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Sex differences in overall and cause-specific mortality among HIV-infected adults on antiretroviral therapy in Europe, Canada and the US

The Antiretroviral Therapy Cohort Collaboration (ART-CC) *

* The members of the Writing Committee are listed at the end of the paper. The contributors to the ART-CC Collaboration are listed in the Acknowledgement section.

Running head: Sex differences in mortality from cART in Europe, Canada and US

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ABSTRACT

Background: To evaluate regional differences in all-cause, AIDS- and non-AIDS-related mortality in HIV-positive men and women started on combination antiretroviral therapy (cART) in Europe, Canada and US.

Methods: The ART Cohort Collaboration (ART-CC) combines 19 cohorts of individuals started on cART in Europe and North America (NA). We analyzed patients infected via injecting drug use (IDU) or heterosexual sex using Cox proportional hazards models.

Results: 32,443 European (45.9% women), 1,162 (32.5% women) Canadian and 2,721 (15.5% women) US patients were included. In Europe and NA, women were younger, more likely to have acquired HIV heterosexually, be AIDS-free and have higher CD4 counts and lower HIV-1 RNA at baseline. European women had lower rates of all-cause (adjusted Hazard Ratio:0.76; 95%CI: 0.68–0.84) and non-AIDS mortality (0.67; 0.57–0.78) than men, but AIDS-mortality rates were similar (0.90; 0.75–1.09). Women had lower mortality due to non-AIDS infections (0.6 versus 1.3 per 1000 person-years), liver diseases (0.4 versus 1.7), non-AIDS malignancies (0.6 versus 2.0) and cardiovascular diseases (0.6 versus 1.0). Between-sex differences in all-cause mortality were larger in heterosexuals (0.70; 0.61–0.80) than in IDU (0.88; 0.73–1.05) (interaction p-value=0.043). No sex differences in all-cause mortality were found in Canada (HR women 1.13; 0.82–1.56) or US (HR women 1.12; 0.79–1.58).

Conclusions: The increasing importance of non-AIDS mortality is leading to emergent sex differences among HIV-positive patients in Europe, as in the general population. In spite of the better clinical characteristics at cART initiation, women in NA had similar mortality to men.

INTRODUCTION

Higher life expectancy in women compared with men has been well documented since the early and mid 20th century in the general population of industrialised countries [1-3], and since 2006 in developing countries [4]. The reasons are not fully understood, but important reductions in between-sex mortality differences have occurred in countries with high female smoking rates and high levels of female participation in the work-force, supporting a strong contribution of lifestyle factors and gender roles [1-4].

Among HIV-positive people, the introduction of combination antiretroviral therapy (cART) has led to dramatic reductions in mortality rates [5-6], with an increasing proportion of deaths in treated HIV-positive people being due to causes not conventionally considered HIV-related [7]. Such changes may lead to emergent differences between mortality rates in treated HIV positive men and women but, unfortunately, sex-stratified analyses are not commonly reported given the low proportion of women among the Western HIV epidemics.

Studies reported to date have produced contradictory results. Reports from the United States, largely based on seroprevalent cohorts, continue to report worse outcomes in HIV-infected women than men [8-10]. In Canada, no sex differences in disease progression have been found [11]. Conversely, evidence has been increasing, largely from European seroconverter cohorts [12-16], and more recently from a Southern Africa Collaboration [17], that HIV-infected women fare better than men. The CASCADE (Concerted Action on SeroConversion to AIDS and Death in Europe) Collaboration, restricted to seroconverters infected through injecting drug use (IDU) and sex between men and women, reported that from 1997 onwards, women experienced lower risks of most AIDS conditions as well as death [12].

Most studies have been conducted in cohorts that recruited high proportions of men who have sex with men (MSM) and low numbers of women. Transmission category is a marker for unmeasured confounders of HIV related outcomes; compared to heterosexuals, the gay community tends to have more established support networks to cope with the consequences of chronic HIV infection, whereas Injecting Drug Users (IDU) have higher prevalence of smoking and other life styles that put them at risk of non-HIV chronic conditions diseases. Because of that, and given that the distribution of these unmeasured confounders would be very different between men and women, it seems appropriate to exclude MSM from analyses of between-sex differences in HIV positive people, and focus on differences between men and women infected through the same routes. We examined differences in rates of all-cause and cause-specific mortality among men and women infected through heterosexual intercourse or injecting drug use, using data from a large collaboration of cohorts of HIV-positive people treated with cART in Europe, Canada and the US.

METHODS

Study population

The ART Cohort Collaboration (ART-CC) combines data from cohorts of HIV-positive persons started on cART from three regions with different HIV epidemics and health care systems: Europe, Canada and the US. Details of the collaboration appear elsewhere [18-19] (<http://www.art-cohort-collaboration.org>). Briefly, it includes patients with confirmed HIV infection, aged ≥ 16 years who started cART (a combination of at least 2 nucleoside reverse transcriptase inhibitors plus boosted protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor) after 1st January 1998. Participating cohorts have been approved by their ethics committees or institutional review boards, use standardized methods of data collection, and schedule follow-up visits at least every six months. Nineteen cohorts contributed to the present analyses, which were restricted to patients infected through heterosexual intercourse or injecting drug use.

Statistical analyses

We performed separate analyses for Europe, Canada and the US, because of the different contexts regarding population composition and health care delivery. Sex differences in socio-demographic and clinical characteristics at start of cART were assessed through the Mann-Whitney test for continuous variables and the chi squared test for independence for categorical variables.

Death and date of death were ascertained by cohorts through chart review and, in some cases, cross-checks with mortality registers. Individuals not known to have died during the follow-up period were censored on the last date the individual was known to be alive or on the cohort-specific date to which follow-up was assumed to be complete, whichever arose first.

Cause of death was ascertained and classified centrally by ART-CC investigators in all but the VACS cohort [20]. VACS obtained causes of death from the National Death Index using the International Classification of Diseases, 10th Revision (ICD-10). Causes of death were classified as AIDS and non-AIDS (non-AIDS infections, liver-related, malignancies, cardiovascular disease, pulmonary, external cause, substance abuse and other).

We calculated overall and cause-specific mortality rates per 1000 persons-year of follow-up. Deaths which were unclassifiable were excluded from the calculation of cause-specific death rates. We used Cox proportional hazards models to estimate hazard ratios (HR), comparing women with men, for all-cause, AIDS and non-AIDS related mortality from the start of cART.

All models were stratified by cohort to allow for between cohort heterogeneity in mortality and adjusted for age at cART initiation (16-29, 30-39, 40-49, 50+); transmission category (IDU, heterosexual); geographical origin (Europe, Sub-Saharan Africa, Latin America, North Africa/Middle East, Asia, North America/Australia/New Zealand) among persons from cohorts in Europe, race/ethnicity (White, Black, Hispanic, Other/Unknown) among persons from cohorts in the US and a combination of geographical origin and race/ethnicity (White Canadian, Aboriginal Canadian, White non-Canadian, Asian non-Canadian, Other/Unknown) among persons from cohorts in Canada; AIDS at cART initiation (no, yes); CD4 count (0-24, 25-49, 50-99, 100-199, 200-349, 350-499, 500+) and HIV viral load (<100,000, ≥100,000) at the start of cART. Tests for non-proportional hazards were derived using Schoenfeld residuals. We tested for interaction between sex and transmission category in multivariable models. Wald tests were used to derive p-values. We repeated analyses of cause-specific mortality using competing risks regression models [21].

Patients were considered lost to follow-up if there was a lag of more than 2 years between the last date the patient was known to be alive and the administrative censoring date, which varied between cohorts from 31st December 2006 to 31st December 2009. For the majority of patients (58%) the censoring date was 31st Dec 2009. We explored whether there were sex differences in the immunological, virological and clinical status of patients lost to follow-up.

All statistical analyses were performed using Stata software (Version 12.0, College Station, Texas).

RESULTS

Socio-demographic characteristics

Of 36,326 patients included, 32,443 (45.9% women) were from 12 European cohorts, 1,162 (32.5% women) from 2 Canadian and 2,721 (15.5% women) from 5 US cohorts. In both Europe and North America, median age at start of cART was younger in women than men. Women were more likely than men to have acquired HIV infection through heterosexual intercourse, to be AIDS-free and to have started cART at higher CD4 counts and with lower HIV-1 RNA (Table 1).

All-cause mortality in men and women

In Europe, during 152,630 persons-years of follow-up, there were 1,809 deaths: 1,301 in men and 508 in women. The all-cause mortality rate was 11.9 (95% confidence interval [CI]: 11.3 – 12.4) per 1000 person-years: 15.5 (14.7 – 16.4) in men and 7.4 (6.8 – 8.1) in women. The crude all-cause mortality HR comparing women with men was 0.47 (95% CI: 0.42 – 0.52): this attenuated to 0.76 (0.68 – 0.84) after adjustment for prognostic factors at start of cART. We found some evidence ($p=0.043$) of an interaction between sex and transmission category: the between-sex difference in mortality was greater in heterosexually infected people (adjusted HR: 0.70; 0.61 – 0.80) than in injecting drug users (0.88; 0.74 – 1.05) (Table 2).

In Canada, during 5,189 persons-years of follow-up, there were 188 deaths (129 in men and 59 in women), resulting in an all-cause mortality rate of 36.2 (95% CI: 31.4 – 41.8) per 1000 person-years: 37.0 (31.2 – 44.0) for men and 34.6 (26.8 – 44.6) for women. The crude and adjusted HR for all-cause mortality were 0.95 (95% CI: 0.70 – 1.30) and 1.13 (0.82 – 1.56), respectively. We found no evidence ($p=0.31$) of an interaction between sex and transmission category.

In the US cohorts, there were 552 deaths (505 in men and 47 in women) during 13,495 persons-years of follow-up, resulting in an all-cause mortality rate of 40.9 (95% CI: 37.6 – 44.5) per 1000

person-years: 42.9 (39.3 – 46.8) in men and 27.2 (20.5 – 36.3) in women. The crude and adjusted HR for all-cause mortality were 0.83 (95% CI: 0.59 – 1.16) and 1.12 (0.79 – 1.59), respectively. There was no evidence ($p=0.81$) of an interaction between sex and transmission category.

We found no evidence of non-proportional hazards in the effect of gender on mortality in any of the three regions (all $P > 0.1$).

AIDS- and non AIDS-related causes of death in men and women

Information on cause of death was available for 1,526 (84%) patients in Europe, 174 (93%) in Canada and 510 (92%) in the US.

In Europe, rates of AIDS-related mortality were 4.4 (95% CI: 4.0 – 4.9) per 1000 person-years in men and 2.8 (2.4 – 3.2) in women; respective values for non AIDS-related mortality were 8.8 (8.2 – 9.4) and 3.4 (3.0 – 3.9) (Table 3). After adjustment, the HR comparing women with men were 0.90 (95% CI: 0.75 – 1.09) for AIDS- and 0.67 (0.57 – 0.78) for non AIDS-related mortality (Table 4). The lower non-AIDS-mortality in women appeared attributable to reduced rates of non-AIDS infections [0.6 (95% CI: 0.5 – 0.8) in women versus 1.3 (1.1 – 1.6) in men], liver related diseases [0.4 (0.3 – 0.6) vs. 1.7 (1.5 – 2.0)], malignancies [0.6 (0.4 – 0.8) versus 2.0 (1.7 – 2.4)] and cardiovascular disease [0.6 (0.4 – 0.8) versus 1.0 (0.8 – 1.3)]. We found weak evidence of an interaction between sex and transmission category for AIDS- ($p=0.11$) and non-AIDS- ($p=0.10$) related mortality.

In Canada, rates of AIDS-related mortality were 17.1 (95% CI: 13.2 – 22.0) per 1000 person-years in men and 14.3 (9.6 – 21.3) in women; values for non AIDS mortality were 18.2 (14.2 – 23.3) and 16.7 (11.5 – 24.1) respectively (Table 3). Adjusted HR for AIDS- and non-AIDS-related mortality were 1.00 (95% CI: 0.61 – 1.65) and 1.16 (0.73 – 1.86), respectively (Table 4).

In the US, rates of AIDS-related mortality were 23.1 (95% CI: 20.5 – 26.0) per 1000 person-years in men and 7.8 (4.5 – 13.4) in women: rates of non-AIDS mortality were 17.8 (15.6 – 20.4) and 12.0 (7.7 – 18.6) respectively. Adjusted HR for AIDS and non-AIDS mortality were 0.84 (0.46 – 1.55) and 1.24 (0.73 – 2.11) respectively.

For Europe, Canada and the US, HR estimated using competing risks regression were similar to those estimated using Cox regression (results available from the authors on request).

Analyses of losses to follow-up by sex

Rates of loss to follow-up differed between regions ($P < 0.001$): Europe 53.1 (95% CI: 52.0 – 54.3) per 1000 persons-years of follow-up, Canada 16.4 (13.2 – 20.3) and US 16.2 (14.2 – 18.5). The rate of loss to follow-up was slightly higher in men than women in Europe (55.0 (53.4 – 56.6) versus 50.8 (49.2 – 52.5), $P < 0.001$) and Canada (19.0 (14.9 – 24.1) versus 11.1 (7.1 – 17.5), $P = 0.033$), but lower in the US (13.5 (11.6 – 15.8) versus 34.8 (27.0 – 44.8), $P < 0.001$).

Amongst people lost to follow-up, the median (IQR) CD4 cell counts (cells/mm³) in the 6 months prior to the last date the person was known to be alive was slightly lower in men than in women in Europe [347 (205, 532) vs. 393 (253, 568), $P < 0.001$], in Canada [308 (160, 482) vs. 367 (100, 564), $P = 0.50$] and in the US [333 (223, 557) vs. 446 (220, 618), $P = 0.11$].

DISCUSSION

HIV-positive women in Europe have lower mortality rates after cART initiation than men, with larger between-sex differences in mortality among heterosexually infected patients than among injecting drug users, and larger between-sex differences in non-AIDS than AIDS mortality. By contrast, we found little evidence of between-sex differences in all-cause or cause-specific mortality in Canada and in the US. However, compared with Europe, data on fewer patients were available and the proportion of women was lower in North America. Because values of prognostic factors such as CD4 cell count and HIV-1 RNA at start of cART were more favorable in women than men in Europe, Canada and the US, adjusted mortality hazard ratios comparing women with men were greater than crude hazard ratios.

Previous studies have reported lower mortality in HIV-positive women than men in European settings [1-2, 22], but only some of the patients included in these studies were on cART. Our study confirms that this observation also holds after cART initiation and is therefore not attributable solely to between-sex differences in access to care [12-13, 15]. These are the first pan-European data on cause-specific mortality according to sex, and demonstrate that, in Europe, lower mortality in women than men was mainly due to non-AIDS-related causes: in particular non-AIDS infections, liver-related death, cardiovascular diseases and non-AIDS malignancies. These last two conditions, which are strongly linked to smoking, are the commonest causes of death in men and women in the general population, with markedly higher rates in men than women [1, 22-23]. By contrast with the general population, rates of mortality due to non-AIDS related infections in our study were as high as for cardiovascular disease mortality [1, 22]. The higher rates of malignancies and of non-AIDS related infections, relative to cardiovascular diseases, are consistent with the immunopathogenesis of HIV infection.

HIV-positive women in Europe, Canada and the US had more favorable values of prognostic factors such as CD4 cell count and HIV-1 RNA, and a lower proportion of previous AIDS diagnoses, compared with men. This, as well as the younger median age at which women started cART, may reflect earlier HIV diagnosis through routine antenatal testing, implemented since the late 90s in Europe and North America. These factors mediated some of the between-sex differences reflected in crude hazard ratios comparing women with men: adjusted hazard ratios were consistently greater than crude hazard ratios. Consistent with other publications; a high proportion of the HIV-positive women recruited to European cohorts were from Sub-Saharan Africa and Latin-America [24]. HIV-positive migrants have been reported to fare better than autochthonous populations [25-26]. In Canada, a higher proportion of women than men were of aboriginal origin, although numbers are low. This is an indicator of worse prognosis given the profound socio-economic deprivation of the aboriginal communities in Canada [27]. In the US, proportions of Black Americans among HIV-positive men and women were similar, with a higher proportion of male than female Hispanics, though numbers are low [28].

By contrast with European patients, we found little evidence of lower mortality after starting cART for women, compared with men, in Canada and the US in spite of their earlier HIV diagnoses. The smaller between-sex differences in Canada and the US, compared with Europe, are likely to reflect differences between the socioeconomic profiles of HIV-positive women in the three regions. In Europe, the HIV epidemic in women is probably associated with a lower degree of social exclusion than in Canada and the US, where HIV/AIDS disproportionately impacts Aboriginal and African-American women, respectively [29-30].

Limitations of our study include the potential for misclassification of causes of death because of incomplete information in cohort data. Cause-specific death rates in this study are an underestimate of the true rates and comparisons may be biased because deaths which were

unclassifiable were excluded. However, the percentage of missing causes death was very small for the three regions and the characteristics of those with and without a cause of death is very similar. We lack data on socio-economic status (for example educational level, income or housing instability), obesity, smoking, alcohol and current use of illegal drugs. These variables, well established confounders, may account for some of the observed associations but are often missing in very large cohort collaborations which, on the other hand, have the statistical power to detect these differences. Smaller numbers of participants from North America than from Europe were included in the dataset analyzed: this limited the precision of estimates of between-sex differences in Canada and the US and calls for larger collaborations to gain deeper understanding of the differences identified in this study. To date, this is the first collaboration to explore outcomes in HIV-positive women across two continents. The men and the women of the ART-CC are not necessarily representative of the HIV-positive population of their respective countries, though they all originate from well-established cohorts and their only selection criterion is to be naïve at ART initiation [19]. Mortality rates in the North American cohorts were higher than for European cohorts, both for the women and for the men. The ART Collaboration has recently described how this heterogeneity is partially due to lower losses to follow-up rates, higher death ascertainment and differential inclusion criteria of very socially deprived HIV-positive patients in cohorts from North-America (31). This, however, should not be different for the men and the women and would not bias our results.

Losses to follow-up were considerably higher in Europe than in North-American cohorts, and men lost to follow-up in Europe had lower CD4 cell counts than women. Similar patterns were observed for men lost to follow-up in Canada and the US, though differences were less marked.

Nonetheless, it is unlikely these patterns account for the marked sex differences observed in Europe, particularly since these mainly relate to non-AIDS mortality.

In summary, there are differences in overall and cause-specific mortality between HIV-positive men and women on ART in Europe, but such differences were not seen in Canada and the US. Patterns of non-AIDS mortality in HIV-infected cohort members in Europe are coming to resemble those of the general population, with malignancies and cardiovascular diseases the commonest causes of death, and sex mortality ratios in treated HIV positive people may increasingly resemble those in the general population, but sex differences in access to care may lead to continuing higher mortality in HIV positive men than women.

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Conflicts of interest

No conflicts of interest

Study groups for each of the cohorts contributing to ART-CC

[French Hospital Database on HIV \(ANRS CO4 FHDH\)](#)

[Italian Cohort of Antiretroviral-Naive Patients \(ICONA\)](#)

[Swiss HIV Cohort Study \(SHCS\)](#)

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Table 1. Socio-demographic and clinical characteristics at the start of cART in men and in women in Europe, Canada and the US

	Europe (N=32,443)		Canada (N=1,162)		US (N=2,721)	
	Men	Women	Men	Women	Men	Women
N	17,539	14,904	784	378	2,300	421
Median (IQR ^a) age, years ^b	38 (33–45)	33 (28–40)	40 (34–46)	35 (28–42)	45 (39–50)	38 (30–45)
Transmission category						
IDU	6,143 (35.0)	1,736 (11.6)	585 (74.6)	233 (61.6)	2,004 (87.1)	115 (27.3)
Heterosexual	11,396 (65.0)	13,168 (88.4)	199 (25.4)	145 (38.4)	296 (12.9)	306 (72.7)
AIDS diagnosis ^b						
No	13,044 (74.4)	12,313 (82.6)	575 (73.3)	304 (80.4)	1,634 (71.0)	331 (78.6)
Yes	4,495 (25.6)	2,591 (17.4)	209 (26.7)	74 (19.6)	666 (29.0)	90 (32.4)
Median (IQR ^a) CD4 count, cells/ μ l ^b	190 (70–306)	229 (120–348)	170 (60–280)	192 (109–299)	200 (67–326)	227 (86–352)
Viral Load, copies/mL ^b						
< 100,000	9,771 (55.7)	10,039 (67.4)	396 (50.5)	227 (60.0)	1,391 (60.5)	280 (66.5)
\geq 100,000	7,768 (44.3)	4,865 (32.6)	388 (49.5)	151 (40.9)	909 (39.5)	141 (33.5)
Geographical origin			Geographical origin/ethnicity		Race/Ethnicity	
Europe	10,991 (62.7)	7,361 (49.4)	White Canadian	287 (36.3)	White	555 (24.1)
Sub-Saharan Africa	2,488 (14.2)	4,239 (28.4)	Aboriginal Canadian	101 (12.9)	Black	1449 (63.0)
Latin America	637 (3.6)	814 (5.5)	White non-Canadian	26 (3.3)	Hispanic	142 (6.2)
North Africa and Middle East	382 (2.2)	192 (1.3)	Asian non-Canadian	13 (1.7)	Other/Unknown	154 (6.7)
Asia	129 (0.7)	252 (1.7)	Other/Unknown	357 (45.5)		7 (1.7)
North America, Australia & NZ ^c	15 (0.1)	11 (0.1)				
Unknown	2,897 (16.5)	2,035 (13.6)				

^a IQR: Interquartile range

^b At cART initiation

^c NZ: New Zealand

Table 2. Number of deaths, all-cause mortality rates (95% confidence intervals) per 1000 person-years and mortality hazard ratios for women compared to men in Europe, Canada and the US

		No. of deaths	Person-years follow-up	Rate (95% CI) per 1000 person-years	Crude HR (95% CI)	Adjusted HR (95% CI) ^a
Europe						
All	Men	1301	83901	15.5 (14.7–16.4)	1.00	1.00
	Women	508	68729	7.4 (6.8–8.1)	0.47 (0.42–0.52)	0.76 (0.68–0.84)
Heterosexuals	Men	674	52911	12.7 (11.8–13.7)	1.00	1.00
	Women	355	59918	5.9 (5.3–6.6)	0.46 (0.40–0.52)	0.70 (0.61–0.80)
Injecting drug use	Men	627	30999	20.2 (18.7–21.9)	1.00	1.00
	Women	153	8811	17.4 (14.8–20.3)	0.82 (0.69–0.98)	0.88 (0.73–1.05)
Canada						
All	Men	129	3483	37.0 (31.2–44.0)	1.00	1.00
	Women	59	1706	34.6 (26.8–44.6)	0.95 (0.70–1.30)	1.13 (0.82–1.56)
Heterosexuals	Men	11	785	14.0 (7.8–25.3)	1.00	1.00
	Women	12	590	20.3 (11.6–35.8)	1.43 (0.63–3.26)	1.68 (0.73–3.87)
Injecting drug use	Men	118	2697	43.7 (36.5–52.4)	1.00	1.00
	Women	47	1116	42.1 (31.6–56.1)	0.97 (0.69–1.36)	1.06 (0.74–1.50)
US						
All	Men	505	11770	42.9 (39.3–46.8)	1.00	1.00
	Women	47	1725	27.2 (20.5–36.3)	0.83 (0.59–1.16)	1.12 (0.79–1.58)
Heterosexuals	Men	28	1082	25.9 (17.9–37.5)	1.00	1.00
	Women	27	1174	23.0 (15.8–33.5)	0.87 (0.51–1.48)	1.18 (0.69–2.01)
Injecting drug use	Men	477	10688	44.6 (40.8–48.8)	1.00	1.00
	Women	20	551	36.3 (23.4–56.2)	0.87 (0.55–1.38)	1.08 (0.68–1.71)

All models are stratified by cohort

^a Adjusted for age at cART initiation (16-29, 30-39, 40-49, 50+), transmission category (IDU, Heterosexual), Geographical origin in Europe (Europe, Sub-Saharan Africa, Latin America, North Africa and Middle East, Asia and North America, Australia and New Zealand), Race/Ethnicity in the US (White, Black, Hispanic, Other/Unknown) and a combination of Geographical origin and Race/Ethnicity in Canada (White Canadian, Aboriginal Canadian, White non-Canadian, Asian non-Canadian and Other/Unknown), AIDS at cART initiation (yes/no), CD4 cell count (0-24, 25-49, 50-99, 100-199, 200-349, 350-499, 500+) and HIV Viral Load (<100,000 and ≥100,000) at the start of cART and stratified by cohort

Table 3. Frequency and cause-specific mortality rates (95% confidence intervals) per 1000 person-years in men and in women in Europe, Canada and the US

	Europe				Canada				US ^a			
	Men		Women		Men		Women		Men		Women	
Person-years	83,297		68,521		3,459		1,680		11,663		1,665	
	No.	Rate (95% CI)	No.	Rate (95% CI)	No.	Rate (95% CI)	No.	Rate (95% CI)	No.	Rate (95% CI)	No.	Rate (95% CI)
AIDS related ^b	370	4.4 (4.0 – 4.9)	192	2.8 (2.4 – 3.2)	59	17.1 (13.2 – 22.0)	24	14.3 (9.6 – 21.3)	269	23.1 (20.5 – 26.0)	13	7.8 (4.5 – 13.4)
Non-AIDS related	731	8.8 (8.2 – 9.4)	233	3.4 (3.0 – 3.9)	63	18.2 (14.2 – 23.3)	28	16.7 (11.5 – 24.1)	208	17.8 (15.6 – 20.4)	20	12.0 (7.7 – 18.6)
Infection	112	1.3 (1.1 – 1.6)	42	0.6 (0.5 – 0.8)	12	3.5 (2.0 – 6.1)	7	4.2 (2.0 – 8.7)	3	1.4 (0.5 – 4.3)	2	1.5 (0.4 – 6.1)
Liver related ^c	144	1.7 (1.5 – 2.0)	28	0.4 (0.3 – 0.6)	14	4.0 (2.4 – 6.8)	6	3.6 (1.6 – 8.0)	7	3.3 (1.6 – 6.9)	1	0.8 (0.1 – 5.4)
Malignancy	169	2.0 (1.7 – 2.4)	40	0.6 (0.4 – 0.8)	2	0.6 (0.1 – 2.3)	5	3.0 (1.2 – 7.2)	3	1.4 (0.5 – 4.3)	2	1.5 (0.4 – 6.1)
Cardiovascular ^d	85	1.0 (0.8 – 1.3)	39	0.6 (0.4 – 0.8)	8	2.3 (1.2 – 4.6)	2	1.2 (0.3 – 4.8)	2	0.9 (0.2 – 3.7)	3	2.3 (0.7 – 7.1)
Pulmonary ^e	22	0.3 (0.2 – 0.4)	9	0.1 (0.1 – 0.3)	2	0.6 (0.1 – 2.3)	0	-	2	0.9 (0.2 – 3.7)	2	1.5 (0.4 – 6.1)
External ^f	38	0.5 (0.3 – 0.6)	12	0.2 (0.1 – 0.3)	6	1.7 (0.8 – 3.9)	0	-	3	1.4 (0.5 – 4.3)	3	2.3 (0.7 – 7.1)
Substance abuse	69	0.8 (0.7 – 1.0)	25	0.4 (0.2 – 0.5)	16	4.6 (2.8 – 7.6)	8	4.8 (2.4 – 9.5)	1	0.5 (0.1 – 3.3)	1	0.8 (0.1 – 5.4)
Other ^g	92	1.1 (0.9 – 1.4)	38	0.6 (0.4 – 0.8)	3	0.9 (0.3 – 2.7)	0	-	3	1.4 (0.5 – 4.3)	1	0.8 (0.1 – 5.4)

^a In US, mortality rates for each non-AIDS related cause of death are calculated excluding VACS cohort; persons-year of follow up are 2,139 in men and 1,312 in women

^b AIDS related: AIDS, AIDS infection, AIDS malignancy

^c Liver related: Hepatitis, Gastro-intestinal haemorrhage, Liver failure

^d Cardiovascular: Myocardial infarction/ischemic heart disease, Stroke, Lung embolus, Heart/vascular

^e Pulmonary: Pulmonary hypertension, Chronic obstructive pulmonary disease-COPD, Respiratory

^f External cause: Accident/violent, suicide

^g Other: Diabetes, Pancreatitis, Lactic acidosis, Renal failure, Haematological, Psychiatric, CNS, Digestive, Skin/motor system, Other

Table 4. AIDS and non-AIDS related mortality hazard ratios for women compared to men in Europe, Canada and the US

	AIDS related mortality ^a		Non-AIDS related mortality ^b	
	Crude HR (95% CI)	Adjusted HR (95% CI) ^c	Crude HR (95% CI)	Adjusted HR (95% CI) ^c
Europe				
Men	1.00	1.00	1.00	1.00
Women	0.59 (0.50–0.71)	0.90 (0.75–1.09)	0.40 (0.34–0.46)	0.67 (0.57–0.78)
Canada				
Men	1.00	1.00	1.00	1.00
Women	0.85 (0.53–1.37)	1.00 (0.61–1.65)	0.94 (0.60–1.46)	1.16 (0.73–1.86)
US				
Men	1.00	1.00	1.00	1.00
Women	0.63 (0.34–1.15)	0.84 (0.46–1.55)	0.94 (0.56–1.58)	1.24 (0.73–2.11)

^a AIDS related mortality: AIDS, AIDS infection, AIDS malignancy

^b Non-AIDS related mortality: Liver related (Hepatitis, Gastro-intestinal haemorrhage, Liver failure), Cardiovascular (Myocardial infarction/ischemic heart disease, Stroke, Lung embolus, Heart/vascular), Pulmonary (Pulmonary hypertension, Chronic obstructive pulmonary disease-COPD, Respiratory), External cause (Accident/violent, suicide), Other (Diabetes, Pancreatitis, Lactic acidosis, Renal failure, Haematological, Psychiatric, CNS, Digestive, Skin/motor system, Other)

^c Adjusted for age at cART initiation (16-29, 30-39, 40-49, 50+), transmission category (IDU, Heterosexual), Geographical origin in Europe (Europe, Sub-Saharan Africa, Latin America, North Africa and Middle East, Asia and North America, Australia and New Zealand), Race/Ethnicity in the US (White, Black, Hispanic, Other/Unknown) and a combination of Geographical origin and Race/Ethnicity in Canada (White Canadian, Aboriginal Canadian, White non-Canadian, Asian non-Canadian and Other/Unknown), AIDS at cART initiation (yes/no), CD4 cell count (0-24, 25-49, 50-99, 100-199, 200-349, 350-499, 500+) and HIV Viral Load (<100,000 and ≥100,000) at the start of cART and stratified by cohort.