Acta Biomed 2018; Vol. 89, Supplement 10: 5-18 DOI: 10.23750/abm.v89i10-S.7965

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).

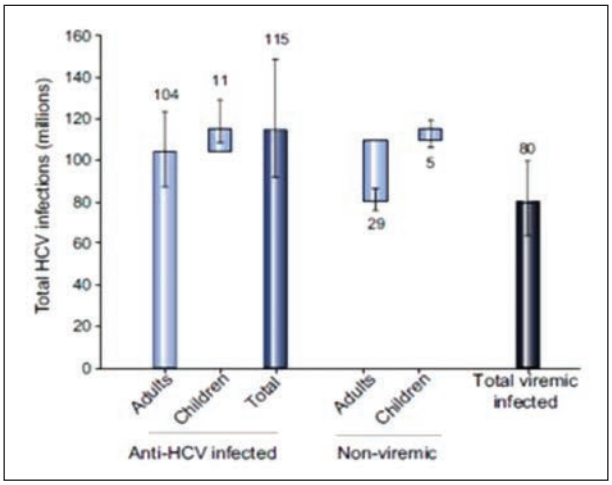
In 2016, the 69th World Health Assembly approved the Global Health Sector Strategy to eliminate hepatitis infection by 2030, (4) and WHO introduced global targets for the care and management of HCV including "a 90% reduction in new cases of chronic hepatitis C, a 65% reduction in hepatitis C deaths, 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),

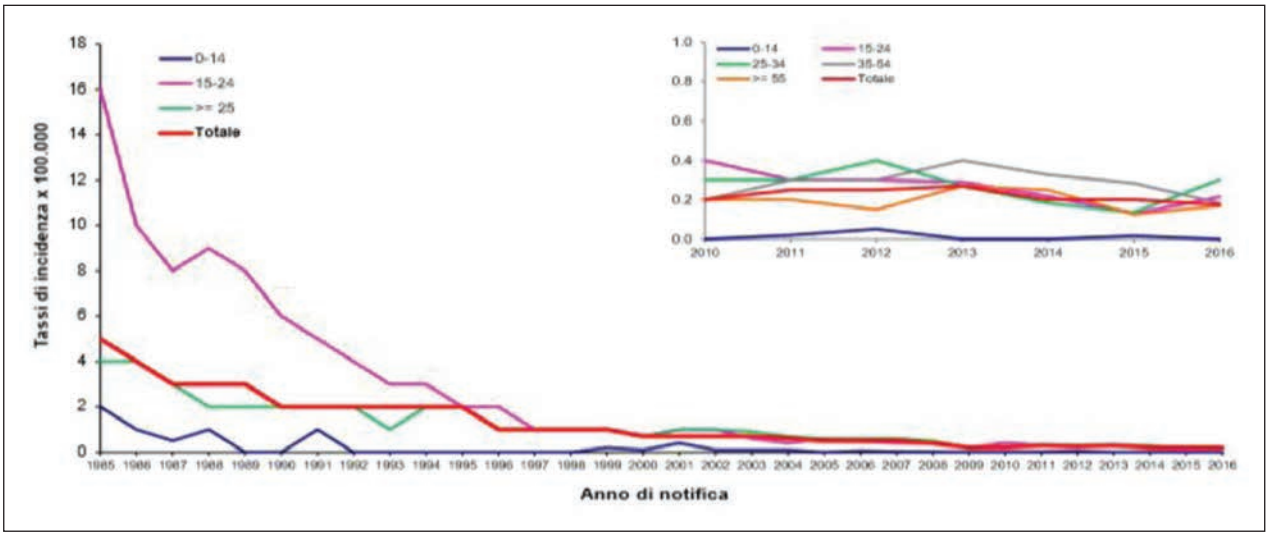
In Italy, the incidence of HCV has decreased from 5 per 100,000 in 1985 to 1 per 100,000 in 1996 (15).

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

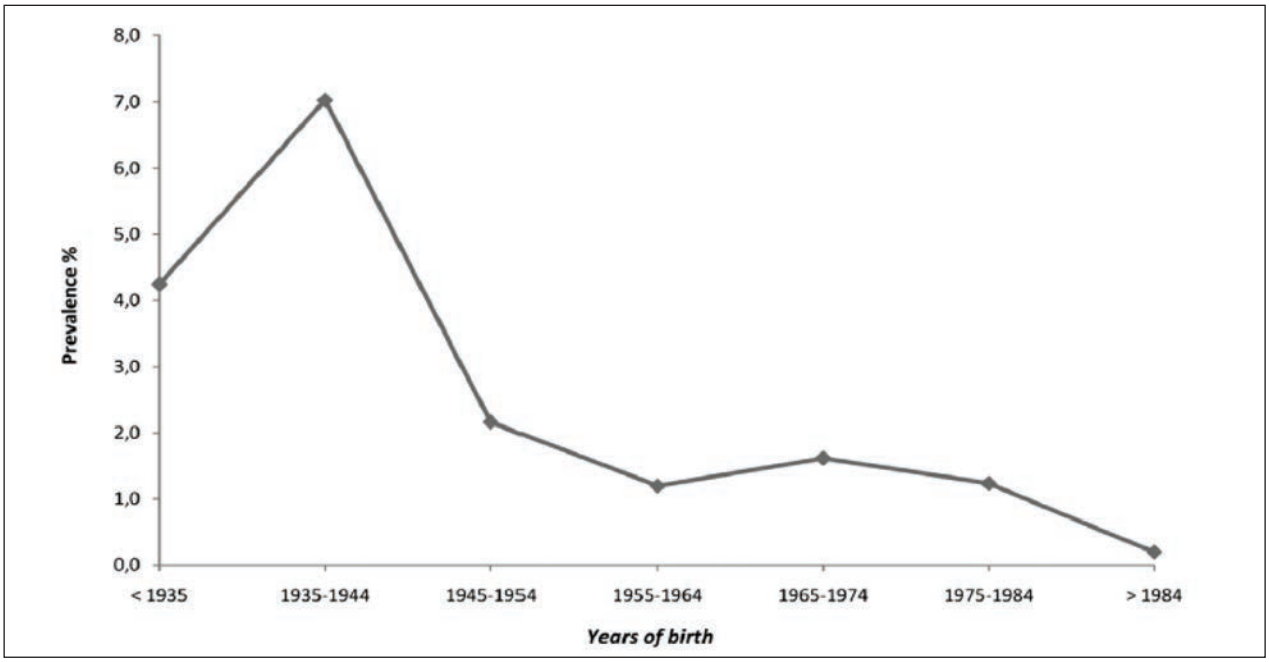
* fino al 2008 Epatite NonA-NonB

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

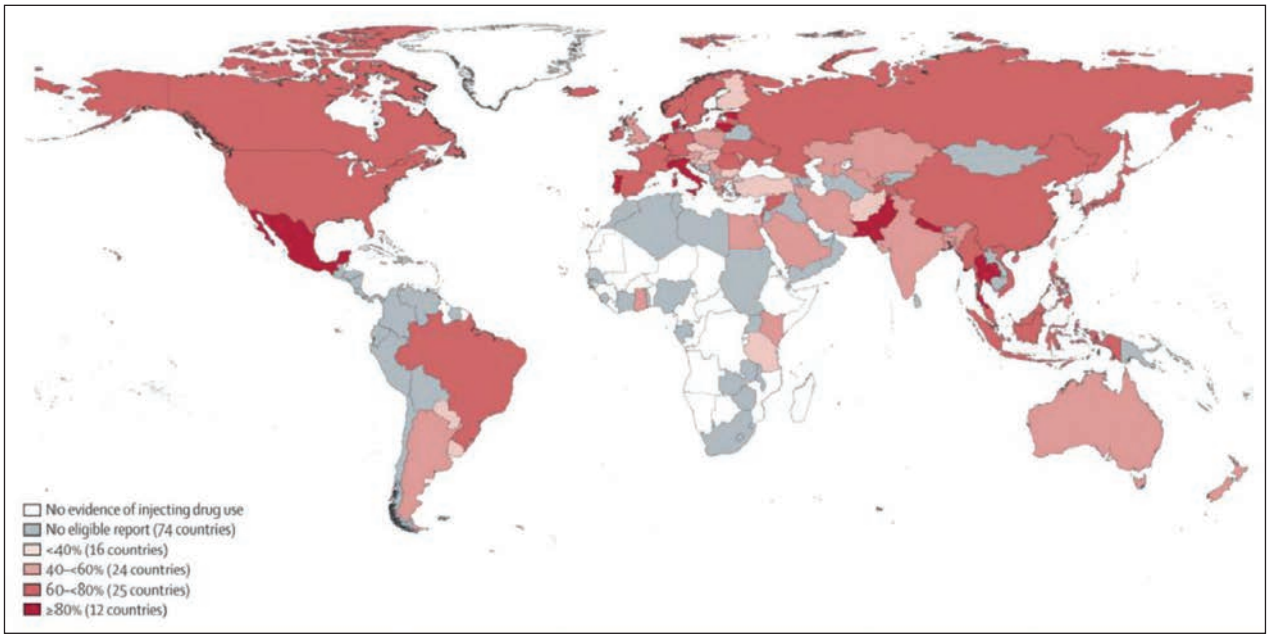


Figure 1. Prevalence of anti-HCV in PWID (29)

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

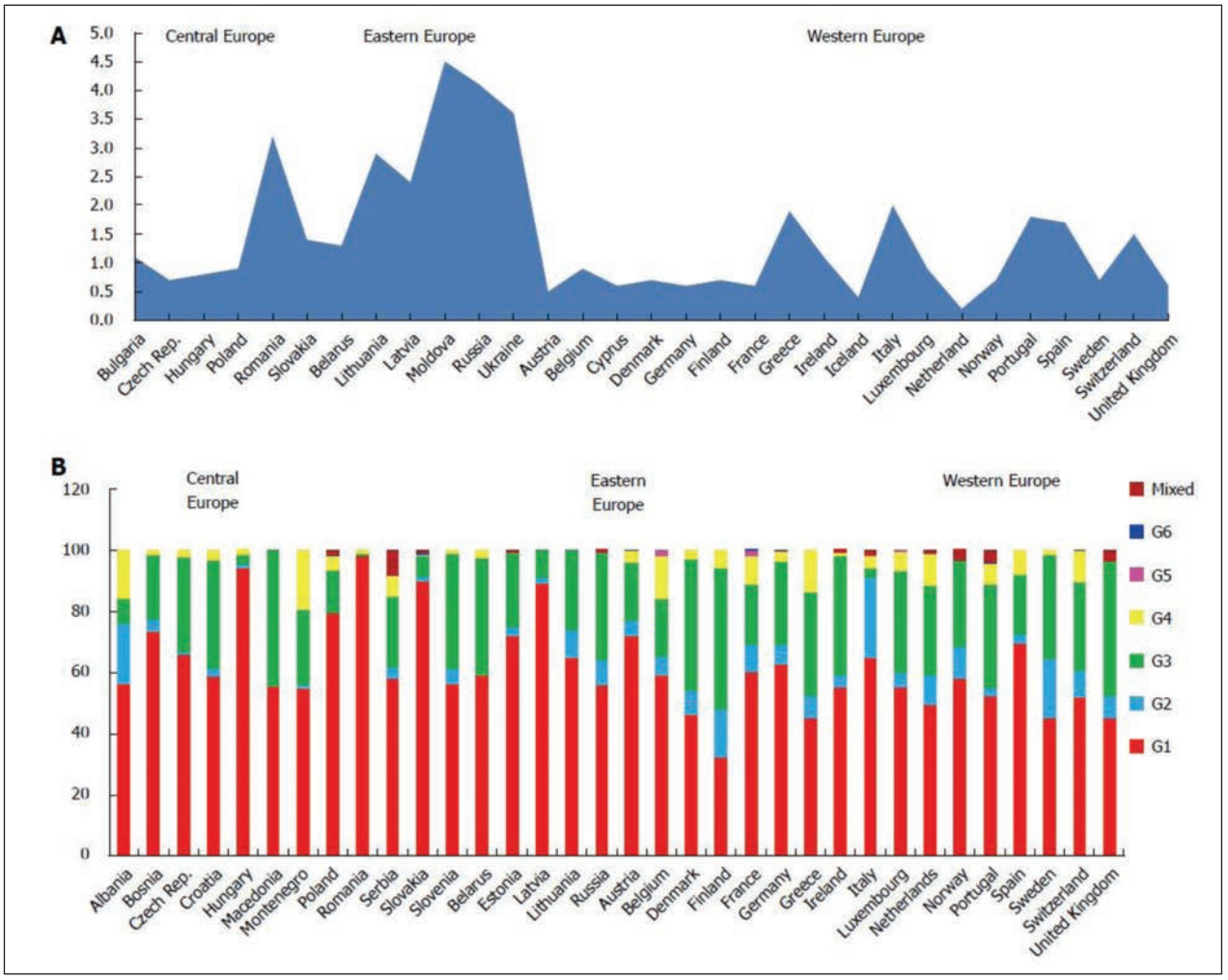
The distribution of HCV genotypes/subtypes differs significantly between people who inject drugs (PWID) and the general population. HCV genotypes that previously exhibited a limited geographical distribution (3a, 4) are becoming more prevalent in this high-risk group. Immigration from HCV-endemic countries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

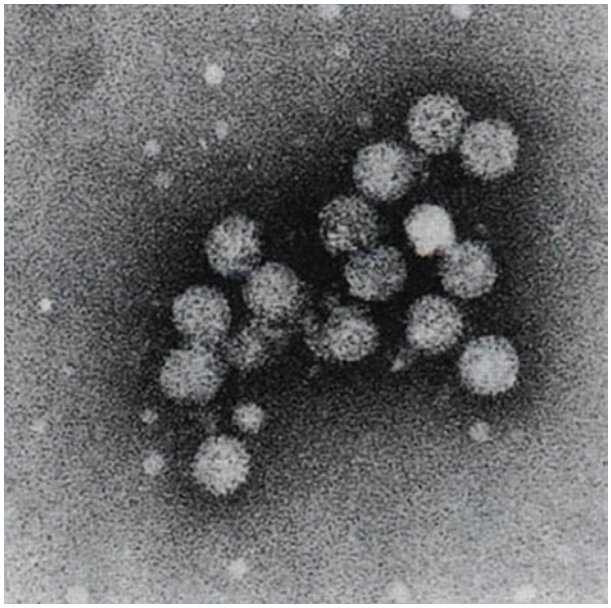


Figure 4. Hepatitis C Virus

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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Received: 29 September 2018
Accepted: 25 October 2018
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