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ORIGINAL RESEARCH

# Epidemiological trends of HIV/HCV coinfection in Spain, 2015–2019

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[Correction added on 21 March 2022, after first online publication: the affiliations of Antonio Rivero-Román have been corrected in this version.]

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## Abstract

**Objectives:** We assessed the prevalence of anti-hepatitis C virus (HCV) antibodies and active HCV infection (HCV-RNA-positive) in people living with HIV (PLWH) in Spain in 2019 and compared the results with those of four similar studies performed during 2015–2018.

**Methods:** The study was performed in 41 centres. Sample size was estimated for an accuracy of 1%. Patients were selected by random sampling with proportional allocation.

**Results:** The reference population comprised 41 973 PLWH, and the sample size was 1325. HCV serostatus was known in 1316 PLWH (99.3%), of whom 376 (28.6%) were HCV antibody (Ab)-positive (78.7% were prior injection drug users); 29 were HCV-RNA-positive (2.2%). Of the 29 HCV-RNA-positive PLWH, infection was chronic in 24, it was acute/recent in one, and it was of unknown duration in four. Cirrhosis was present in 71 (5.4%) PLWH overall, three (10.3%) HCV-RNA-positive patients and 68 (23.4%) of those who cleared HCV after anti-HCV therapy ($p = 0.04$). The prevalence of anti-HCV antibodies decreased steadily from 37.7% in 2015 to 28.6% in 2019 ($p < 0.001$); the prevalence of active HCV infection decreased from 22.1% in 2015 to 2.2% in 2019 ($p < 0.001$). Uptake of anti-HCV treatment increased from 53.9% in 2015 to 95.0% in 2019 ($p < 0.001$).

**Conclusions:** In Spain, the prevalence of active HCV infection among PLWH at the end of 2019 was 2.2%, i.e. 90.0% lower than in 2015. Increased exposure to DAAs was probably the main reason for this sharp reduction. Despite the high coverage of treatment with direct-acting antiviral agents, HCV-related cirrhosis remains significant in this population.

**KEYWORDS**
coinfection/*epidemiology, hepatitis C/drug therapy/*epidemiology, HIV infection/*epidemiology

## INTRODUCTION

Coinfection by hepatitis C virus (HCV) is a common complication in people living with HIV (PLWH) acquired mainly through injection drug use (IDU) [1] or sexual practices with a high risk of mucosal transmission in the case of men who have sex with men (MSM) [2]. HIV infection modifies the natural history of HCV, increasing

chronic infection rates [3], accelerating liver fibrosis [4] and hastening progression to end-stage liver disease [5]. However, the harmful effect of HIV infection on the natural history of hepatitis C can be mitigated with effective ART [6].

The introduction of direct-acting antiviral agents (DAAs) against HCV has revolutionized the treatment of hepatitis C, particularly among HIV/HCV-coinfected patients and those with decompensated cirrhosis, both of which are groups that were considered difficult to treat in the interferon + ribavirin era [7]. The benefits of HCV clearance following anti-HCV therapy in coinfected people include a reduction in liver-related complications and mortality [8], a decrease in HIV progression and morbidity and mortality not related to liver disease [9], and a reduced risk of transmission of HCV [10].

The epidemiology of HIV/HCV coinfection is poorly known in many European countries and is subject to variability depending on testing and changes in the factors that determine the transmission of each virus [11]. Of great significance has been the decrease in IDU as a mechanism fuelling the HIV and HCV epidemics in some countries, including Spain [12], and the greater mortality associated with HIV/HCV coinfection than with HIV monoinfection [13]. In addition, the lack of protective immunity against HCV favours reinfection after viral clearance when practices with a high risk of transmission are maintained [14]. This phenomenon is even more concerning because of the growing number of HCV infections among HIV-negative MSM on pre-exposure prophylaxis against HIV [15] who engage in transmission networks involving HIV-infected MSM [16]. One mitigating factor is the scale-up of DAA treatment, which can decrease the population HCV burden and, consequently, the risk of new HCV infections despite ongoing high-risk transmission practices [17]. All these factors provide solid arguments for active monitoring of the burden of HIV/HCV coinfection.

Here, we present data from a nationwide study of the prevalence of HIV/HCV coinfection in Spain in 2019 and compare the results with those of four similar studies performed during 2015–2018.

## PATIENTS AND METHODS

The study was carried out by AIDS Study Group ['Grupo de Estudio del SIDA' (GeSIDA) of the Spanish Society of Infectious Diseases and Clinical Microbiology ('Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica' (SEIMC)] between 1 October 2019 and 30 November 2019. The Institutional Ethics Committee of Hospital General Universitario Gregorio Marañón approved the study and waived the requirement for written informed consent, as it was based on anonymous, routine clinical data intended for scientific publication.

### Study design and sample size estimation

The study was performed in 41 hospitals throughout Spain following a methodology similar to that used in four previous studies performed yearly from 2015 to 2018 [18–21].

The reference population consisted solely of PLWH in active follow-up in the participating centres, defined as at least one visit to the centre in the previous 12 months. Before the study was initiated, the total number of PLWH in active follow-up at the participating centres was 41 973, and the prevalence of active HCV infection according to the most recent survey carried out by GeSIDA in 2018 was 3.7% [22]. Based on these figures, we estimated that a sample of at least 1325 PLWH was needed for a confidence level of 95%, a design effect of 1.0, and an accuracy for the sample size of 1.0%. The PLWH were selected by simple random sampling with proportional allocation.

### Investigations

The sources of data were the medical records. We collected demographics, HIV transmission category, Centers for Diseases Control and Prevention (CDC) disease category, current CD4 T-cell counts, current HIV-RNA load, whether PLWH were on ART, and the ART regimen used. We also enquired about the presence of hepatitis B virus surface antigen (HBsAg), the presence of HCV antibodies, and – if applicable – HCV-RNA. Those PLWH receiving anti-HCV therapy at the time the study was performed were considered to be HCV-RNA-positive. In PLWH who were HCV-RNA-positive, information was requested regarding the time since diagnosis of HCV infection (< 12 months or ≥ 12 months) and HCV genotype and subtype. In PLWH with HCV antibodies, information was also obtained about prior anti-HCV therapy and, if applicable, the regimens used and their outcomes. In PLWH with active HCV infection who were not receiving anti-HCV therapy, the reasons for not receiving treatment were requested. In PLWH with HCV antibodies and negative HCV-RNA, we queried whether this was due to spontaneous clearance or anti-HCV treatment. In PLWH who were positive for HCV-RNA or HBsAg, transient elastography results and the date the procedure was performed were recorded.

Cirrhosis was investigated in all PLWH, as was the method of diagnosis, namely, liver biopsy, transient elastography (liver stiffness > 12.5 kPa) or clinical/biological findings. The Fibrosis-4 (FIB-4) score was also calculated, and values ≥ 3.25 were considered indicative

of advanced liver fibrosis/cirrhosis. In PLWH with cirrhosis, current Child-Pugh and model for end-stage liver disease (MELD) scores were recorded. We calculated anti-HCV treatment uptake, defined as the percentage of PLWH with current infection or past chronic HCV infection exposed to anti-HCV therapy. All the information was recorded at each institution using an online electronic case report form.

## Statistics

A descriptive analysis was carried out using frequency tables for categorical variables and mean and standard deviation (SD) or median and interquartile range (IQR), respectively, for normally and non-normally distributed continuous variables. We used the $\chi^2$ test of independence to detect significant differences in categorical variables and the *t*-test or Mann–Whitney test for differences in normally or non-normally distributed continuous variables, respectively. All statistical analyses were performed using Stata (v.14.0; StataCorp).

# RESULTS

A total of 41 centres participated in the study. The reference population consisted of 41 973 PLWH, and the sample size was 1325 PLWH.

## Prevalence of HIV/HCV coinfection

In the 2019 prevalence study, HCV serostatus was known in 1316 of 1325 PLWH (99.3%), 376 of whom were HCV-seropositive. Of these 376 PLWH, 29 were HCV-RNA-positive, 291 were HCV-RNA-negative following anti-HCV therapy, and 55 cleared HCV spontaneously; HCV-RNA results were unknown in one. Therefore, the prevalence of anti-HCV antibodies was 28.6% [95% confidence interval (CI): 26.1–31.1%], and the prevalence of active HCV infection was 2.2% (1.5–3.1%).

## Characteristics of PLWH

The characteristics of the PLWH included in the 2019 seroprevalence study are summarized in Table 1. No significant differences were found for sex between HCV-seronegative PLWH and HCV-seropositive PLWH, although the latter were, on average, 7 years older than the former. The frequency of IDU was significantly higher among HCV-seropositive PLWH than among HCV-seronegative PLWH. HBsAg positivity was more frequent in HCV-seropositive PLWH than in HCV-seronegative PLWH (4.3% vs. 2.3%; $p = 0.036$).

More HCV-seropositive than HCV-seronegative PLWH were in CDC category C (25.0% vs 18.3%; $p = 0.015$). Overall, 98.0% were on ART, with a small but statistically significant difference between HCV-seronegative and HCV-seropositive patients (98.5% vs. 96.8%; $p = 0.024$). Compared with HCV-seronegative PLWH, a lower proportion of HCV-seropositive PLWH were on a first-line ART regimen (17.6% vs. 4.9%, respectively; $p < 0.001$). Significant differences were also found between HCV-seronegative and HCV-seropositive PLWH in the distribution of ART regimens, with a higher frequency of integrase strand transfer inhibitors and nonnucleoside reverse transcriptase inhibitors as the anchor drugs among the former ($p = 0.03$). The proportion of PLWH with an HIV-RNA load < 50 copies/mL was 91.5% overall and 92.6% in those receiving ART, with no significant differences in this regard between HCV-seropositive and HCV-seronegative PLWH. Statistically significantly lower CD4 T-cell counts were found among HCV-seropositive PLWH than among HCV-seronegative PLWH overall (643 vs. 707 cells/μL; $p < 0.001$) and in those on ART (640 vs. 710 cells/μL; $p < 0.001$).

## Characteristics of liver disease in HIV/HCV-coinfected PLWH

The characteristics of liver disease in the 29 PLWH with active HCV infection identified in 2019 are shown in Table S1. None were considered to have HCV reinfection. The infection had occurred within the previous 12 months in only one out of 25 with a known date of diagnosis. Eleven of the 29 PLWH with active HCV infection (37.9%) received oral DAA therapy during the study period but were considered infected by definition, and four (13.8%) were due to initiate treatment. The main reasons for not being on or having programmed therapy were physician decision ($N = 5$), unknown ($N = 4$), loss to follow-up ($N = 3$) and patient refusal ($N = 2$). Liver cirrhosis was present in three out of 29 (10.3%) PLWH with active HCV infection, all with compensated liver disease, and in 68 out of 291 (23.4%) PLWH who cleared HCV following anti-HCV therapy. The main features of liver cirrhosis in PLWH with active HCV infection and those who cleared HCV infection following anti-HCV therapy are shown in Table S2.

## Trends in HIV/HCV coinfection, 2015–2019

We compared the 2019 results with those from studies carried out yearly from 2015 to 2018 in a similar number of

**TABLE 1** Baseline characteristics of the 1325 individuals with HIV included in the study

| Characteristic | HCV antibodies | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | | Positive | | | | | | | |
| | Unknown $N = 9$ | HCV RNA+ $N = 29$ | HCV RNA-negative post treatment $N = 291$ | HCV RNA-negative spontaneous clearance $N = 55$ | HCV RNA unknown $N = 1$ | Total HCV positive $N = 376$ | Negative $N = 940$ | $p$[a] | $N = 1325$ |
| Sex [*n* (%)] | | | | | | | | | |
| Male | 8 (88.9) | 23 (79.3) | 224 (77.0) | 34 (61.8) | 1 (100.0) | 282 (75.0) | 709 (75.4) | 0.894 | 999 (75.4) |
| Female | 0 | 6 (20.7) | 67 (23.0) | 20 (36.4) | 0 | 93 (24.7) | 227 (24.1) | | 320 (24.1) |
| Unknown | 1 (11.1) | 0 | 0 | 1 (1.8) | 0 | 1 (0.3) | 4 (0.4) | | 6 (0.5) |
| Age (years) [mean (SD)] | 50 (18) | 53 (7) | 54 (7) | 54 (7) | 64 (-) | 54 (7) | 47 (12) | < 0.001 | 49 (12) |
| HIV transmission category [*n* (%)] | | | | | | | | | |
| Injection drug use | 0 | 25 (86.2) | 231 (79.4) | 40 (72.7) | 0 | 296 (78.7) | 44 (4.7) | < 0.001 | 340 (25.7) |
| Heterosexual | 2 (22.2) | 2 (6.9) | 18 (6.2) | 9 (16.4) | 0 | 29 (7.7) | 307 (32.7) | | 338 (25.5) |
| MSM | 5 (55.6) | 2 (6.9) | 24 (8.2) | 3 (5.4) | 0 | 29 (7.7) | 500 (53.2) | | 534 (40.3) |
| Contaminated blood products | 0 | 0 | 6 (2.1) | 1 (1.8) | 0 | 7 (1.9) | 4 (0.4) | | 11 (0.8) |
| Mother-to-child transmission | 0 | 0 | 2 (0.7) | 0 | 0 | 2 (0.5) | 17 (1.8) | | 19 (1.4) |
| Other | 2 (22.2) | 0 | 9 (3.1) | 2 (3.6) | 1 (100.0) | 12 (3.2) | 67 (7.1) | | 81 (6.1) |
| Unknown | 0 | 0 | 1 (0.3) | 0 | 0 | 1 (0.3) | 1 (0.1) | | 2 (0.2) |
| CDC clinical category C [*n* (%)] | | | | | | | | | |
| No | 6 (66.7) | 17 (58.6) | 219 (75.3) | 39 (70.9) | 1 (100.0) | 276 (73.4) | 758 (80.6) | 0.015 | 1040 (78.5) |
| Yes | 2 (22.2) | 11 (37.9) | 70 (24.0) | 13 (23.6) | 0 | 94 (25.0) | 172 (18.3) | | 268 (20.2) |
| Unknown | 1 (11.1) | 1 (3.5) | 2 (0.7) | 3 (5.5) | 0 | 6 (1.6) | 10 (1.1) | | 17 (1.3) |
| HBsAg [*n* (%)] | | | | | | | | | |
| Negative | 3 (33.3) | 25 (86.2) | 274 (94.2) | 49 (89.1) | 1 (100.0) | 349 (92.8) | 904 (96.2) | 0.036 | 1256 (94.8) |
| Positive | 0 | 2 (6.9) | 10 (3.4) | 4 (7.3) | 0 | 16 (4.3) | 22 (2.3) | | 38 (2.9) |
| Unknown | 6 (66.7) | 2 (6.9) | 7 (2.4) | 2 (3.6) | 0 | 11 (2.9) | 14 (1.5) | | 31 (2.3) |
| ART [*n* (%)] | | | | | | | | | |
| No | 0 | 0 | 5 (1.7) | 3 (5.5) | 0 | 8 (2.1) | 13 (1.4) | 0.024 | 21 (1.6) |
| Yes | 8 (88.9) | 29 (100.0) | 283 (97.3) | 51 (92.7) | 1 (100.0) | 364 (96.8) | 926 (98.5) | | 1298 (98.0) |
| Unknown | 1 (11.1) | 0 | 3 (1.0) | 1 (1.8) | 0 | 4 (1.1) | 1 (0.1) | | 6 (0.4) |

(Continues)

TABLE 1 (Continued)

| Characteristic | HCV antibodies | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | | Positive | | | | | | | |
| | Unknown $N = 9$ | HCV RNA+ $N = 29$ | HCV RNA-negative post treatment $N = 291$ | HCV RNA-negative spontaneous clearance $N = 55$ | HCV RNA unknown $N = 1$ | Total HCV positive $N = 376$ | Negative $N = 940$ | $p$[a] | $N = 1325$ |
| Category of ART regimen [*n* (%)] | | | | | | | | | |
| First-line therapy | 1 (12.5) | 4 (13.8) | 10 (3.5) | 4 (7.8) | 0 | 18 (4.9) | 163 (17.6) | < 0.001 | 182 (14.0) |
| Switch unrelated to toxicity/ failure | 3 (37.5) | 17 (58.6) | 172 (60.8) | 36 (70.6) | 1 (100.0) | 226 (62.1) | 546 (59.0) | | 775 (59.7) |
| Switch following failure | 2 (25.0) | 3 (10.3) | 21 (7.4) | 3 (5.9) | 0 | 27 (7.4) | 45 (4.9) | | 74 (5.7) |
| Switch following toxicity | 2 (25.0) | 5 (17.2) | 72 (25.4) | 7 (13.7) | 0 | 84 (23.1) | 155 (16.7) | | 241 (18.6) |
| Clinical trial | 0 | 0 | 4 (1.4) | 1 (2.0) | 0 | 5 (1.4) | 15 (1.6) | | 20 (1.5) |
| Unknown | 0 | 0 | 4 (1.4) | 0 | 0 | 4 (1.1) | 2 (0.2) | | 6 (0.5) |
| Type of ART regimen [*n* (%)] | | | | | | | | | |
| Two NRTIs + one NNRTI | 1 (12.5) | 0 | 47 (16.6) | 13 (25.5) | 0 | 60 (16.5) | 190 (20.5) | 0.034 | 251 (19.3) |
| Two NRTIs + one PI | 1 (12.5) | 13 (44.8) | 49 (17.3) | 9 (17.6) | 0 | 71 (19.5) | 123 (13.3) | | 195 (15.0) |
| Two NRTIs + one integrase inhibitor | 5 (62.5) | 11 (37.9) | 121 (42.8) | 19 (37.2) | 0 | 151 (41.5) | 446 (48.2) | | 602 (46.4) |
| Dual therapy: DTG + 3TC or RPV | 0 | 1 (3.4) | 25 (8.8) | 1 (2.0) | 1 (100.0) | 28 (7.7) | 59 (6.4) | | 87 (6.7) |
| Dual therapy: PI + 3TC | 0 | 0 | 9 (3.2) | 3 (5.9) | 0 | 12 (3.3) | 25 (2.7) | | 37 (2.8) |
| Other dual therapy combinations | 1 (12.5) | 1 (3.4) | 11 (3.9) | 5 (9.8) | 0 | 17 (4.7) | 32 (3.5) | | 50 (3.8) |
| PI-based monotherapy | 0 | 0 | 13 (4.6) | 1 (2.0) | 0 | 14 (3.8) | 23 (2.5) | | 37 (2.8) |
| Other | 0 | 3 (10.3) | 8 (2.8) | 0 | 0 | 11 (3.0) | 28 (3.0) | | 39 (3.0) |
| CD4+ – T cells/μL [median (IQR)] | | | | | | | | | |
| All patients | 809 (510–920) | 604 (365–744) | 640 (398–872) | 691 (470–881) | 724 (724–724) | 643 (404–866) | 707 (530–947) | < 0.001 | 694 (481–930) |
| Patients on ART | 809 (510–920) | 604 (365–744) | 640 (398–867) | 669 (470–890) | 724 (724–724) | 640 (402–866) | 710 (536–951) | < 0.001 | 696 (486–930) |

TABLE 1 (Continued)

| Characteristic | HCV antibodies | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | | Positive | | | | | | | |
| | Unknown $N = 9$ | HCV RNA+ $N = 29$ | HCV RNA-negative post treatment $N = 291$ | HCV RNA-negative spontaneous clearance $N = 55$ | HCV RNA unknown $N = 1$ | Total HCV positive $N = 376$ | Negative $N = 940$ | $p$[a] | $N = 1325$ |
| HIV RNA copies/mL [$n$ (%)] | | | | | | | | | |
| All patients | | | | | | | | | |
| < 50 | 8 (88.9) | 23 (79.3) | 266 (91.4) | 53 (96.4) | 1 (100.0) | 343 (91.2) | 861 (91.6) | 0.860 | 1212 (91.5) |
| 50–200 | 0 | 2 (6.9) | 13 (4.5) | 0 | 0 | 15 (4.0) | 42 (4.5) | | 57 (4.3) |
| > 200 | 0 | 4 (13.8) | 10 (3.4) | 2 (3.6) | 0 | 16 (4.3) | 34 (3.6) | | 50 (3.8) |
| Unknown | 1 (11.1) | 0 | 2 (0.7) | 0 | 0 | 2 (0.5) | 3 (0.3) | | 6 (0.4) |
| Patients on ART | | | | | | | | | |
| < 50 | 8 (100.0) | 23 (79.3) | 262 (92.6) | 50 (98.0) | 1 (100.0) | 336 (92.3) | 858 (92.7) | 0.516 | 1202 (92.6) |
| 50–200 | 0 | 2 (6.9) | 11 (3.9) | 0 | 0 | 13 (3.6) | 42 (4.5) | | 55 (4.2) |
| > 200 | 0 | 4 (13.8) | 9 (3.2) | 1 (2.0) | 0 | 14 (3.8) | 23 (2.5) | | 37 (2.9) |
| Unknown | 0 | 0 | 1 (0.3) | 0 | 0 | 1 (0.3) | 3 (0.3) | | 4 (0.3) |

Abbreviations: ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; IQR, interquartile range; MSM, men who have sex with men; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; RNA, ribonucleic acid; SD, standard deviation.

[a]$p$-values for the comparisons between HCV-positive patients ($N = 385$) and HCV-negative patients ($N = 940$) derived from the $\chi^2$ test for independence for categorical variables and the $t$-test or the nonparametric Mann–Whitney test for normally or non-normally distributed continuous variables, respectively.

centres distributed throughout Spain [20–23]. A summary of participating centres, the reference population and the sample size of the previous GeSIDA prevalence studies is shown in Table 2.

Men who have sex with men and IDU were the main HIV transmission categories among PLWH in all the prevalence studies. From 2015 to 2019, the proportion of MSM increased from 35.1% to 40.3% ($p$ trend = 0.004), and the proportion of IDU declined from 30.7% to 25.7% ($p$ trend = 0.004) (Figure S1).

Prevalence trends of anti-HCV antibodies and active HCV infections among PLWH from 2015 to 2019 are shown in Figure 1. The prevalence of anti-HCV antibodies decreased steadily from 37.7% in 2015 to 28.6% in 2019 ($p$ trend < 0.001), whereas the prevalence of active HCV infection decreased sharply from 22.1% in 2015 to 2.2% in 2019 ($p$ trend < 0.001).

Prevalence trends of HCV seropositivity and active HCV infections among PLWH categorized by HIV transmission category groups are shown in Figure 2. Over the years, HCV coinfection has been at its highest in those acquiring HIV by IDU, while MSM have contributed little to the total burden of HCV infection among PLWH. Decreasing trends in HCV markers, particularly HCV-RNA, were observed among IDUs (from 55.7% in 2015 to 7.3% in 2019) and those in other/unknown transmission categories (from 13.4% in 2015 to 0.4% in 2019). A decreasing trend in HCV markers of infection was not observed among MSM. In this group, the prevalence of active HCV infection remained under 2.5% throughout the study period, with a peak of 2.2% in 2016 and a trough of 0.4% in 2019.

As shown in Figure 3, uptake of anti-HCV treatment increased significantly from 59.3% in 2015 to 95.0% in 2016.

## DISCUSSION

In this cross-sectional study performed in Spain at the end of 2019, almost one-third of PLWH were seropositive for HCV, and approximately 2% had active HCV infection. We also found that over the period 2015–2019, the prevalence of active HCV declined by 90% and the uptake of DAA treatment increased significantly, reaching 95%.

**TABLE 2** Centres and patients included in the nationwide hepatitis C virus (HCV) prevalence studies carried out by the 'Grupo de Estudio del SIDA' (GeSIDA) (2015–2019)

| Year [reference] | 2015 | 2016 | 2017 | 2018 | 2019 |
|---|---|---|---|---|---|
| Centres | 41 | 43 | 43 | 43 | 41 |
| Reference population | 35 791 | 38 904 | 40 322 | 40 650 | 41 973 |
| Sample size | 1867 | 1588 | 1690 | 1733 | 1325 |
| Tested for HCV antibodies | 98.7% | 99.8% | 99.1% | 99.3% | 99.3% |

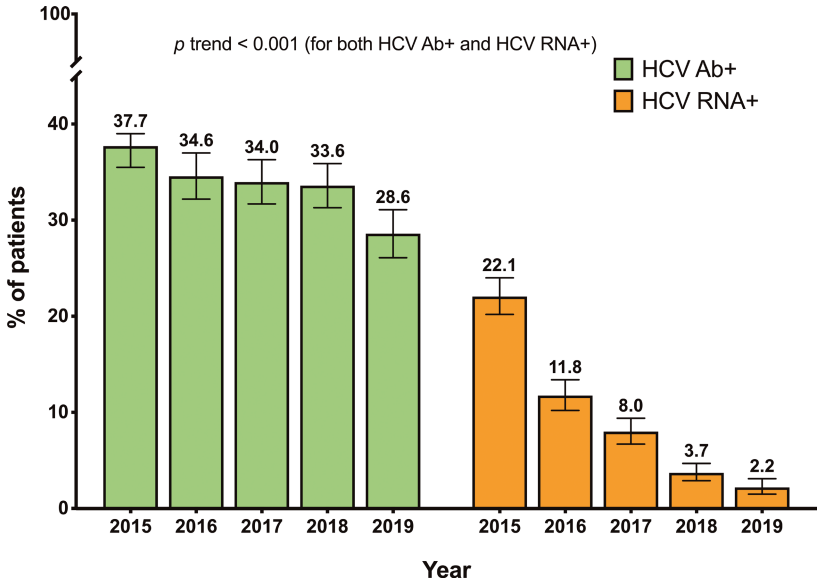


**FIGURE 1** Prevalence of hepatitis C virus (HCV) seropositivity and active HCV infection in the annual cross-sectional studies carried out by 'Grupo de Estudio del SIDA' (GeSIDA) from 2015 to 2019. HCV Ab+, presence of antibodies against HCV; HCV-RNA+, detectable HCV-RNA

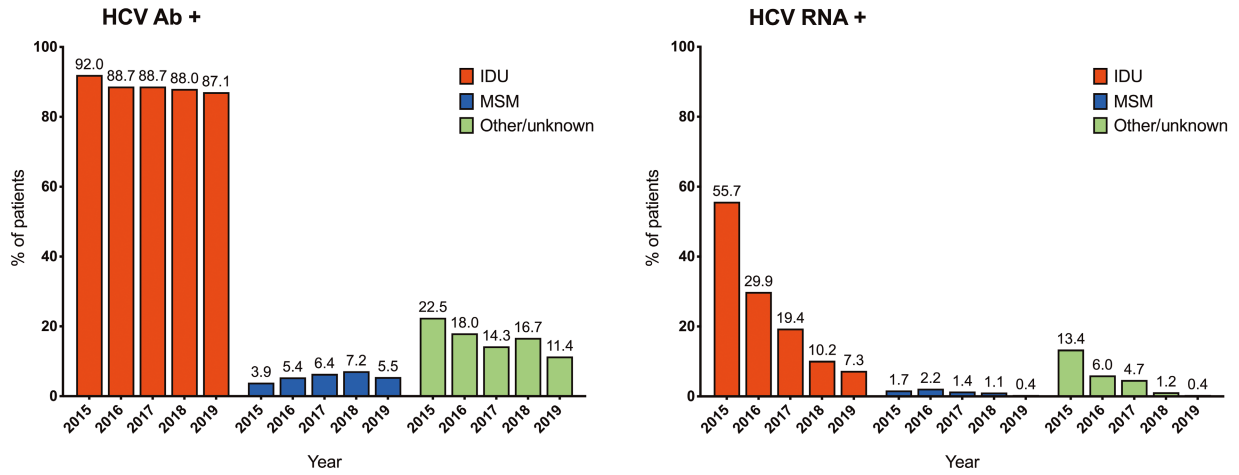


**FIGURE 2** Prevalence of hepatitis C virus (HCV) seropositivity and active HCV infection in the annual cross-sectional studies carried out by 'Grupo de Estudio del SIDA' (GeSIDA) from 2015 to 2019, categorized by HIV transmission category groups. HCV Ab+, presence of antibodies against HCV; HCV-RNA+, detectable HCV-RNA, IDU, injection drug use; MSM, men who have sex with men

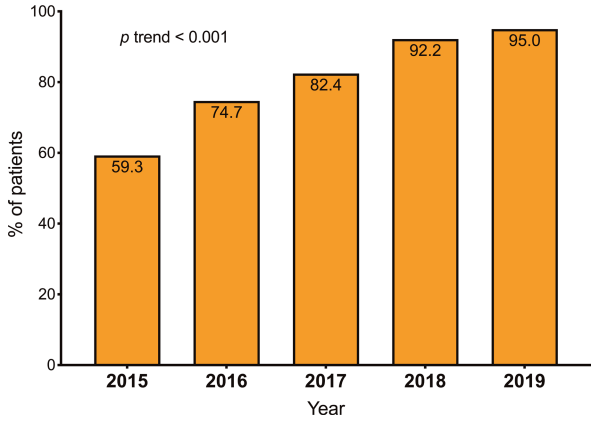


**FIGURE 3** Uptake of anti-hepatitis C virus (HCV) treatment in the annual cross-sectional studies carried out by the 'Grupo de Estudio del SIDA' (GeSIDA) from 2015 to 2019. Treatment uptake was defined as the proportion of people living with HIV with current or past chronic HCV infection exposed to anti-HCV therapy

The prevalence of HCV seropositivity and active HCV infection found among PLWH in 2019 are 41 and 13 times higher than the prevalence among the general population in Spain (0.69% and 0.17%, respectively) [24], underscoring yet again that PLWH comprise a population that is at higher risk of infection by HCV.

After introduction of highly active ART, coinfection by HCV emerged as a leading cause of morbidity and mortality among PLWH in Spain, a country where IDU was the primary driver of the HIV epidemic for many years [12]. In the first nationwide cross-sectional study on HCV performed by GeSIDA in 2002, the prevalence rates of HCV seropositivity and active HCV infection among PLWH were 61% and 54%, respectively [25], which fell to 38% and 22%, respectively, in 2015 [20]. The main factor contributing to this decrease in the first 15 years of this century was the decline in IDU as a mechanism of HIV transmission [12] owing to preventive drug programmes [26]. The higher mortality rates in HCV-infected PLWH than in non-HCV-infected PLWH and the anti-HCV treatment available during this period also helped to decrease the prevalence of HCV infection [13]. Notwithstanding this, the main factor contributing to the sharp reduction in active HCV infection found in recent years in Spain has been the increased uptake of treatment with DAAs, an approach whose effectiveness among HCV-infected PLWH has been > 90% [27]. In 2015, Spain implemented a National Strategic Plan for chronic hepatitis C, which contemplated that all HCV-infected patients were eligible for DAA therapy. However, due to the extent of HCV infection in Spain, it was decided to prioritize patients with advanced liver fibrosis or cirrhosis, transplant recipients or patients on transplant waiting lists, and those with a high risk of transmission such as MSM with ongoing transmission behaviours. Universal access to DAA therapy was approved in June 2017, including acute/recent infections and reinfections.

In 2019, most active HCV infections in PLWH were chronic and were detected among those involved in IDU, whereas fewer than 10% were identified among MSM. In a European survey performed in 2015, those involved in IDU were the leading HCV-seropositive PLWH population group, whereas the proportion of MSM varied from 16.3% in southern Europe to 36.4% in northern Europe [28]. It is notable that, in the GeSIDA 2019 study, almost one-quarter of PLWH who cleared HCV following anti-HCV therapy had liver cirrhosis, indicating that the burden of HCV-related cirrhosis will remain a substantial problem even if the desired goal of eliminating HCV among this population group is achieved.

Taken together, the results of the GeSIDA studies indicate that Spain is on the right track towards achieving microelimination of HCV among PLWH. However, achieving this goal is not without its obstacles, mainly because of ongoing risk transmission behaviours among MSM. Although MSM contributed little to the total burden of HCV infection among PLWH, it is noteworthy that in contrast to the sharp decline in active HCV infections among those involved in IDU, a clear decreasing trend was not observed among MSM. Besides, real-world data for PLWH who received all-oral DAA as treatment for HCV in Spain have shown reinfection rates 28 times higher for MSM than for IDU [14]. Our study reveals additional obstacles to eliminating HCV. In 2019, almost half of PLWH with active HCV infection were receiving or were programmed to receive DAA therapy; among the other half, the main reasons for not being on or not having programmed therapy were unknown/loss to follow-up or physician decision, whereas patient refusal was uncommon. This finding emphasizes the importance of addressing patient-related and healthcare provider-related barriers to and misconceptions regarding HCV treatment [29].

The design of our study was limited mainly by its inability to assess the incidence of HCV infection, which can only be appraised within a prospective cohort. However, repeated cross-sectional studies over time in a defined population (not necessarily the same individuals) provide a measure of incidence and are frequently used by public health agencies to assess secular trends in infection or changes in disease burden [30].

In conclusion, this study showed that the prevalence of active HCV infection among PLWH in Spain has decreased sharply, reaching approximately 2% in 2019, due to increased uptake of DAA treatment over the last 5 years. Our findings suggest that eliminating HCV infection among PLWH in Spain is an achievable goal in the short term, provided we successfully address the barriers to HCV treatment and the prevention of infection and reinfection in key transmission groups. Notwithstanding this, the burden of HCV-related cirrhosis will continue to be significant among PLWH.

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## CONFLICTS OF INTEREST

JB reports honoraria for advice or public speaking from AbbVie, Gilead, MSD, Janssen and ViiV Healthcare; and grants from AbbVie, Gilead, MSD and ViiV Healthcare. AR-R reports honoraria for advice or public speaking from AbbVie, Gilead, MSD, Janssen and ViiV Healthcare, and grants from AbbVie, Gilead, MSD, Janssen and ViiV Healthcare. IJ reports honoraria for advice or public speaking from Gilead and ViiV Healthcare. JGG reports honoraria for advice or public speaking from AbbVie, Gilead, MSD, Janssen and ViiV Healthcare, and grants from Gilead, MSD and ViiV Healthcare. The rest of the authors have nothing to disclose.

## AUTHOR CONTRIBUTIONS

JB and JGG conceived of the work. JB, MdM, JB, and JGG designed the database. IJ analysed the data. All authors interpreted the data. JB drafted the manuscript. All authors critically revised the manuscript for important intellectual content and gave final approval. The authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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## APPENDIX

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