Estrategias de identificación y tratamiento de la infección por virus D

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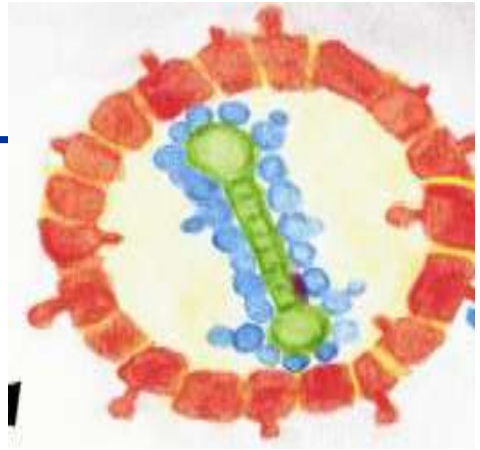
Disclosures

- MB speaker and/or Advisor Gilead, Abbvie, Altimmune, GSK, Janssen and Assembly

Hepatitis D (delta) Virus



- The «Delta agent» was discovered in 1977 by Mario Rizzetto
- Defective virus that needs HBsAg for its propagation
- Causes the most severe form of chronic viral hepatitis

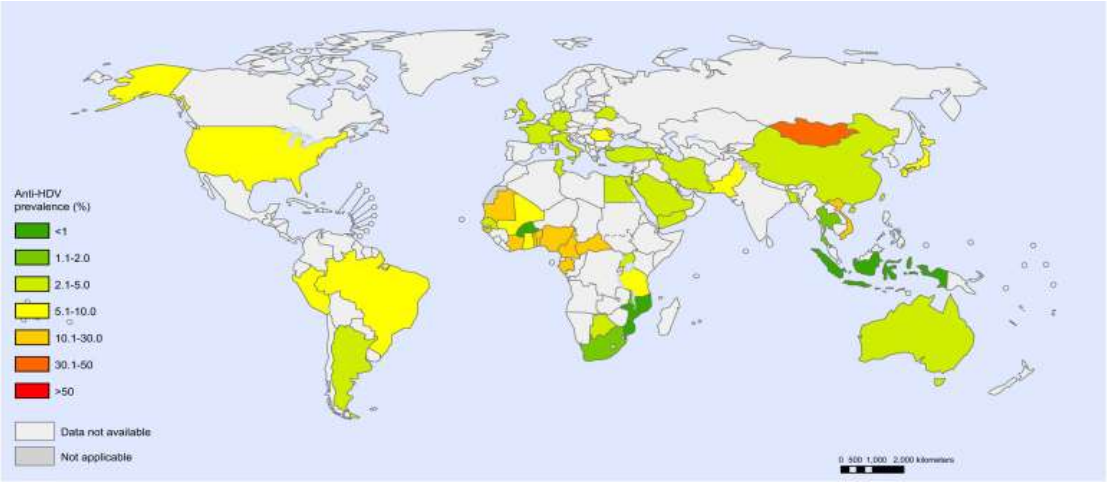
  More rapid progression to liver cirrhosis and liver cancer; 5-7x more likely to develop cirrhosis and HCC vs HBV

- Current standard anti-HDV therapy: NUC not effective, PegIFNα effective in only 20% of the patients (not EMA or FDA approved)

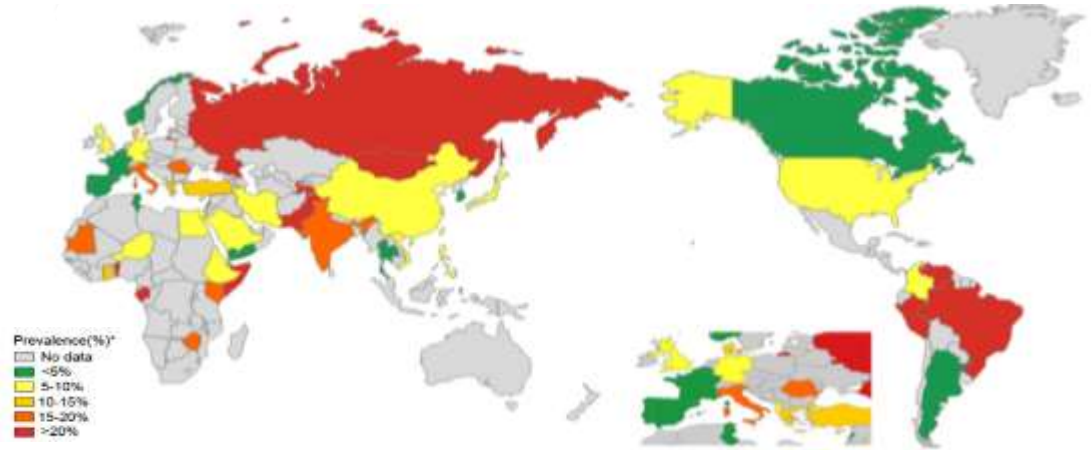
Calle Serrano et al, Semin Liver Dis. 2012 Lempp et al, Nat Rev. 2016

Hepatitis D is infradiagnosed

Anti-HDV prevalence among HBsAg-positive subjects = **4.5% (12 million people)**[1]



Anti-HDV prevalence among HBsAg-positive subjects = **14.6% (43 million people)**[2]



[1] Stockdale AJ. *J Hepatol.* 2020;73:523-32 | [2] Chen H-Y. *Gut.* 2019;68:512-21

Cribado del VHD: recomendación de las guías nacionales e internacionales

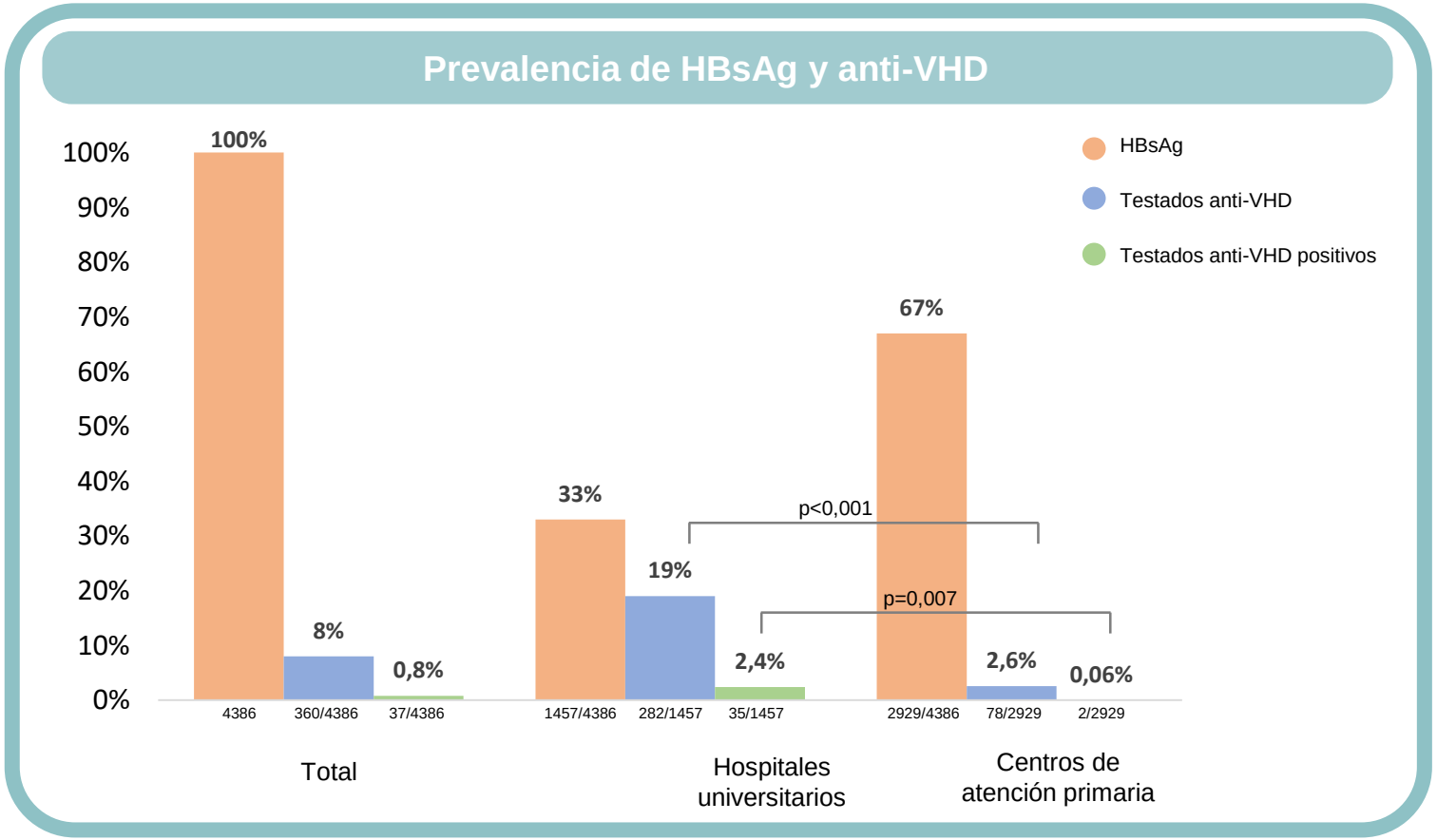
Guía	A quién testar	Cómo testar
AASLD 2018[1]	• HBsAg+ con factores de riesgo VHD • ADN del VHB bajo/indetectable y ALT alta	• Anti-VHD • ARN-VHD
EASL 2017[2]	• Todos los pacientes HBsAg+	• Sin recomendación
AEEH[3]	• Todos los pacientes HBsAg +	• Sin recomendación
APASL 2016[4]	• Pacientes con VHB crónica y enfermedad hepática crónica	• HDAg o anti-VHD • ARN VHD
WHO 2015[5]	• Sin recomendación	• Anti-VHD • ARN VHD

VHD: virus de la hepatitis delta; HBsAg: antígeno de superficie del virus de la hepatitis B; ADN: ácido desoxirribonucleico; VHB: virus de la hepatitis B; ALT: alanina aminotransferasa; Anti: anticuerpos; ARN: ácido ribonucleico; HDAg: antígeno del VHD; AASLD: American Association for the Study of Liver Diseases; EASL: European Association for the Study of the Liver; AEEH: Asociación Española para el Estudio del Hígado; APASL: The Asian Pacific Association for the Study of the Liver; WHO: World Health Organization

1. AASLD HBV Guidelines. April 2018. 2. EASL HBV Guidelines. August 2017. 3. Rodríguez M, et al. Gastroenterol Hepatol. 2020. 4. APASL HBV Guidelines. November 2015. 5. WHO HBV Guidelines. March 2015.

Cribado del VHD en pacientes portadores del HBsAg en el área Norte de Barcelona: ¿están implementadas las guías EASL?

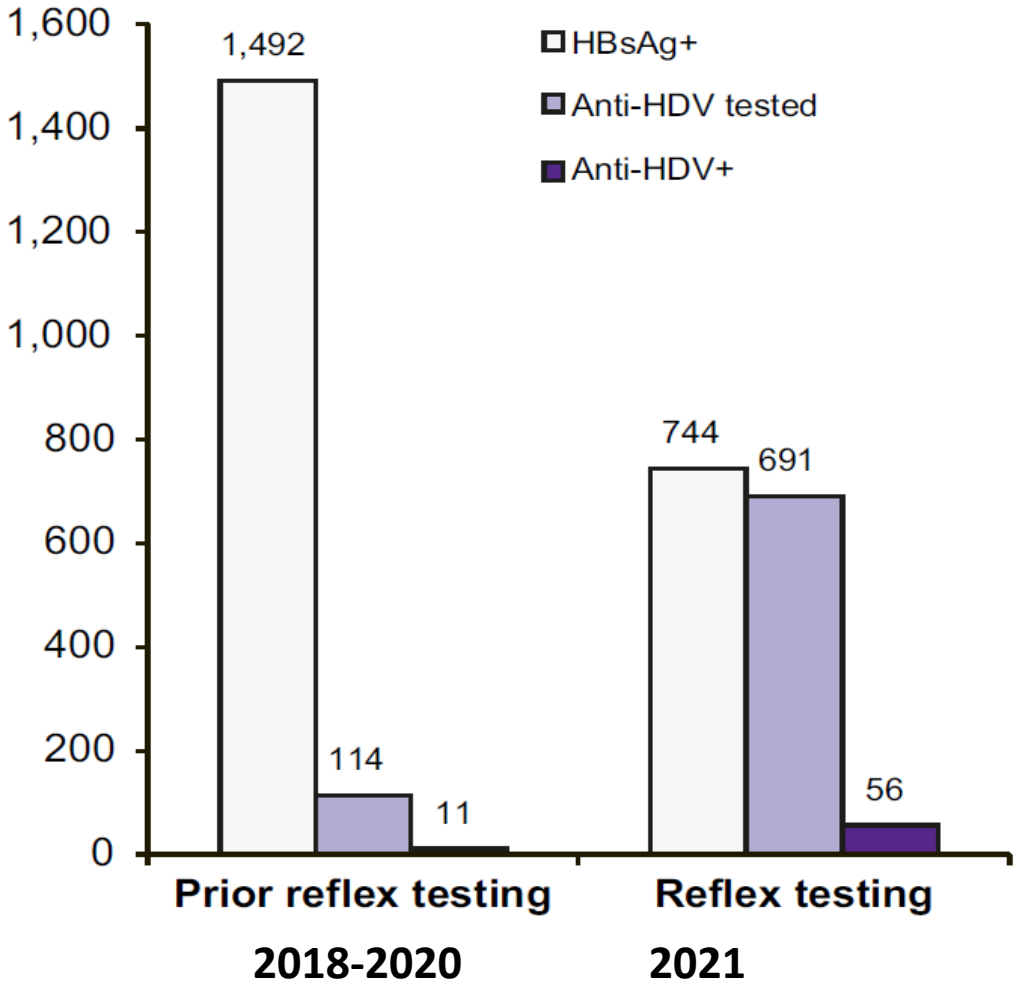
Análisis retrospectivo de muestras HBsAg+ del laboratorio central de Barcelona
(enero 2015 – mayo 2021)



VHD: virus de la hepatitis delta; HBsAg: antígeno de superficie del virus de la hepatitis B; EASL: European Association for the Study of the Liver; Anti: anticuerpos; ARN: ácido ribonucleico;
Palom. AASLD 2021. CO73.

Low adherence to guidelines recommendations for hepatitis D testing in HBsAg-positive patients leads to high undiagnosis rates

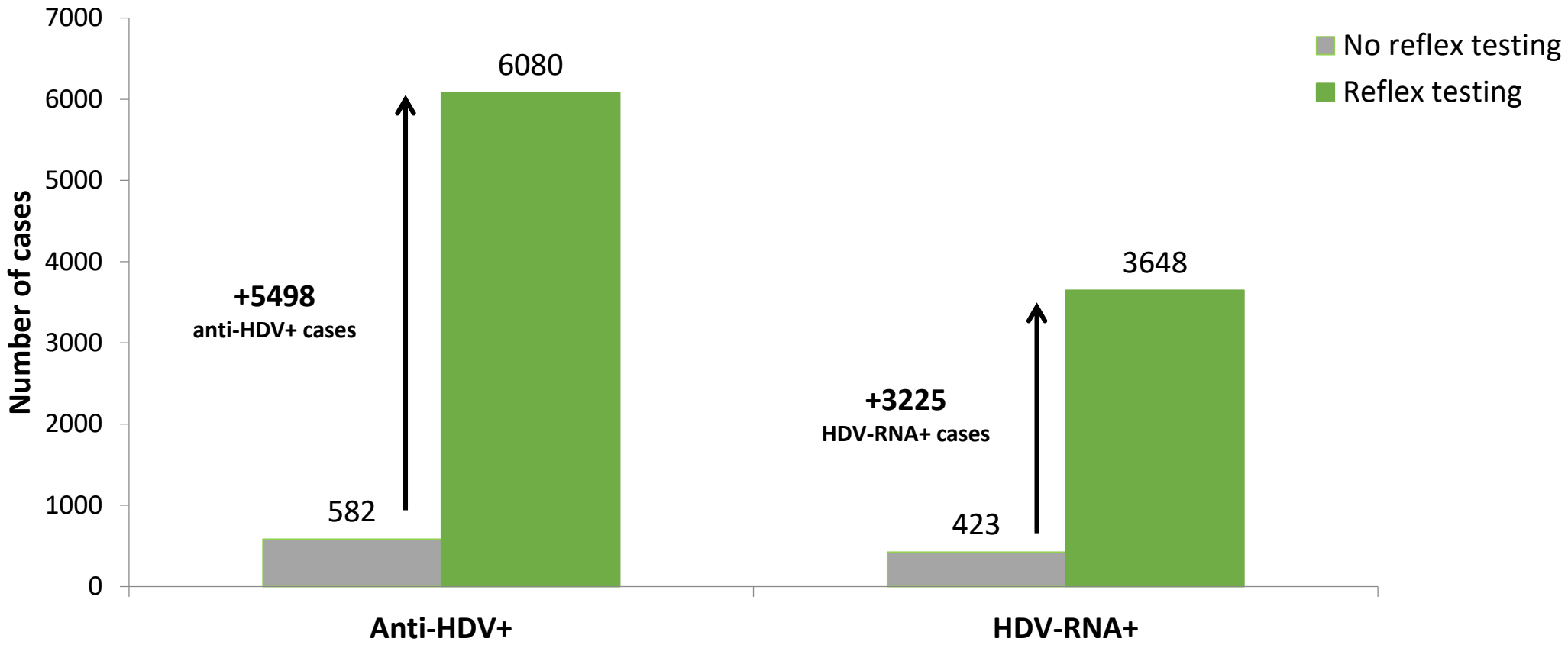
La implementación del test reflejo Anti-VHD aumenta x5 el número de pacientes identificados



- **Anti-HDV reflex testing quintupled the absolute diagnoses of chronic hepatitis D.**
- **60% of the anti-HDV positive patients did not have any risk factor**
- **65% had detectable HDV RNA**

[1] Palom A. *JHEP Rep*. 2022; 4(10): 100547.

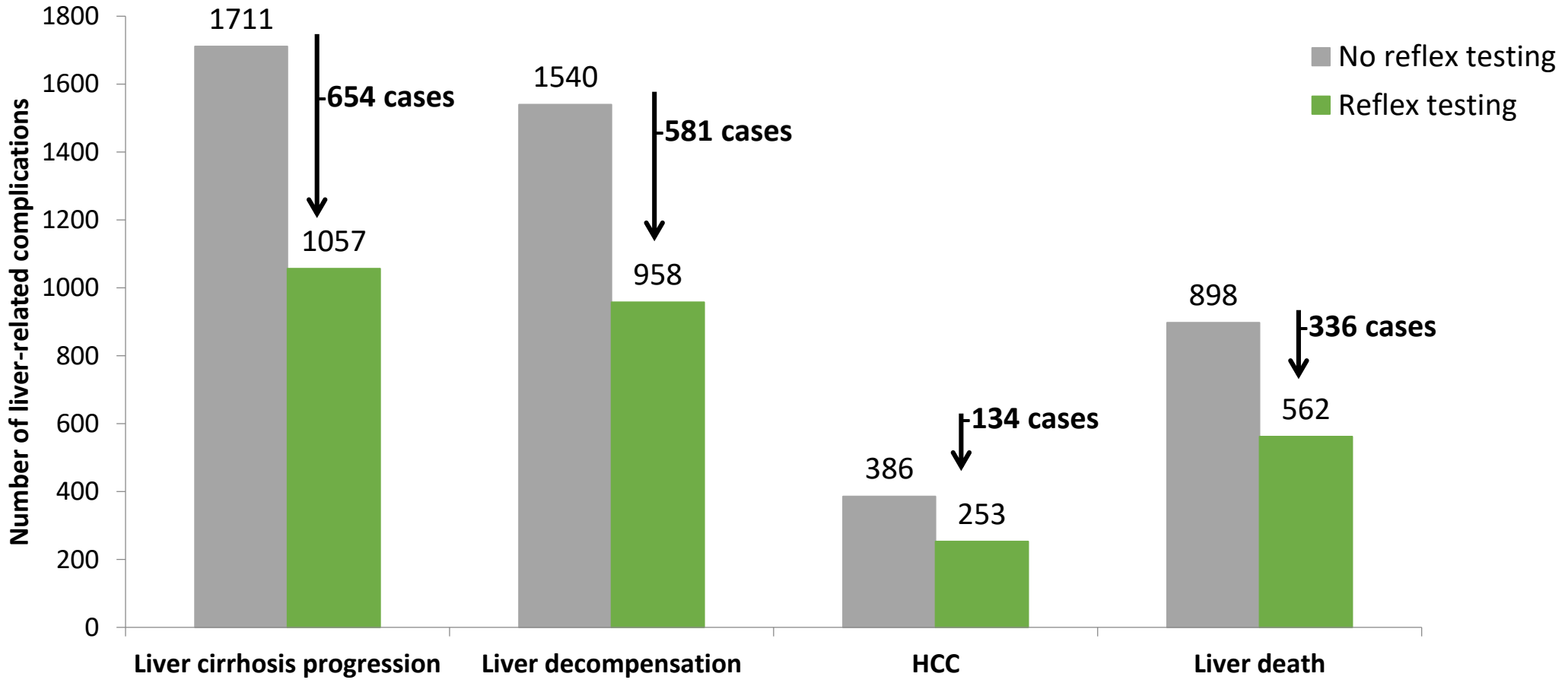
Reflex testing increases hepatitis D diagnosis x9 in Spain



The additional cost per anti-HDV+ patient detected with reflex testing in all HBsAg+ subjects would be **129€**

Buti M, et al. EASL 2023 abs accepted

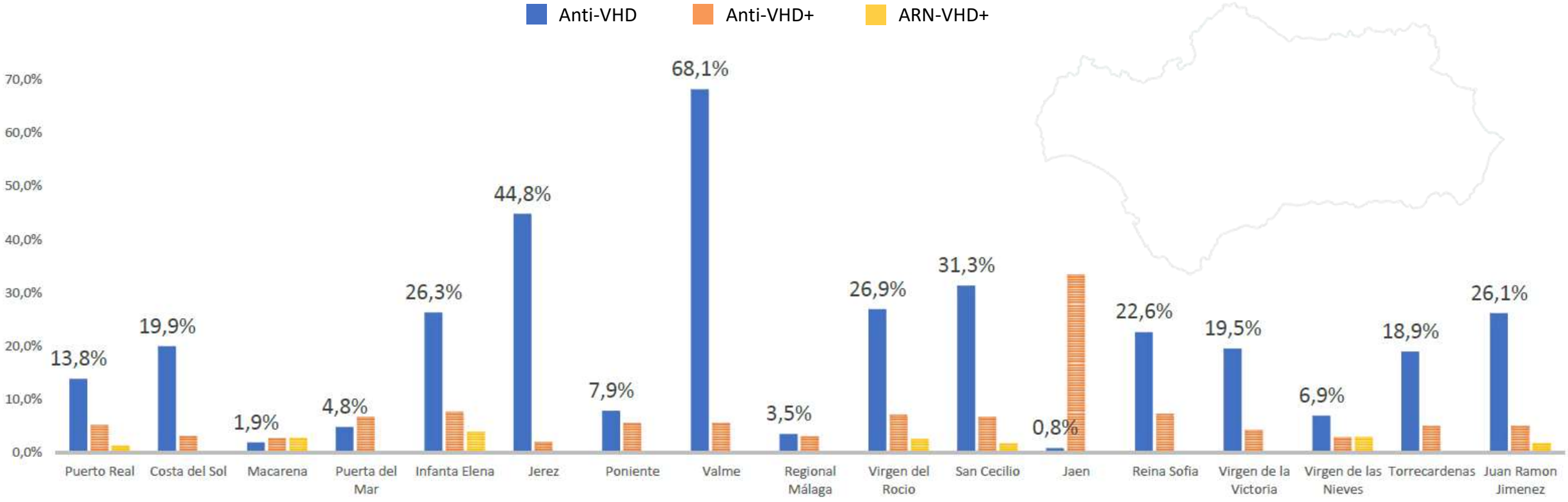
Reflex testing reduces hepatitis D liver complications
Is it cost-effective?



Liver-related complications would be reduced between 31-37% with the use of anti-HDV reflex testing, saving **36M €**

Buti M, et al. EASL 2023 abs accepted

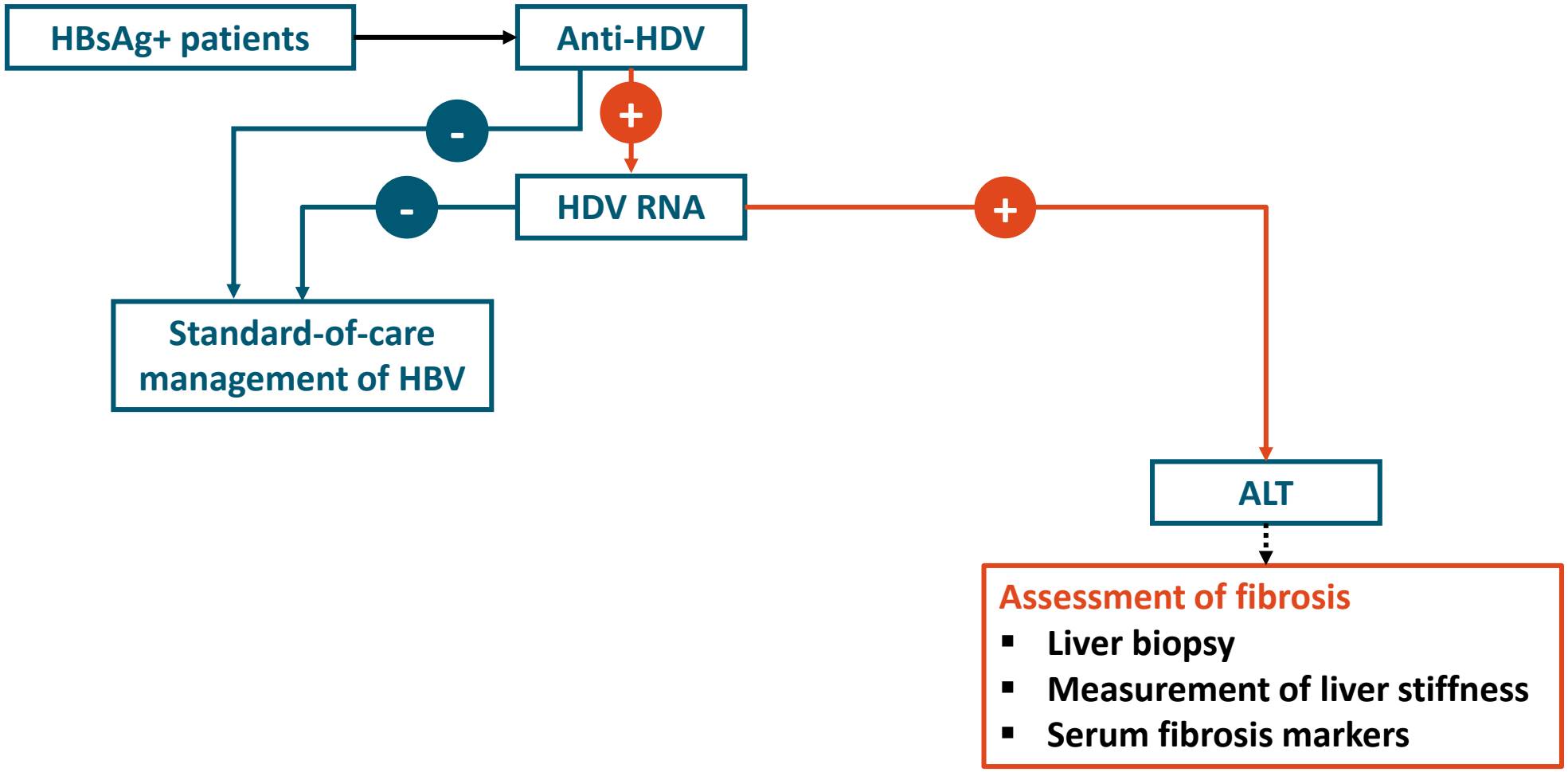
Datos de Andalucía demuestran el infradiagnóstico del VHD: solo se criban el 18% de las personas HBsAg positivas



VHD: virus de la hepatitis delta; HBsAg: antígeno de superficie del virus de la hepatitis B; Anti: anticuerpos; ARN: ácido ribonucleico

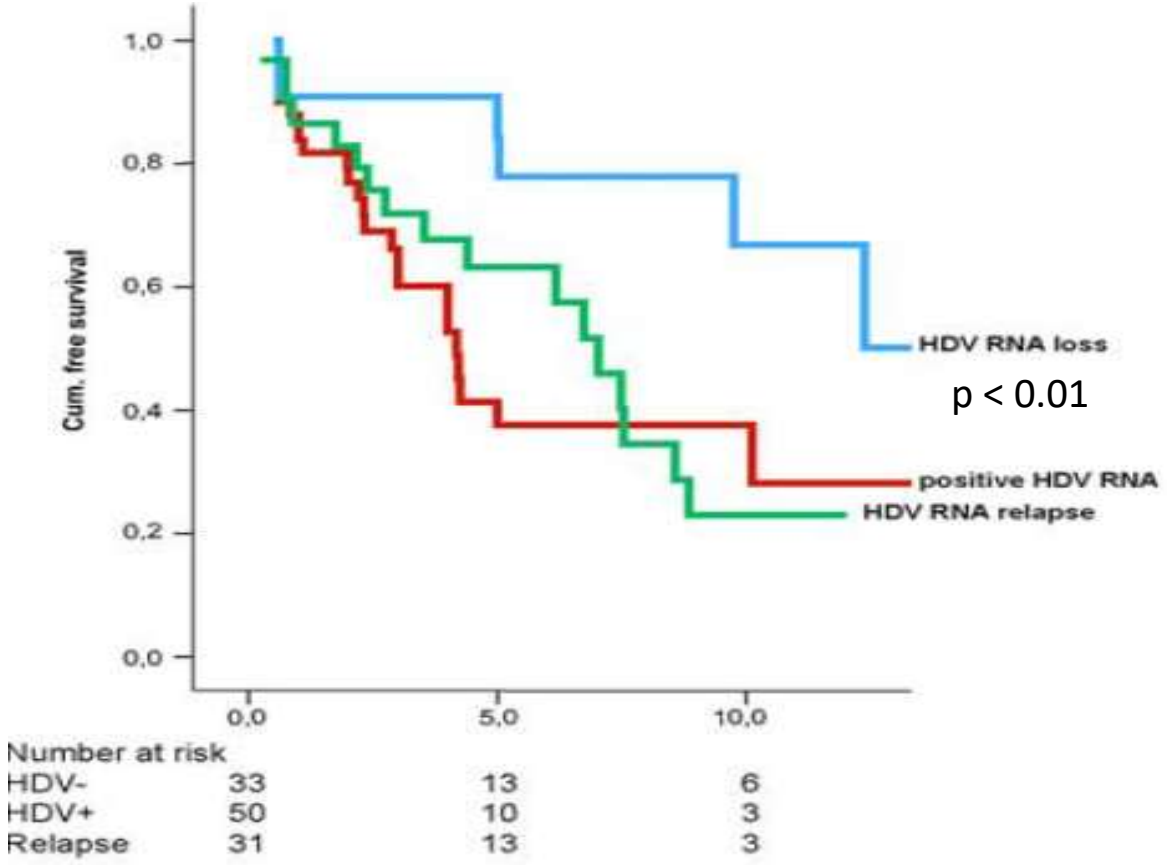
Fuentes A, et al. GEHEP 2022. CO18.

Algorithm for the Evaluation of HDV



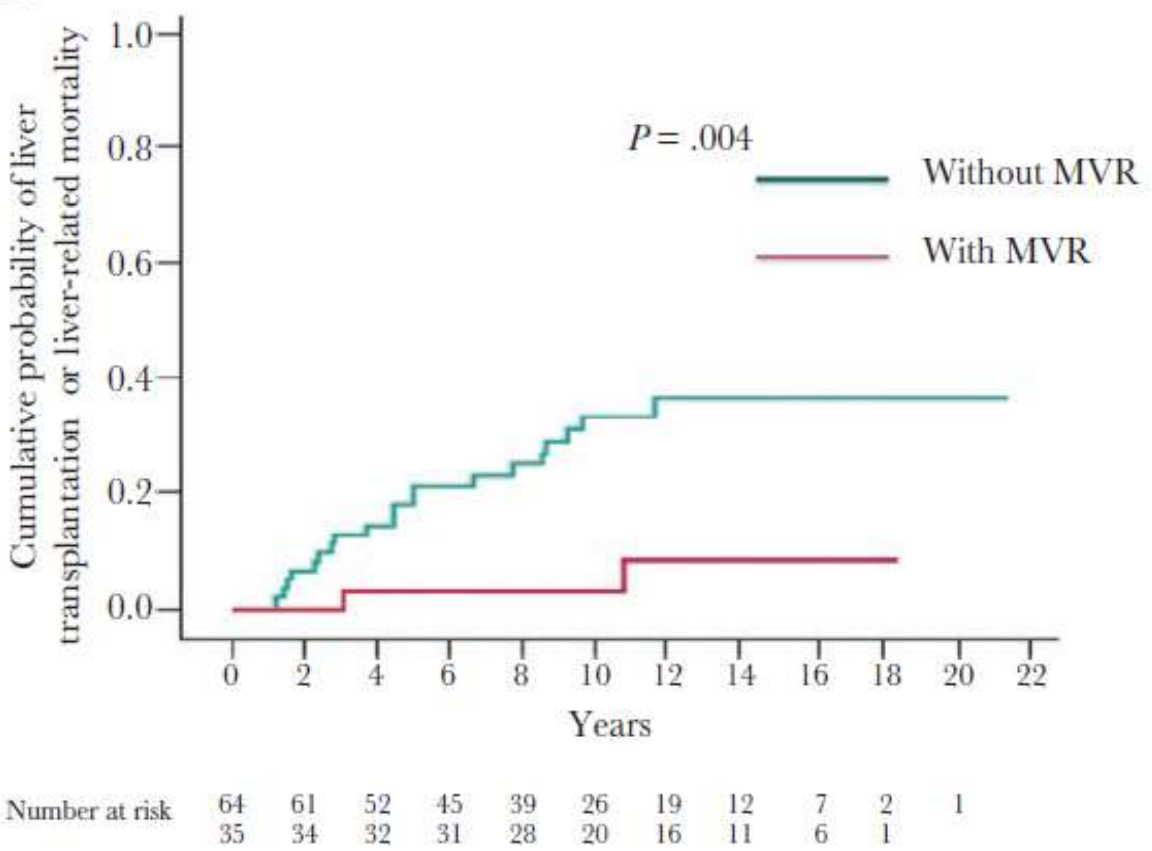
Adapted from: Shah. Gastroenterol Rep (Oxf). 2019;7:396.

Long-term survival in patients with undetectable HDV RNA



p < 0.01

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



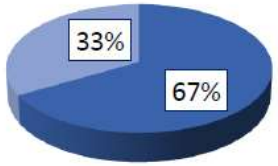
Yurdaydin C et al. J Infect Dis. 2018;217:1184-1192

Registro multicéntrico de hepatitis D en España: el 13% de los centros (2/15) dispone de test ARN-VHD cuantitativo

HEPATITIS DELTA REGISTRO

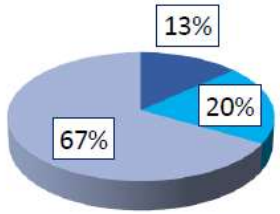
AEEH Asociación Española para el Estudio del Hígado

HBsAg cuantificado



ARN-VHD

ARN-VHD cuantitativo



Disponible
Externalizado
No disponible

Hepatitis D en el registro N=213 casos

- **Hombres:** 51%
- **Edad media:** entre 40-60 (62% de los pacientes)
- **Extranjeros:** 45%
- **VHC / VIH coinfectados**: 16% / 10%
- **Situación en la primera visita médica**:
  - Cirrosis: 38%
  - Hipertensión portal: 13%
  - Descompensado: 4%

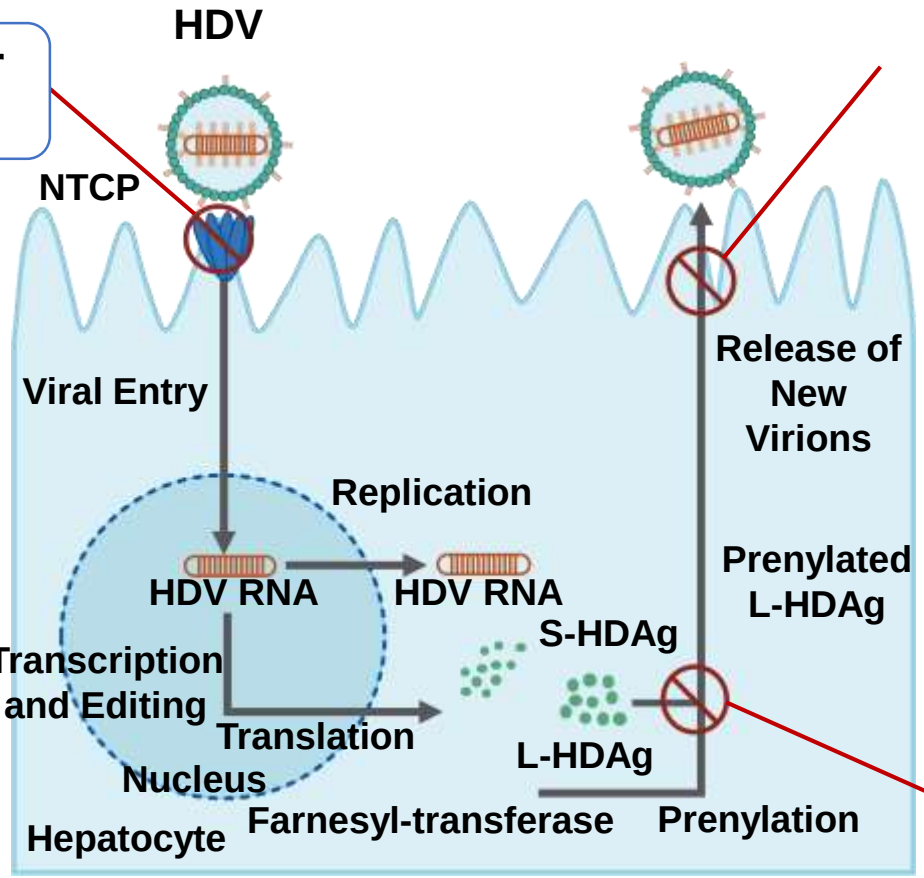
ARN: ácido ribonucleico; VHD: virus de la hepatitis delta; HBsAg: antígeno de superficie del virus de la hepatitis B; VHC: virus de la hepatitis C; VIH: virus de la inmunodeficiencia humano

Rodríguez-Tajes S. Congreso Anual AEEH 2022. Comunicación Oral 01392

Therapeutic Targets for HDV Infection

Entry Inhibitor
Bulevirtide

Inhibitors of HBsAg Release (NAPs)
REP-2139
REP-2165



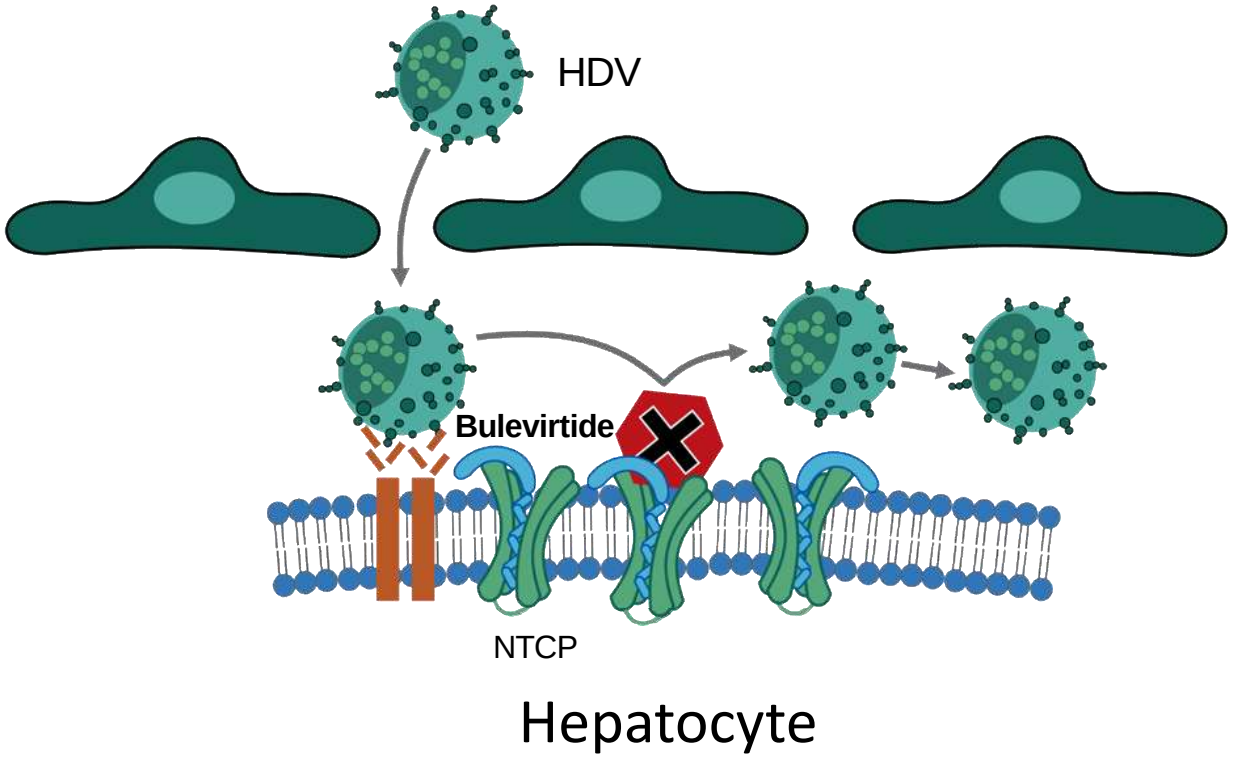
Immunomodulators
PEG-IFN-λ
PEG-IFN-α

Prenylation Inhibitor
Lonafarnib

PEG-IFN-λ: pegylated interferon lambda; L-HDAg: large form HDV antibody; NAP: nucleic acid Polymer.
Loureiro D et al. *Liver Int*. 2021;41:30-37.

Bulevirtide: Mechanism of Action

- 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
  - Conditionally approved in Europe by the EMA



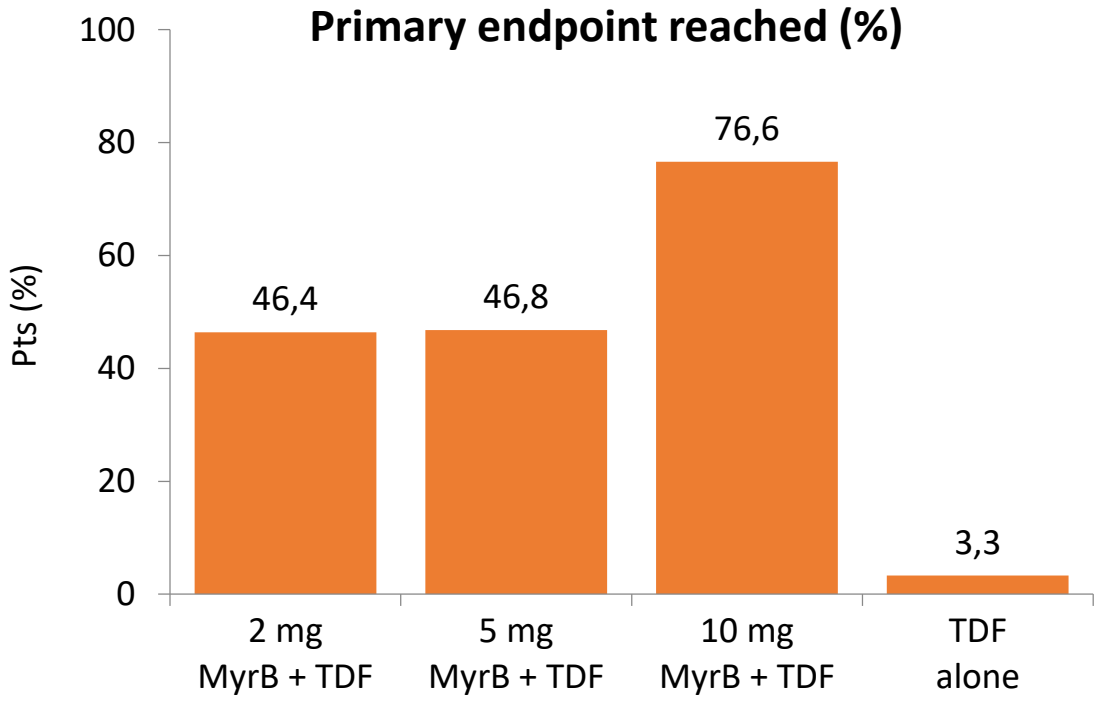
EMA: European Medicines Agency; SC: subcuataneous.

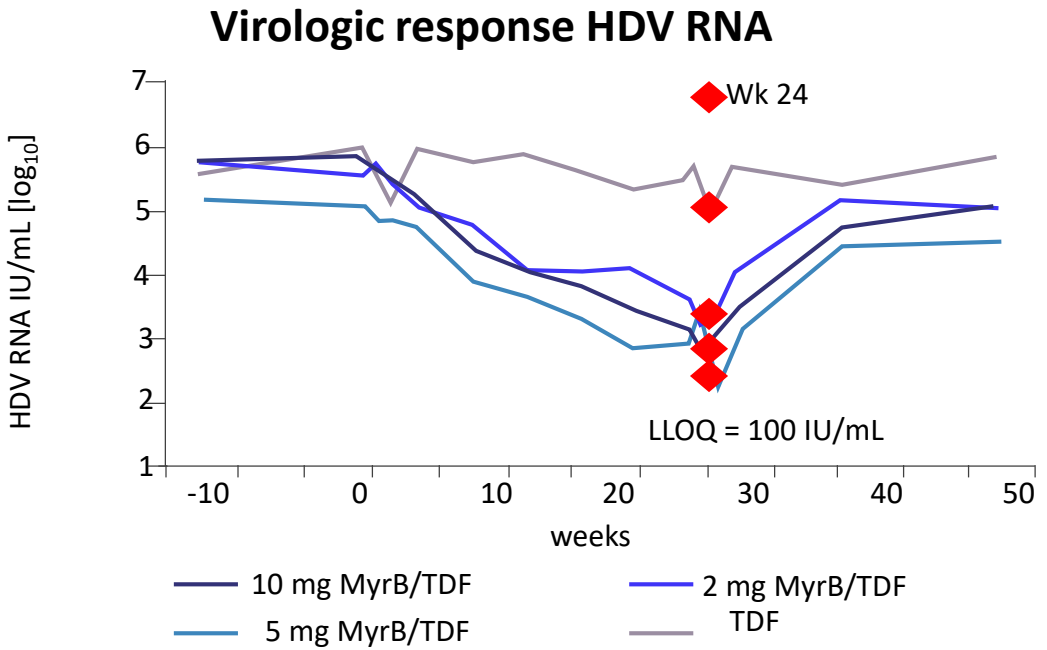
Yardeni D, Koh C. *Drugs Today (Barc)*. 2021;57:433-448. Gilead press release. November 19, 2021. https://www.gilead.com/news-and-press/press-room/press-releases/2021/11/gilead-submits-biologics-license-application-to-us-food-and-drug-administration-for-bulevirtide-an-investigational-treatment-for-people-living-with

Efficacy and Safety of Bulevirtide + TDF for 24 weeks in patients CHD (Phase 2b MYR 202)

Study design

- 120 patients (30 per arm) 50% cirrhosis
- Myrcludex B SC QD in vViral suppress TDF (oral QD) during entire study period
- Primary endpoint: HDV RNA ≥2 log_{10} from BL to Wk 24

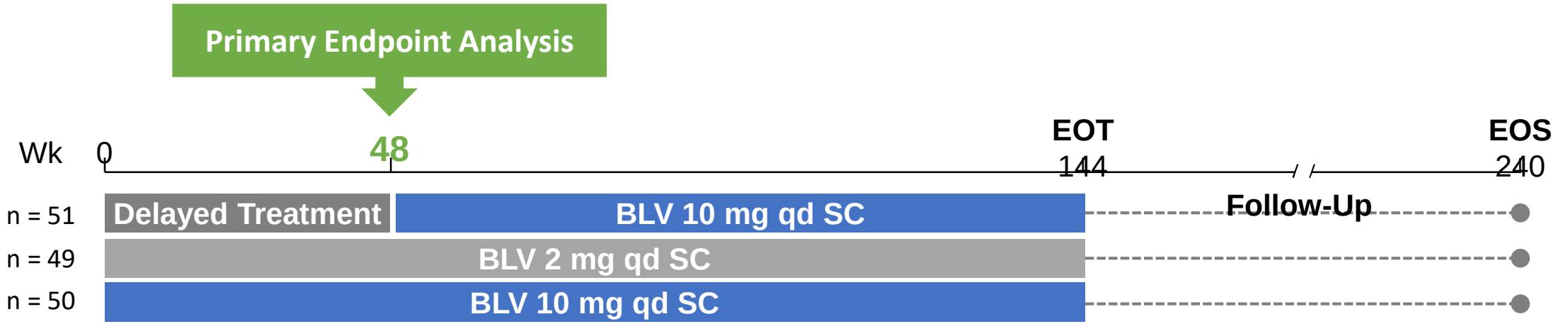




Wedenmeyer H et al. Lancet Gastro Hepatol 2023

MYR301: Study Design

Multicenter, open-label, randomized phase III trial conducted in 4 countries (Germany, Italy, Russian Federation, and Sweden) including 150 patients with CHD



Key Inclusion Criteria

- CHD without or with cirrhosis and CPT ≤7
- ALT >1x to <10x ULN
- Platelets ≥60,000 cells/mm^3

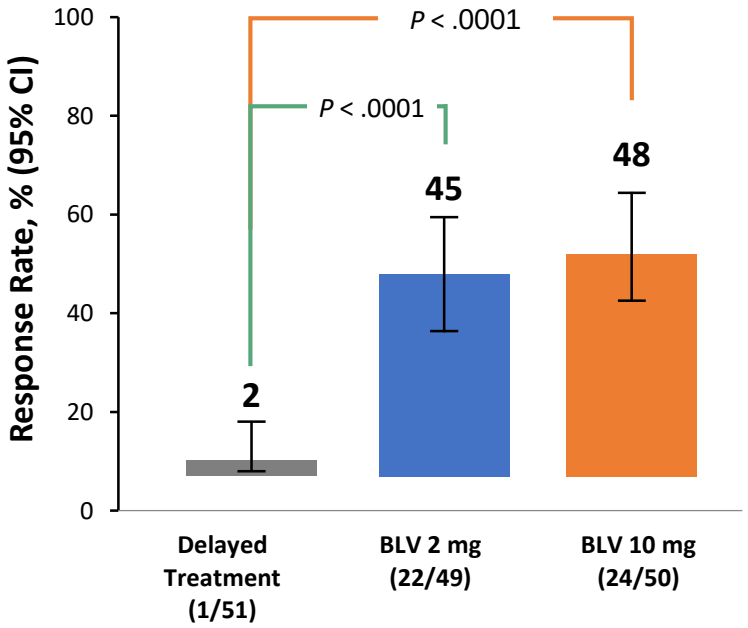
- Combined response at Wk 48: HDV RNA undetectable *or* decrease by ≥2 $\log_{10}$ IU/mL from BL *and* ALT normalization (FDA draft guidance for development of HDV treatment)

BLV: bulvirtide; EOS: end of study; EOT: end of treatment; qd: once daily.

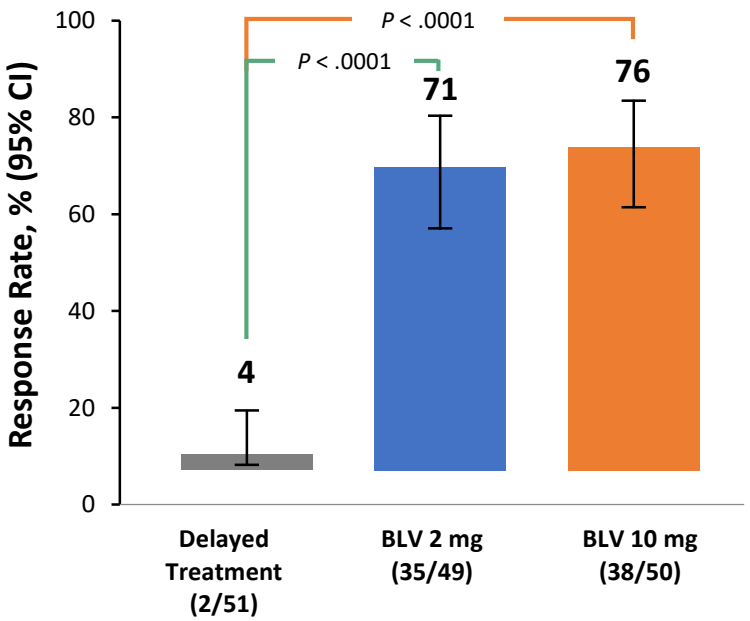
Wedemeyer H et al. International Liver Congress. 2022. Oral 509; ClinicalTrials.gov Identifier: NCT03852719. https://clinicaltrials.gov/ct2/show/NCT03852719. Accessed November 1, 2022.

MYR301: Response at Week 48

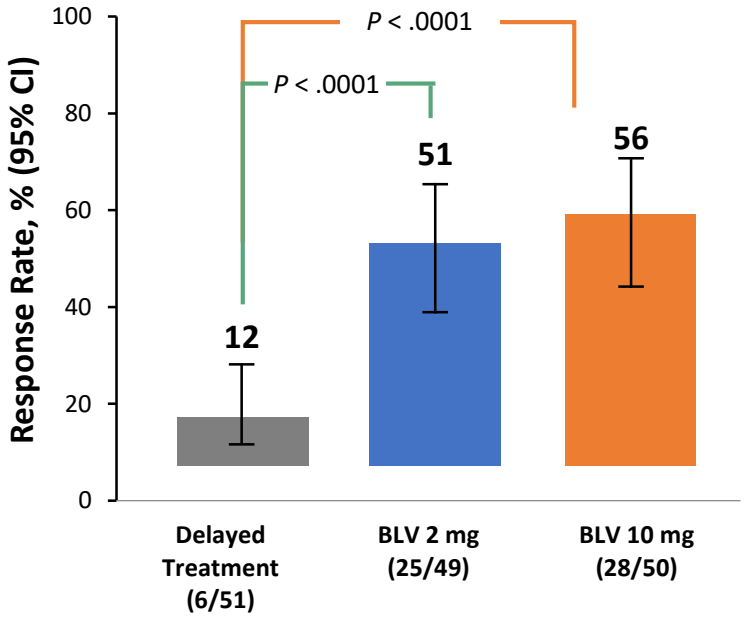
Primary Endpoint



HDV RNA Response



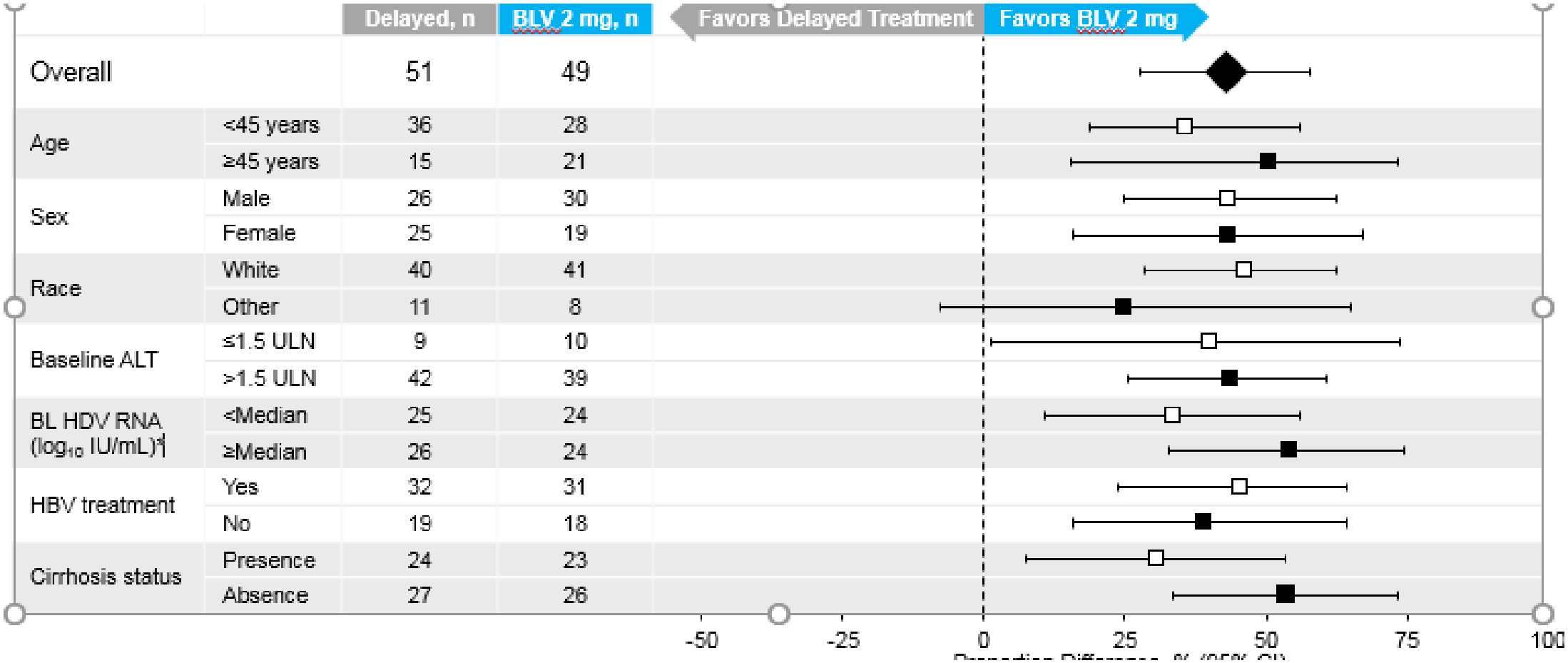
Biochemical Response



Wedemeyer H et al. International Liver Congress. 2022. Oral 509.

Primary Endpoint: Combined Response at Week 48

		Delayed, n	BLV 2 mg, n
Overall		51	49
Age	<45 years	36	28
	≥45 years	15	21
Sex	Male	26	30
	Female	25	19
Race	White	40	41
	Other	11	8
Baseline ALT	≤1.5 ULN	9	10
	>1.5 ULN	42	39
BL HDV RNA (log_{10} IU/mL)[1]	<Median	25	24
	≥Median	26	24
HBV treatment	Yes	32	31
	No	19	18
Cirrhosis status	Presence	24	23
	Absence	27	26



Combined response defined as undetectable HDV RNA or ≥2 log10 IU/mL decline from BL and ALT Normalization
Undetectable HDV RNA defined as below LOD (6 IU/mL).
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). CI, confidence interval.

MYR301: Safety

BLV Monotherapy in Patients With Chronic Hepatitis Delta, Wk 48 Analysis

Overall Safety Summary		Delayed Treatment, n = 51	BLV 2 mg, n = 49	BLV 10 mg, n = 50
Any AE		39 (77)	40 (82)	44 (88)
Any Grade 3-4 AE		3 (6)	5 (10)	4 (8)
Any SAE		1 (2)[a]	2 (4)[b]	1(2)[c]
Any AE leading to withdrawal of BLV		0	0	0
Any AE related to BLV		0	24 (49)	36 (72)
Death		0	0	0
AEs of Interest[d]	Headache	0	9 (18)	10 (20)
	Dizziness	0	2 (4)	2 (4)
	Nausea	2 (4)	3 (6)	4 (8)
	Pruritis	0	6 (12)	8 (16)
	Fatigue	1 (2)	5 (10)	8 (16)
	Injection site reactions[e]	0	8 (16)	15 (30)

- No SAEs related to BLV or AEs leading to discontinuation of study drug
- Asymptomatic elevations in total serum bile acids observed in BLV groups
- Injection site reactions were mild to moderate and occurred at a higher frequency with BLV 10 mg
- **No case of Grade 3 or 4 elevation in bile acids**

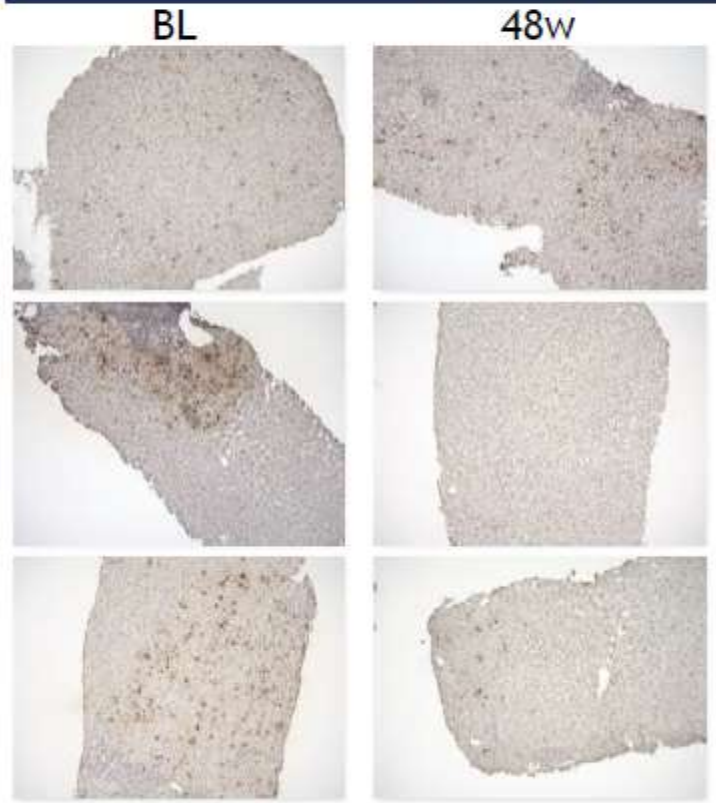
[a]Cholelithiasis (n = 1), COVID-19 (n = 1); [b]Asthenia and depression (n = 1), foot fracture (n = 1); [c]COVID-19 pneumonia (n =1); [d]AEs with higher frequencies in BLV groups compared to delayed treatment; [e]Grouped term including injection site reaction, injection site erythema, injection site pruritis, injection site swelling, injection site pain, injection site haematoma, injection site rash, injection site abscess, injection site dermatitis, injection site irritation. [f]Grade >3 AEs: 1 participant each, BLV 10 mg: COVID-19, leukopenia, pneumonia; BLV 2 mg foot fracture, neutrophil count decreased, osteopenia, depression; Grade >3 AEs related to BLV: 1 participant each, BLV 10 mg: thrombocytopenia, neutropenia, leukopenia; BLV 2 mg: neutrophil count decreased.

AE: adverse event; SAE: serious adverse event.

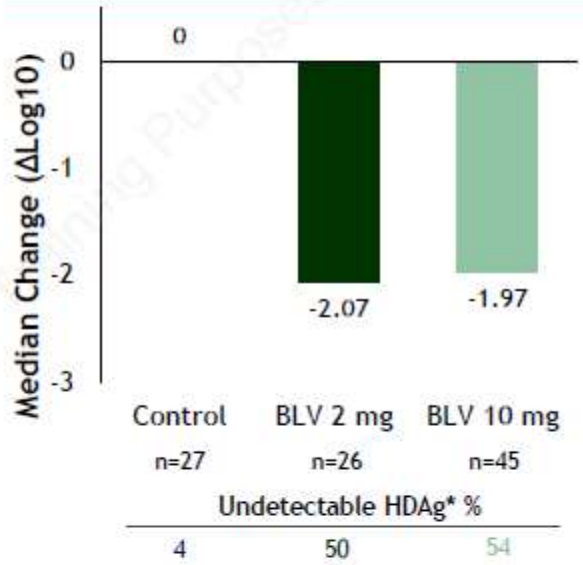
Wedemeyer H et al. International Liver Congress. 2022. Oral 509.

Integrated Paired Biopsy Analysis at 48 Weeks

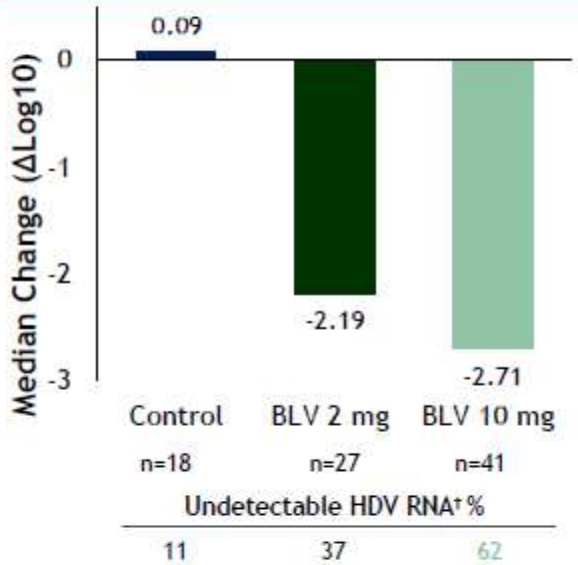
Intrahepatic analysis of HDV biomarkers at 48 weeks of BLV treatment



HDAg-Positive Hepatocytes



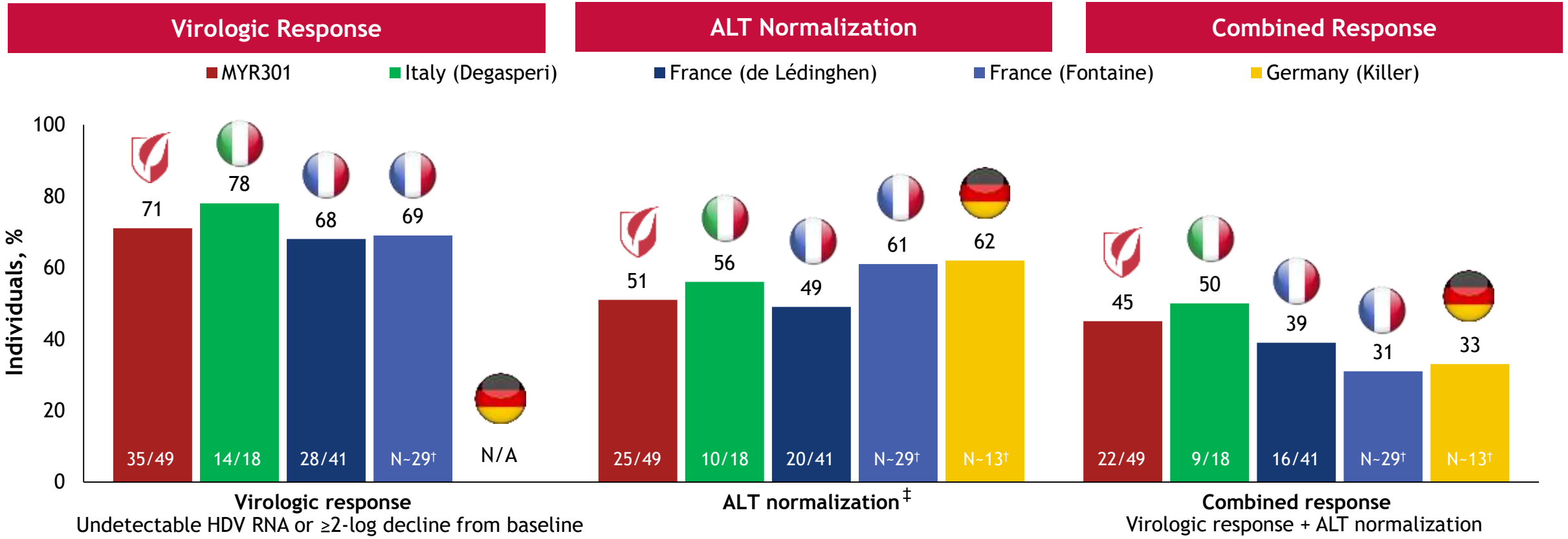
Intrahepatic HDV RNA Levels



48 weeks of BLV led to a marked drop in HDV-infected hepatocytes

*Lower limit of detection = 0.01% of positive cells; †Lower limit of detection not provided
BLV, bulevirtide; BL, baseline; HDAg, hepatitis delta antigen.
Allweiss L, et al. International HBV Meeting 2022. Presentation #49

BLV 2 mg monotherapy in CHD: efficacy at week 48 MYR301 and RWD Sets



Week 48 RWD support the efficacy of BLV 2 mg observed in MYR301

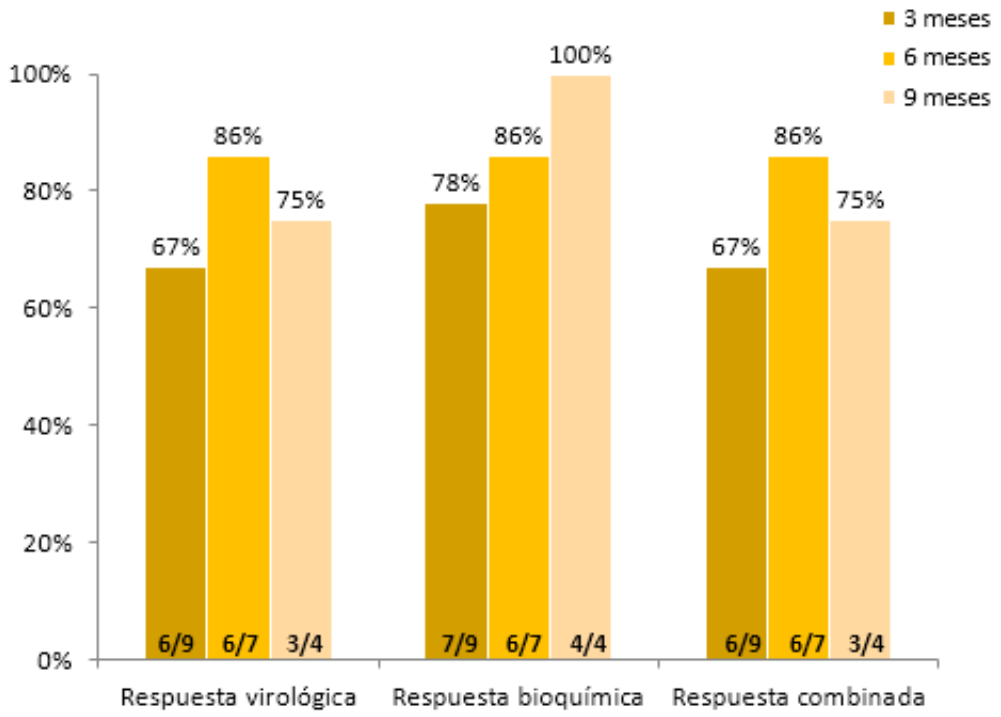
*NOT HEAD-TO-HEAD COMPARISONS. †n/N are not provided/unclear in the source document; ‡See slide notes for ALT cutoff values. BLV, bulevirtide; RWD, real-world data.

1) . Wedemeyer H, et al. EASL 2022. Oral #GS006; 2. Degasperi A, et al. EASL 2022. Poster #SAT429; 3. de Lédinghen V, et al. AASLD 2021. Oral #21; 4. Fontaine H, et al. EASL 2022. Oral #OS093; 5. Killer A, et al. EASL 2022. Poster #SAT345

Experiencia Preliminar de Bulevertide en España

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%)



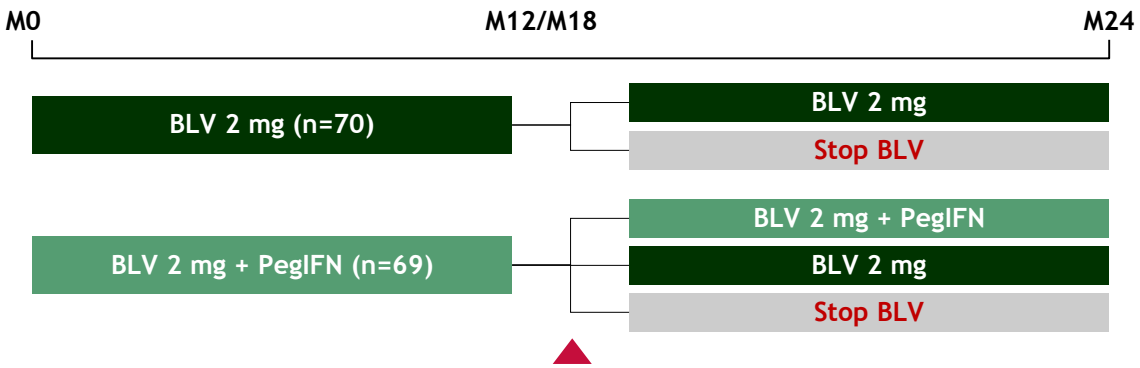
En un paciente se interrumpió el tratamiento a los 9 meses por persistencia de ALT elevadas e incremento en los niveles de ARN-VHD.

La tolerancia fue buena. No se observaron descompensaciones de la enfermedad hepática ni desarrollo de carcinoma hepatocelular.

Buti M et al. AEEH 2023.

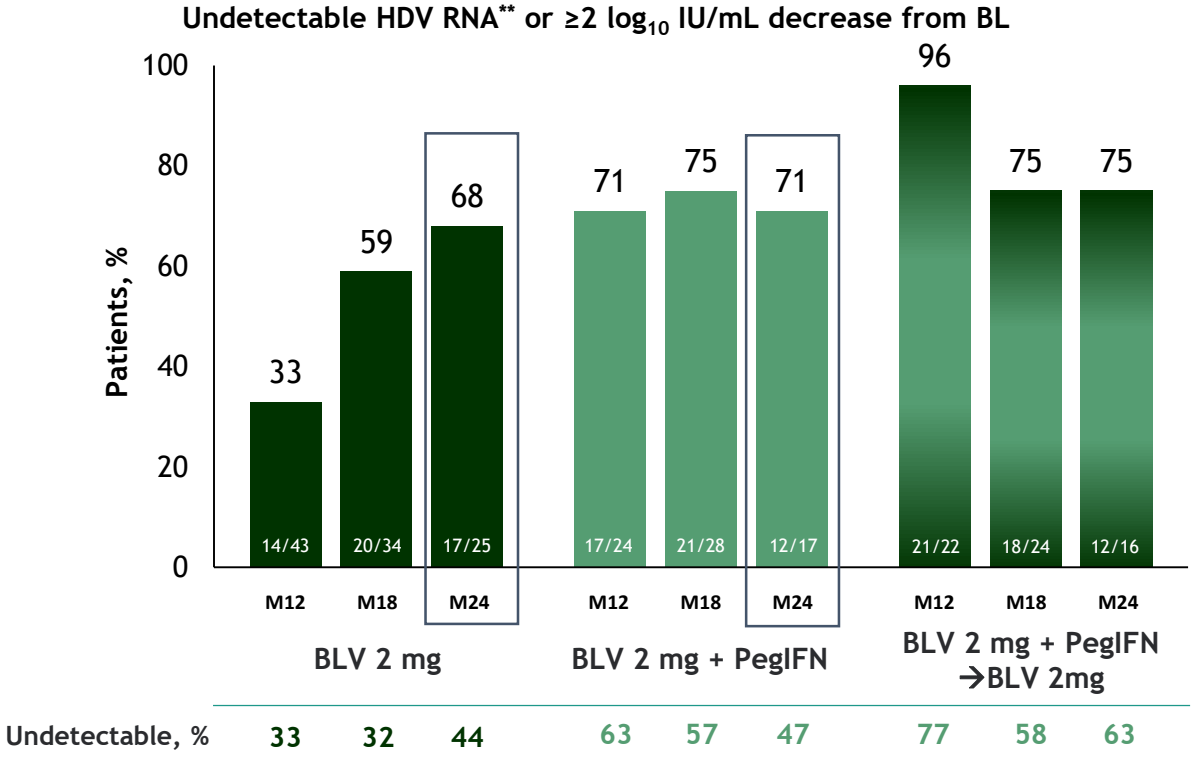
Two-Year Early Access Program RWD from France

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.

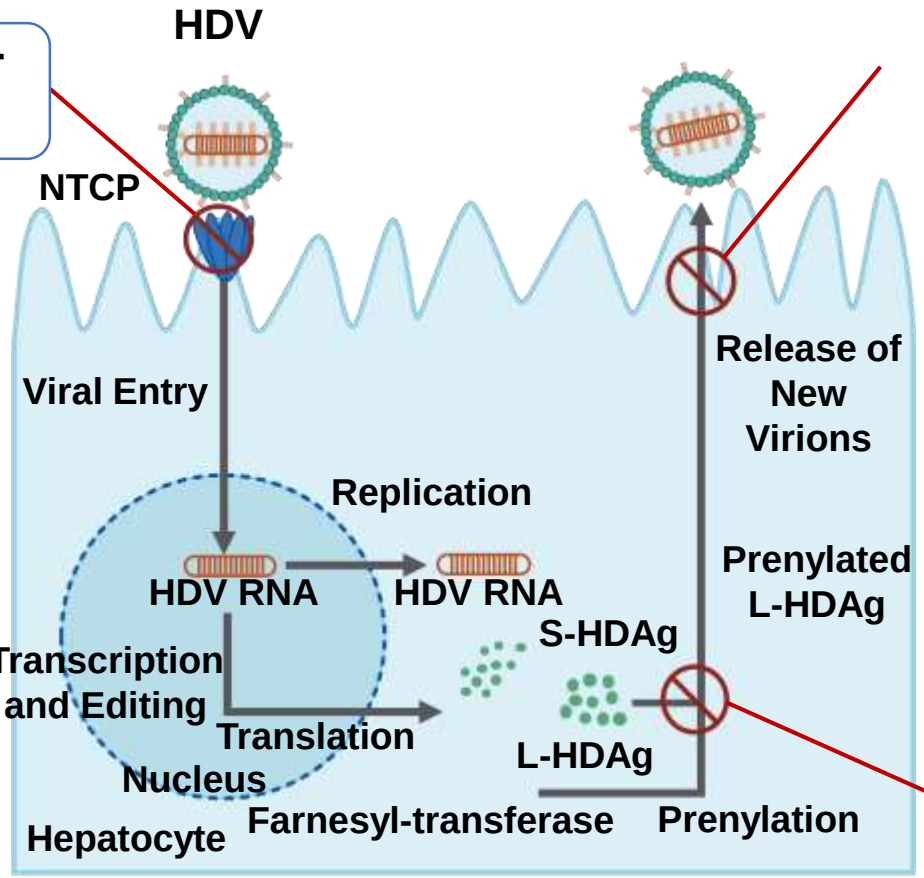
de Lédinghen V, et al. AASLD 2022. Oral #28

‡ Cohort Temporary Authorization for Use (cATU)

Therapeutic Targets for HDV Infection

Entry Inhibitor
Bulevirtide

Inhibitors of HBsAg Release (NAPs)
REP-2139
REP-2165

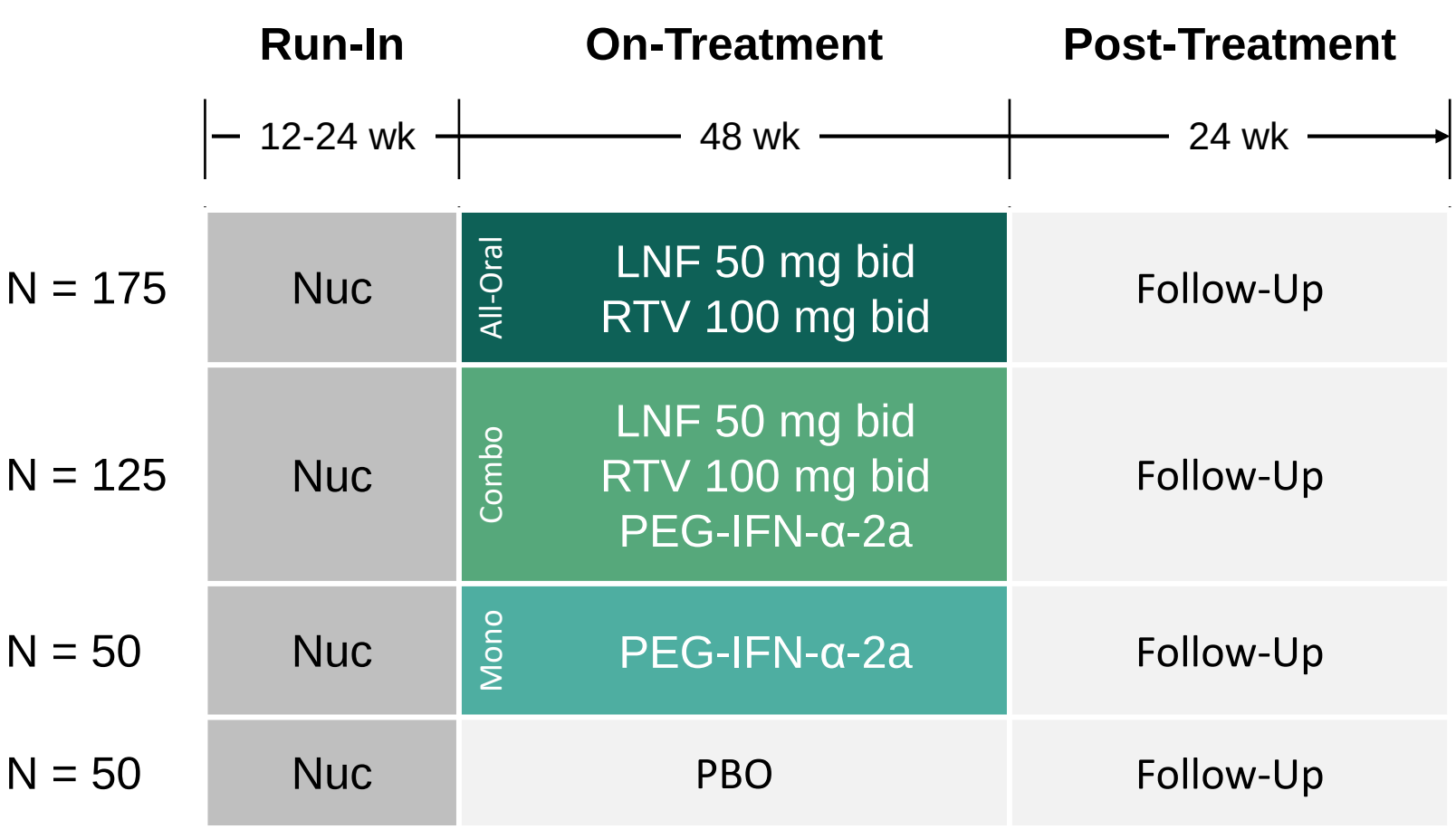


Immunomodulators
PEG-IFN-λ
PEG-IFN-α

Prenylation Inhibitor
Lonafarnib

PEG-IFN-λ: pegylated interferon lambda; L-HDAg: large form HDV antibody; NAP: nucleic acid Polymer.
Loureiro D et al. *Liver Int*. 2021;41:30-37.

D-LIVR: Phase 3 Global Study



- Primary endpoint at Wk 48
  - ≥2 log decline in HDV RNA+
  - Normalization of ALT

Eiger Announces both Lonafarnib-based Treatments achieved Statistical Significance Against Placebo in Composite Primary Endpoint

December 2022

All patients will be run-in and maintained on background HBV nucleoside therapy.
HAI: hepatic activity index; PBO: placebo.
ClinicalTrials.gov Identifier: NCT03719313. https://clinicaltrials.gov/ct2/show/NCT03719313. Accessed November 2, 2022.

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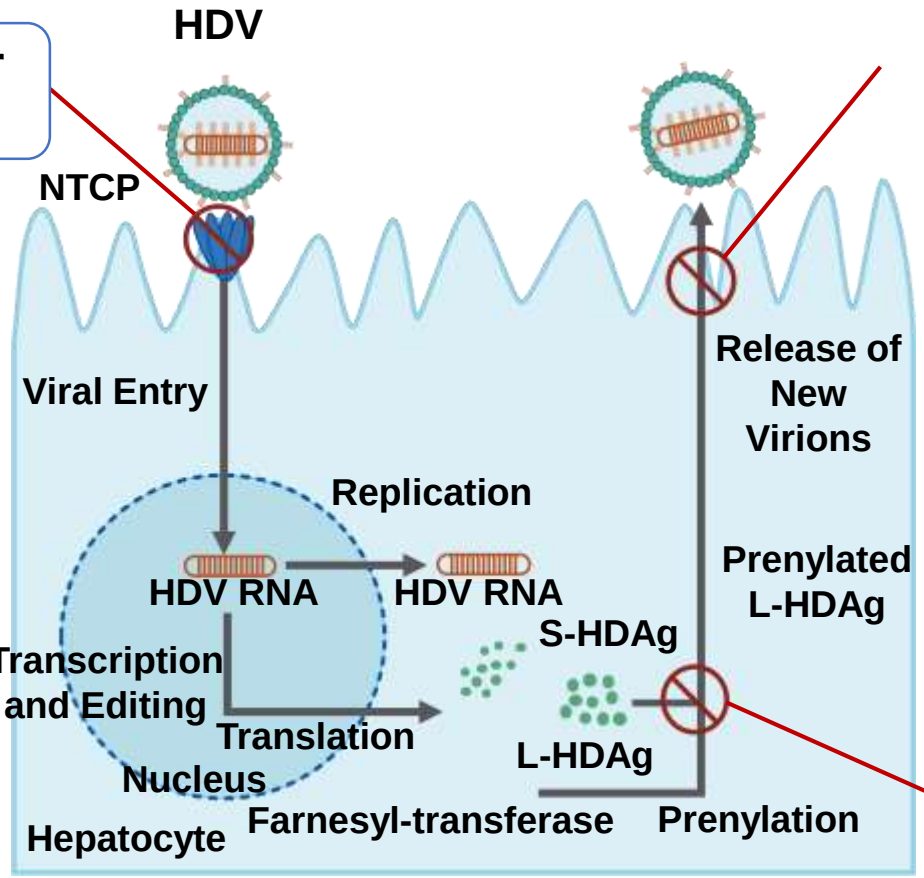

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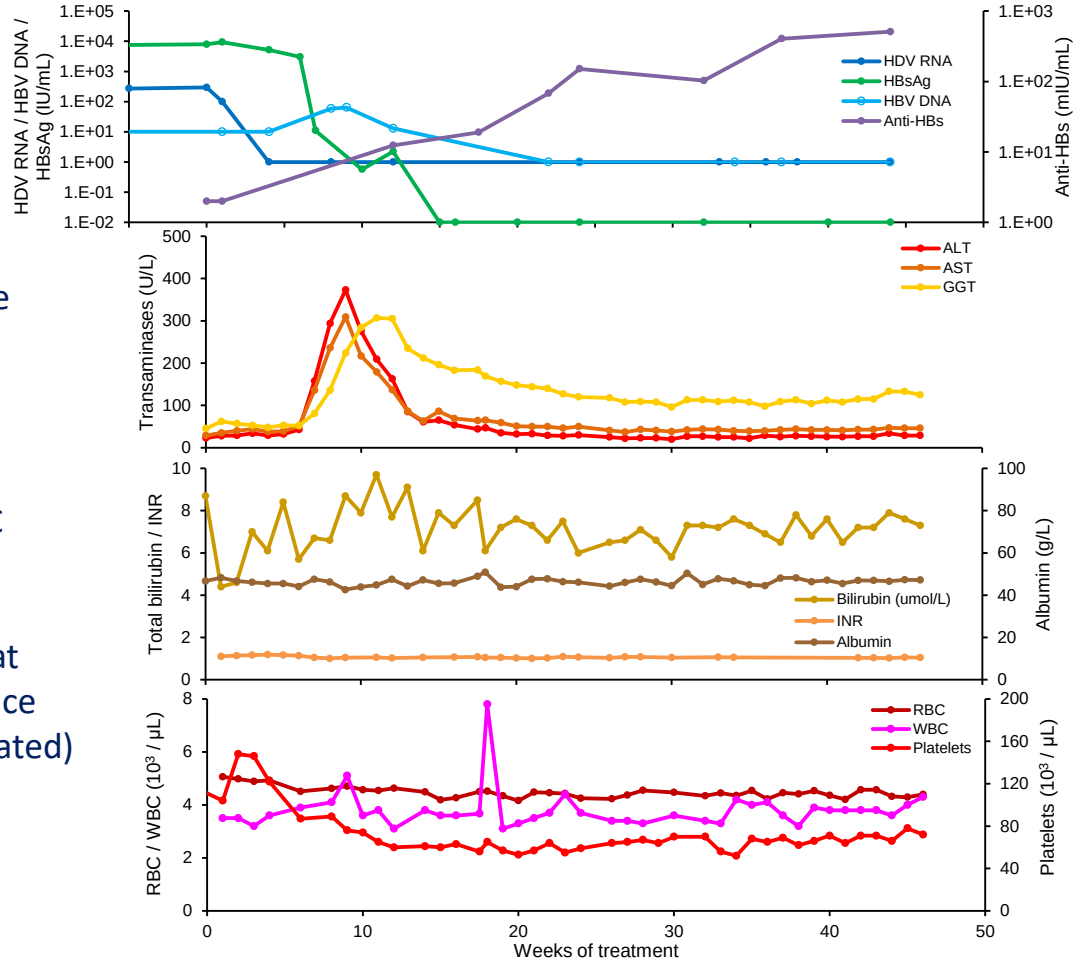
Transition of REP 2139-Mg to subcutaneous administration

Compassionate use program in France

Senegalese
51 years old male
Compensated cirrhosis
HBV / HDV (GT5)
Previous failure on:
- TDF + pegIFN
- TDF + pegIFN + bulvertide

Currently receiving:
- TDF
- low dose pegIFN (90ug)
- REP 2139-Mg (250mg) SC (once every week)

Transition to 125mg REP 2139-Mg IV at week 14 to maintain patient compliance (despite SC injections being well tolerated)



HBsAg loss at week 15
HBsAg seroconversion @ week 12 (508 IU/mL at EOT)
HDV DNA TND @ week 4
HBV DNA TND before week 22

Host mediated transaminase flare coincident with HBsAg clearance and HBV DNA flare

Normal liver synthetic / secretory function throughout

Stable hematology

SC REP 2139-Mg dosing initiated in two additional HBV / HDV cirrhotic patients with poor / no response to previous pegIFN and pegIFN + bulvertide therapy

A Vaillant, M Bourliere personal communication

Take-home Points

- All patients positive for HBsAg should be tested for hepatitis delta and those positive for HDV RNA
- Reflex anti-HDV testing and other strategies should be employed to increase HDV testing rates and reduce loss to follow-up in persons positive for HBsAg
- Patients with CHD should receive ongoing monitoring for liver damage and HCC since they experience more rapid progression vs those with HBV monoinfection
- Bulevertide, the first approved therapy for CHD, is efficacious and safe. However, more studies are needed to define best dose, therapy duration and the role of PegIFN in combination with BLV
- More studies with Bulevertide and other drugs are ongoing