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Title: Differences in the HCV cascade of care and time to initiation of therapy among vulnerable sub-populations using a mobile unit as point-of-care

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Abbreviations:
HCV: Hepatitis C virus
PWID: People who inject drugs
PoC: Point-of-care
MHD: Mental health disorder
AUD: Alcohol use disorder
DAA: Direct-acting antivirals
SVR: Sustained virological response
CoC: Cascade of care
PCR: Polymerase chain reaction
VL: Viral load
ART: Antiretroviral therapy
Ab: Antibodies

OR: Odds ratio

ICD: International diagnosis code

MoC: Model of care

REDCap: Research Electronic Data Capture

EDTA: Ethylenediaminetetraacetic acid

LTFU: Lost to follow-up

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Conflict of interest disclosure

JV has received honoraria for lectures/consultancy from AbbVie, Gilead and ViiV Healthcare outside the submitted work. JVL has received grants from Gilead Sciences and MSD, and speaker fees from AbbVie, Genfit, Gilead, Intercept, and Merck outside the submitted work. PR has received research grants from AbbVie and Gilead. In addition, he has received honoraria for lectures/consultancy from AbbVie, Gilead and ViiV Healthcare.

Ethics approval and patient consent statement

The study was conducted following the Declaration of Helsinki, and participants gave their written informed consent to participate. The Institutional Review Board and the Research Ethics Committee of the Hospital General Universitario Gregorio Marañón approved the study with registry number MP-001/2019 on January 9, 2019.

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Abstract

Background & Aims: People who inject drugs (PWID) and other marginalized populations with high hepatitis C virus (HCV) infection rates represent a unique challenge for treatment initiation due to health, administrative and social barriers. We analyzed the HCV cascade of care (CoC) in vulnerable populations in Madrid, Spain, to identify gaps and barriers to improve HCV elimination efforts in these populations.

Methods: From 2019 to 2021, a mobile unit was used to screen active HCV using a linkage-to-care and two-step point-of-care-based strategy. Viremic participants were grouped into four subgroups: PWID, homeless individuals and people with a mental health disorder (MHD) and alcohol use disorder (AUD). Logistic regression, and Cox and Aalen's additive models were used to analyze associated factors and differences between groups.

Results: A prospectively recruited cohort of 214 HCV infected individuals (73 PWID, 141 homeless, 57 with a MHD and 91 with AUD) participated in the study. The overall HCV CoC analysis found that: 178 (83.1%) attended a hospital, 164 (76.6%) initiated direct-acting antiviral therapy and 141 (65.8%) completed therapy, of which 99 (95.2%) achieved sustained virological response (SVR). PWID were significantly less likely to initiate treatment, while people with AUD and PWID were significantly less likely to complete HCV treatment. Individuals with AUD waited a longer time before treatment.

Conclusions: Overall, SVR was achieved in the majority of the participants treated. However, PWID need better linkage to care and treatment, while PWID and AUD need more support for treatment completion.

Keywords: Cascade of care; hepatitis C virus; point-of-care test; marginalized populations

Lay summary

This cohort study describes the entire cascade of care of the hepatitis C virus (HCV) in vulnerable populations and includes subgroups not often previously studied, such as people with a mental health disorder and alcohol use disorder (AUD). It identified gaps and barriers in order to improve HCV elimination efforts in these populations. These results provide evidence of differences in the time to HCV treatment initiation among these subgroups and demonstrate that using a mobile unit as a linkage-to-care and point-of-care-based strategy is a successful model of care to reach marginalized populations in Madrid, Spain. Furthermore, they highlight the importance of patient centered care so as to allow for treatment initiation and completion, especially in people who inject drugs and those with AUD.

Introduction

Hepatitis C virus (HCV) infection has a major global impact in terms of morbidity, mortality and economic costs, with about 58 million people having chronic HCV worldwide [1]. The risk of HCV infection has been linked to alcohol and injecting drug use, homelessness, incarceration, severe mental illness and socioeconomic status.[2-5] HCV infection rates are substantially higher in some vulnerable populations,[6] such as inmates and people who inject drugs (PWID), both of which represent the highest HCV burden in Madrid, Spain and the rest of the world.[4] The prevalence of active HCV infection in the homeless and other vulnerable subgroups such as PWID, prisoners and people with a mental health disorder (MHD) is also high, as these groups face barriers to access healthcare and social services[7,8] resulting in disproportionately high rates of viral hepatitis.[9] Therefore, HCV eradication should be prioritized in these populations.[6]

Despite the availability of highly effective therapeutic regimens based on direct-acting antivirals (DAAs), challenges to HCV elimination still remain due to inequalities in the HCV cascade of care (CoC) of PWID and other vulnerable groups such as prisoners and homeless people.[2,10] These populations face barriers to access healthcare when using traditional models of care (MoCs),[11,12] due to drug use criminalization, stigma and discrimination, and the stress surrounding their precarious living circumstances, which cause and amplify health inequalities [9,13]. Therefore, it is important to monitor the HCV CoC in these groups so as identify and address gaps in order to advance HCV elimination efforts.[10]

Alternative MoCs utilizing novel screening (e.g., onsite HCV polymerase chain reaction (PCR) tests) and linkage to care (e.g., using peer-navigators) strategies and others such as nurse-led, telemedicine, pharmacist-led and mobile van units have been used with PWID and homeless people with success.[11,14,15] One of the hallmarks of these MoCs is their simplicity, which, along with other elements such as effective linkage to care and integration of services, are key to the scaling up of interventions and widely considered as predictors of success [11,16]. However, due to biosocial determinants and transient lifestyles, it remains difficult to reach and treat some groups such as people with a MHD and alcohol use disorder (AUD).[17-19] In addition, studies on completion rates of HCV treatment in the homeless and people with a MHD and AUD are scarce in the literature.[20-22]

The amount of time elapsed between the HCV-RNA test result and treatment initiation (time to HCV treatment) is a useful parameter to measure success in treating HCV in vulnerable groups, in spite of it not being considered part of the HCV CoC consensus.[10] A recent study showed that the time to HCV treatment is lower in the general population compared to vulnerable populations such as prisoners, people with a MHD and homeless people.[23]

To date, there are no studies comparing the time to HCV treatment among vulnerable subgroups. More studies are needed to evaluate this and the whole HCV CoC in PWID and other vulnerable subgroups, using integrated test-and-treat MoCs. Therefore, the aim of this study was to identify gaps in time to HCV treatment and barriers to achieving SVR along the CoC.

Methods

Study population

We carried out a prospective study on vulnerable populations in Madrid from 1 February 2019, to 28 February 2021, using a screening mobile unit. Individuals were engaged in a wide variety of locations or hotspots including harm reduction and addiction centers, institutions that provide social assistance, parks and other public areas, homeless shelters and places where street prostitution and mendicity are practiced.

Participants (18 years of age or older) were screened for HCV and HIV, in a first come first serve basis. For this study, only those viremic belonging to these subgroups were included: PWID with recent drug use, homeless individuals and people with a MHD and AUD. A signed informed consent form was also required to be included.

Design

The screening phase was carried out at the mobile unit, consisting of an adapted van and a car, serving the hot spots following a predefined schedule. A nurse and an educator performed HCV and HIV rapid tests for antibodies using capillary whole blood sampling. Those participants who tested positive in the HCV rapid test were offered HCV-RNA detection using the Xpert HCV Viral Load Fingerstick (Xpert-HCV-VL-FS) assay. This was done in order to confirm active infection and to obtain a viral load. Anti-HCV antibody (Ab) and onsite HCV-RNA test results were processed in 20 and 60 minutes, respectively. While participants waited for their results, their sociodemographic and epidemiological data were collected through questionnaires. In addition, they were counseled on prevention of blood-borne infections and harm reduction practices.

In the linkage to care phase, all participants with a positive HCV-RNA test were offered a referral to hospital the same day. Those who accepted the referral were transported by car and accompanied by a team member to any hospital in Madrid (mainly the Infanta Leonor Hospital), where they were examined by an infectious disease specialist or a hepatologist. At the hospital, prescription of HCV therapy was carried out according to national guidelines. No scheduled appointment was needed, and treatment was prescribed without host restrictions based on liver disease stage, drug and alcohol use or insurance status as per usual practice at this hospital. Regardless of location, all fast-track clinics are dedicated to streamlining referral visits by facilitating blood tests, elastography and consultations within a single visit.

Even though in Madrid access to HCV therapy is universal and free, regardless of the level of liver fibrosis, it can only be prescribed in a hospital setting. In this study, HCV treatment procurement was facilitated by the hospital pharmacy to a team member in all cases, who negotiated with the participant about the most convenient way for medicine pick-up/delivery through outreach and addiction services, as a directly observed therapy strategy or as self-administered.

HCV-RNA positive participants who refused to be referred to hospital were subsequently contacted by phone or actively sought by a navigator, by physically looking for them at the site(s) that the participant was known to frequent, to reattempt engaging them in care. HIV-infected patients who refused to be referred to hospital underwent this same process and, at the very least, those who were not taking antiretroviral therapy (ART) were encouraged to reinitiate HIV therapy care at the hospital.

Data sources

Epidemiological data were collected through a questionnaire on a mobile unit with an internet connection. Clinical data were collected from hospital medical records. Data were stored using Research Electronic Data Capture (REDCap, Vanderbilt University, Nashville, TN, USA), [24] hosted at the Asociación Ideas Health, Madrid, Spain.

HCV screening tests: anti-HCV Ab and HCV-RNA

OraQuick HCV Rapid Ab Test (OraSure Technologies, Bethlehem, PA, USA) were used, which uses a fingerstick capillary whole-blood sample (100 µL blood). After approximately 20 minutes, the test result was available and reported. Patients with a negative anti-HCV Ab test were not eligible to continue participating in the study.

The Xpert-HCV-VL-FS assay was offered to all individuals with a positive anti-HCV Ab test at the PoC. For this on-site PCR, a 100µl of fingerstick capillary blood sample was collected using an Ethylenediaminetetraacetic acid (EDTA)-coated minivette device (Sarstedt Minivette) and analyzed using a GeneXpert instrument (Cepheid, CA, USA) in the mobile unit. The limit of quantification was 100 IU/mL and of detection 40 IU/mL. After 60 minutes, the results were immediately reported to each individual.

Only participants with both positive results (anti-HCV Ab test and HCV-RNA) were selected for the analysis of this study. Reinfections were self-reported in those participants who had previously been treated or cleared infection spontaneously and were confirmed in all cases by clinical reports and a positive Xpert HCV-RNA result.

Evaluating the HCV CoC

Four events were taken into account for the HCV CoC: I) being seen in hospital; II) starting HCV therapy; III) completing HCV therapy; and IV) achieving SVR. Time to HCV treatment was also considered as a parameter to evaluate as good practice to incorporate into the CoC.

The study population was grouped into four subgroups defined as follows: I) PWID: those who self-reported injecting drug use in the last six months; II) homeless people: those who lived in the street, shelters or experienced recent homelessness; III) people with a MHD: those who had a previous diagnosis of psychiatric disease according to ICD-10 and registered medical records; and IV) people with AUD: those with a history of heavy alcohol use diagnosed or treated in the last six months. AUD diagnoses were collected from the medical records (diagnosis code ICD-10, F10) of at least one AUD-related hospital admission or outpatient treatment, coded in the principal or secondary diagnosis of the ICD-10 code.

Treatment was classified as incomplete when it was permanently discontinued or the patient was lost to follow-up (LTFU). Participants who missed dosing days were encouraged to continue attending until treatment was completed, extending the planned treatment time as needed. Adherence to treatment, planned extended dosing time and missed medication during treatment were variables not collected in this study.

SVR was defined as an HCV-RNA load under the lower limit of quantification in the first sample at least 12 weeks after the end of treatment or from the last dose taken after uncompleted treatment.

Liver stiffness was evaluated using transient elastography at the hospital. Liver disease staging was based on established liver stiffness cut-offs. Cirrhosis (liver fibrosis stage 4 (F4)) was diagnosed when liver stiffness was ≥12.5 kPa.

Calculating the time to treatment initiation

Time to HCV treatment (time elapsed between HCV-RNA measurement by Xpert-HCV-VL-FS at the mobile unit and treatment initiation) was estimated based on available data, measured in days and stratified per subgroup. If treatment started on the same day of diagnosis, time to HCV treatment was considered as 0 days.

Statistical analysis

The four steps of the HCV CoC (being seen in hospital, HCV treatment initiation, HCV treatment completion and SVR) were considered as outcomes in this study. We considered as predictor variables, recent injection drug use, AUD, a MHD and homelessness for the descriptive data; differences between groups were analyzed using Chi-square with a Monte Carlo simulated p-value for categorical and the Kruskal-Wallis test for continuous variables. Logistic regression models were used to estimate the odds ratio (OR) for: (1) factors associated with being seen in hospital among all individuals of the cohort, (2) factors associated with HCV treatment initiation among the total cohort, and (3) factors associated with treatment completion among those who initiated therapy. Sex and age were added as covariables to complete the multivariable model.

All variables, even those of patients with missing data, were analyzed using the Chi-square test with the Monte Carlo p-value simulation to identify differences between the four subgroups.

The median time to HCV treatment was calculated for the overall cohort and by vulnerable subgroups. Survival models were used to explore the effect of the different predictor variables over the time elapsed between HCV diagnosis date at the mobile unit and treatment initiation date. Fifty individuals that did not initiate HCV treatment by February 2021 were censored. The Kaplan Meier method and log rank test were performed to assess univariate differences in the probability of initiating treatment among the different subgroups. The hazard ratio for initiating treatment was estimated with the Cox Proportional-Hazard and Aalen's additive models.

Two-sided tests were used for all statistical methods. Analyses and figures were performed using R 4.0.3 software.

Results

Characteristics of participants

Of the 2,890 screened people, 549 (18.9%) were positive for anti-HCV Ab, and 214 (39.0%) of them were HCV-RNA positive and grouped into one of the four vulnerable subgroups. Participants could belong to one or more subgroups.

The median age was 48 years, 79.4% were male, 23.8% were migrants, 22.4% were coinfected with HIV and 14.5% had hepatic cirrhosis. Regarding drug use, 91.1% of participants had at some point used illegal drugs, 66.4% reported using in the last 6 months, with heroin (72.6%) and cocaine (93.0%) being the most consumed drugs, and 19.5% used benzodiazepines without prescription. Baseline characteristics of the participants included in the study are shown in **Table 1**.

Table 1. Sociodemographic, clinical and epidemiological characteristics of the study population according to the steps of the HCV cascade of care.

	Global	Seen in Hospital		Initiated HCV treatment		Completed HCV treatment		Achieved SVR	
		NO	YES	NO	YES	NO	YES	NO	YES
N	214	35	179	50	164	21	143	5	99
Age, median (IQR)	48 (12.7)	47 (13)	48 (13)	47 (13.2)	48 (12.7)	46 (13)	48 (12.5)	42 (10)	48 (11)
Gender, men	170/214	28/35	142/179	42/50	128/164	15/21	113/143	3/5	75/99
Non-Spaniards	51/214	8/35	43/179	10/50	41/164	6/21	35/143	0/5	25/99
Undocumented migrants	11/214	0/35	11/179	1/50	10/164	3/21	8/143	0/5	8/99
No-income	129/214	21/35	108/178	28/48	100/166	14/21	85/143	5/5	58/99
Ever used drugs	195/214	33/36	162/178	48/50	147/164	18/21	129/143	5/5	88/99
Recent drug use*	142/214	28/38	114/178	38/50	104/164	13/21	91/143	3/5	65/99
Ever injecting drug use*	163/195	31/33	132/162	44/48	119/147	15/18	104/129	4/5	72/88
Recent injecting drug use	73/214	16/36	57/178	24/50	49/164	7/21	42/143	3/5	34/99
Opioid agonist treatment	125/194	21/33	104/162	34/48	91/147	10/18	81/129	5/5	55/88
HIV co-infection	48/214	10/36	38/178	16/50	32/164	6/21	26/143	1/5	23/99
Chronic hepatitis B	6/184	0/34	6/150	2/47	4/137	0/18	4/119	0/4	2/81
HCV reinfection	28/199	4/33	24/166	8/47	20/152	2/21	18/131	1/5	12/93
Cirrhosis**	31/214	5/36	26/178	8/50	23/164	6/21	17/143	2/5	11/99

* Last six months; ** Defined as liver stiffness ≥12.5 kPa. Abbreviations: HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus; SVR, sustained virological response; IQR, interquartile range.

The cohort (n=214) was grouped in these four subpopulations: PWID (n=73), homeless individuals (n=141) and people with a MHD (n=57) and AUD (n=91). PWID were significantly more likely to be undocumented immigrants and to have no economic income. HCV reinfections were found to be more frequent in PWID compared with those without a history of injecting drug use, but this result was not statistically significant (p=0.06). People with AUD were more frequently diagnosed with cirrhosis, compared to those without AUD, while homeless people were significantly more likely to have no economic income compared to those who were not homeless (**Table 2**).

Table 2. Sociodemographic, clinical and epidemiological characteristics of the study population according to vulnerable subgroups

	People who inject drugs¥		People with alcohol use disorder		Patients with a mental health disorder		Homeless patients	
	NO	YES	NO	YES	NO	YES	NO	YES
N	141	73	123	91	157	57	73	141
Age, median (IQR)	50(12)	44(10)	47(11.5)	51(11)	48(13)	48(11)	50(10)	47(13)
Gender, men	108/141	62/73	96/123	74/91	131/157	39/57	61/73	109/141
Non-Spaniard	26/141	25/73	38/123	13/91	44/157	50/57	9/73	42/141
Undocumented migrants	2/141	9/73	8/123	3/91	11/157	0/57	1/73	10/141
No-income	71/141	14/73	40/123	45/91	56/157	29/57	46/73	39/141
OST	115/141	48/73	85/123	78/91	113/157	50/57	64/73	99/141
Chronic HBV infection	3/122	3/62	2/106	4/78	5/139	1/45	2/68	4/116
HCV reinfection	11/129	17/70	20/115	8/84	20/148	8/51	6/66	22/133

HIV infection	111/141	54/73	99/123	66/91	125/147	40/57	58/73	107/141
Cirrhosis	98/141	61/73	101/123	58/91	115/157	44/57	47/73	112/141
SVR (cure)	65/67	34/37	60/64	39/40	71/75	28/29	32/33	67/71

¥Patients can be either homeless, people with AUD, people with a MHD or none of them. Abbreviations: HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus; OST, opiate substitution therapy; SVR, sustained virological response; IQR, interquartile range.

Whole HCV CoC

Seen in hospital: Among the 214 individuals who were diagnosed with HCV at the mobile unit, 178 (83.1%) were seen in hospital for evaluation of HCV treatment. There was no association between the different sociodemographic variables or vulnerable subgroups with being seen in hospital.

HCV treatment initiation: Over the study period, 164 (76.6%) individuals started HCV treatment and 50 did not initiate therapy until the end of follow-up. The follow-up censoring date was February 28, 2021. Treatment regimens and reasons for not initiating HCV treatment are shown in **Supplementary Table 1**. No sociodemographic baseline factors were associated with the initiation of HCV treatment in an analysis (**Table 1**); however, participants who belonged to the subgroup of PWID were significantly less likely to initiate treatment (OR 0.40; CI95%, 0.24-0.61; p=0.003) than those who did not inject drugs (Figure 3).

HCV treatment completed: Among those individuals who started treatment, 141 (85.9%) completed therapy and 23 (14.0%) withdrew from treatment. No association was found between sociodemographic factors and compliance to treatment in an analysis with the Kruskal–Wallis test (**Table 1**); however, PWID (OR 0.49; 95% CI, 0.30-0.73; p=0.001) and people with AUD (OR 0.45; CI 95%, 0.29-0.67; p=0.004) were significantly less likely to complete treatment than those who did not belong to these groups (Figure 3).

SVR: Of the 164 individuals who initiated treatment, 104 (63.4%) returned for testing and SVR assessment. We found that participants without a sample for assessment of SVR had similar characteristics with respect to all baseline characteristics shown in **Table 1** and in the stratified subgroups (data not shown).

Of those participants treated and tested after therapy, 99 (95.2%) achieved SVR. By subgroup the results were: PWID, 91.9%; people with AUD, 97.5%; people with a MHD, 96.5%; and homeless people, 94.4%. The study had no statistical power to evaluate differences among the subgroups due to only having five cases of no-SVR.

Time to HCV treatment initiation

The overall median time to HCV treatment initiation among the four subpopulations who received treatment was 35.5 days [IQR 17.7-108.2]. The longest median time to HCV treatment of 40.5 days [IQR 17.0-99.2] was observed in patients with AUD and the shortest median time to HCV treatment was 30 days [IQR 15.0-90.0] in PWID. The median time to HCV treatment in people with a MHD was 39 days [IQR 21.5-131.5] and 36 days [IQR 18.5-120.5] among the homeless. One participant out of all 214 viremic patients was treated on the same day of HCV diagnosis.

A Kaplan-Meier graph of the time to HCV treatment by each vulnerable subgroup is shown in Figure 3. In the multivariable analysis of Cox proportional hazards and Aalen's additive model, people with AUD remained associated with longest time to HCV treatment initiation (HR 0.63; CI 97.5%, 0.45-0.88; p= 0.001) (**Table 3**).

Table 3. Survival analysis. Cox's Proportional Hazard and Aalen's Additive Regression Model of the time to HCV treatment initiation

	HR	2.5%	97.5%	p-value
Cox Hazard Model				
Age	1.001	0.982	1.020	0.9412
Sex	1.161	0.788	1.709	0.4513
Recent injecting drug use	0.706	0.488	1.022	0.0649
Alcohol use disorder	0.637	0.457	0.888	**0.0017**
Mental health disorder	0.811	0.570	1.156	0.2468
Homelessness	0.943	0.672	1.322	0.7327
Aalen's Additive Model	**Estimate**			
Age	0.0001	-0.0001	0.0001	0.9220
Sex	0.0012	-0.0020	0.0043	0.4749
Recent injecting drug use	-0.0026	-0.0052	0.0005	0.0552
Alcohol use disorder	-0.0031	-0.0055	-0.0005	**0.0158**
Mental health disorder	-0.0013	-0.0037	0.0012	0.3258
Homelessness	0.0008	-0.0035	0.0018	0.5505

Discussion

This hepatitis C study was carried out among diverse vulnerable subpopulations in Madrid, using a PoC-based strategy and referring patients to hospital with the help of a team member. This strategy demonstrated that the vast majority of patients traditionally considered difficult to engage in care and eligible for DAA therapy can be treated and cured, even among some subgroups with the lowest reported rates of treatment completion, PWID and people with AUD. We also described some differences and gaps in the HCV CoC and inequalities in the time between HCV diagnosis and treatment initiation among these subgroups.

Clinical trials and real-life cohorts have demonstrated high rates of SVR amongst people receiving opioid agonist therapy (OAT), homeless people and in those with recent injecting drug use; [15,22,26] however, few studies have explored the differences in the CoC steps analyzed in this study in other vulnerable subgroups. In the present cohort, we found that cure rates were high across all treated vulnerable subgroups, which is consistent with previously reported cure rates in some evaluated vulnerable populations. [27-29] Nevertheless, the main gap occurred in the initial phase of the CoC, which led a quarter of the participants to not initiate treatment in our study despite utilizing an alternative MoC based on a screening mobile unit.

New MoCs implementing a test-and-treat strategy and HCV care delivery on-site in OAT programs have been used in PWID, [2,30] the homeless[31] and inmates,[32] and report similar rates of treatment initiation found in our cohort (76.6%). However, treatment initiation

remains a challenge in some vulnerable populations such as PWID.[33] Indeed, we found that PWID were less likely to start DAA treatment compared to people who did not inject drugs. We also noted that the two main reasons for not initiating HCV treatment were loss to follow-up and patient refusal, as reported in previous studies;[2,34] another reason was death, which happened in 18.0% of our participants who did not initiate treatment. This previous finding supports the inequality and greater risk of liver-related mortality in HCV-infected people with AUD, even in the DAA era.[35] In previous work using traditional MoCs, the homeless and people with a MHD have been associated with a lower likelihood of HCV treatment initiation.[36,37] However, we could not reproduce these findings, which suggests that the support and holistic approach used in alternative MoCs like the one in this study could lead to a higher uptake of HCV treatment in these vulnerable subgroups. Nonetheless, reducing the proportion of PWID LTFU in order to increase treatment completion among diagnosed PWID continues to be a challenge.

In the DAA era, AUD is common in patients diagnosed with decompensated cirrhosis and hepatocellular carcinoma and remain as a major contributor to the HCV-related liver disease burden.[35] In our study, we confirmed that cirrhosis occurred more frequently in people with AUD in comparison to people without AUD. This suggests that alcohol abuse could result in a more rapid progression of liver disease severity in HCV positive people due to the synergic hepatotoxic effect of HCV and alcohol, leaving this group of patients at a particularly high risk for liver related adverse outcomes even after DAA treatment.[35,38] Based on high DAA treatment effectiveness, regardless of the alcohol abuse found in our study and another previous study[18] we suggest that strategies must be developed to combine DAA therapy with the management of AUD without restrictions or delays in DAA access, to avoid fatal liver outcomes or liver-related mortality. Furthermore, new models should be implemented to facilitate DAA delivery to enhance adherence while alcohol consumption continues.[39,40] Future research could explore if HCV treatment impacts alcohol consumption and whether the implementation of harm reduction services specific for AUD can increase treatment completion.

Low rates of non-compliance and suboptimal adherence have been described in previous studies in vulnerable populations such as homeless and people with a MHD;[27,41] however, alcohol abuse, drug use and mental illness are associated with HCV treatment non-completion.[18,42,43] Conversely, other studies have reported high rates of HCV treatment completion in the homeless or people with unstable housing when support activities and a holistic approach are implemented.[31,44] In the present study, we found that only 23 individuals (14.0% of those who initiated treatment) discontinued DAA treatment. This figure is comparable to the findings of other studies treating vulnerable subgroups such as PWID,[27,45] but a little higher than in studies like the Iceland cohort[46] and the SIMPLIFY trial.[26] We also found that PWID, compared to people who do not inject drugs, and people with AUD, in comparison to those without AUD, were less likely to complete treatment, although SVR was higher than 90% in both groups. We could not demonstrate differences in the cure rates according to treatment completion due to the weak statistical power of the sample inherent to the low number of cases of no-SVR; however, high rates of treatment success, even among patients with unhealthy alcohol use and ongoing drug use, have been reported previously.[18,27,29]

According to other findings, the high effectiveness of treatment despite incomplete treatment rates suggests that missed doses and early discontinuation do not impede achieving SVR,[45,47] although extension of therapy due to missed doses could play a role as well,[45] and so suboptimal adherence in these groups may still lead to a cure in the DAA

era.[47] We did not measure adherence in this study, but other publications targeting highly marginalized populations, such as PWID or homeless people, have reported acceptable levels of DAA adherence.[45] However, factors such as having a MHD and AUD have been related to poor adherence[45,47] As the effectiveness of DAAs is well established, we believe that efforts should be aimed towards initiating treatment and enhancing its completion, instead of focusing on testing for SVR post-treatment in vulnerable people with a lower reinfection risk and in those without cirrhosis. Nevertheless, in people with a higher risk of reinfection such as PWID and in those with cirrhosis, it is necessary to balance the need for further SVR monitoring. This is reinforced by the fact that we found that reinfections accounted for 11.2% of the HCV diagnosis in the global cohort sample and up to a quarter of the sample from PWID.

The implementation of PoC-based rapid screening in combination with a simplification of the linkage-to-care process has the benefit of significantly reducing diagnosis time and improves the likelihood of and reduces the time to HCV treatment initiation[2,29,30] even in prisons settings.[32] Nevertheless, the time to HCV treatment initiation using rapid PoC screening among different vulnerable subgroups has not been well described. Studies have reported that the median time to HCV treatment was more than 120 days in general population[21,48] but a recent United States' study among the homeless and incarcerated and people with a MHD who received sofosbuvir/velpatasvir showed a median time to HCV treatment of 60 days,[23] and that patients with a MHD had the longest median time to HCV treatment (66 days), while homeless patients had the shortest (27 days). We found a global median time to HCV treatment of 35.5 days and that people with AUD had the longest time to HCV treatment initiation (40.5 days), when compared to other subgroups. Future challenges include starting HCV treatment on the same day of diagnosis and decentralizing DAA procurement so that they are available outside of hospital settings. In the present study, only one patient started treatment on the same day of diagnosis. Had this occurred more, it could have decreased the proportion of individuals LTFU. Our findings are comparable to a previous study which showed that the proportion of patients who start treatment on the same day of diagnosis is very low (8%)[23]

Strengths and limitations

Strengths of our study include the inclusion and follow-up of some vulnerable subgroups such as people with an MHD or AUD that have not been evaluated previously in terms of the whole HCV CoC, which allowed for the identification of barriers. We were also able to calculate the time to HCV treatment initiation when using a mobile unit utilizing a PoC strategy including rapid treatment and diagnosis. However, there are several limitations to our study that should be considered. First, we present findings from a single mobile unit that carried out screening in a big city with a diverse population, so these results may not be generalizable to all settings in Spain and other countries. Second, a high loss to follow-up (36%) between treatment completion and SVR testing occurred; however, unavailability for SVR testing is common in this population and this rate of loss to follow-up for SVR testing is similar to other cohorts of PWID initiating DAA therapy.[44,45] Third, the number of cases of people with no-SVR was too small to assess the factors associated with SVR between the vulnerable subgroups and evaluate if there are any existing influences on non-completion of treatment and SVR. Fourth, the diagnoses of AUD and a MHD were obtained and matched by clinical reports of the electronic system of hospitals of Madrid at the moment of treatment initiation, and based in ICD-10 codes; it is possible, though, that some individuals had poor contact with the health system and so they remained unevaluated and undiagnosed; this could have led to an underestimation of

cases of AUD and MHDs. Fifth, we were unable to make distinctions between no-SVR and possible reinfection at SVR testing, and assumptions were based only on genotyping of HCV-RNA results. It seems reasonable to assume that patients with higher-risk behaviors would become reinfected after the end of treatment and before SVR testing. Although the gold standard would be sensitive sequencing methods, all our cases of no-SVR were switched genotypes. Finally, although self-reporting is considered a reliable source of data collection among people who use drugs, some may not have provided accurate answers.[49]

Conclusions

In conclusion, the mobile unit was a successful MoC to reach marginalized people in Madrid and demonstrates that curing HCV is possible in diverse patient subpopulations traditionally considered hard to reach. Ultimately, it is important to support patients, focusing on their priorities, and to utilize a holistic approach towards HCV management, to allow for treatment initiation and completion, especially for PWID and people with AUD.

Authors' contributions

Funding body: JV and PR.

Study concept and design: JV and PR.

Patients' selection and clinical data acquisition: PR, JV, GC and JTM.

Laboratory assays: SR.

Statistical analysis and interpretation of data: FC.

Writing of the manuscript: JV.

Critical revision of the manuscript for relevant intellectual content: PR, JT and JVL.

Supervision and visualization: JV, PR and FC.

All authors read and approved the final manuscript.

Originality

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

Availability of data and materials

Datasets used and analyzed during the current study may be available from the corresponding author upon reasonable request.

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Figure legends:

Figure 1. Global hepatitis C cascade of care, using a screening mobile unit.

Figure 2. Multivariable logistic regression analysis of factors associated with initiation of DAA treatment and treatment completion.

Figure 3. Kaplan Meier analysis. Kaplan Meier curves for time to HCV treatment initiation according to vulnerable groups: PWID with recent drug use, the homeless, people with a MHD and AUD.

Figure 4. Mosaic Plots of the different risks according to the patient treatment status. All individuals of the study cohort were considered (n=214)

Figure 5. Mosaic Plots of the different risks according to the patient treatment status. Only individuals who initiated treatment were considered (n=164).

Supplementary table

Table 1. Characteristics HCV Treatment

	HCV Treatment
Treatment regimens	
Glecaprevir/pibrentasvir	78/164
Sofosbuvir/velpatasvir	81/164
Sofosbuvir/velpatasvir/voxilaprevir	4/164
Elbasvir/gazoprevir	1/164
Reasons for not initiating HCV treatment	
Medical indication	2/50
Patient refusal	17/50
Death	9/50
Loss to follow-up	19/50
Spontaneous clearance	3/50