Hepatitis D, la hepatitis olvidada

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Disclosures

Maria Buti, MD, FAASLD, has a financial interest/relationship or affiliation in the form of:

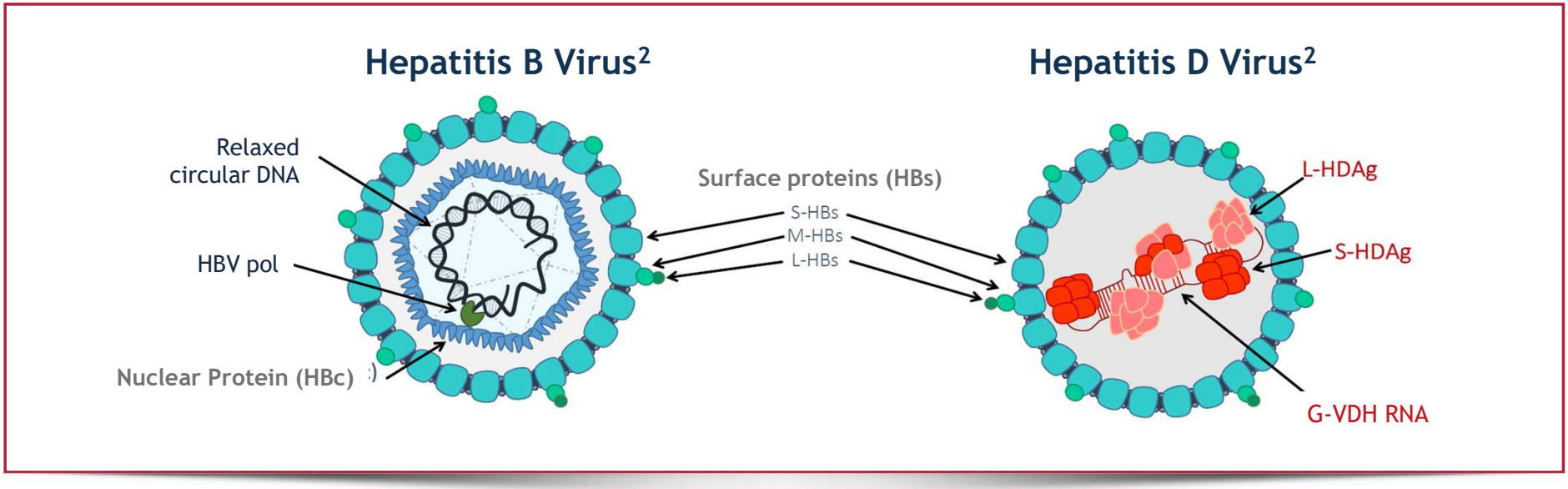
Speakers Bureau participant with AbbVie Inc. and Gilead Sciences, Inc.

Advisory Board for AbbVie Inc.; Altimmune, Inc; Assembly Biosciences, Inc.; Gilead Sciences, Inc.; GlaxoSmithKline plc.; and Janssen Inc.

¿Cuál es la hepatitis viral más agresiva… y la menos diagnosticada?

- 1-Hepatitis B
- 2.- Hepatitis C
- 3.- Hepatitis D
- 4. Hepatitis E

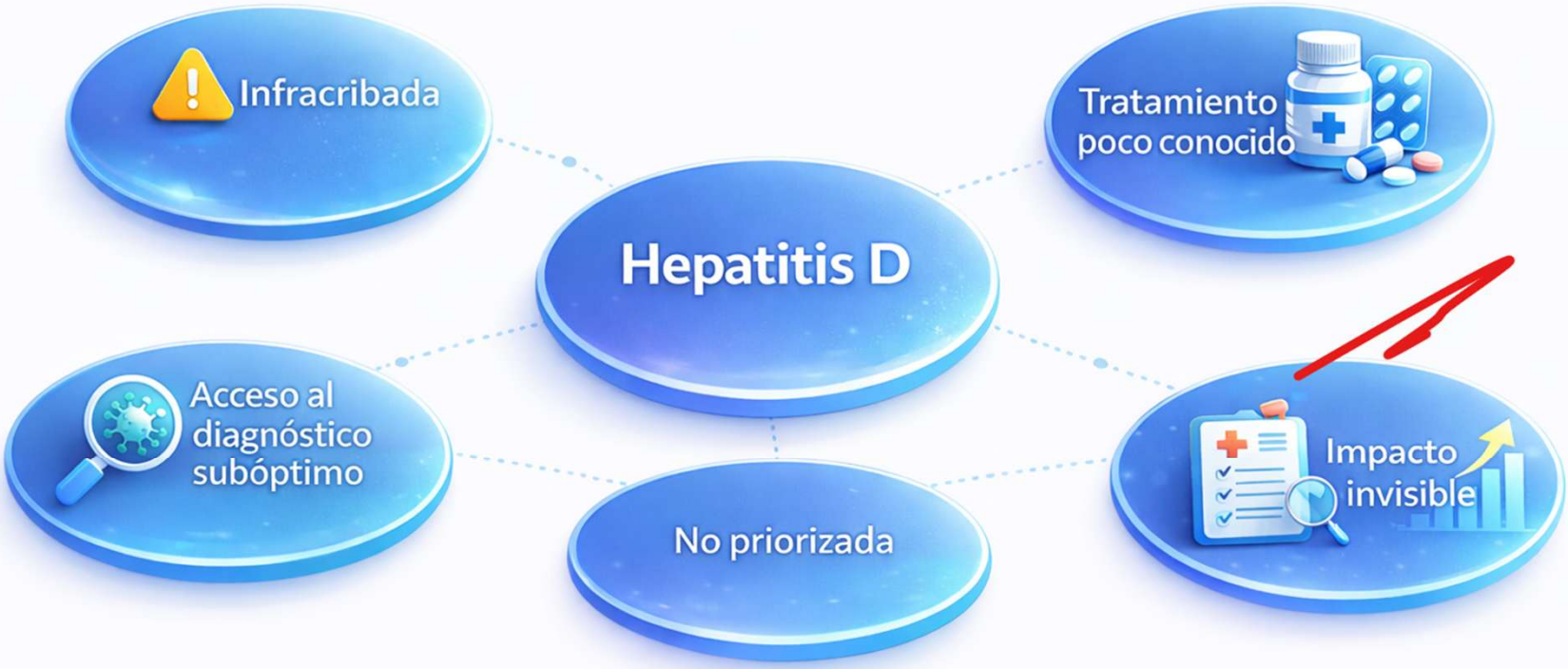
El Virus de la Hepatitis B y el olvidado Virus de la Hepatitis D



- El virus de la hepatitis B es el segundo carcinógeno después del tabaco.[3]
- El VHD precisa de la presencia del VHB para infectar y terminar la replicación. [4-6]

- **1.** Levrero & Zucman-Rossi, J Hepatol 2016;64(S1):S84-S101. **2.** Lucifora J, et al. Current knowledge on Hepatitis Delta Virus replication. Antiviral Res. 2020;179:104812. **3.** Risk of developing cancer-comparison of HBV, HCV and smoking. Razavi, Journal of Hepatology 2023 78:S934-S935 **4.** Hughes SA, et al. Hepatitis delta virus. Lancet. 2011;378(9785):73-85. **5.** Koh C, et al. Gastroenterology. 2019;156(2):461-476.e1 5. Stockdale AJ, et al. J Hepatol. 2020;73(3):523-32. **6.** Lempp FA, et al. Viruses. 2017;9(7):172.

La hepatitis D, la gran olvidada



¿Por qué importa? La gravedad clínica

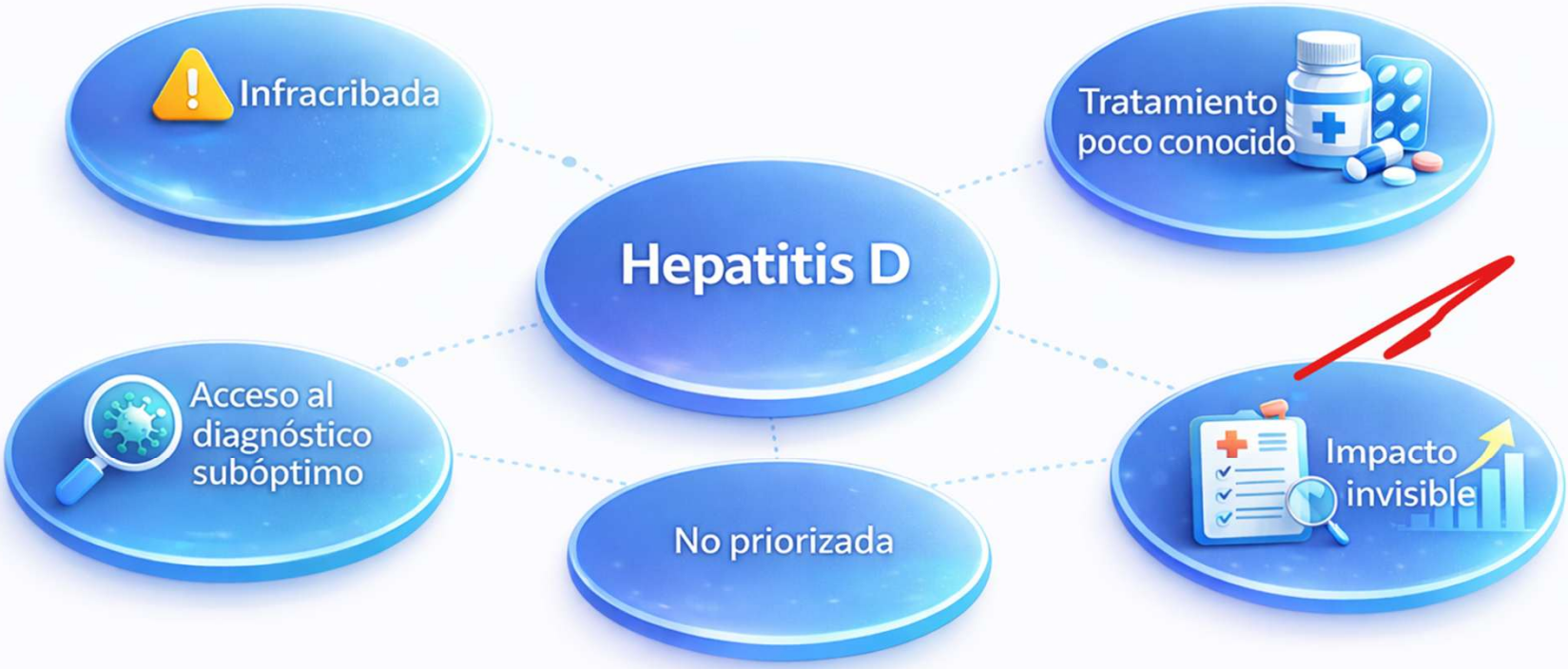
- La hepatitis crónica D presenta un **progresión de la enfermedad** más rápida que la mono-infección por hepatitis B.

El 75% de los pacientes con hepatitis crónica D desarrollarán una cirrosis hepática → 15 años

"El virus de la hepatitis D convierte una Hepatitis B estable en una enfermedad agresiva."

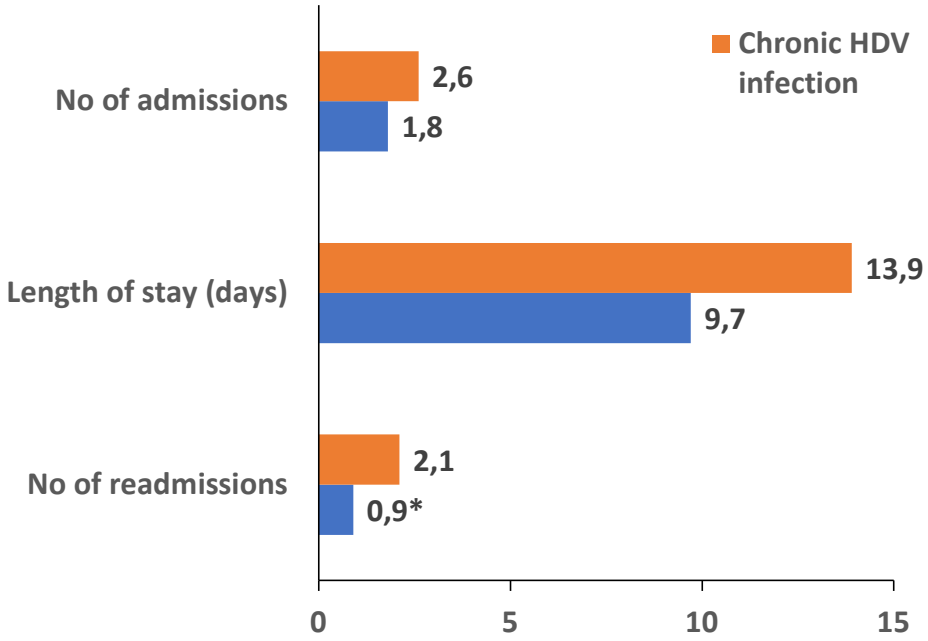
Da *et al. Gastroenterol Rep*. 2019 | Miao *et al. J Infect Dis*. 2020 | Hercun *et al. Gastroenterol Clin North Am*. 2020

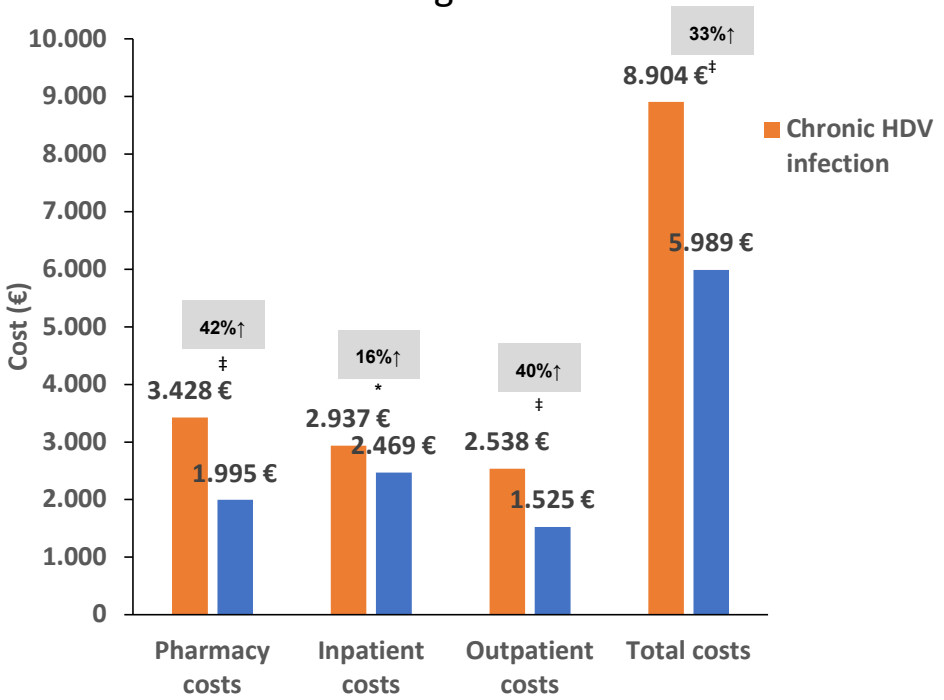
La hepatitis D, la gran olvidada



Utilizacion de Recursos del Cuidado de la Salud por paciente y año post diagnóstico

Retrospective cohort study used the Spanish National Health System's Hospital Discharge Records Database between 2001 and 2018 and followed for 12 months before and after the index diagnosis date.





CHD infection is associated with substantially higher HCRU and costs compared with CHB in Spain

Hepatitis D no solo es clínicamente más grave, también es económicamente más costosa."

Factores de riesgo de progresión en hepatitis D crónica

Pacientes con Hepatitis D crónica **con mayor riesgo de progresión hepática** [1,2]

ALT y gammaGT elevada[1]

Persistencia de la viremia por VHD[1]

Enfermedad hepática avanzada[1]

Fibroscan ≥ 7Kpa[2]

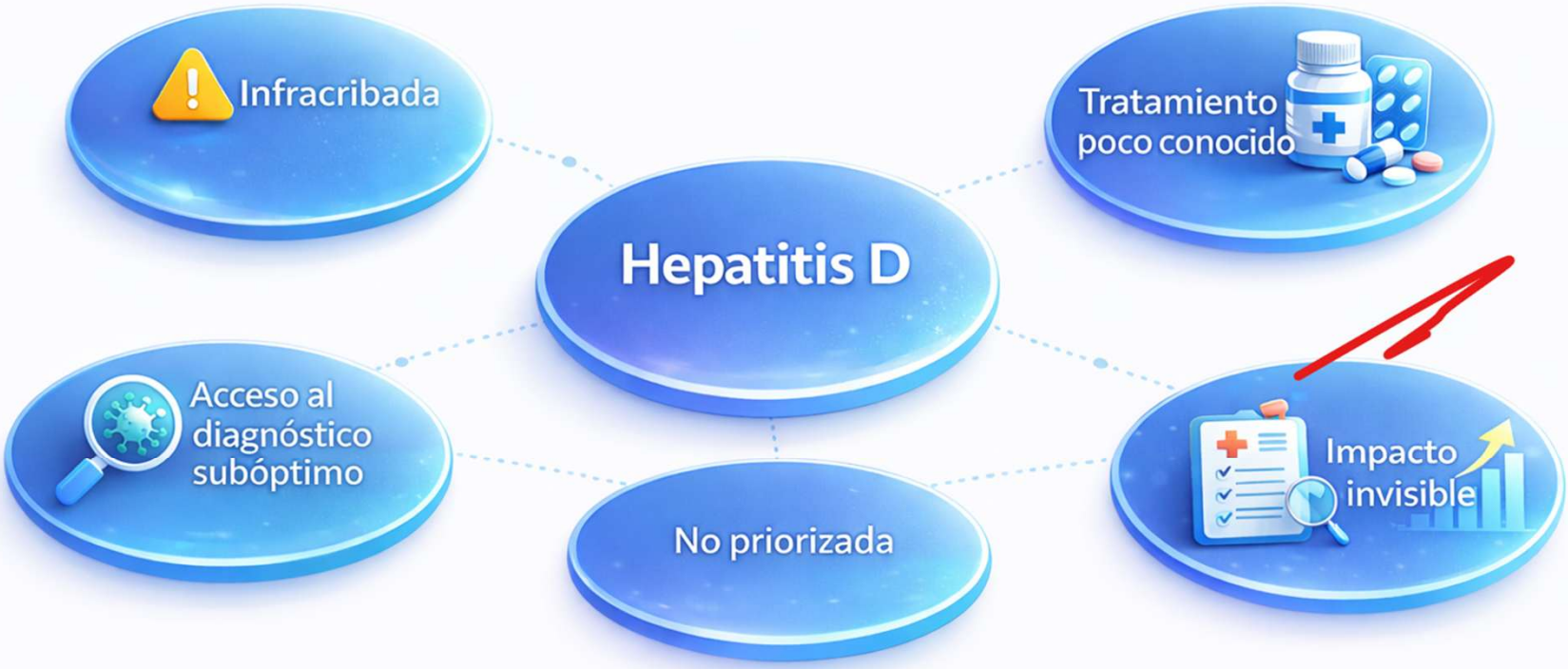
Consumo de alcohol, obesidad y diabetes[1]

Coinfecciones virales, ej. VIH[1]

Es critico la identificación precoz de las personas con mayor riesgo de progresión

1. EASL. EASL Clinical Practice Guidelines on hepatitis delta virus. J Hepatol. 2023;79(2)433-460. **2.** Lens AASLD 2024 poster 1155

La hepatitis D, la gran olvidada



Las guías recomiendan el cribado del VHD en todas las personas HBsAg positivo[1]

World Health Organization 2024

EASL The Home of Hepatology 2023

AEEH AEHVE seimc SEPD GEHEP 2022

EASL The Home of Hepatology 2023

¿A quién se debe cribar? [1]

- Todos los **individuos HBsAg+** al menos una vez en su vida.
- En individuos con HBsAg+ **repetir siempre que esté clínicamente indicado**, como por ejemplo ALT Flares
- **Anualmente** en pacientes **en riesgo de infección**

¿Qué pruebas deben realizarse? [1]

- Determinación **Anti-VHD**
- **Realizar ARN-VHD** en caso de anticuerpo positivo
- Disponer de **al menos 2 determinaciones** de **ARN negativas** para descartar infección activa.

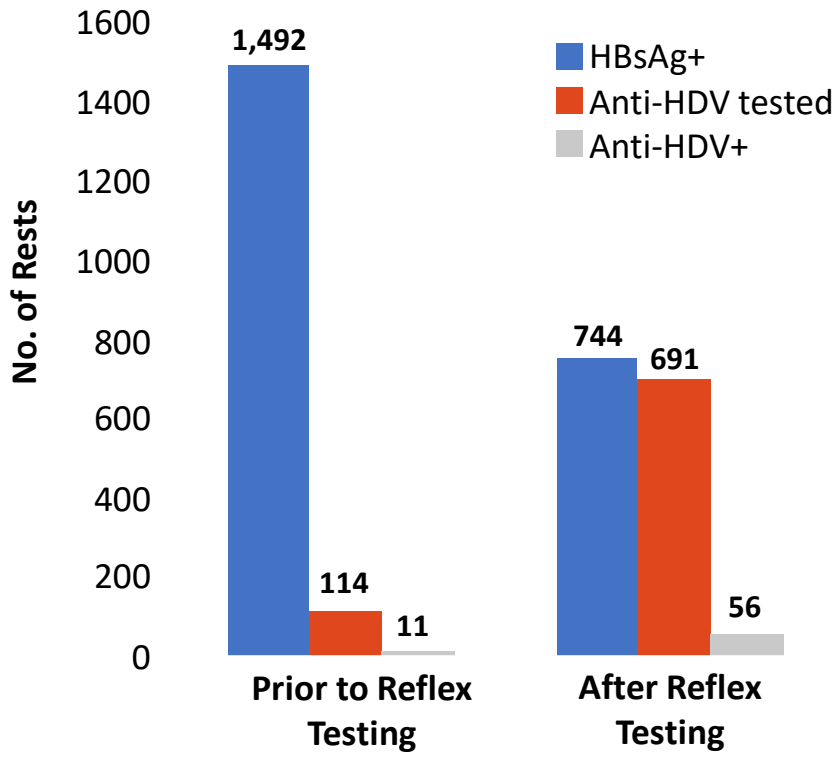
Sin embargo, la adherencia a estas recomendaciones es heterogénea.

Ag: antígeno; **ARN**: ácido ribonucleico; **HBsAg**: antígeno de superficie de la hepatitis B (por sus siglas en inglés); **VHD**: virus de la hepatitis D.

1. EASL. EASL Clinical Practice Guidelines on hepatitis delta virus. J Hepatol. 2023;79(2)433-460.

Test reflejo de la Hepatitis D en personas HBsAg positivo

- Retrospective of HDV screening implementation
- Only 8% of screening
- Anti-HDV reflex testing resulted in a **5-fold increase** in HBV cases diagnosed with HDV
- 60% of anti-HDV and HDV RNA–positive patients had **no HDV risk factors identified**



Palom. JHEP Rep. 2022;4:100547.

Prevalence of Hepatitis Delta Virus Infection in Galicia: Results of the Universal Implementation of Double Reflex Testing

Study population

All **chronic HBsAg carriers** who visited any hospital within the Galician health service during the period **between January 2023 and December 2024**

Methods and results

Delta double reflex testing:

HBsAg+ → **1962**

↓

Anti-VHD + → **85 +**

LIAISON® XL MUREX Anti-HDV Assay; Diasorin

↓

HDV viral load → **20 +**

Hepatitis Delta Real Time PCR Kit; Vircell

Outcomes

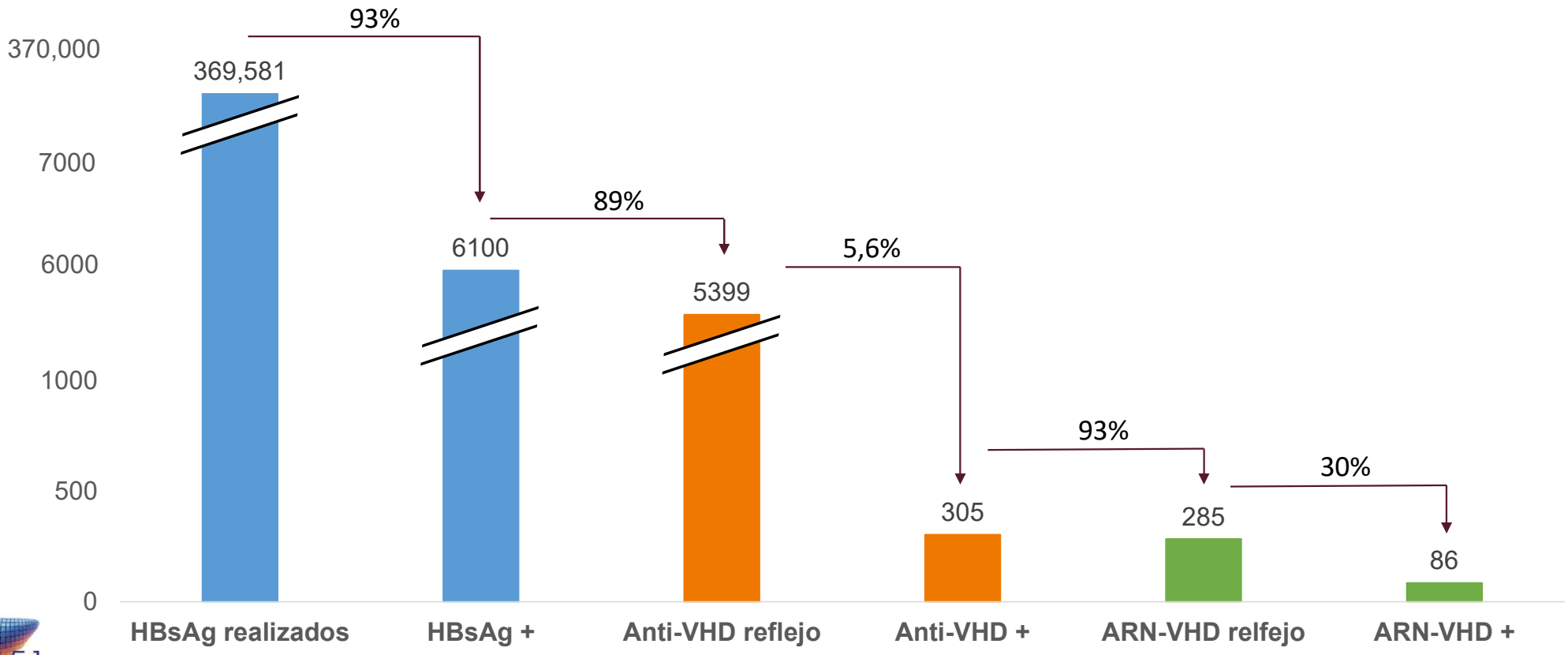
In our setting, the **seroprevalence of HDV in HBsAg carriers is 4,3%.** Despite the low prevalence, a significant proportion of patients have **active infection (23,5%),** which places them at risk of complications. Consequently, they could benefit from **early diagnosis and novel treatments** such as Bulevirtide.

Carracedo, et al.

Revista Española de Enfermedades Digestivas (REED)
The Spanish Journal of Gastroenterology

Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

Programa de Cribado y atención de la hepatitis D en Cataluña

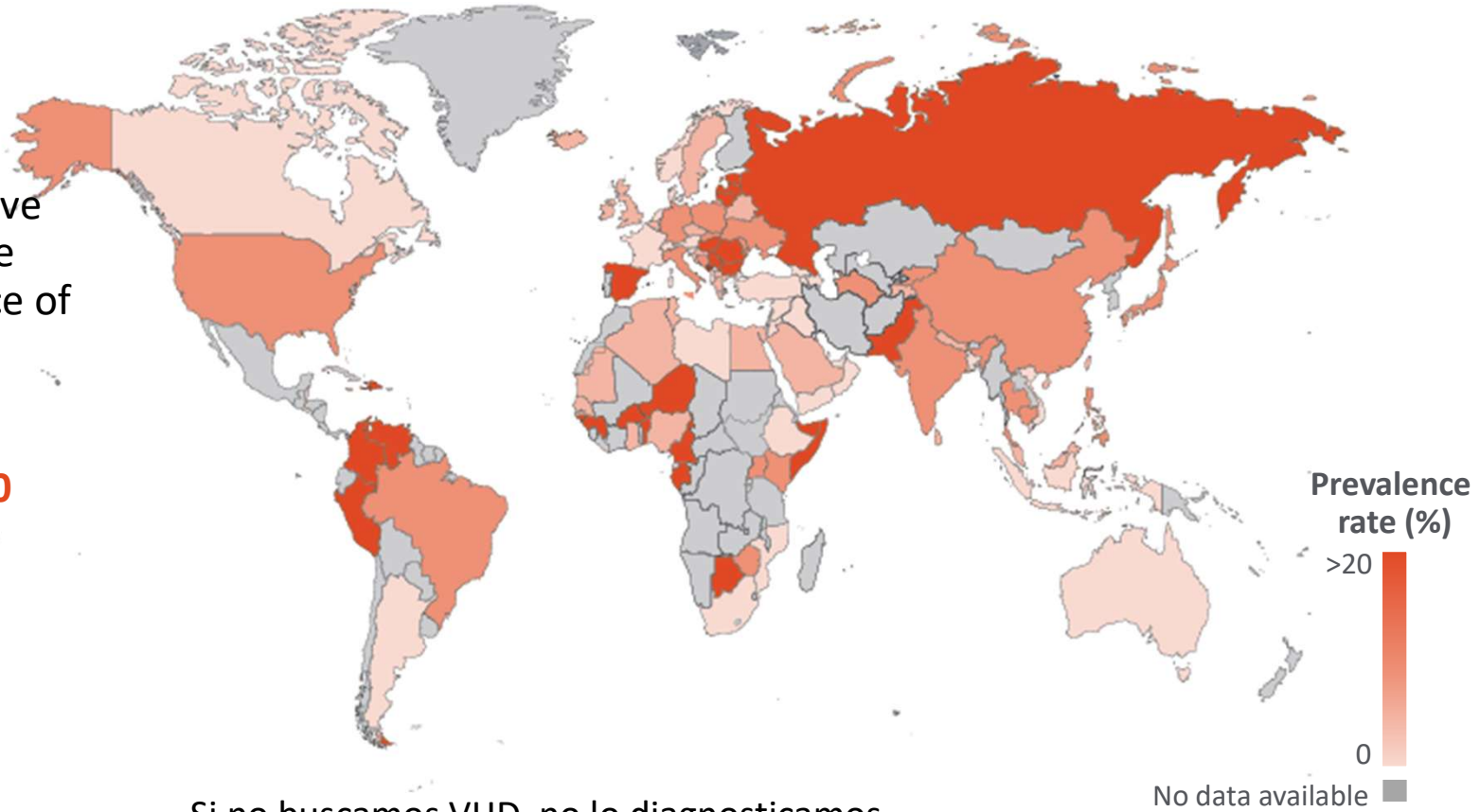


51 congreso anual

AEEH Asociación Española para el Estudio del Hígado

Epidemiologia de la Hepatitis D

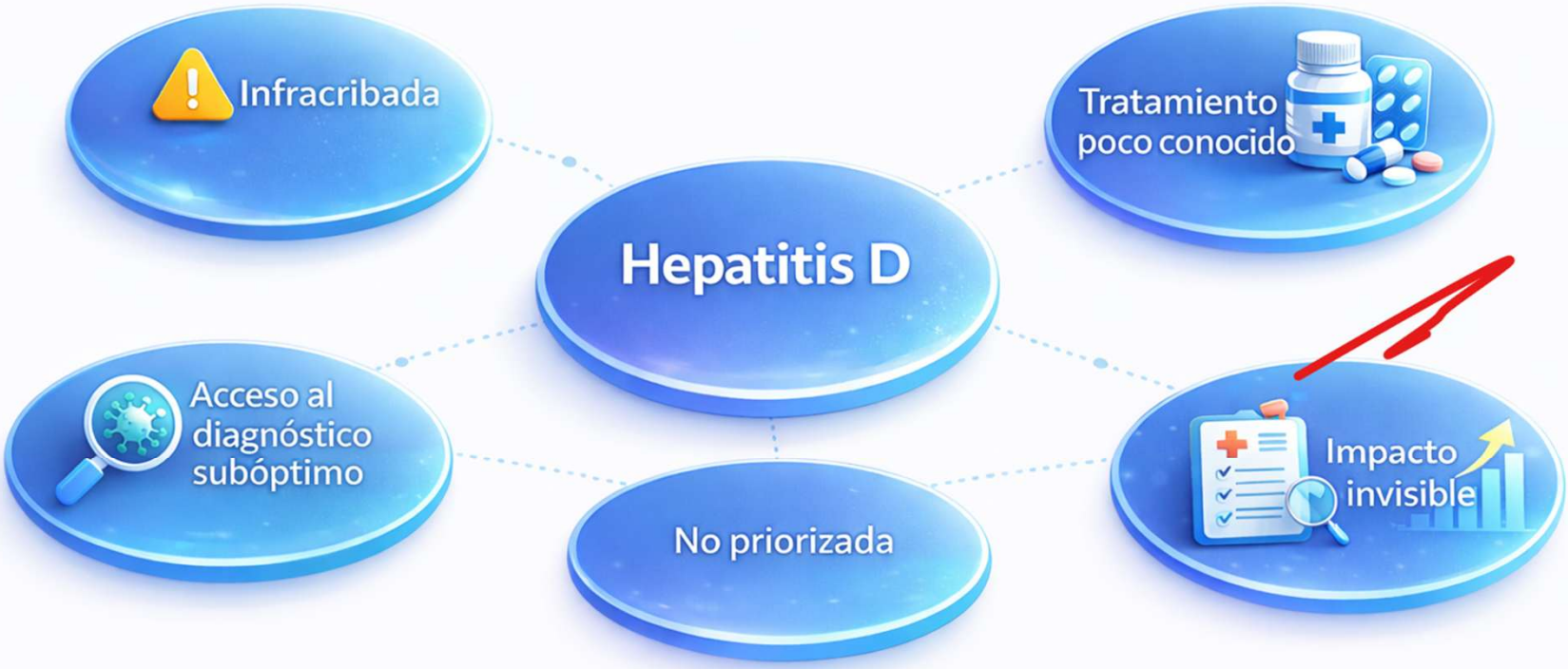
- Among HBsAg positive people with HBV, the estimated prevalence of HDV is **4.5%-13%**
- Approximately **48-60 million people** are infected with HDV worldwide



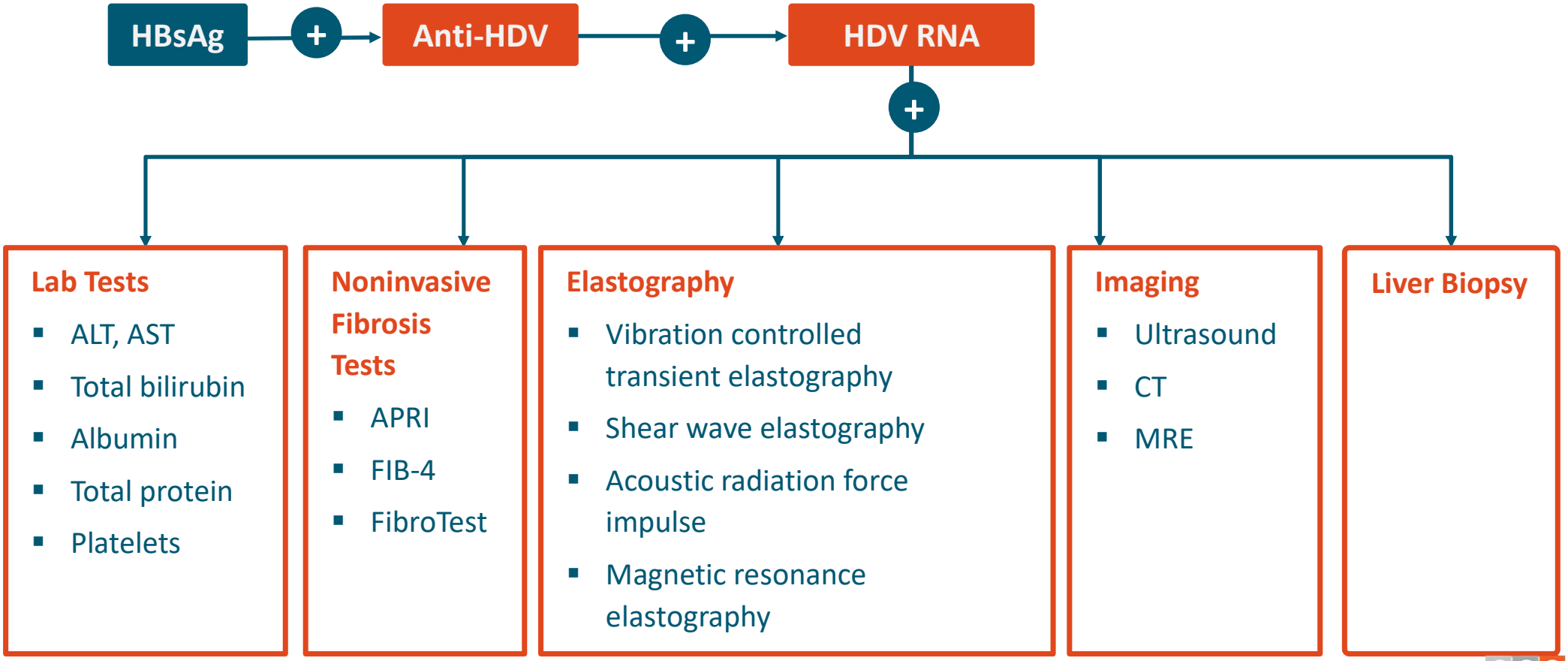
Si no buscamos VHD, no lo diagnosticamos

Stockdale. J Hepatol 2020;73:523; Miao. J Infect Dis 2020;221:1677.

La hepatitis D, la gran olvidada



Diagnostico de la Hepatitis D



Shah. Gastroenterol Rep (Oxf). 2019;7:396.

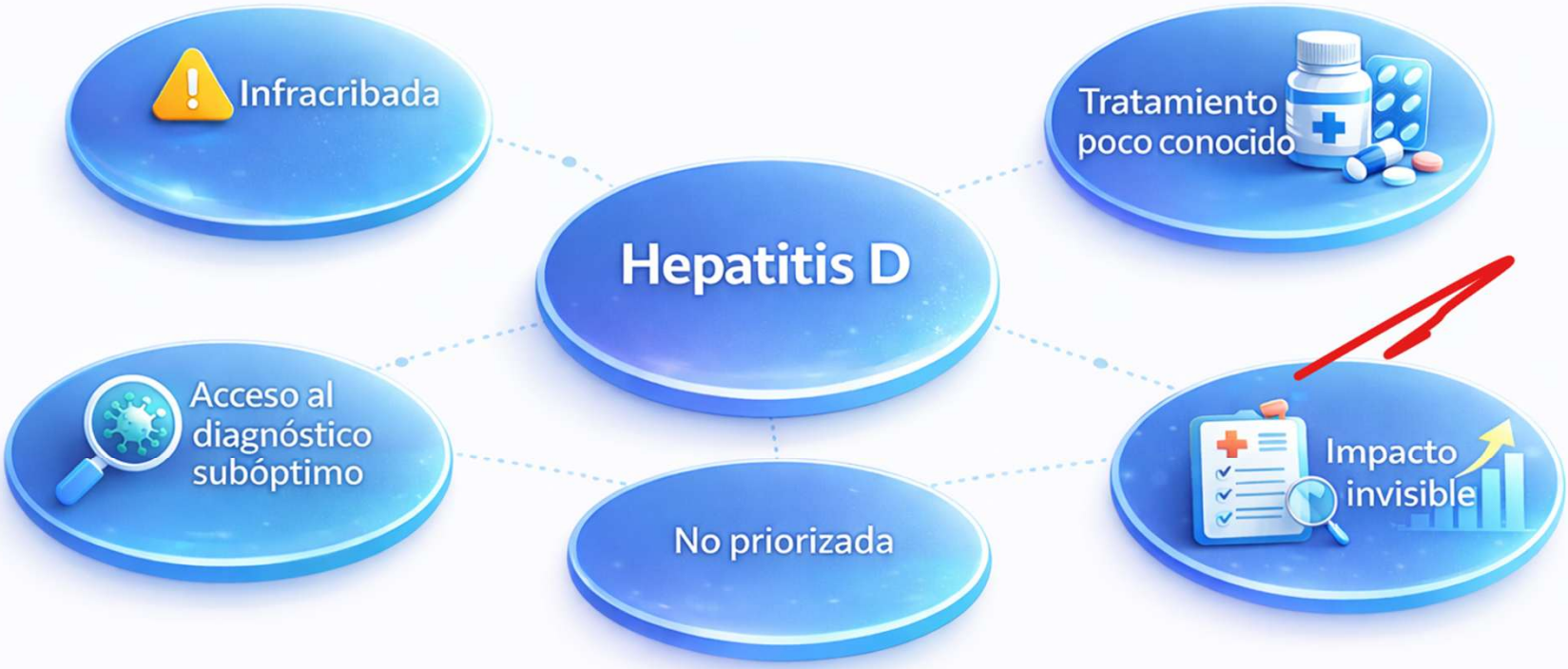
Slide credit: clinicaloptions.com

Pruebas para la determinación del RNA-VHD

Nombre de la prueba	Fabricante	LOD	LLOQ	Rango lineal	Genotipos	Certificación
Robogene® HDV RNA Quantification kit 2.0	Roboscreen GmBH	6 UI/ml	60 UI/ml	5 – 1x10^8 UI/ml	1-8	CE
AltoStar® HDV RT-PCR	Altona Diagnostics	9,48 UI/ml	N/D	40 – 4x10^8 UI/mL	1-8	RUO
EurobioPlex HDV qRT-PCR EBX-004	Eurobio Scientific	100 UI/ml	100 UI/ml	10^2 –10^8 UI/ml	1-8	CE
Bosphore® HDV Quantification-Detection kit	Anatolia Geneworks	45 copias/ml	100 copias/ml	10^2 – 10^8 copias/ml	1-8	CE
Lightmix HDV kit	Roche Diagnostics	10 copias/ml	10 copias/ml	10^1 – 10^6 copias/ml	1	RUO
DiaPro HDV RNA quantification kit	Diagnostic Bioprobes	100 copias/ml	100 copias/ml	10^2 – 10^7 copias/ml	1-8	CE
HDV Genesig standard kit	Primerdesign Ltd	100 copias/ml	N/D	10^2 – 10^7 copias/ml	1-8	RUO
HDV Realtime PCR kit	Vircell Microbiologists	23 copias/ml	N/D	N/D	N/D	RUO

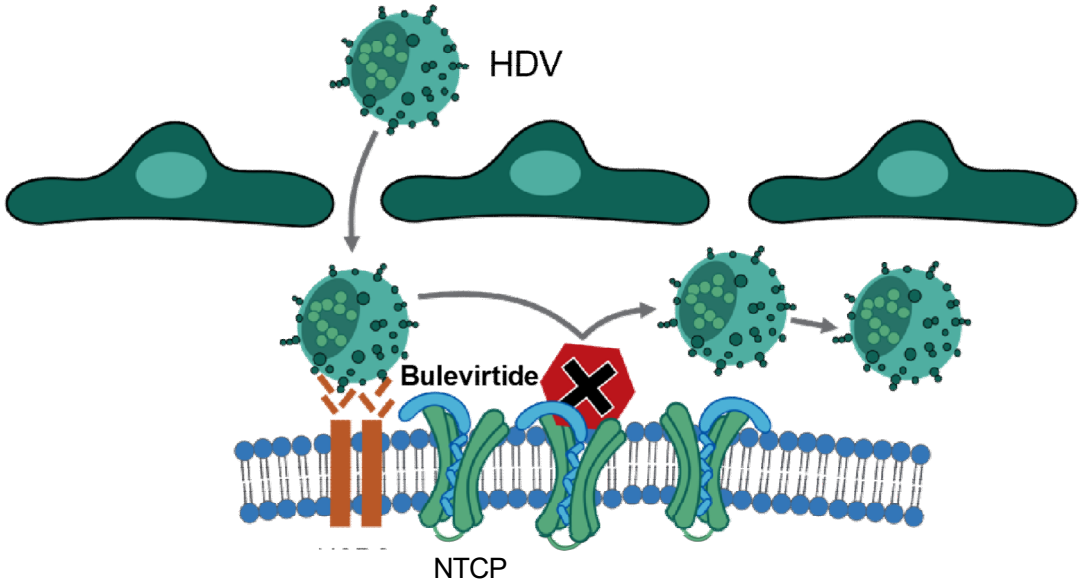
CE: Conformidad Europea; LLOQ: *Lower Limit Of Quantification*; LOD: *Limit Of Detection*; N/D: No Disponible; RUO: *Research Use Only*; UI: Unidades Internacionales; VHD: Virus de la Hepatitis D.

La hepatitis D, la gran olvidada



Bulevirtide

- HBV and HDV entry inhibitor
  - Binds and blocks the hepatocyte surface protein NTCP, which is the receptor for HBV/ HDV entry
  - Mechanism of action increases bile acids (NTCP is also a receptor for bile acids)
  - Daily SC injection
  - Approved BLV 2 mg in Europe by the EMA in July 2020



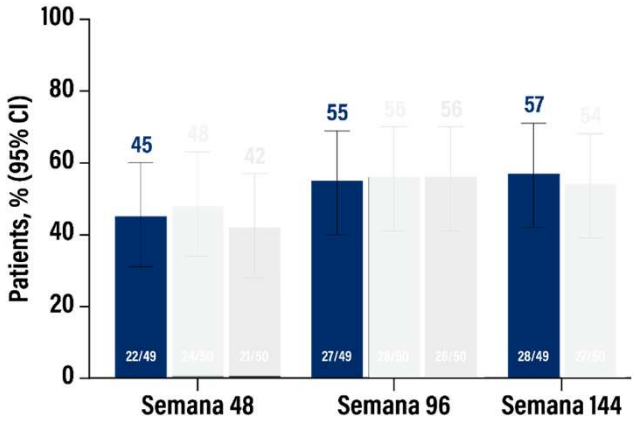
EMA: European Medicines Agency; SC: subcuataneous.

Yardeni D, Koh C. *Drugs Today (Barc)*. 2021;57:433-448. Gilead press release. November 19, 2021. https://www.gilead.com/news-and-press/press-room/press-releases/2021/11/gilead-submits-biologics-license-application-to-us-food-and-drug-administration-for-bulevirtide-an-investigational-treatment-for-people-living-with

Estudio fase III: MYR301
El tratamiento con BLV muestra incremento de las respuestas virológica y bioquímica durante 144 semanas

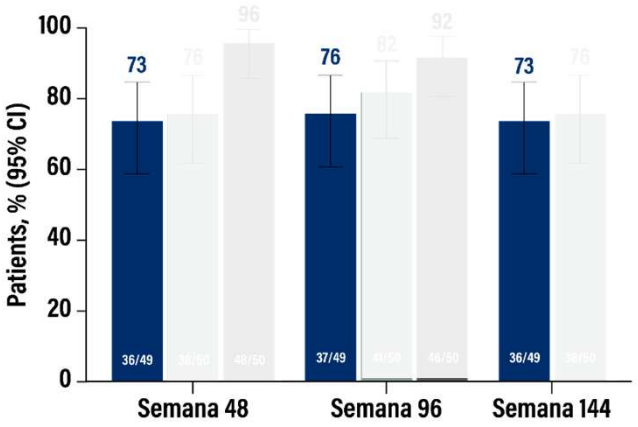
Combined Response

Undetectable HDV RNA* or ≥2 log_{10} IU/mL decline from BL and ALT normalization**

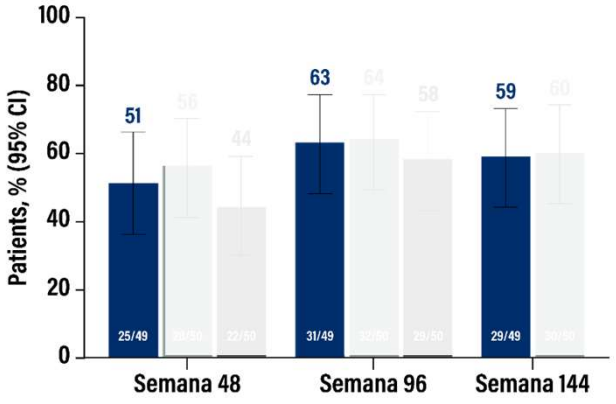


Virologic Response

Undetectable HDV RNA* or ≥2 log_{10} IU/mL decrease from BL



ALT Normalization**



Undetectable HDV RNA (TND), %

12	20	29

Bulevirtide 2 mg
Bulevirtide 10 mg
Deferred treatment/Bulevirtide 10mg

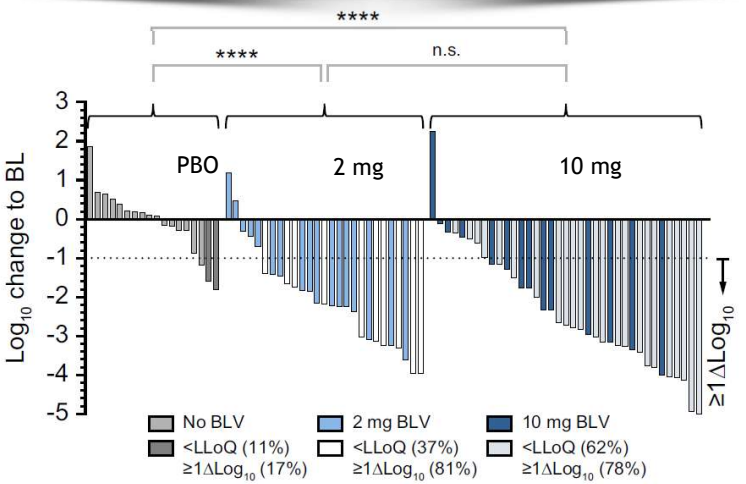
No HBsAg decline !

BLV 2 mg es la única dosis aprobada en España

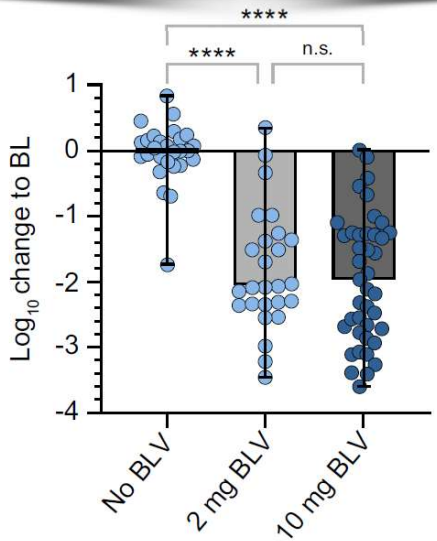
Data shown here are BLV treatment by duration. *Undetectable HDV RNA was defined as <LLOQ (50 IU/ml) and target not detected; **ALT normalization: ≤31 U/L for females and ≤41 U/L for males (Russian sites) or ≤34 U/L for females and ≤49 U/L for males (all other sites); †Delayed treatment arm did not receive any BLV in the first 48 weeks of the trial. ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; LLOQ, lower limit of quantification; LOD, limit of detection;
Tx, treatment; W, week. Lampertico P, et al. EASL 2024. Poster #LBP-029

Estudio MYR203 y 301
Respuesta Intrahepática después de 48 Semanas de monoterapia con BLV

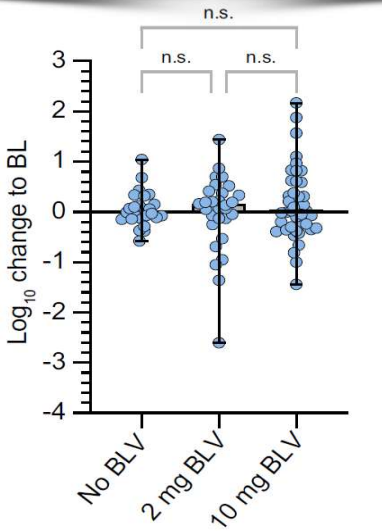
Intrahepatic HDV RNA levels



Intrahepatic HDAg levels



Intrahepatic HBsAg levels



- **Serum and liver HDV RNA** levels strongly correlated (Spearman r: 0,62, p <−0.0001).
- **Liver HDV RNA negative (<LLOQ)**: **37%** and 62% in 2 and 10 mg arms, respectively.
- **Liver HDAg negative staining**: **50%** and 54% in 2 and 10 mg arms, respectively.

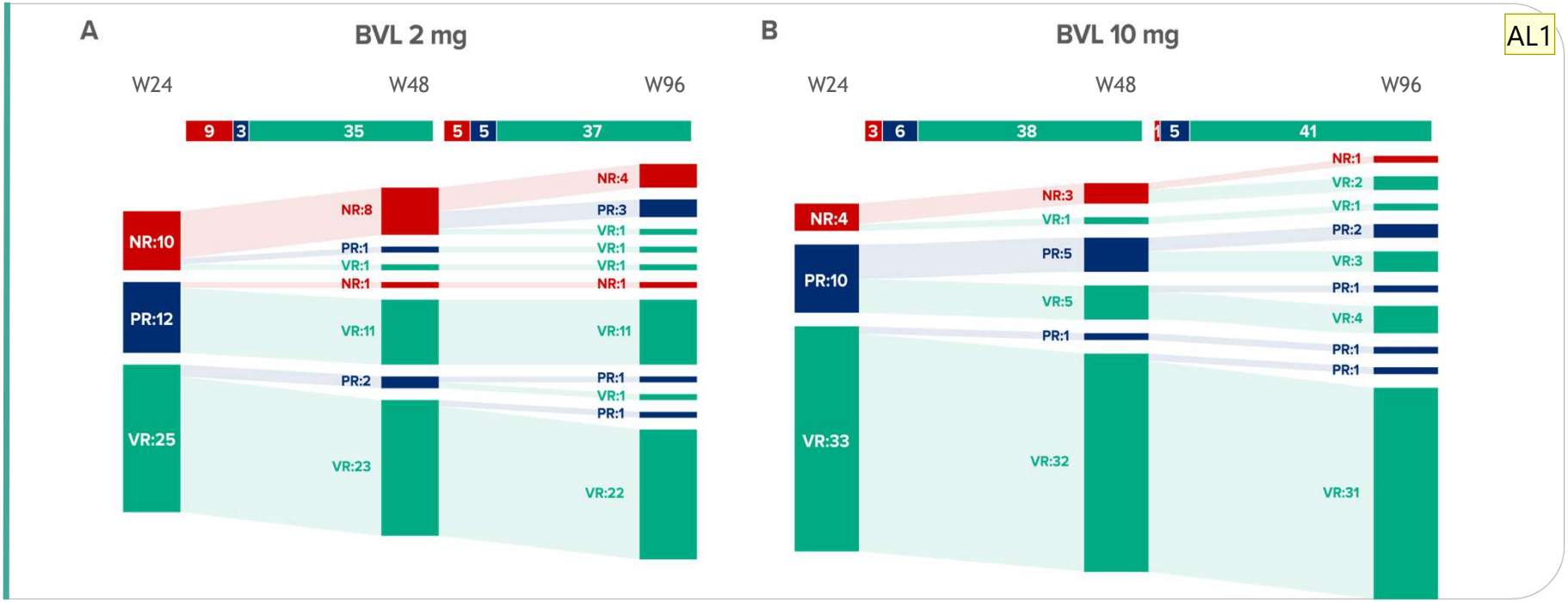
Blocking viral entry diminishes signs of liver inflammation and promotes a strong reduction of HDV infection within the liver, thus suggesting that some patients may achieve HDV cure with long-term treatment

BLV 2 mg es la única dosis aprobada en España

Allweiss L. et al, J Hepatol 2024

En pacientes con una respuesta subóptima precoz, el tratamiento con BLV mejora la respuesta a las 96 semanas

Treatment response in patients with suboptimal virological response at week 24*



60% of NR achieved partial or virological response with Bulevirtide 2mg at week 96
92% of RP achieved virological response with Bulevirtide 2mg at week 96

BLV 2 mg is the only approved dose; BLV 10 mg is not indicated in the label. *NR: non-responders (HDV RNA reduction <1 log_{10} IU/mL from baseline); PR: partial response (HDV RNA reduction ≥1 and <2 log_{10} IU/mL from baseline); VR: virological response (HDV RNA undetectable or reduction ≥2 log_{10} IU/mL from baseline); Suboptimal response: NR or PR at week 24.*

1. Wedemeyer H. et al.. Bulevirtide monotherapy in patients with chronic HDV: Efficacy and safety results through week 96 from a phase III randomized trial. J Hepatol. 2024;81(4):621-629. doi:10.1016/j.jhep.2024.05.001.

Diapositiva 23

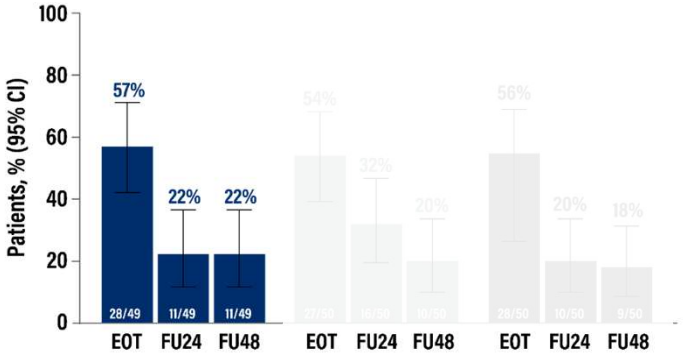
AL1 diapositiva maquetada

Adriana Lazcoz; 2025-11-18T18:43:18.528

Estudio MYR301
Impacto de la discontinuación del tratamiento

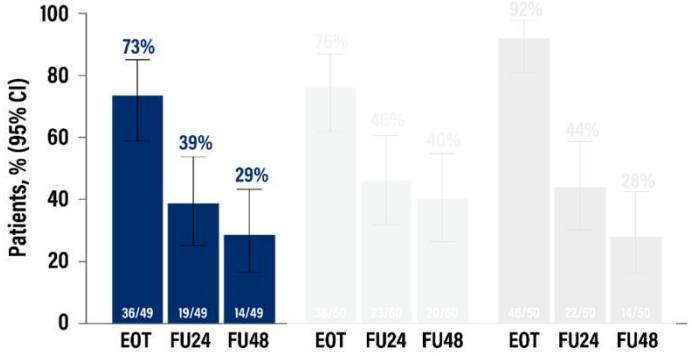
Combined Response

Undetectable HDV RNA or ≥2 log_{10} IU/mL decrease from BL and ALT normalization*

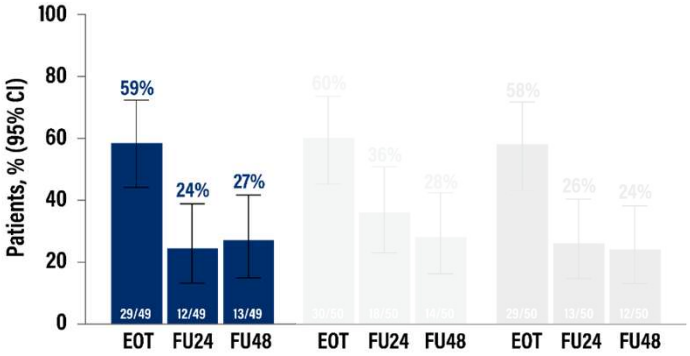


Virologic Response

Undetectable HDV RNA or ≥2 log_{10} IU/mL decrease from BL



ALT Normalization



Undetectable HDV RNA,* %

29	18	16
50	26	24
52	18	16

FU96[2] Undetectable HDV RNA ➡ 20%

- **Bulevirtide 2 mg**
- **Bulevirtide 10 mg**
- **Deferred treatment/Bulevirtide 10mg**

Response rates across all outcomes were sustained between follow-up weeks 48[1] and 96[2].

BLV 2 mg es la única dosis aprobada en España

Data shown here are BLV treatment by duration. *HDV RNA was quantified using the RoboGene®, version 2.0, with limit of detection 6 IU/ml; ALT normalization was defined at Russian sites as ≤31 U/L for female patients and ≤41 U/L for male patients and at all other sites as ≤34 U/L for female patients and ≤49 U/L for male patients; **Includes 1 responder who restarted BLV prior to the visit; †Includes 2 responders who restarted BLV prior to the visit; ‡Delayed treatment arm did not receive any BLV in the first 48 weeks of the trial. ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; EOT, end of treatment; F/U48, follow-up at 48 weeks after EOT; F/U96; follow-up at 96 weeks after EOT; Tx, treatment.

"Bulevirtide 2 mg is the only approved dose. The 10 mg was a comparator arm in the phase 3 clinical study and is not approved anywhere."

1. Aleman S, et al. AASLD 2024. Poster 1147. 2. Wedemeyer H and Aleman S, et al. EASL 2025. Oral LBO-004

Estudio MYR301. Analisis de Seguridad al final del tratamiento y del seguimiento

Patients, n (%)	Delayed Tx*/BLV 10 mg		BLV 2 mg		BLV 10 mg	
	W48 to EOT** (n=50)	EOT to FU48 (n=49)	EOT (n=49)	EOT to FU48 (n=46)	EOT (n=50)	EOT to FU48 (n=47)
Any AE	46 (92)	30 (61)	48 (98)	31 (67)	48 (96)	34 (72)
Any AE related to BLV	23 (46)	NR	27 (55)	NR	37 (74)	NR
Grade 3–4 AE	5 (10)	11 (22)	12 (24)	6 (13)	10 (20)	6 (13)
Any SAE	3 (6)	6 (12)	3 (6)	3 (7)	6 (12)	4 (9)
Any AE leading to withdrawal of BLV	0	NA	0	NA	0	NA
Death	1 (2)	0	0	0	0	0
Hepatic AEs	5 (10)	22 (45)	14 (29)	21 (46)	10 (20)	20 (43)
Hepatic SAEs	0	5 (10)	0	3 (7)	0	3 (6)

- Post-treatment, 47/140† (34%) reported ALT >5x ULN and14/140‡ (10%) reported ALT >10x ULN
- Of the 47 patients reporting ALT >5x ULN, 10 were retreated
- One death due to plasma cell myeloma was not related to study treatment

11 patients with hepatic SAEs associated with:

ALT >5x ULN	10 patients
Liver-related hospitalization	3 patients
HDV viremia rebound	8 patients
BLV required	8 patients
TDF required	1 patient

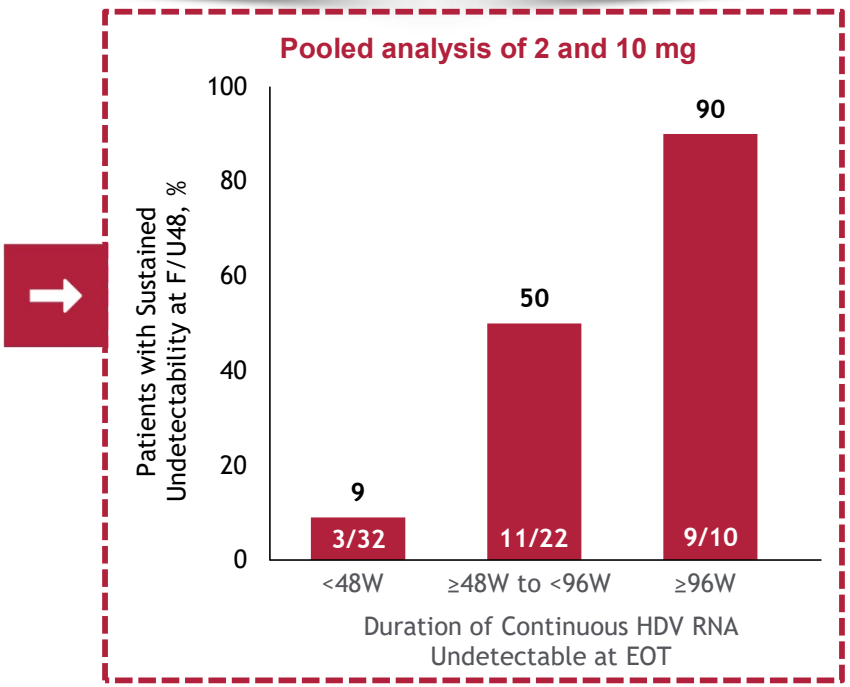
BLV 2 mg es la única dosis aprobada en España

BLV discontinuation may lead to virological relapse and ALT flares !

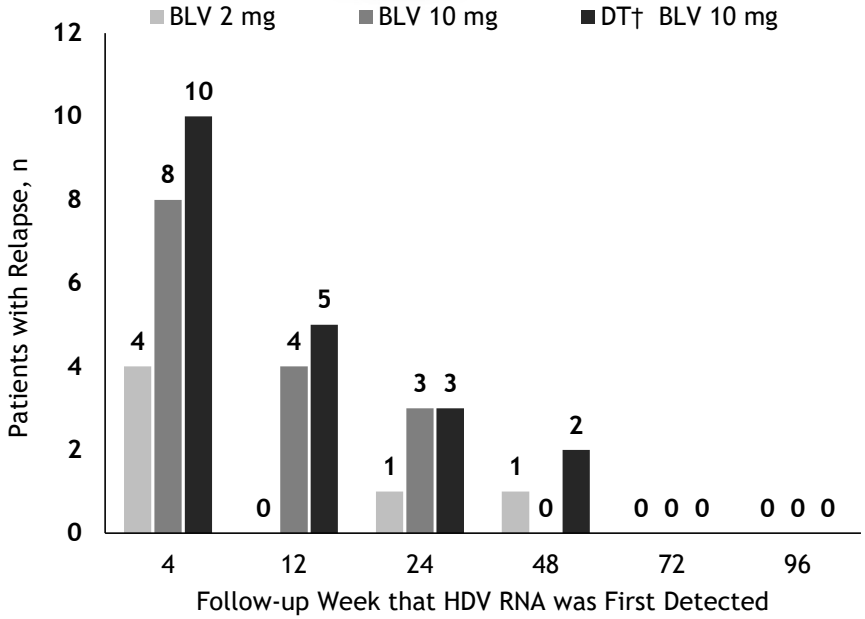
Aleman S, et al. AASLD 2024. Poster #1147

Estudio MYR301 Predictores de Respuesta a BLV tras discontinuar el Tratamiento

Predictor of Off-Tx Sustained Undetectability* through F/U48



Off-Tx HDV RNA Relapse** Through F/U96



"Bulevirtide 2 mg is the only approved dose. The 10 mg was a comparator arm in the phase 3 clinical study and is not approved anywhere."

Patients with more than 96 weeks of undetectable HDV RNA on-treatment had the highest rates of sustained, off-treatment undetectable HDV RNA; no patients relapsed after F/U48

BLV 2 mg es la única dosis aprobada en España
*HDV RNA was quantified using the RoboGene®, version 2.0, with limit of detection 6 IU/ml; Includes all treatment groups **HDV RNA relapse was defined as HDV RNA undetectable at EOT and ≥1 HDV RNA sample during the follow-up period with observed detectable HDV RNA; †Delayed treatment arm did not receive any BLV through Week 48.
Wedemeyer H and Aleman S, et al. EASL 2025. Oral LBO-004

Registro de Hepatitis D de la AEEH

603 pacientes incluidos en el registro VHD

135 iniciaron BLV

70 con visita al año de tratamiento

60 con ARN-VHD cuantificado

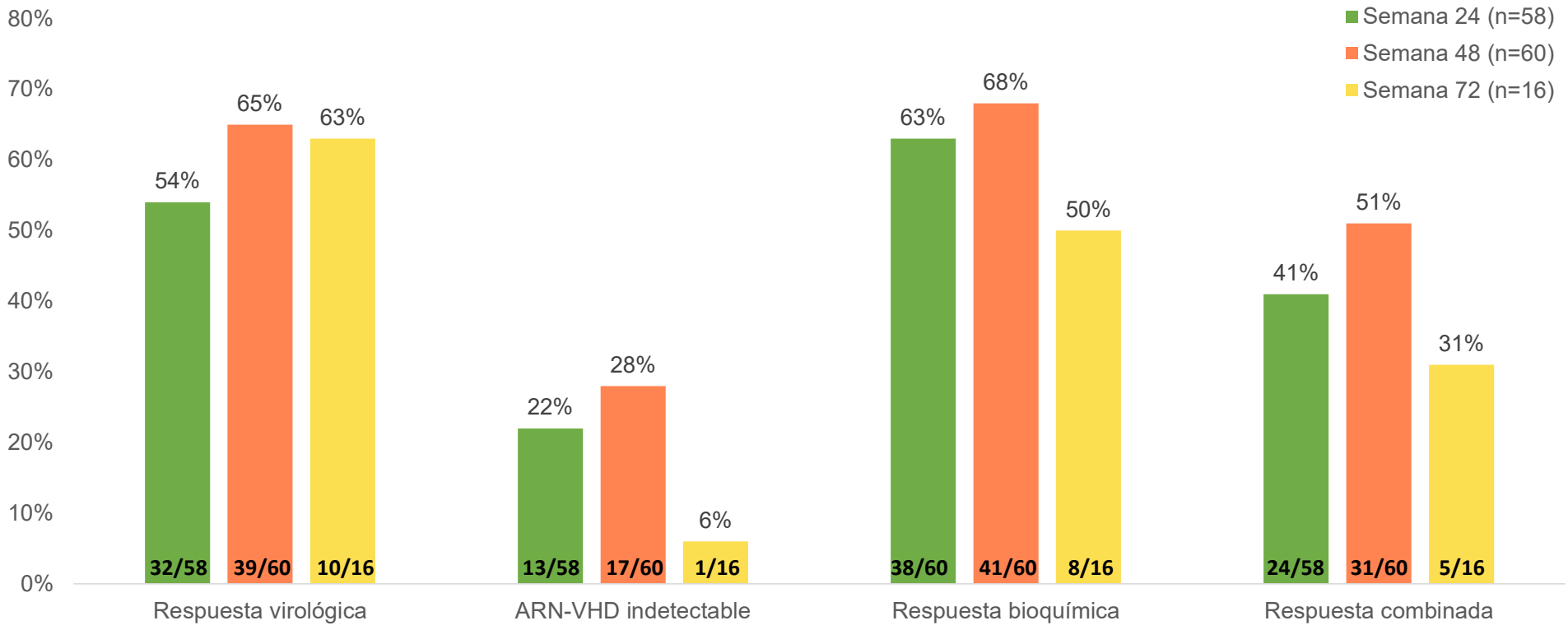
Características basales	Participantes (N=60)
Edad, años	51 (40-57)
Hombres	41 (68%)
Nacidos en el extranjero	36 (60%)
Factores de riesgo reportados	11 (18%)
ALT > LSN	47 (78%)
Elastografía hepática, kPa*	13,8 (11,2-21)
Cirrosis hepática**	46 (77%)
Descompensación hepática previa	3 (5%)
Hepatocarcinoma	2 (3%)
Tratamiento previo con IFN	35 (58%)
Tratamiento análogos de nucleós(t)ido	51 (85%)
Tenofovir	34 (57%)
Entecavir	15 (25%)
Lamivudina	2 (3%)

**disponible en 50 pacientes; **definida mediante histología (METAVIR F4), evaluación no invasiva (elastografía hepática >12,5 kPa) o criterios clínicos, que incluyen superficie hepática nodular, esplenomegalia y trombocitopenia.*
Las variables cualitativas están expresadas como n(%), y las cuantitativas como md (RI).

51 congreso anual

AEEH Asociación Española para el Estudio del Hígado

Respuestas al año de tratamiento con Bulevertide



51 congreso anual

AEEH
Asociación Española para el Estudio del Hígado

Impacto de BLV en el Desarrollo de eventos hepaticos en pacientes con Cirrosis Compensada

European case-control study of BLV-treated patients* from SAVE-D[1] versus an HDV natural history cohort[2]

Incidence of Liver Events[1]

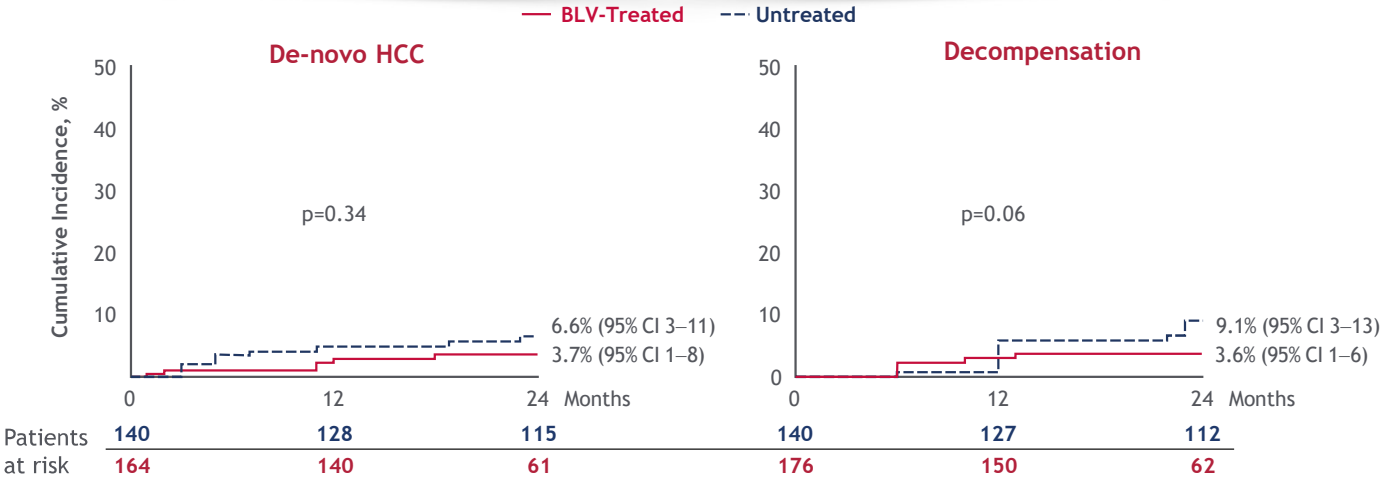
The **2-year cumulative probability** of overall **LRE** was **15.6% in untreated** patients *vs* **7.3%** in **BLV-treated** patients in SAVE-D study (**p-value = 0.05**)

The **2-year cumulative incidence** of de **novo HCC** was **6.6% in untreated** patients *vs* ***3.7%*** in **BLV-treated** patients (**p-value = 0.34**)

The **2-year cumulative incidence** of de-novo **decompesation** was **9.1% in untreated** patients *vs* ***3.6%*** in **BLV-treated** patients (**p-value = 0.06**)

The **decompensation events** in patients with **CTP-A5 at baseline** was **9.2% in untreated** patients *vs* ***0%*** in **BLV-treated** patients (**p-value = 0.003**)

2-Year Cumulative Incidence of Liver Events[1]



IPTW-Adjusted Cox Regression Analysis

The **HR** for **liver related events** was **0.38** (CI 95%: 0.23-0.62; **p-value: <0.0001**)

The **HR** for **decompensation** was **0.32** (CI 95%: 0.16-0.63; **p-value: 0.0001**)

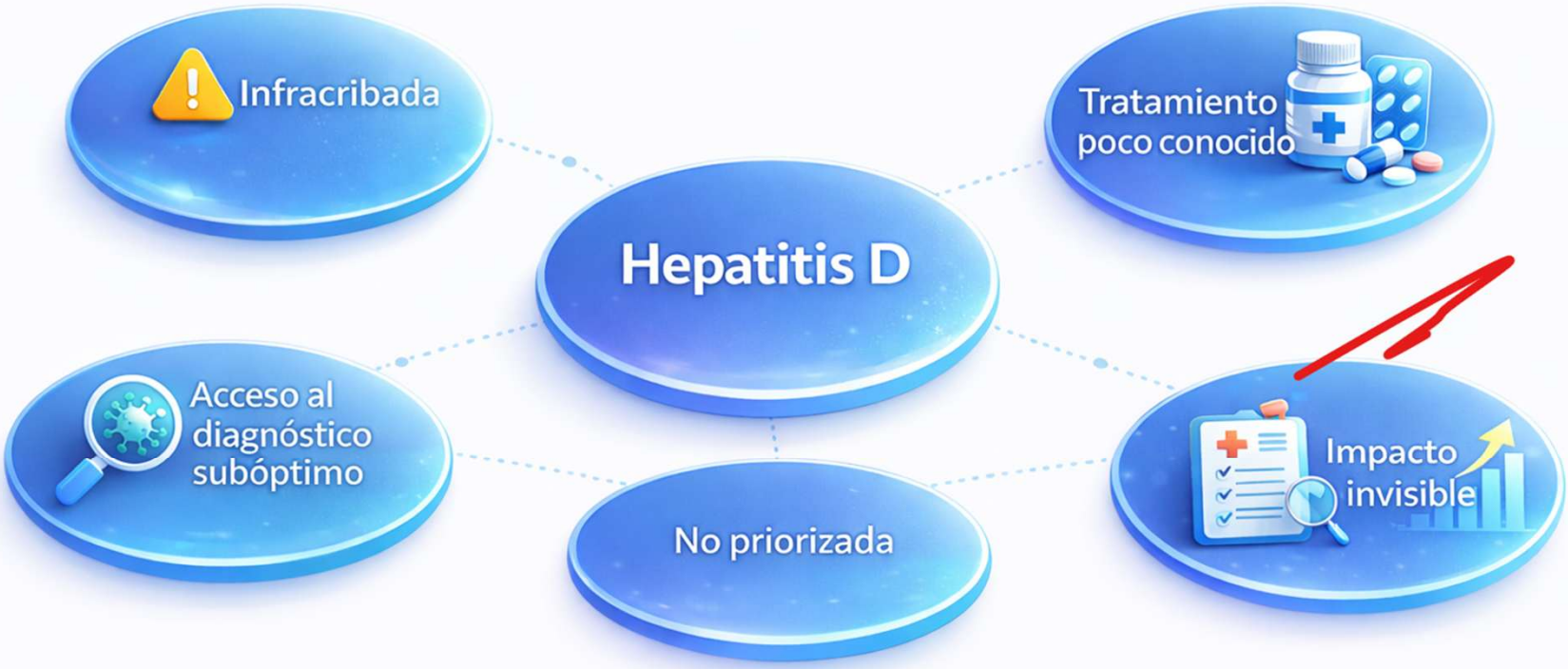
The **HR** for **de-novo HCC** was **0.50** (CI 95%: 0.24-1.06; **p-value: 0.07**)

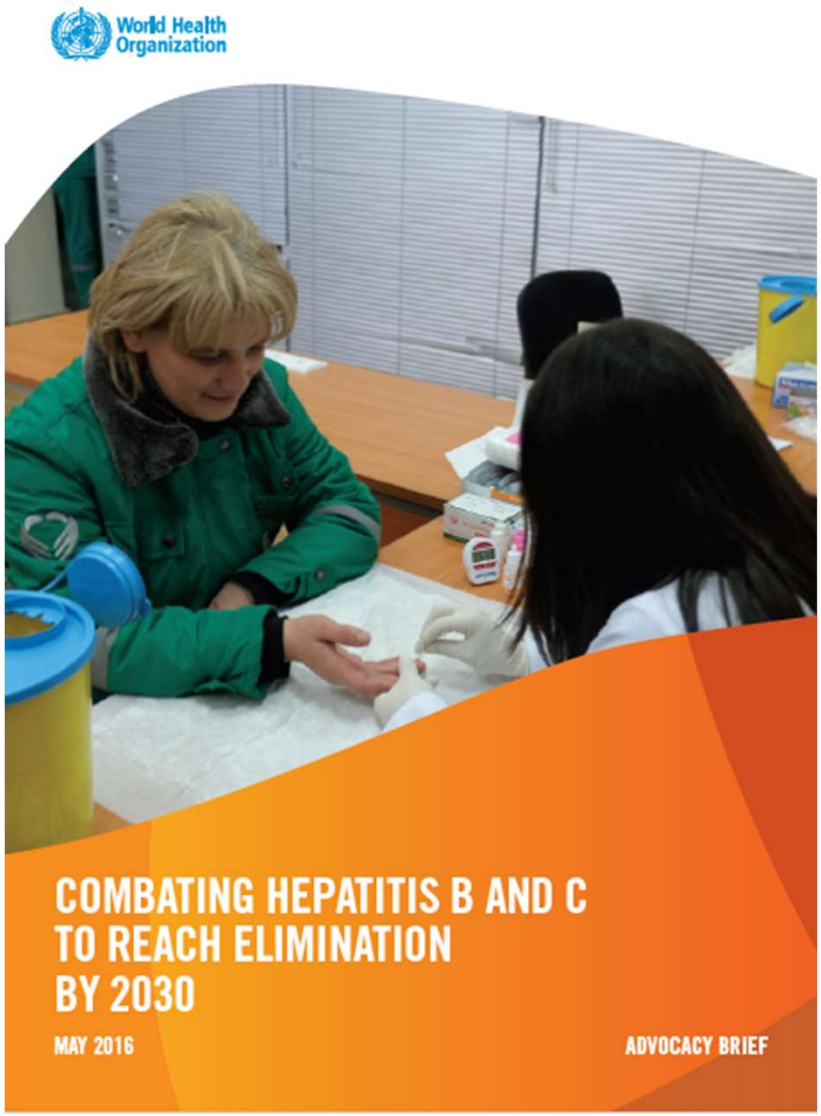
BLV treatment associated with significantly lower decompensation rates over 2 years versus no treatment

BLV 2 mg es la única dosis aprobada en España

The untreated cohort was enrolled between 1978-2006 in a single center, retrospective, natural history study[2]. *Patients were followed-up from baseline to event, last visit, or censoring (24 months–interim analysis). ALT, alanine aminotransferase; BLV, bulevirtide; CI, confidence interval; CTP, Child-Turcotte-Pugh; HR hazard ratio; HCC, hepatocellular carcinoma; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LRE, liver-related events. 1. Degasperi S, et al. AASLD 2024. Poster #1166; 2. Romeo R, et al. Gastroenterology. 2009;136(5):1629–1638.

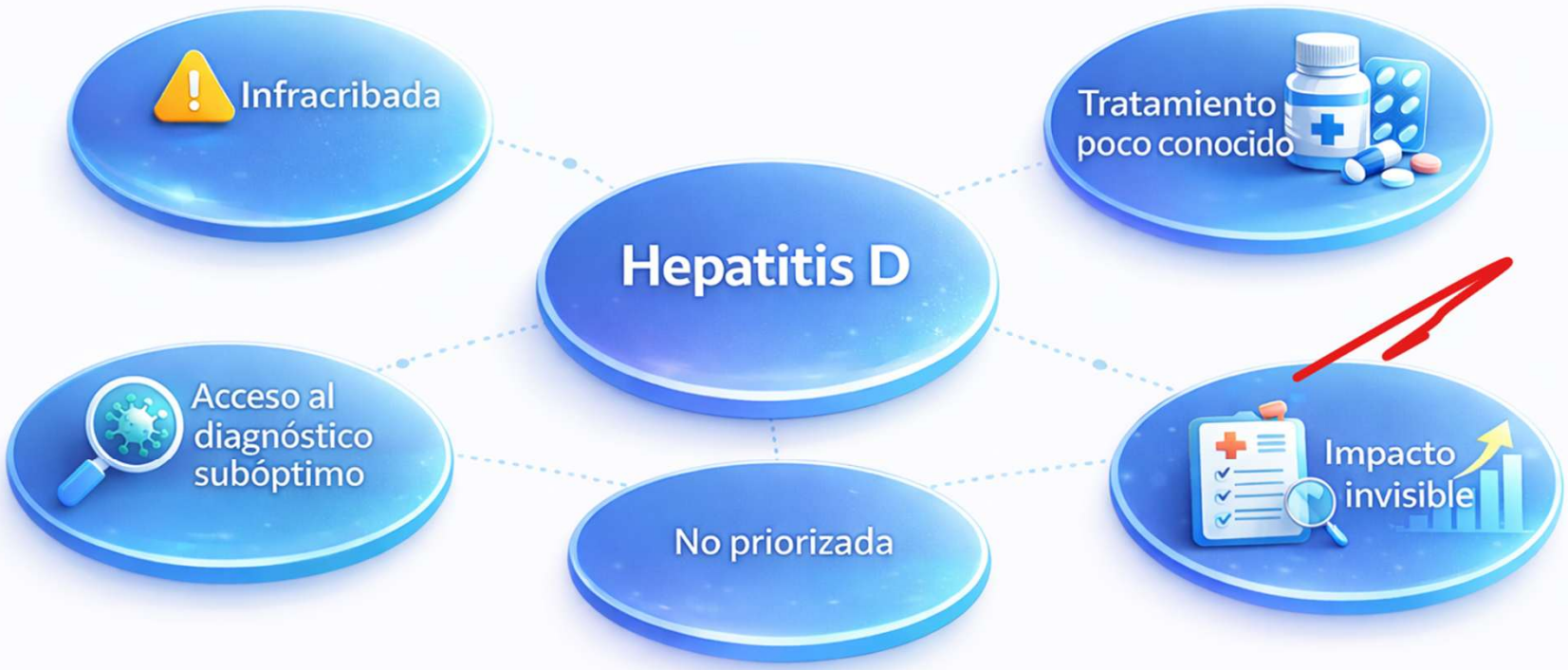
La hepatitis D, la gran olvidada





No Hepatitis Delta!!!!

La hepatitis D, la gran olvidada



Por primera vez, tenemos herramientas. Lo que falta es pensar en la Hepatitis Delta