Out-of-hospital treatment of Hepatitis C increases retention in care among people who inject drugs and homeless persons: an observational study.

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ABSTRACT

BACKGROUND
Nowadays, main viral reservoir of HCV infection are people who inject drugs (PWID) and homeless (HL). HCV elimination programs barely reach these difficult to treat subgroups.
Aim of our retrospective study was to compare the retention in care rate between a group of PWIDs and/or HLs with Hepatitis C treated in a traditional hospital setting and a group treated in out-of-hospital setting ("Stop HCV project" in Bologna, Italy).

METHODS
We categorized patients into two groups according to whether the treatment was offered in a hospital or in an out-of-hospital setting. All the patients received treatment with Direct Antiviral Agents (DAAs). Retention in care rate was defined as the completion of DAAs therapy.

RESULTS
We enrolled 56 patients: 27/56 subjects in the out-of-hospital group. Thirty-tree out of 56 patients started and completed therapy with DAAs, with a higher rate of retention in care in the out-of-hospital group ($p = 0.001$). 93.9% achieved SVR 12.
At the univariate analysis, retention in care was associated with a shorter time between the first visit and the start of therapy ($p = 0.003$).

CONCLUSION
The choice of treatment models that can better adapt to difficult to treat populations will be important for achieving the eradication of HCV infection.

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Keywords

PWIDs, HLs, HCV eradication, DAAs, retention in care

Introduction

The worldwide incidence and prevalence of HCV infection has been decreasing since the introduction of the new Direct Antiviral Agents (DAAs) as a form of standard of care [1] [2].
The World Health Organization (WHO) has established the global goal of eradicating hepatitis C infection as a public health threat by 2030. [3]

Currently, injection drug use represents the primary route of transmission of HCV infection and the main viral reservoir are people who inject drugs (PWID) [4] [5].
An anti-HCV seroprevalence of 52.3% has been estimated among PWID [6].
Prevalence studies have reported that homeless persons are at high risk for HCV, mostly as a result of injection drug use [7]. Indeed, PWID tend to experience homelessness or unstable housing with prevalence ranging from 6.7% in Eastern Europe to 50.3% in North America [6].
Homelessness and unstable housing have been recently associated to a greater risk for acquiring infections like HCV and HIV among PWID when compared to PWID who had stable house [8]. A large meta-analysis has estimated a prevalence of HCV infection ranged from 3.9% to 36.2% in homeless people, based on the results of 12 eligible studies [7].

However, there is a lack of epidemiological data on the real prevalence of HCV infection in these difficult to treat subgroups [5]. HCV elimination programs barely reach these populations. Targeted screening programs are necessary to achieve the goal set by the WHO [4].

For a long time, PWID has been regarded as a neglected population because of the concerns about adherence to treatments and poor treatment outcome. Among others, the MISTRAL study has shown how a safe and effective pan-genotypic treatment regimen, particularly with a short duration, could facilitate an increase in accessing treatments for high-risk populations. [9] [10]

Currently, guidelines for Hepatitis C treatment from both the American and the European Association for the Study of Liver Diseases recommends to treat PWID with chronic HCV infection. [11][12]
Factors complicating access to care in this population must be addressed: the stigma, the risk for reinfection in PWID, challenges related to incarceration, and housing instability. [5] [13]
It is also widely recognized that an integrated harm reduction strategy is needed to control HCV transmission and to reduce community viral load. [6] [14] By reducing risk behaviors, HCV testing programs that combine screening and counseling can decrease HCV transmission and reinfection after treatment with DAAs. [15] [16] The provision of sterile injecting equipment through needle and syringe programs (NSP) and the enrolment in opioid substitution treatment (OST) are among the primary interventions for reducing HCV reinfection rate among PWID. [17]

Recent data have shown that the incidence of HCV reinfections in PWID after achieving sustained viral response (SVR) is low (1.85-22.32 / 1000 person-years), with higher rates in active drug users. [18][19]
Screening and confirmation tests, linkage to care, retention in care, prescription of DAAs and adherence to HCV treatment are priorities for fighting the silent epidemic of chronic HCV infection in PWID and homeless people [9] [20].

However, PWID and homeless persons have poor access to hospital care due to reduced retention in care and difficulties in accessing traditional screening programs. Therefore, alternative treatment programs for PWID and homeless people are emerging in Europe. [17] [20] [21] [22] [23]
In Italy, out-of-hospital care models are emerging with the presence of dedicated doctors, nurses, and peer-educators with experience in drug addiction. [24] [25] [26] In Italy, the “Stop HCV” project was conceived and conducted in the city of Bologna with the help of the “Open Group-Unità di Strada”, a non-profit organization of harm reduction. The project consisted in offering HCV screening and treatment for hepatitis C using DOT (directly observed therapy), in a population of PWID and homeless people, with this occurring in an out-of-hospital setting.

The primary aim of our retrospective study was to measure and compare the retention in care rate, (defined as the completion of DAAs therapy), achieved in a group consisting of PWID and/or homeless persons with Hepatitis C treated in a traditional hospital setting (i.e. outpatient services) with the retention in care rate achieved in a group of PWID and/or homeless persons but treated in an out-of-hospital setting.
The secondary aim of the study was to estimate prevalence of patients who started treatment after their linkage-to-care, the time between first visit and start of therapy, and the rate of sustained virological response 12 weeks after the end of treatment (SVR 12).

Materials and Methods

We retrospectively included in this study patients with HCV chronic infection (i.e. with documented detectable HCV RNA), considered therefore eligible for DAAs treatment, who were active intravenous drug users and/or who experiencing homelessness. We categorized the enrolled patients into two groups according to whether the treatment was offered in a hospital or in an out-of-hospital setting and we compared the outcomes between the two groups. While the patients treated for Hepatitis C in the standard setting received therapy from May 2017 to August 2018 at our clinic of Infectious Diseases in Bologna (Italy), differently, the patients treated in an out-of-hospital setting underwent treatment between January 2019 and June 2019. In the latter setting, DOT (under the supervision of medical and not-medical staff) was applied, with the support of peer-educators with expertise in management of PWID, in the context of the “Stop HCV” project, which we have already mentioned.
All the patients received treatment with DAAs for 8 or 12 weeks, according to international guidelines.
Retention in care rate was defined as the completion of the established DAAs therapy.
We also measured the *expected waiting time,* which was defined as the time between the first visit and the start of therapy with DAAs.
For each subject, we collected the following data at baseline: demographics (age, sex, BMI), stage of liver fibrosis (measured by transient elastography, FibroScan), prior failures to anti-HCV treatment, HCV genotype, HCV RNA, DAAs regimen, data on HIV coinfection when present (i.e. HIV RNA viremia, CD4+T-cells count, current antiretroviral (ART) regimen), HBV coinfection, psychiatric comorbidity, OST, drug use status (current or previous). INR, bilirubin, ALT, creatinine, HCV RNA were then evaluated at each scheduled visit.

Statistical analysis
Patient characteristics were expressed as median [and Interquartile range, IQR] and percentage when appropriate.
To compare the characteristics between groups (i.e. in hospital and out-of-hospital setting), we performed the Mann–Whitney U-test and the Chi-squared test (or Fisher Test) for continuous and categorical variables, respectively. A p-value < 0.05 was considered statistically significant. To evaluate the variables associated with our retention in care we performed regression analysis, including in the multivariable model demographics characteristics, as age and gender, and variables which presented a p-value ≤ 0.1 at univariate analysis. All the analysis were performed by using SPSS (24.0 version).

Results

Patient characteristics at baseline

We enrolled 56 patients who met the inclusion criteria: 29 subjects in the in-hospital group and 27 subjects in the out-of-hospital group. The baseline characteristics are shown in **Table 1.**
The median age was 44.5 years and 92.9% of patients were male.
All the subjects in the in-hospital group actively used drugs at enrollment, while only 44.4% of those in the out-of-hospital were PWID ($p< 0.001$). An overall of 71.4% of individuals (40/56) used OST, with a lower percentage in the out-of-hospital setting rather than the comparison setting ($p = 0.003$).
Psychiatric comorbidity was found in 26.8% (15/56) of patients; 58.8% (30/56) of subjects was

infected with HCV genotype 1. Five out of 56 patients (8.9%) had F3 fibrosis according to Metavir score, while 15.7% (8/56) had documented liver cirrhosis: 2 out of these 8 subjects with an advanced liver disease had decompensated cirrhosis (B8 Child-Pugh class). None of the patients had hepatocellular carcinoma. There was a statistically significant difference in creatinine values between the two groups, with higher levels among those who were treated in the standard in-hospital setting ($p = 0.003$).
Thirteen patients (24,5%) were HCV-HIV coinfected: their characteristics are shown in **Table 2.**

Primary and secondary outcomes

Thirty-tree out of 56 patients started therapy with DAAs. The most used HCV regimen was Glecaprevir/Pibrentasvir (73% treated for 8 weeks, 9% for 12 weeks). The other patients received therapy with Sofosbuvir/Velpatasvir. Thirty-tree patients (60% of the overall population) completed the treatment with DAAs, with a higher rate of DAAs treatment completion (defined a retention in care, as specified before) in the out-of-hospital group ($p = 0.001$). The expected waiting time was significantly longer in subjects referring to standard in-hospital services ($p < 0.001$), in comparison with the other group **(Figure 1).**

Among the 33 patients who were treated for Hepatitis C, 93.9% achieved SVR 12 (31/33), with SVR12 rate of 91% among subjects treated in the traditional in-hospital setting and a rate of 94% among those treated in the out-of-hospital setting (**Table 3**). The two patients (one in each of the two compared groups) did not achieve sustained virological response: one experienced a relapse after 4 weeks after end of treatment (in-hospital group) and was diagnosed with HCV reinfection over the follow-up (out-of-hospital group).

At the univariate analysis, retention in care was associated only with the out-of-hospital management ($p= 0.002$) and with a shorter expected waiting time ($p = 0.003$), as shown in **Table 4**. Despite a significantly higher prevalence of PWID as well as of patients in OST among those included in the in-hospital group, these particular conditions were not associated with retention in care.
When we included the covariate “expected waiting time” in the model with out-of-hospital management as an exposure variable, the out-of-hospital management did not remain statistically significant as a predictor of retention in care ($p=0.69$). This could potentially suggest that our primary outcome (i.e. retention in care) might be driven by a shorter expected waiting time rather than the setting where patients were managed.

Discussion

HCV infection is efficiently spread by injection drug use, and this represents an important public health issue. Furthermore, PWID are very challenging patients to treat because of their difficulties in accessing traditional care in hospital settings and the frequent co-occurrence of alcohol abuse, HIV infection, and psychiatric comorbidities [5] [6].
Due to the difficulties in treating PWID, along with often asymptomatic course of HCV infection, there is a risk of underestimating individuals affected by hepatitis C [1].
Similarly, hepatitis C infection represents one of the most prevalent infectious diseases among homeless people, who should be considered a high-risk group, for which diagnosis and treatment of HCV should be a priority [7].
This lack of data on the real prevalence of HCV infection limits the WHO's goal of eradicating hepatitis C around the world [2].
Attempts to associate harm reduction interventions simultaneously with the administration of safe and shorter therapeutic regimens may favor a lower transmission of the virus and a reduction of liver damage in these populations. [9] [10]
For these reason alternative models of care in out-of-hospital setting are spreading in Europe [25] and Italy, with encouraging results [24] [25] [26].

Our study showed how an out-of-hospital care model might guarantee a better retention in care for difficult-to-reach groups with HCV infection.

In our population, the patients with diagnosis of chronic C hepatitis managed in the out-of-hospital setting were more likely to complete the therapy, achieving the primary outcome, in comparison to the individuals treated in hospital.
Consistently with that, those who were scheduled to start a treatment with DAAs earlier after their first visit were more likely to complete the treatment for HCV infection than those who had to start DAAs with delay. We can reasonably assume from our analysis and results that a shorter expected waiting time is the key for the success of out-of-hospital approach, suggesting that it may play a role as a mediator for a higher proportion of retention in care in the out-of-hospital setting.
The presence of peer educators may have contribute to improve the linkage to care in the out-of-hospital setting.

Starting treatment quickly and in a more individualized way improved the retention in care of PWID. [26][17] [20] [24].

In agreement with our findings, a recent research conducted in Vienna on DAAs administration as DOT (given at OST facilities) in PWID showed excellent SVR12 rates (99%) in this difficult-to-treat population, similar to patients with expected high treatment compliance in a standard setting [27].

In our study, although the rate of DAAs therapy completion was lower among patients treated in hospital, when we consider the entire subset of subjects who completed treatment, we observed similarly high virological success rates regardless from treatment setting, with no statistically significant differences.
The 93.9% of SVR 12 in our overall treated population confirmed the efficacy of regimens with DAAs as reported in the real-world published studies. [28]

Small sample size and its retrospective nature are limitations of the study. Moreover, this is a real-world study and we have to acknowledge some baseline differences between the two groups that we compared in the analysis. In particular, all the patients in the in-hospital group were active IDUs, while less than 50% of the out-of-hospital group was currently using intravenous drugs: nevertheless the active use of drugs was not associated with our primary outcome. In addition, the “Stop HCV project” was interrupted in November 2019 due to lack of funds. A prolongation of this program would have added relevant data, such as reinfection rate.
The results of an effective anti-HCV treatment can be compromised by the risk of reinfection, associated with the persistence of risk behaviors after achieving SVR. For this reason, for a long time, PWID has been regarded as a neglected population because of poor treatment outcome.
In fact, recently published data show how the incidence of HCV reinfection in PWID after the achievement of SVR is low (1.85 to 22.32 / 1000 person-years). [18] [29]
Longer follow-up periods could certainly provide further data on this population.

Conclusions

In conclusions, our study demonstrated that underserved patients with chronic C hepatitis, historically defined as “difficult to treat” groups due to their social instability and risky behaviors, might benefit from new integrated healthcare approaches, such as an out-of-hospital setting where patients may be diagnosed with chronic HCV infection and cured shortly afterwards.

The choice of treatment models that can better adapt to difficult populations, such as PWID and homeless people, will be important for achieving the WHO’s goal and therefore further studies are needed.

Tables

Table 1. Baseline patients' characteristics

Characteristics	Total population (n=56)	In-hospital group (n = 29)	Out-of-hospital group (n= 27)	P value
Age (year), median [IQR]	44.5 [35.5- 51]	45 [36.5- 50.5]	41 [35.0-51]	0.941
Male, n (%)	52.0 (92.9%)	27 (93.1%)	25 (92.6%)	1.000
BMI, median [IQR]	22.8 [20.8- 24.8]	23.2 [21.0- 27.2]	22.6 [20.1- 24.5]	0.154
Active PWID	41 (73.2%)	29 (100%)	12 (44.4%)	**< 0.001**
OST, n (%)	40.0 (71.4%)	26.0 (89.7%)	14.0 (51.9%)	**0.003**
Psychiatric comorbidity, n (%)	15.0 (26.8%)	6.0 (20.7%)	9.0 (33.3%)	0.370
HBV coinfection, n (%)	1.0 (1.9%)	1 (3.4%)	0.0 (0.0%)	1.000
HIV coinfection, n (%)	13.0 (24.5%)	10.0 (34.5%)	3.0 (12.5%)	0.108
Stiffness, kPa, median [IQR]	6.5 [5.1-8.2]	6.8 [5.1-8.6]	6.35 [5.0-8.1]	0.434
HCV genotype, n (%) **1** **3** **4**	 30.0 (58.8%) 16.0 (31.4%) 5.0 (9.8%)	 14.0 (53.8%) 9.0 (34.6%) 3.0 (11.5%)	 16.0 (64 %) 7.0 (28 %) 2.0 (8 %)	0.754
Prior Peg-IFN/RBV failure, n (%)	8.9 (14.8%)	2.0 (7.4%)	6.0 (22.2%)	0.250
HCV RNA, log_{10} IU/ml, median [IQR]	6.1 [5.2-6.3]	6.1 [5.4-6.4]	6.0 [5.0-6.3]	0.741
ALT, UI/L, median [IQR]	45.0 [29.0-110]	44.0 [28.3-110]	55.0 [30.0-110]	0.899
Total bilirubin, mg/dl, median [IQR]	0.6 [0.4- 0.8]	0.6 [0.4- 0.9]	0.6 [0.4- 0.8]	0.381
Creatinine, mg/dl, median [IQR]	0.8 [0.7- 0.9]	0.9 [0.8- 1]	0.7 [0.6- 0.8]	**0.003**
Platelets, 10^9L, median [IQR]	218 [177- 266]	202 [152- 253]	234 [185- 273]	0.108

Table 2. Patients with HIV/HCV coinfection

Parameters	Total population (n 13)	In-hospital group (n 10)	Out-of-hospital group (n 3)	P value
Undetectable HIV RNA, n (%)	9 (75%)	8 (88.9%)	1 (33.3%)	0.127
CD4+ cell count/mm^3, median [IQR]	632 [419-849]	575 [377-891]	688 [545-746]	1.000
ART regimen, n (%) **2NRTI+NNRTI** **2NRTI+INSTI** **2NRTI+PI** **Others**	 4 (33.3%) 3 (25 %) 1 (8.3%) 4 (33.3%)	 3 (33.3%) 2 (22.2%) 1 (11.1%) 3 (33.3%)	 1 (33.3%) 1 (33. 3%) none 1 (33.3%)	0.931

Abbreviation: ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non- nucleoside reverse transcriptase inhibitors; INSTI: Integrase Strand Transfer Inhibitors; PI, Protease Inhibitors.

Table 3. Comparison of primary and secondary outcomes between in-hospital and out-of-hospital settings.

Outcomes	Total population (n 56)	In-hospital group (n 29)	Out-of-hospital group (n 27)	P value
Retention in care, n (%)	33 (58.9%)	11 (37.9%)	22 (81.5%)	**0.001**
Expected waiting time, days, median [IQR]	42 [28.0-215.3]	215.5 [168.5-314.8]	28.0 [21.0-28.0]	**<0.001**
	Treated population (n 33)	**In-hospital group (n 11)**	**Out-of-hospital group (n 22)**	
SVR12, n (%)	31 (93.9%)	10 (90.9%)	21 (94.5%)	0.6

Abbreviation: SVR12, Sustained Virological Response 12 weeks after end of treatment.

Table 4. Univariate analysis of factors associated to the completion of DAAs (defined as retention in care).

VARIABLES	Univariate analysis		
	Exp(B)	95 % CI	p-value
Age	1.042	0.989; 1.099	0.123
Male sex	0.68	0.088; 5.19	0.71
Metavir F4	0.281	0.031; 2.552	0.26
BMI	0.91	0.79; 1.047	0.18
OST	2.71	0.747; 9.87	0.129
Psychiatric comorbidity	0.64	0.19; 2.2	0.48
HIV coinfection	1.43	0.40; 5.1	0.58
Prior Peg-IFN/RBV failure	3.13	0.66; 14.8	0.15
ALT	1.002	0.99; 1.01	0.71
Bilirubin	1.25	0.453; 3.46	0.67
Creatinine	0.128	0.006; 2.77	0.19
Platelets	0.997	0.99; 1.004	0.434
Expected waiting time, days	0.992	0.987; 0.997	**0.003**
SERD	2.11	0.713; 6.249	0.117
Out-of-hospital management	0.139	0.041; 0.474	**0.002**

Figure legends

Figure 1
Expected days of waiting before DAAs treatment start in the standard in-hospital setting group and in the out-of-hospital setting group (Panel A); retention in care rates among patients treated for HCV in hospital and out of hospital (Panel B).

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