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ORIGINAL RESEARCH

Incidence of recently acquired hepatitis C virus infection among HIV-infected patients in southern Spain

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Objectives

Spain is close to HCV microelimination, so rates of recently acquired HCV infection (RAHC) should decrease. Nowadays, men who have sex with men (MSM) carry the highest risk of HCV acquisition. Our aim was to estimate the incidence of and the factors associated with RAHC, together with reinfection rates, among patients sexually infected by HIV.

Methods

Primary RAHC infection was diagnosed when anti-HCV antibody seroconversion was documented. In anti-HCV positive patients, initially without HCV viraemia, a diagnosis of reinfection was established if plasma HCV RNA was detected.

Results

All 350 patients tested negative for anti-HCV at baseline and had at least one follow-up visit. Among them, there were 16 RAHC cases from 2016 to 2019. RAHC incidence rates [IR (95% confidence interval, CI)] per 100 person-years were 3.77 (0.5–12.9) in 2016, 1.85 (0.6–4.3) in 2017, 1.49 (0.4–3.8) in 2018 and 1.98 (0.6–4.5) in 2019. Only previous sexually transmitted infections [incidence rate ratio (IRR) = 18.23, 95% CI: 1.93–172.1; $P = 0.011$], male sex (IRR = 8.33, 95% CI: 1.38–54.15; $P = 0.026$) and sharing chem-sex drugs (IRR: 4.93, 95% CI: 1.17–20.76; $P = 0.030$), were independently associated with RAHC. Four out of 42 (9.5%) patients became reinfected.

Conclusions

The incidence of RAHC among HIV-infected patients showed a decrease after 2016, although a lower but steady incidence of residual cases still remains. HCV reinfections showed a similar pattern. New infections were associated with sharing chem-sex drugs among MSM.

Keywords: hepatitis C virus, HIV, men who have sex with men, microelimination, risk factors

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Introduction

In the last decade, numerous outbreaks of recently acquired hepatitis C virus infection (RAHC) have been described among people living with HIV (PLWH) worldwide, mainly in HIV-positive men who have sex with men (MSM) [1–9]. The increased incidence of RAHC in HIV-positive MSM has been attributed to several factors such as a higher hepatitis C virus (HCV) load in blood and semen [10], sexual practices with an increased risk of mucosal damage, the presence of ulcerative sexually transmitted diseases, a larger number of sexual partners and the use of chem-sex [11].

Some studies conducted in very specific areas within the largest Spanish cities have reported an increase in the number of cases of RAHC among HIV-infected MSM [1,7,12]. However, the number of RAHC episodes among PLWH in southern Spain remained stable until 2015 [13,14], in spite of the fact that over one-third of HIV-infected subjects bore an active HCV coinfection [15]. This lack of RAHC outbreaks in southern Spain may reflect a different epidemiological situation in our area to what has been reported from other Spanish urban areas [1,20] and in many European cities, as well as in Australia and the United States [3–6].

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The direct-acting antiviral drugs (DAAs) currently used yield sustained virological response rates of > 95% [16,17]. The widespread use of DAAs in Spain may ultimately lead to the elimination of HCV in the country. Indeed, the Polaris Observatory reported that Spain is on track to eliminate HCV infection by 2030 [18]. Therefore, if the burden of HCV infection declines due to DAA use, a decrease of RAHC episodes during recent years should be observed in our area. Nowadays, MSM carry the highest risk of HCV acquisition [19]. Because of this, the expected decline in the incidence of RAHC should be primarily seen in this particular subset. Due to this, our aim was to estimate the incidence of RAHC and the factors associated with RAHC during recent years among PLWH in southern Spain infected through sexual intercourse. We also evaluated the rates of reinfections in those patients.

Methods

This was a prospective cohort study conducted at four hospitals in Spain. MSM and non-MSM patients consecutively attending these hospitals were included. Primary RAHC infection was diagnosed when anti-HCV antibody seroconversion was documented. In anti-HCV positive patients, initially without HCV viraemia, a diagnosis of reinfection was established if plasma HCV RNA was detected.

Study population

This study was a prospective cohort study conducted in four hospitals throughout Southern Spain. Eight hundred sixty-one PLWH consecutively attended in the Infectious Diseases Units of the participating centers from January 2016 to December 2019 were analyzed. Of them, three hundred and fifty PLWH infected through sexual intercourse, i.e. MSM and PLWH infected through sexual intercourse who are not MSM (non-MSM individuals), with at least 12 months of follow-up and available serum samples were finally included in the study. PLWH infected by other routes, i.e. people who inject drugs (PWID), than through sexual intercourse were excluded. A questionnaire of behavioural risk factors and sexual practices associated with HCV infection was filled out for every patient at the first visit and every 12 months. All patients with at least one follow-up visit were evaluated. HCV serum antibodies were determined, at the least, at baseline and every 12 months, and plasma HCV-RNA was determined if seroconversion occurred during the follow-up. For seropositive patients for anti-HCV at baseline, plasma HCV-RNA was determined, at the least, at baseline and every 12 months. The last participant was included in December 2018 in order to achieve 1-year follow-up.

Definition of RAHC and HCV reinfection

An episode of RAHC was diagnosed if anti-HCV seroconversion was observed during the follow-up among patients who showed negative plasma immunoglobulin G antibody against HCV at baseline.

In those patients who tested positive for anti-HCV and negative for HCV RNA plasma at baseline, a definite diagnosis of reinfection was established if HCV RNA was detected during a subsequent visit.

Management of DAA combinations in Spain (2016–2019)

Interferon-free DAA combinations have been available and reimbursed by the Spanish Health System since January 2015, restricting the use to patients with advanced liver fibrosis, extrahepatic manifestations and women of childbearing age and high risk of transmission [20]. Since June 2017, all HCV-infected patients could be treated without restrictions.

Laboratory determinations

Plasma HCV antibodies were tested by enzyme immunoassay (ADVIA Centaur XP, Siemens Healthcare Diagnostics S.L., Tarrytown, NY, USA; or ELECSYS® Anti-HCV II, Roche Diagnostics, Basel, Switzerland). A PCR assay was conducted to determine HCV RNA levels in plasma (Cobas AmpliPrep/Cobas TaqMan HCV test v.2.0; Roche Diagnostic Corporation, Pleasanton, CA, USA), lower limit of quantification (LLOQ) = 15 IU/mL.

Statistical analyses

Descriptive statistics of demographic factors, HIV transmission route and biological data were carried out. Incidence rates (IRs) and the 95% confidence intervals (95% CIs) of RAHC were calculated and presented as cases per 100 person-years. IRs of RAHC in 2016 and 2017–2019 periods were compared using the STATA command 'irr'. Continuous variables are expressed as median (Q1–Q3), whereas categorical variables are presented as numbers (percentages). Continuous variables were compared by means of the Student's *t*-test or the Mann–Whitney *U*-test, depending on the normality tests. The χ^2 and Fisher tests, when appropriate, were used for comparisons between categorical variables. Factors associated with

RAHC with a univariate P-value < 0.1 were entered in a Poisson regression, adjusted by age and sex. Incidence rate ratios (IRRs) were calculated. Analyses were carried out by means of the SPSS statistical software package release 25.0 (IBM Corporation, Somers, NY, USA) and STATA 12.0 (StataCorp LP, College Station, TX, USA).

Ethical aspects

Both the study design and development complied with the Helsinki Declaration and were approved by the local Ethics Committee of the Hospital Universitario Virgen de Valme (Seville). All patients gave their written informed consent to participate in the study.

Results

Patient characteristics

Three hundred and fifty MSM and non-MSM patients with at least one follow-up visit were anti-HCV negative at baseline. Their median (interquartile range, IQR) time of follow-up was 34.9 (20.7–37.7) months. A total of 1064 anti-HCV tests (3.4 tests per patient) were performed during the follow-up. The characteristics of these patients at baseline are described in Table 1.

RAHC episodes during the follow-up

A total of 16 cases of RAHC were detected. The characteristics of patients at baseline according to RAHC are described in Table 2. Over a follow-up period of 845 py from 2016 to 2019, the overall IR (95% CI) of RAHC was 1.89 (1.1–3.1) per 100 py. The IRs according to the year of seroconversion are depicted in Fig. 1. Losses to follow-up were 9/201 (4.5%) in 2016, 42/332 (12.6%) in 2017, 38/296 (12.8%) in 2018 and 0/256 (0%) in 2019. The IRs (95% CI) of RAHC per 100 py were 3.77 (0.5–12.9) in 2016, 1.85 (0.6–4.3) in 2017, 1.49 (0.4–3.8) in 2018 and 1.98 (0.6–4.5) in 2019. The incidence of RAHC tended to decrease from 3.77 (0.5–12.9) per 100 py in 2016 to 1.77 (0.9–2.9) per 100 py in 2017–2019 [IRR (95% CI) = 2.15 (0.5–9.1), P = 0.170)].

Table 1 Characteristics of the patients at baseline (n = 350)

Characteristic	Value	RAHC (%)
Sex [*n* (%)]		
Male	290 (82.9)	14 (4.8)
Female	60 (17.1)	2 (3.3)
Age (years)*	44.7 (36.4–53.3)	
Risk factor for HCV acquisition [*n* (%)]		
Non-MSM	108 (30.9)	2 (1.9)
MSM	242 (69.1)	14 (5.8)
Previous STIs [*n* (%)]	178 (50.9)	12 (6.7)
Recreational drugs during sex [*n* (%)]	28 (8)	7 (25)
Sharing chem-sex drugs† [*n* (%)]	13 (3.7)	3 (23.1)
No condom use [*n* (%)]	159 (45.4)	12 (7.5)
Group sex [*n* (%)]	13 (3.7)	6 (46.2)
Sexual practices with high risk of bleeding [*n* (%)]	43 (12.3)	4 (9.3)
Sexual partners ≥ 2 in last 6 months [*n* (%)]	99 (28.3)	8 (8.1)

RAHC, recently acquired HCV infection; MSM, men who have sex with men; STIs, any sexually transmitted disease ever suffered before baseline.
*Median (interquartile range).
†Sharing chem-sex drugs or equipment.

Factors associated with RAHC

Several behavioural risk factors such as sharing chem-sex drugs, two or more sexual partners during the last 6 months, never use condom during sex, group sex, use recreational drugs during sex and previous sexually transmitted infections (STIs) were associated with RAHC in the univariate analysis (Table 2). After multivariate analysis, only previous STIs, male gender and sharing chem-sex drugs were identified as independently associated with RAHC.

HCV reinfections

Forty-two patients showed positive anti-HCV and undetectable HCV RNA at baseline and had at least one follow-up visit afterwards. The characteristics of these patients at baseline are described in Table 3. Four (9.5%) of them were reinfected with HCV during the study period (Fig. 2). The characteristics of these four patients at baseline are described in Table 4. All reinfected patients were MSM with two or more sexual partners during the last 6 months and previous STIs. Most of them used recreational drugs during sex. All of them achieved sustained virological response (SVR) with DAA and subsequently were reinfected after achieving SVR. The incidence of reinfection per 100 py (IR 95% CI) was 25 (3.2–65) in 2016, 2.95 (0.1–14.5) in 2017, 0 (0–0) in 2018 and 2.94 (0.1–15.3) in 2019.

Discussion

We have found a trend to a decrease in the incidence of RAHC among HIV-infected patients in our area after 2016, with a steady incidence of residual cases afterwards. These episodes of RAHC were overwhelmingly observed among MSM who share chem-sex drugs. Likewise, we found that HCV reinfections numerically decreased during the same time periods in parallel with primary infections.

Table 2 Risk factors for recently acquired hepatitis C virus infection (n = 350)

Characteristic	RAHC (n = 16)	No RAHC (n = 334)	Univariate P-value	IRR (95% CI)	Multivariate P-value
Male sex [n (%)]	14 (87.5)	276 (82.6)	1	0.125 (0.019–0.784)	0.026
Age (years) [median (IQR)]	44.1 (32.2–48.3)	44.9 (36.4–53.9)	0.386	0.992 (0.937–1.045)	0.788
Risk factor for HCV acquisition [n (%)]					
MSM	14 (87.5)	228 (68.3)	0.164		
Non-MSM	2 (12.5)	106 (31.7)			
Sharing chem-sex drugs* [n (%)]	3 (25)	10 (3)	0.008	4.925 (1.168–20.759)	0.030
Sexual partners ≥ 2 in last 6 months [n (%)]	8 (80)	91 (28.2)	0.001	1.059 (0.247–4.533)	0.939
No condom use [n (%)]	12 (85.7)	147 (44)	0.022	0.558 (0.142–2.191)	0.403
Group sex [n (%)]	6 (40)	7 (2.1)	<0.001	3.992 (0.643–24.761)	0.137
Recreational drugs during sex [n (%)]	7 (43.8)	21 (6.3)	<0.001	1.262 (0.234–6.797)	0.786
Previous STIs [n (%)]	12 (100)	166 (50.9)	0.001	18.23 (1.931–172.05)	0.011
Sexual practices with high risk of bleeding [n (%)]	4 (33.3)	39 (14.1)	0.087	1.126 (0.245–4.533)	0.879

RAHC, patients with an episode of recently acquired HCV infection; no RAHC, patients without an episode of recently acquired HCV infection; CI, confidence interval; IRR, incidence rate ratio; MSM, men who have sex with men; STIs, any sexually transmitted infection ever suffered before baseline.
*Sharing chem-sex drugs or equipment.

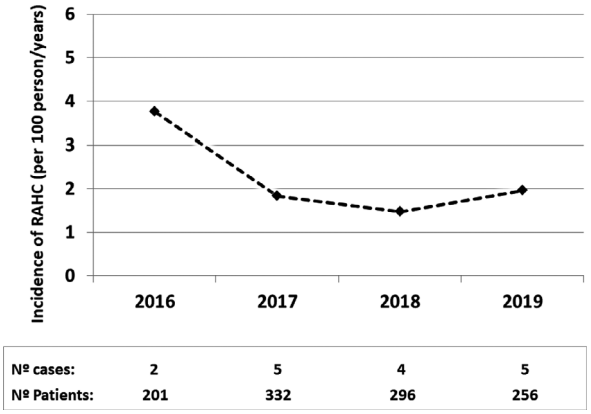

Fig. 1 Incidence rate distribution of recently acquired hepatitis C virus infection (RAHC) among HIV-infected individuals according to the year of seroconversion (P = 0.170 for comparison of 2016 *vs.* 2017–2019 period)

Table 3 Characteristics of the patients seropositive for HCV at baseline (n = 42)

Characteristic	Value
Male sex [n (%)]	30 (71.4)
Age (years) [median (IQR)]	49.8 (45.4–56.9)
Risk factor for HIV acquisition [n (%)]	
MSM	21 (50)
Non-MSM	21 (51)
Previous STIs [n (%)]	14 (35.9)
Recreational drugs during sex [n (%)]	5 (18.5)
Sharing chem-sex drugs* [n (%)]	7 (17.1)
No condom use [n (%)]	15 (57.7)
Group sex [n (%)]	2 (7.4)
Sexual practices with high risk of bleeding [n (%)]	5 (17.9)
Sexual partners ≥ 2 in last 6 months [n (%)]	13 (31.7)
Spontaneous clearance of HCV [n (%)]	6 (14.3)

MSM, men who have sex with men; STIs, any sexually transmitted infection ever suffered before baseline.
*Sharing chem-sex drugs or equipment.

The WHO goal is to eliminate viral hepatitis worldwide by 2030 [21]. According to the Polaris Observatory, Spain is in a leading position to achieve this objective [18]. One key aspect of HCV elimination is wide access to DAA combinations. In Spain, DAA therapy was administered if spontaneous clearance was not achieved, but since June 2017 all patients with HCV infection were candidates to receive DAA therapy without restrictions. In our study, we show a 52% decrease in RAHC among HIV-infected patients after 2016. This relevant decrease in incidence of RAHC should be mostly attributable to a reduction in the burden of active HCV infections associated with unrestricted DAA treatment. Although these results are promising, residual incident RAHC cases and reinfections, are observed in our study after 2016. These RAHC cases have the potential to reseed the HCV epidemic and, consequently, preclude HCV elimination.

Our findings are in agreement with other studies that have reported a decrease in the incidence of RAHC after widespread treatment of HIV/HCV-infected patients [22–24]. Thus, in the Netherlands, unrestricted DAA availability in the country was followed by a 51% decrease in the incidence of RAHC infections among HIV-positive MSM, while the incidence of STIs increased during the same period of observation [22]. Similarly, in the Swiss HIV cohort, after intensive screening for HCV, the majority of HIV/HCV-coinfected MSM received successful therapy and, as a consequence, a 49% reduction in incident RAHC was observed [23]. In the same way, in the UK, a 78% reduction in the incidence of RAHC episodes has been reported, after a peak in 2015, which coincides with

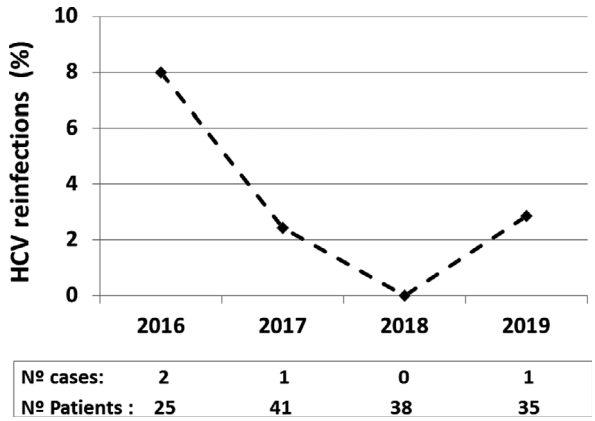

Fig. 2 Prevalence rate distribution of hepatitis C virus (HCV) reinfections among HIV-infected individuals according to the year of seroconversion. Two patients of 25 (8%) were reinfected in 2016, 1/41 (2.5%) was reinfected in 2017, 0/38 (0%) were reinfected in 2018 and 1/35 (2.9%) was reinfected in 2019.

Table 4 Characteristics of hepatitis C virus (HCV) reinfection episodes

Patient no.	1	2	3	4
Risk	MSM	MSM	MSM	MSM
Drugs during sex	Yes	Yes	Yes	No
Sharing chem-sex drugs*	Yes	Yes	No	No
Group sex	No	No	No	Yes
Sexual practices with high risk of bleeding	No	Yes	Yes	No
Condom use	No	No	Yes	No
Sexual partners ≥ 2	Yes	Yes	Yes	Yes
Previous STIs	Yes	Yes	Yes	Yes
Spontaneous clearance of HCV [*n* (%)]	No	No	No	No
Year of reinfection	2016	2016	2017	2019

MSM, men who have sex with men; STIs, any sexually transmitted infection ever suffered before baseline.
*Sharing chem-sex drugs or equipment.

wider access to DAAs in the UK [24]. However, HCV reinfection among HIV-infected MSM in the UK remained challenging, probably because early treatment of HCV infection remained challenging, which is probably because second treatment of HCV infection was not permitted until September 2019 [25]. It is notable that, although all these studies show a decrease in the incidence of RAHC after wider access to DAAs, here we show for the first time that a low but steady incidence of HCV infections has been reached in our area after widespread treatment of HIV/HCV-infected patients. Moreover, the IR in our study, all above 1 per 100 py, is comparable but higher than those in the studies mentioned earlier [22–24]. All these reports and our study fall short of WHO targets for reductions in new diagnoses to reach HCV elimination [21].

Given that DAA treatment is widely available in Spain, further reductions in the incidence of RAHC should have been observed in more recent years. Indeed, the prevalence of HIV-infected patients with HCV viraemia has drastically decreased over time in our area, reaching HCV microelimination targets [26]. A possible explanation for our findings is that the sources of RAHC in recent years might be individuals outside the follow-up of our practices. Thus, the undiagnosed fraction of active HCV infection was 29.4% according to the Spanish Ministry of Health in 2019 [27]. In the Swiss HIV Cohort, both international and domestic transmission networks were the source of HCV infections among HIV-infected MSM [28]. In Spain, RAHC in HIV-infected MSM followed in a single centre in Barcelona were linked to a large international HCV transmission network [1]. Therefore, incident RAHC among HIV-infected MSM in our study could be related to transmission networks beyond our area.

We found that RAHC was linked to MSM with high-risk sexual habits. Sexual transmission of HCV is not frequent among HIV-infected patients [4]. However, certain MSM sexual practices, such as unprotected anal sex with bleeding, fisting and group sex, have been associated with HCV transmission [3,29]. In addition to previous STIs, a marker of high-risk sexual habits, we found that sharing chem-sex drugs was independently associated with RAHC. HCV infection is strongly linked to parenteral exposure, with very high rates of transmission among people who share unsterile injection equipment [30]. Nowadays, sexualized injecting drug use is a high-risk drug use pattern emerging among MSM [31]. In Spain, an anonymous online survey on sexual behaviour and recreational drug use among HIV-infected MSM reported a rate of sexualized injecting drug use of 16% [32]. This relatively small group of sex-enhancing drug users may ultimately maintain a residual rate of HCV infection among HIV-infected MSM.

Providing behavioural interventions addressing high-risk sexualized drug use practices should be part of a comprehensive HCV management in HIV-infected MSM. However, drug addiction treatment programmes do not meet the needs of chem-sex users. Specific behavioural and educational programmes are required, but such interventions may be difficult to implement because MSM using chem-sex usually do not identify themselves as drug users [33]. Enrolment in HIV pre-exposure prophylaxis (PrEP) programmes might reduce HCV incidence due to a reduction in risky behaviour [34], but they do not seem to achieve it, probably because HIV-infected MSM and HIV-negative MSM using PrEP share similar risk practices [35]. In fact, a recent study in a cohort of HIV-negative MSM using PrEP in the Netherlands reported

high IR of RAHC and of HCV reinfection, similar to the rates that we have found herein [36]. Mass screening at population level and linkage to care, with fast access to therapy for those with active HCV infection, is feasible, and it could be more successful than behavioural interventions, as proved with treatment-as-prevention for HIV infection [37].

This study might have some limitations. First, as episodes of RAHC are frequently asymptomatic [32], and tests were performed annually and spontaneous clearance is not an unlikely outcome [38], we cannot rule out the possibility that some reinfections could have gone unnoticed. However, this does not affect our main aim of estimating RAHC. In addition, most RAHC among HIV-infected patients do not clear spontaneously [39]. Also, losses to follow-up could bias our results toward patients with better adherence. In this sense, incidence of RAHC and/or reinfection might be even higher than that reported here. The prospective design, including a detailed questionnaire about sexual habits, is the main strength of the present study.

In conclusion, to achieve HCV elimination in Spain, the estimations of active HCV infections might need correction for the reseeding of the overall burden of HCV infection by RAHC. As virtually all HIV-infected patients with HCV infections have been treated in our country, early detection by massive screening and immediate treatment of HIV-uninfected MSM with HCV infection to access potential reservoirs of HCV is needed to keep Spain on track for HCV elimination by 2030.

Acknowledgements

Conflict of interest: JM has been an investigator in clinical trials supported by Bristol-Myers Squibb, Gilead and Merck Sharp & Dome. He has received lecture fees from Gilead, Bristol-Myers Squibb and Merck Sharp & Dome, and consulting fees from Bristol Myers-Squibb, Gilead and Merck Sharp & Dome. JAP reports having received consulting fees from Bristol-Myers Squibb, Abbvie, Gilead, Merck Sharp & Dome and Janssen Cilag. He has received research support from Bristol-Myers Squibb, Abbvie and Gilead and has received lecture fees from Abbvie, Bristol-Myers Squibb, Janssen Cilag and Gilead.

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Author's contributions

JG-M, AG-S, JAP and JM were responsible for concept and design. JM, RP, CG-A, FT, AR-J, JS, CMG-D, JG-M and JAP were responsible for the patients' follow-up and data recording. Laboratory determinations were carried out by AG-S and MF. AG-S and JM were responsible for writing the article.

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