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The earlier the better. The cost of health services in treating PWIDs with chronic hepatitis C: Results from a non-interventional study

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SUMMARY

■ *The World Health Organization (WHO) has set up the elimination of hepatitis C virus (HCV) worldwide by 2030. The main aims of this study were to evaluate in HCV positive PWIDs: 1) the cost of patient's journey of treated subjects; 2) the cost saving induced by HCV treatment for the public health system; 3) the potential cost for a national HCV elimination plan in drug users.*

We performed a non-interventional study including 1,333 PWIDs attending the Drug Abuse Units of the Public Health Service ASST Melegnano-Martesana (Milan, Italy), over one year (January-December 2017). The direct cost for the health services received by each patient during HCV treatment (excluding the cost of drug treatment) was collected using the electronic clinical database of the public health service.

In the cohort of 1,333 patients we found 257 RNA HCV-positive PWIDs, 65 of which were treated. The mean health direct cost per each treated patient was € 1,418, while the mean the annual cost for each patient in waiting list for treatment was € 214. Considering that a HCV-positive PWID may infect within 3 years from infection at least 20 other new subjects, we may suppose that a HCV treatment may save about € 30,000 for the public health system.

The study shows that HCV treatment in PWIDs can significantly reduce both individual and community health costs and that HCV elimination plans may be sustainable for the public health system by avoiding the enormous costs of the disease burden. ■

Keywords: HCV, Health Cost, PWIDs, DAAs, Patient's journey.

Parole chiave: Epatite C, Costi sanitari, Persone che usano sostanze in vena, Farmaci a azione diretta, percorso del paziente.

Introduction

Hepatitis C virus (HCV) infection is an important cause of morbidity and mortality in the world and affects millions of people, with a high prevalence in West Africa, Eastern Europe and Central Asia. The disease is the most common indication for liver transplantation (Ponziani *et al.*, 2011; Ponziani *et al.*, 2017). The introduction into clinical practice of direct-acting antiviral (DAA) drugs has revolutionized the treatment of HCV infection, reducing the health-care costs (Axelrod *et al.*, 2018).

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In May 2016, the World Health Organization (WHO) developed a series of actions aimed at reducing new infections and deaths and achieving global HCV elimination by 2030 (WHO, 2016). For this reason, DAA therapy is currently included among the essential drugs, i.e. those that “meet the health priorities for the world's population”. The elimination of HCV has become for the governments one of the most important public health priorities, in particular for countries that have a public health system. In this context, modern health-care systems are encouraged to implement HCV elimination plans able of combining both effectiveness and saving costs (AIFA, 2019; Grebely *et al.*, 2017; Lazarus *et al.*, 2014). Italy belongs to the group of countries where access to antiviral treatment is guaranteed to all HCV-infected patients, regardless of the severity of the disease (AIFA, 2019). Despite this, DAA drugs are still denied to many HCV positive subjects belonging to “special populations” (Grebely *et al.*, 2017; Lazarus *et al.*, 2014; Molinaro *et al.*, 2019).

Today, the main barrier for the treatment of People Who Inject Drugs (PWIDs) with HCV infection is the lack of an effective multidisciplinary model of care (Konerman, Lok, 2016; Molinaro *et al.*, 2019; Nava *et al.*, 2018).

Since one of the primary objectives of public health systems is to treat the largest number of infected individuals with risky behaviors, the treatment of PWIDs represents one of the most important public health priorities of the next years (Grebely *et al.*, 2017; Lazarus *et al.*, 2014; WHO, 2017).

HCV is a disease with high health and social costs (Stanaway *et al.*, 2013; WHO, 2017). This is due to at least three factors: 1) HCV is often asymptomatic and in most cases the disease is treated only in the advanced stages (Stanaway *et al.*, 2016); 2) the disease affects between 130 and 210 million people in the world and represents the seventh cause of death globally (Fagiuoli *et al.*, 2015; Lee *et al.*, 2014); 3) HCV has significant hepatic manifestations, causing cirrhosis, hepatocellular carcinoma, and liver failure (requiring liver transplant), as well as important systemic consequences that may impact infected patients (Lee *et al.*, 2014; Stanaway *et al.*, 2016).

Italy has the highest number of HCV positive patients in Western Europe and the highest rate of deaths due to cirrhosis and hepatocellular carcinoma (EASL, 2014; WHO, 2017). Today, in Italy it is estimated that HCV positive subjects eligible for treatment are about 300,000 and most of them are drug users (Gardini *et al.*, 2016).

The literature shows that the cost of the disease is very relevant. An Italian study estimated that the costs of the disease amount to more than 1 billion of euros of which € 418 million for direct costs (e.g. medical examinations, first aid items, hospitalizations, etc.) and € 643 million for indirect costs (e.g. loss of productivity and days of work) (Marcellusi *et al.*, 2015). Another study evaluated the direct and indirect costs of the disease on a sample of 286 HCV positive patients from five European countries (Italy, France, Germany, United Kingdom and Spain) compared to a homogeneous control group for socio-demographic characteristics (Vietri *et al.*, 2013). The study showed that in Italy the indirect costs are higher than in other countries. In particular, indirect costs per patient were € 7,532.54 in HCV positive patients and € 4,576.43 in the control group, while direct costs for HCV positive and HCV negative subjects were € 1,147.06 and € 652.07, respectively (Vietri *et al.*, 2013).

An interesting Italian pharmacoeconomic study based on the costs of first generation of DAA drugs assessed the potential economic consequences of HCV infection on the public health system, in the next 30 years (Mennini *et al.*, 2014). The authors estimated a reduction, due to the treatment, of more than 156,000 critical events related to the disease and a costs reduction of € 13,000 and € 18,000 per patient over a time horizon of 10 and 30 years, respectively. Also, a recent study has shown that the full access to DAA therapy can induce, over a 20-year time horizon, a cost saving corresponding to 50 millions of euros for 1,000 patients treated (Marcellusi *et al.*, 2019). Comparable cost saving is expected also for the patients in the early-stage fibrosis (Ruggeri *et al.*, 2018), which are the majority of the drug users with HCV infection.

Moreover, several studies have also shown that HCV treatment in PWIDs is cost-effective and that an early-treatment could prevent a significant number of liver-related death (Scott *et al.*, 2016; van Santen *et al.*, 2016). In addition, treatment associated with harm reduction policies can help to reduce HCV spread and to improve the quality of life of drug users (Gountas *et al.*, 2017; Hellard *et al.*, 2018).

The main aims of this study were: 1) to evaluate the direct health cost of HCV treatment in drug users; 2) to establish if the HCV

treatment in PWIDs may be cost-saving for the public health system; 3) to determine the cost of a potential national HCV elimination plan in drug users.

Methods

We performed a non interventional study involving the drug users attending the four Drug Abuse Units of the Public Health Service ASST Melegnano-Martesana (Milan), over one year (January-December 2017).

Patients' data were collected through an online system and only physicians who had patients in care had access to patient's personal information. In particular, the data were collected using the electronic clinical database able to register every medical service correlated with HCV infection received by each patient during the year.

The patients with HCV were matched to control drug users (those without evidence of HCV) on demographic and clinical characteristics.

The costs considered in the study refer only to the direct cost covered by Italian National Health System (NHS) for the health services correlated with HCV treatment. The costs were calculated for the patient's journey (excluding the cost of drug treatment) and included specialist examinations, hospital admissions, screening, diagnosis and follow-up processes. The HCV screening was performed using an HCV-Ab test, while test confirmation was obtained with an RNA test. Follow up and re-infection tests were carried out using an RNA test. The cost of the real patient's journey was also evaluated for "health care silos", considering the costs of diagnostics (e.g. laboratory analysis, fibroscan® evaluation, etc.), specialist examinations, and health personnel.

To estimate direct costs, a bottom-up approach was followed (Bai *et al.*, 2012; Marcellusi *et al.*, 2016). This method measures the direct cost of the patient's management, obtained by multiplying the average cost by the disease prevalence.

In order to verify the uncertainty of the model results, a probabilistic sensitivity analysis (PSA) was performed (Briggs, 1999). The analysis consists in using the differences found in the examined data indicating a minimum and maximum value of the uncertainty distribution of each parameter. The probabilistic distribution was prepared applying what is normally reported for the development of probabilistic models in economic evaluations, distinguishing between costs (gamma distribution) and epidemiological parameters (beta distribution) (Briggs *et al.*, 2007; Taylor, 2009).

Data on patient populations are expressed as number, percentage, or mean \pm S.D. To determine whether the group of patients analyzed were different in terms of demographic and clinical characteristics we performed a One-Way ANOVA test for continuous variables and a Chi-square test for categorical variables. Significant levels were set at $p < 0.05$. Data were analyzed using GraphPad Prism v. 8.2.0.

The study was conducted according to the principles of Helsinki declaration, the good clinical practice consolidated guidelines and the Italian law on privacy of personal data. The study was approved by director board of the clinical studies of the Public Health Service ASST Melegnano-Martesana and by the scientific and ethical board of the Italian Society of Addiction Medicine (FeDerSerD). The data accessed were freely available by clinicians and they were taken from administrative reports which, by their nature, to be used in a clinical research are not subjected to approval by the ethics committee of the experimental studies.

Results

The three groups considered in the study (HCV negative, HCV positive treated and HCV positive not treated patients) did not differ in demographic and clinical characteristics (Table 1). Of the 1,333 PWIDs attending the Drug Abuse Units during 2019, 257 (19%) were HCV-positive PWIDs (19%); and 65 (25%) were treated (Fig. 1).

Of the treated patients 44 (68%) reached a complete sustained viral response (SVR) (Table 2).

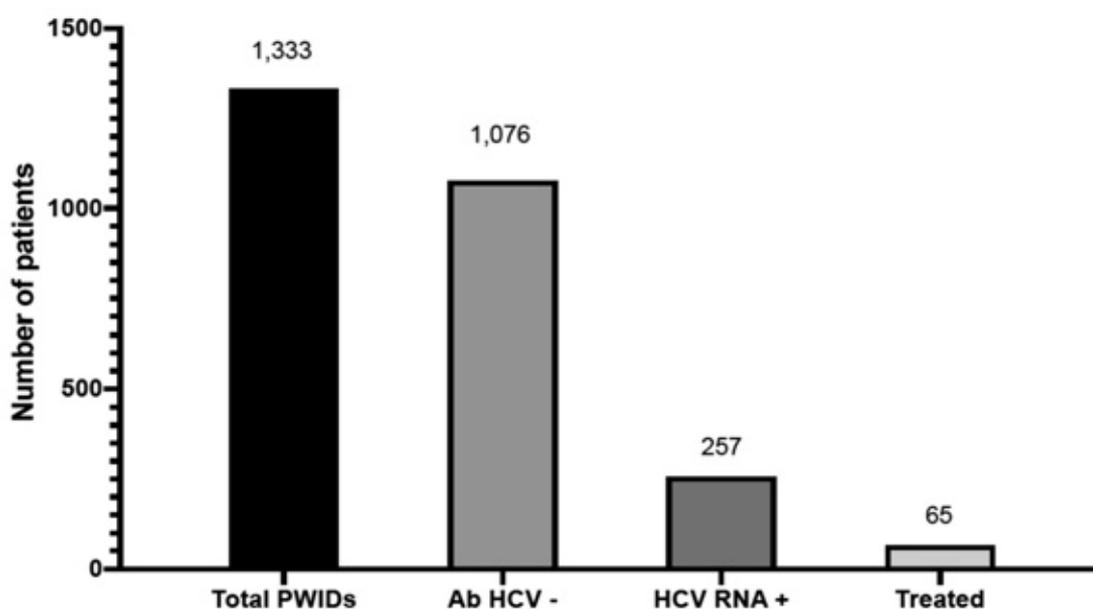
Achievement of SVR was not higher, as expected, because not all patients were treated with DAAs (some of them were yet treated with interferon + ribavirin), not being all medical doctors inside the Drug Abuse Units authorized to prescribe the DAA therapy. Moreover, the low rate of HCV treatment was also due to the existence of some important barriers limiting the cure of PWIDs

Tab. 1 - Comparison between groups in terms of demographic and clinical characteristics

		PWIDs HCV negative (n = 1,076)	PWIDs HCV RNA positive not treated (n = 257)	PWIDs HCV RNA positive treated (n = 65)
Sex (%)				
Male	78%	76%	81%	Chi2 = 0.74; p = 0.68
Female	22%	24%	19%	
Age	37.88 + 6.57	38.93 + 8.66	38.40 + 7.33	F = 2.37; p = 0.09
Duration of Addiction (Years)	12.4 + 2.5	14.3 + 5.3	15.8 + 2.8	F = 2.03; p = 0.13
Dual Diagnosis (%)				
Yes	26%	30%	29%	Chi2 = 0.42; p = 0.80
No	74%	70%	71%	
Severe and chronic internal diseases (%) (e.g. diabetes, severe cardiovascular diseases, cirrhosis, etc.)				
Yes	13%	16%	21%	Chi2 = 2.35; p = 0.30
No	87%	84%	79%	
Opiate Substitution Treatment (OST) (%)				
Yes	77%	82%	85%	Chi2 = 2.15; p = 0.34
No	23%	18%	15%	

Data analysis using One-Way ANOVA for continuous variables (age, duration of addiction) or Chi-square test (Chi2) for categorical variables (sex, dual diagnosis, severe and chronic internal diseases, OST) showed that the differences among groups were not statistically significant ($p > 0.05$).

Fig. 1 - Treatment cascade for People Who Inject Drugs (PWIDs) with chronic HCV infection attending the Drug Abuse Units of Public Health Service ASST Melegnano-Martesana during 2017



Tab. 2 - Therapy outcomes of the HCV treated patients

	N	%
Therapy Outcomes:	65	100%
SVR	44*	68%
No SVR	11	17%
Ongoing	4	6%
NN	6	9%

NN: Not determined; SVR: Sustained Viral Response. * Data analysis using Chi-square test showed that SVR response was statistically significant (Chi2 = 44.33; p < 0.001).

inside the Drug Abuse Units, such as the impossibility to make the fibroscan® analysis and the difficulty for the patients to reach the specialized centers.

The mean direct cost per treated patients, excluding the cost of the drug, was € 1,418, including the cost of the harm reduction activities corresponding to € 171 (12% of the entire cost of the patient’s journey) (Table 3). In particular, the data suggest that diagnostics represent the greatest cost, followed by the costs for specialists and other healthcare personnel (Table 3).

The mean of the annual cost for patient in waiting list for HCV treatment was € 214, considering that these patients need of periodic visits to monitor the disease and its complications. In

other words, in one year a HCV treated patient costed as about 5 not treated drug users.

Moreover, considering that literature shows that a drug user is able to infect, within 3 years from the time of infection, other 20 subjects (Magiorkinis *et al.*, 2013), the HCV treatment of a single infected PWID may save about € 30.000 of direct health cost.

On the basis of the costs of the HCV-positive patient’s journey, we can hypothesize the value of an effective national plan for HCV elimination in PWIDs, on the time horizon 2020-2030 (excluding the cost of the drug). Since the Italian epidemiological data suggest that there are about 450,000 high-risk drug users, but only about 150,000 are in care in the Drug Abuse Units (Nava *et al.*, 2018) and, considering that the prevalence of HCV in drug users can be around 60% (Stroffolini *et al.*, 2012), we may assume that the costs of HCV treatment for the entire high-risk drug users may correspond to about 380 million euros (excluding the cost of the drug), including a cost of about 46 millions of euros for harm reduction measures (Table 4).

Given the costs of management of HCV positive PWIDs described above, in order to achieve the elimination target by 2030 established by the WHO (i.e. the treatment of the 80% of HCV positive patients), we may assume that the annual resources required – in the period 2020-2030 – for the treatment of HCV infected high-risk drug users may amount to about 30 million euros per year (Table 5).

Tab. 3 - Costs of the patient’s journey of HCV treated drug users

Management of PWID with Chronic Hepatitis C	Costs for “health care silos” (€)				Costs of the harm reduction activities (included in the total cost per capita) (€)		
	Min	Max	Mean	%	Min	Max	Mean
Patient’s journey:	1,297	1,540	1,418	100	84	258	171
Diagnostics	376	571	620	43			
Specialists	531	579	521	37			
Other healthcare personnel (nurses, pharmacists, etc.)	390	390	390	23			

Tab. 4 - Costs for the management of PWIDs with hepatitis C in Italy (excluding the cost of the drug treatment) – time horizon 2020-2030

In care in the SerDs:		
90,000	127,620,000	15,390,000
Not in care in the SerDs:		
180,000	255,240,000	30,780,000
Total:		
270,000	382,860,000	46,170,000

Tab. 5 - Annual investments required to reach the WHO HCV elimination target among drug users in Italy – time horizon 2019-2030

High-risk drug users (number) (mean)	Annual Cost (€)
In care in the SerDs:	
90,000	10,209,600
Not in care in the SerDs:	
180,000	20,419,200
Total:	
270,000	30,628,800

Discussion

Currently, there are many barriers that limit the access for treatment of HCV infected PWIDs (Konerman, Lok, 2016; Nava *et al.*, 2018). The most important are due to the lack of an organized health-care system based on a multidisciplinary, and cooperative model of work, able to make an effective linkage to care. This evidence is well proven by our study, showing that Drug Abuse Units are able to treat, over one year, only 24% of HCV positive patients. The main priority for the public health system is to include PWIDs in HCV elimination plans, in order to reduce new infections (treatment as prevention), contributing to eliminate the spread of the infection also in general population (Cousien *et al.*, 2016; Hickman *et al.*, 2019; Grebely & Dore, 2017; Grebely *et al.*, 2017).

To our knowledge, this is the first study that determines the cost of the patient's journey of the HCV positive patients in Italian Drug Abuse Units and that shows how it may be cost-saving for the public health system.

This study is also the first that makes a cost analysis for "health-care silos", permitting to evaluate the cost of each step of the patient's journey.

Moreover, our study is the first that defines, based on available epidemiological data, the potential cost (excluding the cost of the drug) for an HCV elimination plan in Italian drug users. Interestingly, our data show that the cost for HCV elimination plan in drug users (corresponding to about 380 million euros) is lower than the cost of disease burden (corresponding to 1 billion euros) (Marcellusi *et al.*, 2015). Moreover, over a time horizon 2020-2030, the annual cost of HCV elimination plan may correspond to about 30 million euros, making the eradication program in PWIDs suitable for the public health system.

The harm reduction actions are essential measures in order to reduce reinfection rate in PWIDs. Recent studies have shown that the reinfection rate in PWIDs is low and it corresponds to 3.1/100 per person-year, if associated with harm reduction measures like opioid agonist therapy (Metzig *et al.*, 2017; Rossi *et al.*, 2018). On the other hand, some recent studies have shown that DAA treatment is also cost-effectiveness when associated with a syringe exchange programs and a medication assisted therapy for opioid use disorders (Barbosa *et al.*, 2019; Stevens *et al.*, 2019). At this regard our study demonstrates that the cost of harm reduction measures (including OST) associated with HCV treatment may be sustainable for the health-care system, corresponding to the 12% of the entire cost of the patient's journey.

This study has some limitations. The first is that the data are extracted from a single public health service. The second is the impossibility to estimate in PWIDs the indirect costs associated with the disease, such as the loss of productivity and competitiveness, as well as the costs incurred directly by patients (out-of-pocket costs). The third is that the cost of the drug treatment was not included in our cost analysis because there is a high variability of the reimbursed prices that constantly changed over the years and that depend by a dedicated fund of the Ministry of Economy (Italian Budget Law, 2019).

Considering all the above issues, we may assume that the HCV treatment of PWIDs can produce a substantial reduction of the incidence of new infections and the decrease of disease burden, with a significant impact for the public health system.

In conclusion, the HCV treatment in PWIDs is a priority in term of public health and it may be cost-saving for the public health systems.

Our study shows that the treatment of drug users with HCV infection determines a return of health and avoidable costs for the public health system. To our knowledge our study is the first that fix the direct health costs for the patient's journey of HCV-positive PWIDs and the cost-benefits for the public health system.

Today, we have limited data on the epidemiology of HCV in PWIDs and we have no information on the disease stages in drug users affected by HCV. However, since HCV is a "disease that induces disease", specially in drug users, and PWIDs are the reservoir of the disease we may assume that the investment in HCV treatment for drug users may be certainly cost-saving for the health-care system.

Finally, this study can be of reference for the health authorities and policy decision-makers who will be able to carry out more realistic hypothesis about costs and investments on the HCV elimination plans including drug users.

Notes

The authors declare no conflicts of interest.

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