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HCV point-of-care screening programme and treatment options for people who use drugs in a metropolitan area of Southern Italy

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Abstract

Background and aims: People who use drugs (PWUD) represent an active reservoir of HCV infection. The prevalence of chronic HCV infection in PWUD in Italy remains unknown because of the lack of systematic screening. Thanks to direct-acting antiviral agents (DAAs), hepatitis C can now be cured in most patients. Thus, the next challenge is to provide linkage-to-care for these patients.

Methods: In this scenario, we conducted a screening programme in PWUD attending seven Addiction Centers in Southern Italy, as well as a treatment programme in the Liver Unit of the University Hospital of Salerno. We used the OraQuick HCV antibody test to screen the PWUD (from 1 April to 30 September 2018).

Results: 593 subjects were consecutively enrolled in the programme; 250 (41.8%) were HCV-Ab-positive. 143 (24.1%) were aware of their infection and had been HCV-RNA-tested: 83 were positive and 60 negative. The remaining 107 subjects (18.1%) had never previously been tested and were unaware of their infection. A total of 160 (26.9%) HCV RNA-positive patients were found and offered antiviral therapy with DAAs. The sustained virological response rate was 98.5% and no adverse events were recorded. Two patients voluntarily discontinued treatment. No reinfections have been recorded to date.

Conclusions: The prevalence of HCV-Ab positivity was high in the PWUDs enrolled in this study, and almost half the patients were unaware of being HCV-positive. The linkage-to-care provided was safe and effective, and no case of reinfection was recorded.

KEYWORDS
direct antiviral agents, HCV infection, people who inject drugs, point-of-care screening, sustained virological response

Abbreviations: ALT, alanine aminotransferase; ANOVA, analysis of variance; AST, aspartate aminotransferase; CHE, choline esterase; DAAs, direct antiviral agents; EASL, European Association for the Study of the Liver; HCV, hepatitis C virus; INR, International normalized ratio; PWID, persons who inject drugs; PWUD, people who use drugs; SVR, sustained virological response; WHO, World Health Organization.

1 | INTRODUCTION

HCV-related hepatitis is a chronic indolent insidious process that can progress to cirrhosis and hepatocellular carcinoma,[1-3] and is highly prevalent worldwide.[1,4] The advent of direct-acting antiviral agents (DAAs) against genomic viral sequences was a breakthrough in the treatment of HCV infection. In fact, this treatment eliminates the infection in almost all patients irrespective of viral genotype.[5] Another advantage of DAAs is that treatment is short, and in some cases lasts only 8 weeks.[6] Most developed countries and some developing countries offer access to DAA treatment to all HCV-infected subjects regardless of the severity of liver disease, and about 1.5 million HCV-positive patients have undergone DAA treatment since 2016.[7] In Italy almost 175 000 patients have received DAA therapy with a success rate of almost 98%.[8]

The challenge, as set by the WHO in 2016, is now to eliminate HCV infection and block its spread worldwide by 2030.[9] To achieve this goal, new cases of infection and HCV-related deaths should be reduced by 80% and 60% respectively.[9] In 2018, the Polaris Observatory reported that only 12 countries were on the track of achieving this result, and Italy is among these.[10,11] Notably, many countries have already started special programmes to meet this challenge.[12-19] In this optics, the European Association for the Study of Liver (EASL) International Liver Foundation proposed "micro-elimination" as a way to eliminate HCV infection. This strategy breaks down major elimination goals into smaller objectives for specific population segments in which prioritized and simplified treatment strategies can be quickly applied.[20] This promising approach to eliminate HCV infection is based on implementing 'case-finding' strategies to identify the infection in people at high risk of HCV, such as people who inject drugs (PWID), HIV-infected subjects, convicts and the homeless who also help to maintain an active reservoir of the disease.[20] To be effective, case-finding strategies must be associated to appropriate linkage-to-care programmes in such high-risk populations in order to provide antiviral treatment to HCV-positive patients as soon as possible.[21,22] This approach was found to reduce the burden of HCV in the general population, and was cost-effective in settings with moderate HCV prevalence.[23-26]

The aim of our study was to determine the prevalence of HCV infection in a large population of people who use drugs (PWUD) patients attending seven centres of the Department of Drug Addictions of the city area of Salerno in Southern Italy, and to propose a simplified linkage-to-care model with which to rapidly diagnose and treat HCV infection.

Keypoints

- People who use drugs (PWUD) have a high prevalence of HCV, are an active reservoir of infection, and a target population for HCV elimination.
- However, there is a lack of systematic screening and treatment programmes worldwide.
- Herein, we report the results of a point-of-care screening and treatment programme of a PWUD population from a network of Centers of a Department of Drug Addictions in Southern Italy.

2 | PATIENTS AND METHODS

A network of seven centres of the Department of Drug Addictions of the city area of Salerno coordinated by the Liver Unit of the University of Salerno was set-up to screen and treat HCV-infected subjects. Members of the network and of the Liver Unit of Salerno University met periodically throughout the study to discuss the programme proceedings, to exchange data sheets of the patients enrolled and to check the results of the screening and treatment programme. When an HCV-infected subject was identified, he/she was directed to the Liver Unit of the University of Salerno for further diagnostic procedures (HCV-RNA, genotyping, complete blood tests, liver ultrasonography, transient elastography) and antiviral treatment with DAAs. Applying this diagnostic/therapeutic algorithm, we consecutively enrolled 598 subjects over a period of six months (April-September 2018). All subjects were followed up in the seven centres of the network (Figure 1), and all but five who refused informed consent, underwent a rapid oral salivary test for HCV antibodies detection. Subjects who were found to be HCV-Ab positive underwent an HCV-RNA test and genotyping to identify the most appropriate therapy. The therapy of choice was the shortest DAA regime possible as indicated by the Italian Drug Regulatory Agency and EASL guidelines.[5] The prevalence of enrolment was similar in the seven centres taking into account the size and clinical capacity of each centre (Figure S1). All enrolled patients provided written informed consent. The study protocol was approved by the Ethics Committee of Campania Sud, and conducted in conformity with the 1975 Declaration of Helsinki.

2.1 | Oral salivary test

The oral saliva test was performed with a fast HCV antibody test (OraQuick, OraSure Technologies, Inc, Bethlehem, PA, USA), which is a single-use lateral-flow indirect immunoassay FDA-approved for use in symptomatic and high-risk asymptomatic patients.[27,28]

2.2 | HCV-RNA, genotyping and clinical assessment

HCV-Ab-positive subjects underwent HCV-RNA and HCV genotyping by PCR (Cobas TaqMan v2.0, CAP/CTM HCV v2, Roche Molecular Systems, Pleasanton, CA). All HCV-RNA-positive subjects were tested for liver fibrosis using transient elastography (Echosense Fibroscan® device, model 502; EchoSense, Paris, France),[29] prior to treatment. Transient elastography scans were considered reliable if there was an interquartile range <30% of the mean value, and a success rate of at least 60% of the measurements.[30] Finally, a complete laboratory assessment was performed with routine laboratory assays for liver functionality testing (ALT, AST, blood count, bilirubin,

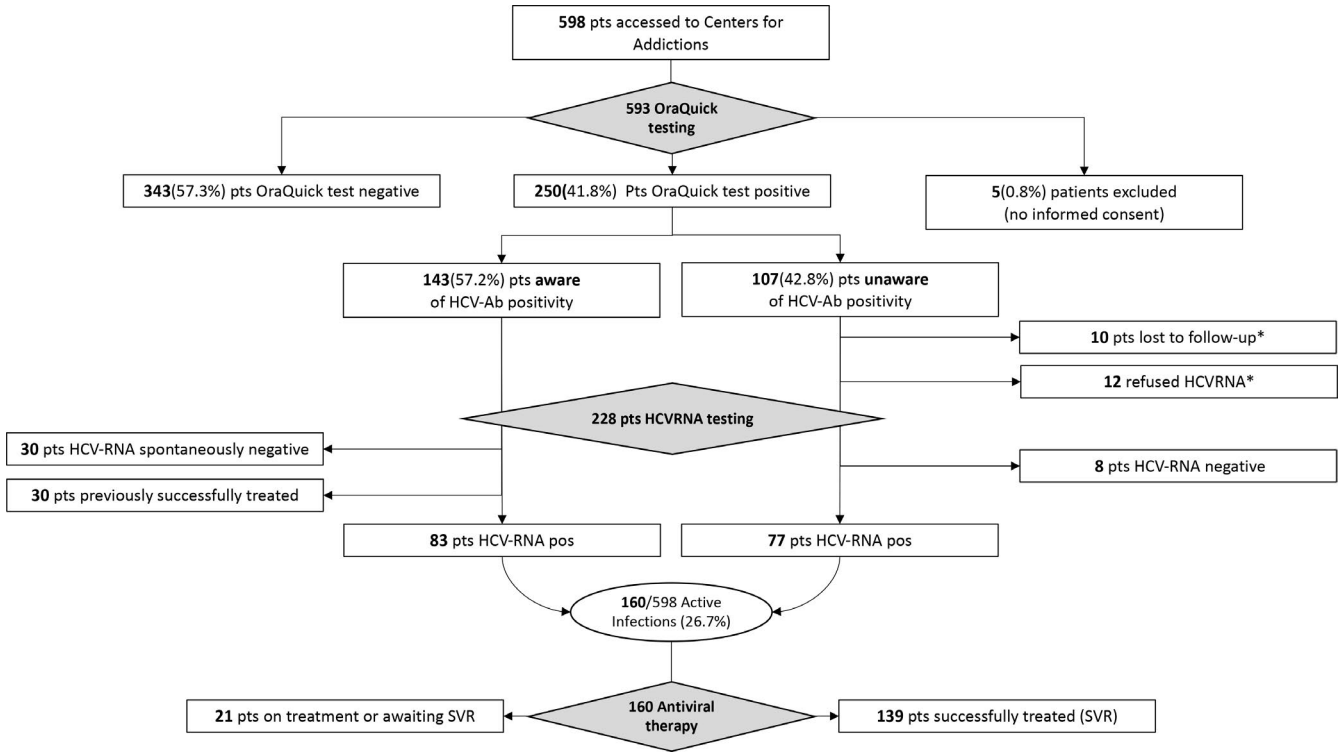

FIGURE 1 Study flowchart. 593 patients were tested for HCV-Ab. Of the 250 HCV-Ab-positive, 228 patients were tested for HCVRNA. A total of 160 patients were HCV-RNA-positive. All of them underwent antiviral treatment (98.5% of SVR). *22 patients out of the 107 first diagnosed with OraQuick (20.5%) were either lost to follow-up or refused HCVRNA testing

TABLE 1 Demographic features of the study population in relation to the results of the OraQuick test

	Overall N = 593	OraQuick-positive N = 250	OraQuick-negative N = 343	*P*
Age (±SD)	42 ± 9	45 ± 8	40 ± 9	ns
Male sex (%)	510 (86.0)	217 (86.7)	293 (85.4)	ns
BMI (±SD)	25.8 ± 6.2	25.8 ± 4.3	25.6 ± 4.5	ns
PWUD (%)				
PWID	420 (70.8)	220 (88.0)	200 (58.3)	**<0.0001**
Non-IV	173 (29.2)	30 (12.0)	143 (41.7)	
OST (%)	499 (84.1)	206 (82.4)	293 (85.4)	ns
Non-active addiction (%)	421 (71.0)	173 (69.2)	248 (72.3)	ns
HIV coinfection (%)	3 (0.5)	1 (0.4)	2 (0.6)	ns
HBV coinfection (%)	14 (2.4)	8 (3.2)	6 (1.7)	ns

Bold indicates statistically significant value.
Abbreviations: BMI, body mass index; Non-IV, non-intravenous drugs users; OST, opioid substitution treatment; PWID, people who inject drugs; PWUD, people who use drugs.

total proteins, CHE, INR) in order to select the most appropriate DAA for each patient according to Italian and European guidelines for the treatment of HCV.[5]

2.3 | Statistical analysis

Student's *t* test, the Mann-Whitney U test, ANOVA and linear correlations were used to compare continuous variables, and the chi-square test with Yates correction or the Fisher-exact test was used to compare categorical variables. To assess if continuous variables were normally or not normally distributed, we performed a Kolmogorov-Smirnov 'Goodness of fit' test for normality. Statistical analyses were performed using the Statistical Program for Social Sciences (SPSS®) v.20 for MacIntosh® (IBM Corp, Armonk, NY, USA). Statistical significance was defined when "$P < 0.05$" in a two-tailed test with a 95% confidence interval.

3 | RESULTS

Five of the 598 subjects enrolled in the study refused informed consent. The epidemiological characteristics of the remaining 593 subjects are reported in Table 1. A total of 250 (41.8%) subjects were HCV-Ab-positive. There were no differences between HCV-Ab-positive and -negative people in terms of age, gender, BMI, active addictions or coinfections. Significantly more PWID were HCV-Ab-positive than non-intravenous drug users ($P < 0.01$). As shown in Figure 2, at the time of OraQuick screening, of the 250 HCV-Ab-positive subjects, 60 (10.1% of the total) were aware of being HCV-RNA-negative and, of those, 30 (5.6%) had been previously treated. Of the remaining 190 HCV-Ab-positive subjects, 83 (14%) were aware of being HCV-RNA-positive (but had never been treated) and 107 (18%) were unaware of being HCV-Ab-positive and consequently had never previously been tested for HCV-RNA.

TABLE 2 Characteristics of OraQuick-positive patients in relation to HCV RNA testing

	HCV RNA-positive n = 160	HCV RNA-negative n = 68	*P*
Age (±SD)	43 ± 8	44 ± 11	ns
Male Sex (%)	141 (88.1)	58 (85.3)	ns
BMI (±SD)	25.6 ± 4.3	26.3 ± 4.6	ns
Addiction (%)			
IV	142 (88.8)	61 (89.7)	ns
Non-IV	18 (11.2)	7 (10.3)	
OST (%)	133 (83.1)	56 (82.4)	ns
Non-active addiction (%)	111 (69.4)	48 (70.6)	ns
HIV coinfection (%)	1 (0.6)	0 (0.0)	ns
HBV coinfection (%)	6 (3.8)	2 (2.9)	ns
Fibrosis		—	—
F0-F1 n (%)	82 (51.2)	—	—
F2-F3	39 (24.4)	—	—
F3-F4	39 (24.4)	—	—
DAA-treated patients with 12 w follow-up (SVR %)	139 (98.5%)	—	—

Abbreviations: BMI, body mass index; DAA, direct-acting antiviral agent; Non-IV, non-intravenous drugs users; OST, opioid substitution treatment; SVR, sustained virological response.

Quantitative HCV-RNA testing and genotyping was performed in 228 of the 250 subjects found to be HCV-Ab-positive. The clinical and epidemiological data of the 228 subjects tested for HCV-RNA and genotypes are reported in Table 2. There were no differences in any of the variables evaluated. At transient elastography, 75% of patients had mild or no-fibrosis (F0-F2) whereas the others had significant fibrosis or cirrhosis (F3-F4: 25%). Genotype distribution in HCV-RNA-positive subjects is shown in Figure S2. As already reported in other PWID populations, the most frequent HCV genotypes were 1a and 3a, which accounted for 78.1% of active infections (36.2% and 41.9% respectively).[31] Immediately after HCV-RNA screening, all the 160 HCV-RNA-positive patients were offered and agreed to undergo antiviral therapy with DAAs. Of the 139 subjects who reached the 12th post-treatment week, 137 were HCV-RNA-negative, which corresponds to an SVR rate of 98.5% (2 patients voluntarily discontinued the therapy after 1 and 3 weeks respectively). No adverse events or reinfections have been reported in these patients to date. The remaining 21 subjects are currently under treatment or awaiting the SVR screening visit. As shown in Figure 1, 10 HCV-Ab-positive patients were lost to follow-up, and 12 refused HCV-RNA testing. In practice, 22 of the 250 HCV-Ab-positive patients (8.8%) left the programme, thereby remaining a possible reservoir of HCV infection.

4 | DISCUSSION

The World Health Organization estimated that the mean global prevalence of chronic HCV infection is 1.5% with some differences in terms of age and geographical area.[9] In Italy, no large epidemiological

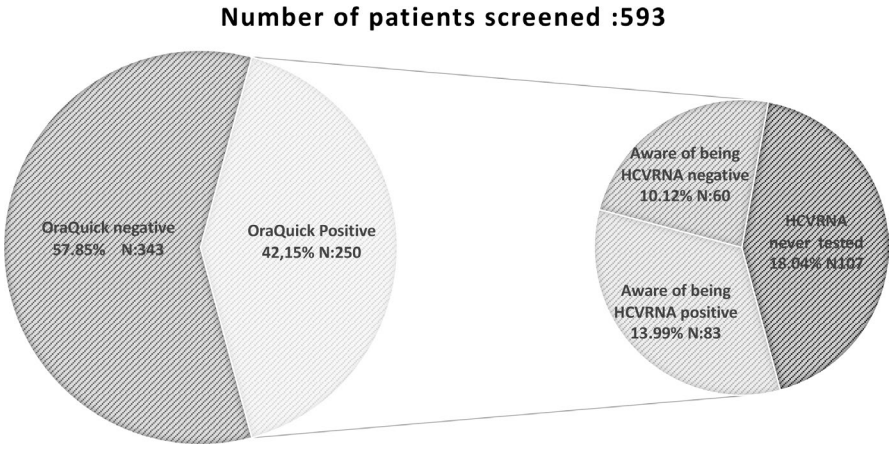

FIGURE 2 Screening results of our study population. 593 patients were screened with the oral salivary test, 250 (41.8%) were HCV-Ab-positive

studies of HCV infection have been conducted, but it is estimated that its prevalence in the general population ranges between 0.7% and 1.7%, with hidden infection in 20% of cases.[32,33] Therefore, although a large number of patients have already been treated, and have achieved a very high SVR rate, HCV elimination remains elusive. One way to address this issue is to improve the diagnosis and treatment of infected subjects, and those at risk of infection/reinfection. For example PWUD are at a very high risk of HCV infection. In fact, the prevalence of HCV in this population can reach 70%, with the highest rates occurring in PWID (80%).[34] In 2016, the European Monitoring Centre for Drugs and Drug Addiction estimated an HCV prevalence in Italy (2014-2015) of 45% in PWID, 30% of whom were below the age of 25 years.[35,36] Notwithstanding this situation, only 20.5% of subjects in follow-up in the Italian centres for drug addictions are screened for HCV infection.[37] Therefore, we designed a HCV screening programme in a population of PWUD using a quick and efficient HCV-Ab oral salivary test.[27,28]

As most of the patients were undergoing drug substitution therapy, we started screening the first time that drug substitution was administered, or during the first visit after the start of the study. Of the 593 enrolled subjects, 250 (41.8%) were HCV-Ab-positive, 107 (42.8%) of whom were unaware of being so, and 87 (33.2%) knew they were positive but had not been treated or allocated to a treatment programme. Notably, 160/593 subjects (26.7% of the total), irrespective of whether or not they were active or non-active substance users, were infected and not yet treated. This finding is consistent with the previously reported prevalence of 40% in other Drug Addiction Centers in Italy.[38] Recent epidemiological studies performed in other countries report a prevalence of active infection ranging from 35% to 50% depending on epidemiological area.[39-41]

All our HCV-positive patients started DAA therapy as set out in the Italian guidelines, using the shortest treatment available (8 weeks with the Glecaprevir/Pibentrasvir association) when indicated.[42] The rate of SVR was 98.5%, which is comparable to the 'general' HCV-infected population, although there was a high prevalence of genotypes 1a and 3a.[5] Compliance to treatment was excellent and no minor or serious adverse events were reported. Moreover, no re-infections were recorded at the last visit, unlike previous studies, in which reinfection were reported.[43,44] This discrepancy might reflect the fact that most of our population was undergoing substitution therapy, whereas the previous studies were conducted in patients enrolled in community and needle syringe programmes in which most subjects are active substance users and are therefore at a higher risk of reinfection than our patients.[44] Also the shorter follow-up period (6 months) in our study versus 18 months and beyond in other studies could also explain this discrepancy.[43,44] However, there is now extensive evidence that PWUD affected by HCV can be successfully targeted and treated.[45-48]

The strategy we propose, namely, rapid diagnosis, shortest treatment available as first choice (ie Glecaprevr/pibrentasvir for 8 weeks) and good coordination between the Centers for Drug Addiction and the Liver Unit proved to be effective. In fact, almost all HCV infections were identified and promptly treated, and, moreover, compliance was very good.

The question now arises as to whether or not an even more simple diagnostic work-up might further accelerate access to treatment. Given that current DAAs are pangenotypic, and result in SVR rates not lower than 95%,[42] HCV genotyping may be omitted, at least in a setting such as the one we describe, in which timing is crucial in maintaining the patient's linkage-to-care high. Notably, PWUD are often reluctant to accept medical help, frequently have no permanent address and do not keep appointments. In fact, about 20% (22/107) of subjects that were unaware of being HCV-Ab positive, did not undergo further evaluations because they were lost to follow-up. Moreover, as previously reported, a point-of-care prescribing strategy may help to ensure adherence of patients to screening and treatment programmes.[49] We did not adopt this strategy because, in Italy, DAA prescription is strictly regulated and is restricted to specially selected prescribing centres in which a specialist in internal medicine, gastroenterology or infectious diseases must be present, as well as essential medical devices (ie transient elastography and ultrasonography devices). On the contrary, the follow-up of subjects attending addiction centres is usually carried out by nursing staff or psychiatrists, and the personnel and equipment required for HCV therapy prescription are often not available. The scientific community and healthcare authorities should address these problems. As is now applied to vaccination programmes of other diseases, it might be useful to introduce a mandatory screening programme for HCV infection, at least in the groups of subjects who have been shown to be at high risk. Currently, the high number of PWIDs eluding healthcare control, together with the unknown number of active PWUDs who do not attend drug addiction centres, represent a large potentially HCV-infected population.[47,50] This dramatic reality may jeopardize all the efforts being made to achieve the ambitious target of elimination of HCV.[9,21]

In conclusion, this study confirms the tight link between PWUDs and HCV infection, and demonstrates that a fast diagnosis and treatment strategy (the shortest possible) is a crucial factor in the elimination of HCV infection. In this setting, a structured linkage-to-care system is recommended, in which tertiary centres collaborate with addiction centres in terms of treatment and follow-up management after HCV has been detected. Finally, the data reported herein reinforce the need to identify infected patients within high-risk populations in order to reach subjects who are not under any sanitary control and are unaware of the risks they face.

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CONFLICT OF INTEREST

The authors declare no conflict of interests for the present work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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