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Clinical outcomes of patients infected with HIV through use of injected drugs compared to patients infected through sexual transmission: late presentation, delayed anti-retroviral treatment and higher mortality

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ABSTRACT

Aims To compare patients who acquired HIV infection through use of injected drugs (HIV-IDU) with patients who acquired HIV by sexual transmission (HIV-ST) in terms of late presentation (LP), delay in anti-retroviral treatment (ART) initiation, virological and immunological response to ART, mortality and progression to AIDS. **Design** Prospective multi-centre cohort study of HIV-infected subjects naive to ART at entry (Cohort of the Spanish HIV Research Network: CoRIS). **Setting** Thirty-one centres from the Spanish public health-care system. **Participants** A total of 9355 patients were included (1064 HIV-IDU and 8291 HIV-ST) during 2004–13. **Measurements** We compared LP (defined as presentation for care with a CD4 cell count < 350/μl and/or AIDS-defining illness), delayed ART initiation (defined as initiating treatment more than 6 months after the date when treatment was indicated by the guidelines, or not initiating treatment at all when it was indicated), virological and immunological response to ART (defined as viral load < 50 HIV-1 RNA copies/ml and a CD4 count increase of at least 100 cells/μl, respectively, after 1 year of treatment), mortality and progression to AIDS in HIV-IDU and HIV-ST. **Findings** Compared with HIV-ST, HIV-IDU had higher risk of LP [odds ratio (OR) = 1.76; 95% confidence interval (CI) = 1.41–2.18], delayed ART initiation (OR 1.87; 95% CI = 1.46–2.40) and higher mortality [hazard ratio (HR) = 1.43; 95% CI = 1.03–2.01] and risk of progression to AIDS [subhazard ratio (SHR) = 1.68; 95% CI = 1.29–2.18]. Virological suppression due to ART was lower in HIV-IDU than in patients with HIV-ST only among patients without hepatitis C virus (HCV) infection [adjusted OR (aOR) = 0.59; 95% CI = 0.36–0.95]; among patients with HCV infection, virological suppression due to ART did not show significant differences between HIV-IDU and HIV-ST. There were no significant differences in immunological response after adjusting by HCV (aOR = 0.74; 95% CI = 0.52–1.06). **Conclusions** In Spain, patients who acquire HIV infection through use of injected drugs appear to have a higher risk of late presentation, delayed initiation of anti-retroviral treatment and progression to AIDS and death than patients who acquire HIV by sexual transmission.

Keywords Cohort studies, drug users, HIV infections, mortality.

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INTRODUCTION

HIV-infected patients who inject drugs have a worse prognosis compared with patients infected with HIV by other transmission routes [1,2]. Previous studies have shown poorer engagement to care, a delay in the initiation of anti-retroviral treatment, low adherence to anti-retroviral treatment (ART), poorer virological response to ART, high

prevalence of other comorbidities and higher mortality in this group [1–3]. Many of these studies have been conducted in settings without a universal health-care system or with restricted access to ART.

The use of injected drugs shaped the HIV epidemic in Spain, where the proportion of people who inject drugs (PWID) among the HIV-infected population was one of the highest in Europe during the 1990s [4]. This proportion has been declining during recent years [5,7]. However, the situation of HIV-infected PWID in Spain has not been studied sufficiently. Very few studies from earlier years showed that PWID had delayed initiation of treatment and poor prognosis [8,9]. In recent years, when the proportion of PWID among newly diagnosed cases has decreased, little is known about their situation and whether they continue to show poor outcomes despite having a universal health-care system and free access to ART.

The aim of this study was to describe the clinical management and prognosis of patients who acquired HIV through the use of injected drugs (HIV-IDU) compared to patients who acquired HIV by sexual transmission (HIV-ST) during the years 2004–13 in a prospective cohort of HIV-infected patients naive to ART at study recruitment (Cohort of the Spanish HIV Research Network: CoRIS) in Spain. The specific aims were to compare HIV-IDU with HIV-ST in terms of: (1) late presentation to health care, (2) delay in the initiation of ART, (3) response to ART (taking into account the presence of primary antiretroviral resistance), (4) mortality (all-cause and cause-specific) and (5) progression to AIDS.

METHODS

Participants

Patients were included from January 2004 to May 2013. CoRIS is a prospective multi-centre cohort of adult HIV-positive subjects naive to ART at entry, recruited from 31 centres in the Spanish public health-care system [10]. The cohort details are explained in the Supporting information, Appendix S1. All patients were included for the analysis of temporal trends of the proportion of HIV-IDU in the cohort; for all the remaining analyses, we included only HIV-IDU and HIV-ST [men who have sex with men (MSM) and heterosexual], and patients with other or unknown transmission categories were excluded.

Measures

Data for the following variables were collected: date of enrolment, follow-up hospital, sex, transmission category (HIV-IDU, MSM, heterosexual, other and unknown), country of origin, education level, CD4 cell count and viral load at enrolment and at follow-up, hepatitis B [defined as positive hepatitis B virus (HBV) surface antigen (HbsAg)], hepatitis C [defined as positive hepatitis C virus (HCV) antibodies], date of treatment initiation, date of stage B or C clinical events according to the Centers for Disease Control and Prevention (CDC) classification [11], date of last follow-up visit or death and cause of death. Causes of death were coded using a modification of the CoDe protocol developed by the Copenhagen HIV programme [12]. A death was classified as AIDS-related if it was due to a disease of category C of the CDC classification [11] or Hodgkin's lymphoma, or if the cause was unknown with a CD4 count < 50 cells/μl at the time of death [13].

Patients were considered lost to follow-up if they were enrolled into the cohort at least 1 year before the end of the study (31 May 2013), there was no evidence of their death and they did not have a follow-up visit in the last year before the end of the study.

Late presentation was defined as presentation for care with a CD4 cell count < 350/μl and/or AIDS-defining illness [14].

Date of ART indication was defined as the day on which a patient first fulfilled criteria for ART initiation according to the Spanish national guidelines [15–25] current at that time (Table 1). Delayed ART initiation was defined as initiating ART more than 6 months after the date when it was indicated by the guidelines, or not initiating ART at all when it was indicated. Patients were included in this analysis only if they fulfilled criteria for ART initiation and had at least 6 months of follow-up after ART indication. Patients who started ART before it was indicated were excluded.

Virological and immunological responses were defined as viral load < 50 HIV-1 RNA copies/ml and a CD4 count increase of at least 100 cells/μl, respectively, after 1 year of treatment (closest value between 10 and 14 months).

In order to explore whether virological and immunological responses to ART were influenced by resistance to anti-retrovirals, we collected information on primary resistance for a subset of patients for which FASTA sequences were available. Resistance-associated mutations were evaluated following the World Health Organization (WHO) surveillance list [26] and resistance to any anti-retroviral group (nucleoside or non-nucleoside reverse transcriptase inhibitors, or protease inhibitors) was analysed; the detailed methodology has been described elsewhere [27].

Statistical analysis

Baseline characteristics of HIV-IDU and HIV-ST were compared using χ^2 or Fisher's exact tests.

The risk of late presentation, delayed ART initiation and virological and immunological responses were compared in HIV-IDU and HIV-ST using a multivariate logistic regression model, adjusting for potential confounding factors (age, sex, education level, country of origin, CD4 cell count, viral load, HBV and HCV infections and, for the analysis of

Table 1 Spanish guidelines' indications for initiating anti-retroviral therapy for patients with chronic HIV infection according to CD4 cell count.

	CD4 count (cells/μl)[a]			
Period	*< 200*	*< 350*	*350–500*	*> 500*
Feb 2004–Jan 2008	Always recommended	Recommended on most occasions	Not recommended	Not recommended
Feb 2008–Jan 2009			Consider in the presence of: viral load > 100,000 copies/ml, CD4 < 14%, cirrhosis, hepatitis B when its treatment is indicated, or chronic hepatitis C	Not recommended
Feb 2009–Dec 2010		Always recommended	Recommended in the presence of: viral load > 100,000 copies/ml, CD4 < 14%, cirrhosis, hepatitis B when its treatment is indicated, chronic hepatitis C, age > 55 years, high cardiovascular risk or HIV nephropathy	Consider in the presence of: viral load 100,000 copies/ml, CD4 < 14%, cirrhosis, hepatitis B when its treatment is indicated, chronic hepatitis C, age > 55 years, high cardiovascular risk or HIV nephropathy[b]
Jan 2011–Dec 2011	Always recommended	Always recommended	Always recommended	Consider in the presence of: viral load 100 000 copies/ml, CD4 < 14%, cirrhosis, hepatitis B when its treatment is indicated, chronic hepatitis C, age > 55 years, high cardiovascular risk or HIV nephropathy[b]
Jan 2012–May 2013	Always recommended	Always recommended	Always recommended	Recommend in the presence of viral load 100,000 copies/ml, CD4 < 14%, cirrhosis, hepatitis B when its treatment is indicated, chronic hepatitis C, age > 55 years, high cardiovascular risk or HIV nephropathy, or neurocognitive disorders[c]

[a]Initiation of anti-retroviral therapy is always indicated in the presence of symptoms of B or C events according to Centers for Disease Control and Prevention (CDC) classification [11] or pregnancy, regardless of CD4 count. [b]During the period from January 2010 to December 2011, the guidelines recommend considering treatment initiation in patients with CD4 count > 500 cells/μl in case of having a serodiscordant partner. [c]During the period from January 2012 to May 2013, the guidelines recommend treatment initiation in patients with CD4 count > 500 cells/μl in case of having a serodiscordant partner. Treatment of primary HIV infection is only recommended by the guidelines in these situations: severe clinical manifestations including C events according to CDC classification [11], or prolonged duration of symptoms. From 2011 treatment of primary HIV infection is also recommended if CD4 count is < 200 cells/μl or severe risk of HIV transmission. From 2012 treatment of primary HIV infection is also recommended if CD4 count is < 350 cells/μl.

delayed initiation of treatment, date of treatment indication) and evaluating interactions.

Mortality was analysed using the Kaplan–Meier method and was compared in HIV-IDU and HIV-ST with multivariate Cox regression. Patients with no follow-up were excluded from the mortality analysis. Progression to AIDS was analysed using multivariate competing risks proportional hazards regression models [28], with death being a competitive event. Patients with no follow-up or with AIDS at diagnosis were excluded from the analysis of progression

to AIDS. These analyses were adjusted for potential confounders (see above), assessing interactions between covariates and exposure group and checking the assumption of proportional risks.

In order to explore a possible misclassification bias if patients with HCV infection included in the HIV-ST group might not have disclosed use of injected drugs (and therefore should be included in the HIV-IDU group), we performed three sensitivity analyses: first, not adjusting our results by HCV (but adjusting for other variables where appropriate); secondly, excluding all patients with HCV from the HIV-ST group and thirdly, assuming that all patients with HCV in the HIV-ST group were really HIV-IDU. Robust methods were used to estimate confidence intervals (CI), assuming correlation between the subjects in each centre [29]. Wald tests were used to calculate *P*-values. All analyses were performed with a 95% confidence level. Statistical analyses were performed in STATA version 13.1 (StataCorp, College Station, TX, USA).

Ethics

All patients signed informed consent forms. The study was approved by the ethics committees of all participating hospitals.

RESULTS

Proportion of HIV-IDU over time, baseline characteristics and losses to follow-up

A total of 9667 patients were included in CoRIS during the study period, 1064 of whom (11%) had acquired HIV infection by use of injected drugs, 5312 (55%) were MSM, 2979 (31%) were heterosexuals, 118 (1%) had other transmission categories and in 194 (2%) the transmission category was unknown. The proportion of HIV-IDU among all the patients included each year declined progressively from 21.3 to 3.8% (Fig. 1).

After eliminating patients with other and unknown transmission categories, 9355 patients were included (1064 HIV-IDU and 8291 HIV-ST) into the study. Their baseline characteristics are shown in Table 2. Compared to HIV-ST, HIV-IDU had a lower proportion of university education and higher proportion of primary or no education, were more frequently of Spanish origin and had a much higher proportion of HCV infection (Table 2).

A total of 341 (33.4%) HIV-IDU and 1599 (21.5%) HIV-ST were lost to follow-up. Compared to HIV-IDU who remained in the cohort, HIV-IDU who were lost to follow-up were younger (37.9 versus 45.7%, aged < 30 years, respectively; $P = 0.041$), were more frequently foreign-born (9.6 versus 16.5% of foreign origin, respectively; $P = 0.002$) and had higher CD4 counts (41.1 versus 31.4% had < 200 cells/μl; $P = 0.007$). Compared to HIV-ST who remained in the cohort, HIV-ST who were lost to follow-up were younger (36.8 versus 48.5%, aged < 30 years, respectively; $P < 0.001$), were more frequently foreign-born (28.9 versus 48.9% of foreign origin, respectively; $P < 0.001$), had lower educational level (7.2 versus 9.8% had primary or no education; $P = 0.006$), had higher CD4 counts (24.4 versus 21.1% had < 200 cells/μl; $P = 0.019$) and had lower viral loads (33.8 versus 23.9% had viral loads > 5 $\log_{10}$ copies/ml; $P < 0.001$); these were the only significant differences.

Late presentation

Among 9245 patients who had information on CD4 count at cohort enrolment, 603 663 (63.8%) HIV-IDU and 3688 (44.9%) HIV-ST had late presentation. Compared to HIV-ST, HIV-IDU had a higher risk of late presentation [odds ratio (OR) = 2.16; 95% confidence interval (CI) = 1.58–2.95]. This risk decreased, but continued to be significantly higher, after adjusting for age at inclusion and HCV infection [adjusted OR (aOR) = 1.58 1.76; 95% CI = 1.27–1.96 1.41–22.18)] (Table 3).

Delay in ART initiation

A total of 5793 patients fulfilled criteria for treatment initiation and had a minimum of 6 months of follow-up. In univariate analysis, the risk of delayed ART initiation was not significantly different in HIV-IDU compared to HIV-ST. However, after adjusting by CD4 cell count at enrolment and HCV infection, the risk of delayed ART initiation was significantly higher in HIV-IDU (aOR = 1.87; 95% CI = 1.46–2.40) (Table 3).

Virological and immunological response to ART

ART was initiated in 6748 patients, 3897 and 4182 of whom had information on immunological and virological response after 1 year, respectively. HIV-IDU had a lower probability of immunological response compared to patients with HIV-ST in univariate analysis (OR = 0.46; 95% CI = 0.35–0.62); however, after adjusting for HCV infection, the OR of immunological response was no longer statistically significant (aOR = 0.74; 95% CI = 0.52–1.06) (Table 4). HIV-IDU had also a lower probability of virological response compared to HIV-ST in univariate analysis (OR = 0.68; 95% CI = 0.53–0.86). In the multivariable analysis of virological response we detected an interaction between transmission category and HCV infection: among patients without HCV infection, HIV-IDU continued to have a lower probability of virological response than HIV-ST (aOR = 0.59, 95% CI = 0.36–0.95), but among patients with HCV infection the probability of virological response was no longer significantly different in HIV-IDU and HIV-ST.

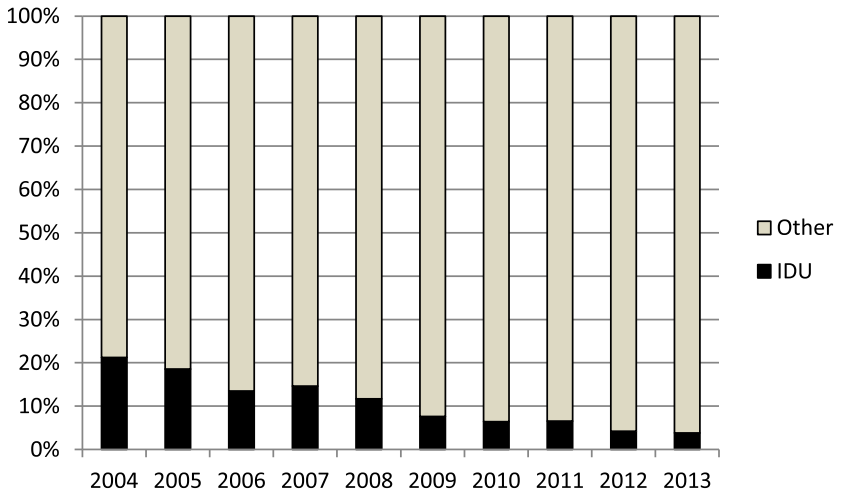

Figure 1 Proportion of injecting drug users (IDU) compared to all other transmission categories included in the cohort during the study period, by year of inclusion

In order to explore whether or not primary anti-retroviral resistance might have influenced response to treatment in HIV-IDU, we performed a subanalysis with 3576 patients for whom this information was available. Fifteen (7.6%) of 196 HIV-IDU had primary resistance to at least one class of anti-retrovirals, compared to 257 (7.6%) of 3380 HIV-ST ($P = 0.980$).

Mortality

There were 343 deaths [123 (1.5% 11.5%) among HIV-IDU and 220 (2.6%) among HIV-ST]. The cause of death was unknown in 50 patients. Among the 293 in which the cause of death was known (104 HIV-IDU and 189 HIV-ST), the number of deaths due to AIDS-related causes was 36 (34.6%) in HIV-IDU and 100 (52.9%) in HIV-ST ($P = 0.003$). The proportional causes of death are shown in Fig. 2.

After excluding patients with no follow-up, 9056 patients were followed for a median of 3.1 years (31 042 person-years). The mortality rates were 31.06 (95% CI = 26.03–31.07) in HIV-IDU and 8.12 (95% CI = 7.12–9.27) in HIV-ST per 1000 person-years, respectively (Table 5). The mortality rate was significantly higher in HIV-IDU than in HIV-ST [hazard ratio (HR) = 3.97; 95% CI = 3.20–4.93), and it remained significantly higher after adjusting for HCV infection, age and CD4 cell count at enrolment (aHR = 1.43, 95% CI = 1.03–2.01).

Progression to AIDS

After excluding patients with no follow-up or with AIDS at enrolment, 7944 patients were followed during a median of 2.8 years (25 606 person-years), 396 of whom developed AIDS during follow-up (Table 5). The risk of progression to AIDS was significantly higher in HIV-IDU compared to HIV-ST [subhazard ratio (SHR) = 2.87; 95% CI = 2.29–3.59]. This risk remained significantly higher after adjusting for HCV infection, age and CD4 cell count at enrolment (aSHR = 1.68, 95% CI = 1.29–2.18).

Sensitivity analyses for possible misclassification of patients with HCV infection

The results of the sensitivity analyses are shown in Supporting information, Appendix S2. The first sensitivity analyses (not adjusting for HCV infection) increased all risk ratios for the HIV-IDU group and also increased their statistical significance for all outcomes, particularly for mortality.

The second and third sensitivity analyses for all outcomes showed very similar results: when excluding all patients with HCV infection from the HIV-ST group (second analysis), and when assuming that all patients with HCV infection from the HIV-ST group would be in the HIV-IDU group (third analysis), our estimates were only slightly changed, with a minor decrease in statistical significance. Mortality HR decreased slightly, but lost statistical significance.

DISCUSSION

This study has analysed the clinical management and outcome of patients who acquired HIV by the use of injected drugs compared to those who acquired HIV by sexual transmission in a Spanish multi-centre cohort during the last 10 years. Although the proportion of HIV-IDU among new cohort enrolments has been declining steadily, this group continues to show late presentation, delayed HIV diagnosis and ART initiation, poorer immunological response to ART and higher risk of progression to AIDS or death compared to patients with HIV-ST.

The proportion of HIV-IDU among all other transmission categories shows a progressive decline in the last 10 years, with very similar ranges to those found among new HIV

Table 2 Baseline socio-demographic and clinical characteristics of patients who acquired HIV through the use of injected drugs (HIV-IDU) and patients with sexual HIV transmission (HIV-ST).

	HIV-IDU	*HIV-ST*	*Total*	*P*
Sex				
Male	844 (79.3)	6866 (82.8)	7710 (82.4)	0.005
Female	220 (20.7)	1425 (17.2)	1645 (17.6)	
Age at HIV diagnosis				
< 30 years	429 (40.3)	3255 (39.3)	3684 (39.4)	0.635
31–40 years	383 (36.0)	2966 (35.8)	3349 (35.8)	
> 40 years	252 (23.7)	2070 (25.0)	2322 (24.8)	
Median age at HIV diagnosis (IQR) in years	33 (27–40)	33 (27–40)	33 (27–40)	
Education				
Primary/no education	155 (14.6)	560 (6.8)	715 (7.6)	< 0.001[b]
Secondary	638 (60.0)	4333 (52.3)	4971 (53.1)	
University	41 (3.9)	2052 (24.7)	2093 (22.4)	
Unknown	230 (21.6)	1346 (16.2)	1576 (16.9)	
Country of origin				
Spain	935 (87.9)	5546 (66.9)	6481 (69.3)	< 0.001[b]
Other countries	127 (11.9)	2741 (33.1)	2868 (30.7)	
Unknown	2 (0.2)	4 (0.05)	6 (0.06)	
CD4 count at enrolment				
< 200 cells/μl	394 (37.0)	1922 (23.2)	2316 (24.8)	< 0.001[b]
201–350 cells/μl	238 (22.4)	1698 (20.5)	1936 (20.7)	
> 350 cells/μl	407 (38.3)	4586 (55.3)	4993 (53.4)	
Unknown	25 (2.3)	85 (1.0)	110 (1.2)	
Median CD4 count at enrolment (IQR), cells/μl	270 (115–477)	388 (214–586)	377 (200–576)	
Viral load at enrolment				
< 4 $\log_{10}$ copies/ml	308 (28.9)	1915 (23.1)	2223 (23.8)	< 0.001[b]
4–4.99 $\log_{10}$ copies/ml	398 (37.4)	3551 (42.8)	3949 (42.2)	
> 5 $\log_{10}$ copies/ml	339 (31.9)	2746 (33.1)	3085 (33.0)	
Unknown	19 (1.8)	79 (1.0)	98 (1.0)	
Median viral load at enrolment (IQR), $\log_{10}$ copies/ml	4.54 (3.83–5.16)	4.65 (4.05–5.15)	4.64 (4.02–5.16)	
Clinical stage at enrolment[a]				
Primary infection	16 (1.5)	208 (2.5)	224 (2.4)	< 0.001[b]
A	696 (65.4)	6332 (76.4)	7028 (75.1)	
B	124 (11.7)	625 (7.5)	749 (8.0)	
C	189 (17.8)	842 (10.2)	1,031 (11.0)	
Unknown	39 (3.7)	284 (3.4)	323 (3.5)	
HCV infection				
Yes	896 (84.2)	438 (5.3)	1334 (14.3)	< 0.001[b]
No	117 (11.0)	7514 (90.6)	7,631 (81.6)	
Unknown	51 (4.8)	339 (4.1)	390 (4.2)	
HBV infection				
Yes	61 (5.7)	332 (4.0)	393 (4.2)	0.018[b]
No	903 (84.9)	6900 (83.2)	7803 (83.4)	
Unknown	100 (9.4)	1059 (12.8)	1,159 (12.4)	
Total	1064	8291	9355	

[a]According to Centres for Disease Control and Prevention (CDC) classification [11]. [b]The categories 'unknown' were not taken into account in the comparison test. Values are expressed as *n* (%) unless stated otherwise. IDU = injected drug users; MSM = men who have sex with men; IQR = interquartile range; HCV = hepatitis C virus; HBV = hepatitis B virus.

diagnoses by the Spanish National AIDS Plan [6,7]. This confirms that the declining trend detected in previous years in the CoRIS and CoRIS-MD cohorts still continues [5]. The explanations for this decline include an overall decrease in heroin consumption as well as the use of inhaled instead of injected routes, and decreases in sharing of injection equipment due to harm reduction programmes [30–32].

PWID frequently face a number of social problems, including unemployment, low educational level, previous or present imprisonment [32], economic difficulties, lack of social and family support and associated psychiatric comorbidities [33,34]. All these factors could impair access to health services and cause a delay in HIV diagnosis and treatment initiation and lower adherence to treatment.

Table 3 Risk of late presentation and delayed initiation of treatment in patients who acquired HIV through the use of injected drugs (HIV-IDU) compared with patients with sexual HIV transmission (HIV-ST).

		Crude OR		*Adjusted OR*	
Variable	*n (%)/total*	*OR (95% CI)*	*P*	*OR (95% CI)*	*P*
Late presentation					
HIV-ST	3688 (44.9)/8206	1	<0.001	1	< 0.001
HIV-IDU	663 (63.8)/1039	2.16 (1.58–2.95)		1.76 (1.41–2.18)[a]	
Total	4351 (47.1)/9245				
Delayed treatment initiation					
HIV-ST	1416 (27.9)/5076	1	0.277	1	< 0.001
HIV-IDU	232 (32.4)/717	1.23 (0.84–1.81)		1.87 (1.46–2.40)[b]	
Total	1648 (28.5)/5793				

OR = odds ratio; CI = confidence interval. [a]Adjusted for hepatitis C virus infection and age at inclusion; [b]adjusted for CD4 cell count at enrolment and hepatitis C virus infection.

Table 4 Virological and immunological response to anti-retroviral treatment in patients who acquired HIV through the use of injected drugs (HIV-IDU) compared to patients with sexual HIV transmission (HIV-ST).

	Patients with response [n (%)]/total	*Crude OR (95% CI)*	*P*	*Adjusted OR (95% CI)*	*P*
Immunological response					
HIV-ST	2809 (80.2)/3504	1	< 0.001	1	0.098
HIV-IDU	256 (65.1)/393	0.46 (0.35–0.62)		0.74 (0.52–1.06)[a]	
Total	3065 (78.7)/3897				
Virological response					
HIV-ST	3197 (85.3)/3746	1	< 0.001	1	
HIV-IDU	348 (79.8)/436	0.68 (0.53–0.86)		No HCV: 0.59 (0.36–0.95)	0.031
				With HCV: 1.37 (0.81–2.33)	0.238
Total	3545 (84.8)/4182				

OR = odds ratio; CI = confidence interval. [a]Adjusted for hepatitis C virus infection.

Our study shows that HIV-IDU have a high risk of late presentation to clinical care. This could be due not only to the high risk of late diagnosis, but also to lack of access to health-care services after HIV diagnosis. Although diagnostic delay has been described in Spanish PWID [9,35], other studies from Spain [36,37] and elsewhere [38–42] show a lower risk of late presentation and delayed HIV diagnosis compared to other transmission categories. These discrepancies could be due to the analysis of different populations that can vary in the access of PWID to health services, the perception of risk of HIV among different groups or the programmes for HIV diagnosis in specific risk groups.

The delayed initiation of ART in PWID has been described in several studies [1,3,43–45], including one in this same cohort [46]. The HIV-IDU in our sample are a select group of patients who have already accessed the medical system, and their delayed treatment initiation cannot be explained by the diagnostic delay or lack of first contact with a health-care provider. Socio-economic reasons would probably have a limited effect in a health-care system with universal access and free ART. The reasons for delayed treatment are probably multiple, and could include individual factors (such as lack of confidence in the treatment or the health-care system), structural factors [1] that limit the retention in health care of HIV-IDU and factors associated with the prescribing physicians, who might withhold the treatment due to concerns about perceived risk of low adherence, interactions with other drugs or methadone or liver toxicity in patients with chronic hepatitis.

Response to treatment was lower in HIV-IDU than in HIV-ST, and this was due in large part to co-infection with HCV. In univariate analysis, virological and immunological responses were lower in HIV-IDU than in HIV-ST; however, after adjusting by HCV infection, immunological response was no longer significantly different, and virological response was lower in HIV-IDU only among patients without HCV infection. Previous studies found conflicting results, showing either a lower virological [3,47,48] and immunological [47] response or no differences in PWID compared to other transmission categories [44,49,50]. However, these results are limited, because none of these studies considered HCV infection in their analysis. A recent meta-analysis found that patients co-infected with HIV and HCV had a lower immunological response but a similar virological response than HIV-infected patients without hepatitis C [51]. HCV could impair response to anti-

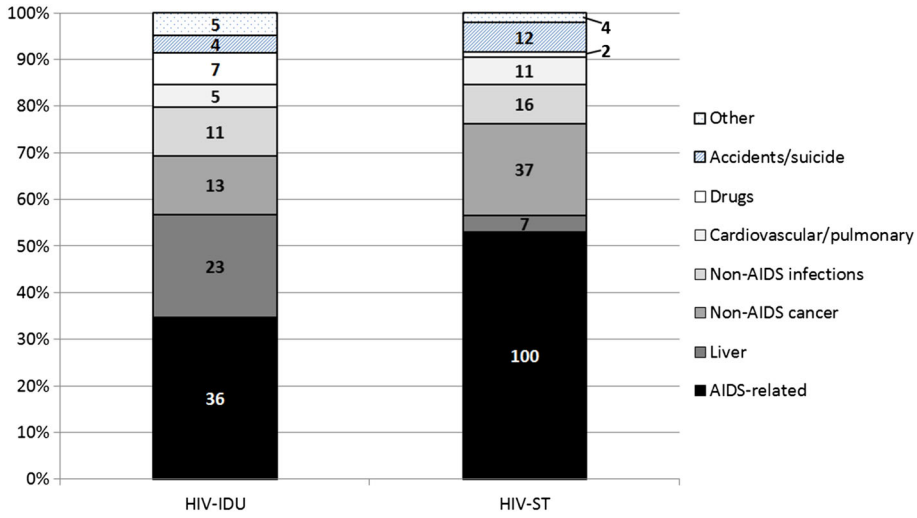

Figure 2 Causes of death in patients who acquired HIV through injection drug use (HIV-IDU) compared to patients with sexual HIV transmission (HIV-ST), displayed as proportion of total deaths in patients with known death cause. Total number of deaths due to each cause are displayed in the bars. The number of deaths (%) due to AIDS-related causes was distributed as follows: in HIV-IDU, 13 (36.1%) tuberculosis, seven (19.4%) non-Hodgkin lymphoma, six (16.7%) progressive multi-focal leucoencephalopathy, four (11.1%) *Pneumocystis jiroveci* pneumonia, three (8.3%) cerebral toxoplasmosis, one (2.8%) esophageal candidiasis, one (2.8%) recurrent pneumonia, one (2.8%) unknown cause with CD4 count < 50 cells/μl. In HIV-ST, 25 (25%) non-Hodgkin lymphoma, 21 (21%) *P. jiroveci* pneumonia, 14 (14%) chronic progressive multi-focal leucoencephalopathy, eight (8%) Kaposi's sarcoma, six (6%) tuberculosis, five (5%) cerebral toxoplasmosis, five (5%) cytomegalovirus disease, three (3%) Hodgkin's lymphoma, three (3%) HIV wasting syndrome, two (2%) cervical carcinoma, two (2%) recurrent pneumonia, two (2%) unknown cause with CD4 count < 50 cells/μl, one (1%) extrapulmonary cryptococcosis, one (1%) disseminated histoplasmosis, one (1%) oesophageal candidiasis, one (1%) candidiasis of bronchi, trachea or lungs. The number of deaths classified as 'Other' was distributed as follows: in HIV-IDU, one lactic acidosis, one digestive haemorrhage, one acute pancreatitis, one viral central nervous system infection, one hypoxic encephalopathy. In HIV-ST, one digestive haemorrhage, one intestinal ischaemia, one renal failure, one meningitis of unknown cause

Table 5 Risk of death and progression to AIDS in patients who acquired HIV through the use of injected drugs (HIV-IDU) compared to patients with sexual HIV transmission (HIV-ST).

Mortality

Transmission	*Events (n)*	*Rate per 1000 person-years*	*Crude HR (95% CI)*	*P*	*Adjusted HR (95% CI)*	*P*
HIV-ST	220	8.12 (7.12–9.27)	1		1	0.037
HIV-IDU	123	31.06 (26.03–31.07)	3.97 (3.20–4.93)	<0.001	1.43 (1.03–2.01)[a]	
Total	343	11.05 (9.94–12.29)				

Progression to AIDS

Transmission	*Events (n)*	*Rate per 1000 person-years*	*Crude SHR (95% CI)*	*P*	*Adjusted SHR (95% CI)*	*P*
HIV-ST	293	12.87 (11.48–14.43)	1	<0.001	1	<0.001
HIV-IDU	103	36.25 (29.88–43.97)	2.87 (2.29–3.59)		1.68 (1.29–2.18)[a]	
Total	396	15.46 (14.01–17.07)				

HR = hazard ratio; SHR = subhazard ratio; CI = confidence interval. [a]Adjusted for hepatitis C infection, CD4 count and age at enrolment.

retroviral treatment by different mechanisms, such as induction of CD4 cell apoptosis, increased immune activation [51] or hepatotoxicity of anti-retroviral drugs that could impair adherence to treatment.

As found by previous research [3,39,45], the risk of progression to AIDS and death was higher in HIV-IDU than in HIV-ST. The proportion of deaths due to non-AIDS related causes was significantly higher in HIV-IDU: this was due largely to liver-related mortality, which is not surprising considering the high prevalence of HCV co-infection in these patients. Liver diseases were responsible for almost a quarter of deaths among HIV-IDU, a proportion which was much higher than deaths due to external causes or drug effects. However, HCV does not fully explain the higher risk of death and progression to AIDS, as these risks were still significantly higher in HIV-IDU after adjusting for HCV infection.

Our cohort has several strengths: a large number of patients with long-term prospective follow-up, a representative sample of the Spanish territory, thorough quality control for data collection and free unrestricted access to ART. However, it has several limitations. We have information on patients who acquired HIV by the use of injected drugs, but we do not know whether these patients were still using injected drugs at cohort entry: therefore, we cannot analyse the effect of active drug use in our results. We do not have information on adherence to therapy, on associated consumption of alcohol or non-injected drugs or whether the patients are receiving opioid substitution therapy. All these variables can influence the delay of ART initiation, response to ART and progression to AIDS or death. It is likely that many of our patients in the HIV-IDU group might not be using injected drugs actively: a small study with 421 patients in our cohort found that only 12% of HIV-UDI declared recent use of injected drugs [52].

That the definition of chronic HCV infection was based on positive serology is a limitation of our study. However, as spontaneous clearance of HCV is infrequent in HIV-infected patients [53,54], we believe this is unlikely to influence our results strongly. Also, there is a possibility of misclassification bias if patients with HCV infection who were included in the HIV-ST group might have not disclosed previous use of injected drugs, and therefore should really be included in the HIV-IDU group. Our sensitivity analyses suggest that this would not modify our results substantially: even assuming that all patients with HCV infection from the HIV-ST group would be in the HIV-IDU group, our estimates were barely changed, except for the adjusted mortality analyses which lost statistical significance.

The generalizability of our findings is limited, as this cohort includes only patients who have contacted a health-care centre. Because the clinical follow-up of HIV-infected patients in Spain is conducted almost entirely in hospitals, it is reasonable to assume that HIV-IDU who have not accessed the health-care system would have even worse outcomes than our patients. Also, we have a high number of patients lost to follow-up, especially among HIV-IDU, which could affect our estimates of mortality and progression to AIDS. However, this does not modify our findings substantially. Among HIV-ST (but not among HIV-IDU), patients lost to follow-up had lower education level and had lower viral loads than those who remained in the cohort: this could bias our estimates of progression to AIDS or death towards the unit. We could therefore assume that, had there been fewer losses to follow-up, the risk of progression to AIDS or death in HIV-IDU would have been even higher. In order to investigate the effects of losses to follow-up in our results, we repeated the mortality analysis using competing risks proportional hazards regression, considering losses to follow-up a competitive event: our results were not changed (data not shown).

This study shows that although the proportion of HIV-IDU among all HIV-infected patients is declining, they merit special attention due to late presentation, late initiation of treatment and higher mortality and risk of AIDS. Although specific strategies targeting these patients are needed to improve their clinical care, recommendations aimed specifically at PWID are extremely scarce in HIV clinical practice guidelines [1,33,55]. Several strategies have been shown to improve adherence and response to ART in HIV-IDU, such as methadone substitution programmes, access to multi-disciplinary support centres and directly observed therapy [1,33,49,56–59]. Given that the present system of HIV diagnosis in health-care settings is not providing an early diagnosis in these patients, alternative diagnostic strategies such as outreach services should also be considered. Mortality remains higher in HIV-IDU, and liver diseases have become an important cause of death.

Declaration of interests

None.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Appendix S1 Centres and investigators involved in CoRIS.
Appendix S2 Sensitivity analyses for possible misclassification of patients with HCV infection.