Original article

Relevant gender differences in epidemiological profile, exposure to first antiretroviral regimen and survival in the Spanish AIDS Research Network Cohort

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Background: The possible differences in the disease spectrum and prognosis of HIV infection in women and men is a major point of concern. Women are under-represented in randomized clinical trials and in some cohorts. Discordant results have often been obtained depending on the setting. Methods: We assessed gender differences in clinical and epidemiological features, antiretroviral treatment (ART) exposure and survival in two multicentre cohorts of HIV-positive subjects in Spain: CoRIS-MD and CoRIS. Competing risk regression models were used to assess gender effect on time to start ART and time to first ART change, and a Cox regression model to estimate gender effect on time to death. Results: Between January 1996 and December 2008, 1,953 women and 6,072 men naive to ART at study entry were included. The trend analysis over time showed the percentage of women in the younger (<20 years) and older (>50 years) strata increased significantly (P<0.001) from 0.5% and 1.8% in 1996 to 4.9% and 4.2% in 2008, respectively. By competing risk analysis women started ART earlier than men (adjusted subhazard ratio [ASHR] 1.21, 95% CI 1.11, 1.31) in CoRIS cohort, while in CoRIS-MD none of these differences were observed. In both cohorts women showed a shorter time to the first ART change (ASHR 1.10, 95% CI 1.01, 1.19). Pregnancy and patient’s/physician’s decisions as reasons for changing were more frequent in women than in men in CoRIS. In the Cox regression model, gender was not associated with differences in survival. Conclusions: In two large cohorts in Spain, we observed relevant gender differences in epidemiological characteristics and antiretroviral exposure outcomes, while survival differences were not attributable to gender.

Introduction

Worldwide, UNAIDS estimated that the proportion of women living with HIV is around half of the global HIV-positive population [1]. The AIDS epidemic has had a unique impact on women, which has been exacerbated by their role within society and their biological vulnerability to HIV infection [2]. Frequently, in developing countries women with HIV infection encounter great difficulty in accessing health care and carry a heavy burden of caring for children and other family members who may also be
HIV-infected [3,4]. They often lack social support and face other challenges that might interfere with their ability to adhere to treatment regimens [5–7]. Moreover, the detrimental effect of lipodystrophy on body image is an important stigmatizing factor, with a high impact on the emotional well-being and quality of life of women living with HIV [8]. Other issues are related to the impact of HIV infection on the different life stages from adolescence and child-bearing years to peri- and post-menopause, HIV testing, treatment access, HIV prevention strategies, differential responses to therapy and prevention [9], as compared with men, and the factors behind the under-representation of women in clinical trials [10]. For all these reasons, current research interests focus on investigation of mechanisms underlying gender differences to HIV infection.

The possible differences in the disease spectrum and prognosis of HIV infection in men and women is a major point of concern, with conflicting reports about the effect of gender-related differences on mortality [11–13]. To what extent differences between women and men in baseline characteristics, disease severity, age or behavioural habits when presenting for care may explain gender differences in survival is still poorly understood. A number of studies dealing with potential differences in the clinical, immunological and virological features of HIV infection that could exist between women and men, both before and after the introduction of highly active antiretroviral treatment (ART) regimens, have shown discordant results [14–24]. Of note, HIV-positive women were under-represented in clinical trials [10,25] and most studies did not have sufficient statistical power to make gender comparisons. Therefore, information gaps and regional peculiarities may be explored by analysis of the full spectrum of HIV infection and clinical outcomes in large cohorts with similar characteristics regarding important aspects, such as access to medical care and ART use. Identifying whether men and women benefit equally from ART and ascertaining the reasons underlying any difference could inform strategies to address these differences and optimize ART delivery.

To contribute further to defining gender differences in HIV infection, a study was performed using two cohorts of the Spanish Network on HIV research (CoRIS-MD and CoRIS, see Methods) which were recruited between January 1996 and December 2008. The objectives of the study were the following: to describe the epidemiological and clinical profile of women and their trends over time and to compare them with those of men, to assess gender-related differences in the exposure to initial ART regimen prescribed and to investigate gender survival differences.

### Methods

**Cohort description, patient selection and data collection**

CoRIS (Cohorte de la Red de Investigación en SIDA, AIDS Research Network Cohort) and CoRIS-Merge Dataset (MD) are a joint activity of the Research Network of Excellence (Red de Investigación en SIDA [RIS], AIDS Research Network, Spain), which is a coordinated and organized structure for HIV/AIDS research funded by the Institute of Health Carlos III and the Spanish Ministry of Science and Innovation (Madrid, Spain) and co-funded by the European regional development fund (ERDF).

Each patient was only included in one of the two cohorts of the Spanish AIDS Research Network: CoRIS-MD or CoRIS. CoRIS-MD was a retrospectively assembled multicentre cohort, from January 1996 to December 2003, comprising 10 hospitals from 7 of 17 Autonomous Communities in Spain. CoRIS is an ongoing prospective cohort from January 2004 to present from 28 hospitals and HIV diagnosis centre of 13 Autonomous Communities; for these analyses, however, only subjects followed until 31 December 2008 were included. A detailed description of both cohorts was previously published [23,26,27]. Both cohorts recruited subjects seen for the first time at any of the participating HIV care units and they were followed according to each hospital’s clinical routine, usually every 3 to 6 months. For this analysis follow-up of patients was administratively censored on 31 December 2004 for CoRIS-MD and on 31 December 2008 for CoRIS or at the date of their last clinical visit if it was previous to the censoring date. In CoRIS internal quality controls were performed twice annually and 10% of data (randomly selected) were externally audited every year. An extensive codification data clean-up process was performed for CoRIS-MD. Data of participants included in CoRIS were collected from personal medical records. No further testing or visits from their usual follow-up were requested. Patients moving forward to another CoRIS hospital continued their follow-up in the new hospital in order to minimize loss of follow-up. In a previous study using data from this cohort, loss of follow-up was less than 20% [27].

To be eligible for these analyses, subjects had to be ART-naïve at study entry (except for women who received ART for the prevention of vertical transmission in previous pregnancies and had discontinued ART at the end of pregnancy), be more than 18 years old and have had at least 6 months of follow-up.

Variables considered in this study were: sociodemographic data (age, gender), epidemiological data (category of transmission, date of entry in the cohort),
clinical data on admission (CDC categories), laboratory data at entry (CD4+ T-cell count and plasma HIV RNA), treatment-related data (date of each ART start and stop, antiretroviral drugs prescribed and follow-up data such as vital status at the end of follow-up (lost contact, death and cause of death). The variables on geographical origin, education level, serological tests for HCV and syphilis infections, and the main reasons for switch/withdrawal of treatment were only available for the prospective CoRIS cohort because they were not captured in the CoRIS-MD retrospective cohort.

The study protocol was approved by the Ethics Committees of the participating hospitals. Patients in the CoRIS cohort agreed to participate by signing a written informed consent form. The Spanish National Health System provides universal and free access to HIV clinical care and ART.

Data analyses and statistics

Overall population baseline characteristics were described and compared according to gender. For assessing trends over time of baseline categorical variables a χ² Mantel–Haenszel was used, while a linear regression test was used for age analyses by gender over the 1996–2008 period of time, considering annual values for each variable. A separate analysis for variables available only in CoRIS was also carried out for 2004–2008.

Dichotomized variables were created for category of transmission (intravenous drug user [IDU] versus others), HIV stage (AIDS versus non-AIDS), geographical origin (Spanish versus immigrants), study level (university degree versus others), CD4+ T-cell count (CD4+ T-cell count <200 cells/µl versus others) and HIV RNA (HIV RNA>10⁵ log₁₀ copies/ml versus others). Age was categorized for some analyses as <20, 20–50 and >50 years old. Belonging to CoRIS-MD or CoRIS was also considered for some analyses. Categorical variables were compared with the χ² or the Fisher’s exact test using contingency tables, whereas continuous variables were compared with the Student’s t-test or the Mann–Whitney U test for non-parametric data.

We described and compared the first antiretroviral regimens prescribed and these were categorized by individual drugs for some analyses and by protease inhibitors (PI), boosted PI, non-nucleoside reverse transcriptase inhibitors (NNRTI), three nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) and suboptimal NRTI-based therapies for others.

For all time to event analyses we considered only patients with at least 6 months of follow-up. To estimate gender effect on time to start ART and time to first ART change competing risk regression models were carried out (death was considered as the competing event), cumulative incidence curve was computed by the method of Fine and Gray [28]. Variables included as possible confounders were age, category of transmission, HIV stage, percentage of patients with CD4+ T-cell counts <200 cells/µl and HIV RNA>10⁵ log₁₀ copies/ml at baseline, belonging to CoRIS-MD or CoRIS cohort and the two interactions between gender*cohort, and gender*category of transmission. To estimate the gender effect on time to death, Kaplan–Meier survival curve (log-rank test) and Cox estimative regression models were carried out including the same confounders and interactions as in the above mentioned analysis. The proportional hazard assumption was tested graphically and by creating interactions of the predictors. A function of survival time was included in the model. Reason for first ART change was analysed only in CoRIS. The Statistical Package for Social Sciences (SPSS 17.0; SPSS Inc., Chicago, IL, USA) and STATA 11 software (StatCorp LP, College Station, TX, USA) were used. Everything was calculated for a 95% CI and P<0.05 values were considered statistically significant.

Results

Baseline characteristics and trends

Between 1996 and 2008, 1,953 women and 6,072 men with a mean age (± standard deviation) of 35 ±8.9 years were included in both cohorts. As shown in Table 1, statistically significant differences were observed in all baseline variables except AIDS HIV stage and HCV coinfection. Overall, women were younger than men, with a lower proportion of IDUs, HIV-1 RNA>10⁵ copies/ml and CD4+ T-cell counts <200 cells/µl when presenting for care. Analysing only the 4,386 CoRIS patients (998 women and 3,388 men), a higher proportion of immigrants, a lower education level and a lower proportion of syphilis coinfection were observed in women (Table 1).

The trend analysis over time showed a statistically significant yearly decrease in the number of women recruited in the cohorts, from 33.9% in 1996 to 23.3% in 2008 (P<0.01), although the percentage of women in the younger (<20 years) and older (>50 years) strata increased significantly (P<0.001) from 0.5% and 1.8% in 1996 to 4.9% and 4.2% in 2008, respectively. In both men and women, there was a significant decreasing trend of AIDS HIV stage and IDUs, and a significant increasing trend of the mean age and the percentage of patients with HIV-1 RNA>10⁵ copies/ml (Figure 1A). In relation to those baseline variables that were only available in the CoRIS cohort (2004–2008), the number of immigrants increased in both sexes but this was more pronounced in women (female immigrants accounted for more than 50% in 2008). A decrease of HCV coinfection was observed over time and this trend was observed in both women and men. The proportion of baseline syphilis coinfection and having a higher
educational level remained stable for women, whereas for men it increased significantly in the same period (Figure 1B).

**Antiretroviral exposure**

Overall, 5,704 (71.1%) patients started ART during follow-up, 1,451 (74.3%) women and 4,253 (70.0%) men. An NNRTI regimen was initially prescribed for 2,254 patients, 509 (35.1%) women and 1,745 (41%) men (unadjusted odds ratio [UOR] 1.29, 95% CI 1.13, 1.45; \( P < 0.0001 \)), however analysing separately CoRIS-MD and CoRIS, a difference in NNRTI use by gender was only significant in CoRIS (UOR of starting a non-NNRTI regimen in men versus women [1.55, 95% CI 1.32, 1.85; \( P < 0.001 \)]; Figure 2). Considering each NNRTI regimen separately, efavirenz was used as initial therapy in 1,776 patients, but less frequently in women than in men (68% versus 82%; UOR 0.83, 95% CI 0.78, 0.88; \( P < 0.0001 \)), while nevirapine was used more frequently in women than in men (32% versus 18.1%; UOR 2.1, 95% CI 1.7, 2.7; \( P < 0.001 \)). A boosted PI regimen as initial treatment was given to 1,421 patients, 369 (25.4%) women and 1,052 (24.7%) men, lopinavir/ritonavir being the most frequent medication (60% of women, 64.5% of men).

Considering only patients with at least 6 months of follow-up (7,832 patients), 5,640 (1,431 women and 4,209 men) started treatment with a median time to ART initiation of 4 months (95% CI 3.5, 4.5). The effect of gender on time to start ART was investigated separately in both cohorts, as an interaction between gender and belonging to CoRIS-MD or CoRIS was shown (\( P = 0.002 \)) in the competing risk regression.
Figure 1. Yearly trend over time in women and men

(A) Yearly trends over time of age, category of transmission (intravenous drug user [IDU] versus others), HIV stage (AIDS versus non-AIDS), CD4+ T-cell count (% CD4+ T-cells <200 cells/µl versus others) and HIV RNA (% HIV RNA >10^5 copies/ml versus others), by gender (1996–2008).

(B) Yearly trends over time of educational level (university degree versus others), geographic origin (Spanish versus immigrants), syphilis and HCV coinfection by gender (2004–2008).
model. In CoRIS-MD ART treatment was not started earlier in women (adjusted subhazard ratio [ASHR] 0.96, 95% CI 0.88, 1.04; \( P=0.302 \)), while in CoRIS women started treatment earlier than men (ASHR 1.21, 95% CI 1.11, 1.31; Figure 3). No interaction between gender and category of transmission was found (\( P=0.641 \)).

At 12 months, the percentage of patients with HIV-1 RNA<50 copies/ml was similar in women (68%) and men (71.3%).

For the whole cohort, the median time to ART change was shorter in women (13 months, IQR 11.3–14.6) than in men (19 months, IQR 17.7–20.2; \( P<0.001 \); ASHR 1.10, 95% CI 1.01, 1.19). Neither interactions between cohort and gender (\( P=0.684 \)) nor gender and category of transmission (\( P=0.309 \)) were found (Figure 4). In CoRIS, ART regimen was changed more frequently in women as compared with men because of pregnancy and patient’s or physician’s decision (Figure 5).

**Survival**

For a median follow-up of 47.4 months for women and 45.5 for men, there were 73 (3.7%) deaths among women (54.8% related to HIV infection) and 322 (5.3%) among men (54.1% related to HIV infection). Four years after being admitted in the cohort the probability of survival was 97% for women and 94.7% for men. In the Cox regression model, gender was not associated with higher survival (HR=1.08; \( P=0.596 \)) and no interaction between either gender and CoRIS-MD or CoRIS (\( P=0.363 \)), or gender and category of transmission (\( P=0.432 \)) were found.

**Discussion**

In this Spanish cohort of HIV-infected patients most women’s baseline characteristics differ from those of men when presenting for care. At enrolment into the cohort women were younger than men but there was a trend for initial diagnosis of HIV at older ages in recent years. The mean age of the HIV-infected population is increasing because patients live longer, particularly women, and because a greater number of new diagnoses are established in patients over 50 years of age [29–31].

The increased survival of HIV-infected patients, the late recognition of older subjects with missed or delayed diagnosis are responsible for a further expected rise in mean age of HIV-infected individuals, so that the patient population aged 60–70 years or more is expected to increase in coming years [30].

In Spain, although women only account for about one-quarter of people with HIV/AIDS, among persons newly diagnosed with HIV, the proportion of women in the older strata (>50 years) has increased significantly in recent years, from 1.8% in 1996 to reach 4.2% in 2008. This finding in our study is consistent with data of the 2009 report on HIV/AIDS surveillance in Europe [32].

Other two important characteristics observed in this study were: the increase in HIV-infected women younger than 20 years of age and a more pronounced increase in the population of immigrants among women than men. Both aspects need to be considered from a public health perspective [33].

At the time of inclusion in the cohort, women were in a better virological condition than men, with a significantly lower percentage of women with HIV...
Figure 3. Time to start initial ART regimen in CoRIS-MD 1996–2003 and CoRIS 2004–2008

Variables included as possible confounders were age, category of transmission, HIV stage, percentage of patients with CD4+ T-cell counts <200 cells/µl and HIV RNA >10^5 log_10 copies/ml at baseline, belonging to CoRIS-MD or CoRIS cohort. ART, antiretroviral treatment; ASHR, adjusted subhazard ratio.
RNA\textsuperscript{$>10^5$} copies/ml. The majority of studies demonstrated that women have lower numbers of circulating HIV RNA copies than do men. Given that women and men progress to AIDS and death at similar rates, it has been suggested that the rate of increase in viral load over time may be presumably greater for women [34]. Women were diagnosed in a better immunological situation in our cohort and this was stable throughout the study period, while men were worse initially but this has improved in recent years. The better immunological condition of HIV-infected women at the time of diagnosis may be due to the universal screening performed before delivery in Spain [35], while other factors such as the higher proportion of immigrants observed in the female group in our cohort is unlikely to explain this because a previous analysis of the CoRIS cohort for the period 2004–2006 showed that the immunological status of immigrants at entry and initiation of ART was not different from that of Spaniards [36].

A decreasing trend in prevalence of intravenous drug use as a probable route of transmission was observed in both cohorts. We could only investigate HCV prevalence at diagnosis in CoRIS and a decreasing trend was observed in both genders. This finding has been already described in a previous analysis of these cohorts, but women and men were not considered separately [37].

Both the lower education level, not improving over time, and the higher proportion of immigrants observed in the female group could be factors which increase vulnerability in this group [38,39].

In CoRIS, women showed a different pattern of ART use than men, starting earlier and less frequently with NNRTI than men. Efavirenz was the first NNRTI used as initial therapy, but less frequently in women than in men, while nevirapine was used more frequently in women. Of note, both differences were observed in women more recently admitted in the cohort, CoRIS but not in CoRIS-MD, indicating a differentiation between women and men from an early ART to a recent ART pattern of use. As women were in a better immunological condition, this cannot explain the earlier starting of ART. A possible explanation could be pregnancy or pregnancy desire, influencing both the earlier exposure independent of CD4\textsuperscript{+} T-cell count and the use of less efavirenz because it is contraindicated in pregnancy [36].

Figure 4. Time to change initial ART regimen in men and women in CoRIS-MD 1996–2003 and CoRIS 2004–2008

Variables included as possible confounders were age, category of transmission, HIV stage, percentage of patients with CD4\textsuperscript{+} T-cell counts <200 cells/µl and HIV RNA\textsuperscript{$>10^5$} log\textsubscript{10} copies/ml at baseline, belonging to CoRIS-MD or CoRIS cohort. ART, antiretroviral treatment; ASHR, adjusted subhazard ratio.
In our study, durability of the first ART regimen was lower for women in both cohorts. In CoRIS, where reasons for change were captured, differences in the rates of failure or toxicity were not observed. Similarly, an FDA meta-analysis of gender differences did not find differences of viral response [40], while different clinical trials [41–43] have also shown that the rates of discontinuation are higher among women for different reasons. A particular reason is that pregnant women are excluded from participating in clinical research, and also in clinical practice it is a reason for treatment discontinuation, as is observed in CoRIS. Not only have clinical trials shown higher discontinuation rates, but also different cohort analyses have documented this fact [44]. In a study of the role of gender on response to efavirenz-containing regimens in previously ART-naive patients, women seemed to have comparable virological and immunological outcomes, although the risk of discontinuing the drug was 34% lower in men [45].

In CoRIS, reasons for change observed with higher frequency in women than men were pregnancy (4.4% of all the reasons) and women’s or physician’s decision. The higher discontinuation rate in women, driven by reasons other than virological failure was also observed in the GRACE study, which highlights the need to explore gender differences in barriers to continuous medical care for HIV-infected patients [41]. In a recent meta-analysis, including clinical trials of lopinavir/ritonavir in naive and pretreated patients, virological efficacy was similar for both sexes, but more women discontinued for any reason especially because of being lost to follow-up. Of note, those differences were not seen in pretreated patients [46]. In a retrospective cohort study of 631 HIV-positive subjects, women and men were equally likely to discontinue treatment within 12 months but reasons for discontinuation were different, with poor adherence, rash, neurotoxicity, constitutional symptoms and concurrent medical conditions (pregnancy, delivery of a child) being more frequent among women [47].

Similar adjusted survival time was observed for women and men after presenting for care in the era of potent ART in this Spanish cohort, with similar results in the CoRIS-MD and CoRIS cohorts. A lower risk of death for women as compared with men has been reported in a partial analysis of this cohort and in other studies [17,48], including a cohort of IDUs [24]. However, in our cohort, crude differences in survival are not explained by gender but by other baseline clinical and epidemiological characteristics, such as disease severity, age and possibly behavioural habits of women and men when presenting for care. Regardless of gender, we observed very high survival rates and a high percentage of deaths not related to AIDS.

ART, antiretroviral treatment.

**Figure 5.** Reasons for change of ART according to sex

![Graph showing reasons for change of ART according to sex]
Several limitations were identified in our cohort analyses. In CoRIS-MD four variables were not captured (geographical origin, education level, serological tests for HCV and syphilis infections, and the main reason for switch/withdrawal of treatment); these variables were not used in the multivariate analyses involving both cohorts. Other variables that might have some influence on the main outcomes considered, such as frequency of clinic visits, number of women with pregnancies during follow-up, and/or women with ART to prevent vertical transmission prior to being admitted in the cohort, were not available in either of the two cohorts. However, the high number of patients, plus the quality of data captured and the verification of data permitted us to adjust for main independent variables influencing treatment outcomes and survival.

In summary, this study in two large cohorts in Spain showed gender-related differences in baseline characteristics when presenting for care, as well as in the time-course of distinctive features. This means that when talking of HIV-infected women and men, we are really facing two distinctive epidemics and therefore different health responses should be implemented. Furthermore, exposure to ART treatments differ, mostly in recent years, with an earlier starting and a lower durability in women, and also with different drugs used. Finally, the better crude survival observed in women, was not dependent on the gender but on other baseline characteristics. These results support the special need for research and clinical management targeted to HIV-infected women.

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Disclosure statement

The authors declare no competing interests.

Additional file

Additional file 1: A list of the members of the CoRIS Study group can be found at http://www.intmedpress.com/uploads/documents/3052_Perez-Elias_Additional_file_1.pdf

References


