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All-cause and liver-related mortality in HIV positive subjects compared to the general population: Differences by HCV co-infection

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Background & Aims: We aimed at comparing overall and liver-related mortality rates, observed in HIV positive subjects followed-up in the Cohorts of Spanish Network on HIV/AIDS Research stratified by HCV co-infection status, with the expected mortality of the general population of same age and sex in Spain, for the period 1997 – 2008.

Methods: We estimated standardized mortality ratio (SMR) and excess mortality, comparing death rates from our cohort (globally and by HCV co-infection) with death rates from the general population standardized by sex in 5 year-age bands.

Results: Overall, 5914 HIV positive subjects were included, 37.3% of which were co-infected with HCV; 231 deaths occurred, 10.4% of which were liver-related. SMR for all causes mortality for the HIV positive subjects was 5.6 (CI 95% 4.9–6.4), 2.4 (1.9–3.1) for HCV negative subjects and 11.5 (9.9–13.4) for HCV positive ones. Having HCV co-infection and AIDS yielded an SMR of 20.8 (16.5–26.1) and having AIDS and being HCV negative had an SMR of 4.8 (3.5–6.7). SMR for liver-related mortality was 1.8 (0.6–5.7) for HCV negative subjects *vs.* 22.4 (14.6–34.3) for HCV positive ones. Overall, both mortality rates as SMR and excess mortality rates were higher for injecting drug users (IDUs) than men having sex with men (MSM) and heterosexuals, patients with AIDS, with and without cART and for subjects included between 1997 and 2003.

Conclusions: There was an excess of all-cause and liver-related mortality in our cohorts compared with the general population. Furthermore, HCV co-infection in HIV positive patients increased the risk of death for both all causes and liver-related causes.

Keywords: HIV; HCV; Mortality; Cause of death; Standardized mortality ratio.
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Abbreviations: CoRIS, Prospective Cohort of Spanish Network on HIV/AIDS Research (in Spanish Cohorte de la Red de Investigación en SIDA); CoRIS-MD, Retrospective Cohort of Spanish Network on HIV/AIDS Research (in Spanish Cohorte de la Red de Investigación en SIDA); cART, combined antiretroviral treatment; HIV, Human Immunodeficiency Virus; SMR, standardized mortality ratio; IDU, injecting drug user; AIDS, Acquired Immunodeficiency Syndrome; HCV, Hepatitis C Virus; MSM, men having sex with men; NBDF, National Basic Death File; NSI, National Statistics Institute; ICD, International Classification of Diseases; p-y, persons-year; IQR, Interquartile rate; HIV VL, HIV viral load.

Introduction

Since the introduction of combined antiretroviral treatment (cART), important reductions in all cause-mortality in HIV positive subjects have been observed [1,2]. Nevertheless, HIV positive subjects still have higher mortality rates than the general population standardized for age and sex [3,4]. These standardized mortality ratios (SMRs) have been reported to be higher in women, injecting drug users (IDUs), people with AIDS and in those with lower CD4 cell counts [5–7]. In HIV positive subjects within 5 years of seroconversion, no difference in mortality is observed as compared to the general population, and in individuals on cART with high CD4 counts, excess HIV-related mortality seems to be similar to other chronic conditions [4,8].

This increase in life expectancy, together with the co-morbidities often associated with HIV infection such as co-infection by hepatitis B and C, alcohol, tobacco, and drug use, are responsible for increases in non-AIDS defining causes of death [2,9,10]. Liver-related deaths are one of the commonest causes of death in the post cART era [11–13]. HIV and HCV co-infection have detrimental effects on the natural history of each virus: HIV infection has been reported to accelerate HCV progression [14,15], and higher mortality is described in HIV positive subjects with HCV co-infec-

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tion [16,17]. In Spain, despite the continuous decrease of HCV co-infection due to declines in the proportion of injecting drug users (IDUs), HCV prevalence in HIV positive subjects remains high, and mortality due to liver diseases in HIV populations partly replaces mortality from AIDS prior to cART [18–21]. Liver-related deaths were the second commonest cause of death in CoRIS, the Cohort of the Spanish Research Network on AIDS, accounting for 10% of all events [22,23].

Higher SMRs in HIV positive people co-infected with HCV have been reported by Lewden *et al.* [6]. In HIV positive populations with high HCV co-infection rates, as is the case in Spain, stratification by HCV infection would help understand whether the elevated mortality ratios, observed in HIV positive men and women of different age-groups and transmission categories as compared to the general population, differ significantly by HCV status. In this study, we compare the overall and liver-related mortality rates observed in HIV positive subjects followed-up in the cohorts of the Spanish Network on HIV/AIDS Research – CoRIS-MD and CoRIS, stratified by HCV co-infection status, with the expected mortality in the general population of the same age and sex in Spain from 1997 to 2008. We calculate both SMRs and excess mortality rates.

Materials and methods

Study design, setting, and participants

Data on HIV positive adults from two multicenter cohort studies in Spain (CoRIS-MD and CoRIS) were analyzed. CoRIS-MD is a retrospectively assembled multicenter cohort, from January 1997 to December 2003, and CoRIS is an ongoing prospective cohort from January 2004 to present; for these analyses, however, only subjects followed until December 31st, 2008 were included. A detailed description of both cohorts has been published previously [24,25]. Both cohorts recruited subjects seen for the first time at any of the participating HIV care units. To be eligible for these analyses, subjects had to be cART naïve at study entry, less than 20 years old, and to have had at least one HCV test and at least 6 months of follow-up.

Patient characteristics

For the purpose of this study, we considered the following variables: (1) age at entry; (2) gender; (3) year of cohort entry; (4) HIV transmission category classified as heterosexual contact, men having sex with men (MSM), IDU and other or unknown risk pattern; (5) HCV serological status classified as positive or negative antibodies; (6) CD4 count at entry (measured over a period of six months from inclusion in the cohort); (7) HIV viral load at entry (measured over a period of six months from inclusion in the cohort); (8) changes in AIDS status during follow-up (Yes/No); (9) cART initiation during follow-up (Yes/No); and (10) cohort – CoRIS-MD (patients included between 1997 and 2003) and CoRIS (patients included between 2004 and 2008).

Ascertainment and classification of deaths in the cohorts and in the general population

Vital status in CoRIS-MD and CoRIS was reported by the study sites. For CoRIS-MD a cross-check with the National Death Index was performed, and for CoRIS, active surveillance for deaths is conducted at cohort level. Causes of death for all deceased subjects were obtained from the National Basic Death File (NBDF) provided by the National Statistics Institute in 2010 for the period 1997–2008. For 1997 and 1998, cause of death was coded according to the 9th revision of the International Classification of Diseases (ICD 9) and was converted to ICD 10 codes.

Death rates in the general population for all causes and liver-related causes of death were downloaded in December 2010 from the NIS webpage (www.ine.es), stratified in 5-year age groups for men and women, for deaths occurring between January 1st, 2004 and December 31st, 2008. The causes of death were also coded according to ICD 10.

We used the same procedure to classify deaths at numerators and denominators. For deaths that occurred in 1997 and 1998, we classified as liver-related mortality all causes that were provided in an aggregated form as 'viral hepatitis', 'malignant neoplasm of the liver', 'cirrhosis', and 'other chronic diseases of the liver'. For the period from 1999 to 2008, we classified as liver-related mortality all causes of death with the following ICD-10 codes: (B15-B19) viral hepatitis, (C22) malignant neoplasm of the liver and (K70-K76) diseases of the liver.

Statistical analyses

We calculated mortality rates, overall and according to socio-demographic and clinical characteristics, as the number of deaths by 100 persons-year (py) of follow-up. Individuals were followed-up from study entry to death or the administrative censoring date (31/12/2003 in CoRIS-MD and 31/12/2008 in CoRIS), whichever arose first.

We estimated SMRs by comparing all-cause mortality rates in our cohorts stratified by HCV co-infection status with all-cause mortality rates in the general population standardized by sex in 5-year age bands. To calculate death rates and SMR, AIDS, and cART were treated as time-dependent variables. We also estimated SMRs for liver-related deaths compared to liver-related mortality in the general population. We assumed a constant death rate within each 5-year age stratum. SMRs were estimated as the ratio of the observed number of deaths divided by the expected number of deaths; the expected number of deaths was calculated by applying the mortality rates of the general population to the p-y distribution of the HIV cohort. Confidence intervals at 95% level were also calculated.

Excess mortality was calculated as the difference between observed deaths in our cohorts and expected deaths according to mortality in the general population, divided by the number of p-y of follow-up. Confidence intervals at 95% level were also calculated using the exact Poisson method.

All analyses were performed using STATA 11 (StataCorp LP, College Station TX, USA).

Results

Overall, 5914 subjects, 18,951 p-y of follow-up and 231 deaths, 24 (10.4%) of which liver-related, were observed in our cohorts. Over three quarters (76.0%) were men, 71.6% were under 40 years, 31.3% were or had been IDUs, 32.4% were MSM, 30.6% were heterosexuals, and 37.3% were co-infected with HCV (Table 1). Information on baseline CD4 cell count was available for 5,229 subjects, and the median was 334 (IQR 150–540): 344 (IQR 152–547) for HCV negative and 319 (IQR 147–525) for HCV positive individuals ($p = 0.02$). Although all patients included in the cohorts have to be naïve for antiretroviral treatment at entry, 74.7% began cART anytime during the follow-up.

Death rates, SMR, and excess mortality rates for all-cause mortality in HCV negative and HCV positive subjects

All-cause mortality was 1.22 per 100 p-y (95% CI: 1.07–1.39): 0.61 per 100 p-y (95% CI: 0.47–0.78) in HCV negative subjects and 1.96 per 100 p-y (95% CI: 1.68–2.28) in those who were HCV positive. For both HCV negative and HCV positive subjects, death rates were higher in men, subjects over 40 years of age, IDUs, those with an AIDS diagnosis, baseline CD4 counts below 200 cells, HIV VL values over 100,000 copies and those on cART (Table 2).

The SMR for all cause-mortality for all subjects was 5.6 (95% CI: 4.9–6.4). However, marked differences by HCV status were seen: the SMR was 2.4 (95% CI: 1.9–3.1) for HCV negative subjects and 11.5 (95% CI: 9.9–13.4) for those HCV positive (Table 2).

Compared to the general population, higher SMRs were observed in both HCV negative and HCV positive cohort members for men and women, people over and under 40 years of age, dif-

Table 1. Baseline socio-demographics and clinical characteristics, globally and by HCV status.

	Total		HIV+/HCV-		HIV+/HCV+	
	n	%	n	%	n	%
Total	5914	100	3710	100	2204	100
Gender						
Male	4492	76.0	2859	77.1	1633	74.1
Female	1422	24.0	851	22.9	571	25.9
Age (yr) category at entry						
<40	4236	71.6	2549	68.7	1687	76.5
≥40	1678	28.4	1161	31.3	517	23.5
Transmission category						
IDU	1851	31.3	134	3.6	1717	77.9
MSM	1919	32.4	1824	49.2	95	4.3
Heterosexual	1812	30.6	1517	40.9	295	13.4
Others/unknown	332	5.6	235	6.3	97	4.4
AIDS						
No	4483	75.8	2931	79.0	1552	70.4
AIDS before entry	769	13.0	462	12.5	307	13.9
AIDS during follow-up	662	11.2	317	8.5	345	15.7
CD4 at entry						
<200	1648	27.9	1075	29.0	573	26.0
200-349	1074	18.2	689	18.6	385	17.5
≥350	2507	42.4	1714	46.2	793	36.0
Unknown	685	11.6	232	6.2	453	20.5
Median (IQR)	334 (150-540)		344 (152-547)		319 (147-525)	
Viral load at entry						
<20,000	1955	33.1	1256	33.8	699	31.7
20,000-100,000	1464	24.8	1061	28.6	403	18.3
≥100,000	1459	24.7	1083	29.2	376	17.1
Unknown	1036	17.5	310	8.4	726	32.9
Antiretroviral treatment during follow-up						
No	1499	25.3	990	26.7	509	23.1
Yes	4415	74.6	2720	73.3	1695	76.9
Cohort						
CoRIS (2004-2008)	3461	58.5	2745	74.0	716	32.5
CoRIS-MD (1997-2003)	2453	41.5	965	26.0	1488	67.5

ferent transmission categories, with different baseline CD4 cell counts and HIV VL, with or without cART, in both cohorts. Nearly all SMRs showed statistically significant increases except those categories with a low number of observed deaths (Table 2). As expected, SMRs were markedly higher in HCV positive people than in HCV negative ones. Fig. 1 shows the SMRs observed in subjects according to HCV infection and AIDS diagnosis. Having HCV co-infection and AIDS yielded an SMR of 20.8 (16.5–26.1) and having AIDS and being HCV negative had an SMR of 4.8 (3.5–6.7).

The overall excess mortality rate for cohort members was 1.0 (95% CI: 0.8–1.1) per 100 p-y: 0.35 (95% CI: 0.26–0.49) in HCV negative subjects and 1.79 (95% CI: 1.53–2.10) in HCV positive ones. Excess mortality for HCV negative subjects was of similar magnitude in men and women, and was higher in people over 40 years of age, IDUs, people with a previous AIDS diagnosis, individuals with CD4 cell counts below 200 cells, those with over 100,000 copies of HIV VL, and those on cART. The excess mortality rate was also higher in CoRIS-MD than in CoRIS. Excess mortality rates for HCV positive subjects were higher in men, people over 40 years of age, IDUs, people with an AIDS diagnosis, individuals with CD4 cell counts below 200 cells, those with over 100,000 copies of HIV VL, and those on cART. Moreover, the excess mortality rate was higher in CoRIS than in CoRIS-MD (Table 2).

Death rates, SMR, and excess mortality rates for liver-related deaths

There were 24 liver-related deaths during 18,951 p-y of follow-up, leading to a mortality rate of 0.13 per 100 p-y (95% CI: 0.08–0.19), which was 0.03 per 100 p-y (95% CI: 0.01–0.09) in HCV negative subjects compared to 0.24 (95% CI: 0.16–0.38) in HCV positive ones (Table 3). Similar liver-related mortality rates were seen in men and women. Liver-related mortality was higher in subjects over 40 years of age, IDUs and heterosexuals, individuals with an AIDS diagnosis, subjects with CD4 cell counts below 200, those with over 100,000 copies HIV VL, and those on cART.

The SMR for liver-related mortality for all subjects was 9.4 (95% CI: 6.3–13-9). However, marked differences by HCV status

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Table 2. Death rates per 100 p-y and standardized mortality ratios (SMRs) for all deaths according to the HCV status.

	HIV+/HCV-					HIV+/HCV+				
	p-y	Deaths	Death-rate (95% CI)*	SMR (95% CI)	Excess mortality rate (95% CI)**	p-y	Deaths	Death-rate (95% CI)*	SMR (95% CI)	Excess mortality rate (95% CI)**
Total	10,379	63	0.61 (0.47-0.78)	2.4 (1.9-3.1)	0.35 (0.26-0.49)	8571	168	1.96 (1.68-2.28)	11.5 (9.9-13.4)	1.79 (1.53-2.10)
Gender										
Male	7778	51	0.66 (0.50-0.86)	2.2 (1.6-2.8)	0.35 (0.24-0.51)	6295	137	2.18 (1.84-2.57)	10.6 (8.9-12.5)	1.97 (1.65-2.34)
Female	2601	12	0.46 (0.26-0.81)	4.5 (2.5-7.8)	0.36 (0.19-0.68)	2276	31	1.36 (0.96-1.94)	18.8 (13.2-26.7)	1.29 (0.90-1.85)
Age (yr) category										
<40	6473	18	0.28 (0.17-0.44)	3.1 (1.9-4.9)	0.19 (0.11-0.33)	5975	95	1.59 (1.30-1.94)	12.8 (10.5-15.7)	1.47 (1.19-1.81)
≥40	3906	45	1.15 (0.86-1.54)	2.2 (1.6-2.9)	0.63 (0.42-0.93)	2596	73	2.81 (2.23-3.53)	10.2 (8.1-12.8)	2.53 (2.00-3.23)
Transmission category										
IDU	421	6	1.43 (0.64-3.18)	6.7 (3.0-14.9)	1.21 (0.51-2.89)	6918	148	2.14 (1.82-2.51)	12.8 (11.0-15.2)	1.97 (1.67-2.33)
Homosexual	4807	26	0.54 (0.37-0.79)	2.4 (1.7-3.6)	0.32 (0.19-0.53)	294	4	1.36 (0.51-3.62)	6.1 (2.3-16.1)	1.14 (0.39-3.32)
Heterosexual	4454	27	0.61 (0.42-0.88)	2.2 (1.5-3.2)	0.33 (0.20-0.55)	979	15	1.53 (0.92-2.54)	8.6 (5.1-14.2)	1.35 (0.78-2.32)
Others/ unknown	697	4	0.57 (0.22-1.53)	1.5 (0.6-4.1)	0.20 (0.04-1.05)	380	1	0.26 (0.04-1.87)	1.3 (0.2-9.1)	0.06 (0.00-3.79)
AIDS										
No	8409	27	0.32 (0.22-0.47)	1.4 (0.9-2.1)	0.10 (0.05-0.19)	6659	94	1.41 (1.15-1.73)	8.5 (6.9-10.4)	1.25 (1.00-1.54)
Yes	1670	36	1.83 (1.32-2.53)	4.8 (3.5-6.7)	1.45 (1.00-2.09)	1913	74	3.87 (3.08-4.86)	20.8 (16.5-26.1)	3.68 (2.92-4.65)
CD4 at entry										
<200	2937	35	1.19 (0.86-1.66)	3.5 (2.5-4.9)	0.85 (0.57-1.26)	1782	64	3.59 (2.81-459)	17.9 (14.0-22.9)	3.39 (2.64-4.36)
200-349	1780	6	0.34 (0.15-0.75)	1.4 (0.6-3.1)	0.09 (0.02-0.43)	1320	22	1.67 (1.10-2.53)	9.8 (6.5-15.0)	1.49 (0.96-2.33)
≥350	4607	14	0.30 (0.18-0.51)	1.7 (1.0-2.8)	0.12 (0.05-0.28)	2961	38	1.28 (0.93-1.76)	7.9 (5.8-10.9)	1.12 (0.79-1.57)
Unknown	1054	8	0.76 (0.38-1.52)	2.2 (1.1-4.4)	0.41 (0.16-1.06)	2508	44	1.75 (1.30-2.36)	10.9 (8.2-14.7)	1.59 (1.17-2.17)
Viral load at entry										
<20,000	3226	13	0.40 (0.23-0.69)	2.0 (1.1-3.3)	0.19 (0.09-0.42)	2216	33	1.49 (1.06-2.09)	8.4 (5.9-11.8)	1.31 (0.91-1.89)
20,000-100,000	2711	16	0.59 (0.36-0.96)	2.7 (1.6-4.3)	0.37 (0.19-0.69)	1203	29	2.41 (1.67-3.47)	14.2 (9.8-20.4)	2.24 (1.54-3.27)
≥100,000	2948	23	0.78 (0.52-1.17)	2.7 (1.8-4.0)	0.49 (0.29-0.82)	1089	37	3.40 (2.46-4.69)	16.5 (11.9-22.8)	3.19 (2.29-4.45)
Unknown	1494	11	0.74 (0.41-1.33)	2.3 (1.3-4.1)	0.41 (0.19-0.91)	4063	69	1.69 (1.34-2.15)	10.8 (8.5-13.7)	1.54 (1.20-1.97)
Antiretroviral treatment										
No	3540	12	0.34 (0.19-0.60)	1.9 (1.1-3.4)	0.17 (0.07-0.38)	3399	47	1.38 (1.04-1.84)	8.6 (6.5-11.5)	1.27 (0.90-1.73)
Yes	6839	51	0.75 (0.57-0.98)	2.5 (1.9-3.3)	0.45 (0.32-0.64)	5172	121	2.34 (1.96-2.79)	13.2 (11.1-15.8)	2.16 (1.80-2.60)
Cohort										
CoRIS (2004-08)	6784	32	0.47 (0.33-0.67)	2.1 (1.5-3.0)	0.25 (0.16-0.41)	1851	42	2.27 (1.68-3.07)	10.9 (8.0-14.7)	2.06 (1.50-2.83)
CoRIS-MD (1997-03)	3595	31	0.86 (0.61-1.23)	2.8 (1.9-3.9)	0.55 (0.35-0.85)	6720	126	1.87 (1.57-2.23)	11.7 (9.9-13.9)	1.72 (1.43-2.06)

*Death rates per 100 person-years.
**Excess mortality rates per 100 person-years.

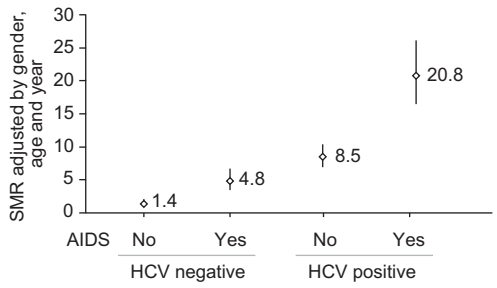

Fig. 1. SMR according to HCV status and AIDS diagnosis in HIV positive subjects.

were observed: the SMR for HCV negative subjects was 1.8 (95% CI: 0.6–5.7) *vs.* 22.4 (95% CI: 14.6–34.3) for those HCV positive (Table 2). The SMRs for liver-related mortality were higher in women, people under 40 years of age, IDUs and heterosexuals compared to MSM, those on cART, and for CoRIS-MD.

Excess liver-mortality rates were 0.11 per 100 p-y (95% CI: 0.07–0.17): 0.01 per 100 p-y (95% CI 0.00–0.07) for HCV negative subjects and 0.23 per 100 p-y (95% CI 0.15–0.36) for HCV positive ones (Table 3).

Discussion

The all-cause mortality in HIV positive subjects in the Cohorts of the Spanish AIDS Research Network of Excellence between 1997 and 2008 is nearly six times higher than that of the general population of the same age and sex. However, remarkable differences are observed according to the HCV co-infection status: mortality in HCV negative subjects is two and a half times higher than in the general population while death rates in HCV positive individuals are eleven times higher. Liver-related mortality in HIV positive subjects in CoRIS is nearly ten times higher than in the general population of the same age and sex, and again, notable differences by HCV co-infection status are seen. While non-significant increases in liver-related mortality are observed in HCV negative people, liver-related mortality is twenty-two times higher in HCV infected subjects compared to the general population of the same age and sex.

As previously reported, HIV-infected populations have higher mortality rates than the general population of the same age and sex. Our data are consistent with these findings, but they also highlight the remarkable excess mortality in subjects with HCV co-infection [3,17,26,27]. We observe that the all-cause mortality in HIV positive HCV negative subjects who were AIDS-free was 1.4 times higher than the general population and increased to 20.8 times higher in HCV positive subjects who had an AIDS defining condition.

Despite the sustained reduction of HCV serial prevalence from 1997 onwards in our cohort of HIV positive subjects, overall HCV prevalence was 37.3%, similar to figures reported by EuroSIDA for Southern European countries [17]. HIV and HCV are well established causes for death from all causes [17,22,28,29]. In addition to this, people infected with HIV and/or HCV have been reported to have higher rates of drug, alcohol, and tobacco use than the general population [26,30,31]. Data from a subset of CoRIS members shows that 42% of the men and 54% of the women reported current smoking [32], while these proportions were 31% and 21% for the general population between 16 and 64 years of age, according to the National Health Survey [33]. Therefore, it is likely that higher smoking rates are responsible for part of the excess mortality observed in our population. Regarding alcohol use, preliminary data in our cohort show that 75% of the men and 44% of the women had drunk alcohol in the preceding 12 months [32]. This is slightly lower than the figures for the general population, (80% and 57% [33]), which may be due to sick people drinking less alcohol than those in the general population. A recently published study on the cardiovascular risk in the patients from our cohort has shown a prevalence of smoking of 47% as well as of other co-morbidities, such as diabetes and hypertension (3% and 9%, respectively [34]).

SMRs for all-cause mortality were higher for people less than 40 years old, and this was observed both in subjects co-infected with HCV and those not co-infected. As mortality rates in the general population rise, mortality in our cohort increasingly resembles that of the general population. As expected, excess mortality rates increased with age, highlighting the value of using both relative and absolute measures to estimate excess mortality.

Regarding liver-related mortality, we observed an important difference between men and women. In women, liver-related SMR was 38 times higher than for women of the general population of the same age. These differences may be explained by the relative low liver-related death in women from the general population [35], together with the special characteristics of the HIV positive women; a higher prevalence of co-morbidities (29.5% of women in this study were current or former injecting drug users and 40.2% were co-infected with HCV) and their lower socio-economic level [36].

As far as we know, only one previous study has estimated SMRs in HIV positive populations by the HCV infection status [6]. Lewden *et al.* found that all-cause mortality in HIV positive subjects co-infected with HCV was 14 times higher than in the general population, whereas the SMR for those not co-infected was 4.4. Our results are similar, although slightly lower for the HCV negative population. Various studies have estimated the SMR for all-cause mortality in cohorts of HIV-infected subjects and have found that their mortality rates are 3–14 times higher than in the general population [3–5,7]. In interpreting these findings, the composition of the cohort, the background HCV prevalence, and the mortality rates of the general population have to be taken into account. Lower SMRs have been reported in large international cohorts made up of heterogeneous populations, whereas higher SMRs are derived from smaller cohorts with larger proportions of injecting drug users [3,4]. Regarding excess mortality, our rate of 1.0 per 100 p-y, is slightly higher than the 0.6 per 100 p-y for the period 2004–2006, reported by the CASCADE Collaboration [8]; overall HCV prevalence in that study was lower than ours, and it was composed exclusively of seroconverters with longer periods of disease-free follow-up. Our data are consistent with previous publications reporting important reductions in mortality in the cART era in settings, such as Spain, where access to cART is universal [6,37].

Treatment for HCV infection in co-infected individuals has been more recent in our setting [38]. In a short survey of 24 European countries, Salmon *et al.* showed that this treatment has been prescribed to only 10% of the subjects who need it [39]. Nowadays, this treatment is widely recommended since successful treatment of chronic hepatitis C, besides preventing the development of

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Table 3. Death rates per 100 p-y, standardized mortality ratios (SMRs) and excess mortality rates for liver-related deaths.

		Liver-related deaths			
	p-y	Deaths	Death-rate (95% CI)	SMR (95% CI)	Excess mortality rate (95% CI)
Total	18,951	24	0.13 (0.08-0.19)	9.4 (6.3-13.9)	0.11 (0.07-0.17)
Gender					
Male	14,073	17	0.12 (0.08-0.19)	7.1 (4.4-11.5)	0.10 (0.06-0.17)
Female	4878	7	0.14 (0.07-0.30)	37.9 (18.1-79.6)	0.14 (0.06-0.29)
Age (yr) category					
<40	12,449	10	0.08 (0.04-0.15)	17.9 (9.6-33.3)	0.07 (0.04-0.14)
≥40	6502	14	0.21 (0.13-0.36)	7.0 (4.1-11.8)	0.18 (0.10-0.32)
Transmission category					
IDU	7339	14	0.19 (0.11-0.32)	17.9 (10.6-30.3)	0.18 (0.10-0.31)
MSM	5101	2	0.04 (0.01-0.16)	2.7 (0.7-10.7)	0.02 (0.00-0.14)
Heterosexual	5434	7	0.13 (0.06-0.27)	8.5 (4.1-17.9)	0.11 (0.05-0.25)
Others/unknown	1077	1	0.09 (0.01-0.66)	4.6 (0.6-32.3)	0.07 (0.01-0.67)
AIDS					
No	15,068	14	0.09 (0.06-0.16)	7.6 (4.5-12.9)	0.08 (0.05-0.14)
Yes	3882	10	0.26 (0.14-0.48)	13.7 (7.4-25.5)	0.24 (0.12-0.45)
CD4 at entry					
<200	4719	10	0.21 (0.11-0.39)	20.8 (5.8-20.1)	0.19 (0.10-0.37)
200-349	3100	5	0.16 (0.07-0.39)	11.6 (4.8-27.8)	0.15 (0.06-0.37)
≥350	7569	5	0.07 (0.03-0.16)	6.2 (2.6-14.9)	0.06 (0.02-0.14)
Unknown	3562	4	0.11 (0.04-0.30)	9.8 (3.7-26.2)	0.10 (0.04-0.28)
Viral load at entry					
<20,000	5442	3	0.06 (0.02-0.17)	4.3 (1.4-13.5)	0.04 (0.01-0.15)
20,000-100,000	3914	3	0.08 (0.02-0.24)	5.7 (1.8-17.6)	0.06 (0.02-0.22)
≥100,000	4038	11	0.27 (0.15-0.49)	15.1 (8.3-27.2)	0.25 (0.14-0.47)
Unknown	5557	7	0.13 (0.06-0.26)	11.2 (5.4-23.6)	0.11 (0.05-0.25)
Antiretroviral treatment					
No	4690	1	0.01 (0.00-0.10)	1.5 (0.2-10.6)	0.005 (0.00-0.14)
Yes	12,011	23	0.19 (0.13-0.29)	12.1 (8.0-18.2)	0.17 (0.11-0.27)
Cohort					
CoRIS (2004-2008)	8635	6	0.07 (0.03-0.16)	4.7 (2.1-10.6)	0.05 (0.02-0.14)
CoRIS-MD (1997-2003)	10,316	18	0.17 (0.11-0.28)	13.8 (8.7-21.9)	0.16 (0.10-0.26)
HCV test					
Negative	10,379	3	0.03 (0.01-0.09)	1.8 (0.6-5.7)	0.01 (0.00-0.07)
Positive	8571	21	0.24 (0.16-0.38)	22.4 (14.6-34.3)	0.23 (0.15-0.36)

*Death rates per 100 person-years.
**Excess mortality rates per 100 person-years.

end-stage liver disease, may also reduce the risk of subsequent liver toxicity during antiretroviral therapy in HIV/HCV-co-infected patients [40].

There are some study limitations that merit discussion. We are aware that variables other than age and sex may account for the higher mortality rates found in our cohort, such as current use of injecting drugs. Unfortunately, this information was not available, but adjustment for this factor would probably have resulted in lower SMRs. Nevertheless, the SMRs for transmission categories other than IDUs also showed an excess mortality. Similarly, information on socio-economic status and alcohol and tobacco use is missing from both numerators and denominators, which means the SMRs found in this study may be an overestimation. Approximately 15% of the subjects with HCV infection will clear the infection spontaneously, but this can only be detected by PCR, which was available for only a minority of our patients [41]. Therefore, the assumption that these HCV antibody positive but PCR negative subjects are HCV positive, underestimates the magnitude of the association. We are aware that additional data on chronic hepatitis C and HCV treatment data would be very important, but those data were not uniformly collected during all the study period and were available only for few patients.

Deaths were coded in the same way for both numerators and denominators, based on information provided by the National Basic Death File using ICD-9 and ICD-10 coding algorithms. This is an important asset of this study as the majority of previous studies have coded deaths in cohort members using algorithms different from those used for denominators. Concordance between different death coding algorithms has been insufficiently studied [23]. With respect to subjects excluded from the analysis, we believe that they do not introduce important biases. In the first place, if we perform a sensitivity analysis considering all unknowns as positive, the SMRs are similar to the results obtained. Second, by eliminating those with less than 6 months of follow-up, we are losing subjects who die shortly after cohort

entry. Since people included in the cohort are new cases in hospitals, these early deaths during follow-up would be represented by people dying from AIDS who have been diagnosed very late, and these represent only a small percentage of the cohort. Finally, the association between HCV infection and liver-related death could be overestimated if the physician who certified the cause of death knew the HCV status of the subject; those with positive HCV serology would be more likely assigned a liver-related death [42]. While this bias may, indeed, account for some of the observed associations, it has to be highlighted that we obtained the cause of death for all cohort members from the National Basic Death File and that it is unlikely that all doctors certifying deaths had the information on the HCV status of the subject.

To conclude, we have shown an excess of all-cause and liver-related mortality in HIV positive people compared to the general population in the last decade, despite improvements in the management of both HIV and HCV infections. Co-infection with HCV seems to play a very important role in all-cause and liver-related excess mortality. Rapid changes in the epidemiology of HCV co-infection and major advances in the treatment of these infections are likely to shape future patterns of excess mortality in the coming years.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Appendix 1

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