Associazione Coagulopatici Emofilici Piemontesi "Massimo Chesta"
PROMUOVE IL CONGRESSO

COAGULOPATIE CONGENITE:
bisogni espressi, organizzazione
del Centro Multidisciplinare di Città della Salute

Torino, 25 novembre 2017
Starhotels Majestic

Epidemiologia dell'epatopatia da HCV e HBV correlata nel paziente affetto da Malattie Emorragiche Congenite (MEC)

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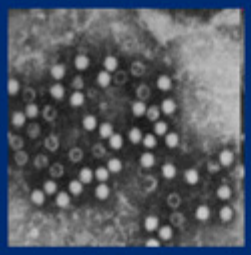
Outlines
Congenital Bleeding Disorders (CBD)
(Hemophilia, won Willebrand disease and others)

- Prevalence of HBV e HCV infection
- Currently available tests for viral diagnosis
- Prevalence of chronic Hepatitis B and C
- Liver Disease progression (cirrhosis, HCC, LF, tranplants , Death)

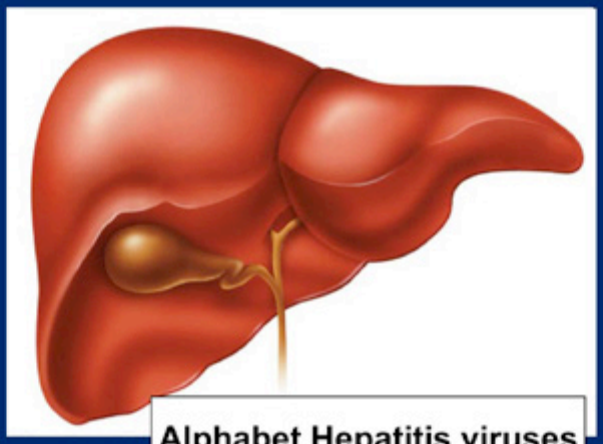
- Therapy for HBV e HCV Liver diseases (Dott.ssa Alessia Ciancio)

HEPATOTROPIC VIRUSES: YEAR OF DISCOVERY



HAV
1973

HEV
1991



Alphabet Hepatitis viruses

HBV
1969

HDV
1977

HCV
1989

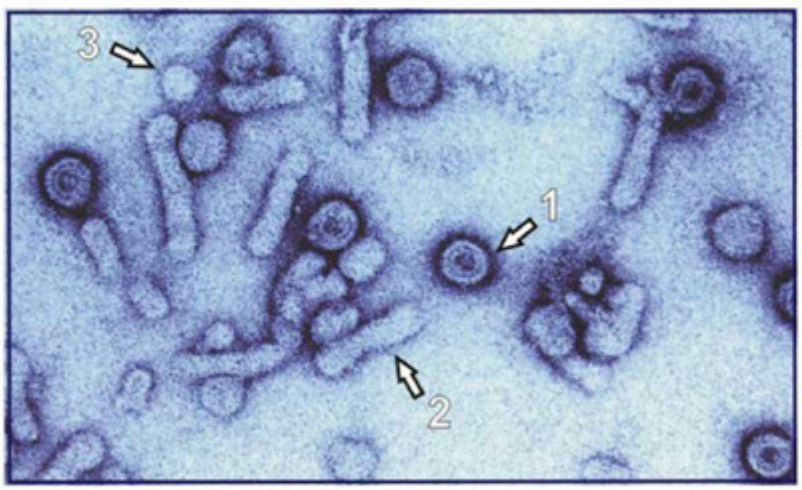
HGV
1996

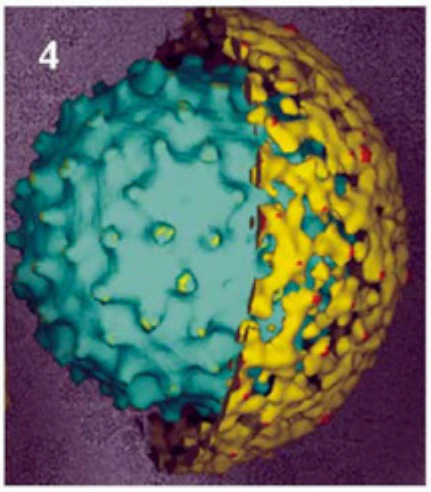
TTV
1997

SENV
2001

?

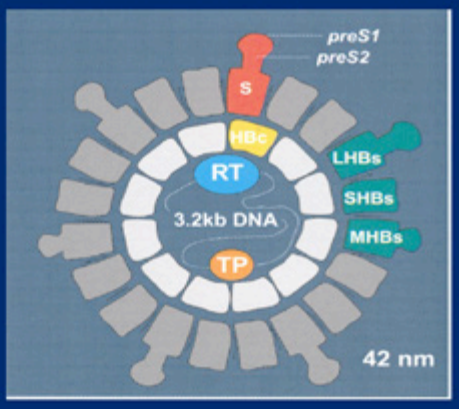
The human Hepatitis B Virus (HBV) is the causative agent for Hepatitis B and the most frequently naturally occurring carcinogen

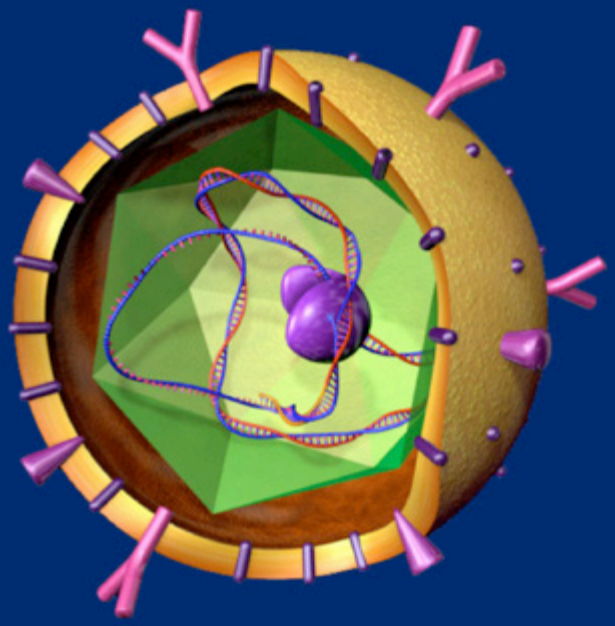




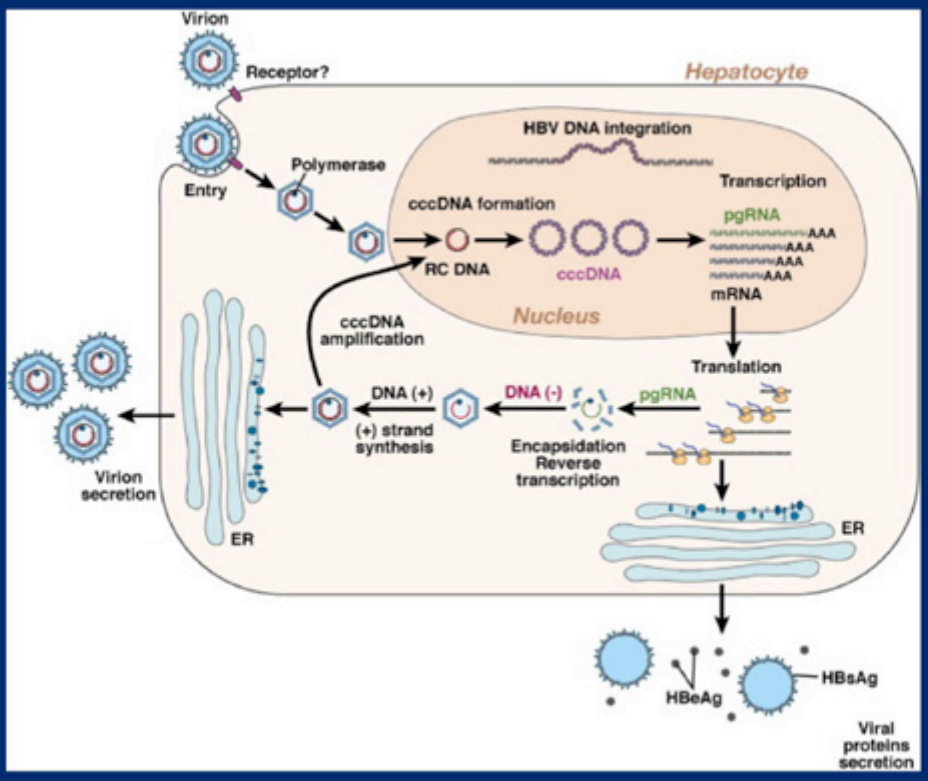
Electron microscopic picture of Hepatitis B Virus particles from the serum of an infected patient:
(1)infectious virions (Dane particles), (2) non-infectious filaments, (3) non infectious 22 nm spheres, (4) cryo-EM reconstruction of a Dane-particle (Seitz et al., EMBO J, 2007)

HBV particle and genome strucure





The HBV Replication cycle



Zoulim F. and Locarnini S. Gastroenterology 2009

The Etiologies of Liver Diseases Worldwide and in China

	Worldwide
HBV infection history	2 billion
HBsAg+	***350-400 million***
Anti-HCV positive	200 million (3%)
ALD (adult)	> 150 million
NAFLD	>600 million
Total	> 1300 million

	Euro-America
HBsAg+	***< 10 million (< 1%)***
Anti-HCV positive	> 30 million (2-3%)
ALD (adult)	84 million (7.4%)
NAFLD	400 million (20-33%)
Total	> 500 million

	China
HBsAg+	***93 million (7.18%)***
Anti-HCV positive	13 million (1%)
ALD (adult)	60 million (4.5%)
NAFLD	200 million (15%)
Total	> 400 million

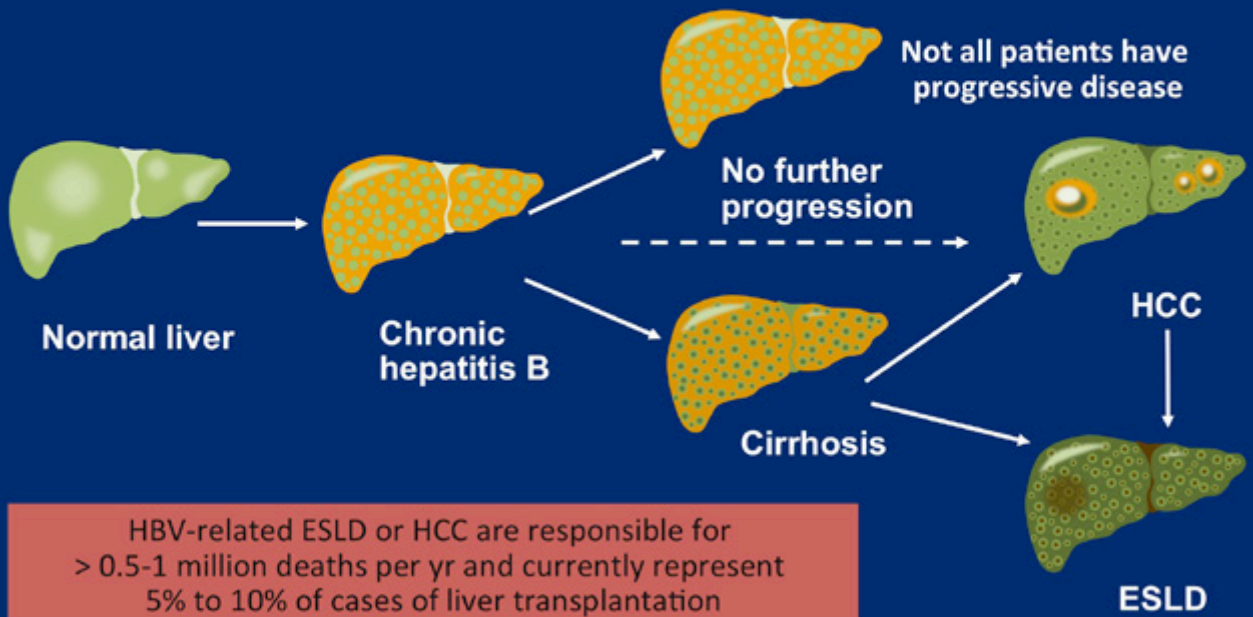
Wang Fu-Sheng et al, Hepatology 2014

Genotypes and Subtypes of HBV

Genotype	Subtypes	Geographic Location
A	Adw2, ayw1	Europe, India, Africa, N.America
B	Adw2, ayw1	Asia
C	Adw2, adr, ayr	Asia
D	Adw2, ayr3	Worldwide, Italy
E	ayw4	W.Africa, Madagascar
F	adw4	Central America, S.America
G	adw2	S.America, Europe
H	adw4	Central America, USA

Geographic distribution of hepatitis B virus genotypes

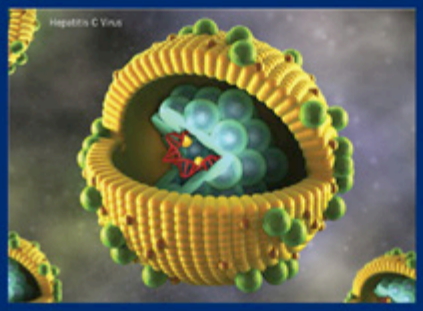
Natural History of Chronic Hepatitis B

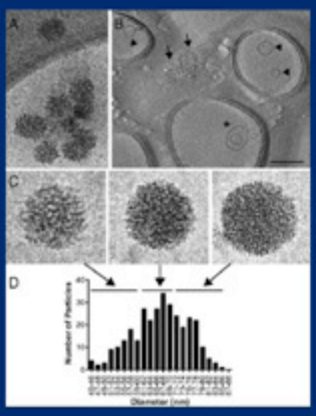


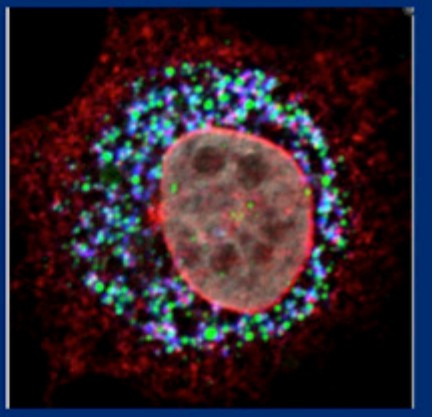
HBV-related ESLD or HCC are responsible for
> 0.5-1 million deaths per yr and currently represent
5% to 10% of cases of liver transplantation

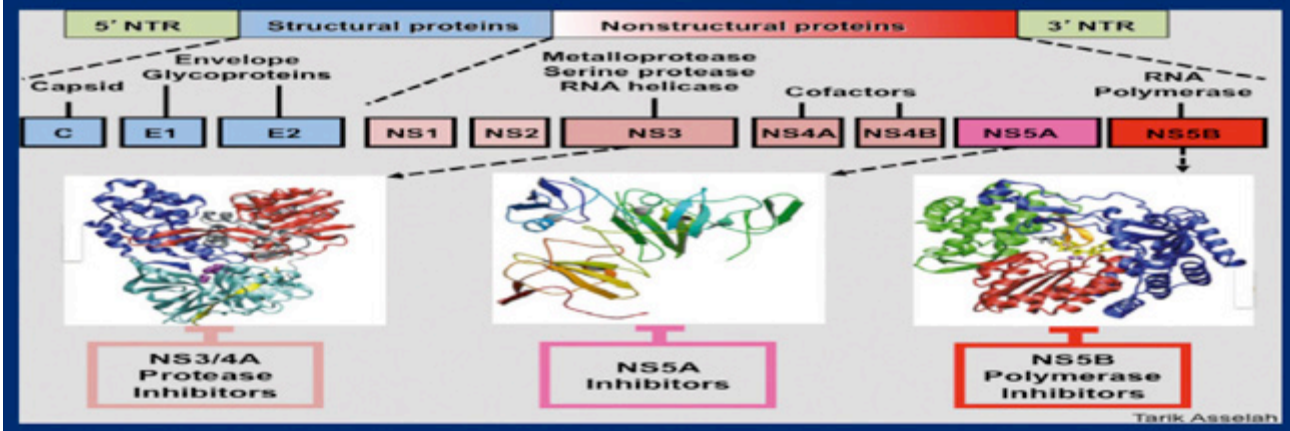
1. EASL. J Hepatol. 2012;57:167-185.

Hepatitis C Virus particle and genome structure

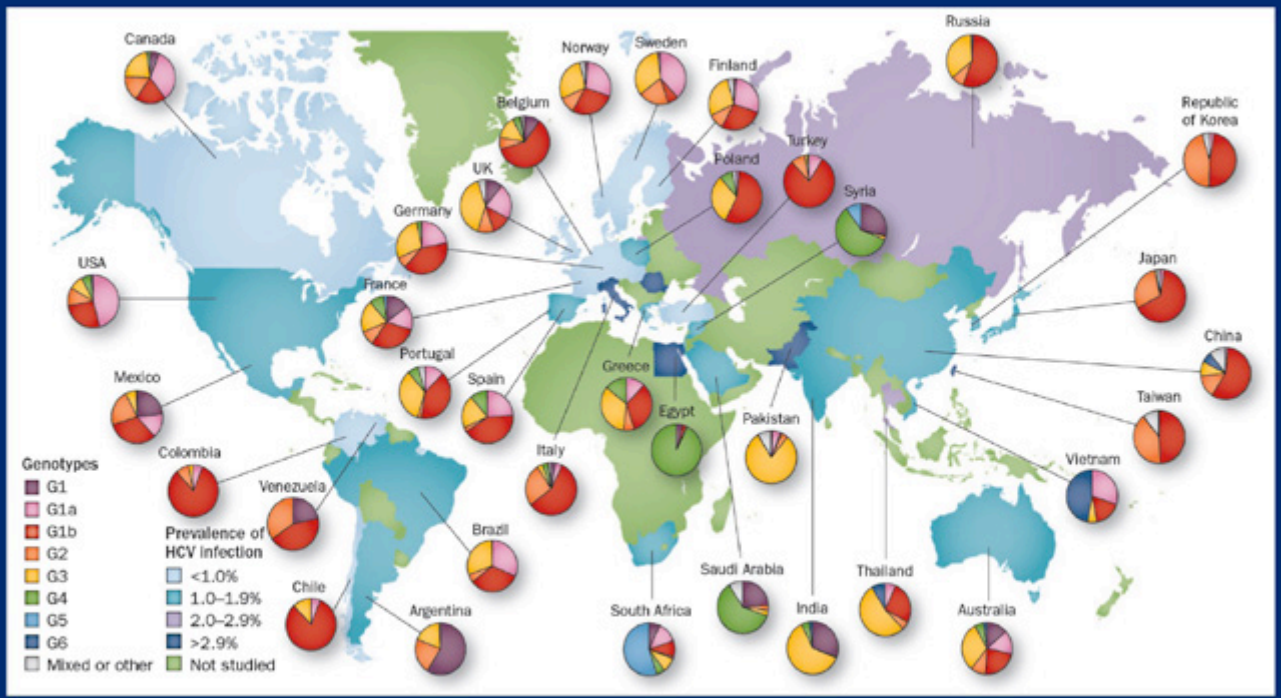






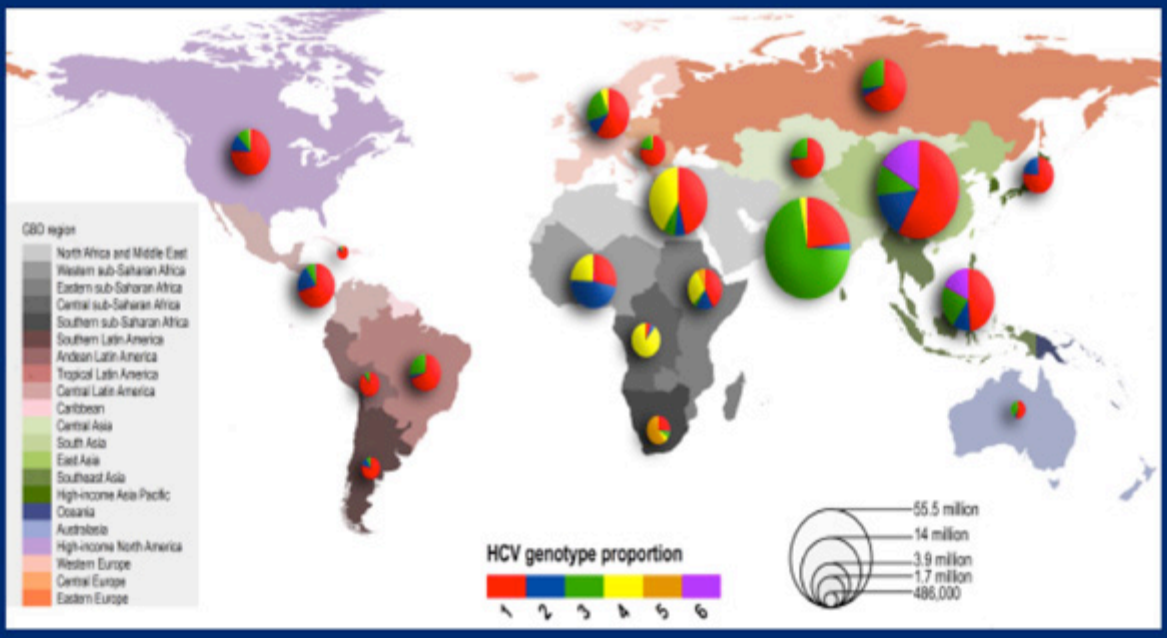


HCV infects >185 million people worldwide

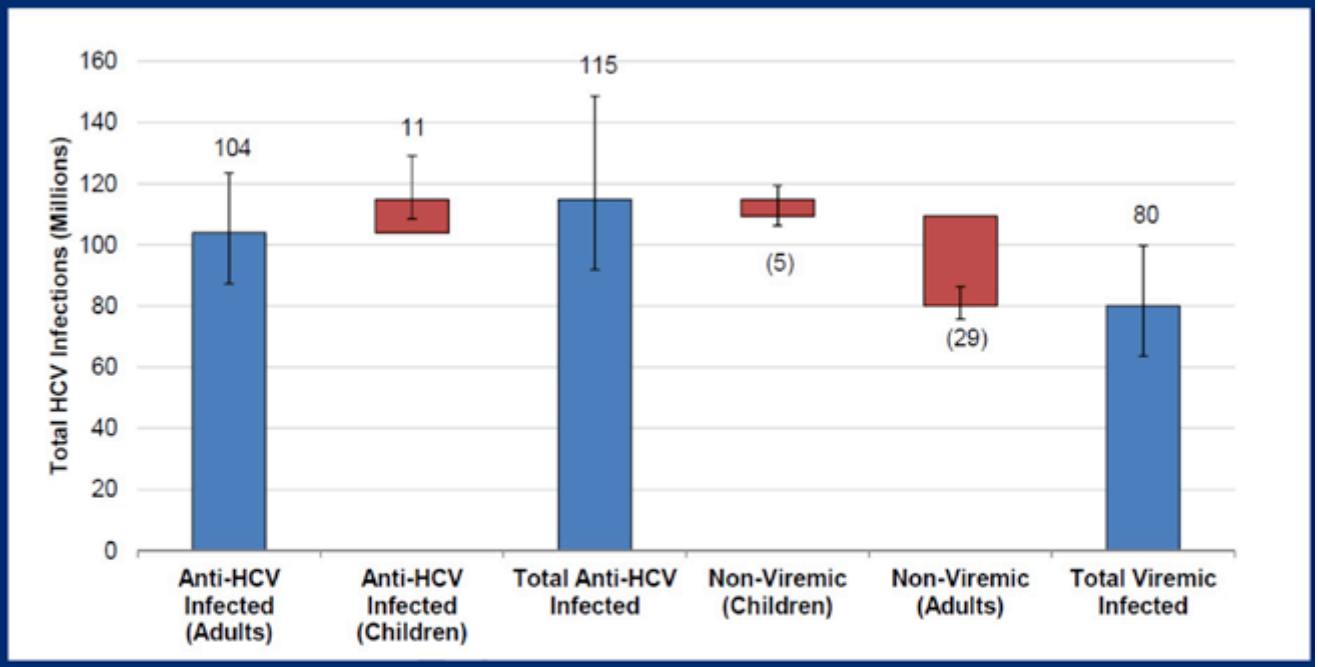


HAJARIZADEH *et al*. Nat Rev Gastroenterol Hepatol 2013;10:553-562; NEGRO and ALBERTI, Liv Int 2011;31 Suppl 2:1-3
HANAFIAH *et al*. Hepatology 2013;57:1333-1342

Global Distribution and Prevalence of Hepatitis C virus genotypes



Messina et al, Hepatology 2014



Messina et al, Hepatology 2014

Major drivers of the HCV prevalence

	Resource-rich settings	Resource-poor settings
Old infections	**Iatrogenic** (Blood transfusions, unsafe medical procedures)	**Iatrogenic** (Unsafe injections during mass parenteral therapies)
New infections	**IVDU** Immigration from resource-poor settings	**Iatrogenic** (IVDU)

Unsafe blood (and blood derivatives) transfusion as major driver of the HCV epidemic

- Before 1990, ~10% of all blood transfusion recipients were infected with HCV, and up to 99% of hemophiliacs were anti-HCV+

  KOZIOL *et al*, Ann Intern Med 1986; DONAHUE *et al*, N Engl J Med 1992
  MAUSER-BUNSCHOTEN *et al*, J Med Virol 1995

- Screening assays and use of recombinant clotting factors have virtually eliminated transmission of CV via blood and blood products

  SCHREIBER *et al*, N Engl J Med 1996; PIPE. Semin Hematol 2006;43(suppl 2):S23-7

- Current risk: <1 per 1,000,000 transfused units

  POMPER *et al*, Curr Opin Hematol 2003;10:412-8

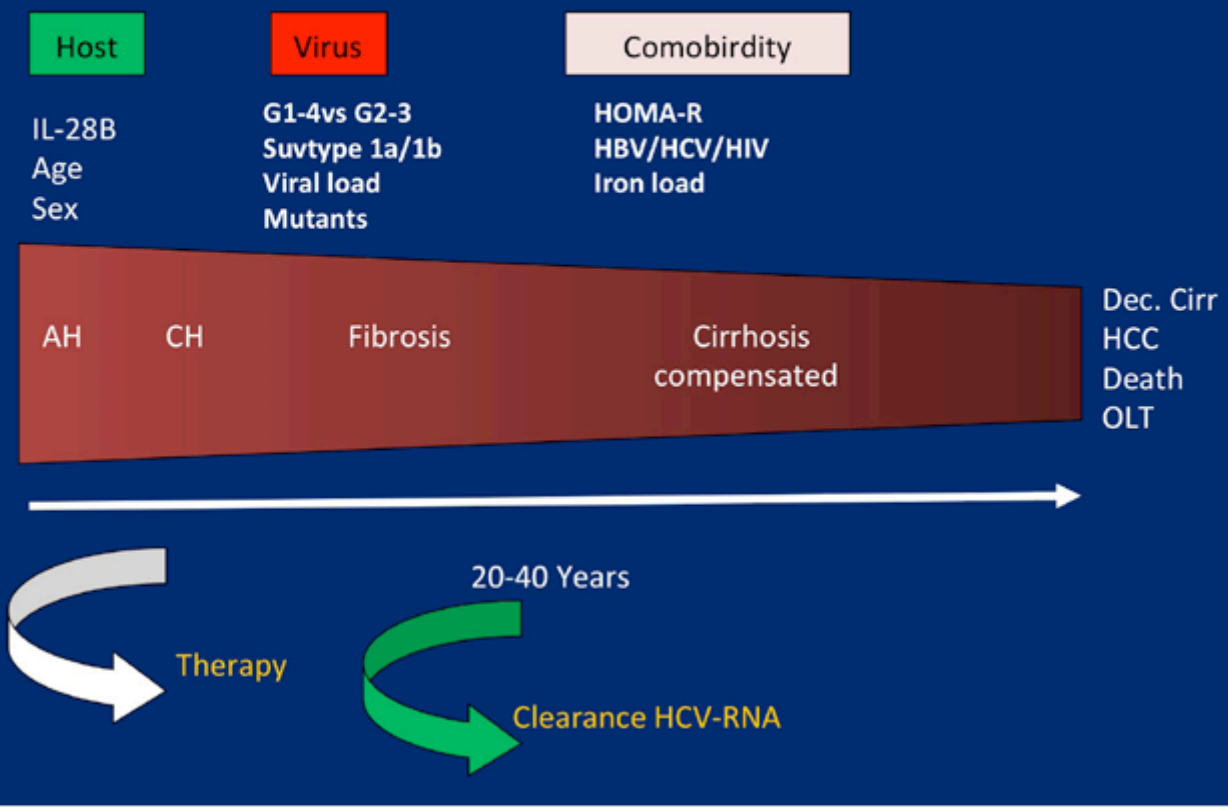
Epidemiology provides data for policy and action

	HIV[1]	HCV[2,3]	HBV[4]
Prevalence	34M	185M	400M
Incidence	2.5M	4M	?
Mortality	1.7M	0.35M	0.62M

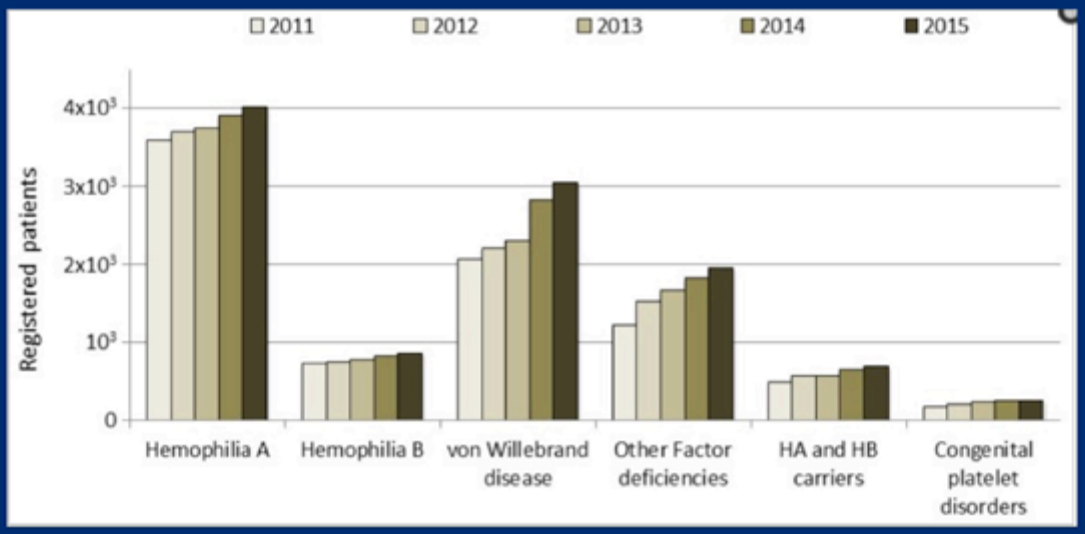
4-5M coinfected patients, depending on location and routes of transmission

[1]UNAIDS Global Report 2012; [2]HANAFIAH *et al*, Hepatology 2013
[3]PERZ *et al*, J Hepatol 2006; [4]GOLDSTEIN *et al*, Int J Epidemiol 2005

HCV: Natural History

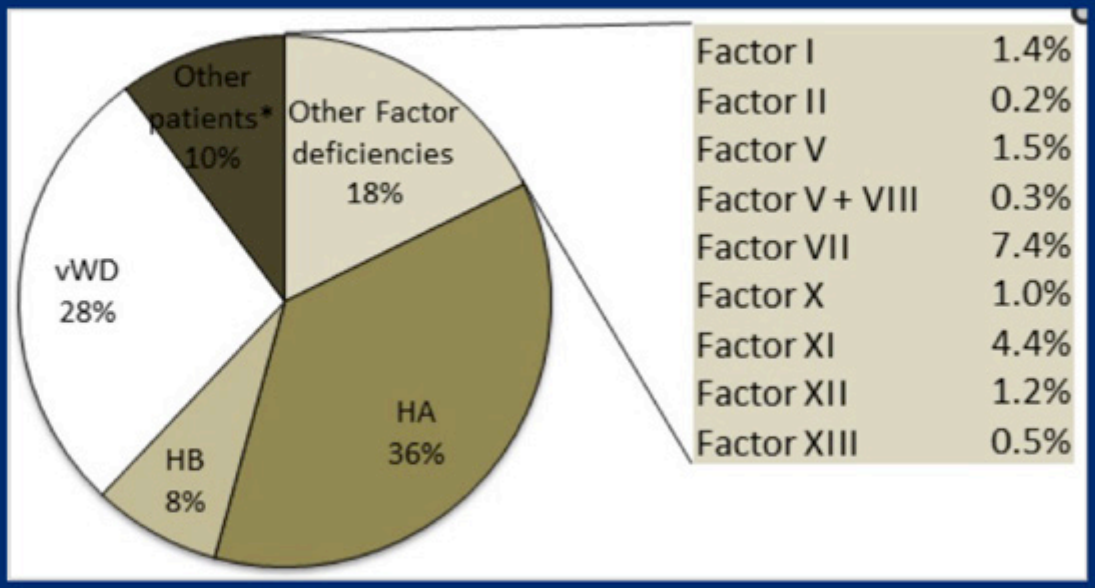


Trend in the total number of patients with bleeding disorders registered in the National Registry of Congenital Coagulopathies (NRCC) from 2011 to 2015



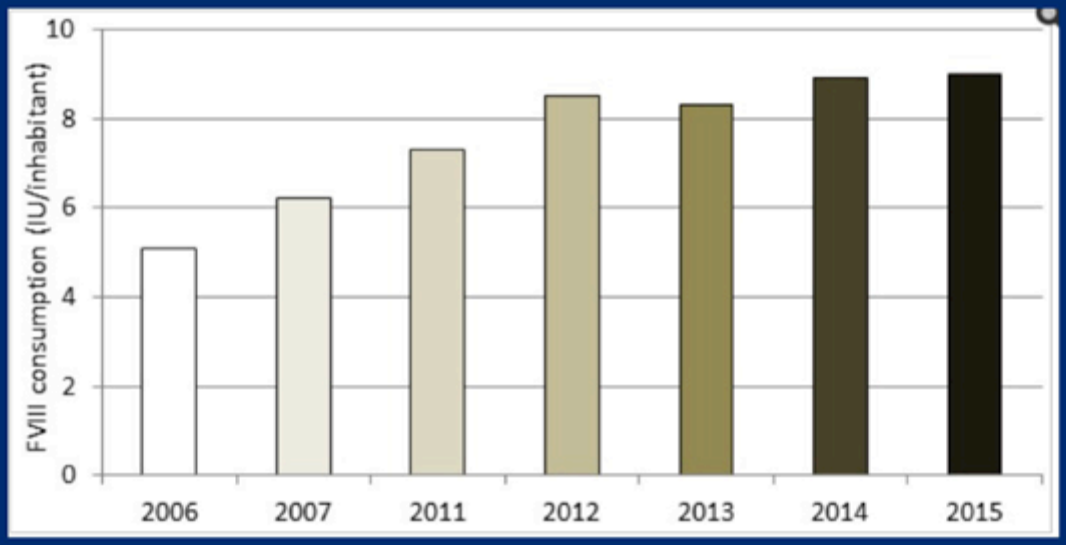
Gianpaolo A. et al, ISS Registry 2017

National Registry of Congenital Coagulopathies (NRCC) from 2011 to 2015



Gianpaolo A. et al, ISS Registry 2017

Trend of estimated FVIII used in Italy over the years based on the entire population of severe HA



Gianpaolo A. et al, ISS Registry 2017

National Registry of Congenital Coagulopathies (NRCC) from 2011 to 2015

Table 1. Distribution of patients with HA, HB and vWD, according to disease severity.

Pathology	Total Patients	<18 Years Old	Median Age (0–90 Years Old)
Severe HA	1838	406 (22.1%)	35
Moderate HA	552	107 (19.4%)	37
Mild HA	1630	210 (12.9%)	42
Hemophilia A	**4020**	**723 (18.0%)**	**38**
Severe HB	311	78 (25.1%)	32
Moderate HB	184	34 (18.5%)	38
Mild HB	364	71 (19.5%)	38
Hemophilia B	**859**	**183 (21.3%)**	**36**
vWD type 1	2307	248 (10.8%)	42
vWD type 2	621	66 (10.6%)	46
vWD type 3	119	10 (8.4%)	41
Von Willebrand Disease	**3047**	**324 (10.6%)**	**43**

Gianpaolo A. et al, ISS Registry 2017

Table 2. Patients with major adverse events (presence of HIV and Hepatitis C Virus (HCV) infection and of alloantibodies to FVIII and FIX) recorded in the NRCC-2015.

Pathology	HIV Infection	HCV Infection	Alloantibodies
Severe HA	166	743	345
Moderate HA	13	178	20
Mild HA	10	293	15
Severe HB	40	101	13
Moderate HB	10	44	-
Mild HB	2	37	-
vWD type 1	4	54	-
vWD type 2	2	30	-
vWD type 3	3	23	-
Factor I	-	4	-
Factor II	-	1	-
Factor V	-	3	-
Factor V + FVIII	-	6	-
Factor VII	3	21	-
Factor X	-	1	-
Factor XI	-	16	-
Factor XII	-	1	-
Factor XIII	-	2	-
Not indicated	-	3	-
Total	253	1561	393

HCV Prevalence in Multitrasfused Patients (Before 1985-1990)

Italy 85% G1>

U.K. 23%

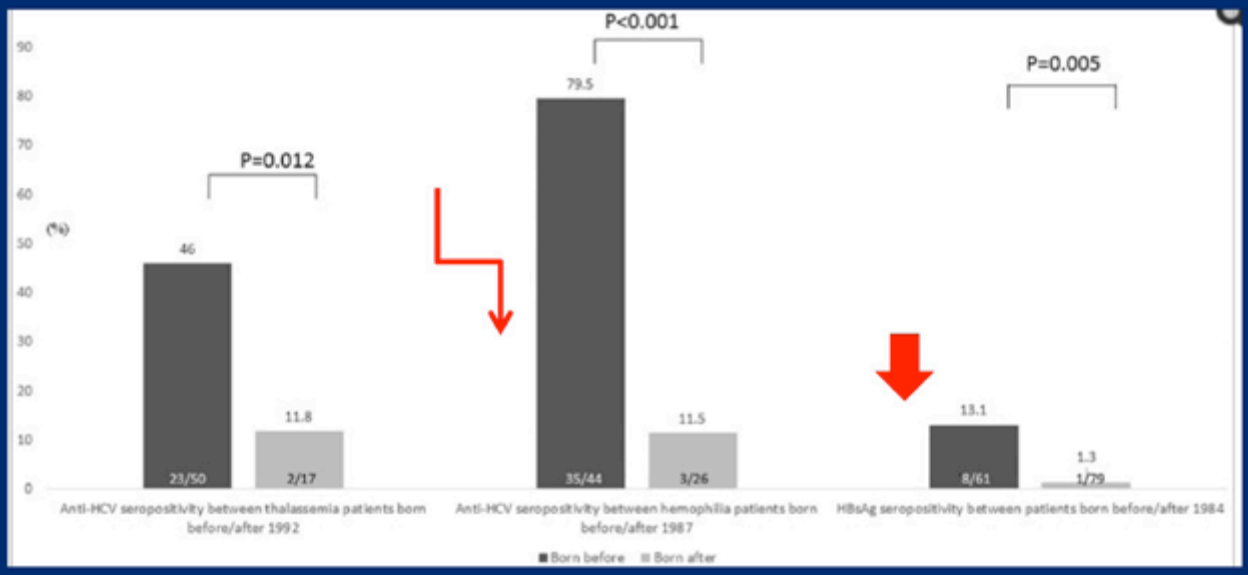
U.S.A. 35%

Indipendent factors affecting outcome in PWH:

- HIV positive status
- HCV infection
- Age at HCV infection

Therapeutic products for **haemophilics sindromes** have a very good safety profile
No cases of blood-borne viruses through plasma-derived prodcuts have been recorded in the last 25 years

Seroprevalence of anti-HCV and HBsAg seropositivity in thalassemic and hemophilic patients with different age groups



Taiwan 2014-2015
N =140 (Thalassemic 67 ; **Hemophiliac 70)**

Thing Yan Jang et al, PlosOne 2017

Univariate and multivariate analysis of factors associated with anti-HCV seropositivity

	Anti-HCV(+) (n = 64, 45.7%)	Anti-HCV(-) (n = 76, 54.3%)	P value	Logistic regression analysis		
				OR	95% CI	*P* value
Age (years, mean(SD))	34.0 (10.3)	24.4 (8.9)	<0.001	1.12	1.07–1.18	<0.001
Born before 1992, n (%)	60 (93.8)	43 (56.6)	<0.001			
Male gender, n (%)	49 (47.1)	55 (52.9)	0.57			
Body weight (kg, mean (SD))	57.5 (11.8)	56.1 (13.0)	0.62			
Thalassemia/hemophilia, n (%)	25/38 (39.1/60.9)	42/32 (55.3/44.7)	0.13			
AST (IU/L, mean (SD))	49.6 (36.1)	24.9 (11.8)	<0.001			
ALT (IU/L, mean (SD))	77.2 (79.5)	25.7 (15.9)	<0.001	1.04	1.02–1.06	<0.001
Serum creatinine ((mg/dL, mean (SD))	0.72 (0.23)	0.71 (0.22)	0.81			
Hemoglobin (g/dL, mean (SD))	12.7 (2.7)	11.6 (2.9)	0.02			
Platelet count ($x10^3$u/L, mean (SD))	270 (153)	339 (140)	0.007	0.995	0.991–0.998	0.002
HBsAg (+), n (%)	7 (10.9)	2 (2.6)	0.08			
HBV DNA (log IU/mL, mean (SD))	2.77 (1.73)	3.42 (1.24)	0.66			
IL-28B rs8099917 TT genotype, n/N(%)	48/54 (88.9)	44/47 (93.6)	0.41			

SD: standard deviation; OR: odds ratio; CI: confidence intervals; AST: aspartate aminotransferase; ALT: alanine aminotransferase. HBsAg: Hepatitis B surface antigen. Anti-HCV: hepatitis C antibody. IL-28B: Interleukin 28B.

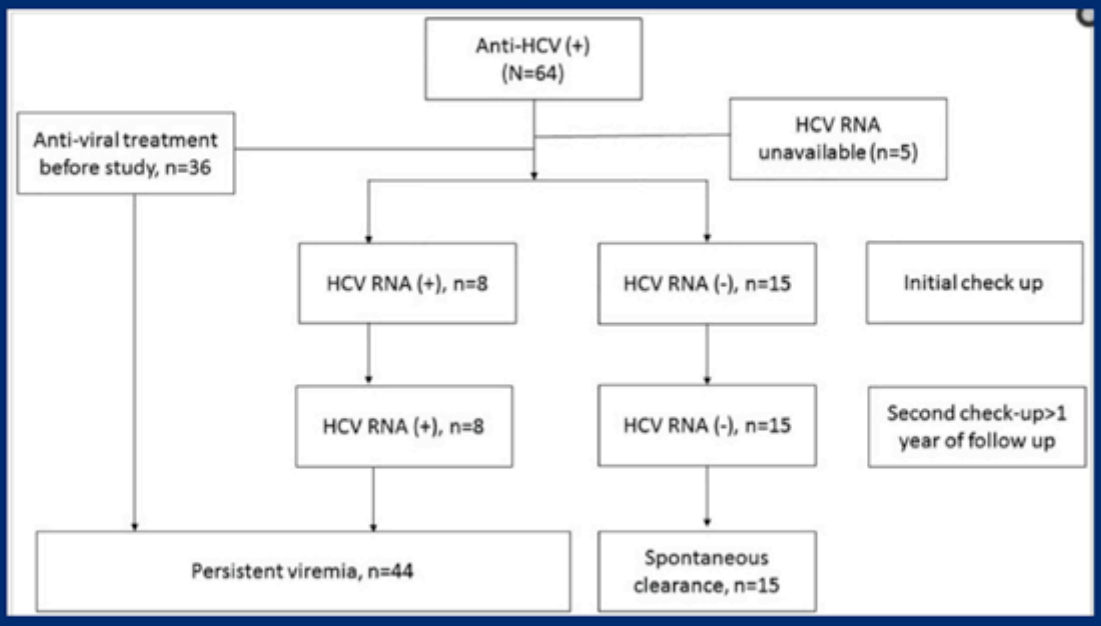
Differences of characteristics between subjects with or without HBsAg seropositivity

Differences of characteristics between subjects with or without HBsAg seropositivity.

	HBsAg (+) (n = 9, 6.4%)	HBsAg (-) (n = 131, 93.6%)	P value	Logistic regression analysis		
				OR	95% CI	*P* value
Age (years, mean(SD))	40.0 (10.7)	28.4 (10.4)	0.02	1.08	1.02–1.14	0.007
Male gender, n (%)	7 (87.5)	97 (73.5)	0.38			
Born before 1984, n (%)	8 (88.9)	53 (40.5)	0.01			
Body weight (kg, mean (SD))	62.7 (26.6)	56.5 (11.8)	0.40			
Thalassemia/hemophilia, n (%)	2/6 (22.2/66.7)	65/64 (49.6/48.9)	0.34			
AST (IU/L, mean (SD))	49.1(35.6)	35.5(28.2)	0.17			
ALT (IU/L, mean (SD))	61.1 (67.1)	48.4 (60.3)	0.59			
Serum creatinine ((mg/dL, mean (SD))	0.67 (0.22)	0.71 (0.23)	0.64			
Hemoglobin (g/dL, mean (SD))	12.8 (3.0)	12.1 (2.8)	0.49			
Platelet count ($x10^3$u/L, mean (SD))	288 (21)	309 (146)	0.71			
IL-28B rs8099917 TT genotype, n/N(%)	4/4 (100)	88/97 (90.7)	0.52			
Anti-HCV(+)	7 (77.8)	57 (43.5)	0.08			
HCV RNA (log IU/mL, mean (SD))	5.07 (1.27)	5.27(1.19)	0.82			

SD: standard deviation;OR: odds ratio; CI: confidence intervals; AST: aspartate aminotransferase; ALT: alanine aminotransferase.HBsAg: Hepatitis B surface antigen. Anti-HCV: hepatitis C antibody. IL-28B: Interleukin-28B.

Flow chart of the patients with H anti-HCV seropositive



Years of infection and FW

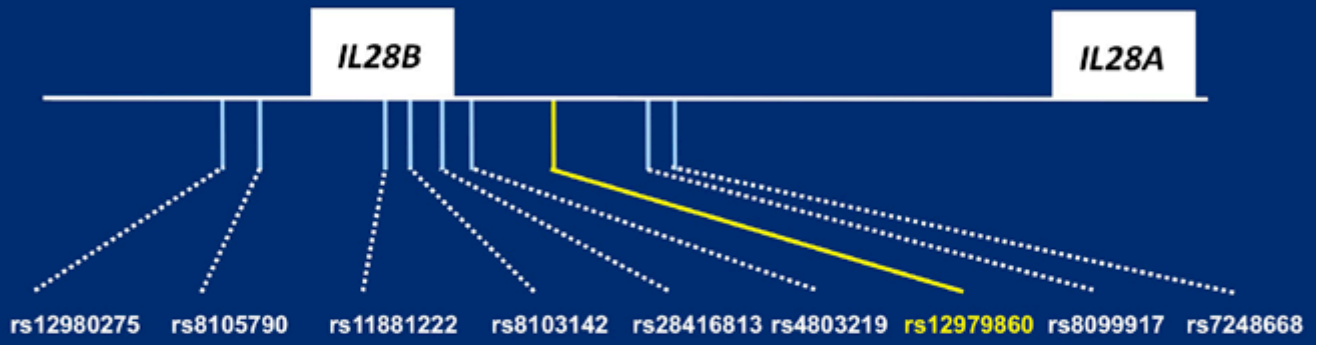
Factors associated with spontaneous HCV seroclearance in 59 anti-HCV (+) patients

	Spontaneous HCV seroclearance (n = 15, 25.4%)	HCV viremia (n = 44, 74.6%)	P value	Logistic regression analysis		
				OR	95% CI	*P* value
Age (years, mean(SD))	34.8 (10.2)	33.3 (9.9)	0.62			
Male gender, n (%)	11(73.3)	33 (75)	0.90			
Thalassemia/hemophilia, n (%)	4/10(26.7/66.7)	21/23 (47.7/52.3)	0.10			
Born before 1992, n (%)	13 (86.7)	42 (95.5)	0.24			
AST (IU/L, mean (SD))	35.2 (34.0)	55.8 (36.3)	0.06			
ALT (IU/L, mean (SD))	39.0 (42.4)	95.4 (89.8)	0.002	0.98	0.96–1.00	0.02
Serum creatinine ((mg/dL, mean (SD))	0.72 (0.21)	0.68 (0.18)	0.47			
Hemoglobin (g/dL, mean (SD))	13.0 (2.9)	12.7 (2.6)	0.70			
Platelet count (x10^3u/L, mean (SD))	301(132)	269 (164)	0.44			
HBsAg (+), n (%)	3 (20.0)	3 (6.8)	0.15			
HBV DNA (log IU/mL, mean (SD))	3.41 (2.15)	1.68 (1.45)	0.30			
HBV DNA detectatble,** n (%)	3 (20.0)	2 (4.5)	0.06			
IL-28B rs8099917 TT genotype, n/N (%)	12/12 (100)	36/42 (85.7)	0.17			

SD: standard deviation; OR: odds ratio; CI: confidence intervals; BMI: body mass index; AST: aspartate aminotransferase; ALT: alanine aminotransferase. HBsAg: Hepatitis B surface antigen. Anti-HCV: hepatitis C antibody. IL-28B: Interleukin 28B * history and data available in 51 patients.

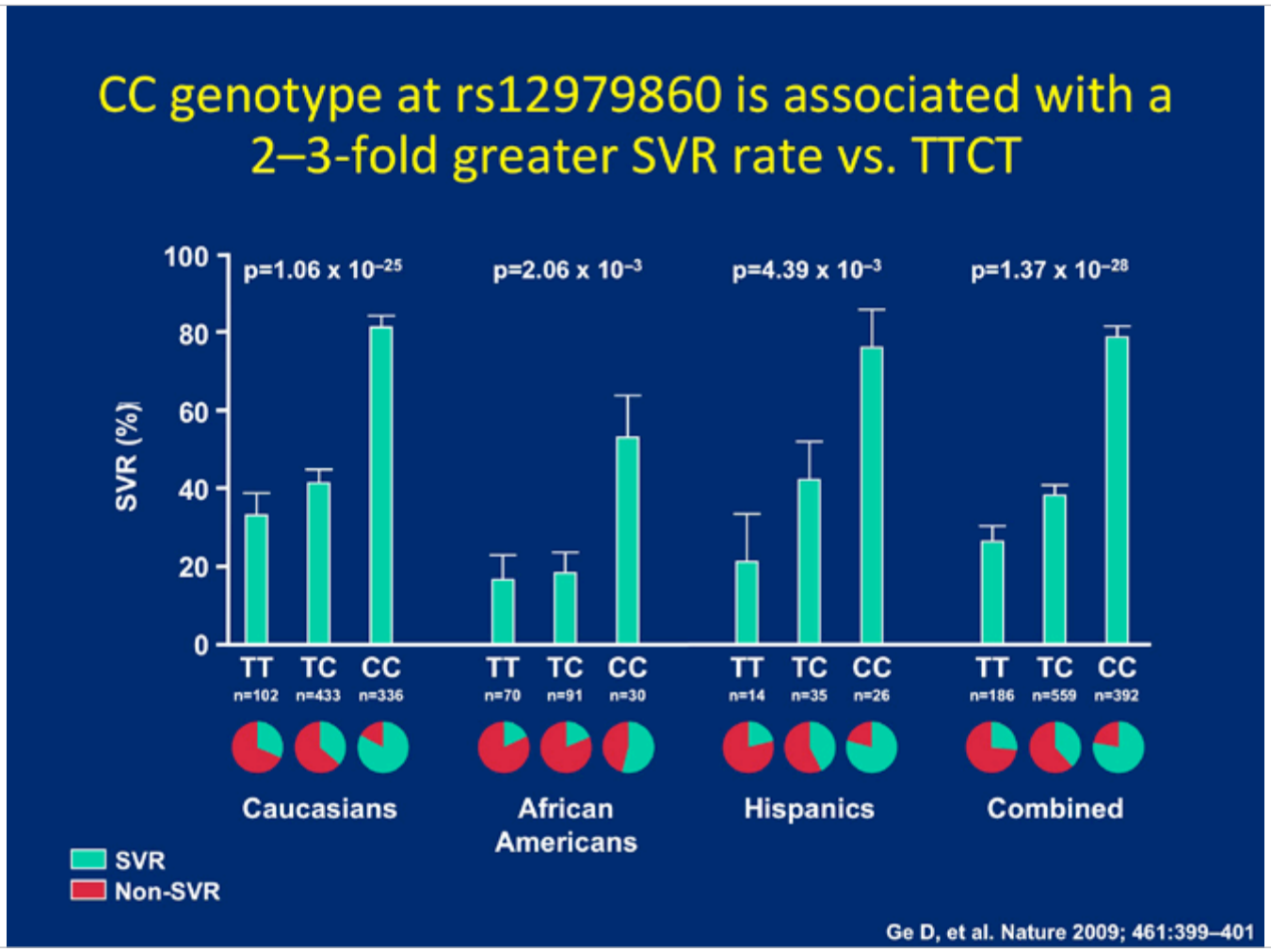
**Detectatble HBV DNA defined as >20 IU/mL

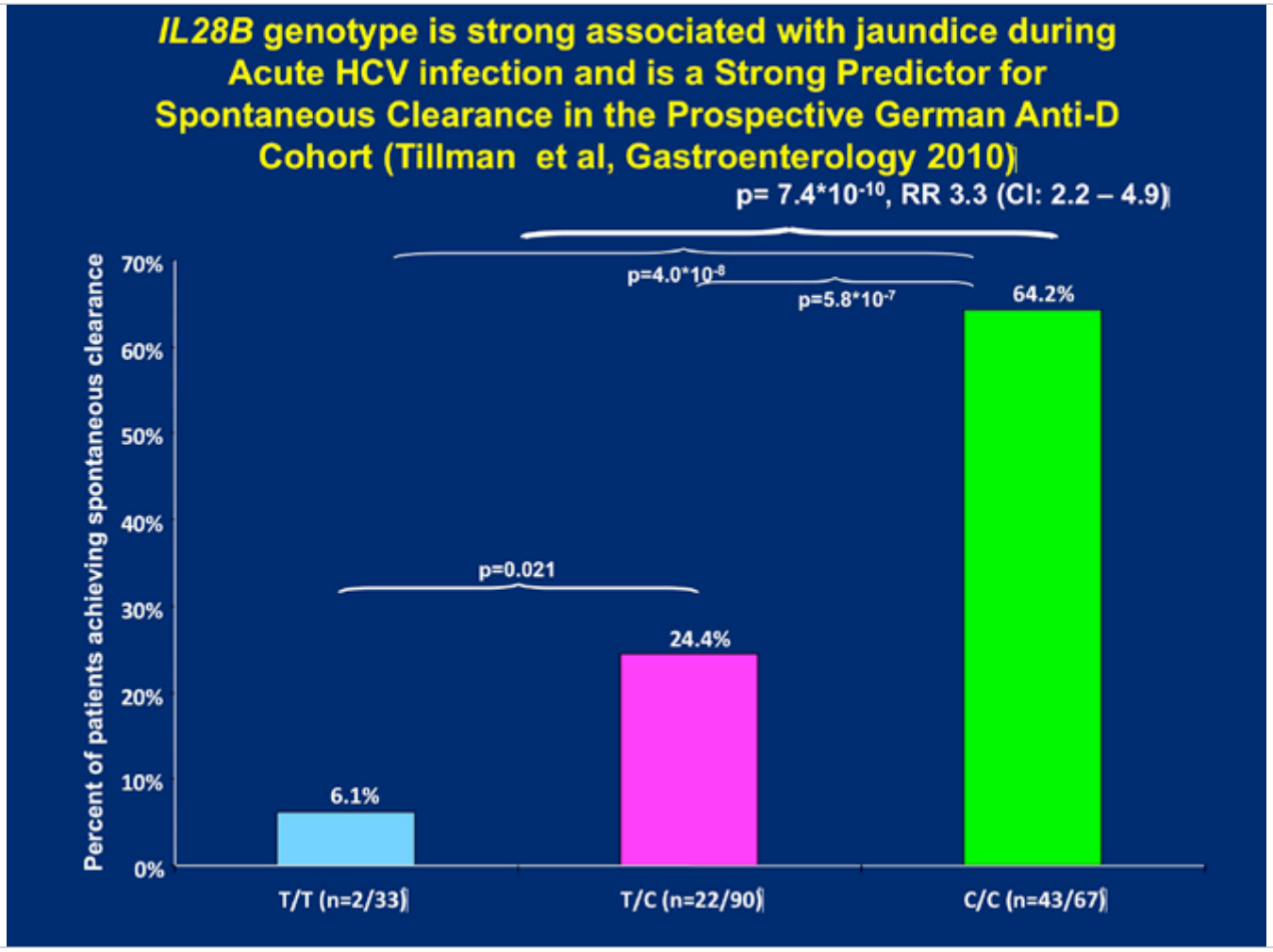
IL28B SNPs associated with CHC treatment response



- Associations between CHC treatment response and several *IL28B* variants have been shown in over 15 studies since Ge D, et al. was published in Nature in 2009
- At 61st AASLD 2010, at least 16 oral presentations and 57 posters were presented on *IL28B*

Ge D, et al. Nature 2009; 461:399–401
Goldstein DB. 61st AASLD 2010. State-of-the-art lecture


CC genotype at rs12979860 is associated with a 2–3-fold greater SVR rate vs. TTCT
SVR (%)
100
80
60
40
20
0
p=1.06 x 10−25
p=2.06 x 10−3
p=4.39 x 10−3
p=1.37 x 10−28
TT TC CC
n=102 n=433 n=336
TT TC CC
n=70 n=91 n=30
TT TC CC
n=14 n=35 n=26
TT TC CC
n=186 n=559 n=392
Caucasians
African Americans
Hispanics
Combined
SVR
Non-SVR
Ge D, et al. Nature 2009; 461:399–401


IL28B genotype is strong associated with jaundice during Acute HCV infection and is a Strong Predictor for Spontaneous Clearance in the Prospective German Anti-D Cohort (Tillman et al, Gastroenterology 2010)
p= 7.4*10-10, RR 3.3 (CI: 2.2 – 4.9)
Percent of patients achieving spontaneous clearance
70%
60%
50%
40%
30%
20%
10%
0%
p=4.0*10-8
p=5.8*10-7
64.2%
p=0.021
24.4%
6.1%
T/T (n=2/33)
T/C (n=22/90)
C/C (n=43/67)

HBV Diagnosis: Serum and Liver Markers

Serum:

- **HBsAg (qHBsAg)**
- HBeAg
- anti-HBe
- anti-HBc IgG
- **HBV-DNA levels**
- Genotpypes HBV(A-H), subtypes

Liver : HBcAg, HBV-DNA

Inactive HBV

HBV-DNA -
Anti-HBc IgM –
Anti-HBe+

Active HBV

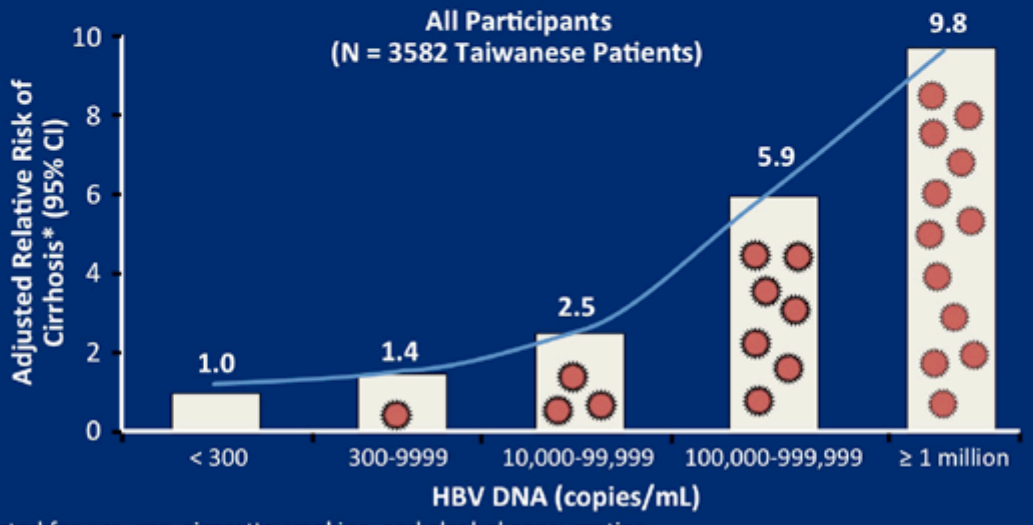
HBV-DNA +
Anti-HBc IgM +
Anti-HBe+/HBeAg+

New markers for HBV:
HBcrAg, HBV-RNA, cccDNA
Anti-HBc IgG levels

HDV assays: anti-HDV IgG, Anti-HDV IgM , HDV-RNA

REVEAL: Higher HBV DNA Associated With Higher Risk of Cirrhosis Over Time

- Serum HBV DNA ~ 2000 IU/mL (≥ 10^4 copies/mL) is an independent predictor of cirrhosis development

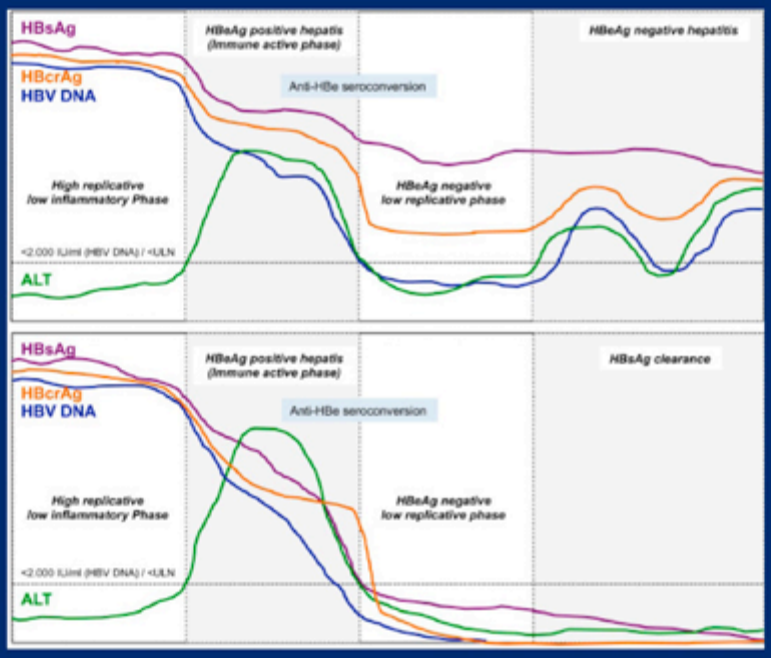


*Adjusted for age, sex, cigarette smoking, and alcohol consumption.

5. Iloeje UH, et al. Gastroenterol. 2006;130:678-686.

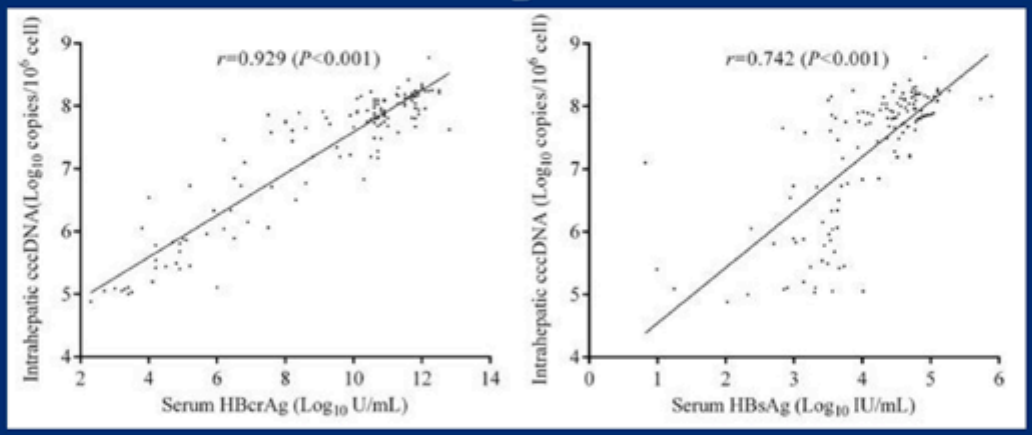
What is new on HBsAg and other diagnostic markers in HBV infection?

Christoph Höner zu Siederdissen, Benjamin Maasoumy, Markus Cornberg



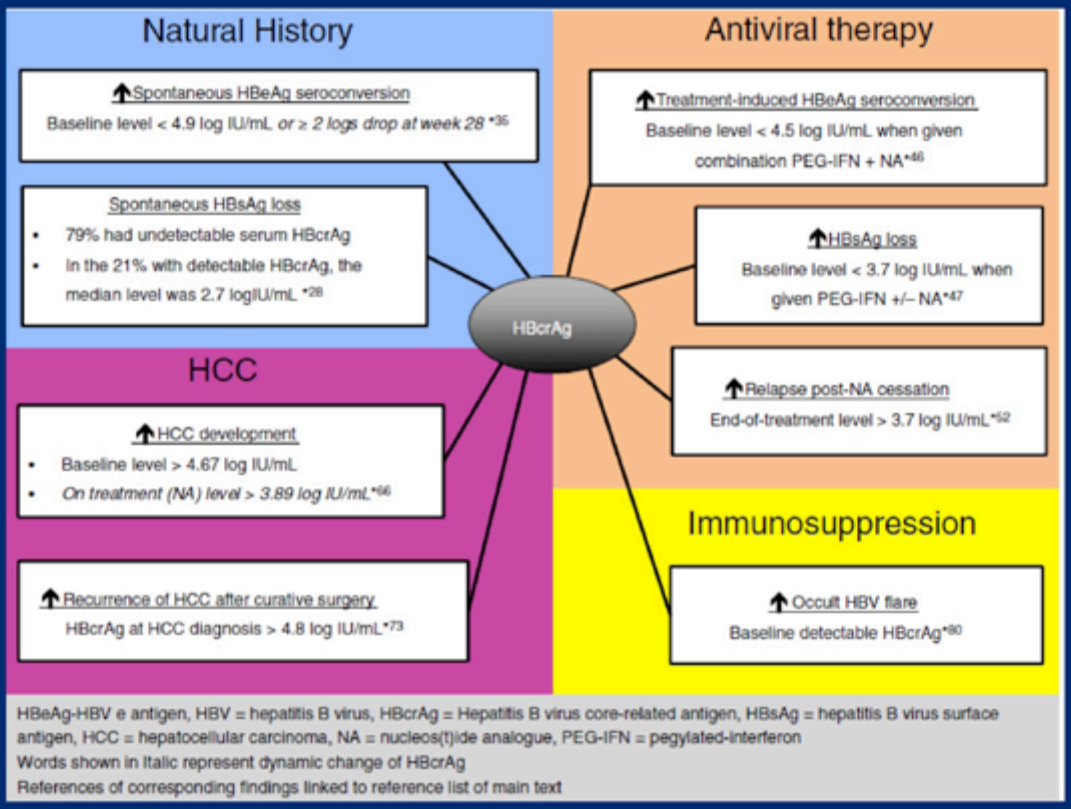
Best Practice & Research Clinical Gastroenterology, 2017

The correlations of serum HBcrAg (A) and HBsAg (B) with intrahepatic cccDNA



Chen EQ, Sci Rep 2017

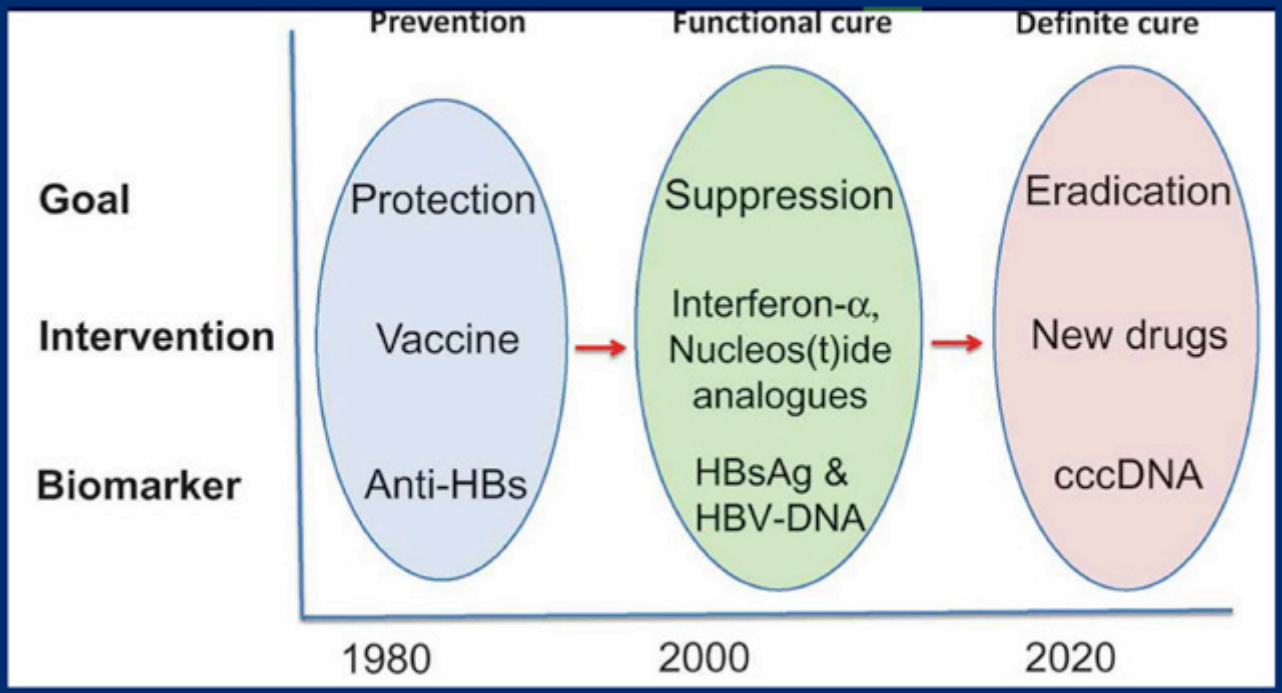
HBcrAg a Novel marker: Clinical applications



HBeAg-HBV e antigen, HBV = hepatitis B virus, HBcrAg = Hepatitis B virus core-related antigen, HBsAg = hepatitis B virus surface antigen, HCC = hepatocellular carcinoma, NA = nucleos(t)ide analogue, PEG-IFN = pegylated-interferon
Words shown in Italic represent dynamic change of HBcrAg
References of corresponding findings linked to reference list of main text

Mak L.-Y. Et al, Aliment Pharmacol Ther 2017

The path toward HBV cure



HCV Screening and Diagnosis

anti-HCV antibody pos
HCV-RNA –

anti-HCV antibody pos
HCV-RNA +

Genotpyes 1-6 /Subtypes

HCV-RNA quantitation assays

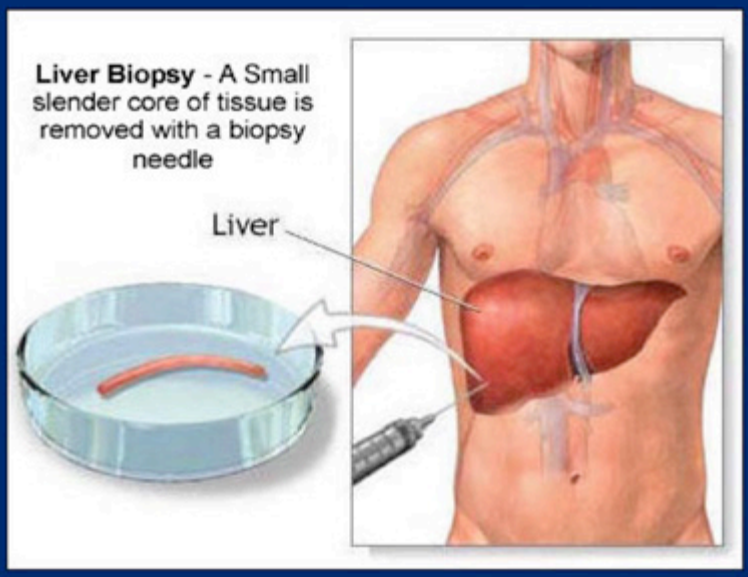
Genotype 1 through 6 with fully automated sample extration and real-time PCR amplification and detection

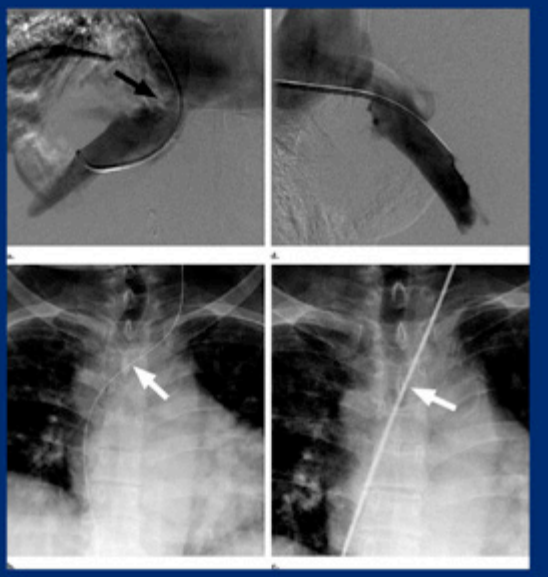
Aptima HCV quant Dx (the last available)
(LoD was 5.1 IU/mL or lower for serum and 4.8 IU/mL or lower for plasma depending on the HCV genotype)

Abbott RealTime HCV (LoD 25 UI/mL)

Roche COBAS AmpliPrep/COBAS TaqMan HCV quantitative test v2.0
(LoD 15UI/mL)

PLB and TJLB Procedures





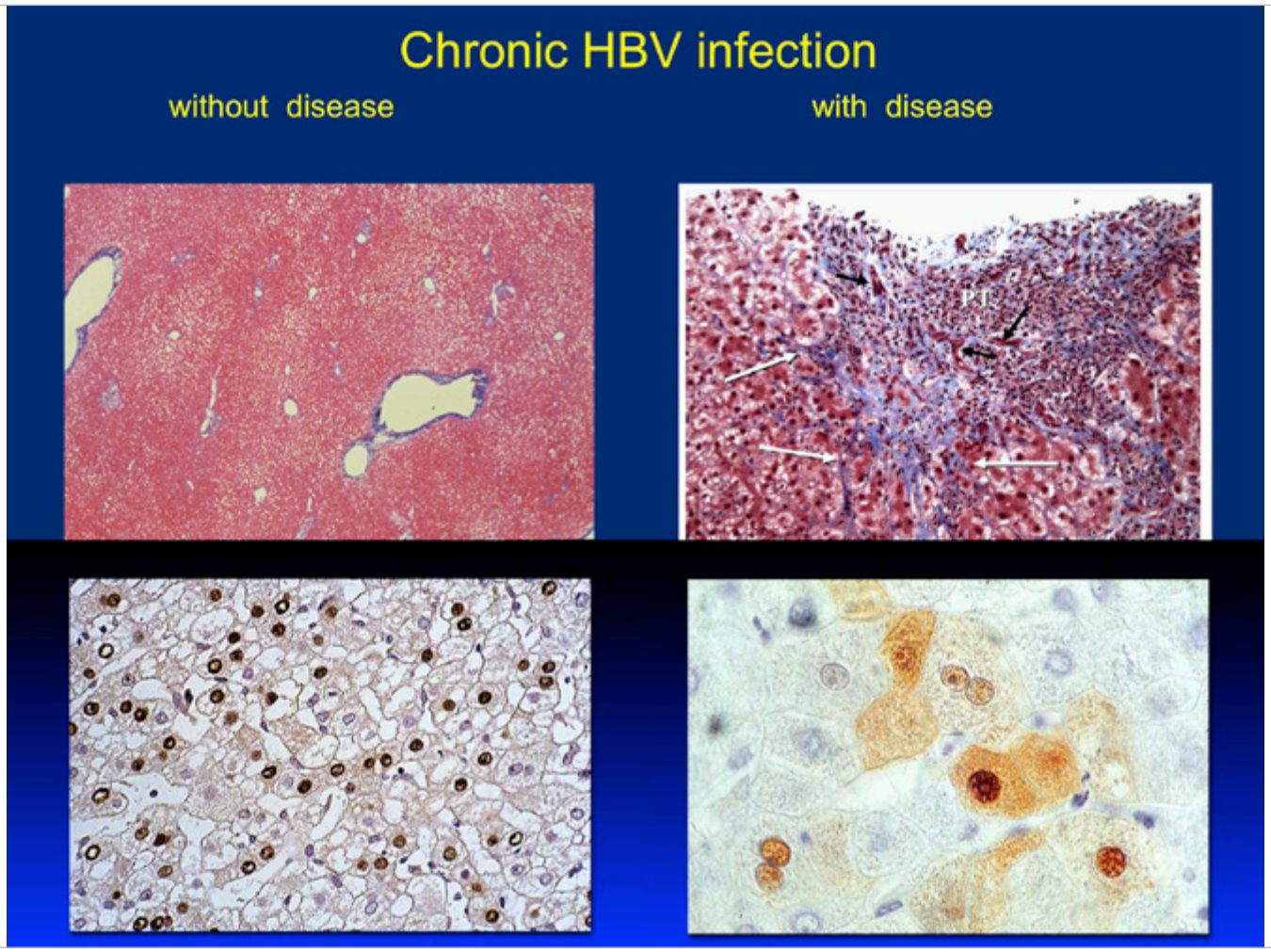
Menghini needle: 16 G
Tru-cut needle : 16-18 G; >18 G

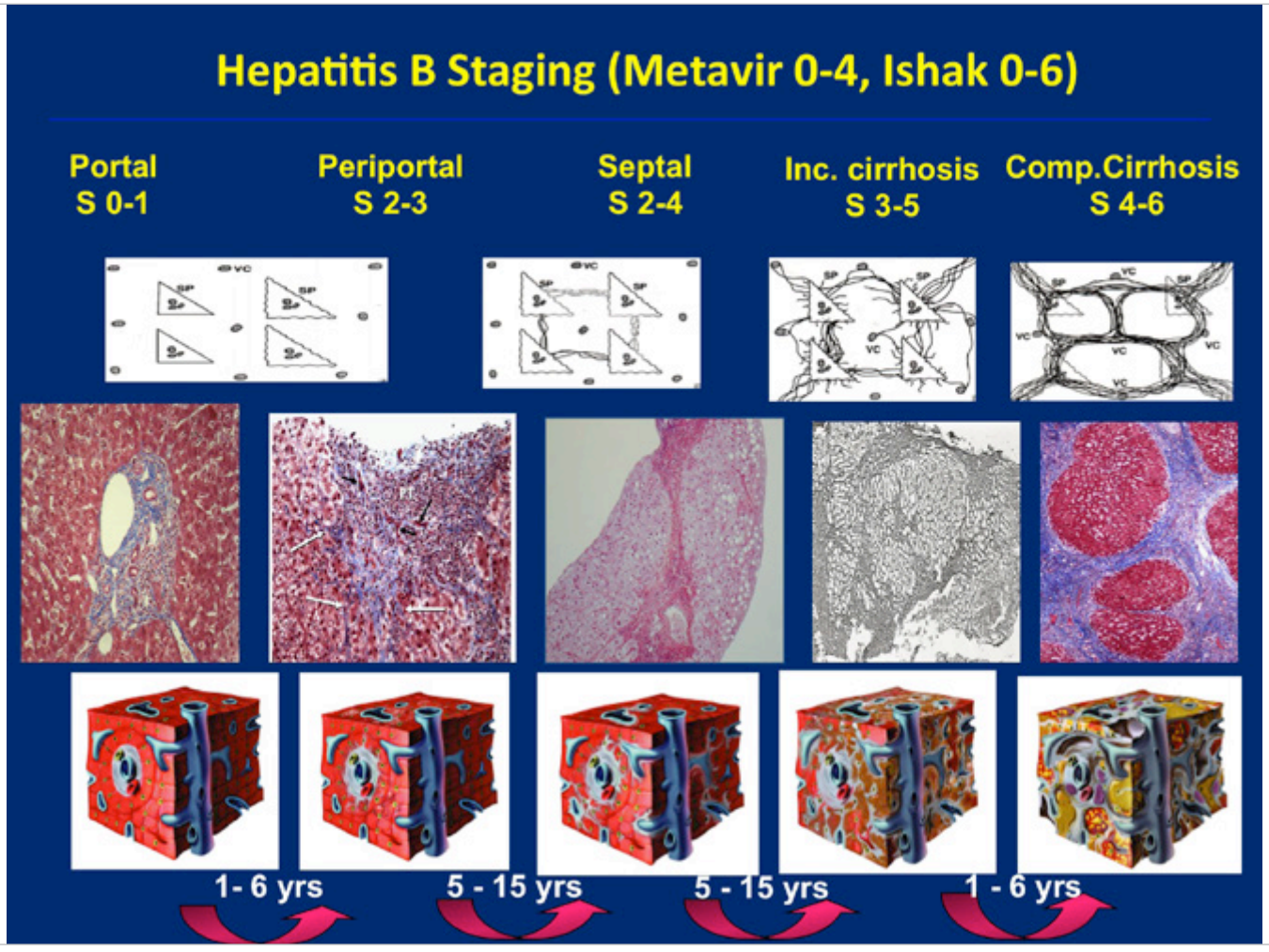
Liver Biopsy: TJLB

- PLB vsTJLB= 2462 (n=2156 vs n=306)
- Period 1994-2004
- Adequate sample: 91%
  Cirrhosis present vs absent :87%
- Menghini technique: 16 G needle;1-3 passes
- Fragmentation rate:37%
- Complications: 2% minor (atrial arritymia)
- HVPG measure

TJLB safe procedure not to be considered second rate procedure biopsies compared to PLB

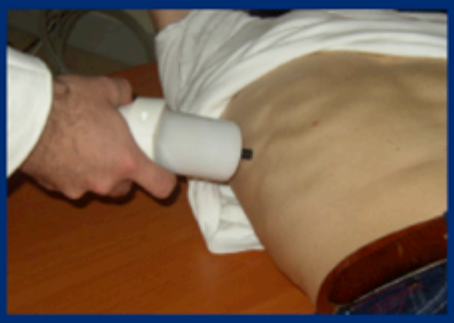
Alessandria et al, J Hepatol 2007


Chronic HBV infection
without disease
with disease
PT


Hepatitis B Staging (Metavir 0-4, Ishak 0-6)
Portal
S 0-1
Periportal
S 2-3
Septal
S 2-4
Inc. cirrhosis
S 3-5
Comp.Cirrhosis
S 4-6
1- 6 yrs
5 - 15 yrs
5 - 15 yrs
1 - 6 yrs

Fibroscan

- Il Fibroscan valuta il grado di rigidità del fegato.
- Utilizza una sonda con un vibratore a bassa frequenza (50 Hz) e un trasduttore di ultrasuoni (5 MHz).
- La vibrazione produce onde elastiche che si propagano nel tessuto esplorato.
- La velocità di propagazione dell'onda è proporzionale alla rigidità del fegato: quanto più è rigido tanto più velocemente si propaga l'onda meccanica.



Fibroscan range from 2005 -2017

With its patented Vibration Controlled Transient Elastrography (VCTE technology), the FibroScan is the most recommended non-invasive device to use in the clinical management of patients with liver disease. **Mass screening with ultra mobility**

ROC Curve for significant Fibrosis in H with Fibroscan and different non invasive scores

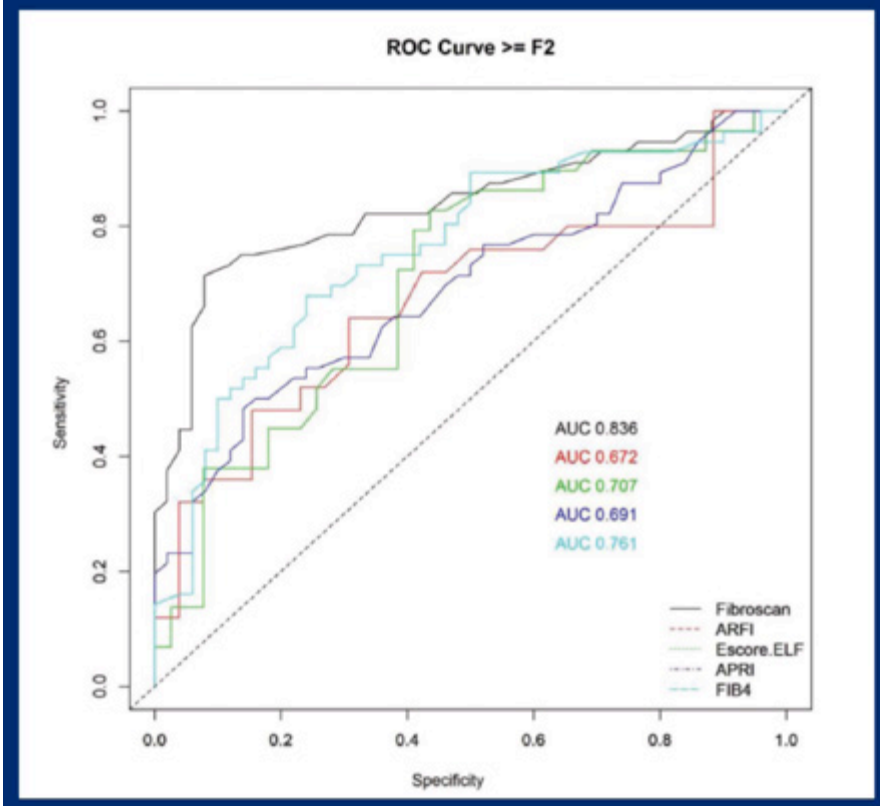


Table 1. Selected non-invasive models to assess liver fibrosis

FibroTest	alfa 2-macroglobulin, GGTP, apolipoprotein A-1, haptoglobin, total bilirubin, age, sex
APRI	GOT, PLT
Hepascore	bilirubin, GGTP, hyaluronic acid, sex, age
Fibrometer	PLT, prothrombin time, GOT, alfa 2-macroglobulin, hyaluronic acid, urea, age
Forns Index	age, PLT, cholesterol, GGTP
ELF (Enhanced Liver Fibrosis score)	age, hyaluronic acid, MMP-3, TIMP-1
FibroSpect	alfa 2-macroglobulin, hyaluronic acid, TIMP-1
MP3	MMP-3, TIMP-1
FIB-4	ALT, AST, PLT, age

Ragazzo TG et al, Clinics Science 2017

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection

Natural history and assessment of patients with chronic HBV infection

HBV markers
HBsAg
HBeAg/anti-HBe
HBV DNA

Liver disease
Biochemical parameters: ALT
Fibrosis markers: non-invasive markers of fibrosis (elastography or biomarkers) or liver biopsy in selected cases

	HBeAg positive		HBeAg negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBsAg	High	High/intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10^7 IU/ml	10^4-10^7 IU/ml	<2,000 IU/ml**	>2,000 IU/ml
ALT	Normal	Elevated	Normal	Elevated*
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis

Lampertico P. et al, J Hepatol 2017

CHRONIC HEPATITIS B IN SOUTHERN ITALY

The Gr.E.Ca.S Hospitals'Collaborating Group

February-July

2010

Baseline characteristics of 247 HBsAg + subjects

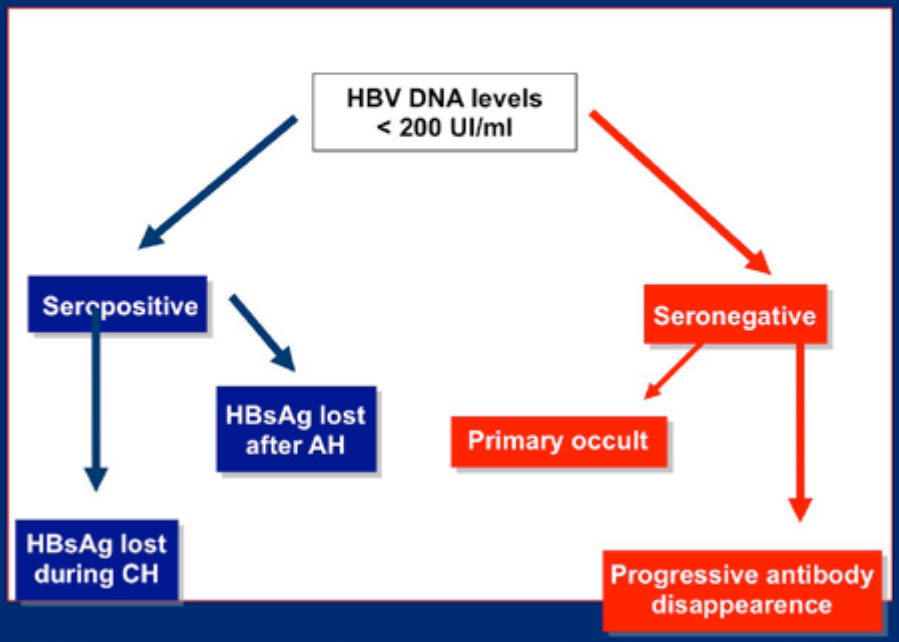
Diagnostic category:

- Inactive carrier 108 (43.7%)
- Chronic hepatitis 103 (41.7%)
- Liver cirrhosis 36 (14.6%)

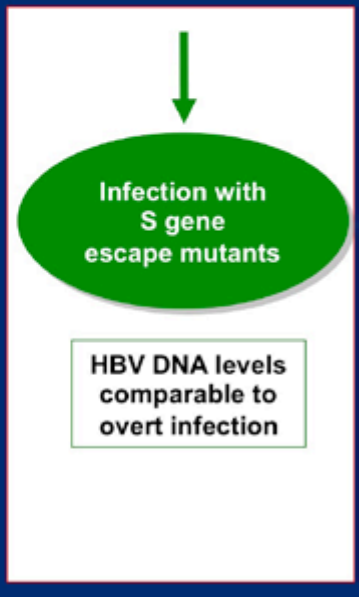
Stroffolini T. et al. EJIM 2012

Occult HBV carrier

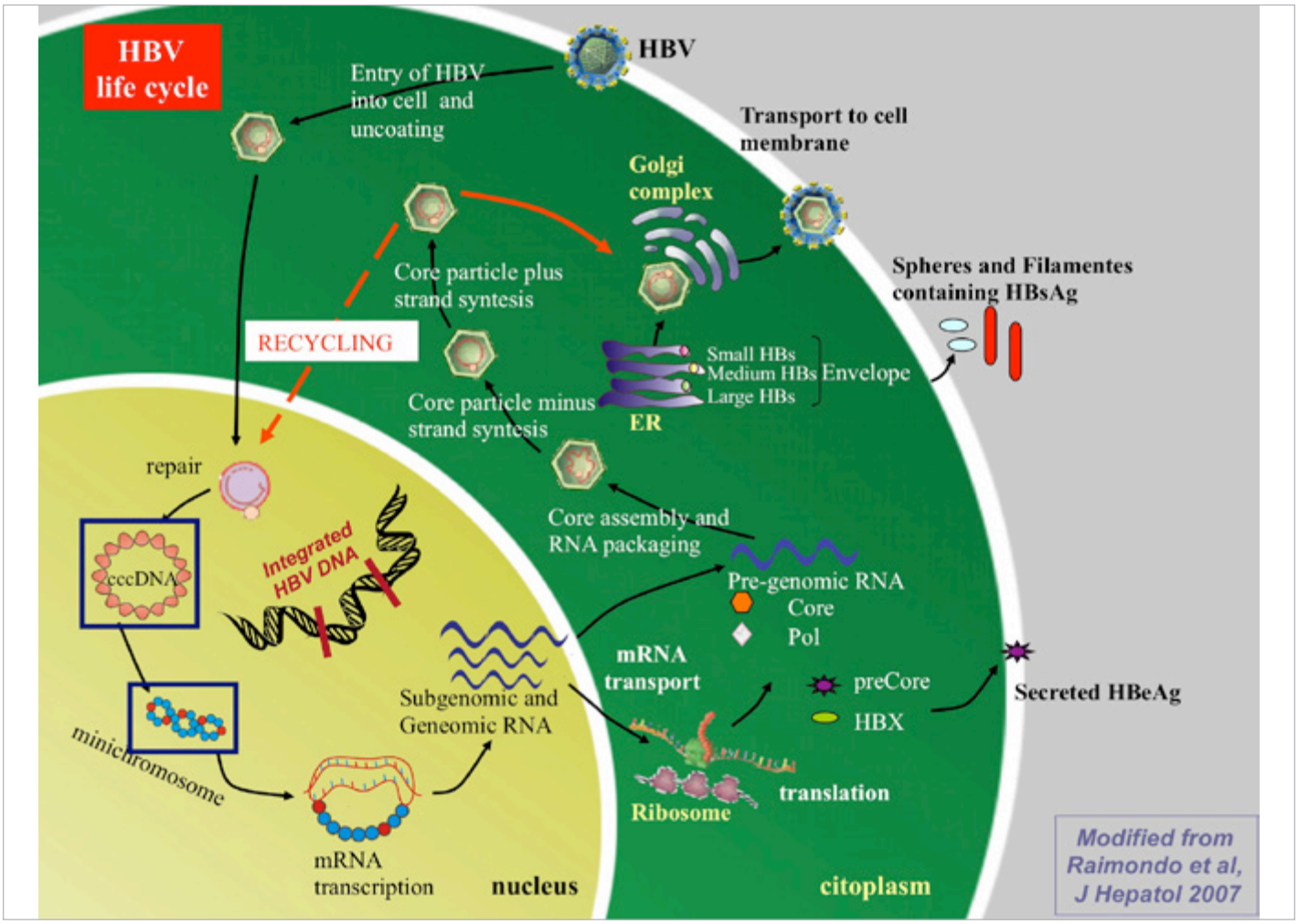
OBI



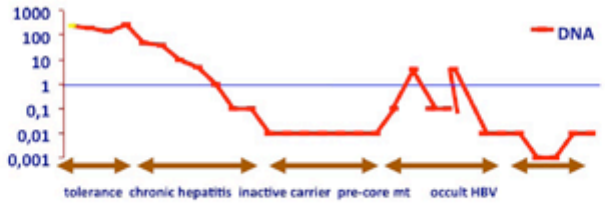
„false" OBI

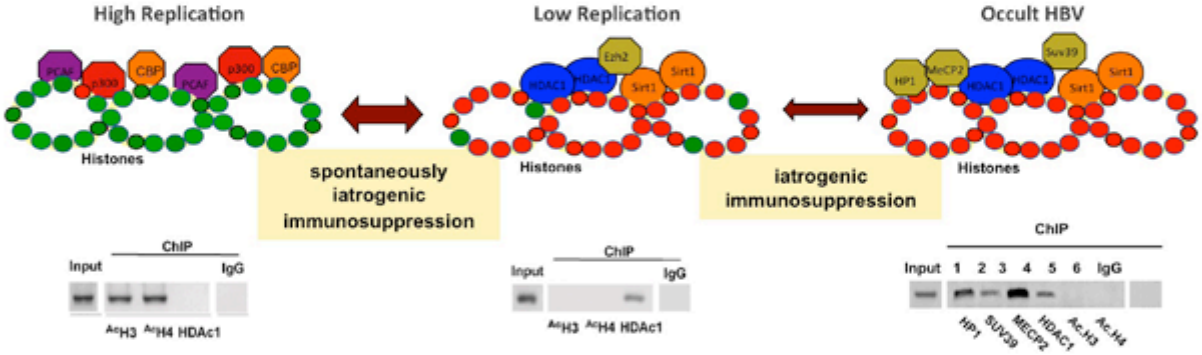


EASL Concensus Conference Taormina, 7-8 Marzo 2008



cccDNA status in HBV patients





Low-replicative to latent infection

Epigenetic control

HBsAg-Negative: Occult-HBV Carrier

Anti-HBc+ Alone

Anti-HBc+ Anti-HBs+

OLT

Blood Banks

Oncology Unit

HBV-DNA liver cccDNA

Anti-HBs+

HBV Markers -

OLT

Cryptogenic Cirrhosis
Cryptogenic HCC
Occult acute hepatitis

Marzano et al, AISF Guidelines 2007-2011
AISF Revision 2017

Occult B Infection (OBI)

Hepat Mon 2012

The Prevalence of OBI and HBV Serological Markers Among Blood Recipient Patients

	Disease	Country	Region, City	Prevalence of OBI [a], %	Prevalence, %		
					Anti HBc	Anti HBs	HBs Ag
Toyoda et al. [11] (2004)	Hemophilia	Japan	ND	51.2	86	62.8	0
Borhany et al. [12] (2011)	Hemophilia	Pakistan	Karachi	1.73	ND [a]	ND	ND
Windyga et al. [13] (2006)	Hemophilia	Polish	ND	0	69.5	49.5	7.8

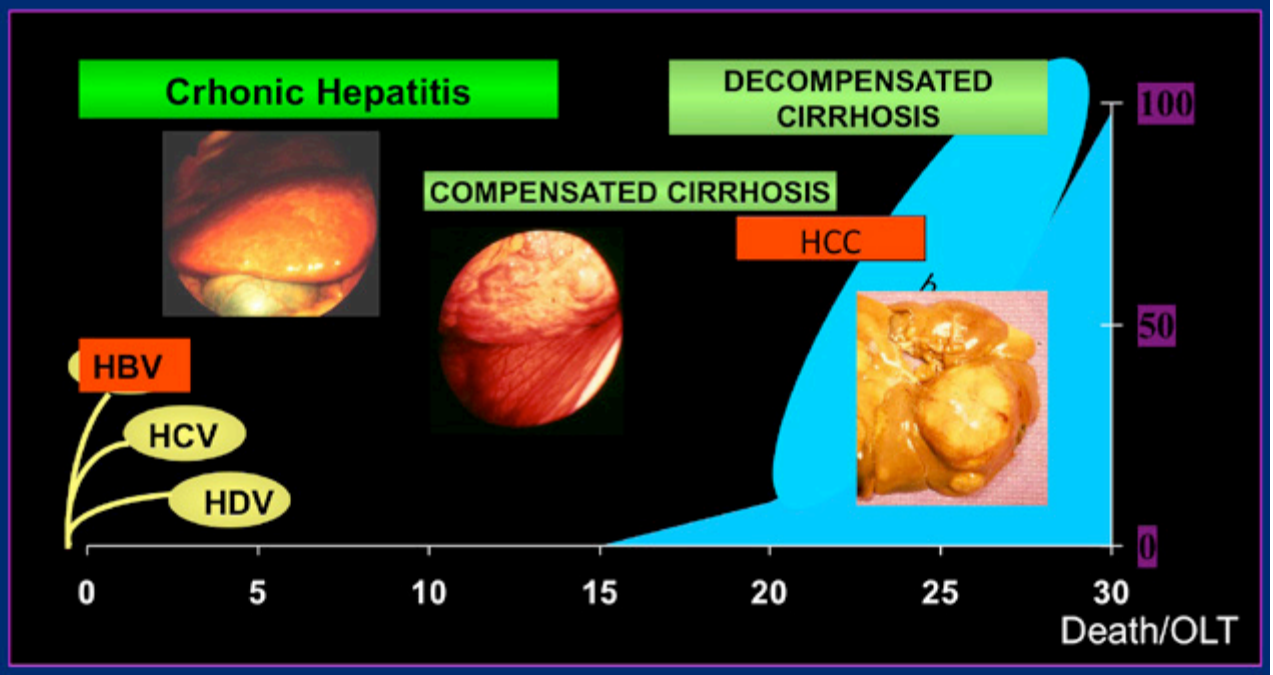
Greek patients (H)
N= 112
OBI+ : N= 2/112 (1.8%) HBsAg negative, anti-HBc+ (46.5%)

Agoritsa Varacklioti et al, 2017

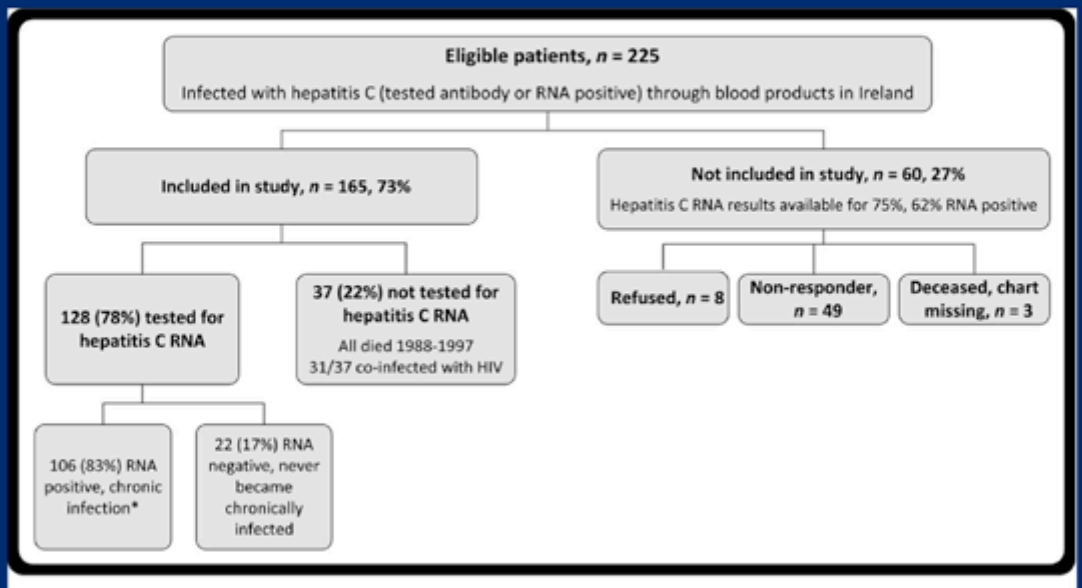
Diagnosis (anti-HBc + surrogate marker for OBI+)
Clinical Significance
Risk factors for: HBV Reactivation -Fibrosis-Cirrhosis -HCC

Raimondo et al H Hepatol 2008
Squadrito et al, Ann. Gastoenterol 2014
Caviglia GP et. al, DLD 2014

Chronic Viral Hepatitis
Natural History



Progression of hepatitis C in the haemophiliac population in Ireland, after 30 years of infection in the pre-DAA treatment era



*5 of the 106 HCV chronically infected patients included in the study had late spontaneous resolution

Murphy N. et al, Haemophilia 2017

Age and HIV status

	HIV positive (*n* = 36, 34%)		HIV negative (*n* = 70, 66%)		All (*n* = 106)	
	N	%	*N*	%	*N*	%
Age at infection (*n* = 106)						
<20 years	29	80.6	43	61.4	72	67.9
20–29 years	5	13.9	15	21.4	20	18.9
30+ years	2	5.6	12	17.1	14	13.2
Median (range)	11	(0–35)	17	(0–53)	14	(0–53)
Age at end of follow-up (*n* = 106) [a]						
0–39 years	12	33.3	15	21.4	27	25.5
40–54 years	17	47.2	31	44.3	48	45.3
55+ years	7	19.4	24	34.3	31	29.3
Median (range)	43.5	(30–63)	49.0	(18–81)	47	(18–81)

Murphy N. et al, Haemophilia 2017

Time since Infection and HCV Genotypes (n= 106)

Time since infection (*n* = 106) [b]						
<20 years	1	2.8	4	5.7	5	4.7
20–29 years	6	16.7	22	31.4	28	26.4
30+ years	29	80.6	44	62.9	73	68.9
Median (range)	36.5	(17–42)	32	(14–50)	34	(14–50)
HCV genotype (*n* = 92)						
Genotype 1	18	58.1	42	68.9	60	65.2
Genotype 2	5	16.1	4	6.6	9	9.8
Genotype 3	7	22.6	13	21.3	20	21.7
Genotype 4	1	3.2	1	1.6	2	2.2
Genotype 5			1	1.6	1	1.1

Murphy N. et al, Haemophilia 2017

Hepatitis B Status (N=99)

Hepatitis B status (*n* = 99)						
Current infection	6	18.2	3	4.6	9	9.1
Past infection	15	45.5	28	42.4	43	43.4
Not infected	12	36.4	35	53.0	47	47.5
Highest alcohol intake (*n* = 92)						
Non drinker	5	18.5	12	18.5	17	18.5
Within recommended limits	9	33.3	33	50.8	42	45.7
Moderately high	7	25.9	11	16.9	18	19.6
High	6	22.2	9	13.9	15	16.3

[a] End of follow-up is the date of last test or hospital attendance or date of death.

[b] Time from infection to the end of latest follow-up for each patient. The duration of hepatitis C RNA positivity is less than this for patients with resolved infection.

Murphy N. et al, Haemophilia 2017

	HIV positive (*n* = 36, 34%)		HIV negative (*n* = 70, 66%)		All (*n* = 106)	
	N	%	*N*	%	*N*	%
Signs of advanced liver disease [a]	23	63.9	16	22.9	39	36.8
Cirrhosis	10	27.8	11	15.7	21	19.8
Hepatocellular carcinoma	4	11.1	6	8.6	10	9.4
Deceased	16	44.4	20	28.6	36	34.0
Liver-related death [b]	6	17.1	7	10.1	13	12.5
HIV/immunodeficiency/NHL [c]	5	14.3			5	4.8
Haemophilia	3	8.6	2	2.9	5	4.8
Other	1	2.9	10	14.5	11	10.6
Missing death certificates	1		1		2	

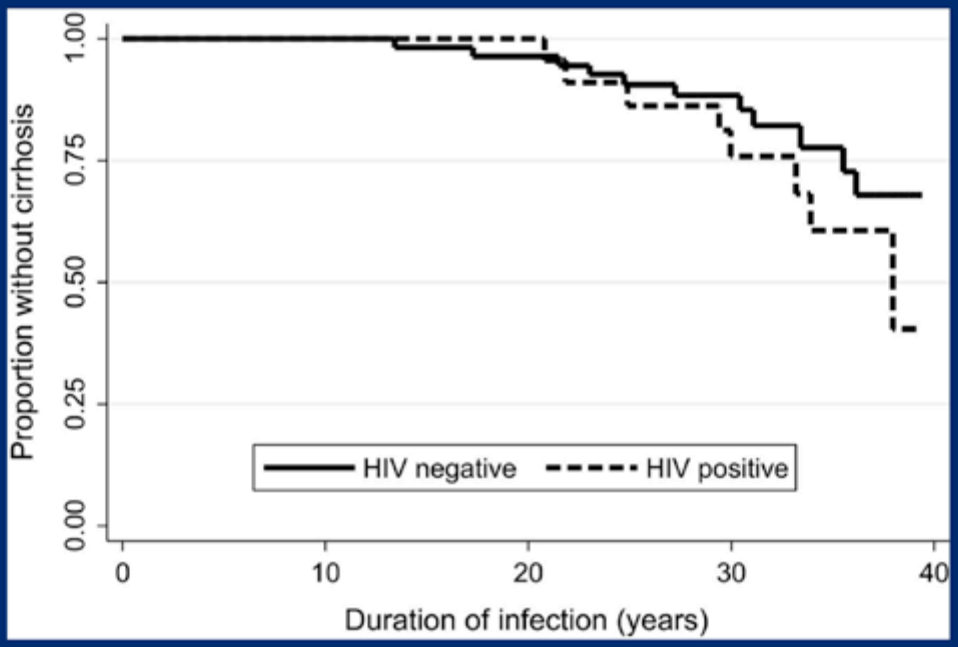
[a] Signs of liver disease include cirrhosis, HCC, varices, ascites, portal hypertension, encephalopathy, hepatomegaly, splenomegaly or hepatosplenomegaly. Counts of cirrhosis and HCC are not mutually exclusive.

[b] The denominator for the percentage who died from liver-related causes (and other specified causes) is the total number of patients excluding cases with missing death certificates.

[c] Non-Hodgkin's lymphoma.

Murphy N. et al, Haemophilia 2017

Progression of hepatitis C in the haemophiliac population in Ireland, after 30 years of infection in the pre-DAA treatment era



Murphy N. et al, Haemophilia 2017

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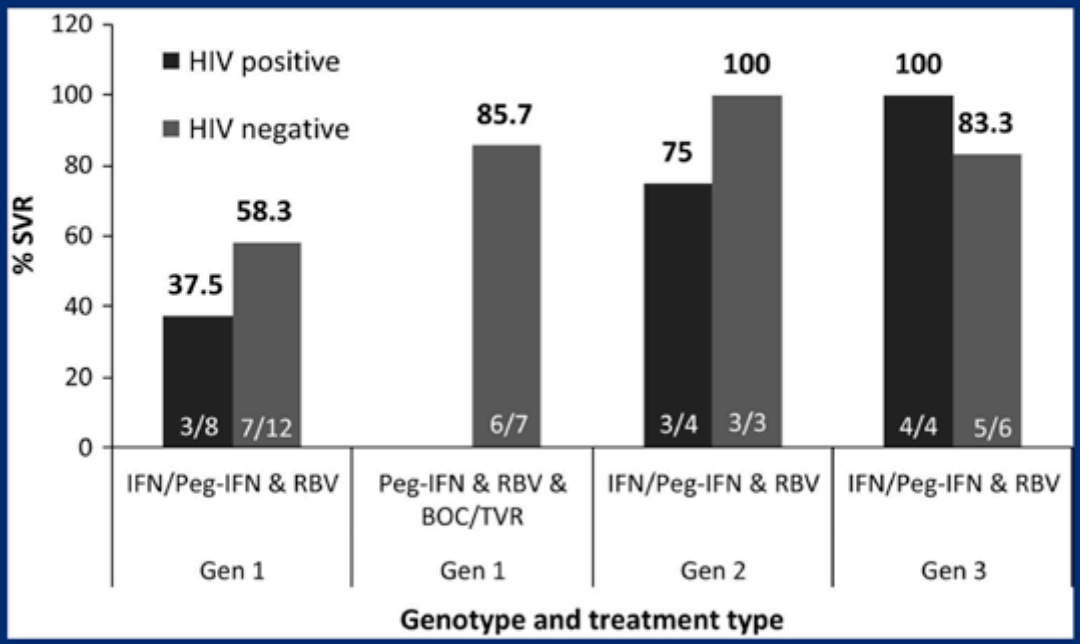
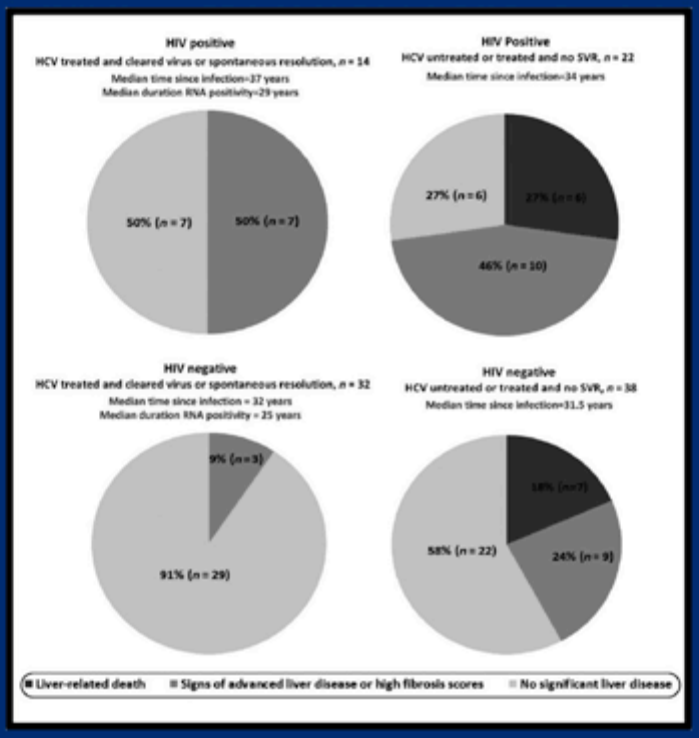


Murphy N. et al, Haemophilia 2017

Progression of hepatitis C in the haemophiliac population in Ireland, after 30 years of infection in the pre-DAA treatment era

Liver-related disease status by HCV therapy and HIV status



Long-term FW of hepatitis C infection in a large cohort of patients with inherited bleeding disorders

Sites: Netherland (1), U.K.(2) FW (30 years)

	Overall (n = 863)	Spontaneous clearance (n = 163)
Male sex	815 (94%)	153 (94%)
Hemophilia A	654 (76%)	112 (68%)
Hemophilia B	129 (15%)	31 (19%)
Von Willebrand disease	53 (6%)	14 (9%)
Other bleeding disorder	27 (3%)	6 (4%)
Severe bleeding disorder	544 (65%)	91 (57%)
Mean age in yr (range)		
At HCV infection	16.2 (0-76)	15.8 (0-61)
At end of follow-up	46.2 (10-93)	44.8 (10-93)
HCV genotype		
1	372 (43%)	5 (3%)
2	70 (8%)	1 (0.5%)
3	92 (11%)	1 (0.5%)
4	14 (2%)	-
5	8 (1%)	-
unknown	307 (35%)	156 (96%)
Co-infection with HIV	212 (25%)	21 (13%)
Co-infection with hepatitis B	16 (2%)	7 (4%)
History of alcohol abuse	77 (10%)	10 (8%)
Total number of follow-up yr	26,216	4815

HCV, hepatitis C; HIV, human immunodeficiency virus.

Fransen van de Putte D.E.et al J Hepatol 2014

Adverse liver –related outcomes in 863 HCV infected patients with inherited bleeding disorders

	Overall (n = 863)	Chronic HCV infection (n = 700)*	Spontaneous clearance (n = 163)	Never treated (n = 344)
ESLD	11% (9-13)	13% (10-16)	0.6% (0-3)	16% (13-21)
Decompensated cirrhosis	9% (7-11)	11% (9-13)	0.6% (0-3)	14% (11-18)
Hepatocellular carcinoma	3% (2-4)	3% (2-5)	0.6% (0-3)	3% (2-6)
Liver transplantation	1.5% (0.8-3)	2% (1-3)	0% (0-2)	2% (0.6-4)
Liver-related death	8% (6-10)	9% (7-12)	0.6% (0-3)	13% (10-17)

Values are proportions (95% CI).

ESLD, end-stage liver disease.

* Includes all patients without spontaneous clearance of the hepatitis C virus.

Fransen van de Putte D.E.et al J Hepatol 2014

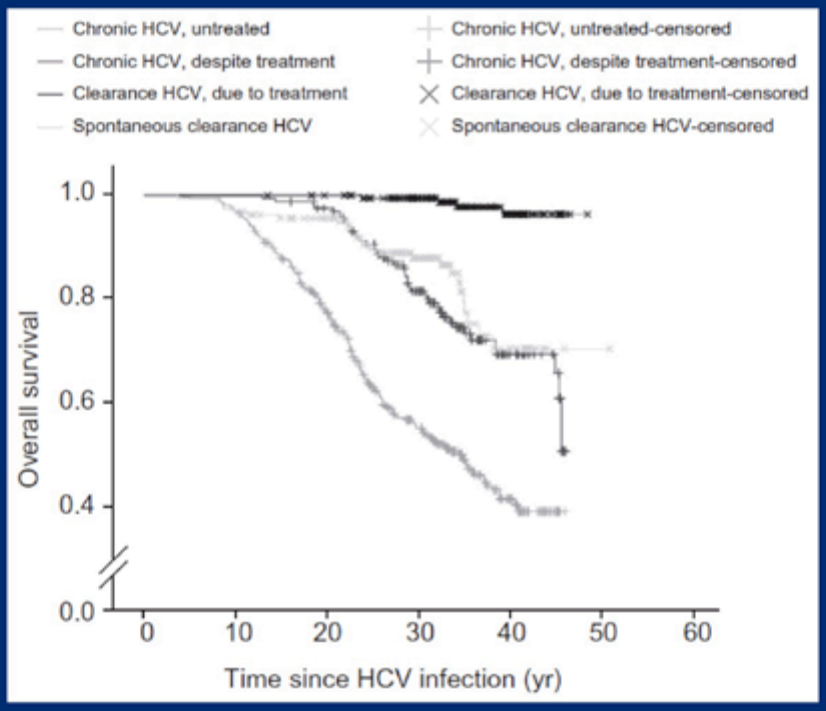
Univariate and multivariate analyses of ELD in 700 Patients with inherited bleeding disorders and Chronic Hepatitis C

	Univariate analysis			
	Crude HR	(95% CI)	*p* value	Adjusted HR
Male sex	1.46	0.46-4.63	0.52	-
Age at HCV infection (per yr)	1.05	1.04-1.07	<0.001	1.09
Age at end of follow-up (per yr)	1.01	0.99-1.03	0.20	-
HCV genotype 1	1.80	1.00-3.24	0.05	1.56
HIV co-infection	5.14	3.40-7.78	<0.001	10.85
History of alcohol abuse	2.57	1.56-4.23	<0.001	4.34
Successful antiviral treatment	0.04	0.01-0.17	<0.001	0.14

HR, hazard ratio; CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

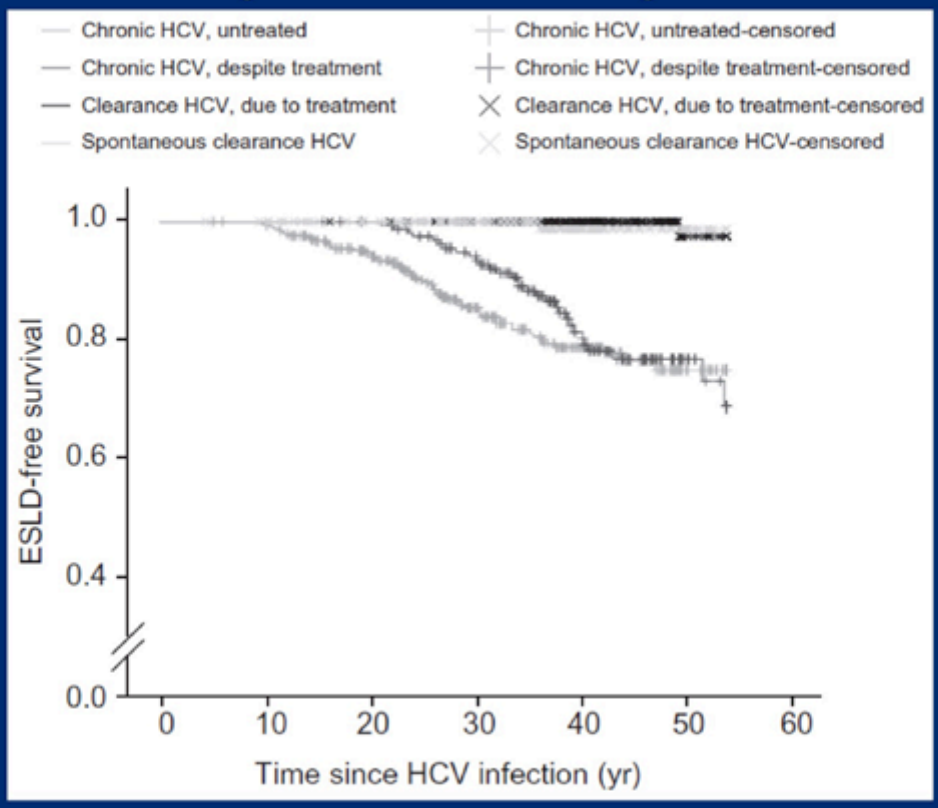
Fransen van de Putte D.E.et al J Hepatol 2014

Overall survival in 863 HCV infected patients with inherited bleeding disorders according to infection status



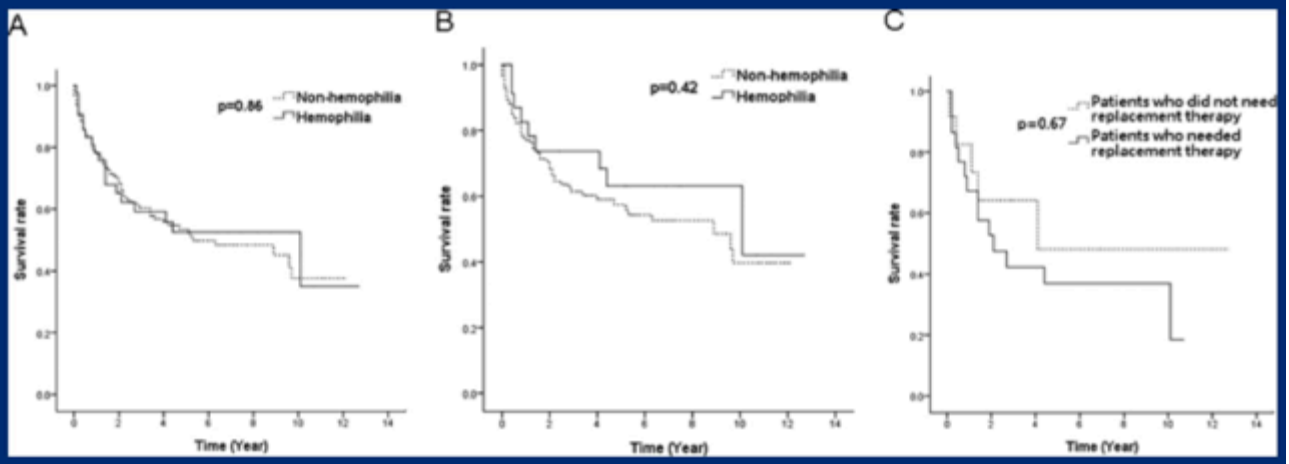
Fransen van de Putte D.E.et al J Hepatol 2014

ESLD-free survival in 863 HCV infected patients with inherited bleeding disorders according to infection status.



Fransen van de Putte D.E.et al J Hepatol 2014

Incidence and survival of cancers among 1,054 hemophilia patients: A nationwide and 14-year cohort study



The study showed that the cumulative incidence of cancer was higher in PWH than the general population (HCC /Leukemia /Lymphoma). PWH with cancer were younger and had few comorbidities at the time of diagnosis, but the survival rates were similar in PWH and the general male population (N= 10.540)

Yung-Chien Huang. et al, A J of Hematology 2015

Number, type, and diffusion of cancers according to the patients' VWD type and viral infection status

Type of cancer	Total *n* (%)	VWD type *n*	Metastasis[a] *n*	HCV+/HIV+ *n*
Solid	87 (82)	53 type 1; 11 type 2A; 10 type 2B; 8 type 2M; 3 type 2N; 2 [illegible]3	23	13/2
Urogenital tract	19 (22)	9 type 1; 2 type 2A; 3 type 2B; 3 type 2M; 2 type 2N	5	3/1
Gastrointestinal tract	17 (19)	14 type 1; 1 type 2A; 2 type 2B	4	2/0
Breast cancer	16 (18)	8 type 1; 3 type 2A; 1 type 2B; 3 type 2M; 1 type 3	4	0/0
Hepatocellular carcinoma	6 (7)	4 type 1; 1 type 2B; 1 type 2M	1	6/0
Respiratory system	9 (10)	5 type 1; 2 type 2A; 2 type 2B	5	0/0
Pancreas	3 (3)	3 type 1	1	0/0
Other cancers[b]	17 (19)	11 type 1; 3 type 2A; 1 type 2B; 1 type 2M; 1 type 3	3	2/1[c]
Hematological	19 (18)	11 type 1; 2 type 2A; 4 type 2B; 1 type 2M; 1 type 3	–	4/0
Non-Hodgkin lymphoma	10 (54)	6 type 1; 1 type 2A; 3 type 2B		3/0
Myeloproliferative disorders	5 (26)	2 type1; 1 type 2A; 1 type 2M; 1 type 3		0/0
Multiple myeloma	2 (10)	1 type 1; 1 type 2B		1/0
Chronic lymphocytic leukemia	1 (5)	1 type 1		0/0
Acute myeloid leukemia	1 (5)	1 type 1		0/0

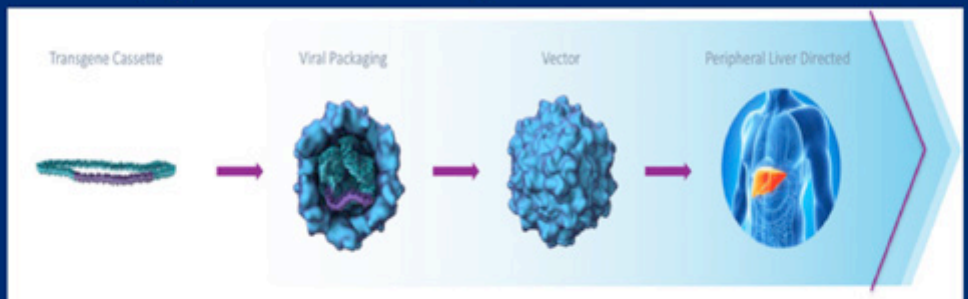
Franchini M. et al, Italian Association of Haemophilia Centres (AICE)

Semin Thromb Hemost 2016

Proposed machanisms for increased/decreased prevalence of malignancies in PWH Schimati Chetty et.al, 2017

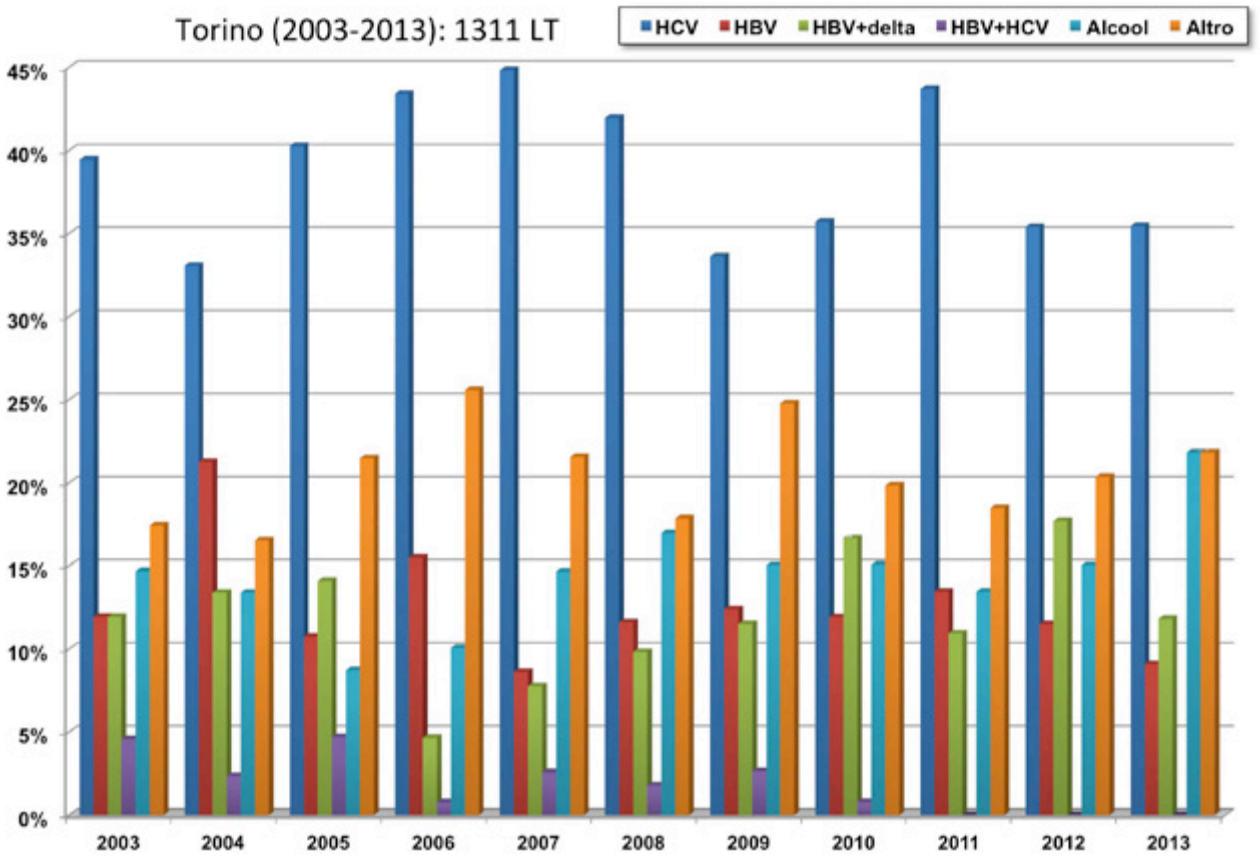
Observation	Hypothesis	Mechanism
Increased cancer incidence	Viral infection (HCV/HBV/HIV)	Immune dysfunction,progressive liver disease with development of liver disease which in turn increases the prevalence of HCC or NHL
	Multiple transfusion with blood or plasma	Immune modulation, chronic inflammation and immune system dysregulation
	Transfusion with recombinant products with albumin	Inhibition of lymphocyte transformation
	Frequent exposure to radiation or radionuclide joint injections	Acquired chromosomal changes
Decreased cancer incidence	Reduced thrombin generation	Thrombin has a role in activation of platelet tumor aggregation, tumor associated angiogenesis and metastasis
	Mortality related to viral infections	Malignancies are underrepresented due to high rates of death
	Reduced number of diagnostic tests, specifically biopsies	Underrepresentation of patients with cancers

Therapy for Hemophilia: Gene therapy



AAV and the Liver	Monogenic Diseases Best Suited for Gene Therapy
• Enhanced liver targeting	• Known disease biology
• Durable expression	• Restoration to 5–10% of normal activity is meaningful
• Well-established safety	• Well-described biomarkers
• 25% population NAbs	• Highly predictive animal models
	• Readily identifiable patients

Pipe SV. Pediatric s Blood and Cancer 2017



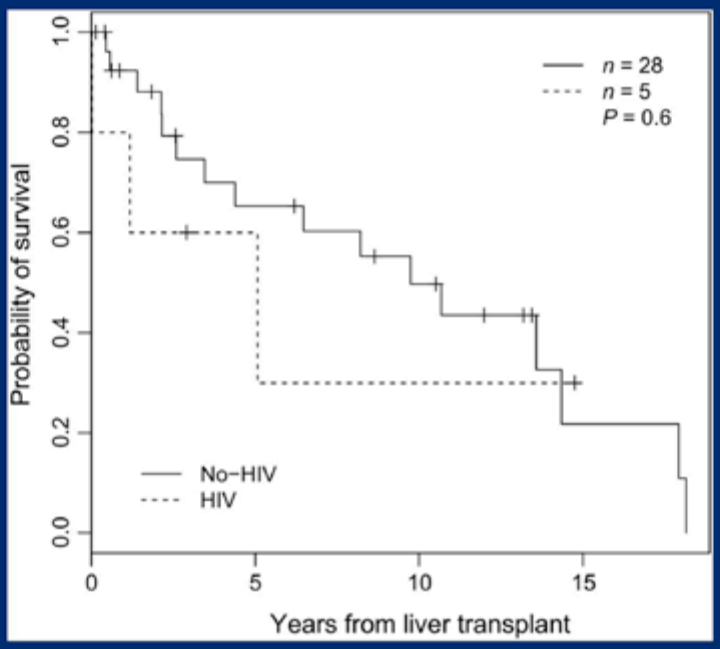
Survival Following Liver Transplantation in viral hepatitis and Haemophilia patients (U.K experience single center)

	n	1 year	3 years	5 years	5 years
		% (*n*)	% (*n*)	% (*n*)	% (*n*)
Overall survival	33	91 (26)	73 (18)	64 (16)	47 (10)
HCC	12	83 (10)	42 (4)	31 (3)	31 (3)
No-HCC	21	95 (16)	95 (14)	88 (13)	58 (7)
HIV	5	80 (4)	60 (2)	60 (2)	30 (1)
No-HIV	28	92 (22)	75 (16)	65 (14)	50 (9)

HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus.

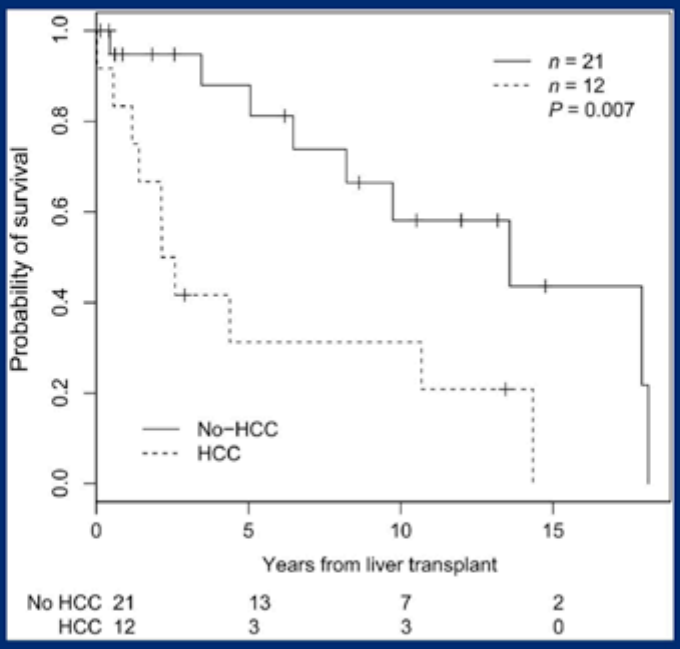
Muthy V. et al Haemophilia 2016

Outcome of liver transplantation in patients with hereditary bleeding disorders: a single centre UK experience



Muthy V. et al Haemophilia 2016

Outcome of liver transplantation in patients with hereditary bleeding disorders: a single centre UK experience



Muthy V. et al Haemophilia 2016

CONCLUSIONS

Patients with inherited bleeding disorders who were treated with blood products before the introduction of virus inactivation procedures (1985) were highly infected with HCV, HBV and HIV viruses

Staging liver disease in Hemophilia was difficult because LB was unsafe. Nowdays Fibroscan and non-invasive fibrosis score are used for staging fibrosis and monitoring

Natural history of HCV and HBV infection in Hemophilia is not different than non-H

Clinical events include CAH, cirrhosis and HCC. Risk factors for worse outcome are:1) HCV; age at HCV diagnosis; HIV positive status

CONCLUSIONS

Advances in the therapy for HBV and HIV and pre-era DAAs for HCV proposed to these «difficult to treat patients «have partially modified the natural history. Liver transplantation is the last option for LF

Antiviral therapy for HCV with DAAs is effective and safe in hemophilic patients with SVR >95%

Long-term outcome of hemophlic patients who cleared HCV will furhter improve

Surveillance for HCC occurrence in hemophlic cirrotic Is reccomanded for HCV responder and CHB under permanent antiviral therapy for residual risk of HCC

Associazione Coagulopatici Emofilici Piemontesi "Massimo Chesta"
PROMUOVE IL CONGRESSO

COAGULOPATIE CONGENITE:

bisogni espressi, organizzazione del Centro Multidisciplinare di Città della Salute

Torino, 25 novembre 2017
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