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Rate of hepatitis C reinfection after successful direct-acting antivirals treatment among people who inject drugs in Spain: the LIVERate study

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Abstract

Background Hepatitis C virus (HCV) reinfection following successful treatment threatens the achievement of HCV elimination. The primary aim of this study is to assess reinfection rate three years after sustained virologic response (SVR) in people who inject drugs (PWID) that are on opioid agonist treatment (OAT) who underwent anti-HCV treatment with interferon-free regimens.

Methods Observational, non-interventional, prospective, descriptive study carried out in Spanish tertiary public hospitals between 2017 and 2022. Participants comprised 186 adult HCV infected individuals, 85.5% males with a mean age (Standard Deviation, SD) of 50.1 (5.9). All were enrolled in an OAT program at baseline and had attained SVR 12 weeks after therapy completion with an interferon-free treatment. Baseline data were abstracted from medical chart information collected through the routine clinical practice.

Results The overall rate of HCV reinfection three years after SVR12 among PWID was 1.2 new cases per 100 person-years of follow-up at a median of 15.9 months. In the subgroup analyses, those with injection drug practice and without a stable housing had higher reinfection rates.

Conclusion Although PWID in OAT present a low rate of reinfection by HCV after successful treatment, a closer monitoring in the first year and strengthening inter-consultations with services responsible for monitoring addiction in these patients will be crucial to reduce risky behaviors avoiding HCV reinfection.

Keywords Hepatitis C, Reinfection, People who inject drugs, Opioid substitute therapy, Risk behaviors, Direct-acting antivirals, Sustained viral response

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Background

People who inject drug (PWID) are at high risk of viral Hepatitis C (HCV) [1]. Approximately 40% of PWID have HCV infections worldwide [2] and 5–22% reinfect annually [3]. In 2016, the World Health Organization (WHO) set the goal of eliminating viral hepatitis by 2030 [1] and Spain developed a "Strategic Plan for the Approach to Hepatitis C (PEAHC)" [4] to support it, which recommends equitable access to direct-acting antivirals. These drugs have replaced the usual therapy until that moment, pegylated interferon (IFN) and ribavirin (RBV). Direct-acting antivirals are much more efficacious, easy to administer [5] and with high pan-genotypic efficacy on HCV [3]. In addition, they offer more convenient administration and shorter treatment regimens as well as better tolerability [6]. This type of therapy is also effective in patients who have received treatment with opioid agonists (OAT, e.g., methadone or buprenorphine) and active PWID [7]. Nevertheless, their success may be weakened by the risk of reinfection [3, 8].

Although these treatments have shown efficacy in people who use drugs, there are several barriers to achieving HCV elimination. The issue arises from the fact that people who use drugs frequently decline medical care and engage risky behaviors that impair disease monitoring, as well as raise the chance of reinfections after the achievement of sustained viral response (SVR) [3, 5, 7, 8]. Risky practices include sharing needles and injection equipment, and engaging in risky sexual practices, especially unprotected intercourse or having multiple sexual partners [1]. In addition, stigmatization and discrimination of this vulnerable population affects their acceptance of treatment and, the psychiatric and social problems they suffer (unstable housing, poverty, incarceration, and marginalization) affect their adherence to therapy [9]. Because reinfection may jeopardize the advantages of HCV treatment for both the individual and the population, it is a serious concern [7].

In a meta-analysis by Simmons B, et al.., in addition to risky practices, HCV-HIV (Human Immunodeficiency Virus) coinfection was highlighted as a risk factor for reinfection. Thus, they reported a reinfection rate of 1.91 (95% CI: 11.4–28.2) and 3.2 (95% CI: 0.0-123.5) per 100 person-years (PYs) in mono-infected persons performing high-risk practices and in those coinfected (HCV-HIV), respectively [10].

Most trials of direct-acting antiviral (DAA) therapies for HCV have excluded people with recent drug use. However, some data exist among people receiving OAT. In phase II/III clinical trials, SVR rates are similar among people receiving OAT compared with those not receiving OAT [11–13].

There is a lack of actual real-world data on the durability of SVR and long-term reinfection rates in HCV-infected PWID treated with IFN-free regimens. The aim of this study is to assess reinfection rate three years after SVR12 in PWIDs that are on OAT who underwent anti-HCV treatment with IFN-free regimens. It also measures time to reinfection and analyzes multiple variables to characterize the HCV-PWID patients.

Methods

Study design

Observational, non-interventional, prospective, descriptive, and multicenter study involving chronic HCV-infected patients who achieved SVR12 with any IFN-free antiviral regimen in Spain. Follow-up occurred at baseline (once SVR12 was confirmed), at 6, 12, 24 and 36 months. All data were extracted from medical history information collected through routine clinical practice. Given the observational and non-interventional nature of the study, variables were collected through medical chart review and were entered into the eCRF through a web page.

Recruitment was carried out between December 2017 and April 2019 in 19 Spanish tertiary public hospitals, specifically, in the outpatient clinics of the Hepatology or Infectious Diseases Departments. The study was approved by an Independent Ethics Committee (IEC) and no specific COVID-19 contingency measures were implemented to manage the study.

Eligible patients were adult (>18 years) women and men, that were previously infected with any HCV genotype, on opioid agonist therapy (OAT; methadone, levomethadone, buprenorphine, naloxone, naltrexone), who had achieved SVR12 from 1st January 2017. Co-infected with HIV individuals were also included. Written informed consent was obtained from all participants. Subjects were excluded if they were not able or unwilling to sign the informed consent.

Study endpoints and variables

Demographic and clinical characteristics (age, gender, race, education level, employment, and residence) were recorded at enrollment. The primary objective was to assess reinfection rate three years after SVR12 post-IFN-free treatment in PWID who were on OAT. SVR12 was defined as undetectable plasma HCV RNA 12 weeks after the end of HCV treatment. HCV reinfection was defined as a positive HCV RNA test preceded by SVR12 development or a negative test result after other reinfection during follow-up, if the genotype detected was different than the one found in the prior infection. In case both genotypes were the same, reinfection was diagnosed according to the phylogenetic analysis of the strains at the first and second episode. The reinfection rate was expressed as person-year (PYs) of follow-up reinfection incidence rate (number of new cases of reinfection during follow-up/

total persons-follow-up time [years] of all patients). In the survival analyses (where events have been considered to be reinfections occurring for the first time after SVR12), there were event-free survival times > 3 years because reinfection analyses described at the last visit but dated > 36 months have been reported. Follow-up time was considered as the last reinfection analysis date. Also, reinfection rates analysis by subgroups (participation in other harm reduction programs, comorbidities, OAT, accommodation, drug use and sexual practices) were performed. High risk sexual factors were defined as men who have sex with men (MSM), unprotected intercourse, multiple sex partners, chemsex, slamming and fisting after achieving SVR12.

Secondary objectives included assessing reinfection rate during follow-up (6 months [mo], 12 mo, 24 mo) and time to reinfection defined as the number of months elapsed from SVR12 date and reinfection date. Also, the influence of comorbidities (HIV-HCV and HBV (Hepatitis B Virus)-HCV coinfections and psychiatric disease), drug use and harm reduction programs (other than OAT) in reinfection rates were evaluated at 6 mo, 12 mo, 24 mo and 3 years. Psychiatric comorbidities were defined as a diagnosis of one of the following: bipolar, psychotic, affective, anxiety or personality disorder, non-opiate dependencies or others unclassified disorders, as well as compliance with psychiatrist visits. High risk sexual practices were also collected. Additionally, compliance with scheduled post-SVR12 appointments was estimated.

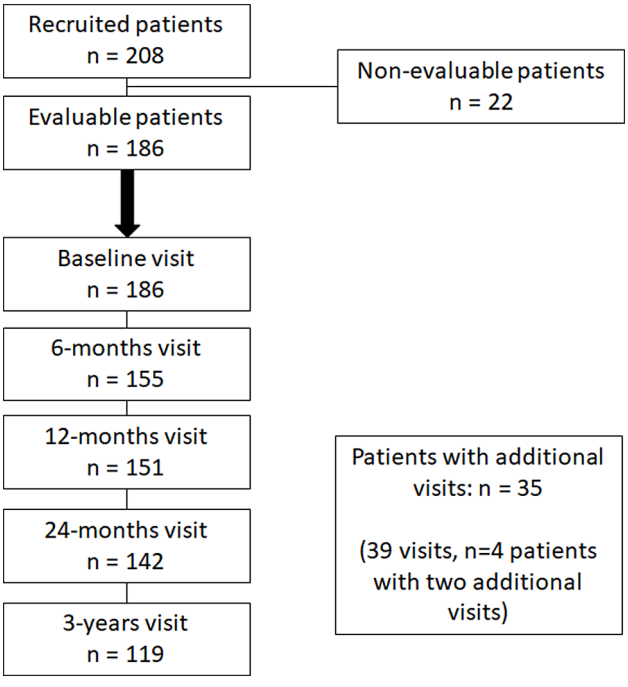

Fig. 1 Patient flow diagram. Additional visits registered until the database closure have been recorded. However, they were only considered to study reinfection rates

Sample size determination and statistical analysis

The sample size was determined according to the primary objective, i.e., reinfection rate three years after 12 weeks of SVR in PWIDs who underwent anti-HCV treatment with IFN-free regimens. Based on the COSTAR-study it was estimated that 200 patients could provide an accuracy of ±3% in the proportion of patient characteristics (COSTAR: 4%); with a confidence of 0.95. The percentage of necessary replacements is expected to be 10%.

Continuous variables were expressed as mean, standard deviation (SD) and confidence interval of the mean (95% CI); whereas categorical ones as absolute and relative frequencies. Comparisons of sociodemographic and clinical characteristics of patients were performed using the Mann-Whitney U test, in continuous variables, and Fisher´s exact tests, in categorical ones. Incidence rate person-year was calculated using the following formula: New cases of reinfection / Total person – time at risk (person-year units). The Kaplan-Meier method was selected for survival analysis (log-rank test), to evaluate global reinfection free survival and, also, by study groups, through the follow-up period. Considering, the time since SVR12 until the onset of the first reinfection and censoring the last reinfection analysis date.

Statistical significance was set at $p < 0.05$. All statistical procedures were carried out with SAS 9.4.

Results

Sample inclusion and baseline characteristics

A total of 208 patients were included in the study, of which 186 were valid for the sample description and the study outcomes analyses (Fig. 1). Of these, 155 underwent the 6-month follow-up visit (median 6.2 months from SVR12), 151 completed the 1-year follow-up (12.5 months), 142 the 2-year follow-up (24 0.3 months) and, finally, 119 were followed up for 3 years (36.3 months).

Baseline characteristics are summarized in Table 1. In the overall population, 85.5% were men with a mean age (Standard Deviation, SD) of 50.1 (5.9) mostly of Caucasian origin (99.5%). Regarding education level, a total of 47.8% had completed primary school and 16.7% secondary school. Employment and residence status data showed that 63.4% were unemployed and the majority had stable housing (87.1%). Coinfection with HIV and HBV was observed in 52.2% and 3.8% of patients, respectively, and 34.9% had psychiatric problems.

At baseline, risky sexual practices after SVR12 were reported from 8.1% patients, of which 73.3% had unprotected sex and 33.3% had more than one sexual partner. Regarding drug use, 32.3% were active people who use drugs, defined as patient using drugs (in addition to OAT) regardless of the consumption frequency (cannabinoids 31.9%, cocaine 27.7% and opioids 26.6%) mainly smoked (52.1%).

Table 1 Sociodemographic characteristics and baseline comorbidities

***N* (%)**	**186 (100.0%)**
Gender n (%)	
Man	159 (85.5%)
Woman	26 (14.0%)
Transgender	1 (0.5%)
Age, Mean (SD)	50.1 (5.9)
Education level n (%)	
Unavailable	38 (20.4%)
No studies	4 (2.2%)
Primary	89 (47.8%)
Secondary	31 (16.7%)
High school	17 (9.1%)
Higher studies	7 (3.8%)
Employment n (%)	
Yes	46 (24.7%)
No	118 (63.4%)
Unavailable	22 (11.8%)
Residence n (%)	
Unstable	21 (11.3%)
Stable	162 (87.1%)
Unavailable	3 (1.6%)
HIV	
Yes	97 (52.2%)
No	89 (47.8%)
HBV	
Yes	7 (3.8%)
No	179 (96.2%)
Psychiatric diseases	
Yes	65 (34.9%)
No	121 (65.1%)
Psychiatric diseases type[1,2]	**65 (100.0%)**
Bipolar disorder	1 (1.5%)
Psychotic disorder	12 (18.5%)
Affective disorder	18 (27.7%)
Anxiety disorder	12 (18.5%)
Personality disorder	10 (15.4%)
Abuse other than opioids	6 (9.2%)
Other psychiatric disorders	9 (13.8%)

[1]A patient could have more than one category marked

[2]Percentages calculated over the total number of patients with psychiatric comorbidities ($n=65$)

To be included in the study, all participants were required to be enrolled in an OAT. They were mainly treated with methadone (91.4%). Also, 41.9% patients self-reported to be in a harm reduction program at baseline visit and counseling was the most frequent (78.2%), followed by low intervention threshold (28.2%), meeting and support centers (16,7%), distribution of syringes (2.6%), community outreach (1.3%), and clean rooms (self-injection supervised) (1.3%).

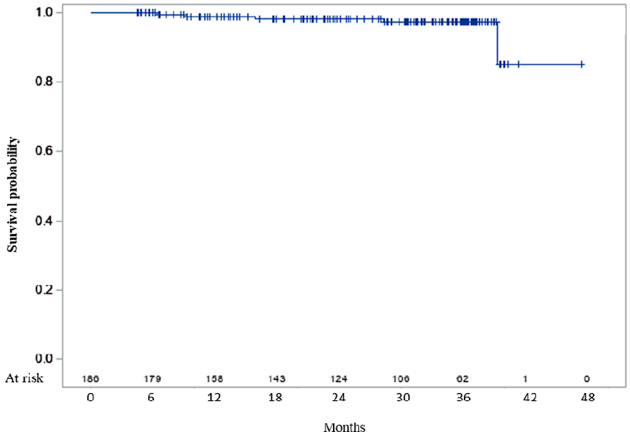

Fig. 2 Reinfection free period after reaching SVR12. Kaplan-Meier method (log-rank test)

Primary endpoint: reinfection rate after 3 years

Since SVR12, reinfection was observed in five people out of 186 assessable patients (2.7%) during follow-up period, considering the follow-up time as date of last available patient visit. During this period, the incidence rate was 1.15 new cases/100 person-years (PYs) (95% CI: 0.48–2.76). No patient had more than one episode of infection during the study. After 3 years, the survival probability of no occurrence of reinfection after reaching SVR12 was 85.2% (Fig. 2).

Subgroup analysis

In the subgroup analysis of reinfection according to the present comorbidities, none of the patients reinfected during follow-up had HBV coinfection, however, two patients of the five reinfected had HIV-HCV comorbidities. On the other hand, the incidence rate of reinfection in patients with HIV-HCV comorbidities ($n=2/97$; 2.1%) was 0.85/100 PYs of follow-up (95% CI: 0.21–3.40); while this rate was 1.5/100 PYs in patients without HIV ($n=3/89$; 3.4%) (95% CI: 0.48–4.64), noting an incidence ratio rate (IRR)=0.6 (95% CI: 0.1–3.4; $p=0.5361$). Thus, patients without VIH the reinfection rate was 1.76 times higher than the one obtained for the other patients (Fig. 3).

Two patients reinfected had psychiatric comorbidities ($n=2/65$; 3.1%), showing reinfection rates 1.5 times higher than patients without them ($n=3/121$; 2.5%) (incidence rate of reinfection: 1.5/100 PYs, 95% CI: 0.38–6.02) vs. 0.99 new cases/100 PYs of follow-up, 95% CI: 0.32–3.07 respectively; IRR: 1.5, 95% CI: 0.3–9.1; $p=0.6477$).

During the follow-up period, 44.1% actively used drugs (cannabinoids 54.3%, opioids 46.9% and cocaine 40.7%), and the most frequent route of administration in the 4 follow-up visits was smoked, in more than 50% of the reported drugs. Four of these patients who actively used drugs, reinfected with an incidence rate of 2.09 cases per

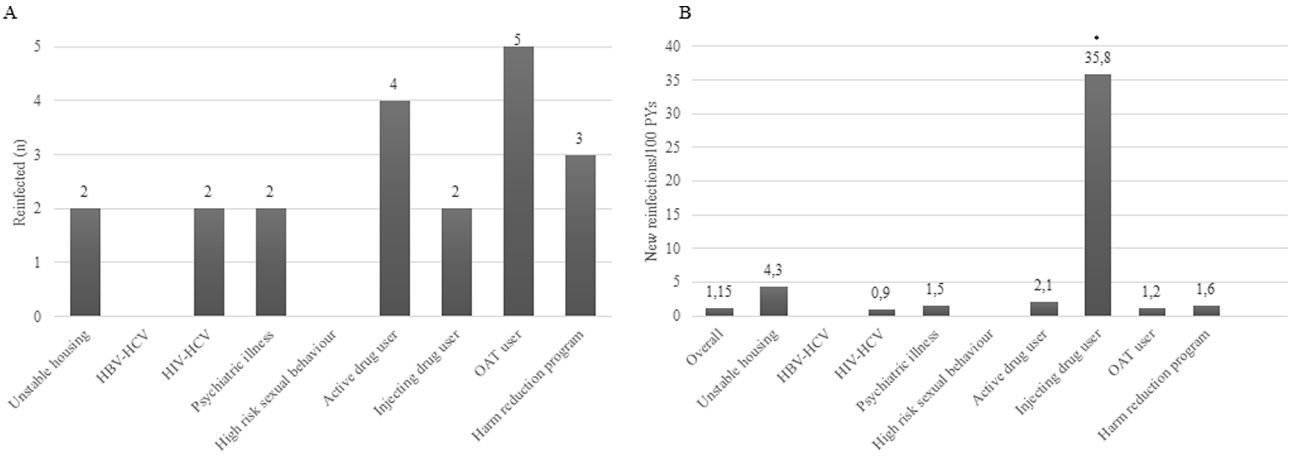

Fig. 3 Reinfection in each group studied among the overall number of reinfected ($n=5$). (**A**) Number of new cases. (**B**) New cases per 100 person-years. *IRR statistical significance, $p<0.01$ (view Table 2)

100 PYs (95% CI: 0.78–5.57) during follow-up (versus 0.4 in people who do not use drugs, 95% CI: 0.06–2.99), with a reinfection rate almost five times higher than in those who did not use drugs (IRR: 5.0; 95% CI: 0.6–44.4; $p=0.1517$). Among these, two used the injectable route for administration resulting in an incidence rate of reinfection of 35.8/100 PYs (95% CI: 8.95–143.01). PWID showed a 66-fold higher reinfection rate than the rest of the patients (IRR 65.7; 95% CI: 6.0–724.1; $p=0.0006$).

All participants were required to be enrolled in an OAT program and most of them maintained it through follow-up. In fact, everyone reinfected during follow-up was in OAT at the time of reinfection ($n=5$) registering an incidence rate of reinfection of 1.2/100 PYs of follow-up (95% CI: 0.50–2.86). Patients participating in harm reduction programs other than OAT at some point of the study (44.6%) showed an incidence reinfection rate 1.84 times higher (1.6/100 PYs; 95% CI: 0.51–4.93; $n=3/83$, 3.6%) than the reinfection rate in the patients who did not (0.86/100 PYs; 95% CI: 0.22–3.45, $n=2/96$, 2.1%) (IRR: 1.8; 95% CI: 0.3–11.0; $p=0.5029$).

Regarding sexual behavior during follow-up, 6.5% reported high-risk sexual behavior (75.0% unprotected sexual intercourse and 16.7% multiple partners). No data confirming risky sexual practices were collected among those who were reinfected during follow-up. There were three cases of reinfection (1.9%) among those without risky sexual behavior showing an incidence rate of reinfection of 0.8 new cases per 100 person-years (95% CI: 0.26–2.47).

Finally, in patients with unstable accommodation the incidence reinfection rate was five times higher than in the rest of patients (4.25 new cases per 100 person-years, 95% CI: 1.06–16.98, $n=2/21$ vs. 0.79 per 100 person-years, 95% CI: 0.25–2.43, $n=3/162$; IRR: 5.4; 95% CI: 0.9–32.4; $p=0.0644$).

Secondary endpoints

The reinfection incidence rate along the follow-up was 1.49, 1.28 and 1.27 new cases per 100 PYs at 6-, 12- and 24-months, respectively. Median time to reinfection was 15.9 months from SVR12.

Reinfection after SVR12 during follow-up (according to harm reduction programs other than OAT, comorbidities, and drug use) are shown in Table 3. Completion of all four follow-up visits was carried out by 44.1% of those included for evaluation.

Discussion

Our study primary aim was to assess reinfection rate three years after successful IFN-free treatment in PWID who were on OAT, analyzing other harm reduction programs, accommodation and comorbidities status, drug use and sexual behaviors. Most trials of DAA therapies for HCV exclude people with recent drug use [15]. However, some data exist among OAT recipients [16]. Our results showed that the overall reinfection rate in those people who inject drugs evidenced significantly higher rates (35.8/100 PYs), nevertheless these values must be observed with caution because the total number of reinfections during the follow up period was low ($n=5$). Similarly, a 3 -year extension of the CO-STAR Study, randomized, controlled, double-blind trial was performed in 12 countries to evaluate the combination of elbasvir-grazoprevir in the treatment of HCV in PWID receiving OAT. This study estimated a low overall rate of 1.7 reinfections/100 PYs (95% CI: 0.8-3.0) noting higher values for recent people who inject drugs (1.9/100 PYs [95% CI: 0.5 to 4.8]) mostly in the first 24 weeks after treatment completion [17]. A meta-analysis assessing the rate of HCV reinfection following treatment among people with recent drug use and those receiving OAT, found similar HCV reinfections outcomes (1.4 per 100 person-years [95% CI: 0.8–2.6]) in people receiving OAT alongside

Table 2 Reinfection rate three years after SVR12 according to different factors

		Reinfection, *n* (%)				Number of reinfection person-year				
		n (%)	Yes[1]	No	P[3]	New cases (n)	Person-year units (n)	Incidence rate person-year[2]	IRR, IC 95%	p
Type of housing	*Unstable*	21 (100.0)	2 (9.5)	19 (90.5)	0.102	2	47.06	0.043	5.4 (0.9–32.4)	0.0644
(*n* = 183)	*Stable*	162 (100.0)	3 (1.9)	159 (98.1)		3	381.82	0.008		
HBV-HCV coinfection	*Yes*	7 (100.0)	-	7 (100.0)	1.000	0	18.37	-	-	-
(*n* = 186)	*No*	179 (100.0)	5 (2.8)	174 (97.2)		5	416.8	0.012		
HIV-HCV coinfection	*Yes*	97 (100.0)	2 (2.1)	95 (97.9)	0.671	2	234.89	0.009	0.6 (0.1–3.4)	0.5361
(*n* = 186)	*No*	89 (100.0)	3 (3.4)	86 (96.6)		3	200.28	0.015		
Psychiatric illness	*Yes*	65 (100.0)	2 (3.1)	63 (96.9)	1.000	2	132.82	0.015	1.5 (0.3–9.1)	0.6477
(*n* = 186)	*No*	121 (100.0)	3 (2.5)	118 (97.5)		3	302.34	0.01		
High-risk sexual behavior at the reinfection time	*Yes*	12 (100.0)	-	12 (100.0)	1.000	0	30.56	-	-	-
(*n* = 172)	*No*	160 (100.0)	3 (1.9)	157 (98.1)		3	376.86	0.008		
Active drug user at the reinfection time	*Yes*	82 (100.0)	4 (4.9)	78 (95.1)	0.175	4	191.26	0.021	5.0 (0.6–44.4)	0.1517
(*n* = 183)	*No*	101 (100.0)	1 (1.0)	100 (99.0)		1	237.44	0.004		
People who inject drugs[4] (*n* = 81)	*Yes*	2 (100.0)	2 (100.0)	-	0.001	2	5.59	0.358	65.7 (6.0–724.1)	0.0006
	No	79 (100.0)	1 (1.3)	78 (98.7)		1	183.52	0.005		
OAT user[5]	*Yes*	179 (100.0)	5 (2.8)	174 (97.2)	1.000	5	419.58	0.012	-	-
(*n* = 181)	*No*	2 (100.0%)	-	2 (100.0)		0	6.15	-		
Harm reduction program	*Yes*	83 (100.0)	3 (3.6%)	80 (96.4%)	0.664	3	188.47	0.016	1.8 (0.3–11.0)	0.5029
(*n* = 179)	*No*	96 (100.0)	2 (2.1)	94 (97.9)		2	231.62	0.009		

Note unavailable data have been excluded (type of accommodation *n* = 3, high-risk sexual behavior *n* = 13, patients with high-risk sexual behavior who suffered reinfection *n* = 2, people who use drugs *n* = 3, people who inject drugs *n* = 1, OAT *n* = 5, harm reduction program *n* = 7)

[1]Number of new reinfection episodes during follow-up

[2]Incidence rate person-year: # New cases of reinfection / Total person – time at risk (person-year units)

[3]Fisher's exact test

treatment with no recent drug use. However, rates were higher for those receiving the substitution therapy with recent drug use (5.9/100 person-years [95% CI; 4.0-8.6]) or people with recent drug use but not receiving OAT (6.6/100 person-years [95% CI: 3.4–12.7]) [18]. Rossi et al. [19], in a large cohort study, evaluated different factors and their association with the risk of HCV reinfection post-DAA. They reported that incidence of reinfection was higher among recent PWIDs (3.1/100 PYs; IRR: 6.7, 95% CI: 1.9–23.5) vs. former PWIDs (1.4/100 PYs; IRR: 3.7, 95% CI: 1.1–12.9) vs. non-PWIDs (0.3/100 PYs), noting that only a participant from a post-treatment OAT program presented reinfection. Therefore, reinfection rates are low but injecting drugs seems to increase it. Inclusion in OAT programs has been shown to improve outcomes. Additionally, they evaluated the association between reinfection and comorbidities. A higher reinfection rate was observed in those patients coinfected with HIV (5.7/100PYs [2.6–10.8]) and psychiatric illness (3.0 [1.45–5.6]) in PWID [19]. In Spain, a study of 84 HIV/HCV-coinfected patients who had previously achieved SVR after HCV treatment, 72 of whom were people who inject drugs, reinfection was documented in 4 (4.76%) patients, 3 of whom were injecting drug users, with 1.2 cases per 100 PYs in the overall study population and 8.7 in people who inject drugs [20]. Our results showed an incidence rate of reinfection five times higher in patients with unstable accommodation than the rest of patients (IRR: 5.4; 95% CI: 0.9–32.4; $p=0.0644$). Similar results were recently described in a real-world cohort of homeless or unstable housed individuals in Boston. HCV reinfection rate was 12.0/100 PYs (95% CI: 9.5–15.1) overall, 18.9/100 person-years (95% CI: 13.3–26.7) among individuals with unstable accommodation and 14.6/100 person-years (95% CI: 10.0–21.3) among those experiencing homelessness [21]. In another prospective study, various socioeconomic factors, and drug use behaviors, specifically being homeless, HIV coinfection, daily drug injection and syringe, or paraphernalia sharing were linked to a higher risk of reinfection. A multivariate regression analysis was performed and only HIV (adjusted odds ratio [OR]: 5.6; 95% CI: 1.9–15.9); $p=0.001$) and daily injection practice (OR 2.8; 95% CI: 1.1–7.2; $p=0.03$) appeared to be independent predictors of contracting a disease again [22].

Since the population included in OATs and other harm reduction programs present higher risk practices to suffer from HCV reinfections, several studies call for the development of prevention and mitigation strategies [7, 8, 19, 21]. Other strategies such as promotion of psychotherapy, social services dedicated to improving stable accommodation and employment could be useful in reducing HCV reinfection [23]. In the study conducted by Lens et al. [22], inclusion in an anti-HCV program had a positive impact on PWID with high-risk practices by decreasing daily injection ($p<0.001$), sharing of materials (syringe $p=0.009$ and paraphernalia $p=0.012$) and risky sex ($p=0.001$), and improving linkage to OAT programs ($p=0.045$) as well as homelessness ($p=0.001$). As stated in the book "Clinical Dilemmas in Viral Liver Disease", people at risk of reinfection should be assessed for risk behaviors and provided with medical education. Also, facilitate access to harm reduction programs and conduct annual follow-up. Retreatment for reinfection should be offered without stigma or discrimination [24], including patients in OAT with other mental disorders (dual disorders) that has been claim as special risk group for having HCV [25].

The results of this first study on the rate of reinfections of HCV in a Spanish population after successful DAA treatment suggest the need of appropriate strategies for education, counseling, and linkage to care services to help reduce the risk of post-treatment reinfection. HCV microelimination programs should include easy access to treatment and harm reduction and behavioral interventions in marginalized patients to achieve the goal of disease elimination [14, 22].

Our study has some limitations. Among them, the loss of follow-up stands out, as 36% of the initial 186 participants unreachable for assessment at the 3-year follow-up, what could lead to an under detection of HCV reinfections This can be explained by these patients' profile, since they are not very compliant with medical follow-up and health care. Nevertheless, the existence of missing data was considered low because the study variables are usually recorded in the medical file. Regarding the low cumulative incidence rate of the primary outcome, it not only posed limitations on the robustness of the estimates but also may have impacted the overall statistical reliability and generalizability of the findings. Also, since there were limited occurrences of HCV reinfection, despite calculating the incidence rate ratios across various sub-groups, it was unfeasible to determine the relative risk in the study. Therefore, the analyses are descriptive and p-values in the statistical models should be interpreted as exploratory and taken with caution. However, this real-world, multi-center study provides valuable insights into the actual clinical practice. Also, conducting extensive long-term follow-ups poses significant challenges and we were able to follow-up patients 36 months.

Conclusion

In conclusion, although reinfection rate for people following OAT programs who inject drugs is low, it can be elevated significanly in homeless and parenteral drug use, beeing afected in lower rate for by different sociodemographic factors and risky behaviors such as mental

Table 3 Influence of different factors in reinfection rates. Reinfection after SVR12 during follow-up according to harm reduction programs, comorbidities, and drug use

		Follow-up							
		6 months		12 months		24 months		3 years	
		N (%)	Reinfected n (%)	N (%)	Reinfected n (%)	N (%)	Reinfected n (%)	N (%)	Reinfected n (%)
Harm reduction programs[2]	Yes n (%)	58 (100.0)	0 (0.0)	58 (100.0)	1 (1.7)	47 (100.0)	1 (2.1)	31 (100.0)	1 (3.2)
	No n (%)	75 (100.0)	1 (1.3)	73 (100.0)	0 (0.0)	76 (100.0)	1 (1.3)	71 (100.0)	0 (0.0)
	P[1]	1.000		0.443		1.000		0.304	
HIV-HCV[3]	Yes n (%)	69 (100.0)	1 (1.4)	76 (100.0)	0 (0.0)	75 (100.0)	1 (1.3)	61 (100.0)	0 (0.0)
	No n (%)	73 (100.0)	0 (0.0)	64 (100.0)	1 (1.6)	62 (100.0)	1 (1.6)	53 (100.0)	1 (1.9)
	P[1]	0.486		0.457		1.000		0.465	
Psychiatric illness[3]	Yes n (%)	52 (100.0)	1 (1.9)	51 (100.0)	0 (0.0)	43 (100.0)	1 (2.3)	30 (100.0)	0 (0.0)
	No n (%)	90 (100.0)	0 (0.0)	89 (100.0)	1 (1.1)	94 (100.0)	1 (1.1)	84 (100.0)	1 (1.2)
	P[1]	0.366		1.000		0.531		1.000	
People who use drugs actively[2]	Yes n (%)	53 (100.0)	0 (0.0)	53 (100.0)	1 (1.9)	45 (100.0)	2 (4.4)	36 (100.0)	1 (2.8)
	No n (%)	84 (100.0)	1 (1.2)	81 (100.0)	0 (0.0)	85 (100.0)	0 (0.0)	69 (100.0)	0 (0.0)
	P[1]	1.000		0.396		0.118		0.343	
People who inject drugs	Yes n (%)	6 (100.0)	0 (0.0)	8 (100.0)	1 (12.5)	8 (100.0)	1 (12.5)	5 (100.0)	0 (0.0)
	No n (%)	47 (100.0)	0 (0.0)	45 (100.0)	0 (0.0)	36 (100.0)	0 (0.0)	31 (100.0)	1 (3.2)
	P[1]	-		0.151		0.182		1.000	

n = 2 reinfected patients described at additional visit have been considered within 2-years follow-up, because they have occurred at 15.9 and 28.3 months

[1]Fisher's exact test

[2]At reinfection time

[3]At baseline

illness, HIV coinfection. Therefore, these patients should be closely followed up the first year after reinfection by offering access to harm reduction programs as well as to mental health and social services.

Abbreviations

DAA	Direct-Acting Antiviral
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IEC	Independent Ethics Committee
IFN	Interferon
IRR	Incidence Rate of Reinfection
mo	Months
OAT	Opioid Agonist Treatment
PEAHC	Strategic Plan for the Approach to Hepatitis C
PWID	People Who Inject Drugs
PYs	Person-Year
RBV	Ribavirin
SD	Standard Deviation
SVR	Sustained Virologic Response
WHO	World Health Organization

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Author contributions
The conception, design or planning of the study was conducted by TAE, JC, EV, FC, NS and CR. The acquisition of the data was provided by TAE, JC, EV, LM, LEA, JN, NS, MP and PR. The analysis of the data was performed by JC, EV and CR. The interpretation of the results was provided by TAE, JC, EV, FC, JML, LEA, JN and CR. The drafting of the manuscript was performed by TAE, JC, EV, and CR. Its review was conducted by JC, EV, FC, JML, LM, LEA, JN, NS, MP, CR and PR. All authors read and approved the final manuscript.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted in conformance with Good Clinical Practice standards and applicable to the Spanish and Autonomous Communities legal regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. Vall d´Hebron University Hospital´s clinical research ethics committee approved this study on September 8th, 2017 and written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
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