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Barriers for HCV treatment in Italian Drug Abuse Service: Data from a multicentric observational study (SCUDO Project)

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SUMMARY

■ *The epidemiological data suggests that people who use drugs (PWUDs) are the most important “reservoir” for the spread of HCV infection. For this reason PWUDs should be included in all HCV elimination plan as priority target for treatment.*

We performed an observational study in 5 Italian Drug Abuse Services (SerDs) with the main aims to determine: 1) the prevalence of HCV infection in PWUDs; 2) the most important barriers to HCV treatment.

Of the about 4,000 drug users included in the study only about the 36% was tested and of them the 20% were anti HCV positive; only about the 60% of the HCV RNA positive patients were treated.

The study showed several important barriers to the screening, especially when cannot used rapid tests and/or if test is not proposed periodically, and to the linkage to care, in particular when the HCV treatment cannot be given inside the SerDs.

The study has also revealed as the harm reduction measures as suggested by WHO are not offered to all PWUDs. In conclusion the study suggests how inside the SerDs the barriers for HCV treatment that can be overcome with a simpler model of treatment as represented by the point of care. ■

Keywords: HCV, PWUDs, Point of care, DAAs, Harm reduction.

Parole chiave: Epatite C, Persone che utilizzano sostanze, Point of care, Farmaci antivirali ad azione diretta, Riduzione del danno.

Introduction

The epidemiological data suggests that in the developed countries about 20 millions of people who use drugs (PWUD) are HCV positive (WHO, 2017). Between drug users the most important risk factor is represented by intravenous drug use (Nelson *et al.*, 2011). In Europe the epidemiological data suggests that there are about 3 millions of people who inject drugs (PWIDs), corresponding to

about 67% of HCV positive subjects (Nelson *et al.*, 2011). The majority of infected PWIDs are unaware of their status (Heimbach *et al.*, 2017; WHO, 2017). The clinical evidence has also shown that the drug users are the most important “reservoir” of the infection and they may contribute to the maintenance of HCV infection in the general population (Taherkhab, Farshadpour, 2017).

PWIDs are a key population in the global HCV control and they, independently of their disease severity, should be treated as priority target (Grebely, Dore, 2017; Martin *et al.*, 2013). Fortunately, the Direct Antiviral Agents (DAAs) have shown to be efficacy and well tolerated in drug users and their use, together the harm reduction measures, are “powerful weapons” able to contribute to eliminate HCV in drug users (Alimohammadi *et al.*, 2018).

In Italy there is one of the most elevated prevalence of HCV. The data estimates that up to 60% of drug users are HCV positive and that about of 90,000 people that use drugs live with HCV (Nava *et al.*, 2018a). The most of them are not yet tested, diagnosed and/or treated (Nava *et al.*, 2018a) due to existence of important barriers for the treatment (Grebely *et al.*, 2017).

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The main aim of this study is to determine the prevalence of HCV in the PWUDs treated in the Italian Drug Abuse Services (SerDs) and to identify the most important barriers for treatment in order to remove them and make simpler the HCV treatment in drug users.

Methods

Between January and December 2017 was conducted an observational study in 5 representative Italian Drug Services (SerDs) of North and Centre Italy.

The main aims of the study were: 1) to collect the HCV cascade data inside the SerDs at 31 December 2017 (pre-intervention period); 2) to align the clinical procedures of the SerDs to Italian

best practice for HCV treatment in drug users; 3) to collect the HCV cascade data inside the SerD at 31 December 2018 (post-intervention period); 4) to identify inside SerDs the main barriers to treatment in order to develop specific actions able to remove them. The alignment on the best practice inside the SerDs was conducted during the 2018 through three periodic prospective audits conducted by clinical experts and the principal investigators of the study. As gold standard were considered the best clinical practices for HCV treatment approved by the Italian Societies of Addiction Medicine (FeDerSerD), Infection Diseases (SIMIT) and Penitentiary Medicine (SIMSPE) (Nava *et al.*, 2018a) (Table 1). The statistical analysis was performed using the Graph Pad vers. 8.4.3. Continuous variables were summarized as mean and stan-

Tab. 1 - Patient's journey of HCV infected drug users according an integrated and multidisciplinary management as suggested by the Italian best practices (Nava et al., 2018a)

<i>Who</i>	<i>Action</i>	<i>Description</i>	<i>Frequency</i>	<i>When</i>
<i>Screening</i>				
Addiction Specialists	Screening test	Test proposal (HCV-Ab) to the patient for the screening of HCV infection	Periodical	At entry and if negative every 6 months
	Counseling (Harm reduction)	Information about disease, the methods of transmission, ecc.	Periodical	At entry and at every test
	Diagnostic analysis	Diagnosis confirmation (HCV RNA test, genotype, ALT, etc.)	One time	After a positive test
<i>Referral</i>				
Addiction Specialists	Motivational counseling to treatment (Harm reduction)	Motivates the patient to undertake the treatment, illustrating to the patient the advantages of DAAs therapy	One time	At the end of the diagnostic evaluation process
	Referral to specialist	Send the patient to the specialists of infection disease/hepatologists for treatment start	One time	When the patient is ready from the motivational point of view
<i>Treatment, Monitoring, Follow up</i>				
Specialists of Infection Diseases/Hepatologists	Treatment's eligibility criteria evaluation	Evaluate the patient requisites to access to DAAs treatment (e.g. Fibroscan® analysis)	One time	When the patient is sent by the SerD
	Counseling (Harm reduction)	Inform the patients how DAA act and how to prevent re-infection	One time	Before the start of treatment
	DAAs treatment	Treatment choice on the bases of clinical need	One time	After patient consent of treatment
	Treatment monitoring	Evaluate treatment compliance and the presence of eventual comorbidities	Periodical	During the treatment
	Treatment monitoring	Evaluate the SVR (HCV RNA test)	One time	12 weeks after starting treatment
	Follow up (in cirrhotic and complex patients)	Serological control (HCV RNA test) and clinical evaluation	Periodical	3 and 6 months after the end of the treatment

Tab. 1 - Continued

Who	Action	Description	Frequency	When
Addiction Specialists	Treatment monitoring	Evaluate the presence of psychiatric, behavioral and substance abuse co-morbidities	Periodical	During the treatment
	Follow up (in not cirrhotic patients)	Serological control (HCV RNA test)	Periodical	3 and 6 months after the end of the treatment
	Screening monitoring and harm reduction measures	Control of re-infection (HCV RNA test) and re-infection prevention	Periodical	Every 6 months

dard deviation, and categorial variables as absolute and relative frequencies. For continuous variables, the differences were evaluated by t test; categorical variables were compared by the chi-square test, as appropriate. Comparison between group was made using the paired t test. Differences were considered statistically significant at $P < .05$.

The study was conducted in accordance with the international guidelines and with the Helsinki Declaration. All patients signed an informed consent for the collection and storage of their data for research purpose.

Results

The subjects followed up at the SerDs in the pre-intervention and post-intervention period were 4,486 and 5,579, respectively, and their demographic characteristics are shown in Table 2.

Only some SerDs took in treatment the “vulnerable people” (i.e. subjected that show individual, familiar and/or environmental

vulnerable factors that induce to use drugs of abuse) and/or “occasional users” (i.e. persons with risk behaviors that use sometimes drugs) (Table 3).

Fig. 1 shows the HCV cascade in the two periods considering all the PWUD population evaluated. Compared with the pre-intervention period, the number of subjects tested for anti-HCV, referred and treated was similar, although the HCV cascade was higher in the post-intervention period.

The main barriers detected in the SerDs in the pre-intervention and post-intervention periods are shown in Table 4. The data indicate that the most important barriers are correlated with the screening (lacking of rapid tests and of the test-retest procedures), the referral (lacking specific inter-professional collaboration procedures between specialists), the treatment (lacking HCV specialist inside SerDs), and the harm reduction measures (that are not fully applied inside the SerDs). As shown in Table 2 the audit sessions made inside the SerDs in order to develop the best practices for HCV treatment were able to improve the actions only in some areas, such as the counseling interventions and to increase of the points for blood-samples collection inside the SerDs.

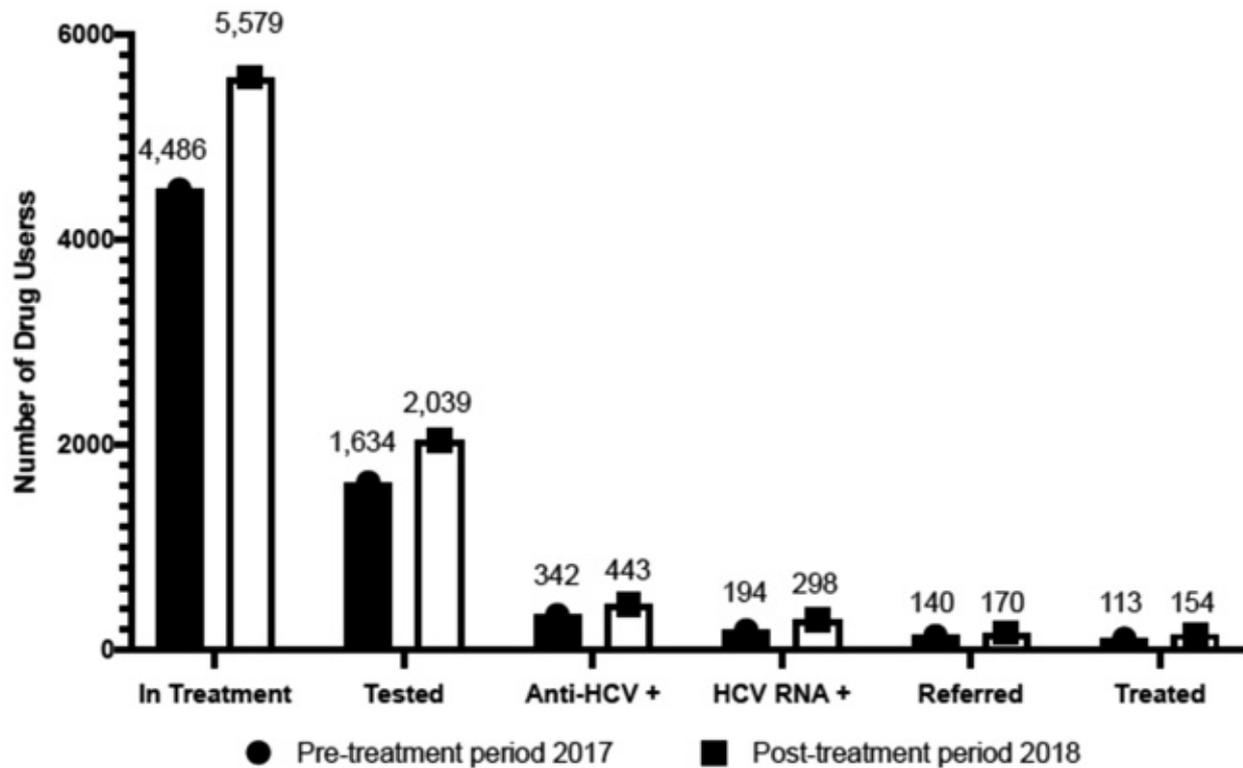
Tab. 2 - Characteristics of subjects follow up at the SerDs in the pre-intervention (2017) and post-intervention period (2018)

	2017	2018
N. subjects	4,486	5,579
Male (%)	89	92
Age (mean + S.D.)	41.2 + 8.5	42.4 + 6.9
Years of drug uses (mean + S.D.)	15.5 + 3.2	16.7 + 2.5
OST (%)	84	87
PWIDs (%)	55	58
Non-PWIDs (%)	45	42

Tab. 3 - Typologies of people take in treatment at the SerDs in the pre-intervention and post-intervention period

	SerD ASST Melegnano-Martisana		SerD Bergamo		SerD Novara		SerD Chieti		SerD Sud Est Firenze	
	2017	2018	2017	2018	2017	2018	2017	2018	2017	2018
People take in treatment										
Vulnerable people	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
Occasional drug users	No	Yes	Yes	Yes	No	Yes	No	Yes	No	No

Fig. 1 - HCV cascade in the PWUDs in the pre-intervention (2017) and post-intervention (2018) periods (Paired t test $p < 0.14$)



Tab. 4 - Main barriers for HCV treatment inside the SerDs in the pre-intervention (2017) and pos-intervention period (2018)

	SerD ASST Melegnano-Martisana		SerD Bergamo		SerD Novara		SerD Chieti		SerD Sud Est Firenze	
	2017	2018	2017	2018	2017	2018	2017	2018	2017	2018
Screening										
Rapid test	No	No	No	No	No	No	No	No	No	No
Test – Re-test	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Counseling	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No
Blood sample collection point	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Referral										
Referral per all HCV positive	No	Yes	No	Yes	No	No	No	No	No	Yes
Treatment										
Trattamento inside SerDs	Yes	Yes	No	No	No	No	No	No	No	No
Drug treatment monitoring	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes
Harm reduction										
All HR actions	No	No	No	No	No	No	No	No	No	No
Some HR actions	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Discussion

The study shows that only the 36% of people in treatment inside the SerDs are tested for anti HCV both in 2017 and in 2018. Of the tested people the 20% and 21% were resulted anti-HCV positive, respectively at 2017 and 2018. These data does not fit completely with last national epidemiological report (Relazione al Parlamento, 2019) that show that only the 22% of people treated

inside the SerDs are tested and of them the 41% are anti-HCV positive. This discrepancy may be due to the well know methodological bias contained in the annual national report (that does not include in the data all Italian Regions and does not provide a quality control of the data collection).

A previous epidemiological study conducted in 25 Italian SerDs have shown that the prevalence of HCV positive drug users is about 60% (Stroffolini *et al.*, 2012), confirming that the sero-

prevalence of HCV may be varying inside the SerDs by different variables such as age of the patients, the years of drug use, the typologies of the drugs used and their route of administration. In any case the above data confirm that the prevalence of HCV infection in Italian drug users is very high with a range varying of 20-60%.

On the other hand the study confirms that only a very few percentage of drug users are tested inside the SerDs. This is due to the several reasons including the lacking of rapid test, points of blood-collection and by the fact that often the SerDs do not test the subjects at higher risks (such as PWIDs) or the “hidden” at risk population that is represented by vulnerable people and/or occasional users.

The study shows also that another important barrier for HCV treatment is represented by referral that is not offered to all HCV positive patients for several reasons; the most important are the well-known difficulty of the HCV specialist to go inside the SerDs to treat the patients and the lack of inter-collaboration procedures able to facilitate the contact of the patients with the external specialized centers.

Another important limit for HCV treatment is represented by the harm reduction measures that are only partially offered at the drug abusers (Nava *et al.*, 2018a; 2018b). A lack of harm reduction measures may extremely increase the number of re-infection. The literature shows that the re-infection rate in drug users is low (0-5 cases per 100 subjects-year) only if associated with effective harm reduction measures (Cunningham *et al.*, 2015). At this regard the data indicate that the drug users that receive the Opiate substitutive therapy (OST) have a lower rate of re-infection (Rossi *et al.*, 2018).

The study reveals also that several barriers may block the HCV treatment inside of SerDs. The evidence that even an evident effort to align the SerDs to the best practices may not improve the HCV cascade underlines how the main important barriers are due to “structural” (e.g. lacking of rapid tests) and “organizational” limitations (e.g. lacking of HCV specialists inside the SerDs) (Nava, 2019).

The evidence of the present study suggest that only a model of point of care may overcome the barriers for HCV treatment in drug users. The point of care is a model of treatment able to test and treat the drug users inside the SerDs in few and rapid steps. Moreover, the point of care may be included in the outreach programs and may be able to test and treat also the “hidden” drug users that are not yet in treatment in the SerDs.

Another important point raised by the study is the DAAs together the harm reduction measures must be proposed to all drug users independently to the severity of their drug use disorder. Several important study have indicated that harm reduction measures are synergic to DAAs treatment to contribute to HCV elimination (Valencia La rosa *et al.*, 2018). Only the ability of DAAs to cure the HCV infection together to the capacity of the harm reduction measures to reduce the re-infection rate may contribute to the “eradication” of HCV infection in drug users.

The barriers to HCV treatment in drug users may be also overcoming from the elimination of the Italian Drug Agency (AIFA) criteria (AIFA, 2019) that actually require for DAAs treatment of drug users (independently if with a mild and middle severity of the disease - F0-F2) the need of the genotyping and reserve the DAAs prescription only to the HCV specialists.

Finally the study have permitted to identify the main barriers of treatment inside the SerDs suggesting how the point of care may be the most effective model to test and treat the drug users and may contribute to HCV elimination programs.

Notes

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References

- AIFA criteria for HCV treatment (2019). Available from: www.aifa.gov.it/aggiornamento-epatite-c.
- Alimohammadi A., Holrksa J., Thiam A., Truong D., Conway B. (2018). Real-world efficacy of direct-acting antiviral therapy for HCV infection affecting people who inject drugs delivered in a multidisciplinary setting. *Open Forum Infect Dis.*, 5/6: ofy120. doi: 1.1093/ofid/ofy120.eCollection 2018 Jun.
- Cunningham E.B., Applegate T.L., Lloyd A.R., Dore G.J., Grebely J. (2015). Mixed HCV infection and reinfection in people who inject drugs – impact on therapy. *Nat. Rev. Gastroenterol Hepatol.*, 12(4): 218-230.
- Grebely J., Dore G.J. (2017). Treatment of HCV in persons who inject drugs: Treatment as prevention. *Clin. Liver Dis.*, 9(4): 77-80.
- 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? *Journal of the International AIDS Society*, 20: 22146.
- Heimbach J.K. (2017). Overview of the updated AASLD guidelines for the management of HCC. *Gastroenterol. Hepatol. (NY)*, 13(12): 751-753.
- Martin N.K., Vickerman P., Grebely J. *et al.* (2013). Hepatitis C virus treatment for prevention among people who inject drugs: modeling treatment scale-up in the age of direct-acting antivirals. *Hepatology*, 58(5): 1598-1609.
- Nava F.A. (2019). I Ser.D. come presidi sul territorio: il ruolo dei Servizi nell'eliminazione di HCV. *Quaderno di ReAdfiles*, 20(Suppl. 2): 10-15.
- Nava F.A., Alberti A., Andreoni M., Babudieri S., Barbarini G., D'Egidio P.F., Leonardi C., Lucchini A. (2018a). For a program of eradication of hepatitis C in the population at risk (drug users and convicts). *Acta Biomed.*, 89(Suppl. 10): 33-41.
- Nava F.A., Alberti A., Andreoni M., Babudieri S., Barbarini G., D'Egidio P.F., Leonardi C., Lucchini A. (2018b). Position paper. Per un programma di eliminazione dell'epatite C nella popolazione a rischio dei consumatori di sostanze e dei detenuti. *Mission - Italian Quarterly Journal of Addiction*, 49: 56-61.
- Nelson PK, Mathers B.M., Cowie B., Hagan H., Des Jarlais D., Horyniak D., Degenhardt L. (2011). Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic review. *Lancet*, 378: 571-583.
- Relazione annuale al Parlamento sullo stato delle tossicodipendenze (2019). Available from: www.politicheantidroga.gov.it/it/dpa-in-sintesi/relazioni-annuali-al-parlamento/relazione-annuale-al-parlamento-sul-fenomeno-delle-tossicodipendenze-in-italia-anno-2019-dati-2018.
- Rossi C., Butt Z.A., Wong S., Buxton J.A., Islam N., Yu A., Darvishian M., Gilbert M., Wong J., Chapinal N., Binka M., Alvarez M., Tyndall M.W., Krajden M., Janjua N.Z., BC Hepatitis Testers Cohort Team. *J. Hepatol.*, 69(5): 1007-1014.
- Stroffolini T., D'Egidio P.F., Aceti A., Filippini P., Puoti M., Leonardi C., Almasio P.L., DAVIS drug Addictd, HCV prevalence in Italy and epidemiological observational, cross-sectional, multicenter study participating centers. *J. Med. Vir.*, 84(10): 1608-1612.
- Taherkhani R., Farshadpour F. (2017). Global elimination of hepatitis C virus infection: progress and the remaining challenges. *World J. Hepatol.*, 9(33): 1239-1252. doi: 10.4254/wjh.v9.i33.1239.
- Valencia La Rosa J,m Ryan P., Alvaro-Meca A., Troya J., Cuevas G., Gutiérrez J., Moreno S. (2018). HCV seroconversion in a cohort of people who use drugs followed in a mobile harm reduction unit in Madrid: breaking barriers fo HCV elimination. *PLoS One*, 13(10): e0204795. doi: 1.1371/journal.pone.0204795.
- WHO (2017). Global Hepatitis Report 2017. Geneva, Switzerland: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO. 2017. Available from: <https://doi.org/10.1149/2.030203jes>.