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Hepatitis C management and treatment among people who inject drugs in Italy: An exploratory pilot survey

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SUMMARY

■ Background

People Who Use Drugs (PWID) play a crucial role in the goal of eradicating hepatitis C and, despite the high efficacy and tolerability of Direct Acting Antivirals, many PWID still have to be treated and there are many barriers that slow down the process. An exploratory pilot survey was conducted to determine service providers' current condition and the barriers experienced by PWID in accessing HCV treatment.

Methods

Seven selected clinical centres completed a 27-item online survey addressing the current treatment situation in PWID hepatitis C treatment, related barriers and linkage to care.

Results

The survey mainly involved central-northern Italian clinical centres (71.4%), with less than 4 prescribers (71.4%) despite they are currently treating around 500-1000 patients for Hepatitis C (> 50% current or former PWID). In most cases, they carried out the necessary checks (100% blood sample, 85.7% fibroscan and 43% ultrasound) in few visits (85.7%) to deliver drugs in about one month (71.4%). They all agree on the need for fast-track for PWID and therefore they are all engaged in dedicated projects. The commitment to eradication is, in most cases, based on personal efforts, which despite the few prescribers, the lack of institutional support (85.7%) and the impossibility to use simplification scores since prescription and drug delivery portals (AIFA and regional) still require a lot of information. Although the centres questioned express the need for a simplification of the bureaucratic processes, however, they scrupulously follow PWID. For 57.4% of the centres, Linkage to Care remains the most problematic moment, to follow equally the lack of a correct epidemiological estimate and the implementation of the harm reduction policies. Finally, most of the centres don't find particular barriers related to PWID's features, but analysing them individually the main ones are: the difficult social background, the reinfection risk and the patient's poor motivation.

Conclusions

The needs emerged from this survey are: to work on PWID de-stigmatization, to simplify the prescription/drug delivery portals in order, to increase PWID social assistance network and institutions support in HCV eradication programs. ■

Keywords: PWID, Key population, HCV elimination, Hepatitis C virus, Injection drug use.

Parole chiave: PWID, popolazione target, eliminazione HCV, Virus dell'Epatite C, Uso di droghe iniettabili.

Introduction

In Europe, Hepatitis C virus (HCV) infection is very common among people who inject drugs (PWID) through the sharing of injection equipment, such as needles, syringes and other equipment (paraphernalia) (Palmateer *et al.*, 2014).

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In 2017, anti-HCV prevalence among people who inject drugs varied from 15% to 82% and in eight out of the 14 countries with national data reported by the European Monitoring Centre for Drugs and Drug Addiction (EMCCDA), more than half of PWID have been infected with HCV.

In Italy there are no reliable and documented data on the extent of the phenomenon: in 2017 there were about 235,000 high-risk PWID and HCV seroprevalence was estimated 64.33% (EMCCDA, 2019).

To eliminate viral hepatitis as a public health threat, the WHO target aims for 50% of people with chronic hepatitis C to be diagnosed by 2020, and 75% of eligible patients to be receiving treatment. The WHO recommends offering treatment to all people with chronic hepatitis C infection (≥ 12 years of age or older, except for pregnant women), irrespective of hepatic disease stage, also stressing that treating PWID along with provision of harm reduction interventions is cost-effective (WHO, 2017).

Nevertheless, yet many PWID with chronic HCV infection are still (Wiessing *et al.*, 2014). Treatment rates in European PWID with HCV infection have been estimated to be between 10% and 30% (Maticic *et al.*, 2019).

According to the data recently available in Italy (February 2020), since 2015, over 200,000 thousand treatments with DAAs (Direct Acting Antivirals) for chronic hepatitis C started and in the majority already successfully concluded, but even in our country there are at least as many people who are not yet treated, even if access to care is guaranteed to all persons with HCV infection (AIFA, 2020).

Without finding and treating those “missing” patients (often among the most marginalized and vulnerable groups of population as PWID) all other efforts will have only marginal success. In this scenario it is therefore necessary to focus on the key populations, as PWID, in which the infection is found to circulate more and which act as a reservoir of the virus. Furthermore, globally, 23% of new HCV infections are attributable to injecting drug use (Grebely *et al.*, 2017).

Although, results from clinical trials (Foster *et al.*, 2019; Flamm *et al.*, 2019; Cunningham *et al.*, 2018; Kattakuzhy *et al.*, 2018; Dore *et al.*, 2016) showed high success of HCV treatment also in PWID, however, real world data on knowledge, attitudes, and practices, including barriers and facilitators, of HCV treatment among PWID are limited. Moreover, there are still health system, structural, social, patient-level and provider-level barriers that are hindering DAAs access to PWID (Grebely *et al.*, 2013).

The aim of this exploratory and descriptive analysis is to evaluate, through a questionnaire survey, the barriers perceived related to HCV management and treatment by physicians prescribing DAAs in Italy.

Methods

Seven selected clinical centres (Infectious Diseases Clinic of Tor Vergata University of Rome, Unit of Infectious Diseases University of Sassari, Villa Maraini Foundation in Rome, Infectious Diseases Clinic of Policlinico San Martino Hospital of Genoa, Infectious Diseases Unit of Pescara General Hospital, Penitentiary Infectious Diseases Unit of Santi Paolo and Carlo Hospital, Infectious Diseases Clinic of University of Foggia, Hepatology Unit of Sapienza University of Rome, Institute of Tropical and Infectious Diseases of University of Milan) engaged in the treatment of PWID with chronic hepatitis C, completed a 27-items online survey addressing the current DAAs treatment situation for PWID. All physicians involved in the survey were infectious diseases specialists.

The selection of questionnaire items took into account the following issues (see attached content):

1. characteristics of the clinical centers: evaluation of the prevalence of the PWID population affected by Chronic Liver Disease C in infectious disease clinics (pre-DAAs, post-DAAs and trends over the past four years) (n = 9 questions);

2. Linkage to Care: access modality of PWID to the infectious diseases clinics, analysis of the relationship between DAAs prescribers and public drug use disorders units (SerD – Servizi per le Dipendenze) and non-governmental organization (NGOs) otherwise associations engaged in harm reduction in out-of-hospital setting such as for example Needle Exchange Program, overdose treatment and prevention, drop-in activity, counseling, prevention activities (n = 7 questions);
3. management and treatment: tools for the assessment of liver disease, timing of start of therapy for PWID, visits and controls during and at the end of treatment (n = 7 questions);
4. barriers: evaluation of the barriers to treatment (n = 4 questions).

The survey consisted of multiple-choice questions, specifically n = 18 included only one choice between the answers, n = 7 included more than one choice between the answers and n = 2 were classification questions that allowed respondents to choose the order of answers options that most closely matched their experience.

Statistical analysis

Data are given as frequencies and percentages. Our complete data analysis is exploratory. Hence, no sample size calculation was performed. Data were analyzed using Excel.

Results

Characteristics of the clinical centers

The survey mainly involved central-northern clinical centers (3 centers from Central Italy, 2 centers from Northern Italy, 1 center from the Islands, 1 center from Southern Italy) with fewer than four AIFA (Agenzia Italiana del Farmaco) authorized Infectious Diseases specialist prescribers (71.4%) despite counting more than 500 chronic hepatitis C patients in over half of the cases (500-1000 patients 57.14%). The populations most represented in the seven clinical centers explored, are PWID (47%) and more precisely current PWID (24%) and former PWID (23%), following general population (26%), nephropatic patients (15%), liver transplanted/waiting list (12%) (Figure 1).

The era before the availability of DAAs is characterized by a reduced number of treated patients (<500) in 57.1% of clinical centers, and PWID represented, respectively, < 30% and > 50% of the whole treated population in 57.15% and 42.86% of the clinical centers.

Four years after the introduction of DAAs, 71.4% of the surveyed centers reports having treated 200-1000 patients with chronic hepatitis C, and 42.8% of the centers reports that they are PWID for over 50% (Table 1).

Planning and Linkage to Care

All the surveyed clinical centers expressed the need to dedicate a fast track (preferential and rapid) for the treatment with DAAs to PWID with chronic hepatitis C and all of them declare that they have ongoing HCV micro-elimination projects for this key population also because with the DAAs arrival, PWID access to the clinical centers has increased (so declares 87.51%). Specifici-

cally, these projects are to be referred to informal agreements with public drug dependency service units and organizations engaged in harm reduction programs (71.34%), regional institutional programs (42.86%), grants from pharmaceutical companies (14.29%), other nature (28.57%).

As regards projects with SerD and associations, 57.14% of clinical centers declare that the request to formulate a referral model by meeting the territorial services for drug use disorder and associations arose from themselves, the reverse is declared by 28.57% and in 42.86% of cases, clinical centers, SerD and associations were convened and brought together by an institutional technical committee.

The referral models that emerged from the survey are: 57.14% a direct call and give an appointment as soon as possible, 42.86% organize periodical visits going directly to SerD/associations, 14.29% receive a direct call and give an appointment in dedicated days (Table 2).

Management and treatment

The clinical centers report in the survey to have most of the main tools for the assessment of the liver disease, in particular: 100% (7/7) perform blood samples, 87.51% (6/7) use fibroscan, 42.86% (3/7) did liver ultrasound; and 42.86% (3/7) of them use also noninvasive scores for the liver fibrosis evaluation.

57.14% of the clinical center declares that PWID in charge has predominantly an F0-F1 liver fibrosis according to Metavir score (28.57% F2, 14.29% F3).

The average waiting time to start DAAs in PWID patients is one month for five clinical center, three months for one center, while one clinical center is able to guarantee liver disease assessment and start of treatment in a single visit.

Regarding the timing of treatment and follow-up visits, 57.14% of the involved centers visit PWID HCV patients and perform blood exams at baseline, every month during treatment, at 4, 12 and 24 weeks after the End of Treatment (EOT), 42.86% at baseline, 12 weeks after the EOT and 28.57% at baseline, EOT, 12 weeks after the EOT (Table 3).

Barriers to treatment

The majority (87.51%) of the centers involved in the study associated the lack of treatment with PWID DAAs, primarily, with the lack of interest from the institutions, while less than 50% (42.86%) reported difficulties in reaching this key population that is still highly stigmatized. When the survey explores the PWID Care Cascade, more than half of the clinical centers (57.14%) recognizes the most difficult step in Linkage to Care, while for other three centers lack of an accurate estimate of HCV seroprevalence among PWID, screening and prevention of HCV reinfection are problematic according to their experience (Table 4).

Most of the centres doesn't find particular barriers related to PWID's features (62%), but analysing them individually the main ones are: the difficult social background (88%), the reinfection risk (76%) and the patient's poor motivation (69%) (Figure 2).

Four out of seven centers agree with the need to make the prescription of DAAs accessible to general practitioners (GP) and physicians who work in public drug dependency service units.

Discussion

This pilot survey study made it possible to draw up a partial picture of the DAAs treatment of PWID with chronic hepatitis C subjects in seven Italian clinical centers. Compared to the interferon era, the introduction of DAAs in HCV infection therapy has led to an increase in treatments in both PWID and non-PWID patients: prior the DAAs availability, over half of the centers treated less than 500 patients, compared to 200-1000 patients in the DAAs era, and, if before DAAs, the number of PWID treated patients was less than 30% (57.1% of the clinical centers) currently they mainly represent more than half of the treated population (42.8% of the clinical centers). In addition, almost all of the clinical centers (87.51%) reports an overall increase of PWID among their patients since 2015 (introduction of DAAs). The increase of PWID access to DAAs prescribing clinical centers is certainly due to the availability of the interferon-free regimens, which are more effective, tolerable and with a shorter duration. Such innovative characteristics of DAAs facilitate the PWID population, until then excluded from interferon-based protocols for incompatibility between drug use disorder and interferon side effects. Even clinical trials included PWID patients and both dedicated and post-hoc analyses showed high sustained virologic response after 12 weeks (SVR12) and adherence rates (Foster *et al.*, 2019; Flamm *et al.*, 2019; Cunningham *et al.*, 2018; Kattakuzhy *et al.*, 2018; Dore *et al.*, 2016). The seven surveyed clinical centers demonstrate a significant commitment for the treatment of chronic hepatitis C in the key population of PWID: they all agree on the need for a fast-track for PWID and therefore they are all involved in dedicated projects.

The commitment to eradication is based, in most cases, on the efforts and personal initiatives of each individual center, materializing in the cooperation of infectious disease centers, SerD and organizations engaged in drug use disorders, in the discussion of the most difficult clinical/social cases in order to take charge in the shortest possible time. Integrated care networks are the key to improving HCV treatment of PWID. An integrated model of care, incorporating partnerships between hospital-based services prescribing DAAs and the drug use disorder services is recommended for the provision of HCV treatment to PWID (Harris *et al.*, 2012).

The hospital-based setting is one evidenced barrier to HCV treatment uptake among PWID and in order to counter this barrier, fast track and integrated care networks play a fundamental role. The integrated approach is certainly at the basis of the micro-elimination programs, which have demonstrated to be less daunting, less complex and less costly than full-scale, country-level initiatives to eliminate HCV, and it can build momentum by producing small victories that inspire more ambitious efforts. Furthermore, a micro-elimination approach, which entails pursuing elimination goal through integrated initiatives that tailor interventions to the need of specific populations such as PWID (Lazarus *et al.*, 2014).

If on the one hand different experiences and best practices demonstrate how the integrated collaboration between the different figures that revolve around PWID and the facilitated paths increase DAAs access for this key population, on the other hand the possibility of reaching them in out of hospital settings may prove a better intervention capillarity.

The efforts of each clinical center to increase access to treatment to PWID develop despite a) the small number of AIFA authorized prescribers (less than four in 71.4% of clinical centers); b) the

lack of support from the institutions (87.51% recognizes it as a major cause of unsatisfactory proposal of therapy to PWID); c) the impossibility of using simplification scores as the prescription and drug delivery online portals (AIFA and regional) still require a lot of information, though 42.86% already use noninvasive scores too.

In most cases, clinical centers have the possibility to carry out the necessary checks for the delivery of DAAs in single-visit, especially blood samples and fibroscan (100% and 87.51%) and, with some more difficulties, liver ultrasound (42.86%). However, it should be considered that over half of the clinical centers reports that PWID they follow has mainly an F0-F1 liver fibrosis according to Metavir score. Despite this, at the moment only one in seven clinical centers is potentially able to always guarantee diagnostic confirmation, staging and DAAs dispensing in single-visit mode; the average time for starting DAAs varies from one month to a maximum of three months.

If the clinical centers questioned express the need for simplification of the bureaucratic processes, on the other hand they follow their patients scrupulously with a complete baseline staging with samples/liver ultrasound/fibroscan and also blood examens at the end of treatment and to evaluate SVR12 (42.8%), and 57.1% also performs monthly blood examens during treatment and then for SVR4, SVR12 and SVR24.

Simplification process of HCV screening and management are fundamental for the DAA treatment scale-up, especially for a vulnerable population such as PWID. The importance of simplification is explicit in its primary goals, that are to better identify infected individuals, increase rates of retention and linkage to care and treatment, reduce the costs of diagnosis for patients and the healthcare system with the ultimate goal of reducing viral transmission at a population level (treatment as prevention), and progression of liver disease and hepatitis-related mortality at an individual level (Fourati *et al.*, 2018).

Although the aforementioned centers established preferential routes with great results in the growing access to the prescriber centers of PWID, chorally considered victims of stigmatization, the complex social background remains a consistent barrier and linkage to care is the most delicate moment of Continuum of Care.

It is known that many of the highest HCV prevalent populations (i.e., PWID, homeless and socioeconomically disadvantaged) often lack access to HCV testing and continuity of care. Case

management and regular sources of care attenuates social vulnerability, and robust support systems are needed in response to these complex and challenging demands (Franco *et al.*, 2018). Finally, despite several studies of task shifting treatment from specialists to primary care providers such as GPs and physicians working in the territorial dependency service units demonstrated its success in improving access to HCV care (Kattakuzhy *et al.*, 2017), among the clinical centers involved in the survey this topic remains an open question as it 42.86% doesn't agree.

Conclusions

To date, chronic hepatitis C remains a challenge in terms of elimination, which does not involve the rather proven efficacy and tolerability of antiviral drugs such as in the interferon era, but the analysis of barriers and facilitators of access to diagnosis and treatment in vulnerable population such as that of PWID.

Despite the well-known role of PWID in keeping the pandemic of chronic hepatitis C active and despite the literature and guidelines ask health care providers to care for these patients with professional and non-judgmental attitude, the survey confirms that this key population remains today highly stigmatized.

As a key population, that of PWID presents numerous vulnerable points, but certainly the most delicate and comprehensive one of the others is the difficult socio-economic background. In this regard, institutions should assist healthcare professionals in this difficult task of welcoming PWID in the continuum of care, from diagnosis to treatment, for example by intensifying the social care network and facilitating the work of prescribers by promoting micro-elimination programs and simplifying the DAAs online prescription portals.

The active collaboration between SerDs and NGOs engaged in the territory with PWID and hospitals represents a valid tool to overcome the main barriers, allowing to reach a quota of PWID otherwise excluded from screening programs and difficult to reach by the health system.

It is essential to create or, where already in place, intensify a diffused screening models in the territory thanks to the NGOs and SerDs and a fast track in hospital for PWID as simple as possible and free from bureaucracy, to pave the way for decentralization of treatment (out-of-hospital setting) which is certainly the most effective strategy to increase access to care for PWID.

Tab. 1 - Characteristics of the clinical centers which participated to the survey
PWID: People Who Inject Drugs; DAAs: Direct Acting Antivirals

<i>Characteristics of the clinical centers</i>	<i>N</i>	<i>%</i>
<i>Provenience</i>		
Northern Italy	2	28.57
Central Italy	3	42.86
Southern Italy	1	14.29
Islands	1	14.29
<i>Patients currently in charge</i>		
<500	2	28.57
500-1000	4	57.14
1000-1500	–	–
>1500	1	14.29
<i>Number of prescribers per clinical center</i>		
1	1	14.29
2	2	28.57
3	2	28.57
>4	2	28.57
<i>Patients treated in pre-DAAs era</i>		
<500	4	57.14
500-1000	2	28.57
1000-1500	1	14.29
>1500	–	–
<i>PWID among patients treated in pre-DAAs era</i>		
<10%	3	42.86
10-30%	1	14.29
30-50%	–	–
>50%	3	42.86
<i>Patients treated in DAAs era</i>		
<200	1	14.29
200-500	3	42.86
500-1000	2	28.57
>1000	1	14.29
<i>PWID among patients treated in DAAs era</i>		
<10%	1	14.29
10-30%	2	28.57
30-50%	1	14.29
>50%	3	42.86

Tab. 2 - Planning and Linkage to Care models

PWID: People Who Inject Drugs; SerD: Servizi per le Dipendenze, otherwise local services for drug use disorders; DAAs: Direct Acting Antivirals; HR: Harm Reduction

<i>Planning and Linkage to Care</i>	<i>N</i>	<i>%</i>
<i>HCV microelimination programs for PWID</i>		
Yes	7	100
No	–	–
<i>Type of HCV microelimination programs for PWID</i>		
Informal agreement with SerD/associations engaged in HR programs	5	71.43
Regional institutional program	4	42.86
Grant by pharmaceutical company	1	14.29
Other	2	28.57
<i>Increased access of more PWID with the arrival of DAAs</i>		
Yes	6	87.51
No	1	14.29
<i>PWID access the clinical center via</i>		
Regional booking system	1	14.29
SerD of belonging with which arrangements have been made	6	85.71
Associations engaged in HR programs	3	42.86
Already followed by the center for some time	2	28.57

Tab. 2 - Continued

<i>Planning and Linkage to Care</i>	<i>N</i>	<i>%</i>
<i>First contact with SerD/associations</i>		
The clinical center asked to meet to establish a referral model	4	57.14
SerD/associations asked to meet to establish a referral model	2	28.57
By institutional technical committee	3	42.86
There were no contacts	1	14.29
<i>Referral model</i>		
Direct call to the clinical center and appointment the first day available	4	57.14
Direct call to the clinical center and appointment in dedicated days	1	14.29
The staff of the clinical center periodically visits SerD/associations	3	42.86

Tab. 3 - Management and treatment

*DAA*s: Direct Acting Antivirals; *PWID*: People Who Inject Drugs; *EOT*: End of Treatment; *SerD*: Servizi per le Dipendenze, otherwise local services for drug use disorders

<i>Management and Treatment</i>	<i>N</i>	<i>%</i>
<i>Use of noninvasive scores for the evaluation of liver fibrosis</i>		
Yes	3	42.86
No	4	57.14
<i>Assessment tools liver disease available by center</i>		
Blood samples	7	100
Fibroscan	6	87.51
Liver ultrasound	3	42.86
<i>Average waiting time for the start of DAAs for PWID</i>		
Single visit	1	14.29
1 month	5	71.43
3 months	1	14.29
>3 months	–	–
<i>PWID liver fibrosis (Metavir score)</i>		
F0-F1	4	57.14
F2	2	28.57
F3	1	14.29
F4	–	–
<i>Timing of visits for treatment and follow up</i>		
Baseline, every month during treatment, 4-12-24 weeks after the EOT	4	57.14
Baseline, EOT, 12 weeks after the EOT	2	28.57
Baseline, 12 weeks after the EOT	3	42.86

Tab. 4 - Barriers to treatment

PWID: People Who Inject Drug; *DAA*s: Direct Acting Antivirals; *GP*: General Practitioner

<i>Barriers</i>	<i>N</i>	<i>%</i>
<i>Reasons why the treatment proposal remains unsatisfactory</i>		
Lack of interest from institutions	6	87.51
<i>PWID</i> are hard to reach	3	42.86
<i>PWID</i> are still stigmatized	3	42.86
Don't know	1	14.29
<i>The most difficult step of the Care Cascade for PWID</i>		
Lack of an accurate estimate of HCV seroprevalence among <i>PWID</i>	1	14.29
Screening	1	14.29
Linkage to Care	4	57.14
Diagnostic confirmation (HCV-RNA)	–	–
Staging	–	–
Engagement in Care	–	–
Prevention of reinfection	1	14.29
<i>Need to make the prescription of DAAs accessible to GP and physicians who work in drug use disorders services</i>		
Yes	4	57.14
No	3	42.86
Not sure	–	–

Fig. 1 - Patient populations most represented in the clinical centers that participated to the survey

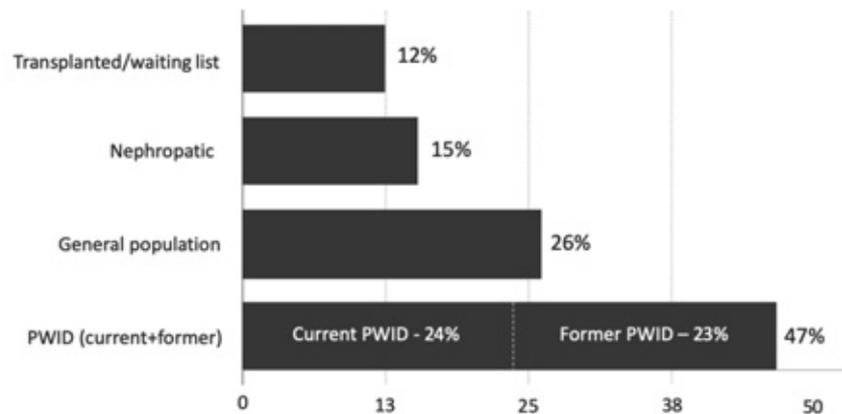
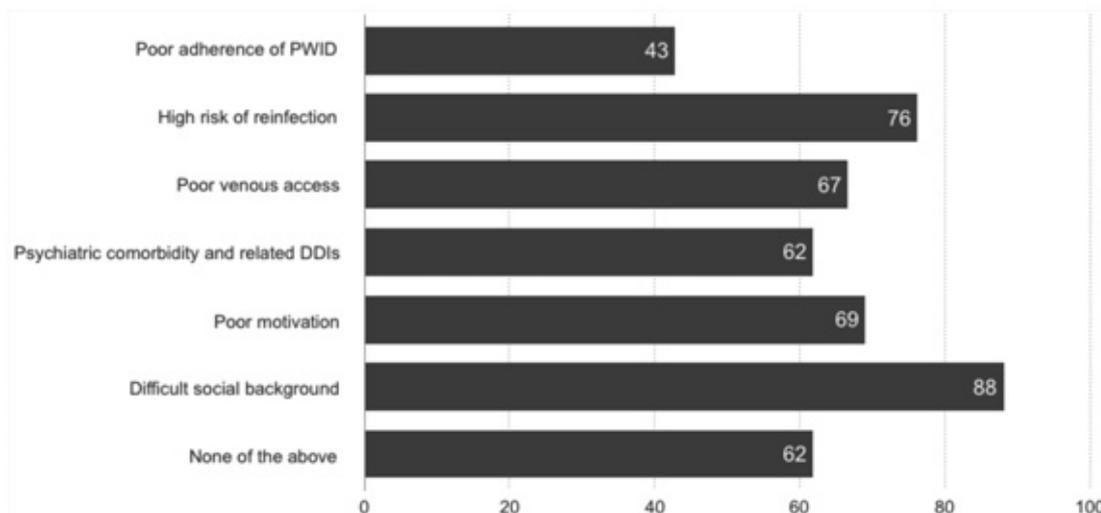


Fig. 2 - Most relevant barriers reported by the clinical centers that participated to the survey



Attached content. The 27-items questionnaire used for the online survey

1. What is your specialization?
 - a) Infectious Diseases specialist
 - b) Hepatology specialist
 - c) Internal Medicine specialist
 - d) Other
2. Can you report the area of belonging to your clinical center?
 - a) North
 - b) Center
 - c) South
 - d) Islands
3. How many patients affected by HCV Chronic Hepatitis are currently in charge at your clinical center?
 - a) <500
 - b) 500-1000
 - c) 1000-1500
 - d) >1500
4. How many DAAs prescribers does your clinical center provide?
 - a) 1
 - b) 2
 - c) 3
 - d) >4
5. Indicate the current composition of the population of your clinical center: (in descending order, where 1 is the least represented and 5 the most represented)
 - a) Nephropathic
 - b) Liver transplanted/waiting list
 - c) PWID
 - d) Former PWID
 - e) Other
6. How many patients did your clinical center treated in the pre-DAAs era?
 - a) <500
 - b) 500-1000
 - c) 1000-1500
 - d) 1500
7. Of these, how many were current PWID?
 - a) <10%
 - b) 10-30%
 - c) 30-50%
 - d) >50%
8. How many patients did your clinical center treated with Direct Acting Antivirals:
 - a) <200
 - b) 200-500
 - c) 500-1000
 - d) >1000
9. Of these, how many were current PWID?
 - a) <10%
 - b) 10-30%
 - c) 30-50%
 - d) >50%

10. Do you believe it is necessary to dedicate a fast track path (preferential and rapid) for PWID affected by Chronic Liver Disease C?
 - a) Yes
 - b) No
11. Does your clinical center have any plans for HCV eradication dedicated to PWID?
 - a) Yes
 - b) No
 - c) Don't know
12. If you answered Yes, please specify:
 - a) Informal convention with public drug use disorders units (SerD - Servizi per le Dipendenze) or NGOs engaged in harm reduction in out-of-hospital setting
 - b) Institutional regional program
 - c) Project financed by a pharmaceutical company
 - d) Other
13. Did you noticed an increase in access to your clinical center for more PWID?
 - a) Yes
 - b) No
 - c) Don't know
14. PWID affected by HCV Chronic Hepatitis access your center (multiple answers can be selected):
 - a) Using regional booking system
 - b) Through the public drug use disorders units (SerD- Servizi per le Dipendenze) to which they belong
 - c) Though NGOs engaged in harm reduction in out-of-hospital setting
 - d) These are patients who have already been followed by my clinical center for some time
15. In case of answer B, C: how did you get in touch with them? (multiple answers can be selected)
 - a) They organize a meeting with my clinical center to define a referral model
 - b) We organize a meeting with them to define a referral model
 - c) We met at an institutional technical meeting to organize referral model
 - d) There were no contacts
16. How do you plan appointments for PWID?
 - a) SerD or NGOs call my clinical center directly which gives them an appointment the first day available
 - b) SerD or NGOs call my clinical center directly which gives them an appointment on dedicated days
 - c) The staff of my clinical center goes periodically to SerD
17. Do you use scores to simplify the evaluation of the PWID with HCV Chronic Hepatitis to start treatment quickly?
 - a) Yes
 - b) No
18. Does your clinical center have the possibility to perform blood samples, fibroscan and liver ultrasound in a single visit?
 - a) Blood sample: Yes/No
 - b) Fibroscan: Yes/No
 - c) Liver ultrasound: Yes/No
19. What it the average time to star treatment for PWID?
 - a) Single-visit
 - b) One month
 - c) Three months
 - d) More than three months
20. If you answered more than 3 months, please specify why:
 - a) It is the time necessary to carry out all the clinical investigations
 - b) The patient is asked to start therapy only after detoxification from drugs and/or Opioid Substitution Therapy (OST)
 - c) Waiting lists are long due to the small number of staff
21. On average, PWID at your clinical center have liver fibrosis (according to Metavir score):
 - a) F0-F1
 - b) F2
 - c) F3
 - d) F4
22. How many visits do PWID at you clinical center during and after treatment:
 - a) Baseline, every 4 weeks during treatment and 4-12-24 weeks after the end of treatment
 - b) Baseline, end of treatment, 12 weeks after the end of treatment
 - c) Baseline, 12 weeks after the end of treatment
23. Do you contact SerD/NGOS colleagues to discuss the patient's clinical case?
 - a) Yes
 - b) No
24. Although it is known that PWID are a reservoir of HCV infection, the treatment proposal remains unsatisfactory. Why do you think? (multiple answers can be selected)
 - a) There is little interest from the institutions
 - b) It is part of the psychopathology of the patient who has difficulty taking care of himself PWID are still stigmatized
 - c) Don't know
25. Barriers to treatment are numerous, numbers from 1 (the most important) to 6 (the least important) according to the experience of you clinical center:
 - a) Poor adherence of PWID
 - b) High risk of reinfection of PWID
 - c) PWID poor venous access
 - d) PWID psychiatric comorbidity and related Drug Drug Interactions
 - e) Poor motivation of PWID
 - f) PWID difficult social background
 - g) None of the above
26. Which step of the care cascade do you think is most problematic in your area?
 - a) Accurate evaluation of PWID HCV prevalence
 - b) Screening
 - c) Linkage to Care
 - d) HCV-RNA diagnostic confirmation
 - e) Liver evaluation (ultrasound, fibroscan, ...)
 - f) Engagement in care
 - g) Reinfection prevention (Harm Reduction)
27. Do you think it is necessary to make the prescription of DAAs accessible to GP (General Practitioner) and doctors who work in drug use disorders services?
 - a) Yes
 - b) No
 - c) I'm not sure

References

Agenzia Italiana del Farmaco. Registri AIFA DAAs – Epatite C cronica, uffici registri di monitoraggio, 03/02/2020. www.aifa.gov.it/documents/20142/847506/Aggiornamento_dati_Registri_AIFA_DAA_s-03-02-2020.pdf/a2474474-bf00-e737-23a0-58fe11eb7143.

AASLD, IDSA (2020). Key Populations: Identification and Management of HCV in People Who Inject Drugs. www.HCVGuidance.org on January 30.

Cunningham E.B., Amin J., Feld J.J., Bruneau J., Dalgard O., Powis J., Hellard M., Cooper C., Read P., Conway B., Dunlop A.J., Norton B., Litwin A.H., Hajarizadeh B., Thurnheer M.C., Dillon J.F., Weltman

- M., Shaw D., Bruggmann P., Gane E., Fraser C., Marks P., Applegate T.L., Quiene S., Siriragavan S., Matthews G.V., Dore G.J., Grebely J., SIMPLIFY study group (2018). Adherence to sofosbuvir and velpatasvir among people with chronic HCV infection and recent injection drug use: The SIMPLIFY study. *Int J Drug Policy*, Dec, 62: 14-23. doi: 10.1016/j.drugpo.2018.08.013.
- Dillon J.F., Lazarus J.V., Razavi H.A. (2016). Urgent action to fight hepatitis C in people who inject drugs in Europe. *Hepatol Med Policy*, Jun 30, 1: 2. doi: 10.1186/s41124-016-0011-y.
- Dore G.J., Altice F., Litwin A.H., Dalgard O., Gane E.J., Shibolet O., Luetkemeyer A., Nahass R., Peng C.Y., Conway B., Grebely J., Howe A.Y., Gendrano I.N., Chen E., Huang H.C., Dutko F.J., Nickle D.C., Nguyen B.Y., Wahl J., Barr E., Robertson M.N., Platt H.L., C-EDGE CO-STAR Study Group (2016). Elbasvir-Grazoprevir to Treat Hepatitis C Virus Infection in Persons Receiving Opioid Agonist Therapy: A Randomized Trial. *Ann Intern Med.*, Nov 1, 165(9): 625-634. doi: 10.7326/M16-0816.
- European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2019). Hepatitis C: models of care for drug services in Europe. www.emcdda.europa.eu/system/files/attachments/11482/Hepatitis-C-new-models-of-care-for-drugs-services_WEB.pdf.
- European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2019). Monitoring the elimination of viral hepatitis as a public health threat among people who inject drugs in Europe. www.emcdda.europa.eu/system/files/publications/11796/Technical%20report_The%20elimination%20barometer%20for%20viral%20hepatitis%20among%20PWID%20in%20Europe_0.pdf.
- European Monitoring Centre for Drugs and Drug Addiction. European drug report 2019, trends and developments. www.emcdda.europa.eu/system/files/publications/11364/20191724_TDAT19001E_NN_PDF.pdf.
- Flamm S., Mutimer D., Asatryan A., Wang S., Rockstroh J., Horsmans Y., Kwo P.Y., Weiland O., Villa E., Heo J., Gane E., Ryder S.D., Welzel T.M., Ruane P.J., Agarwal K., Ng T.I., Xue Z., Lovell S.S., Krishnan P., Kopecky-Bromberg S., Trinh R., Mensa F.J., Wyles D.L. (2019). Glecaprevir/Pibrentasvir in patients with chronic HCV genotype 3 infection: An integrated phase 2/3 analysis. *J Viral Hepat.*, Mar, 26(3): 337-349. doi: 10.1111/jvh.13038.
- Fourati S., Feld J.J., Chevaliez S., Luhmann N. (2018). Approaches for simplified HCV diagnostic algorithms. *J Int AIDS Soc.*, Apr, 21(Suppl. Suppl. 2): e25058. doi: 10.1002/jia2.25058.
- Franco R.A., Galbraith J.W., Overton E.T. (2018). Saag MS. Direct-acting antivirals and chronic hepatitis C: towards elimination. *Hepatome Res*, 4: 74. doi: 10.20517/2394-5079.2018.94.
- Grebely J., Sherman K.E., Baumgarten A., Conway B., Jackson D., Asselah T., Gschwantler M., Tomasiewicz K., Aguilar H., Asatryan A., Hu Y., Mensa F.J. (2019). Glecaprevir/pibrentasvir in patients with chronic HCV and recent drug use: An integrated analysis of 7 phase III studies. *Drug Alcohol Depend.*, Jan 1, 194: 487-494. doi: 10.1016/j.drugalcdep.2018.11.007.
- Grebely J., Dore G.J., Morin S., Rockstroh J.K., Klein M.B. (2017). Elimination of HCV as a public health concern among people who inject drugs by 2030 – What will it take to get there? *J Int AIDS Soc.*, 20(1): 22146. doi: 10.7448/IAS.20.1.22146.
- Grebely J., Oser M., Taylor L.E., Dore G.J. (2013). Breaking down the barriers to hepatitis C virus (HCV) treatment among individuals with HCV/HIV coinfection: action required at the system, provider, and patient levels. *J Infect Dis.*, Mar, 207(Suppl. 1): S19-25. doi: 10.1093/infdis/jis928.
- Grebely J., Haire B., Taylor L.E., Macneill P., Litwin A.H., Swan T. *et al.* (2015). Excluding people who use drugs or alcohol from access to hepatitis C treatments – is this fair, given the available data? *J Hepatol.*, 63: 779-82.
- Grebely J., Dore G.J., Zeuzem S. *et al.* (2016). Efficacy and safety of sofosbuvir/velpatasvir in patients with chronic hepatitis C virus infection receiving opioid substitution therapy: analysis of phase 3 ASTRAL trials. *Clin Infect Dis.*, 63(11): 1479-1481.
- Grebely J., Hajarizadeh B., Dore G.J. (2017). Direct-acting antiviral agents for HCV infection affecting people who inject drugs. *Nat Rev Gastroenterol Hepatol.*, 14(11): 641-651.
- Harris M., Jolly E., Martin A., Wells H., Rhodes T. (2012). Barriers and facilitators to Hepatitis C treatment for People who inject drugs A qualitative study. www.euro.who.int/__data/assets/pdf_file/0011/179750/Barriers-and-facilitators-to-hepatitis-C-treatment-for-PWID-A-qualitative-study-June-2012-rev-5.pdf.
- Kattakuzhy S., Mathur P., Gross C. *et al.* (2018). High SVR in PWID with HCV despite imperfect medication adherence: data from the anchor study. *Hepatology*, 68(S1). doi: 10.1002/hep.30256.
- Kattakuzhy S., Gross C., Emmanuel B., Teferi G., Jenkins V., Silk R., Akoth E., Thomas A., Ahmed C., Espinosa M., Price A., Rosenthal E., Tang L., Wilson E., Bentzen S., Masur H., Kottlil S. (2017). Expansion of Treatment for Hepatitis C Virus Infection by Task Shifting to Community-Based Nonspecialist Providers: A Nonrandomized Clinical Trial. *Ann Intern Med.*, Sep 5, 167(5): 311-318. doi: 10.7326/M17-0118.
- Lazarus J.V., Sperle I., Maticic M., Wiessing L. (2014). A systematic review of Hepatitis C virus treatment uptake among people who inject drugs in the European Region. *BMC Infect Dis.*, 14(Suppl. 6): S16. doi: 10.1186/1471-2334-14-S6-S16.
- Lazarus J.V., Safreed-Harmon K., Thursz M.R., Dillon J.F., El-Sayed M.H., Elsharkawy A.M., Hatzakis A., Jadoul M., Prestileo T., Razavi H., Rockstroh J.K., Wiktor S.Z., Colombo M. (2018). The Micro-Elimination Approach to Eliminating Hepatitis C: Strategic and Operational Considerations. *Semin Liver Dis.*, Aug, 38(3): 181-192. doi: 10.1055/s-0038-1666841.
- Litwin A.H., Drolet M., Nwankwo C., Torrens M., Kastelic A., Walcher S., Somaini L., Mulvihill E., Ertl J., Grebely J. (2019). Perceived barriers related to testing, management and treatment of HCV infection among physicians prescribing opioid agonist therapy: The C-SCOPE study. *J Viral Hepat.*, Sep, 26(9): 1094-1104. doi: 10.1111/jvh.13119. Epub 2019 Jun 11.
- Marinho R.T., Barreira D.P. (2013). Hepatitis C, stigma and cure. *World J Gastroenterol*, 19: 6703-9.
- Stein J.A., Nyamathi A. (2004). Correlates of hepatitis C virus infection in homeless men: a latent variable approach. *Drug Alcohol Depend*, 75: 89-95.
- Maticic M., Videcnik Zorman J., Gregorcic S., Schatz E., Lazarus J.V. (2019). Changes to the national strategies, plans and guidelines for the treatment of hepatitis C in people who inject drugs between 2013 and 2016: a cross-sectional survey of 34 European countries. *Harm Reduct Journal*, May, 9, 16(1): 32. doi: 10.1186/s12954-019-0303-9.
- Molinaro S., Resce G., Alberti A., Andreoni M., D'Egidio P.P.F., Leonardi C., Nava F.A., Pasqualetti P., Villa S. (2019). Barriers to effective management of hepatitis C virus in people who inject drugs: Evidence from outpatient clinics. *Drug Alcohol Rev.*, Sep, 38(6): 644-655. doi: 10.1111/dar.12978.
- Murdock M., Brizzi M.B., Perez O., Badowski M.E. (2019). Public Health Considerations among People who Inject Drugs with HIV/HCV Co-Infection: A Review. *Infect Dis Ther*, 8: 23-32. doi: 10.1007/s40121-018-0228-8.
- Norton B.L., Fleming J., Bachhuber M.A., Steinman M., DeLuca J., Cunningham C.O., Johnson N., Laraque F., Litwin A.H. (2017). *Int J Drug Policy*, 47: 196-201.
- Palmateer N., Hutchinson S., McAllister G., Munro A., Cameron S., Goldberg D., Taylor A. (2014). Risk of transmission associated with sharing drug injecting paraphernalia: analysis of recent hepatitis C virus (HCV) infection using cross-sectional survey data. *J Viral Hepat*, Jan, 21(1): 25-32. doi: 10.1111/jvh.12117.
- Stein J.A., Andersen R.M., Robertson M., Gelberg L. (2012). Impact of hepatitis B and C infection on health services utilization in homeless adults: a test of the Gelberg-Andersen behavioral model for vulnerable populations. *Health Psychol*, 31: 20-30.
- Terrault N.A. (2019). Hepatitis C elimination: challenges with under-diagnosis and under-treatment. *F1000Res.*, Jan 14, 8, pii: F1000 Faculty Rev-54. doi: 10.12688/f1000research.15892.1.
- World Health Organization Europe (2017). Action plan for the health sector response to viral hepatitis in the WHO European region. www.euro.who.int/data/assets/pdf_file/0008/357236/Hepatitis-9789289052870-eng.pdf.
- Wiessing L., Ferri M., Grady B., Kantzanou M., Sperle I., Cullen K.J., EMCDDA DRID group, Hatzakis A., Prins M., Vickerman P., Lazarus J.V., Hope V.D., Matheï C. (2014). Hepatitis C Virus Infection Epidemiology among People Who Inject Drugs in Europe: A Systematic Review of Data for Scaling Up Treatment and Prevention. *PLoS One*, 9(7): e103345. doi: 10.1371/journal.pone.0103345.