Hepatitis Delta

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Disclosures

M Buti

Speaker: Gilead, Abbvie

Advisory board: Gilead, Janssen, Spring Bank, Abbvie

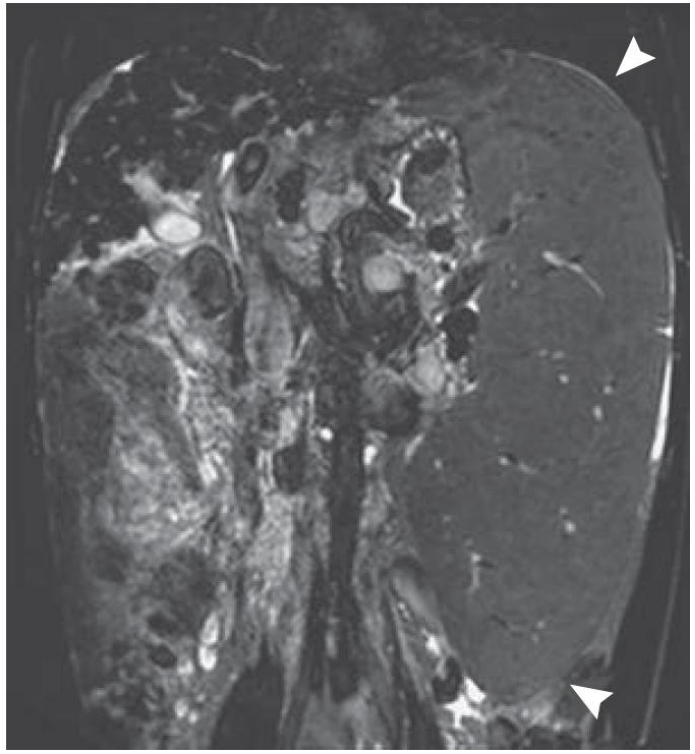
Caso Clínico

- Varon de 34 años
- Nacio en **Romania**
- Diagnosticado Hepatitis crónica B y D hace 2 ñaos
- HBsAg positivo, antiHBe positivo,DNA-VHB indetecable UI/ml
- AntiHD positivo, RNA-VHD 479.600 UI/ml
- ALT 96 UI/L, AST 72 UI/L, plaquetas 74,000
- Funcion hepática conservada
- Fibroscan de 19 Kpa

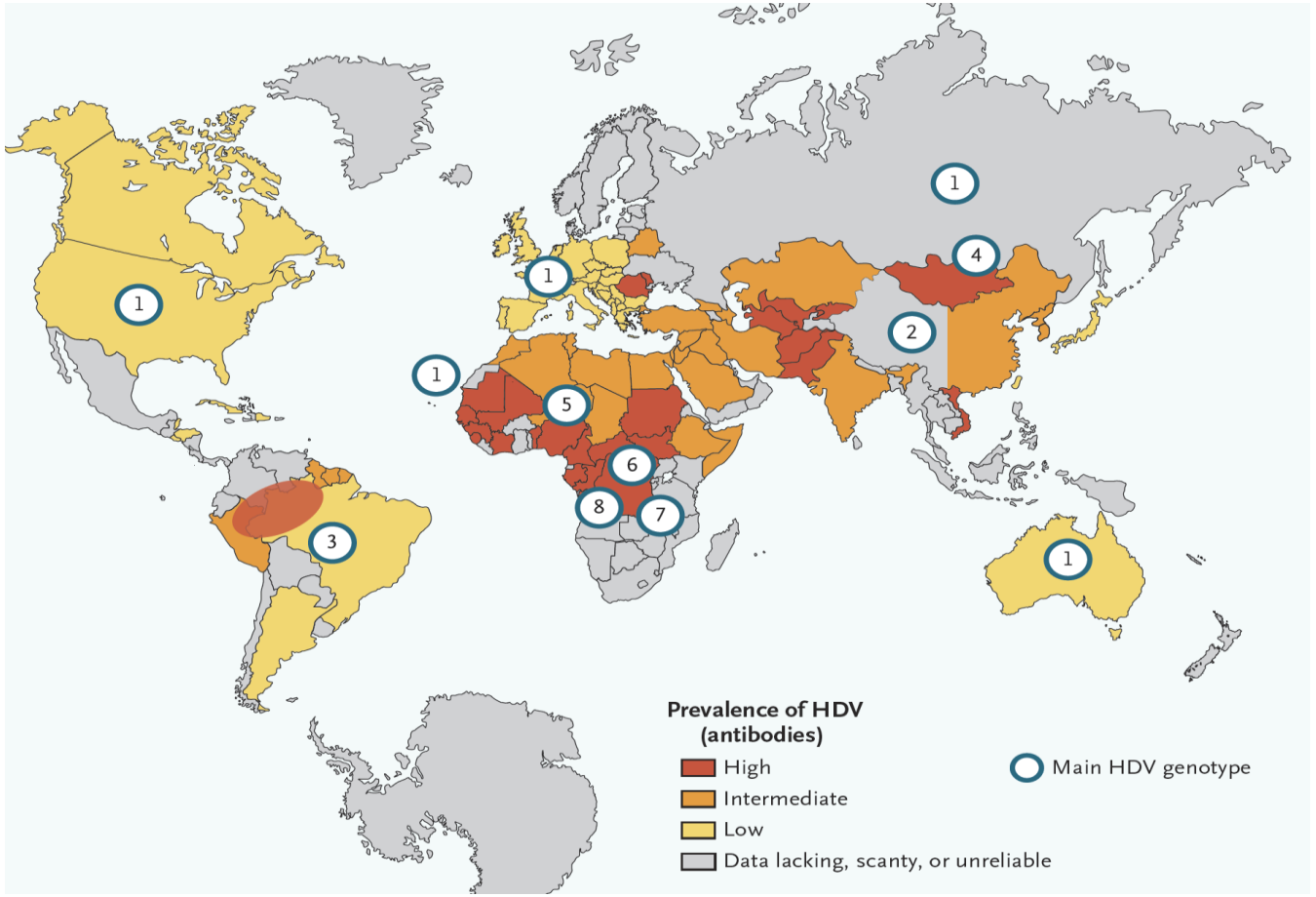
Caso Clínico

- Ecografia: hígado nodular, gran esplenomegalia
- Endoscopia varices grado 2
- No biopsia hepática
- No descompensaciones previas

- Remitido en 2022 para valorar Bulevertide



Pasises con alta Prevalencia de Hepatitis D en los ultimos 10 años



Spanish Registry of Hepatitis D

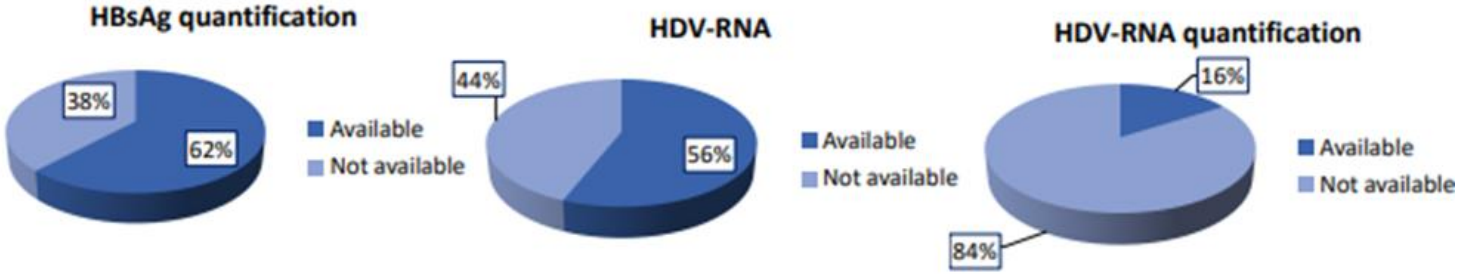
HEPATITIS DELTA REGISTRO

AEEH Asociación Española para el Estudio del Hígado

Participating centres in the registry (total 30 centers)

Table 1. Main characteristics

	Total 329
Sex (male)	194 (59%)
Age at last visit	51.1 (41.7-56.4)
Age 40-60 yo	210 (63%)
Follow-up (years)	6,4 (2,6-10,0)
Origin: Spain Origin: East Europe Origin: Africa	173 (53%) 79 (24%) 48 (15%)
Ex-PWID	48 (15%)
Anti-HCV	58 (18%)
HIV	30 (9%)
TE (kPa)	8.3 (6-12.4)



Test availability: HDV-RNA determination was available in 56% of centers (performed externally in the rest) and its quantification only in 16%. During follow-up, HDV-RNA was assessed in 278 (84%) patients

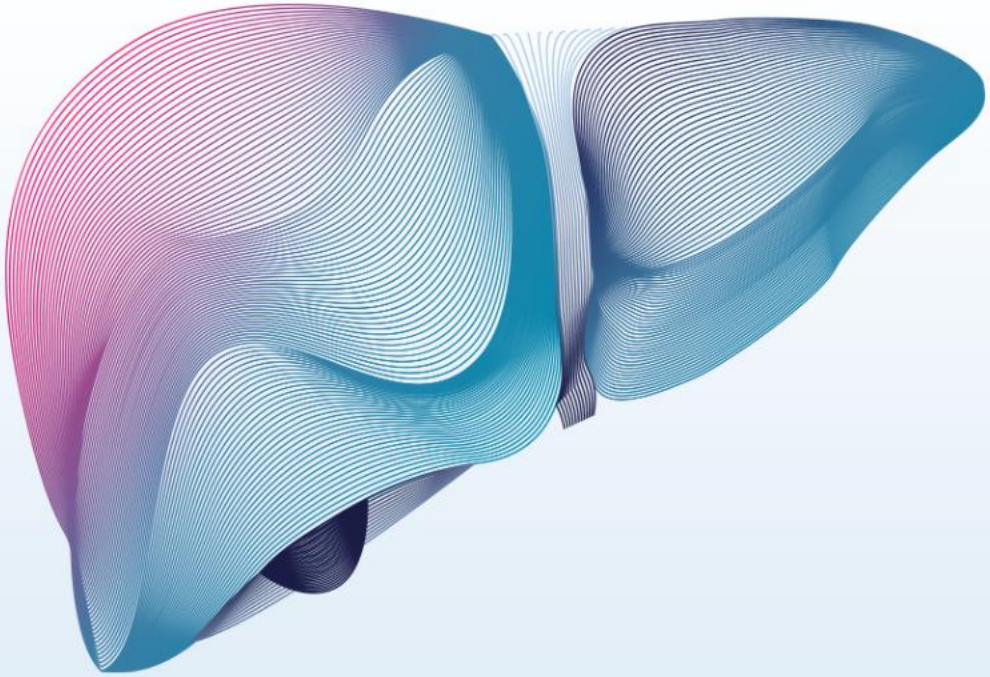
15ª EDICIÓN AULA ABIERTA MULTIDISCIPLINAR EN HEPATOLOGÍA

Around 1/3 had liver cirrhosis

GILEAD Creating Possible

EASL CONGRESS 2023
Vienna, Austria
21–24 June

The International Liver Congress™



EASL Clinical Practice Guidelines on hepatitis delta virus

Clinical Practice Guideline Panel: Chair: Maurizia Rossana Brunetto; Secretary: Gabriele Ricco; Panel members: Kosh Agarwal, Tarik Asselah, Patrizia Farci, Liana Gheorghe, Francesco Negro, George Papatheodoridis, Heiner Wedemeyer, Cihan Yurdaydin; EASL Governing Board representative: Maria Buti.

Clinical Practice Guidelines

JOURNAL
OF HEPATOLOGY

EASL Clinical Practice Guidelines on hepatitis delta virus☆

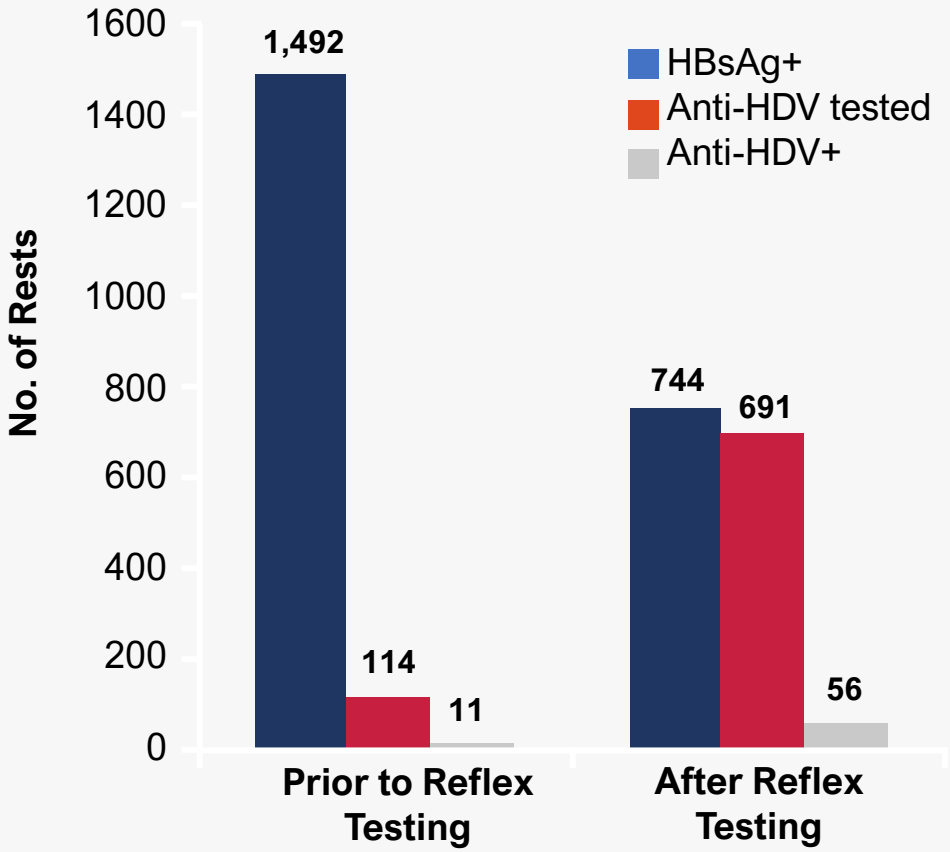
European Association for the Study of the Liver*

Recommendations

- Screening for anti-HDV antibodies should be performed with a validated assay at least once in all HBsAg-positive individuals **(LoE 3, strong recommendation, strong consensus).**
- Re-testing for anti-HDV antibodies should be performed in HBsAg-positive individuals whenever clinically indicated (*e.g.*, in case of aminotransferase flares, or acute decompensation of chronic liver disease) **(LoE 3, strong recommendation, strong consensus),** and may be performed yearly in those remaining at risk of infection **(LoE 5, weak recommendation, strong consensus).**

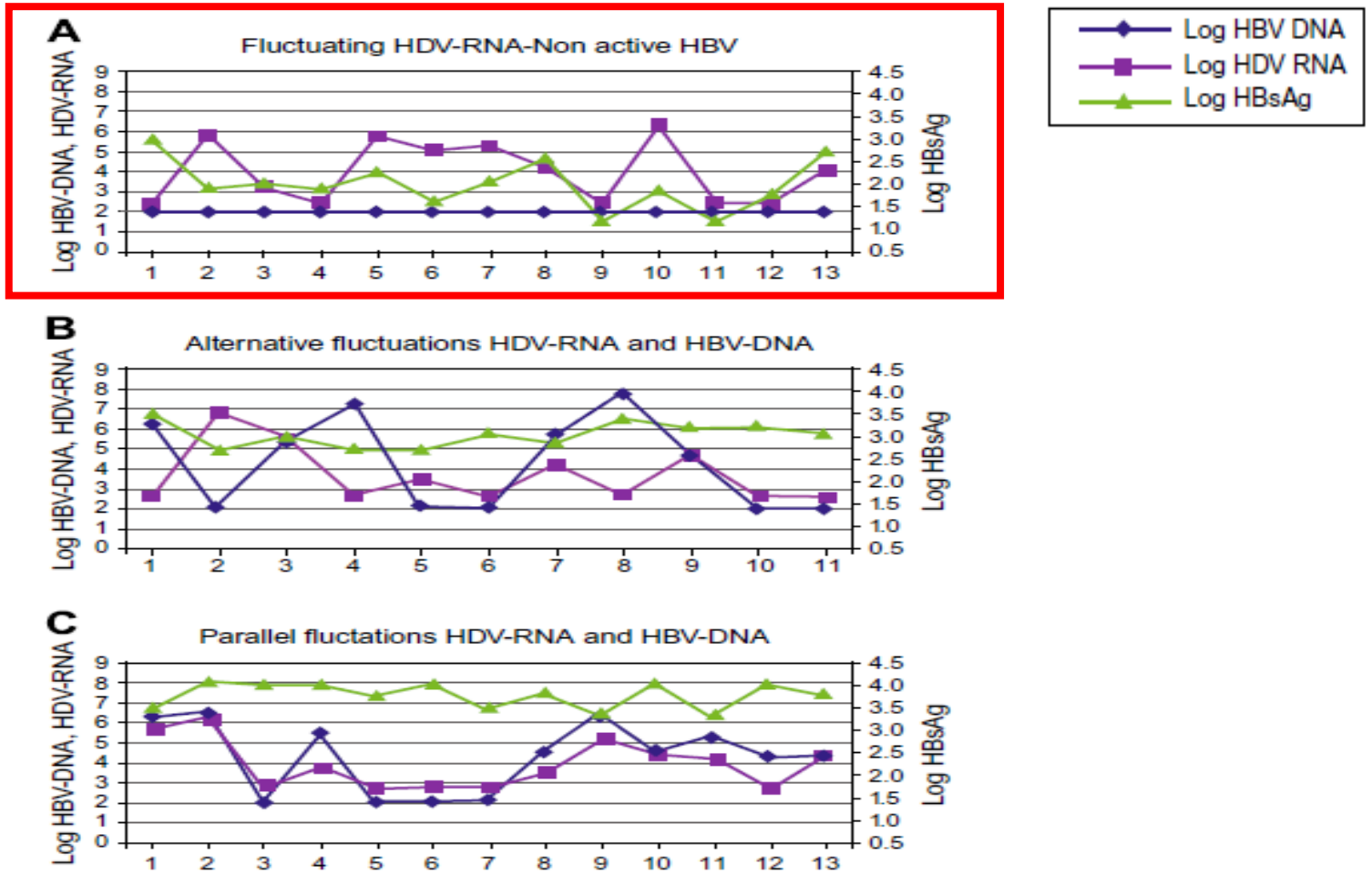
HDV Reflex Testing in HBsAg-Positive Individuals: Barcelona

- Retrospective analysis of HBsAg positive samples before and after anti-HDV reflex test implementation in an academic hospital and 17 primary care centers
- 60% of anti-HDV and HDV RNA–positive patients had **no HDV risk factors identified**
- Anti-HDV reflex testing resulted in a **5-fold increase** in HBV cases diagnosed with HDV



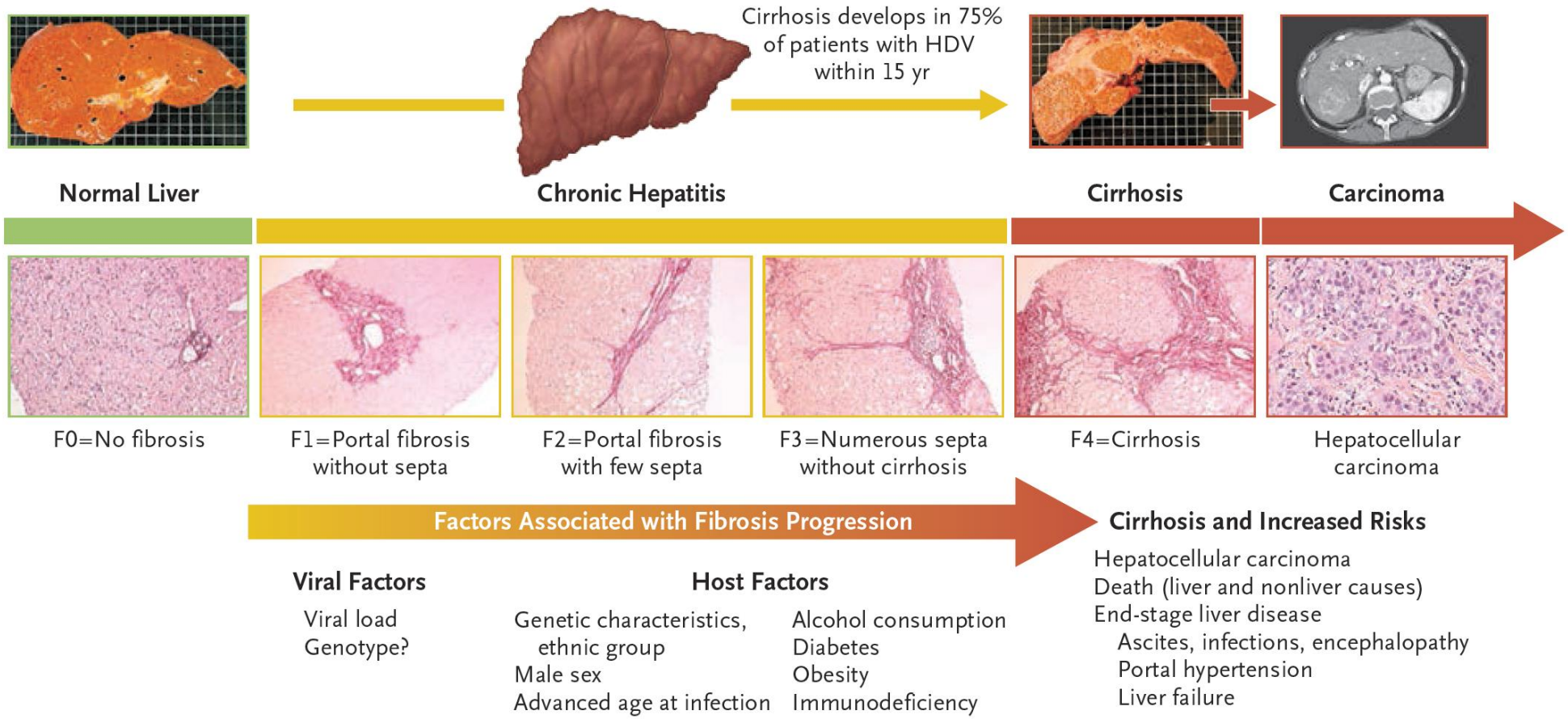
Palom. JHEP Rep. 2022;4:100547.

Patrones de replicación del VHB/VHD durante la historia natural



(Schaper et al J Hepatol 2010)

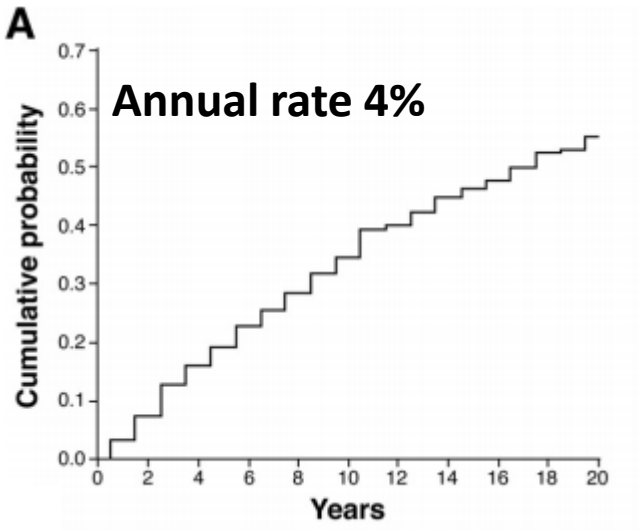
Factors associated with disease progression



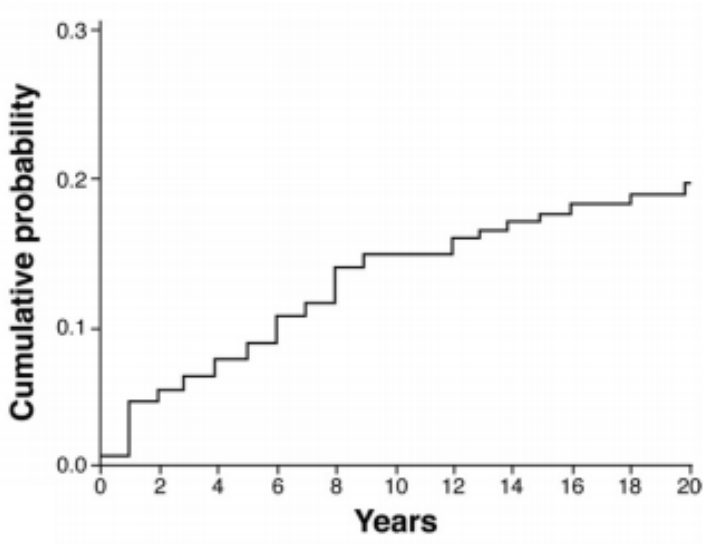
Probability of developing clinical events in chronic hepatitis delta

Mean follow-up of 19 years

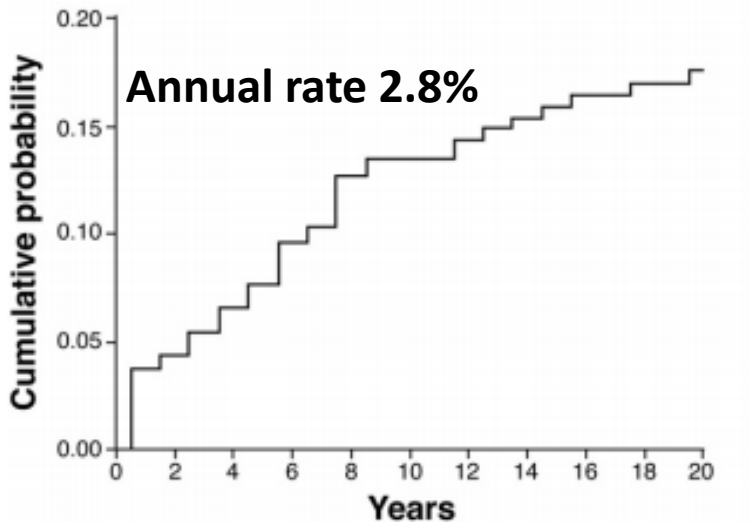
Cirrhosis
(N=299)



Decompensation
(N=186)



Hepatocelullar Carcinoma
(N=299)



Factors associated with worse outcome in chronic hepatitis Delta

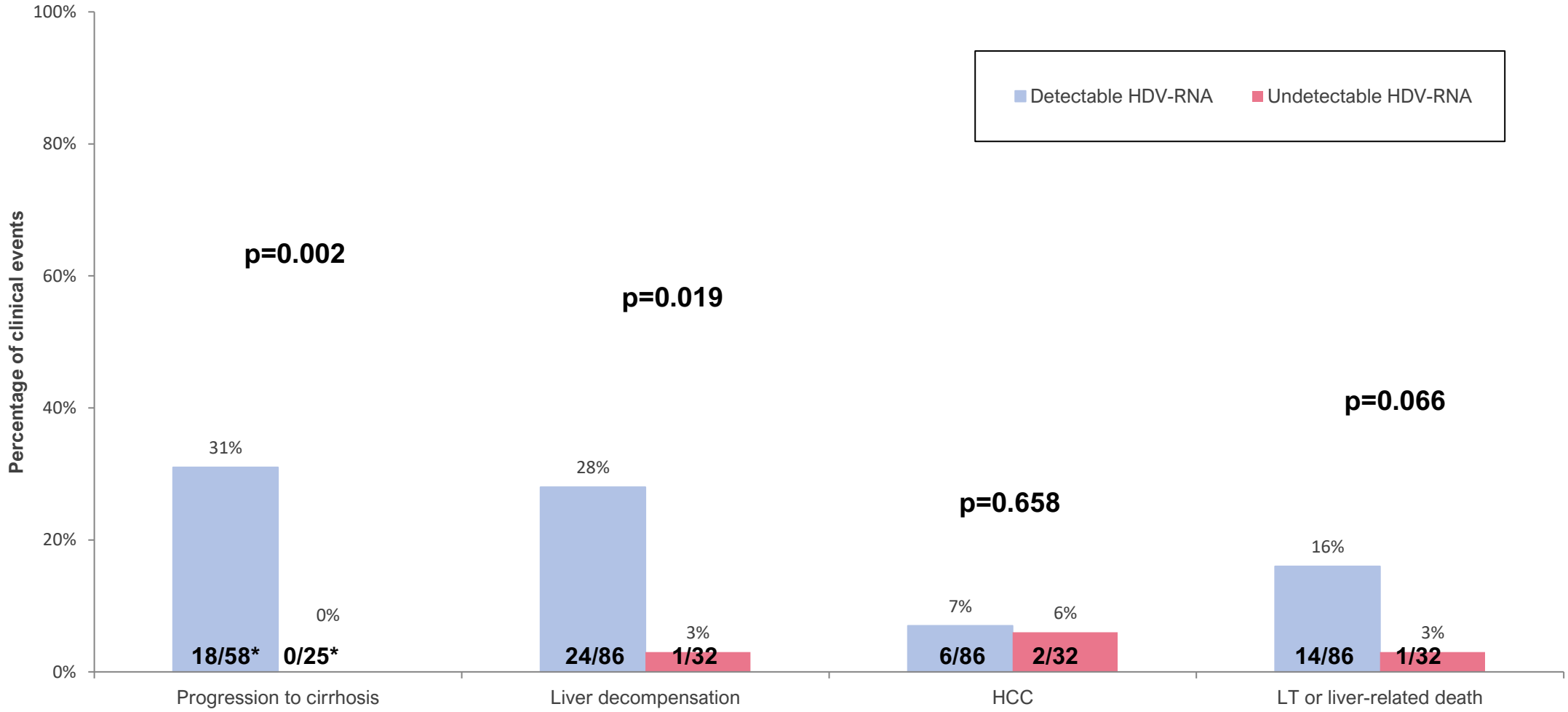
Persistent HDV RNA

Male gender
Cirrhosis at diagnosis
Lack of antiviral therapy

Romeo F et al Gastroenterology 2009;136:1629-1638; Niro GA, et al. J Hepatol. 2010;53(5):834-40

Probability of developing clinical events in chronic hepatitis delta

Multicentre study including 118 anti-HDV subjects followed for a median of 8 years



Palom A, *et al.* Aliment Pharmacol Ther 2019.

Debemos tratar la hepatitis B?

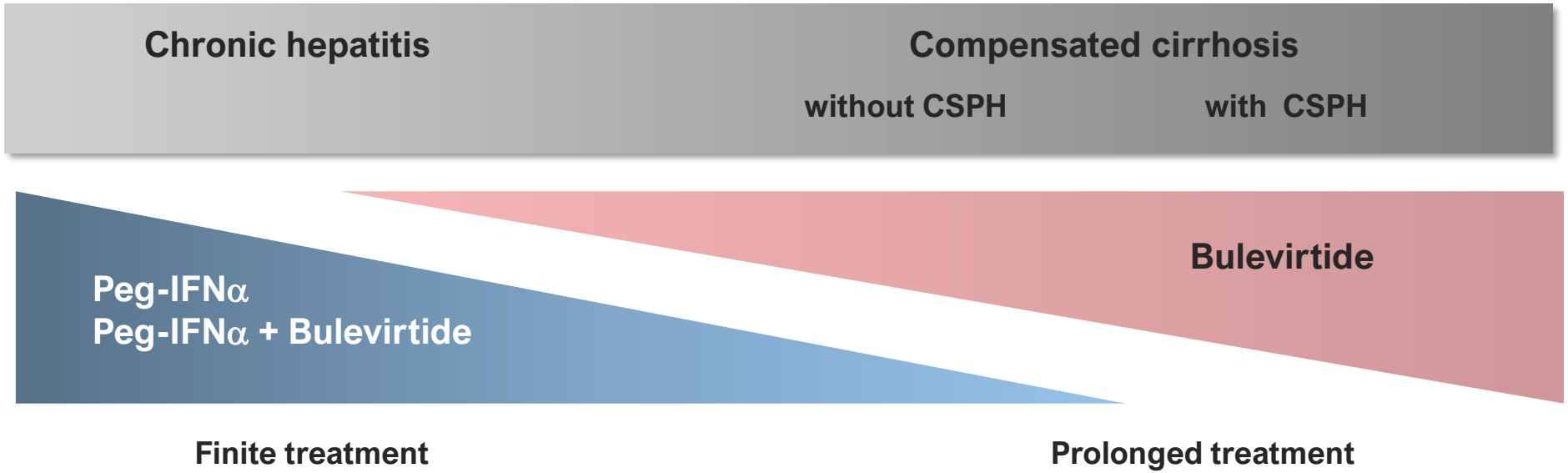
Como tratar la hepatitis D?

When should NAs be used in patients with CHD?

Recommendations

- NAs should be given in patients with decompensated cirrhosis irrespective of the presence of detectable HBV DNA **(LoE 5, strong recommendation, strong consensus).**
- NAs should be given in patients with compensated cirrhosis and detectable HBV DNA **(LoE 5, strong recommendation, strong consensus).**
- NAs should be given in patients without cirrhosis if HBV DNA levels are higher than 2,000 IU/ml **(LoE 5, strong recommendation, strong consensus).**

Treatment of Chronic Hepatitis Delta



To cure the infection/disease

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

PegIFNα no está indicado para el tratamiento de la hepatitis delta. La combinación de bulevirtida y PegIFNα no está indicada para el tratamiento de la hepatitis delta. Bulevirtida: medicamento aprobado por la Comisión Europea y sin financiación y precio en España

48 wks course of PegIFN+ADV vs PegIFN vs ADV in Chronic Hepatitis Delta

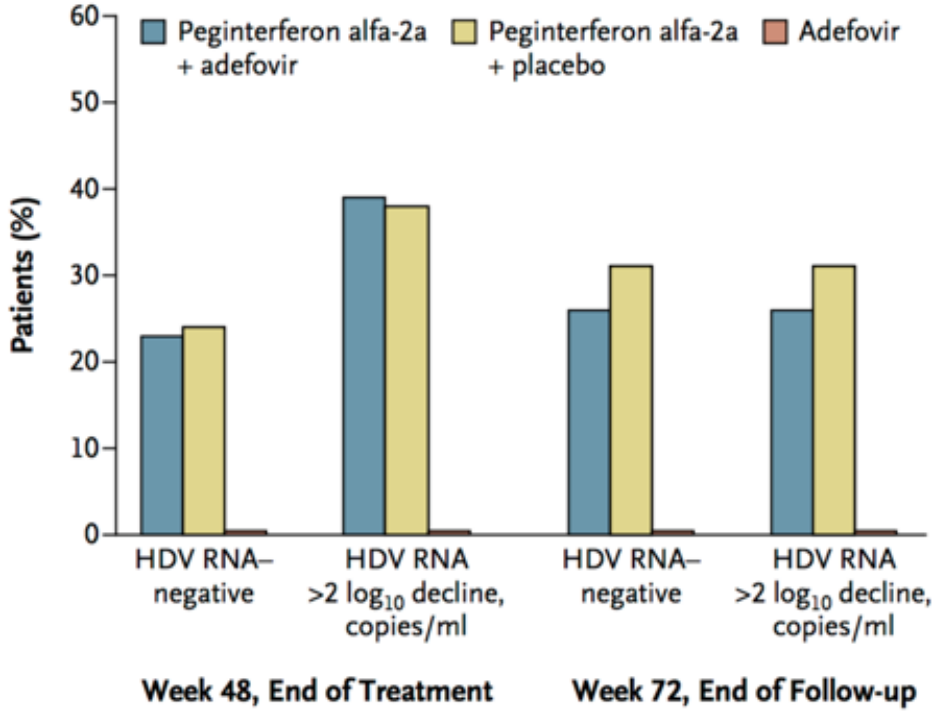
N=90 Chronic Hepatitis Delta

PEG-IFNα-2a (180 µg/wks) + ADV 10 mg/day (n = 31)

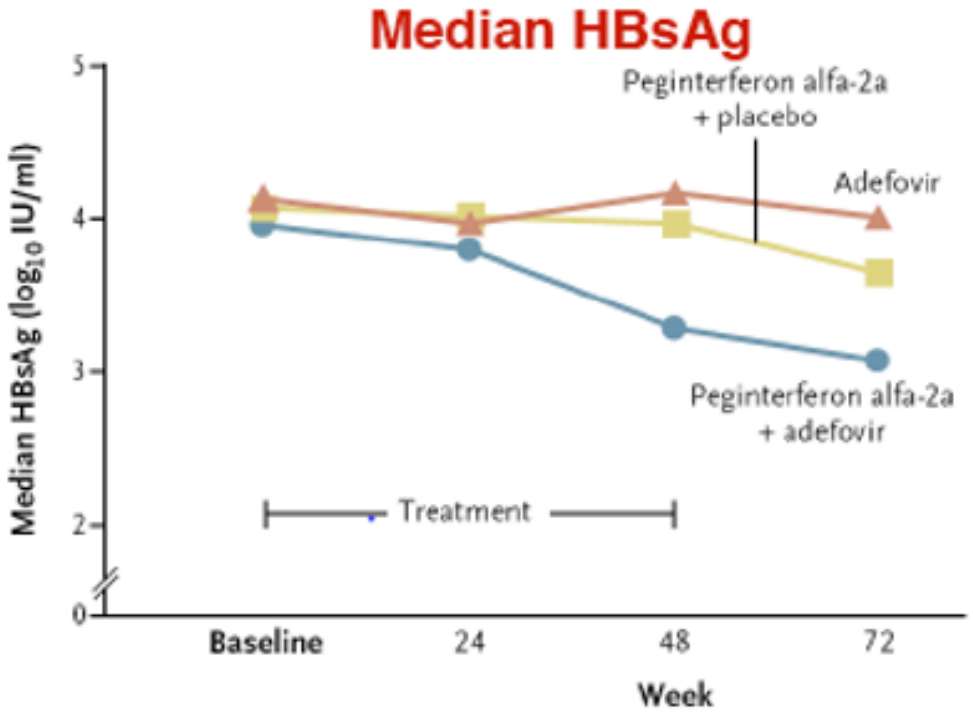
PEG-IFNα-2a (180 µg/wks) + placebo (n = 29)

ADV 10 mg/day (n = 30)

Primary End-Point: HDV RNA undetectable and Normal ALT at week 48



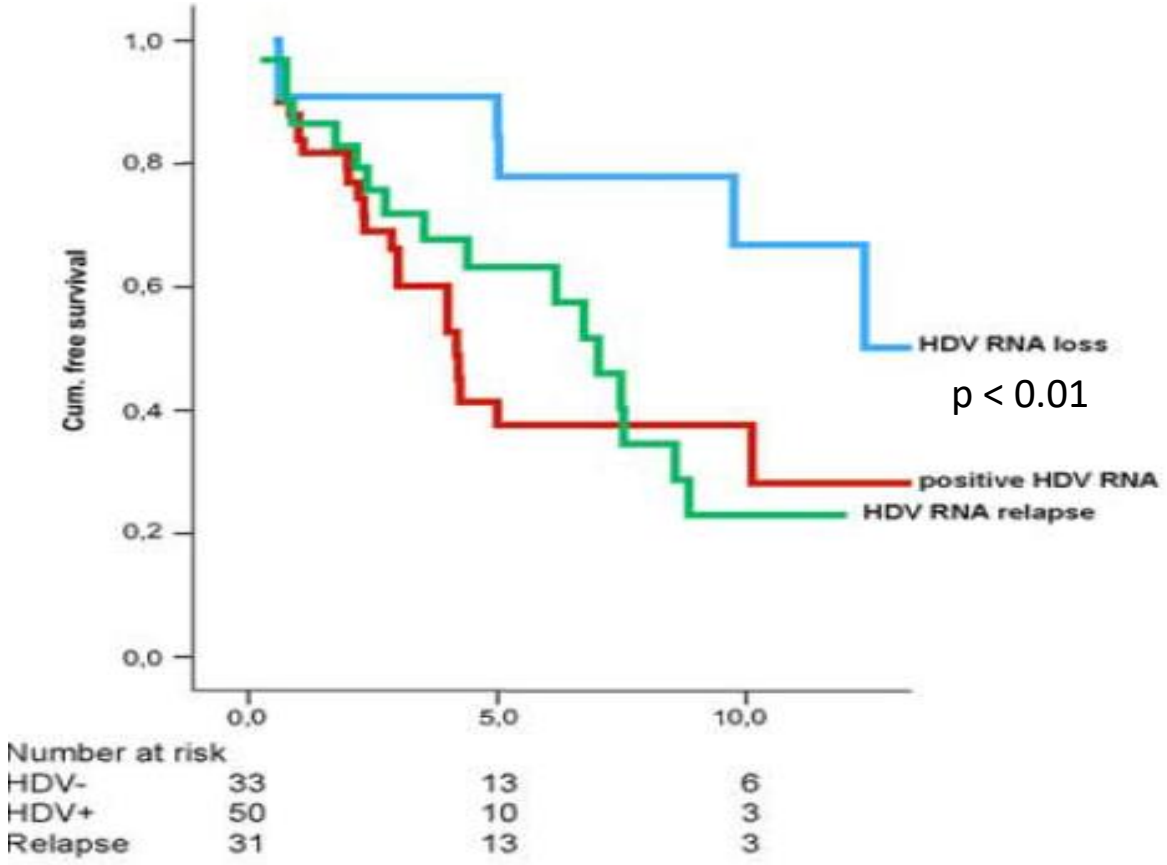
All HDV GT 1
14-24% cirrhosis

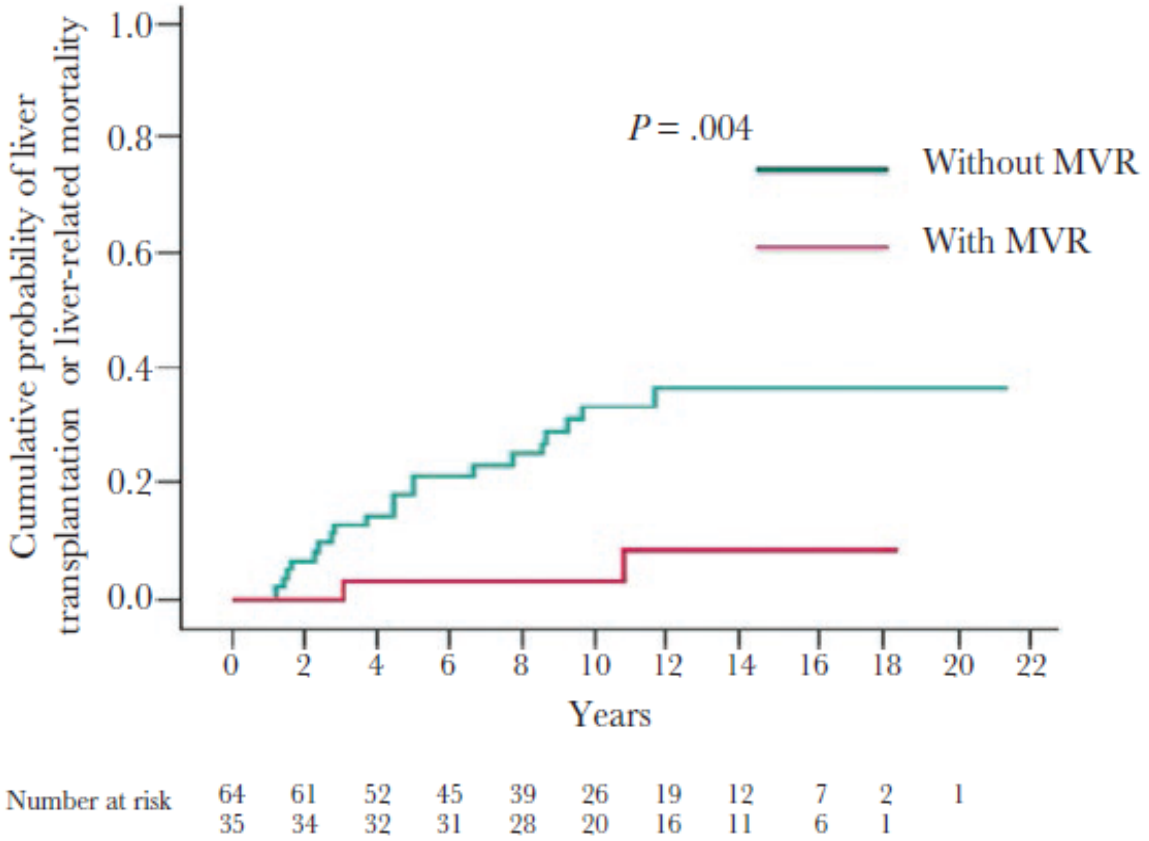


%0% of initial responders relapsed during a 5 years follow-up

Wedemeyer H. et al, N Eng J Med 2011;364:322-331

Long-term survival in patients with undetectable HDV RNA





Wranke A et al. Hepatology 2017;65:414-425

Yurdaydin C et al. J Infect Dis. 2018;217:1184-1192

Which patients with CHD can be treated with PegIFNα?

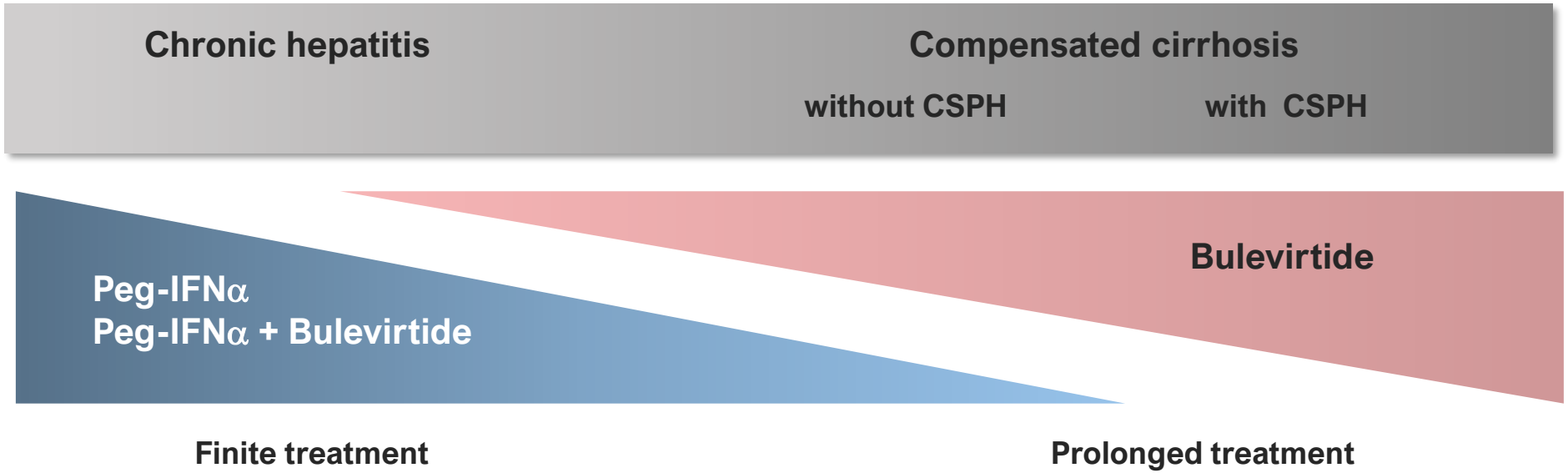
Statement

- IFNα has been used since the ‘90s for the treatment of CHD. Mono- and multicentre studies have been conducted with IFNα, with only two randomised phase II studies published. Nevertheless, long-term data on clinical benefit and safety are available **(LoE 2, strong consensus).**

Recommendations

- All patients with CHD and compensated liver disease, irrespective of whether they have cirrhosis or not, should be considered for treatment with PegIFNα **(LoE 2, strong recommendation, consensus).**
- PegIFNα for 48 weeks should be the preferred treatment schedule **(LoE 3, strong recommendation, consensus).**
- Personalised treatment durations may be considered based on HDV RNA and HBsAg kinetics and treatment tolerability **(LoE 3, weak recommendation, strong consensus).**

Treatment of Chronic Hepatitis Delta



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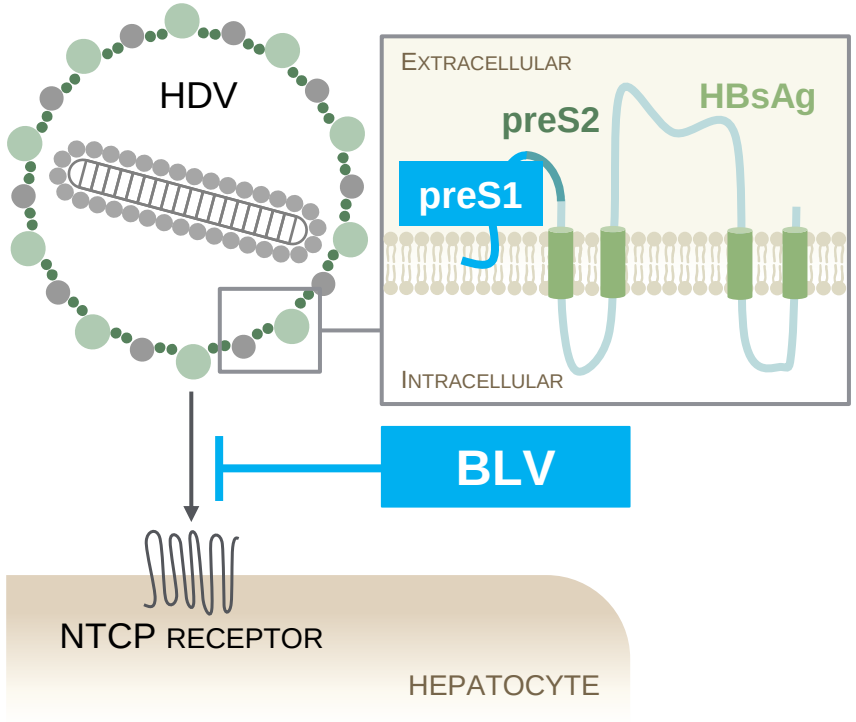
Bulevertide (BLV)

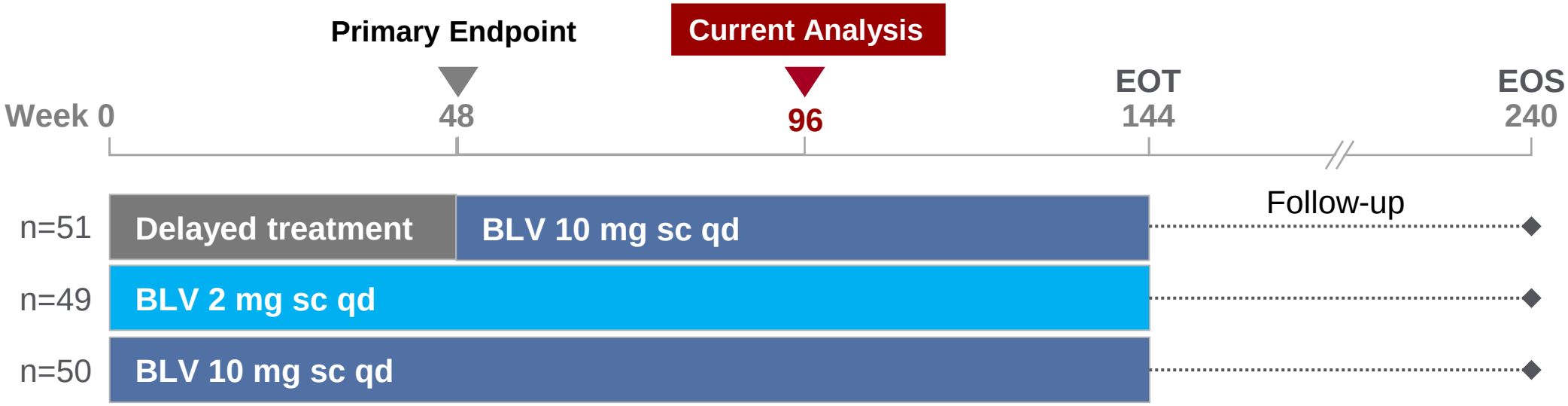
- First-in-class entry inhibitor for treatment of CHD
- Linear 47-amino acid chemically synthesized lipopeptide
- Binds to NTCP at the basolateral membrane of hepatocytes; NTCP is used by HBV and HDV to enter hepatocytes[1]
- Conditionally approved in Europe in 2020 for treatment of CHD in patients with compensated liver disease[2,3]



HBsAg, hepatitis B surface antigen; NTCP, sodium taurocholate cotransporting polypeptide.

1. Ni Y, et al. Gastroenterology 2014;146:1070-83; 2. Lampertico P, et al. J Hepatol 2022;77 (5):1422-30; 3. Wedemeyer H, et al. NEJM 2023;388(25)

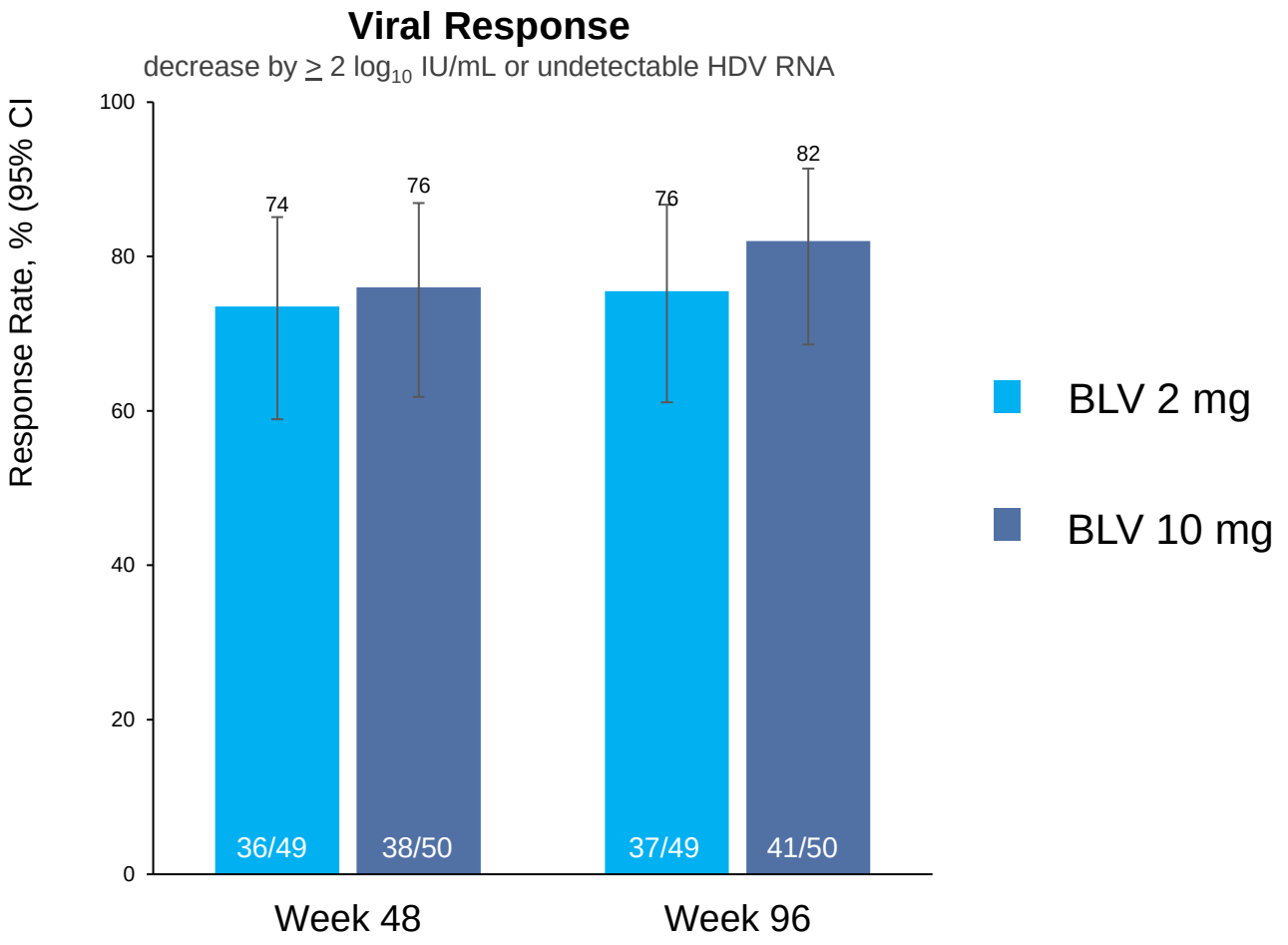
Study Design

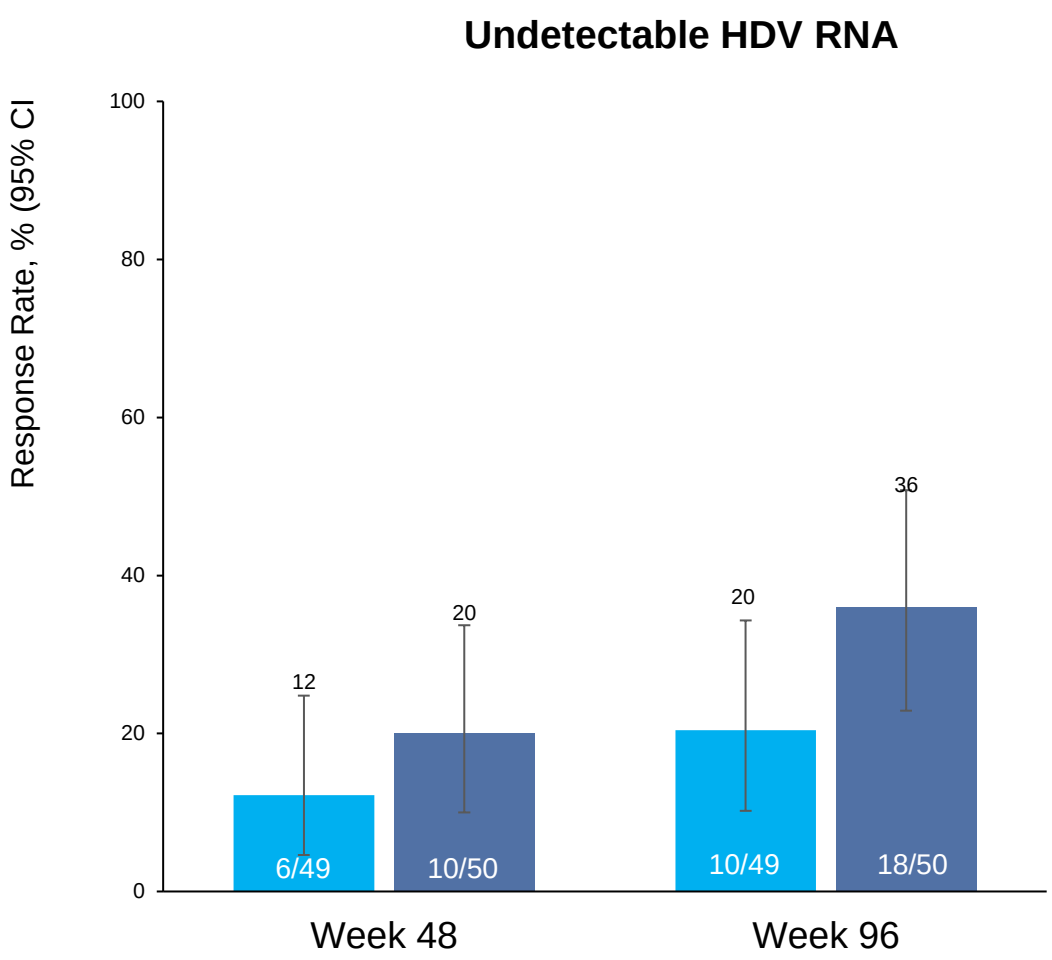


- Multicenter, open-label, randomized, Phase 3 study (NCT03852719) conducted in 16 sites across 4 countries (Germany, Italy, Russian Federation, and Sweden)
- **Key Inclusion Criteria:**
  - CHD without or with cirrhosis and CPT ≤7
  - ALT >1X to <10X ULN
  - Platelets ≥60,000 cells/mm^3
  - Controlled HIV coinfection allowed

ALT, alanine transaminase; BLV, bulevirtide; CHD, chronic hepatitis delta; CPT, Child-Pugh-Turcotte; EOS, end of study; EOT, end of treatment; ULN, upper limit of normal; sc, subcutaneous; qd, once daily.

Results: Virologic Endpoints

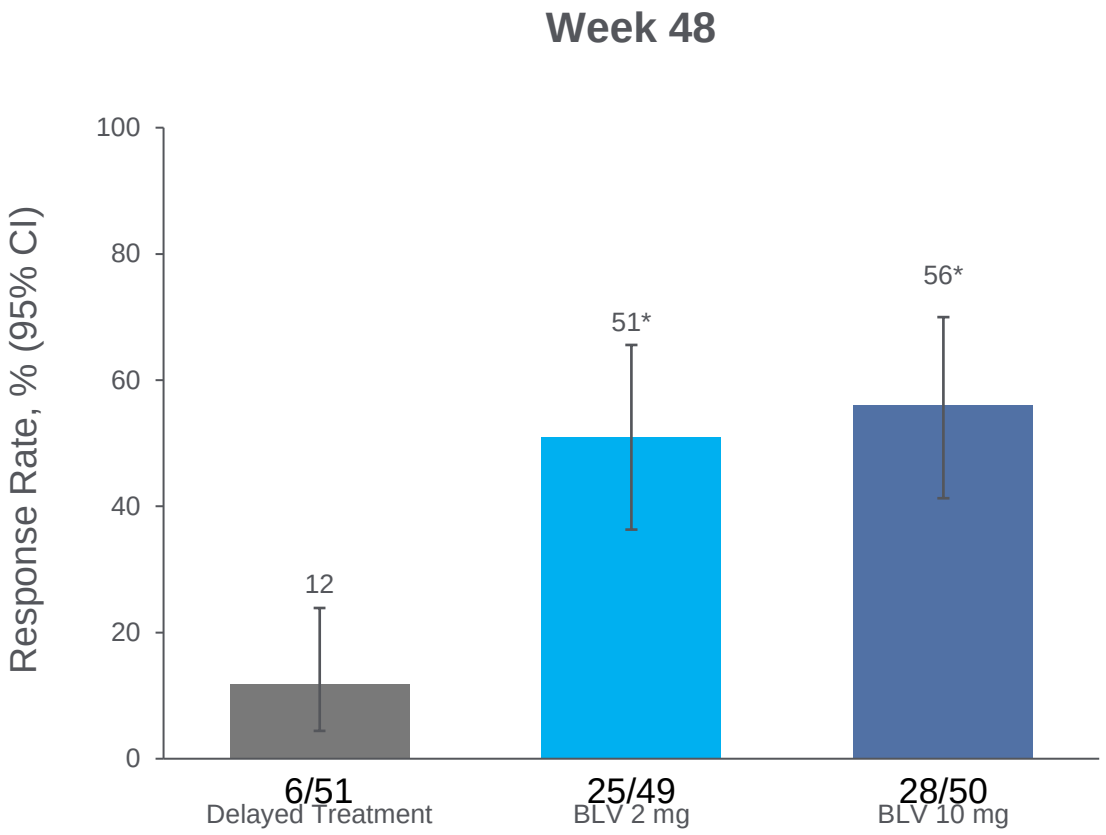


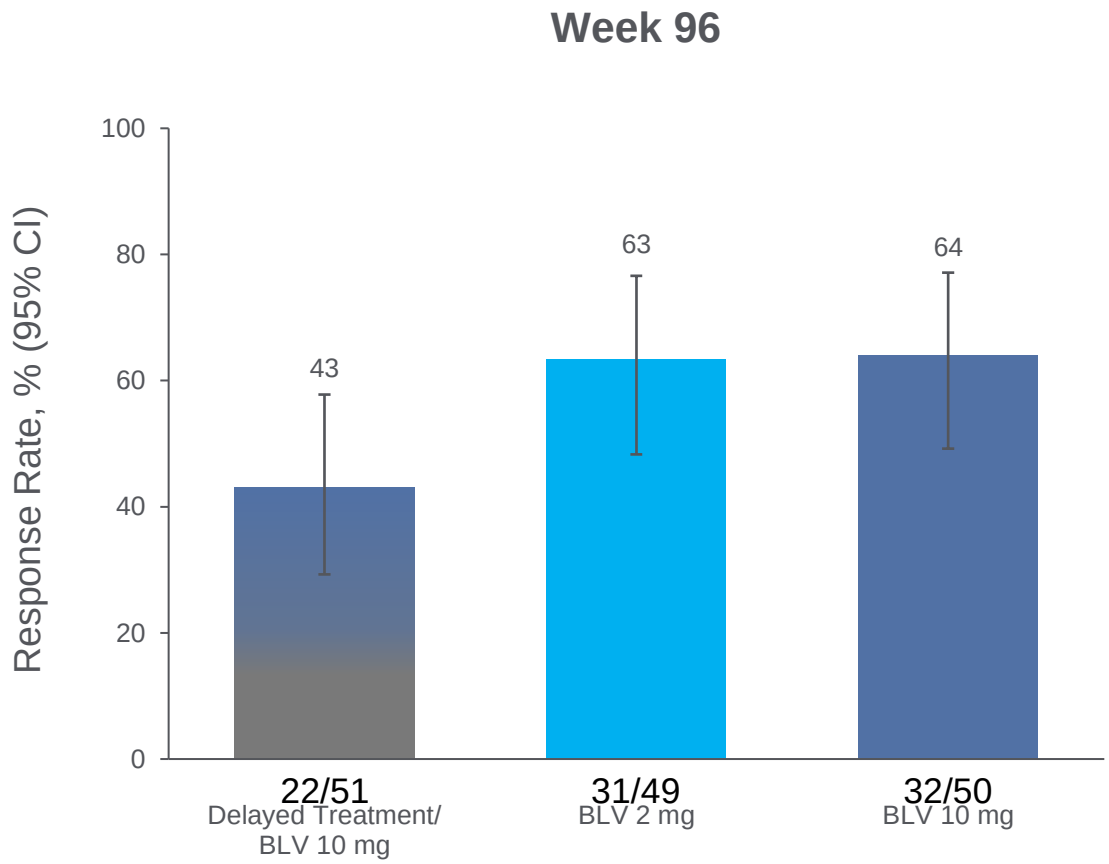


- Rates of virological response in BLV arms increased over time

Viral response defined as HDV RNA decrease by ≥ 2 log10 IU/mL or undetectable HDV RNA; Undetectable HDV RNA defined as <LLOQ (50 IU/mL) (target not detected). BLV: bulevirtide; HDV, hepatitis delta virus.

Results: ALT Normalization

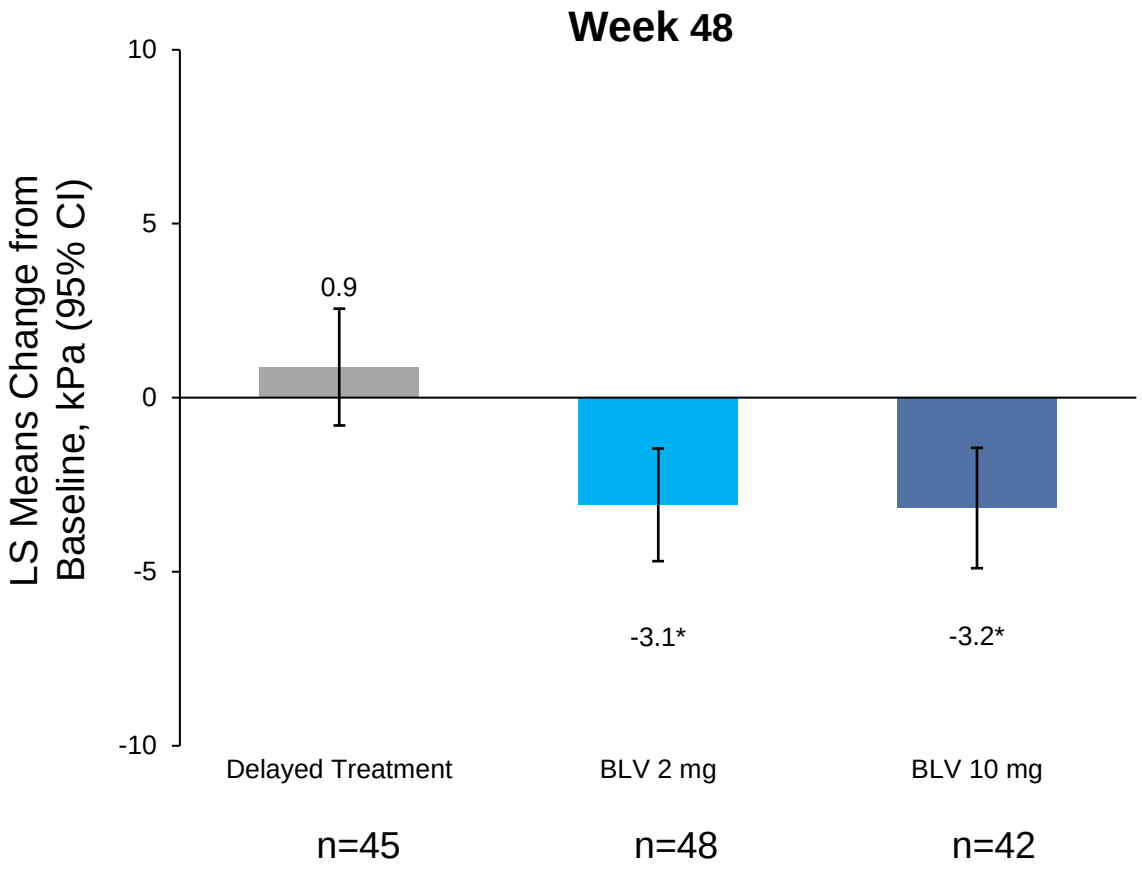


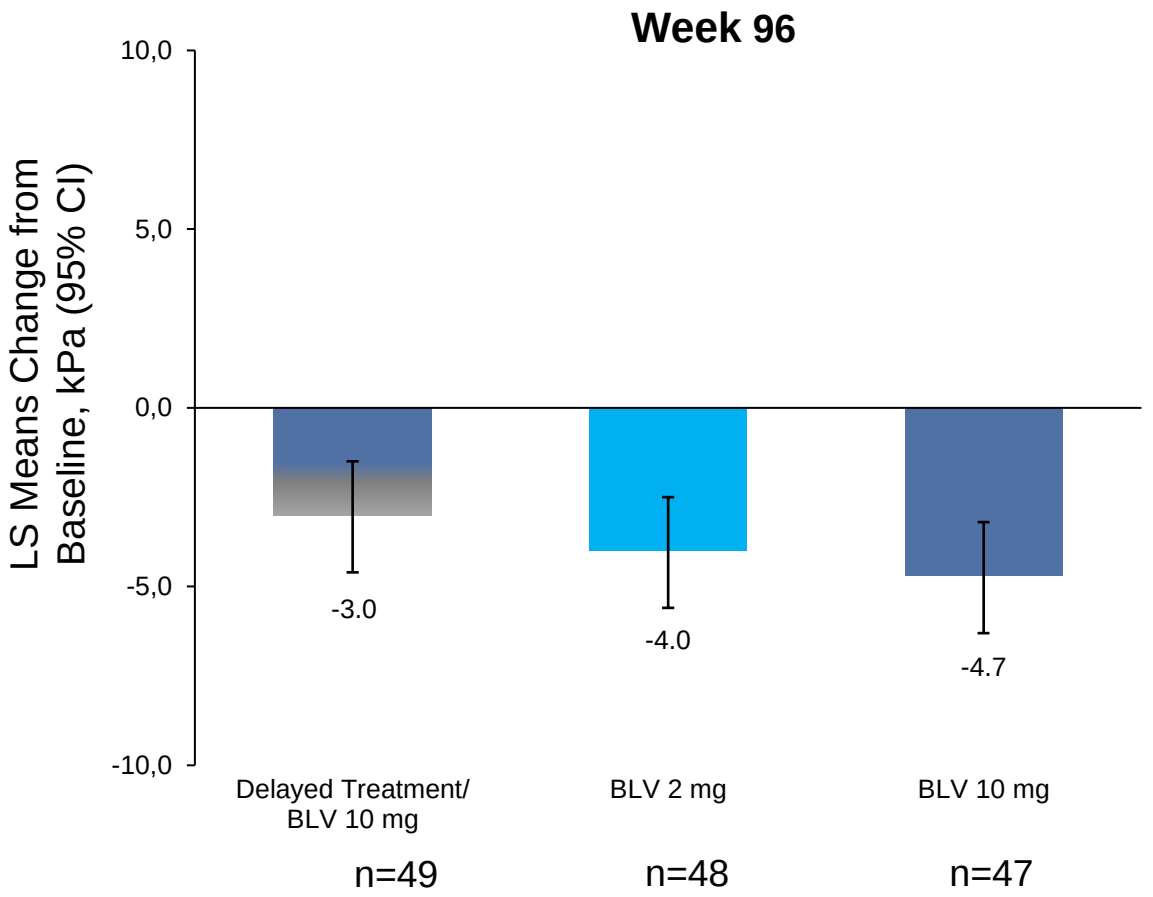


- Rates of biochemical response improved over time and were similar between doses

*p<0.0001 vs Delayed treatment arm. ALT ULN: ≤31 U/L for females and ≤41 U/L for males (Russia sites); ≤34 U/L for females and ≤49 U/L for males (all other sites). ALT, alanine transaminase; BLV, bulevirtide.

Results: Change in Liver Stiffness at Weeks 48 and 96

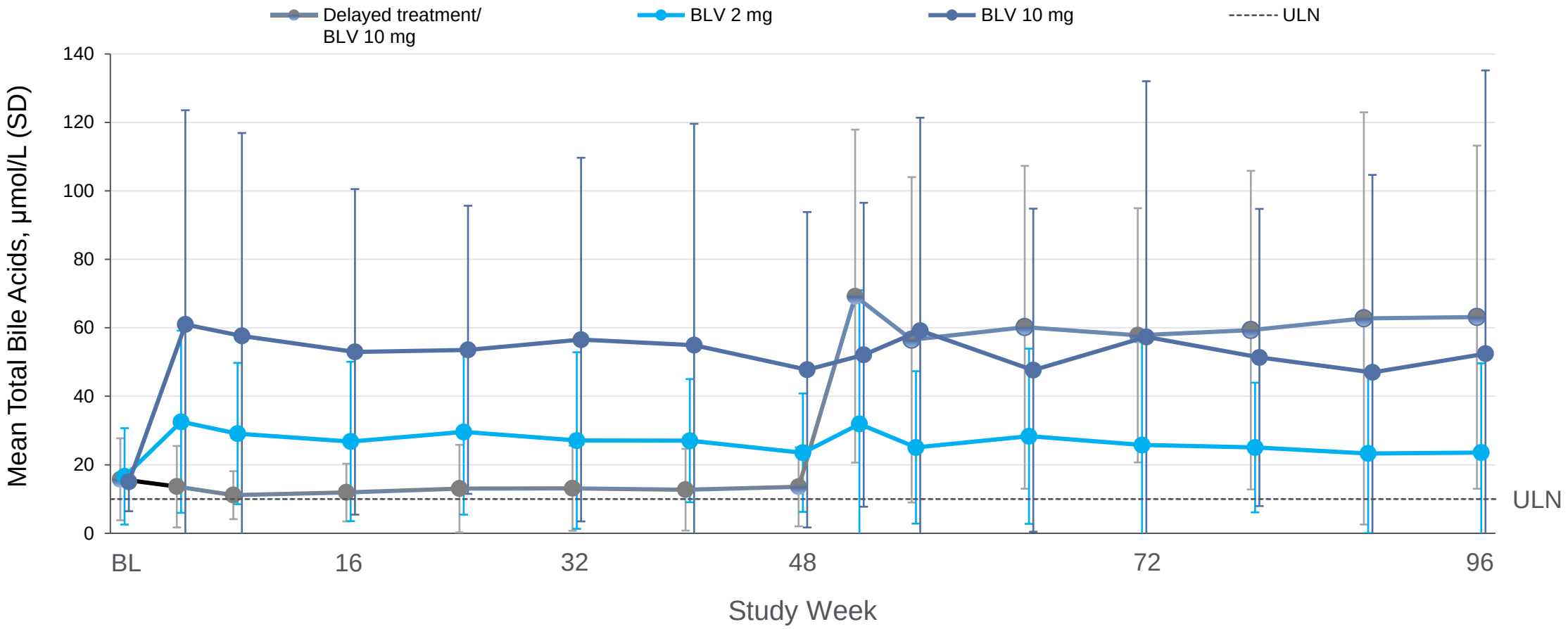




- BLV was associated with continued reductions in liver stiffness by transient elastography

*p=0.0010 vs Delayed treatment arm. BLV, bulevirtide; LS, least-squares.

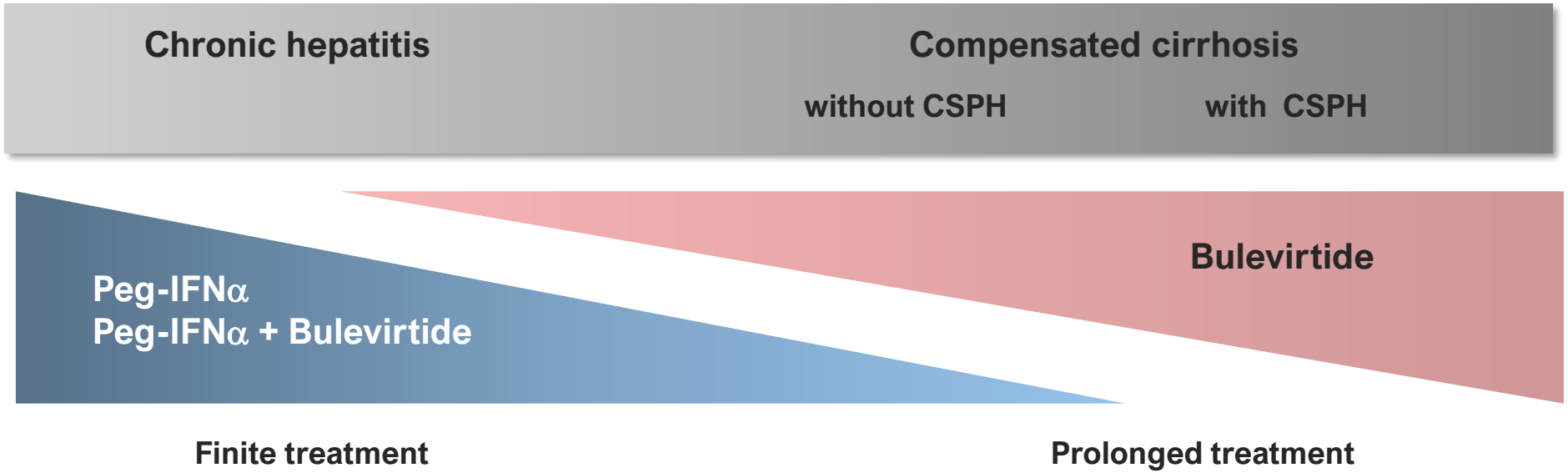
Results: Total Bile Acids Levels Over 96 Weeks



- Dose-dependent asymptomatic elevations in total bile acids were observed with BLV treatment which were less pronounced in the 2 mg dose group

Safety analysis set. BLV, bulevirtide; ULN, upper limit of normal.

Treatment of Chronic Hepatitis Delta



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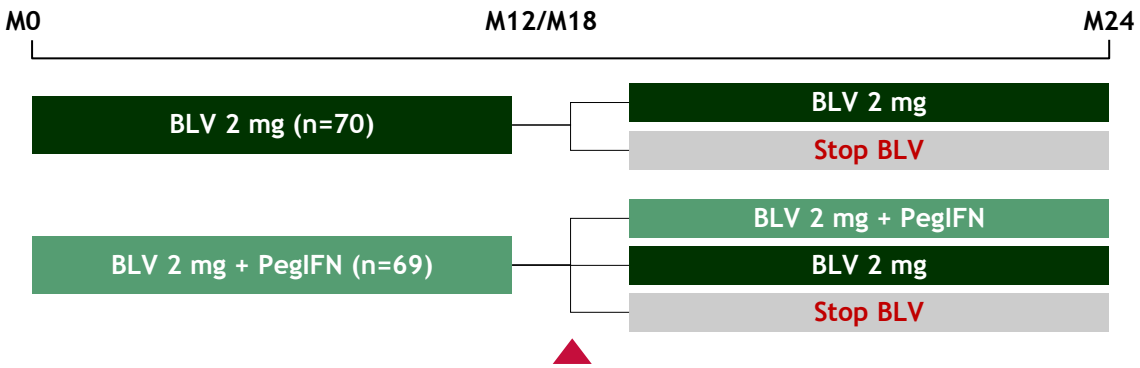
‡

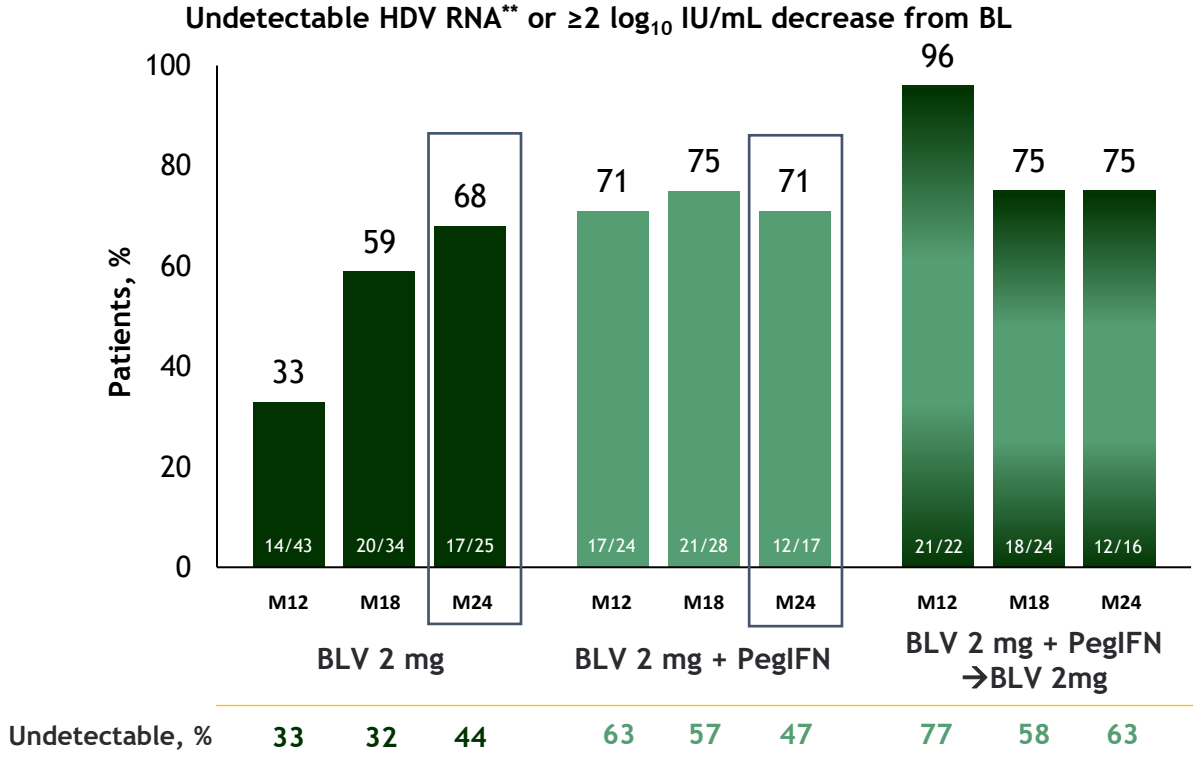
Two-Year Early Access Program RWD from France

A multicenter, open-label, observational prospective study of 139 patients treated with BLV 2 mg ± PegIFN*



Baseline Characteristics	BLV 2 mg n=70	BLV 2 mg + PegIFN n=69
Age, mean years (range)	42 (12)	40 (11)
Male, n (%)	50 (71.4)	45 (65.2)
Country of birth (Europe/Africa)**, n (%)	47 (67)/21 (30)	35 (52)/32 (48)
Cirrhosis, n (%)	44 (62.9)	42 (60.9)
Liver stiffness**, mean kPa (SD)	16.7 (14)	13.3 (9)
ALT†, mean IU/L, (SD)	94 (54)	124 (97)
HDV RNA, median log_{10} IU/mL, (IQR)	6.52 (1)	6.52 (1)
Current NA use, n (%)	56 (80)	51 (73.9)
HIV infection, n (%)	13 (18.6)	6 (8.7)

On Treatment Virologic Response



Virologic response increased with BLV 2 mg monotherapy over time, leading to similar response rates at 24 months compared to combination regimens

*Study not powered to compare all treatment regimens; **Missing data; †17 patients had ALT <40 IU/L at baseline and were included in the analysis. ALT, alanine aminotransferase; BLV, bulevirtide; NA, nucleos(t)ide analogue; PegIFN, pegylated interferon.

de Lédinghen V, et al. AASLD 2022. Oral #28

Which patients with CHD can be treated with BLV?

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 pegIFNa and BLV may be considered in patients without pegIFNa intolerance or contraindications **(LoE 5, weak recommendation, consensus)**

¿Cómo tratar la hepatitis D?

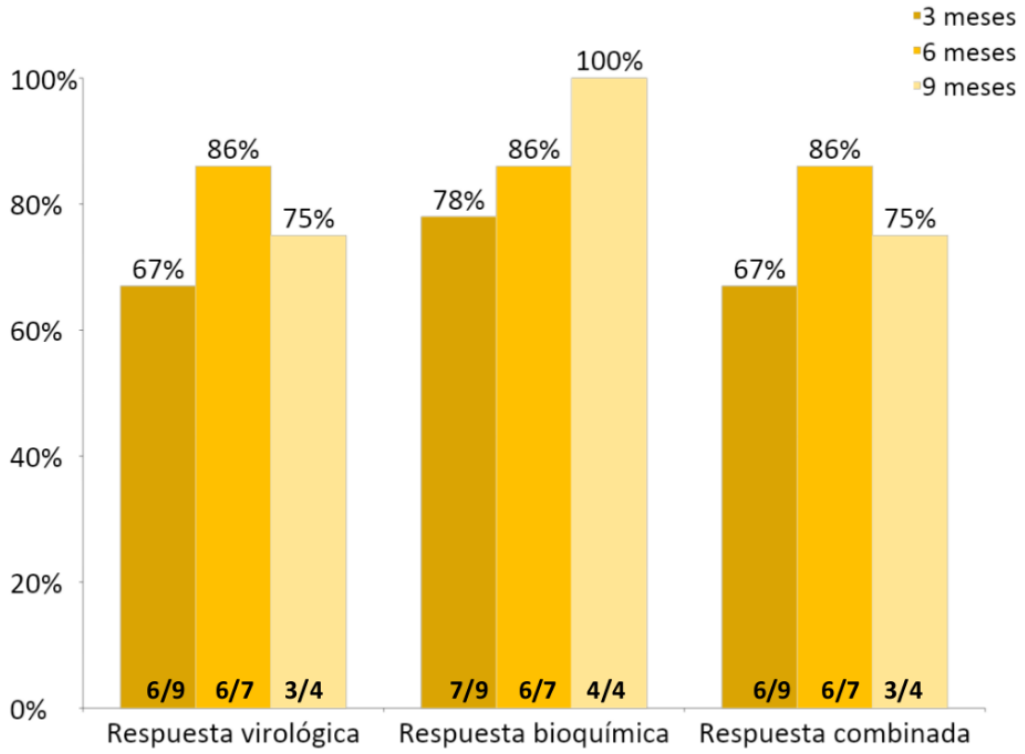
- PegIFN 180 mcg/semanal 12 meses
- Mala tolerancia al tratamiento
- Plaquetas 25.000 a los 2 meses
- Eltrombopag
- RNA-VHB negativo semana 24 y 48 de tratamiento

- Recaida????

Experiencia BLV en España hasta febrero 2023

Nueve pacientes se incluyeron en total, y la duración media de tratamiento con Bulevirtide 2mg fue de 8.7 meses.

Tabla 1. Características basales al inicio del tratamiento con BLV	
Mujeres, n(%)	6 (66%)
Caucásicos, n(%)	6 (66%)
Edad media, años	54.77
ALT elevadas, n(%)	9 (100%)
Cirrosis hepática, n(%)	9 (100%)
Tratados previamente con IFN, n(%)	7 (78%)
Tratados con NUC, n(%)	7 (78%)
ADN-VHB detectable, n(%)	0 (0%)
ARN-VHD detectable, n(%)	9 (100%)



Summary

In our country the majority of patients with hepatitis D are foreign-born or have liver cirrhosis[2]

Patients with HDV viremia have more rapid progression to cirrhosis, hepatic decompensation and hepatocellular carcinoma[3]

Reflex testing increases the rate of HDV screening, helps to better understanding the global burden of the disease and can improve HDV outcomes in Spain[5]

EASL guidelines recommend treatment with Peg-IFN or bulevirtide for HDV[1]

Bulevirtide 2 mg is efficacious and safe in patients with compensated chronic hepatitis D[2]

Real World studies confirm the results of clinical trials even in advanced compensated cirrhosis[3]

1. Stockdale. J Hepatol 2020;73:523; Miao. J Infect Dis 2020;221:1677. 2. Rodríguez-Tajes S. Congreso Anual AEEH 2022. Comunicación Oral 01392. 3. Palom A, *et al.* Aliment Pharmacol Ther 2019. 4. Buti M, *et al.* JHEP Rep 2021;3:100280. 5. Palom. JHEP Rep. 2022;4:100547.