Manejo en vida real de la infección por Hepatitis Delta

XIX CURSO EN AVANCES EN INFECCION VIH Y HEPATITIS VIRALES 2024

Vigo, 30 y 31 de mayo 2025

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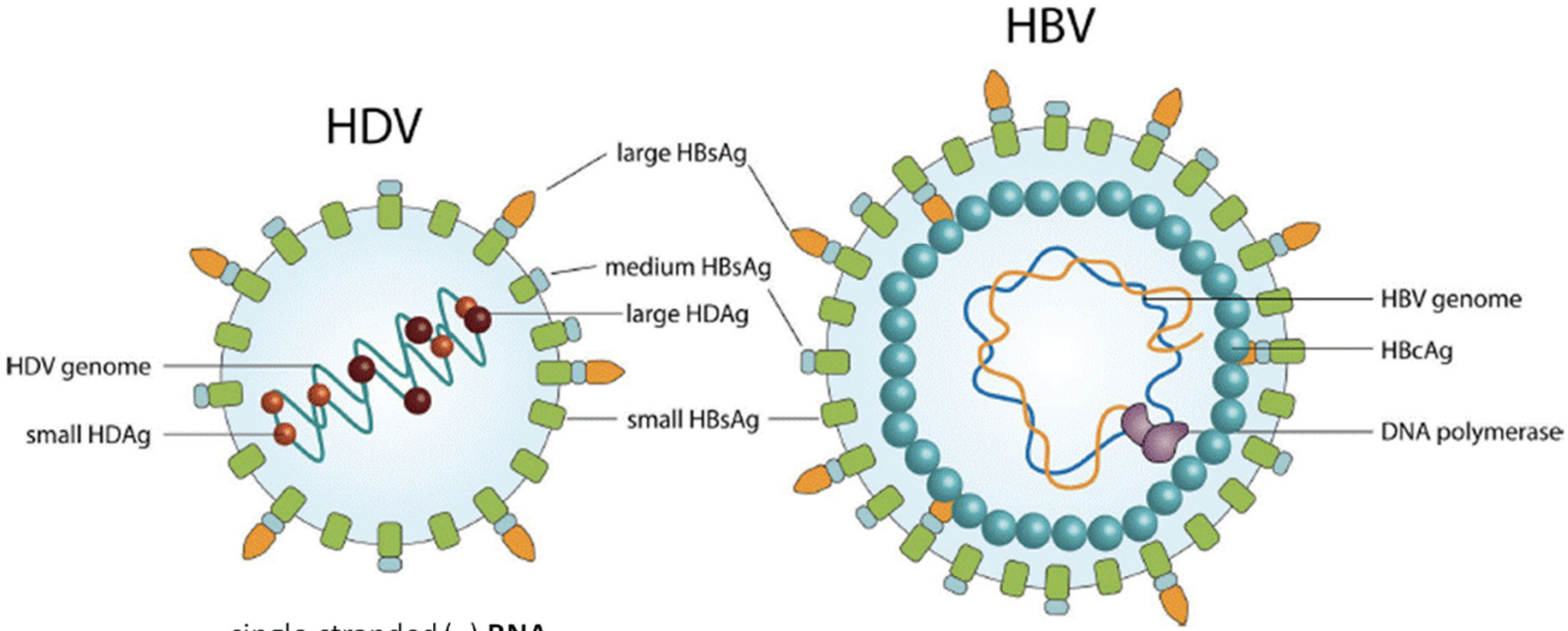
FCRB/IDIBAPS, CIBERehd

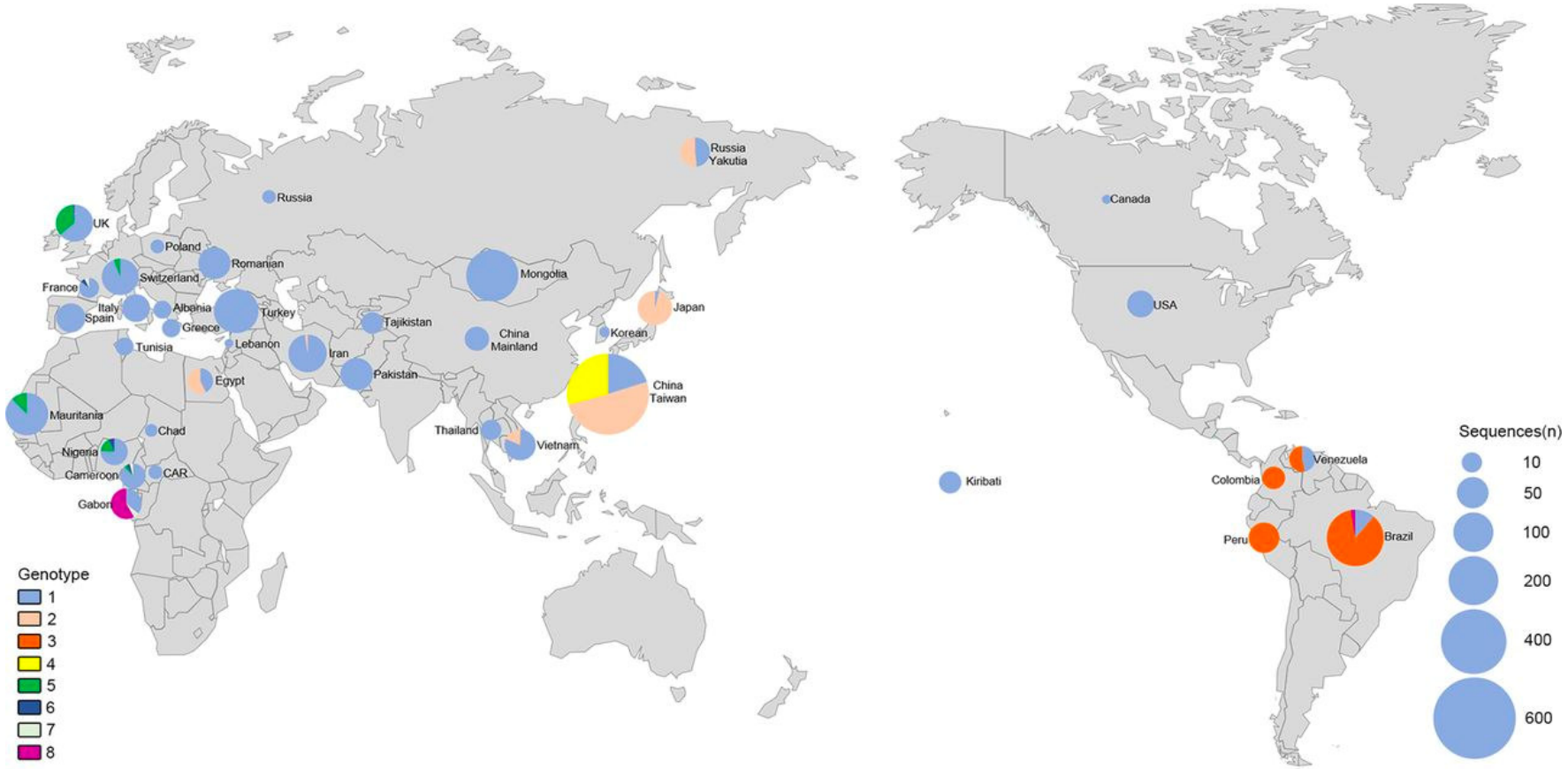
Hepatitis Delta



single-stranded (–) **RNA**
~1.7kb

relaxed circular partially double-stranded **DNA**, ~3.2kb

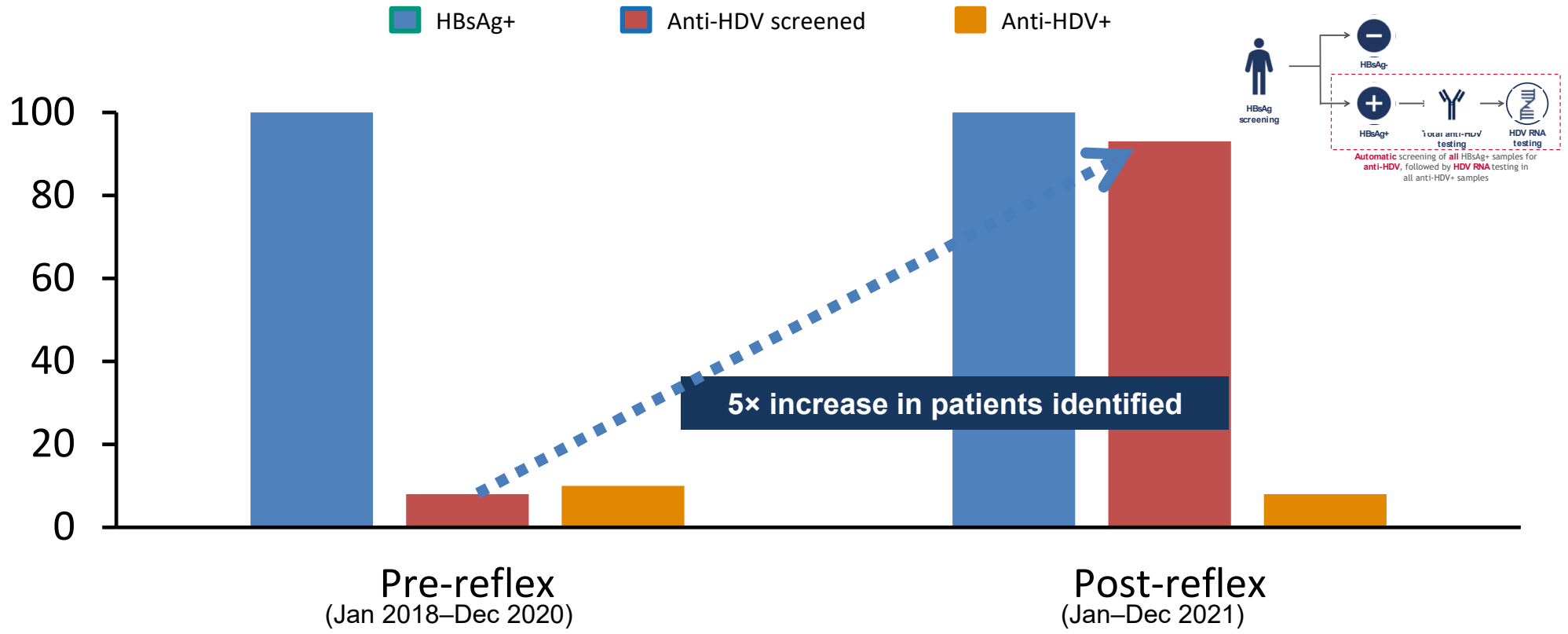
Hepatitis Delta



Anti-VHD+ en 5% de HBsAg → Cribar VHD en todos los HBsAg+

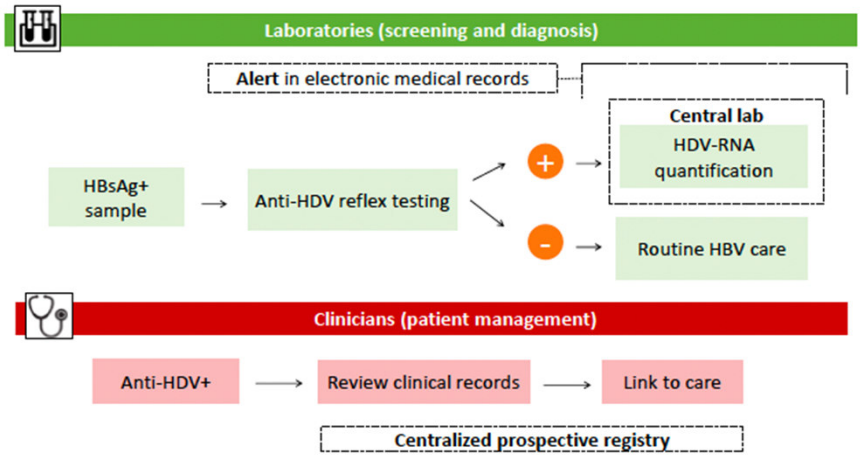
Hepatitis Delta: optimizando el cribado

Analysis of HBsAg+ samples before and after anti-HDV reflex test implementation in an academic hospital and 17 primary care centres



Palom A, et al. JHEP Rep 2022;4:100547.

Hepatitis Delta: optimizando el cribado



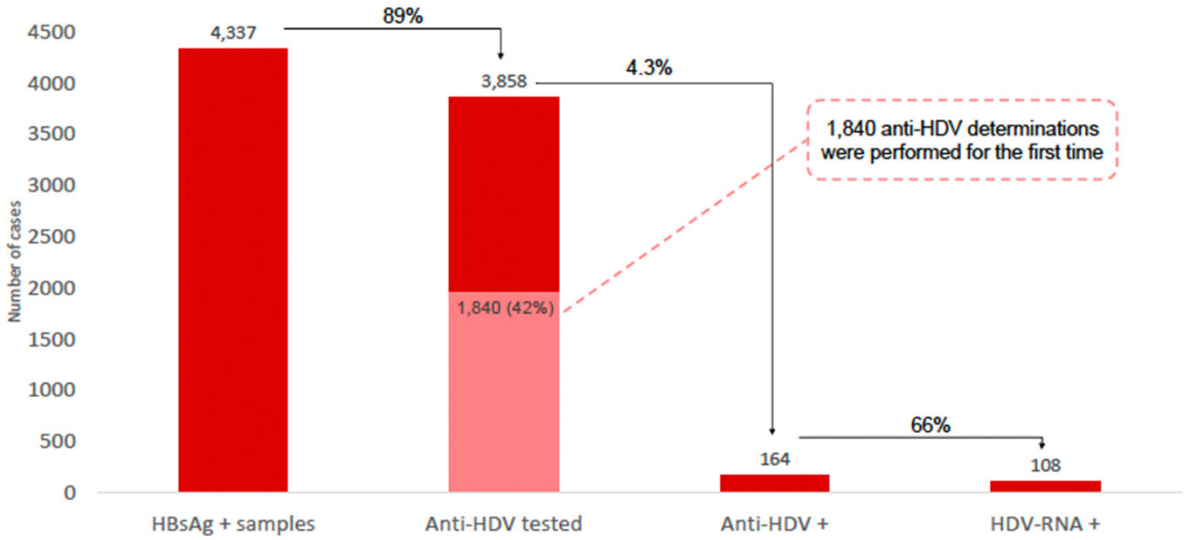


Fig 2. Cascade of samples tested on the program.

Palom A, et al. AASLD 2024

Hepatitis Delta en España

Table 1 Baseline patients' characteristics of the overall cohort at first visit.

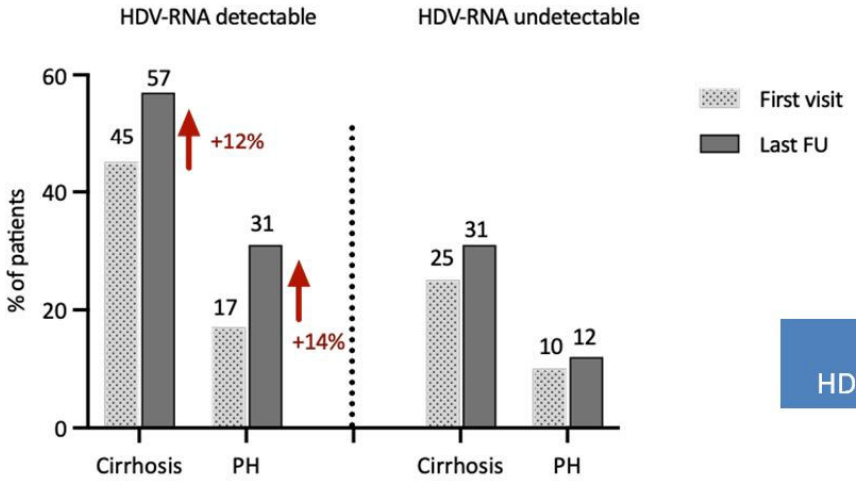
Variables	All *n* = 329
Sex (female), n (%)	135 (41)
Age (years), median (IQR)	51 (42–56)
Age (years) categories, n (%)	
<18	2 (0.6)
18–29	19 (5.8)
30–39	49 (15)
40–49	78 (24)
50–59	133 (41)
60–69	41 (12)
70–79	6 (1.8)
Origin, n (%)	
Spain	173 (53)
East Europe	79 (24)
Africa	48 (15)
Others	27 (8)
PWID, n (%)	48 (15)
HCV coinfection, n (%)	58 (18)
HIV coinfection, n (%)	30 (9)
Virological markers	
HDV-RNA positive[a], *n* (%)	138 (62)
HBeAg positive, *n* (%)	54 (16)
HBV-DNA positive, *n* (%)	216 (70)
Antiviral treatment	
Interferon experienced, *n* (%)	94 (29)
Nucleos(t)ide analogs[b], *n* (%)	191 (66)
Liver disease	
TE-LSM (kPa)[c], median (IQR)	9.2 (6.1–14.3)
Cirrhosis, *n* (%)	108 (33)
Portal hypertension, *n* (% of cirrhosis)	44 (41)
Liver decompensation, *n* (% of cirrhosis)	15 (14)
Hepatocellular carcinoma, *n* (%)	4 (1.2)

HEPATITIS DELTA REGISTRO

n=329 patients with CHD and active follow-up

33% had cirrhosis at diagnosis

After a median FU of 6 years +12% of those **HDV RNA +** progressed to cirrhosis



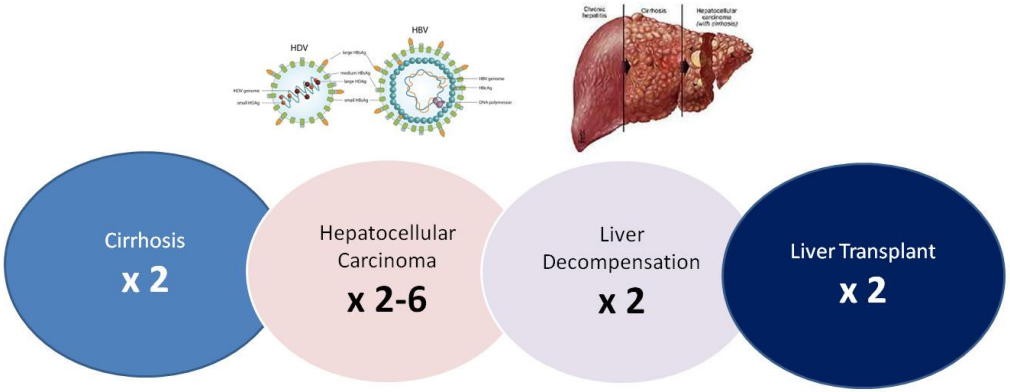
PH: portal hypertension

1/3 of patients = late diagnosis
HDV RNA is associated to disease progression

Roríguez-Tajes et al. Gastroent Hepatol 2024

A quién tratar?

- En todos los pacientes debería considerarse iniciar tratamiento antiviral



Kamal H et al. J Viral Hep 2021;28:1431–1442.

- Considerar el grado de la enfermedad hepática y potenciales contraindicaciones
- Análisis (parámetros función hepática, transaminasas, parámetros virológicos)
- Pruebas de imagen (elastografía, ecografía)

Riesgo de progresión fibrosis hepática

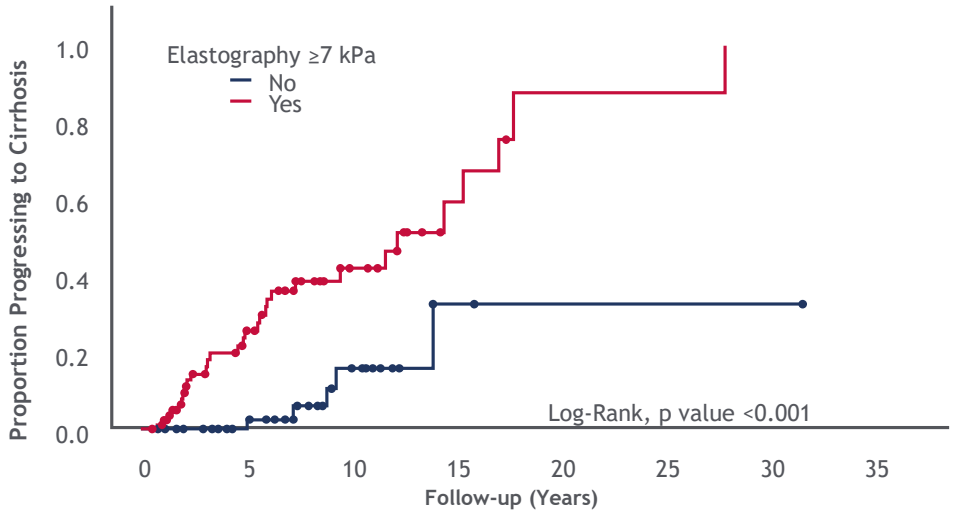
Retrospective, multicenter*, study of 177 F0–F2 patients with HDV

Table 1. Baseline characteristics

Variable	n=177
Sex (female)	84 (48%)
Age (years)	38 (31-45)
BMI > 30 kg/m^2	18 (15%)
Diabetes Mellitus	6 (3%)
Anti-HIV	7 (4%)
Anti-HCV	16 (9%)
Liver Biopsy	81 (46%)
F0-1 F2	41 (50%) 40 (50%)
TE-LSM (Kpa) n=156	7.7 (6-9)

Liver tests	n=177
AST (IU/L)	48 (36-69)
ALT (IU/L)	67 (42-112)
GGT (IU/L)	34 (23-64)
INR	1.08 (1-1.1)
Albumin (g/dl)	4.1 (3.9-4.3)
Platelets (10^9/L)	192 (152-233)
Viral parameters	
HBeAg+	20 (11%)
qHDV-RNA log^{10} IU/mL	5.6 (4-7)
Antiviral Therapy	
Previous IFN therapy	22 (12%)

Survival curve for cirrhosis according to baseline LSM greater than (gt) 7 kPa or not

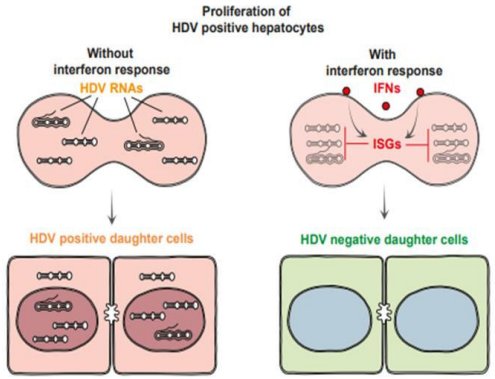


1 out of 5 HDV patients with mild-to-moderate fibrosis at BL are at high risk of progression to cirrhosis, with TE-LSM ≥7 kPa at BL being a significant predictor

S Lens AASLD 2024

Opciones terapéuticas

	Análogos nucleós(t)idos	Peg-IFN alfa
Recomendación	ADN VHB > 2000 IU/mL Fibrosis significativa Todos?	Pacientes ARN VHD+ Revisar contraindicaciones Regular tolerancia
Duración	Hasta negativización HBsAg	48 semanas
Limitaciones	Sin eficacia directa contra VHD	Contraindicaciones: cirrosis avanzada, enf autoinmunes, psiquiátricas.. Ef adversos hematológicos Recaídas tardías Eficacia limitada

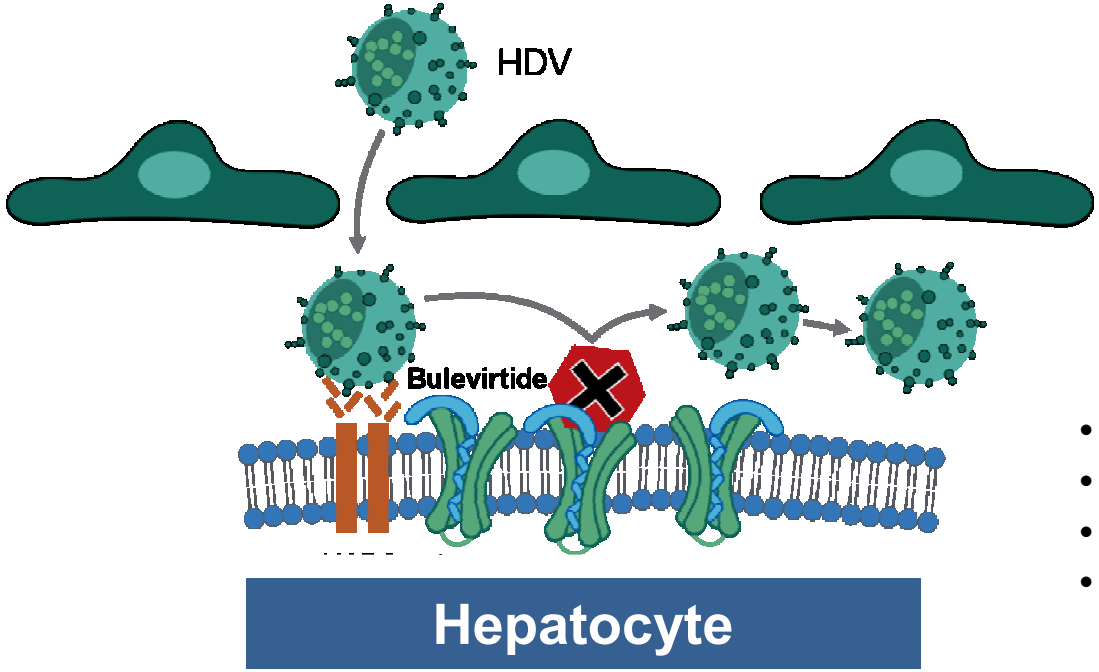


Effects of IFN in HDV infection:

- Viral entry
- Viral replication
- HDV spread
- Innate and adaptive immune responses

Zhang et al. J Hepatol 2022

Opciones terapéuticas

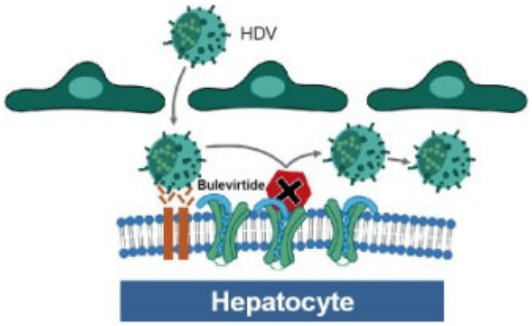


- Blocks NTCP receptor
- 2 mg, subcutaneous, daily injection
- Conditional approval by EMA in Jul/20
- Reimbursed in Spain since Feb/24

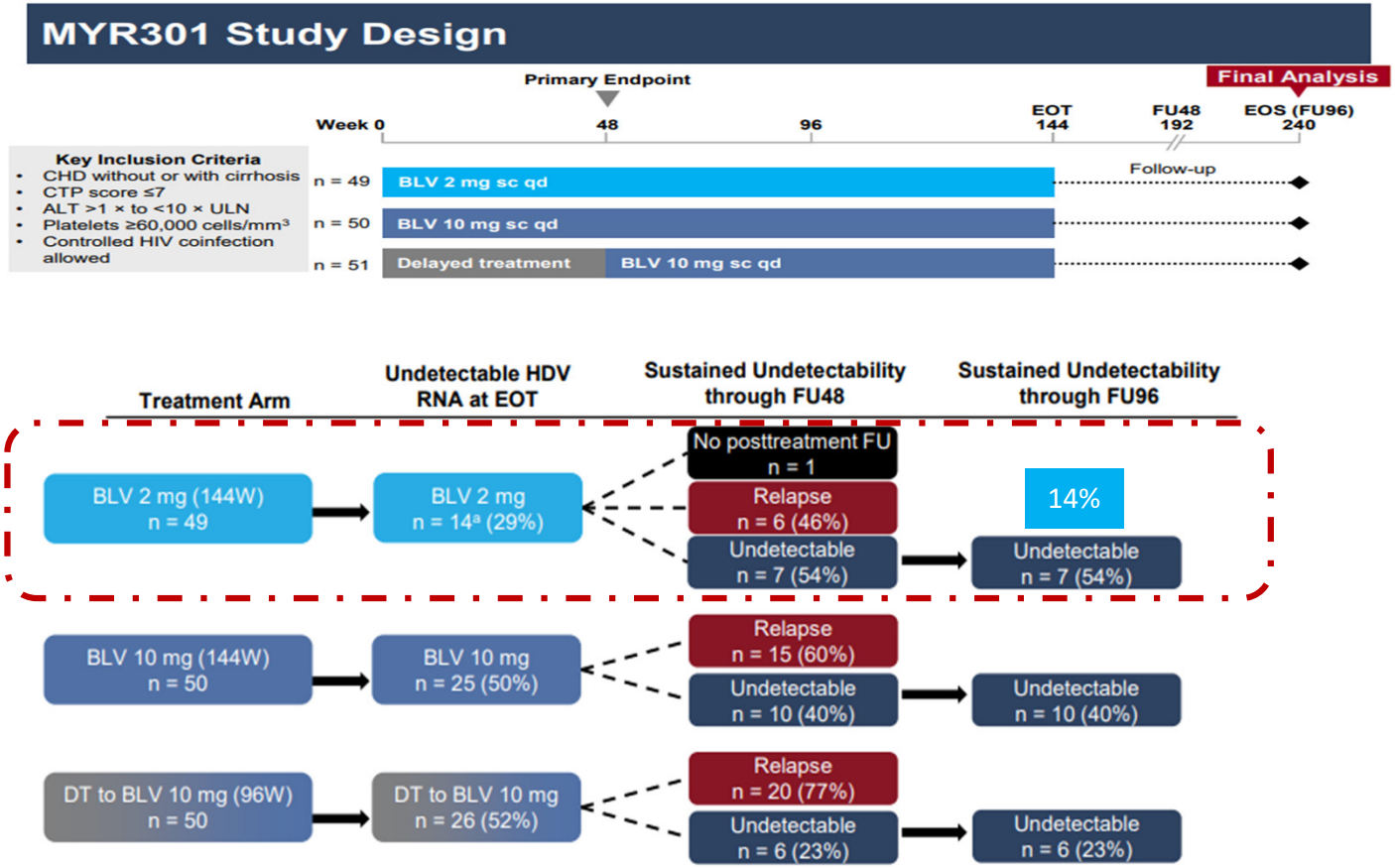
1. Kang C, Syed YY. Bulevirtide: first approval. Drugs. 2020;80:1601-1605. **2.** Alweiss L, *et al.* Journal of Hepatology 2024. **3**. Ficha técnica HEPCLUDEX®. Disponible en: https://ftgileadspain.com/filesRepositorio/68/Hepcludex_FT.pdf. **4.** https://www.sanidad.gob.es/profesionales/medicamentos.do?metodo=verDetalle&cn=732023. **5.** EMA. https://cima.aemps.es/cima/pdfs/ipe/1201446001/IPE_1201446001.pdf.

Opciones terapéuticas

	Análogos nucleós(t)idos	Peg-IFN alfa	Bulevirtide
Recomendación	ADN VHB > 2000 IU/mL Fibrosis significativa	Pacientes ARN VHD+ Revisar potenciales contraindicaciones Regular tolerancia	Pacientes ARN VHD+ **F2 o más, NR o intolerantes a Peg-IFN** **Cirrosis compensada** Buena tolerancia Con/sin VIH+
Duración	Hasta negativización HBsAg	48 semanas	Mientras dure beneficio clínico? 3 años?
Limitaciones	Sin eficacia directa contra VHD	Contraindicaciones: cirrosis avanzada, enf autoinmunes, psiquiátricas.. Ef adversos Recaídas tardías Eficacia limitada	Sin efecto en HBsAg Reglas parada? Duración óptima? Elevación ARN VHD (y ALT) tras stop Combinación Peg-IFNa? 2mg o 10 mg?



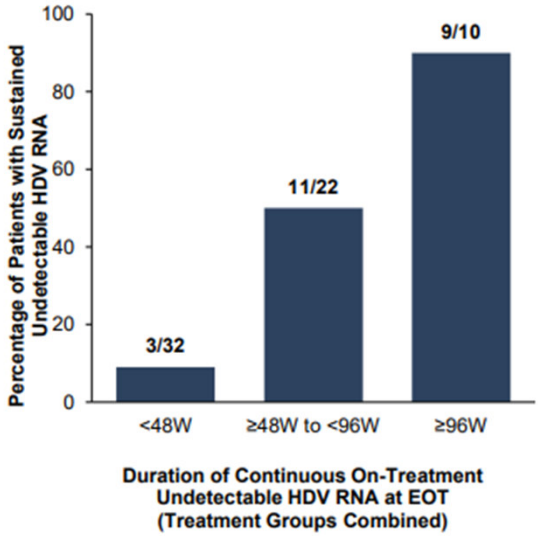
BLV monoterapia



93% (38/41) of relapses occurred within 24 weeks after EOT

50% cirrosis, 50% NR a PegIFN

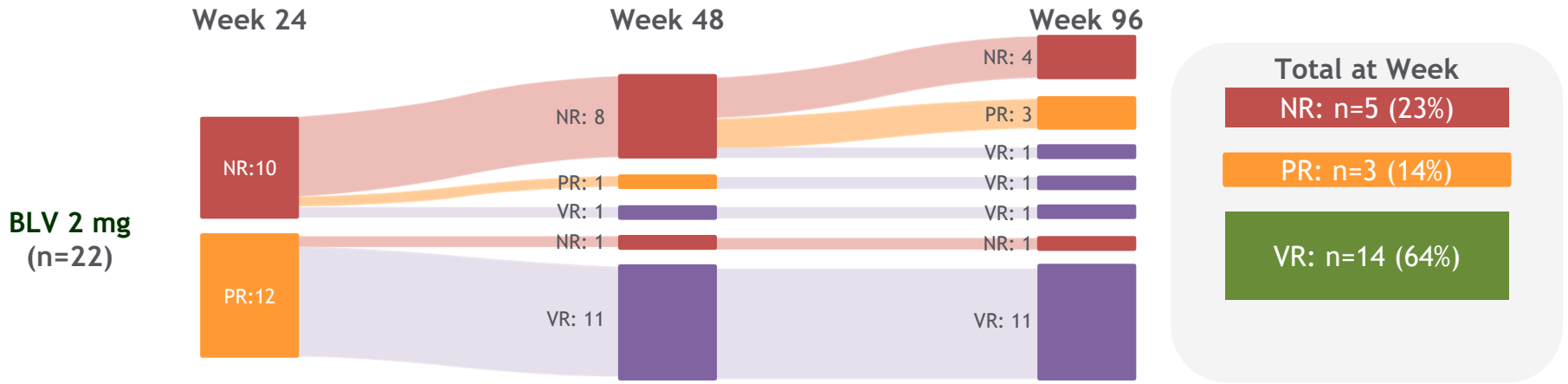
Respuesta combinada: ↓2log ARN-VHD o UND & normalización ALT (50% a las 48 sem)



Wedemeyer H, et al. EASL 2025

BLV monoterapia

Week 24 NR and PR treatment response through Week 96



Virologic response (**VR**): Undetectable HDV RNA or ≥2 log_{10} IU/mL decline from BL

Virologic partial response (**PR**): HDV RNA decline of ≥1 but <2 log_{10} IU/mL from BL

Virologic nonresponse (**NR**): HDV RNA decline of <1 log_{10} IU/mL from BL

Most early PR and NR at Week 24 experience virologic response with continued BLV therapy

Early suboptimal virologic response was defined as nonresponse or partial response at Week 24.
BL, baseline; BLV, bulevirtide; NR, virologic nonresponder; PR, partial virologic responder; VR, virologic responder; W, week.
Lampertico P, et al. AASLD 2023. Oral #63

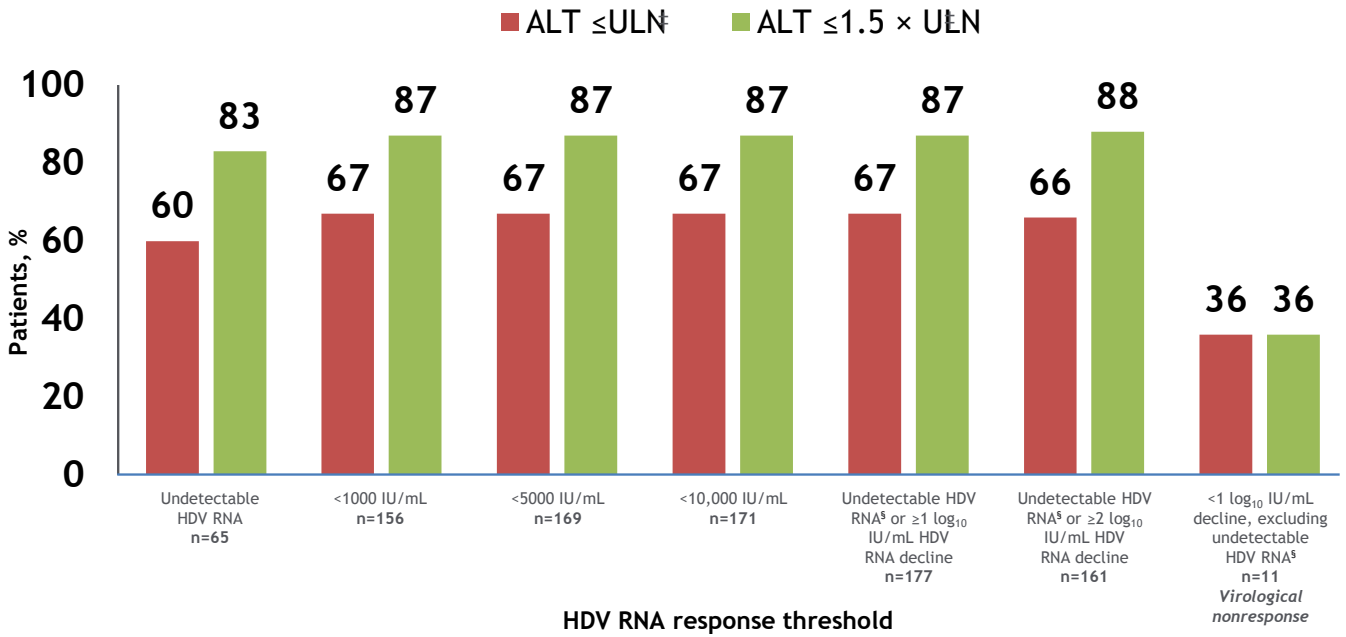
BLV monoterapia

Pooled analysis of patients with HDV from Phase 2 MYR204[2] and Phase 3 MYR301[3,4] trials

Baseline characteristics

Variable	BLV 2 mg + 10 mg* n=190
Age, mean years (SD)	42 (8)
Male, n (%)	120 (63)
Cirrhosis, n (%)	84 (44)
HBeAg positive, n (%)	22 (12)
HDV RNA, log_{10} mean IU/mL (SD)	5.2 (1.3)
Previous IFN therapy, n (%)	99 (52)
Concomitant HBV NA treatment, n (%)	110 (58)
ALT, mean U/L (SD)	109 (81)
Baseline ALT category, n (%)†	
≤ULN‡	14 (7)
>ULN‡ to ≤1.5 × ULN‡	34 (18)
>1.5 × ULN‡	142 (75)

ALT Improvement at W96 by virologic response†



BLV treatment led to ALT improvement regardless of virologic response

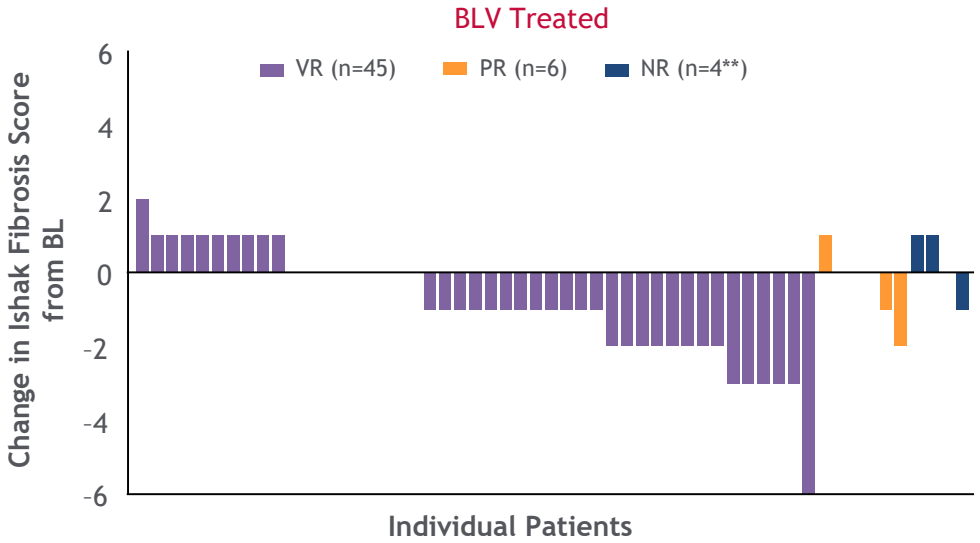
BLV 2 mg is the only approved dose, BLV 10 mg is off-label. *BLV 2 mg (n=47), BLV 10 mg (n=143); †Key eligibility criteria included positive HDV RNA and ALT between 1 and 10 × ULN. Despite this criteria, some patients had ALT ≤ULN. Two patients did not have HDV RNA results at Week 96; ‡ALT ULN: ≤31 U/L for females and ≤41 U/L for males (Russian sites) and ≤34 U/L for females and ≤49 U/L for males (all other sites); §Undetectable HDV RNA is defined as less than the LLOQ (50 IU/mL) with target not detected, LOD = 6 IU/mL.
ALT, alanine aminotransferase; BLV, bulevirtide; HBsAg, hepatitis B surface antigen; IFN, interferon; LLOQ, lower limit of quantification; LOD, limit of detection; NA, nucleos(t)ide analogue; SD, standard deviation; ULN, upper limit of normal; W, week.

1. Lampertico P, et al. AASLD 2024. Poster #1172; 2. Asselah T, et al. N Engl J Med 2024;391:133–43. 3. Wedemeyer H, et al. N Engl J Med 2023;389:22–32; 4. Wedemeyer H, et al. J Hepatol 2024;81:621–29.

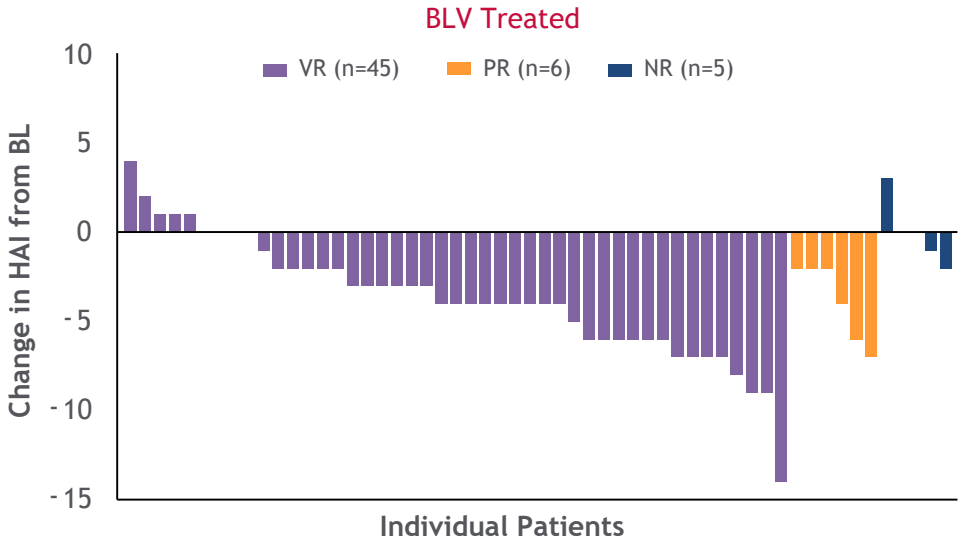
BLV e impacto en fibrosis

Paired biopsy analysis of chronic HDV patients treated with BLV 2 mg or 10 mg (n=56*) over 48 weeks

Change in Ishak Fibrosis Score by Viral Response at W48



Change in HAI by Viral Response at W48



Virologic response (VR): Undetectable HDV RNA or ≥2 $\log_{10}$ IU/mL decline from BL to W48

Virologic partial response (PR): HDV RNA decline of ≥1 but <2 $\log_{10}$ IU/mL from BL to W48

Virologic nonresponse (NR): HDV RNA decline of <1 $\log_{10}$ IU/mL from BL to W48

Treatment with BLV improved fibrosis score and histology

Lampertico P, et al. EASL 2024. Poster #WED-392

Allweiss et al. J Hepatology 2024

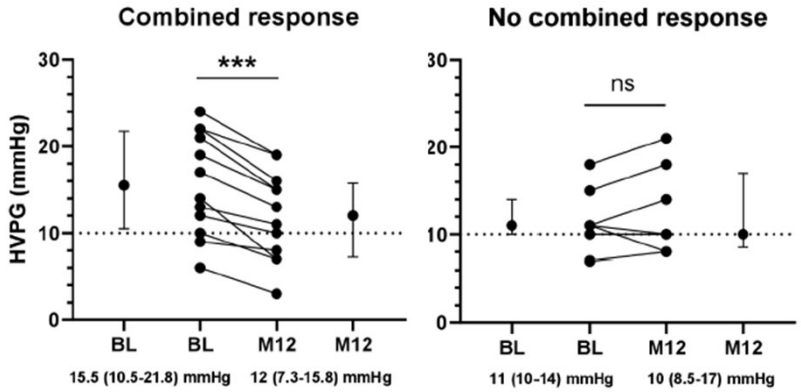
Hipertensión Portal

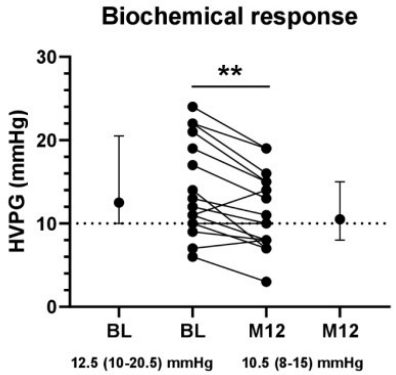
N=20 HVPG pre- and 12Mo post-BLV

	Total cohort (n=20)		
	Baseline	M12	p value
Male	13 (65)		
Age (years)	48 (41.3-57.0)		
BMI (kg/m²)	25.8 (22.3-29.0)		
HDV RNA (log_{10} IU/ml)	4.45 (3.35-5.57)	1.21 (0.21-2.21)	<0.001
HBV DNA (IU/ml)	10 (2.5-20)	0 (0-10)	0.015
HBsAg (IU/ml)	4.14 (3.67-4.33)	4.0 (3.57-4.19)	0.004
AST (U/L)	70 (47-148)	41 (30-62)	0.001
ALT (U/L)	72 (62-117)	33 (23-45)	<0.001
Bilirubin (µmol/L)	16 (13-23)	16 (9-28)	0.896
Creatinine (µmol/L)	66 (54-82)	71 (51-85)	0.401
Albumin (g/L)	36.9 (33-40)	37.5 (34.8-42)	0.064
gGT (U/L)	55 (34-91)	34 (19-51)	<0.001
Platelets (x1000/µl)	80 (39-109)	62 (39-125)	1.0
INR	1.3 (1.2-1.4)	1.3 (1.2-1.5)	0.900
Bile acids (µmol/L)	22 (6-46)	36 (20-61)	0.001
MELD	10 (9-12)	10 (9-13)	0.524
Child Pugh Score			1.0
A	17 (85)	17 (85)	
B	3 (15)	3 (15)	
LSM (kPa)	24 (13.5-28.5)	13.5 (9.0-22.7)	<0.001
HVPG (mmHg)	12.5 (10-18.8)	10.5 (8-15.8)	0.013
PH	20 (100)	19 (95)	1.0
CSPH	17 (85)	14 (70)	0.248

12 (60%)

HVPG response -2.5 (-4, 0) mmHg, 70% HVPG decline



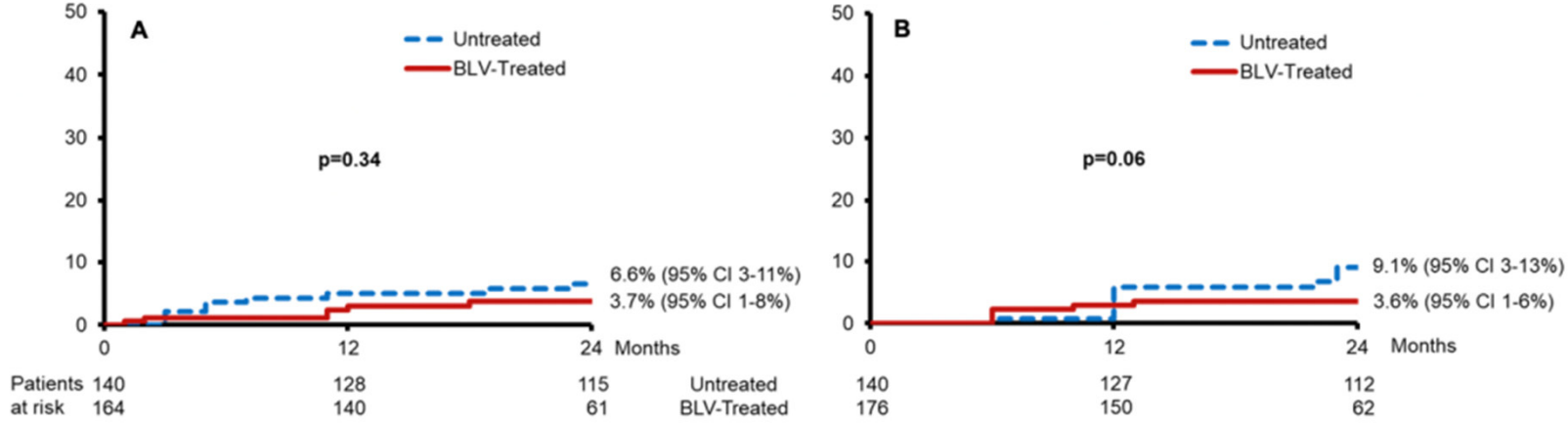


16 (80%)

Sandmann L, et al. EASL 2025

Prevención descompensación

Figure 1. 2-Year Cumulative Incidence of De-novo HCC (A) and Decompensation (B)



No liver decompensations occurred among baseline CPT-A5 patients in the BLV-Treated cohort *vs.* 9.2% in the Untreated cohort (p=0.003)

By inverse probability of treatment weighting analysis adjusted for confounding baseline factors and competing mortality risks, the BLV-treated cohort had a significantly decreased risk of all-type liver-related events (HR 0.38; 95% CI 0.23-0.62, p<0.0001) and decompensation (HR 0.32; 95% CI 0.16-0.63, p<0.0001) compared to untreated patients. Conversely, the HCC risk was similar in the two cohorts (HR 0.50; 95% CI 0.24-1.06, p=0.07) (**Table 2**).

Outcomes	Category	Unadjusted Cox Regression ANalysis		IPTW-Adjusted Cox Regression Analysis		IPTW-Adjusted Competing Risk 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

BLV: Bulevirtide; IPTW: Inverse Probability of Treatment Weighting; HR: Hazard Ratio; SHR: Sub-distribution Hazard Ratio; CI: Confidence Interval; HCC: Hepatocellular Carcinoma

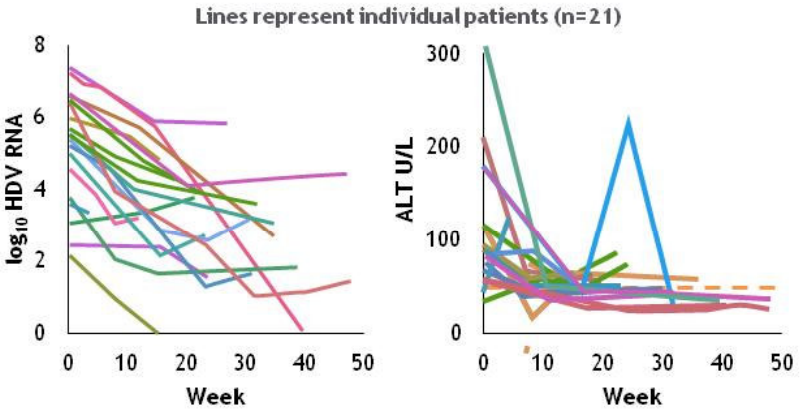
Degasperi E, et al. AASLD 2024 Poster #1166

Cirrosis descompensada

Retrospective, multicenter*, real-world analysis of BLV in 21 patients

Baseline Characteristic	Cohort (n=21)
Age (mean)	50.9 ± 9.6
Child-Pugh Stage, n (%)	
A	3 (14)†
B	17 (81)
C	1 (5)
Ascites, n (%)	12 (57)
Esophageal varices present, n (%)	15 (71)
Variceal bleeding history, n (%)	2 (10)
Bilirubin, median µmol/L (range)	30.8 (8.0–82.0)
Albumin, median g/L (range)	31 (28–51)
ALT median IU/L (range)	72 (31–307)

Efficacy Responses



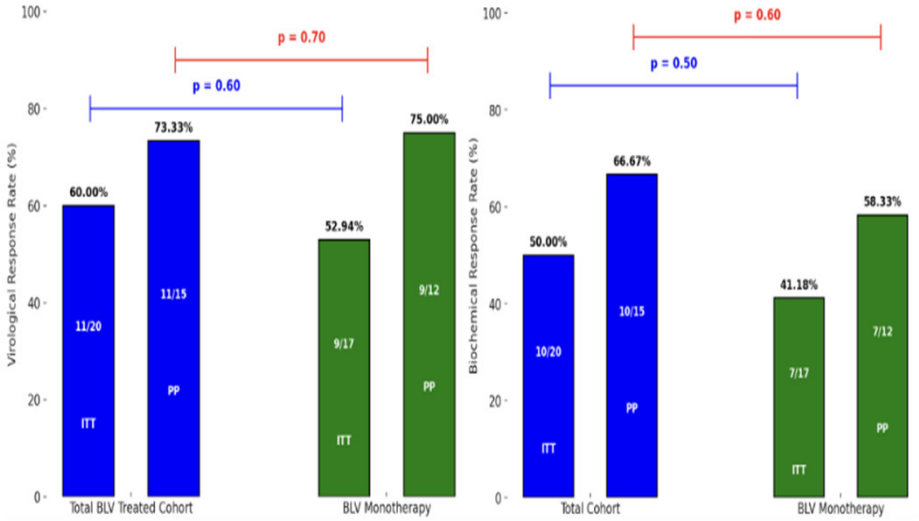
67%	14 of 21 patients had virologic response**
86%	18 of 21 patients had normal ALT
41%	7 of 17 patients improved from Child-Pugh B to A
50%	6 of 12 patients had improvement of ascites

*Centers in Austria, Italy, and Germany; **HDV RNA decline of ≥2 log; †Given presence of ascites in previous months, the patients were considered as decompensated following the Baveno VII recommendations. ALT, alanine aminotransferase; BLV, bulevirtide; RWD, real-word data.

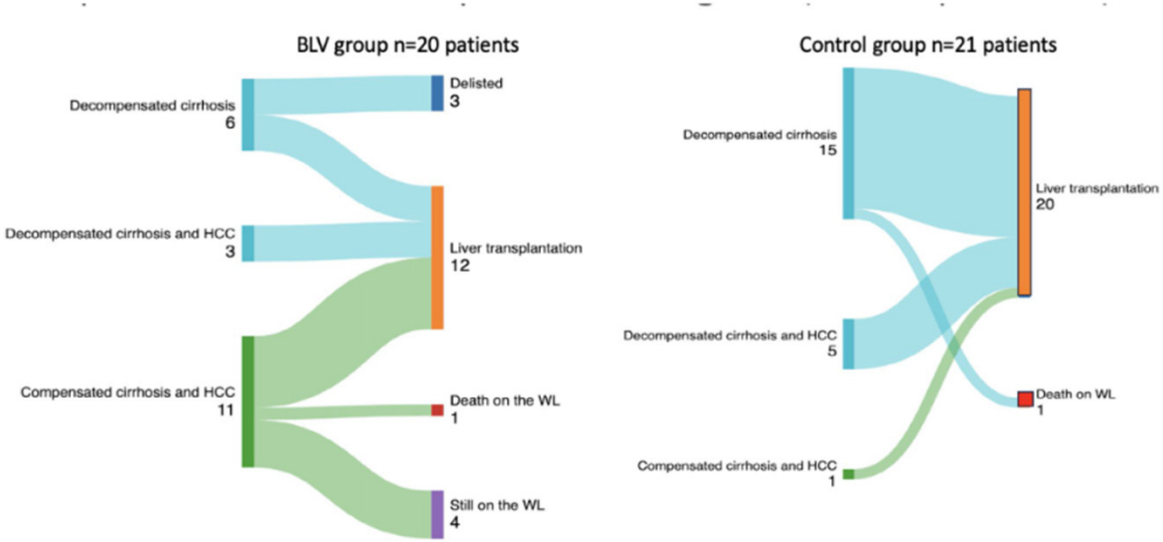
Dietz-Fricke C, et al. DeltaCure 2023. Poster #43
J Hep Reports 2024

Lista de espera de TH

Efficacy while on the waiting list



Outcomes while on the waiting list

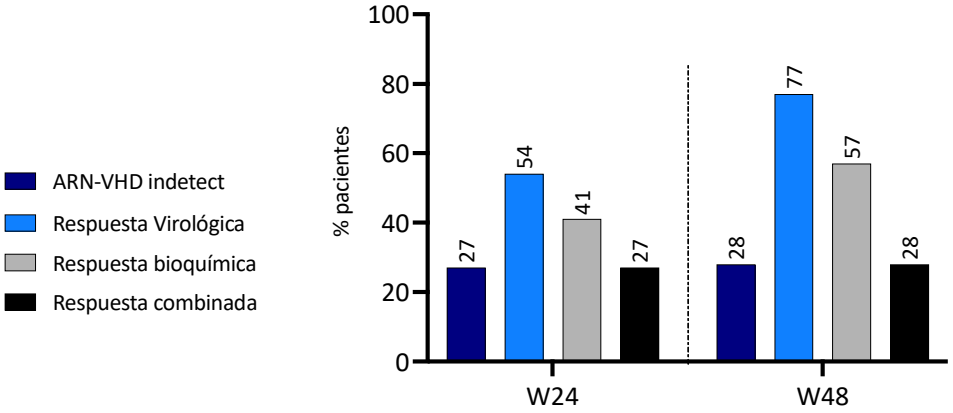


Meszaros M, et al. Liver Int 2025

BLV datos vida real España

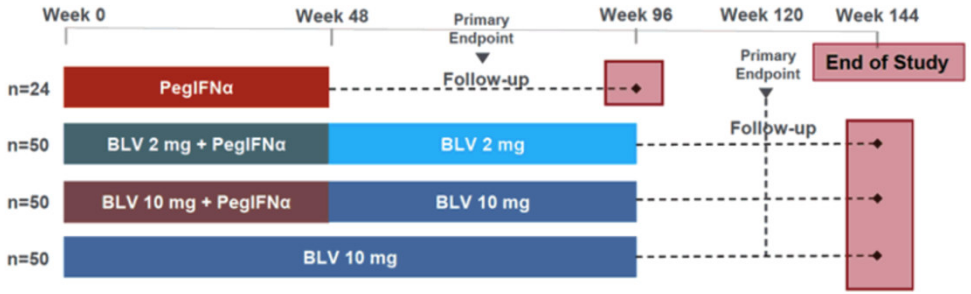
Variable	Inicio BLV n=57
Edad (años)	53 (42-57)
Sexo (mujer)	14 (25%)
Origen (España)	23 (40%)
UDVP	8 (14%)
VHC, VIH	6 (10%), 3 (5%)
Elastografía Hepática (kPa)*	18 (11-22)
Cirrosis	42 (70%)
Varices Esofágicas	17/21 (80%)
Descompensación / HCC	Ascitis (2), HDA (2), HCC (1)
AST UI/L	60 (43-93)
ALT UI/L	69 (54-106)
ALT > 2 LSN	22 (39%)
Bi (mg/dl)	0.7 (0.6-1)
Albúmina (g/dl)	4.1 (3.7-4.4)
Plaquetas (x10^9)	143 (91-261)

Efectos Adversos
Eritema (2)
Cefalea (2)
Astenia (1)
Prurito (1)
HCC (1)
TOH (1)



Palom A,.., Lens S, et al. AEEH 2025

BLV + PegIFN

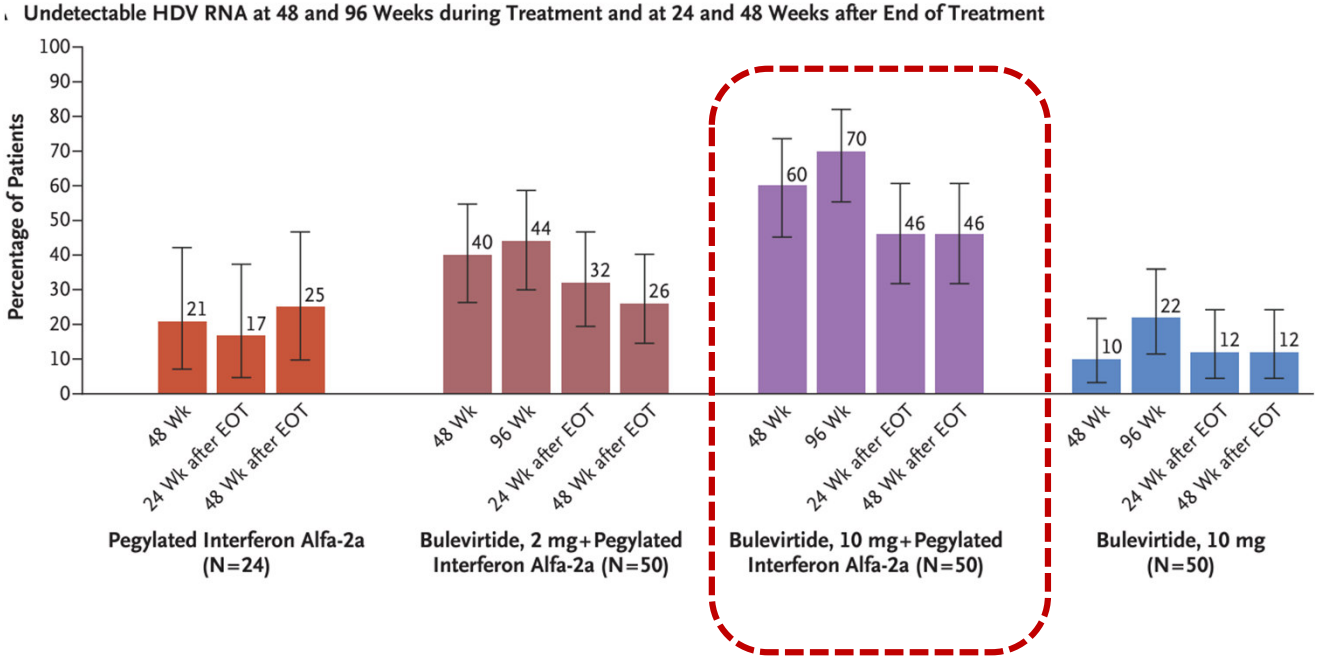


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bulevirtide Combined with Pegylated Interferon for Chronic Hepatitis D

T. Asselah, V. Chulanov, P. Lampertico, H. Wedemeyer, A. Streinu-Cercel, V. Păntea, S. Lazar, G. Placinta, G.S. Gherlan, P. Bogomolov, T. Stepanova, V. Morozov, V. Syutkin, O. Sagalova, D. Manuilov, R.-C. Mercier, L. Ye, B.L. Da, G. Chee, A.H. Lau, A. Osinusi, M. Bourliere, V. Ratziu, S. Pol, M.-N. Hilleret, and F. Zoulim



Asselah T, et al. NEJM 2024

BLV, PegIFN o ambos?

	Bulevirtide monoterapia	Bulevirtide+ PegIFNa
Ventajas	•Autorizado por ficha técnica EMA (2mg/d sc) •Buena tolerancia •50% respuesta combinada sem 48 •Bajo % ARN VHD UND post EOT	•No autorizado por EMA •Datos vida real en otros países •Aumento posibilidad de ARN VHD neg y mayor efecto sobre VHB
Inconvenientes	•Administración diaria •Preparación de la medicación •Sin efecto en HBsAg •Baja tasa ARN VHD neg •Duración?	•Predictores de respuesta, duración y dosis todavía en análisis •Selección de pacientes •Ef secundarios / Ajuste dosis PegIFN •Inyecciones diarias y semanales •Disponibilidad?

Conclusiones

- Debemos cribar de Hepatitis Delta a todos las personas HBsAg+, el test reflejo es una herramienta eficaz para incrementar las tasas de cribado. En caso de factores de riesgo o incremento ALT repetir test.

- Todos los pacientes con infección activa (ARN-VHD+) son candidatos a recibir tratamiento antiviral. Debemos usar técnicas diagnósticas sensibles.

- El tratamiento con Bulevirtide monoterapia presenta un buen perfil de seguridad y tolerancia (incluso en caso de hepatopatía avanzada) y hasta un 50% respuesta combinada al año de tratamiento. Algunos pacientes logran la curación del VHD tras 3 años de tratamiento.

- Perspectivas futuras: duración óptima? Adición Peg-IFN? Impacto en la enfermedad hepática y QoL? Nuevas terapias contra VHD (y VHB)?

Muchas gracias!

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