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MAJOR ARTICLE

Human Immunodeficiency Virus/Hepatits C Virus Coinfection in Spain: Elimination Is Feasible, but the Burden of Residual Cirrhosis Will Be Significant

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Background. We assessed the prevalence of antibodies against hepatitis C virus (HCV-Abs) and active HCV infection in patients infected with human immunodeficiency virus (HIV) in Spain in 2016 and compared the results with those of similar studies performed in 2002, 2009, and 2015.

Methods. The study was performed in 43 centers during October–November 2016. The sample was estimated for an accuracy of 2% and selected by proportional allocation and simple random sampling. During 2016, criteria for therapy based on direct-acting antiviral agents (DAA) were at least significant liver fibrosis, severe extrahepatic manifestations of HCV, and high risk of HCV transmissibility.

Results. The reference population and the sample size were 38 904 and 1588 patients, respectively. The prevalence of HCV-Abs in 2002, 2009, 2015, and 2016 was 60.8%, 50.2%, 37.7%, and 34.6%, respectively (*P* trend <.001, from 2002 to 2015). The prevalence of active HCV in 2002, 2009, 2015, and 2016 was 54.0%, 34.0%, 22.1%, and 11.7%, respectively (*P* trend <.001). The anti-HCV treatment uptake in 2002, 2009, 2015, and 2016 was 23.0%, 48.0%, 59.3%, and 74.7%, respectively (*P* trend <.001). In 2016, HCV-related cirrhosis was present in 7.6% of all HIV-infected individuals, 15.0% of patients with active HCV, and 31.5% of patients who cleared HCV after anti-HCV therapy.

Conclusions. Our findings suggest that with universal access to DAA-based therapy and continued efforts in prevention and screening, it will be possible to eliminate active HCV among HIV-infected individuals in Spain in the short term. However, the burden of HCV-related cirrhosis will continue to be significant among HIV-infected individuals.

Keywords. coinfection/*epidemiology; hepatitis C/drug therapy/*epidemiology; HIV infection/*epidemiology; Spain/epidemiology.

Coinfection by hepatitis C virus (HCV) is one of the most common comorbidities in patients infected by the human immunodeficiency virus (HIV), particularly in areas in which HIV infection has been acquired mainly through injection drug use (IDU) [1, 2]. However, since 2000, a substantial increase in the number of new HCV infections has been reported among men who have sex with men (MSM) involved in high-risk practices, particularly in metropolitan areas of Northern Europe, the United States of America, and Australia [3–5].

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In the last few years, the introduction of direct-acting antiviral agents (DAAs) has revolutionized the treatment of HCV [6] and has provided new opportunities for treatment of coinfected individuals, a population considered to be difficult to treat in the interferon plus ribavirin era.

In countries like Spain, where sexually acquired HCV infection has contributed little to the burden of HIV/HCV coinfection to date, the prevalence of HCV antibodies and active HCV infection among HIV-infected individuals has decreased substantially over the years owing to several factors, including the decline in IDU as a mechanism of transmission of HIV infection, the greater mortality in HIV/HCV-coinfected patients than in HIV-monoinfected patients, and the increased uptake of anti-HCV treatment [7, 8]. All these factors provide strong arguments in favor of actively monitoring the burden of HIV/HCV coinfection. In this study, we present data from a nationwide prevalence study of HIV/HCV coinfection in Spain carried out in 2016.

SUBJECTS AND METHODS

The study was carried out by "Grupo de Estudio del SIDA" (AIDS Study Group; GeSIDA) of the "Sociedad Española de Enfermedades Infecciosas y Microbiologıa Clınica" ([SEIMC] Spanish Society of Infectious Diseases and Clinical Microbiology) between October 1, 2016 and December 30, 2016 after a methodology similar to that used in 3 previous studies performed in 2002, 2009, and 2015 and reported in full elsewhere [7, 9, 10].

Design and Sample Size Considerations

This cross-sectional study was performed in 43 hospitals throughout Spain. The reference population was all HIV-infected patients in active follow-up in the participating centers. Active follow-up was defined as at least 1 visit to the center in the previous 12 months. Before the study was initiated, the total number of patients in active follow-up at the participating centers was 38 904 and the prevalence of active HCV infection was 22.1%, according to the most recent survey carried out by GeSIDA in 2015 [7]. Based on these figures, a confidence level of 95%, a design effect of 1.0, and an accuracy for the sample size of 2.0%, we estimated that a sample of at least 1588 patients was needed.

Patient Selection

The number of patients to be included at each center was determined by proportional allocation, and patients were selected by simple random sampling (full details in [7]). The Institutional Ethics Committee of Hospital General Universitario Gregorio Marañón approved the study and waived the requirement for written informed consent, because the study was based on anonymous routine clinical data intended for scientific publication.

Variables and Statistical Analysis

We collected demographic data, HIV transmission category, Centers for Diseases Control and Prevention (CDC) disease category, current $CD4^+$ T-cell counts, current HIV-ribonucleic acid (RNA), whether patients were on combination antiretroviral therapy (cART), and the regimen used. We also inquired about the presence of hepatitis B virus surface antigen (HBsAg), the presence of HCV antibodies, and—if applicable—the presence of HCV-RNA. In patients with HCV antibodies, information was also obtained about anti-HCV therapy and—if applicable—the regimens used and their outcomes. Patients receiving anti-HCV therapy at the time the study was performed were considered to be HCV-RNA positive. In the case of patients with HCV antibodies and negative HCV-RNA, we inquired whether this was due to spontaneous clearance or to anti-HCV treatment. In patients with HCV antibodies and who were HCV-RNA positive, we collected HCV genotype and subtype. In patients who were positive for HCV-RNA and/or HBsAg, transient elastography results and the date the procedure was performed were recorded.

The presence of liver cirrhosis was investigated in all patients, as was the method of diagnosis, namely, liver biopsy, transient elastography (liver stiffness >12.5 kPa), or clinical/biological findings. Patients with prior or current episodes of ascites, hepatic encephalopathy, or variceal bleeding were considered to have decompensated liver disease. In patients with cirrhosis, current Child-Pugh and Model for End-Stage Liver Disease (MELD) scores were recorded. We also recorded whether patients had been diagnosed with hepatocellular carcinoma and whether they had undergone liver transplantation. We calculated anti-HCV treatment uptake, defined as the percentage of patients with current or past chronic HCV infection exposed to anti-HCV therapy.

All the information was entered into a shared database at each institution using an online electronic case report form. A descriptive analysis was carried out using frequency tables for categorical variables and mean and standard deviation (SD) or median and interquartile range (IQR) for normally and nonnormally distributed continuous variables. We used the χ^2 test of independence to detect significant differences in categorical variables and the *t* test or the nonparametric Mann-Whitney test for differences in normally or nonnormally distributed continuous variables, respectively. All statistical analyses were performed using Stata, version 14.0 (StataCorp, College Station, TX).

RESULTS

A total of 43 centers participated in the study. The reference population was 38 904 HIV-infected patients, and the sample size was 1588 patients.

Patients' Characteristics

The characteristics of the 1588 patients included in the study are summarized in Table 1. No significant differences were found for sex between HCV-seronegative and HCV-seropositive patients; however, the latter were 4 years older than the former, on average. The frequency of IDU was significantly higher among

HCV-seropositive patients than among HCV-seronegative patients, whereas the frequency of both transmission via heterosexual relations and sexual relations between MSM was significantly higher among HCV-seronegative than among HCV-seropositive patients. Hepatitis B virus surface antigen positivity was more frequent in HCV-seronegative patients than in HCV-seropositive patients (4.4% vs 2.5%; $P < .019$).

More HCV-seropositive patients were in CDC category C than HCV-seronegative patients (30.3% vs 22.8%; $P < .001$). Overall, 96.7% of patients were on cART. In comparison with HCV-seronegative patients, a small but significantly higher proportion of HCV-seropositive patients were on cART (98.2% vs 95.8%, respectively; $P = .014$). In comparison with HCV-seronegative patients, a significantly lower proportion of HCV-seropositive patients were receiving a first-line cART regimen (22.9% vs 7.2%, respectively; $P < .001$). The proportion of patients with an HIV-RNA load <50 copies/mL was 89.5% overall and 92.2% in patients receiving cART. Among the latter, no significant differences were found between HCV-seropositive and HCV-seronegative patients. In the full data set, statistically significantly lower $CD4^+$ T-cell counts were found among HCV-seropositive patients than among HCV-seronegative patients (671 vs 654 cells/μL; $P = .045$) and in patients on cART (678 vs 659 cells/μL; $P = .039$), although the differences were small.

Prevalence of Anti-Hepatitis C Virus (HCV) Antibodies and Active HCV Infection

Hepatitis C virus serostatus was known in 1585 (99.8%) patients, 548 of whom were HCV seropositive. Of these 548 patients, 186 were HCV-RNA positive, 292 were HCV-RNA negative after sustained viral response after anti-HCV therapy, 68 cleared HCV spontaneously, and HCV-RNA results were unknown in 2. The prevalence of anti-HCV antibodies was therefore 34.6% among tested patients (548 of 1585 patients whose serostatus was known), and the prevalence of active HCV infection was 11.7% (186 of 1583 patients with known HCV serostatus and with known HCV-RNA among those with HCV antibodies).

Comparison With Previous Prevalence Studies

We compared the results of this study with those of 3 national studies carried out by GeSIDA in 2002, 2009, and 2015 in a similar number of centers across the same geographical areas of Spain [7, 9, 10]. A summary of participating centers, reference population, and sample size of the studies performed in 2002, 2009, 2015, and 2016 is shown in Table 2.

The main HIV transmission categories among HIV-infected individuals in the 4 prevalence studies are shown in Figure 1. From 2002 to 2015, there was a significant decrease in the proportion of IDU (from 55.2% to 30.7%) and a significant increase in the proportion of MSM (from 17.2% to 35.1%). However, no significant changes were observed from 2015 to 2016.

The prevalence of anti-HCV antibodies and the prevalence of active HCV infection in the 4 studies are shown in Figure 2. The prevalence of anti-HCV antibodies decreased significantly from 60.8% in 2002 to 37.7% in 2015 (P trend <.001) and remained almost unchanged in 2016 (34.6%). In addition, the prevalence of active HCV infection decreased significantly from 54.0% in 2002 to 11.7% in 2016 (P trend <.001). Of note, a 47.1% reduction in the prevalence of active HCV infection was observed from 2015 to 2016. In contrast, the decrease in the prevalence of active HCV infection was 37.0% in the 8-year period from 2002 to 2009 and 35.0% in the 7-year period from 2009 to 2015.

Anti-HCV treatment uptake in the 4 prevalence studies is shown in Figure 3. The proportion of patients with current or past chronic HCV infection exposed to anti-HCV therapy increased significantly from 23.0% in 2002 to 74.7% in 2016.

Characteristics of Patients With Active Hepatitis C Virus Infection

The characteristics of the 186 patients with active HCV infection are summarized in Table 3. A total of 121 (65.1%) were naive for anti-HCV therapy, and 41 (22.0%) were receiving oral DAA therapy during the study. Two patients (1.1%) with active HCV infection had reinfections after sustained viral response with pegylated interferon plus ribavirin. The HCV genotype was unknown in 10 patients (5.4%). Among the remaining 176 patients, the most common infecting genotypes were 1a (46.6%), 4 (22.2%), 3 (15.9%), and 1b (13.6%). Transient elastography was performed in 150 patients (80.6%) a median of 10 months before data were collected. The median liver stiffness value was 6.6 kPa. The distribution of liver stiffness by cutoff was as follows: <7.1 kPa (absent or mild liver fibrosis), 58.0%; >9.5 kPa (advanced fibrosis), 23.3%; and >12.5 kPa (cirrhosis), 16.0% [11]. In addition, the fibrosis-4 (FIB-4) score was available for 185 (99.5%) patients, 13.0% of whom had values ≥3.25 (indicative of advanced liver fibrosis) [12].

The main features of liver cirrhosis in patients with active HCV infection and in those who cleared HCV infection after anti-HCV therapy are summarized in Table 4. Liver cirrhosis was present in 28 of 186 (15.0%) patients with active HCV infection and in 92 of 292 (31.5%) patients who cleared HCV after anti-HCV therapy. Thus, we can assume that of the 1588 HIV-infected patients included in the study, a diagnosis of HCV-related liver cirrhosis had been made at some point in 120 (7.6%) patients.

DISCUSSION

This study showed that at the end of 2016, the prevalence of active HCV infection among HIV-infected individuals in Spain was 11.7%. This represents an approximately 50% decrease in comparison with the prevalence found in 2015. This sharp decrease occurred concurrently with increased access to oral DAAs for treatment of HCV. The study also showed that approximately 7.6% of all HIV-infected individuals in Spain had HCV-related cirrhosis, a condition that was twice as common in coinfected patients with a sustained viral response than in those with active HCV infection.

Table 1. Baseline characteristics of the 1588 Patients Included in the Study

	HCV Antibodies								
	Unknown	Positive					Negative		Total
Characteristic	n = 3	HCV-RNA Positive n = 186	HCV-RNA Negative Posttreatment n = 292	HCV-RNA Negative Spontaneous Clearance n = 68	HCV-RNA Unknown n = 2	Total HCV-Positive n = 548	n = 1037	P^a	n = 1588
Male sex, n (%)	3 (100.0)	140 (75.3)	233 (79.8)	41 (60.3)	1 (50.0)	415 (75.7)	805 (77.6)	.39	1223 (77.0)
Age years, mean (SD)	51 (4)	50 (7)	52 (6)	51 (8)	50 (5)	51 (7)	47 (12)	<.001	49 (11)
HIV transmission category, n (%)									
Injection drug use	0	140 (75.3)	231 (79.1)	44 (64.7)	2 (100.0)	417 (76.1)	53 (5.1)	<.001	470 (29.6)
Heterosexual	0	22 (11.8)	22 (7.5)	14 (20.6)	0	58 (10.6)	318 (30.7)		376 (23.7)
Men who have sex with men	3 (100.0)	12 (6.4)	14 (4.8)	4 (5.9)	0	30 (5.5)	523 (50.4)		556 (35.0)
Contaminated blood products	0	2 (1.1)	2 (0.7)	0	0	4 (0.7)	1 (0.1)		5 (0.3)
Mother-to-child transmission	0	2 (1.1)	0	1 (1.5)	0	3 (0.5)	8 (0.8)		11 (0.7)
Other	0	8 (4.3)	23 (7.9)	5 (7.3)	0	36 (6.6)	134 (12.9)		170 (10.7)
HBsAg, n (%)									
Negative	1 (33.3)	171 (91.9)	278 (95.2)	64 (94.1)	2 (100.0)	515 (94.0)	973 (93.8)	.019	1489 (93.8)
Positive	0	5 (2.7)	5 (1.7)	4 (5.9)	0	14 (2.5)	46 (4.4)		60 (3.8)
Unknown	2 (66.7)	10 (5.4)	9 (3.1)	0	0	19 (3.5)	18 (1.7)		39 (2.5)
CDC clinical category C, n (%)	0	54 (29.0)	92 (31.5)	20 (29.4)	0	166 (30.3)	236 (22.8)	.001	402 (25.3)
cART, n (%)	3 (100.0)	181 (97.3)	289 (99.0)	66 (97.1)	2 (100.0)	538 (98.2)	994 (95.8)	.014	1535 (96.7)
Type of cART regimen, n (%)									
2 NRTI + 1 NNRTI	1 (33.3)	45 (24.9)	75 (25.9)	16 (24.2)	0	136 (25.2)	376 (37.8)	<.001	513 (33.4)
2 NRTI + 1 PI	0	32 (17.7)	31 (10.7)	9 (13.6)	1 (50.0)	74 (13.7)	118 (11.9)		191 (12.4)
2 NRTI + 1 integrase inhibitor	2 (66.7)	61 (33.7)	101 (34.9)	21 (31.8)	0	183 (33.9)	312 (31.4)		497 (32.4)
PI-based monotherapy	0	13 (7.2)	19 (6.6)	4 (6.1)	0	36 (6.7)	49 (4.9)		85 (5.5)
PI-based bitherapy	0	15 (8.3)	30 (10.4)	8 (12.1)	0	53 (9.8)	56 (5.6)		109 (7.1)
Other	0	15 (8.3)	33 (11.4)	8 (12.1)	1 (50.0)	57 (10.6)	83 (8.3)		140 (9.1)
Category of cART regimen, n (%)									
First-line therapy	0	15 (8.3)	17 (5.9)	7 (10.6)	0	39 (7.2)	228 (22.9)	<.001	267 (17.4)
Switch unrelated to toxicity/ failure	1 (33.3)	100 (55.2)	168 (58.1)	28 (42.4)	1 (50.0)	298 (55.3)	436 (43.9)		734 (47.8)
Switch after failure	0	24 (13.3)	19 (6.6)	8 (12.1)	1 (50.0)	52 (9.6)	60 (6.0)		112 (7.3)
Switch after toxicity	2 (66.7)	40 (22.1)	80 (27.7)	22 (33.3)	0	142 (26.3)	240 (24.1)		384 (25.0)
Unknown	0	2 (1.1)	5 (1.7)	1 (1.5)	0	8 (1.5)	30 (3.0)		38 (2.5)
HIV-RNA copies/mL, n (%)									
All patients									
<50	3 (100.0)	158 (84.9)	276 (94.5)	57 (83.8)	2 (100.0)	493 (90.0)	926 (89.3)	.15	1422 (89.5)
50–200	0	7 (3.8)	9 (3.1)	7 (10.3)	0	23 (4.2)	30 (2.9)		53 (3.3)
>200	0	21 (11.3)	7 (2.4)	4 (5.9)	0	32 (5.8)	81 (7.8)		113 (7.1)
Patients on cART									
<50	3 (100.0)	157 (86.7)	273 (94.5)	56 (84.8)	2 (100.0)	488 (90.7)	924 (93.0)	.28	1415 (92.2)
50–200	0	7 (3.9)	9 (3.1)	7 (10.6)	0	23 (4.3)	30 (3.0)		53 (3.4)
>200	0	17 (9.4)	7 (2.4)	3 (4.5)	0	27 (5.0)	40 (4.0)		67 (4.4)
$CD4^+$ T cells/μL, median (IQR)									
All patients	744 (522–805)	600 (372–826)	680 (455–909)	764 (438–925)	205 (185–225)	654 (429–882)	671 (492–904)	.045	670 (470–895)
Patients on cART	744 (522–805)	605 (390–826)	684 (455–911)	764 (448–925)	205 (185–225)	659 (431–886)	678 (495–910)	.039	670 (472–897)

Abbreviations: cART, combination antiretroviral therapy; CDC, Centers for Disease Control and Prevention; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; PI, protease inhibitor; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; RNA, ribonucleic acid; SD, standard deviation.

[a] *P* values for the comparisons between HCV-positive patients (n = 548) and HCV-negative patients (n = 1037) derived from the χ^2 test for independence for categorical variables and the *t* test or the Mann-Whitney test for normally or nonnormally distributed continuous variables, respectively.

Table 2. Centers and Patients Included in the Nationwide HCV Prevalence Studies Carried out by GeSIDA in 2002, 2009, 2015, and 2016

Variable	2002	2009	2015	2016
Participating centers	39	43	41	43
Reference population	31 800	29 559	35 791	38 904
Sample size	1260	1458	1867	1588
Tested for HCV antibodies	99.5%	99.8%	98.7%	99.8%
Reference	9	10	7	Current study

Abbreviations: GeSIDA, Grupo de Estudio del SIDA; HCV, hepatitis C virus; IQR, interquartile range; RNA, ribonucleic acid; TE, transient elastography.

The results of this study and previous GeSIDA studies [7, 9, 10] showed remarkable differences between the seroprevalence of HCV and the prevalence of active HCV infection among HIV-infected individuals in the 14-year period from 2002 and 2016. The seroprevalence of HCV dropped sharply from 2002 to 2015 but remained practically unchanged from 2015 to 2016 (approximately 35%). However, the prevalence of active HCV infection decreased steadily from 54.0% in 2002 to 11.7% in 2016. Of note, a 47% drop was observed from 2015 to 2016. This is a huge decrease if we consider that the decline in the prevalence of active HCV infection was 37.0% in the 8-year period from 2002 to 2009 and 35.0% in the 7-year period from 2009 to 2015, respectively.

Several factors contributed to the declining trends in HCV seropositivity and active infection among HIV-infected individuals from 2002 to 2016. In the early years, the main factor was the reduction in the frequency of IDU as a mechanism of HIV transmission [13], together with the development of preventive drug programs [14]. The higher mortality rates in coinfected patients compared with HIV-monoinfected patients in this period also contributed to a decrease in the prevalence of HCV infection [15]. Over the last few years, however, the reduction of active HCV infection may be attributable to the increase in the frequency of anti-HCV treatment uptake, which went from 23.0% in 2002 to 59.3% and 74.7% in 2015 and 2016, respectively. Of note, in the last 2 years, anti-HCV therapy in Spain consisted of DAA-based regimens. Under real-life conditions, these regimens yielded high rates of sustained viral response that were similar to those of HCV-monoinfected patients and showed an excellent safety and tolerance profile, even in patients with end-stage liver disease [16, 17].

All of the above findings raise the question of whether the goal of elimination of HCV among HIV-infected individuals can be achieved in Spain in the short term. Elimination of an infection means the reduction to zero of the incidence of the disease caused by a specific agent in a defined geographical area because of deliberate efforts, requiring continued measures to prevent re-establishment of transmission [18]. If one considers that prevention, screening, and universal access to treatment are essential for the elimination of HCV infection [19], Spain appears to be on the right track towards the achievement of this goal.

As previously mentioned, the preventive programs of the National Drug Strategy in Spain have proven effective for reduction of drug-related risk and harm [14]. These programs have included social and health services offering preventive educational interventions, overdose prevention activities, sterile needles and syringes, testing for drug-related infections, vaccination against viral hepatitis, emergency care and assistance to injecting drug users (who do not usually have contact with support interventions), and a scaling up of opioid substitution treatment. The National Drug Strategy for the period 2017–24 covers many illicit and licit substances [14]. As this and previous studies show, HCV infection acquired through sexual relations contributes little to the burden of coinfection in Spain and

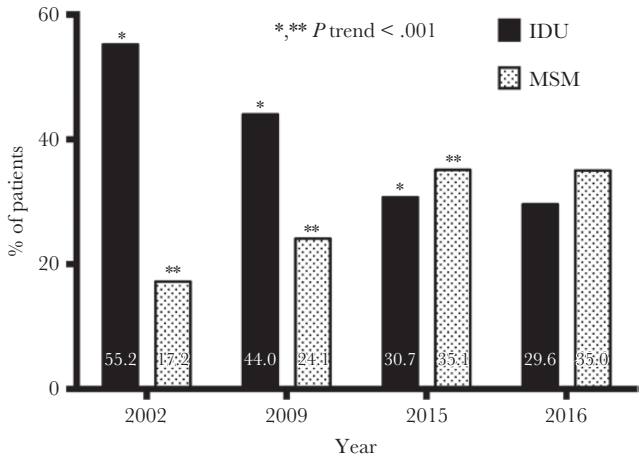

Figure 1. Principal human immunodeficiency virus transmission categories in the cross-sectional studies carried out by Grupo de Estudio del SIDA in 2002, 2009, 2015, and 2016. IDU, injection drug use; MSM, men who have sex with men.

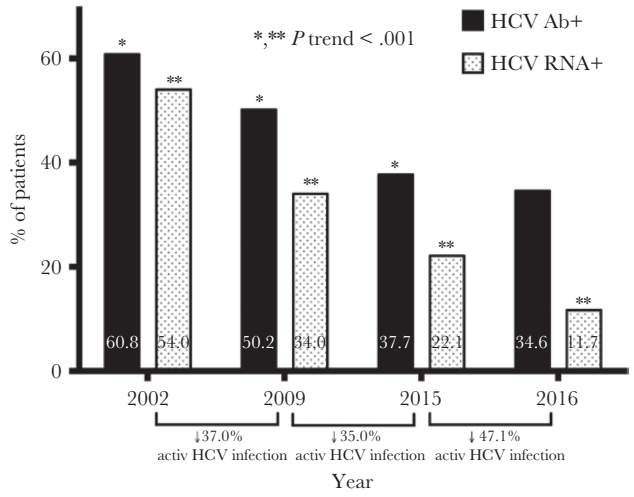

Figure 2. Prevalence of hepatitis C virus (HCV) seropositivity and active HCV infection in the cross-sectional studies carried out by Grupo de Estudio del SIDA in 2002, 2009, 2015, and 2016. HCV Ab$^+$, presence of antibodies against HCV; HCV-RNA$^+$, detectable HCV-RNA; RNA, ribonucleic acid.

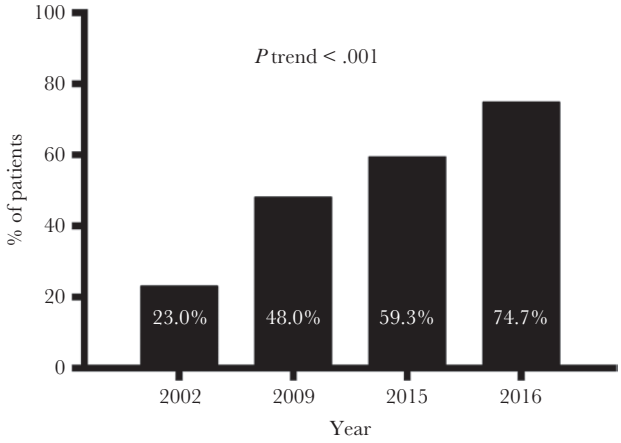

Figure 3. Anti-hepatitis C virus (HCV) treatment uptake in the cross-sectional studies carried out by Grupo de Estudio del SIDA in 2002, 2009, 2015, and 2016. Treatment uptake was defined as the proportion of patients with current or past chronic HCV infection exposed to anti-HCV therapy

remains restricted to specific areas of Madrid and Barcelona [20, 21]. However, prevention activities should also be undertaken to reduce high-risk behavior among both HIV-infected and non-HIV-infected MSM who engage in high-risk practices for sexual transmission of HCV [5].

Hepatitis C virus screening practices among HIV-infected individuals appear to be of a high standard according to the results of the 4 prevalence studies performed over the last 14 years, which have consistently shown that 99% of HIV-infected individuals are tested for HCV antibodies [7]. However, it is important to perform regular screening for HCV among HIV-infected people who engage in high-risk practices. In addition, testing should be considered in migrants from regions with a high prevalence of HCV, such as sub-Saharan Africa and Eastern Europe [22, 23].

As for universal access to therapy, a total of 63 075 patients with HCV—20% of whom were coinfected—were treated with all oral DAA-based regimens in Spain from January 1, 2015 to September 31, 2016 [24]. During the first months, access to therapy was prioritized for patients with advanced liver fibrosis or cirrhosis; however, in 2015, in most autonomous regions of Spain, access to DAA therapy was available for patients with significant fibrosis (METAVIR F ≥2 in liver biopsy or equivalent by transient elastography). Furthermore, irrespective of liver fibrosis stage, DAA-based therapy could also be administered to patients with clinically significant extrahepatic manifestations of HCV (such as symptomatic mixed cryoglobulinemia) and to patients at risk of transmitting HCV (active injection drug users, MSM with high-risk sexual practices for acquiring HCV, and women of childbearing age who wish to become pregnant). In June 2017, the Spanish Ministry of Health committed to providing access to DAA-based therapy for all individuals with HCV, irrespective of the stage of fibrosis [25].

Table 3. Characteristics of Liver Disease in the 186 Patients Who Were HCV-RNA Positive

Characteristic	N = 186
Anti-HCV Therapy, n (%)[a]	
Never	121 (65.1)
Ongoing[b]	41 (22.0)
In the past	34 (18.3)
Null response or partial response	26 (76.5)
Relapse	1 (2.9)
Abandonment or interruption due to adverse events	5 (14.7)
Sustained viral response	2 (5.9)
HCV Genotype, n (%)	
Unknown	10 (5.4)
Known	176 (94.6)
1[a]	82 (46.6)
4	39 (22.2)
1[b]	24 (13.6)
3	28 (15.9)
2	3 (1.7)
Mixed	0
TE Results	
Patients with TE, n (%)	150 (80.6)
Months from TE to study date, median (IQR)	10.0 (5.6–21.9)
TE value–kPa, median (IQR)	6.6 (5.4–9.1)
TE distribution according to cutoff values–kPa, n (%)	
<7.1	87 (58.0)
7.1–9.5	28 (18.7)
9.6–12.5	11 (7.3)
>12.5	24 (16.0)
FIB-4 Index Results	
Patients with FIB-4, n (%)	185 (99.5)
FIB-4 value, median (IQR)	1.5 (1.1–2.2)
FIB-4 Distribution According to Cutoff Values, n (%)	
≤1	39 (21.1)
1–3.25	122 (65.9)
≥3.25	24 (13.0)

Abbreviations: DAA, direct-acting antiviral agent; FIB-4, fibrosis 4; HCV, hepatitis C virus; IQR, interquartile range; RNA, ribonucleic acid; TE, transient elastography.

[a]The number of patients in the "never", "ongoing", and "in the past" categories total more than 186 because the groups overlap. Of the 186 patients, 121 were naive for anti-HCV therapy, 31 are currently receiving therapy but had not received it previously, 24 are not currently receiving therapy but had received it in the past, and 10 are currently receiving treatment and received it in the past.

[b]All 41 patients in this category were receiving oral DAA therapy during the study.

An important observation in this study was the finding that almost 8% of all HIV-infected individuals had been diagnosed at some time with HCV-related liver cirrhosis. Of note, cirrhosis was more common in patients who had achieved a sustained viral response than in those with active HCV infection. This finding underscores the fact that despite the well known benefits of eradicating HCV among coinfected individuals in terms of reduced morbidity and mortality [26], there persists a residual risk for liver-related events, especially hepatocellular carcinoma, in patients with cirrhosis in whom HCV has been eradicated [27, 28]. Therefore, even if we achieve the probable and desired goal of eliminating HCV among HIV-infected individuals, the burden of HCV-related cirrhosis will remain

Table 4. Features of Liver Cirrhosis in Patients With Active HCV Infection and in Those Who Cleared HCV Infection After Anti-HCV Therapy

Feature	Active HCV Infection N = 186	Clearance of HCV After Anti-HCV Therapy N = 292	P^a
Liver cirrhosis, n (%)	28 (15.0)	92 (31.5)	<.001
Method of diagnosis (Mutually Exclusive), n (%)			.30
Transient elastography	25 (89.3)	82 (89.1)	
Liver biopsy	0	5 (5.4)	
Clinical/biological diagnosis	3 (10.7)	5 (5.4)	
Decompensated cirrhosis, n (%)	4 (14.3)	8 (8.7)	.39
Hepatocellular carcinoma, n (%)	1 (3.6)	1 (1.1)	.37
Child-Pugh Stage, n (%)			.13
Stage A (5–6)	22 (78.6)	80 (87.9)	
Stage B (7–9)	5 (17.9)	11 (12.1)	
Stage C (10–15)	1 (3.6)	0	
MELD score, median (IQR)	8.4 (7.0–10.8)	7.6 (6.4–10.3)	.22
Serum albumin, median (IQR)	4.0 (3.5–4.6)	4.4 (4.0–4.7)	.046
FIB-4 Index			
Patients with FIB-4, n (%)	28 (100.0)	92 (100.0)	
FIB-4 value, median (IQR)	2.8 (1.6–5.1)	2.0 (1.4–3.2)	.047
FIB-4 distribution, n (%)			.085
≤1	3 (10.7)	10 (10.9)	
1–3.25	12 (42.9)	59 (64.1)	
≥3.25	13 (46.4)	23 (25.0)	
Transient Elastography			
Patients with TE, n (%)	27 (96.4)	84 (91.3)	
Months from last TE to study date, median (IQR)	10.9 (3.2–25.4)	14.7 (7.7–34.3)	.29
Last TE value–kPa, median (IQR)	18.4 (14.0–34.3)	16.7 (11.1–26.0)	.30
Last TE value distribution–kPa, n (%)			.062
<7.1	2 (7.4)	3 (3.6)	
7.1–9.5	1 (3.7)	10 (11.9)	
9.6–12.5	0 (0)	13 (15.5)	
>12.5	24 (88.9)	58 (69.0)	

Abbreviations: FIB-4, fibrosis-4; HCV, hepatitis C virus; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; TE, transient elastography.

[a] *P* values derived from the χ^2 test for independence for categorical variables and the Mann-Whitney test for continuous variables.

substantial. Considering the 130 000 to 160 000 people who live with HIV in Spain [29] and the 7.6% prevalence of HCV-related cirrhosis, between 9120 and 12 160 HIV-infected individuals with cirrhosis will need indefinite surveillance for hepatocellular carcinoma according to current recommendations [30, 31].

CONCLUSIONS

In conclusion, this study showed that at the end of 2016, the prevalence of active HCV infection among HIV-infected individuals in Spain was 11.7%, ie, an almost 50% decrease in comparison with the prevalence for 2015. This decrease was accompanied by a sharp increase in the uptake of oral DAAs against HCV. We believe that the universal treatment of HCV and the continued efforts in prevention and screening will make it possible to eliminate active HCV infection among HIV-infected individuals in Spain in the short term. However, despite the elimination of active HCV infection, HCV-related liver cirrhosis will continue to generate a significant burden among HIV-infected individuals in Spain.

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