
Peer reviewed version
License (if available): Unspecified
Link to published version (if available): 10.3851/IMP2768

Link to publication record in Explore Bristol Research
PDF-document

This is the author’s version of a work accepted for publication by International Medical Press. Changes resulting from the publishing process, including peer review, editing and formatting, might not be reflected in this document. A definitive version was published in Antiviral Therapy, (20, 21-28), 27 March, ©2014 International Medical Press

University of Bristol - Explore Bristol Research
General rights
This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available: http://www.bristol.ac.uk/pure/about/ebr-terms
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

Corresponding author: Inma Jarrin, National Center of Epidemiology, Instituto de Salud Carlos III, Avenida Monforte de Lemos 5 28029 Madrid, Spain. Telephone number: 0034 918222142. E-mail: ijarrin@isciii.es.
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/mm\(^3\)) 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.
Acknowledgments

Sources of funding

The ART Cohort Collaboration is supported by the UK Medical Research Council grants G0700820 and MR/J002380/1. Sources of funding of individual cohorts include the Agence Nationale de Recherche contre le SIDA (ANRS), the Institut National de la Santé et de la Recherche Médicale (INSERM), the French, Italian, Spanish and Swiss Ministries of Health, The Swiss HIV Cohort Study, supported by the Swiss National Science Foundation, the Stichting HIV Monitoring, the European Commission, the British Columbia and Alberta Governments, the Michael Smith Foundation for Health Research, the Canadian Institutes of Health Research, the VHA Office of Research and Development and unrestricted grants from GlaxoSmithKline, Roche and Boehringer-Ingelheim. Inma Jarrin is employed by the “Spanish Network for AIDS Research (RIS; ISCIII-RETIC RD06/006)

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)

AIDS Therapy Evaluation project Netherlands (ATHENA)

The EuroSIDA Study Group

Vanderbilt-Meharry Center for AIDS Research, Nashville, Tennessee, US

Frankfurt HIV Cohort, Germany

ANRS CO3 Aquitaine Cohort, France

British Columbia Centre for Excellence in HIV (BCCfE-HIV), Canada

Royal Free Hospital Cohort, London UK

South Alberta Clinic, Canada
Köln / Bonn Cohort, Germany

PISCIS, Catalonia and Balearic islands, Spain

1917 Clinic Cohort, University of Alabama, Birmingham US

University of Washington HIV Cohort, Seattle, US

Veteran Aging Cohort (VACS), Connecticut, US

HIV Atlanta Veterans Affairs Cohort Study (HAVACS), US

CoRIS, Spain

VACH, Spain

Österreichische HIV-Kohortenstudie (OEHIVKOS), Austria
French Hospital Database on HIV (ANRS CO4 FHDH)


Statistical analysis center: U943 INSERM et UPMC (S Abgrall, D Costagliola, S Grabar, M Guiguet, E Lanoy, L Lièvre, M Mary-Krause, H Selinger-Leneman), INSERM Transfert (JM Lacombe, V Potard)


Overseas: Corevih Guadeloupe (CHRU de Pointe-à-Pitre: M Strobel; CH Saint-Martin: F Bissuel), Corevih Guyane (CHG de Cayenne: R Pradinaud, M Sobesky), Corevih Martinique (CHRU de Fort-de-France: A Cabié), Corevih de La Réunion (CHD Félix Guyon: C Gaud, M Contant).

Italian Cohort of Antiretroviral-Naive Patients (ICONA)

GOVERNING BODY

SCIENTIFIC SECRETARY
A d’Arminio Monforte

STEERING COMMITTEE

STATISTICAL AND MONITORING TEAM
A Cozzi-Lepri, I Fanti, T Formenti, Laura Galli, Patrizia Lorenzini

PARTICIPATING PHYSICIANS AND CENTERS
Italy M. Montroni, A. Giacometti, A Costantini, A. Riva (Ancona); U. Tirelli, F. Martellotta (Aviano-PN); G. Angarano, L Monno, N. Ladisa, (Bari); F. Maggiolo, G Lazzari (Bergamo); PL. Viale, M Borderi, G. Verucchi (Bologna); F Castelli, A Scalzini, C. Torti, C. Minardi, D. Bertelli (Brescia); T. Quirino, C Abeli (Busto Arsizio); P.E. Manconi, P. Piano (Cagliari); J Vecchiet, K Falasca (Chieti); G Carnevale, S Lorenzotti (Cremona); L. Sighinolfi, D. Segala (Ferrara); F. Leoncini, F. Mazzotta, M. Pozzi, S. Lo Caputo (Firenze); G. Cassola, G Viscoli, A. Alessandrini, R. Piscopo, G Mazzarello (Genova); C. Mastroianni, V. Belvisi (Latina); P. Bonfanti, I. Caramma (Lecco); A. Chiodera, P. Castelli (Macerata); M Galli, A. Lazzarin, G. Rizzardini, M. Puoti, A. d’Arminio Monforte, AL Ridolfo, A Foschi, A Castagna, S Salpietro, A Galli, A Bigoloni, V Spagnuolo, S. Merli, L Carenzi, M.C. Moioli, P Cicconi, T Formenti (Milano); C. Mussini, L Bisio (Modena); A Gori, G Lapadula (Monza), N. Abrescia, A. Chirianni, M. De Marco, M Gargiulo (Napoli); C. Ferrari, R Borghi (Parma); F Baldelli, B Belfiori (Perugia); G. Parruti, T Ursini (Pescara); G. Magnani, M.A. Ursitti (Reggio Emilia); R. Cauda, M Andreoni, A. Antinori, P. Narciso, V Tozzi, V. Vullo, A. De Luca, A. d’Avino, M. Zaccarelli, L Gallo, R. Acinapura, M Capozzi, R Libertone, M.P. Trotta, M. Lichtner, G Tebano, (Roma); AM Cattelan (Rovigo); M.S. Mura, G Madeddu (Sassari); P. Caramello, G. Di Perri, G.C. Orofino, M Sciandra (Torino); E. Raise, F. Ebo (Venezia); G. Pellizzer, V. Manfrin (Vicenza).

The Icona Foundation Study is supported by unrestricted educational grants of Abbott, Bristol-Myers Squibb, Gilead
Swiss HIV Cohort Study (SHCS)


AIDS Therapy Evaluation project Netherlands (ATHENA)

L.A. Gras (bio-statistician), A.I. van Sighem (senior researcher), C. Smit (epidemiologist), F. de Wolf (director)

Treating physicians

The EuroSIDA Study Group

The multi-center Study Group on EuroSIDA (national coordinators in parentheses)

Argentina: (M Losso), C Elias, Hospital JM Ramos Mejia, Buenos Aires. Austria: (N Vetter) Pulmologisches Zentrum der Stadt Wien, Vienna; (R Zangerle) Medical University Innsbruck, Innsbruck. Belarus: (I Karpov), A Vassilenko, Belarus State Medical
Buzunova, Novgorod Centre for AIDS, Novgorod. Serbia: (D Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade.

Slovakia: (M Mokráš) D Staneková, Dérer Hospital, Bratislava. Slovakia: (J Tomazic) University Clinical Centre Ljubljana, Ljubljana. Spain: (J González-Lahoz) V Soriano, L Martin-Carbonero, P Labarga, Hospital Carlos III, Madrid; (S Moreno) Hospital Ramon y Cajal, Madrid; B Clotet, A Jou, R Paredes, C Tural, J Puig, I Bravo, Hospital Germans Trias i Pujol, Badalona; JM Gatell, JM Miró, Hospital Clinic i Provincial, Barcelona; P Domingo, M Gutierrez, G Mateo, MA Sambeat, Hospital Sant Pau, Barcelona.

Sweden: (A Karlsson), Karolinska University Hospital, Stockholm; PO Persson, Karolinska University Hospital, Huddinge; L Flamholc, Malmö University Hospital, Malmö. Switzerland: (B Ledergerber) R Weber, University Hospital, Zürich; P Francioli, M Cavassini, Centre Hospitalier Universitaire Vaudois, Lausanne; B Hirschel, E Boffi, Hospital Cantonal Universitaire de Geneve, Geneve; H Furrer, Inselspital Bern, Bern; M Battegay, L Elzi, University Hospital Basel. Ukraine: (E Kravchenko) N Chentsova, Kiev Centre for AIDS, Kiev; (G Kutsyna) Luhansk AIDS Center, Luhansk; (S Servitskiy), Odessa Region AIDS Center, Odessa; (S Antoniak) Kiev; (M Krasnov) Kharkov State Medical University, Kharkov. United Kingdom: (S Barton) St. Stephen’s Clinic, Chelsea and Westminster Hospital, London; AM Johnson, D Mercey, UCL Medical School, London (University College Campus); A Phillips, MA Johnson, A Mocroft, UCL Medical School, London (Royal Free Campus); M Murphy, Medical College of Saint Bartholomew’s Hospital, London; J Weber, G Scullard, Imperial College School of Medicine at St. Mary’s, London; M Fisher, Royal Sussex County Hospital, Brighton; C Leen, Western General Hospital, Edinburgh.

Virology group: B Clotet, R Paredes(Central Coordinators) plus ad hoc virologists from participating sites in the EuroSIDA Study.

Steering Committee: F Antunes, B Clotet, D Duiculescu, J Gatell, B Gazzard, A Horban, A Karlsson, C Katlama, B Ledergerber (Chair), A D’Arminio Montforte, A Phillips, A Rakhmanova, P Reiss (Vice-Chair), J Rockstroh

Coordinating Centre Staff: J Lundgren (project leader), O Kirk, A Mocroft, N Friis-Møller, A Cozzi-Lepri, W Bannister, M Ellefson, A Borch, D Podlekareva, J Kjær, L Peters, J Reekie, J Kowalska

Vanderbilt-Meharry Center for AIDS Research, Nashville, Tennessee, US

Principal Investigator: Timothy R. Sterling


Data management: Samuel Stinnette, Sally Bebawy, Megan Turner, Daniel Rasbach, Ashley Tillman, Henry Heaton, Cathy Jenkins

Frankfurt HIV Cohort, Germany

Hans-Reinhard Brodt, Schlomo Staszewski, Eike B. Helm, Amina Carlebach, Axel Müller, Annette Haberl, Gabi Nisius, Tessa Lennemann, Christoph Stephan, Markus Bickel, Manfred Mösch, Peter Gute, Leo Locher, Thomas Lutz, Stephan Klauke, Gabi Knecht, Pavel Khaykin (Clinical Group); Hans W. Doerr, Martin Störmer (Virology Group); Errol Babacan (Scientific Advisor and Data Management); Nils von Hentig (Pharmacology Group).
ANRS CO3 Aquitaine Cohort, France

Epidemiology, Methodology
M. Bruyand, G. Chêne, F. Dabis (Principal Investigator), S. Lawson-Ayayi, R. Thiébaut.

Infectious diseases, Internal Medicine

Immunology, Virology, Pharmacology, Pharmacovigilance
Pharmacovigilance: G. Miremont-Salamé.

Data collection

Data management
S. Geffard, G. Palmer, D. Touchard.

Scientific committee

British Columbia Centre for Excellence in HIV (BCCfE-HIV), Canada

Royal Free Hospital Cohort, London UK
Data management: C Chaloner, J Holloway, J Puradiredja, S Scott, R Tsintas.
Biostatistics/Epidemiology: V Cambiano, E Harris, F Lampe, R Lodwick, A Phillips, C Smith.
Laboratory: E Amoah, C. Booth, G Clewley, A Garcia Diaz, B Gregory, W Labbett, J Libaste, F Tahami, M Thomas, Y Zhong

South Alberta Clinic, Canada
John Gill, Ron Read, Brenda Beckthold
Köln / Bonn Cohort, Germany

Gerd Fätkenheuer, Jürgen Rockstroh, Caro Hertenstein, Janne Vehreschild, Jan-Christian Wasmuth

PISCIS, Catalonia and Balearic islands, Spain

Coordinators

J. Casabona (CEEISCAT, CIBER Epidemiología y Salud Pública, CIBERESP, Spain) y JM. Miró (Hospital Clinic-Idibaps, Universitat de Barcelona)

Field coordinator: Virginia Isern

Steering committee: J. Casabona, A. Esteve, A. Alquézar (CEEISCAT, CIBER Epidemiología y Salud Pública, CIBERESP, Spain); JM. Miró (Hospital Clinic-Idibaps, Universitat de Barcelona); D. Podzamczer (Hospital de Bellvitge de Barcelona); J. Murillas (Hospital Son Dureta de Mallorca).

Scientific committee: A. Romero y C. Agustí (CEEISCAT, CIBER Epidemiología y Salud Pública, CIBERESP, Spain); JM Gatell, F. Agüero (Hospital Clinic-Idibaps, Universitat de Barcelona); C. Tural, B. Clotet (Hospital Universitari Germans Trias i Pujol, Universitat Autónoma de Barcelona); E. Ferrer (Hospital de Bellvitge de Barcelona); M. Riera (Hospital Son Dureta de Mallorca) F. Segura G. Navarro (Corporació Parc Taulí de Sabadell); L. Force (Hospital de Mataró ); I. García (Hospital General de Sabadell); J. Vilaró (Hospital de Vic); A. Masabeu (Hospital de Palamós); I. García (Hospital General d’Hospitalet); M. Guadarrama (Hospital Alt Penedès de Vilafranca).

Data Management and statistical analysis: A. Esteve, A. Montoliu y N. Ortega (CEEISCAT, CIBER Epidemiología y Salud Pública, CIBERESP, Spain), E. Lazzari (Hospital Clinic-Idibaps, Universitat de Barcelona).

Technical support: E. Puchol, (CEEISCAT, CIBER Epidemiología y Salud Pública, CIBERESP, Spain); M. Sanchez (Hospital Clinic-Idibaps, Universitat de Barcelona).

Clinicians

JL Blanco, F. Garcia-Alcaide, E. Martinez, J. Mallolas M. López-Dieguez, JF García-Goez, (Hospital Clinic-Idibaps, Universitat de Barcelona); G. Sirera, J. Romeu, A. Jou. E. Negredo, C. Miranda, MC Capitan (Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona); M. Olmo, P. Barragan, M. Saumoy, F. Bolao, C. Cabellos, C. Peña. (Hospital Universitari de Bellvitge, L’Hospitalet, Barcelona), M. Sala, M. Cervantes, M Jose Amengual, M. Navarro y E Penelo (Corporació Sanitària Parc Taulí), P. Barrufet (Hospital de Mataró ); M. Guadarrama (Hospital Alt Penedès de Vilafranca)

1917 Clinic Cohort, University of Alabama, Birmingham US

Steering Committee: Michael S. Saag, Michael J. Mugavero, James H. Willig, James L. Raper, Jeroan J. Allison, Mirjam-Colette Kempf, Joseph E. Schumacher, Andrew O. Westfall

Faculty Investigators: Hui-Yi Lin, Maria Pisu, Linda Moneyham, David Vance, Laura Bachmann, Susan L Davies, Eta Berner, Edward Acosta, Jennifer King, Richard A. Kaslow
Research Support Team
Karen Savage, Christa Nevin, Frances B. Walton, Malcolm L. Marler, Sarah Lawrence, Barbara Files-Kennedy, D. Scott Batey
Informatics Team: Manoj A. Patil, Ujava Patil, Mohit Varshney, Eugene Gibson, Alfredo Guzman, Dustin Rinehart

University of Washington HIV Cohort, Seattle, US

Veteran Aging Cohort (VACS), Connecticut, US
Cynthia Brandt, Kristina Crothers, Robert Dubrow, David Fiellin, Matthew Freiberg, Neel Gandhi, Joseph Goulet, Amy Justice, Joseph Lim, Vincent LoRe, Kathleen McGinnis, Michael Ohl, Chirag Parikh, David Rimland (Atlanta PI), Melissa Skanderson, Janet Tate, Julie Womack, Sheldon Brown (Bronx PI), Adeel Butt (Pittsburgh PI), Cynthia Gibert (Washington DC PI), Matthew Goetz (Los Angeles PI), Kris Ann Oursler (Baltimore PI), Maria Rodriguez-Barradas (Houston PI), Michael Simberko (New York PI)

HIV Atlanta Veterans Affairs Cohort Study (HAVACS), US
Jodie L. Guest, PhD, MPH - Director of HIV Research
David Rimland, MD - Chief of Infectious Diseases
Abeer Moanna, MD, - HAVACS physician
Alicia Hidron, MD - HAVACS physician
Kathryn E. DeSilva, Pharm.D. - HAVACS pharmacist
Michelle Moorfield, PA-C - HAVACS clinician
Martha Dorsey, NP - HAVACS clinician
Rondeen Mindley, MPH - research coordinator
Susan Schlueter Wirtz, MPH - research coordinator
Patrick Brown - Program assistant
Rene Dozier, RN - HAVACS nurse
Yvette Robinson, RN - HAVACS nurse

CoRIS, Spain
Steering committee: Juan Berenguer, Julia del Amo, Federico García, Félix Gutiérrez, Pablo Labarga, Santiago Moreno, María Ángeles Muñoz.
Pulido, Silvana Fiorante, Jara Llenas, Violeta Rodríguez, Mariano Matarranz Hospital Doce de Octubre (Madrid). José Antonio Iribarren, Julio Arrizabalaga, María José Aramburu, Xabier Camino, Francisco Rodríguez-Arrondo, Miguel Ángel von Wichmann, Lidia Pascual Tomé, Miguel Ángel Goenaga, Mª Jesús Bustinduy, Harkaitz Azkune Galparsoro Hospital Donostia (San Sebastián). Félix Gutiérrez, Mar Masiá, José Manuel Ramos, Sergio Padilla, Andrés Navarro, Fernando Montolio, Yolanda Peral, Catalina Robledano García Hospital General Universitario de Elche (Elche). Juan Berenguer, Juan Carlos López Bernaldo de Quirós, Pilar Miralles, Jaime Cosín Ochaita, Matilde Sánchez Conde, Isabel Gutiérrez Cuellar, Margarita Ramírez Schacke, Belén Padilla Ortega, Paloma Gijón Vidaurreta Hospital Gregorio Marañón (Madrid). Francesc Vidal, Joaquín Peraire, Consuelo Viladés, Sergio Veloso, Montserrat Vargas, Miguel López-Dupla, Montserrat Olona, Alba Aguilar, Joan Joseph Sirvent, Antoni Soriano, Rami AA. Qaneta Hospital Universitari de Tarragona Joan XXIII, IISPV, Universitat Rovira i Virgili (Tarragona). Ignacio de los Santos, Jesús Sanz Sanz, Johana Rodríguez, Ana Salas Aparicio, Cristina Sarriá Cepeda Hospital de la Princesa (Madrid). José Antonio Oteo, José Ramón Blanco, Valvanera Ibarra, Luis Metola, Mercedes Sanz, Laura Pérez-Martínez Hospital San Pedro-CIBIR (Logroño). Julio Sola Boneta, Javier Uriz, Jesús Castiello, Jesús Reparaz, María Jesús Arraiza, Carmen Irigoyen, David Mozas Hospital de Navarra (Pamplona). Santiago Moreno, José Luis Casado, Fernando Dronda, Ana Moreno, María Jesús Pérez Elías, Dolores López, Carolina Gutiérrez, Beatriz Hernández, María Pumares, Paloma Martí Hospital Ramón y Cajal (Madrid). Federico García García, José Hernández Quero, Alejandro Peña Monje, Leopoldo Muñoz Medina, Jorge Parra Ruiz Hospital San Cecilio (Granada).

VACH, Spain

ASTURIAS

➤ Hospital de Cabueñes
M.Interna_Enf Infecciosas
Investigador Principal: Dra. Mª Luisa García-Alcalde Fernández

e-mail: garcialcalde@gmail.com
Investigador Colaborador: Dra. Belén de la Fuente García

e-mail: garcialcalde@gmail.com, aylabe@terra.es
Dirección del hospital: Calle de los Prados 395. 33203 Gijón, Asturias
Teléfono: 985185000; Extensión UEI: 85292

BADAJOZ

➤ Hospital Universitario Infanta Cristina
M.Interna_Enf Infecciosas
Investigador Principal: Dr. Agustín Muñoz Sanz

e-mail:
BARCELONA

➤ Hospital Universitari Vall d’Hebron

Enfermedades Infecciosas

Investigador Principal: Dr. Esteban Ribera

e-mail: eribera@vhebron.net

Telef.: 699224271

Paseo Vall d’Hebron 119_129 08005 Barcelona

➤ Hospital de la Santa Creu i Sant Pau

Jefe de Sección, Unidad de Enfermedades Infecciosas

Pere Domingo

Investigador Principal: Dr. Pere Domingo

e-mail:

Telef.: Av San Atoni Mª Claret 167 08025 Barcelona

➤ Hospital General de Granollers

Unitat de Malalties Infeccioses – VIH

Investigador Principal: Elisabeth Deig Comerma

e-mail: edeig@fhag.es

Telef.:938425055

Avda Francesc Ribas sn, 08400 Granollers (Barcelona)

BILBAO

➤ Hospital de Basurto
Servicio de Enf Infecciosas
Investigador Principal: Dra. Pepa Muñoz Sanchez
Investigador colaborador:
e-mail:josefa.munozsanchez@osakidetza.net
Telef.: 944006000
Avda. Montevideo 18, 43013. Bilbao

CÁDIZ

Hospital Clínico Universitario
Unidad de Gestión Clínica Enfermedades Infecciosas
Investigador Principal: Dr. Antonio Vergara Campos
e-mail: antonio.vergara.sspa@juntadeandalucia.es
Crtra NA 4 KM 665 s/n, 11510 Puerto Real, Cádiz

Hospital SAS de Jerez
M. Interna. Sección de Enf. Infecciosas
Investigador Principal: Dr. José Alberto Terrón Pernía
e-mail: jaterron@hotmail.com
Telef.: 956 03 22 00 (Hospital) 669 525 974
Crtra.Circunvalación SN 11407 Jerez de la Frontera (Cádiz)

CARTAGENA

Hospital Virgen del Rosell
M. Interna-Sección Infecciosos
Investigador Principal: Dr. Trinitario Sánchez
e-mail:
Telef.: tariosanchez@ono.com
Carmen Conde 63,4ºA, 30204 Cartagena, Murcia

CASTELLON
Hospital General
Servicio de Medicina Interna e Infecciones
Investigador Principal: Dr. Bernardino Roca Villanueva
e-mail: brocav@meditex.es
Telef.: 964 726 530
Cataluña 33-A, 4, 12004 Castellón

CUENCA

Hospital Virgen de la Luz
Sección M.Interna - Infecciosas
Investigador Principal: Dra. Paloma Geijo Martinez
Investigador Colaborador: Dra. Carmen Rosa Herranz
e-mail: mgeijo@sescam.jccm.es
Telef.: 969179900 –ext 58792
Herrmandad Donantes Sangre 1 16004 Cuenca

HUELVA

Hospital Infanta Elena
Unidad de Infecciosos-M Interna
Coordinador Grupo VACH: Dr. Ignacio Suárez Lozano
Investigador Principal: Dr. Ignacio Suárez Lozano
Investigador Colaborador: Dr. J Mª Fajardo
E-mail: ochanzer@vach.es
Telef.: 959015170
Carretera de Huelva-Sevilla s/n 21080 Huelva

LLEIDA

Hospital Universitari Arnau de Vilanova
Unidad de Infecciosos-M Interna
Investigador Principal: Dra. Teresa Puig Ganau
Investigador Colaborador:

E-mail: tpuig@arnau.scs.es
Telef.: 
Av. Alcalde Rovira Roure 80, 25198 Lleida

MADRID

➤ Hospital Clínico San Carlos
Consulta de VIH. Hospital de día de Enfermedades Infecciosas
Investigador Principal: Dr. Vicente Estrada
Investigador Colaborador: Dra. Mónica Fuster
e-mail: vestrada.hcsc@salud.madrid.org
Telef.:913303538
Dirección C/Prof. Martín Lagos, SN. 28040 Madrid

➤ Hospital Gregorio Marañón
Unidad Enf.Infecciosas
Investigador Principal: Jaime Cosín Ochaita
e-mail: jcosin.hgugm@salud.madrid.org
Telef.:91.5868591 / 8592
Esquerdo 46, 28007 Madrid

MALAGA

➤ Hospital Regional Universitario Carlos Haya
Servicio de Enfermedades Infecciosas
Investigador Principal: Dr. Manuel Castaño Carracedo
Investigador Colaborador: Dr. Juan de Dios Colmenero Castillo
e-mail: ensayosminte@yahoo.es
Telef.:951291775
Avda Carlos Haya s/n, 29010 Málaga

SANTANDER
Hospital de Sierrallana
Servicio de MI - Enfermedades Infecciosas
Investigador Principal: Dr. Ramón Teira Cobo
e-mail: rteira@hsll.scsalud.es
Telef.: 942847400
c/ Ganzo s/n, 39300 Torrelavega, Santander

Hospital Virgen del Rocío Sevilla
Servicio de Enfermedades Infecciosas
Investigador Principal: Dr. Pompeyo Viciana
Investigador Colaborador: Dr. Luis López Cortés
e-mail: pompeyo.viciana.sspa@juntadeandalucia.es
Telef.: +34955013096
Avda Manuel Siurot s/n, 41013 Sevilla

Hospital de Valme
Unidad Clínica de Enfermedades Infecciosas
Investigador Principal: Dr. Fernando Lozano
e-mail: fernandolozano@telefonica.net
Telef.: 955015738, 955015757
Avenida de Bellavista, s/n. 41014 Sevilla

TARRAGONA

Hospital Universitari de Tarragona Joan XXIII
Medicina Interna
Unitat de Malalties Infeccioses - VIH
Investigador Principal: Dr. Francisco Vidal Marsal
e-mail: fvidalmarsal.hj23.ics@gencat.cat
Telef.: 977295833
C/ Dr Mallafré Guasch nº4, 43007 Tarragona
Hospital Xarxa Sanitaria i Social de Santa Tecla

Medicina Interna
Unitat de Malalties Infeccioses - VIH
Investigador Principal: Dr. Enric Pedrol Clotet
Investigadores Colaboradores: Dr. Antonio Delegido; Dra. Mariona Tasias; Dra. Sheila Ruiz

e-mail: epedrol@xarxatecla.cat
Telef.: 977 25 99 00 Ext. 4037
Rambla Vella, 14 • 43003 Tarragona

VALENCIA

Hospital Clínico Valencia
M. Interna_ Enf. Infecciosas
Investigador Principal: Dra. Mª José Galindo

e-mail: med001021@saludalia.com
Telef.: 963862600 Ext. 51377-51289
AV. Blasco Ibáñez 17, 46010 Valencia

Hospital Universitario La Fe
Unidad Enfermedades Infecciosas
Investigador Principal: Dr. José López Aldeguer
Investigador Colaborador: Dr. Blanes, Dr. José Lacruz, Dra. Marta Montero, Dr. Miguel Salavert, Dra Sandra Cuéllar

e-mail: pepelopezal@gmail.com
Telef.: 961973210
AV. Campanar 21, 46009 Valencia

Osterreichische HIV-Kohortenstudie (OEHIVKOS), Austria

Chair: Robert Zangerle, Innsbruck
Coordinating Centre: University Hospital Innsbruck
Steering committee: Alexander Egle, Maria Geit, Bernhard Haas, Manfred Kanatschnig, Armin Rieger, Andrea Steuer, Robert Zangerle

HIV treatment centres (*site coordinating physicians):
University Hospital Innsbruck: Martin Gisinger, Maria Kitchen, Mario Sarcletti*, Robert Zangerle


AKH Linz: Maria Geit*, Angela Öllinger

AKH Wien: Regina Aichwalder, Florian Breitenecker, Armin Rieger*, Veronique Touzeau

Otto-Wagner Hospital: Piotr Cichon, Brigitte Schmied, Wolfgang Stefflitsch, Andrea Steuer*

LKH Graz West: Bernhard Haas*, Andreas Kapper

LKH Klagenfurt: Manfred Kanatschnig*

Virology: Elisabeth Puchhammer-Stöckl (Vienna)

Data management: Heinz Appoyer (IT-related), Stefanie Gogl (AHIVCOS), Margret Jöchl (AGES)

Data safety and protection: Klaus Schindelwig (TILAK Innsbruck)

Scientific advisory board: Bruno Ledergerber (Zurich), Gerd Fätkenheuer (Cologne)
Writing group: Inma Jarrin, Santiago Moreno, Sue Ingle, Margaret T May, Timothy R. Sterling, Amy Justice, Markus Bickel, Heidi Crane, Michael J Mugavero, Frank De Wolf, Norma Jung, Angela Cescon, Isabel Garcia, Luigia Elzi, Antonella d’Arminio, Murielle Mary-Krause, Colette Smith, Jodie Guest, Mojgan Hessamfar, John Gill, Jonathan A C Sterne and Julia del Amo

Writing committee affiliations

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amy Justice</td>
<td>Yale University School of Medicine, New Haven, CT, USA; VA Connecticut Healthcare System, West Haven, CT, USA</td>
</tr>
<tr>
<td>Angela Cescon</td>
<td>British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada</td>
</tr>
<tr>
<td>Antonella d’Arminio Monforte</td>
<td>Clinic of Infectious Diseases &amp; Tropical Medicine, San Paolo Hospital, University of Milan, Italy</td>
</tr>
<tr>
<td>Colette Smith</td>
<td>Research Department of Infection and Population Health, UCL, London, UK</td>
</tr>
<tr>
<td>Frank De Wolf</td>
<td>HIV Monitoring Foundation, Academic Medical Centre, University of Amsterdam, Amsterdam</td>
</tr>
<tr>
<td>Heidi Crane</td>
<td>School of Public Health, University of Washington</td>
</tr>
<tr>
<td>Inma Jarrin</td>
<td>National Centre of Epidemiology, Instituto de Salud Carlos III, Spain</td>
</tr>
<tr>
<td>Isabel Garcia</td>
<td>Hospital General de l'Hipresalet, L'Hipresalet de Llobregat, Barcelona, Spain</td>
</tr>
<tr>
<td>Jodie Guest</td>
<td>HIV Atlanta VA Cohort Study (HAVACS), Atlanta Veterans Affairs Medical Center, Decatur, GA, USA</td>
</tr>
<tr>
<td>John Gill</td>
<td>Division of Infectious Diseases, University of Calgary, Calgary, Canada</td>
</tr>
<tr>
<td>Jonathan Sterne</td>
<td>School of Social and Community Medicine, University of Bristol, Bristol, UK</td>
</tr>
<tr>
<td>Julia del Amo</td>
<td>National Centre of Epidemiology, Instituto de Salud Carlos III, Spain</td>
</tr>
<tr>
<td>Luigia Elzi</td>
<td>Division of Infectious Diseases &amp; Hospital Epidemiology, University Hospital Basel, Basel, Switzerland</td>
</tr>
<tr>
<td>Margaret May</td>
<td>School of Social and Community Medicine, University of Bristol, Bristol, UK</td>
</tr>
<tr>
<td>Name</td>
<td>Institution</td>
</tr>
<tr>
<td>---------------------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Markus Bickel</td>
<td>Department of Infectious Disease, Johann Wolfgang Goethe-Universität,</td>
</tr>
<tr>
<td></td>
<td>Frankfurt, Germany</td>
</tr>
<tr>
<td>Michael J Mugavero</td>
<td>Division of Infectious Disease, Department of Medicine, University of Alabama,</td>
</tr>
<tr>
<td></td>
<td>Birmingham</td>
</tr>
<tr>
<td>Mojgan Hessamfar, MD, PhD</td>
<td>1. Univ. Bordeaux, ISPED, Centre Inserm U897- Epidemiologie-Biostatistique, F-</td>
</tr>
<tr>
<td></td>
<td>33000 Bordeaux, France.</td>
</tr>
<tr>
<td></td>
<td>2. INSERM, ISPED, Centre Inserm U897- Epidemiologie-Biostatistique, F-33000</td>
</tr>
<tr>
<td></td>
<td>Bordeaux, France.</td>
</tr>
<tr>
<td>Murielle Mary-Krause</td>
<td>1 INSERM U943, Paris, F75013, France</td>
</tr>
<tr>
<td></td>
<td>2 UPMC Univ-Paris 06, UMR S943, Paris, F75013, France.</td>
</tr>
<tr>
<td>Norma Jung</td>
<td>First Department of Internal Medicine, Medical Hospital of the University of</td>
</tr>
<tr>
<td></td>
<td>Cologne, Germany</td>
</tr>
<tr>
<td>Santiago Moreno</td>
<td>Hospital Universitario Ramon y Cajal, Madrid, Spain</td>
</tr>
<tr>
<td>Suzanne Ingle</td>
<td>School of Social and Community Medicine, University of Bristol, Bristol, UK</td>
</tr>
<tr>
<td>Timothy R. Sterling</td>
<td>Vanderbilt University School of Medicine</td>
</tr>
</tbody>
</table>
REFERENCES


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

<table>
<thead>
<tr>
<th></th>
<th>Europe (N=32,443)</th>
<th>Canada (N=1,162)</th>
<th>US (N=2,721)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>N</td>
<td>17,539</td>
<td>14,904</td>
<td>784</td>
</tr>
<tr>
<td>Median (IQR) age, years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>38 (33–45)</td>
<td>33 (28–40)</td>
<td>40 (34–46)</td>
</tr>
<tr>
<td>Transmission category</td>
<td></td>
<td></td>
<td>45 (39–50)</td>
</tr>
<tr>
<td>IDU</td>
<td>6,143 (35.0)</td>
<td>1,736 (11.6)</td>
<td>585 (74.6)</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>11,396 (65.0)</td>
<td>13,168 (88.4)</td>
<td>199 (25.4)</td>
</tr>
<tr>
<td>AIDS diagnosis&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>2,004 (87.1)</td>
</tr>
<tr>
<td>No</td>
<td>13,044 (74.4)</td>
<td>12,313 (82.6)</td>
<td>575 (73.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>4,495 (25.6)</td>
<td>2,591 (17.4)</td>
<td>209 (26.7)</td>
</tr>
<tr>
<td>Median (IQR) CD4 count, cells/μl&lt;sup&gt;a&lt;/sup&gt;</td>
<td>190 (70–306)</td>
<td>229 (120–348)</td>
<td>170 (60–280)</td>
</tr>
<tr>
<td>Viral Load, copies/mL&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>200 (67–326)</td>
</tr>
<tr>
<td>&lt; 100,000</td>
<td>9,771 (55.7)</td>
<td>10,039 (67.4)</td>
<td>396 (50.5)</td>
</tr>
<tr>
<td>≥ 100,000</td>
<td>7,768 (44.3)</td>
<td>4,865 (32.6)</td>
<td>388 (49.5)</td>
</tr>
<tr>
<td>Geographical origin</td>
<td></td>
<td></td>
<td>1,391 (60.5)</td>
</tr>
<tr>
<td>Europe</td>
<td>10,991 (62.7)</td>
<td>7,361 (49.4)</td>
<td>287 (36.3)</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>2,488 (14.2)</td>
<td>4,239 (28.4)</td>
<td>101 (12.9)</td>
</tr>
<tr>
<td>Latin America</td>
<td>637 (3.6)</td>
<td>814 (5.5)</td>
<td>26 (3.3)</td>
</tr>
<tr>
<td>North Africa and Middle East Asia</td>
<td>382 (2.2)</td>
<td>192 (1.3)</td>
<td>13 (1.7)</td>
</tr>
<tr>
<td>North America, Australia &amp; NZ&lt;sup&gt;c&lt;/sup&gt;</td>
<td>129 (0.7)</td>
<td>252 (1.7)</td>
<td>357 (45.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>15 (0.1)</td>
<td>11 (0.1)</td>
<td>555 (24.1)</td>
</tr>
<tr>
<td></td>
<td>2,897 (16.5)</td>
<td>2,035 (13.6)</td>
<td>149 (63.0)</td>
</tr>
</tbody>
</table>

<sup>a</sup>IQR: Interquartile range
<sup>b</sup>At cART initiation
<sup>c</sup>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

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

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, Aborginal 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

<table>
<thead>
<tr>
<th>Europe</th>
<th>Canada</th>
<th>US*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Men</td>
</tr>
<tr>
<td>Person-years</td>
<td>83,297</td>
<td>68,521</td>
</tr>
<tr>
<td>No.</td>
<td>Rate (95% CI)</td>
<td>No.</td>
</tr>
<tr>
<td>AIDS relatedb</td>
<td>370</td>
<td>4.4 (4.0 – 4.9)</td>
</tr>
<tr>
<td>Non-AIDS related</td>
<td>731</td>
<td>8.8 (8.2 – 9.4)</td>
</tr>
<tr>
<td>Infection</td>
<td>112</td>
<td>1.3 (1.1 – 1.6)</td>
</tr>
<tr>
<td>Liver relatedc</td>
<td>144</td>
<td>1.7 (1.5 – 2.0)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>169</td>
<td>2.0 (1.7 – 2.4)</td>
</tr>
<tr>
<td>Cardiovasculard</td>
<td>85</td>
<td>1.0 (0.8 – 1.3)</td>
</tr>
<tr>
<td>Pulmonary*</td>
<td>22</td>
<td>0.3 (0.2 – 0.4)</td>
</tr>
<tr>
<td>Externalf</td>
<td>38</td>
<td>0.5 (0.3 – 0.6)</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>69</td>
<td>0.8 (0.7 – 1.0)</td>
</tr>
<tr>
<td>Otherg</td>
<td>92</td>
<td>1.1 (0.9 – 1.4)</td>
</tr>
</tbody>
</table>

*In US, mortality rates for each non-AIDS related cause of death are calculated excluding VACS cohort; persons-years 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 hemorrhage, Liver failure
d Cardiovascular: Myocardial infarction/ischemic heart disease, Stroke, Lung embolus, Heart/vascular

*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

<table>
<thead>
<tr>
<th></th>
<th>AIDS related mortality a</th>
<th>Non-AIDS related mortality b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude HR (95% CI)</td>
<td>Adjusted HR (95% CI)c</td>
</tr>
<tr>
<td>Europe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Women</td>
<td>0.59 (0.50–0.71)</td>
<td>0.90 (0.75–1.09)</td>
</tr>
<tr>
<td>Canada</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Women</td>
<td>0.85 (0.53–1.37)</td>
<td>1.00 (0.61–1.65)</td>
</tr>
<tr>
<td>US</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Women</td>
<td>0.63 (0.34–1.15)</td>
<td>0.84 (0.46–1.55)</td>
</tr>
</tbody>
</table>

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, Aborginal 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.