy (cART) and is associated with a dramatic decrease in AIDS-related mortality.^{1–4} For the first time, it has become conceivable that treated HIV-infected individuals may experience mortality rates that are similar to those seen in HIV-negative individuals of the same age and gender.^{5,6} Indeed, among individuals in high-income countries with a known date of HIV seroconversion who were followed between 2004 and 2006, mortality in the first 5 years after seroconversion was similar to that in the general population.⁴ The absolute number of circulating CD4+ cells/ mm^3 (the 'CD4 count') is the most commonly used marker of HIV disease progression and of immune reconstitution after cART, with a lower CD4 count predicting the occurrence of both AIDS and non-AIDS-defining diseases.^{7–9} A trend towards improved survival among those with higher CD4 counts is apparent even among untreated patients with a CD4 count $>350/\text{mm}^3$.^{10,11}

Currently, in most resource-rich countries, mortality in HIV-infected individuals receiving cART remains higher than in the general population^{12–16} even among individuals who experience a good initial response to cART.¹⁷ However, some subgroups do have a more favourable prognosis, including men who have sex with men (MSM) who initiated treatment for the first time, whereas AIDS-free⁶ and individuals who have maintained a high CD4 count while on cART for >6 years.⁵ Beyond the immune restoration

measured in routine practice by the CD4 count, the reconstitution of the T-cell subsets may, however, remain incomplete despite several years of treatment.¹⁸ In a large European collaboration of HIV cohorts, we aimed to identify the optimal circumstances in which treated HIV-infected individuals will experience similar mortality rates to those of the general population. In particular, we wished to explore the impact on the mortality rate of attaining and maintaining over a long period, a CD4 count $\geq 500/\text{mm}^3$ in different subgroups.

Methods

Study population

The Collaboration of Observational HIV Epidemiological Research in Europe (COHERE, <http://www.cohere.org>) was established in 2005 with the objective of conducting epidemiological research on the prognosis of HIV-infected people across Europe.¹⁹ The 33 participating observational cohorts have been approved by local ethics committees or institutional review boards according to local regulations. Each cohort submits information using a standardized data format to one of two coordinating centres at the Copenhagen HIV Project (CHIP), Copenhagen, Denmark or the Institut de Santé Publique d'Épidémiologie et de Développement (ISPED), University Bordeaux Segalen, France. Our analyses were based on data merged in November 2008. Patients were eligible if they met the following

criteria: at least 18 years of age at cART initiation, cART initiation in 1998 onward, followed in an European country, known date of birth and gender, at least one CD4 measurement within 6 months prior to cART initiation and at least 1 day of follow-up.

Statistical analysis

We used three complementary estimates to express mortality.

- (i) Mortality rates were expressed as number of deaths per 100 person-years (PY) with 95% confidence intervals (95% CIs) calculated using the exact Poisson method. These reflect mortality incidence over time.
- (ii) Standardized mortality ratios (SMRs) were used to compare, in a multiplicative way, the mortality rates with those of the general population. The SMR is the ratio of the number of observed deaths to the number of expected deaths. Expected deaths were obtained by applying country-, calendar year-, gender- and age-specific mortality rates for the general population to the PY of follow-up of the HIV cohort. Mortality rates for the general population were extracted from the Human Mortality Database, www.mortality.org, or from the World Health Organisation statistical information system (WHOSIS, <http://apps.who.int/whosis/data>). SMRs were computed through Poisson models offsetting expected mortality rates, and adjusted for gender, age, HIV transmission group and history of AIDS at cART initiation. A random-effect for cohort studies was included to account for heterogeneity. An interaction term was included in the model to take into account an effect modification between HIV transmission category and age. SMRs were then estimated for the whole study population and separately by gender, age (18–39 years; 40–59 years; ≥ 60 years), HIV transmission group [injecting drug users (IDUs), MSM, heterosexual], clinical AIDS at cART initiation and the current CD4 count. To allocate PY and events to the current CD4 count, each year of age during follow-up was categorized according to the lowest CD4 measurement during the corresponding year. Where the CD4 count was missing for a particular age-year (1.3, 4.1 and 0.6% of overall PY, at the beginning, during and end of follow-up, respectively), a last-observation-carried-forward method or other simple methods were used to impute the missing values (these methods were judged to provide reliable estimates of SMRs in sensitivity analyses designed to assess the robustness of the method, data not shown).

Our specific interest was in assessing mortality rates and SMRs during periods where the CD4 count was $\geq 500/\text{mm}^3$. Within this

subanalysis, we aimed to identify whether a longer time spent with a CD4 count $\geq 500/\text{mm}^3$ was associated with a higher likelihood of similar mortality rates to those reported in the general population. We thus estimated SMRs accounting for all years of age with CD4 counts $\geq 500/\text{mm}^3$ with the following time thresholds: ≥ 1 year spent with CD4 $\geq 500/\text{mm}^3$; ≥ 2 consecutive years spent with CD4 $\geq 500/\text{mm}^3$, ..., ≥ 5 consecutive years spent with CD4 $\geq 500/\text{mm}^3$.

Mortality rates were considered as similar to the general population when the 95% CI for the SMR included the value 1 and when the point estimate was close to 1, i.e. < 1.2 .

- (iii) Excess mortality rates quantified, in an additive way, the observed death beyond those expected. These were estimated by subtracting the expected number of deaths from the observed number, and dividing this by the total PY; 95% CIs were computed using the exact Poisson method assuming that the reference mortality rates were fixed.²⁰ All statistical analyses were performed using Statistical Analysis System software (SAS, 9.1).

Results

In the COHERE database, 80 642 patients from 23 cohorts and 31 European countries were eligible for this analysis out of a total of 94 295 HIV-infected adults who initiated cART between 1998 and 2008 (Figure 1 and Supplementary Figure 1, available as Supplementary Data at *IJE* online). Patients excluded from the analysis (due to missing data on gender, CD4 measures within 6 months prior cART initiation or follow-up) did not differ from included patients in terms of their gender, age, transmission category, clinical stage, year of cART initiation or mortality rate (data not shown). Overall, 70% of eligible participants were men and the median age at cART initiation was 37 years (men 38 years, women 34 years) (Table 1). IDU was the HIV transmission category in 16%, of whom 1% were ≥ 60 years of age. Among men, 48% were MSM. Overall, 19% of individuals had AIDS at cART initiation, the median CD4 count was $225/\text{mm}^3$ (inter-quartile range: 107–357) and 44% had a CD4 count $< 200/\text{mm}^3$ (men 45%, women 40%). The median CD4 count at cART initiation was lower in individuals aged ≥ 60 years as compared with younger individuals. The median delay between HIV diagnosis and cART initiation was shorter in older individuals and was 0.3 and 1.2 years for patients starting cART with CD4 cell count $< 200/\text{mm}^3$ and $\geq 500/\text{mm}^3$, respectively. The median duration of follow-up was 3.5 years. Of the total duration of follow-up of 315 340 PY, 29% was spent with a CD4 count $\geq 500/\text{mm}^3$.

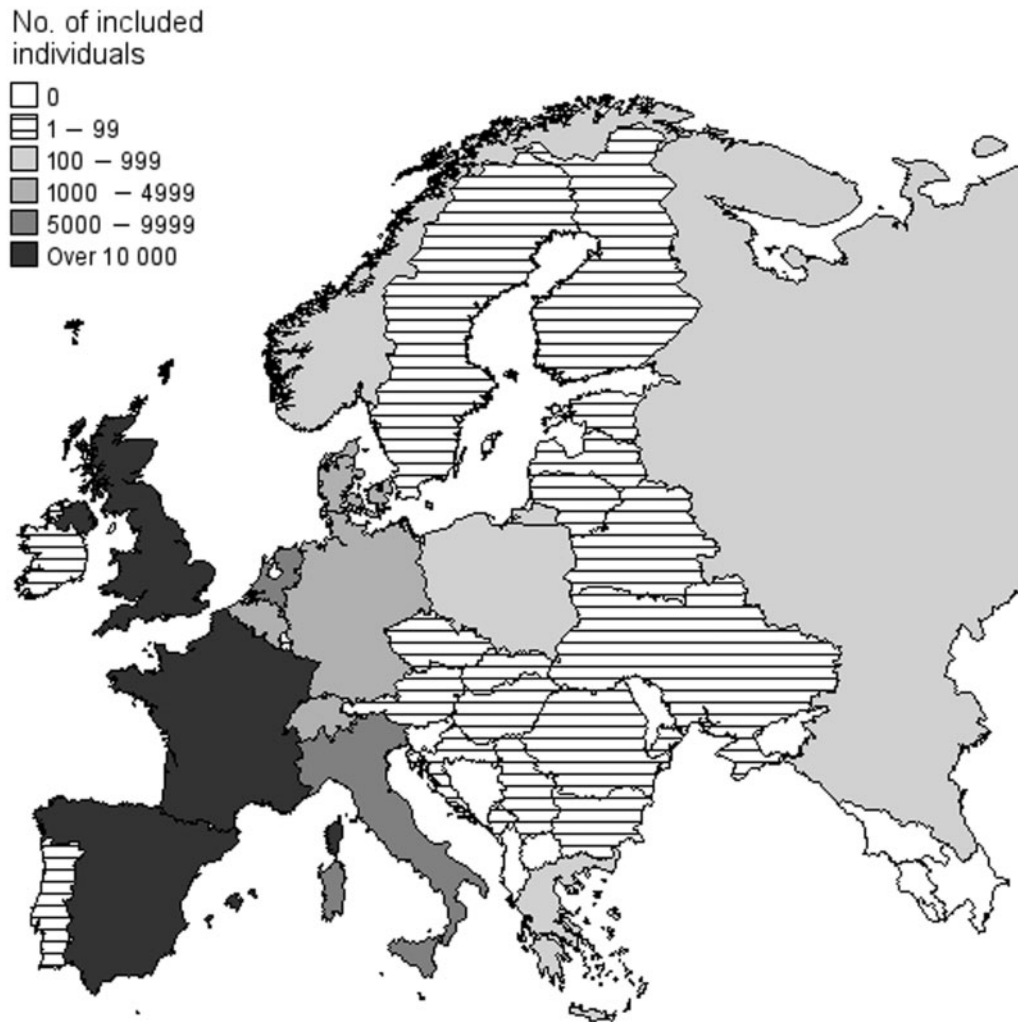


Figure 1 European country distribution of the study population within mortality analysis, the COHERE Collaboration 1998–2008

Mortality rates, SMRs and excess mortality rates overall

Gender

Mortality rates were 1.15/100 PY overall, 1.29 in men and 0.86 in women (Table 1). Overall, mortality was higher than in the general population (SMR 4.2, 95% CI 3.5–5.2), both in men (SMR 3.8, 95% CI 3.1–4.7) and women (SMR 7.4, 95% CI 6.0–9.1). Conversely, excess mortality rates were slightly lower in women [0.74/100 PY (95% CI 0.60–0.92)] than in men [0.95/100 PY (95% CI 0.78–1.16)].

Age

As expected, mortality rates increased with age, whereas SMRs decreased with age from 8.5 at ages <40 years to 1.7 at ages ≥ 60 years. Conversely, the excess mortality rates increased with age from 0.73/100 PY at ages <40 years to 1.19/100 PY at ages ≥ 60 years (Table 1). The excess mortality

represented 88, 75 and 41% of the observed mortality among individuals <40 years, 40–59 years and ≥ 60 years, respectively. Thus, whereas older HIV-infected individuals had mortality rates that were closer to those of a general population of the same age and gender when considered in relative terms, absolute excess mortality was higher in older individuals and this represented a smaller proportion of the observed mortality rates (Table 1 and Figure 2).

Mortality rates, SMRs and excess mortality rates with CD4 counts $\geq 500/\text{mm}^3$

As the CD4 count increased, mortality rates dropped and were closer to those of the general population. Among 35 316 individuals with a CD4 count $\geq 500/\text{mm}^3$, the mortality rate was 0.37/100 PY (SMR 1.5, 95% CI 1.2–1.8) and excess mortality rate 0.12 (95% CI 0.10–0.15) (Table 2). Overall, mortality rates among the 24 479 HIV-infected men with a CD4

Table 1 Characteristics of HIV-infected patients at cART initiation, duration of follow-up, mortality rates compared with the general population, COHERE Collaboration, 1998–2008

	Overall N = 80 642	Men N = 56 417	Women N = 24 225	18–39 years N = 51 400	40–59 years N = 26 562	≥60 years N = 2680
Women (%)	30			36	20	21
Median age (years) (IQR)	37 (31–43)	38 (33–45)	34 (29–40)			
Mode of HIV transmission (%)						
Drug injection	16	17	12	18	13	1
Homo or bisexual	33	48		32	36	30
Heterosexual	42	27	79	43	41	53
Other/unknown	9	9	9	8	10	16
Median time between HIV diagnosis and cART initiation (years) (IQR)	1.0 (0.2–4.6)	1.1 (0.2–4.8)	0.9 (0.2–4.1)	1.1 (0.2–4.4)	1.0 (0.1–5.3)	0.3 (0.1–2.0)
Baseline AIDS (%)	19	21	16	17	24	27
Median baseline CD4 count (/mm ³) (IQR)	225 (107–357)	220 (98–349)	239 (128–377)	242 (121–380)	200 (86–317)	186 (79–298)
Year of starting cART (%)						
1998–99	28	29	25	31	23	23
2000–02	32	32	33	33	32	31
2003–04	21	20	23	20	23	23
2005–08	19	19	19	17	22	23
Median duration of follow-up (years) (IQR)	3.5 (1.5–6.1)	3.6 (1.6–6.2)	3.4 (1.5–5.9)	3.7 (1.7–6.3)	3.3 (1.4–5.7)	3.0 (1.3–5.4)
PY	315 340	223 333	92 007	166 456	134 331	14 553
PY with CD4 ≥ 500/mm ³ (% of total PY)	91 891 (29)	65 697 (29)	26 194 (28)	50 129 (30)	38 154 (28)	3 608 (25)
Mortality rates (per 100 PY) (95% CI)	1.15 (0.94–1.14)	1.29 (1.05–1.57)	0.86 (0.70–1.06)	0.83 (0.67–1.03)	1.38 (1.11–1.70)	2.91 (2.32–3.66)
SMR (95% CI)	4.2 (3.5–5.2)	3.8 (3.1–4.7)	7.4 (6.0–9.1)	8.5 (6.8–10.5)	4.2 (3.4–5.1)	1.7 (1.3–2.1)
Excess mortality rates (per 100 PY) (95% CI)	0.88 (0.72–1.07)	0.95 (0.78–1.16)	0.74 (0.60–0.92)	0.73 (0.59–0.91)	1.04 (0.84–1.29)	1.19 (0.95–1.50)

cART: combination antiretroviral therapy; CI: confidence interval; HIV: human immuno-deficiency virus; IQR: interquartile range; PY: person-years.

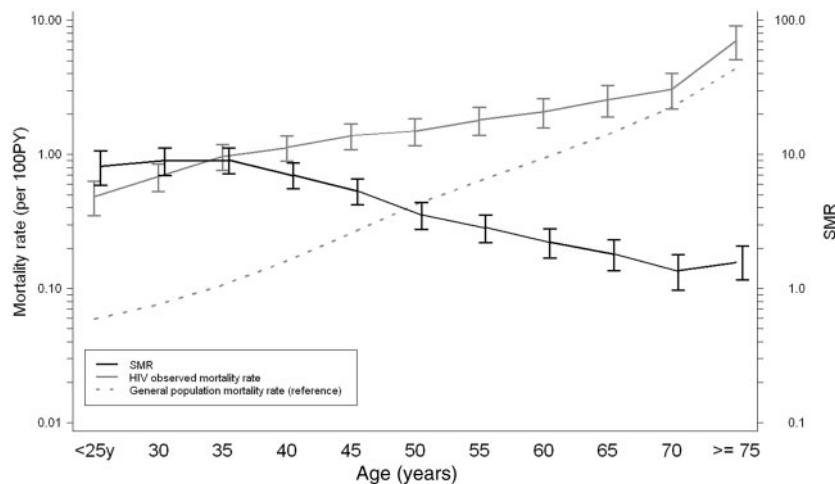


Figure 2 SMRs and mortality rates according to age in HIV-infected individuals after initiation of cART and in the general population, the COHERE Collaboration 1998–2008 (logarithmic scale)

Table 2 SMR and excess mortality rates in HIV-infected individuals with a CD4 count $\geq 500/\text{mm}^3$ after cART initiation, according to gender and age

	PY	Mortality rate/ 100 PY (95% CI)	SMR (95% CI)	Excess mortality rate/ 100 PY (95% CI)
Global	91 891	0.37 (0.30–0.46)	1.5 (1.2–1.8)	0.12 (0.10–0.15)
Men (years)	65 697	0.43 (0.35–0.53)	1.4 (1.1–1.7)	0.12 (0.10–0.15)
18–39	32 565	0.31 (0.24–0.40)	2.5 (1.9–3.2)	0.18 (0.14–0.24)
40–59	30 216	0.48 (0.38–0.62)	1.3 (1.0–1.7)	0.12 (0.09–0.15)
≥ 60	2916	1.27 (0.88–1.82)	0.7 (0.5–1.0)	
Women (years)	26 194	0.23 (0.17–0.32)	2.2 (1.6–3.0)	0.13 (0.09–0.17)
18–39	17 564	0.17 (0.12–0.24)	3.4 (2.5–4.8)	0.12 (0.09–0.17)
40–59	7938	0.32 (0.23–0.45)	1.9 (1.3–2.6)	0.15 (0.10–0.21)
≥ 60	692	0.77 (0.50–1.21)	1.0 (0.6–1.5)	–0.03 (–0.04 to 0.02)

cART: combination antiretroviral therapy; CI: confidence interval; HIV: human immuno-deficiency virus; PY: person-years.

count $\geq 500/\text{mm}^3$ reached similar levels to those of the general male population after 3 years in this CD4 strata: SMR 1.0 (95% CI 0.8–1.4) (Figure 3a). Among the 10 837 HIV-infected women with a CD4 count $\geq 500/\text{mm}^3$, mortality rates did not reach similar levels to those of the general female population, even after 5 years spent above this threshold (Figure 3b). These results were similar in the subgroup of individuals with a high CD4 count at cART initiation.

Non-IDUs

Among non-IDUs, mortality rates were similar to those of the general population in men with CD4 count $\geq 500/\text{mm}^3$: SMR 0.9 (95% CI 0.7–1.2) (Figure 3e and g). In women with a CD4 count $\geq 500/\text{mm}^3$, mortality rates were similar to those of

the general population after 3 years in this CD4 strata, SMR 1.1 (95% CI 0.7–1.7) (Figure 3f).

IDUs

Among 12 503 IDUs, mortality was 13.1 times (95% CI 10.5–16.5) higher than in the general population, 11.7 times (95% CI 9.4–14.7) higher in men and 22.7 times (95% CI 18.0–28.7) higher in women; the excess mortality rate was 2.29/100 PY (95% CI 1.83–2.87). Even when the CD4 count was $\geq 500/\text{mm}^3$, mortality rates remained higher than those seen in the general population, SMR 5.7 (95% CI 4.2–7.8), with an excess mortality rate of 0.76 (95% CI 0.56–1.04). This was apparent even after 5 years spent above this threshold, though SMRs tended to decrease as individuals attained a CD4 count $\geq 500/\text{mm}^3$ for longer periods of time (Figure 3c and d).

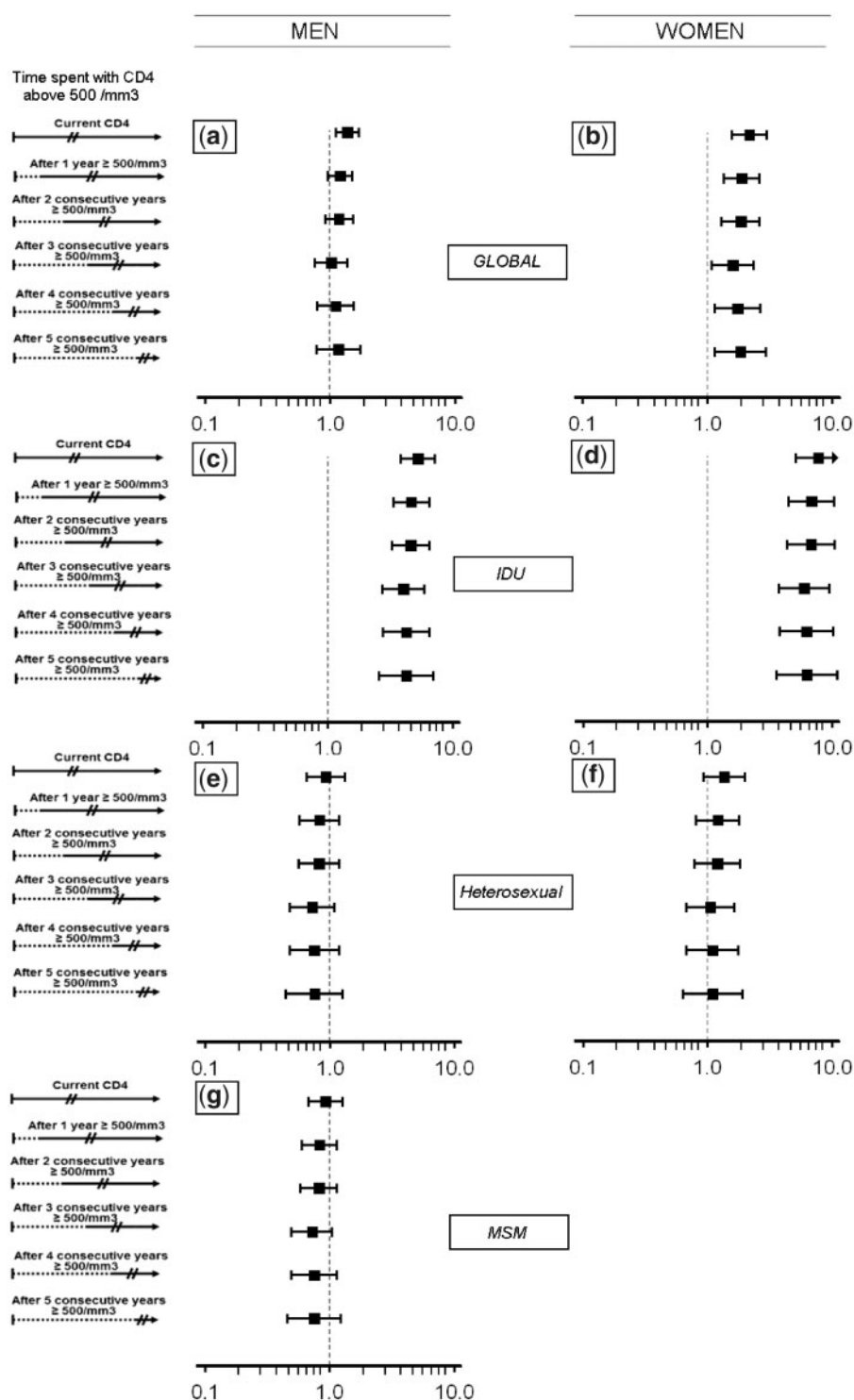


Figure 3 SMRs according to gender, transmission group and time spent with CD4 count $\geq 500/\text{mm}^3$ among HIV-infected individuals with CD4 count $\geq 500/\text{mm}^3$ after initiation of cART, the COHERE Collaboration 1998–2008. (a) men global; (b) women global; (c) men IDU; (d) women IDU; (e) men heterosexual; (f) women heterosexual; (g) men who have sex with men

Age and baseline AIDS

The 1717 individuals aged ≥ 60 years who achieved a CD4 count $\geq 500/\text{mm}^3$ experienced mortality rates that were similar to the general population; this was true

for both genders (Table 2). Nevertheless, in the group of older women who reached CD4 counts $\geq 500/\text{mm}^3$, the SMR was 1.7 (95% CI 0.7–4.0) among those who had AIDS at cART initiation (Figure 4h).

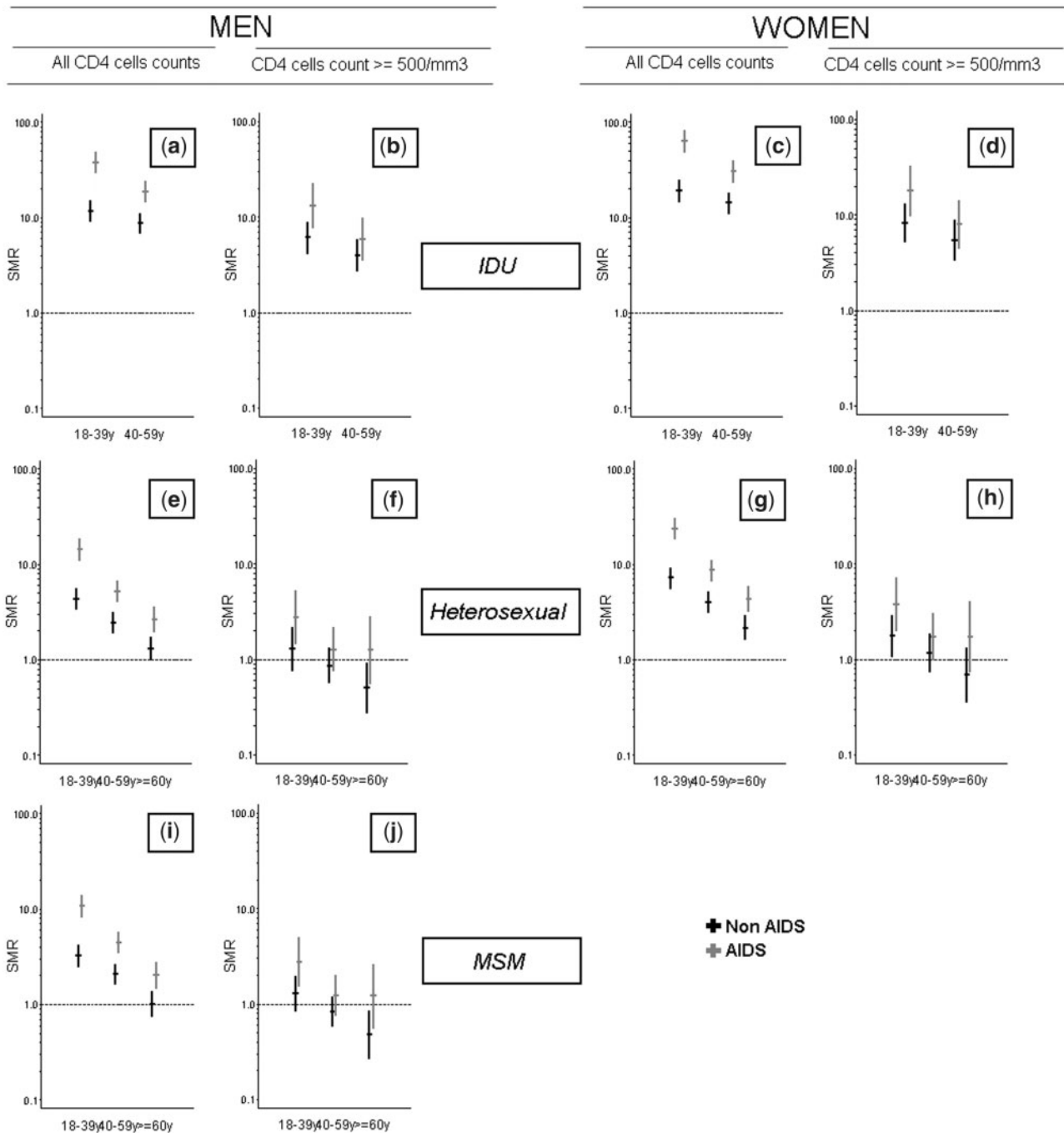


Figure 4 SMRs according to gender, age, transmission group and AIDS at baseline among HIV-infected individuals after initiation of cART, overall and during periods with CD4 count $\geq 500/\text{mm}^3$, the COHERE Collaboration 1998–2008. All CD4 cell counts: (a) men IDU; (c) women IDU; (e) men heterosexual; (g) women heterosexual; (i) men who have sex with men. CD4 cell count $\geq 500/\text{mm}^3$: (b) men IDU; (d) women IDU; (f) men heterosexual; (h) women heterosexual; (j) men who have sex with men

Among non-IDU men who had a CD4 count $\geq 500/\text{mm}^3$, mortality rates were similar to those in the general population at ages ≥ 40 years but were higher at ages < 40 years. Nevertheless, among men aged 40–59 years who had high CD4 counts but who had AIDS at cART initiation, the SMR was 1.3 (95%

CI 0.8–2.1) in heterosexuals and 1.2 (95% CI 0.8–2.0) in MSM (Figure 4f and j).

Among non-IDU women aged < 60 years who had a CD4 count $\geq 500/\text{mm}^3$, mortality rates were higher than those of the general female population (Figure 4h). However, after 1 year with a CD4 count

$\geq 500/\text{mm}^3$, 40- to 59-year-old non-IDU women experienced similar mortality rates as those of the general population, SMR 1.1 (95% CI 0.7–1.7); in contrast, women aged 18–39 years never experienced similar mortality rates as those in the general population.

Overall, AIDS at cART initiation was associated with higher SMRs. This remained the case in all groups even when the current CD4 count was $\geq 500/\text{mm}^3$ (Figure 4).

Discussion

This large cohort collaboration includes more than 80 000 patients from 31 countries. Given this large number of patients, as well as the inclusion of patients from 31 different European countries, and the fact that many of the participating cohorts are based within health-care delivery systems in these countries, the results presented may be considered to provide a fair representation of the wider situation of HIV-infected individuals in Europe over the first 10 years of widespread cART use. Between 1998 and 2008, the mortality rate in cART-treated European HIV-infected adults was 1.2/100 PY on average. Although IDUs continued to experience greater mortality than that seen in the general population, even when they had attained a CD4 count $\geq 500/\text{mm}^3$ for more than 5 years, non-IDUs who attained a CD4 $\geq 500/\text{mm}^3$ experienced mortality rates that were similar to those of the general population; this effect was seen immediately after reaching the threshold in men and after 3 years among women. AIDS at cART initiation was, however, associated with higher SMRs, regardless of the CD4 count attained.

The overall SMR among HIV-infected individuals on cART in our study is close to recent reports^{6,21} but lower than those from previous studies,^{5,14} consistent with a decrease in mortality reported in the most recent years of the cART period.⁴

Gender

Higher SMRs in women compared with men have already been reported.^{12,17,21} Non-IDU males aged ≥ 40 years with CD4 counts $\geq 500/\text{mm}^3$ reached similar mortality rates as men in the general population. Although the same was generally true of non-IDU women, SMRs did remain high in some specific subgroups, e.g. those aged 18–39 years. This may reflect differences between HIV-infected women and women of the general population that may lead to a higher mortality risk (e.g. lower socio-economic status^{22,23}, increased frequency of smoking²⁴) which are not captured within the COHERE study. Of note, mortality rates among women in the general population are much lower than those among similarly aged men. Conversely, the excess mortality rates were slightly higher in men than in women, representing the

burden of mortality associated with HIV infection or associated conditions from a public health standpoint.

Age

The higher SMRs seen in younger individuals are partly explained by a higher proportion of IDUs in this age group. After excluding IDUs, the age trend remained, however, suggesting that other characteristics (e.g. smoking or socio-economic level) may also play a role. Older individuals had lower SMRs as compared with younger ones, due to higher mortality rates in the older general population, and higher excess mortality rates, as previously described.^{15,17} From a public health perspective, these higher excess mortality rates should lead to further exploration of the causes of death in older HIV-infected individuals. In the French 'Mortalité 2000-2005' surveys, diversification of the causes of death was particularly marked in older individuals, with higher proportions of cancer- and cardiovascular-related deaths.²⁵

IDUs

Our results confirm that IDUs generally have a poor prognosis, though those who experience a good immunological response to cART for sufficiently extended periods of time have the best prognosis. Since adherence is a strong predictor of mortality,²⁶ HIV-infected IDUs should therefore be reminded that the ability to adhere to ART over the long term is especially important for their health. In addition, these results emphasize the importance of sustained prevention of HIV infection in IDUs. In addition to high-risk behaviours, the role of co-infection with hepatitis C deserves further research.²⁷

Baseline AIDS

Occurrence of AIDS before cART initiation resulted in a poorer prognosis even in individuals who attained CD4 counts $\geq 500/\text{mm}^3$. Our findings provide further arguments for early cART initiation in order to prevent the occurrence of AIDS-defining events that may still occur (albeit at low frequency) in high CD4 strata¹⁰ and which may have a long-term effect on subsequent prognosis. In fact, the median CD4 count at starting cART was $225/\text{mm}^3$ (lower in older individuals), highlighting the importance of widespread HIV testing in order to increase earlier HIV diagnosis.

Current CD4 count

We initially hypothesized that a longer time spent with CD4 counts $\geq 500/\text{mm}^3$ might permit treated HIV-infected patients to attain mortality rates that were similar to those of the general population. When considering the overall sample of treated individuals, this was verified after 3 years in this CD4

strata for men but not in women, even after 5 years with a CD4 count $\geq 500/\text{mm}^3$. Nevertheless, the effect of time spent with a high CD4 count was weaker when compared with the impact of other characteristics such as IDU status or age. While some subgroups (e.g. those aged ≥ 60 years or non-IDU men aged ≥ 40 years) experienced mortality rates that were similar to the general population when their CD4 count was high, regardless of the time spent with a high CD4, other subgroups did not (e.g. IDUs, non-IDUs aged < 40 years), even with a high CD4 nadir. This is in accordance with other studies which have reported that CD4 measurement most strongly predictive of death, non-AIDS-related mortality²⁸ or AIDS and non-AIDS-defining cancers²⁹ was the most recent one. Of note, the effect of time spent with a high CD4 count was apparent in female non-IDUs aged 40–59 years, who experienced similar mortality rates as the general population after 1 year with a CD4 count $\geq 500/\text{mm}^3$.

In the subgroups where we see a higher risk of death despite a CD4 count $\geq 500/\text{mm}^3$, we suggest that any excess mortality may be driven by behavioural or socio-economic characteristics. If this is the case, then a treatment target of a CD4 count $\geq 500/\text{mm}^3$ may not necessarily improve the prognosis of this group, as suggested by a recent pooled analysis among non-treated individuals in high-income settings.¹¹ When compared with our study of treated individuals, these authors report a similar SMR among MSM with a CD4 count $\geq 500/\text{mm}^3$ and a higher SMR among heterosexuals.¹¹

Strengths and generalizability

Only one previous study has analysed SMRs according to updated CD4 in treated individuals from two French cohorts.⁵ The current study provides further evidence on this topic with greater potential for extrapolation across Europe.

For the purpose of this analysis, which was to identify conditions associated with low mortality rates, we selectively identified patients who succeeded in attaining a high CD4 count on cART. Our selection means that these individuals had to survive long enough for the count to reach this high level. Other studies with similar aims to our own selected individuals treated with cART for at least 24 weeks.¹⁷ Identification of the optimal conditions was useful in order to define a target for complete success of treatment in some subgroups and to advance research as to how these favourable outcomes may be achieved in other subgroups (e.g. younger individuals, women, IDUs). Despite the selection of individuals with a good response to treatment, however, the mortality among some subgroups remained substantially higher than in the general population of the same age and gender.

Our results apply to the follow-up of HIV-infected individuals over the first 10 years of cART. Further

studies will be necessary to analyse mortality rates across several decades of cART. Early aging, which involves immune, cerebral, cardiovascular, bone and metabolic systems, may lead to earlier mortality in this population over the long term.³⁰

In order to compare mortality rates we used two estimators. The main analysis was based on SMRs that identified conditions that allow HIV-infected adults to reach mortality rates similar to those of the general population and provided a multiplicative figure which may be interpreted as a relative risk. When mortality was higher than in the general population and when the reference mortality rates in the general population differed according to subgroups, in particular for gender and age, excess mortality rates were also used in order to interpret the results in terms of public health burden.

Limitations

A description of the causes of death would help to determine if the excess mortality in some subgroups of HIV-infected individuals was related to AIDS conditions, to comorbidities such as hepatitis C or B or to emerging morbidities such as cardiovascular disease or cancer. Nevertheless, such a description requires standardized collection and determination of the underlying cause of death.^{25,31} Such a valid determination of the causes of death was not available in our study, though investigators of HIV cohorts should make every possible effort to incorporate standardized collection and validation of data on causes of death. Increasing use of the Coding Causes of Death in HIV (CoDe) protocol for describing the causes of death among those with HIV is likely to result in improvements in cause of death records in the future.³¹

We acknowledge that our results do not directly apply to HIV-infected individuals living in low-resource settings, due to differences in HIV care management, socio-economic conditions, characteristics of patients and the spectrum of morbidities, with active tuberculosis and invasive bacterial diseases being more frequent in these settings than in high-income countries.³²

We chose to refer to all-cause mortality rates in the general population, which include HIV-related deaths. However, HIV-related mortality represents only a small proportion of all-cause mortality in the general population in Europe, allowing us to consider the general population mortality rates as a reasonable proxy for the mortality rates in a non-HIV-infected population.

Although data available from the general population did not allow us to take into account other risk for mortality such as smoking, socio-economic level or IDU, we considered the mortality rates in the general population of the same age and gender as low mortality rates that could be a rational target for therapy to achieve for all subgroups of patients.

Clinical relevance

In conclusion, among treated HIV-infected individuals who attained a CD4 count $\geq 500/\text{mm}^3$, mortality rates were similar to those of the general population in non-IDU men and after 3 years in this CD4 strata in non-IDU women. Among IDUs, mortality rates remained higher than those in the general population, even after 5 years spent with a CD4 count $\geq 500/\text{mm}^3$, though SMRs tended to decrease with longer durations above this threshold. Further studies will be necessary to confirm this trend across several decades of cART. The persistent influence of a prior AIDS diagnosis even among those attaining a high CD4 count, underlines the importance of the current public health calls for earlier identification of HIV infection and entry into care. Our results emphasize the fact that factors other than quantitative immune restoration are necessary in order to reach low mortality rates in HIV-infected individuals.

Supplementary Data

Supplementary Data are available at *IJE* online.

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KEY MESSAGES

- The mortality rate in HIV-infected adults after cART initiation in Europe between 1998 and 2008 was 1.2/100 PY on average, consistent with a decrease in mortality reported in the most recent years of the cART period.
- In a large European collaborative study, non-IDUs infected by HIV and treated by cART who attained a CD4 count $\geq 500/\text{mm}^3$ experienced mortality rates that were similar to those of the general population, immediately after reaching the threshold in men and after 3 years among women.
- Mortality rates in treated IDUs remained elevated, though they tend to decrease with longer durations with high CD4 count. AIDS at cART initiation was associated with higher SMRs, regardless of the CD4 count attained.

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Commentary: Can mortality rates among adult antiretroviral therapy patients in Europe reach levels similar to those experienced in the general population?

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Since 1996, widespread availability of combination antiretroviral therapy (ART) has significantly improved survival of HIV-infected persons in industrialized countries.^{1,2} This has prompted researchers in Europe^{2,3} and North America^{1,2,4} to investigate whether mortality among HIV-infected persons receiving ART

might reach levels similar to those in the general population.

In this paper by Lewden *et al.*,⁵ more than 80 000 patients from 31 European countries are included in an analysis to estimate crude ART patient mortality rates for persons ≥ 18 years of age, who initiated ART