I Jornada de Otoño en Enfermedades Infecciosas

“Hepatitis Delta”

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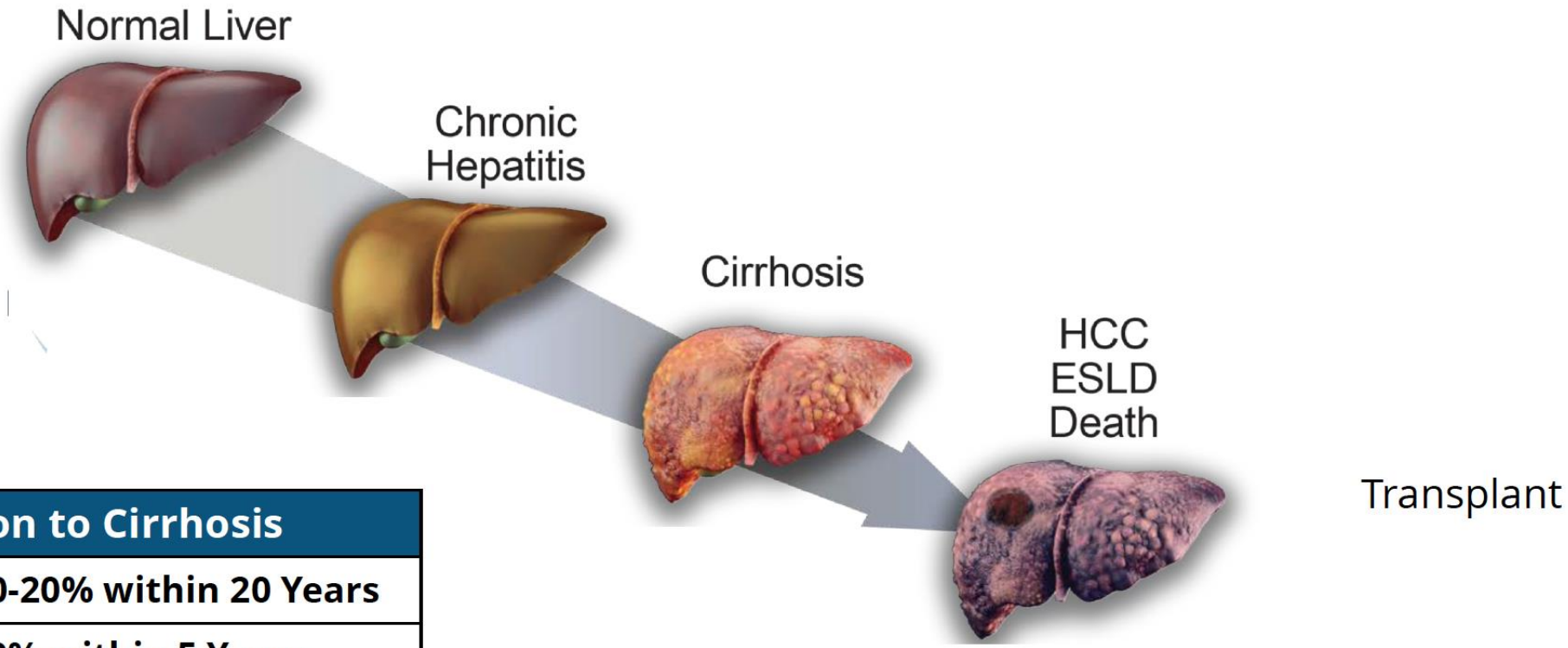
HDV
Most Rapid Progression of Viral Hepatitis

50% of HDV-Infected Patients are Cirrhotic at Diagnosis



Progression to Cirrhosis	
HCV	10-20% within 20 Years
HBV	20% within 5 Years
HDV	70% within 5-10 Years

1.-Westbrook et al. J Hepatology 2014; 61(1 Suppl):S58-68. 2.-Fattovich et al. Seminars in Liver Diseases 2003; 23(1):47-58. 3.-Nourredin et al. Curr Gastroenterol Rep. 2014 Jan;16(1):365

What Is Delta Hepatitis?

- First discovered in 1977 by Mario Rizzetto and colleagues
- Known as a “satellite virus” or an “incomplete virus”
  - Can only infect people who are also infected with the hepatitis B virus (HBV)
  - Uses HBsAg* to form the HDV envelope
- The smallest human RNA virus
- May be acquired simultaneously with HBV as co-infection OR by chronically infected HBV patients as super infection

***HBsAg = hepatitis B surface antigen.**

The First Paper Describing “Delta”

Gut, 1977, **18**, 997-1003

Immunofluorescence detection of new antigen-antibody system (δ/anti-δ) associated to hepatitis B virus in liver and in serum of HBsAg carriers

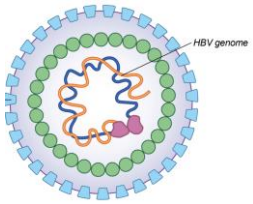
M. RIZZETTO,[1] M. G. CANESE, S. ARICÒ, O. CRIVELLI, C. TREPO, F. BONINO, AND G. VERME

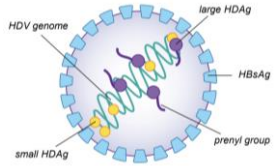
From the Department of Gastroenterology, Ospedale Mauriziano Umberto I, Turin, Italy, the Electron Microscopy Centre of the Faculty of Medicine, University of Turin, Italy, and INSERM U45, and Laboratory of Hygiene, University Claude Bernard, Lyon, France

SUMMARY A new antigen-antibody system associated with the hepatitis B virus and immunologically distinct from the HB surface, core, and *e* systems is reported. The new antigen, termed δ, was detected by direct immunofluorescence only in the liver cell nuclei of patients with HBsAg positive chronic liver disease. At present, the intrahepatic expression of HBcAg and δ antigen appears to be mutually exclusive. No ultrastructural aspect corresponding to the δ antigen could be identified under the electron microscope. δ antibody was found in the serum of chronic HBsAg carriers, with a higher prevalence in patients with liver damage. The nuclear fluorescence patterns of HBcAg and δ antigen were similar; it is only possible to discriminate between the two antigens by using the respective specific antisera.

Noureddin M, Gish R. *Curr Gastroenterol Rep.* 2014(1); 16: 365. DOI 10.1007/s11894-013-0365-x

Characteristics of HBV and HDV



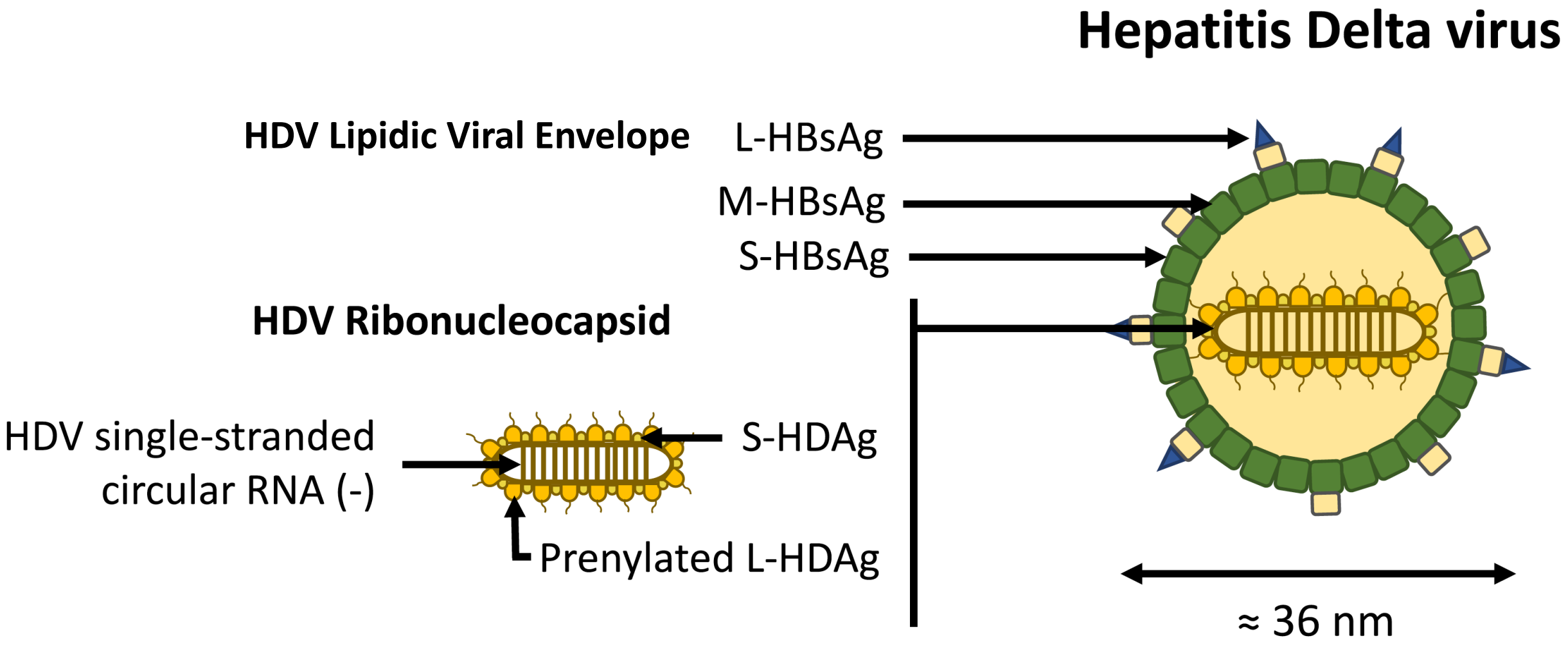


Characteristic	HBV[1]	HDV[1-4]
Family	*Hepadnaviridae*	*Kolmioviridae*
Genus	*Orthohepadnaviruses*	*Deltavirus*
Genome	Relaxed, circular, partially double-stranded DNA 3.2 kbp	Single-stranded (-) RNA 1.7 kbp
Virus-encoded proteins	HBcAg, HBeAg, polymerase, HBx, L-/M-/S-HBsAg	L-/S-HDAg
Cellular receptors	HSPG, NTCP*	HSPG, NTCP*
Chronically infected individuals worldwide	**296 million**	**12-60 million**
Vaccine available?	Yes	No
Curative therapy available?	No	No

***HSPG, heparan sulfate proteoglycans. NTCP, sodium taurocholate cotransporting polypeptide**

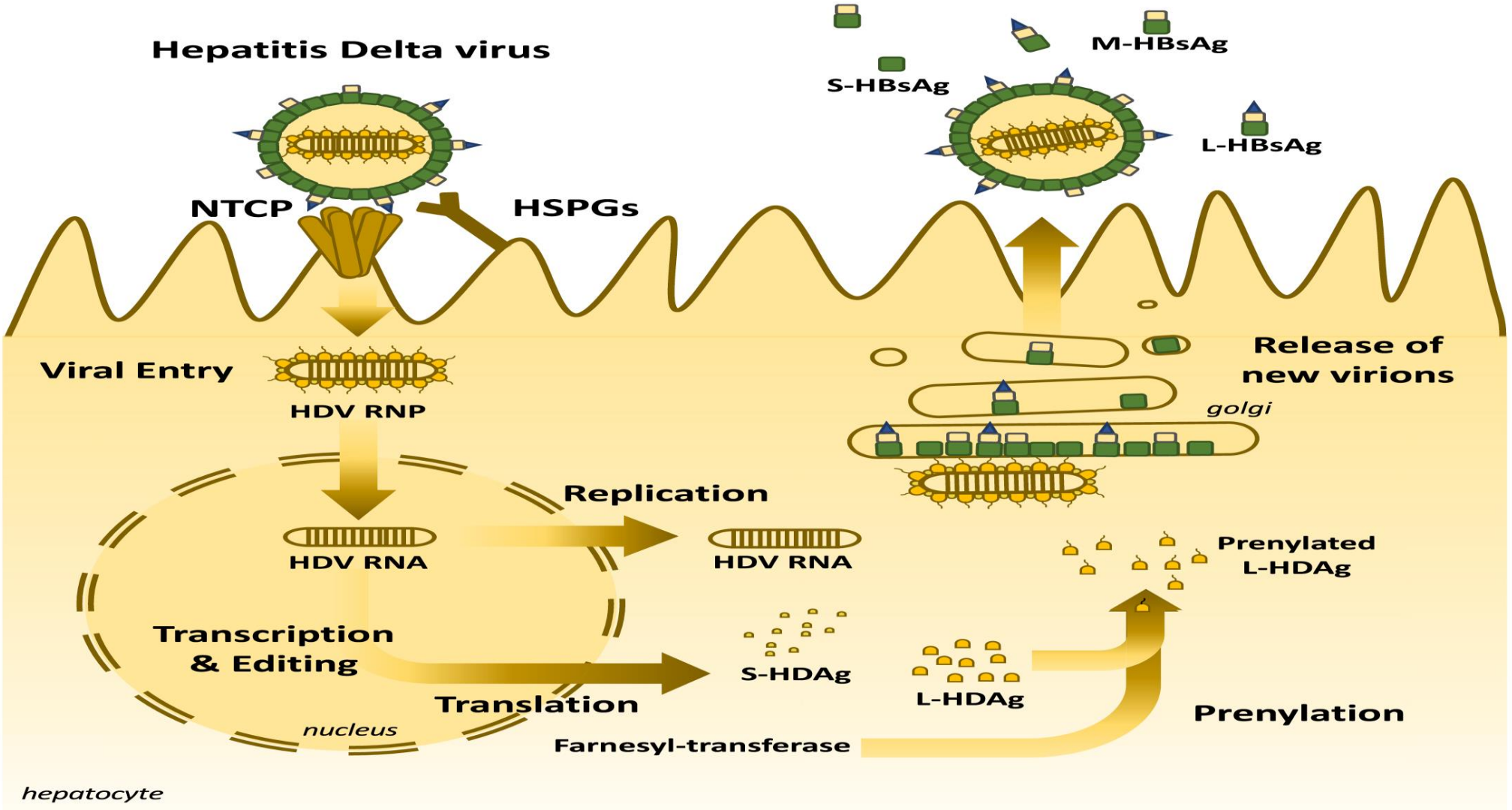
1. Lempp. Viruses. 2017;9:172. 2. Netter. Front Microbiol. 2021;12:652962.
3. Stockdale. J Hepatol. 2020;73:523. 4. Miao. J Infect Dis. 2020;221:1677.

Hepatitis Delta Virus (HDV) Viral Structure



Loureiro D, et al. Liver International. 2021;41(Suppl. 1):30–37.

Hepatitis Delta Virus (HDV) Viral Structure



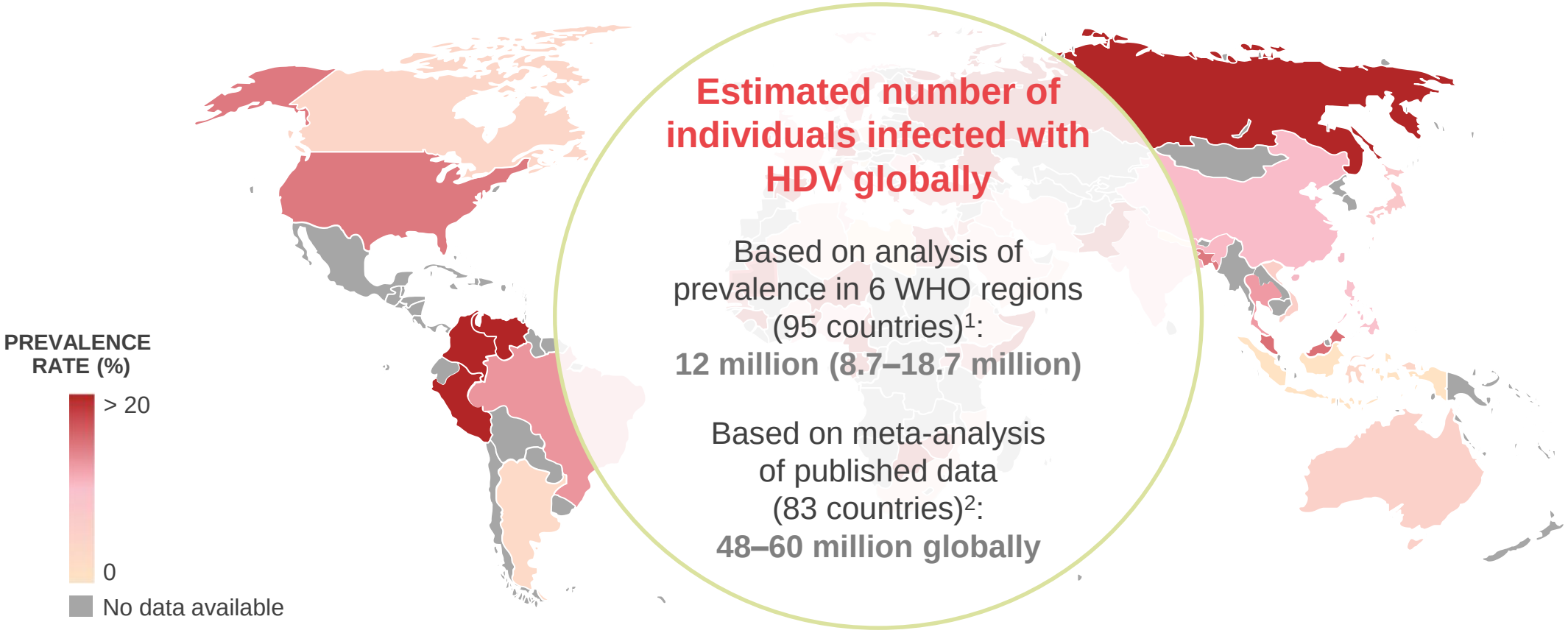
*HSPGs: Heparin Sulfate GlycoProtein

**NTCP: Sodium taurocholate co-transporting polypeptide

Loureiro D, et al. Liver International. 2021;41(Suppl. 1):30–37.

EPIDEMIOLOGIA
y
FACTORES de RIESGO

Approximately 4.5%-13% of HBsAg-Positive Carriers Are Coinfected With HDV



Prevalence of HDV in HBsAg-positive patients from Ref 2.
WHO: World Health Organization.

1. Stockdale AJ et al. *J Hepatol*. 2020; 73(3): 523–532; 2. Miao Z, et al. *J Infect Dis*. 2020(10); 221: 1677–1687.

PREVALENCIA Y CARACTERÍSTICAS DE PACIENTES CON VHD EN EE.UU.

Estudio de cohorte retrospectivo para estimar la prevalencia del VHD y las características de los individuos coinfectados con el VHD y el VHB a partir de la BBDD de "The Agency for Healthcare Research and Quality". (APCD; 2014-2020)

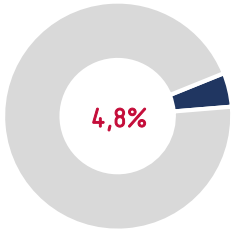
Adultos con VHB o VHD

194.573

VHD diagnosticado con VHB

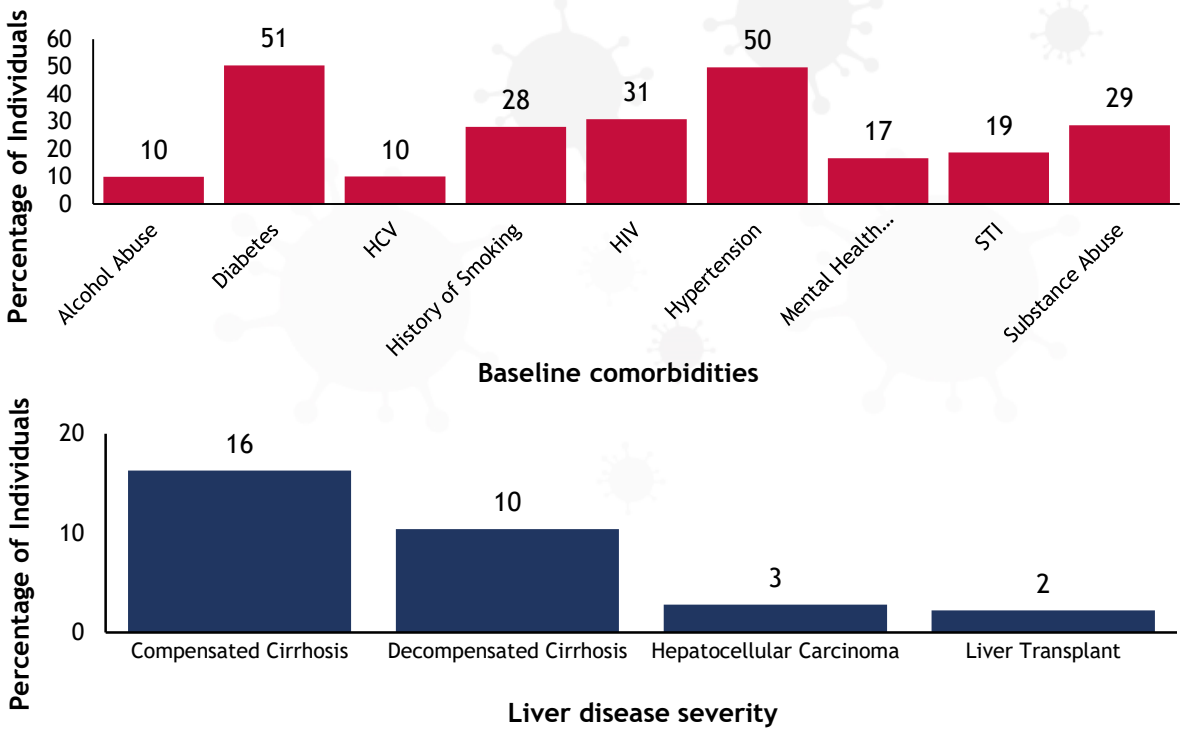
9.376

Prevalencia del VHD con VHB



Características de los adultos con VHD y VHB		N=6,719*
Mean age (SD)		51.9 (15.1)
Women, n (%)		3,391 (50)
Race**, n (%)	White	1,500 (49)
	Black	1,127 (37)
	Asian	420 (14)
	Other	29 (1)
Ethnicity**, n (%)	Hispanic	581 (21)
	Non-Hispanic	2,140 (79)
Level of education**, n (%)	High school or less	1,279 (67)
	College or post-graduate	625 (33)
Insurance, n (%)	Commercial	2,871 (43)
	Medicare	1,338 (20)
	Medicaid	2,295 (34)
	Other†	215 (3)
Mean CCI score (SD)‡		1.7 (2.3)

Comorbilidades iniciales y gravedad de la enfermedad hepática en adultos con coinfección por el VHD y el VHB



De los más de 194.500 adultos identificados con el VHB, el ~5% estaban coinfectados con el VHD y tenían altas tasas de comorbilidades y complicaciones hepáticas de base

*Personas con VHD y datos continuos de 12 meses antes y después de la fecha del índice; **La raza, el origen étnico, la educación y los ingresos no estaban disponibles para todos los pacientes; †Otros pagadores incluyen el VA y los planes de seguro que no especifican el canal de pago; ‡CCI pondera 15 condiciones comórbidas para determinar el riesgo de morbilidad de un paciente a 1 año (una puntuación más alta equivale a un mayor riesgo de muerte). BBDD: Base de daots; APCD: All-payer claims databases; CCI: Índice de comorbilidad de Charlson; STI, Infección de transmission sexual. Gish RG, *et al*. EASL 2022. Poster #THU376

PREVALENCIA Y CARACTERÍSTICAS DE PACIENTES CON VHD EN ESPAÑA

Estudio de cohorte retrospectivo a partir de la base de datos de registros de altas hospitalarias del Sistema Nacional de Salud español, que abarca 192 hospitales privados y 313 públicos (2001-2018)[1]

Todos los diagnósticos de VHB o VHD en adultos (Jun 2000 – Dic 2019)
n=11.939

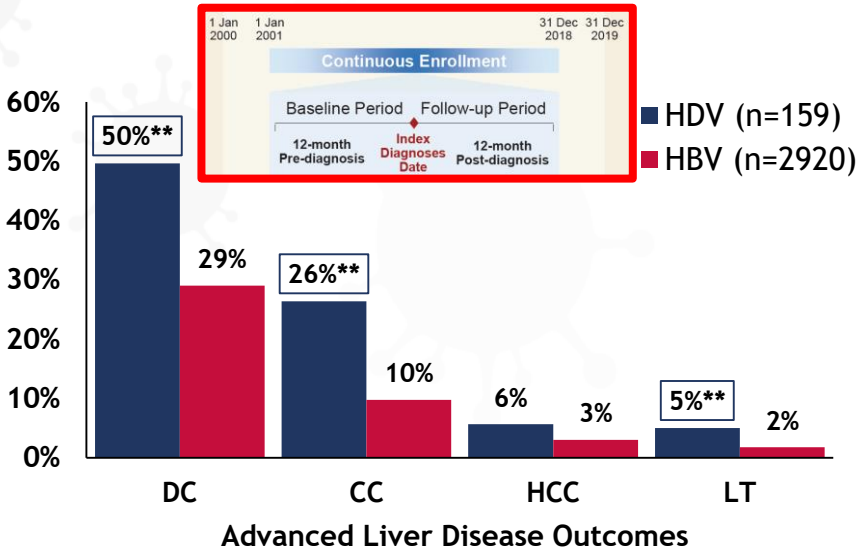
↓

Diagnósticos de VHD
N=597

↓

Diagnósticos nuevos en el periodo de estudio
N=536

Los individuos con coinfección por el VHD eran significativamente más propensos a tener cirrosis y a recibir un LT*.



Los individuos hospitalizados con coinfección por el VHD tenían mayores tasas de comorbilidad y gravedad de la enfermedad que los individuos con monoinfección por el VHB

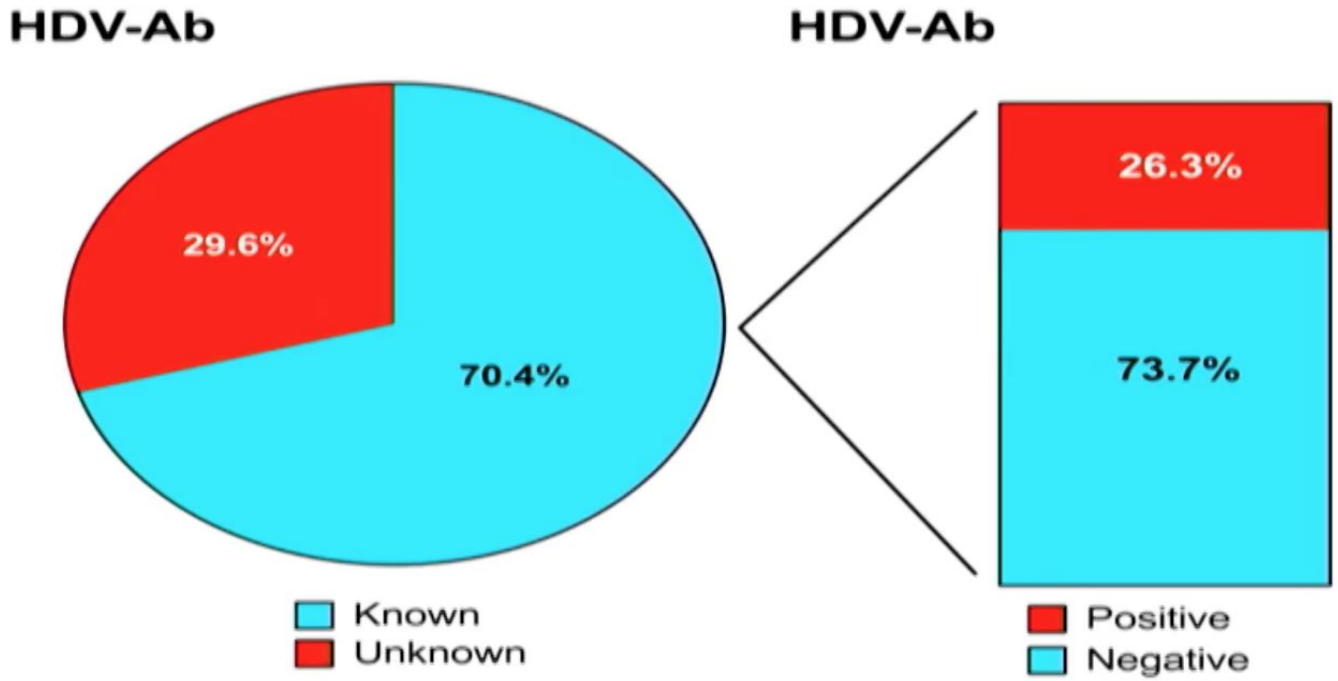
Perfil del paciente (registro AEEH)[2]

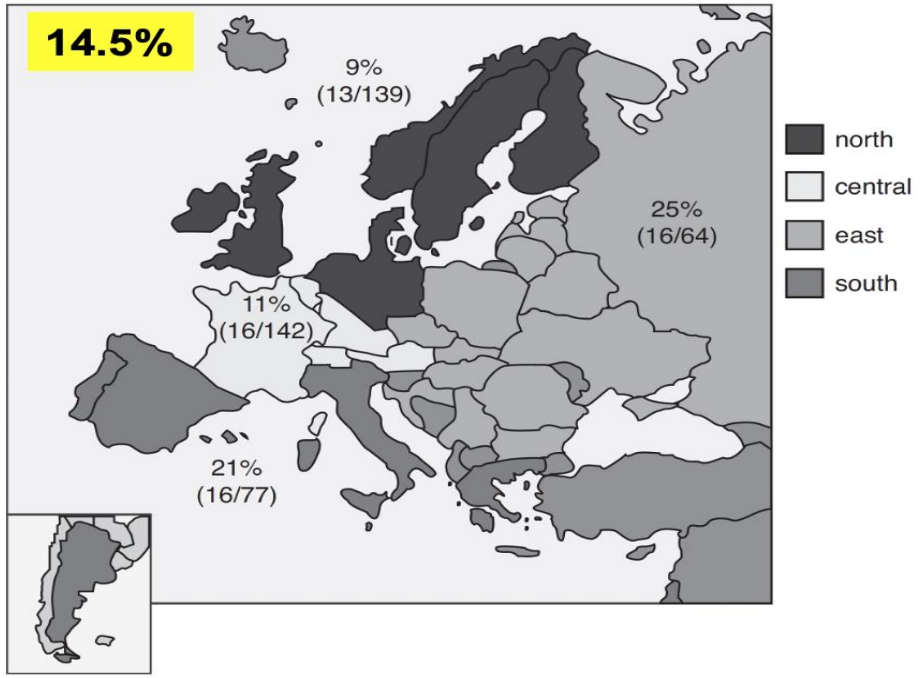
- **Hombres:** 51%
- **Edad media:** entre 40-50 años (62% de los pacientes)
- **Extranjeros:** 45%
- **Coinfectados con VHC / VIH**: 16% / 10%
- **Situación en la primera visita**:
  - Cirrosis: 38%
  - Hipertensión portal: 13%
  - Descompensacion: 4%

*En comparación con los pacientes diagnosticados con monoinfección por el VHB; **valor-p < 0,05 para las comparaciones (HDV vs HBV). AAD/AUD, trastorno por abuso de alcohol/trastorno por consumo de alcohol; CC, cirrosis compensada; DC, cirrhosis descompensada; LT, trasplante de hígado.

1. Buti M, *et al*. EASL 2022. Poster #THU384. 2. Registro AEEH hepatitis delta: Rodríguez Tajes et al. Registro multicéntrico de la hepatitis crónica delta en España. Situación actual y retos pendientes. AEEH 2022, comunicación oral

HDV in Patients HBsAg Positive among PLHIV, Spain, 2018

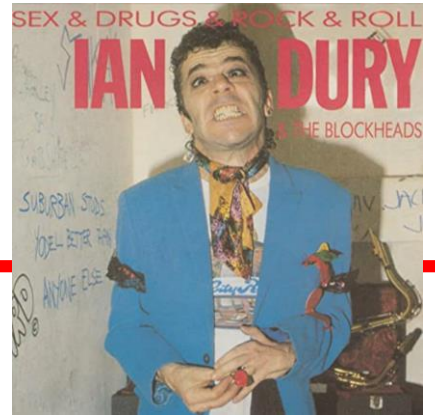




1.-Pérez-Latorre L, et al. Euro Surveill 2021 Jun; 26 (25): 20000236. doi: 10.2807/1560-7917.ES.2021.26.25.2000236. 2.-Soriano V, et al. AIDS 2011; 25: 1987-92

TRANSMISIÓN

Risk Factors for Delta Hepatitis

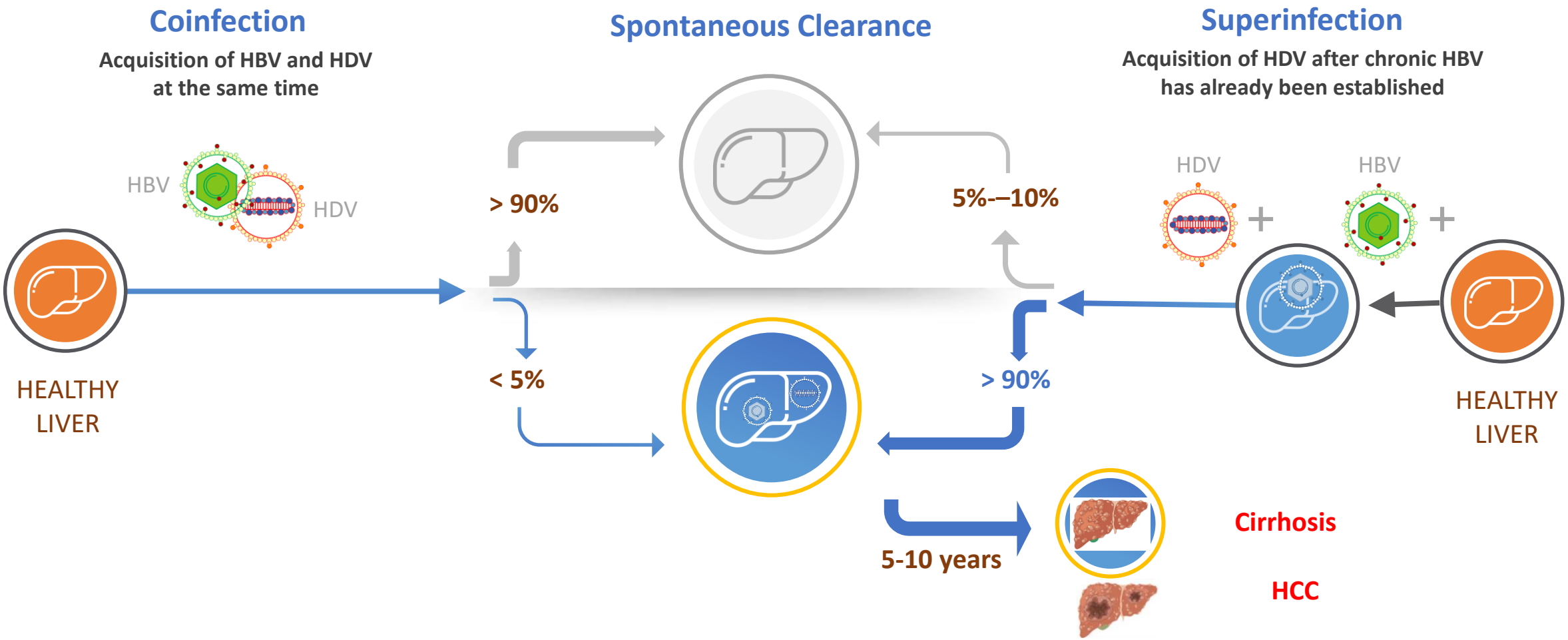


- Sexual transmission with infected partner (high-risk sexual behavior)
- Injection Drug use
- Mother-to-child transmission (rare)
- Men who have sex with men
- Needle sticks/exposures
- Household contacts with HDV infection
- Hemodialysis patients

CDC. Updated March 9, 2020. Accessed March 2021. https://www.cdc.gov/hepatitis/hdv/hdvfaq.htm#section1.

Clínica/Historia Natural

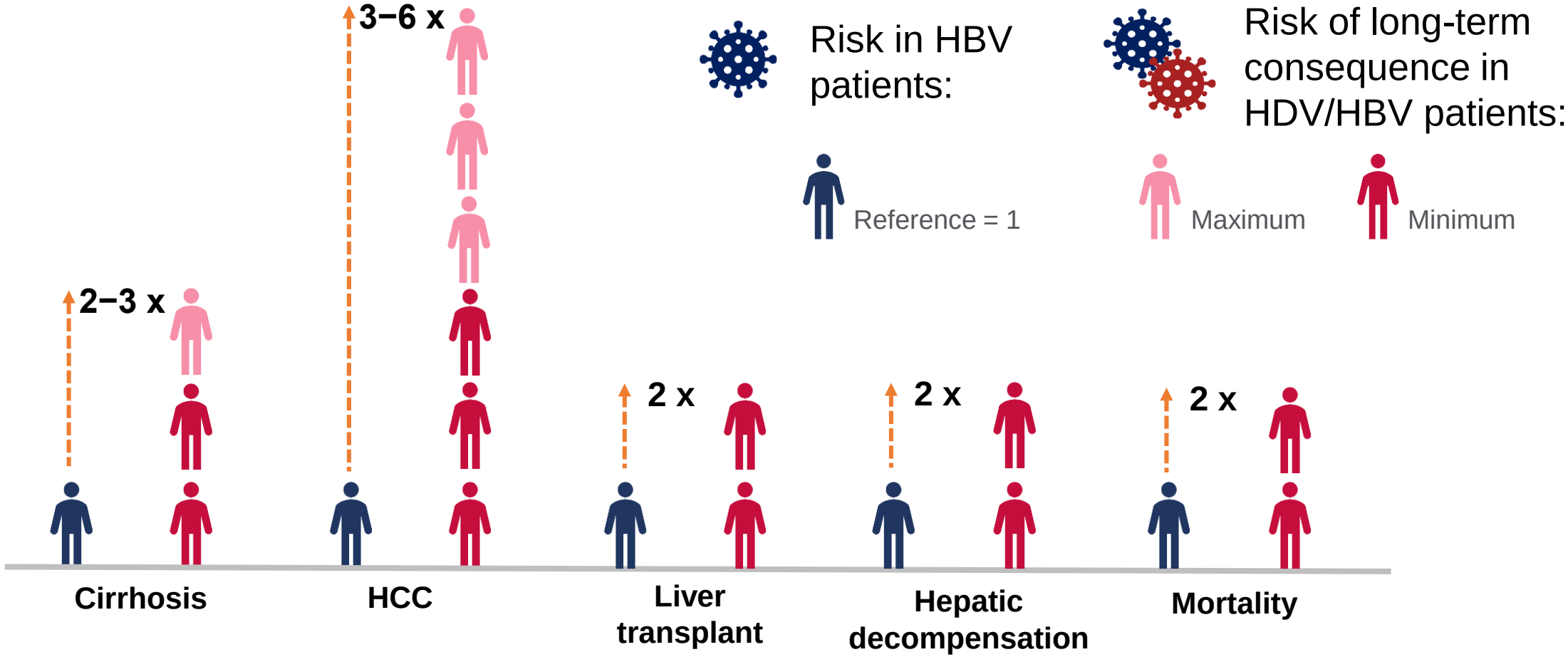
Differences in Major Clinical Outcomes for Adults Based on Coinfection vs Superinfection[1-6]



1. Tseligka ED et al. *Viruses*. 2021; 13(5): 778; 2. Jung S et al. *World J Gastroenterol.* 2020; 26(21): 2781–2791; 3. Farci P, Niro GA. *Semin Liver Dis.* 2012; 32(3): 228–236; 4. Buti M et al. *J Viral Hepat.* 2011; 18(6): 434–442; 5. Gilman C et al. *World J Gastroenterol*. 2019; 25(32): 4580–4597; 6. Buti, M et al. *J Hepatol.* 1987; 5(1): 59–64; 7. Urban S et al. *GUT*. 2021.

Por qué es Importante Diagnosticarla

Compared with hepatitis B mono-infection



Da BL, et al. Gastroenterol Rep 2019;7:231-45.

Diagnostico

Diagnostico

- Todas las personas con HBsAg positivo
- Sospecha Clínica:
  - Hepatitis B Aguda
  - Hepatitis aguda y/o reactivación o agravamiento en un paciente HBsAg positivo
  - Paciente HBsAg (+) con ADN VHB bajo o indetectable y ALT elevadas

LAS GUÍAS DE HEPATITIS B RECOMIENDAN EL CRIBADO DE LA HEPATITIS DELTA

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

Se recomienda realizar pruebas a personas con HBsAg positivas en riesgo de contraer VHD[1]:

- Con infección por VIH
- Consumo de drogas por vía intravenosa
- Hombres que tienen Sexo con Hombres
- Inmigrantes de zonas de endémicas de VHD HBsAg
- Con ADN VHB bajo o indetectable y ALT elevadas

EASL™
The Home of Hepatology

En todos los casos HBsAg positivos

AEEH
Asociación Española para el Estudio del Hígado

El VHD infecta sólo a los pacientes HBsAg positivos y esto requiere la detección de la infección por VHD en todos los pacientes con hepatitis B[3].

1. AASLD. Hepatology. 2018 Apr;67(4):1560-1599. 2. EASL. J Hepatol. 2017;67(2):370-398; 3. AEEH. Gastroenterol Hepatol. 2020;43(9):559-587

Diagnostic Test for HDV

Diagnostic test	Detection	Significance	Comments
Liver HDAg	Detects HDV antigen on liver histology via immunohisto-chemical staining	Indicates active infection	Lack of availability. Poor sensitivity
Serum HDAg	Detects HDV antigen in the serum	Indicates active infection but disappears quickly	Rarely performed. May be unde-tectable in chronic HDV
Anti-HDV IgM	Detects the presence of IgM antibodies against HDV in the serum	Indicates active infection, usually found in acute but can be found in chronic HDV	Often negative in chronic HDV but can be positive during periods of increased HDV replication
Anti-HDV IgG	Detects the presence of IgG antibodies	Usually indicates previous infection or chronic HDV	Appears late in acute HDV but persistent in chronic HDV
HDV RNA PCR (Qualitative)	Detects HDV RNA in the serum	Indicates active infection, can be found in acute or chronic HDV	LLOD depends on the assay. Useful for diagnosis
HDV RNA PCR (Quantitative)	Quantifies HDV RNA in the serum	Indicates active infection, can be found in acute or chronic HDV	LLOQ depends on the assay. Useful for treatment monitoring
HDV genotyping	Determines HDV genotype	Distinguish specific HDV genotype (1–8) with possible prognostic significance	Not commercially available

HDAg, hepatitis D antigen; HDV, hepatitis d virus; RNA, ribonucleic acid; PCR, polymerase chain reaction; LLOD, lower limits of detection; LLOQ, lower limits of quantification.

Da BL et al. Gastroenterology Report, 7(4), 2019, 231–245

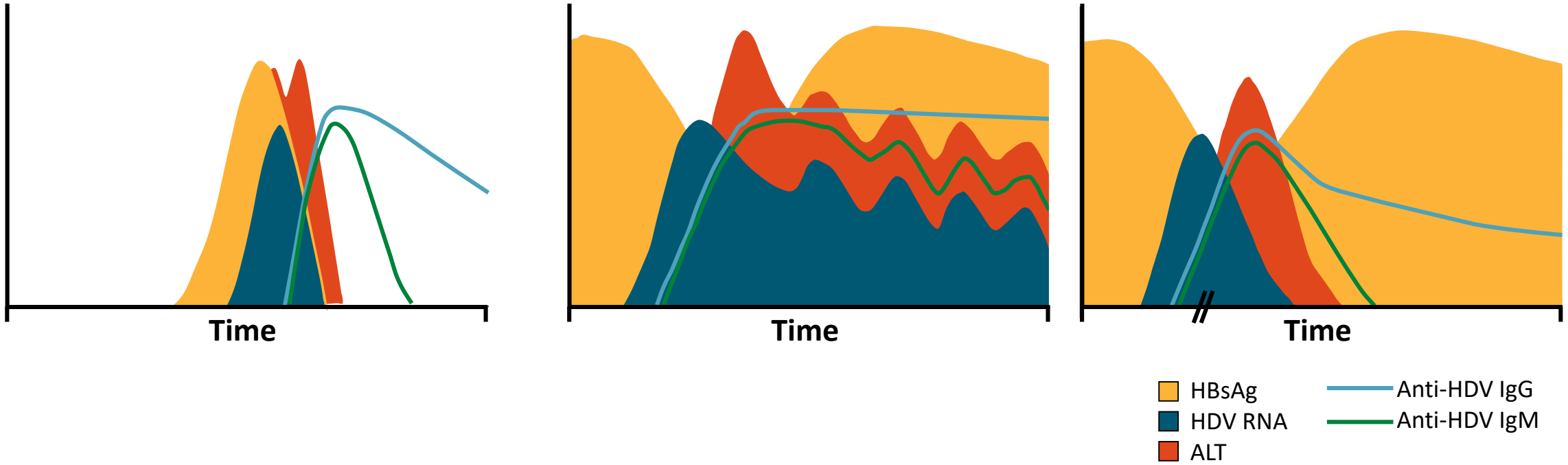
HBV and HDV Serology Varies Depending on Timing of HDV Infection

Simultaneous Coinfection With HBV and HDV
Usually results in spontaneous clearance of both viruses

HDV Superinfection in HBV Carrier

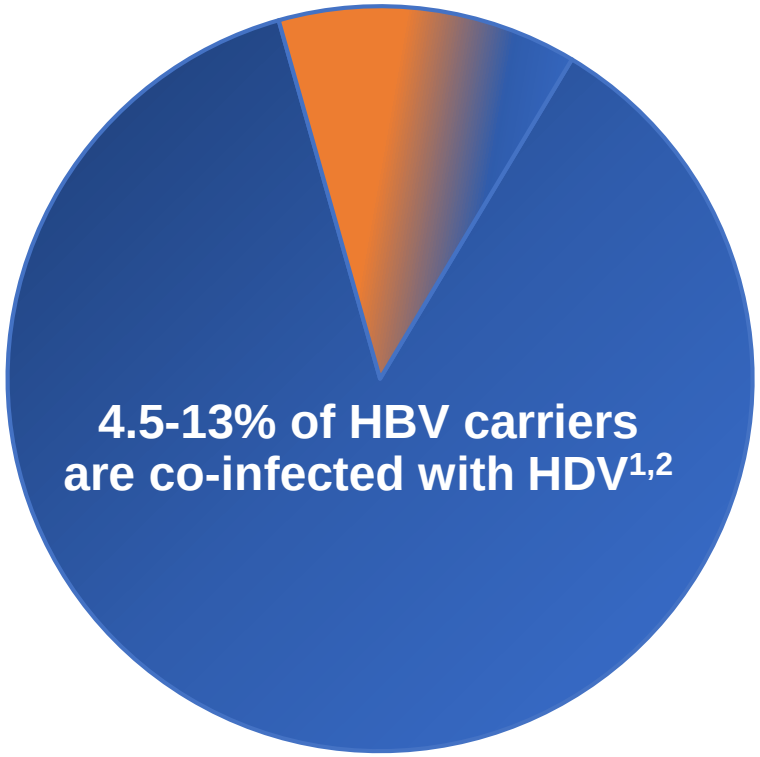
Usually results in persistent viral replication

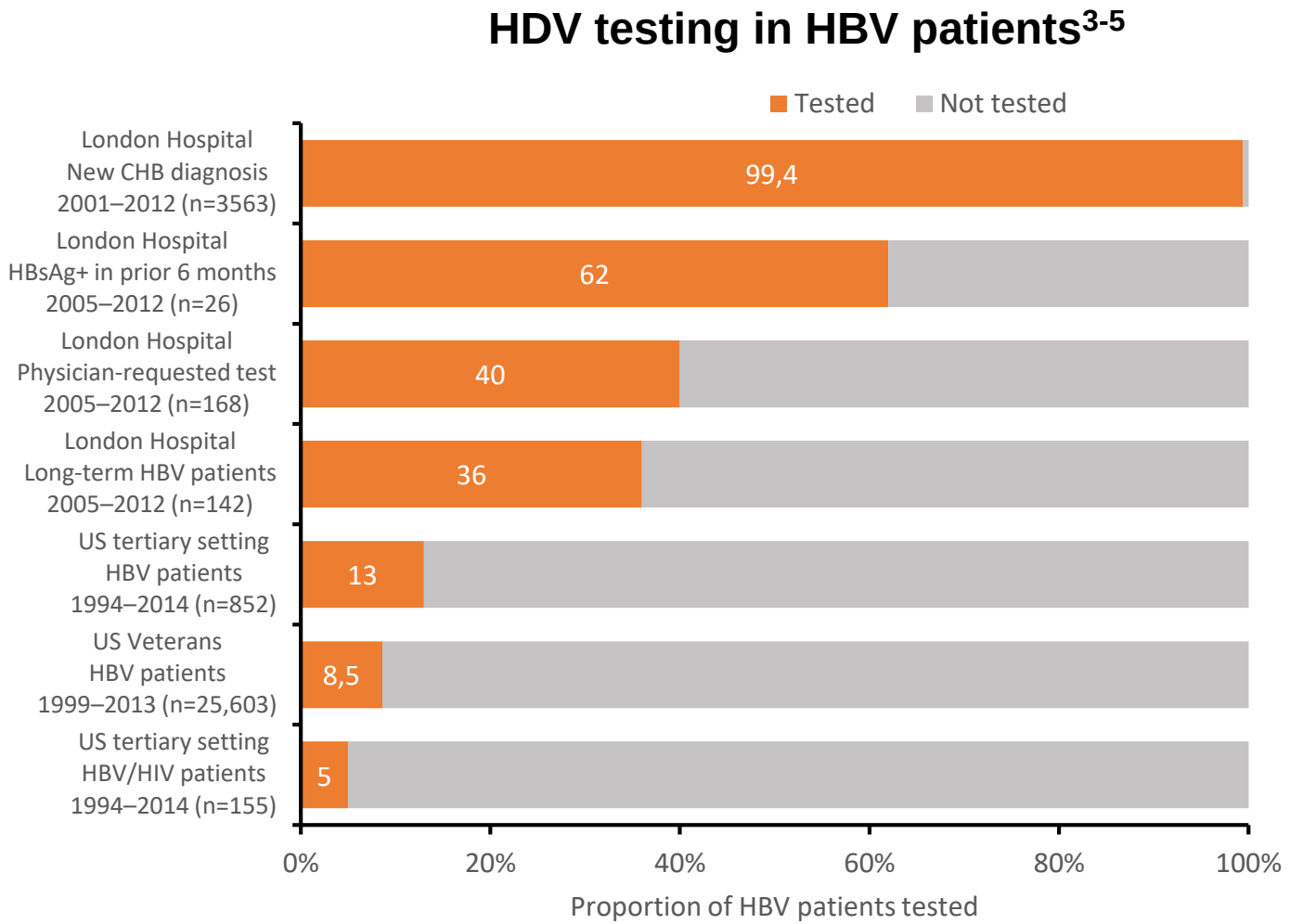
May occasionally result in HDV RNA clearance after many yr



Hughes. Lancet. 2011;378:73.

Y en la Práctica … qué Hacemos?





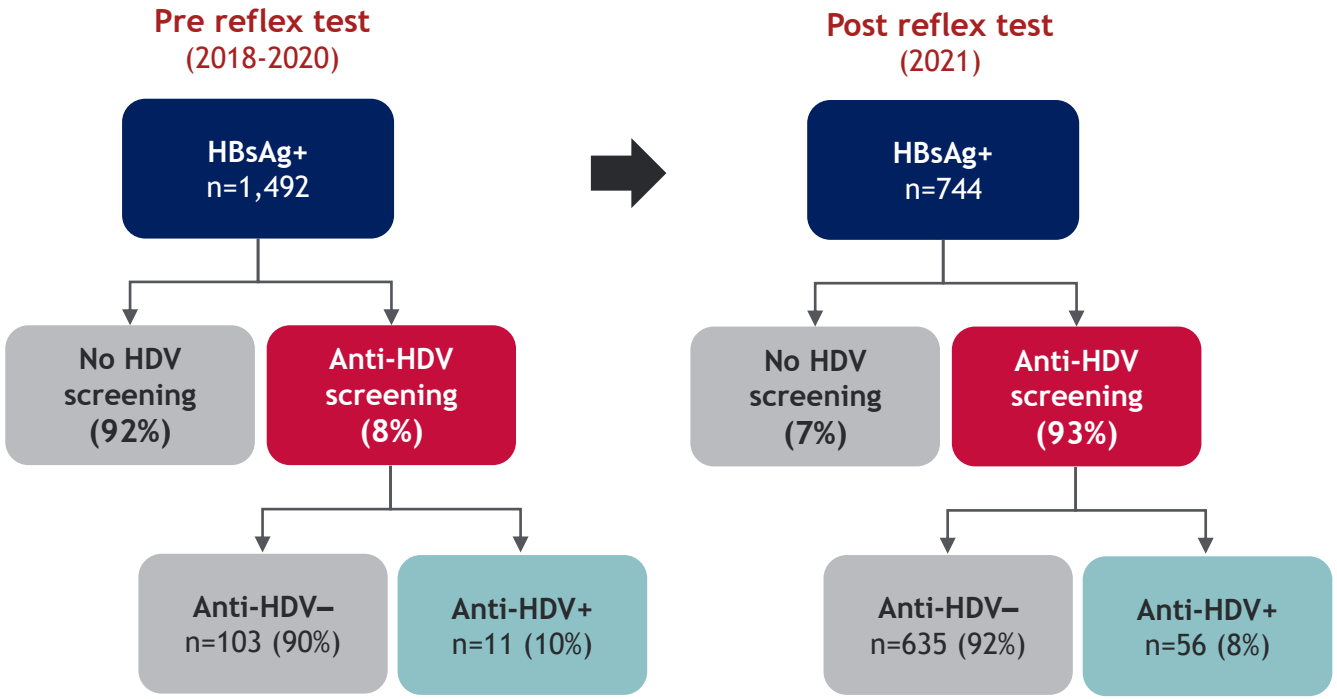
Tenemos margen de mejora!

1. Miao Z, et al. J Infect Dis 2020;221:1677-87; 2. Stockdale AJ, et al. J Hepatol 2020;73:523-3;
3. Safaie P, et al. Virus Res 2018;250:114-7; 4. Kushner T, et al. J Hepatol 2015;63:586-92;
5. Bouzidi KE, et al. J Clin Virol 2015;66:33-7.

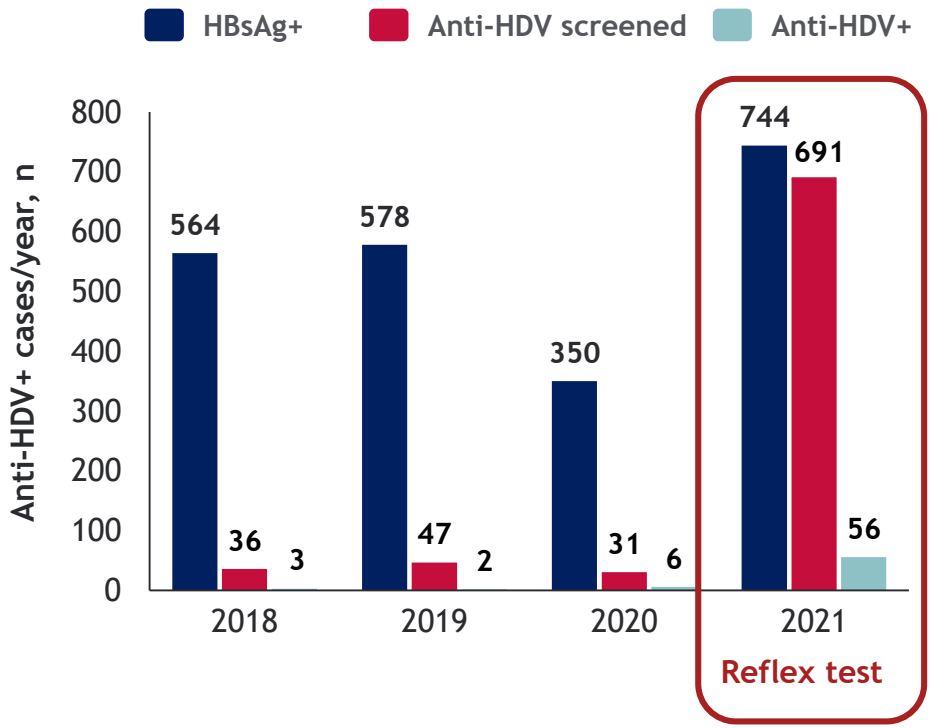
Implementation of HDV Reflex Testing in HBsAg+ Patients

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

HDV Screening Cascade



Anti-HDV+ Cases Detected

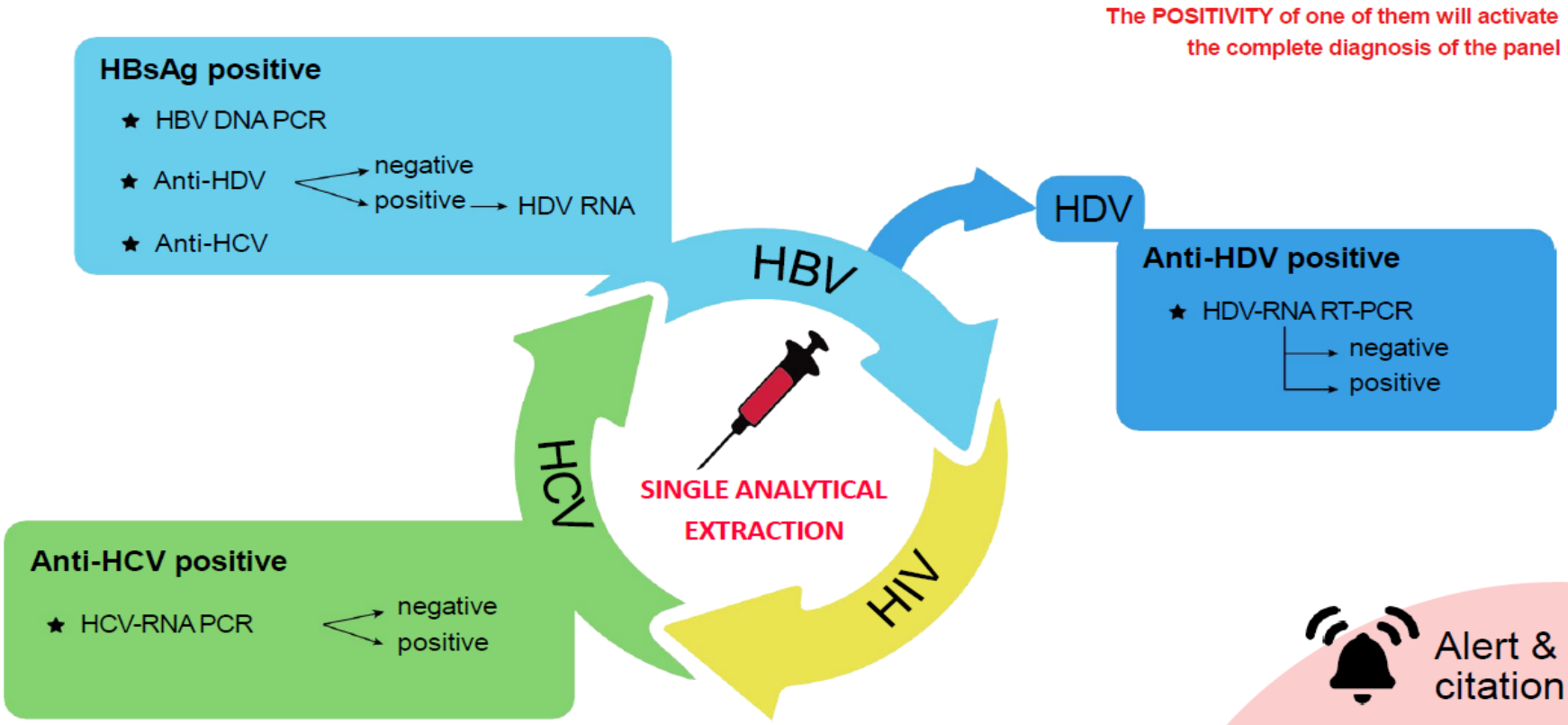


CHD diagnoses increased five-fold following introduction of reflex testing of all HBsAg+ individuals

HBsAg, hepatitis B surface antigen.

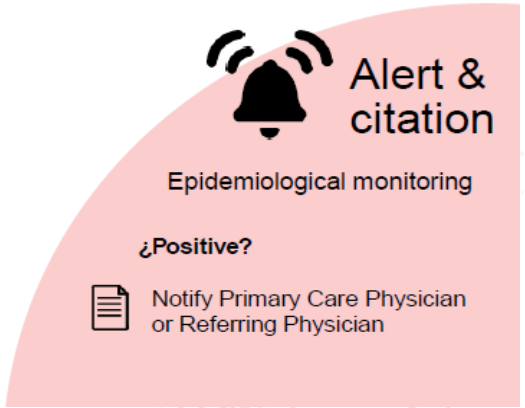
Palom A, et al. EASL 2022. Poster #THU367

RECOMENDACIONES PARA EL DIAGNÓSTICO INTEGRAL DE LAS HEPATITIS VIRALES CRÓNICAS EN UNA ÚNICA EXTRACCIÓN ANALÍTICA



Other recommendations:

Determine the existence of antibodies against HAV (anti-HAV)
Rule out the presence of antibodies against HIV (anti-HIV)
Perform HBsAg and anti-HCV in all patients with positive HIV serology
→ If possible, this should be done in the same analytical extraction



Avalado por:

Con la colaboración de:

Recomendaciones para el diagnóstico integral de las hepatitis virales crónicas en una única extracción analítica. Disponible en https://seimc.org/contenidos/documentoscientificos/recomendaciones/seimc-dc-2022-Hepatitis_Virales_una_unica_extraccion_analitica.pdf

Tratamiento

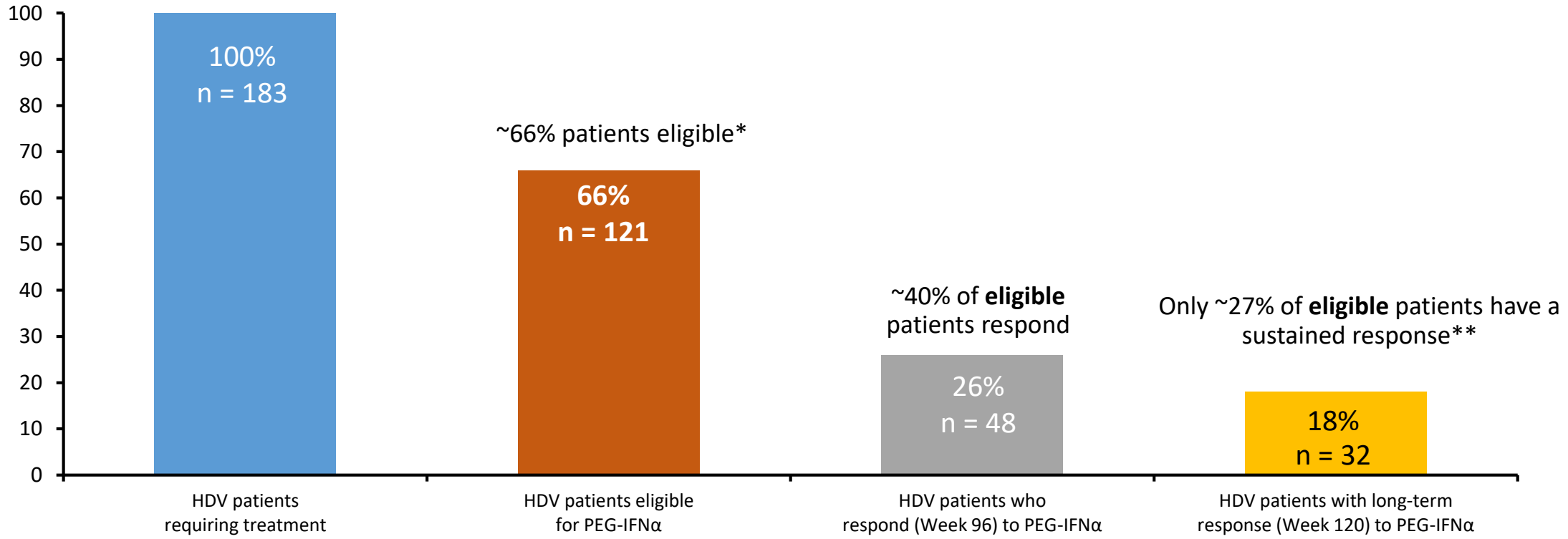
Guideline Recommendations for Management of HDV – Treatment

	Treatment options	Treatment endpoint	Management
AASLD[1] (2018)	• PEG-IFNα for 1 year • Patients with elevated HDV RNA and ALT elevation	• Undetectable HDV RNA • ALT normalisation/ improved histology	• Test for HDV relapse if ALT increases • Manage in specialist centres
APASL[2] (2016)	• PEG-IFNα for ≥ 1 year • Optimal duration of therapy not well defined	• Undetectable HDV RNA	• Monitor for ≥ 6 months post-treatment
EASL[3] (2017)	• PEG-IFNα for ≥ 48 weeks • HDV/HBV patients with compensated liver disease	• Undetectable HDV RNA	• Long-term HDV RNA monitoring required
WHO[4] (2015)	• PEG-IFNα for ≥ 1 year	• Undetectable HDV RNA	No recommendation

NOTE: Treatment of HDV with PEG-IFNα is off-label. AASLD: American Association for the Study of Liver Diseases; ALT: alanine aminotransferase; APASL: Asian Pacific Association for the Study of the Liver; EASL: European Association for the Study of the Liver; HDV: hepatitis D virus; PEG-IFN: pegylated interferon; RNA: ribonucleic acid; WHO: World Health Organization.

1.-Terrault N et al. *Hepatology*. 2018; 67: 1560–99; 2. Sarin SK et al. *Hepatol Int*. 2016; 10: 1–98; 3. European Association for the Study of the Liver. *J Hepatol*. 2017; 67: 370–98; 4. WHO HBV guidelines. March 2015. Available at: https://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf?sequence=1 (Accessed March 2021).

Response to PEG-IFNα Treatment



Only a subset of patients are treated with PEG-IFNα, of which a small proportion respond to treatment

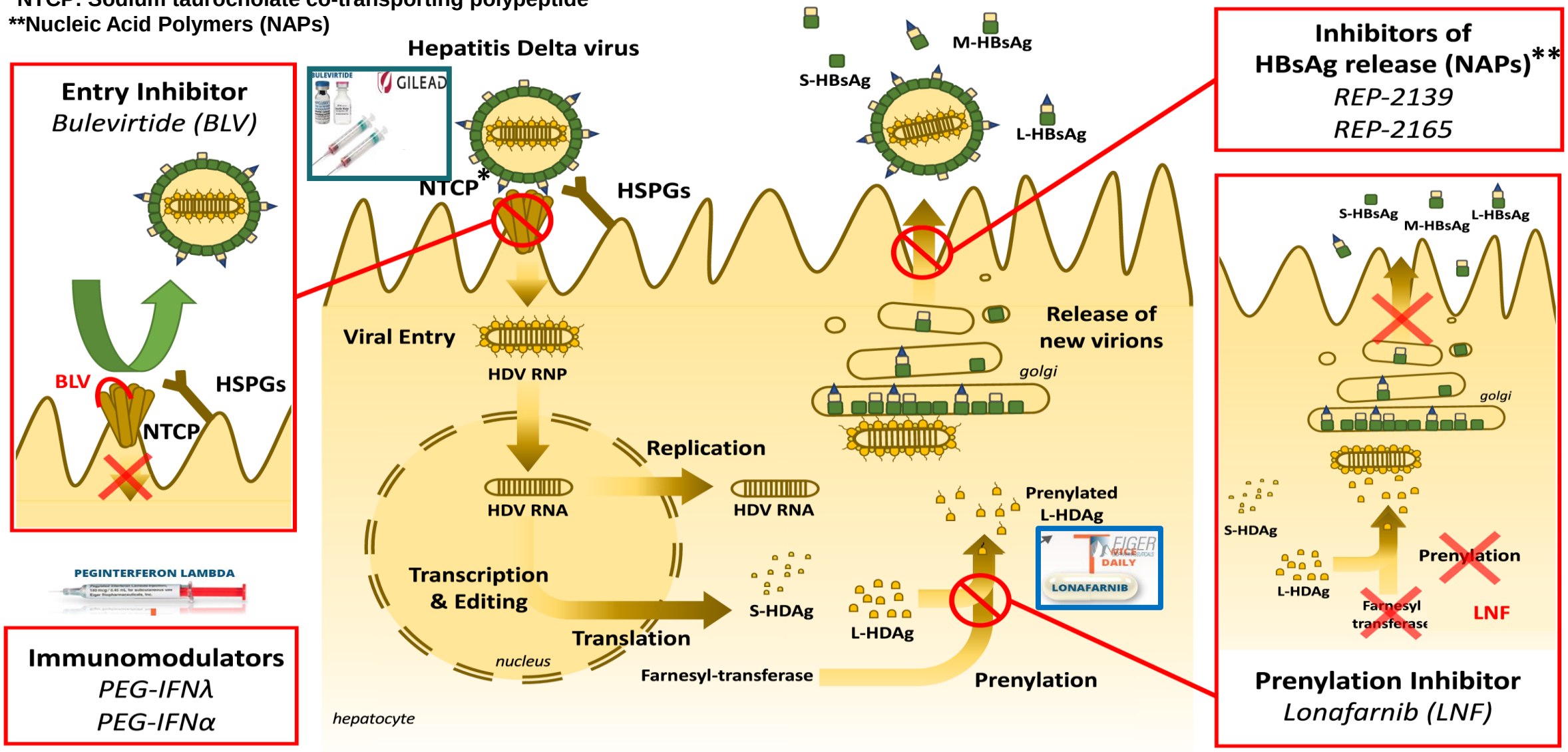
*Ineligibility based on contraindications, intolerance and presence of advanced liver disease in HIDIT-II (62 of 183 screened did not meet inclusion criteria or met exclusion criteria) **Response defined as undetectable HDV RNA after 120 weeks of treatment.
HDV: hepatitis D virus; PEG-IFNα: pegylated interferon alpha..

Wedemeyer H et al. Lancet Infect Dis. 2019; 19: 275–86

Emerging Therapeutics for HDV Infection

Therapeutics Targets for HDV Infection

*NTCP: Sodium taurocholate co-transporting polypeptide
**Nucleic Acid Polymers (NAPs)



** NAPs. Nucleic Acid Polymers

Loureiro D, et al. Liver International. 2021;41(Suppl. 1):30–37.

Drug Classes by Therapeutic Target in Clinical Development

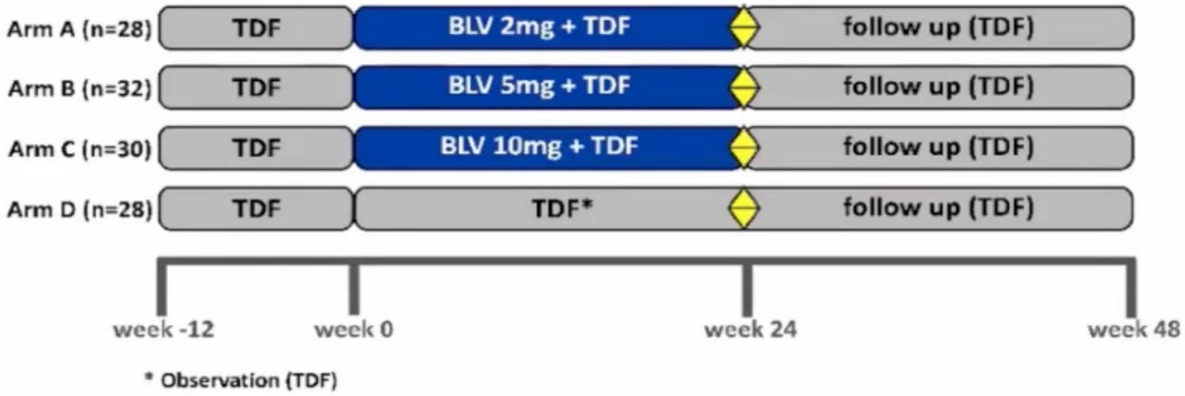
	HBsAg secretion inhibitors	Prenylation inhibitors	Immune modulators	Entry Inhibitors
Therapies in development	• REP2139-REP2165	• Lonafarnib *	• PEG-IFNλ	• Bulevirtide
Stage of replication cycle affected	• Broad-spectrum antiviral activity	• Inhibits L-HDAg prenylation	• Induces IFN-stimulated genes and activates JAK and STAT	• Blocks uptake at the NTCP receptor
Consequence(s)	• Inhibits export of HBsAg to serum • HDV virions cannot be formed without HBsAg	• Essential for interaction with HBsAg • Lack of prenylation prevents HDV virion formation	• General broad antiviral response	• Blocks uptake of virus into liver cell
Progress	• Phase 2 trials	• Phase 3 trials	• Phase 2 trials	• Late Phase 3 trial; • Approval in Europe

*Lonafarnib is boosted with ritonavir; REP: Nucleic Acid Polymers (NAPs)
HBsAg: hepatitis B surface antigen; HDV: hepatitis D virus; IFN: interferon; JAK-STAT: Janus-kinase-signal transducer and activator of transcription; L-HDAg: large hepatitis D antigen; PEG-IFN: pegylated interferon; NTCP: Sodium taurocholate co-transporting polypeptide.

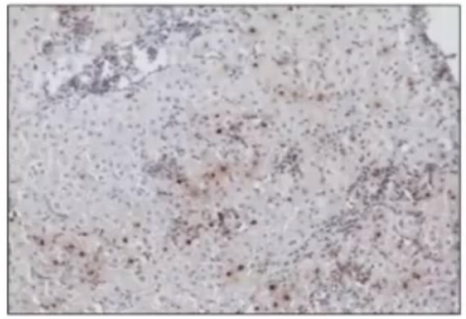
1.-Gilman C, et al. World J Gastroenterol 2019;25:4580-97. 2.-Koh C, et al. Gastroenterology 2019;156:461-6.

Bulevirtide: Approval Studies MYR202

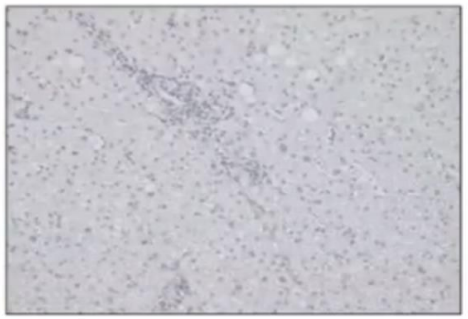
- **120 patients** randomized in 4 groups
- Multicenter, open label, randomized trial with study centers in Germany and Russia
- **Primary endpoint**: HDV RNA undetectable or decrease by ≥2log$_{10}$ IU/mL in week 24



Baseline:



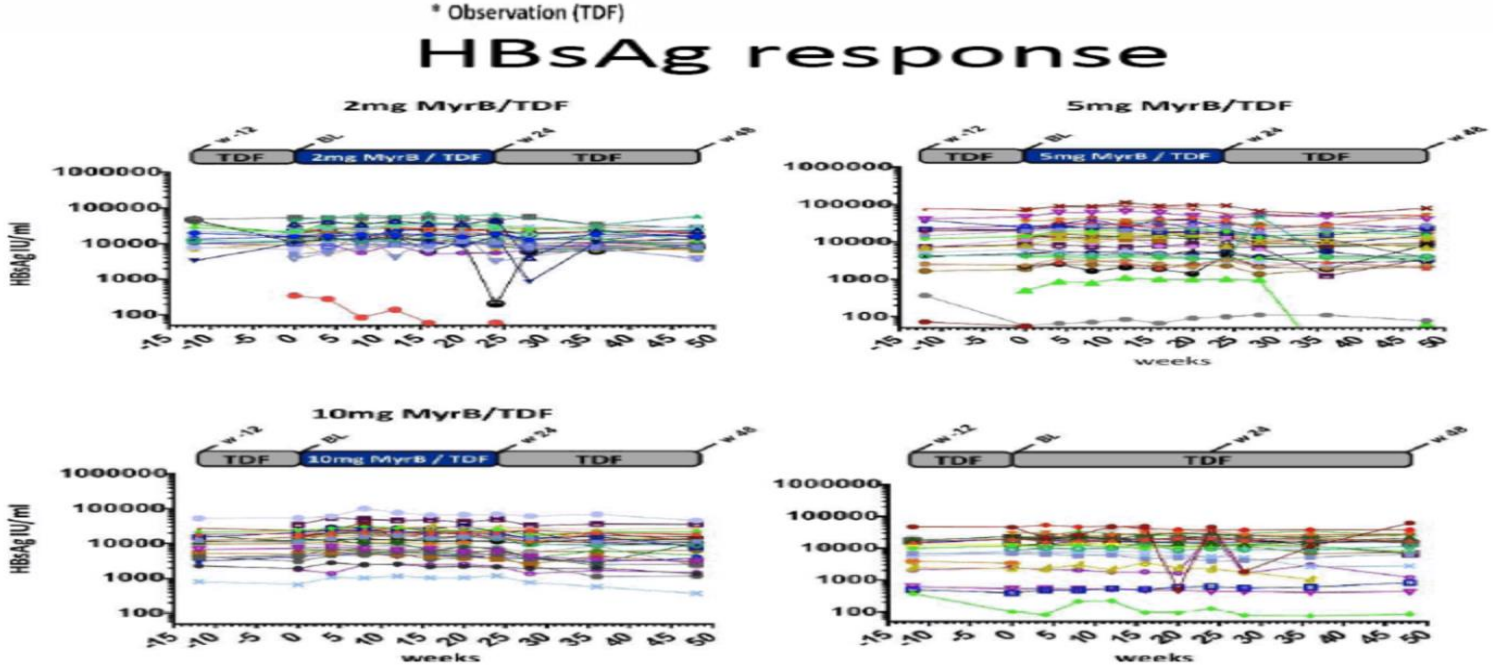
Week 24:



HDAg; HE staining; treatment with 10 mg BLV for 24 weeks compared to the patient's baseline level

→ Decrease of HDAg-positive hepatocytes

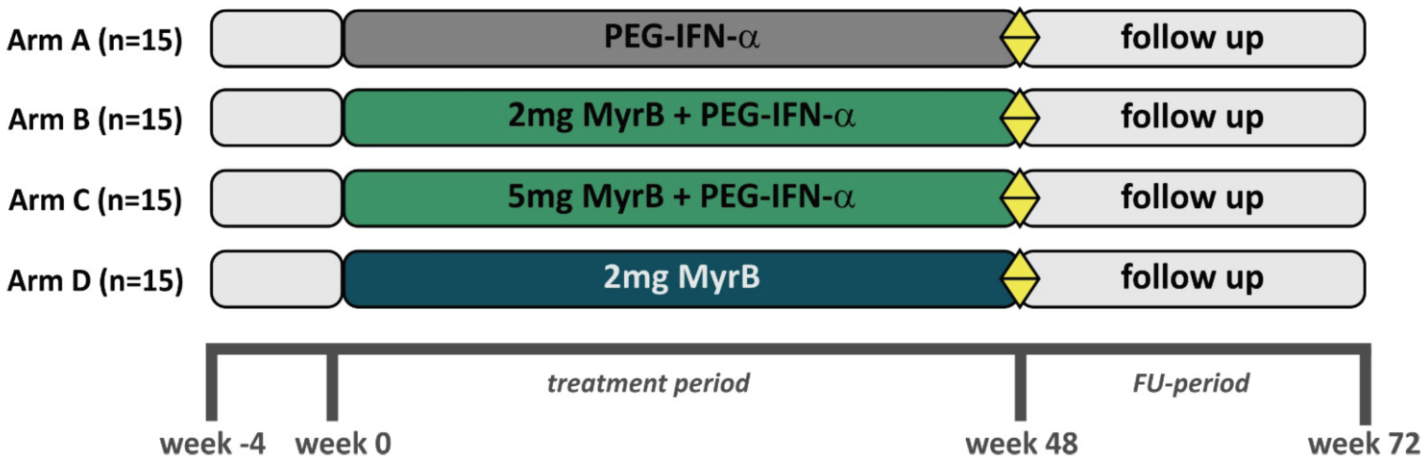
→ I
e



Wedemeyer H, et al. J Hepatol 2018;68:S3

Bulevirtide: Approval Studies MYR203

- Myrcludex B (MyrB, Bulevirtide) is a first-in-class entry inhibitor for HBV/HDV infection
- In a phase 2 study MYR202, MyrB monotherapy led to HDV RNA decline and improvement of ALT levels
- End-of-treatment data from a MyrB ± PegIFNα2a 48 weeks combination study (MYR203) have been reported[1]
- Here, the 24-week treatment-free follow-up data are presented



- Primary endpoint: undetectable serum HDV RNA at Week 72 (w72)
- Secondary endpoints: ALT normalization, combined treatment response*, and HBsAg reduction >1 $\log_{10}$

*≥2 log serum HDV RNA decline + normal ALT levels

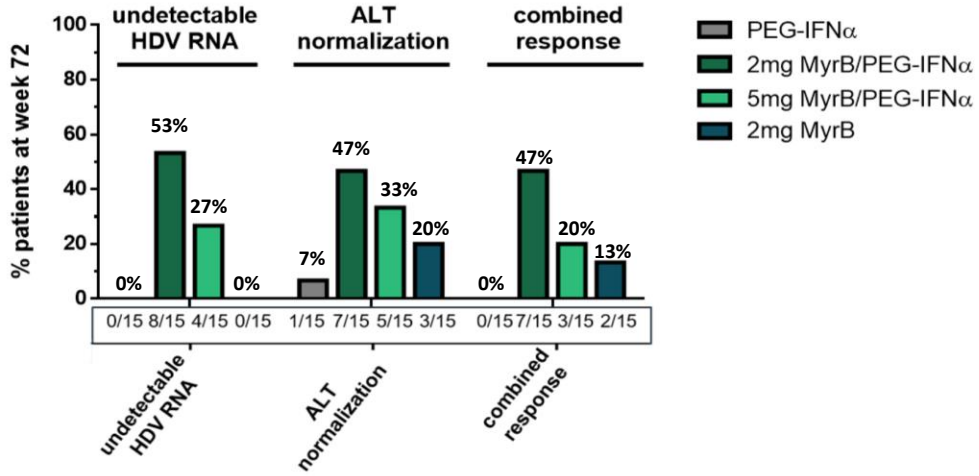
1.- Wedemeyer H, et al. Hepatology 2018;68(Suppl):11. 2.-Wedemeyer H, et al. ILC 2019; GS-13

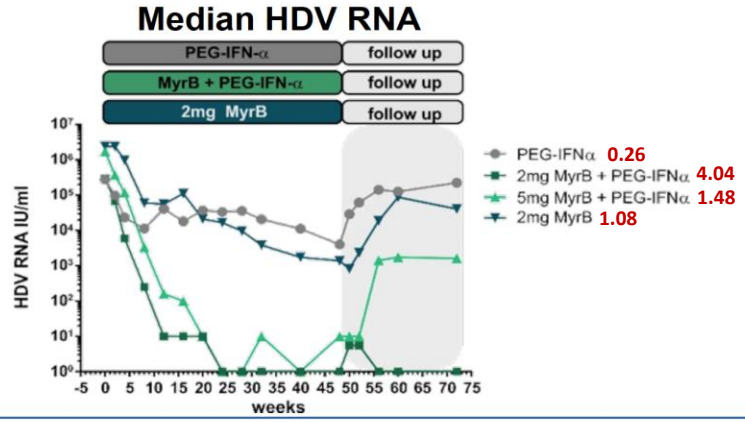
Bulevirtide: Approval Studies MYR203

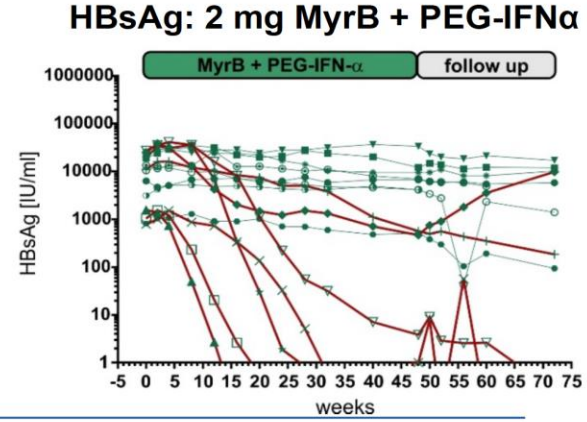
- **Safety:** MyrB was well tolerated, with 155 drug-related AEs up to w72 (mild n=122, moderate n=28, serious n=5), primarily increased total bile salts
  - Most AEs (n=524) related to PegIFNα2a
  - All cases resolved; bile salts returned to baseline by follow-up Week 50
  - Two SAEs (anal fistula and proctitis) not-related to MyrB occurred in 1 patient of Arm B in follow-up
- **Efficacy:** MyrB + PegIFNα2a induced a significant enhancement of HDV RNA response
  - 40% (12/30) patients had undetectable HDV RNA at Week 72

2 mg MyrB + PegIFNα2a induces HBsAg response in HBeAg negative patients at Week 72

- 40% of patients experienced HBsAg response
- In this group 27% lost HBsAg and 20% seroconverted





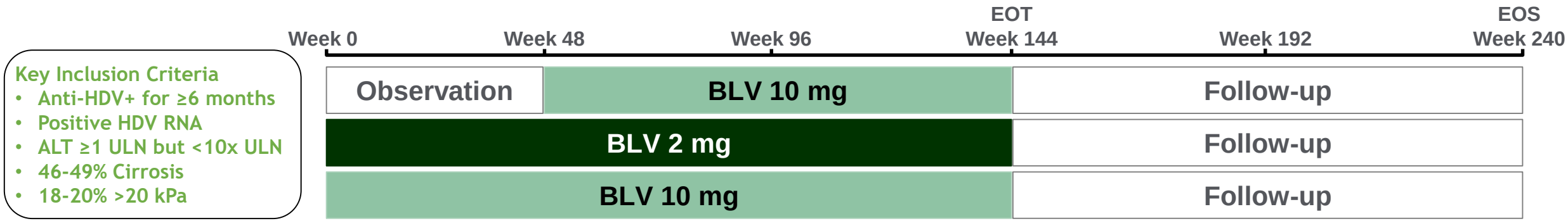


In contrast to PegIFNα2a monotherapy, MyrB + PegIFNα2a demonstrated high rates of HDV RNA suppression. HBsAg loss was achieved in 27% of patients, indicating a potential role for MyrB in future HBV cure regimens

1.- Wedemeyer H, et al. Hepatology 2018;68(Suppl):11. 2.-Wedemeyer H, et al. ILC 2019; GS-13

MYR301: Immediate vs Delayed Bulevirtide Monotherapy for Chronic HDV

Ongoing, Phase 3, randomized, multi-center, open-label study



Primary endpoint:

- Combined response HDV RNA undetectable *or* decrease by ≥2 log IU/mL from baseline and ALT normalization (week 48)

Secondary endpoints:

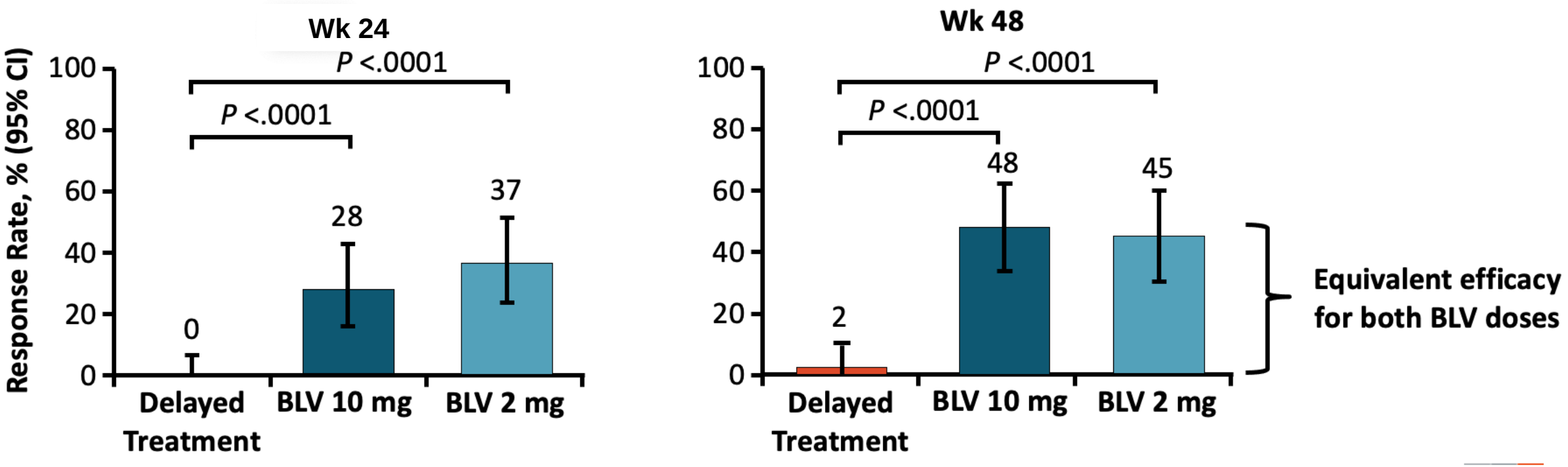
- Undetectable HDV RNA
- ALT normalization
- HDV RNA undetectable 24 weeks after EOT
- HDV RNA undetectable 48 weeks after EOT
- Change in liver stiffness

ALT, alanine aminotransferase; BLV, bulevirtide; EOS, end of study; EOT, end of treatment; HDV, hepatitis D virus.

1. Gilead, Data on File. 2. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT03852719

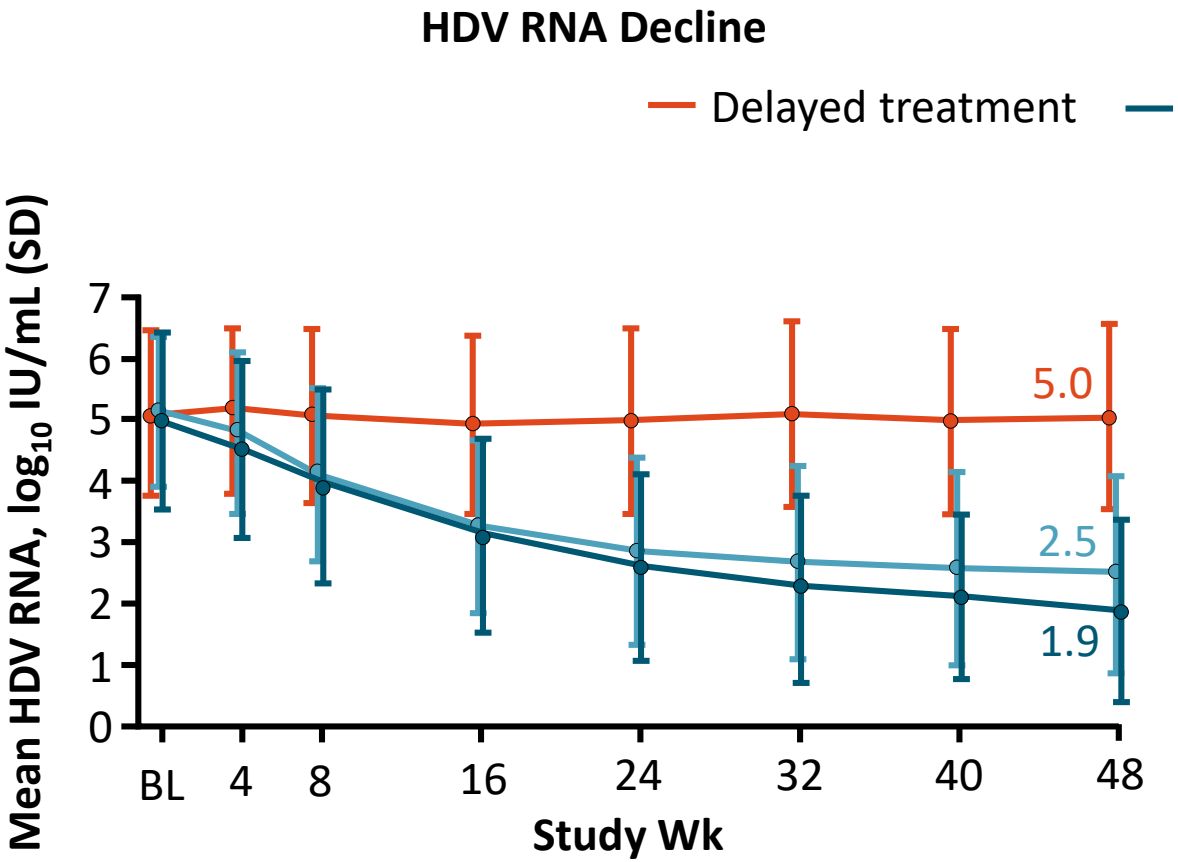
MYR301: Immediate vs Delayed Bulevirtide Monotherapy for Chronic HDV

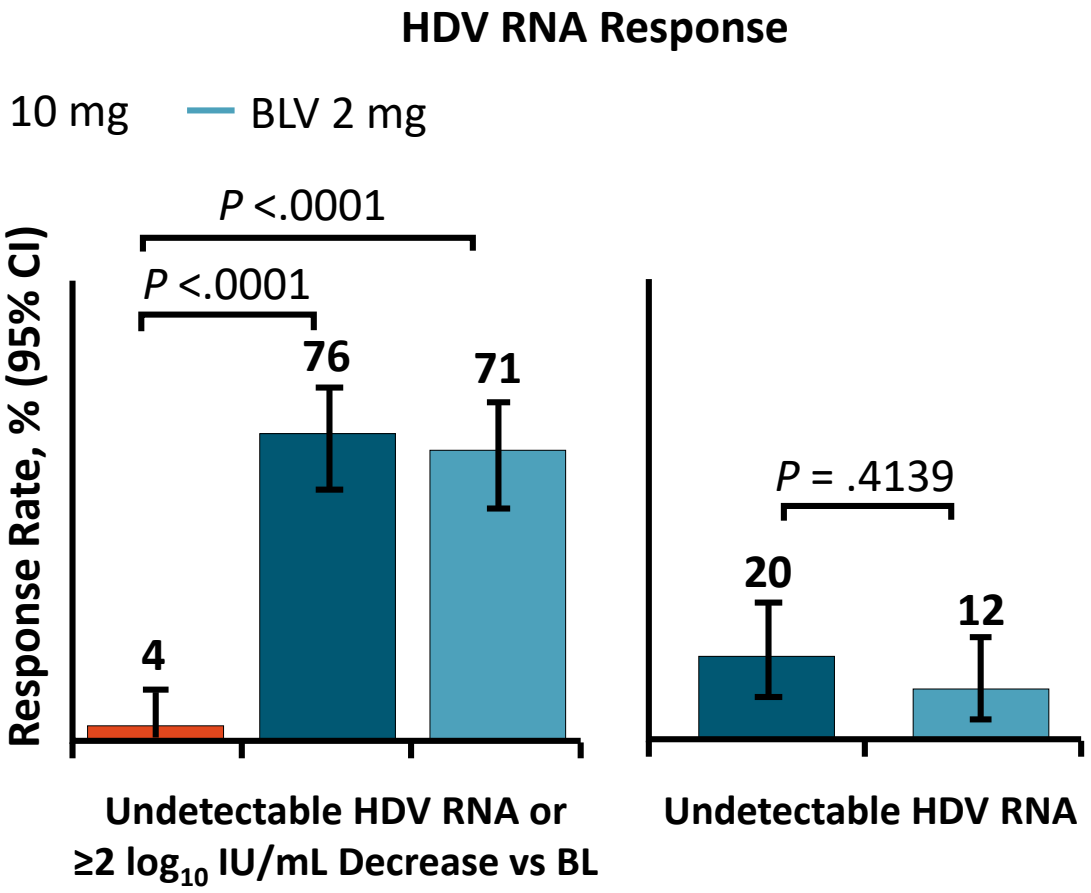
- Multicenter, randomized, phase III trial of BLV 2 mg or 10 mg SC QD for 48 wk vs delayed BLV treatment (10 mg SC QD beginning Wk 48) in patients with chronic HDV (N = 150)
  - Primary endpoint: combined response at Wk 48 (HDV RNA undetectable or ≥2 $\log_{10}$ copies/mL decrease vs baseline with ALT normalization)



Wedermeyer. EASL 2022. Abstr GS006.

MYR301: HDV RNA Response at Wk 48



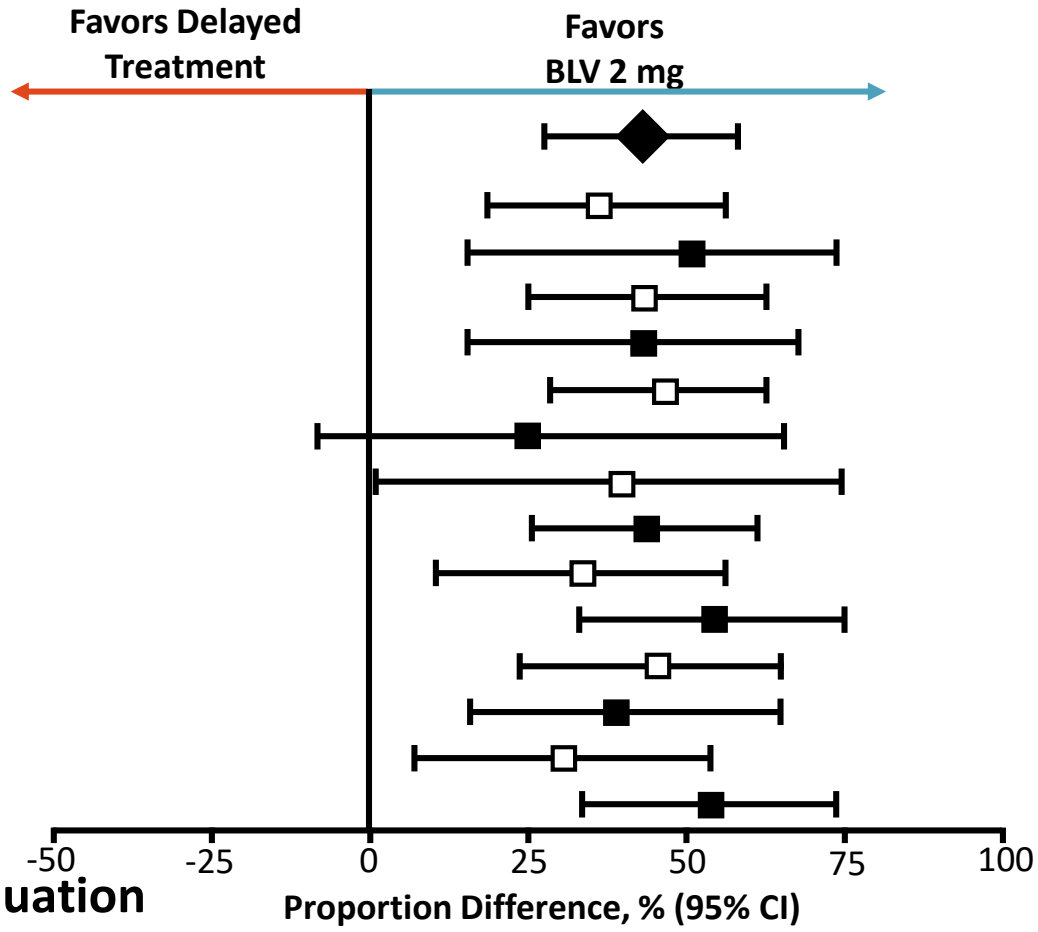


Wedermeyer. EASL 2022. Abstr GS006.

MYR301: Combined Response at Wk 48 by Subgroup

Immediate Treatment With BLV 2 mg vs Delayed Treatment

		Delayed, n	BLV 2 mg, n
Overall		51	49
Age	<45 yr	36	28
	≥45 yr	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)*	< Median	25	24
	≥ Median	26	24
HBV Treatment	Yes	32	31
	No	19	18
Cirrhosis status	Presence	24	23
	Absence	27	26



- **No SAEs related to BLV or AEs leading to discontinuation**
- Consistent results observed with immediate treatment with BLV 10 mg

Wedermeyer. EASL 2022. Abstr GS006.

MYR301: Effect of Bulevirtide on HBV

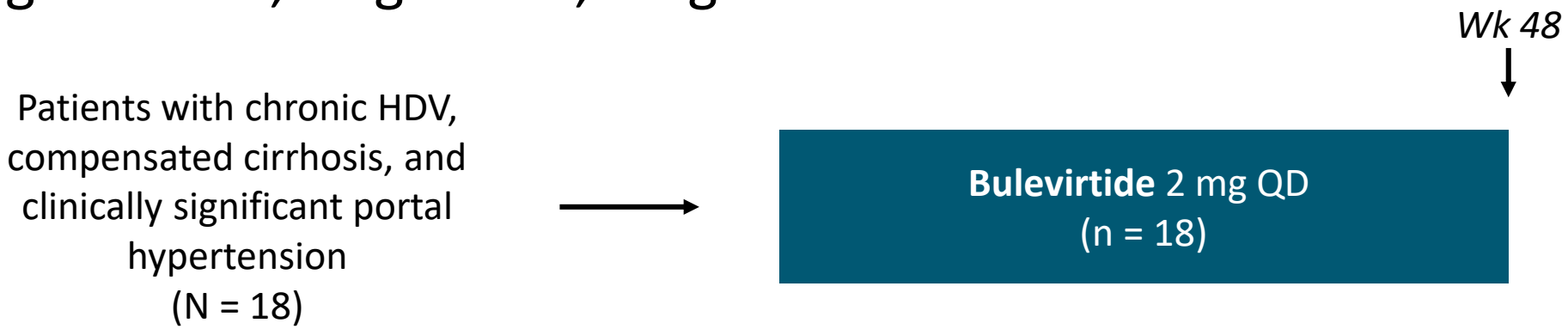
		Delayed Treatment n=51	BLV 2 mg n=49	BLV 10 mg n=50
HBsAg	HBsAg loss, n (%)	0	0	0
	HBsAg response: >1 log_{10} IU/mL decrease, n (%)	1 (2)	0	0
	LS mean change in HBsAg, log_{10} IU/mL (95% CI)	0.006 (-0.085, 0.097)	0.053 (-0.041, 0.147)	0.115 (0.019, 0.211)
HBV DNA	LS mean change in HBV DNA, log_{10} IU/mL (95% CI)	-0.16 (-0.404, 0.078)	-0.38 (-0.634, -0.134)	-0.64 (-0.898, -0.387)
	P-value vs delayed treatment	—	0.210	0.008
	Patients with HBV DNA positivity at baseline and no concomitant NUC treatment, n	12	13	13
	Mean change from BL in HBV DNA, log_{10} IU/mL (SD)	-0.15 (0.655)	-0.42 (0.599)	-0.88 (0.690)

- No patients in any group experienced HBsAg loss and changes in HBsAg levels were minimal
- Small declines in HBV DNA levels were observed with BLV treatment in patients not on NUC treatment

Wedermeyer. EASL 2022. Abstr GS006.

Bulevirtide for Patients With HDV, Cirrhosis, and Portal Hypertension: Study Design

- Single-center, single-arm, longitudinal trial



- Endpoints:
  - Virologic response: HDV RNA undetectable or ≥2 log IU/mL decline vs baseline
  - Combined response: HDV RNA undetectable or ≥2 log IU/mL decline vs baseline with ALT normalization
  - Safety

Degasperi. EASL 2022. Abstr SAT249.

Bulevirtide for Patients With HDV, Cirrhosis, and Portal Hypertension: Responses Through Wk 48

- BL characteristics: male, 67%; white, 100%; CPT score A, 100%; esophageal varices, 78%; median spleen diameter, 17 cm (10-25 cm); median liver stiffness, 16.4 kPa (7.8-57.8 kPa); active HCC, 11%; prior NA, 100%

Outcome	Baseline	Wk 8	Wk 24	Wk 32	Wk 48
ALT normalization, n (%)	1 (6)	9 (50)	13 (72)	14 (78)	15 (83)
Median HDV RNA, log IU/mL (range)	4.9 (3.3-6.6)	3.5 (1.2-5.9)	2.3 (0.7-5.8)	2.0 (0.7-5.8)	2.2 (0.3-6.0)
Median HDV RNA decline, log IU/mL (range)	--	1.4 (0.4-3.1)	2.7 (0.6-3.9)	2.8 (0.4-3.9)	3.1 (0.2-4.3)
HDV RNA decline ≥2 log IU/mL, n (%)	--	2 (11)	15 (83)	15 (83)	14 (78)
Virologic nonresponse, n (%)	--	2 (11)	2 (11)	2 (11)	2 (11)
Virologic response*, n (%)	--	2 (11)	15 (83)	15 (83)	14 (78)
Combined response†, n (%)	--	0	12 (67)	11 (61)	12 (67)

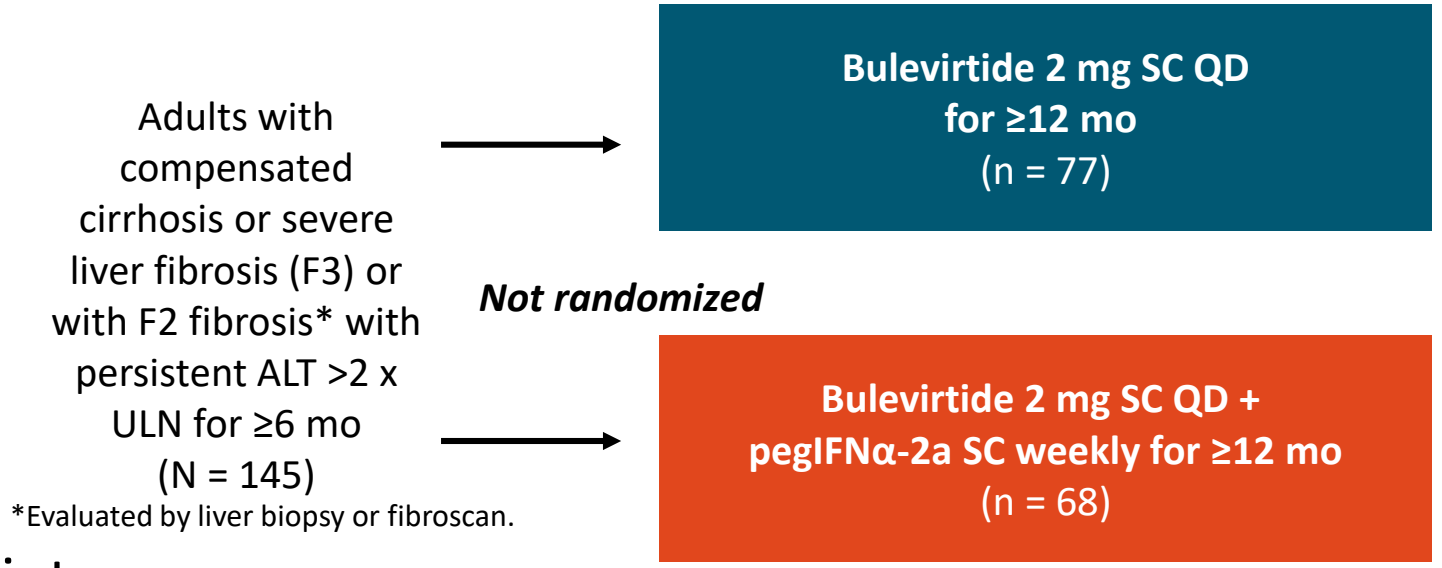
*Virologic response: HDV RNA undetectable or ≥2 log IU/mL decline vs BL. †Combined response: HDV RNA undetectable or ≥2 log IU/mL decline vs BL with ALT normalization.

- Median bile acids increased significantly at Wk 48 vs baseline (63 µmol/L vs 23 µmol/L; *P* = .04)

Degasperi. EASL 2022. Abstr SAT249.

French Early Acces Program: Virologic and Biochemical Efficacy

- Multicenter, prospective, retrospective, observational study in patients with chronic HDV from French cATU program



Efficacy endpoints:

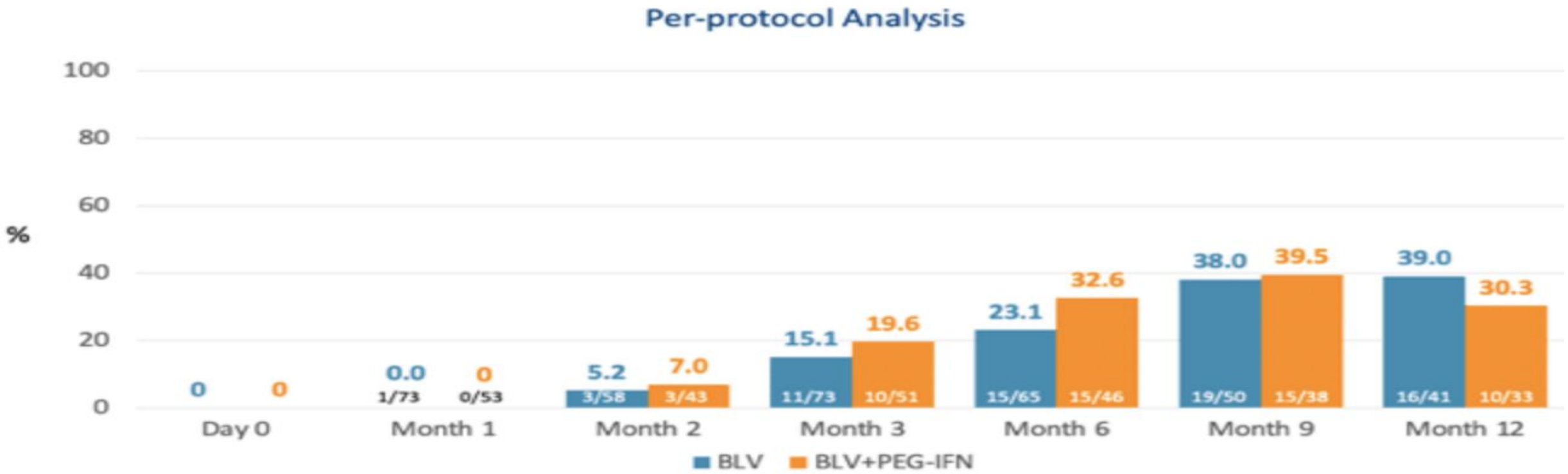
- **Virologic efficacy** defined as HDV RNA undetectable or decrease by ≥2 $\log_{10}$ from baseline

- **Biochemical efficacy** defined as normal ALT levels (ALT <40 IU/L)

De Ledinghen. AASLD 2021. Abstr OA21.

French Early Acces Program: Virologic and Biochemical Efficacy

Efficacy: Combined Response: Undetectable HDV RNA or ≥2 log_{10} IU/mL Decrease From Baseline and Normal ALT



Normal ALT defined as < 40 IU/L. missing does not equal failure. Study not powered to compare the two treatment regimens

De Ledinghen. AASLD 2021. Abstr OA21.

Current Treatment Options for HDV

In EU in some countries: Bulevirtide[1,2]	Global: PEG-IFNα[3,4]
• HDV entry inhibitor • Daily subcutaneous injections • EMA approved (commercially available in Germany, France, Austria) • **Spain:** Access to Medications in Special Situations	• Immune modulator • Weekly injections • 12–18 months' treatment duration • Off-label use

HDV: hepatitis D virus; EMA: European Medicines Agency; PEG-IFN: pegylated interferon.

1.-EMA. Hepcludex. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/hepcludex#authorisation-details-section. Accessed March 2021; 2. MYR GmbH. HEPCLUDEX (bulevirtide), Summary of Product Characteristics. October 2020; 3. Terrault N et al. *Hepatology*. 2018; 67: 1560–99; 4. Wedemeyer H et al. *N Engl J Med*. 2011; 364: 322–31.

Bulevirtide European Label

Indication

- Treatment of chronic hepatitis delta virus (HDV) infection in HDV RNA-positive adult patients with compensated liver disease

Administration

- Administered at 2 mg once daily (every 24 hours ± 4 hours) by subcutaneous injection
- Monotherapy or in co-administration with a nucleoside/nucleotide analogue for treatment of underlying HBV infection

Instructions for Use

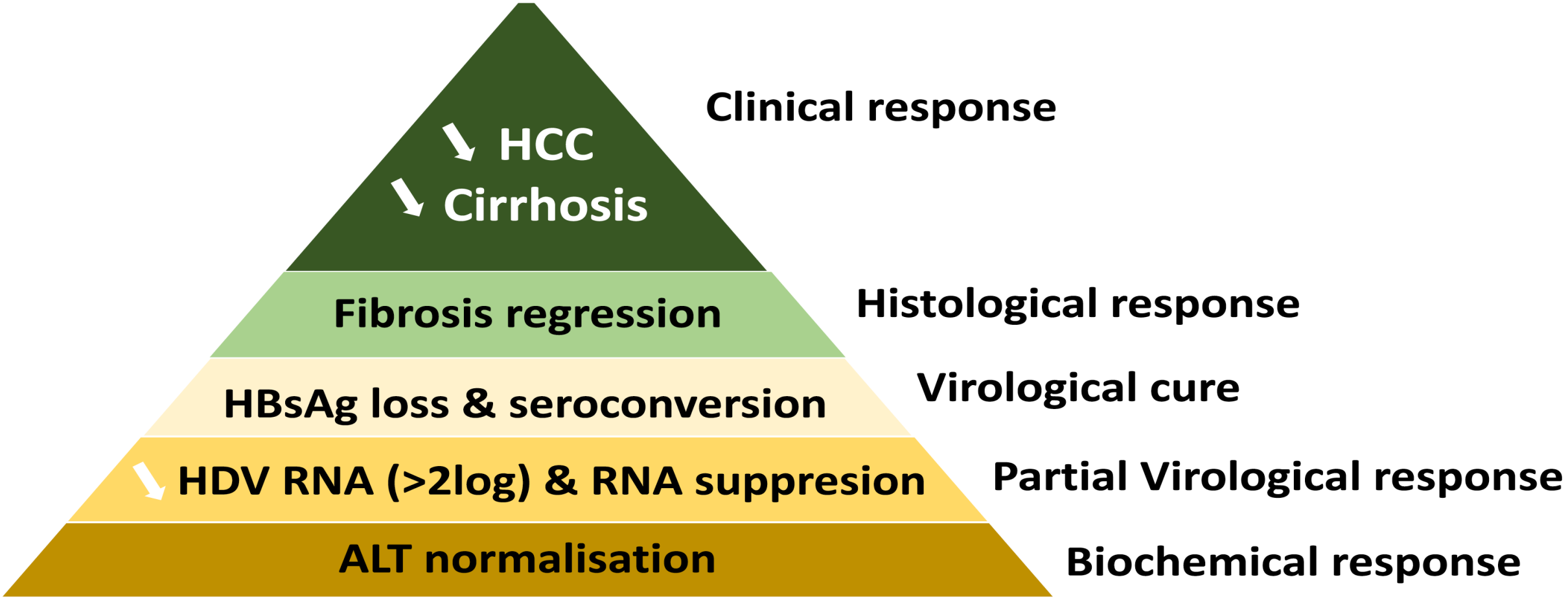
- Treatment should be initiated only by a physician experienced in the treatment of patients with HDV infection
- Optimal treatment duration is unknown. Treatment should be continued as long as associated with clinical benefit

Reference: Summary of Product Characteristics, available at www.eua.europa.eu.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Endpoints for Clinical Trials for HDV Drug Development

↗ Survival & Quality of life



Loureiro D, et al. Liver International. 2021;41(Suppl. 1):30–37.

Conclusiones

- La Hepatitis Delta representa la forma mas grave de hepatitis crónica
- EL VHD esta infradiagnosticada:
  - El sreening del VHD debería de realizarse en todos los pacientes HBsAg positivo
- IFN es el tratamiento recomendado pero tiene una eficacia limitada en pacientes con infección crónica por VHD:
  - Efectos adversos no despreciables
- Bulevirtide (BLV) ha sido recientemente aprobado para tratar la Hepatitis D Crónica en pacientes con enfermedad hepática compensada
- Los fármacos en Desarrollo para tratar al VHD incluyen:
  - Los inhibidores de la prenilación / inhibidores de la secreción del HBsAg / Nuevos interferones
  - Fármacos en desarrollo para el tratamiento de la infección crónica por el VHB