

# Hepatitis delta infection in Italian patients: towards the end of the story?

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## Abstract

**Background** The endemicity of hepatitis delta virus infection in Italy has decreased in the last decades.

**Aim** To evaluate the current epidemiology of chronic delta infection in Italy and to compare the present findings with the corresponding figures from the previous studies.

**Methods** A cross-sectional study involving 16 referral centres scattered all over the country in 2014.

**Results** Out of the 513 hepatitis B surface antigen-positive subjects enrolled, 61 (11.9%) were anti-delta positive, with

a sex ratio (M/F) of 2.05. The majority (80.3%) of them was 50 years or older, while the proportion of subjects younger than 30 years of age was as low as 3.3%. No difference was detected by geographical area of residence. The presence of liver cirrhosis was diagnosed in 52.4% of cases. In comparison to previous studies, a further shift towards the oldest age groups and an increasing proportion of subjects having liver cirrhosis among all anti-delta-positive subjects are observed.

**Conclusions** Currently, hepatitis delta infection mostly affects old people who have an advanced but indolent liver disease, reflecting a survival effect. The defective hepatitis delta virus is near to disappear in the country, where it has been discovered in the second half of 70s.

The members of EPACRON study group are listed in Acknowledgements.

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**Keywords** HDV infection · HBsAg · Cirrhosis · Epidemiology

## Abbreviations

HDV	Hepatitis delta virus
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
anti-HDV	Antibodies to delta virus
HCC	Hepatocellular carcinoma
AFP	Alpha-fetoprotein

## Introduction

Hepatitis delta virus (HDV) discovered in the 1970s [1, 2] is a defective RNA virus requiring the helper function of hepatitis B virus (HBV) to establish its own infection. This discovery opened a new window for the knowledge of liver diseases adding important new issues even to the natural history of HBV infection. At that time, HDV was endemic

in Italy, particularly in Southern areas, accounting for the majority of cases of juvenile cirrhosis [3]. High prevalence rates of HDV infection were worldwide reported, especially in Mediterranean areas, Eastern Europe, the Amazon basin and central Asia [4].

In Italy, after the introduction of the mass immunization campaign against HBV in 1991 for 3-month-old infants and for subjects of 12 years of age (the latter limited to the first 12 years of campaign), a control even of HDV infection was expected. In fact, since the second half of 80s the incidence rate of acute HDV per million of inhabitants progressively declined from 3.1 cases in 1987 to 0.5 cases in 2004 [5, 6]. The downward trend was mostly affecting the 15–24 years old age group, both reflected the decreased pool of chronic hepatitis B surface antigen (HBsAg) carriers [7], and the impact of mass immunization campaign against HBV.

Similarly, the prevalence of antibodies to delta virus (anti-HDV) evaluated among cohorts of chronic HBsAg carriers referring Italian hospitals progressively declined over time, being 23.4% in 1987 [8], 14.0% in 1992 [9], 8.3% in 1997 [10], 5.7% in 2001 [11], and 8.1% in 2006 [12], respectively.

In this paper, we report the results of a further national survey performed in 2014 on the epidemiology of chronic HDV infection in Italy. Moreover, the present findings have been compared with the corresponding figures from the previous studies [8–12] to detect changes, if any.

## Materials and methods

All HBsAg-positive subjects consecutively referring in 2014, as either inpatients or outpatients, to 16 Liver Units were recruited. Patients with acute B hepatitis were excluded from the study. The Liver Units participating were located throughout the country.

Liver cirrhosis was diagnosed by liver biopsy or on the presence of the characteristics of clinical, biochemical and ultrasound signs [13]. The diagnosis of hepatocellular carcinoma (HCC) was based on histological and/or imaging findings and on serum alpha-fetoprotein (AFP) levels, according to accepted criteria [14].

The collection of personal data was made in full compliance with the Italian law on personal data collection, and each patient gave his/her informed consent to participate. All procedures applied in the study were in accordance with the international guidelines, with the standards of human experimentation of the local Ethics Committees, and with the Helsinki Declaration of 1975, revised in 1983. Each patient signed informed consent for the collection of personal data, established in full agreement with the rules of the Ethic Committee of the coordinating centre (A.O.U.P.

of Palermo, Italy). Patients who agreed to undergo liver biopsy signed informed consent before this procedure was performed. All patients were included only once, i.e. at the first observation during the study period. For each patient, demographic, clinical, and etiological data were recorded using a pre-coded questionnaire (Air-Tel telematica, Italy).

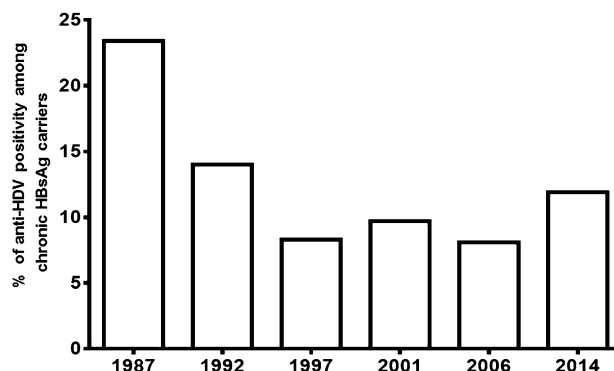
HBV serum markers and antibodies to hepatitis D virus (anti-HDV) were determined by commercial immunoenzymatic assays.

## Statistical analysis

Categorical variables were summarized as absolute counts and proportions. Differences in proportion were evaluated by Chi square test or Fisher's exact test. A  $p$  value  $<0.05$  was considered to be significant. Crude odds ratios (ORs) for the association of anti-HDV positivity with different variables were calculated by univariate analysis. The reference category for ORs estimates was no exposure or the most favourable level of exposure.

## Results

During the study period, 513 chronic HBsAg carriers were enrolled. All were tested for anti-HDV. Among them, 61 (11.9%) had an anti-HDV-positive test result, a figure slightly higher than those reported in the studies performed since the year 1997 (Fig. 1). The main characteristics of the 61 anti-HDV-positive subjects are reported in Table 1. Sex ratio (male/female) was 2.05, and the majority (80.3%) of subjects were 50 years or older, while the proportion of subjects younger than 30 years of age was as low as 3.3%. Twelve (19.7%) of these 61 were anti-HCV positive. Liver biopsy was performed in 24.6% of cases, liver cirrhosis was diagnosed in 32 subjects (52.4%) and in three of them HCC was detected.



**Fig. 1** Prevalence of anti-HDV positivity among chronic HBsAg carriers in Italy over time

**Table 1** Study population of 61 anti-HDV-positive subjects

Characteristic	No (%)
Anti-HDV prevalence (HDV+/HBsAg+)	61/513 (11.9)
Sex ratio (M/F)	41/20 (2.05)
Age-distribution (years)	
0–29	2 (3.3)
20–49	10 (16.4)
>49	49 (80.3)
Liver biopsy	15 (24.6)
Presence of cirrhosis <sup>a</sup>	32 (52.4)

<sup>a</sup> Three subjects with hepatocellular carcinoma

The age-distribution of anti-HDV-positive subjects in Italy over time plotted in Fig. 2 provides interesting information. During the period 1987–2014, the proportion of cases in the age group of 0–29 and 30–49 years strongly decreased from 39.8 to 3.3% and from 50.6 to 16.4%, respectively. In contrast, the proportion of cases in subjects with 50 years or older increased from 9.6 to 80.3% (Table 2).

Anti-HDV prevalence was slightly higher in Northern/Centre than Southern/Islands areas (13.6 vs. 12.0%), a finding completely different from that observed in the previous surveys, which have shown a much higher prevalence than the latter regions.

Table 3 reports the sociodemographic characteristics of anti-HDV-positive subjects, the potential risk factors and the crude ORs with their 95% Confidence Intervals (CI) derived from univariate analysis. The presence of cirrhosis resulted the sole variable significantly associated with HDV infection (OR 2.6, 95% CI 1.5–4.5). Since only one variable resulted associated, multiple logistic regression

**Table 2** Prevalence of anti-HDV positivity among chronic HBsAg carriers in Italy by geographical area, over time (1987–2014)

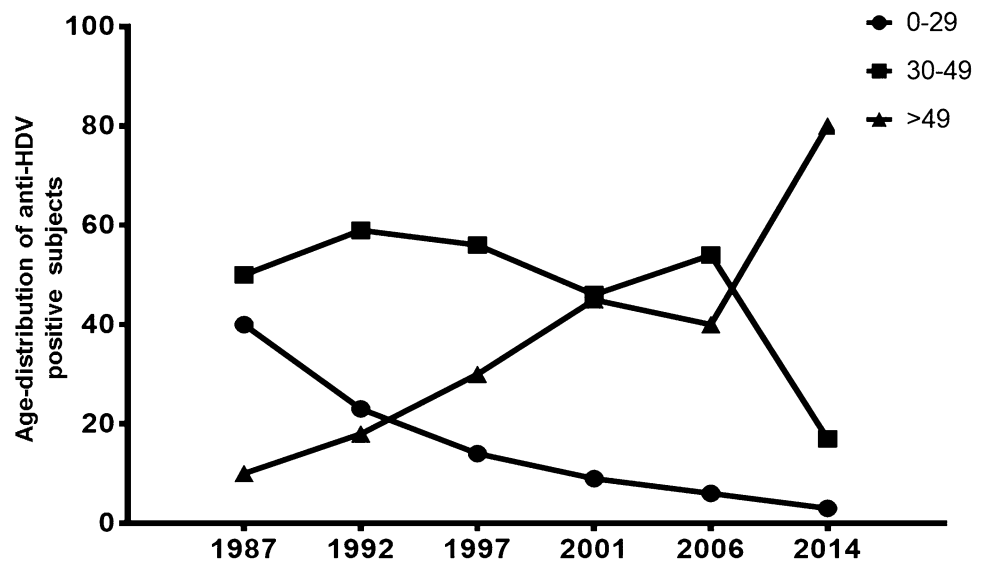
Year	Percent of patients with anti-HDV positivity among chronic HBsAg carriers		
	North/Centre (%)	South/Islands (%)	References
1987	13.1	26.6	[7]
1992	9.0	18.5	[8]
1997	1.9	11.3	[9]
2001	6.6	8.3	[10]
2006	8.7	6.7	[11]
2014	13.6	12.0	Present study

was not performed. Finally, the proportion of subjects with anti-HDV-positive patients with liver cirrhosis increased from 35.7% in 1987 to 52.4% in 2014 ( $p < 0.05$ ) (Table 4).

### Discussion

The data herein reported complete the picture of chronic HDV infection in Italy over a very long period (1987–2014). Since several units participating in the current survey took also part in all previous investigations, current findings are suitable to be compared with the previous ones. Despite the current anti-HDV prevalence is slightly higher than that observed in the previous study performed in 2006 (11.9 vs. 8.1%), we may assert that the spread of HDV infection in Italy is vanishing. Some lines of evidence support this evidence. Firstly, the age distribution of cases is mostly confined to people with more than 50 years of age, whilst people younger than 30 years account for only 3.3% of cases, Secondly, the proportion of

**Fig. 2** Age distribution of anti-HDV-positive subjects in HBsAg carriers in Italy from 1987 to 2014



**Table 3** Prevalence of anti-HDV positivity by sociodemographic characteristics and potential risk factors in 513 HBsAg-positive subjects, 2014

Characteristic	HBsAg-positive No of cases	Anti-HDV-positive % of cases	OR (95% CI)
Sex			
Females	183	10.9	1
Males	330	12.4	1.2 (0.7–1.5)
Age (years)			
0–29	15	13.3	1
30–49	126	7.9	0.6 (0.1–2.8)
>49	371	13.2	0.99 (0.2–4.5)
Area of residence			
North/Centre	103	13.6	1.2 (0.6–2.2)
South/Islands	375	12.0	1
Country of birth			
Italy	478	12.3	2.3 (0.5–9.9)
Outside Italy	35	5.7	1
Educational level			
High	113	11.5	1
Medium–Low	400	12.0	0.7 (0.4–1.6)
Blood transfusion	51	11.8	0.99 (0.4–2.4)
IVDU	32	9.4	1.3 (0.4–4.5)
Presence of cirrhosis	166	19.3	2.6 (1.5–4.5)

Crude odds ratio (OR) derived by univariate analysis  
 IVDU intravenous drug use

**Table 4** Proportion of subjects with liver cirrhosis among anti-HDV positive in Italy (1987–2014)

Year	Presence of cirrhosis No (%)	References
1987	130/364 (35.7%)	[7]
1992	61/143 (42.6%)	[8]
1997	30/69 (43.5%)	[9]
2001	43/104 (41.4%)	[10]
2006	37/95 (38.9%)	[11]
2014	32/61 (52.4%)	Present study

cirrhotic patients among all HDV-infected subjects has significantly increased over time reaching the current rate of 52.4%, likely reflecting a so-called “survival effect”. Taken together, these findings evidence a low current spread of HDV infection with an accumulation of cases having an advanced, slowly evolving disease. Actually, HDV infection in Italy is an ageing disease with a long-term survival, which explains the observed slightly higher overall anti-HDV prevalence observed in the present study as compared to previous ones. This is in agreement with a follow-up study of subjects with biopsy-proven chronic HDV infection in two Italian medical centres showing a stable clinical cirrhosis for more than a decade [15].

The low proportion of cases in people younger than 30 years is an expected finding due to the mass vaccination campaign against HBV started in 1991, which depleted

in the youngest age group the HBsAg carrier reservoir that represents the necessary substrate for the replication of HDV defective virus [16]. A second effect to explain the decline in HBV endemicity is the successful treatment of HBV infection with nucleoside analogues or other drugs with low adverse events since 1998. Indeed, this treatment has been extensively administered in Italy in the latter 15 years, but in the absence of a national register we may not be accurate on this point.

For several years, HDV infection has been characterized by a higher prevalence in Southern than in Northern Italian areas [8–11]. However, since the survey of 2006 [12], the prevalence has become higher in the latter ones. This evolving geographical pattern may reflect changes in the modes of transmission. Intrafamilial spread was the main source of HDV infection in Southern areas, whereas illicit drug abuse was the predominant risk factor in Northern Italy [8, 10, 17]. The reduced family size even in the South has affected the spread of infection in these areas, while i.v. drug use has continued to be practised, particularly in Northern areas, where it has been responsible for some epidemic peaks [6]. Although the majority of HDV-infected subjects have liver cirrhosis, its contribution to the entire pool of cirrhosis in Italy should be considered minimal. The last published survey [18] has shown that 13% of cirrhosis are HBV related and nearly 20% of these cirrhosis are caused by simultaneous HDV infection. Therefore, a little more than 2.5% of all cirrhosis cases in Italy are attributable to HDV infection.

The decreasing endemicity of HDV infection in Italy has led to a downgrading alert about the risk of its spreading. In fact, it has been shown that 35.3% of HBsAg-positive subjects in Southern Italy in 2005 [19], and as many as 53.8% of acute HBV cases during the period 1993–2004 [6] were not tested for anti-HDV. More attention should be addressed to HDV infection testing for all subjects who are found to be HBsAg positive.

In conclusion, current HDV infection in Italy mostly affects old people who have an advanced but indolent liver disease, as a consequence of survival effect. Based on this epidemiological survey, we can hypothesize that this defective virus is near to disappear in the Country where it has been firstly discovered in the second half of 70s.

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#### Compliance with ethical standards

**Conflict of interest** All the authors of the manuscript declare that they have no conflict of interest in connection with this paper.

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