RESEARCH REPORT

Gender differences in progression to AIDS and death from HIV seroconversion in a cohort of injecting dug users from 1986 to 2001

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Background: Although the consensus is that gender does not influence HIV progression, its relevance may depend on the setting.
Aim: To study gender differences in HIV progression to AIDS and death from 1986 to 2001 in a cohort of injecting drug user (IDU) seroconverters in Spain.
Methods: Risk of AIDS and death in persons infected for the same length of time were compared through Kaplan-Meier, allowing for late entry, and Cox regression adjusting for gender, age, and calendar period (before 1992, 1992–1995, 1996–1998, 1999–2001) fitted as time dependent covariates.
Results: Of 929 IDU, 24.7% were women. Median seroconversion year was 1993.3 for men and women. 44% of women and 34% of men received antiretroviral therapy. Risk of AIDS was lower in women in univariate (hazard ratio (HR) 0.72; 95%CI:0.51 to 1.01) and multivariate analyses (HR 0.73 95%CI:0.52 to 1.03). A 46% reduction in risk of AIDS for period 1999–2001 compared with 1992–1995 was seen in both men and women (HR: 0.56 (95%CI:0.36 to 0.87). As for mortality, women's risk of death was lower univariately (HR 0.67 95%CI:0.45 to 0.99) although compared with 1992–95, men experienced a 34% reduction in mortality during 1999–2001 (HR 0.66 95%CI:0.40 to 1.01), which was not statistically significant in women.
Conclusions: HIV progression was lower in female IDU before and after 1997 and their uptake of antiretroviral therapy was higher than male IDU. The inability to detect a reduction in mortality for women during 1999–2001 is probably attributable to lack of power. Differences in severity of addiction, drug using patterns, and competing causes of death may explain these findings.

The use of highly active antiretroviral treatment (HAART) in western countries has considerably improved the prognosis of HIV infected subjects with access to these therapies.[1–3] However, HAART can make inequality in HIV care more visible even in countries with free and universal access to antiretroviral drugs as its benefits at population level will largely depend on the patterns of access to, and utilisation of, HIV care.[4] Although the consensus seems to be that gender does not influence HIV progression, its relevance may vary depending on the setting.

Women have been reported to have higher lymphocyte CD4 cell counts and lower viral load measurements at equal duration of HIV infection, but these findings seem to have no translation in overall progression rates or response to HAART.[5–9] Most studies have found no differences in HIV progression to AIDS and death by gender, although some have found differences both before and after HAART.[10–16] Some have reported faster[17] and others have reported slower HIV progression.[18–20] To what extent the underlying mechanisms for these findings are biological or behavioural is difficult to elucidate but the differences in lymphocyte CD4 cell counts and viral load have been detected in women from different transmission categories from different countries[5–8] and the slower HIV progression has been seen in both heterosexual seroconverters in France and Spanish seroconverters from different transmission categories.[18 20]

Although some of the observed discrepancies may be attributable to differences in study design, biased progression estimates by gender may have also resulted from residual confounding by socioeconomic status resulting from the differences in the transmission categories in both the men and the women being compared. Injecting drug users (IDU) and heterosexual partners of IDU in some countries have poorer access to health care, lower uptake of HAART,[21] and higher pre-AIDS mortality than gay men.[22] Few studies have specifically studied the influence of gender on HIV progression among IDU after HAART.[23]

Spain has had one of the largest HIV epidemics in western Europe, which has been largely associated to intravenous drug use.[24 25] HIV/AIDS has also been, until recently, the leading cause of death among young adults.[26] GEMES, Spanish Multicentre Study Group of Seroconverters, has consistently reported slower HIV progression rates in women before and after HAART,[20 27] although no differences in the population effectiveness of HAART by gender have been shown.[20] Nevertheless, the heterogeneity of transmission categories within GEMES and the low number of women who are not IDU may hamper the comparisons. The objective of this work is to study differences by gender in HIV progression to AIDS and death in subjects who acquired HIV though injecting drug use from 1986 to 2001.

Abbreviations: IDU, injecting drug user; HAART, highly active antiretroviral treatment

*See the appendix for members of GEMES

Table 1 Descriptive statistics of 929 injecting drug users

	Total	Men		Women	
	Number	Number	%	Number	%
Subjects (n)	929	700	75.4	229	24.7
Cohorts integrating GEMES					
CIPS Valencia	280	203	29.1	77	33.6
Sandoval-Madrid	64	50	7.1	14	6.1
HUGTIP-Badalona	213	1622	23.1	51	22.3
CAS-Barcelona	157	114	16.3	43	18.8
Prisons-Barcelona	215	171	24.4	44	19.2
Level of education					
No formal education	74	61	6.4	13	5.2
Primary education	357	265	27.8	92	36.8
Secondary education	169	141	14.8	28	11.2
University studies	75	71	7.5	4	1.6
Unknown	528	415	43.5	113	45.2
AIDS (%)	215	172	24.5	43	18.7
AIDS incidence per 100 person years		5.1		3.8	
Deaths (%)	160	130	18.6	30	13.1
Death rate per 100 person years		3.5		2.5	
Pre-AIDS deaths (%of total deaths)	64	52	40	12	30
Year of seroconversion (median)		July 1992		October 1992	
Seroconversion interval (median in years)	929	700 1.07		229 1.00	
Year of beginning of treatment (median)		April 1997		January 1997	
Age at seroconversion (median)		25.1		24.1	
Proportion prescribed antiretrovirals	337	237	33.9	100	43.7
Subjects in each calendar period*					
Before 1992		225	76.8	68	23.2
1992–95 (reference)		483	74.4	166	25.6
1996–98		488	74.3	169	25.7
1999–2001		456	75.6	147	24.4

*Calendar period for which each patient contributes to the analysis.

METHODS

Data from 929 IDU with well recorded HIV seroconversion dates from five established seroconverter cohorts included in GEMES were analysed. The cohorts within GEMES have identified HIV seroconverters either retrospective or prospectively from the 1980s to current date and follow them up over time. All subjects who fulfilled the criteria of seroconverter were included in the study. A seroconverter was defined as a person who had had an HIV negative test previous to the first HIV positive one or had a reported seroconversion illness. Seroconversion was estimated as the midpoint between the last HIV negative and the first HIV positive tests.[28]

Current analyses have used data from five cohorts within GEMES; two cohorts from HIV counselling and testing centres: CIPS (Centres for AIDS Information and Prevention) within the Valencian Community and Centro Sanitario Sandoval (Centre for Sexually Transmitted Diseases and HIV in Madrid), one cohort from the CAS (centres for care and monitoring drug addicts of Barcelona) led by the Municipal Institute for Public Health (IMSP) of Barcelona, one cohort from Badalona Hospital Universitary Germans Trias i Pujol (detoxification unit), and a cohort recruited in prisons of the autonomous government of Catalonia. More information on the characteristics of these cohorts can be obtained from individual publications.[29–31]

Information on sociodemographic characteristics (age, gender, transmission category (IDU, men who have sex with men: MSM, heterosexuals) and educational level) as well as clinical and inmunological data (number and type of AIDS events, antiretroviral treatments prescribed, lymphocyte CD4 cell counts, HIV-RNA viral load, vital status, and cause of death) were collected.

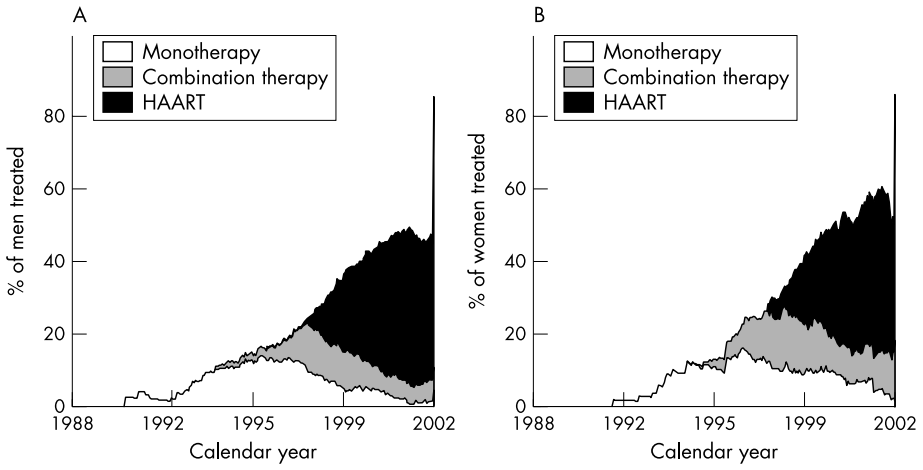

Figure 1 Distribution of treatments over time for (A) men and (B) women in GEMES cohorts of injecting drugs users.

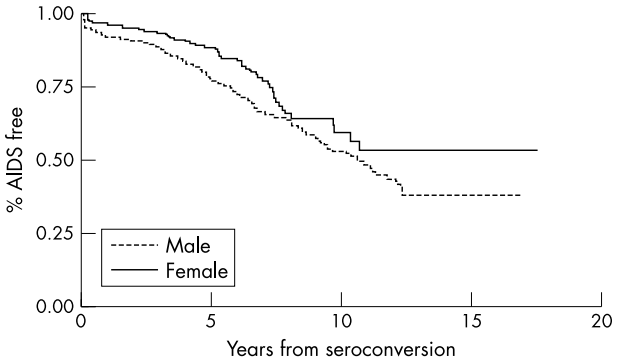

Figure 2 Time to AIDS from seroconversion by gender.

Each of the cohorts within GEMES follows up its seroconverters at the recruiting centres and referral hospitals and follow up is updated yearly.

Additionally, to increase the completeness of the data, cross checks with local and/or national AIDS registers and mortality registers from the different autonomous communities are also performed.[32] Regional AIDS registers in Spain report to the National AIDS Register and the overall underreporting, 13%, is similar to other European countries.[33] Cause of death was coded according to the 9th Revision of International Classification[34] and was further divided into four groups: (a) death from AIDS, (b) death from non-AIDS defining organic causes, (c) death from drug overdose, accidents, and/or violence, (d) death from indeterminate cause.

Statistical analyses

The demographic and clinical differences by gender were analysed using the two sample *t* test for normally distributed continuous data, the Mann-Whitney test for non-parametric data, and the χ^2 test for frequencies. The analysis of progression to AIDS and death from HIV seroconversion was analysed, allowed for late entry to the date of the first HIV positive test. For these analyses, people who were AIDS free and alive by March 2001 were censored. People with pre-AIDS mortality were censored as AIDS free at the moment of death for time to AIDS analysis. Survival of HIV positive men was compared with that of HIV positive women infected by HIV for the same length of time through extended Kaplan-Meier curves and log rank tests. Cox proportional hazards models were used to examine the risk of AIDS and death by gender adjusting for age at seroconversion, transmission category, calendar period, and educational level in those with that information available, testing for effect modification. Calendar year at risk was divided in four periods reflecting the availability of antiretroviral drugs in Spain; the reference period, 1992–1995, (double therapy), before 1992 (zidovudine monotherapy), 1996–1998, and 1999–2001, (potent antiretroviral therapy and protease inhibitors).[20] Calendar period is used as a proxy to measure the population impact of different antiretroviral regimens available during those years. Calendar period was modelled as a time dependent covariate so each person contributes to the analyses with as many registers of ''time periods'' he/she has been at risk. Each of these registers has the duration of HIV infection the seroconverter had at the beginning and at the exit of that calendar period, and what was the outcome in terms of AIDS or death. The resulting relative hazard should be interpreted as the excess or the absence in the risk of AIDS and death had the conditions in each period been constant in subjects infected for the same length of time.

Analyses were performed in Stata 7.0 (StataCorp, College Station, TX, USA) using robust methods to estimate confidence intervals.[26]

Table 2 Relative risk of AIDS from HIV seroconversion in 929 injecting drug users adjusting for calendar period, age, and sex

	Time to AIDS	
	Hazard ratio (95% CI)	**p Value**
Calendar period*		
Before 1992	1.10 (0.65 to 1.84)	0.2
1992–95	1.00	
1996–98	0.96 (0.66 to 1.39)	
99–2001	0.56 (0.36 to 0.87)	
Age (per year increase in age)	1.00 (0.97 to 1.03)	0.858
Sex		
Women	0.73 (0.52 to 1.02)	
Men	1.00	0.071

*Calendar period for which each patient contribute to the analysis.

Figure 3 Time to death from HIV seroconversion by gender.

RESULTS

These analyses included 929 IDU, 24.7% of whom were women. Median age at seroconversion was 25 years for men (range 13–49) and 24 years for women (range 15–49). A lower proportion of women had received secondary (11.2%) and university education (1.6%) compared with the men; 15% and 8% respectively. No differences by gender were observed in either the median year of seroconversion ($p = 0.711$) or in the year of the start of antiretroviral treatment ($p = 0.814$) (table 1).

We classified someone as lost to follow up when no further data were available on that person after two years from his/her last contact with the healthcare facility. There were no significant differences in these proportions in men and women (26% and 31% respectively; $p = 0.119$).

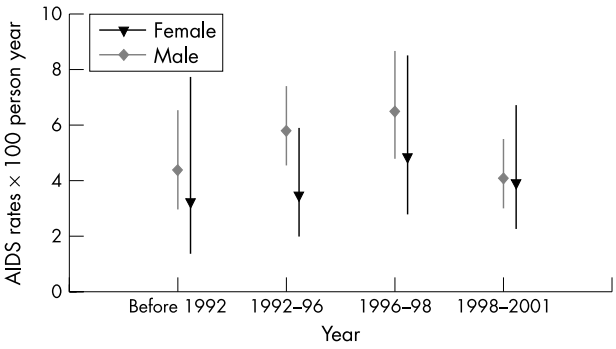

Figure 4 AIDS rates in men and women by calendar period.

Table 3 Relative risk of death from HIV seroconversion in 929 injecting drug user by sex adjusting for calendar period and age

	Time to death	
	Women	Men
	Hazard ratio (95%CI)	Hazard ratio (95%CI)
Calendar period*		
Before 1992	3.28 (0.90 to 11.89)	0.56 (0.25 to 1.22)
1992–95	1	1
1996–98	2.83 (0.98 to 8.11)	1.08 (0.67 to 1.72)
1999–2001	1.23 (0.40 to 3.77)	0.66 (0.40 to 1.08)
Age (per year increase in age)	1.03 (1.00 to 1.07)	

*Calendar period for which each patient contributes to the analysis.

Incidence of AIDS was 5.1 per 100 person years (172 cases) for men and 3.8 per 100 person years (43 cases) for women. There were 130 deaths among the men giving a mortality rate of 3.5 per 100 person years and 30 deaths in the women, resulting in a mortality rate of 2.5 per 100 person years. The proportion of pre-AIDS deaths was 40% for men and 30% for women.

A higher proportion of women (44%) received antiretroviral therapy compared with the men (34%) (table 1). Figure 1A and B show the evolution in the uptake of antiretroviral therapy by gender and how the uptake of HAART is higher among women. Of all subjects ever receiving treatment, 40% received monotherapy as their first option, 26% combination therapy, 34% HAART, and there were no differences by gender ($p = 0.79$). Among subjects prescribed HAART, 50% were naive (52% of the women and 50% of the men) and 21% had received combination therapy and 29% monotherapy previously, and no gender differences were observed ($p = 0.82$). No differences were observed either in the median time from seroconversion to the start of any antiretroviral treatment between women and men (4.0 and 4.40 years respectively, $p = 0.170$) or in time from seroconversion to start of HAART.

There were CD4 count data before 24 months from seroconversion in 125 (55%) women and 371 (53%) men. There were no significant differences in the median CD4 count by sex; 527 cells/ml in women and 484 cells/ml in men, $p = 0.097$. Differences were not significant in the median values within six months of the initial AIDS condition in 38 women and 164 men; 221 cells/ml in women and 169 cells/ml in men, $p = 0.465$ or in values at death in nine women and 63 men; 353 cells/ml in women and 161 cells/ml in men, $p = 0.168$. However, women started antiretroviral treatment at higher CD4 counts than men; for 189 women and 490 men, CD4 counts within six months of starting treatment were 440 cells/ml and 356 cells/ml respectively, $p<0.001$.

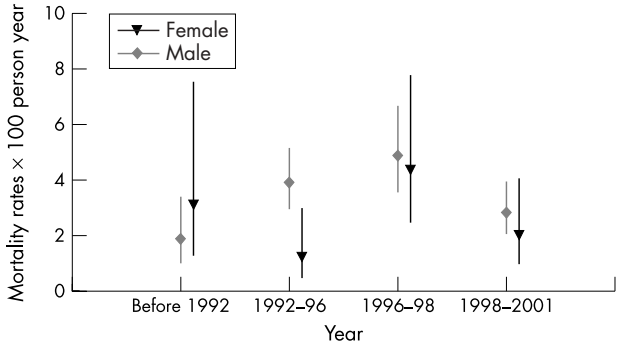

Figure 5 Mortality rates in men and women by calendar period.

Table 4 Effect of gender on calendar period in time to death from HIV seroconversion

	Time to death
	Hazard ratio (95%CI) women/men*
Calendar period†	
Before 1992	2.00 (0.70 to 5.63)
1992–95	0.34 (0.13 to 0.85)
1996–98	0.89 (0.47 to 1.70)
1999–2001	0.63 (0.29 to 1.35)

*Adjusted by age; †calendar period for which each patient contributes to the analysis.

The prevalence of HCV was known in 88% of the subjects, 89% of the women and 87% of the men. HCV prevalence was 73% in women and 72% in men, $p = 0.700$.

Time to AIDS from HIV seroconversion

Women had a lower risk of AIDS compared with men in crude analyses although differences did not reach statistical significance. Kaplan-Meier survival curves show how the risk of AIDS was lower in women compared with men (log rank $p = 0.065$); 47% of men had developed AIDS 10 years after seroconversion compared with 41% of women (fig 2).

Seventy per cent of all initial AIDS diagnoses were attributable to *Pneumocystis cariini* pneumonia (PCP) (11%), pulmonary tuberculosis (TB) (25%), and extrapulmonary TB and oesophageal candidiasis (34%). No important gender differences were observed in the pattern of initial AIDS defining illnesses except for extrapulmonary TB, which was commoner in men (15%) compared with women (0%) ($p<0.005$).

Women had a lower hazard of AIDS compared with men in both univariate (hazard ratio (HR) 0.72; 95%CI:0.51 to 1.01) and multivariate analyses that adjusted for age and calendar period (HR 0.73 95%CI:0.52 to 1.03). Again, differences were in the limit of statistical significance. No interaction was detected between gender and calendar period (log rank test $p = 0.657$) suggesting that the observed effect of calendar period on time to AIDS, a statistically significant 44% reduction in the risk of AIDS for calendar period 1999–2001 compared with period 1992–1995, is not different for men and women (table 2 and fig 4). Additional analyses in the subset of persons with information on educational level showed no effect of this variable in progression to AIDS (data not shown).

Survival from HIV seroconversion

Women showed a lower risk of death compared with men in crude analyses. Kaplan-Meier survival curves show how the risk of death was lower in women compared with men (log rank $p = 0.0479$); 36% of the men had died 10 years after

Key points

- Among injecting drug users, progression to AIDS and death from HIV seroconversion was slower in women compared with men.
- Compared with men, a higher proportion of female IDU were prescribed antiretroviral regimens and were also started with treatment at higher lymphocyte CD4 counts.
- It is unlikely that these findings are attributable to biological sex differences and healthier behaviours may account for some of the observed differences in the IDU population

seroconversion compared with 24% of the women (fig 3). Also, univariate Cox regression showed a 33% reduction in the risk of death for the women (HR 0.67 95%CI:0.45 to 0.99) compared with men.

Crude mortality rates, as shown in figure 5, increase progressively up to calendar period 1996–98 to decrease thereafter, although they follow a different temporal pattern for men and women. The crude risk of death is lower for women in all calendar periods except for before 1992, although differences in that period are not statistically significant; there were only five deaths in women and 11 deaths in men (table 4 and fig 5). From 1992 onwards, female mortality is lower that male mortality although differences are only significant for calendar period 1992–95 ($p = 0.022$) (table 4 and fig 5).

It can be deduced from the above that gender modified the effect of calendar period on survival although the interation test was of borderline significance (log rank test $p<0.085$) (table 3). Multivariate Cox regression adjusting for age and calendar period showed that compared with 1992–95, men experienced a 34% reduction in the risk of death for calendar period 1999–2001 (HR 0,66 95%CI:0.40 to 1.01) while this pattern is not observed in women because their mortality reaches its minimum by 1992–95 (table 3). Nevertheless, compared with calendar period 1996–98, women did experience a reduction in their risk of death by 1999–2001, although it did not reach statistical significance.

Four of the five cohorts had well reported causes of death. No important gender differences were observed in the main groups of causes of death; 60% of the women and 63% of the men died of AIDS, 27% of the women and 21% of the men died of drug overdose, accidents and/or violence, 4% of the women and 6% of the men died from non-AIDS defining illness, and 13% of the women and 8% of the men died from unknown causes. Further descriptive analyses looking at causes of death in different calendar periods were difficult to interpret because of small numbers, but it was noticeable that the proportion of deaths from overdose, accidents, and/or violent causes in men was very high (33%) in 1996–1998 and in women (13%). Also, an increase in the proportion of deaths attributable to non-AIDS illness was seen for both men (11%) and women (17%) in the last period 1999–2001.

DISCUSSION

These data show that among persons who acquired HIV though injecting drug use, progression from HIV seroconversion to AIDS and death (1986 to 2001) was lower in women compared with men, although some of these differences were of borderline statistical significance in some calendar periods. Women had slower progression to AIDS compared with men in all calendar periods, as well as higher overall survival, although the relative survival ratio by gender varied overtime; before 1992, mortality was higher in women, although not statistically significant, to become smaller than men thereafter.

Slower HIV progression in female IDU, before and after HAART, had been previously reported in Spain.[20 27 28] It is unlikely that these findings are attributable to biological differences or underreporting of AIDS and death in women,[32] and it seems more plausible that healthier behaviours, as suggested by the higher proportion of women prescribed any antiretroviral drugs and their higher uptake of HAART, may account for some of the observed differences in the IDU population. The fact that a higher proportion of female IDU received more treatment than men could be either the cause or the consequence of their better prognosis. As these are observational data, it is not possible to draw firm conclusions on their directionality. However, as slower HIV progression was also seen in female seroconverters in our setting before HAART,[20 27] it is more likely that some unmeasured characteristics women have, such as not being a current drug user, make them more suitable to be prescribed treatment. This is also supported by the fact that women were started on treatment at higher lymphocyte CD4 counts than men, not detecting further lymphocyte CD4 differences by sex at seroconversion, AIDS, or death.[35]

Previous research in IDU conducted in Valencia, Spain, showed no differences in access to and utilisation of health services by gender.[36] In our study, among those who were treated, no gender differences were observed in the time from seroconversion to the start of treatment. HAART in Spain is free of charge for any person, national or foreign, registered in civil registry. Being an active drug user is not a contraindication in itself although there are recommendations to consider starting treatment only in persons who are likely to comply with the regimens and mentions that active drug users should be treated first for their drug related problems. This is why, although data on current drug use in this cohort are not available, we think that the lower proportion of men receiving HAART is likely to be related to their continuation of their injection practices.

Gender differences in HIV related behaviours in IDU have been previously reported both in Europe[37 38] and the USA.[39] Women IDU were more likely to have regular partners who injected drugs[37 38] and had a higher risk of HIV infection because of overlapping sexual and injection partnerships.[39] Few studies have examined gender differences in HIV progression among IDU after HAART and only studies conducted in Spain have reported better outcomes in women. Muga *et al* reported lower mortality in HIV positive women compared with HIV positive men in a large cohort of HIV seroprevalent IDU in Spain, but these differences were not observed among HIV negative subjects.[31 40] Prins *et al* found a slower progression to AIDS and death in IDU women registered in the European IDU seroconverter study (where some of the women in GEMES participated) although differences were not statistically significant in the era before HAART. In an Italian seroconverter study, with a large proportion of IDU, no gender differences in HIV progression were observed, although women seemed to have no reduction in AIDS rates after HAART.[14 15] The CASCADE collaboration (where women within GEMES are included) the study with the largest number of seroconverters, has recently reported a slower progression to AIDS and death in women.[41]

A statistically significant reduction of 44% in the risk of AIDS for calendar period 1999–2001 compared with 1992–95 was observed for both men and women and a 34% reduction in overall mortality in calendar period 1999–2001 was seen in men. For women, a non-statistically significant reduction in mortality is seen in 1999–2001 compared with 1996–98

although because of small numbers it is not possible to draw firm conclusions. The effect of calendar period in progression to AIDS and death in our cohort of IDU is observed only for years 1999–2001 and not before, despite HAART being freely available from 1997 onwards. We have previously reported that the population effectiveness of HAART in Spain is delayed in IDU compared with homo/bisexual men and that higher pre-AIDS competing mortality and lower uptake of HAART could be the likeliest causes for it.[20]

While the decrease in the incidence of AIDS related deaths after HAART has been extensively reported[1 13 20 42 43] fewer studies have explored the decrease in pre-AIDS deaths after HAART.[44] In our study, the proportion of pre-AIDS deaths was very high as it has been at length described in IDU before HAART.[22] Pre-AIDS deaths seemed to be attributable to different causes over time with a suggestion of a decrease in the number of overdoses, accidents, and/or violent deaths and an increase of non-AIDS illness, although because of small numbers this could not be verified. Therefore, grouping pre-AIDS deaths as it has been done so far seems incorrect in the HAART era given that some of these deaths may be related to drug use (such as drug overdose) and others because of the benefits of the extended survival attributable to HAART (such as hepatitis C liver disease). The low number of events in GEMES did not permit the exploration of this in more detail and collaborative analyses with other seroconverter cohorts are needed to conduct competing risk models analyses.

The methodology used in HIV seroconverters cohorts allows us to obtain a public health indicator of the evolution of HIV progression trends in different calendar periods in persons infected by HIV for the same length of time.[45 46] To minimise losses to follow up, cross checks with AIDS and mortality registers were carried out and these strategies are the same for men and women.[32] Some of the analyses were underpowered to detect statistically significant differences although in all instances, all trends suggested slower HIV progression in the women. An important limitation is the high rate of losses to follow up but this is inevitable in such difficult to reach populations such as IDU. However, as we crossed check with AIDS and mortality registers, the hard end points of this study, it is unlikely that the results are gender biased.

In summary, the gender differences in HIV disease progression found in IDU in this study are probably attributable to differences in severity of addiction and/or drug using patterns and not biological factors. Further research into behavioural differences in IDU by gender and more detailed cause of death are needed to fully understand the observed trend.

CONTRIBUTORS

Manuela García de la Hera, Julia del Amo, Patricia García de Olaya, Santiago Pérez-Hoyos, and Ildefonso Hernández initiated this project. Manuela García de la Hera, Patricia García de Olaya, Roberto Muga, Jorge del Romero, Julia del Amo, Rafael Guerrero, and other members of GEMES were responsible for data collection. Inmaculada Ferreros and Santiago Pérez-Hoyos were responsible for data management and statistical analyses. Manuela García de la Hera wrote the first draft of the paper together with Julia del Amo. All authors were involved in the study design and commented on interim drafts. All authors have reviewed the final manuscript.

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Conflicts of interest: none declared.

APPENDIX

THE MEMBERSHIP OF GEMES INCLUDES

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Participating centres

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