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Abstract

Background: The burden of hepatitis C virus (HCV) infection among marginalized people in Spain is high, despite the fact that HCV prevalence has decreased in recent years. We aimed to assess the effectiveness of a simplified point-of-care (PoC) model for screening for active HCV infection via a mobile unit and subsequent linkage to care with the assistance of navigators.

Methods: We carried out a prospective study on 2,001 participants from Madrid, Spain. A nurse and a navigator/educator screened for hepatitis C in a mobile unit, using the OraQuick HCV Rapid Antibody Test and Xpert HCV VL Fingerstick assay. Participants with active HCV were referred to the hospital the same day with a navigator for evaluation and treatment of HCV.

Results: Overall, 1,621 (81%) participants had not been exposed to HCV, 380 (18.9%) were positive for HCV antibodies, and 136 (6.8%) had active hepatitis C. Among the latter, 134 (98.5%) received the HCV screening results, 133 (97.8%) had an appointment at the hospital, 126 (92.8%) were seen by a physician once they were at the hospital, and 105 (77.2%) started HCV treatment. Being over 50 years old and a person who uses drugs, particularly people who inject drugs (PWID), was directly associated with active hepatitis C ($p<0.05$). PWID were the only patients with HCV reinfection (4.3% in people without recent injecting drug use and 5.9% in people with recent injecting drug use). Among PWID, no income and daily alcohol intake were also directly associated with active hepatitis C. People with recent injecting drug use showed the lowest rates of attendance at the hospital (91.8%) and starting HCV treatment (70.4%).

Conclusion: HCV screening using a two-step PoC-based strategy and its linkage to care was extremely efficient for identifying and treating marginalized people with active hepatitis C, thanks to the use of a mobile unit with personnel and technical equipment, an interdisciplinary team, and collaboration between institutions.

Keywords: Hepatitis C; screening mobile unit; people who use drugs; point-of-care; linkage-to-care; HCV testing; HCV treatment; Spain

Introduction

Despite significant advances in hepatitis C virus (HCV) screening and treatment, the burden of HCV infection is high among marginalized people, such as the homeless and people who use drugs (PWUD) (Surey, et al., 2019). Homelessness and injecting drug use history are associated with an increased risk of HCV acquisition (Arum, et al., 2021; Valencia, et al., 2019). The burden of active hepatitis C is exceptionally high in people who inject drugs (PWID) (Morris, et al., 2017; Zibbell, et al., 2018), among whom the prevalence of active hepatitis C in Spain is about 40-50% (Grebely, et al., 2019; Ryan, et al., 2021). Transmission of HCV is frequent in PWID due to ongoing risk behaviors (Platt, et al., 2016; Valencia, et al., 2019), marginalization, and limited access to the health system, all of which result in inadequate HCV screening and linkage to care (Lazarus, et al., 2019; Valerio, et al., 2020).

Injection drug users who initiate opioid agonist therapy are more likely to be diagnosed with HCV infection, initiate HCV therapy, and have a low risk of HCV reinfection after HCV therapy (Norton, Akiyama, Zamor, & Litwin, 2018). In this regard, many studies on HCV linkage to care often include PWID on opioid agonist therapy (S. Chevaliez, et al., 2020; Lazarus, Sperle, Maticic, & Wiessing, 2014). Therefore, it is important to continue evaluating the HCV screening and linkage to care among those who report current or previous injecting drug use.

Mathematical modeling estimates indicate that HCV screening and linkage to care are cost-effective strategies because early identification of HCV-infected patients enables HCV treatment, limiting transmission and preventing or reducing the liver disease (Eckman, Ward, & Sherman, 2019). In this regard, micro-elimination is a pragmatic approach to eliminating HCV infection in marginalized populations (Grebely, Bruneau, et al., 2017; Lazarus, et al., 2018), but perhaps not for all PWID populations in every country. Micro-elimination implies expanded detection, reduction in risk behaviors, and unrestricted access to HCV treatment in well-defined population segments (Grebely, Dore, Morin, Rockstroh, & Klein, 2017; Hollande, Parlati, & Pol, 2020). As such, policies should be developed and implemented to support the prevention of infection and harm reduction among PWID, including needle and syringe programs, opioid agonist therapy, and other evidence-based drug dependence treatment.

The standard strategy for diagnosing and treating HCV infection requires multiple visits to the hospital, resulting in loss to follow-up in marginalized people with active hepatitis C (Grebely, Bruneau, et al., 2017; Lazarus, et al., 2018). Therefore, linkage to care has become an essential component in achieving HCV elimination goals for marginalized people (Grebely, Bruneau, et al., 2017; Lazarus, et al., 2018; Safreed-Harmon, et al., 2019; World Health Organization, 2016). Furthermore, in Spain, HCV treatment is only prescribed in hospital settings, and marginalized populations often do not have access to health care services, making their access to HCV treatment inadequate in many cases (Grebely, Applegate, Cunningham, & Feld, 2017; Yehia, Schranz, Umscheid, & Lo Re, 2014).

HCV testing at the point-of-care (PoC) increases test acceptance and linkage to care in marginalized populations (Grebely, Applegate, et al., 2017). A two-step PoC-based strategy is a cost-effective option for diagnosing HCV infection at a single visit among marginalized people (Stéphane Chevaliez, 2019; Saludes, et al., 2019). Anti-HCV antibodies are first detected using a rapid test, and then, active HCV infection is confirmed using an HCV-RNA test, such as the Xpert HCV Viral Load Fingerstick assay (Xpert-HCV-VL) (Grebely, Applegate, et al., 2017). This strategy reduces the time from sample collection to diagnosis of active hepatitis C at the same visit, thus improving the acceptability of testing and linkage to care (Bajis, et al., 2018; Stéphane Chevaliez, 2019). Moreover, trained peer support workers using a mobile unit to assist in diagnosing and preventing HCV infection are essential for reaching vulnerable people (Surey, et al., 2019). In this study, we aimed to assess the effectiveness of a simplified model for HCV screening at PoC and its linkage to care among marginalized people using a mobile unit.

Methods

Study Population

We carried out a prospective study in Madrid, Spain, from February 1, 2019, to March 15, 2020. We conducted screening of active HCV infection in 2001 participants with a high risk for acquiring HCV infection in Madrid's hot spots, namely, mobile harm reduction units, institutions providing social assistance, public areas, homeless shelters, and places where street prostitution is practiced. Participants were selected consecutively in the order of appearance. We included participants who fulfilled the following criteria: 1) age ≥ 18 years; 2) discrimination because of social, health, economic, and cultural issues; 3) capacity to sign the informed consent.

Ethics statement

The study was conducted according to the Declaration of Helsinki, and participants gave their written informed consent to participate. The Institutional Review Board and the Research Ethics Committee of Hospital General Universitario Gregorio Marañón (378/18).

Study groups

We stratified the study population according to drug use history in order to analyze outcome variables. Thus, the groups formed were the following: i) people without a history of drug use were those who had never used drugs; ii) PWUD without a history of injecting drug use were those who had been drug users but never injected; iii) people without recent injecting drug use were those who had been injecting drug users at least one year before the study period, but not in the previous year; and iv) people with recent injecting drug use were those who had injected drugs in the previous year.

In order to evaluate the predictors of HCV test results, we also stratified the study population according to their HCV infection status. The groups formed were the following: i) persons not exposed to hepatitis C were those who had a negative anti-HCV antibody test result; ii) persons exposed to hepatitis C were those who had a positive anti-HCV antibody test result; iii) persons with active hepatitis C were those who had a positive anti-HCV antibody test and positive HCV-RNA result.

HCV screening

A mobile unit consisting of a van adapted for the project (**Supplementary File 1**) and a satellite car, approached the hot spots following a predefined schedule. In the mobile unit, a nurse and a navigator/educator performed HCV screening with a capillary whole-blood sample.

We used the OraQuick HCV Rapid Antibody Test (OraSure Technologies, Bethlehem, PA, USA), a single-use immunoassay for the qualitative detection of HCV antibodies using a finger-stick capillary whole-blood sample (100 μL blood). The test took approximately 20 minutes to process, after which the result was reported. Individuals with negative HCV antibodies ended their participation in the study. A navigator/educator counseled all participants on ways to prevent HCV transmission, and those with a positive result were offered immediate HCV RNA detection. The navigator/educator was a social worker science graduate trained in infectious disease screening and outreach programs with extensive experience in social interventions for the homeless, PWID, and other marginalized people.

The PoC Xpert-HCV-VL was offered to all individuals with a positive anti-HCV antibody test. For this onsite PCR, 100 μL of the finger-stick capillary blood sample was collected using an EDTA-coated minivette device (Sarstedt Minivette) and analyzed using a GeneXpert instrument (Cepheid, CA, USA) in the mobile unit. The GeneXpert system was powered using a solar battery as well as a charge controller. The limit of quantification was 100 IU/mL; the limit of detection was 40 IU/mL. HCV-RNA results were returned within 60 minutes. While the participant waited for the test results, sociodemographic and epidemiological data were collected through questionnaires. Participants were also given advice on prevention and harm reduction.

Linkage to care

All participants with a positive HCV-RNA test were offered a referral to the hospital the same day because HCV treatment in Spain can only be prescribed at hospitals by a specialist physician. HCV-infected patients who accepted were transported by car by a navigator/educator to the hospital. Due to the geographic proximity and the established protocols for referral and care within the health system in Madrid, most of the patients were transported to the Fast-Track Clinic at "Infanta Leonor" Hospital. Here, patients were examined by a physician who could prescribe HCV treatment the same day according to international guidelines (European Association for the Study of the Liver, 2020). If a participant with a positive HCV-RNA test result refused to be referred to the hospital on the same day, the participant was subsequently contacted to try referral another day. Later, patients who started HCV therapy were given an appointment to confirm the cure of HCV infection 12 weeks after the planned completion date (SVR, sustained virological response).

Data sources

Epidemiological data (age, sex, nationality, income, homeless status, and immigrant status), substance abuse (daily alcohol intake, benzodiazepine, and illegal drugs), sexual risk behavior (sexual relationships and condom use), and previous anti-HCV testing were collected through a questionnaire (see **Supplementary File 2**) on a mobile device with an Internet connection. Data were stored using the Research Electronic Data Capture system (REDCap, Vanderbilt University, Nashville, TN, USA) (Harris, et al., 2009), which is hosted at the Ideas for Health Association. Homeless participants were those who lived on the street or who lived in a homeless shelter. A marginalized person was one who had a social disadvantage or was marginalized in terms of education, health, or sociological, psychological, political, and economic aspects. The daily alcohol intake (>50 g/day) was self-reported by the participant. Clinical data (HCV reinfection, hospital care, HCV treatment started) were obtained from medical records. HCV reinfection was defined as those cases with positive results in HCV serology and negative results in HCV-RNA in plasma documented in the medical records and who now had a positive PoC Xpert-HCV-VL test result.

Outcome variables

According to the results of the screening tests, we considered four outcomes: i) having a previous rapid anti-HCV test performed; ii) having a positive result in the rapid anti-HCV test; iii) having a positive result in the Xpert-HCV-VL test; iv) having HCV reinfection. In the cascade of care for patients with active hepatitis C, we considered four events: i) receiving the HCV test results; ii) having an appointment at the hospital; iii) being seen by a physician once at the hospital; iv) starting HCV therapy.

Statistical analysis

All analyses were performed with IBM SPSS v24 (IBM Corp, Armonk, NY, USA). All p-values were two-tailed and $p < 0.05$ was considered statistically significant. Figures were generated using GraphPad Prism v8.0 (GraphPad Software, Inc., San Diego, CA, USA).

The HCV infection rates were calculated from all participants who underwent the HCV screening tests, and the cascade of care was calculated from all participants with active hepatitis C.

We analyzed the distribution of outcome variables among the drug user populations because the injection of opioids, particularly in recent times, is likely to impact the rate of active infection and the cascade of care. This analysis was performed using the chi-square test or Fisher's exact test (differences between groups). We also evaluated the associations between drug user populations and outcome variables using the Mantel-Haenszel linear-by-linear association test, employing people without a history of drug group as a reference. This test yielded the linear trend between variables.

We also analyzed the association between patient's characteristics (sex, age, Spanish nationality, no income, homeless status, irregular migrant status, daily alcohol intake, benzodiazepine use, drug user ever, injecting drug user ever, people with recent injecting drug use, and sexual relationships in the previous year) and HCV infection groups (unexposed to hepatitis C, exposed to hepatitis C, and active hepatitis C) using multivariate logistic regression, employing the unexposed to hepatitis C group as a reference. The test yielded the adjusted odds ratios (aOR).

Results

Participant characteristics

The median age was 43 years, 68% were male, 48% were migrants (mainly from Latin America [25%]), 58% had no income, and 66% were homeless (**Table 1**). Regarding substance use, 26% had a daily alcohol consumption >50 g/day, and 21% were using benzodiazepines illegally. As for the use of illegal drugs, 43% were PWUD, of whom 50% were PWID (33% people with recent injecting drug use), and heroin and cocaine were the most frequently consumed drugs (**Table 1**). Overall, 44% were receiving opioid agonist therapy. Regarding sexual risk behaviors in the previous year, 56% of the participants had had sexual intercourse with their partners, 82% of whom were unprotected (**Table 1**).

Table 1. Sociodemographic and epidemiological characteristics of the study population.

Characteristics	Data
No.	2001
Age, median (IQR)	43 (34; 52)
<30 years	287 (14.5%)
30-40 years	471 (23.9%)
40-50 years	578 (29.3%)
≥50 years	637 (32.3%)
Male, N (%)	1367 (68.4%)
Nationality, N (%)	
Spain	1046 (52.3%)
Eastern Europe	165 (8.2%)
Western Europe	40 (2%)
North Africa	141 (7.1%)
Sub-Saharan Africa	74 (3.7%)
Middle East	25 (1.2%)
Latin America	497 (24.8%)
Other	13 (0.6%)
No income, N (%)	1167 (58.3%)
Homeless, N (%)	1321 (66%)
Undocumented immigrant, N (%)	116 (5.8%)
Daily alcohol intake >50 g/day, N (%)	516 (25.8%)
Benzodiazepine use, N (%)	424 (21.2%)
Illicit use of benzodiazepines	101/424 (23.8%)
Use of illegal drugs, N (%).	
Had ever used drugs (PWUD)	854 (42.7%)
PWUD (active in last year)	558/854 (65.3%)
Had ever injected drugs (PWID)	430/854 (50.3%)
PWID (active in last year)	142/430 (33%)
Type of illegal drug used	
Cocaine	563/854 (65.9%)

Heroin	359/854 (42.0%)
Marihuana	113/854 (13.2%)
Recreational drugs	28/854 (3.3%)
Opioid agonist therapy	376/854 (44%)
Sexual risk behavior, N (%)	
Sexual relationships (last year)	1121 (56%)
Without a condom (last year)	924/1121 (82.4%)

Statistics: Values are expressed as number (percentage) and median (interquartile range). **Abbreviations**: IQR, interquartile range; PWUD, people who use drugs; PWID, people who inject drugs.

Results of the intervention (HCV screening and linkage to care)

Approximately 32% of participants had previously been screened for HCV infection. Overall, 19% of people were positive for HCV antibodies (exposed to hepatitis C), 7% had a positive result in the HCV-RNA assay (active hepatitis C), and 4% of those with previous HCV antibodies had HCV reinfection (**Figure 1A**). The median HCV viral load was 706,000 IU/mL (109,000; 2,300,000). Additionally, HCV-RNA assay data were not available for 19/380 (5%) individuals who were positive for HCV antibodies (15 not tested for HCV-RNA and four had an indeterminate result).

Among the 136 individuals with active hepatitis C, 134 (98%) received the HCV screening results (two participants did not wait to receive their results), 133 (98%) had an appointment at the hospital (one participant was not located), 126 (93%) attended their appointment and were seen by a physician once they were at the hospital (seven participants missed the appointment), and 105 (77%) started HCV therapy (21 participants were not located to deliver HCV treatment) (**Figure 1B**). Furthermore, SVR data were available in 66.6% (70/105) of patients, of whom 94.3% (66/70) had been cured of HCV infection.

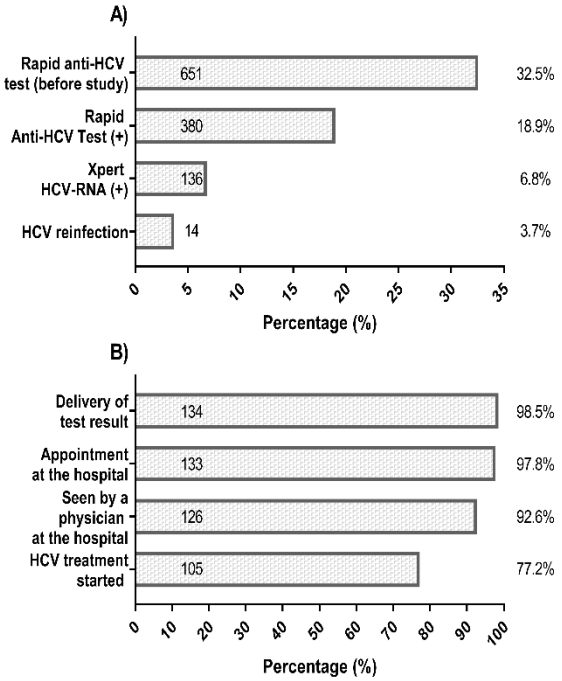

Figure 1. Summary of HCV screening (A) and linkage to care (B) among marginalized populations in Madrid. **Abbreviations**: HCV, hepatitis C virus; RNA, ribonucleic acid.

HCV screening and linkage to care according to drug user populations

Supplementary Table 1 shows the study population's characteristics stratified by drug use (people without a history of drug use, PWUD without a history of injecting drug use, people without recent injecting drug use, and people with recent injecting drug use).

For HCV screening (**Figure 2A**), we found significant differences (chi-square test) and significant linear trends (Mantel-Haenszel association test) between injection drug use and having a rapid anti-HCV test before the study (p<0.001), a positive HCV rapid test (p<0.001), and a detectable HCV-RNA measured by GeneXpert (p<0.001). People without a history of drug use had the lowest percentages of rapid anti-HCV tests before this study (22%), positive HCV antibody testing (3%), and positive HCV-RNA test results (1%). Conversely, PWUD had higher frequencies, particularly PWID. Besides, 54% of people without recent injecting drug use had rapid anti-HCV tests before the study, 64% had positive HCV antibodies, and 22% were HCV-RNA–positive. PWID in the previous year had the highest percentages of rapid anti-HCV tests before this study (56%), positive HCV rapid tests (72%), and positive HCV-RNA tests (27%). Additionally, PWID were the only patients with HCV reinfection (4% in people without recent injecting drug use and 6% in people with recent injecting drug use).

Concerning linkage to care (**Figure 2B**), we found no significant differences between groups and no linear trends. The frequency of people who received the test results and people who were seen by a physician at the hospital was higher than 95% in the four study groups. The percentage of people who were seen by a physician once they were at the hospital was lowest for PWID (92% in people without recent injecting drug use and 89% in people with recent injecting drug use) and people who started HCV treatment (75% in people without recent injecting drug use and 70% in people with recent injecting drug use).

Factors related to the type of exposure to HCV

Supplementary Table 2 shows the study population stratified by HCV infection group (unexposed to hepatitis C, exposed to hepatitis C, and active hepatitis C). Using multivariate logistic regression, with the group of unexposed to hepatitis C as a reference, we analyzed the factors (patient characteristics) associated with being exposed to hepatitis C and having active hepatitis C (**Figure 3**; full description in **Supplementary Table 3**). For the entire population (**Figure 3A**), the factors associated with being exposed to hepatitis C and having active hepatitis C were drug use (aOR=15.8 [p<0.001] and aOR=9.8 [p<0.001], respectively) and being over 50 years of age (aOR=2.7 [p<0.001] and aOR=2.3 [p<0.001], respectively). Considering only PWUD (**Figure 3B**), the factors associated with being exposed to hepatitis C and having active hepatitis C were injecting drug use (aOR=11.3 [p<0.001] and aOR=11.5 (p<0.001), respectively] and being over 50 years of age (aOR=2.7 [p<0.001] and aOR=2 [p=0.019], respectively). Having no income (aOR=1.9; p=0.024) was also associated with having active hepatitis C. When only PWID were analyzed (**Figure 3C**), the factors associated with being exposed to hepatitis C and having active hepatitis C were recent injecting drug use (aOR=1.8 [p=0.019] and aOR=1.9 [p=0.050], respectively), being over 50 years of age (aOR=2.6 [p<0.001] and aOR=2.7 (p=0.006), respectively), and daily alcohol intake (aOR=1.7 [p=0.032] and aOR=1.9 [p=0.038], respectively).

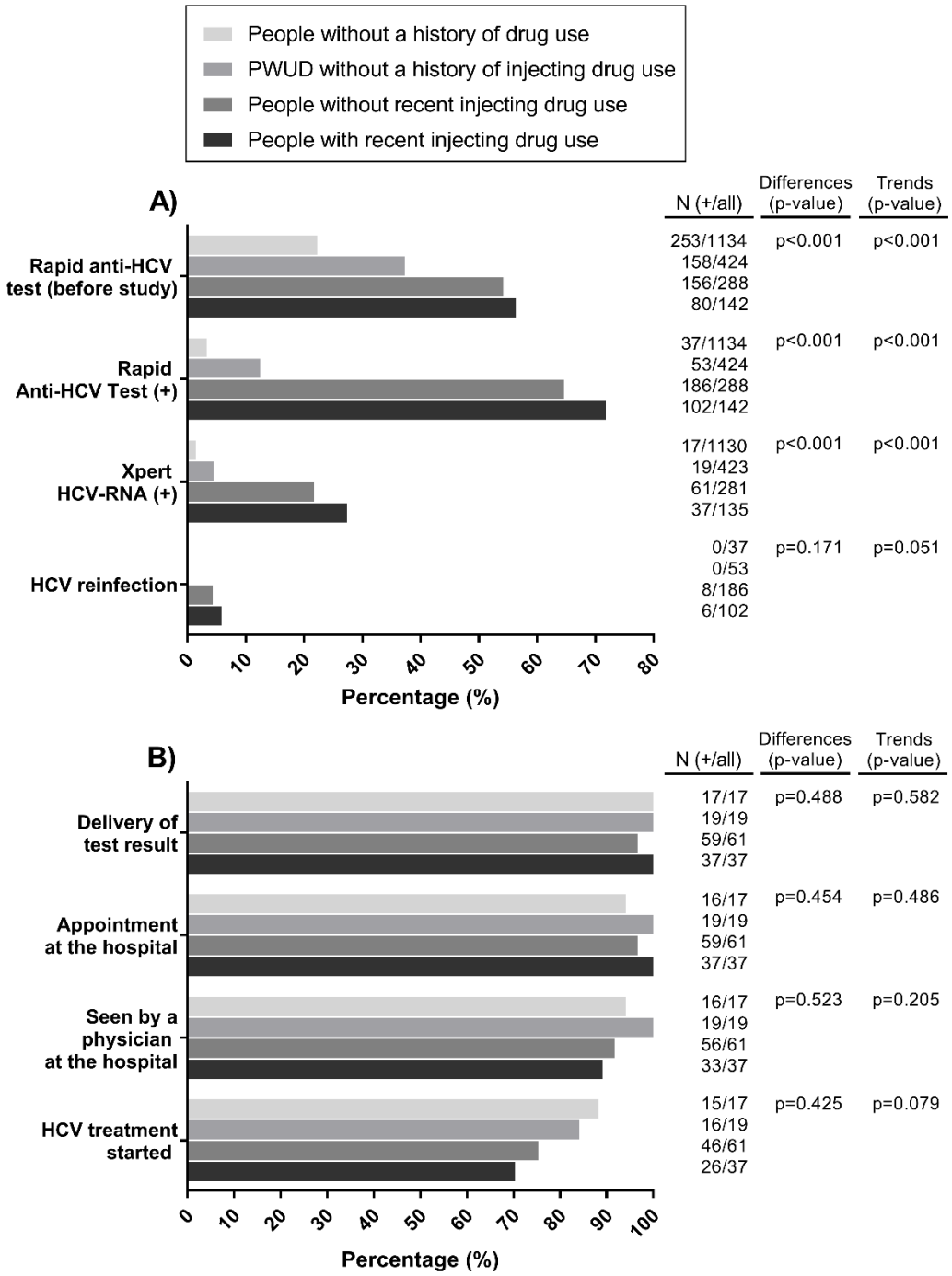

Figure 2. Univariate association between the groups of participants according to drug use and outcome variables related to HCV screening (A) and linkage to care (B) in marginalized populations. **Statistical analysis**: Differences were evaluated using the chi-square test or Fisher's exact test. Linear trends between variables were assessed using the Mantel-Haenszel linear-by-linear association test. **Abbreviations**: HCV, hepatitis C virus; RNA, ribonucleic acid; PWUD; people who use drugs.

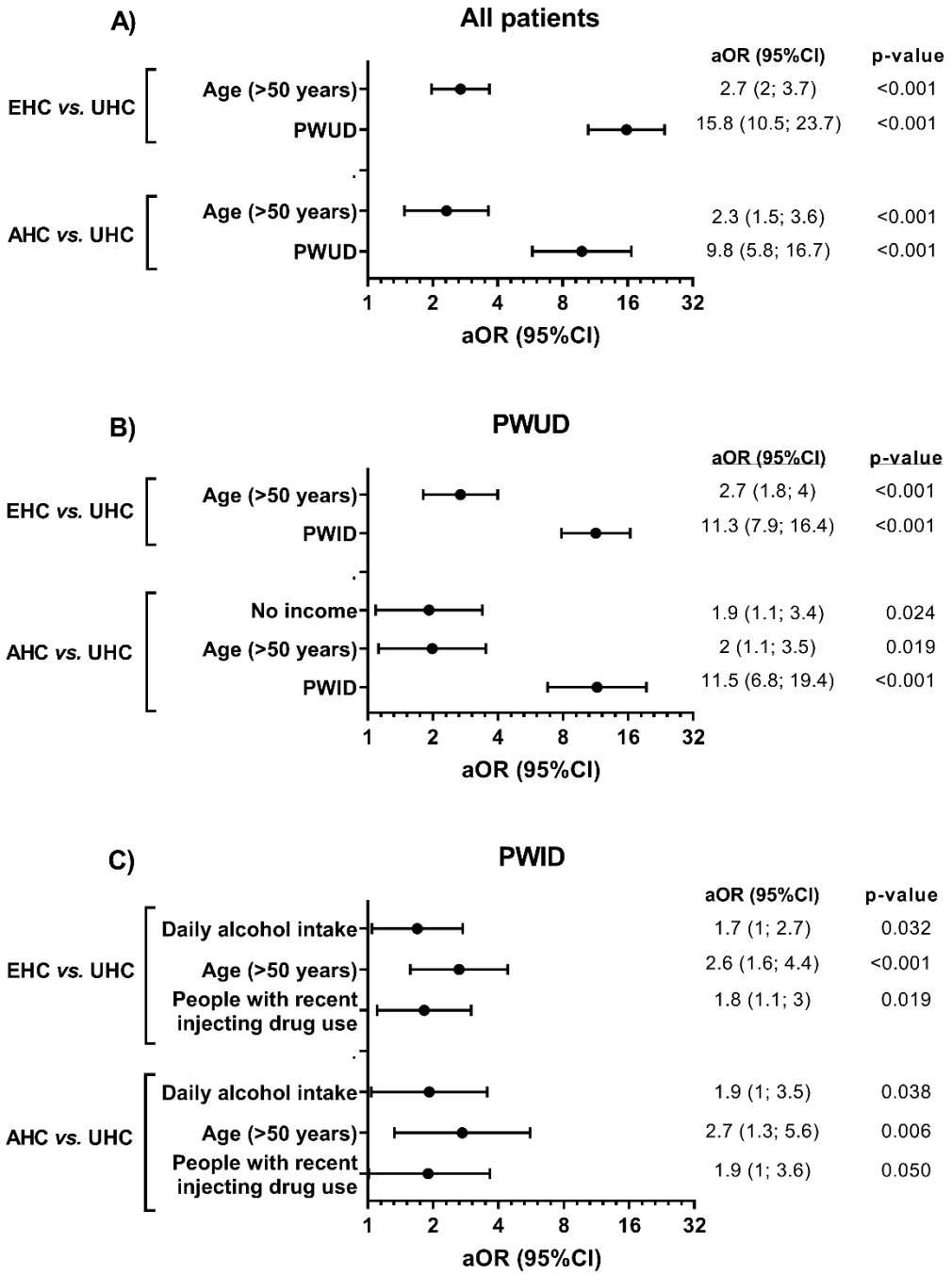

Figure 3. Summary of factors linked to HCV infection among marginalized populations in Madrid stratified by drug users. **Statistical analysis**: The association between the patient's characteristics and belonging to a study group according to HCV infection was evaluated by multivariate logistic regression (see the statistical analysis section). **Abbreviations**: HCV, hepatitis C virus; RNA, ribonucleic acid; PWUD; people who use drugs; PWID, people who inject drugs; UHC, unexposed to hepatitis C; EHC, exposed to hepatitis C; AHC, active hepatitis C; aOR, adjusted odds ratio; 95%CI, 95% confidence interval.

Discussion

We conducted a prospective study on marginalized people from Madrid to evaluate the effectiveness of active hepatitis C screening and linkage to care through a mobile unit. This strategy involved performing rapid tests with a two-step PoC-based strategy and referring

participants to the hospital with the help of a navigator. We found that the prevalence of active hepatitis C and that of HCV reinfection among patients with previous HCV antibodies were both high in PWID (6.8% and 3.7%, respectively). Second, linkage to care was high, as about 77% of participants started HCV therapy. Third, having active hepatitis C was linked to the use of drugs—mainly intravenous drugs—being over 50 years of age, having no income, and daily alcohol intake.

Access to HCV screening can be facilitated by making virologic testing quick and easy through simplification of the HCV testing algorithm and increasing diagnostic rates (Stéphane Chevaliez, 2019). In a previous study in Madrid using a mobile unit and DBS to collect samples, which were later sent to the laboratory to confirm active hepatitis C infection, only 85.2% of the participants were contacted to report their results 19 days later (Ryan, et al., 2021). However, the current study found only 2 participants did not wait to receive their results on the same day, demonstrating that a single-visit PoC-based strategy for HCV screening was useful and quick for the diagnostic of active hepatitis C infection in marginalized people and with similar results to a recently initiated mobile unit–based testing initiative reported elsewhere (Lazarus, Ovrehus, Demant, Krohn-Dehli, & Weis, 2020). We confirmed viremia in 95% of the participants with positive antibodies against HCV, and only 4% were lost (15 not tested for HCV-RNA). The percentage of patients whose possible active HCV infection could not be confirmed was very low in our study, similar to a previous report from Sydney, Australia, using the PoC Xpert-HCV-VL assay for confirmation of HCV infection (1.5% (3/202) (Bajis, et al., 2020), and better than in other studies in Spain, again using the PoC Xpert-HCV-VL assay (Saludes, et al., 2020) or confirmation of HCV-RNA in a central laboratory on DBS (Ryan, et al., 2021; Saludes, et al., 2019).

We found an overall prevalence of active hepatitis C of 6.8% in 2019-2020, although this varied according to drug use. Among participants who had never used drugs, the prevalence of active hepatitis C was 1.5%. This was slightly higher in PWUD who never injected drugs had (4.5%) and much higher in PWID (21.7%), particularly in people with recent injecting drug use (27.4%). In Western Europe, the prevalence of active hepatitis C in PWID has ranged between 27% and 40% in recent years (S. Chevaliez, et al., 2020; Grebely, et al., 2019; Persico, et al., 2019). In Spain, the prevalence of active hepatitis C was 58% in PWID from Catalonia in 2017-2018 (Saludes, et al., 2019). Differences in prevalence between our study and previous reports in Spain (Saludes, et al., 2019) and neighboring countries (S. Chevaliez, et al., 2020; Persico, et al., 2019) could be explained in part by the different inclusion criteria and the years in which HCV screening was carried out (widespread access to treatment in PWUD varied by region). We performed a proactive search among marginalized people in Madrid's hot spots, where 42.7% were PWUD, but only 21.5% were PWID. In contrast, the studies by Saludes *et al.* (Saludes, et al., 2019), Chevaliez *et al.* (S. Chevaliez, et al., 2020), and Persico *et al.* (Persico, et al., 2019) were based on PWID from harm reduction services. Another factor to consider may be regional or local differences in HCV prevention strategies (Heffernan, Cooke, Nayagam, Thursz, & Hallett, 2019), which may have reduced HCV prevalence in PWUD and PWID. For example, Ryan *et al.* (Ryan, et al., 2021) recently found the prevalence of active hepatitis C to be 7.3% among PWUD who had never injected drugs and 40.2% in PWID in Madrid for 2017-2018. These values are higher than those reported in the current study. The increase in proactive HCV screening and in access to HCV treatment in these marginalized populations in recent years could explain the decline in the rates from 2017-2018 to 2019-2020. Moreover, changes in drug use behaviors that have led to a decrease in injection drug use among PWID in Madrid may be another factor to consider (EMCDDA, 2019).

We also carried out multivariate analyses to determine the factors associated with having HCV antibodies and HCV-RNA. We found that drug use—mainly intravenous drugs—and being over 50 years of age were associated with these two clinical outcomes. The burden of hepatitis C

among drug users is high, mainly due to ongoing risk behaviors such as sharing needles/syringes and paraphernalia (Morris, et al., 2017; Nelson, et al., 2011). In fact, injecting drug use led to a large epidemic from the 1980s and 1990s, although this decreased considerably in the 2000s (EMCDDA, 2019; Fuente, et al., 2006), leading in turn to a decrease in active hepatitis C in PWID in Spain (Degenhardt, et al., 2017; Grebely, et al., 2019). Additionally, people aged over 50 years were born before the 1970s, when the global hepatitis C epidemic began, and chronic HCV infection among this population increased dramatically in Spain (Bruguera & Forns, 2006). There are two main factors related to the peak of HCV prevalence in people over 50 years. First, Spanish patients were mainly infected with HCV through blood transfusions before systematic HCV screening was implemented in the 1990s. Second, injecting drug use led to a large epidemic from the 80s and 90s, causing a significant expansion of hepatitis C, but decreased sharply from the 2000s onward. Other factors associated with active infections are homelessness, incarceration in the previous year, and daily injection frequency (Valerio, et al., 2020). These findings are consistent with our results for PWUD and PWID, although no data related to prison history were collected in our cohort to demonstrate the association. Finally, we found that people with high alcohol consumption were more likely to have active hepatitis C. We think these individuals have significant barriers to starting HCV treatment since the rate of a successful response to therapy is independent of unhealthy alcohol consumption (Tsui, et al., 2016). However, more studies are required to evaluate the treatment completion rate and the time to treatment initiation in this population.

When we analyzed the subgroup of drug users (PWUD and PWID), having no income was significantly associated with having active hepatitis C. Having no income is linked to vulnerability and is a critical feature when assessing HCV infection in marginalized populations (Arasteh, Des Jarlais, Feelemyer, & McKnight, 2020; Bartholomew, et al., 2020). PWID who are homeless is more frequently infected with HCV (Beijer, Wolf, & Fazel, 2012; Morris, Yen, Shiboski, Evans, & Page, 2020). Homeless people and who inject drugs are also more frequently evaluated by a hepatologist at the hospital than non-homeless and who inject drugs (Ingiliz & Tacke, 2019), probably owing to the implementation of specific programs or alternative models of support and care for the homeless. Our finding highlights the need to implement alternative HCV care models to address the specific difficulties and barriers to HCV treatment among homeless persons who use drugs (Fazel, Geddes, & Kushel, 2014; Lambert, et al., 2019). These alternative care models would make it possible to offer HCV treatment to homeless people in their own environment or to other vulnerable groups who are addicted to illicit drugs, thus removing many of the barriers that result in their exclusion from treatment and providing an alternative to the centralized and traditional clinical approach. Finally, in our study, daily alcohol intake was also associated with having active hepatitis C in PWID. Alcohol use is related to risk behaviors that can lead to acquisition and transmission of HCV (Harrell, Mancha, Petras, Trenz, & Latimer, 2012; Keen, Khan, Clifford, Harrell, & Latimer, 2014), and moderate/heavy alcohol intake is prevalent in PWID with HCV (Irvin, et al., 2019). Two studies reported an association between reduced alcohol consumption or abstinence and more frequent initiation of HCV therapy (Dieperink, et al., 2010; Knott, et al., 2006). However, more studies are needed to evaluate the impact of alcohol intake on HCV infection in PWID who had alcohol use disorder during the DAA era.

PoC-based testing of hepatitis C at a single visit may improve linkage to care in marginalized populations (Stéphane Chevaliez, 2019; Grebely, Applegate, et al., 2017). Our study shows that linkage to care in marginalized people was high. Over 95% of participants with active hepatitis C received the test results and had an appointment at the hospital, over 90% were seen by a physician once they were at the hospital, and over 75% started HCV treatment. In addition, 33% of patients who started HCV therapy did not attend the HCV cure confirmation test 12 weeks after SVR. The main reason for not beginning HCV therapy and not performing the HCV cure confirmation test was the loss of contact with the participants. However, when the population

was stratified by drug use, PWID had the lowest rates of initiation of HCV treatment, although the differences were not significant. Larger sample size could reveal significant differences with other study groups. This significant number of losses to follow-up before initiating HCV treatment for PWID shows that linkage to care is more challenging to manage in this marginalized population and still seems to be a barrier to improving HCV treatment and eliminating the disease (Stéphane Chevaliez, 2019).

We report robust data on linkage to care in marginalized people when using a trained navigator/educator for linkage to healthcare services, increasing the likelihood of favorable treatment outcomes. Our findings are superior to those reported elsewhere, regardless of the intervention of a navigator. Broad *et al.* found no change in rates of engagement in HCV care using peer outreach workers (Broad, et al., 2020). Hsiang *et al.* engaged 25% of patients on HCV treatment when used direct access at the hospital through a hotline number to call to arrange for an immediate clinic appointment (Hsiang, et al., 2020). Hutton *et al.* reported a low linkage to care when using a screening and treatment strategy at the emergency department presentation (Hutton, et al., 2019). Surey *et al.* found that 52.8% of individuals were engaged with treatment centers when using highly trained peer support workers for linkage to specialist care (Surey, et al., 2019). In any case, they always used a rapid HCV antibody test with confirmation in a central laboratory. Other authors used the Xpert-HCV-VL assay at the PoC, albeit without a navigator, and also reported lower rates of linkage to care (Williams, et al., 2019). Therefore, our results may be considered an improvement over those of previous studies on PWID, probably because of the two-step PoC-based strategy for HCV screening, which enables the HCV result to be reported at a single visit, and the navigator, who accompanies the participant to the hospital to strengthen the linkage to care. Nonetheless, we think that our model has room for improvement because about 15% of the participants who had an HCV-RNA result were lost between attending hospital and starting HCV treatment. Our study highlights the need to expand strategies to improve linkage to care in marginalized people, especially in PWID. In this regard, we did not consider a series of factors that could have increased the effectiveness of linkage to care, such as incentives or peer-based support. Moreover, in Spain, the prescription and administration of HCV treatment are exclusively hospital-based. As such, another strategy could be decentralized HCV treatment to enable physicians to provide HCV therapy at the PoC (test-and-treat strategy). This will require the removal of prescription restrictions for DAA therapy so that it can be administered outside the hospital setting, for example, in primary care centers and drug treatment centers (Applegate, Fajardo, & Sacks, 2018; Lazarus, et al., 2019; Valerio, et al., 2020).

The rates of initiation of HCV treatment and the improvement of linkage to care reported in our study were exceptionally high among PWIDs thanks to this new model of HCV care at the PoC. Our strategy also makes it possible to decrease the prevalence of active hepatitis C among vulnerable populations, thus removing the barriers faced by PWID when accessing HCV treatment. According to our findings, the single-vist with two-step PoC-based strategy should be part of the HCV standard of care among PWID and other marginalized populations that remain viremic and out of reach of traditional HCV care approaches. Implementing this strategy in local or regional HCV micro-elimination plans will lead to higher success rates and shorten the time to the WHO's proposed objectives in this specific population.

Limitations and strengths of the study

Our study is subject to a series of limitations. First, it was performed on marginalized people in a high-income country, limiting the generalizability of our findings. However, our model might be applicable to marginalized populations in low- to middle-income countries where geographic or cultural barriers may make medical care and treatment difficult and laboratory capacity is limited. Second, some patients may have gone to another hospital outside the scope of our study, registering as if they had not received treatment, although this seems likely in only

a small percentage, since almost all patients were referred on the same day. Third, risk behavior data may be incomplete or contain biases. However, the fact that data were collected by trained personnel would have minimized errors. Fourth, some people may not have been included in our study since we did not offer incentives, although higher-risk participants, such as people with recent injecting drug use, may have been more interested in being included in the sample. Fifth, the route and frequency of drug use were self-reported and, as such, could be subject to recall bias. Therefore, the odds of some associations may have been underestimated. In any case, other studies have reported that self-reported drug use is both accurate and reliable (Golub, et al., 2005; Latkin, Vlahov, & Anthony, 1993; McElrath, 1994).

Several aspects of this project for screening and treatment in marginalized populations should be highlighted. First, the implementation of the model was feasible thanks to the work of an interdisciplinary team and close collaboration with the various institutions that care for drug users and homeless people. Second, the use of a mobile unit to search and access hot spots where these populations gather is a useful strategy for reaching people where they are in the community. Third, an on-site HCV PCR was used to detect HCV active infections. Lastly, the use of navigators to refer and accompany patients to HCV treatment also helped to improve linkage to care.

Conclusion

HCV screening using a two-step PoC-based strategy and linkage to care proved highly efficient for identifying and treating marginalized people with active hepatitis C, thanks to the use of a mobile unit with trained personnel and technical equipment, an interdisciplinary team, and collaboration between institutions. New approaches are needed to enhance HCV treatment rates among PWID, particularly those who consume alcohol and report no income.

Declarations and Ethics

Ethics approval and consent to participate

The study was conducted following the Declaration of Helsinki, and participants gave their written informed consent. The Institutional Review Board and the Research Ethics Committee of Hospital General Universitario Gregorio Marañón, Madrid, Spain approved the study (378/18).

Consent for publication

Not applicable.

Originality

The authors confirm that the material contained herein is entirely original.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Funding body: PR and SR.

Study concept and design: PR, JV, and SR.

Patient selection and clinical data acquisition: PR, JV, GC, JT, NMR, AP, and JTM.

Laboratory assays: SV and MJMG.

Statistical analysis and interpretation of data: SR.

Drafting of the manuscript: PR, JV, and SR.

Critical revision of the manuscript for relevant intellectual content: IM and JL.

Supervision and visualization: PR and SR.

All authors read and approved the final manuscript.

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Supplementary Data

Supplementary File 1. The mobile screening unit used to approach marginalized populations

NOTE: The mobile unit approaches the hot spots following a predefined schedule. This mobile unit consists of a van adapted for the project and a car. HCV screening of vulnerable individuals is performed by a nurse and a social worker hired specifically for that purpose. All individuals who are approached are offered information on prevention and the importance of early diagnosis and referral to health centers. If a positive HCV PCR test is found, participants are provided the possibility of the same-day referral to the hospital and are accompanied by an educator.

Supplementary File 2. Questionnaire items.

Questions	Response
How old are you? (years)	
Sex (Male or female)	
Were you born in Spain? (Yes or no)	
If you were not born in Spain	
What is your nationality?	
Do you have legal documentation to reside in Spain? (Yes or no)	
Where do you live now? (Home or homeless)	
If you have no home, do you have a fixed or temporary address? (on the street/platform, shelter, unstable housing, hotel, sofa, etc.)	
Have you received income in the last year? (Yes or no)	
Drug use questionnaire	
Had you ever used drugs? (Yes or no)	
What drugs have you used? (Heroin, cocaine, methamphetamine, alcohol, cannabis, other drugs [which ones]).	
Do you drink > 50 g of alcohol daily? (equivalent to 2 glasses of brandy, vodka, tequila, whiskey or rum, or three-quarters of a bottle of wine or one liter of beer) (Yes or no)	
If you use benzodiazepines, do you take them with a prescription? (Yes or no)	
Have you ever used injection drugs? (Yes or no)	
What kinds of drug have you injected?	
Have you used drugs during the last year? (Yes or no)	
What drugs have you used? (heroin, cocaine, methamphetamine, alcohol, cannabis, benzodiazepines, other [which ones]).	
Have you ever injected drugs? (Yes or no)	
What kind of drugs have you injected?	
Have you shared injecting equipment (needles, syringes, spoons, cookers, and washouts)? (Yes or no)	
Sexual risk behavior	
Have you had sex in the last year? (Yes or no)	
Did you use condoms? (Yes or no)	
If you used condoms, how often? (Frequently, sometimes, hardly ever)	

Supplementary Table 1. Characteristics of the study population stratified by type of drug addiction.

Characteristics	Non-PWUDs	PWUDs/non-PWIDs	Inactive PWIDs	Active PWIDs
No.	1134	424	288	142
Age, median (IQR)	42 (32; 53)	42 (34; 50)	50 (44; 55)	40 (35; 48)
<30 years	216 (19.22%)	59 (14.05%)	4 (1.43%)	6 (4.32%)
30-40 years	279 (24.82%)	101 (24.05%)	34 (12.19%)	53 (38.13%)
40-50 years	277 (24.64%)	150 (35.71%)	95 (34.05%)	53 (38.13%)
≥50 years	352 (31.32%)	110 (26.19%)	146 (52.33%)	27 (19.42%)
Male, N (%)	718 (63.43%)	318 (75%)	210 (73.17%)	112 (78.87%)
Nationality, N (%)				
Spain	380 (33.51%)	308 (72.64%)	252 (87.50%)	99 (69.72%)
Eastern Europe	92 (8.11%)	28 (6.60%)	14 (4.86%)	31 (21.83%)
Western Europe	15 (1.32%)	9 (2.12%)	10 (3.47%)	5 (3.52%)
North Africa	98 (8.64%)	35 (8.25%)	5 (1.74%)	2 (1.41%)
Sub-Saharan Africa	63 (5.56%)	10 (2.36%)	0 (0.00%)	0 (0.00%)
Middle East	20 (1.76%)	1 (0.24%)	1 (0.35%)	1 (0.70%)
Latin America	458 (40.39%)	30 (7.08%)	5 (1.74%)	3 (2.11%)
Other	8 (0.71%)	3 (0.71%)	1 (0.35%)	1 (0.70%)
No income, N (%)	726 (64.02%)	216 (50.94%)	102 (35.42%)	83 (58.45%)
Homeless, N (%)	828 (73.02%)	237 (55.90%)	157 (54.51%)	91 (64.08%)
Undocumented migrant, N (%)	97 (8.55%)	9 (2.12%)	4 (1.39%)	5 (3.52%)
Benzodiazepine use, N (%)	0 (0%)	234 (55.2%)	119 (41.32%)	71 (50.00%)
Illicit use of benzodiazepines	0 (0%)	42/234 (17.9%)	35/119 (29.4%)	24/71 (33.8%)
Sexual risk behavior, N (%)				
Sexual relationships (last year)	597 (52.6%)	272 (64.1%)	147 (51.1%)	99 (69.7%)
Without a condom (last year)	479/597 (80.2%)	228/272 (83.8%)	126/147 (85.7%)	87/99 (87.9%)

Statistics: Values are expressed as number (percentage) and median (interquartile range). **Abbreviations**: IQR, interquartile range; PWUD, people who use drugs; PWID, people who inject drugs.

Supplementary Table 2. Sociodemographic and epidemiological characteristics of the study population stratified by HCV infection.

Characteristics	Unexposed to HCV	Exposed to HCV	Active HCV infection
No.	1621	361	136
Age, median (IQR)	42 (33; 51)	49,5 (42,5; 54)	48 (40; 54)
<30 years	284 (17.71%)	3 (0,85%)	1 (0.75%)
30-40 years	410 (25.56%)	56 (15,91%)	29 (21.80%)
40-50 years	458 (28.55%)	117 (33,24%)	43 (32.33%)
≥50 years	452 (28.18%)	176 (50,00%)	60 (45.11%)
Male, N (%)	1073 (66.32%)	277 (76,73%)	107 (78.68%)
Nationality, N (%)			
Spain	746 (46.02%)	287 (79,50%)	102 (75.00%)
Eastern Europe	114 (7.03%)	48 (13,30%)	24 (17.65%)
Western Europe	28 (1.73%)	11 (3,05%)	6 (4.41%)
North Africa	134 (8.27%)	7 (1,94%)	1 (0.74%)
Sub-Saharan Africa	72 (4.44%)	1 (0,28%)	0 (0.00%)
Middle East	23 (1.42%)	2 (0,55%)	0 (0.00%)
Latin America	492 (30.35%)	5 (1,39%)	3 (2.21%)
Others	12 (0.74%)	0 (0,00%)	0 (0.00%)
No income, N (%)	963 (59.41%)	158 (44,76%)	76 (55.88%)
Homeless, N (%)	1100 (67.86%)	208 (57,94%)	87 (63.97%)
Undocumented immigrant, N (%)	104 (6.42%)	9 (2,51%)	4 (2.94%)
Alcohol intake, N (%)	379 (23.38%)	130 (36,31%)	55 (40.44%)
Benzodiazepine use, N (%)	266 (16.41%)	151 (41,83%)	53 (38.97%)
Illicit use of benzodiazepines	51 (3.15%)	47 (13,02%)	19 (13.97%)
Use of illegal drugs, N (%),			
Had ever used drugs (PWUDs)	513 (31.65%)	326 (90,30%)	117 (86.03%)
PWUDs (active in last year)	345/513 (67.25%)	204/326 (62,58%)	75/117 (64.10%)
Had ever injected drugs (PWIDs)	142/513 (27.68%)	274/326 (84,05%)	98/117 (83.76%)
PWIDs (active in last year)	40/142 (28.17%)	95/274 (34,67%)	37/98 (37.76%)
Type of drug used			
Cocaine	340/513 (66.28%)	212/117 (181,20%)	80/117 (68.38%)
Heroin	179/513 (34.89%)	174/117 (148,72%)	65/117 (55.56%)
Marijuana	91/513 (17.74%)	21/117 (17,95%)	8/117 (6.84%)

Recreational drugs	24/513 (4.68%)	3/117 (2,56%)	2/117 (1.71%)
Opioid agonist therapy	151/513 (29.43%)	220/117 (67,48%)	79/117 (67.52%)
Sexual risk behavior, N (%)			
Sexual relationships (last year)	937 (57.80%)	173 (47,92%)	65 (47.79%)
Without a condom (last year)	769/937 (82.07%)	147/173 (84,97%)	56/65 (86.15%)

Statistics: Values are expressed as number (percentage) and median (interquartile range). **Abbreviations**: IQR, interquartile range; PWUD, people who use drugs; PWID, people who inject drugs.

Supplementary Table 3. Sociodemographic and epidemiological characteristics associated with HCV infection among marginalized populations in Madrid stratified by drug users.

A) All participants				**Univariate**		**Multivariate**	
AHC vs. UHC	**No.**	**AHC**	**UHC**	**OR (95%CI)**	**p-value**	**aOR (95%CI)**	**p-value**
PWUD ever	1744	117 (86%)	513 (31.6%)	9.2 (6.1; 14)	**<0.001**	9.8 (5.8; 16.7)	**<0.001**
Age (over 50 years)	1737	60 (45.1%)	452 (28.2%)	2.1 (1.5; 3)	**<0.001**	2.3 (1.5; 3.6)	**<0.001**
Sex (male)	1754	107 (78.7%)	1073 (66.3%)	1.9 (1.2; 2.9)	**0.004**	1.4 (0.9; 2.3)	0.161
Spanish nationality	1757	102 (75%)	746 (46%)	3.5 (2.4; 5.3)	**<0.001**	1.4 (0.9; 2.4)	0.154
No income	1728	76 (57.6%)	963 (60.3%)	0.9 (0.6; 1.3)	0.533	1.5 (1; 2.4)	0.064
Homeless	1744	87 (64.9%)	1100 (68.3%)	0.9 (0.6; 1.2)	0.418	1 (0.7; 1.6)	0.859
Irregular migrant	1731	4 (3%)	104 (6.5%)	0.4 (0.2; 1.2)	0.114	0.9 (0.3; 2.9)	0.879
Daily alcohol intake	1744	55 (40.7%)	379 (23.6%)	2.2 (1.6; 3.2)	**<0.001**	1.5 (1; 2.2)	0.075
Benzodiazepine use	1757	53 (39%)	266 (16.4%)	3.3 (2.2; 4.7)	**<0.001**	1 (0.6; 1.5)	0.962
Sexual relationships in the last year	1720	65 (47.8%)	937 (57.8%)	0.8 (0.6; 1.1)	0.162	0.8 (0.6; 1.3)	0.427
EHC vs. UHC	**No.**	**EHC**	**UHC**	**OR (95%CI)**	**p-value**	**aOR (95%CI)**	**p-value**
PWUD ever	1969	326 (90.3%)	513 (31.6%)	14.7 (10.6; 20.4)	**<0.001**	15.8 (10.5; 23.7)	**<0.001**
Age (over 50 years)	1956	176 (50%)	452 (28.2%)	2.5 (2; 3.2)	**<0.001**	2.7 (2; 3.7)	**<0.001**
Sex (male)	1979	277 (76.7%)	1073 (66.3%)	1.7 (1.3; 2.2)	**<0.001**	1.2 (0.9; 1.7)	0.191
Spanish nationality	1982	287 (79.5%)	746 (46%)	4.5 (3.5; 6)	**<0.001**	1.3 (0.9; 1.9)	0.161
No income	1949	158 (44.8%)	963 (60.3%)	0.5 (0.4; 0.7)	**<0.001**	1 (0.7; 1.4)	0.952
Homeless	1969	208 (57.9%)	1100 (68.3%)	0.6 (0.5; 0.8)	**<0.001**	1 (0.7; 1.3)	0.853
Irregular migrant	1956	9 (2.5%)	104 (6.5%)	0.4 (0.2; 0.7)	**0.005**	1.1 (0.5; 2.6)	0.782
Daily alcohol intake	1967	130 (36.3%)	379 (23.6%)	1.9 (1.4; 2.4)	**<0.001**	1.3 (1; 1.7)	0.084
Benzodiazepine use	1982	151 (41.8%)	266 (16.4%)	3.7 (2.9; 4.7)	**<0.001**	1 (0.7; 1.4)	0.928
Sexual relationships in the last year	1940	173 (47.9%)	937 (57.8%)	0.7 (0.6; 0.9)	**0.007**	0.8 (0.6; 1)	0.101

B) PWUD				**Univariate**		**Multivariate**	
AHC vs. UHC	**No.**	**AHC**	**UHC**	**OR (95%CI)**	**p-value**	**aOR (95%CI)**	**p-value**
PWID ever	621	98 (83.8%)	142 (27.7%)	9 (5.6; 14.5)	**<0.001**	11.5 (6.8; 19.4)	**<0.001**
Age (over 50 years)	622	48 (41.7%)	123 (24.3%)	2.2 (1.5; 3.4)	**<0.001**	2 (1.1; 3.5)	**0.019**
Sex (male)	629	91 (77.8%)	379 (74%)	1.2 (0.8; 2)	0.400	1.4 (0.8; 2.5)	0.265

Spanish nationality	630	89 (76.1%)	381 (74.3%)	1.1 (0.7; 1.8)	0.687	0.9 (0.5; 1.6)	0.607
No income	618	67 (59.3%)	249 (49.3%)	1.5 (1; 2.3)	0.056	1.9 (1.1; 3.4)	**0.024**
Homeless	623	74 (64.3%)	293 (57.7%)	1.3 (0.9; 2)	0.190	1.1 (0.6; 1.9)	0.840
Irregular migrant	619	4 (3.5%)	11 (2.2%)	1.6 (0.5; 5.2)	0.419	1.7 (0.4; 6.8)	0.441
Daily alcohol intake	626	47 (40.2%)	155 (30.5%)	1.5 (1; 2.3)	**0.043**	1.4 (0.8; 2.3)	0.184
Benzodiazepine use	630	53 (45.3%)	266 (51.9%)	0.8 (0.5; 1.2)	0.202	1 (0.6; 1.6)	0.910
Sexual relationships in the last year	617	59 (50.4%)	346 (67.4%)	0.6 (0.4; 0.9)	**0.009**	0.7 (0.4; 1.1)	0.149
EHC vs. UHC	**No.**	**EHC**	**UHC**	**OR (95%CI)**	**p-value**	**aOR (95%CI)**	**p-value**
PWID ever	830	274 (84%)	142 (27.7%)	10.6 (7.6; 14.9)	**<0.001**	11.3 (7.9; 16.4)	**<0.001**
Age (over 50 years)	825	153 (48.1%)	123 (24.3%)	2.9 (2.1; 3.9)	**<0.001**	2.7 (1.8; 4)	**<0.001**
Sex (male)	838	248 (76.1%)	379 (74%)	1.1 (0.8; 1.5)	0.505	1.1 (0.7; 1.7)	0.628
Spanish nationality	839	266 (81.6%)	381 (74.3%)	1.5 (1.1; 2.2)	**0.014**	0.9 (0.6; 1.4)	0.649
No income	823	142 (44.7%)	249 (49.3%)	0.8 (0.6; 1.1)	0.193	1.3 (0.9; 1.9)	0.230
Homeless	832	183 (56.5%)	293 (57.7%)	1 (0.7; 1.3)	0.734	0.9 (0.6; 1.3)	0.455
Irregular migrant	828	7 (2.2%)	11 (2.2%)	1 (0.4; 2.6)	0.983	1.2 (0.4; 3.9)	0.710
Daily alcohol intake	833	117 (36.1%)	155 (30.5%)	1.3 (1; 1.7)	0.090	1.2 (0.8; 1.8)	0.321
Benzodiazepine use	839	151 (46.3%)	266 (51.9%)	0.8 (0.6; 1.1)	0.118	1 (0.7; 1.4)	0.967
Sexual relationships in the last year	821	163 (50%)	346 (67.4%)	0.6 (0.4; 0.7)	**<0.001**	0.7 (0.5; 1)	0.062

C) PWID

				Univariate		**Multivariate**	
AHC vs. UHC	**No.**	**AHC**	**UHC**	**OR (95%CI)**	**p-value**	**aOR (95%CI)**	**p-value**
PWID recently	240	37 (37.8%)	40 (28.2%)	1.5 (0.9; 2.7)	0.119	1.9 (1; 3.6)	**0.050**
Age (over 50 years)	236	42 (43.3%)	40 (28.8%)	1.9 (1.1; 3.3)	**0.022**	2.7 (1.3; 5.6)	**0.006**
Sex (male)	239	77 (78.6%)	98 (69.5%)	1.6 (0.9; 2.9)	0.121	1.4 (0.7; 2.8)	0.317
Spanish nationality	240	72 (73.5%)	117 (82.4%)	0.6 (0.3; 1.1)	0.099	0.7 (0.3; 1.4)	0.270
No income	237	58 (61.1%)	59 (41.5%)	2.2 (1.3; 3.7)	**0.003**	1.8 (0.9; 3.6)	0.071
Homeless	238	66 (68%)	80 (56.7%)	1.6 (0.9; 2.8)	0.079	1.3 (0.7; 2.5)	0.434
Irregular migrant	238	4 (4.1%)	2 (1.4%)	3 (0.5; 16.7)	0.211	1.8 (0.3; 11.4)	0.521
Daily alcohol intake	239	42 (42.9%)	42 (29.8%)	1.8 (1; 3)	**0.038**	1.9 (1; 3.5)	**0.038**
Benzodiazepine use	240	45 (45.9%)	55 (38.7%)	1.3 (0.8; 2.3)	0.268	1.4 (0.8; 2.6)	0.230
Sexual relationships in the last year	236	51 (52%)	97 (68.3%)	0.6 (0.4; 1.1)	0.086	0.8 (0.4; 1.5)	0.420
EHC vs. UHC	**No.**	**EHC**	**UHC**	**OR (95%CI)**	**p-value**	**aOR (95%CI)**	**p-value**

PWID recently	414	95 (34.7%)	40 (28.2%)	1.4 (0.9; 2.2)	0.111	1.8 (1.1; 3)	**0.019**
Age (over 50 years)	406	126 (47.2%)	40 (28.8%)	2.2 (1.4; 3.4)	**<0.001**	2.6 (1.6; 4.4)	**<0.001**
Sex (male)	415	212 (77.4%)	98 (69.5%)	1.5 (1; 2.4)	0.082	1.4 (0.8; 2.2)	0.238
Spanish nationality	416	222 (81%)	117 (82.4%)	0.9 (0.5; 1.5)	0.733	0.8 (0.4; 1.5)	0.525
No income	409	117 (43.8%)	59 (41.5%)	1.1 (0.7; 1.7)	0.659	1.1 (0.7; 1.8)	0.751
Homeless	414	160 (58.6%)	80 (56.7%)	1.1 (0.7; 1.6)	0.715	1.1 (0.7; 1.8)	0.725
Irregular migrant	414	7 (2.6%)	2 (1.4%)	1.8 (0.4; 8.9)	0.455	1.8 (0.3; 9.6)	0.491
Daily alcohol intake	413	104 (38.2%)	42 (29.8%)	1.5 (0.9; 2.3)	0.089	1.7 (1; 2.7)	**0.032**
Benzodiazepine use	416	129 (47.1%)	55 (38.7%)	1.4 (0.9; 2.1)	0.105	1.6 (1; 2.5)	0.060
Sexual relationships in the last year	408	141 (51.5%)	97 (68.3%)	0.6 (0.4; 0.9)	**0.016**	0.7 (0.5; 1.2)	0.190

Statistical analysis: The association between the patient's characteristics and belonging to a study group according to HCV infection was evaluated using multivariate logistic regression.
Abbreviations: HCV, hepatitis C virus; RNA, ribonucleic acid; PWUD; people who use drugs; PWID, people who inject drugs; UHC, unexposed to hepatitis C; EHC, exposed to hepatitis C; AHC, active hepatitis C; OR, odds ratio; aOR, adjusted odds ratio; 95%CI, 95% confidence interval.