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High rates of early HCV reinfection after DAA treatment in people with recent drug use attended at mobile harm reduction units

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ABSTRACT

Background and Aims: The World Health Organization recently called for the elimination of hepatitis C virus (HCV) and has identified people who inject drugs (PWID) as a key target population. Clinical trials analyzing currently available all-oral regimens have demonstrated a high degree of efficacy in this population, with a relatively low reinfection rate. There is an urgent need to confirm these data in a harm reduction and active consumption setting. The primary aim of this study was to evaluate the HCV reinfection rate in people with recent drug use followed at low-threshold mobile harm reduction units.

Method: We included people with recent drug use (smoked or injected heroin/cocaine in the previous 6 months) who received HCV treatment and were attended at two low-threshold mobile harm reduction units over 19 months. Sustained virologic response was assessed 12 weeks after therapy (SVR12). The incidence density of HCV reinfection was defined as the number of reinfections per 100-person years (PY) using person-time of observation and was stratified by drug consumption at initiation of HCV treatment. Cox proportional hazard regression analysis was used to assess factors associated with reinfection.

Results: During the study period, 160 people who used drugs in the past 6 months completed HCV therapy. 122 (73.9%) and 88 (53.3%) reported injecting drug use in the 6 months and 30 days prior to HCV treatment, respectively. The overall SVR12 was 68% in the ITT analysis (reinfection = failure) and 90.7% in the modified intent-to-treat analysis (considering reinfections as response and removing people who were missing SVR data). The cohort at-risk for reinfection (n = 121) included 47 (39.2%) people who initiated HCV treatment with recently reported abstinence. Reinfection was identified in 10 persons (8.3%), and the median time to reinfection was 7.2 (IQR 4.2–18) months. Total follow-up time at-risk was 101.1-PY (median 0.6 years, IQR 0.3–1.3). The overall incidence of reinfection was 9.8 per 100-PY (95% CI 4.7,18.2). The incidence of reinfection was higher amongst those who had injected drugs in the previous 6 months (16.7 [95%CI 8.0; 30.7] per 100-PY) and in the previous 30 days (18.9 [95% CI 8.1; 37.2] per 100-PY). In the adjusted analysis, only injecting drugs use in the month prior to initiation of HCV therapy was associated with reinfection (aHR 8.7, 95%CI 1.0; 73.6; p 0.04).

Conclusion: High efficacy of HCV treatment, was found in people with recent drug use attended and followed at low-threshold mobile harm reduction units. The high rate of early HCV reinfections in this setting should promote surveillance for reinfection at 7-month intervals after ending the treatment or earlier.

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Background

The hepatitis C epidemic and injection drug use are public health issues that are interconnected at the level of transmission (Organization WH, 2018). Injecting drug use has now been documented in most countries and territories in the world, and HIV and HCV infection are prevalent in many populations of PWID, representing a substantial challenge to public health (Degenhardt et al., 2017; Grebely & Larney, 2019). With respect to HCV infection, the World Health Organization (WHO) estimated that, in 2017, there were 15.6 million people who inject drugs (PWID) aged 15–64 years and that 52% of PWID have serological evidence of past or current HCV infection (Organization WH, 2018). Most of the 1.75 million new infections in 2015 occur among people with recent injecting drug use, with a global incidence rate of 23.7 per 100,000 (Organization WH, 2017; UNAIDS, 2010). WHO set an ambitious goal of eliminating viral hepatitis by 2030 (Grebely, Dore, Morin, Rockstroh, & Klein, 2017) and thus, there is a need to decrease transmission of HCV associated with injecting drug use. This can be accomplished by harm reduction strategies or by treating HCV infection (ie, treatment as a prevention strategy) (Hickman, De Angelis, Vickerman, Hutchinson, & Martin, 2015; Martin, Vickerman, Dore, & Hickman, 2015).

Harm reduction includes but is not limited to distribution of sterile needles and syringes to PWID (Cousien et al., 2018; Fernàndez-López, Folch, Majó, Gasulla, & Casabona, 2016; Stoicescu, 2012). Low threshold mobile harm reduction units attend heroin- or cocaine-dependent individuals, who do not usually seek medical care and generally engage in behaviors that carry a high risk of transmission of HCV. Low-threshold mobile harm reduction units would reduce barriers to admission for opiate substitution therapy (OST) and help to retain the patients in the center (Strike, Millson, Hopkins, & Smith, 2013). They deliver medical, social, and psychosocial support in an environment free from stigma and discrimination and in an outreach harm reduction and low-threshold setting (La Rosa et al., 2018; Silva et al., 2017).

Novel direct-acting antivirals (DAA) are now the standard of care for the management of HCV infection (Liver EAfTSoT, 2017; Panel et al., 2015). In interferon-free clinical trials, DAAs are associated with high sustained virologic response (SVR) at 12 weeks after completion of treatment (Afdhal et al., 2014; Foster et al., 2015; Martinello et al., 2018; Vallet-Pichard & Pol, 2017; Zeuzem et al., 2014). DAA treatment has also been shown to be effective among PWID receiving and not receiving OST (Alimohammadi et al., 2018; Grebely et al., 2017b; Grebely, Hajarizadeh, & Dore, 2017; Grebely et al., 2018; Robaeys et al., 2017). Curing HCV infection not only brings benefits to an infected individual, but it also provides a collective benefit by reducing the burden of HCV infection at the population level (Organization WH, 2014; Salmon, Mondelli, Maticic, Arends, & Hepatitis, 2018). Moreover, a recent cost-effectiveness study among PWID in Australia showed that treatment with DAA can be cost-effective in this setting (Scott, Iser, Thompson, Doyle, & Hellard, 2016). Mathematical modelling, which includes evaluation of strategies such as “test and treat” and treating PWID and all their contacts, suggests that treating HCV infection in PWID with DAA is cost-effective (Cousien et al., 2018; Hellard et al., 2014, 2015; van Santen et al., 2016).

Reinfection following therapy is an expected finding when HCV treatment is administered to individuals with ongoing risk behaviors (Martinello et al., 2017) and is a concern if HCV elimination is to be achieved when considering scaling up treatment of HCV with DAA without post-treatment surveillance, harm reduction strategies and education in PWID. Martinello et al. and Rossi et al. reported a high incidence of reinfection following treatment for recent HCV infection in individuals with ongoing exposure to risk (Martinello et al., 2017; Rossi et al., 2018). However, few studies have evaluated the incidence of HCV reinfection following treatment in real-world low-threshold harm reduction settings.

The main objective of this study was to estimate the incidence of HCV reinfection among individuals attending low-threshold mobile harm reduction units and to evaluate social and clinical factors associated with reinfection in this population. As a secondary objective, we assessed the efficacy of the DAA treatment.

Materials and methods

Study population

This observational study was based on data from a follow-up cohort of HCV-infected people who use drugs (PWUD) and who consumed heroin and/or cocaine during the previous 6 months and received interferon-free HCV treatment at two low-threshold mobile harm reduction units located in Madrid (Spain) between January 2016 and July 2018 and who were followed until September 2018. All participants had chronic HCV infection confirmed by HCV RNA measurements. Participants received HCV treatment while in active consumption or with recently reported abstinence in a low-threshold setting. Sociodemographic variables and characteristics related to drug use were collected at initiation of HCV treatment and during follow-up. No information on adherence was collected.

In the low-threshold mobile harm reduction units, a comprehensive multidisciplinary team cared for and followed active PWUD who had limited access to standard healthcare. Several services were offered, including needle and syringe exchange, OST, addiction treatment, frequent testing for infectious diseases, treatment of diseases (infectious, psychiatric, and other chronic diseases), prevention counselling, coverage of basic needs, and social support. Furthermore, referral to detoxification services are provided. This population consumes heroin and/or cocaine, usually mixed in different proportions, through smoking, injection, or both. Substance use information was collected by self-report to healthcare personnel before the initiation of HCV treatment. NSP, OST and other harm reduction services were offered seven days a week in two mobile units located at two different places in Madrid, reaching altogether around 1200 individuals per month. All services were free of charge before, during and after of DAA treatment, on demand and as low threshold. This means that there are no entry requirements, admission or readmissions to the OST program are without appointments and non-judgmental in nature, flexible and with onsite healthcare by doctors/nurses on demand. No information related to needle/syringe sharing and injection paraphernalia sharing was measured neither collected. No other places offer needle, syringe and paraphernalia exchange in Madrid; however, OST is offered at other addiction centers.

This specific group of PWUD is characterized by frequent relapses, few or shorter periods of abstinence, impaired physical conditions, poor access to standard medical care and be socially excluded and marginalized.

HCV RNA testing

HCV infection was confirmed in all patients using the enzyme-linked immunosorbent and PCR assays. Serum samples were tested for HCV antibody using the ADVIA Centaur® HCV assay. Plasma samples were tested for HCV-RNA detection using the VERSANT kPCR Molecular System platform (Siemens) and the VERSANT HCV RNA 1.0 Assay kit (kPCR) following the manufacturer’s instructions. Results were reported as international units per milliliter (IU/ml), with a lower limit of detection of 13 IU/ml. HCV genotype was determined by amplification and reverse transcription using the HCV Amplification 2.0 Assay Line Probe Assay (LiPA) kit in a SimpliAmp TM Thermal Cycler followed by reverse hybridization and detection by the HCV Genotype 2.0 Assay (LiPA) in an Auto-LiPA 48 Genotyping Instrument. HCV RNA sequencing was not performed to determine reinfection or relapse.

Patients were scheduled for routine clinical assessment and blood samples at EOT, SVR, and every 3–6 months thereafter. In addition,

HCV RNA could be tested when high risk behaviors were suspected by the physician or self-perceived by individuals while attending our low-threshold mobile harm reduction units.

Case definitions

End-of-treatment response (ETR) was defined as an undetectable HCV RNA at the end of treatment. SVR was defined as undetectable HCV RNA at the first available HCV RNA measurement obtained a minimum of 12 weeks after the end of treatment. Probable virologic relapse was defined as detectable plasma HCV RNA with the same genotype as baseline at or before the date of SVR and supported based on virologic, behavioural and clinical characteristics.

Reinfection was defined as the presence of detectable HCV RNA after an ETR with detection of an HCV genotype that differed from the baseline genotype, or by the presence of detectable HCV RNA after an ETR without sequence data, but occurring after SVR. Sequencing methods to difference relapse or reinfections were not used. All HCV reinfection samples were assessed in the same laboratory. The estimated date of reinfection was calculated as the midpoint between the dates of the last undetectable HCV RNA and the first detectable HCV RNA during follow-up.

Participants with recently reported abstinence was defined as cessation of drug consumption for at least 15 days and no more than 6 months. It was established by direct observation or drug testing in urine performed by healthcare staff when the participants were admitted to detoxification clinics. Relapse in drug use during follow-up was self-reported by participants or by the low-threshold mobile harm reduction units' team.

Liver stiffness was evaluated using transient elastography. Liver disease stage was defined based on established liver stiffness cutoffs. Cirrhosis (F4) was diagnosed when liver stiffness was ≥12.5 kPa (Castera et al., 2005).

Ethical aspects

The databases of both low-threshold mobile harm reduction units were anonymized with an alphanumeric code that was unique for each individual. Thus, the participant could not be identified and linked to the registered information. When entering the low-threshold mobile harm reduction units, all individuals signed various documents, including informed consents for blood tests, forms for standard follow-up at the unit, and inclusion of information in a database for purposes of analysis. In these circumstances, no additional approval from an Ethics Committee was required.

Statistical analysis

The intent-to-treat (ITT) outcome was SVR, that included all participants who initiated an 8- or 12-week course of therapy prior to 30 April 2018 and 30 March 2018, respectively, and received at least one doses of DAA. A modified intent-to-treat analysis (removing people who were missing SVR data and assuming that reinfections were treatment failures) was performed also. Additionally, we performed an efficacy analysis that considered patients with reinfection as responders.

The individuals at risk for reinfection were those with ETR without virologic relapse and who had at least 1 valid HCV RNA measurement after achieving an ETR. The time at risk for reinfection was calculated from the date of the end of treatment in individuals with an ETR to the date of reinfection or the last undetectable HCV RNA.

Categorical variables were compared using the Pearson chi-squared test or Fisher exact test; continuous variables were compared using the Wilcoxon rank-sum test for independent variables. The Kaplan-Meier method was used to estimate the overall incidence density and incidence density of HCV reinfection according to OST, use of drugs at baseline, and HIV status; 95% confidence intervals (CIs) were calculated using the normal approximation, given the frequent events based on person-time of observation.

Cox proportional hazard regression analysis was used to assess factors associated with time to HCV reinfection. In the unadjusted analyses, potential predictors were determined according to previous reports (Martinello et al., 2017; Schulkind et al., 2019), and included: age (per year), sex, income, nationality, HIV infection, social support, homeless status, mental health illness, OST, injector partner, and injecting drug use (previous 6 months and previous 30 days at initiation of HCV treatment). All variables with $p < 0.05$ in the univariate analysis were included in the multivariate regression models using an Akaike Information criterion (AIC) method approach. Statistical significance was set at $p < 0.05$; p-values were 2-sided.

Data were collected and managed using Research Electronic Data Capture (Redcap), and analyses were performed using R software (R Foundation, Vienna, Austria).

Results

A total of 160 individuals completed DAA treatment for HCV infection at the two low-threshold mobile harm reduction units between January 2016 and July 2018. The demographics of the cohort are outlined in Table 1. Notably, 120 patients (72.7%) were homeless, and 122 (73.9%) and 88 (53.3%) reported injecting drug use in the 6 months and 30 days prior to HCV treatment, respectively. In addition, 142 (86.1%) were receiving OST, 59 (36%) had HIV coinfection, 19 (13.6%) had cirrhosis, 31 (18.9%) had mental disorders, and 71 (43%) started therapy in recently reported abstinence. Of those who started therapy in recent abstinence, 39 (55%) relapsed in drug consumption

Table 1
Baseline characteristics of the overall cohort (n = 160).

Characteristics	n (%) or mean (SD)
Age at treatment, mean (SD) years;	44.2 (8)
Gender	
Female	35 (21.9%)
Male	125 (78.1%)
Nationality	
Spaniards	117 (73.1%)
Eastern Europe	25 (15.6%)
Other nationalities	18 (11.2%)
Mental disorder	30 (18.8%)
IDU during the last 6 months	118 (73.8%)
IDU at last month	84 (52.5%)
HIV co-infection	57 (35.6%)
HCV RNA (log), mean (SD)	13.8 (2.4)
HCV genotype	
1a	73 (48.7%)
1b	20 (13.3%)
2	4 (2.7%)
3	43 (28.7%)
4	10 (6.7%)
HCV treatment experienced	17 (10.6%)
Cirrhosis*	19 (11.9%)
HCV treatment regimen	
Sofosbuvir/ledipasvir	41 (25.6%)
Sofosbuvir plus ribavirin	18 (11.2%)
Sofosbuvir/velpatasvir	31 (19.4%)
Ombitasvir/paritaprevir/ritonavir plus dasabuvir	24 (15.0%)
Glecaprevir/pibrentasvir	35 (21.9%)
Elbasvir/grazoprevir	11 (6.9%)
Opiate substitutive treatment	138 (86.2%)
Drugs use at baseline	90 (56.2%)
Familiar support	57 (35.6%)
Employment	24 (15.0%)
Homeless**	116 (72.5%)

Abbreviations: Injecting drug use (IDU; opiate substitution therapy (OST; standard deviation (SD; hepatitis C virus (HCV.

* measured by liver stiffness (LS) ≥12.5 kPa.

** Temporary/ unstable accommodation/hostel/sofa surfing.

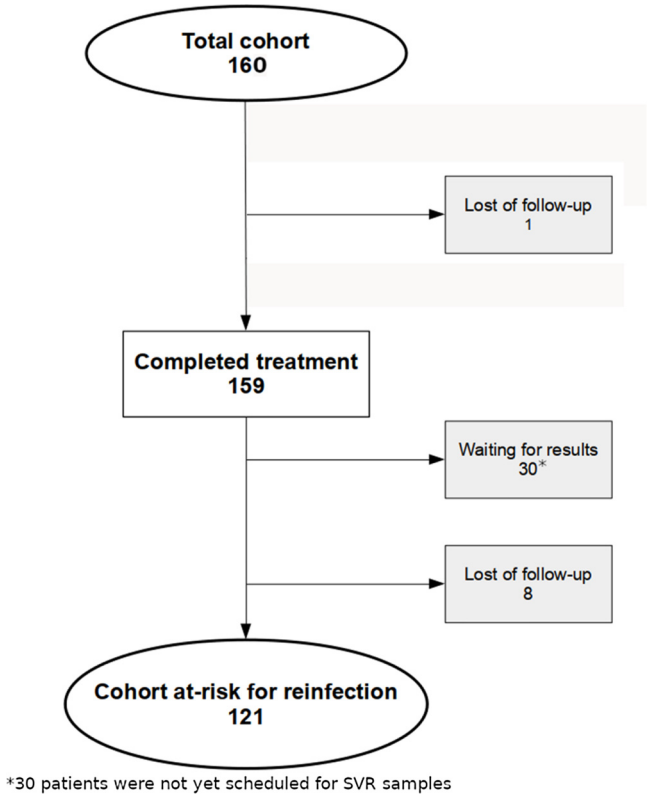

Fig. 1. Flowchart.

during follow-up. Therefore, 129 (80.6%) of individuals consumed heroin and/or cocaine throughout treatment and follow-up.

Overall, 99.4% (159 of 160) completed treatment and had an end of treatment response.1 participant discontinued treatment early and was lost to follow up. The overall SVR by intent to treat was 68% (108 of 160) and the modified intent-to-treat analysis (removing people who were missing SVR data and considering reinfections as treatment failures) was 83.1% (108 of 130). Among people who did not have SVR (n = 51), virologic relapse was recorded in 3 participants, reinfection in 10 and 38 participants were lost to follow-up after achieving ETR, and did not have available SVR results (Fig. 1). Additionally, assuming that people who had reinfection had SVR and considering reinfections as response, the SVR by intent to treat was 74% (118 of 160) and in the modified intent-to-treat analysis (removing people who were missing SVR data) was 90.7% (118 of 130).

All patients with virologic relapse had a positive HCV RNA with the same baseline genotype after ETR and before SVR.

Participants with virologic relapse and those who were lost to follow-up after ETR were excluded from the analysis of the risk for reinfection. The characteristics of the overall cohort at risk for reinfection and a comparison of those who were and were not re-infected are shown in Table 2. When follow-up was censored at the estimated date of reinfection, total time at risk for reinfection was 101.1-PY (median, 0.6 years; IQR, 0.3–1.3).

During the post-treatment follow-up, we identified 10 reinfections. Detailed demographic and clinical characteristics of the 10 participants with HCV reinfection are shown in Table 3. Six participants reported injecting drug use at initiation of HCV treatment, and another 4 initiated HCV treatment with recently reported abstinence. One participant who had HCV reinfection also seroconverted for HIV during follow-up. HCV genotypes of reinfection changed in all the patients compared with baseline. Low-level quantifiable HCV RNA was detected in an HIV/HCV-coinfected patient with reinfection and, as such, the genotype could not be identified. In this patient, quantifiable HCV RNA

Table 2
Baseline characteristics of the cohort at risk for HCV reinfection.

Characteristics	n (%) or mean (SD) n = 121	No reinfection n = 111	HCV reinfection n = 10
Age at treatment, mean (SD) years	45.3 (7.6)		
Gender			
Female	21 (17.4%)	18 (16.2%)	3 (30%)
Male	100 (82.6%)	93 (83.8%)	7 (70%)
Country of origin			
Spain	91 (75.2%)	85 (76.6%)	6 (60%)
Eastern Europe	17 (14.0%)	13 (11.7%)	4 (40%)
Others	13 (10.8%)	23 (100%)	0
Mental disorder	21 (17.4%)	19 (17.1%)	2 (20%)
IDU during the last 6 months**	87 (71.9%)	77 (69.4%)	10 (100%)
IDU during the last month**	58 (47.9%)	50 (45.0%)	8 (80%)
Homeless/unstable housing***	85 (70.8%)	77 (70.0%)	8 (80%)
HIV coinfection	53 (44.2%)	47 (42.7%)	6 (60%)
HCV RNA (log), mean (SD)	13.7 (2.33)	13.7 (2.2)	13.7 (2.4)
HCV genotype			
1a	49 (43.0%)	45 (42.9%)	4 (44.4%)
1b	18 (15.8%)	16 (15.2%)	2 (22.2%)
2	4 (3.5%)	2,4 (3.8%)	0
3	34 (29.8%)	32 (30.5%)	2 (22.2%)
4	9 (7.9%)	8 (7.6%)	1 (11.1%)
Cirrhosis*	19 (13.6%)	18 (16.2%)	1 (10.0%)
HCV treatment–experienced	13 (10.7%)	12 (10.8%)	1 (10.0%)
HCV treatment regimen			
Sofosbuvir/ledipasvir	39 (32.2%)	35 (31.5%)	4 (40.0%)
ofosbuvir plus ribavirin	17 (14.1%)	14 (12.6%)	3 (30.0%)
Sofosbuvir/velpatasvir	15 (12.4%)	15 (13.5%)	0
Ombitasvir/paritaprevir/ritonavir plus dasabuvir	17 (14.1%)	15 (13.5%)	2 (20.0%)
Glecaprevir/pibrentasvir	19 (15.7%)	18 (16.2%)	1 (10.0%)
Elbasvir/grazoprevir	8 (6.6%)	8 (7.2%)	0
OST	104 (86.7%)	96 (87.3%)	8 (80.0%)
Drug use at baseline	71 (59.2%)	65 (59.1%)	6 (60.0%)
Family support	32 (26.7%)	31 (28.2%)	1 (10.0%)
Employment	32 (26.7%)	29 (26.4%)	3 (30.0%)

* Defined as liver stiffness ≥12.5 kPa.
** Before HCV treatment initiation.
*** Temporary/unstable accommodation/hostel/sofa surfing.

was detected only at week 116 after completion of treatment, with repeatedly negative HCV RNA between SVR and week 88 after treatment. Eight patients (80%) developed persistent infections, while 2 patients cleared the virus spontaneously (the mid-point between the last positive and first negative were 7.2 and 13.8 weeks, respectively). As of September 30, 2018, 5 of the patients with persistent reinfections were subsequently retreated and achieved SVR, 2 were under treatment, and 1 had not received treatment. No symptomatic acute reinfections were reported.

Among the 10 patients with HCV reinfection, median estimated time to HCV reinfection was 7.2 (IQR, 4.2–18) months after the end of treatment. Median time to reinfection was shorter in those who reported injecting drug use at initiation of HCV treatment (5.9 months; IQR, 4.3–7.8, p = 0.01) and the median interval between tests post SVR was 4.9 (IQR, 3.3–7.1) months.

The overall and persistent reinfection rates were 9.8 (95% CI, 4.7; 18.2) (Fig. 2) and 7.9 per 100-PY (95% CI, 3.4; 15.6), respectively. There were no differences in the rate of HCV reinfection among HIV-infected and HIV–uninfected people, in people on OST compared with people who were not receiving OST, or in people with recently reported abstinence compared to people in active consumption at baseline (Table 4). The incidence of reinfection was higher among those who reported injecting drug use in the previous 6 months at baseline: 16.7 (95% CI, 8.0; 30.7) per 100 PY and among those who reported injecting drug use in the previous 30 days at baseline: 18.9 [95% CI, 8.1; 37.2]

Table 3
Demographic, behavioral, and virologic characteristics of 10 individuals with HCV reinfection.

Sex	Age	IDU[a]	HIV infection	Primary HCV genotype	Reinfection HCV genotype	Time between EOT and reinfection (weeks)	Reinfection outcome	Liver stiffness
Male	39	Yes	Yes	1a	4	26	Persistence	6.1 kPa
Female	35	Yes	Yes	1b	4	28	Persistence	5.2 kPa
Female	42	No	Yes	1a	Not identified[b]	117	Retreated (cured)	18.6 kPa
Female	51	Yes	No	1a	1b	16	Spontaneous clearance	5.0 kPa
Male	37	Yes	No	1b	3	28	Spontaneous clearance	5.0 kPa
Male	51	Yes	Yes	3	1b	86	Persistence	5.4 kPa
Male	33	Yes	Yes	1a	2	14	Retreated (cured)	6.7 kPa
Male	48	No	No	4	1a	31	Retreated (cured)	5.8 kPa
Male	40	No	Yes	3	1a	32	Retreated (cured)	8.9 kPa
Male	40	No	No	1a	4	128	Retreated (cured)	4.5 kPa

Abbreviations: IDU, injection drug use; EOT end of treatment; Kpa: Kilopascals; Liver stiffness measured using a FibroScan.
[a] Use of injecting drugs at initiation of HCV treatment.
[b] Unable to sequence owing to low HCV RNA at reinfection.

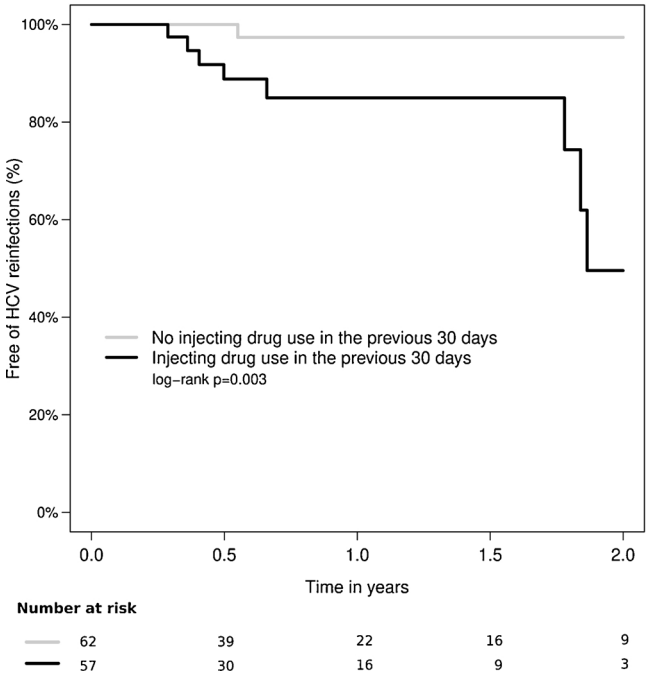

Fig. 2. Kaplan-Meier graph of time to HCV reinfection.

Table 4
HCV reinfection rates in the study population according to different subgroups.

Characteristics at baseline*	Incidence rate (per 100 PY); CI 95%
HIV-positive	11.0 [95% CI, 4.0; 23.9]
HIV-negative	8.6 [95% CI, 2.3; 21.9]
OST	10.0 [95% CI, 4.5; 19.0]
No OST	13.6 [95% CI, 0.3; 75.9]
Recently reported abstinence	9.1 [95% CI, 2.9; 21.3]
Active drugs consumption	10.8 [95% CI, 3.5; 25.2]
Injecting drug use in the previous 6 months	16.7 (95% CI, 8.0; 30.7)
No injecting drug use in the previous 6 months	no cases (not calculated)
Injecting drug use in the previous 30 days	18.9 [95% CI, 8.1; 37.2]
No injecting drug use in the previous 30 days	3.4 [95% CI, 0.4; 12.3]

Abbreviations: opiate substitution therapy (OST); confidence interval (CI); person-year (PY); at baseline*: time of initiation of HCV treatment.

per 100 PY than in people who did not inject in the previous 30 days: 3.4 [95% CI, 0.4; 12.3] per 100 PY, p 0.01. No reinfections were detected in people who did not inject in the previous 6 months.

The variables associated with time to HCV reinfection in the unadjusted analysis were age per year (HR, 0.9; 95% CI, 0.8; 0.9) and injecting drug use at 30 days previous to HCV treatment initiation (HR,11.69; 95%CI,1.5; 93.9). Sociodemographic variables, history of mental illness, OST, cirrhosis status, and HIV coinfection were not associated with time to HCV reinfection in the unadjusted analysis. In the adjusted analysis, only active injecting drug use at 30 days before initiation of HCV treatment remained associated with time to HCV reinfection (aHR, 8.73; 95% CI, 1.03; 73.63) (Table 5).

Discussion

This study assessed the HCV reinfection rate following successful HCV treatment among people with recent drug use. All of the patients reported using drugs, either smoked or injected, at least 6 months prior to HCV treatment. Ten cases of reinfection were identified for an overall incidence of reinfection of 9.8 per 100 PY, which increased to 16.7 and 18.9 cases per 100 PY in those who injected drugs in the previous 6 months and 30 days, respectively. All patients with reinfections reported injecting drug use during or after treatment, with the average time to reinfection being 7 months. To our knowledge, this is the first real-life study in the DAA era performed in low-threshold mobile harm reduction units that included marginalized and outreach PWUD and provides important data on HCV reinfection among people who might be less likely to engage in medical care at community-based health services and hospital-based clinics.

Reinfection is common when HCV treatment is given to individuals with ongoing risk behavior (Ingiliz et al., 2017). Based on data from

Table 5
Cox proportional hazards analysis of factors associated with time to HCV reinfection among individuals who reported drug use 6 months before HCV treatment (n = 121).

Factors	Unadjusted HR (95% CI)	p value	Adjusted HR (95% IC)	p value
Age (per year)	0.9 (0.82;0.98)	0.013	0.92 (0.84;1.01)	0.090
Gender, male	0.41 (0.1;1.63)	0.207		
HIV infection	0.89 (0.23;3.43)	0.871	0.76 (0.19;3.03)	0.702
IDU 1 month at baseline*	11.69 (1.46;93.91)	0.021	9.17 (1.08;77.77)	0.042
Mental disorder	0.88 (0.18;4.28)	0.876		
Opiate substitution treatment	1.46 (0.18;11.91)	0.723	0.82 (0.05;13.61)	0.891
Employment status	0.69 (0.09;5.51)	0.724		
Drug use at baseline*	1.07 (0.31;3.72)	0.919		
Family support	0.2 (0.03;1.63)	0.134		
Homeless	2.16 (0.27; 17.21)	0.468	3.68 (0.24; 57.60)	0.353

Abbreviations: HR, hazard ratio; CI, confidence interval; IDU, injection drug use.
* baseline: time of initiation of HCV treatment.

studies of interferon-based treatment, the incidence of reinfection after sustained virologic response ranges from 2 to 6/100 PY among PWID (Midgard, Weir et al., 2016). Currently, DAA-based studies in this population have shown the incidence of reinfection to range from 1.2 per 100 PY to 5.7 per 100 PY (Falade-Nwulia, Sulkowski, Merkow, Latkin, & Mehta, 2018; Midgard, Bjøro et al., 2016; Rossi et al., 2018; Weir et al., 2016), which is significantly lower than that found in our study. The differences could be explained by the context in which previous studies were performed. Some were performed in the setting of clinical trials, such as SIMPLIFY (4.8 per 100 PY) and C-EDGE CO-STAR study (2.3 per 100 PY), while others included cohorts composed of mixed populations of HIV-infected men who have sex with men (MSM) and PWID (Martinello et al., 2017; Young et al., 2017) or former injection drug users (Rossi et al., 2018). Two Spanish cohorts of HIV/HCV-co-infected patients also reported low reinfection rates (0.21 [0.09-0.52] and 1.21 [0.3–3.09] cases per 100 PY for PWID) (Berenguer et al., 2018; Pineda et al., 2015); however, both cohorts were constituted by heterogeneous populations including mainly MSM or individuals who reported injecting drugs use once in a lifetime (Pineda et al., 2015). Of note, the reinfection rate was 8.72 (4.8–23.7) cases per 100 PY in a small subset of patients (3 out of 11 [27%]) who used heroin and/or cocaine during follow-up (Pineda et al., 2015). More recently, a UK community needle and syringe program with a population profile similar to that of the present study found an even higher HCV reinfection rate (23.5 per 100 PY), although the regimens used in this study included interferon-based treatment (Schulkind et al., 2018). More studies are clearly needed in outreach PWUD who report recent injecting drug use and who are treated in a harm reduction setting to confirm the real incidence of reinfection in this high-risk population.

Addiction is a chronic neuropsychiatric disease, and relapse is a major characteristic of drug dependence (Goldstein et al., 2000). In the present cohort of PWUD at risk of HCV reinfection, around two thirds of participants who reported abstinence at initiation of HCV treatment subsequently relapsed to drug use during follow-up, as reported elsewhere (Shah, Galai, Celentano, Vlahov, & Strathdee, 2006; West et al., 2016). Given the few therapeutic options to treat severe cocaine dependence (Andraka-Christou, 2016; Ling et al., 2016), this population continues to be at high risk of reinfection even after DAA treatment. The relapsing and remitting nature of drug dependence (Shah et al., 2006; Volkow & Morales, 2015) might explain the lack of differences in the HCV reinfection rate we found between PWUD who initiate HCV treatment in recent abstinence or those who were injecting drugs at baseline. These data argues against waiting for abstinence to begin therapy, assuming a low or null risk of reinfection, being more important the efforts aimed at improving retention in care for HCV and reinforcing adherence during the therapy (Gonzalez, Fierer, & Talal, 2017).

Relapse to injecting drug use clearly predicted reinfection in some studies (Midgard, Weir et al., 2016). Thus, once treated, relapsing individuals should continue to be tested regularly for reinfection. According to AASLD and EASL, testing for HCV reinfection among patients at ongoing risk for HCV infection (e.g., injecting drug use or high-risk sexual exposure) should be performed annually (Liver EAfTSoT, 2017; Panel et al., 2015). However, we found a mean time to HCV reinfection of around 7 months after ETR in patients who reported injecting drug use at initiation of HCV treatment. This short time until reinfection is probably associated with the characteristics of the population evaluated, for example, an unstable lifestyle, relapse, and marginalization, which are not usually represented in previous studies. Therefore, clinicians who treat this population should request post-treatment HCV RNA measurements at 7-month intervals, or even more frequently, based on risk behaviors. Early detection and treatment of reinfection is of paramount importance, since it prevents transmission of HCV to other contacts and reduces the burden of HCV infection at the population level (Grebely, Dore, Morin, Rockstroh, & Klein, 2017; Salmon et al., 2018).

Mathematical models have suggested that dramatic reductions in the prevalence and incidence of HCV are possible by scaling-up treatment of HCV in patients at high risk of transmission (Martin et al., 2015). In addition, the approach is cost-effective (Cousien et al., 2018; Organization WH, 2018; Wisløff et al., 2018). Between 2015 and 2030, WHO targets include reducing new HCV infections by 80%. To achieve this goal, the prevalence of viremia should be reduced among those most at risk of onward transmission, including populations seeking care in low-threshold mobile harm reduction units. An Australian experience shows that high DAA uptake leads to a rapid fall in the prevalence of HCV viremia from 43% to 25% among PWID after unrestricted access to DAAs (Iversen et al., 2018). Similarly, a report from the Netherlands showed a decrease of 52% in acute HCV infections among HIV-infected MSM after 1 year of unrestricted DAA treatment (Boerekamps et al., 2017). In addition, WHO elimination goals will require national or regional strategies and governments investment, reforming drug policies (Grebely et al., 2017d; Lazarus et al., 2019), scaling up and improving funding for harm reduction services (Martin, Hickman, Hutchinson, Goldberg, & Vickerman, 2013; Platt et al., 2017), DAA unrestricted and scale-up access (Grebely et al., 2017d), new models of prescribing (Gunn & Higgs, 2019; Wade et al., 2018), point of care diagnostics that can detect active infection in a single visit (Freiman et al., 2019), and post-treatment surveillance and access to early retreatment strategies.

Some studies have shown SVR rates above 90%, with no differences between active PWID and non-PWID (Alimohammadi et al., 2018; Grebely et al., 2017c, 2018). Our study showed high SVR rates with no differences according to HIV status, injecting drug use status, or OST status (data not shown). Indeed, a recent systematic review and meta-analysis found that the response to DAA treatment was favorable among people with recent drug use (including those who inject) and among those receiving OST, with higher SVR and lower loss to follow-up in clinical trials than in observational studies (Hajarizadeh et al., 2018).

The strengths of our study include its prospective follow-up period and HCV-RNA measurements after SVR, as well as the inclusion of PWUD with significant rates of highly active injectors, homelessness, unemployment, mental disorders, and high-risk behaviors. In most reinfection studies, PWID consists of both former injectors and recent injectors, with variations in the definition of “recent” ranging from 1 month to 1 year (Grebely et al., 2017e). Our findings in people with ongoing risk behaviour should not discourage health professionals from offering HCV therapy to PWUD active. On the contrary, they should move to expand the coverage of harm reduction services, thus prioritizing treatment in people who are actively injecting as a target treatment group in order to reduce the risk of HCV transmission at the population-level, to implement alternative models for access to treatment, and to break the barriers in the HCV care cascade.

Our study is subject to a series of limitations. First, the median follow-up after ETR was relatively short. Reinfection rates could change with a longer follow-up. It seems reasonable to assume that patients with the highest-risk behaviors would become re-infected earlier after SVR, and thus reinfection rates would decrease over time. It is also possible, however, that risk factors did not diminish over time and that high rates of reinfection persist many years after SVR (Young et al., 2017). Additionally, given that the study population engaged in high-risk behaviour, we may have underestimated reinfection rates through missing cases of spontaneous clearance after reinfection. Second, injection behavior during treatment and after SVR was self-reported, thus potentially leading to information bias due to under-reporting. No data on high-risk sexual behaviors was collected also. Third, the distinction between relapse and reinfection was based on genotyping of HCV RNA results during follow-up. Although the gold standard would be sensitive sequencing methods, 9 out the 10 cases of reinfection were confirmed by switched genotypes. Only 1 patient was considered to have reinfection based on the late recurrence at 116 weeks, with no demonstration of change in genotype. This last assumption was based on the findings of a clinical trial in which < 3% of all episodes of sequencing-

confirmed late relapse occurred 12 weeks after treatment and therefore the rates of virologic relapse after the achievement of SVR12 are exceeding low (Falade-Nwulia et al., 2018; Yoshida et al., 2015). Also, there were a possibility of a mixed infection at baseline; however, Dore et al. (2016), using ultradeep sequencing confirmed that all participants of his study with probable reinfection did not have baseline mixed HCV infection, with potential no clearance of the nondominant strain. Four, the 3 cases of probable virologic relapse could have been reinfections with the same genotype, thus increasing the reinfection rate. We could not use sequencing but considered these episodes to be relapses for nonvirologic reasons (clinics and behavioural characteristics) because 2 patients had interruptions and suboptimal adherence to treatment (below 80%), and the other patient, who had cirrhosis caused by genotype 3 HCV, received 18 weeks of sofosbuvir/ledipasvir plus ribavirin for genotype 3 in cirrhosis, an approach considered suboptimal in current guidelines (Liver EAfTSoT, 2017; Panel et al., 2015).

In summary, relapse to injecting drug use was common in injectors who were with recently reported abstinence prior to HCV treatment. The efficacy of treatment was notably high, even in this high-risk marginalized population treated in a low-threshold, harm reduction setting. We found high rates of HCV reinfection following successful DAA treatment, with no differences between active PWUD and those who were with recently reported abstinence. These findings highlight the need to encourage treatment of people with ongoing risk in harm reduction facilities, with frequent testing following successful treatment to detect early reinfections.

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CRediT authorship contribution statement

Jorge Valencia: Formal analysis, Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing - original draft, Writing - review & editing. **Alejandro Alvaro-Meca:** Data curation, Formal analysis, Methodology, Software, Validation. **Jesús Troya:** Formal analysis, Investigation, Methodology, Writing - original draft. **Guillermo Cuevas:** Writing - original draft, Investigation, Formal analysis, Methodology. **Jorge Gutiérrez:** Methodology, Writing - original draft. **Angela Morro:** Investigation, Methodology, Writing - original draft. **Jorge Alvarez:** Methodology, Writing - original draft. **Laura Pulido:** Methodology, Writing - original draft. **Irene Cañamares:** Investigation, Supervision. **Ismael Escobar:** Investigation, Supervision. **Santiago Moreno:** Formal analysis, Funding acquisition, Conceptualization, Investigation, Methodology, Supervision, Writing - original draft, Writing - review & editing. **Pablo Ryan:** Formal analysis, Funding acquisition, Conceptualization, Investigation, Methodology, Supervision, Writing - original draft, Writing - review & editing.

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