HDV: il punto sulla terapia nella real life

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Chronic Hepatitis D

- 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.
- **CHD** is considered the **most severe form of viral hepatitis**
- 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 development 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
- Recent studies partially **challenged** these pictures: in a Swedish cohort of 337 (233 viremic) anti-HDV positive patients the probability of being free of liver cirrhosis among the 164 viremic, non cirrhotic patients was 82%, 64% and 51% at 5, 10 and 15 years respectively

- The outcome of HDV infection and liver disease are strongly influenced by the extent of HBV replication, mainly at the time of infection
- Thus, the endemicity of HBV infection in a given geographical area significantly impacts not only on the spreading of HDV, but also on the course of hepatitis
- Recruitment biases due to dynamic epidemiology of HDV infection may have influenced the findings of the different studies, that were conducted across different times and geographical areas and showed a heterogeneous prevalence of cirrhosis at the time of enrollment (ranging from 25 to 70%)

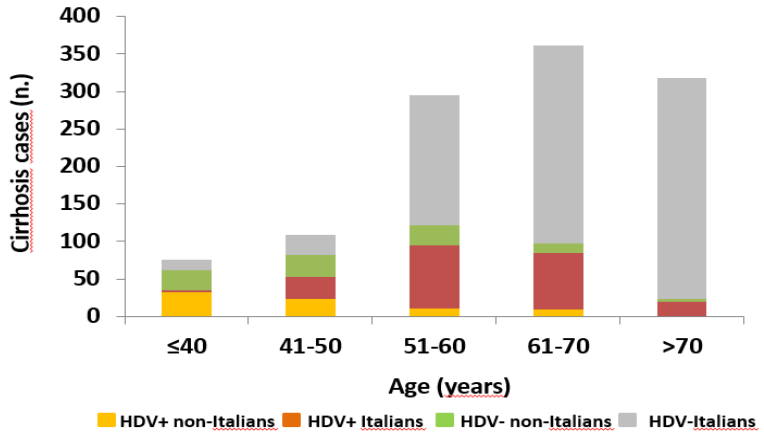
Stockdale AJ et al J Hep 2020 Fattovich G et al J Infect Dis 1987; Mentha N e al J Adv Res 2019; Farci P et al Sem Liv Dis 2012; Rosina F et al Gastroenterology 1999; Kamal H et al Hepatol 2020

A holistic evaluation of patients with chronic hepatitis D virus infection enrolled in the Italina PITER-B and D cohort

	anti-HDV positive N° = 422	anti-HDV negative N° = 3730	p-value
Age median (Q1, Q3)	**55 (**46, 62)	59 (48, 68)	<0.001
Males	253 (60.0)	2335 (62.6)	0.287
Non-Italian natives	**142 (33.6)**	850 (22.8)	<0.001
Injection drug use	**35 (10.0)**	55 (1.7)	<0.001
ALT > 35 IU/L	**243 (59.4)**	566 (15.3)	<0.001
GGT >50 IU/L	**121 (36.3)**	344 (11.1)	<0.001
HBeAg positive	25 (6.1)	253 (6.8)	0.582
Cirrhosis	**299 (70.8)**	892 (23.9)	<0.001
HCC	**42 (10.2)**	106 (2.9)	<0.001
HBV DNA positive	115 (29.1)	1330 (36.5)	0.004
HDV RNA positive (261 tested)	**165 (63.2)**	---	---
Previous IFN	142 (33.6)	580 (15.5)	<0.001
Potential disease co-factors			
Ongoing alcohol use	775 (22.6)	412 (12.0)	0.130
Past use	65 (18.7)	51 (14.7)	
Diabetes	29 (6.9)	375 (10.0)	0.037
BMI 25-30	32 (7.6)	384 (10.3)	0.004
BMI ≥30	109 (25.8)	1.173 (31.4)	
anti-HCV positive	**39 (10.4)**	126 (3.6)	<0.001
anti-HIV positive	**17 (4.8)**	35 (1.1)	<0.001
Ongoing therapy (>95% NUCs)	**323 (76.5)**	2529 (67.8)	<0.001

- **5492** HBsAg positive individuals were enrolled from 12.2019 to 2.2023 in 59 Italian Centers
- 4152 (**75.6%**) were tested for anti-HDV
- **422 (10.2%)** were anti-HDV positive
- **142 (33.6%)** were non Italian natives
- 216 (51.2%) were tested for HDVRNA and 165 (**76.4%**) were positive
- 299 (**70.8%**) anti HDV positive pts have cirrhosis

Cirrhosis by age, presence of anti-HDV antibodies and patients' origin

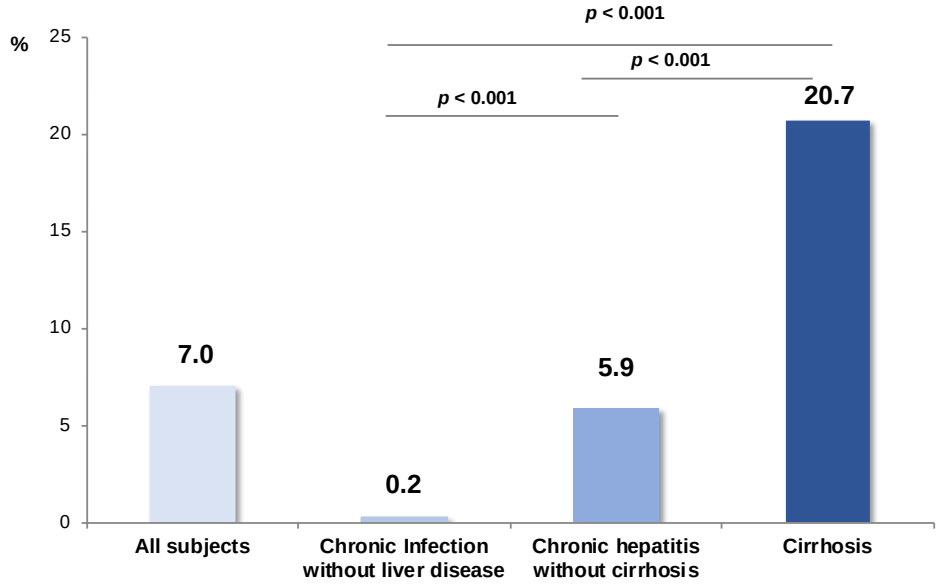


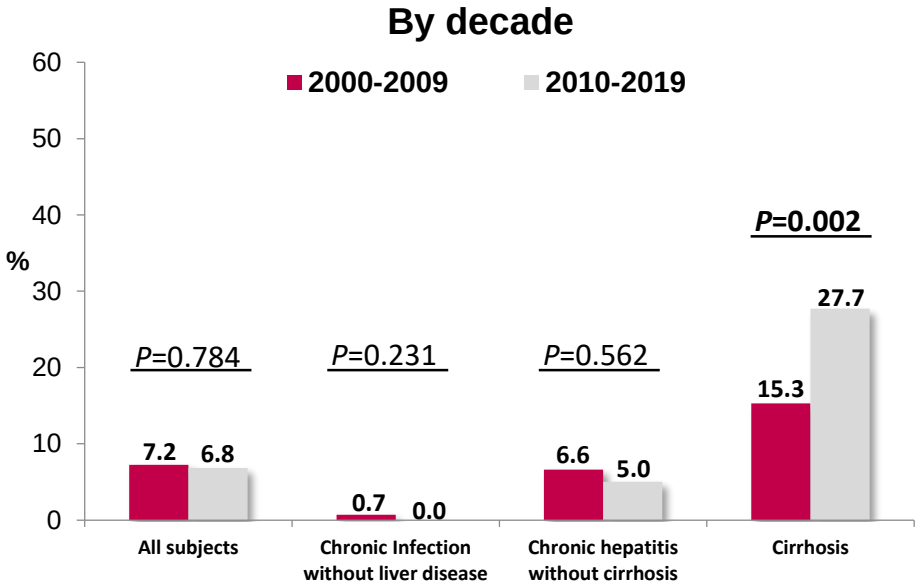
Kondili L and PITER collaborators, Intern J Infect Dis, 2024

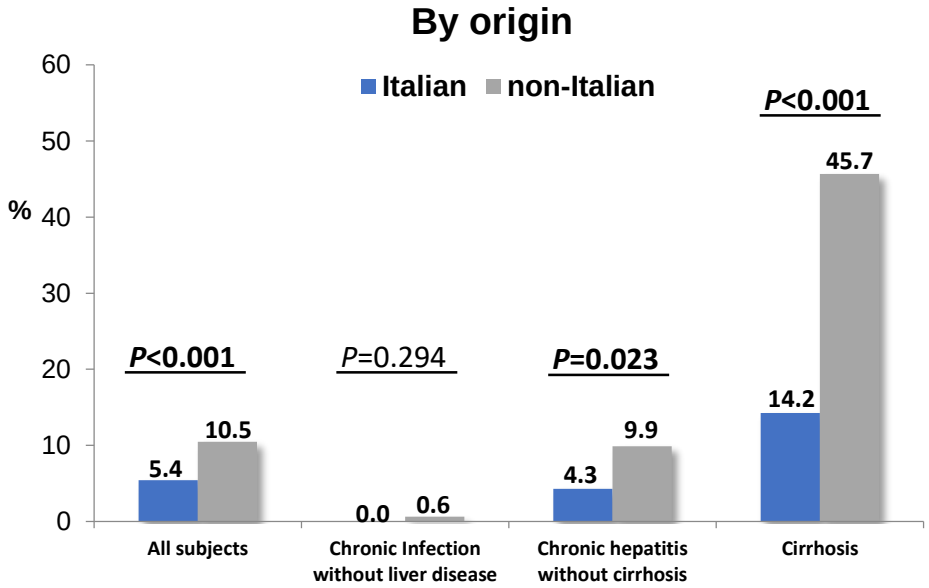
HDV coinfection over a 20 year observation period

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

- 126 (**7%**) patients were **anti-HDV 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)
- **76.1%** and **71.2% of Italian** and **non-Italian** HBV/HDV coinfected patients **had cirrhosis** (P=0.671



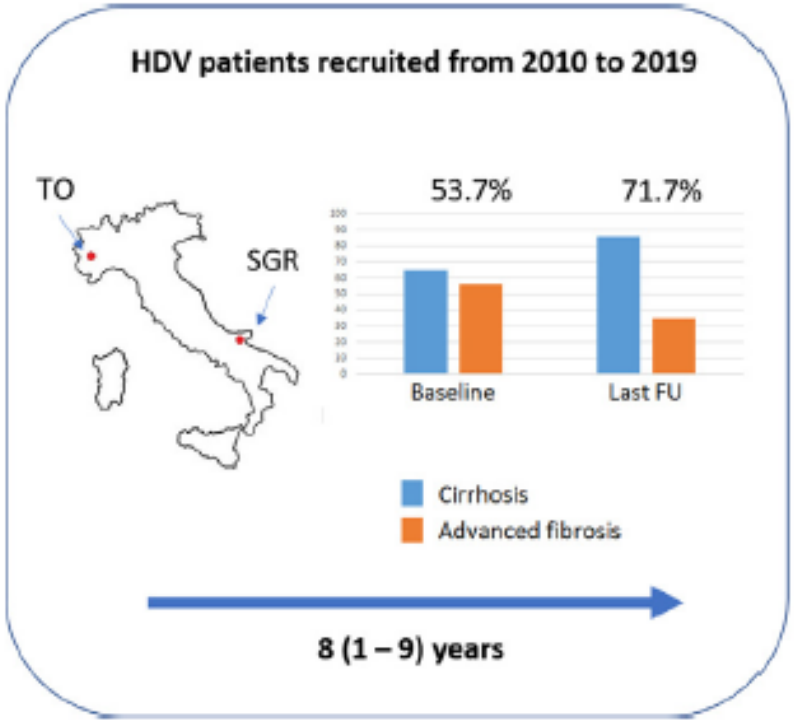




Ricco G et al, DLD 2022

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**

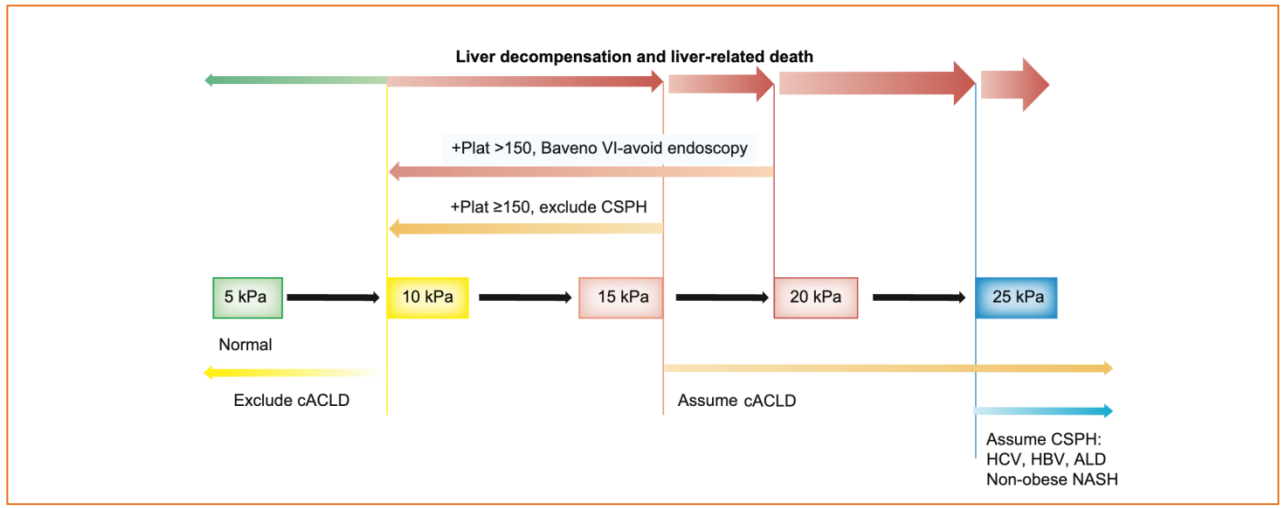


Characteristics of 121 native Italian patients at the first observation and at the last follow-up observation.

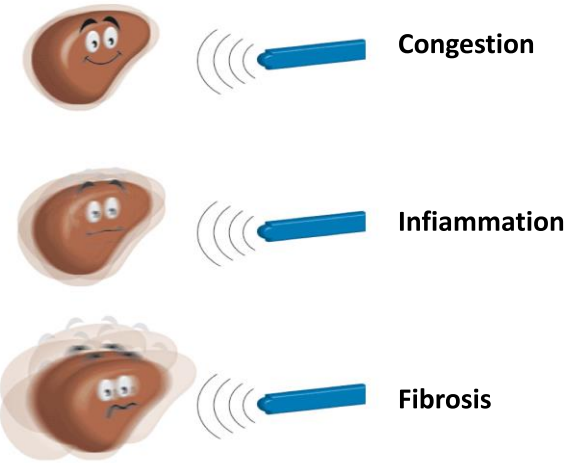
	First observation	Last follow-up	P
Serologic and virologic parameters			
Anti-HD IgM positive, n (%)	74 (61.2%)	46 (38.0%)	<0.001[b]
HBsAg positive, n (%)	121 (100%)	112 (92.6%)	0.003[b]
HDV RNA positive, n (%)	112 (92.6%)	80 (66.1%)	<0.001[b]
HDV RNA positive (<2000 IU/mL), n (%)	16 (14.3%)	18 (22.5%)	
HDV RNA positive (2000–100000 IU/mL), n (%)	24 (21.4%)	26 (32.5%)	<0.001[c]
HDV RNA positive (>100000 IU/mL), n (%)	72 (64.3%)	36 (45.0%)	
HBV DNA positive, n (%)	107 (88.4%)	67 (55.4%)	<0.001[b]
Biochemical parameters			
ALT (U/L), median (range)	76 (14–410)	49 (13–565)	0.002[d]
AST (U/L), median (range)	64 (20–186)	48 (12–248)	0.026[d]
Platelet count (x 10^9/L), median (range)	149 (46–298)	121 (23–331)	0.026[d]
INR, median (range)	1.10 (0.91–1.51)	1.15 (0.90–1.94)	0.380[d]
Albumin (g/dL), median (range)	4.3 (3.5–5.1)	4.0 (2.2–4.9)	0.011[d]
Clinical parameters			
Liver stiffness (kPa), median (95% CI)[a]	11.0 (7.0–12.5)	12.0 (11.2–17.4)	0.081[d]
Cirrhosis, n (%)	65 (53.7%)	86 (71.1%)	<0.001[b]
Ascites, n (%)	0 (0%)	31 (25.6%)	<0.001[b]

Caviglia GP et al J Adv Res 2021

- In the setting of CHD, NITs have not been consistently validated in large multicenter studies
- In **combined scores** that use **indirect markers of liver inflammation** (ALT) or **techniques** (TE and SWE) that are **influenced** not only by fibrosis, but **also by inflammation and congestion**, may **overestimate fibrosis** because of the significant impact of hepatic inflammation that characterizes a substantial proportion of CHD patients.
- **Thresholds** ranging from **12 to 14 kPa** had been proposed to predict cirrhosis with sensitivity 77.8-78% and specificity of 82.5-86%
- As the influence of necro-inflammation on stiffness values declines with the increase of fibrosis, **it's reasonable to use in CHD the TE thresholds proposed by Baveno VII** in order **to identify** patients with compensated advanced chronic liver disease (**cACLD**) and with clinically significant portal hypertension (**CSPH**).



Elastometry of the Liver:
3 vectors condition the liver stiffness



Baveno VII, J Hepatol 2022

Caso clinico 1

Donna di 37 anni, nata in Romania, vive in Italia dal 2012

Cenni anamnestici

- Non familiarità per infezione da HBV/HDV
- All'età di 2-3 anni: morso di cane a livello dell'arcata sopraccigliare destra con necessità di ricovero in Romania e punti di sutura.
- A 13 anni: cure odontoiatriche in Romania.
- A 14 anni (**2001**): dolore in ipocondrio destro riscontro di **HBsAg positività**; riferito **tentativo** di terapia con IFN + lamivudina, sospeso dopo 3 mesi per incremento delle transaminasi.
- 2020: colica renale.
- **2021**: terapia con **TDF**, **sospesa** dopo pochi mesi per riferita comparsa di astenia marcata.

Profilo dell'epatopatia:

Profilo bioumorale

- *Citolisi:* **AST/ALT 28/5 U/L il 08.03.23; GGT/FA 16/43 U/L**
- *Funzionalità:* albumina 4.6 g/dL, bil tot 0.96 mg/dL, PT/INR 100/0.96, PCHE ***4106*** U/L (08.03.23).
- *Crasi ematica* : Hb 14.2 g/dL, GB 4910/mmc, PLTs **167.000/mmc** (08.03.23).
- g-globuline **13.8%** (08.03.23).
- *Funzione renale*: creatinina 0.66 mg/dL (08.03.23); Na 137 mEq/L, K 4.5 mEq/L (02.02.23).
- AFP1.2 ng/mL (08.03.23).

Profilo virologico:

HBV

- Infezione da HBV nota dall'età di 14 anni.
- Genotipo D.
- HBeAg neg/Anti-HBe pos (08.03.23).
- **HBV-DNA 114 IU/mL** (08.03.23).
- qt **HBsAg** 10969 IU/mL (19.11.20) **6762.84** IU/mL (08.03.23).

HDV

- Anti-HDV positività nota dal 12 2020.
- HDV-RNA pos (in house PCR).
- HDV-RNA quantitativo (Real time PCR, Robogene Quantification Kit 2.0): **441.61** IU/mL (08.03.23).

- Anti-HAV IgG pos (30.12.20).
- Anti-HCV neg (08.03.23).
- Anti-HIV neg (30.12.20).

Cofattori di danno:

- **ANA pos 1:160**; AMA, ASMA, anti-LKM neg (08.03.23); in passato autoAb negativi
- Metabolismo glucidico: glicemia 91 mg/dL, insulina 10.45 U/mL, **HOMA 2.34** (08.03.23).
- Metabolismo lipidico: Colesterolo tot 199 mg/dL, TG 59 mg/dL (08.03.23).
- Ferritina 38 ng/mL (08.03.23).

Indagini strumentali

Elastometria epatica con Fibroscan: **8.5 kPa** (20.02.21) 7.5 kPa (08.10.22) 6.5kPa (06.03.23) **7.3 kPa**, CAP 195 dB/m (08.03.23).

ECT epatopancreatica

- Fegato di dimensioni nei limiti, margini a tratti **finemente irregolari**,
- ecostruttura diffusamente disomogenea di **tipo coarse pattern** nel cui contesto si segnalano multiple focalità subcentimetriche tenuemente iperecogene a distribuzione bilobare, la più evidente di circa 7 mm in S6 (angioma? Nodulo rigenerativo?).
- ASP pervio, vena porta di calibro regolare all'ilo (9 mm) con flusso portale epatopeto, **milza megalica** (14 cm). Colecisti scarsamente distesa, apparentemente alitiasica.
- Pancreas indenne da tumefazioni ove esplorabile.
- Minimo film fluido periepatico in assenza di versamento addominale significativo

Biopsia

Frustoli agobioptici frammentati della lunghezza complessiva di 2 cm

- **Mulipli frammenti di parenchima epatico ad architettura conservata** con scarsi e marginali spazi portali nei quali si evidenzia lieve infiltrato infiammatorio, in uno spazio di grado moderato e per lo più confinato entro la lamina limitante, composto da linfociti, rari neutrofili ed eosinofili;
- i dotti biliari mostrano lievi alterazioni citoarchiteturali evidenziate anche con la citocheratina 7 e 19.
- In sede lobulare sono presenti focolai di necrosi litica e confluente, lieve steatosi micro e macrovescicolare valutabile in circa il 2% e un discreto numero di nuclei epatocitari di aspetto iperglicogenato.
- **Dilatazione delle vene portali**, **centrali e dei sinusoidi**, **lieve e focale fibosi perivenosa**.
- Indagine immunoistochimica positiva per HBsAg positiva nel 5% degli epatociti, negativa per HBcAg.
- Colorazione per il ferro negativa.

DIAGNOSI:

Epatite cronica HBV/HDV correlata, associato modesto danno metabolico e disturbo del circolo.

Grado 6/18: infiammazione portale 2, epatite periportale 0, necrosi litica focale 2, necrosi confluente 2.
Stadio 0/6.

Epatite cronica D con cirrosi

Caso Clinico 3

Ragazzo di 24 anni, nato in Russia

Cenni anamnestici

- 9.01 riscontro di infezione da HBV, HBeAg positiva
- 10.01 severa citolisi (ALT 60 x n)
- 2.02 sieroconversione HBeAg/anti-HBe, riduzione della viremia (5100 cp/ml), ma evidenza di anti-HD positività
- '03-'13 mantenimento di minima citolisi (AST/ALT x1.1-1.4)
- '14 incremento della citolisi, Fibroscan 8,8 kPa, valutazione istologica
- '14-'15 trattamento con Peg-IFN

Profilo di infezione e malattia:

Profilo virologico

- Livelli replicativi di HBV bassi, non dosabili in PCR
- **HBsAg 12,667 IU/ml** (11.2016) 12.667 IU/mL (11.2015) --> 24.715 IU/ml (03.2016) --> 32.737,13 IU/mL (07.02.18) --> 25.180,01 (21.08.18) --> 26.376.27 (13.12.18) --> 26849.61 IU/mL (29.10.19) --> **25743** (06.06.23)

- **HDV-RNA: 623126 IU/ml**
- IgM anti-HD: positivo

Profilo biochimico:

- **Citolisi lieve-moderata** AST/ALT 27-42/38-73 U/L ; GGT/FA nn

Istologia

Biopsia epatica (2.14): epatite cronica grado 7/18 (necrosi confluente 0); stadio 1/6

Biopsia epatica (06.06.23): Parenchima epatico ad architettura conservata.

- Nella maggior parte degli spazi portali è presente infiltrato infiammatorio di grado moderato in uno di grado severo, costituito da linfociti, alcuni eosinofili e alcune plasmacellule; le cellule infiammatorie superano la lamina limitante in maniera focale in alcuni spazi portali; diffusa reazione duttulare al confine porto-lobulare.
- In sede lobulare sono presenti numerosi focolai di necrosi litica e confluente, alcuni corpi apoptotici,
- focolai di steatosi micro e macrovescicolare, valutabili in circa il 15% degli epatociti e un discreto numero di nuclei epatocitari di aspetto iperglicogenato.
- Modesta espansione fibrosa di alcuni spazi portali.
- Indagine immunoistochimica per HBsAg positiva nel 20% degli epatociti in sede citoplasmatica; negativa per HBcAg. Colorazione per il ferro negativa.

DIAGNOSI: **Epatite cronica attiva con morfologia principalmente riferibile ad eziologia virale. Associato danno metabolico (steatosi).**
Grado 10/18: infiammazione portale 3, epatite periportale 3, necrosi litica focale 2, necrosi confluente 2.
Stadio 1/6.

Elastometria epatica con Fibroscan:
6.5 kPa, CAP 241 dB/m (2019)
8.0 kPa, CAP 152 dB/m (07.02.24);

RM fegato (11.21):

- Il fegato risulta aumentato per dimensioni, con lieve maggiore evidenza del lobo sinistro.
- Non sono apprezzabili nodularità ipervascolari nel contesto del parenchima epatico.
- Si documenta **la presenza di alterazione di 8mm a carico di S6 (margine inferiore) che presenta caratteristiche orientanti in prima ipotesi per la natura benigna (angioma), ma dato l'aspetto non chiaramente tipico nelle sequenze pesate in T2 appare meritevole di follow up in prima istanza ecografica** (qualora non visibile, indicato follow up RM).
- Asse venoso spleno-portale pervio.
- Colecisti alitiasica a contenuto biliare addensato, vie biliari di calibro regolare.
- Splenomegalia (diam. long. 15 cm).
- Alcuni linfonodi ad asse corto massimo centimetrico a sede interportocavale, celiaca e ilare epatica. Non ascite.

RM fegato (5.24):

Al controllo attuale, in noto quadro di epatopatia cronica, **si rileva lieve maggiore evidenza (11mm, 10mm) della focalità del margine postero-inferiore di S6 che nostra caratteristiche di segnale sovrapponibili ai precedenti controlli (restrizione della diffusività ed aspetto marcatamente ipointenso nella fase epato-biliare)**;
il reperto necessita di ulteriore approfondimento diagnostico mediante biopsia qualora le condizioni cliniche del paziente lo consentono

CEUS (20.6.24)

L'esame ecocontrastografico, condotto sulla base di reperi anatomici, la dimostra in S6 come iperecogena in fase arteriosa
con aspetto isoecongeno nelle successive fasi. Le dimensioni massime sono di 11 mm.
I reperti descritti necessitano di prosecuzione di stretto follow-up.

Discussione GOM 24.6.2024 : Nodulo compatibile con HCC, proposta resezione

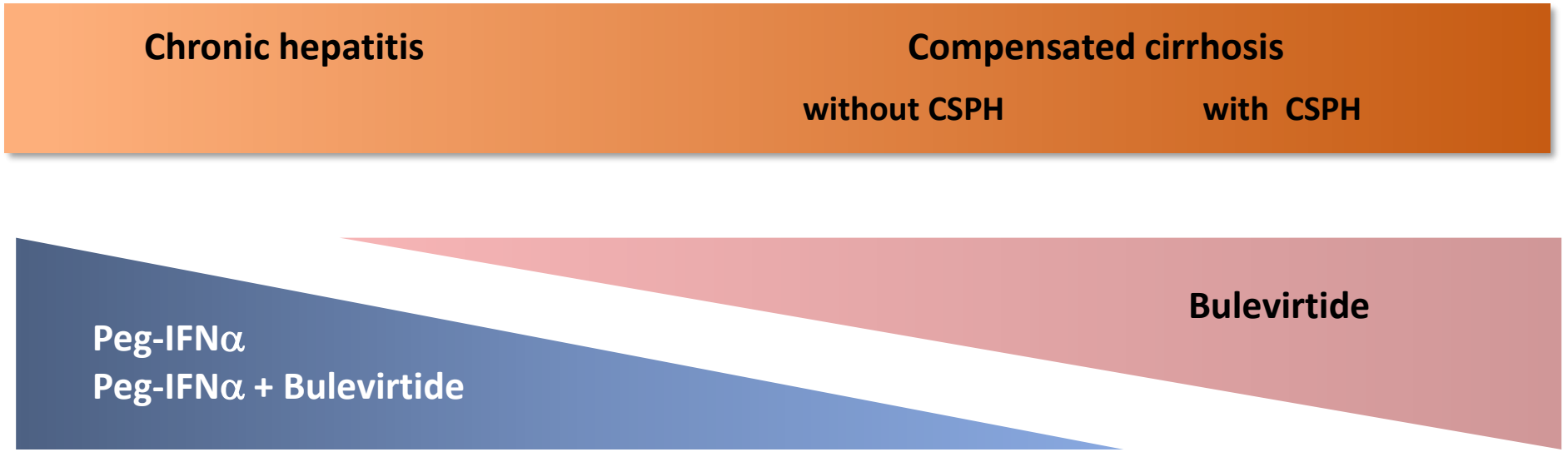
4. Patient monitoring and selection for treatment

Which patients with CHD should be considered for antiviral treatment?

Recommendations

- All patients with CHD should be considered for antiviral treatment **(LoE 3, strong recommendation, consensus).**
- Patients with decompensated cirrhosis should be evaluated for liver transplantation **(LoE 3, strong recommendation, strong consensus).**
- Patients with HCC may be considered for antiviral treatment on an individualised basis **(LoE 5, weak recommendation, strong consensus).**

Treatment of Chronic Hepatitis Delta



Finite treatment

To cure the infection/disease

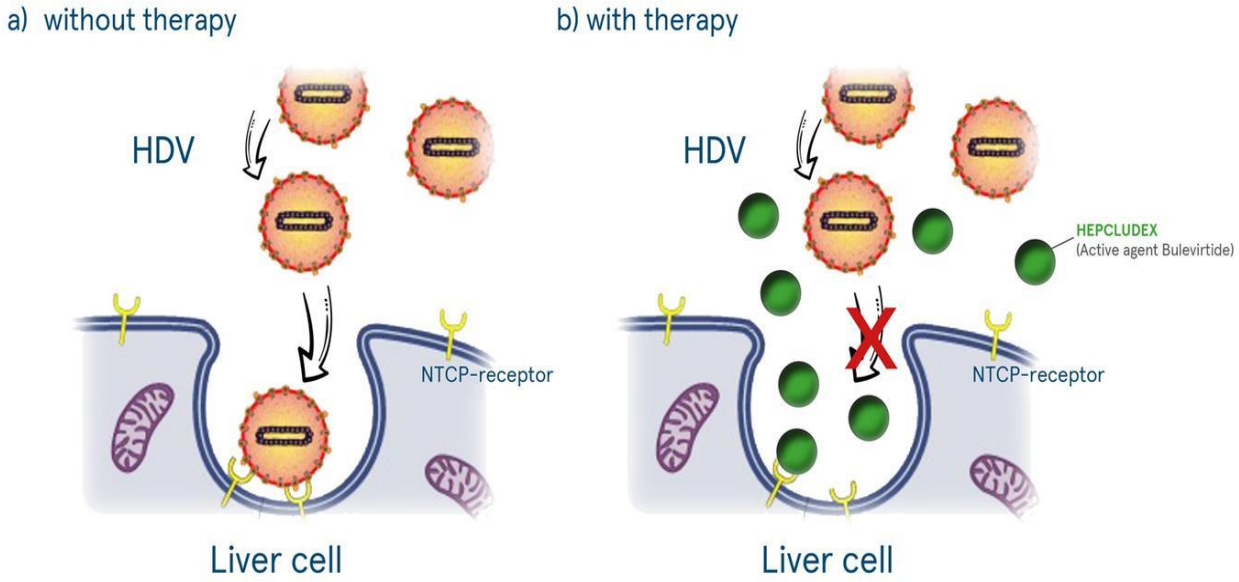
Prolonged treatment

To control the infection/disease

Additional factors influencing the treatment schedule

- ✓ Phase of HBV infection (HBeAg/anti-HBe status; HBV-DNA and HBsAg levels)
- ✓ IFNa contraindiciation, tolerability
- ✓ Patient's will and compliance to treatment

Bulevirtide (BLV) is the first-in-class entry inhibitor



Mode of action:

- BLV is a **synthetic N-acetilated pre-S1 derived lipopeptide that inhibits HBV entry into hepatocytes** in vitro and in vivo, by blocking NTCP, the entry receptor for HBV/HDV
- **New infections and viral spread in the liver prevented**.
- Proliferating virus-free hepatocytes should recolonize the liver, eliminating HBV ccc-DNA and hepatitis D

.

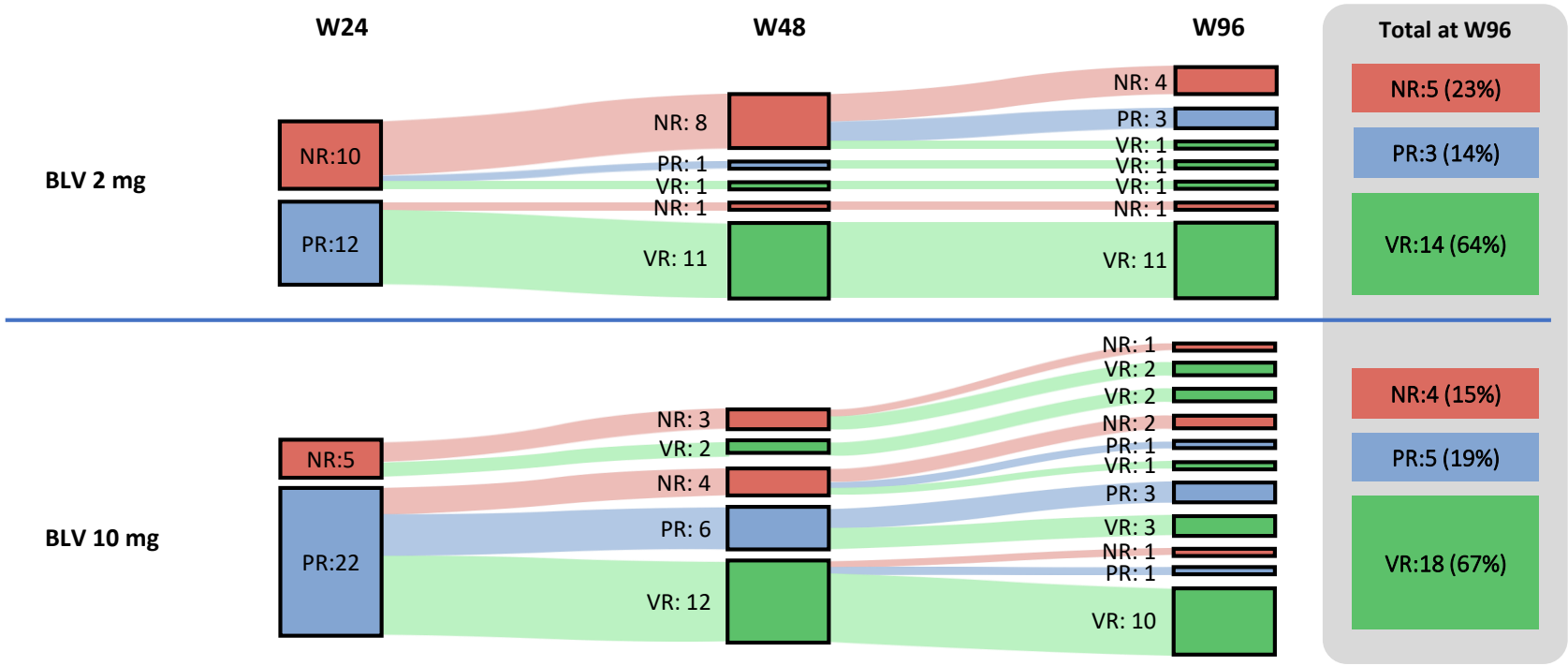
Administration:

- Daily, self administered s.c. injections

The EMA conditional marketing authorisation was switched to a standard marketing authorisation on 18.07.2023.

Lemp and Urban S, 2014 ;*SUMMARY OF RISK MANAGEMENT PLAN FOR HEPCLUDEX (BULEVIRTIDE) _EMA

Treatment Responses Improved in Suboptimal Responders at W24



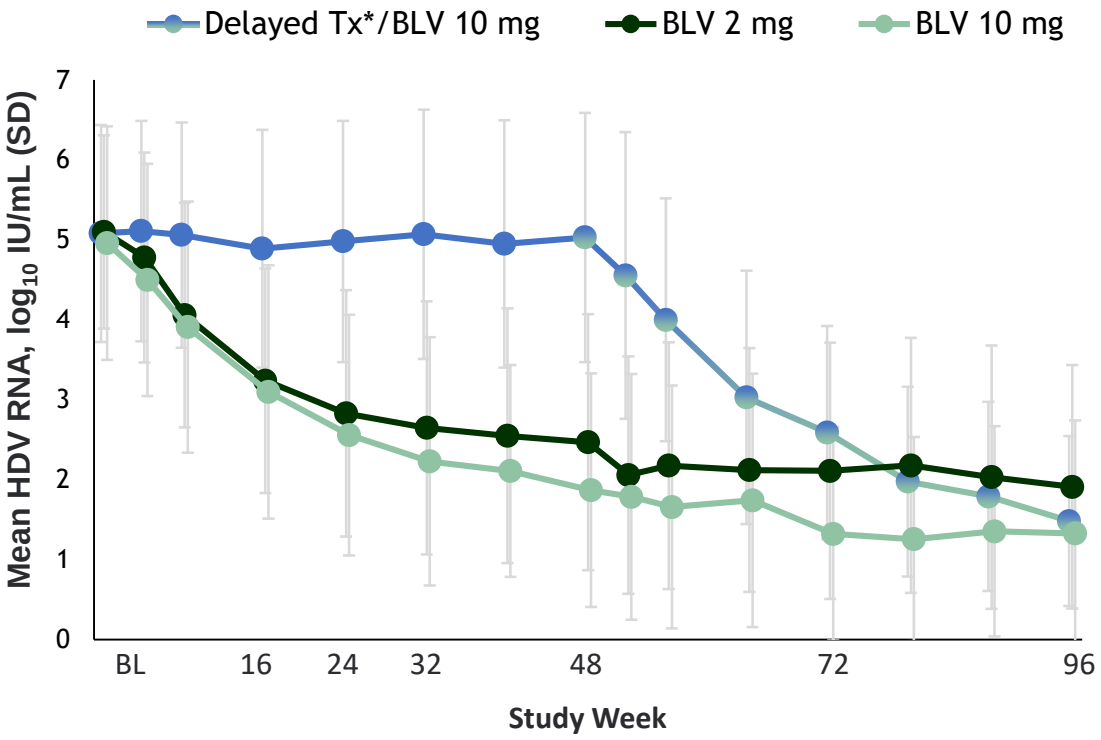
- **Non-responder (NR):** HDV RNA decrease <1 $\log_{10}$ IU/mL from BL
- **Partial responder (PR):** HDV RNA decrease ≥1 and <2 $\log_{10}$ IU/mL from BL
- **Virologic responder (VR):** HDV RNA decrease ≥2 $\log_{10}$ IU/mL from BL or undetectable HDV RNA

64% (BLV 2 mg) and 67% (BLV 10 mg) of W24 suboptimal responders became VRs at W96

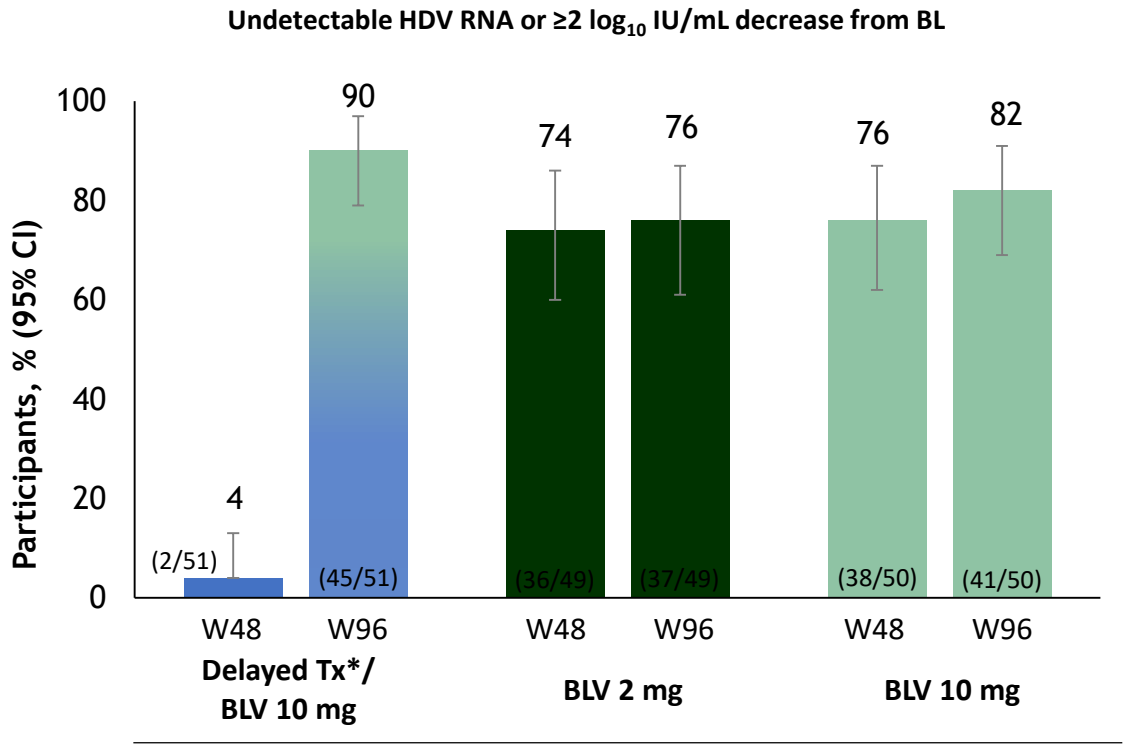
Lampertico P, AASLD 2023

MYR301 Study Design: a multicenter, open-label, randomized, Phase 3 study

HDV RNA Decline Over Time



Virologic Response



Undetectable %	0	24	12	20	20	36

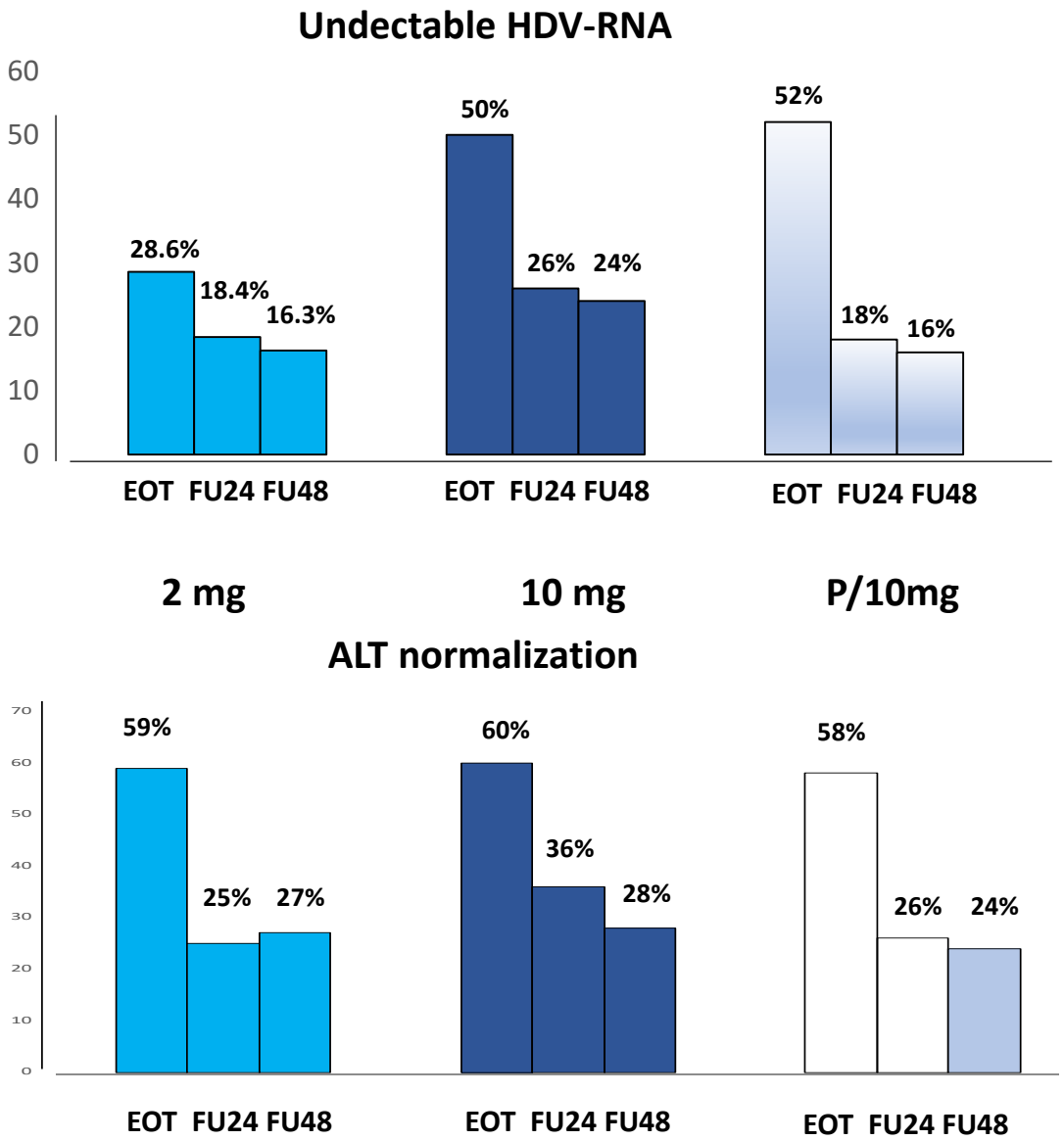
defined as <LLOQ (50 IU/mL) or target not detected

At week 144 the rate of

- **HDV-RNA undetectability** was **29%** and **50%** in BLV 2mg and 10 mg
- **Lower HDV RNA** and **HBsAg levels at BL** were identified as potential **predictors of undetectable** HDV RNA at W144
- **Virologic response** was **73%** and **76%** in BLV 2mg and 10 mg

Wedemeyer H. et al. EASL 2023. Oral #OS-068; Lampertico P et al. EASL 2024 LBP-029

MYR301 Study Design: a multicenter, open-label, randomized, Phase 3 study



Post treatment ALT flares

ALT > 5ULN	47/140 (**34%**)
ALT > 10ULN	14/140 (**10%**)

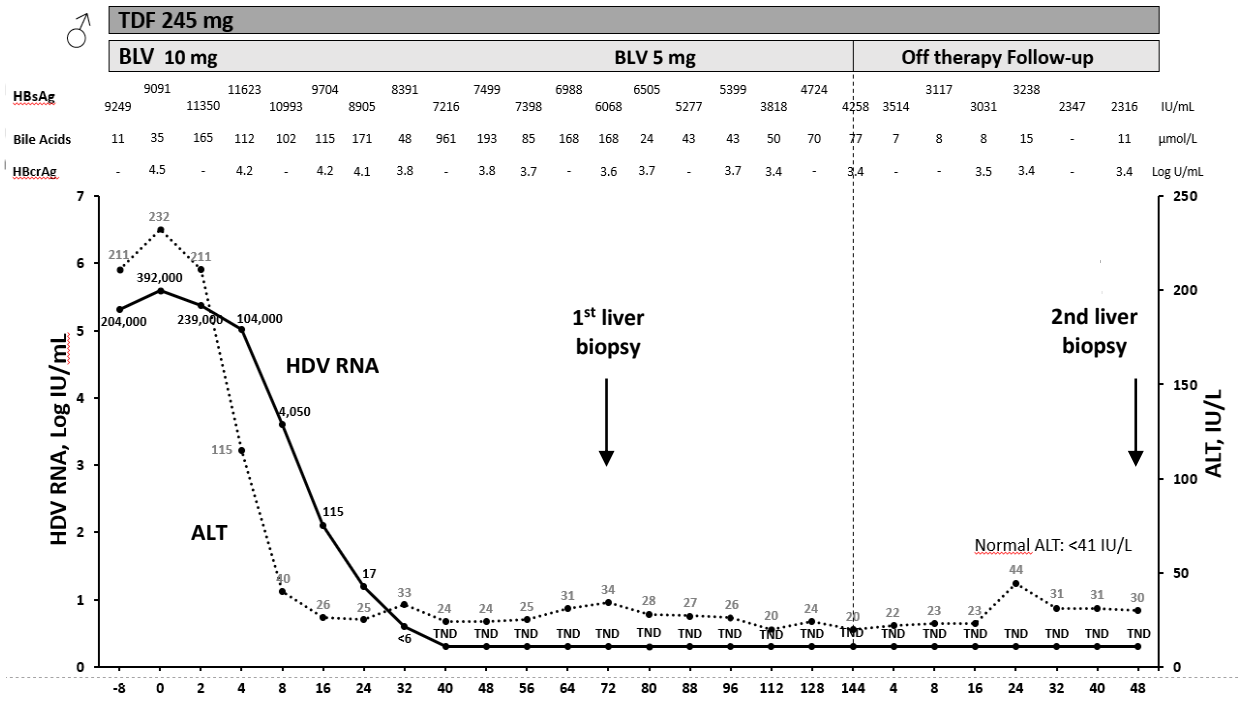
BLV re-treatment in 8 patients
TDF treatment in 1 patient

Aleman S et al AASLD 2024

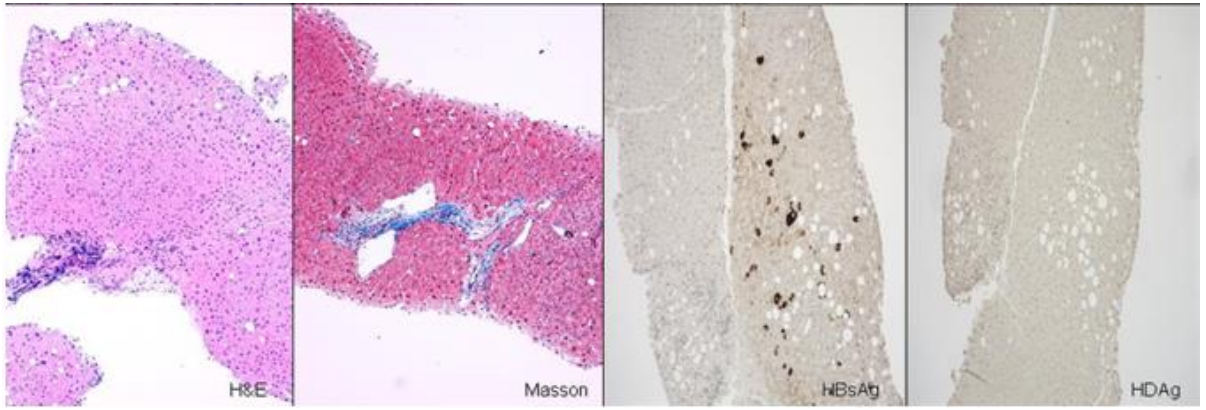
A 3-year course of BLV monotherapy with HDV clearance without HBsAg loss

A 55 year-old patient with HDV-related compensated cirrhosis with F1 esophageal varices and contraindications to pegIFNα

Virological and biochemical response during and off BLV therapy



2nd liver biopsy performed at week 48 off-therapy



H&E staining | Masson staining | HBsAg staining | HDAg staining

- Minimal features of inflammation, improvement of fibrosis (Ishak G1 S4) and resolution of autoimmunity features compared to baseline biopsy (Ishak G9 S6)
- HBsAg staining positive (<1%), HBcAg negative.
- **HDAg, HDV RNA and cccDNA undetectable (Dandri's lab)**
- **HDAg and intrahepatic HDV RNA were already undetectable** in the liver biopsy performed on-therapy at week 72 (Dandri's lab)

Clinical outcomes

- HDV suppression/cure resulted in a significant improvement in biochemistry, liver function parameters, AFP, LSM, and in regression of esophageal varices.
- No specific safety issues, BA normalized after BLV discontinuation

Conclusions

- **A 3-year course of BLV monotherapy may cure HDV infection even in difficult-to-treat patients with advanced compensated cirrhosis**
- **HDV eradication occurred without HBsAg loss**

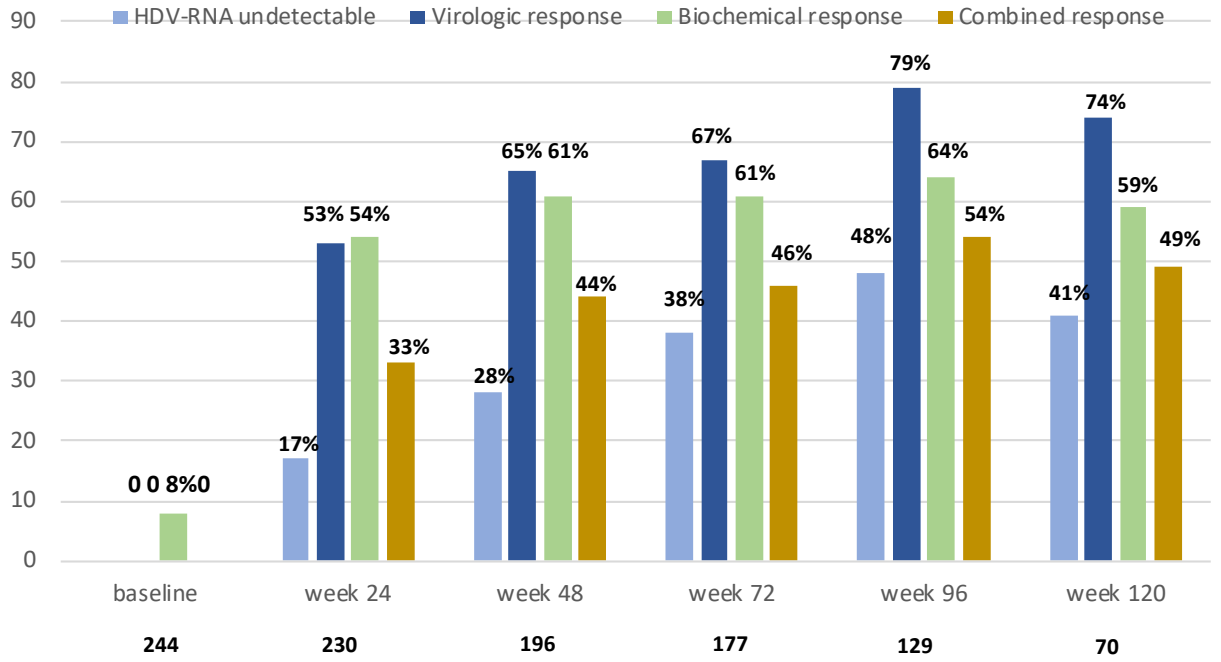
Anolli MP et al, J Hepatol 2023

SAVE-D study: Effectiveness and safety of BLV 2 mg monotherapy up to 96 weeks in a real-world compensated cirrhotic cohort

Retrospective, multicentre, pan-EU cohort of 244 patients from 46 Centers

Baseline Variables	Overall (n=244)
Age, years	49 (40-58)
Males	148 (61%)
Caucasians	201 (82%)
HDV genotype 1*	77 (94%)
HIV coinfection°	24 (10%)
BMI, Kg/m²	25 (23-28)
CPT score A§	233 (95%)
Spleen diameter, cm	15 (12-17)
Esophageal varices@	91 (54%)
Previous decompensation+	37 (15%)
History of HCC#	18 (7%)
Previous IFN treatment	142 (58%)
NUC treatment	224 (92%)

Effectiveness of BLV treatment



Factors associated with virologic response at W 48

- Baseline HBsAg serum levels 3.15 (1.57-6.31) 0.001
- Baseline HDV-RNA serum levels 1.31 (1.07-1.60) 0.01

De Gasperi E et al J Hep i2024 & AASLD

Bulevirtide monotherapy prevents liver decompensation in patients with CHD cirrhosis: a case-control study with propensity score analysis

- **BLV untreated cohort:** pts with compensated CHD cirrosis enrolled (1978-2006) in a single center, retrospective, natural history study *Romeo et al Gastroenterology 2009*
- **BLV treated cohort:** pts with compensated CHD cirrhosis treated with BLV in the multicenter, retrospective , longitudinal European SAVE-D study (37 centers- 2019-2023)

Variables	Untreated (n=140)	BLV-Treated (n=176)	p value
Age, years	40 (34-49)	49 (39-59)	**<0.0001**
Males	109 (78%)	104 (59%)	**0.0004**
Caucasians	136 (97%)	161 (91%)	**0.04**
CPT score A	140 (100%)	176 (100%)	1.00
- A6	22 (16%)	54 (31%)	**<0.0001**
Previous LRE	5 (4%)	35 (20%)	**<0.0001**
- HCC	-	12 (7%)	
- Decompensation	5 (4%)	23 (13%)	
Esophageal varices*	64 (46%)	65 (55%)	0.13
IFN-experienced	56 (40%)	103 (59%)	**0.001**
ALT, U/L	102 (57-176)	77 (53-127)	**0.03**
Bilirubin, mg/dL	0.9 (0.7-1.4)	1.0 (0.7-1.4)	0.40
Albumin, g/dL	3.9 (3.6-4.3)	4.0 (3.7-4.4)	0.08
HBsAg, LogIU/mL	pos	3.7 (3.3-4.1)	na
HBeAg negative	132 (94%)	164 (93%)	0.82
HBV DNA undetectable/low**	109 (78%)	143 (81%)	0.48
HDV RNA, LogIU/mL	pos	5.4 (4.1-6.4)	na

Outcomes	Category	Unadjusted Cox Regression Analysis		IPTW-Adjusted Cox Regression Analysis		IPTW-Adjusted Competing Risks Regression Model	
		HR (95% CI)	p value	HR (95% CI)	p value	SHR (95% CI)	p value
Liver-related Events	Treated vs. Untreated	0.52 (0.25-1.05)	0.07	0.38 (0.23-0.62)	**<0.0001**	0.38 (0.23-0.61)	**<0.0001**
Decompensation	Treated vs. Untreated	0.48 (0.18-1.28)	0.14	0.32 (0.16-0.63)	**0.001**	0.32 (0.17-0.61)	**0.001**
De-novo HCC	Treated vs. Untreated	0.57 (0.20-1.62)	0.29	0.50 (0.24-1.06)	0.07	0.50 (0.24-1.04)	0.06

Total Events: Untreated n=21; BLV-Treated: n=12

IPTW-Adjusted Cox Regression Analysis results confirmed in the CPT-A subclasses

IPTW analysis covariates: age, gender, varices, ALT, albumin

2 year - cumulative incidence of de novo HCC

Untreated 6.6% (95% CI 3-11%)
BLV treated 3.7% (95% CI 1-8%)

2 year - cumulative incidence of decompensation

Untreated 9.1% (95% CI 3-13%)
BLV treated 3.6% (95% CI 1-6%)

By IPTW-adjusted analysis, BLV treated patients has a significantly lower risk of Liver related Events (HR 0.38) and decompensation (HR 0.32), while HCC risk and survival were similar between the 2 cohorts

Degasperi E et al EASL 2024

Safety and efficacy of off-label bulevirtide monotherapy in patients with HDV with decompensated Child-B cirrhosis—A real-world case series

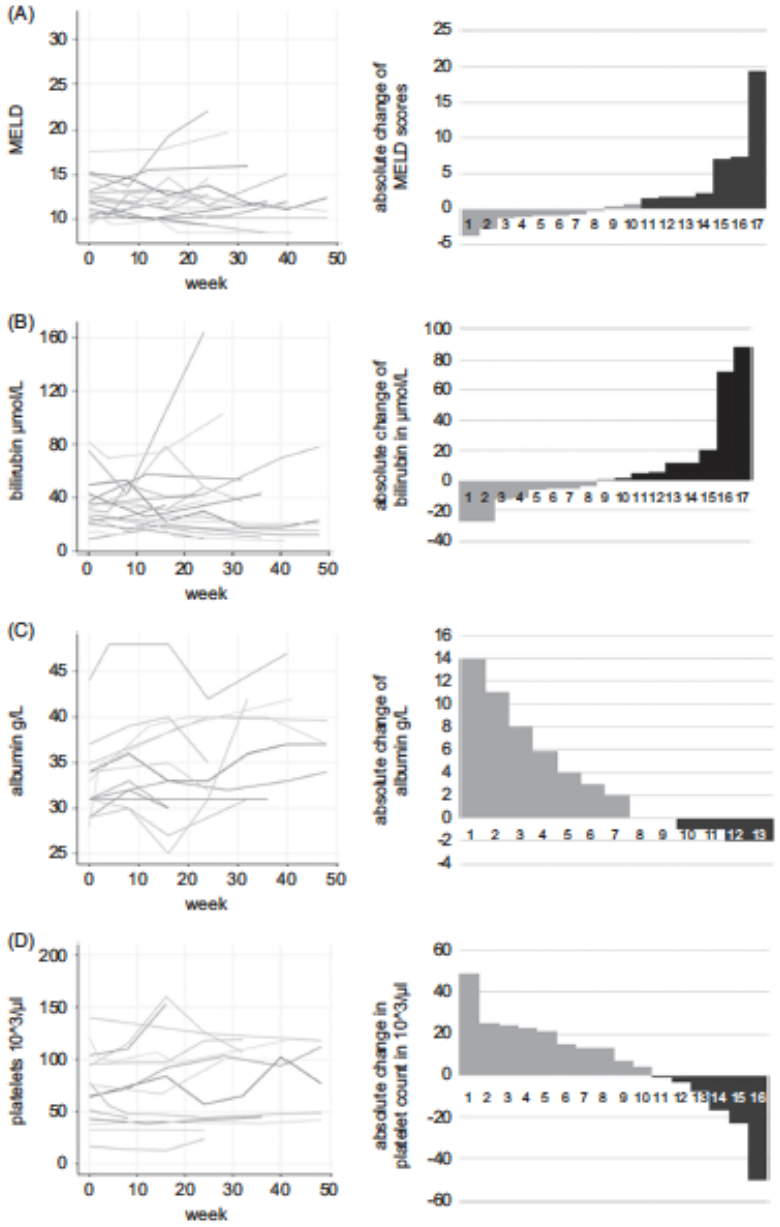
- **19 CHD** patients (47% male, mean age: 51 years) with decompensated liver disease (**Child-Pugh B**; MELD score 12, 9-17) at German, Austrian, and Italian centers.
- **41 weeks of median follow-up**

- ✓ 74% virologic response and ALT normalization
- ✓ 42% of combined response
- ✓ 47% (9/19) improvement from Child-Pugh B to A
- ✓ 58% (7/12) improvements of amount of ascites

- ✓ The most relevant adverse events included self-limited ALT flares, an asymptomatic increase in bile acids, and the need for liver transplantation.

The response was heterogenous and clinical improvement did not occur in all patients: 2 of the 3 cases who developed ascites had already responded virologically.

The subset of decomensated patients who might benefit from BLV treatment need to be identified.



Diets-Fricke C et al, Hepatology 2024

Which patients with CHD can be treated with BLV?

Statement

- Despite the lack of data on long-term efficacy and safety, or on the optimal duration of BLV treatment, preliminary results from phase II studies (with BLV given as monotherapy or in combination with pegIFNα), on-treatment data from a phase III trial of BLV monotherapy and real-life studies suggest consideration of BLV as a treatment option for CHD whenever available **(LoE 3, consensus).**

Recommendations

- All patients with CHD and compensated liver disease should be considered for treatment with BLV **(LoE 3, strong recommendation, consensus).**
- The optimal dose and duration of treatment have not yet been defined **(LoE 5, consensus).** Until further data become available, long-term treatment with BLV, 2 mg once daily, may be considered **(LoE 5, weak recommendation, consensus).**
- The combination of pegIFNα and BLV may be considered in patients without pegIFNα intolerance or contraindications **(LoE 5, weak recommendation, consensus).**

Which parameters should be monitored during and after treatment? (1 of 5)

Recommendations

Virologic markers:

- Virological response to treatment of CHD should be determined during and after therapy **(LoE 3, strong recommendation, strong consensus).**
- HDV RNA should be quantified every 6 months during treatment and whenever there is a clinical indication **(LoE 5, strong recommendation, consensus).**
- For pegIFNα-based finite therapy, HDV RNA should be tested at the end of treatment, after 6 and 12 months and yearly thereafter **(LoE 4, strong recommendation, strong consensus).**
- In case of BLV discontinuation, HDV RNA should be tested at the time of treatment discontinuation, after 1, 3, 6, 12 months and yearly thereafter to monitor the relapse of viral replication **(LoE 4, strong recommendation, consensus)**

(continues…)

Which parameters should be monitored during and after treatment? (4 of 5)

Recommendations

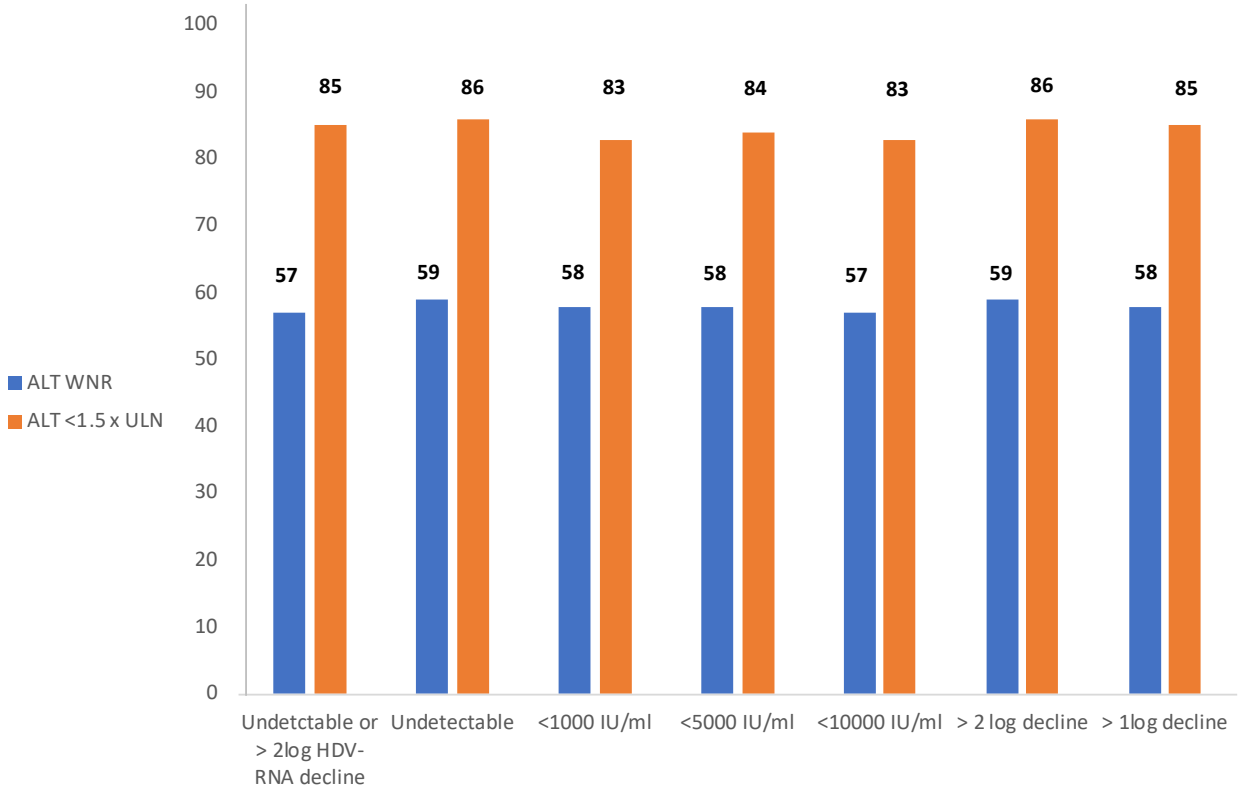
Biochemical markers:

- For pegIFNα-based finite therapy, testing should be performed at the end of treatment, at least at month 6 and 12 after the end of treatment and yearly thereafter **(LoE 4, strong recommendation, consensus).**
- In case of BLV discontinuation, testing should be performed at the time of treatment discontinuation and at least after 1, 3, 6 and 12 months or more frequently according to clinical need **(LoE 4, strong recommendation, strong consensus).**

Relationship Between ALT Normalization Rates and Different Virologic Response Criteria in Chronic HDV Patients Treated With Bulevirtide Monotherapy

A pooled analysis using data from **229 patients** with CHD treated with BLV 2 mg or 10 mg monotherapy for **48 weeks in 3 clinical trials** was performed: the Phase 2 MYR203 (NCT02888106) and MYR204 (NCT03852433), and the Phase 3 MYR301 (NCT03852719) studies

Biochemical response according to virologic response cut-offs at Week 48 (N:229)



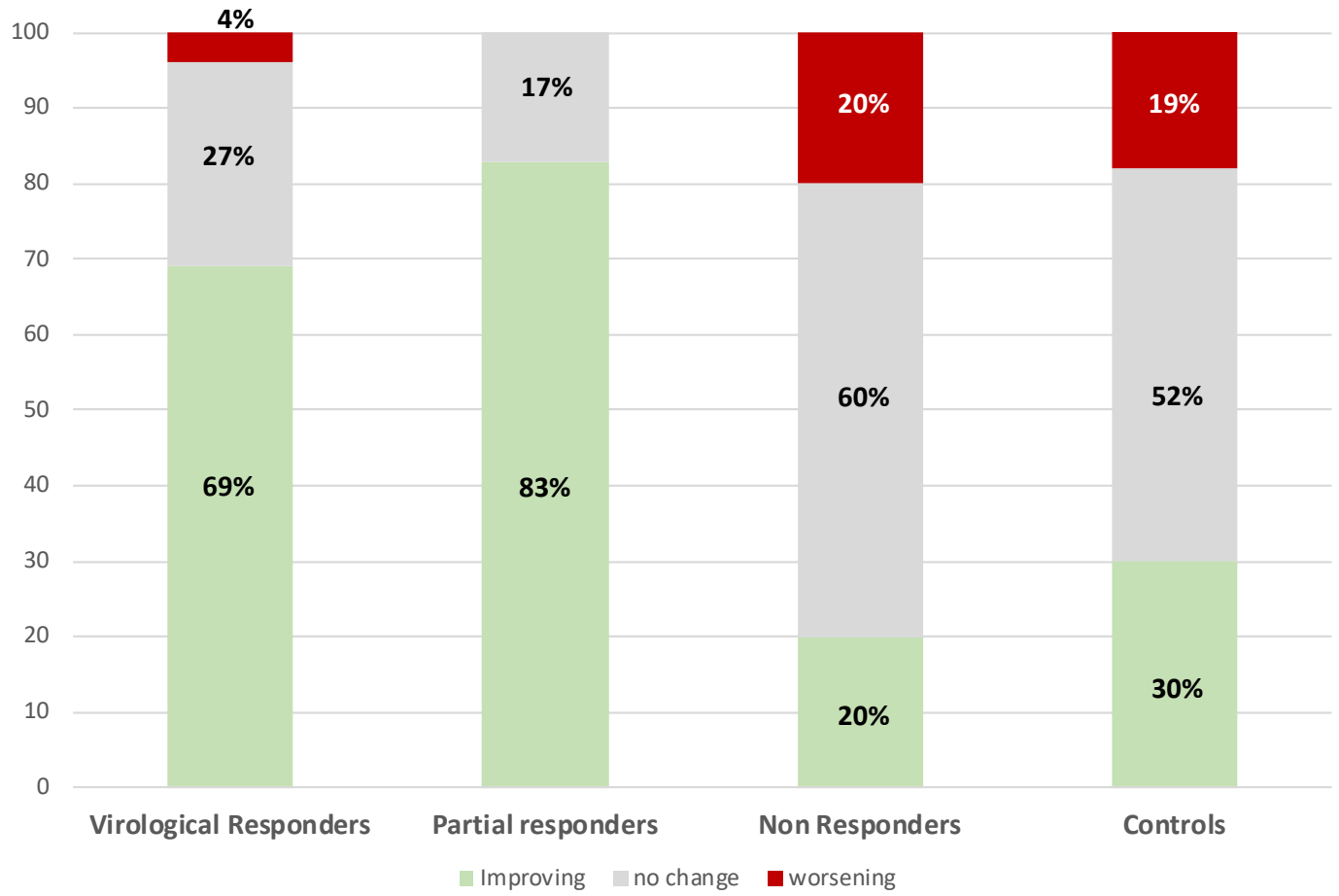
Virological Response	**79%** 180/229	**18%** 42/229	**71%** 163/229	**80%** 184/229	**85%** 94/229	**76%** 174/229	**87%** 200/229

- Viral response rates as high as 87% at 48 weeks were observed when the lowest viral response threshold (HDV RNA decline of ≥1 log10 IU/mL from BL) was used
- **Most patients had biochemical improvement** (as high as 60% for ALT ≤ ULN and 86% for ALT ≤1.5 x ULN depending on criteria), **including those who only achieved a 1-2 log10 IU/mL HDV RNA decline from BL**
- Among patients who did not achieve ALT ≤ ULN despite improvement in HDV viral load with BLV therapy, 84% (16 of 19) had ALT ≤1.5 x ULN
- Improvements in ALT were consistently observed in all viral response subgroups; **those with ≥1 log10 IU/mL decline in HDV RNA from BL had similar improvements in ALT to those with undetectable HDV RNA at W48**

Lampertico P et al, AASLD 2023

Liver Histology changes from baseline to week 48

2 liver biopsies were performed in 83 patients (45 VR, 6 PR, 5 NR, 27 Controls)



Histological improvement occurred more frequently in Virological Responders and Partial responders

Lampertico P et al, EASL 2024 P392

Which parameters should be monitored during and after treatment? (2 of 5)

Recommendations

Virologic markers:

- HBsAg testing should be performed every year during and after therapy **(LoE 3, strong recommendation, consensus).**
- For pegIFNα-based finite therapy, quantitative HBsAg may be determined every 6 months during and every 12 months after treatment **(LoE 3, weak recommendation, strong consensus).**
- HBV DNA should be determined every 6 months in all treated patients who are not on NA therapy **(LoE 3, strong recommendation, strong consensus);** in case of BLV discontinuation, more frequent HBV DNA testing may be required **(LoE 5, weak recommendation, strong consensus).**

Which parameters should be monitored during and after treatment? (5 of 5)

Recommendations

Liver Imaging:

- Liver stiffness determination may be performed yearly during and after antiviral treatment of CHD **(LoE 5, weak recommendation, strong consensus).**

Histology:

- Liver biopsy should be performed in patients during and/or after antiviral treatment where histological diagnosis would aid clinical management **(LoE 3, strong recommendation, consensus).**

Clinical events:

- Patients with CHD should be monitored during and after treatment for the development of liver-related clinical events **(LoE 3, strong recommendation, strong consensus).**

Which parameters should be monitored during and after treatment? (3 of 5)

Recommendations

Biochemical markers:

- Testing for biochemical markers of liver disease activity (*i.e.* aminotransferases), full blood count and, in addition, liver function tests, whenever clinically indicated, should be performed during antiviral treatment **(LoE 3, strong recommendation, strong consensus).**

- Frequency of testing should be at least every 3-6 months, with the timing modulated according to the stage of liver disease and type of treatment **(LoE 3, strong recommendation, strong consensus).**

(continues…)