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Mortality of HIV-infected patients starting potent antiretroviral therapy: comparison with the general population in nine industrialized countries

The Antiretroviral Therapy Cohort Collaboration*†

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Background Mortality in HIV-infected patients has declined substantially with combination antiretroviral therapy (ART), but it is unclear whether it has reached that of the general population. We compared mortality in patients starting ART in nine countries of Europe and North America with the corresponding general population, taking into account their response to ART.

Methods Eligible patients were enrolled in prospective cohort studies participating in the ART Cohort Collaboration. We calculated the ratio of observed to expected deaths from all causes [standardized mortality ratio (SMR)], measuring time from 6 months after starting ART, according to risk group, clinical stage at the start of ART and CD4 cell count and viral load at 6 months. Expected numbers of deaths were obtained from age-, sex- and country-specific mortality rates.

Results Among 29 935 eligible patients, 1134 deaths were recorded in 131 510 person-years of follow-up. The median age was 37 years, 8162 (27%) patients were females, 4400 (15%) were injecting drug users (IDUs) and 6738 (23%) had AIDS when starting ART. At 6 months, 23 539 patients (79%) had viral load measurements $\leqslant$500 copies/ml. The lowest SMR, 1.05 [95% confidence interval (CI) 0.82–1.35] was found for men who have sex with men (MSM) who started ART free of AIDS, reached a CD4 cell count of $\geqslant$350 cells/μL and suppressed viral replication to $\leqslant$500 copies/ml by the sixth month. In contrast, the SMR was 73.7 (95% CI 46.4–116.9) in IDUs who failed to suppress viral replication and had CD4 cell counts <50 cells/μL at 6 months. The percentage of patients with SMRs <2 was 46% for MSM, 42% for heterosexually infected patients and 0% for patients with a history of injection drug use. Corresponding percentages for SMRs >10 were 4, 14 and 47%.

Conclusions In industrialized countries, the mortality experience of HIV-infected patients who start ART and survive the first 6 months continues to be higher than in the general population, but for many patients

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excess mortality is moderate and comparable with patients having other chronic conditions. Much of the excess mortality might be prevented by earlier diagnosis of HIV followed by timely initiation of ART.

Keywords HIV-infection, antiretroviral therapy, mortality, general population, standardized mortality ratio, meta-analysis, industrialized countries

Introduction

The widespread use since 1996 of combination antiretroviral therapy (ART) has substantially improved the prognosis of human immunodeficiency virus (HIV)-infected patients.[1–3] Recent studies have suggested that all-cause mortality in patients successfully treated with ART might approach that of the general population, and that in many patients mortality rates are comparable with other chronic conditions, such as diabetes.[4–8] Such comparisons are important to gain a better understanding of the treated history of HIV infection, to monitor and predict the progress of the HIV/acquired immunodeficiency syndrome (AIDS) epidemic and to plan health services in the era of potent ART. These data are also important in the context of life insurance: an increasing number of people living with HIV/AIDS wish to obtain life insurance, but many find that such insurance is either not on offer, of limited scope or expensive.[9]

Several prognostic factors of mortality have been identified in HIV-infected patients starting ART. The ART Cohort Collaboration (ART-CC), an international collaboration of cohort studies of HIV-1-infected patients starting ART, defined prognostic groups based on the CD4 cell count and viral load at baseline, age, infection through injection drug use and a prior diagnosis of AIDS. The probability of death 3 years after starting ART ranged from 0.8% in the group at lowest risk to 43% in the highest risk group.[10] A subsequent analysis showed that baseline CD4 cell count and viral load were no longer prognostic once the 6-month measurements had been taken into account.[11] The immunological and virological responses after 6 months of treatment are therefore important factors predicting disease progression over subsequent years.

Previous studies comparing the mortality of HIV-1-infected patients with that of the general population were based on single cohort studies and therefore had limited power to compare mortality rates across prognostic groups.[4] In the present study we analysed the ART-CC database to compare mortality rates observed in 13 cohort studies of HIV-1-infected patients with those observed in the general populations of the nine countries concerned. Standardized mortality ratios (SMRs) were calculated from 6 months after starting ART, thus taking the initial response to treatment into account.

Methods

ART-CC

The ART-CC is a collaboration of cohort studies and clinical databases from North America and Europe, which was established in 2001 to estimate prognosis in adult HIV-infected patients initiating ART. Eligibility criteria and methods have been reported in detail elsewhere.[10–13] Briefly, prospective cohort studies were eligible if they had enrolled at least 100 patients with HIV-1 infection aged $\geqslant$16 years who had not previously received antiretroviral treatment (treatment-naive) and initiated ART with a combination of at least three drugs, including nucleoside analogue reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs) and non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs), with a median duration of follow-up of $\geqslant$1 year. The present analysis was based on the most recent database, which was assembled in 2007. All patients with known date of starting ART and who had a CD4 count and HIV-1 RNA measurement at 6 months were included. We restricted the analysis to the three most important transmission groups (via homosexual sexual contacts, via heterosexual sexual contacts and injection drug use). These three groups comprise 80% of all patients in the ART-CC database. Patients who died or were lost to follow-up within the first 6 months after ART were excluded. All cohorts follow patients actively, using telephone, postal reminders or both.

Clinical stage at baseline (the time of starting ART) was classified as less advanced disease (CDC stage A/B) or AIDS (CDC stage C).[14] Most viral load determinations were done with the Amplicor Monitor PCR method (Roche Molecular Systems, Branchburg, NJ, USA), but the branched DNA assay (Chiron Diagnostics, Emeryville, CA, USA) and the NASBA-QT assay (Organon Teknika, Durham, NC, USA) were also used in some cohorts. We considered 500 copies/ml as the lower limit of detection in order to overcome heterogeneity in the assays' detection levels.

Patient selection and data extraction were performed at the data centres of the participating cohort studies. Anonymized data on a predefined set of demographic, laboratory and clinical variables were then pooled and analysed centrally. Data managers checked for duplicated records, and ensured that

patients included in more than one cohort had only one record in the combined dataset. At all sites institutional review boards had approved the collection of data.

Country-specific general population mortality rates

Sex- and age-specific mortality rates for the general populations were obtained from the Human Mortality Database (http://www.mortality.org), a collaborative project between the Department of Demography at the University of California, Berkeley, USA, and the Max Planck Institute for Demographic Research, Rostock, Germany.

Statistical analysis

We used an 'intent-to-continue-treatment' approach and thus ignored subsequent changes to treatment, including treatment interruptions and terminations. We used indirect standardization of rates. Time was measured from 6 months after starting ART to the last follow-up visit or death. SMRs were calculated as the ratio of the number of observed deaths to the number of expected deaths from all causes, in strata defined by sex, risk group—injecting drug users (IDUs), heterosexuals and men who have sex with men (MSM)—clinical stage at baseline (CDC A/B, C) and the CD4 cell count and viral load at 6 months. The expected number of deaths for the corresponding year was calculated by multiplying the age-specific (in 1-year age bands) and sex-specific death rates from the corresponding general population with the observed follow-up time starting at 6 months for each participant. 95% confidence intervals (CIs) for the SMRs were calculated according to Chiang.[15] In a sensitivity analysis we repeated analyses excluding the largest cohort, which contributed 42% of the deaths and 46% of the patients.

Results

The database of the ART-CC includes 49 040 eligible patients of 10 cohorts from Europe, two cohorts from Canada and three cohorts from the USA. We excluded 1658 (3.4%) patients from the EuroSIDA study,[16] which includes patients from 20 European countries; and 4980 (10.2%) patients from the Veterans Ageing Cohort Study (VACS), which has incomplete information on transmission group in a large proportion of patients. We also excluded 4347 (8.9%) patients whose risk group was unknown or other than heterosexual contacts, sex between men or injection drug use, and 4925 (10.0%) patients who did not have both a viral load measurement and CD4 count at 6 months. Finally, we excluded 3195 (6.5%) patients not followed beyond 6 months, including 347 patients who died in the first 6 months of ART. The analyses were thus based on 29 935 (61.0%) patients from the following 13 cohorts of nine countries: AIDS Therapy Evaluation Project Netherlands (ATHENA);[17] Aquitaine Cohort, France;[18] British Columbia Centre for Excellence in HIV/AIDS, Canada;[2] Collaborations in HIV Outcomes Research, United States (CHORUS);[19] Frankfurt HIV Cohort, Germany;[20] French Hospital Database on HIV (FHDH);[21] Italian Cohort of Antiretroviral-Naive Patients (ICONA);[22] Köln/Bonn Cohort, Germany;[23] Proyecto para la Informatización del Seguimento Clínico-epidemiológico de la Infección por HIV y SIDA (PISCIS), Spain;[24] Royal Free Hospital Cohort, UK;[25] South Alberta Clinic, Canada;[26] Swiss HIV Cohort Study (SHCS)[1] and University of Alabama 1917 Clinic Cohort, United States.[27]

The characteristics of the 13 participating cohorts are shown in Table 1. The number of patients ranged from 279 to 13 645. The median CD4 cell count at the start of ART ranged from 159 to 297 cells/μL, and the proportion of patients with a history of injection drug use ranged from 2 to 44%. A total of 8155 (27%) patients were lost to follow-up by study end. Compared with those who were alive and in follow-up at the end of the study period patients who were lost to follow-up had similar median CD4 counts at 6 months (330 compared with 328 cells/μL), and the proportion with AIDS at baseline was also similar (21% compared with 22%). The proportion of patients who were infected via injection drug use was slightly higher in those lost to follow-up (18%) compared with those who remained in follow-up (13%). In patients who died the median CD4 cell count at 6 months was 188 cells/μL, 41% had AIDS and 31% had a history of injection drug use.

Patient characteristics are shown in Table 2. The median age was 37 years [interquartile range (IQR) 32–44 years], 8162 (27%) patients were females, 4400 (15%) had a history of injection drug use and 6738 (23%) had AIDS when starting ART. The initial antiretroviral regimen contained a PI in 18 648 (62%) patients and an NNRTI in 9561 (32%). At start of the therapy, 27 937 patients (93%) were on three antiretroviral drugs (counting ritonavir boosted PI as one drug), the remaining patients were on four or more drugs. At 6 months, data on drug regimen prescribed were available in 27 514 patients (92%). In the remaining patients, data were missing or treatment was stopped before 6 months. A regimen including a PI was used in 16 315 patients (55%) and an NNRTI in 8861 patients (30%). Overall, 19 826 (66%) patients remained on their initial combination at 6 months. The median CD4 cell count increased in the first 6 months, from 216 (IQR 90–348) to 322 cells/μL (IQR 185–489). At 6 months, 23 539 patients (79%) had viral load measurements $\leqslant$500 copies/ml. This proportion varied by outcome status: 59% in those who died, 73% in those lost to follow-up and 82% in those remaining in follow-up and alive at the end of the study.

Table 1 Characteristics of the 13 cohorts from nine countries that participated in the analyses

Cohort	No. of patients, no. of deaths and no. lost to follow-up	Crude mortality rate per 100 person-years of follow-up[a] (95% CI)	No. of women (%)	No. with history of injection drug use at baseline (%)	No. with AIDS at baseline (%)	Median CD4 cells/μL at 6 months (IQR)	No. with viral load ⩽500 copies/ml at 6 months
A	279, 23, 73	1.97 (1.31–2.96)	93 (33)	34 (12)	47 (17)	296 (143–487)	214 (77)
B	648, 22, 80	0.88 (0.58–1.34)	148 (23)	78 (12)	78 (12)	433 (261–589)	535 (83)
C	4380, 154, 732	0.87 (0.74–1.01)	1082 (25)	171 (4)	972 (22)	340 (210–500)	3788 (86)
D	672, 73, 32	2.29 (1.82–2.89)	81 (12)	295 (44)	286 (43)	320 (180–500)	498 (74)
E	434, 17, 95	1.01 (0.63–1.62)	103 (24)	23 (5)	138 (32)	270 (160–410)	348 (80)
F	1055, 34, 370	0.90 (0.65–1.27)	110 (10)	40 (4)	408 (39)	364 (216–552)	773 (73)
G	13 645, 474, 4890	0.87 (0.79–0.96)	4209 (31)	1599 (12)	2981 (22)	312 (177–468)	10 202 (75)
H	1442, 72, 193	1.12 (0.89–1.41)	307 (21)	221 (15)	279 (19)	285 (160–432)	1190 (83)
I	2252, 66, 880	0.73 (0.58–0.93)	630 (28)	797 (35)	372 (17)	385 (216–572)	1656 (74)
K	1705, 41, 208	0.90 (0.66–1.22)	405 (24)	529 (31)	462 (27)	313 (174–491)	1420 (83)
L	655, 5, 99	0.29 (0.12–0.69)	162 (25)	12 (2)	171 (26)	309 (180–485)	560 (85)
M	291, 14, 71	1.08 (0.64–1.82)	55 (19)	57 (20)	85 (29)	288 (183–447)	240 (82)
N	2477, 139, 432	1.31 (1.11–1.54)	777 (31)	544 (22)	459 (19)	321 (183–484)	2115 (85)
All cohorts	29 935, 1134, 8155	0.95 (0.91–1.02)	8162 (27)	4400 (15)	6738 (23)	322 (185–489)	23 539 (79)

[a]Calculation of time at risk started at 6 months.
CI = confidence interval.

The median duration of follow-up after 6 months of ART was 3.75 years. There were 1134 deaths recorded during a total of 118 975 person-years of follow-up, for a crude death rate of 0.95 per 100 person-years (Table 2). The crude SMR over all cohorts was 3.36 (95% CI 3.16–3.56), with some heterogeneity between cohorts. The cohort-specific, crude SMRs tended to be higher for cohorts with large proportions of IDUs and lower median CD4 cell counts at 6 months (data not shown). SMRs for the three main transmission groups stratified by clinical stage at baseline and viral load and CD4 cell count at 6 months are shown in Table 3. SMRs increased with decreasing CD4 counts at 6 months, were higher if viral load at 6 months was >500 copies/ml, higher in patients with AIDS at baseline and higher in IDUs than in homosexual men and heterosexually infected people. The lowest SMR, 1.05 (95% CI 0.82–1.35), was found for MSM who started ART free of AIDS and reached a CD4 cell count of ⩾350 cells/μL and a viral load of ⩽500 copies/ml by the sixth month (Table 3). At the other end of the spectrum, an SMR of 73.7 (46.4–116.9) was found in IDUs who started ART with a CD4 cell count <50 cells/μL and a viral load >500 copies/ml at 6 months. The group of IDUs with the lowest mortality had an SMR of 5.59 (4.28–7.29).

Figure 1 shows the cumulative frequency distribution of SMRs, separately for the three transmission groups. The figure is based on the number of patients in the different risk groups shown in Table 3. Among homosexual men, 5455 (46%) had an estimated SMR <2, 4937 patients (41%) had an SMR in the range of 2 to <5, and 448 patients (4%) had an SMR of ⩾10. The corresponding figures for heterosexually infected patients were 5714 (42%), 5095 (38%) and 1903 (14%). For IDUs the figures were 0 (0%), 0 (0%) and 2055 (47%), respectively. Finally, sensitivity analyses showed that results were robust and not driven by a single cohort. In particular, excluding the largest cohort did not materially alter results.

Discussion

In this collaborative study involving 13 prospective studies and more than 29 000 treatment-naive patients who were followed up for >6 months, the mortality of HIV-infected patients starting ART could be compared across many prognostic groups with that of the corresponding general population. We found that a substantial proportion of men infected through sex with men and individuals infected through heterosexual contacts had SMRs <2. In other words, in >40% of HIV-infected patients from these transmission groups, mortality was increased by <100% compared with the general population. In MSM who started ART free of AIDS and had a CD4 cell count ⩾350 cells/μL and a viral load of ⩽500 copies/ml at 6 months after starting ART, this increase was estimated at 5% (SMR 1.05). Conversely, mortality was increased >70 times (SMR 73.7) in the small group of patients who were infected through injection drug use, failed to suppress viral replication

Table 2 Characteristics of 29 935 treatment-naive study patients at baseline and 6 months after the initiation of potent combination ART

Characteristic	No. of patients (%)	No. of deaths (%)	Crude mortality rate per 100 person-years of follow-up[a]
Total	29 935 (100)	1134 (100)	0.95
Age at baseline (years)			
16–29	5081 (17)	79 (7)	0.4
30–39	13 376 (45)	457 (40)	0.83
40–49	7646 (26)	343 (30)	1.17
⩾50	3832 (13)	255 (22)	1.75
Sex			
Males	21 773 (73)	931 (82)	1.05
Females	8162 (27)	203 (18)	0.68
Risk group			
MSM	11 960 (40	388 (34)	0.76
Heterosexuals	13 575 (45)	392 (35)	0.79
IDUs	4400 (15)	354 (31)	1.95
Clinical CDC stage at baseline			
A/B	23 197 (77)	668 (59)	0.72
C	6738 (23)	466 (41)	1.77
CD4 count (cells/μl) Baseline measurement			
<25	3007 (10)	219 (19)	1.84
25–49	1913 (6)	123 (11)	1.64
50–99	3088 (10)	170 (15)	1.4
100–199	5849 (20)	229 (20)	1.06
200–349	8635 (29)	226 (20)	0.71
⩾350	7443 (25)	167 (15)	0.49
6-month measurement			
<25	442 (1)	101 (9)	7.41
25–49	599 (2)	88 (8)	3.95
50–99	1923 (6)	147 (13)	1.9
100–199	5189 (17)	255 (22)	1.27
200–349	8092 (27)	261 (23)	0.86
⩾350	13 690 (46)	282 (25)	0.49
Plasma HIV-1 RNA level (copies/ml) Baseline measurement			
⩽500 (undetectable)	433 (1)	15 (1)	0.94
501–9999	3373 (11)	89 (8)	0.67
10 000–99 999	11 931 (40)	350 (31)	0.73
⩾100 000	14 198 (47)	680 (60)	1.22
6-month measurement			
⩽500 (undetectable)	23 539 (79)	674 (59)	0.73
501–9999	3287 (11)	165 (15)	1.14
10 000–99 999	1984 (7)	142 (13)	1.83
⩾100 000	1125 (4)	153 (13)	3.71

[a]Calculation of time at risk started at 6 months.

Table 3 SMRs with 95% CIs by risk group, clinical stage at baseline and CD4 cell count and viral load at 6 months based on 29 935 patients

		Clinical stage at baseline A/B		Clinical stage at baseline C	
Risk group	**6-month CD4 count (cells/μL)**	6-month viral load ⩽500 copies/ml	6-month viral load >500 copies/ml	6-month viral load ⩽500 copies/ml	6-month viral load >500 copies/ml
MSM	0–49	3.41 (0.85–13.7)	23.4 (13.0–42.2)	9.62 (5.80–16.0)	24.91 (16.55–37.48)
	50–99	3.23 (1.68–6.21)	6.59 (2.96–14.7)	4.98 (3.28–7.57)	13.40 (7.93–22.62)
	100–199	2.27 (1.57–3.29)	3.52 (2.09–5.95)	3.29 (2.32–4.65)	6.92 (4.24–11.29)
	200–349	1.47 (1.07–2.01)	3.50 (2.33–5.27)	2.65 (1.79–3.93)	1.92 (0.80–4.61)
	⩾350	1.05 (0.82–1.35)	2.06 (1.37–3.10)	1.73 (1.01–2.98)	2.48 (0.93–6.61)
Heterosexuals	0–49	8.40 (4.65–15.16)	28.03 (17.2–45.8)	11.2 (6.72–18.5)	25.7 (18.5–35.8)
	50–99	4.34 (2.62–7.21)	2.11 (0.68–6.53)	4.24 (2.70–6.64)	12.16 (7.33–20.2)
	100–199	2.18 (1.50–3.18)	3.59 (2.26–5.69)	2.91 (1.99–4.24)	5.25 (3.16–8.71)
	200–349	1.85 (1.35–2.53)	3.26 (2.03–5.24)	2.25 (1.40–3.62)	4.67 (2.59–8.44)
	⩾350	1.33 (1.00–1.75)	1.88 (1.11–3.17)	2.52 (1.36–4.69)	3.91 (1.63–9.39)
IDUs	0–49	19.1 (9.09–40.0)	73.7 (46.4–116.9)	13.5 (6.43–28.30)	52.8 (35.4–78.7)
	50–99	6.31 (3.15–12.6)	20.6 (11.7–36.3)	13.0 (6.47–25.89)	40.5 (23.0–71.3)
	100–199	10.3 (7.00–15.1)	14.6 (9.29–22.8)	8.56 (5.07–14.45)	20.5 (12.2–34.7)
	200–349	6.44 (4.55–9.10)	15.1 (10.4–22.1)	7.40 (4.20–13.03)	14.6 (7.29–29.2)
	⩾350	5.59 (4.28–7.29)	8.31 (5.42–12.7)	9.39 (5.33–16.54)	24.9 (11.2–55.4)

Standardized mortality ratios (95% confidence intervals).

and had very low CD4 cell counts at 6 months (<50 cells/μL). Among IDUs, even the group with the lowest mortality rates had an SMR >5.

How applicable are our estimates to other HIV-infected patients? The database of the ART-CC included patients from many countries of Europe and North America who were treated in different settings. The spectrum of patients was broad: men and women, from teenagers to elderly people and the major exposure categories were well represented. The severity of immunodeficiency at baseline ranged from very severe to non-existent, and viral replication from very low to extremely high. Our results should therefore be applicable to many other patients from industrialized countries. Recording of deaths in ART-CC can be assumed to be near complete: in two cohorts deaths are routinely ascertained from the national mortality register, and mortality rates in these two cohorts are similar to the other cohorts. The large number of patients and deaths analysed are a strength of our study, even though follow-up was limited to ~4 years. It is possible that mortality will increase in HIV-infected patients with longer duration of treatment, although we failed to detect such a trend in a recent analysis of ART-CC data.[13] We stress that our estimates apply only to HIV-infected patients who survived for at least 6 months after starting treatment. Mortality in the first months of ART is high in patients starting ART with low CD4 counts and advanced disease. This early mortality was not considered in the present analysis, but has been described in previous reports from the ART-CC collaboration.[10,13,28] Also, we restricted analyses to patients infected either through heterosexual sex, sex between men or injection drug use. The number of patients infected through other routes, including by blood transfusions or blood products, was too small to allow such detailed analyses.

Our analysis did not consider differences between the HIV-infected population and the corresponding general population other than gender and age. There are important differences in the prevalence of risk factors such as smoking between HIV-infected and non-infected populations. For example, a collaborative analysis of HIV cohort studies found that >50% of HIV-infected patients were smokers.[29] In the countries covered by our study, this proportion will be lower (20–40%) in men and women of the same age from the general population.[30] Clearly, part of the increased mortality relative to the general population may be attributable to other lifestyle factors, and smoking in particular, rather than to HIV infection. In an important minority of patients, infection was associated with the injection of intravenous drugs. Studies of HIV infected IDUs have repeatedly shown that they are at increased risk of death from causes not directly related to HIV infection, including overdose, suicide and homicide.[31,32] Also, these patients are known to be at risk of fatal overdose or liver failure associated with co-infection with hepatitis C virus (HCV).[33,34] We did not consider HCV infection in our analyses. However, because HCV co-infection is

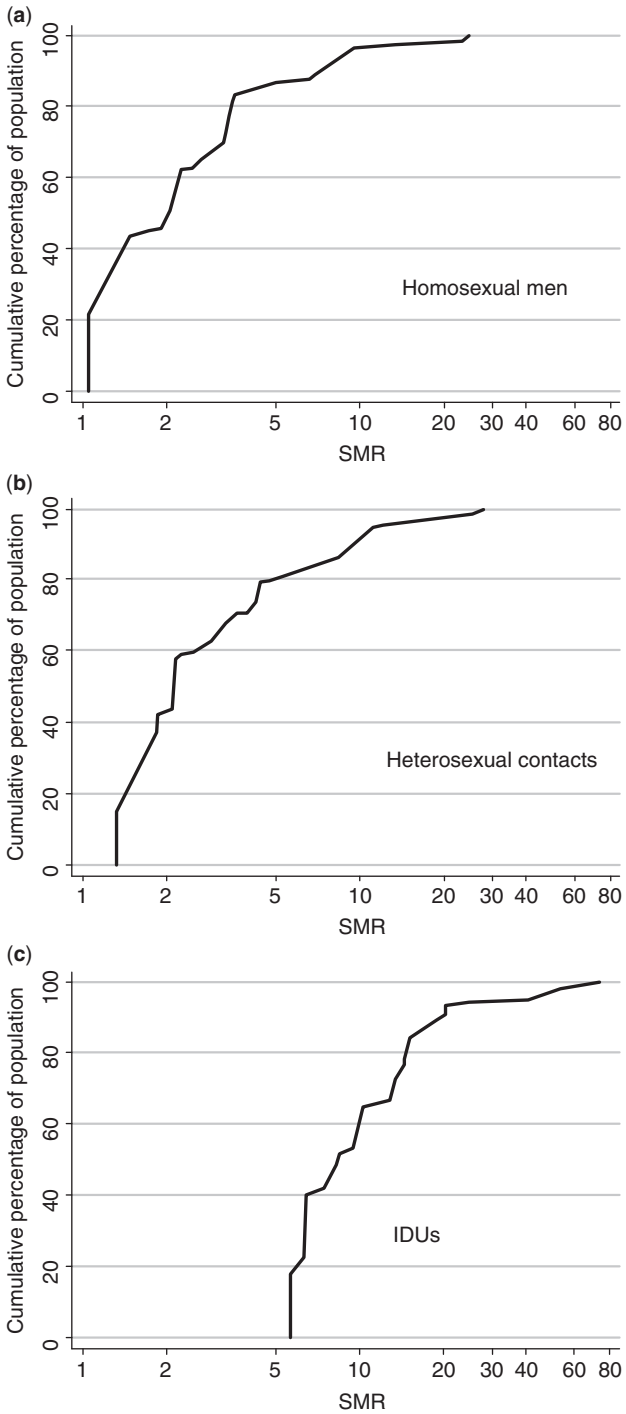

Figure 1 (a–c) Cumulative frequency distribution of SMRs for the three main HIV transmission groups

mainly found in IDUs, its effect will largely be subsumed in the increased hazard for IDUs in our analysis.[35]

There was heterogeneity in the cohort-specific SMRs, which might be explained by differences both in HIV-infected patients and general populations. As noted previously,[8] in this type of study the expected mortality rate for the general population is based on all causes of deaths and thus includes mortality in HIV-infected patients. Mortality due to HIV peaked in the mid-1990s both in Europe[36,37] and the USA.[38] At that time in some urban regions, for example Barcelona or Bologna,[39] HIV-associated mortality was responsible for up to 40% of all deaths in young adults. In 1999 the proportion of deaths attributed to HIV infection in age group 25–44 years ranged from 1.2% in Germany to 6.8% in the USA.[40] The proportion of deaths attributable to HIV will be even lower in older or younger age groups. Therefore, in the era of potent combination ART, mortality due to HIV represents only a small proportion of all-cause mortality in industrialized countries, and substantial bias can be excluded.

How do these SMRs compare with other population groups at increased risk of death due to unhealthy lifestyles or chronic conditions other than HIV infection? For example, among male British doctors born in the 1920s, the probability of dying from any cause in middle age was >3 times in smokers than lifelong non-smokers.[41] Similarly, an analysis of the National Alcohol Survey in the USA showed that regular, heavy drinkers had mortality rates from all causes that were >2.2 times than those observed in lifetime abstainers.[42] The mortality of people with a body mass index (BMI) > 35 kg/m^2 is increased by factor 1.5–2.5, compared with those with a BMI between 20 and 25 kg/m^2, and a similar increase in all-cause mortality is found in physically inactive people compared with physically active individuals.[43] In a population-based study in Turin, Northern Italy, women with type 1 diabetes had an SMR for all causes of 3.4 and men an SMR of 2.[44] The corresponding SMRs for type 2 diabetes was 1.4 for both sexes.[44] The SMRs found in these patients and populations exposed to risk factors are thus quite comparable with those found in some of the patient groups included in our analysis.

What are the implications of this study? Our results are, for example, relevant in the context of insurance protection for HIV-infected individuals. Until recently, life insurance was not available to HIV-infected individuals. This study and other studies support the notion that life insurance plans should be provided at least to some people living with HIV/AIDS. A recent analysis from the Agence Nationale de Recherches sur le Sida et les hépatites virales (ANRS) APROCO and AQUITAINE cohorts in France showed that in patients whose CD4 counts increased to 500 cells/μL, mortality reached that of the general population after the sixth year on ART.[45] The Dutch Association of Insurers has recommended that HIV-positive people responding to antiretroviral treatment who have no other medical complications, and who are not IDUs, should be eligible for life insurance, at reasonable costs.[46] In the USA, an important barrier for HIV-positive people seeking life insurance

policies is high cost: premiums have been found to be two to three times higher for HIV-infected patients, compared with patients of the same age living with cancer.[46] Of note, a South African insurance company recently introduced life insurance for people living with HIV/AIDS.[46]

Although a substantial proportion of HIV-infected patients experienced mortality rates that were comparable with that experienced by other patients with a chronic condition, mortality continues to be much higher in patients who start treatment late, for example, with a history of AIDS-defining illnesses and low CD4 cell counts. Early diagnosis and treatment are of great importance to prevent clinical progression as well as the spread of the infection.[47,48] A survey of new HIV diagnoses in the UK and Ireland showed that many opportunities for earlier diagnosis are missed.[49] Although our study cannot determine the CD4 cell count when ART should be started in order to minimize mortality, much of the excess mortality observed in our study would be preventable with expanded, voluntary screening in health care setting; an approach that has been shown to be cost effective.[50] The ART-CC will continue to monitor the characteristics and mortality of HIV-infected patients starting ART by updating analyses at regular intervals.

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Appendix 1

The Antiretroviral Therapy (ART) Cohort Collaboration

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