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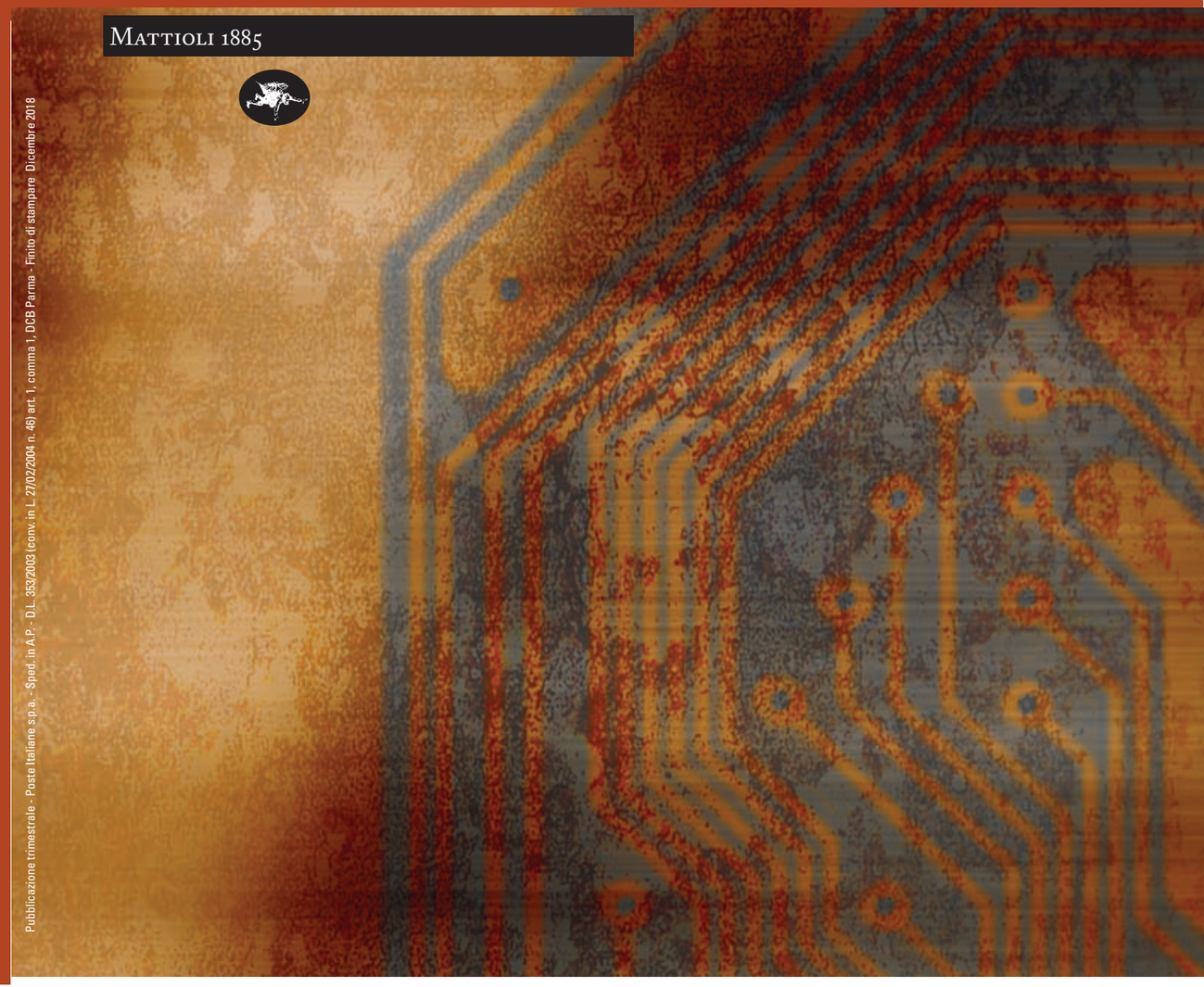

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Review

HCV and drug addiction in the historical scenario of infection entry in Italy

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Summary. The objective of this revision is - through an analysis of the literature – to highlight the relevance and importance of drug addiction in the entry of Hepatitis C virus (HCV) and acquired immunodeficiency (HIV) in Italy, with a review of the history of the HCV various strains that have spread over time through this population (especially in relation to genotypes 3, 4 and in part 1), using the most advanced methods related to the phylogeny and geography of the virus. (www.actabiomedica.it)

Key words: HCV, drug addiction, HCV genotypes, Italy

1) Introduction

Hepatitis C virus (HCV) infection is of growing international concern due to its substantial effect on morbidity and mortality (1). A leading cause of cirrhosis, hepatocellular carcinoma (HCC), liver transplantation, and liver-related death worldwide, the HCV-related disease burden continues to increase as the infected population advances to late stage liver disease (2). The disease inflicts an immense health and economic burden on countries due to the infection's hepatic and extra hepatic effects (3).

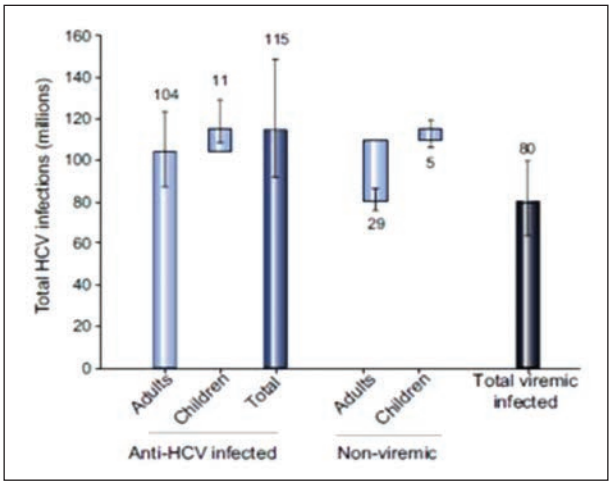
In 2016, the 69th World Health Assembly approved the Global Health Sector Strategy to eliminate hepatitis infection by 2030, (4) and WHO introduced global targets for the care and management of HCV including "a 90% reduction in new cases of chronic hepatitis C, a 65% reduction in hepatitis C deaths, and treatment of 80% of eligible people with chronic hepatitis C infections" (5). To achieve these goals, countries need to develop national policies based on up-to-date and reliable epidemiological evidence (6).

Recently, the World Health Organization set the goal to eliminate the HCV worldwide by 2030. This goal is achieveable thanks to the introduction in the clinical practice of direct anti-viral drugs.(7) At the same time in our and other countries there are organizational difficulties of systematic access to treatment for so-called special populations - ie consumers of substances that use injecting drugs (People Who Inject Drugs - PWIDs) – universally identified as the true reservoir of infection. In fact, a formidable cause of transmission of HCV, widely spread through the globe, is represented by sharing the paraphernalia used by PWIDs.(8) It has been estimated that up to 10,000,000 active drug users may be anti-HCV-positive worldwide (9).

2) HCV epidemiological trends in Italy

The global prevalence of anti-HCV was estimated at 2.0% (1.7–2.3%) among adults and 1.6% (1.3–2.1%) for all ages corresponding to 104 (87–124) million and 115 (92–149) million infections, respectively (Graph 1). The viraemic prevalence was 1.4% (1.2–1.7%) among adults and 1.1% (0.9–1.4%) in all ages corresponding to 75 (62– 89) million and 80 (64–103), respectively.(10)

Three to four million people are newly infected each year (2).



Graphic 1. The global number of HCV infections (anti-HCV and viraemia) (40)

Globally, anti-HCV prevalence is highest in Asia, Africa, Eastern Europe, and North Africa & the Middle East, ranging from 2–4%, whereas in North America, Latin American & the Caribbean, most Western European countries and Australia, the anti- HCV prevalence is less than 1.5% (11).

HCV prevalence has been declining in many countries. It is interesting to note that the most relevant decrease has been observed in the high income zones, especially in Western Europe (-1.5%), Southern Africa (-1.2%) and Australasia (-0.9%), whereas a massive increase it's reported in some of the low income areas as Central Africa (+3.7%) and Central Asia (+2.0%) (12).

In Europe has estimated that the prevalence of HCV varies between 2,4% for western and Central Europe and 2,9% for Eastern Europe. The global population of this area is approximately 740,000,000 persons leading to an estimation of the HCV infected pool of more than 19,000,000 person. The shortcomings of this and other study reside in the fact that evidence is based on surveys often conducted in selected groups, or excluding high risk population such as prison inmates and groups of persons living in social exclusion. The attributable fractions of cirrhosis for HCV are 38% for Western and 34% for Eastern Europe while those for hepatocellular carcinoma are, respectively, 44% and 15% (13).

In Italy anti-HCV prevalence in adult is 2% (1,6-7,3%) and viraemic prevalence is 1,5% (1,2-5,4%), adult anti-HCV population is 1048000 and adult viraemic population is 768000 (10).

In any case, In Italy, the prevalence in the general population is reported to be greater than 5% and 9% among households of HCV-positive patients (14),

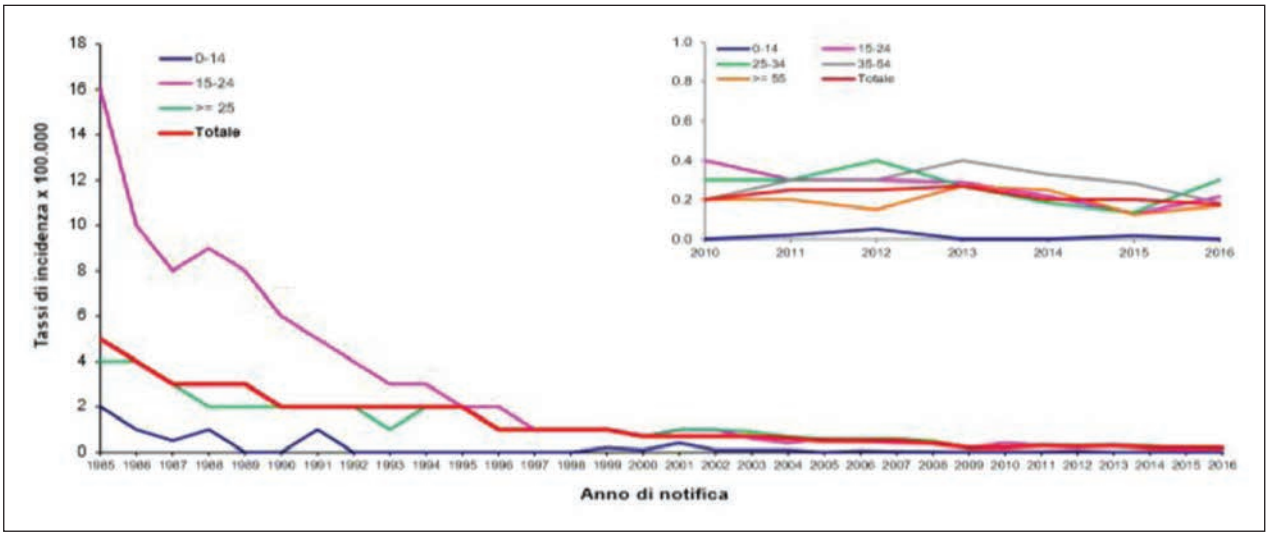
In Italy, the incidence of HCV has decreased from 5 per 100,000 in 1985 to 1 per 100,000 in 1996 (15).

The National Surveillance System too, analyzing period between 1991 and 2010, evaluated that incidence of HCV decreased and reported that in the period 2003- 2010 the mayor risk factor for HCV was injected drug use followed by cohabitation or sexual partnership with HCV carrier. Also the risk of nosocomial acquisition was substantial present in this study (16).

The rates of incidence of Hepatitis C in Italy by age and year of notification are decreasing gradually but steadily from 1985 to 2016 (Graph 2, Table 1) (17).

Unlike other industrialized countries, the burden of clinically relevant HCV-positive cases in Italy is already on the decline and will further reduce in the future. This is due to differences in the age-specific prevalence, most of HCV-positive Italians currently being 65 y of age (18).

A recent study, to up-date the current scenario of HCV in Italy, has performed a survey on the prevalence of HCV infection among the general population in five metropolitan areas of the country. Of the 4097 individuals enrolled 112 subjects resulted anti-HCV positive, generating an overall prevalence of 2.3%. The prevalence was significantly higher in men than in women . It increased with increasing birth cohort, from 0.2% in subjects born after the year 1984, to 4.2% in those born before the year 1935. Two peaks of infection are evident: a bigger one in people born in the decade 1935–1944, and a smaller one in subjects born in the decade 1965–1974 (Graph 3). With the introduction of disposable syringes in medical practice during the 1970s, along with improved socioeconomic conditions, the risk of HCV sharply declined in subjects born after 1955. The intravenous drug use was the strongest independent predictor of the second wave in subjects born from 1965 through 1974 paralleling the historical trend of parenteral illicit drug started in Italy in the 1970s and peaked at the end of the 80s–early 90s.



Graphic 2. Incidence rates (x 100.000) of hepatitis C per year and notification year. SEIEVA 1985-2016 (17)

Table 1. Incidence rates (x 100.000) of hepatitis C per year and notification year. SEIEVA 1985-2016.(17)

ANNO	ETA'			
	0-14	15-24	≥ 25	Totale
1985	2,0	16,0	4,0	5,0
1986	1,0	10,0	4,0	4,0
1987	0,5	8,0	3,0	3,0
1988	1,0	9,0	2,0	3,0
1989	0,0	8,0	2,0	3,0
1990	0,0	6,0	2,0	2,0
1991	1,0	5,0	2,0	2,0
1992	0,0	4,0	2,0	2,0
1993	0,0	3,0	1,0	2,0
1994	0,0	3,0	2,0	2,0
1995	0,0	2,0	2,0	2,0
1996	0,0	2,0	1,0	1,0
1997	0,0	1,0	1,0	1,0
1998	0,0	1,0	1,0	1,0
1999	0,2	1,0	1,0	1,0
2000	0,1	0,7	0,7	0,7
2001	0,4	1,0	1,0	0,7
2002	0,1	1,0	1,0	0,7
2003	0,1	0,6	0,9	0,7
2004	0,1	0,4	0,7	0,6
2005	0,0	0,6	0,6	0,5
2006	0,1	0,5	0,6	0,5
2007	0,0	0,4	0,6	0,5
2008	0,0	0,4	0,5	0,4
2009	0,0	0,2	0,2	0,2
2010	0,0	0,4	0,2	0,2
2011	0,0	0,3	0,3	0,3
2012	0,1	0,3	0,3	0,3
2013	0,0	0,3	0,3	0,3
2014	0,0	0,2	0,3	0,2
2015	0,0	0,1	0,2	0,2
2016	0,0	0,2	0,2	0,2

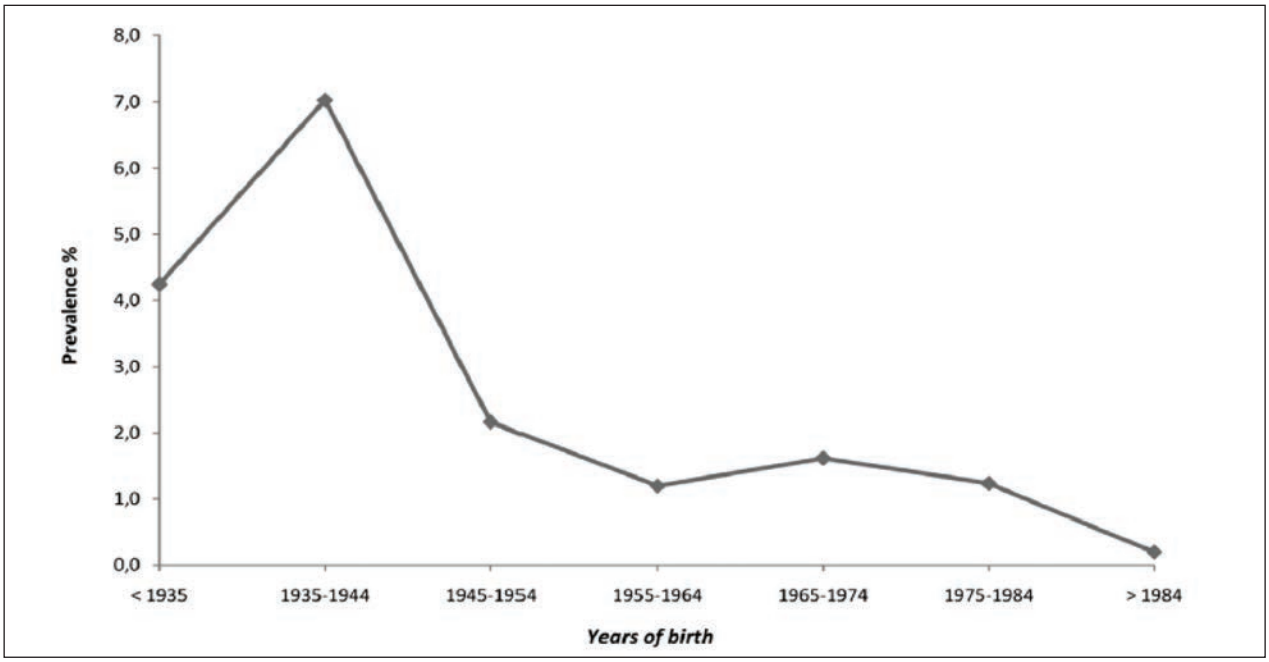
* fino al 2008 Epatite NonA-NonB

The large majority of anti-HCV positive subjects (79.5%) were aware of their infectious status. The estimates of the population attributable risk (PAR) evidence that 32% of anti-HCV positive cases were related to low educational level, 25% to the past use of glass syringes, 14% to previous blood transfusion, 12% to i.v. drug use, and 11% to a household contact with a HCV positive subject.

In conclusion In metropolitan areas in Italy, HCV is prevalent in elderly, reflecting a cohort effect determined by modalities of viral transmission no longer operative. The impact of the infection will further diminish in the years to come due to the natural depletion of the reservoir of the virus (19).

At present, this infection is not eradicable, as a vaccination against hepatitis C is not yet available. Acquisition of HCV infection typically involves the parenteral route (transfusions of blood or blood products from unscreened donors, injection drug use, or unsafe therapeutic injections), but HCV can also be transmitted by occupational injury (contaminated needles or sharp instruments), hemodialysis, and tattooing (20). Another way of nosocomial transmission are digestive endoscopy and invasive radiology procedures (8). Moreover, dental care was found to be associated with HCV seropositivity (21).

Since the late 1980s, the incidence of acute hepatitis C has also declined.



Graphic 3. Prevalence of anti-HCV positivity by cohort of birth in 5 Italian metropolitan areas, 2015 (19)

The decrease was due to a number of factors – increased mortality due to the infected population aging, a reduction in the new infections due to the implementation of blood supply screening and a drop in high-risk behaviour in the early 1990s as the transmission of HIV was better understood (10).

This trend in HCV infections is, in part, attributable to behavioral and social changes. Improved hygiene, use of precautions in medical settings, blood screening, and sexual educational campaign seem to have contributed to reduce the transmission of infection during the last 10 years. In particular, with regard to HCV cases associated with transfusion, this decrease could be attributed to the requirement for blood screening worldwide (22).

However, it is estimated that mortality related to HCV infection (death from liver failure or hepatocellular carcinoma) will continue to increase over the next 2 decades (23)

The relative impact of the different drivers of the HCV viraemic pool has changed over recent decades. Across most of Europe, before the advent of screening assays, most infections were iatrogenic, i.e. due to transfusions with infected blood and its derivates or to unsafe invasive medical and surgical procedures.

A Italian study published in 1999 evaluated the risk factors associated to chronic HCV infection in patients from various areas in Italy: blood transfusion and intravenous drug use emerged as the main risk factors for HCV infection; but also surgery and being the sexual partner of a drug addict have played an important role in the spread of HCV infection in Italy (24). The screening for HCV in blood-donors was introduced in Italy and in many other developed countries in 1990. This reduced the risk of transmitting HCV via blood transfusion to less the 1 per 1.000.000 (before 1990 this risk was 0,45% per unit transfused) and the transmission of HCV via other blood products and even organ transplantation has been reduced to zero.(13) Blood supplies are now very safe in most developed countries. In Italy in 2001-2003, the residual risk of transfusion transmitted HCV vas 2,7/10.000.000 donation and HCV NAT of blood donations in 2001 has reduced the risk even futher (0,2/10.000.000 donations) (25).

Similarly new cases in haemophiliacs have become exceptional after the introduction of recombinant clotting factors (13.)

Iatrogenic transmission of HCV has dramatically decline also after the use of disposable needles and paraphernalia. A strict adherence to standard precautions

is obiously mandatory to prevent nosocomial transmission and this is the case for digestive endoscopy and invasive radiology procedures: transmission of virus can be reduced, if not eliminated with the current mechanical cleaning-washing-disinfection procedures (13).

Transmission of HCV in haemodialysis unit has become rare in most European countries, i.e. in France as low as 0,05% per year, simply by reinforcing of blood-borne pathogens (13).

Routes at risk of transmitting included also acupuncture, beauty treatments, manicure/pedicure and tattooing.(13) In particular tattooing is result associated with HCV infection even among those without traditional risk factors such IDU and blood transfusion (before 1992) (26).

3) The problem of PWIDs

Globally, in 2015 there was 15,6 million people who inject drugs (PWID), amounting to approximately 0,33% (0,21–0,9) of those aged 15–64 years. Globally it was estimated that 52,3% of PWID were anti-HCV positive, equating to 8,2 million people (27).

PWID represent approximately 6.8% of persons infected with HCV (28).

Another review estimated that in 2010 anti-HCV prevalence in PWID varied greatly between 9,8% to 97,4%: it was 60-80% in 25 countries and 80% or higher in a further 12 (fig. 1). Globally about 10 millions of PWID were anti-HCV positive. The largest populations of HCV-positive PWID lived in Eastern Europe (2,3 millions) and East and Southeast Asia (2,6 millions). The three countries with the largest populations of PWID with HCV were China (1,6 millions), Russia (1,3 million) and the USA (1,5 million). In Italy in 2010 the midpoint prevalence of anti-HCV in PWID was 81,1% (29).

In the area of the EU/EFTA region, the number of PWID is about 1,2 million, among which 500,000 (43%) are HCV RNA positive (8).

In 2010 it has been estimated the prevalence of HIV, HBV and HCV infections among injecting and non injecting drug users treated within public drug-treatment centres in Italy (SerT). In the sample of 1330 drug users, the prevalence of HIV was 14.4% among drug injectors and 1.6% among non-injectors; the prevalence of HBV was 70.4% among injecting drug users and 22.8% among non-injectors and the prevalence of HCV was 83.2% among injecting drug users and 22.0% among non-injectors (Table 2). For PWID, the probability of infection increased with the

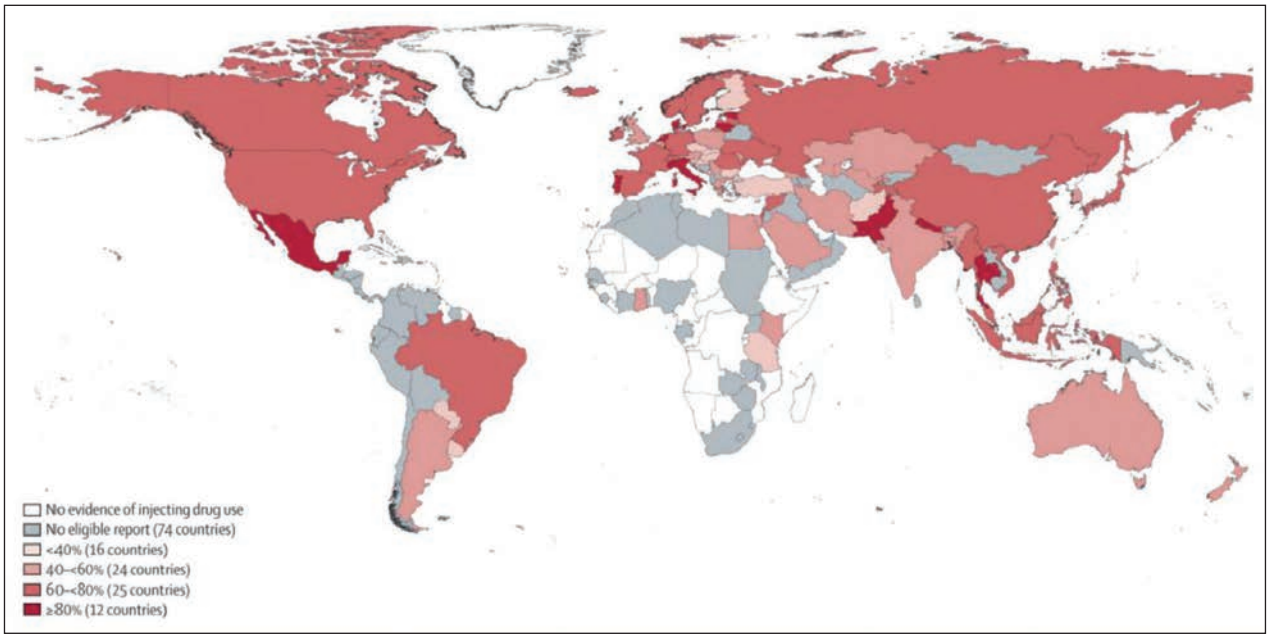


Figure 1. Prevalence of anti-HCV in PWID (29)

Table 2. Prevalence for HIV, HBV and HCV infections among PWIDsattendingSerTin Italy, 2005 (28)

	Tested for HIV	HIV + N	(%)	Crude OR (95% CI)	Adjusted OR (95% CI)	Tested for HBV	HBV+ N	(%)	Crude OR (95% CI)	Adjusted OR (95% CI)	Tested for HCV	HCV+ N	(%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Total	807	93	(11.5)			563	342	(60.7)			1085	772	(71.2)		
Gender															
Male	648	70	(10.8)	1	1*(a)*	465	271	(58.3)	1	1	890	636	(71.5)	1	1*(b)*
Female	156	23	(14.7)	1.43 (0.86-2.37)	1.61 (0.90-2.89)	94	67	(71.3)	1.77 (1.09-2.88)	1.66 (0.92-3.00)	190	132	(69.5)	0.90 (0.64-1.27)	1.09 (0.69-1.72)
Age group															
< 31 years	283	7	(2.5)	1*(c)*	1	136	48	(10.3)	1	1	339	169	(33.6)	1	1
31 - 40 years	344	39	(11.3)	5.04 (2.22-11.46)	4.59 (1.94-10.83)	261	160	(61.3)	2.90 (1.89-4.47)	2.45 (1.51-4.11)	480	371	(77.3)	3.42 (2.53-4.62)	3.55 (2.38-5.29)
> 40 years	180	47	(26.1)	13.93 (6.13-31.65)	11.17 (4.73-26.37)	166	134	(80.7)	7.68 (4.56-12.93)	5.83 (3.21-10.55)	266	232	(87.2)	6.86 (4.51-10.42)	6.58 (3.85-11.26)
Area of SerT															
Central and Southern Italy	438	41	(9.4)	1	1	197	134	59.5%	1	1*(d)*	625	444	(71.0)	1	1
Northern Italy	369	52	(14.1)	1.59 (1.03-2.45)	1.67 (1.04-2.70)	145	87	62.5%	1.13 (0.80-1.60)	1.24 (0.80-1.92)	460	328	(71.3)	1.01 (0.77-1.32)	0.93 (0.66-1.32)
Number of years of education															
< = 8 years	393	56	(14.2)	1	1	309	206	(66.7)	1	1	559	434	(77.6)	1	1
> 8 years	409	37	(9.0)	0.59 (0.38-0.93)	0.76 (0.47-1.24)	253	135	(53.4)	0.57 (0.41-0.80)	0.69 (0.46-1.06)	520	333	(64.0)	0.51 (0.39-0.67)	0.59 (0.42-0.84)
Employment status															
Employed	476	43	(9.0)	1	1	332	178	(53.6)	1	1	642	431	(67.1)	-	-
Unemployed	324	49	(15.1)	1.79 (1.16-2.78)	1.85 (1.14-3.00)	225	158	(70.2)	2.04 (1.43-2.92)	2.10 (1.35-3.28)	432	211	(32.9)	-	-
Marital status															
Single	463	44	(9.5)	1	1	315	183	(58.1)	-	-	613	417	(68.0)	1	1
Married/divorced/separated	337	48	(14.2)	1.58 (1.02-2.44)	1.01 (0.62-1.65)	245	157	(64.1)			464	349	(75.2)	1.42 (1.08-1.87)	0.96 0.66-1.39

Table 2. (continued) –Prevalence for HIV, HBV and HCV infections among PWIDsattendingSerTin Italy, 2005 (28)

	Tested for HIV	HIV + N	(%)	Crude OR (95% CI)	Adjusted OR (95% CI)	Tested for HBV	HBV+ N	(%)	Crude OR (95% CI)	Adjusted OR (95% CI)	Tested for HCV	HCV+ N	(%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Number of lifetime sexual partner															
< 5	235	29	(12.3)	-	-	167	85	(50.9)	1	1	329	220	(66.7)	1	1
> = 5	560	63	(11.3)	-	-	382	249	(65.2)	1.81 (1.25-2.61)	1.47 (0.93-2.31)	735	536	(72.9)	1.33 (1.01-1.77)	1.58 (0.80-1.68)
Injecting drug user (IDU)															
No	184	3	(1.6)	1	1	114	26	(22.8)	1	1	214	47	(22.0)	1	1
Yes	623	90	(14.4)	10.19 (3.18-32.58)	7.78 (2.39-25.38)	449	316	(70.4)	1.14 (1.10-1.18)	5.48 (3.20-9.38)	871	725	(83.2)	17.64 (12.2-25.52)	17.94 (11.78-27.34)
HIV															
Negative	-	-		-	-	495	286	(57.8)	1	1	972	671	(69.0)	1	1
Positive	-	-		-	-	57	52	(91.2)	7.6 (2.98-19.36)	391 (1.41-10.82)	87	85	(97.7)	19.06 (4.66-77.99)	9.13 (1.89-44.09)
Number of years of injecting use															
Less than 10	220	10	(4.5)	1(c)	(e)	102	43	(42.2)	1(c)	(e)	267	167	(62.5)	1(c)	(e)
10-19	224	29	(12.9)	3.12 (1.48-6.58)		179	133	(74.3)	3.97 (2.38-6.65)		325	300	(92.3)	7.19 (4.46-11.58)	
More than 19	144	48	(33.3)	10.50 (5.10-21.63)		141	124	(87.9)	10.01 (5.27-19.01)		213	204	(95.8)	13.57 (6.66-27.66)	
Frequency of injecting heroin use															
Up to twice a week	67	5	(7.5)	-	-	37	19	(51.4)	1	(e)	94	73	(77.7)	-	-
Three or more times a week	507	79	(15.6)	-	-	373	266	(71.3)	2.36 (1.19-4.66)		711	599	(84.2)	-	-

(a) Gender was included in the multivariate analysis as control variable because it was associated to execution of HIV test.

(b) Gender was included in the multivariate analysis as control variable because it was associated to execution of HCV test.

(c) χ^2 for trend p-value < 0.05.

(d) Area of SerT was included in the multivariate analysis as control variable because it was associated to execution of HBV test.

(e) excluded from multivariate analysis: variables associated with injecting drug use (number of years of injecting use, frequency of injecting heroin use) were not included in the multivariate model because related only to the subgroup of IDUs.

Table 3. Fattori di rischio per infezione da HCV. SEIEVA, 2016 (31)

		Fascia di età											
		0-14		15-24		25-34		35-54		55+		TOTALE	
	Fattore di rischio	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%
Parenterale o sessuale	Trasfusione sangue	0	0,0	2	22,2	9	45,0	4	16,7	1	4,0	16	20,5
	Interventi chirurgici	0	0,0	0	0,0	1	6,3	1	4,6	6	23,1	8	11,0
	Ospedalizzazione	0	0,0	1	11,1	4	20,0	3	13,0	6	23,1	14	17,9
	Altre esposizioni parenterali**	0	0,0	3	33,3	3	18,8	5	22,7	5	19,2	16	21,9
	Terapia odontoiatrica	0	0,0	3	37,5	2	12,5	5	22,7	3	12,0	13	18,3
	Uso di droghe E.V.	0	0,0	7	70,0	6	35,3	5	21,7	2	7,7	20	26,3
	Convivente tossicodipendente	0	0,0	3	42,9	1	7,1	0	0,0	0	0,0	4	7,1
	Contatto con itterico nei 6 mesi	0	0,0	4	57,1	1	8,3	1	7,7	0	0,0	6	11,8
	Partner sessuali (>1 nell'ultimo anno)	0	0,0	2	33,3	3	33,3	11	61,1	2	22,2	18	42,9
	Convivente di soggetto HCV+	0	0,0	1	14,3	0	0,0	2	15,4	1	5,6	4	8,5
	TOTALE CASI***	0		10		20		25		26		81	

* I casi possono avere più di un fattore di rischio
** Piercing, tatuaggi, agopuntura, manicure/pedicure, rasatura dal barbiere
*** Per alcuni casi l'informazione relativa ad alcuni fattori di rischio non è disponibile

number of years of injecting use. In the multivariate analysis, the factors significantly correlated with HCV infection were: older age, a low level of education , being HIV-positive and injecting use (28). The results indicate that these infections continue to circulate among drug users, highlighting the need for monitoring of this group in Italy (28) to achieve the WHO goal to eliminate the HCV worldwide by 2030 (7).

As told before, it has been estimated that up to 10,000,000 active drug users may be anti-HCV-positive worldwide. (9) Thisis of the highest concern, as drug dependence and disease burden are highest in young adults (mostly the third decade), (30) confirmed by a SEIEVA survey on the main risk factors reported in case of hepatitis C (Table 3) (31).

HCV infected PWID represent a substantial proportion of patients at risk of advanced liver diseases and the major reservoir for the continuous spread of the epidemic (8).

Considering the slow progression of the disease, the availability of effective drugs, the need to intervene above all on special populations with PWIDs to achieve the goal set by the WHO becomes even more evident. Furthermore, several studies in literature also have established that treating PWIDs with HCV is cost-effective (29). It should also be emphasized that pharmacological treatment aims to achieve both quality of life and economic clinical healthcare outcomes because the new treatments lead to a complete regression of the disease, saving resources by National Health Services (SSN) due to progressive decrease - up to annullment - of newly occurring cases and reduction of costs associated with the progression of diseases or generated by the need for diagnosis and care in the assistive services.

A systematic search of peer-reviewed (Medline/Embase/PsycINFO) and grey literature databases showed that the prevalence of anti-HCV among PWIDs is far greater than HIV (32). Additionally, global numbers of people who inject drugs, as estimated by United Nations Office on Drugs and Crime, WHO, and UNAIDS, have plateaued in recent years but data are not available from many countries with some evidence of heroin use (33). It is therefore crucial that efforts be refocused on evidence-based prevention and treatment programmes.

Injecting drug use is a major contributor to the global burden of disease. In 2013, an estimated 10,08 million DALYs (deaths, and disability-adjusted life-years) were attributable to previous exposure to HIV, HBV, and HCV via injecting drug use, a four-times increase since 1990. In particular, injected drug use was estimated to cause 39,1% (7,05 million) of DALYs due to HCV (34).

We can conclude that the burden from hepatitis C could be substantially educed by effective prevention programmes. The indifference of too many authorities to the plight of people who inject drugs ignores the burden injecting drug use places on families and communities, as well as on the individuals themselves (35.)

The problem of drug addiction is coming back to Italy with the same severity that it has already had in the past, even for the appearance of new forms of drug addiction.

The modalities of transmission in this community are well known: the reuse of syringes and needles, the sharing of "cookers" (small containers to dissolve the drug, even a simple spoon), of cotton filters and of the water used to mix the drug and even of the swabs. If the incidence of HCV in PWID was dramatically high in the early 1990s, the implementation of HIV prevention programs has reduced transmission rates in many countries: access to sterile injection equipment, availability of safe injection facilities with on-site care and professional counseling on harm reduction practices and at facilitating medical and substance-abuse treatment. It has been suggested that HCV infected PWID should be treated aggressively with antiviral administration being considered also as a preventive tool to avoid the spread of the infection within the PWID community (8).

Table 4. Hepatitis C virus genotypes prevalence in the Europe regions (36)

European regions	The most prevalent genotype	Other genotypes	Comments	First author
Northern Europe	1a	1b, 2, 4	G1a frequent among PWID	Bruggmann *et al*[52], 2014
Western Europe	1b	3a (France)	G1b-common in older age groups	Messina *et al*[43], 2015
		4a (United Kingdom, The Netherlands, Germany)		Payan *et al*[53], 2005
Southern Europe	1b	2a, 2b, 2c, 4	G4 is becoming more frequent	Gower *et al*[10], 2014 Cifuentes *et al*[54], 2015
Eastern Europe	1a	1b, 2, 3, 4	Non G1 genotypes reported in migrants	Cornberg *et al*[16], 2011 Messina *et al*[43], 2015

4) The determination of circulating HCV genotypes in high-risk groups

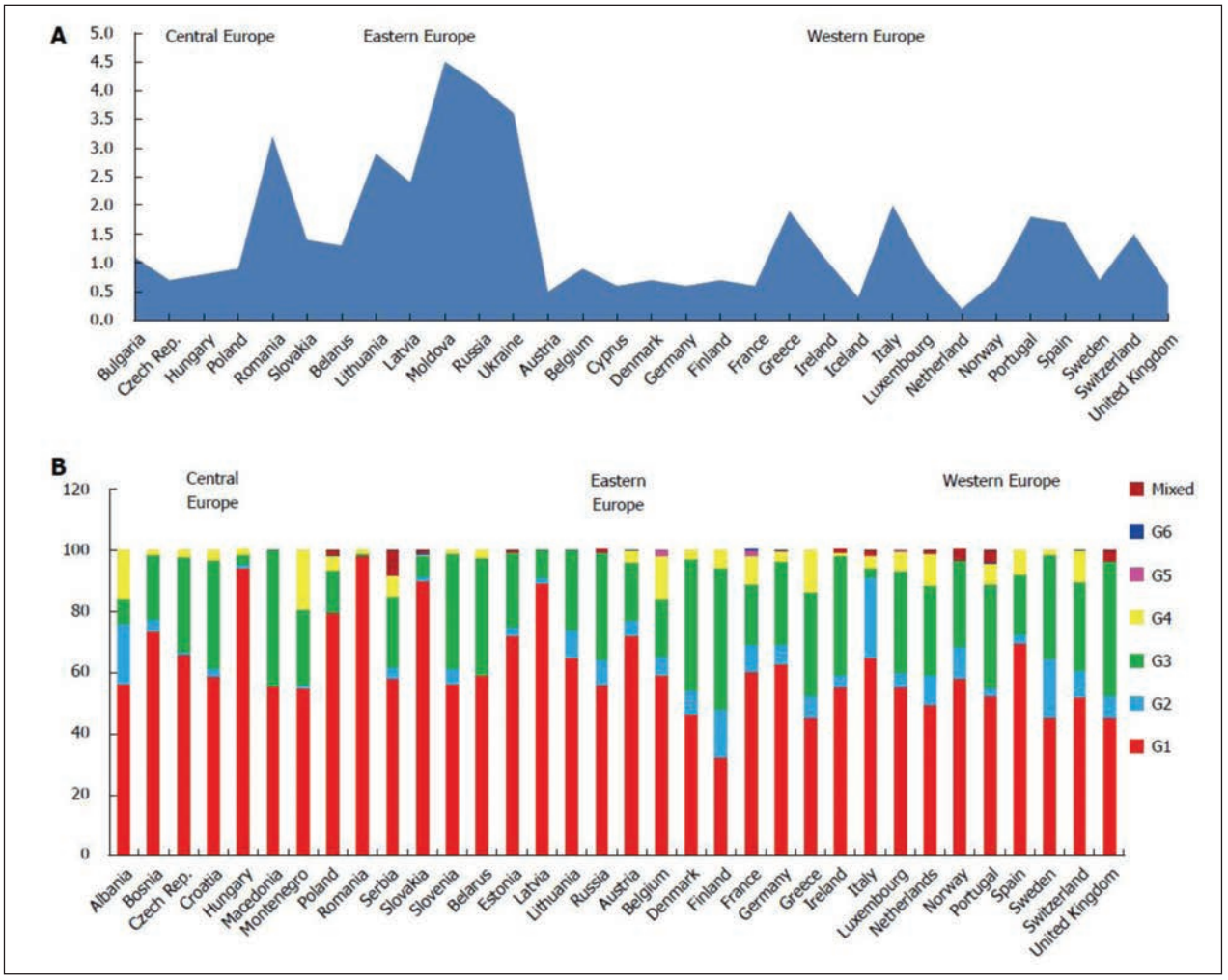
The distribution of HCV genotypes/subtypes differs significantly between people who inject drugs (PWID) and the general population. HCV genotypes that previously exhibited a limited geographical distribution (3a, 4) are becoming more prevalent in this high-risk group. Immigration from HCV-endemic countries and the evolving networks of HCV transmission in PWID influence HCV genotypes distribution in Europe (Tabel 4) (36).

Another recent review analyzed the distribution of genotype worldwide and also in Europe (Graph 4) (37).

Social vulnerabilities (e.g. unemployment, homelessness, and limited access to social and healthcare insurances systems) are important triggers for illicit drug use, which increases the associated risks of HCV infection and the frequent emergence of less prevalent genotypes. The spreading of HCV genotypes/subtypes differs significantly between and within countries, between urban and rural settings, and according to the burden of risk-groups and economic status (36).

Genotype/subtype determination bears important clinical consequences in the progression of liver disease, susceptibility to antiviral therapies and the emergence of resistance-associated variants. The infecting genotype is critical for the natural and on-treatment evolution of the infection.

These data are especially significant for PWID, who are frequently infected with genotypes 1a, 3 and 4 that tend to exhibit less favorable responses to therapies. The current World Health Organization , American Association for the Study of Liver and European Association for the Study of Liver guidelines for HCV treatment are genotype dependent, with several available options for each genotype. An estimated half of the chronically HCV-infected PWID are unaware of their infection. Important barriers to care and treatment are present in vulnerable populations, such as PWID, and it is estimated that only one in ten diagnosed patients enter treatment for hepatitis C. Delays in diagnosis lead to late presentations, with associated high viral loads and significant fibrosis, that represent unfavorable predictors for treatment efficacy. Decisions to treat are taken on a case-by-case basis, and treatments are



Graphic 4. Anti HCV prevalence (A) and genotypes distribution (B) in Europe (37)

accompanied by active counseling to decrease or cease drug and alcohol intake .

The same therapeutic regimens based on DAAs are recommended for PWID, and a history of drug use or recent drug use is not associated with a reduced response rate. PWID, in fact, exhibit high response rates to new antiviral regimens, and the level of HCV reinfection is unexpectedly low (36).

The determination of circulating HCV genotypes in high-risk groups, such as PWID, who frequently have additional risk factors (poverty, imprisonment, and HIV coinfections) will provide a further understanding of the global viral epidemiology. Therefore, knowledge of HCV genotypes will likely remain an essential factor for the correct design of national health programs, even with the introduction of new antivirals (36).

5) A brief history of HCV entry in Italy

To better frame the current role of PWIDs in this clinical setting, a brief history of HCV entry into Italy is described below.

5 a) The first period of HCV diffusion and iatrogenic infections

As a background and to investigate the interrelations with the main theme, the history of HCV infec-

tion in Italy - (essentially hyatrogenic) is reviewed in parallel, when the virus was not known and, as a result, there were not precautions to prevent infection for parenteral route - mainly using non-disposable needles and syringes for intravenous injections.

In this perspective, we can distinguish a wide phase dating back to the great diffusion of HCV starting from the First World War, until the time of transition between the not-disposable and the disposable syringes (monouse material or to lose) (Figures 2, 3), not established with great precision but identifiable around 1970. This change, in fact, took place quite rapidly but there was no universal uniformity in the elimination of non-lost material and in its replacement with the one to be lost. There were instead different temporal scans,

Figure 2. Old not-disposable glass syringes

Figure 3. Modern plastic disposable syringes

with the possibility, for example, of simultaneous use in the same hospital of disposable syringes for the therapy but still of glass syringes for the withdrawals, thus determining the protraction of the problem of viral transmission. There were also many cases of infections in patients who underwent to transplant or transfusion before 1992, the year when improvements in blood screening technologies made a great improvement.

5b) Increasingly safe methods for transfusions after the identification of the virus

In the mid-seventies, Harvey J. Alter, head of the Infectious Diseases section of the Department of Transfusion Medicine at the US National Institutes of Health, along with his research team, showed that most cases of post-transfusion hepatitis were not caused by A or B hepatitis virus. Despite this discovery, international research efforts to identify the virus, initially called hepatitis non A non B (NANBH), were not successful for more than a decade. In 1987, Michael Houghton, Qui-LimChoo and George Kuo, of Chiron Corporation, in collaboration with Dr. D.W. Bradley of the Centers for Disease Control and Prevention (CDC), used a new molecular cloning approach to identify the unknown microorganism (Figure 4) and then develop a diagnostic test (38).

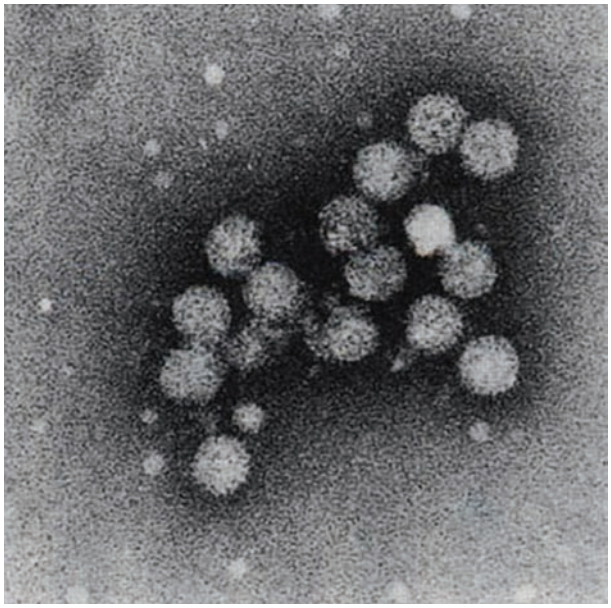


Figure 4. Hepatitis C Virus

In 1988, the existence of the virus was confirmed by Alter verifying its presence in a series of NANBH samples and, in April 1989, the discovery of the HCV virus was published in two articles in the journal Science.(39, 40) The discovery led to significant improvements in diagnosis and improved antiviral treatment (38).

Also in Italy there were a quick progression of further steps in the evolution of knowledge (namely with the identification of the virus in 1989) and growing precautions for transfusions until the progressive introduction of increasingly safe methods for the selection of blood donors. Blood transfusions and organ transplants, in the absence of prior control of the presence of HCV, are procedures that carry a high risk of infection.

In the past three decades, (16) in Italy as in most economically developed countries there has been a progressive decrease in the incidence of HCV infection and a shift in relative importance of different risk factors (41). This change can be attributed to diverse factors: the virtual disappearance of blood transfusion as a mode of transmission, as a result of the anti-HCV screening of blood donors, and, more recently, the use of HCV nucleic acid testing (NAT) on donations; improvements in healthcare standards; and the expansion of the HCV epidemic associated with intravenous drug use, despite harm-reduction interventions (42).

5c) Results of phylogenetics analysis

HCV genotype 1 is the most prevalent genotype worldwide; subtype 1a prevails in Northern America, Japan and Northern Europe, and subtype 1b is dominant in Southern Europe and Japan (44) and exhibits a high frequency in Northern Africa. HCV genotype 2 is reported in North America, Japan, Western Africa and Europe (e.g., 2a/c has been isolated in Northern Italy (45) and 2c has been isolated in Southern Italy (46)). Genotype 2a and 1b were identified as the major HCV genotypes circulating in former blood donors from rural China. HCV subtype 3a is endemic in South Eastern Asia, but it is spreading in PWID in United States and Europe, with Germany, France, Italy, and Portugal reporting an increased prevalence of genotypes 1a and 3a.(47) Mixed infections have been reported in Italy (1b/3a) (36).

Table 5. The worldwide prevalence of Hepatitis C virus genotypes (36)

Area	The most prevalent genotype	Frequency of other genotypes	First author
North America	G1 (80%) 1a- the most common	G2 (11.1%) G3 (7.4%) G4 (1.2%)	Thomas *et al*[13], 2012
Europe	G1 (60%) 1b- the most common	G3 (20%); G4 (18%)	Messina *et al*[43], 2015
South-East Asia	G3 (65%)	G1 (25%) G1 prevails in China, G6 also reported	Mao *et al*[44], 2014 Li *et al*[45], 2015
Middle East and North Africa	G4 (70%)	G1, G2, G6	Ray *et al*[46], 2000 Ramia *et al*[47], 2012
Sub-Saharan and Central Africa	G4	G5 and G6, G1a, 1b, 2a, 2b	Papastergiou *et al*[48], 2015
South Africa	G 5	G1, 2, 3, 4	Gededzha *et al*[49], 2014
Asia Pacific and Latin America	G1a	G 1b, 2a, 2b	Messina *et al*[43], 2015 Ohno *et al*[50], 1997 Villar *et al*[51], 2015

Through recent techniques of phylogenetic analysis it has been established that, in Europe, Italy has the highest HCV prevalence (3 - 4.4%) with peaks of 12.6 - 26% in Southern regions and the major islands. In Italy HCV genotype 1b prevails, and genotype 4 is mainly found in the south of the country where the prevalence is particularly high in regions such as Calabria (43).

6) Conclusions

This brief historical excursus, although not directly related to drug addiction, in addition to containing many information so far little investigated, takes place in parallel to the main topic and is functional to it, because the drug addiction was somehow the external flywheel that, if has not slowed down, certainly has made the path of HCV management more problematic to the present day. In fact, there is a new recovery in the United States of intravenous heroin drug addiction, which could be a prelude to the new recurrence of the problem in Italy.

From analysis of available data is more clearly a scenario that relates on one side the entry of HCV into Italy and the role played from drug addicted in this sense, on the other the comparison of the benefits due to the discovery of the virus and to the development of actions for the reduction of risk in the general popula-

tion. Nevetherless, it must be considered the opposite impact that anyway was registered due the drug addiction, able to overcome the magnitude of these advantages because – while being less dangerous in comparison to the current transfusional security – it involves a population that transmits the infection also through sexual relations.

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Review

HCV and immigration in Italy

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Summary. Aim of this survey is to examine the current situation regarding the various migrant populations in Italy, their consistency, their distribution and the known data in terms of prevalence of HCV infection in the countries of origin, possibly distinguishing by age groups, and evaluate the presumed prevalence of HCV infection in the different areas of Italy in relation to the place of departure, in relation to any comparative data already present in Italy. This in order to construct a sort of Italian geographic map - detailed by Regions or by Provinces - of an estimated or predictable number of migrant people, according to the various groups, who carry the HCV infection, in order to provide a summary of information not yet available and which may constitute the starting point for further studies. This is a rather ambitious work because it intends to reason on a composite reality - making it an instrument of dissemination - such as the multifaceted reality of the presence in Italy of migrant populations who arrive or have already arrived from countries of South America, Africa, Eastern Europe of Asia; this in a vision not linked to the current dramatic arrival of immigrants by sea but which falls within a more general context. (www.actabiomedica.it)

Key words: HCV, immigration, Italy

Introduction

Hepatitis C (HCV) is a major cause of liver cirrhosis and hepatocellular carcinoma (1).

The global prevalence of anti-HCV was estimated at 2.0% (1.7-2.3%) among adults and 1.6% (1.3-2.1%) for all ages corresponding to 104 (87-124) million and 115 (92-149) million infections, respectively. The viraemic prevalence was 1.4% (1.2-1.7%) among adults and 1.1% (0.9-1.4%) in all ages corresponding to 75 (62-89) million and 80 (64-103), respectively (2).

A study conduct in 2013 in Europe has estimated that the prevalence of HCV varies between 2,4% for western and Central Europe and 2,9% for Eastern Europe. The global population of this area is approximately 740,000,000 persons leading to an estimation of the HCV infected pool of more than 19,000,000 person. The shortcomings of this and other study reside in the fact that evidence is based on surveys often conducted in selected groups, or excluding high risk population such as prison inmates and groups of persons living in social exclusion. The attributable fractions of cirrhosis for HCV are 38% for Western and 34% for Eastern Europe while those for hepatocellular carcinoma are, respectively, 44% and 15% (3).

Despite the burden HCV imposes on national healthcare systems and budgets, HCV has failed to attract the type and level of attention it calls for from health policy makers, healthcare workers, and indeed the public at large. WHO resolutions (5) and guidelines (6), as well as a meeting by the Viral Hepatitis Prevention Board (7) have all called for more attention to the problem. All these calls for action have mentioned the growing role of migration as a possible driver of the epidemic.

In 2015 alone, over one million migrants, refugees and asylum seekers arrived in Europe, (7) adding to an existing migrant population of around 72 million people (8). Many of them are from countries where both HBV and HCV are significantly more prevalent than

in Europe. The contribution of migrants to the changing epidemiology of HCV in Europe has been referred to in several studies (3, 9-11).

Proportionately high rates of HCV in migrant populations have been reported in Italy, the Netherlands, Sweden and the UK10-13 and in 2014 the ECDC reported that in Spain the prevalence of HCV ranged between 0.4% and 0.9% among migrants from Latin America, 1.9% among migrants from North Africa and between 9% and 15% among migrants from sub-Saharan Africa and Eastern Europe.14 Similarly in Germany, where between 23 and 37% of all reported HCV is in people of foreign nationality, migration from Turkey and Eastern Europe is thought to be an important factor in changing patterns of HCV (17).

Although rates of HCV among migrant populations typically reflect the prevalence of the disease in countries of origin, there are also reports that HCV rates among migrants in Europe are higher than in home countries (18). This suggests that the migration process itself may prompt behaviors that expose migrants to a higher risk of HCV (19-23). Migrants are also represented in other known HCV risk groups, such as prisoners, (24) and men who have sex with men (25).

A common feature among migrants and refugees is also self perceived loss of power and difficulty in making key decisions on health and healthcare seeking (26). Culturally defined attitudes to disease prevention and treatment vary widely and this can easily complicate public health initiatives. Mass migration into Europe is changing the epidemiology of HCV. To what extent countries are prepared to respond to the challenge is not clear. The public health sectors' response to migration has been slow, and in the case of HCV there is little evidence of concerted action. Although studies have shown the cost effectiveness of screening migrants for HCV, only four countries in the EU have adopted migrant screening policies and while there have been some advances in the form of migrant friendly hospitals, migrants on the whole continue to be ignored as a group that has special psychosocial as well as medical needs. If the goal of HCV eradication is to be achieved much more inclusive policies and practices will be required (26). An imperative need now exists for new thinking, increased resources, and better training of health-care staff working with these new populations (27).

Analysis of literature

The starting point of this analysis is represented by the prevalence data of HCV infection in the places of origin of the migrants (being the local ones relative to Italy scarcely available) from which any problems can be extrapolated (a lower prevalence of infection in one present population with greater consistency on our territory implies a greater impact, in absolute numerical terms, of a higher prevalence in immigrants of another nationality not represented in Italy).

Of particular importance is the analysis of prevalence of HCV infection compared to starting populations also according to age groups, since the clinical condition of a fifty year old compared to that of a thirty year old can be very different. Another aspect to consider, in countries of South America or Africa, is the failure to guarantee the rights to health and care for those not covered by social insurance (a condition that can involve more than half of the less well-off), condition which can promote the transmission of the virus. To this end, after an accurate bibliographic research, an analysis of the costs incurred in health by the most significant epidemiological States of the infection in question is reported.

The HCV seroprevalence among immigrants in Italy

The available data on immigration in Italy of HCV-positive subjects are scarce and not uniformly reported to the entire national territory. However, there are many studies that carefully address individual local realities.

A recent retrospective multicentre study with the aim to evaluate the clinical and epidemiological features of HCV infection in a cohort of immigrants in Italy shown that migrant populations had higher rates of HCV-related chronic hepatitis than the indigenous population; in some cases the infections were contracted in the country of origin, but in others the infection

took place in Italy (Table 1). The most commonly represented genotype, besides 1, was 4, especially among Africans. The therapeutic management of immigrants proved to be very difficult, mostly but not exclusively because of social factors (28).

A series of studies have analyzed the changes in the epidemiology of hepatitis C in the various areas of Italy and how immigration has influenced these changes.

In a study conducted by Chiaramonte M. et al. on HBV and HCV infection among non-European Union immigrants in North-East Italy, resulted that among the 933 individuals screened for HCV infection, prevalence of antibody was much lower (0.9%) than that observed in the Italian general population (3.2 in the North-East Italy, 12.6 % in the South Italy). That's why we can consider the risk of HCV spread from non-EU immigrants very low. No significative differences were observed in the prevalence of anti-HCV according to the age group, sex and region of origin (Table 2). The results of this study demonstrate that the prevalence of HCV infection seems to be similar or lower than the host population, while that HBV infection among immigrants from non-UE countries is still very high because of the high endemicity of HBV in the place of origin. This difference depends on the different way of transimission: iatrogenic for HCV and household or sexual for HBV (29).

Another study, conducted in a community of Sub-Saharan Immigrants living in Verona (Northern Italy) made for analyze the epidemiology of HAV, HBV and HCV, revealed that the HCV positivity rate resulted similar to the prevalence of the Italian population: Of the 182 people enrolled, 5 males (2.7%) who had been in Italy since 2003 were HCV positive. Two of them had a history of HBV infection. No specific parenteral risk factors emerged for these subjects, nor there were any significant differences in their sociodemographic characteristics, though they mostly declared a lower educational level and unemployment (30). The prevalence of HCV infection (2.7%) in this immigrants was a little higher than that reported in a similar study (0.9%) carried out in the mid-1990s by Chiaramonte and colleagues, (29) but it is substantially the same as the estimated prevalence in their geographical area of origin (on average around 3.0%) (31). In any case as the most recent Italian data show an HCV incidence rate of 0.5/100,000 and a prevalence rate that ranges from 3% to 26%, (32) there is no evidence of any particular impact of this infection on the autochthonous population.

A study published in 2001 assessed the prevalence of viral hepatitis infections in a sample of Kosovar refugees that arrived in southern Italy as a result of the 1999 war in the Balkans. This study indicate that the level of endemicity of HCV infection in the

Table 1. HCV-RNA positive patients (119) (29)

	No.	%
Sub-Saharan Africa	24	20.2
Asia	17	14.3
East Europe	71	59.6
North Africa	5	4.2
South America	2	1.7

Table 2. Data on the anti-HCV patient subjects (30)

Age (year)	Sex	Region of origin	HBsAg	Anti-HBc ± anti-HBs	Risk factors
21	m	Eastern Europe	−	+	n.i.*
30	m	Latin America	−	+	n.i.
31	f	Eastern Europe	−	+	n.i.
36	m	North Africa/Middle East	−	+	Multiple surgical interventions
19	f	Eastern Europe	−	−	Presence of STD†
29	m	North Africa/Middle East	−	−	Multiple partners
29	f	Eastern Europe	−	−	Occupational
34	m	Latin America	−	−	Multiple partners, HIV +

* n.i., information not available.
† STDs, sexually transmitted diseases.

Kosovar population was low, in fact the prevalence of anti-HCV antibodies was 0.7%, in agreement with the prevalence rates reported in the population of European countries (33).

Another study in 2003 investigated the prevalence of hepatitis infection in a sample of 1005 refugee Kurds from Iraq and Turkey. In this population the HBV infection is moderately endemic, while the prevalence of HCV infection is low. Only the subject that was confirmed positive for anti-HCV (0.1%) and HCV-RNA showed a 4c/4d genotype (34).

In Italy in 2002 was performed a retrospective multicenter study to evaluate the prevalence of hepatitis in hospitalized immigrants in Italy. It was evinced that 282 of the 2255 immigrants analyze were affected by hepatitis (12.5% of total hospitalised patients). The prevalent form was HBV-related (41.6% in chronic forms and 48.4% in acute), while the rate for HCV were less frequent (37.5% in chronic and 3% in acute). The most part of patient were men (59.6%), with a mean age of 34.2 years and come from east-European countries (34.39%). Viral hepatitis are the third infectious diseases evidenced in immigrated population. HBV-chronic hepatitis is the prevalent form in immigrated patients, as expression of absence of vaccine prophylaxis in many countries (35).

A new picture of HCV epidemiology in Northern Italy is instead offered by a study conducted on a cohort of 965 subjects all resident (including 47 immigrants), anonymously tested for HBV and HCV infections: the overall prevalence of anti-HCV was 2.6%, with a bimodal distribution characterized by the highest prevalence (12%) in subjects over 75 years old; none of the subjects under 25 years old was anti-HCV positive; anti-HCV positivity was similar in males and females (2.4% vs. 2.7%); HCV-RNA was positive in 40% of cases and genotype 1 was the most common. A cohort effect showing a reduction of HCV infection in the elderly, possible due to age-related mortality (36).

A huge study based on screening of undocumented migrants or refugees for HBV, HCV and HIV was conducted from January 2012 to June 2013 at four primary-level clinical centers in Naples and Caserta, in Southern Italy: Of the 882 individuals enrolled, 35 (4%) were anti-HCV positive and seven (1%) had more than one infection (Table 3). All participants with a detectable serum marker of HBV, HCV or HIV infection were unaware of their sierological status. HCV infection was more frequent in individual from Eastern Europe 12/198 (6%), and in those from India-Pakistan area 91/126 (7%) then in those from sub-Saharan 17/144 (4%) and Northern Africa 2/80 (2%). In individual from Eastern Europe, anti-HCV positivity was higher in people aged 16-30 years and 31-45 years, whereas non positive individual was observed in older age group. A high prevalence of anti-HCV positivity was also found in all age groups of individuals from the India-Pakistan area. The prevalence of anti-HCV positivity was 9/183 (5%) in individuals from sub-Saharan Africa aged 16-30 years, 7/229 (3%) in those aged 31-45 years and 1/32 in those aged 46/60 years. Of the 68 individuals from Northern Africa tested for anti-HCV, only two were positive, both in the 31-45 age group. Compared with individuals in the subgroup with no serum markers, those in the four aetiological subgroups were less frequently female, had fewer years of schooling and more frequently came from sub-Saharan Africa. In these aetiological subgroups, the percentages of individuals reporting risk factors for acquiring HBV, HCV or HIV were very high but similar to those found in the subgroup with no serum marker, and, Therefore, infection associated risk factors may be difficult to determine. It is noteworthy that many of the infections were detected in individuals who had experience unsafe healthcare practice and that only a few individuals reported drug use or have a blood transfusions. The HBV, HCV and HIV infections in the undocumented migrants and refugees screened serve as a reminder to the Italian healthcare authorities to carry out extensive screening and educational programmes for these populations (37).

A research conducted among refugees hosted in the Bari Palese CARA (Asylum Seeker Centres) in Southern Italy (Apulian Model) to study seroprevalence of viral hepatitis and HIV in 2008, involving 529 refugees, found that 44 individuals (8.3%) were HBsAg positive, 24 (4.5%) anti-HCV positive, and 8 (1.5%) HIV positive. In the opinion of the authors, these results - such many others - confirmed some traditional concerns about migrant health and especially about the control of infectious diseases among these populations and the need to strengthen screening to

Table 3. Characteristics of study participants by geographical area of origin, Caserta and Naples, Italy, January 2012-June 2013 (n = 848) (37)

Characteristic	Northern Africa n (%)[a]	Sub-Saharan Africa n (%)[a]	Eastern Europe n (%)[a]	India-Pakistan area[b] n (%)[a]
Number of patients	80	444	198	126
Mean age in years (SD)	37(8.6)	33(8)	40.4(12.7)	33 (11)
Number who were male (%)	76 (95.0)	366 (82.4)	66 (33.3)	117 (81.9)
Mean length of time living in Italy in months (SD)	91.8(77.2)	53(46.7)	61.8 (46.4)	43(48)
Number of years of schooling (SD)	8.2(4.7)	5.4(5.1)	9.3(5)	8.7(4.5)
Number using alcohol[c] (%)	21 (26.3)	81 (18.2)	24 (12.1)	4 (3.2)
Status in country, n (%)				
Undocumented migrants[d]	47 (58.8)	304 (68.5)	154 (77.8)	97 (77.0)
Refugees	33 (41.2)	140 (31.5)	44 (22.2)	29 (23.0)
Reported risk factors[e] , n (%)				
Use of drugs	1 (1.2)	0 (0)	2 (1.0)	0 (0)
Unsafe sexual intercourse[f]	20 (25.0)	40 (9.0)	19 (9.6)	7 (5.5)
Surgery/dental care/ abortion	60 (75.0)	226 (50.1)	166 (83.8)	10 (7.9)
Blood transfusion	1 (1.2)	8 (1.8)	7 (3.5)	0 (0)
Other parenteral exposure[g]	54 (67.5)	353 (79.5)	154 (77.8)	8 (6.3)
Not stated	0 (0)	0 (0)	0 (0)	101 (80.2)
Serological status, n (%)				
HBsAg positive	2 (2.5)	62 (14.0)	12 (6.1)	4 (3.2)
HBsAg negative/anti-HBc positive	15 (18.7)	253 (57.0)	60 (30.3)	37 (29.4)
Anti-HCV positive	2 (2.5)	17 (3.8)	12 (6.1)	9 (7.1)
Anti-HIV positive	0 (0)	12 (2.7)	5 (2.5)	1 (0.8)
Any serological marker	19(23.7)	320 (72.1)	89 (44.9)	51 (40.5)
No serological marker	61 (76.3)	124 (27.9)	115 (58.1)	75 (59.5)

aid the development of trust between migrants and resident population (38).

In a previous study, also conducted in a population of refugees of various nationalities, living in forementioned Asylum Seeker Centre in Bari Palese, was assessed the prevalence of HIV, HBV and HCV serological markers and the prevalence of VDRL positive subjects . The study was carried out in the period May-July 2008 and recruited only voluntarily enrolled healthy refugees. A total of 529 refugees, 442 males and 87 females, aged between 7 and 52 years, were studied. Of these, 510 were from Africa and 19 from Asia. A total of 24 (4.5%) individuals, 23 males and 1 female were anti-HCV positive. In detail, the figures were 4.3% for African refugees and 10.5% for Asians. A significant proportion (12.3%) of asymptomatic refugees presented with at least one condition potentially associated with long-term complications and risk of secondary transmission (39).

In another study was assessed the seroprevalence of hepatitis B, C and D markers in a sample of 670 Albanian refugees in Apulia, in 1997: the prevalence of anti-HCV antibodies resulted low (0.3%, 95% CI: 0.0-0.7) (40).

Another study aimed to describe the prevalence of HBV, HCV, and HIV infections in a cohort of immigrants living in Palermo, Sicily. The study was carried out in the period May 2006-June 2010 and recruited a total of 393 patients. Overall, 22/393 (5.6%) immigrants were anti-HCV positive and 13/327 (4.0%)

were infected with HIV. Findings from this study suggest that a suitable screening protocol for the viral blood/sexually transmissible diseases is recommended on entering Italy, and the adoption of health control strategies should also be considered to safeguard the health of the local population (41).

Another study was conducted in three areas of Sothern Italy on undocumented migrants and refugees, it was a screening performed from 2012 to 2015, involved 1,727 immigrants in the Campania and Apulia. 70 (4,1%) of 1727 subjects screened were anti-HCV-positive and 55,7% of this resulted positive to HCV RNA. Patients in the anti-HCV/HCV-RNA-positive subgroup compare with those in the other two subgroups more frequently came from Northern Africa and more frequently declared risk factors associated with parental transmission of HCV infection (Tab.4). The 35,5% of cases showed HCV-genotype 1a or 1b, 23,8% genotype 2 and 22,6% genotype 3. Clinically: 11 (35,5%) HCV-RNA-positive cases were HCV inactive chronic carriers, 18 (58,1%) had chronic hepatitis and 2 (6,4%) liver cirrhosis (42).

The prevalence data of HCV infection in the places of origin of the migrants

According to WHO estimates, an estimated 500 million are living with chronic viral hepatitis, making HBV and HCV one of the top 10 infectious diseases killers globally (43). A recent review that have analyzed data between 2000 and 2015 showed that globally the prevalence and number of HCV infected patients, if compared to a similar study concerning the period 1990-2005, has decreased from 2,8% to 2,5% and from 185 to 177 millions. It's interesting to note that the most relevant decrease has been observed in the high income zones, especially in Western Europe, Southern Africa and Australasia, whereas a massive increase it's reported in some of the low income areas of Central Africa and Central Asia (44).

A meta-analysis published in 2015 that have evalueted seroprevalence of Hepatitis C Antibodies suggest that migrants from intermediate or high HCV prevalence countries represent an important risk group for HCV infection. The overall pooled anti-HCV seroprev-

Table 4. Demographic and initial characteristics of the 1727 immigrates according to HCV sierology and viraemia (42)

	Anti-HCV-positive/ HCV-RNA-negative subjects (A)	Anti-HCV/ HCV-RNA-positive subjects (B)	Anti-HCV-negative (C)	P value
Patients (n)	39	31	1,657	
Age, years, mean ± SD	30 ± 8.2	32.9 ± 7.8	32.1 ± 10.3	0.432
Males, n (%)	35 (89.7)	25 (80.6)	1,315 (79.4)	0.133
Legal status, n (%):				
Undocumented migrants	22 (56.4)	25 (80.6)	1,076 (65)	0,10
Low-income refugees	17 (43.6)	6 (19.3)	581 (35)	
Country of origin, n (%):				0.0306
Eastern Europe, 261 cases	4 (10.2)	11 (35.5)	246 (14.8)	
Northern Africa, 94 cases	1 (2.6)	1 (3.2)	92 (5.5)	A - > B: 0.02653
Sub-Saharan Africa, 990 cases	26 (66.7)	9 (29.0)	955 (57.6)	A - > C: 0.0017
India-Pakistan area, 353 cases	7 (17.9)	9 (29.0)	337 (20.33)	B - > C: 0.0001
Other countries, 29 cases	1 (2.6)	1 (3.2)	27 (1.6)	
In Italy for months, mean ± SD	32.2 ± 41.1	49.5 ± 52.7	38.9 ± 50	0.237
Years of schooling, mean ± SD	7 ± 3.6	6.4 ± 3.9	6.7 ± 4.8	0,520
Declared risk factors,* n (% by column)				0,0001
Drug addiction	0	3 (9.7)	5 (0.3)	A - > B = 0,001
Unsafe sexual intercourse	11 (28.2)	6 (19.3)	408 (24.6)	A - > C: 0,02
Surgery, dental care, abortion	10 (25.6)	27 (87)	774 (46.7)	B - > C: 0,001
Blood transfusion	0	0	21 (1.3)	
Other parenteral exposure**	16 (41.0)	31 (100)	1,216 (73.3)	
Not declaring risk factors	5 (12.8)	0	88 (5.3)	

** Not mutually exclusive. ** The term other parenteral exposure includes unsafe therapy injection, acupuncture, tattoo, piercing and tribal practices.*

alence in migrants in this study was 1.9% (1.4%-2.7%). Globally, anti-HCV prevalence is highest in Asia, Africa, Eastern Europe, and North Africa & the Middle East, ranging from 2-4%, whereas in North America, Latin American & the Caribbean, most Western European countries and Australia, the anti- HCV prevalence is less than 1.5%. The regional HCV seroprevalence estimates for migrants from this meta-analysis were similar or slightly lower than the corresponding HCV seroprevalence estimates from the WHO in the general population in their regions of origin with the exception of Sub-Saharan Africa and South Asia (Fig.1) (45).

Globally, Egypth has the highest prevalence of HCV, with some studies reporting HCV antibody positive rates of up to 15%, with an estimated 10% with chronic viremia.

The largest population of HCV patients worldwide resides in East Asia and the Indian subcontinent, with at least 100 million HCV positive individuals in this region.

The prevalence of HCV in North America and Western Europe is comparatively lower. HCV transmission in Europe and North America is predominantly through IDU. At least 7.3 million people (1.1%) are estimated to be living with HCV in Europe. Estimates suggest that 5.2 million people are anti-HCV positive in the United States. These figures likely underestimate the true prevalence in both regions. These data reveal large differences in the prevalence of these chronic liver diseases among migrant groups and the host nations. In an era of increasing migration, these differences in HBV and HCV prevalence between regions have important implications for public health agencies in host nations. According to UN estimates, the total number of international migrants in 2013 was 231.5 million, making this group larger than the 5th most populous nation. In 1990, 154 million people, or 2.9% of the global population were migrants, whereas the corresponding figure for 2013 was 3.2%. These numbers do not include undocumented migrants of

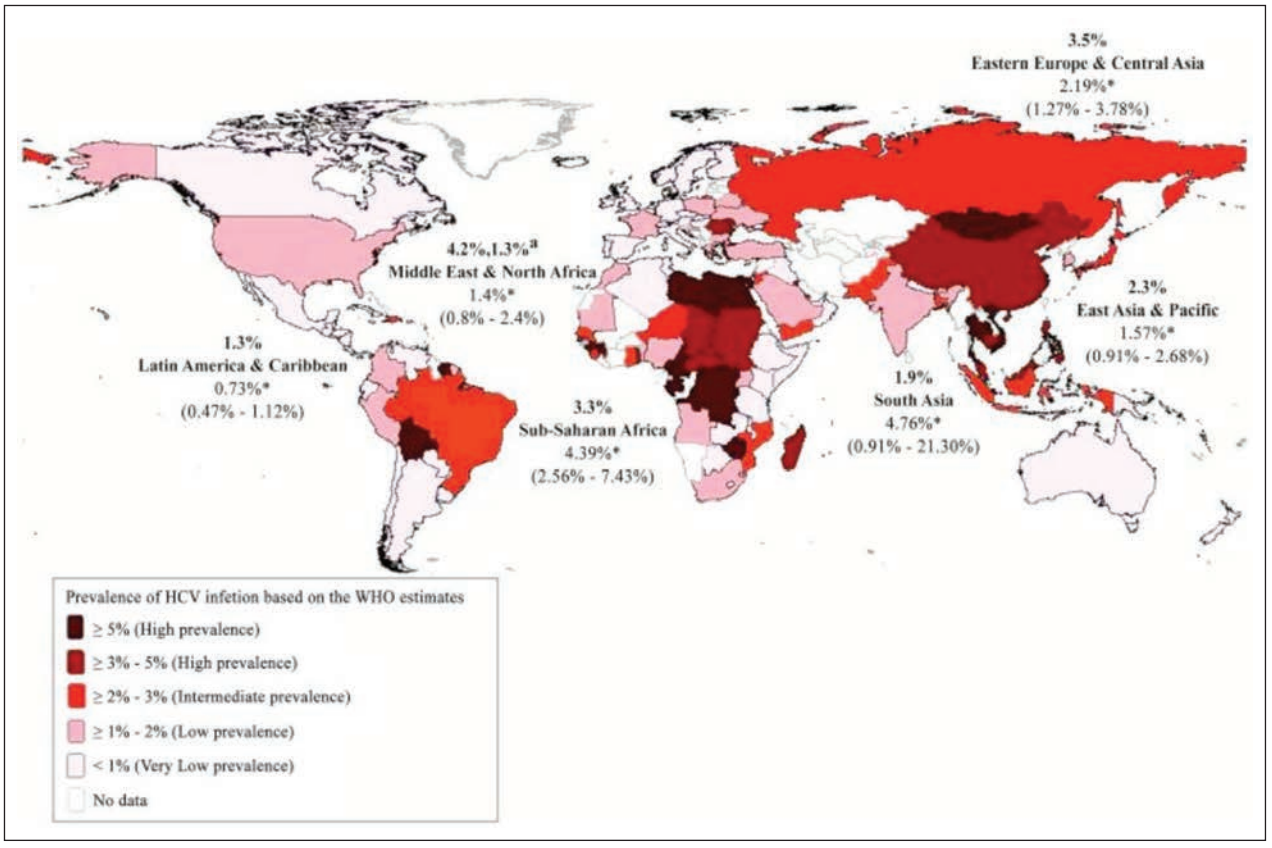


Figure 1. Anti HCV Seroprevalence stratified by region of origin (map) (45)

trafficked persons, and therefore likely underestimate the global migrant population. Many of these migrants move into and remain part of ethnic minority groups where traditional social and cultural behaviors that may have adverse implications for exposure to HBV and HCV are reinforced and persist (16).

Szabo et al. systematically reviewed 25 articles presenting population-based estimates of HCV prevalence from general population or blood donor samples, and supplemented those with publically-available data, to estimate the total number of persons infected with HCV in Latin America at 7.8 million (2010) (46). Of these, 4.6 million would be expected to have genotype 1 chronic HCV. Finally, they calculated that between 1.6 and 2.3 million persons with genotype 1 chronic would potentially benefit from current treatments, based on published estimates of genotype-epidemiologic burden of HCV (46).

Studies focused only on the presence of HCV antibodies generally overestimate the disease burden because they include also patients who have been cured, either spontaneously or through treatment. So, although antibodies to HCV (anti-HCV) are at present the most commonly available marker of HCV infection, used both to estimate its prevalence and to compare HCV infection levels globally, the most important indicator of HCV diffusion seems to be its classification into different genetic variants. At present, in fact, the length of the therapy and the opportunity to associate interferon and/or ribavirin with the new direct-acting antiviral (DAA) therapies still remain partially dependent on HCV genotype. Up to now, HCV is classified into seven recognized genotypes on the basis of sequence of the viral genome.

A recent review of the 2016 tried to quantify global anti-HCV prevalence, viraemic rate and genotype distribution to generate a global estimate of HCV burden disease. From this study results that total global HCV prevalence is nearly 2,5% (ranging from 2,9% in Africa and 1,3% in Americas), the global viraemic rate is 67% and the most prevalent HCV genotype is 1 (49,1%) followed by genotype 3 (17,9%). While genotypes 1 and 3 are common worldwide, the largest proportion of genotypes 4 and 5 is in low-income countries. Below we report tabs (Tab.5-7) and graphics that show the results of this study (44).

In particular the grapichs below show the situation in Europe.

An European Study contributes to secondary prevention planning in the European Union/

European Economic Area (EU/EEA) by estimating the number of CHC (anti-HCV positive and viraemic) cases among migrants living in the EU/EEA and born in endemic countries, defining the most affected migrant populations, and assessing whether country of birth prevalence is a reliable proxy for migrant prevalence. Anti-HCV prevalence in the general population in the EU/EEA is estimated at 1.4% (range of 0.7-2.2%). However, prevalence estimates range from 0.2% in the Netherlands to 4.4% in Italy and 14 EU/EEA countries are considered endemic by the definition adopted in our study (≥1% anti-HCV prevalence). So Italy was considered both endemic area and host country. The migrant populations account for approximately 10.7% of the total adult population in the EU/EEA although the proportion in each country varies. Nearly 80% of the total migrant population were born in HCV endemic countries. The number and propor-

Table 5. Global Anti-Hepatitis C virus prevalence and numbers of infected individuals (44)

Continent	Anti- HCV prevalence (%)	Viraemic rate (%)	2013 population (millions)	Anti- HCV infected (millions)	Viraemic HCV infected (millions)
Africa	2.9	70.5	927.0	26.9	19.0
North Africa/Middle East	2.7	68.8	469.0	12.7	8.7
America	1.3	74.0	953.7	12.4	9.2
Asia	2.8	64.4	3985.0	111.6	71.9
Australasia	1.8	74.8	28.0	0.5	0.4
Europe	1.8	72.4	742.5	13.4	9.7
Total	2.5	67.0	7105.2	177.5	118.9

HCV: Hepatitis C virus.

Table 6. Regional estimates of Hepatitis C virus seroprevalence and viraemia (44)

Regions	Anti-HCV prevalence (%)	Viraemic rate (%)
Central Sub-Saharan Africa	6.0	68.5
EastSub-Saharan Africa	2.4	65.0
Southern Sub-Saharan Africa	0.9	69.0
WestSub-Saharan Africa	2.4	79.6
North Africa and Middle East	2.7	68.8
North America, High Income	1.2	75.7
Caribbean	1.5	70.0
Andean Latin America	1.2	70.0
Central Latin America	1.4	75.8
Southern Latin America	1.5	79.5
Tropical Latin America	1.6	80.2
Central Asia	5.8	48.7
East Asia	2.8	63.6
Pacific Asia, High-income	1.1	70.5
South Asia	2.5	78.5
Southeast Asia	1.6	60.5
Australasia	1.8	74.8
Europe, Central	1.3	76.6
Europe, Eastern	3.1	69.6
Europe, Western	0.9	71.0

tion of all migrants that come from endemic countries, at country level and in the EU/EEA as a whole are shown in Graphic below (Graphic 2) (47).

Across the EU/EEA, the overall anti-HCV prevalence among migrants from endemic countries is estimated at 2.3%, which corresponds to a CHC prevalence of 1.6% and an estimated 580,000 CHC infections. Table 8 lists the ten migrant populations with the highest estimated number of CHC cases and the host EU/EEA countries with the largest populations of migrants born in these countries.

The relative proportion (and range) of infected migrants from endemic countries within the overall CHC burden in EU/EEA countries is shown in the Graphic below (Graphic 3).

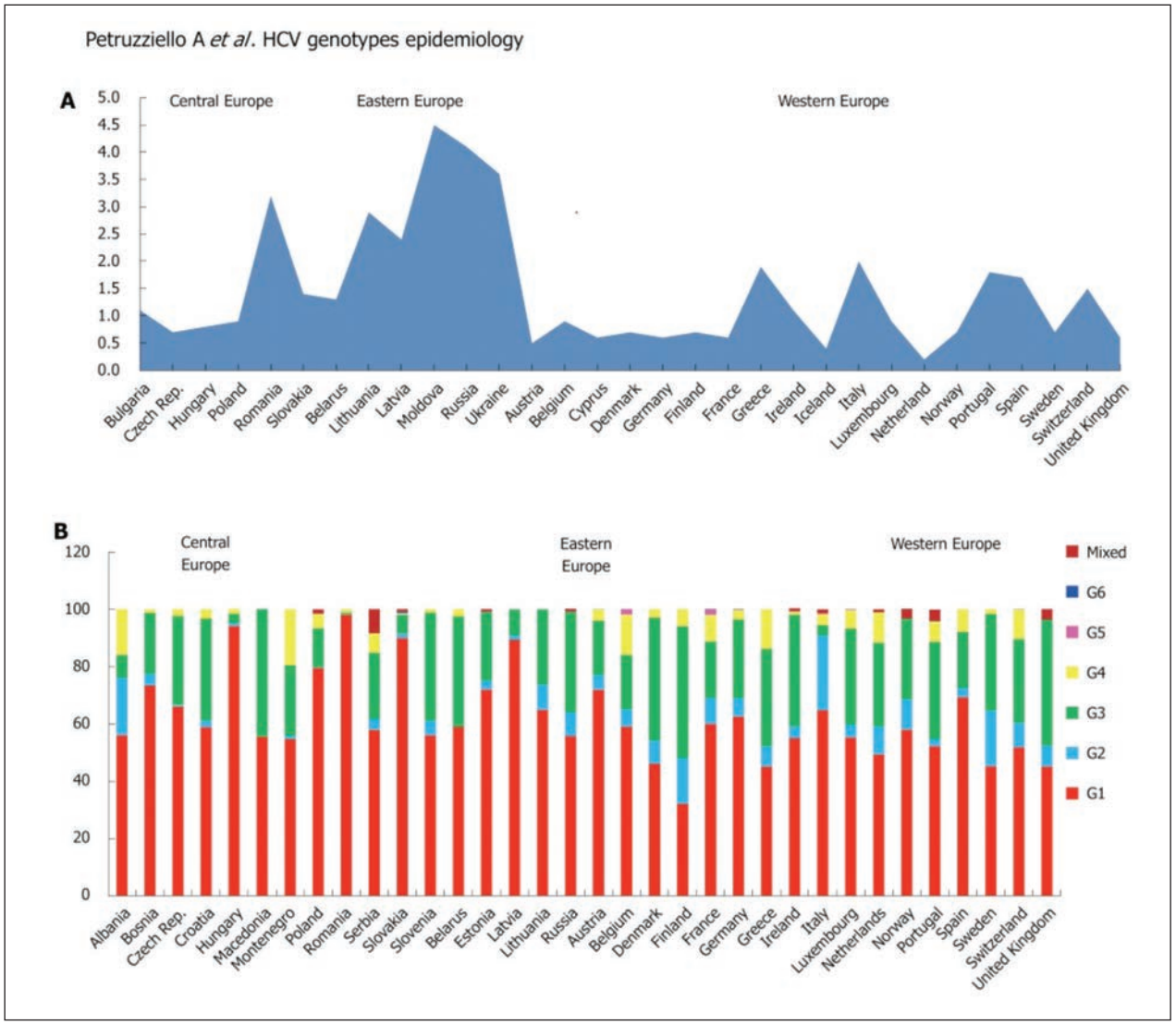
In particular, considering Italy like host country, from this study result that, nearly 10% of migrant population is born in endemic countries; the migrant groups accounting for the highest number of CHC cases are Egypt, Romania, Russia, Polonia, Marocco, Pakistan, Ucraine, Kazakhstan, Nigeria; the relative contribution of migrants to the total number of CHC cases is nearly 4-5% (47).

Discussion

From the data of this work (and from the review on HCV and drug addiction), it is possible to identify the extent of interventions that can be envisaged in the

Table 7. Regional estimates of hepatitis C virus Genotype

Regions	G1 (%)	G2 (%)	G3 (%)	G4 (%)	G5 (%)	G6 (%)	Mixed
Central Sub-Saharan Africa	12.3	4.0	0.8	82.9	-	-	-
East Sub-Saharan Africa	36.2	26.8	7.4	16.6	13.0	-	-
Southern Sub-Saharan Africa	31.4	1.2	12.6	12.4	35.7	-	6.7
West Sub-Saharan Africa	25.5	62.9	4.4	0.6	-	-	6.6
North Africa and Middle East	27.3	0.8	6.3	65.3	0.3	-	-
North America	66.3	13.1	15.7	4.3	-	0.6	-
Caribbean	83.0	7.2	2.1	0.6	-	0.1	7.0
Andean Latin America	86.0	2.0	10.0	-	-	-	2.0
Central Latin America	74.6	21.6	3.3	0.1	0.1	-	0.3
Southern Latin America	72.0	13.3	13.5	0.9	0.1	0.1	0.1
Tropical Latin America	64.8	4.6	30.2	0.2	0.1	-	0.1
Central Asia	70.4	8.6	19.6	-	-	-	1.4
East Asia	53.5	31.7	5.4	0.1	-	3.3	6.0
Pacific Asia, High-Income	58.7	39.7	0.4	0.1	-	0.5	0.6
South Asia	15.5	1.9	66.7	3.7	0.1	0.5	11.6
Southeast Asia	35.2	11.1	19.9	0.9	0.4	30.8	1.7
Australasia	55.0	6.5	36.0	1.2	-	1.3	-
Central Europe	70.0	3.2	21.0	4.9	-	0.1	0.8
Eastern Europe	68.1	4.3	26.6	0.5	-	-	0.5
Western Europe	55.1	8.9	29.0	5.8	0.2	0.1	0.8

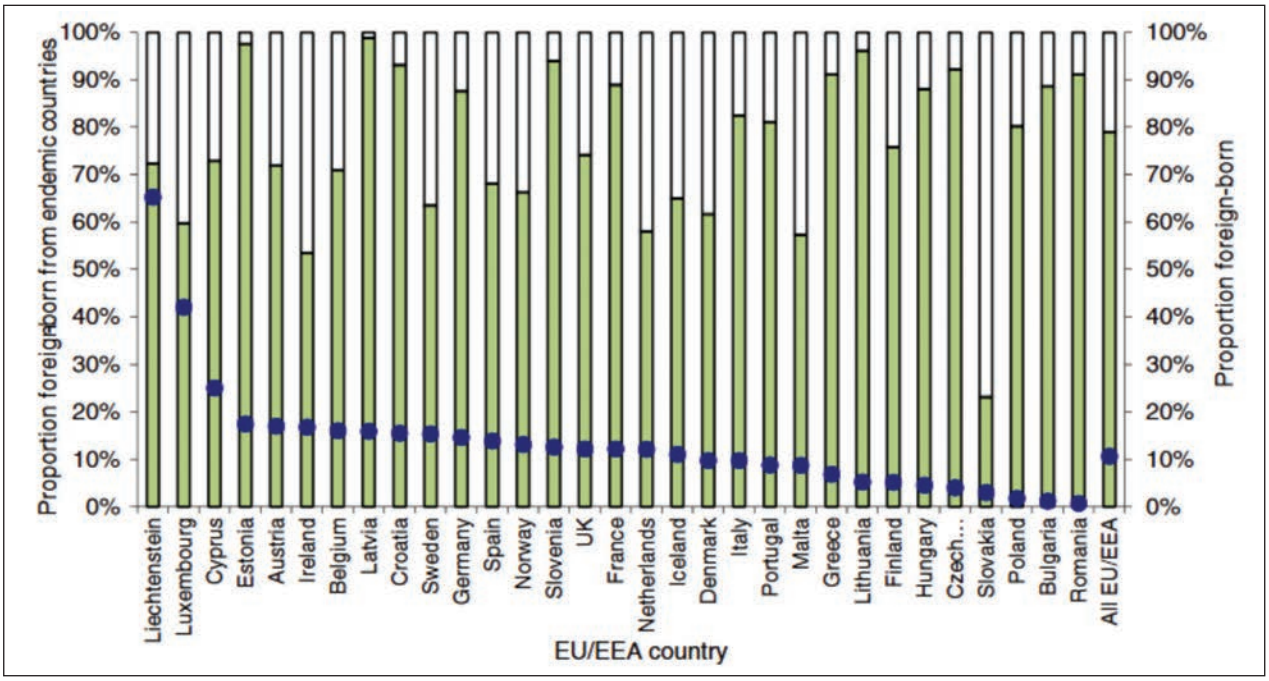


Graphic 1. Anti-Hepatitic C virus prevalence (a) and genotype distribution(b) in Europe (44)

general view of elimination of HCV from the country, which can be substantially theoretically implemented the use of eradicating drugs. In this sense it is possible to proceed with a general population or with a view of a special population. The special populations, precisely because they are delimited, could be an element of intervention from a more immediate part, because they investigate where HCV is expected and a survey is also made to evaluate the emergence of the submerged, on the other they can being an element of greater refractoriness for a number of reasons (many migrant populations, as well as drug addicts, are not easy to manage). To this, in relation to this specific work, other considerations must be added.

Although many data suggest that HCV infection could be eliminated in the next 15-20 years with focused therapeutic strategies, a good understanding of HCV infection should be required to develop strategies to prevent new infections (44).

To achieve the ambitious elimination targets set out by the WHO of a 90% reduction in new infection and a 65% reduction in mortality from viral hepatitis by 2030, significant scale up of our current effort will be required. Effective therapy was critical to even con-



Graphic 2. Total (%) migrant population in each EU/EEA country and the proportion born in endemic countries (47)

Table 8. The ten migrant groups (from endemic countries) accounting for the highest number of CHC cases (47)

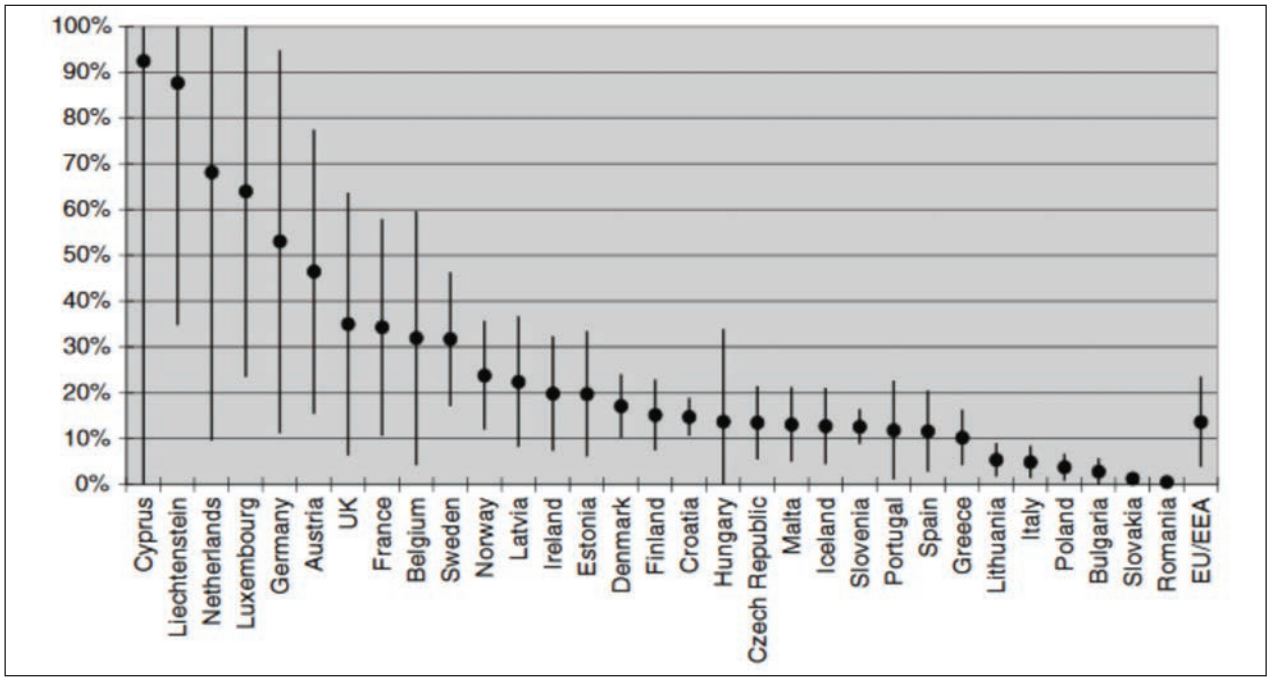
Migrant country of birth	Total adult migrant population	Anti-HCV prevalence	Number (rounded) of CHC cases	Host countries (first 6 with largest populations)[a]
Romania	2,646,392	3.2	59,000	Italy, Spain, Germany, Hungary, UK, Austria
Russia	1,713,636	4.1	49,000	Germany, Latvia, Estonia, Italy, Lithuania, Spain
Italy	1,114,683	4.4	34,000	France, Germany, UK, Belgium, Spain, The Netherlands
Poland	4,103,409	1.1	32,000	Germany, UK, Italy, France, Ireland, The Netherlands
Morocco	2,418,072	1.6	27,000	France, Spain, Italy, Belgium, The Netherlands, Germany
Pakistan	756,170	5.0	27,000	UK, Italy, Spain, Germany, Greece, France
Ukraine	993,459	3.6	25,000	Poland, Germany, Italy, Czech Republic, Spain, Latvia
Egypt	194,852	15.7	21,000	Italy, UK, France, The Netherlands, Austria, Greece
Kazakhstan	807,781	3.3	19,000	Germany, Latvia, Czech Republic, Poland, Lithuania, Estonia
Nigeria	313,212	8.4	18,000	UK, Italy, Spain, Ireland, Austria, The Netherlands

[a]if migrant population is at least 1000

sider elimination but it is important to recognize that therapy is necessary but entirely insufficient on its own to achieve elimination. HCV disproportionately affects marginalized people, like migrants and refugees, but high quality data from such populations are very limited. Such individuals often have very limited or no access to primary health care (48).

Patients in early stages of the disease are generally asymptomatic, and therefore most

patients present in the late stages of HCV disease, when treatments are less effective and complications or death are unavoidable. In recent years, highly effective but very expensive curative treatments have emerged. Early diagnosis and treatment may limit the burden



Graphic 3. Estimated relative contribution (upper/lower range) of migrants to the total number of CHC cases (47)

of the disease in the EU/EEA, for example is necessary to screen migrants when HCV prevalence in their countries of origin is higher than those of European settlement countries. Defining high prevalence regions and determining the effectiveness, acceptability, cost and affordability of screening and treatment from both an EU/EEA migrant and a public health perspective are necessary (49).

A recent review supports the effectiveness and cost-effectiveness of HCV screening in populations at risk for HCV infection, including migrants from intermediate and high HCV prevalence countries (anti-HCV ≥ 2% and ≥5%, respectively). Migrant populations in the EU/EEA face difficulties accessing care and treatment as a result of numerous barriers at the patient, provider, and health system level. To reach HCV elimination goals in the EU/EEA dramatic scale up of HCV testing with diagnosis of all groups at HCV risk, including migrants, and linking those found to be positive to care and treatment will be required. Migrants living in the EU/EEA bear a disproportionate burden of HCV . They are older and more likely to have advanced liver disease and hepatocellular carcinoma compared to non-migrants at the time of HCV diagnosis. The data suggest that early screening of migrants based on the HCV prevalence in the country of origin with linkage to care and treatment could prevent liver related sequelae in the migrant population and would be cost-effective (50).

Other authors, already mentioned, say that in countries where HCV prevalence is high in the general population and the contribution of migrants is low, it may be more cost-effective to implement population-based screening (47).

Conclusion

Italy is a country that has fought hard to allow the diagnosis of HIV free of charge but the infectivologists are now also struggling to ensure the free diagnosis of HCV to the general population since, on this front, foreigners are more likely to be present temporarily in our country while a citizen must pay the exam. Therefore, also to act in a ministerial context in this field, the contained here constitute a possible basis for discussion, since we are able to tell the decision-makers of the health policies the reality we know and, broadly

speaking, what can be expected from the epidemiological profile as a consequence of the implemented interventions.

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For a program of eradication of hepatitis C in the populations at risk (drug users and convicts)

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Summary. Injection drugs are the greater source for HCV infection. About 60% of drug users and about 20-30% of convicts are infected with HCV. HCV infection is often associated with behavioral disorders and drug use. At present, few subjects with HCV belonging to risk groups have been treated with Direct-Acting Antivirals (DAAs). SerDs and prisons should implement the screening for HCV. HCV populations at risk can be successfully treated with DAAs. The primary objective of the linkage to care is the holistic and integrated treatment, and the prevention of reinfections is a priority and essential part of the treatment goals. The removal of the barriers to treatment is a primary goal of the linkage-to-care models and integrated systems; the main action to be undertaken for the linkage to care of the HCV population at risk are screening, referral, treatment and prevention of reinfection. All HCV RNA+ patients may be eligible for treatment, and those with the clinical criteria for starting treatment should be treated with DAAs. All patients should receive a structured harm-reduction program (with skill training). The prevention of the infection is of paramount importance in the linkage to care of the HCV population at risk and is an element which should always be associated with the drug treatment. (www.actabiomedica.it)

Key words: HCV, drug users, direct-activing antivirals (DAAs)

Introduction

Data recently published in the scientific literature identify in the drug use (particularly if intravenous) the most important risk factor for the transmission of HCV, also highlighting how addicts are the most important source of the disease. Another population at risk is the convicts, especially because most of them (34.1% in Italy) have a history of drug use (1).

From the epidemiological point of view, the United Nations estimated that at global level there are about 12 million drug abusers, who inject drugs intravenously (the so-called PWIDs – People Who Inject Drugs) (2). Of these, about 6,000,000 are HCV+, while 80% of HIV+ PWIDs are co-infected with HCV (2).

European data show that 67% of PWIDs – that is, approximately 3 million people – are anti-HCV+ (3). The data also indicate that in Europe 49% of infected PWIDs are not diagnosed (4).

Injection drug use is therefore the most important risk factor for the transmission of the infection. Reports issued by the authority in charge of the protection of the world's health also show that injection drug use is responsible for 23% of the new infections (5)

and that each PWID with HCV infection can infect at least 20 other consumers, within the first 3 years of the start of the infection (6). These data therefore document how PWIDs currently represent the major reservoir of the disease and the main source of infection.

In 2016, the SerDs (*Servizi per le dipendenze* – "Addiction Services") took charge of 143,271 users (2), while it is estimated that about twice as many are the users who are not cared by the Services, but would need a treatment anyway. In other words, in Italy there would be at least 450,000 high-risk consumers, i.e. subjects who, as a result of their problematic use of drugs, could suffer from serious negative consequences (also in infectivological terms) for their health. The data from the Annual Report to Parliament 2017 show that, out of the approximately 150,000 subjects cared by the SerDs, at least 27% are PWIDs (a probably underestimated data), and more than 70% are poly-consumers.

The exact prevalence of HCV in drug users in Italy is unknown. A recent epidemiological study conducted on 21 Italian SerDs which involved 543 drug users showed that 63.9% of users are anti-HCV+ (7). According to this data, it can be assumed that in Italy among the 150,000 users already in treatment in the SerDs, at least 90,000 are HCV+. This figure could go up to 270,000 subjects, when one considers that about 300,000 are the users still not treated by the SerDs and who may require being managed.

Similarly, there are no reliable data on the prevalence of hepatitis C in convicts, but certainly among them the behavior at greater risk for contagion of infection is drug consumption (particularly intravenously), followed by the practices of tattoos and unprotected sex (8). The official figures from the Department of Penitentiary Administration indicate that, in the course of 2016, 101,995 people were restricted to the 190 Italian Penitentiary Institutes, with daily presences oscillating between 53,000 and 55,000. A review of the literature on the prevalence of HCV in prisons quantified the prevalence of infection in a percentage between 22.4% and 38% of the entire prison population (8). These data indicate that it is likely that in the Italian prisons up to 30-35,000 anti-HCV+ subjects may transit each year.

SerDs must implement the activities of screening and diagnosis of HCV infection. The data from the Annual Report to Parliament 2017 indicate that in 2016 the SerDs tested for HCV only 20.5% of their users; 9% of these were positive.

The test for hepatitis C is available in all Italian prisons, but few of them actually manage to test a significant proportion of prisoners. As with the SerDs, the most important reasons limiting the systematic screening of prison inmates are logistical and organizational.

Direct-Acting Antivirals (DAAs) for the treatment of HCV infection represent a huge opportunity to implement the linkage to care of drug users and to improve treatment outcomes (9). More generally, the availability of therapeutic tools capable of eliminating the HCV infection in the patient could allow to develop integrated models of treatment able to implement the screening, prevent reinfections through the increase of harm-reduction actions and improve the quality of life of patients (10). In high risk populations, such as drug users and detainees, DAAs may also be a therapeutic tool that can offer a potential value also as a disease prevention measure (11,12).

Populations at risk, such as drug users and prisoners with HCV infection, can be successfully treated with DAAs. Today, data in the literature indicate that in PWIDs the Sustained Virologic Response (SVR) rate with DAAs is entirely comparable with the general population infected (13), i.e. higher than 98%.

Today in Italy, access to care is ensured to all persons with HCV, regardless of the degree of disease severity (14).

However, at present it is still difficult to reach many of those infected with high-risk behavior – precisely those subjects who, in terms of public health, should be the primary target for the treatment of the disease – and to enable the achievement of the important goal of the eradication of the infection starting from 2030, as suggested by WHO.

Several clinical experiences have shown that drug users, along with the subjects with psychiatric problems, are at a higher risk of developing HCV infection (15). At the same time, there is also evidence showing that people with HCV have a higher chance of developing psychiatric problems (especially depression) and drug use (15,16). More generally, the evidence shows that (16):

- psychiatric co-morbidity and drug use are more prevalent in patients with HCV infection, rather than in the general population
- psychiatric co-morbidity and drug use are associated with a greater risk of contracting HCV infection
- some psychiatric symptoms (eg. depression, neuropsychological deficits) and the use of substances (eg. alcohol) are most frequently associated with HCV infection
- chronic HCV infection can lead to severe psychological "distress" (stigma, anxiety, decreased quality of life)
- chronic HCV infection has significant effects on the neurotransmission at central level, through inflammation mediators
- HCV can penetrate the brain and replicate.

The primary objective for the linkage to care of the subjects belonging to the population at risk, with HCV infection, is the development of a holistic and integrated treatment model able, among other things, also to facilitate access to treatment (17).

Evidence suggests that the development of an "intense" relationship between therapist and patient can produce an appreciable increase in the adherence to treatment (18). The literature and clinical experience have shown that integrated models capable of developing a strong synergy between specialists, through the production and implementation of common procedures and guidelines, can facilitate the access to care for populations at risk (19). Then again, there are many evidences showing that the treatment for hepatitis C in populations at risk can both facilitate the effectiveness of the linkage to care and enhance lifestyles, thus reducing risk behaviors, such as the consumption of substances, and also the commission of crimes (20).

One of the most critical aspects of the treatment of hepatitis C in the populations at risk could be the topic of reinfection. Studies conducted during the interferon era estimated that the risk of reinfection in PWIDs is low, and corresponds to a rate of 2.4 per 100 subject-years (21). In this regard, studies have also shown that the lowest rates are precisely in the North European Countries, where harm-reduction measures are most common and better applied (21). In this regard, harm-reduction measures have been shown to minimize the likelihood of reinfection in the population at risk (22).

The current situation in Italy emphasizes the significant and critical barriers that currently prevent at-risk populations from accessing the treatment for hepatitis C. The most important of these barriers are those which regard: the low screening rate in the population at risk; the systemic lack of an interdisciplinary integrated organization for the linkage to care of patients with HCV, consisting of SerD specialists, prison doctors and hepatologists and infectivologists; the concern about the risk of reinfection (23).

The literature and clinical experience indicate that the main actions to remove the obstacles that prevent the treatment of HCV infection in PWIDs are the following (24):

- develop integrated health and social interventions
- create multidisciplinary interventions, which contain elements of prevention, protection of the patient and the community and fight against the stigma
- facilitate access to treatment, through the development of proximity interventions
- implement the creation of local care networks (connected with the hospitals), such as to facilitate linkage to care and access for people at all levels of health needs, including substitution treatment
- implement programs of individual interventions, focused on the person.

In this regard, the integrated linkage to care of the subject at risk for HCV infection could be a major challenge for modern health care systems, as well as a strong paradigm of integration between hospital and territory, such as to allow an equity of access to health care among all subjects infected with HCV but, above all, to allow the achievement of the important public health goal of eradication of the disease by 2030.

The linkage-to-care structural elements

Clinical experience and evidence from the literature indicate that the main actions to be undertaken for the linkage to care of the HCV population at risk are:

- screening

- referral
- treatment
- prevention of reinfection (through harm-reduction actions).

In this sense, according to the various indications provided by the literature and clinical experience, it seems a priority to propose algorithms for the linkage to care of the HCV population at risk, in order to facilitate the implementation on the territory of networks and effective and efficient organizational models.

Algorithms for the linkage to care of the HCV population at risk

The screening phase (Fig. 1) must be characterized by the following essential elements, that facilitate the execution of the test on the part of the patient, and which consist in the ability by SerDs and Prisons to:

- perform blood samplings for the conventional diagnosis of the disease, possibly with the use of rapid tests also
- inform about the disease, the treatments and the mode of infection (through brochures, websites, public information campaigns, also on social networks)
- provide the user with psycho-educational and motivational counseling, able to optimize the patient's adherence to the test
- offer organizational systems able to ensure to the users the access to and the execution of the test, both at the beginning and then periodically during the linkage to care, so as to be able to intercept in the therapeutic context also any new infections or reinfections.

• Screening for HCV should be **offered to all drug/substance users**

• The screening proposal should be **accompanied by a psycho-educational and motivational counseling**

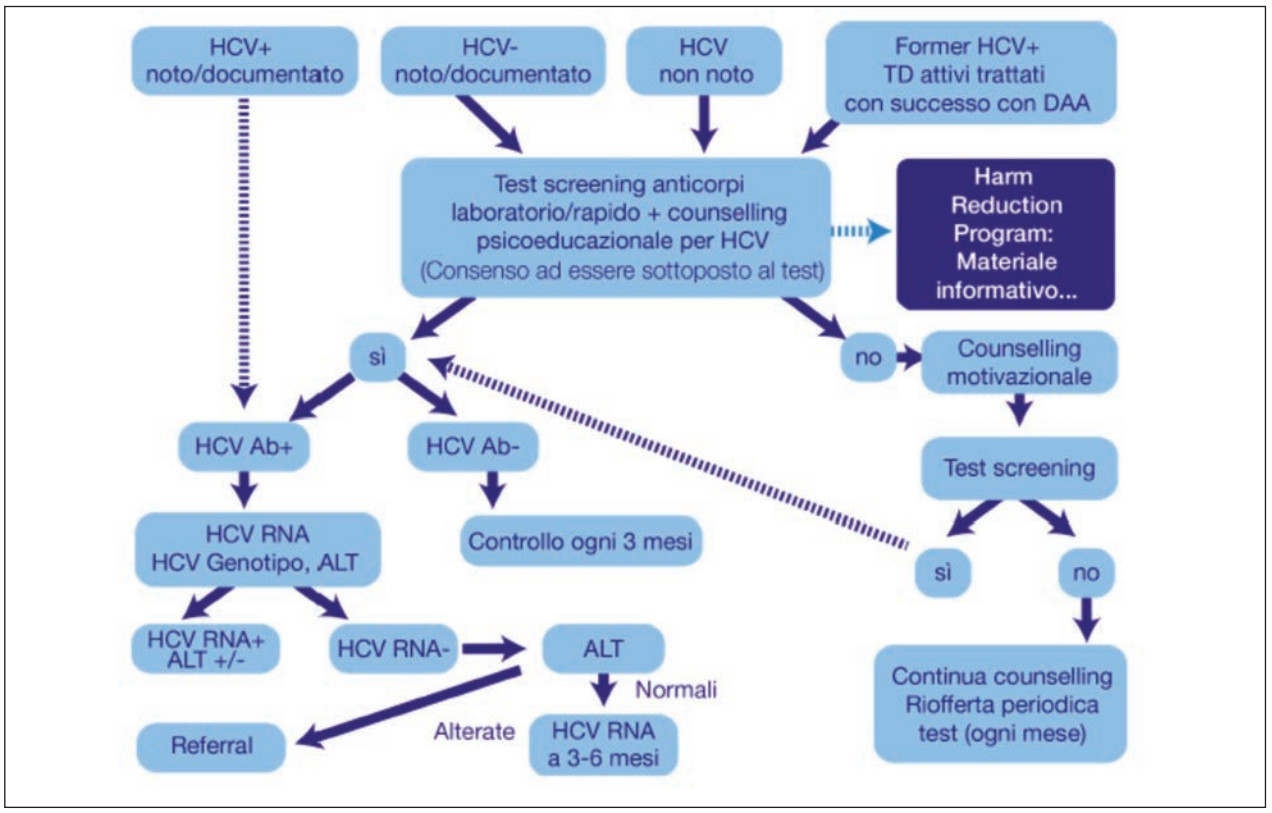

Figure 1.

- The screening proposal should be **associated with the spreading of information about the disease, the treatment and the modes of contagion**
- The screening, **if negative, should be reproposed periodically (at least every three months)**
- The screening, **if refused, should be reproposed periodically, combined with a motivational counseling (at least monthly)**
- **The screening should be proposed to active consumers successfully treated with DAAs for the early detection of reinfection (at least every 3 months)**

The referral phase (Fig. 2) is characterized by the following essential elements, that are intended to motivate the patients to the treatment and to facilitate their contact with the hepatologist-infectious disease specialist; these elements are:

- the patient's motivation to treatment, through motivational interviewing techniques
- the transfer to the patient of basic harm-reduction principles (in order to limit the consequences of the disease, both for themselves and for the community, also in terms of prevention of reinfection)
- the development of organizational models that include the referral, preferably in the same place of the user's linkage to care (SerD or Prison)
- the referral of the patient to a specialist only when "ready" for the treatment from a motivational point of view (while the patient who is still "not ready" should be kept linked to the Service through motivational interviewing techniques aimed at the information and the development of the relationship)
- the periodic proposal of being referred to a specialist for the patients who refuse treatment.

- **All patients eligible for treatment should be referred to the specialist** (infectivologist/hepatologist)

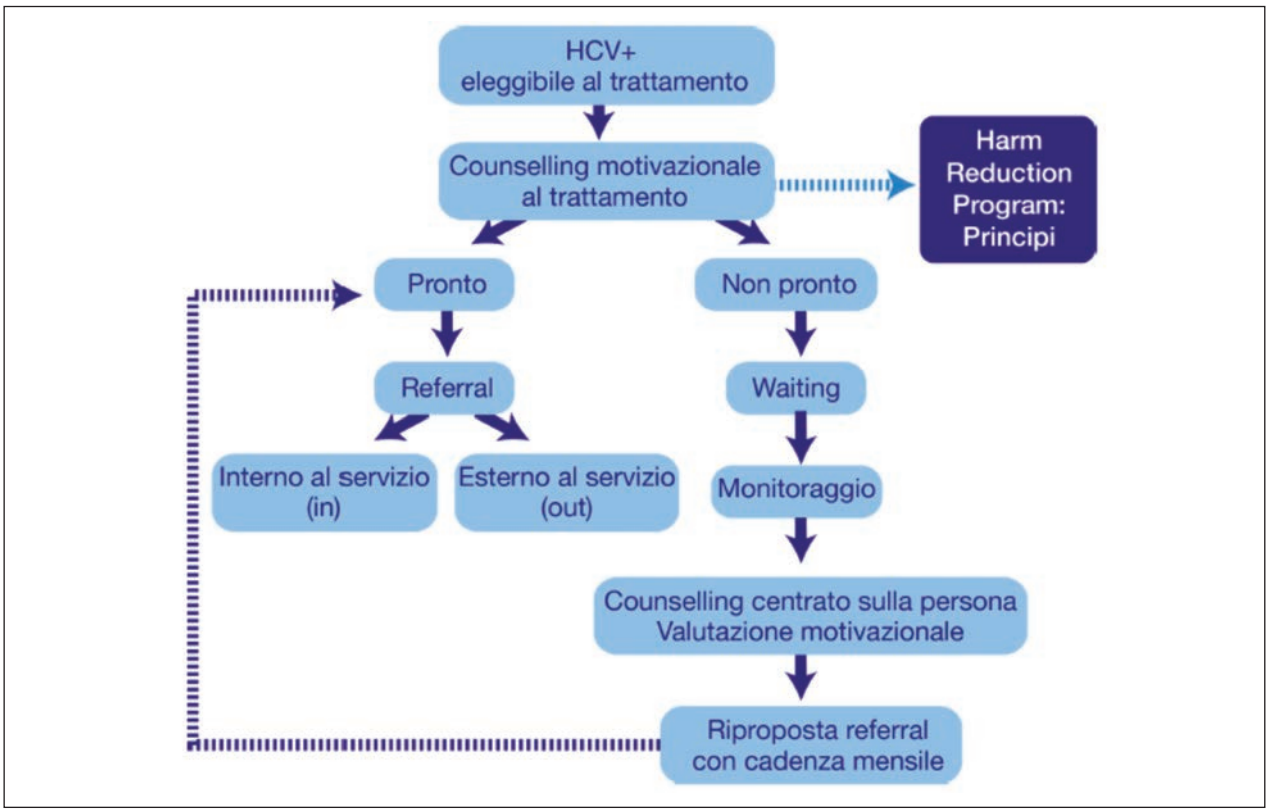

Figure 2.

- **The referral** should be accompanied by a **motivational counseling**
- **All patients who are referred to a specialist** (infectivologist/hepatologist) for treatment should receive a **structured harm-reduction program** (knowledge of the principles and measures, as indicated by WHO)

The treatment phase (Fig. 3) is characterized by the following essential elements, that have the aim of appropriately treating the patient through:

- a complete clinical evaluation carried out by the hepatologists-infectivologists, aimed at the start of treatment (preferably where the linkage to care took place)
- close monitoring (by both specialists) of the compliance with the treatment, based on the therapeutic relationship and the motivational support
- a periodic follow-up assessment (at 3 and 6 months from the start of treatment) by the specialists (individually and/or jointly) for the objectives of virologic and toxicological response and the evaluation of the quality of life
- an offer of harm-reduction programs, aimed at reducing risk behaviors, through the development of skill training in the management of harm-reduction actions and the provision of harm-reduction kits
- a verification of the patient's ability to use the harm-reduction measures

- **All HCV RNA+ patients** may be eligible for treatment
- **All patients with the clinical criteria** for starting treatment **should be treated with DAAs**
- **All patients should receive a structured harm-reduction program** (with skill training)
- **The monitoring of the treatment** should provide for the **evaluation of the adherence to therapy and the assessment of the achievement of the infectivological, toxicological and behavioral outcomes**
- The **end of treatment** should be followed by an **infectivological follow-up** and **by an evaluation on the ability to use harm-reduction measures**
- **All patients being treated with the DAAs should receive a harm-reduction kit**

The prevention of the infection is of paramount

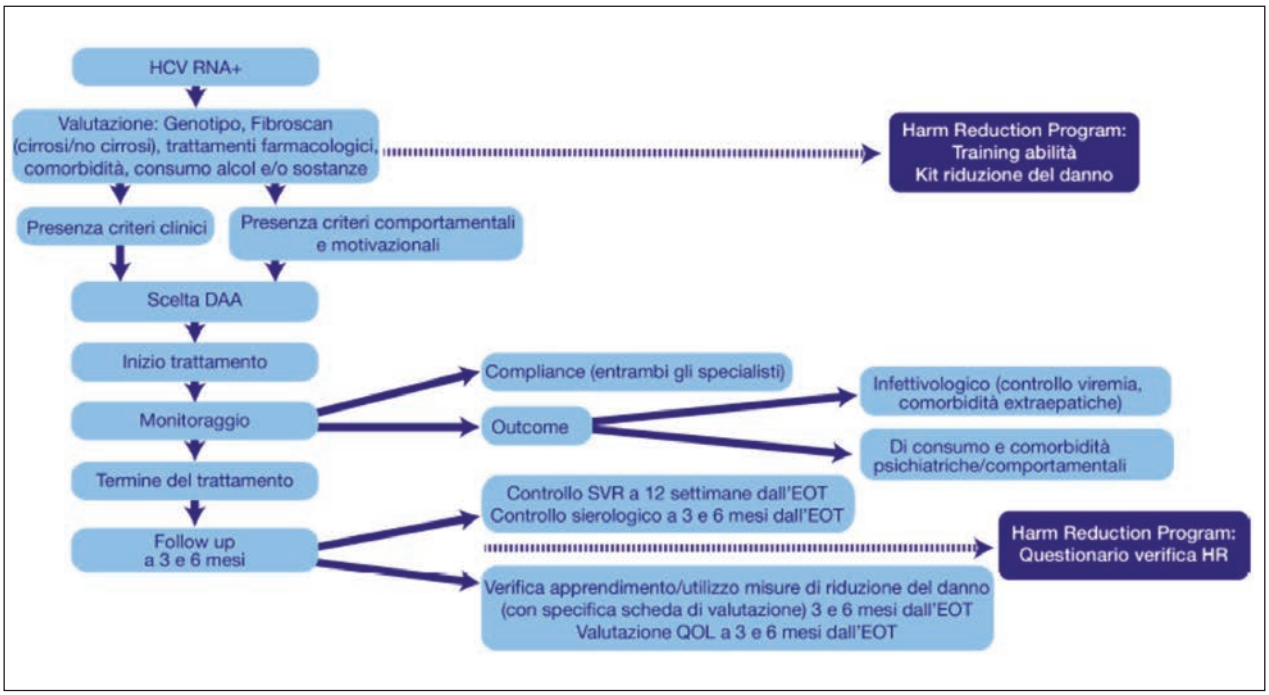

Figure 3.

importance in the linkage to care of the HCV population at risk and is an element which should always be associated with the drug treatment.

The prevention of the infection should occur through the harm-reduction actions, as identified by WHO.

In particular, harm-reduction measures include the use of:

- information and support materials (including online) (to be used on a priority basis in the screening stages)
- specific training on the basic harm-reduction principles (to be used on a priority basis in the referral stage)
- skills training on the harm-reduction actions (to be used on a priority basis in the treatment stages)
- harm-reduction kit, to be supplied to the population at risk (to be used on a priority basis in the treatment stages)
- processes for the verification of the acquisition/use of harm-reduction measures (to be used on a priority basis in the follow-up stages).

Harm-reduction actions should articulate following all the phases of the linkage-to-care "chain" (Fig. 4), with the aim of strengthening the achievement of the objectives set by the individual phases, facilitating the access and the adherence to the treatment but, above all, reducing risk behaviors and minimizing the reinfection rate.

- **Harm-reduction** measures, as suggested by WHO, **should be applied to all drug users** (whether active and/or being treated with DAAs)
- **Harm-reduction measures** should accompany – with specific actions and modes – **all the stages of linkage to care of the drug/substance user with HCV infection** (screening – referral – treatment – follow-up)
- **Harm-reduction kits should be provided to all drug/substance users who are (or have been) in treatment with DAAs**

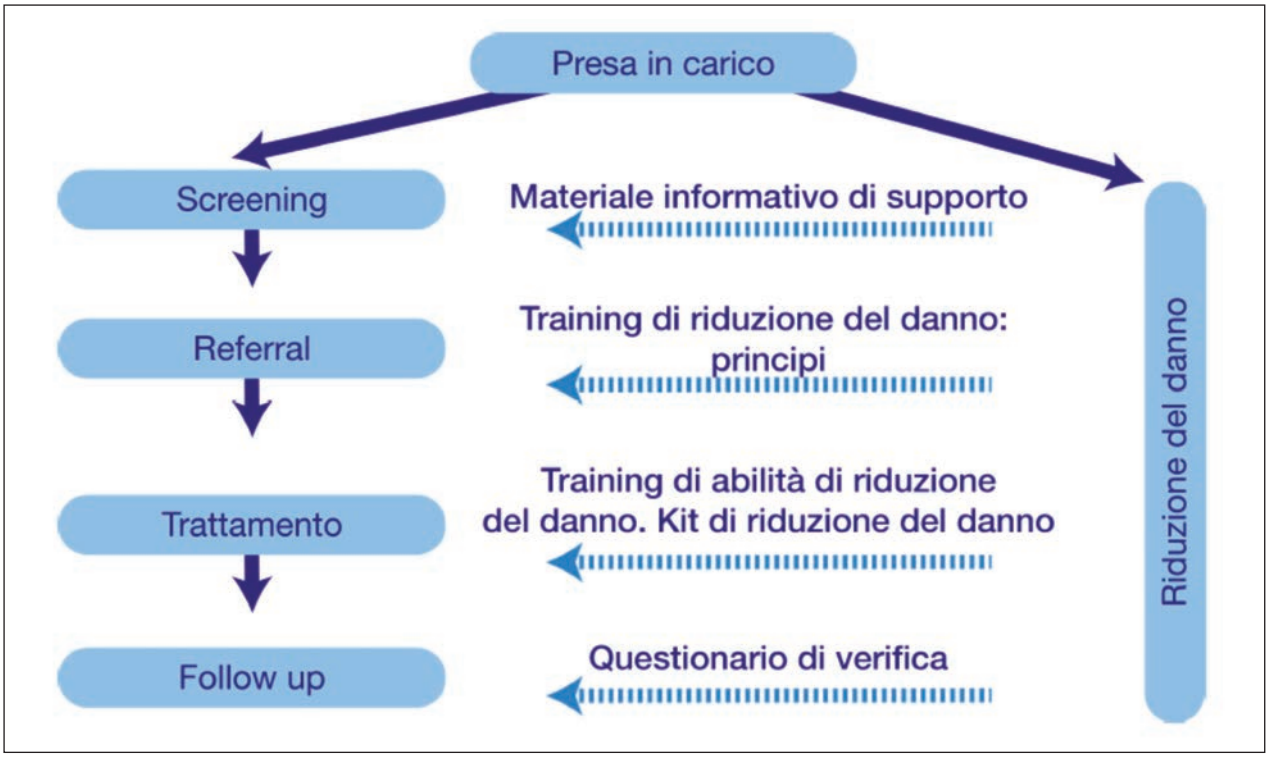

Figure 4.

The basic principles for the linkage to care of drug/substance users and convicts with HCV

- The treatment of the population at risk (drug users and prisoners) should become a priority for the health systems, in order both to ensure equity of access to care and to achieve the public health goal of the eradication of HCV
- Linkage-to-care programs should be integrated, flexible, multi-disciplinary, individual and of proximity
- Linkage-to-care programs should be based on scientific evidence, and should be distributed evenly throughout the national territory
- Linkage to care should be supported by procedures and guidelines which should include also harm-reduction measures, as suggested by WHO.

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Original article

Coordinated hospital-community organisation model for the prevention, monitoring and treatment of patients with addiction and HCV

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Summary. *Background:* Hepatitis C Virus (HCV) infection is a common cause of chronic liver disease, cirrhosis and hepatocellular carcinoma. Epidemiological studies have shown a prevalence amongst the general Italian population that varies between 0.4% and 16.2%, depending on the age bracket and the geographic area considered. The prevalence amongst persons who inject drugs (PWID) is approximately 70%, making this population one of the main reservoirs of the virus. The complex issues of addiction impact access to antiviral therapy, despite the presence of efficacious treatments, with considerable personal, family and social costs. According to the available literature, testing is a critical issue in Drug Addiction Services and at the current time a mere 37.3% of users are screened, which translates into delayed diagnosis and access to antiviral therapies, with a considerable risk of an exacerbation of the clinical situation and of unconscious transmission of the condition to others. *Purpose:* To describe the coordinated organisation model for the therapeutic management of patients who inject drugs with HCV, implemented by Trieste Department of Dependency (DoD); to monitor its clinical efficacy and its ability to guarantee continuing care between hospital and community medicine settings. *Methods:* The aim of the model is to promote certain activities and partnerships that are already implemented by infectious disease/ hepatology specialists as part of the coordinated HCV prevention and treatment programme and to test novel strategies for preventing post-treatment reinfection. The programme is broken down into three different specialised levels: 1. the first level consists of on-site screening, performed at the Department of Dependency outpatient clinic; 2. the second level is characterised by clinical and diagnostic investigations conducted by the infectious diseases/hepatology specialist, to whom the subject is referred when found to be positive at level one; 3. the third level consists of pharmacological treatment and follow-up, which commences when the subject starts treatment with direct-acting antivirals; three different medicinal product management methods are contemplated, depending on the individual's level of self-sufficiency. Follow-up starts at the end of treatment and lasts a year. *Conclusions:* The experience of Trieste DoD demonstrates the feasibility of a coordinated management organisation model with hospital specialists and its efficacy in the clinical management of a population of PWID with viral hepatitis C. The provision by the DoD of daily, highly organised on-site screening managed by a specially- trained medical team has proven strategic for facilitating access to and compliance with the protocol for treatment with new direct-acting antivirals (DAA). In this team, a key role is played by the nurse, as the professional who manages the fiduciary relationship that is closest to the patient. A linkage to care approach that is differentiated according to the level of self-sufficiency and the complexity of the patient's needs makes it possible to avoid drop-out and to complete all pharmacological programmes. Harm reduction activities are important for pursuing changes in at-risk behaviour and preventing reinfection and are implemented at different time points during treatment and follow-up. (www.actabiomedica.it)

Key words: Dependency Service, HCV, epidemiology, direct-acting antivirals, infectious diseases, PWID

Introduction

Hepatitis C virus (HCV) infection is a viral infection of global importance that is transmitted by blood (1,2). Approximately 160 million people, 2-3% of the world's population, have chronic hepatitis C, a condition that single-handedly accounts for one quarter of all cases of cirrhosis and hepatocellular carcinoma (HCC) (1-4). Furthermore, there is evidence that HCV infection is associated with extrahepatic sequelae, such as circulatory disorders, kidney disease and neuropsychiatric disorders (5), and it has been proven that treatment can reduce the complications associated with the infection, including all-cause mortality (6). However, although widespread, this illness is still relatively unknown in both the general population and amongst medical sector professionals (7).

Most incident and prevalent cases of HCV infection worldwide are associated with the use of drugs and substance abuse involving at-risk injection practices (8). This behaviour is concentrated in high-income countries, where there are a significant number of people who inject drugs (PWID) (1,9). In these countries, prevalence ranges from 50-80% in the PWID population, which is chronically infected (1,10).

In Europe (including Russia), it is estimated that the number of subjects with HCV infection is between 11.3 and 14.7 million. Prevalence rates (identified by HCV antibody positivity) in the population vary from 0.5% observed in southern European countries to 7% in eastern Mediterranean countries (11). This population includes both subjects who have previously injected drugs, or "recent injectors", who have injected drugs for no more than one month or one year, depending on the different definitions established in scientific literature. Those subjects with a history of injected substance abuse can also include those on replacement medication for dependence, some of whom potentially continue to inject substances (12).

Every year, worldwide over 1.75 million people contract the disease (with a global incidence rate of 23.7/100,000) and most of these become infected through unsafe use of syringes used to administer drugs (13). In Italy, the prevalence of HCV in the general population varies, depending on the age bracket and geographical area considered, between 0.4% and 16.2%. The figure amongst the PWID population is around 70%, to the extent that it can be said that this target represents one of the main "reservoirs" of the virus (14).

Worldwide, of the 71 million patients with HCV, the impact of the infection amongst PWID with a recent history of injection is particularly significant, with a prevalence of chronic infection of 50%, reflecting an estimated incidence of 5.6 million subjects (8% of all infections worldwide) (1,13). However, although it has not been calculated, there is also a high number of chronic HCV infections amongst those PWID who have stopped injecting drugs (1,15) and that could be accounted for by other at-risk behaviour, such as unprotected sex. In addition, one worrying aspect is represented by the fact that an unquantifiable part of new infections is contracted by people who previously recovered from HCV infection and who become re-infected due to a persistence of at-risk behaviour. This makes it essential to provide harm reduction and counselling initiatives. In this sense, it is important to remember that the morbidity and mortality associated with HCV infection continues to rise in both PWID with a recent history of substance use and in past users (15,16).

However, despite the strong impact of HCV infection, only 1-2% of PWID are on treatment (17-21).

There are a number of viral and subject-related factors that make the identification, diagnosis and treatment of HCV infection difficult in this target (22). Acute infection is usually asymptomatic and chronically infected subjects may not develop significant symptoms for decades after contagion (23). If the disease is not treated, chronic liver disease develops in 60-70% of cases, cirrhosis in 5-20% of cases, and 1-5% die of decompensated cirrhosis or HCC (24). It is estimated that fewer than 5% of PWID are treated for chronic HCV infection (17,25).

It is interesting to observe that in countries in which infection control procedures have been implemented (including counselling and first-level blood test screening), it has been observed that the main means of HCV transmission is at-risk injection practices (2,26). Conversely, in countries in which the adoption of healthcare procedures aimed at preventing the transmission of pathogens in blood is less well or-

ganised, the spread of HCV is extensively related also to nosocomial and iatrogenic causes (27).

Generally speaking, there is a discrepancy between the response of public health services, in terms of primary prevention, and the speed with which HCV is spread, which explains why the prevalence of the virus remains high despite the availability of efficacious and well-tolerated treatments (28,29). It is therefore of paramount importance to promote further research and to invest the resources needed to improve prevention and treatment strategies in PWID populations, also in order to control possible coinfections, in particular, human immunodeficiency virus (HIV) and hepatitis B virus (HBV).

According to the WHO's Global Hepatitis Strategy, the goal is to treat three million subjects with HCV infection by 2030, by implementing a series of resolutive measures: vaccination practices for HBV, HAV and HEV, the prevention of sexual transmission and checks on blood and blood products, long-term treatments for the management to HBV and the treatment of HCV with interferon-free (IFN-free) therapies and the administration of direct-acting antivirals (DAA). Since the achievement of the goal of the HBV and HCV eradication campaign depends above all on the implementation of schemes in "key" contexts and populations, the WHO recommends defining in each country the specific populations that are worst hit by the hepatitis virus epidemic: of these, PWID are a target at a very high risk of contracting HCV infection through blood due to the use of infected syringes or other instruments used to take substances (30).

The new treatments for HCV infection have introduced shorter pharmacological regimens that are associated with manageable side effects and that have high probabilities of healing (31). However, the cost of these treatment options is still high and could clearly orientate guidelines making active substance users ineligible for treatment (4,32-34). One example of this situation is what is happening in many public insurance schemes in the United States (with the exception of Medicaid), which restrict the coverage of the novel treatments to the subjects with the most advanced disease, leading to several years' delay in access to these treatments. These restrictions represent a severe disadvantage for PWID populations and low-income patients (35).

Initially, the guidelines on the treatment of HCV did not take PWID into consideration, justifying this decision by issues concerning compliance with treatment, the increased susceptibility to the side effects (such as depression) and to re-infection. However, there is ever-greater evidence regarding the safety and efficacy of treatment for HCV amongst PWID (36-38). In two systematic reviews evaluating treatment for PWID (one of which focussed on subjects with a recent history of injection at the start of treatment), the overall sustained virologic response (SVR) rate was 56% (37,38). These response rates are similar to those reported in large randomised controlled trials on treatment with pegylated interferon/ribavirin (PEG-IFN/RBV) (39). Therefore, at the current time, international guidelines recommend treating PWID according to an individualised approach (33,40,41). With this in mind, international recommendations have reconsidered the evidence on the relationship between substance use and treatment of HCV infection, stressing that the presence of a history of injected substance abuse does not, in itself, compromise compliance, the completion of treatment or SVR (33).

It has also been demonstrated that early intervention in the PWID population, universally recognised as the true "reservoir" of the infection, with a massive use of DAA, can generate a significant impact on the global HCV epidemic (in terms of a significant decrease) and prevent these subjects from developing cirrhosis, hepatic decompensation and HCC, thereby reducing the impact of its morbidity and mortality (42).

Strong points and limits of coordinated care schemes for the treatment of PWID populations

Therapeutic intervention in PWID, involving referral and management and subsequent HCV clearance, represents a tangible and achievable target in order to motivate the subject to abandon practices that are harmful for his/her health, but also in order to prevent him/her from constituting a universal source of contagion. This makes it possible to achieve a positive impact on the progression of the liver disease, with an improvement in the quality of life and life expectancy.

A number of experiences conducted in different countries have shown that the treatment of PWID, as subjects at a higher risk of acquiring HCV, can contribute to reducing the incidence of HCV infection and therefore prevent its transmission, especially if therapy is associated in a coordinated manner with counselling and harm reduction interventions (replacement opioid therapy and syringe distribution) (42-44). One recent study, for example, calculated that in Edinburgh (where 30% of PWID have HCV), doubling the therapy use rate to 15 per thousand could halve the prevalence and incidence of HCV in 10 years. In other countries such as the United States, on the other hand, a 68% reduction in the prevalence of HCV has been estimated over the next few years with treatment of 20 per thousand PWID/year, with a prevalence of 25% (42).

Despite the obvious usefulness of this approach, in real life the potential results of treatment with DAA would still appear to be limited compared to the benefit that these subjects could obtain from therapy. A number of factors contribute to this situation, including the variability between countries with regard to the organisation and the geographic distribution of specialised drug addiction centres, the presence and absence of screening and harm-reduction intervention, and policy that criminalises and discriminates against PWID, which impacts pleas for help and increases the submerged need (45,46).

Screening, testing and risk assessment counselling activities are important for improving the individual's awareness of his or her serological status and allowing an earlier start to therapy. Specific harm reduction and sexual education schemes are very important also for motivating the individual to adopt safer new behavioural models.

The inadequacy of testing strategies and the limited access by PWID to the new antiviral therapies, has led to the development of combined treatment models, based on cooperation between addiction service specialists and hospital specialists; The individualisation of programmes and their modulation according to the person's actual self-sufficiency have made it possible to trial new ways of managing antiviral therapy in diversified settings, such as outpatient clinics, drug dependency clinics and specialised treatments, also through the use of DOT (directly observed therapy) and peer-based models(47). At the basis of this strategy is a pragmatic, realistic and non-judgemental multidisciplinary approach, guided by public health objectives. The application of integrated models able to develop a strong synergy between specialists, through the drafting and implementation of common procedures and guidelines has facilitated the access to care in at-risk populations.

In Italy, the coordinated care model for HCV infection in PWID was implemented by the different professional figures working in the drug addiction services, namely psychiatrists, psychologists, toxicologists, social workers, nurses and educators.

The Drug Addiction Service is able to guarantee a privileged relationship with the patient: in these facilities, serological tests can be performed in order to guarantee early diagnosis and the introduction of treatment, DAAs can be administered directly and the harm reduction activities needed to eliminate at-risk behaviour and prevent virus transmission and reinfection can be performed. Operational protocols between community and hospital specialists are also useful for follow-up and the monitoring of any adverse event. The importance of a combined management of HCV infection in Addiction Services has long since been assimilated also by the National Health Council, which with its guidelines for screening and early diagnosis of the main infections associated with drug use, published in 2010, envisaged the organisation within the Drug Addiction Service of Special Units for the management of the associated infectious diseases (HIV, HBV, HCV, TB and STDs), also in cooperation with local infectious diseases departments. The aim is to facilitate access to therapy for infectious diseases, to improve treatment compliance and to reduce the dropouts associated with referral to Infectious Diseases units.

The staff working in Drug Addiction Services and dedicated to the management of drug users in 2016 amounted to 7,186 professionals, 75.6% of whom working full time. 51.9% of these professionals are doctors and nurses, 38.5% are psychologists, social workers and educators and the remainder are administrative staff and other professional figures, with an availability rate of between 8 and 24 resources per 100,000 inhabitants, a value that varies greatly from one area to another.

This situation has led to a partial collapse of the Drug Addiction Service system. According to the most recent Report to parliament on the drug addiction situation, which was published last year, in 2016, these Services managed 143,271 users (of whom 21,458 were new users, equal to 15% of the total, and the remaining 121,813 had already been managed in previous years); it is estimated that approximately double this number of users are not treated but would require treatment (Report to parliament on the drug addiction situation 2017). Furthermore, the recent general crisis in the healthcare sector has also had a hefty negative effect on the treatment of PWID and, more generally addiction prevention activities and the lack of resources available is obvious. According to the data available, in 2016 in Italy 28,197 Addition Service users were tested for HCV, a mere 25% of the total number of subjects treated and 275 of PWID. For 9% of users on treatment, i.e. 12,380 subjects, the test was positive, showing significant territorial variability: indeed, the percentage of users testing positive for HCV varies between 0.4% and 36.6%. By analysing subjects who inject heroin and/or cocaine alone, it is observed that the percentage of subjects tested for HCV is approximately 28% for heroin and 30% for cocaine (Report to Parliament on the drug addiction situation 2017). In the drug addiction services, testing therefore still involves significant problems: on average nationwide the number of users who undergo screening is equal to one third of all potentially testable and manageable users (49).

In order to deal with these critical aspects, for some time now Italy's regional authorities have adopted an organisation compatible with a coordinated hospital-community approach to providing diagnosis and care programmes for infectious diseases in PWID. One particularly significant example is that of the Friuli Venezia Giulia Regional Authority that, already in 2014 undertook the "PIT project - Substance use and related disease: Programmes, Identification and Testing", aimed at developing a regional protocol in an attempt to develop procedures in order to standardise the availability of testing and to define a shared diagnosis programme, in concert with infectious diseases experts, with test laboratories, with sexually-transmitted diseases centres and the managements of

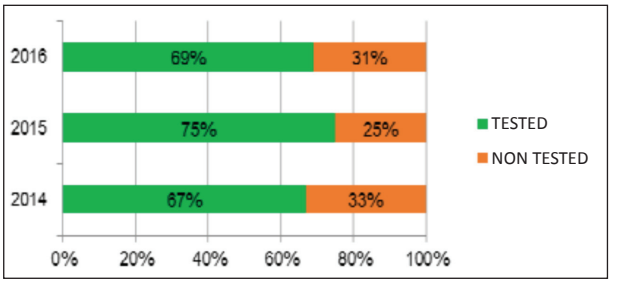

Figure 1. Percentages of users tested for HCV out of total treated by Friuli Venezia giulia Drug Addiction Services in 2014, 2015 and 2016

regional disciplinary facilities. The aim was to improve the availability of testing for HIV, HBV and HCV amongst the substance users followed by the region's addiction services, also through the analysis and reprogramming of the management models. The activity reports for the first two years of introduction of the PIT scheme have shown an improvement in the regional trend (Figure 1).

The experience of Trieste Department of Dependency

The screening work performed by Trieste Department of Dependency (DoD) started in 1985, following the AIDS emergency, with the opening of a dedicated on-site outpatient clinic managed in conjunction with the infectious diseases unit. Considered a strategical part of treatment services, over the years the organisation of this activity has developed, through a gradual increase in the interest dedicated to the impact of the hepatitis viruses (B and "non-A, non-B", then C). In the presence of a low prevalence of HIV, a high prevalence of HCV was observed.

Trieste DoD currently offers an HCV prevention, monitoring, treatment and follow-up service, based on a facilitating and proactive approach and on specific linkage to care activities to prevent drop-out and the development of viral resistance and to favour treatment compliance. Over time, the cooperation with infectious diseases specialists has had a very positive evolution; the introduction of DAAs to the clinic represented a fundamental step for optimising the continuing care pathway. Indeed, up to 2015, an-

tiviral therapy was managed directly by the Infectious Diseases Unit, with an unsatisfactory result in terms of the presence of a great many drop-outs, due to the fragmented and complex nature of the pathway and the difficulties of managing a therapeutic relationship with PWID.

The DoD's work has been reworked and reorganised over the years, with a view to obtaining an ongoing improvement in performance. The DoD headquarters is currently home to a multipurpose facility dedicated to the associated infectious diseases, which operates in close connection with Local Health Authority specialists (infectious diseases, hepatology, cardiology and dermatology specialists). The presence of an infectious diseases expert at the service once a month for scheduled clinical assessments and the availability of a dedicated medical team has allowed greater efficacy and efficiency in the use of resources and time. This activity meets the criteria of clinical appropriateness and is provided in accordance with operational agreements with specialised units, in order to simplify user programmes.

The integrated model implemented in Trieste is made efficacious by a series of organisational and functional "principles", identified on the basis of some of the peculiar characteristics of the target, with the aim of facilitating as far as is possible access to and compliance with the care protocol (Table 1). The screening outpatient service is located next to that for the management of replacement therapy and is open every morning, in order to guarantee testing to all individuals regardless of whether they have an appointment. The staff have a pro-active approach, the HCV test is offered to everyone, free of charge, without a doctor's prescription and whilst respecting the user's anonymity. The team that follows the patient is selected and formed specifically and is capable of managing complex problems that could affect compliance: psychiatric comorbidities, psychosocial unease, fear, difficult venous access, presence of deep skin lesions. In this programme, nurses play a key role in the fiduciary and confidential relationship and in the individualised support provided to patients, in concert with the specialist doctors.

The DoD diagnostic and therapeutic pathway has three different levels of specialisation, which identified in accordance with the clinical assessment. The first (screening) envisages the following activities:

- Pre-test counselling, risk assessment and acquisition of written informed consent (nurse/ doctor);
- Performance of screening serological test (nurse/ doctor);
- Delivery of the results (doctor/ nurse);
- Informative counselling (nurse);
- Support in the event of positive serology (doctor/nurse/psychologist)

The second level (in-depth diagnostic tests and procedures) commences when the subject tests positive for the first level and more detailed diagnostic assessment through clinical and laboratory tests is required. In this case, the Service's pro-active action is expressed: a) by performing the blood draw for the specific test (qualitative and quantitative HCV RNA) directly and by booking an appointment with the infectious diseases specialist at the DoD outpatient clinic; b) by guaranteeing counselling and therapeutic continuity with the Department, if the person if not self-sufficient. The third level (treatment programme) is initiated when the clinical situation requires specialist therapeutic intervention. Once again in these cases the support and counselling provided to improve compliance with the treatment programme and pre-

Table 1. The active "ingredients" of the Trieste DoD coordinated model

- Fully-equipped screening clinic, open every morning, next to the replacement therapies clinic.
- Free, unpaid and anonymous access, no doctor's prescription required.
- Dedicated, specially-trained healthcare team, able to manage complex issues that could affect compliance (psychosocial problems, prejudice/fear, venous access difficulties, presence of skin lesions, etc.).
- Pre- and post-test counseling, personal delivery of results.
- For users who test positive, start of coordinated protocol with Infectious Diseases staff (on-site management of diagnostic work-up and specialist assessment).
- Management of DAA therapy in concert with the infectious diseases specialist, depending on the individual's level of self-sufficiency.
- Specific intervention to improve access to and compliance with treatment (linkage to care), including individualised accompaniment or home visits (service car).

vent dropout involve a series of measurements such as assistance during appointments, consultations in the event of hospitalisation, home help, supervision when taking pharmacological treatment, family-relationship mediation, social support and intervention in conjunction with community services.

Results of HCV screening

Since 2012, Trieste DoD has had a certified database regarding all the activities offered to users, made possible by the implementation of a computerised platform. The data regarding HCV serological screening over the past five years are summarised in Table 2. As is shown, since 2012 there has been an increase in the percentage of users undergoing screening for HCV infection: the percentage of tested subjects out of total users remained above 70%.

The data regarding the DoD's work has shown a decrease in the prevalence of HCV infection amongst the users managed (from 70.52% in 2012 to 67.64% in 2014 and 64.01% in 2016), which may suggest that the continuous and incisive prevention and testing activities are reducing the spread of the virus (Figure 2).

The compliance of HCV+ PWID subjects for the in-depth diagnosis (second-level screening) was very good (equal to 89.2%), showing that, once the patient has been informed and responsibilised, he/she takes adequate care of him/herself. In 2016, 298 were found to have viraemia; of these subjects, almost 60%

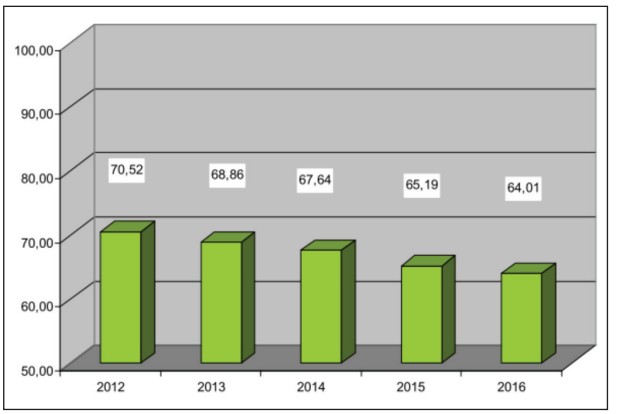

Figure 2. Percentage of users managed by Trieste DoD who tested positive on the HCV antibody test between 2012 and 2016

Table 2. Data and characteristics of users managed by Triests DoD: serology screening for HCV for the five-year period 2012 - 2016

	2012	2013	2014	2015	2016
No. of PWID managed	873	882	892	907	998
No. of users screened for HCV	648	684	717	721	728
% users screened	74,23	77,55	80,38	79,49	72,95
No. of HCV+ users	457	471	485	470	466
% of HCV+ users	70,52	68,86	67,64	65,19	64,01
No. of users HCV positive on HCV-RNA test	423	432	436	427	416
% of users positive on HCV-RNA test	92,56	91,72	89,90	90,85	89,27
No. of users with viraemia	301	311	313	305	298
% of HCV+ users with viraemia	65,86	66,03	64,54	64,89	63,95
No. of viraemic users examined by infectious diseases specialist	106	137	225	263	222
% of viraemic users examined by infectious diseases specialist	35,22	34,08	33,87	34,75	35,57

were infected with genotype 3. In 2016, 222 subjects were examined by the infectious diseases specialist; although this is a good result, it can be improved on, as all subjects with active infection should be examined.

Furthermore, the outcome of the test defines the aims of counselling: in the event of negativity, it aims to promote protective behaviour and raises the individual's awareness regarding serological status monitoring over time; in the presence of a positive result, it promotes the start of a coordinated specialised treatment programme and the modification of at-risk behaviour.

Second-level screening for -Ab+ HCV users is guaranteed on-site with qualitative and quantitative HCV-RNA testing; thanks to the linkage to care approach taken, the offer is taken up in over 90% of cases (Figure 3). Viral genotyping in HCV-RNA-positive subjects showed genotype 3 to be prevalent in the population target studied (Figure 4).

Il 2015, the DoD in concert with the Infectious diseases Unit devised a diagnostic and treatment programme addressing patients with chronic HCV, which was formalised with the protocol titled "Management of continuing care pathways between the Infectious Diseases Unit and the Drug Addiction Unit". This protocol was also stimulated by the availability of new direct-acting antivirals (DAA) and the need to manage the various stages of treatment in a more coordinated manner. The strategic objective was to achieve a standardisation of this activity and to guarantee all users facilitated access to the specialist programme and treatment. The screening clinic staff performs

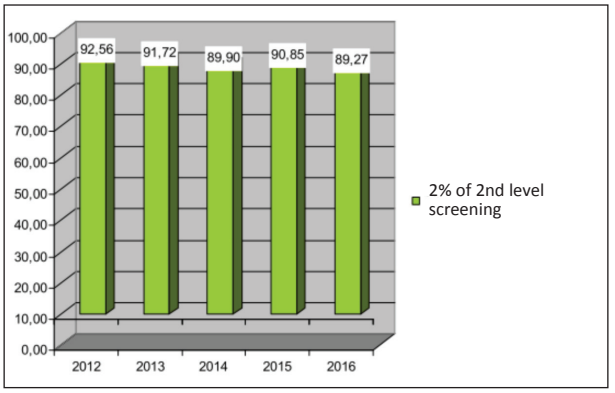

Figure 3. Percentages of subjects with HCV antibodies undergoing second-level screening with qualitative/quantitative HCV-RNA test

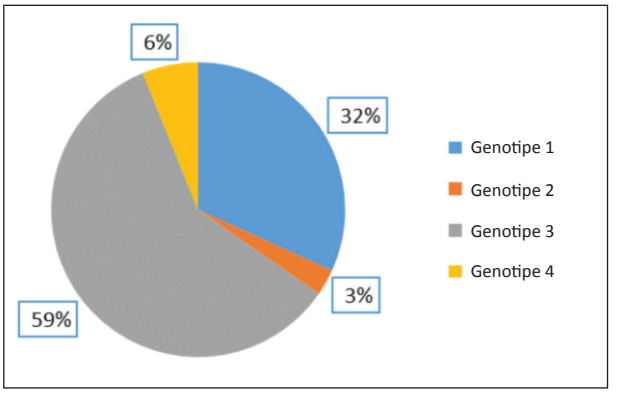

Figure 4. Percentage breakdown for viral genotyping in HCV-RNA-positive subjects managed at DoD between 2012 and 2016

the second-level tests before the appointment with the infectious diseases specialist in order to save time. Until 2015, antiviral therapy was managed directly by the Infectious Diseases Unit, which managed the individual after the diagnostic work-up performed at the DoD screening clinic. This practice was seen to be unsatisfactory given the high dropout rate due to the fragmented and complex nature of the programme and the difficulties managing the therapeutic relationship with drug users.

Until 2017, one of the protocol's critical aspects was the time patients had to wait for a liver ultrasound elastography, which was only performed in 15% of subjects. This led to a delay in the completion of the phase in preparation for the start of pharmacological treatment with DAAs. This critical aspect was overcome in 2018.

The adoption of the protocol permitted good levels of activity and a positive response by users, who did not show reluctance or fear and accepted the programme willingly.

Trials with DAAs

Treatment with DAAS is managed by the infectious diseases specialist/hepatologist, according to the addiction problem and the individual's level of self-sufficiency (the spectrum of operative options ranges from direct and supervised administration to the provision of a supply for a certain period of time). One

strong point is the linkage to care mentioned above, that involves specific intervention in order to improve treatment compliance and prevent drop-out, including individualised accompanying to treatment centres, home visits, telephone reminder activities, supervised medication taking and administration of direct-acting antivirals.

The protocol envisages three types of medication management (Table 3): self-sufficient patients are encouraged to "do it themselves" and the Service's contribution consists in overseeing the administration of the treatment, with reminder calls and communication with the infectious diseases specialist. Treatment can be assigned for a month or week, depending on the reliability of the subject. If the subject is not self-sufficient, the treatment is collected by the Addiction Service and administered, as specified in the treatment plan, daily or twice-weekly (DOT). Counselling is implemented before and during treatment in order to promote the motivation of the subject; follow-up is guaranteed for one year after the end of treatment.

In 2016, 14 people (13 males and 1 female started treatment). All the treatment programmes devised where completed, thanks to the coordinated management approach.

It should be noted that no individual was excluded from treatment for reasons associated with substance use or poor treatment compliance: in accordance with Italian Medicines Agency criteria all patients who were eligible at the time were recruited and treated. In 2016, the "cascade of care" was similar to that of other experiences (Figure 5).

In 2017, 57 people started treatment:

- 27 people, with low self-sufficiency levels and poor compliance, took the medicinal product directly at the Department of Dependency clinic (DOT);
- 20 partially self-sufficient individuals took the treatment themselves, collecting a 7-day supply of treatment from the hospital pharmacy;
- 10 self-sufficient individuals took the treatment themselves, collecting a 28-day supply of treatment from the hospital pharmacy;

Table 3. Activities managed by the Trieste DoD team at the screening clinic, in concert with infectious diseases specialists.

Pre-treatment	Joint, multidisciplinary DoD/ infectious diseases assessment before the patient is included in the pharmacological treatment protocol; during this phase, staff discuss the following with the subject: the pharmacological regimen, the commitment required, the anticipated repercussions, any side effects and the importance of regular blood chemistry monitoring during the treatment. Counselling to promote motivation regarding the treatment, compliance and regular treatment in the long term, as well as to prevent drug and alcohol use. Identification and involvement of any carers.
During therapy	Prescription of the DAA treatment programme by infectious diseases specialist with clinical examination of patient at the DoD screening clinic. Supervision of pharmacological treatment by screening service team. During the first month, the individual's ability to self-manage treatment and follow the treatment regimen is assessed every day; more specifically, depending on the subject's level of self-sufficiency, the following may options may be employed: • Treatment reminder phone calls or texts from the infectious diseases staff; • Collection of medication from the hospital pharmacy and daily of twice-weekly administration c/o the Drug Addiction Service clinic, to avoid leaving non-self-sufficient subjects to manage their therapy alone (DOT – Daily observed therapy) Scheduling and performance of blood chemistry tests c/o DoD screening clinic in accordance with national guidelines with the provision of a home visit service. The outcomes of these tests are discussed with the infectious diseases specialist, who remains in close contact with the screening team and staff of the local DoD unit at all times. Motivational counselling and toxicological and alcohol monitoring
Post-treatment	Serological follow-up (quantitative HCV-RNA test) and clinical follow-up to monitor any re-infection. This phase lasts 1 year. Counselling intended to improve protective behaviour and prevent any at-risk behaviour and re-infection.

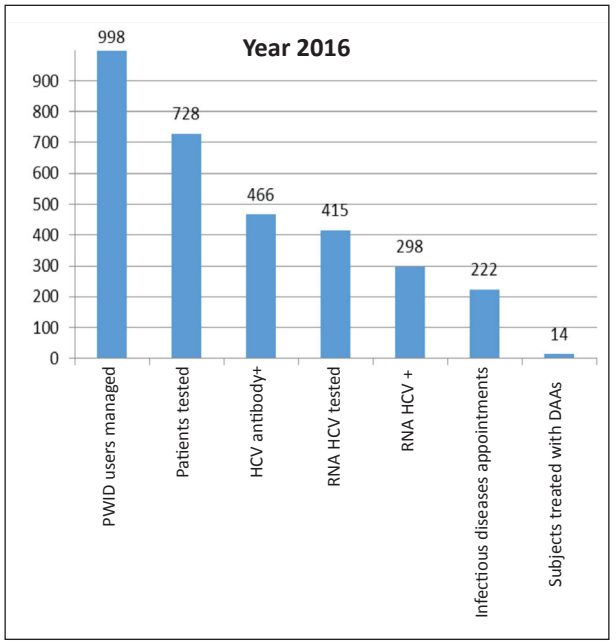

Figure 5. Cascade of care within Trieste DoD. Year 2016

Strong points of the coordinated approach

The preliminary data regarding the sustainability and the outcomes of the DAA treatment programme conducted by the Addiction Service are extremely encouraging. The adoption of a management model coordinated with infectious diseases specialists /hepatologists based on a proactive linkage to care approach that simplifies access to and retention in treatment, is able to avoid drop-outs and the risk of infection. In this approach, a key role is played by the screening clinic nursing staff, who manage the fiduciary relationship that motivates the patient.

The strong points are:

- Trained and dedicated staff (with the appointment of a specific dedicated nurse);
- On-site structured screening service, next to the treatment clinic;
- Pleasant, barrier-free, multipurpose outpatient facility environment;
- Long working hours, free, unpaid access;
- On-site management of the first and second level of the programme, in order to save time and favour an early start to treatment;
- Well-developed linkage activities that also make it possible to recruit individuals with more complex issues;
- Fiduciary partnership with infectious diseases/ hepatology specialists;
- Individualised treatment management, depending on the person's level of self-sufficiency;
- Availability of easy to take medicinal products, including single-dose pangenotypical products.

Financial resources for project consolidation

The coordinated approach proposed by Trieste Department of Dependency is based on a system envisaging dedicated human resources with special skill sets (multidisciplinary team in which a key role is played by the nurse), logistical resources (dedicated outpatient clinic), instrumental resources (medical equipment and material, hard- and software) and organisational resources (operative protocol, swift communication between partners, direction and shared programming of the various phases of activity, collection and dissemination of data, on-going innovation).

Discussion

The PWID population is more exposed to HCV viral infection than the general population. At-risk drug-taking practices, tattoos performed in unsterile conditions and unprotected sex are still the main risk factors. This target can be considered an HCV "reservoir" as prevalence in Italy amongst managed users is higher than 70%, compared to an average of 3% in the general population.

The percentage of untested users in Italian Addiction Services continues to increase and this alarming trend contributes to delaying diagnosis and access to antiviral therapies, with a considerable risk of a deterioration in the subject's clinical situation and unconscious transmission of the disease to others.

According to one study promoted by the Italian National Institute for Health (ISS), the lack of testing performed in Addiction Services would first and foremost appear to be associated with a series of factors such as restricted opening hours, no on-site blood

sample collection facility, the difficulties in identifying a peripheral venous entry portal and user fear/refusal.

The Trieste DoD approach provided a tangible response to these critical aspects by implementing an on-site, free of charge screening clinic that allows user anonymity and is open every morning from Monday to Friday. The close partnership with the local health authority's infectious diseases/hepatology specialists, which led to the preparation of a shared operational protocol, is managed by a purpose-built medical team within the drug Addiction Service. In addition to the specific infection situations, this makes it possible to deal with important health issues that complicate clinical management (psychiatric comorbidity, presence of psychosocial issues, resistance to care due to poor/inadequate information, difficult peripheral venous portals, severe skin lesions caused by "self-injection", feelings of shame and fear).

The rationale of the project is based on the assumption that implementing an HCV prevention, monitoring and treatment service characterised by an approach centring on the specific needs and characteristics of users could facilitate access to and compliance with the specialised programme, even in a high-risk, poorly-compliant population.

Despite the comforting data emerging from the application of the organisational and medical approach and the working method described, this project still has room for improvement. More specifically, the Service intends to increase the number of viraemic subjects who are assessed by the infectious diseases specialist/ hepatologist and those referred for DAA treatment and to reinforce the follow-up and harm-reduction activities, in order to prevent reinfection.

The main methodological and organisational principles of the model could be standardised and exported to other Italian Addiction Services.

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Original article

HCV infection and drug use in Italian detainees: results of validation of EQDP (European Questionnaire on Drug Use in Prison)

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Summary. *Purpose:* The aim of this paper is to describe the results of a survey conducted in Italy amongst detainees by administering a specific questionnaire (EQDP, European Questionnaire on Drug Use in Prison), in order to investigate drug use in prison, any sharing of used needles and, lastly, the degree of self-awareness regarding health (more specifically, in terms of HIV, HBV and HCV infection). *Structure of the article:* The article is split into three parts. The first provides an overview of the methodological guidelines for the EQDP, which were issued in March 2017 by the European Monitoring Centre for Drugs and Drug Addiction. The second describes the structure of the EQDP questionnaire (Italian version). The third provides the results of a survey conducted in Italy using this questionnaire and the health-related implications for the prison community, in particular regarding HCV, HIV and HBV. *Results:* The data were collected by the self-administration of the questionnaire to groups of a sample consisting of 40 male detainees under in normal prisons. In this type of custody, fewer subjects were substance abusers during previous prison terms than amongst subjects in open prisons. The most common forms of dependence (tobacco, alcohol, THC, cocaine, psychostimulants, hallucinogens, opioids, sedatives) detected were significantly different between the two types of imprisonment and they were easier to identify in the open-prison system. The analysis of the state of health with regard to the above viruses demonstrated that, in open-prison conditions, a higher percentage of subjects have been tested for HIV, HBV and HCV, whereas detainees in normal prison conditions were almost all unaware of their infection status and had a poorer awareness of their health in general. *Conclusions:* Health status (HBV, HCV, HIV) is not declared amongst normal detainees, who are less aware of their health conditions and receive less risk-reduction intervention. Amongst open-prison detainees, however, all substance users are subject to risk reduction interventions, which are efficacious in improving self-awareness in terms of a greater use of blood tests and treatments for infectious diseases. (www.actabiomedica.it)

Key words: prison, HCV, HIV, HBV, risk reduction, drug addiction

Introduction

Hepatitis C virus (HCV) infection is an important cause of liver disease worldwide. When untreated, chronic HCV infection progresses to cirrhosis, end-stage liver disease (ESLD) and hepatocellular carcinoma (1-3). The incidence of HCV infection amongst prisoners is many times greater than in the general population: of the more than 11 million detainees around the world at any one time (4), it is estimated that between 3% and 38% have been exposed to HCV, with estimates varying according to the geographic area and the prevalence of people who inject drugs (5). Previous specific investigations conducted on the prison

system, in particular show a sero-prevalence for HCV that ranges from 16% to 42% in the United States (6), from 30% to 50% in European countries (7) and from 31% to 38% amongst detainees in Italian prisons (8,9). HCV infection has a significant importance in mainland Europe: indeed, due to the high prison-population turnover rate, it is estimated that in the 53 countries of Europe there are approximately 6 million detainees in any one year (10). Modelling studies have also confirmed the negative impact of imprisonment on the perpetuation of the epidemic spread of HCV infection (11), and estimates regarding HCV infection amongst detainees with a history of injected drug use indicate a high incidence, equal to 16.4 per 100 person-years (12,13). Nevertheless, routine HCV testing in detention centres is still extremely limited (14,15). Dealing with epidemic HCV infection amongst detainees is therefore an essential component of global response (16). Experts encourage what is known as the "micro-elimination" of HCV, which represents a pragmatic approach for achieving eradication targets in specific populations, in which treatment intervention can be performed more quickly and more efficaciously using targeted methods (17). With the introduction of highly efficacious short-term direct-acting antiviral (DAA) therapy, a 90% reduction in HCV infection amongst detainees by 2030 is deemed a realistic goal (3,18), especially when this treatment is combined with opioid replacement therapy directly in the prison setting (19).

This high prevalence of HCV amongst detainees is the consequence of the forced concentration of high-risk individuals in the penitentiary setting, especially drug addicts and other people who inject drugs (PWID), who represent a significant part of the prison population (20,21). The risk of infection further persists during incarceration, as the prison setting amplifies the adverse conditions for health caused by overcrowding, the inadequacy of the facilities and frequent lack of access to health services (22,23), as well as widespread at-risk behaviour, such as the sharing of syringes and other sharp objects, tattooing and unprotected sex amongst individuals of the same gender (24-26). High-risk behaviour also increases not only the likelihood of catching but also that of spreading HCV – and other sexually-transmitted diseases – on a global level: many exposed patients, although they spend periods in the prison *microenvironment* in which the infection can be detected and treated, re-enter society after their release and are once again at risk of further re-exposure (Figure 1). However, if during their detention they receive treatment for their infection, it is possible that they may constitute less of a risk for others once they are in the *macroenvironment* outside of prison (27).

The prison microenvironment is considered a promising setting for intervention for the treatment of blood-borne disease, since this population presents a high disease prevalence, commonly practices at-risk behaviour and could be readily accessible for testing and treatment. Prisons are a particularly interesting microenvironment for the treatment of HCV, primarily because oral DAA treatment regimens currently require just 8-12 weeks of treatment to achieve a cure (27). It has been demonstrated that the DAA therapy response rates amongst detainees are similar to those achieved amongst ambulatory patients, despite the differences in terms of age, sex and treatment experience, with sustained virologic response at 12 weeks (SVR12) observed in over 95% of patients (28).

Furthermore, the evidence regarding the efforts made to eradicate human immunodeficiency virus (HIV) in the prison system have shown that it is possible to start treatment in these high-risk microenvironments, and that by succeeding in associating patients with care-providers even after their release from prison, it is possible to improve the overall burden of the disease and reduce its transmission and complications (29). Although the validity of this approach has not been proven yet for HCV, on these grounds, it can be postulated that prison could also be the ideal place for identifying, treating and, ultimately, eradicating HCV infection.

Consequently, HIV, HBV and HCV screening should be offered to all detainees when they enter prison. In actual fact, due to a complex series of local and national organisational flaws, prisoners are not always tested for these viruses. The available data on the treatment of chronic hepatitis C in prisons are limited to a few observational studies (30-32), whereas in Italy a number of small case series have been published on this specific topic (33). Generally speaking, it has been

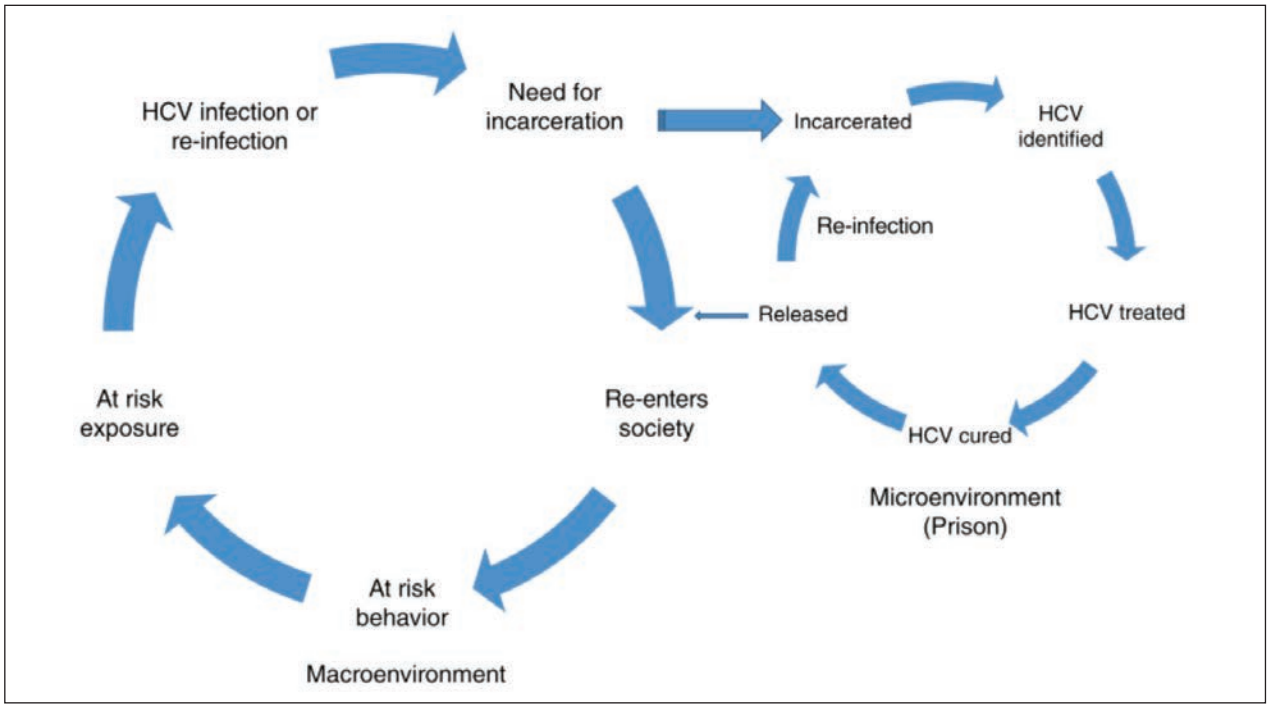

Figure 1. The HCV infection and reinfection "cycle" inside prison (microenvironment) and outside prison (macroenvironment). *(From: Redman JS, Sterling RK. Treating HCV in a Captive Audience: Eradication Efforts in the Prison Microenvironment. Am J Gastroenterol 2018 Jul 24. Epub ahead of print)*

observed that a minority of detainees with hepatitis C are able to complete a cycle of treatment, due to the patient's early release, the onset of side effects or comorbidities restricting access to treatment (31,32).

Given the considerable importance of this issue, a number of different national authorities have published guidelines recommending the screening of all detainees for blood-borne diseases when they enter prison. The Italian Ministry of Health Decree of 21 April 2000, which was issued to protect health in detention facilities (34), recommended not only testing and treating all infections associated with injected drug use, but also promoting programmes in order to improve detainees' awareness regarding preventative measures and treatment needs.

A correct implementation of initiatives to promote the treatment of HCV, HIV, HBV and drug addiction in penitentiary settings therefore requires the identification of efficacious and individualised approaches to service provision (35,36). In order to achieve this, it is necessary that habits regarding substance use and abuse, exposure to at-risk behaviour and the level of health awareness be identified and assessed in the prison setting, in order to facilitate the creation of efficacious local, regional and national intervention, in order to contribute to improving treatment coverage.

The data obtained during our previous pilot survey shows that there is a lack of awareness by users and health services with regard to both HCV screening and at-risk behaviour. In this original contribution, we make available the first Italian data describing the situation in the penitentiary system, as reported directly by the prisoners. In order to do so, we used - and validated for the first time in Italy - the EQDP (European Questionnaire on Drug Use among Prisoners), a tool devised to investigate substance use in detention centres, the possible sharing of used syringes and the degree of self-awareness regarding health, in order to verify in a sample of the prison population, the assessment of HCV and other screened diseases and the assessment of at-risk behaviour, considering both the perception of the problem and the risk factors for infection and spread.

Methods

Methodological guidelines concerning use of the EQDP

The European Questionnaire on Drug Use among Prisoners (EQDP) (original English version available from: www.emcdda.europa.eu/publications/technical-reports/european-questionnaire-drug-use-among-prisoners-eqdp_en) is the result of several years' work in the relationship between substance use and the penitentiary setting, and includes the consensus on a methodological framework and on the monitoring of drugs in prisons in Europe, the analysis of existing questionnaires and a discussion amongst high-level experts from the different European countries and international organisations. The proposed questionnaire represents a minimum essential dataset that could be used in all European countries, in order to guarantee harmonisation and comparisons. Each country could also expand its survey with supplementary items, in order to satisfy national or local information needs.

The questionnaire is completed by methodological guidelines for data collection and reporting. The methodological guidelines aim to guarantee high data quality and comparability between countries and to ensure that high ethical standards are applied. Again, according to national or local requirements, further, broader national guidelines and/or instructions may be produced, as well as rules for conducting the survey and manuals for work "in the field".

The methodological guidelines are split into two sections, those regarding the general principles and those regarding the guidelines themselves.

The first section lists some general principles that are common to all European countries and should be considered when organising and conducting a survey on substance use in prisons, in accordance with the aspects established in the methodological framework. More specifically, it lists a number of important aspects:

a) the information regarding substances and detainees must be collected with a public health perspective, rather than focussing on the control principle;

b) the purpose is to obtain information that can be used to improve the health of and social services for prisoners and therefore the physical, mental and social status of both detainees and the community as a whole.

c) survey planning and management must involve national institutions and the state agencies responsible for health on a nationwide level (Ministries of Health or Institutes for Public Health), for prison-related issues (penitentiary services or Ministries of Justice) and for policy regarding and the monitoring of substance use (drug addiction services, drug use commissions and national drug addiction centres or monitoring agencies);

d) the survey should be conducted by institutions that are independent of the prison service, and that have been recognised as applying rigorous scientific and professional standards;

e) all the fundamental requirements to be presented to the prison's administration department in order to obtain the complex authorisation required to come into contact with prisoners are listed;

f) European guidelines must be harmonised in order to prevent the proliferation of new pilot studies in the different countries and to find a minimum common core that also makes it possible to conduct studies comparing the situations in different countries;

g) the creation of guidelines must guarantee the best possible quality of the information collected and the application of a stringent ethical standard during its conduct, also through the direct involvement of prisoners, in order to increase the perception of the importance of the survey for their health, whilst also guaranteeing their complete anonymity;

h) the results of each survey should be "triangulated" with other potential sources of information, such as other studies, routinely-collected data or other unofficial sources;

i) the language and the terminology used in the questionnaire should consider the specific nature of the prison environment and should therefore aim to maximise comprehension and be suited to the level of education of the prisoners, who may speak a language that is not the official language of the country in which the penitentiary facility is located.

The second section, which includes the guidelines themselves, provides indications regarding the purposes of the survey, the methods and frequency of administration, the characteristics of the target population,

and practical aspects including prison access modalities, data collection methods and interview conduction. It also describes the purposes of the survey, which consist in improving knowledge regarding substance use amongst detainees, their health conditions and the consequences in terms of a better identification of the prisoners' mental health and social needs. This information may favour the appropriate development of social and public health services. It should also be noted that:

a) it is important to explain to the interviewees the purpose of the survey, so that the data can be collected and used to satisfy the general purposes of the research using the method established.

b) the methods used should be based on a transverse survey amongst prisoners regarding drug use both inside and out of prison, the health issues associated with substance use and the involvement of drug-addiction services;

c) the questionnaire should preferably be administered every two years, with a recommended maximum interval between two surveys of four years;

d) the survey's target population should include all the prisoners on the same day or same week in all penitentiary centres, preferably splitting them into categories based on their legal status or the place of detention;

e) the sampling method must be compatible with the targets set, by recruiting the subjects to be interviewed in a randomised manner in order to obtain a sample that is representative of the whole population registered at the prison, where appropriate possibly over-representing in the sample those groups of detainees with a certain state of health or social need;

f) although the interview must be conducted in a completely anonymous and confidential manner, it is essential for each participant to give both verbal and written consent to take part in the survey unless the questionnaire is completed by the respondent him/herself;

g) data quality control must be performed at a very early stage, in order to confirm the completeness and accuracy of the data.

As regards data collection, which is the crucial aspect for the reliability of the survey, the EQDP was designed for detainee self-administration, using either a computer-assisted personal interviewing (CAPI) system or more traditional paper questionnaires. Face-to-face interviews could be considered, although they cannot be conducted in certain countries, due to the regulations applied in some prisons. In connection with this, the methodological guidelines emphasise the fact that the type of data collection procedure chosen defines the quality and quantity of the survey results. Indeed, certain methods could cause unsurmountable problems, whereas others are ideal for their easy and efficacious resolution.

Structure of the EQDP

The EQDP consists of various parts. The first part regards information of a general nature, such as age, nationality, country of birth, judicial status, number of prison terms served and their extemporaneous and overall duration. The second part is dedicated to substance use both outside of and inside prison, and the detainee is asked to specify which substances he/she has used and for how long, as well as the age at which he/she used them for the first time. The next part collects information on the injecting of substances and other behaviour constituting a risk for health (sharing of needles and syringes for the injection of substances, non-professional tattoos), through to, in the fourth and fifth parts, details regarding the detainee's health status and the use of drug addiction services, by investigating HIV, HBV and HCV infection, establishing whether blood tests have been performed for these viruses, infection awareness and any treatment received in- and outside of prison. At the end of the questionnaire, the detainee is asked to declare the presence of any mental health issues or prior overdose episodes. The full Italian translation of the EQDP is provided in the supplementary materials available online.

Results

This experience is based on the data collected by the Penitentiary Health Unit of Padua Local Health Authority no. 16, following the administration of the EQDP to 2 groups of male detainees in normal prisons (November 2016) or, in a previous survey, subject

to detention in open prisons (April 2016). In the survey conducted on detainees subject to normal incarceration, which was self-administered to a group of 40 prisoners in November 2016, some of the prisoners were substance users (who therefore constituted the percentage of users out of the whole detainee population) and were being treated for addiction disorder. In the survey conducted amongst open-prison detainees, which was administered in face-to-face (F2F) interviews in April 2016, all the detainees were known to be substance users, who had entered the open-prison scheme voluntarily and who were receiving more intensive addiction disorder treatment.

The average age of the normal detainees was 34.0±10.3 years. The breakdown of the age brackets in the two groups (normal incarceration vs open-prison) is shown in Figure 2. Data regarding the prisoners' nationality was available for 38 subjects. 14 (36.8%) were Italian, and 24 (63.2%) were foreign nationals (9 from Eastern Europe, 12 from Northern African countries and 3 from other countries). It was possible to ascertain the judicial status of 35 patients: 16 (45.7%) were awaiting trial; 2 (5.7%) had already being tried and were awaiting an appeal, and 17 (48.6%) had been sentenced. Data regarding the duration of incarceration at the time of the survey were obtained for 32 subjects. Of these, 14 (35.0%) had been in prison for <6 months; 13 (32.5%) from 6 months to 1 year; 8 (20.0%) between 1 and 5 years; and 2 (5.0%) longer than 5 years. Two patients (7.5%) did not specify how long they had been detained for.

As regards substance use, the illegal substance most commonly used during the individual's lifetime, the previous year and the 30 days prior to incarceration was cocaine. During imprisonment, the use of illegal substances is around 20%. The most commonly used substances were cannabis, opioids and cocaine. The declared lower consumption of opioids was lower amongst normal detainees than those in open prisons. Furthermore, fewer normal detainees had used abuse substances during prior imprisonment than those in open prisons. Opioid consumption was lower both outside the prison and during incarceration, whereas for cocaine and THC, external use was intense but that inside prison was less so, showing a higher risk of use in prison amongst subjects with overt and recognised addiction problems.

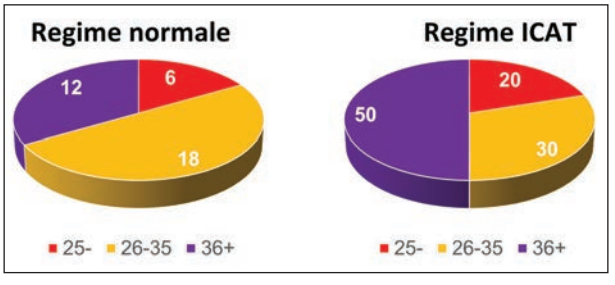

Figure 2. Distribution of the age brackets involved in the survey, broken down according to type of imprisonment.

History of tobacco consumption. The tobacco consumption rate was 82.1% amongst normal detainees and very similar for open-prison detainees (82.5%). Use inside the prison was seen to be considerably higher amongst normal prisoners than those in open prisons, for both the current and previous incarcerations (42.5% and 67.5% vs 20.0% and 5.0%, respectively). In addition, almost half stated they had smoked tobacco in the month prior to incarceration, for both normal and open-prison detainees (48.7% and 42.5%, respectively) (Figure 3).

History of alcohol consumption. The alcohol consumption rate was seen to be 74.4% amongst normal prisoners and very similar for open-prison detainees (77.5%). None of the prisoners said they had consumed alcohol in the current place of imprisonment amongst normal detainees, versus 5.0% amongst those in open prisons, whereas a rate of 10% was declared for previous incarcerations (vs. 17.5% amongst those in open prisons). Consumption was higher during the month preceding imprisonment for both groups (41.0% and 37.5%) (Figure 4).

History of THC consumption 55.6% of normal detainees declared using THC at some point in their lifetime; this percentage was higher amongst individuals in open prisons (77.5%). Just 5% of normal detainees said they used this substance during their current prison sentence (12.5% for those in open prisons), compared to 17.5% during previous prison sentences (30.0% amongst those in open prisons); this figure is slightly lower than that declared for the month prior to incarceration (27.8%; 22. % in open prisons) (Figure 5).

History of cocaine consumption 69.2% of normal detainees declared using cocaine at some point in their

	% Normal regime	% ICAT
Lifetime	82,1%	82,5%
→ *Age at first usage*	*15,7 + 3,8 yrs*	
1 yr before imprisonment	51,3%	45,0%
30 dd before imprisonment	48,7%	42,5%
→ *Frequency of usage (mode)*	*20+ dd in 30 dd (70,0%)*	
Used inside prison	42,5%	20,0%
First usage inside prison	10,0% (12,5% of lifetime users)	
Used during current imprisonment	67,5%	5,0%
→ Used last 12 mm		
→ Used last 30 dd		
→ *Frequency of usage (mode)*	*20+ dd in 30 dd (63,0%)*	

Figure 3. Tobacco consumption rates amongst normal and open-prison detainees.

	% Normal regime	% ICAT
Lifetime	55,6%	77,5%
→ *Age at first usage*	*17,2+5,3 yrs*	
1 yr before imprisonment	41,7%	42,5%
30 dd before imprisonment	27,8%	22,5%
→ *Frequency of usage (mode)*	*20+ dd in 30 dd (29,4%)*	
Used inside prison	17,5%	30,0%
First usage inside prison	2,5% (5,0% of lifetime users)	
Used during current imprisonment	5,0%	12,5%
→ Used last 12 mm		
→ Used last 30 dd		
→ *Frequency of usage (mode)*	*n/a*	

Figure 5. THC consumption rates amongst normal and open-prison detainees.

life. This figure was significantly higher amongst those in open prisons and reached 87.5% (Figure 6). None of them used it during their current prison sentence (5.0% amongst those in open prisons), compared to 7.5% during previous periods in prison (25.0% amongst those in open prisons), and 41.0% in the month before imprisonment (50.0% amongst those in open prisons).

History of psychostimulant use: The use of psychostimulants amongst detainees was absent during both current and previous prison terms, with a usage rate at some point in life of 16.7% and in the month before imprisonment of 8.3%. Once again, use at some point in life was significantly higher amongst those in open prisons (47.5%) (Figure 7).

History of hallucinogen use 8.6% of normal detainees declared using hallucinogens at some point in their lives, whereas none said that they had used this type of substance whilst serving their current or previous prison sentences. Amongst open-prison detainees, the declared consumption of these substances at some

	% Normal regime	% ICAT
Lifetime	69,2%	87,5%
→ *Age at first usage*	*21,6+7,3 yrs*	
1 yr before imprisonment	53,8%	65,0%
30 dd before imprisonment	41,0%	50,0%
→ *Frequency of usage (mode)*	*20+ dd in 30 dd (25,0%)*	
Used inside prison	7,5%	25,0%
First usage inside prison	0,0% (0,0% of lifetime users)	
Used during current imprisonment	0,0%	5,0%
→ Used last 12 mm		
→ Used last 30 dd		
→ *Frequency of usage (mode)*	*n/a*	

Figure 6. Cocaine consumption rates amongst normal and open-prison detainees.

point in life is more than four times greater (37.5%) (Figure 8). Consumption was also low in the month prior to imprisonment in both groups (2.9% and 5.0% amongst normal and open-prison detainees, respectively).

History of opioid consumption. A quarter of all patients (25.0%) said they had used this kind of sub-

	% Normal regime	% ICAT
Lifetime	74,4%	77,5%
→ *Age at first usage*	*17,2+4,4 yrs*	
1 yr before imprisonment	56,4%	50,0%
30 dd before imprisonment	41,0%	37,5%
→ *Frequency of usage (mode)*	*20+ dd in 30 dd (37,8%)*	
Used inside prison	10,0%	17,5%
First usage inside prison	5,0% (6,9% of lifetime users)	
Used during current imprisonment	0,0%	5,0%
→ Used last 12 mm		
→ Used last 30 dd		
→ *Frequency of usage (mode)*	*n/a*	

Figure 4. Alcohol consumption rates amongst normal and open-prison detainees.

	% Normal regime	% ICAT
Lifetime	16,7%	47,5%
→ *Age at first usage*	*20,7+5,0 yrs (MDMA)*	
1 yr before imprisonment	11,1%	7,5%
30 dd before imprisonment	8,3%	2,5%
→ *Frequency of usage (mode)*	*n/a*	
Used inside prison	0,0%	5,0%
First usage inside prison	0,0% (0,0% of lifetime users)	
Used during current imprisonment	0,0%	0,0%
→ Used last 12 mm		
→ Used last 30 dd		
→ *Frequency of usage (mode)*	*n/a*	

Figure 7. Stimulant consumption rates amongst normal and open-prison detainees.

stance at some point in their life; this rate was significantly lower than amongst open-prison detainees (57.5%). 16.7% of normal detainees (22.5% of those in an open prison) used opioids in the month prior to their imprisonment, and the usage rate was identical for the current and previous prison terms (7.5% for both). The rate for previous imprisonment was higher for those in open prisons (27.5% vs 7.5%) (Figure 9).

History of sedative use. Declared use at some point in life by normal detainees is fairly low (8.6%), whereas it is higher for detainees in open prisons (25%) (Figure 10). The usage rate for the current and previous prison terms is the same (2.5%; 2.5% and 5.0% in open-prison detainees, respectively). Use during the previous month is slightly higher (5.7%; 7.5% in the open-prison system).

Figure 11 summarises the consumption rates for the various substances, for some point during life, prior to imprisonment and during imprisonment, for normal and open-prison detainees. The figures comparing normal detainees with those in open prisons with regard to use of abuse substances at some point in life are included in the supplementary online material.

	% Normal regime	ICAT
Lifetime	8,6%	37,5%
→ *Age at first usage*	*18,0+0,0 yrs (mushrooms)*	
1 yr before imprisonment	5,8%	7,5%
30 dd before imprisonment	2,9%	5,0%
→ *Frequency of usage (mode)*	*n/a*	
Used inside prison	0,0%	2,5%
First usage inside prison	0,0% (0,0% of lifetime users)	
Used during current imprisonment	0,0%	0,0%
→ Used last 12 mm		
→ Used last 30 dd		
→ *Frequency of usage (mode)*	*n/a*	

Figure 8. Hallucinogen consumption rates amongst normal and open-prison detainees.

	% Normal regime	% ICAT
Lifetime	25,0%	57,5%
→ *Age at first usage*	*26,5+8,2 yrs*	
1 yr before imprisonment	19,5%	27,5%
30 dd before imprisonment	16,7%	22,5%
→ *Frequency of usage (mode)*	*1-3 dd in 30 dd (11,4%)*	
Used inside prison	7,5%	27,5%
First usage inside prison	2,5% (11,1% of lifetime users)	
Used during current imprisonment	7,5% (meth.)	7,5% (bupr.)
→ Used last 12 mm		
→ Used last 30 dd		
→ *Frequency of usage (mode)*	*n/a*	

Figure 9. Opioid consumption rates amongst normal and open-prison detainees.

	% Normal regime	% ICAT
Lifetime	8,6%	25,0%
→ *Age at first usage*	*22,0+4,2 yrs (BDZ)*	
1 yr before imprisonment	5,7%	10,0%
30 dd before imprisonment	5,7%	7,5%
→ *Frequency of usage (mode)*	*n/a*	
Used inside prison	2,5%	5,0%
First usage inside prison	2,5% (33,3% of lifetime users)	
Used during current imprisonment	2,5%	2,5%
→ Used last 12 mm		
→ Used last 30 dd		
→ *Frequency of usage (mode)*	*n/a*	

Figure 10. Sedative consumption rates amongst normal and open-prison detainees.

An overall analysis of the data shows that substance use is more common amongst open-prison patients, i.e. those with a recognised and confirmed addiction. Indeed, these detainees often continue substance use during imprisonment, showing a composite abuse pattern (stimulants, hallucinogens, opioids), combined with benzodiazepine misuse. Conversely, amongst normal detainees, the high rate of substance use prior to imprisonment drops dramatically during incarceration and there is no evidence of specific composite abuse patterns or benzodiazepine misuse. However, normal detainees deserve special attention, because they often share needles or equipment, most likely because they are less aware of the risks, unlike those in open prisons, amongst whom the higher drug-injection rate is not associated with needle or syringe sharing (Figure 12). Therefore, in our opinion, the specific open prison population could require and benefit from special programmes and schemes, as it is at a greater risk of use during imprisonment, because they are individuals with confirmed and recognised problems.

The collection of data on health in terms of HIV, HBV and HCV revealed a number of differences between the testing performed outside of prison and during imprisonment. With regard to HIV, approximately half of all subjects had already had a test before their imprisonment, whereas during current prison term the percentage rose even further, to more than 2/3 of subjects. All subjects declared testing negative.

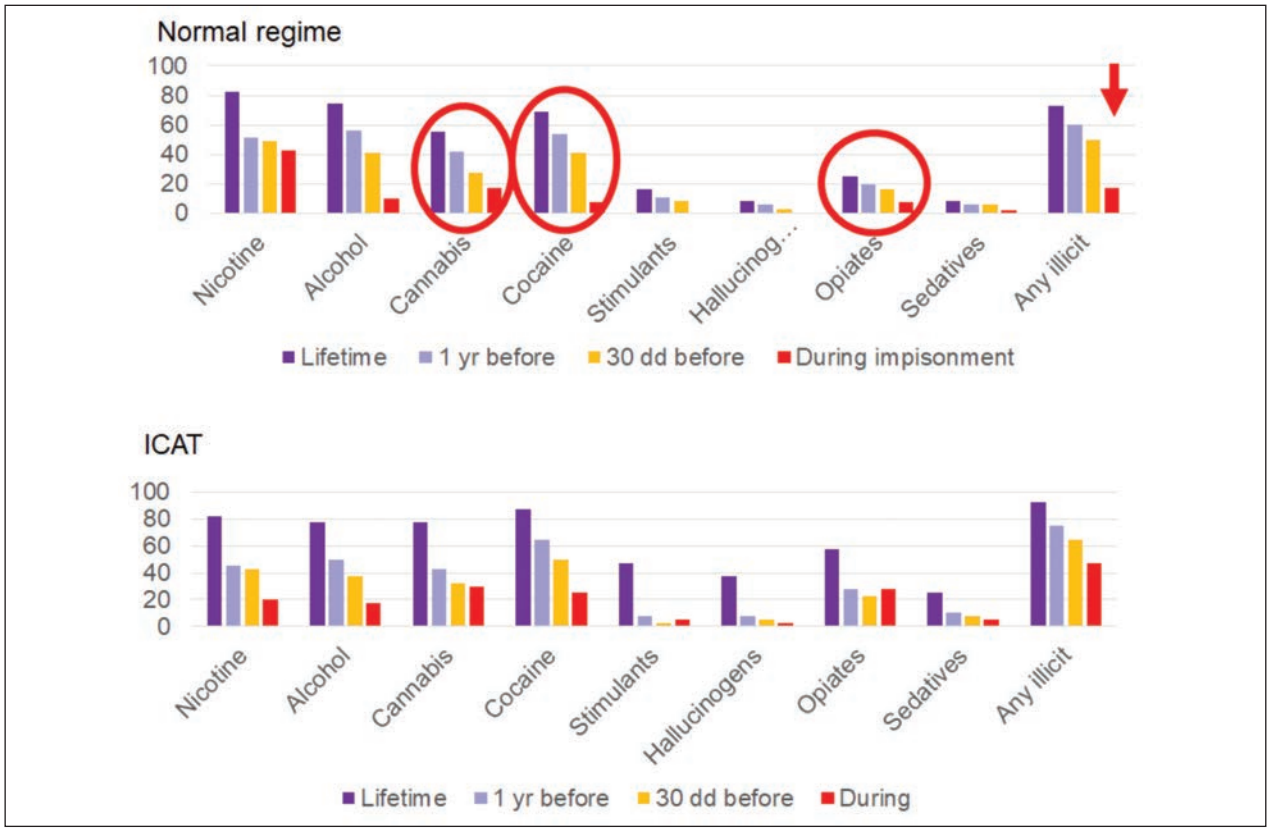

Figure 11. Consumption rates for the various substances, at some point during life, prior to imprisonment and during imprisonment, for normal and open-prison detainees.

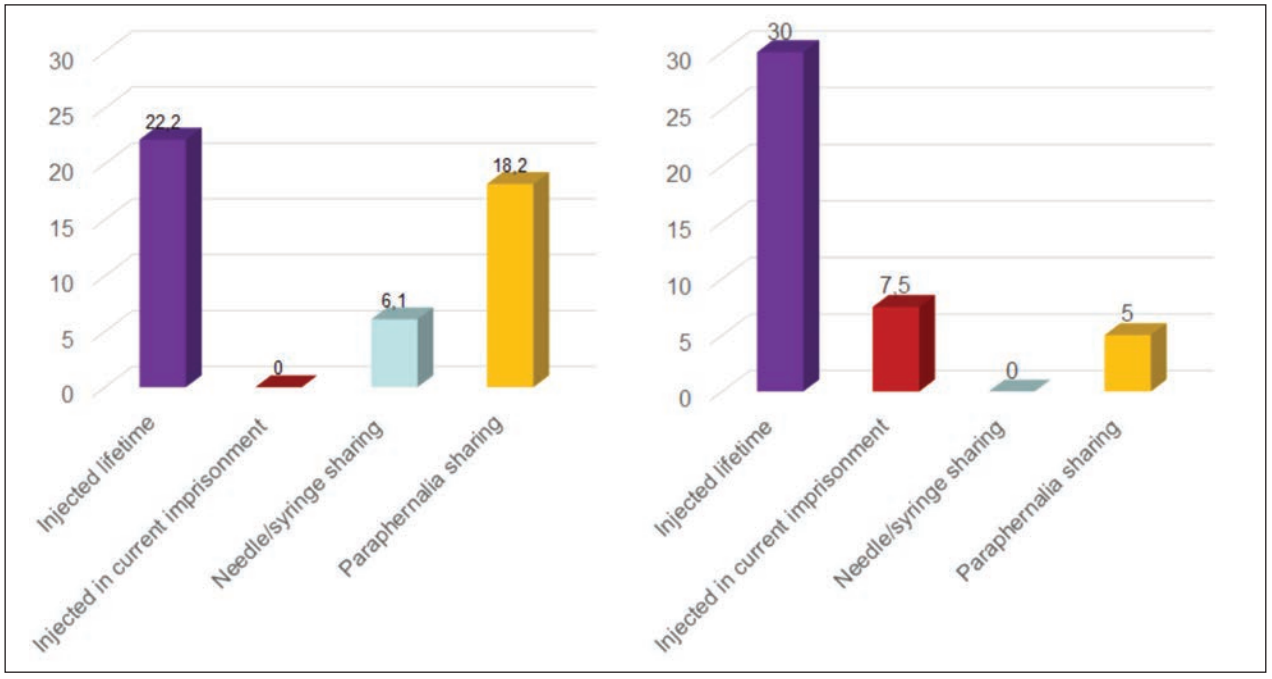

Figure 12. Differences between normal and open-prison detainees with regard to the various at-risk behaviours.

(Figure 13a). The rates for HBV testing out of prison were lower, and only approximately one third of subjects had been tested before imprisonment, whereas the rate for testing in prison was 50%. As for HIV infection, once again all subjects said they were negative for HBV. The vaccination rate is relatively low, as just 1 in 5 subjects said they had been vaccinated (Figure 13b). As far as HCV testing was concerned, just 30% said they had been tested outside of prison; this percentage rose to 60% during imprisonment. As for the other diseases, all subjects said they had tested negative (Figure 13c).

The analysis of the results showed that amongst detainees in open prisons, a higher percentage of subjects have been tested for HIV, HBV and HCV, as detainees under normal imprisonment conditions were almost all unaware of their infection status and less aware of their health conditions in general.

As regards mental/psychiatric health status, more than half had not had any psychiatric assessment during their current prison term and just 11% take medication for mental disorders. Conversely, almost 68% of open-prison detainees have had one, two or more psychiatric assessments during their current prison term, unlike the situation out of prison (30%). A far higher percentage also took medication for mental disorders during their current prison term (52.5%) (Figure 14).

Differences between normal and open-prison detainees were also observed with regard to access to the various social and health services during their current prison term. For instance, whereas all open-prison patients had a check-up upon arrival and received counselling, amongst normal detainees these were not guaranteed in approximately 15% and 30% of cases, respectively. Low rates were also observed for replacement therapy for opioid addiction and detoxification, which were provided in under 20% of cases of normal imprisonment and in under 30% of detainees in open prisons (Figure 15). The analysis of the data collected therefore showed a poor level of use of resources and facilities inside prison for normal detainees with regard to the main areas of care (counselling, psychiatric assessment, screening for infectious diseases). However, the different characteristics of the open-prison system make it easier for this type of detainee to use resources and facilities, although this does not always translate into a great attention with regard to their health, as demonstrated, for example, by the low HBV vaccination rate, despite the at-risk behaviour of this population (Figure 16).

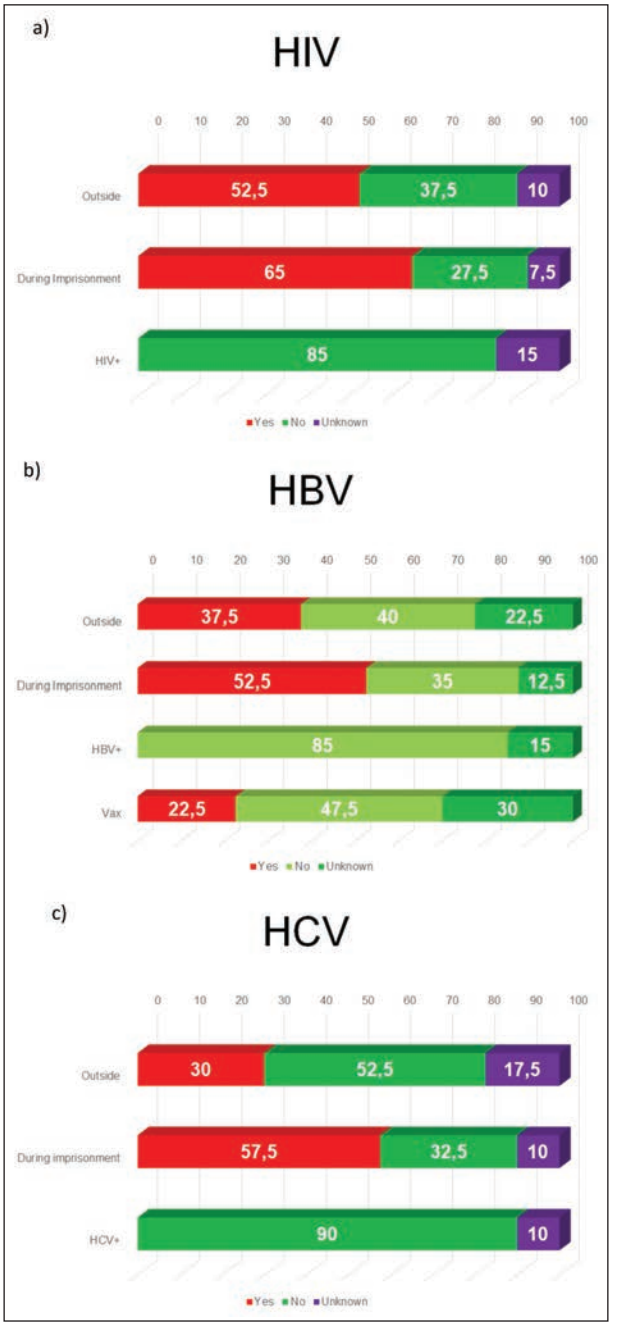

Figure 13. HIV, HBV and HVC screening rates outside of prison and during incarceration.

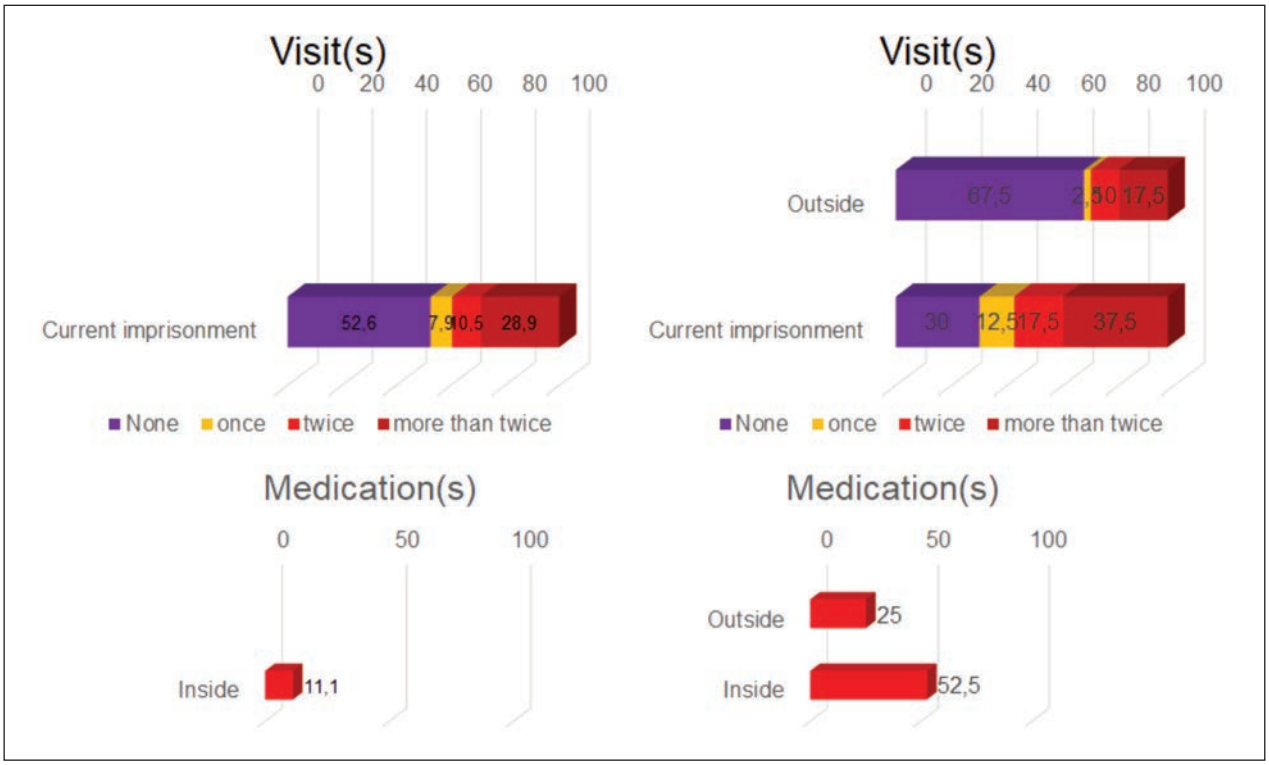

Figure 14. Psychiatric intervention outside of prison and during imprisonment, amongst normal and open-prison detainees.

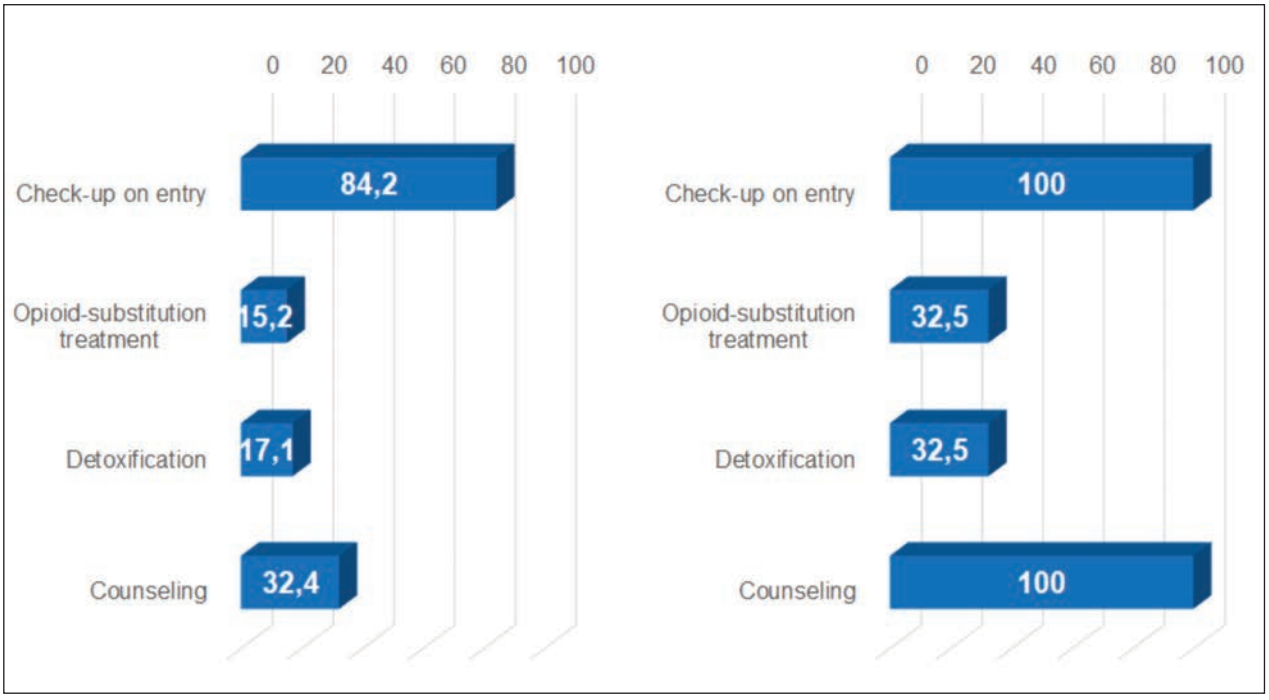

Figure 15. Access to social and healthcare services during imprisonment, amongst normal and open-prison detainees.

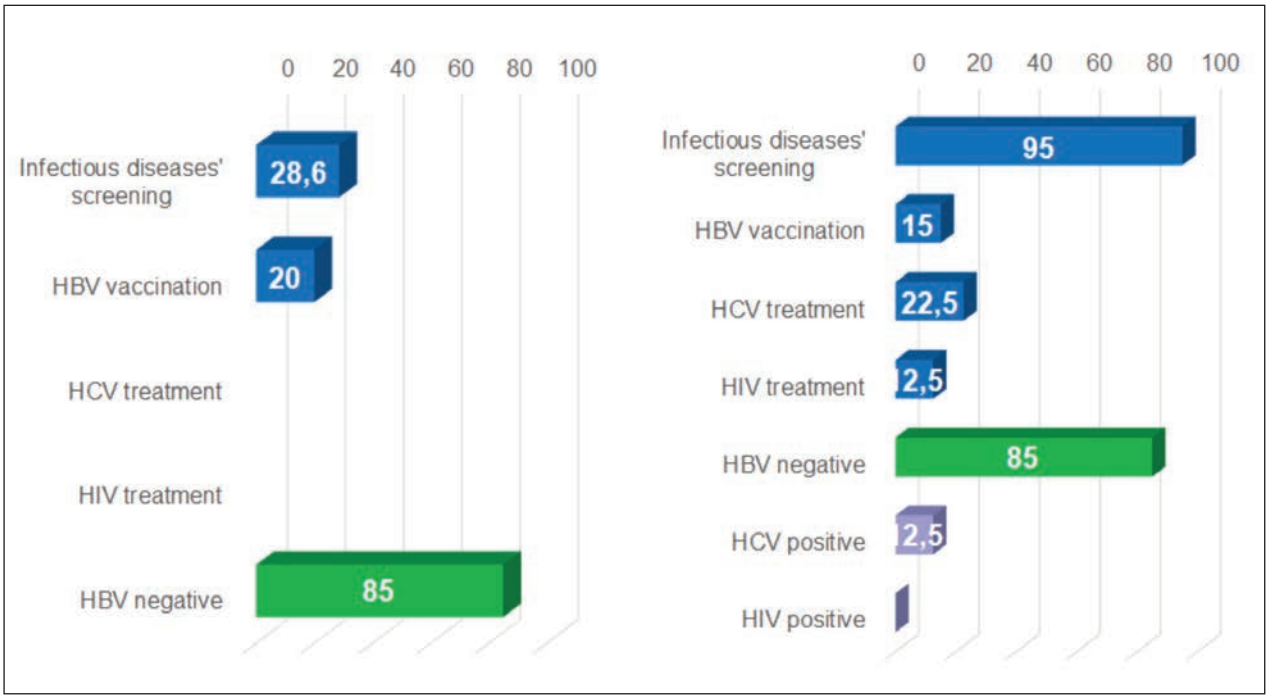

Figure 16. Access to infectious diseases screening services - including for HIV, HBV and HCV infection - during imprisonment, amongst normal and open-prison detainees.

Conclusions

The prison population represents a set of subjects in whom substance use constitutes one of the main health-related issues with regard to both frequency and severity. More specifically, infectious diseases, especially those that are sexually-transmitted or blood-borne, including HIV, HBV and HCV, are common amongst detainees, many of whom are arrested for criminal offences associated with substance use. The high risk of contracting these infections is directly related also to the poor hygiene conditions and inadequate healthcare provided in prison. Previous studies and surveys in this field have shown that the prison population is characterised by higher positivity rates for a number of infectious diseases, including HCV, due primarily to the presence of at-risk lifestyles associated with family, psychiatric and social problems existing prior to imprisonment, to which the problems that are characteristic of incarceration (tattooing, overcrowding, fighting, sexual promiscuity and syringe sharing) are then added.

Our survey, which was conducted using the specially-designed EQDP amongst detainees in two different types of imprisonment, the normal and open-prison systems, showed that in the former case health status is not declared by this group of detainees, which is less aware of their health and receives less intervention to mitigate risks. In the open-prison group, although the detainees say they are more aware of their health, many of them continue to use substances during their prison term, with higher substance use rates than amongst normal detainees. In addition, given the difficulties in obtaining sterile needles and syringes, the sharing of the equipment and tools using for injection increases the risk of infectious disease transmission. Consequently, this situation may constitute the opportunity to implement, amongst open-prison detainees, a series of risk-mitigation measures that are efficacious in improving self-awareness in terms of a greater use of blood tests and treatments for infectious diseases.

The Italian version of the EQDP was administered in two different ways to the two groups of prisoners: in

the normal detainee group it was self-administered by the prisoners, who answered the questions directly and in a confidential manner, whereas in the open-prison system it was administered by face-to-face interviews. Both approaches have advantages and disadvantages: indeed, questionnaire self-administration has advantages over F2F administration in terms of temporal efficiency and confidentiality, but can obtain less accurate answers and a significant amount of missing or inadequate information. Another possible hindrance to the use of the questionnaire is associated with the presence in Italy of a considerable number of foreign prisoners (mainly of North African, Albanian and Romanian), who represent one third of the prison population and whose understanding of questions in another language may be limited. For this reason, we have hypothesised two different options: 1) the creation of a special version for subjects who have been in prison for less than one year (or other period to be defined); 2) F2F administration, which could be useful also for illiterate prisoners.

In short, the results of our survey bring to light not only the inadequacies regarding the identification, control or awareness of diseases associated with the use of substances in prison, but also the need to pursue a number of goals for the future, which could include: extending screening to all prisoners with a history of substance use, regardless of the method of administration or severity of their dependence; targeted patient management; antiviral treatment and the implementation of harm-reduction policies at all stages; prevention activities both inside and outside of prison. This type of approach could be advantageous for both occasional users with mild/moderate dependence and in those with more severe addictions, thanks to the possibility of close-range prevention and treatment strategies that are, therefore, more efficacious and proactive.

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