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HCV prevalence and treatment outcomes among drug users in an outpatient center for drug addiction in Northern Italy

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Abstract

Introduction. We aimed at evaluating hepatitis C virus (HCV) prevalence and treatment referral outcomes in a large population of drug users in Northern Italy.

Material and methods. Each participant underwent a quick capillary blood test. Positive participants underwent HCV RNA quantification. HCV RNA positive subjects were referred to treatment and evaluated immediately at the end of treatment and at 3 and 6 months after treatment.

Results. Of the 636 participants tested, 244 were positive. Intravenous drug use was more frequent among subjects who tested positive for HCV antibodies (99%). Among subjects who tested positive, 68% were HCV-RNA positive while 32% were negative. Among people referred to treatment, nearly 30% did not show up while 70% completed the treatment with success. Over 99% of people who started direct-acting antiviral agent (DAA) have a sustained response.

Discussion. We observed a significant higher prevalence of HCV positive subjects among people who inject drugs (99%) and we observed a high success rate for HCV treatment engagement.

Conclusions. Rapid testing for HCV represents a potential tool for HCV screening among high-risk groups.

Key words

- chronic hepatitis C
- drug abuse
- HCV prevalence
- treatment outcome

INTRODUCTION

HCV-related hepatitis is a chronic and slow-progressing disease that can ultimately lead to cirrhosis and hepatocellular carcinoma. With over 70 million individuals affected worldwide, HCV has become highly prevalent [1]. Among the most affected are people who inject drugs (PWIDs), with an estimated 67% of them infected with HCV [2, 3]. Non-injecting drug users, such as intranasal heroin or cocaine users and crack smokers, also have a higher HCV prevalence than the general population (5-12% *vs* 2%) [4, 5].

Direct-acting antiviral agents (DAAs) have been seen as a breakthrough treatment for HCV. These agents have the ability to eliminate the infection in almost all patients regardless of viral genotype and have a short treatment period, lasting as little as 8 weeks [6]. Many developed countries, as well as some developing countries, now provide access to DAA treatment for all HCV-infected individuals regardless of the severity of liver disease, with approximately 1.5 million patients undergoing DAA treatment worldwide since 2016 [7]. In Italy, almost 175,000 patients have been successfully treated with DAAs [6].

Early diagnosis is essential to avoid the risks associated with disease progression. Unfortunately, diagnosis is often made only when the disease begins to manifest clinically, which can occur years after infection, and asymptomatic individuals can act as carriers of the virus, thereby contributing to its spread [8]. Rapid blood tests, such as the OraQuick® HCV, have shown high reliability and sensitivity of 100%, with a specificity of 89%, and could be used as a safe and economic tool for detecting HCV in high-risk populations like PWIDs [9, 10].

In Italy, it has been estimated that nearly 280,000 HCV patients have yet to be diagnosed and nearly 50% of this patient group are drug users. The Italian Government has recently provided HCV rapid tests to those

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enrolled in the health registry (born between 1969 and 1989), patients followed by Drug Addiction Centers, and individuals detained in prison. In addition, the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) has facilitated access to DAAs for individuals who are unable to perform liver biopsy and/or fibroscan for social welfare reasons, such as drug users.

In this context, our study aims to report preliminary data on HCV prevalence and treatment referral and outcome in a large population of drug users attending the Drug Addiction Center of Pavia (Servizio per le Dipendenze Patologiche, SerD) in Northern Italy. Our study also proposes a simplified linkage-to-care model to rapidly diagnose and treat HCV infection.

MATERIAL AND METHODS

Study enrollment started in August 2020 and is still ongoing. Our results derived from data collected until February 2022.

Patients participated on a voluntary basis, after signing an informed consent. On entry, each subject was interviewed by an infectious disease specialist (AL) about injection behavior, duration of abuse, presence of comorbid infection. Then, each participant underwent a quick capillary blood test.

The capillary blood test was performed with a fast HCV antibody test (OraQuick®) which is a single-use lateral-flow indirect immunoassay FDA-approved for use in symptomatic and high-risk asymptomatic patients [9, 10]. The OraQuick® HCV showed high reliability with a sensitivity of 100% and specificity of 89%. The OraQuick® HCV has an overall accuracy of 98% and provide results in 20 minutes.

All the participants with positive results according to OraQuick® HCV underwent a blood sample for HCV RNA quantification, except for patients who had already started DAAs. When actual infection with HCV was confirmed by positive HCV RNA, further virologic tests were performed: complete blood count, viral genotype, HIV, hepatitis B virus (HBV), syphilis antibodies, aspartate transaminase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT), blood glucose, azotemia, creatinine, prothrombin time, activated partial thromboplastin time and serum electrophoresis. Patients with chronic HCV were offered therapy with DAAs and those who accepted were treated according to the EASL guidelines [2], after staging the liver disease using transient elastography (EchoSense FibroScan ® device; EchoSense, Paris, France). Additionally, the fibrosis-4 (FIB-4) score was calculated for all the patients who started DAAs according to the following formula:

FIB-4 = (age (years) x AST (IU/L))/((PLT [10^9/L]) x ALT (IU/L)) [11].

Patients with HCV infection were referred to three hospitals in Lombardy where DAAs were prescribed. Subjects who completed treatment were followed-up with an HCV-RNA test immediately at the end of treatment and at 3 and 6 months after the end of treatment.

Statistical analysis

Data are presented as median and interquartile ranges or percentages and absolute numbers as appropriate. Differences between groups (i.e., positive and negative at HCV screening test) were determined by using the Mann-Whitney U test or the Chi-square test to compare continuous or categorical variables, respectively. Logistic linear regressions (with HCV antibody status detected by rapid test as a dependent variable) were performed to define factors associated with positive test results.

A two-tailed p-value<0.05 was regarded as statistically significant. Statistical analysis was done using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY, USA).

RESULTS

The recruited sample consisted in 636 drug users, of which 20.1% were female (n=128). Mean age was 40.62 years with a standard deviation (SD) of 12.42 (age range, 15-69). Intravenous (IV) drug use was prominent (n=300, 47.1%), and opioid substitution treatment was present in 63.5% of the sample (n=404). The data flow of the study is depicted in *Figure 1* while sample characteristics are reported in *Table 1*.

Of the 636 participants tested with OraQuick® HCV, 392 patients were HCV antibody negative, while 244 were positive. Intravenous drug use, HIV coinfection, and isolated hepatitis B core antibodies (HBcAb) were more frequent among subjects who tested positive for HCV antibodies compared to the other group (p<0.001). Among the subjects who tested positive with OraQuick® HCV, 70 subjects had already received treatment with DAAs. Of the remaining 174 OraQuick® HCV positive subject, 11 refused to undergo serological confirmation of HCV infection. Among 163 tested subjects, 111 subjects were HCV positive (68%) while the remaining 52 (32%) were negative. HCV genotyping showed the following frequencies: genotype 1 0.9% (n=1); genotype 1A 54.05% (n=60); genotype 1B 4.5% (n=5); genotype 2 0.9.% (n=1); genotype 3 28.8% (n=32); genotype 3A 5.4% (n=6); genotype 4 5.4% (n=6). Gender did not impact HCV positivity as detected with the rapid test (chi-square=0.08, p=0.83). Having HIV did not change the positivity rate to HCV (chi-square=3.09, p=0.08). A logistic linear model using HCV positivity as the dependent variable and age and sex as the independent predictors did not yield significant results (chi-square=3.04, p=0.22). Characteristics of HCV RNA-positive patients are described in *Table 2*.

At univariate analysis, factors associated with anti-HCV antibody positivity (assessed by OraQuick® rapid test) were age (OR 1.09, 95% CI 1.06-1.10, p<0.001), intravenous drug use (OR 58.4, 95% CI 33.5-101.6, p<0.001), HIV infection (OR 14.4, 95% CI 3.4-61.7, p<0.001), opioid substitution treatment (OR 15.1, 95% CI 8.9-25.4, p<0.001). At multivariable analysis, age, intravenous drug use and opioid substitution treatment remained independently associated with positive antibodies for HCV (p<0.001, p<0.00, and p=0.049, respectively).

Patients with chronic C hepatitis

Among the 111 HCV positive subjects, 73 started DAAs during study period: of these, 71 completed

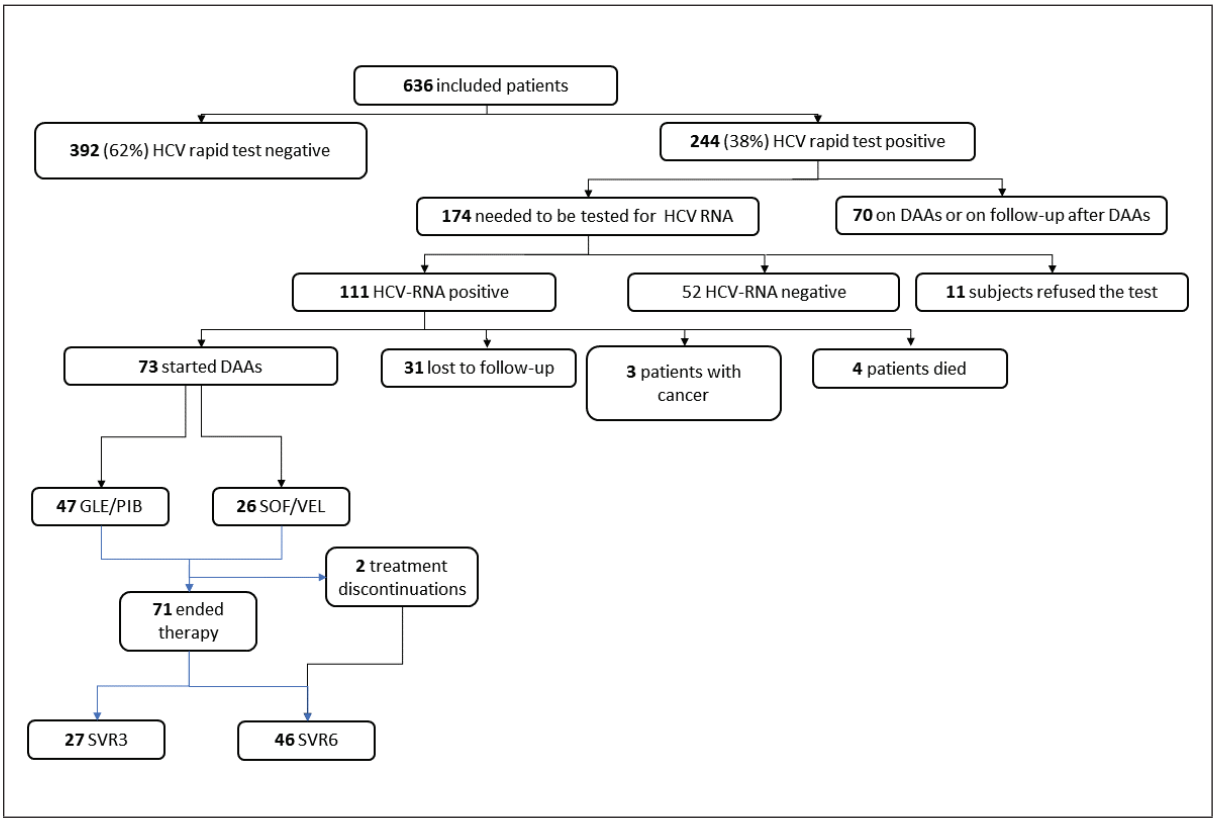

Figure 1
Flow-chart of the prospective study involving people who use drugs in the city of Pavia.
DAA: direct antiviral agents; GLE/PIB: glecaprevir/pibrentasvir; HCV: hepatitis C virus; SOF/VEL: sofosbuvir/velpatasvir; SVR3: sustained viral response at 3 months; SVR6: sustained viral response at 6 months.

Table 1
Characteristics of the total population screened for hepatitis C virus (HCV) in the city of Pavia

	Total screened population (n=636)	Ora-Quick positive (n=244)	Ora-Quick negative (n=392)	p-value
Ora-Quick positive, n (%)	244 (38.4%)	-	-	-
Male sex, n (%)	508 (79.9%)	193 (79%)	315	0.83
Age, median and range (years)	43 (15-69)	48 (25-61)	39 (16-69)	<0.001
Current IV users, n (%)	300 (47.2%)	227 (93%)	73 (18.6%)	<0.001
Current non-IV users, n (%)	33 (5.2%)	2 (0.8%)	31 (7.9%)	<0.001
OST, n (%)	404 (63.5%)	226 (92.6%)	178 (45.4%)	<0.001
HIV coinfected, n (%) (n=357)	28 (7.8%)	26 (14.3%)	2 (1.1%)	<0.001
HBV markers (n=264) **Negative, n (%)** **Isolated HBcAb positive, n (%)** **Isolated HBsAb positive, n (%)**	 91 (34.5%) 84 (31.8%) 89 (33.7%)	 50 (32.5%) 78 (50.6%) 26 (16.9%)	 41(37.3%) 6 (5.5%) 63 (57.3%)	 <0.001

IV: intravenous; OST: opioid substitution treatment; HBcAb: HBV-core antibody; HBsAb: HBV-surface antigen antibody; HBV: hepatitis B virus.

the treatment while 2 interrupted the treatment with DAAs but both showed sustained viral response at 6 months. Of note, three subjects could not be treated as they already had undetected cancer (two hepatocarcinoma and one hematological tumor), four subjects died after screening and before being sent to DAA prescriber, 31 subjects didn't show up at the prescription visit. Subjects who completed treatment were followed-up with an HCV-RNA test immediately after the end of treatment and at 3 and 6 months after the end of treatment. Only one patient with advanced liver disease presented a relapse of HCV at 6 months. As incidental findings, our study detected one case of syphilis, four HIV-positive patients (not yet under

Table 2
Characteristics and treatments of patients diagnosed with chronic C hepatitis in the city of Pavia

	HCV RNA positive (n=111)
Male sex, n (%)	89 (80.2%)
Age, median and range (years)	48 (42-52)
Current IV users	110 (99.1%)
OST, n (%)	106 (95.5%)
HIV coinfection, n (%)	14 (12.6%)
Isolated HBcAb positive, n (%)	52 (48.6%)
Isolated HBsAb positive, n (%)	17 (15.9%)
HCV genotype	
1	66 (59.5%)
2	1 (0.9%)
3	38 (34.2%)
4	6 (5.4%)
Metavir score	
F0-F2	56 (77%)
F3-F4	17 (23%)
FIB-4, median value	1.30
>3.25, n (%)	18 (18.4%)
DAAs initiation, n (%)	73 (65.8%)
Treatment type	
GLE/PIB, n (%)	47 (64.4%)
SOF/VEL, n (%)	26 (35.6%)

DAA: direct antiviral agents; F: fibrosis grade; FIB-4: Fibrosis-4; GLE/PIB: glecaprevir/pibrentasvir; IV: intravenous; HBcAb: HBV-core antibody; HBsAb: HBV-surface antigen antibody; HCV: hepatitis C virus; OST: opioid substitution treatment; SOF/VEL: Sofosbuvir/Velpatasvir.

treatment and who started antiretroviral therapy) and 67 cases of unvaccinated hepatitis B negative patients (who started the vaccination course directly at our outpatient service).

Of the 73 patients who started DAAs, 56 (77%) had absent or mild fibrosis and 17 (23%) had advanced fibrosis in the FibroScan (F3-F4 according to Metavir).

DISCUSSION

In 2016, the World Health Organization (WHO) established the goal of eliminating hepatitis C virus (HCV) by 2030, which requires a significant reduction in new cases of HCV infection and HCV-related deaths (by 80% and 60% respectively) [3].

One of the main barriers to HCV elimination is the large number of people who are unaware of their HCV infection status. Therefore, screening campaigns are critical to detect new infections, especially in high-risk groups such as drug users [2].

Screening campaigns typically involve detecting anti-HCV antibodies and using rapid diagnostic tests (RDTs) at point-of-care centers to improve linkage-to-care for individuals with positive results [2]. This approach has been adopted in Europe and in Italy, and examples of its implementation have been reported in the literature. For instance, Persico and colleagues described a screening program involving 593 drug users who were tested with oral salivary tests at Drug Addiction Centers. Among them, 41.8% were HCV positive, and 160 individuals were HCV RNA positive [7].

Unfortunately, screening campaigns and point-of-care-based approaches are still lacking. According to the last Italian report on active substance users, in 2020, only 22% of all individuals attending drug addiction services were screened for HCV as well as only 26% of the PWIDs [12].

Our study analyzed the prevalence of HCV antibody positivity among a large group of drug users and described a model of screening and linkage to care designed to increase patient engagement in HCV testing and treatment. The model was based on a robust network between Drug Addiction Centers and Infectious Diseases specialists working at the hospitals where patients with chronic HCV could undergo liver elastography and treatment. To our knowledge, we reported data on HCV rapid screening in the largest cohort of drug users in Italy. Similarly, Persico *et al*. tested 593 subjects attending several addiction centers, using the same rapid test but on saliva [7]. We included 636 individuals, with a 38% positivity rate; among subjects using intravenous drugs (n=300), prevalence of HCV antibody-positivity increased to 99%, in line with the data from an ECDC review on hepatitis prevalence in Europe, which reported a prevalence >50% among PWIDs [13]. More specifically, according to a systematic review [14], the median number of positive HCV antibodies among PWID tested for HCV in Europe was 82.9% (interquartile range, IQR 59-100%), and in eight out of the 14 countries in Europe, more than half of the PWID have been infected with HCV [14]. On the other hand, our prevalence of HCV positive subjects among PWID was significantly higher compared to recent estimates in Belgium (43%) [15]. This lower prevalence in Brussels could be attributed to the presence of intensive education programs and several needle exchange programs.

Prior to the beginning of the study, educational and informative material about chronic HCV was made available to all the patients who visited to the outpatient center. This approach might have played a key-role in increasing risk perception in our cohort and improving adherence to testing and treatment.

As expected, opioid substitution treatment and intravenous drug use were independently associated with HCV positivity ($p<0.001$). Likewise, age was independently associated with HCV rapid test positivity, with older age being a risk factor for HCV infection ($p<0.001$).

Despite the efforts to improve the linkage-to-care, only 65.8% of subjects with confirmed HCV (i.e., positive HCV RNA) started treatment with DAAs. This datum could be explained by various obstacles and barriers, including difficulties in reaching the hospitals where the visits were scheduled, long waiting lists due in part to the COVID-19 pandemic, and low compliance of the subjects. We could hypothesize that one possible major barrier to the treatment initiation was the need for individuals to move to a different center, rather than being treated at the drug addiction center by their physicians and nurses. Foschi *et al.* reported

high rates of linkage-to-care and anti-HCV treatment initiation (96.5%) when subjects received DAAs and completed their follow-up in their drug addiction center [16]. Similarly, Granozzi and colleagues described a higher rate of retention in care among drug users and homeless individuals treated with DAAs in an out-of-hospital setting rather than in hospital [17].

An additional incidental finding of our study was the high proportion of individuals who were diagnosed with infections other than HCV (HIV and HBV), of which they were not aware.

Our study has both strengths and limitations. One of the strengths was the large sample size, which is the largest in Italy so far, and the follow-up of treatment outcomes for up to 6 months. A limitation of this study was the lack of long-term follow-up data, which could provide information on reinfection rates and risks in our population. Additionally, administering questionnaires to those who continued to use the service could help identify and overcome treatment barriers and provide important information about the low rate of DAAs therapy initiation.

CONCLUSIONS

In conclusion, our findings highlight the role of RDTs as a tool for HCV screening among high-risk groups such as PWIDs to diagnose HCV infection among individuals unaware of being infected and engage patients with chronic HCV in DAAs therapy. Furthermore, our findings show the impact of a well-designed model to increase access to tests and therapy, based on an educational approach and networking. Further efforts will be necessary to make out-of-hospital treatment possible, in order to improve the linkage-to-care among these patients.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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