XV Workshop Nazionale

Innovazione e Ricerca per la Pratica Clinica

TERAPIE INNOVATIVE DELLE EPATITI CRONICHE VIRALI E DELLE INFEZIONI VIRALI

Firenze, 9-10 Gennaio 2023

Lo scenario italiano dell'infezione da HBV: i dati della coorte PITER

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No Disclosures

2017

Executive Commitee HCV cohort
PITER HBV Promoters:
MR Brunetto,GB Gaeta, M Puoti, M Raimondo

2018

V. Di Marco, C. Ferrari, P. Lampertico, A .Marzano, M. Puoti, G. Raimondo, T. Santantonio, E. Villa,
S. Vella, L. Kondili, B. Coco and MR Brunetto

2019

Session 2
Future Prespectives of PITER
Chairmen: G.B. Gaeta (Napoli), G. Raimondo (Messina)

14.00-14.20 Medium and long term outcomes in HCV infection
P. Andreone (Bologna)

14.20-14.40 Resource utilization: value of anti-HCV treatment screening
F. Mennini (Roma)

14.40-15.00 Refusing HCV screening and treatment: individual vs. social benefit
L. Craxì (Palermo)

15.00-15.20 Presentation of PITER HBV/HDV cohort
M. Brunetto (Pisa)

15.20-16.00 Open Discussion with participating centers

Coordinamento dello studio:
Lo studio è coordinato dall'Istituto Superiore di Sanità (ISS), dall'Associazione Italiana Studio Fegato (AISF) e della Società Italiana di Malattie Infettive e Tropicali (SIMIT) attraverso un Comitato esecutivo

Comitato esecutivo: E. Villa, S. Vella, T. Santantonio, G. Raimondo, M. Puoti, A. Marzano, P. Lampertico, L. Kondili, GB Gaeta, C. Ferrari, V. Di Marco, B. Coco and MR Brunetto
AISF: Alessio Aghemo SIMIT: Massimo Andreone

PITER HBV/HDV si propone come uno *studio prospettico multicentrico nazionale* mirato a valutare complessivamente l'epidemiologia clinica dell'infezione e malattia HBV/HDV correlata in Italia

Disegno dello studio: arruolamento *consecutivo di soggetti con infezione cronica da HBV /HDV con o senza malattia, indipendentemente dallo stato di terapia antivirale*.
Ciascun centro partecipante potrà arruolare i pazienti osservati nell'arco temporale di un anno. I pazienti arruolati saranno seguiti con frequenza annuale per un *periodo di 5 anni*.

Criteri di inclusione:
- Infezione cronica da HBV documentata da HBsAg pos da almeno 6 mesi con o senza coinfezione da HDV, HCV ed HIV

Criteri di esclusione:
- Soggetti con infezione da HBV pregressa ma HBsAg negativo al momento dell'arruolamento
- Pazienti con epatite da HBV acuta

46 centri progressivamente attivati da Nov 2019

Main baseline characteristics of the PITER HBV-HDV cohort

4729 HBsAg carriers enrolled from Oct 2019 to Jun 2022

Interim analysis on 4583 HBsAg positive carriers

		Subjetcs evaluated (n)	% (n) or median (range)
Age	years	4583	58 (16 – 95)
Gender	M	4583	62.2 (2850)
Origin	Italian Non-Italian native	4372	78.2 (3419) 21.8 (953)
Genotype	D non-D	625	77.0 (481) 23.0 (144)
HBeAg	Positive	3817	**7.1 (322)**
Phase of infection	HBe Ag pos infection HBeAg pos CH HBe Ag neg infection HBeAg neg CH	3689	0.3 (11) 5.8 (214) 22.1 (815) 71.8 (2649)
Coinfections	HDV HCV HIV	3566 3491 3305	**9.2 (314)** 4.5 (169) 1.5 (51)
Cirrhosis		4181	24.1 (1107)
HCC		4131	4.6 (210)
Treatment status	Treatment on going	4171	**66.5** (3043)

		% (n)
Familiar exposure	Parents Other family members Partner Community unknown	13.7 (574) 14.9 (624) 2.4 (99) 0.2 (9) 42.5 (1778)
Sexual exposure		5.3 (82)
IV Drug use		1.9 (70)
Alcohol	Absent On going Previous	65.3 (2540) 24.0 (929) 10.8 (420)
Cofactors of liver disease	Steatosis NASH Cholangiopaties AIH other	26.9 (198) 1.6 (69) 0.1 (4) 0.2 (8) 0.1 (5)
Comorbidities	Diabetes Dyslipidemia CV disease Onco-hematologic diseases Tumors	9.4 (385) 8.8 (367) 25.0 (1044) 6.3 (262) 8.6 (360)

MASTER B cohort (2877 HBsAg carriers consecutively observed from 2012 to 2015 at 73 Italian liver specialized centers):

27% subjects were found to be non Italian natives (NINs)

NINs HBV carriers were:

- younger compared to infected native Italians (median age 35.2 vs 54.5 y; $p < 0.0001$)
- more often highly viremic and HBeAg positive (26% vs 8%; $p < 0.001$)
- more often HDV-coinfected (11.1% vs 7.3%; $p = 0.006$)

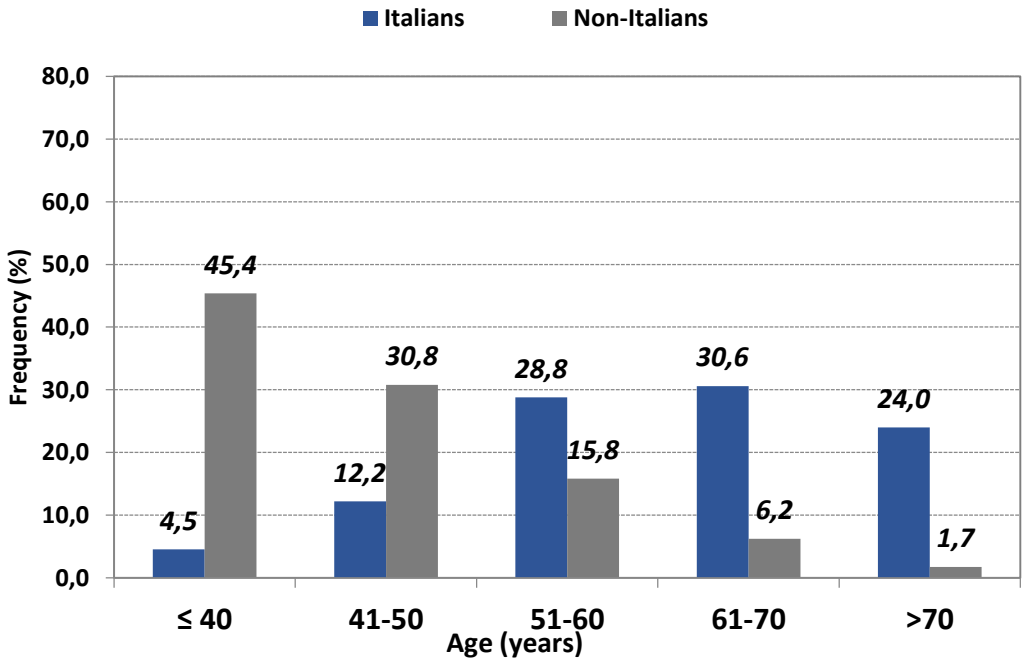
Brancaccio, Dig Liv Dis 2018

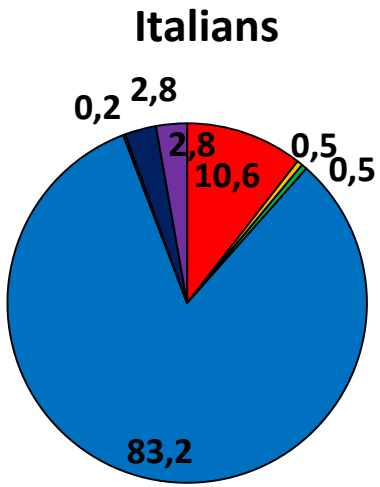
Age and genotype distribution in Italian and non-Italian native HBsAg subjects overall PITER HBV-HDV study cohort

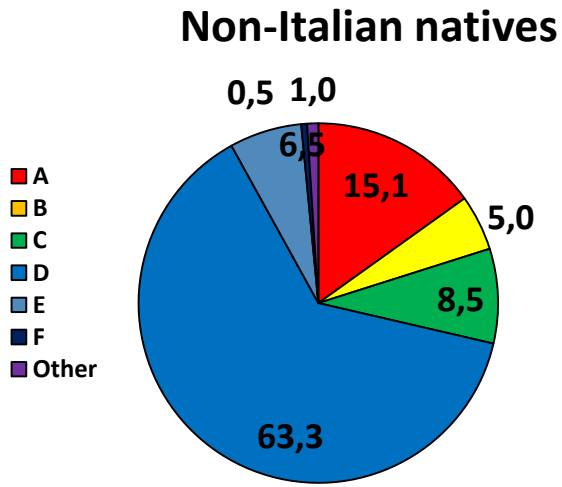
21.8% (953) subjects were non Italian natives

Countries of birth	%
Italy	78,2
Est Europe	12.5
Africa	3,7
Asia	5,0
America	0,5

Living in Italy from
<10 aa :**28%**
10-19 aa: **33%**
>= 20aa: **39%**





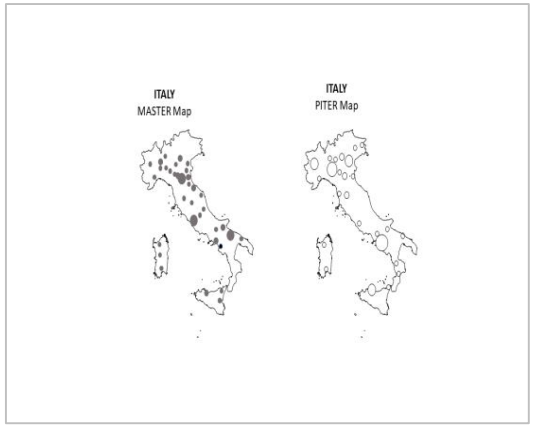


Main characteristics in Italian and non-Italian natives HBsAg subjects overall PITER HBV study cohort

		Italian % (n)	non- Italian natives % (n)	p
Age	years	**62** (16-95)	**42** (19 – 84)	<0.001
Gender	F M	**34.7** (1125) 65.3 (2112)	**47.2** (417) 52.8 (467)	<0.001
Genotype	D non-D	**83.2** (352) 16.8 (71)	63.3 (126) 36.7 (73)	<0.001
HBeAg	Pos Neg	4.4 (128) 95.6 (2798)	**11.9** (100) 88.1 (743)	<0.001
Phase of infection	HBe Ag pos infection HBeAg pos CH HBe Ag neg infection HBeAg neg CH	**0.1** (3) **4.0** (114) **19.2** (540) **76.7** (2161)	**1.0** (8) 11.9 (98) **32.3** (267) **54.8** (453)	<0.001
Coinfections	HDV	7.9 (205)	**12.2** (94)	<0.001
Alcohol	On going In the past	24.0 (716) 10.5 (315)	24.2 (204) 12.1 (102)	0.395
Cofactors of liver damage	Steatosis NASH	26.8 (167) 1.7 (56)	28.0 (30) 1.5 (13)	0.537 0.595
Comordities	Diabetes Dyslipidemia CV disease	**11.0** (357) **9.9** (321) **29.8** (965)	3.9 (35) 4.7 (42) 7.9 (70)	<0.001 <0.001 <0.001
Cirrhosis		**26.1** (896)	**14.8** (141)	<0.001
HCC		**5.06** (171)	**1.2** (12)	<0.001
Treatment status	Treatment on going	**70.3** (2397)	**52.5** (501)	<0.001

	MASTER B *2012- 2015* n = 2920 % (n)	PITER HBV/HDV *2019 - 2022* n = 4583 % (n)	p
Age (median;years)	35.3	**41.7**	0.0001
Gender (male)	68,6 (2003)	**62.2 (2850)**	0.0001
Origin Italian naive East Europe Africa Asia South Central America Central Western Europe	 73.2 (2136) 13.2 (386) 5.9 (173) 6.7 (194) 0.5 (15) 0.4 (12)	 **78.2 (3419)** **12.5 (547)** **3.7 (162)** **5.0 (221)** **0.3 (13)** **0.2 (10)**	
Alchol use	31.1 (783)	**34.2 (1408)**	0.009
HBeAg pos	**12.3 (323)**	7.17 (322)	0.0001
Cirrhosis	24.7 (722)	24.1 (1107)	0.55
Anti HDV	8.3 (161)	9.2 (314)	0.23
On going therapy	34.2 (1000)	**66.6 (3043)**	0.0001

Brancaccio G and PITER investigators, submitted



	MASTER *Cirrhosis* n=722 (24.7%)	PITER *Cirrhosis* n=1107 (24.1%)	*p*-value
Age (Years)	57.2	**63.6**	<0.0001
Gender (Males)	79.9 (577)	73.9 (816)	0.0032
BMI >/= 30	25.5 15.3 (127)	25.5 15.1 (92)	0.90
HBV DNA (pos)	**56.5 (392)**	24.6 (257)	<0.0001
Origin Italian natives East Europe Asia Africa America Central Western Europe	 80.6 (578) 7.7 (56) 5.9 (43) 5.8 (42) 0.42 (3) 0 (0)	 **86.4 (896)** 8.5 (89) 2.9 (31) 1.8 (19) 0.1 (1) 0.1 (1)	<0.0001
Alcohol use (Yes)	29.7 (187)	37.1 (366)	0.0023
HBeAg (Positive)	**12.6 (81)**	4.9 (54)	<0.0001
Anti-HDV (Positive)	17.5 (88)	**24.8 (213)**	0.0017
HCC (Present)	14.0 (99)	16.6 (183)	0.1408
Ongoing therapy (Yes)	50.5 (365)	**91.5 (1012)**	<0.0001

HDV coinfection was the strong factor associated to cirrhosis (OR 10.08; C.I. 7.63-13.43) together with *age, gender, BMI and non Italian origin*

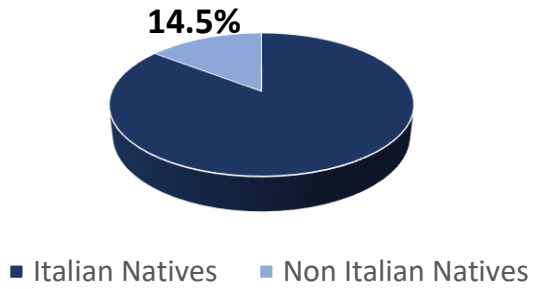
Brancaccio G and PITER investigators, submitted

Highly dynamic changes of regional HBV epidemiology across two decades: a single center cohort study

2003 HBsAg positive carriers (1589 monoinfected) admitted at the Liver Unit from 2000 to 2019

2000-2009

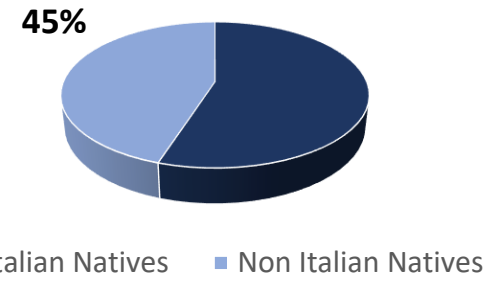
721 HBsAg pos



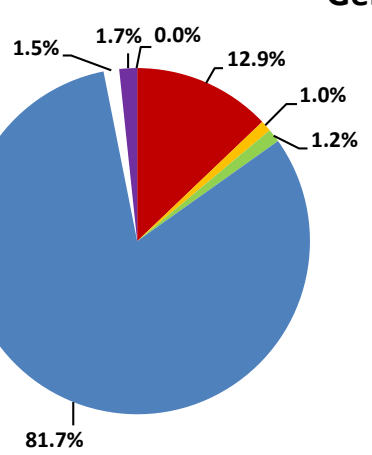
P<0.001

2010-2019

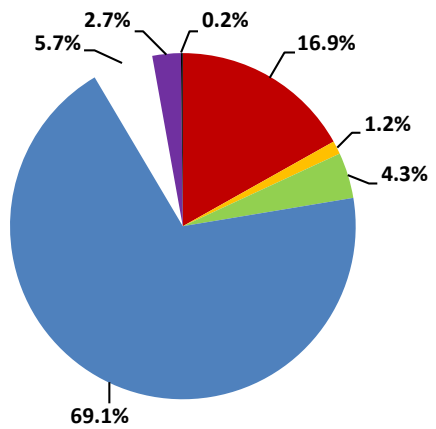
868 HBsAg pos



Genotype distribution



1st vs 2nd decade
P<0.001



A B C D E F G

Country	n	%
Italy	1292	70.0
Albania	202	10.2
Romania	109	5.5
Senegal	64	3.2
China	47	2.4
Moldova	24	1.2
Ukraine	15	0.8

Ricco G et al, Dig Liv Dis 2022

Highly dynamic changes of regional HBV epidemiology across two decades: a single center cohort study

2003 HBsAg positive carriers (1589 monoinfected admitted) at the Liver Unit of Pisa from 2000 to 2019

2000-2009

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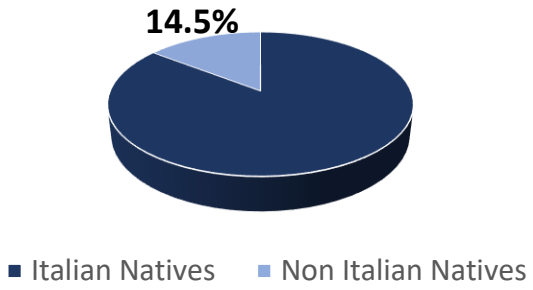

P<0.001

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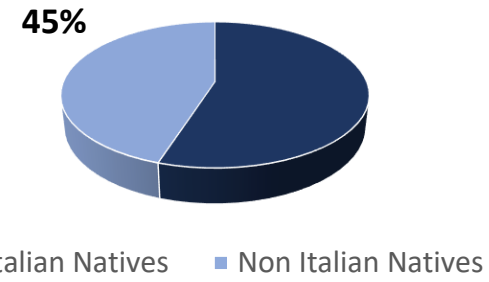
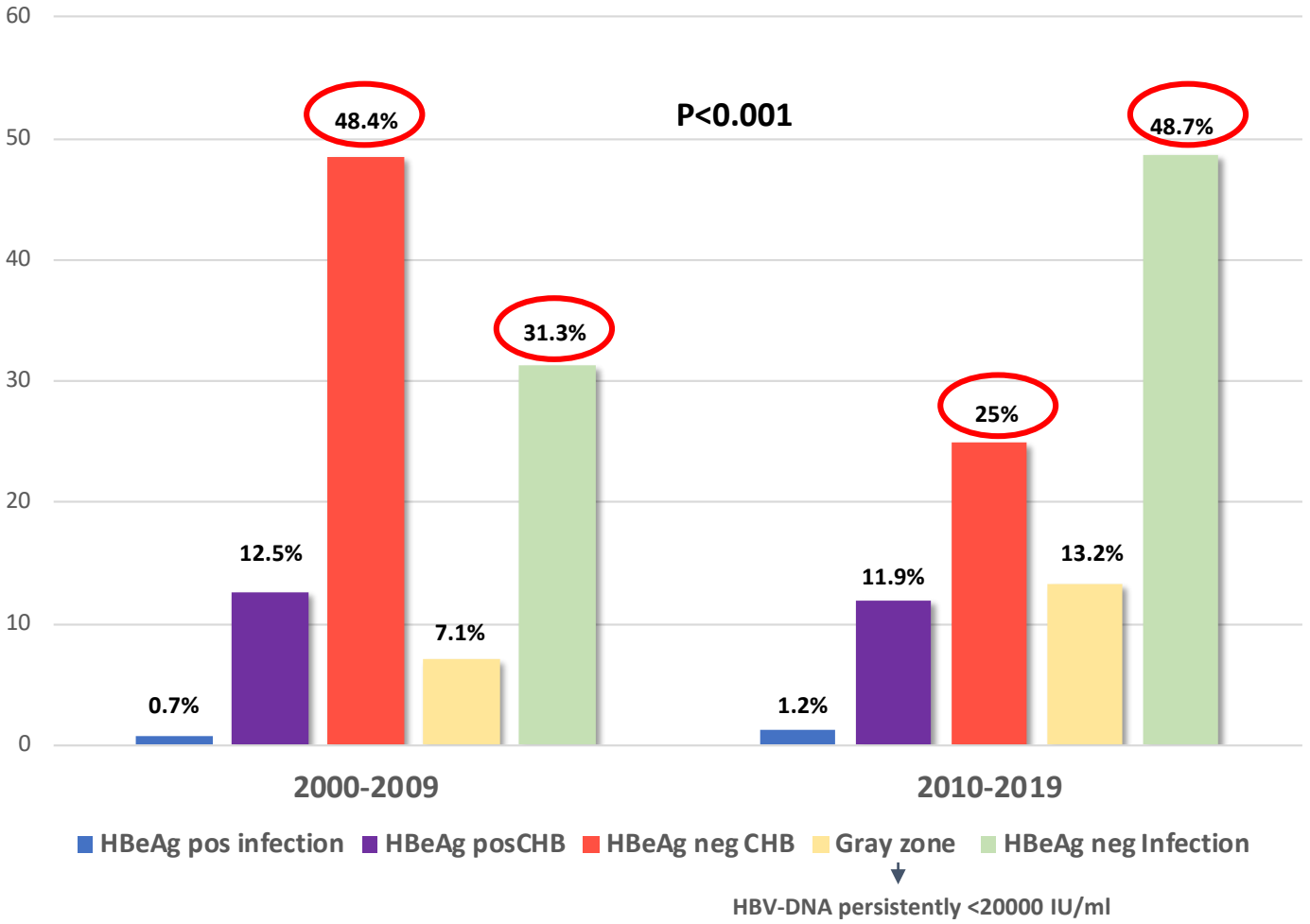


Age	Italian natives	**50.3 years**	**56.2 years**	P<0.001
	Non Italian natives	**33.2 years**	**34.2 years**	n.s.

Ricco G et al, Dig Liv Dis 2022

Distribution of HBV infection phases over time

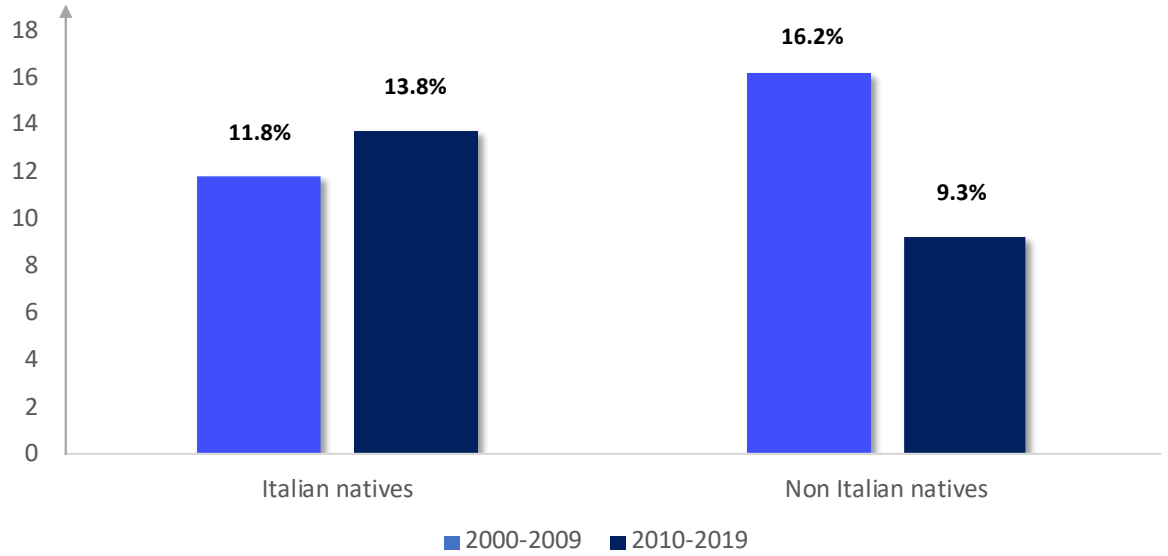


- **Cirrhotic** patients declined form **27%** to **14.4%,** the reduction was observed in both Italians (29.1 to 19.9%) and non Italian natives (15.2 to 7.7%)
- **Non-Italian cirrhotics** were significantly **younger** than Italians with cirrhosis [42 (19.5 ;73.2) *vs* 57.4 (28.2 ; 86.7) years] (P<0.001).
- **Carriers with viremia < 20000 IU/ml** (Gray Zone) were observed more frequently in non Italian natives (16.1% vs 7.9%)
- The prevalence of **HBeAg negative infection** carriers increased over time in both the cohorts (30 to 47.6% -Italians and 39 to 50% -non Italina natives)

Ricco G et al, Dig Liv Dis 2022

HBeAg positive chronic hepatitis B

Overall 193 of 1589 (**12.1%**) HBV monoinfected carriers had HBeAg positive CHB



- HBeAg CHB **prevalence declined** overtime in **non Italians natives** whereas it remained stable in Italians
- The meadian age of **Italians** was **49 years** (as compared to 31.9 y. in non italians), they had the first evidence of HBsAg positive at a median age of 38.9 years
- **Promiscuous sexual behaviour** and **jatrogenic transmission** were present in **23.7** and **13.7%** of cases among Italians as compared to 5.6 and 3.7% of non Italian natives; by convers **intrafamilal infection** was present in **25%** of Italians, but in 75% of non Italian natives

Ricco G et al, Dig Liv Dis 2022

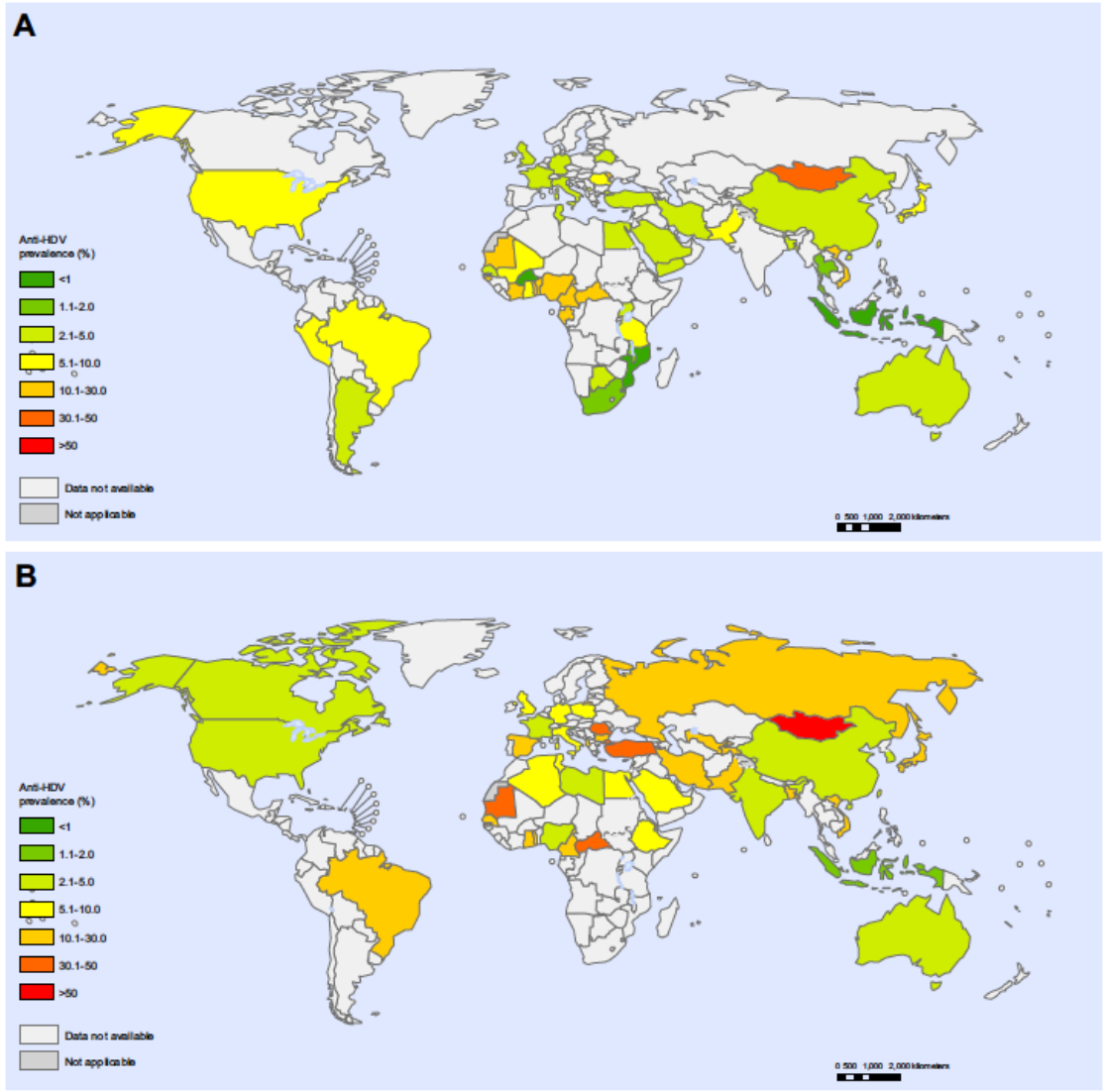
A single center cohort study of HBsAg positive carriers admitted at Hepatology Unit of Pisa over 2 decades

- The **combined effect** of **vaccination policies** and increasing **flows of immigrants** from HBV highly endemic areas were responsible for the highly dynamic changes of HBV epidemiology across the two decades
- Non Italian native HBsAg carriers significantly increased from **14.6%** in the first decade to **43%** in the second
- **Antiviral therapy mitigated** the long lasting infections in **aging Italians with CHB,** as suggested by the reduction of cirrhotic patients in the second decade in spite of the older age of the patients
- A relative **increase** of **HBeAg-positive CHB** and **acute hepatitis B** occurred in adults Italian natives, born before vaccine implementation
- These findings emphasize the need to promote a general awareness on risky behaviors and to recommend vaccination for the non-vaccinated elderly who are still HBV infection naïve.

Ricco G et al, Dig Liv Dis 2022

HDV Epidemiology

HBsAg positive general population

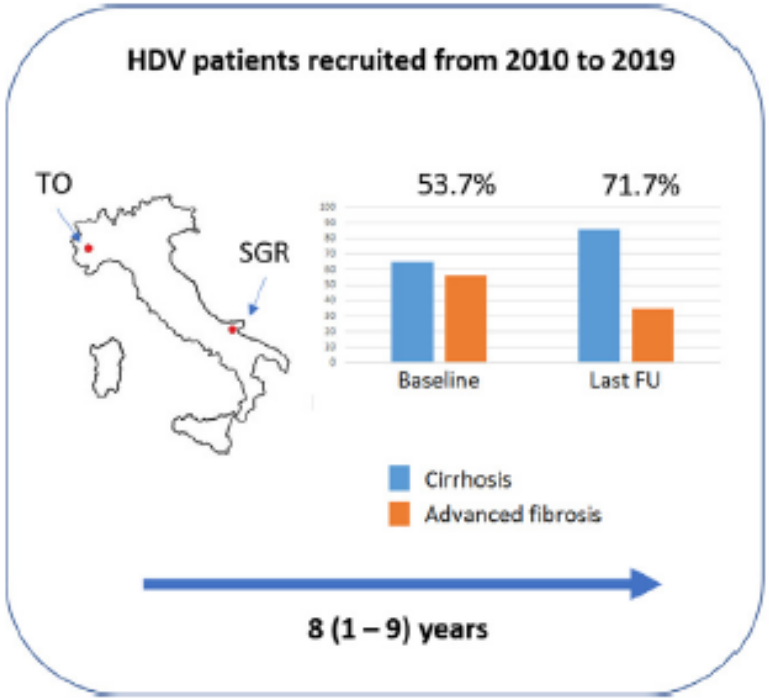


HBsAg positive Hepatology clinic population

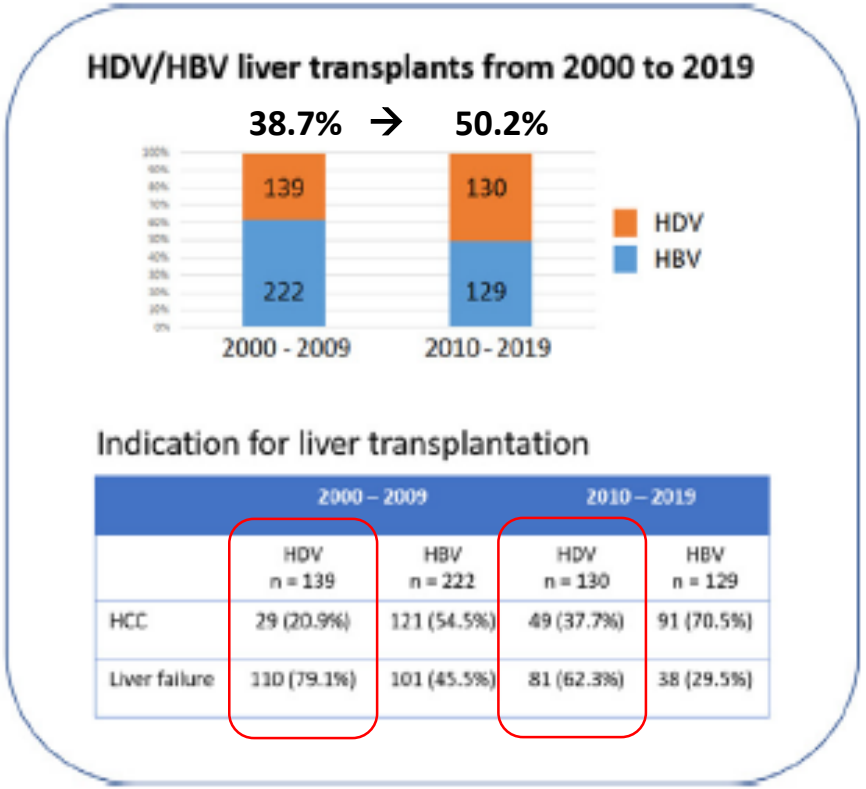
- **15-20 million people** are estimated to **be infected by HDV**, but the global prevalence is not known and recent report suggests up to **62-72 million** infected individuals.
- Globally the estimate of **anti-HDV prevalence among HBsAg positive i**ndividuals is **4.5%** (95% CI 3.6-5.7); 0.16% in the total population.
- The **geographic distribution** of HDV infection is **heterogeneous** with higher prevalences in Mongolia, republic of Moldova, Western and Middle Africa Countries
- Several **population groups** (PWID, haemodialysed patients, CSWs and MSM, patients with HCV and HIV infections) show an association with **higher anti-HD prevalences**
- Methodological issues limit the consistency of the available data and contribute to the heterogeneity ot HDV prevalence, however variation of local risk factors and the occurrence of localized defined foci of transmission could contribute to the findings
- **Among HBsAg chronic carriers the prevalence of HDV infection is higher in patients with more advanced liver disease**

Koh C et al, Gastroenterology 2019; Chen HY et al, Gut 2018 Stockdale AJ et al J Hep 2020

The hepatitis D virus in Italy. A vanishing infection, not yet a vanished disease



- ✓ **121** of 193 (**62.7%**) HBsAg/anti-HD positive patients, who were followed up from 2010 to 2019 at Turin and San Giovanni Rotondo, were **Italian natives**
- ✓ At the last observation:
  - the their **median age** was **58 years**
  - median liver stiffness values were 12.0 kPa (95% CI 11.2-17.4)
  - **86** (**71.1%**) had **cirrhosis**

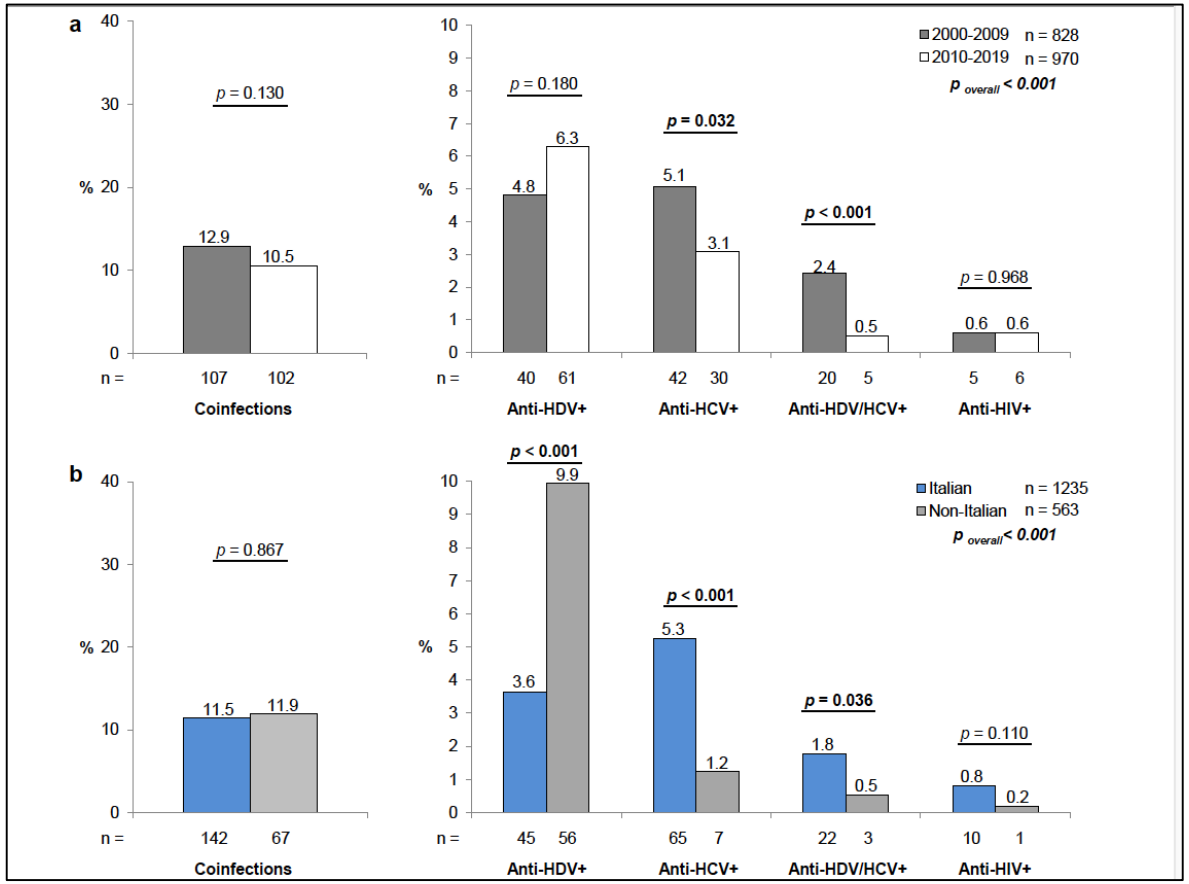


Though HDV is vanishing in Italy, a legacy of ageing native-Italian patients with advanced HDV liver disease still represents an important medical issue and maintains an impact on liver transplantation.

Caviglia GP et al J Adv Res 2021

Highly dynamic changes of regional HBV epidemiology across two decades: a single center cohort study

1878 subjects with HBV chronic infection were observed from 2000 to 2019
1589 (88.4%) HBV had mono-infection and **209 coinfection**:
101 (5.6%) anti-HDV; 72 (4.0%) anti-HCV; 25 (1.4%) anti-HDV/anti-HCV; 11 (0.6%) anti-HIV positive

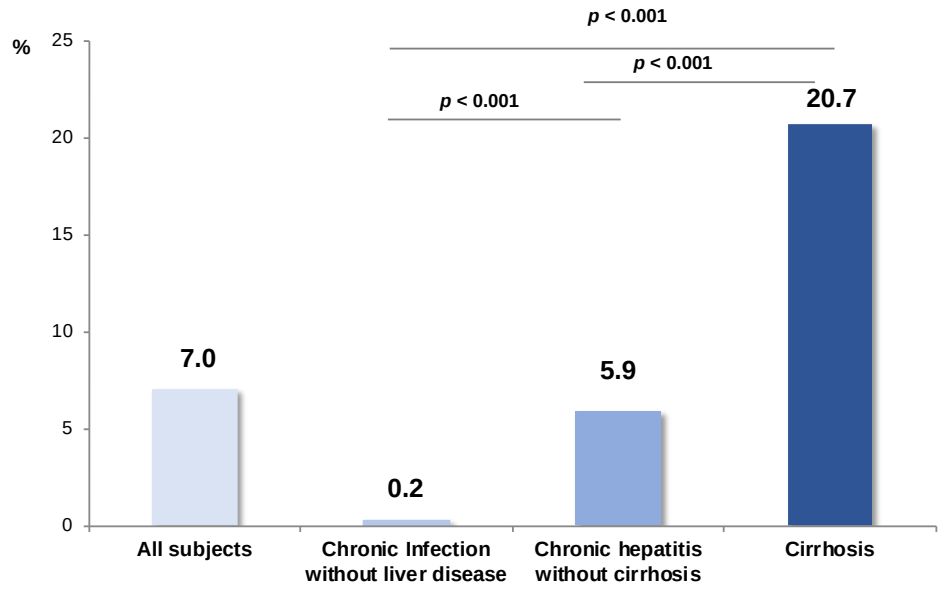


The co-infection prevalence differed across the decades and by origin

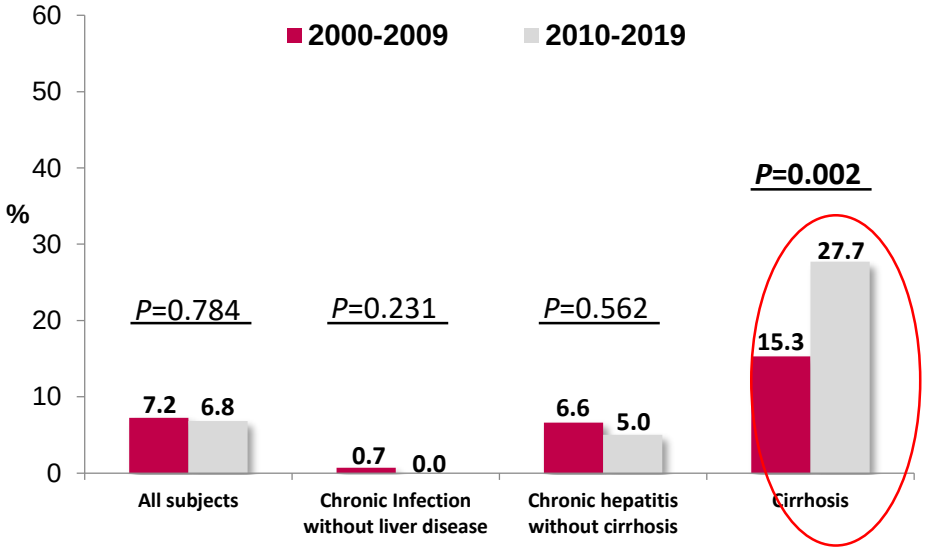
Ricco G , Dig Liver Disease 2022

HDV coinfection over a 20 year observation period

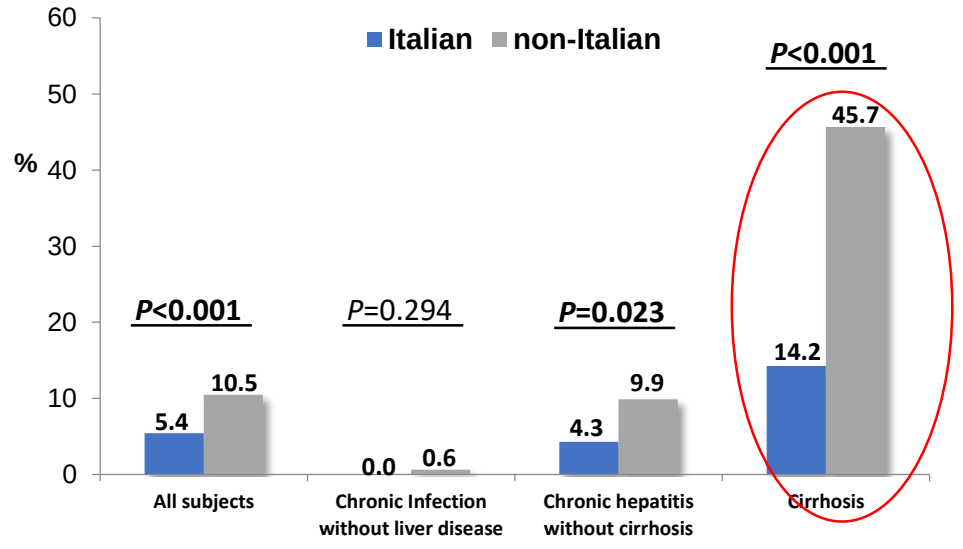
1798 chronic HBsAg positive individuals (828 first decade, 970 second decade)



By decade



By origin



Ricco G , Dig Liver Disease 2022

HDV coinfection over a 20 year observation period

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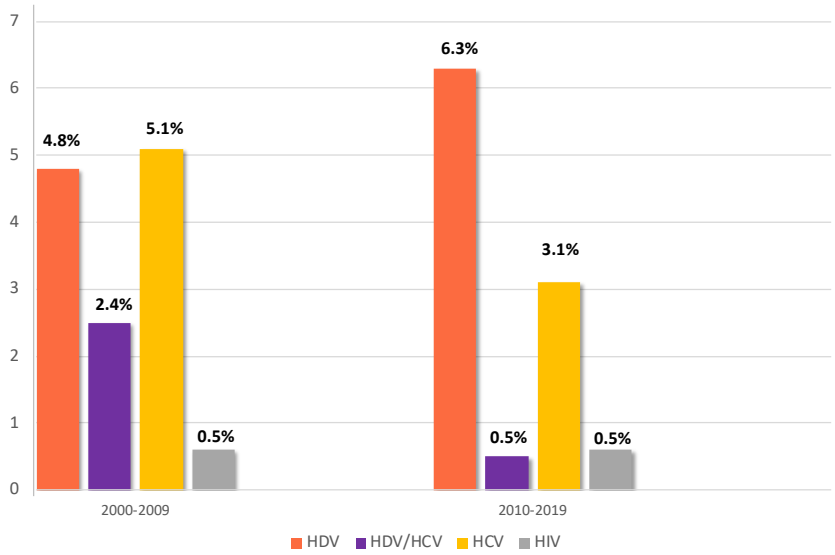
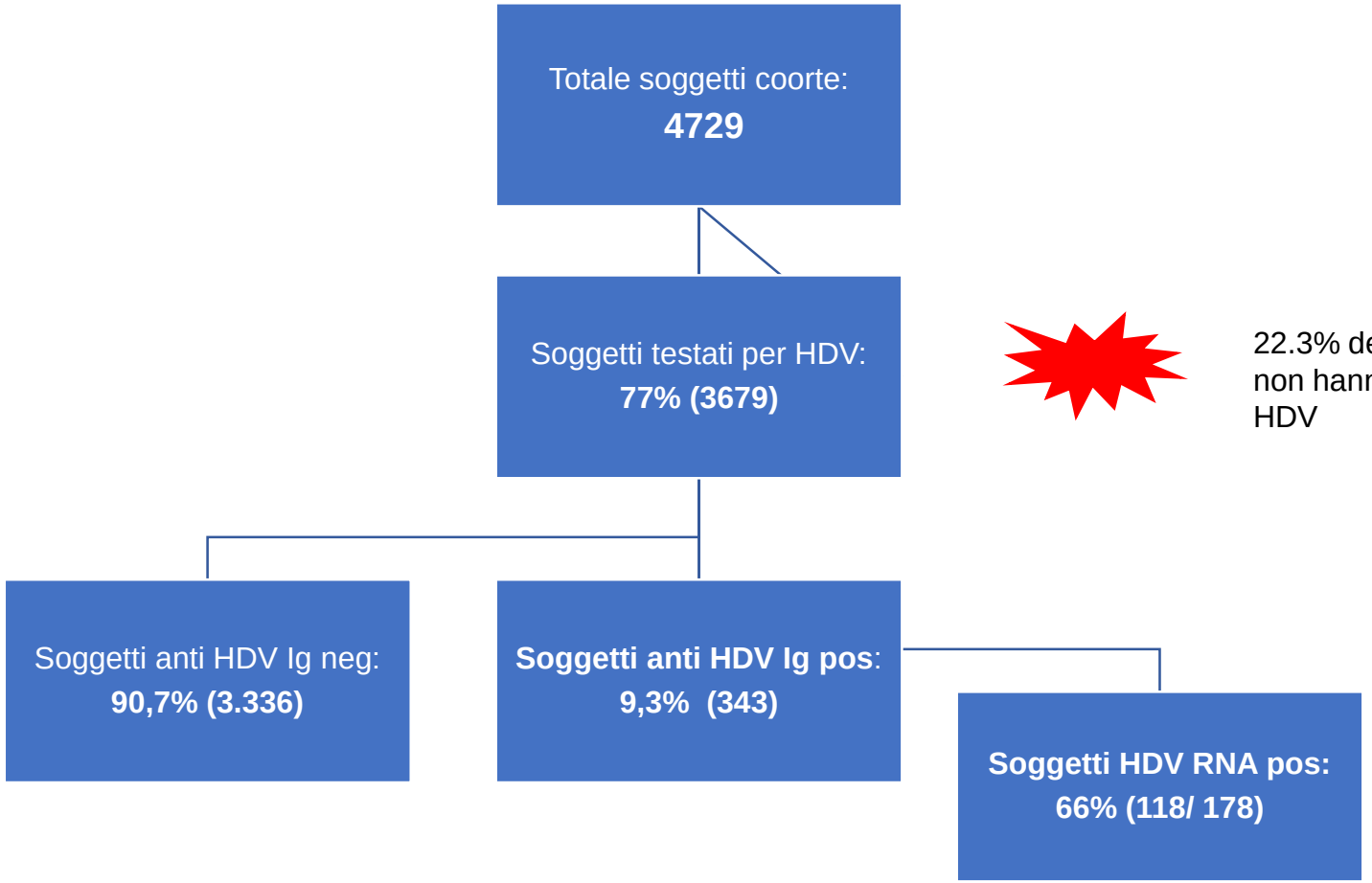


- 126 (**7%**) patients were **anti-HDV positive**, of whom 25 were also anti-HCV positive.
- **46.8%** of the **HBV/HDV** coinfected patients were **non-Italian natives,** their **prevalence** increased significantly in the second decade, from **31.7% to 60.6% (**P=0.002)
- **Non-Italian natives** were **younger** (34.6 vs 50.8 years, P<0.001) and with a **higher prevalence of female gender** (49.2% vs 26.9%, P=0.017)
- **13.5%** of anti-HDV patients were **HDV-RNA negative** (35.3% previous or ongoing IFN treatment).
- **76.1%** and **71.2% of Italian** and **non-Italian** HBV/HDV coinfected patients **had cirrhosis** (P=0.671).
- **Non-Italian** HBV/HDV **cirrhotic** patients were **younger** than Italian HBV/HDV cirrhotics [37.8 *vs* 51.8 years (P<0.001)].
- **HCC** at admission was present in Italian natives only

Ricco G , Dig Liver Disease

Soggetti con coinfezione HBV/HDV arruolati della coorte PITER

Analisi in-itinere di 4729 soggetti HBsAg positivi arruolati dal Dic 2019 -Giu 2022



22.3% dei soggetti HBsAg pos arruolati non hanno effettuato lo screening per HDV

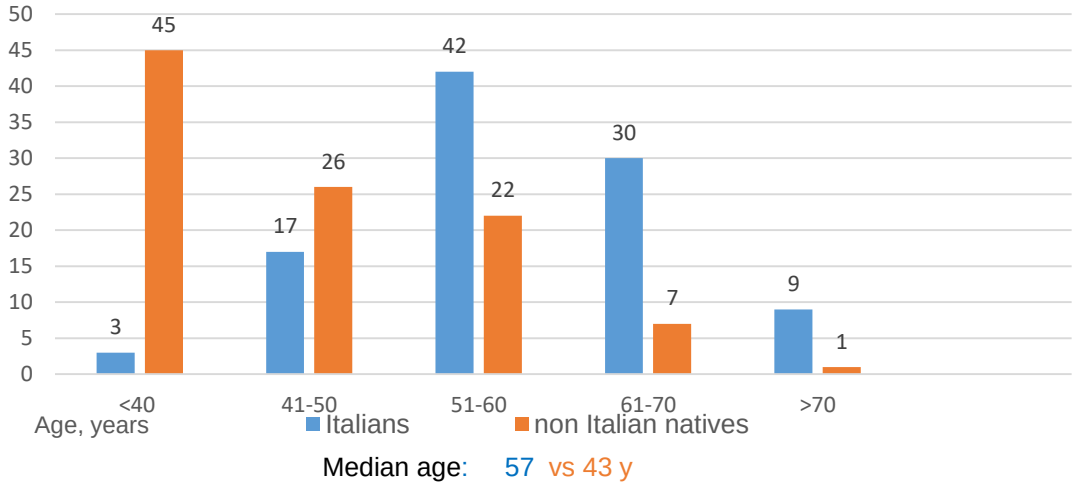
Kondili L et al, SIMIT 2022

Main baseline characteristics of the PITER HDV cohort

Interim analysis on 343 anti HDV positive carriers enrolled from Dec 2019 to Jun 2022:
118 out of 178 subjetcs who were tested had HDV RNA positive

		% (n) or median (range)
Age	years	**55** (21 – 83)
Gender	F M	35.0 (65) **65.0** (120)
Origin	Italian Non-Italian naive	73.9 (141) 26.1 (50)
HBeAg	Positive Negative	4.1 (9) 94.9 (166)
Cirrhosis		**69.9** (240)
Clinical significant portal hypertension		14.2 (49)
Platelet count	< 150.000/mmc	**53.6** (176)
Comorbidities	Diabetes Hypertension	5.7 (19) 16.3 (54)
HCC		7.6 (13)
Treatment status	Untreated Treatment on going unknowm	19.4 (37) 79.0 (151) 31.6 (3)

Treatment on going: 7 pts Peg_IFN
141 pts NUCs
3 pts others



Median age: 57 vs 43 y

non Italian natives HBV HDV coinfected:

- ✓ *57.1% have cirrhosis*
- ✓ *9.5% have portal hypertension*
- ✓ *40% have low platelet count*

Chronic Hepatitis D

- **CHD** is considered the **most severe form of viral he**patitis, because HBV/**HDV** infection is **constantly associated** with **liver damage**
- It has been estimated that the **risk of cirrhosis** and **HCC development** in case of **CHD** is **3** and **2 fold increased** as compared to chronic **hepatitis B** and **C**
- Furthermore, the **time to develpment of cirrhosis** in CHD patients is significantly **shorter** as compared to CHB: **5** to **10 years** in **70%** of cases, but **1** to **2 years** in **about 15%** of the patients
- **Virologic** factors (both HDV and HBV), modality of **HDV acquisition**, **phase of HBV infection** at the time of HDV infection and **co-factors** of liver disease **significantly influnce the clinical course of the disease**

- Currently Italian epidemiological data suggest that there are **2 distinct subsets of CHD patients**: *older Italian patients* with long lasting history of HDV infection with an indolent, but still **slowly progressive course**, and *younger immigrants* with **active and rapidly progressive disease.**

Mentha N e al J Adv Res 2019; Farci P et al Sem Liv Dis 2012; Rosina F et al Gastroenterology 1999, Ricco G et al Dig Liv Dis 2022, Kondil L SIMIT 2022

PITER

Piattaforma Italiana per lo studio della Terapia delle Epatiti viRali.

Grazie!

Comitato Esecutivo e i centri partecipanti disponibili in:
www.progettopiter.it

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INNOVATIVE MODEL OF PERSONALIZED CARE