VI Jornada de Excelencia en VIH

“Hepatitis Delta la Gran Olvidada”

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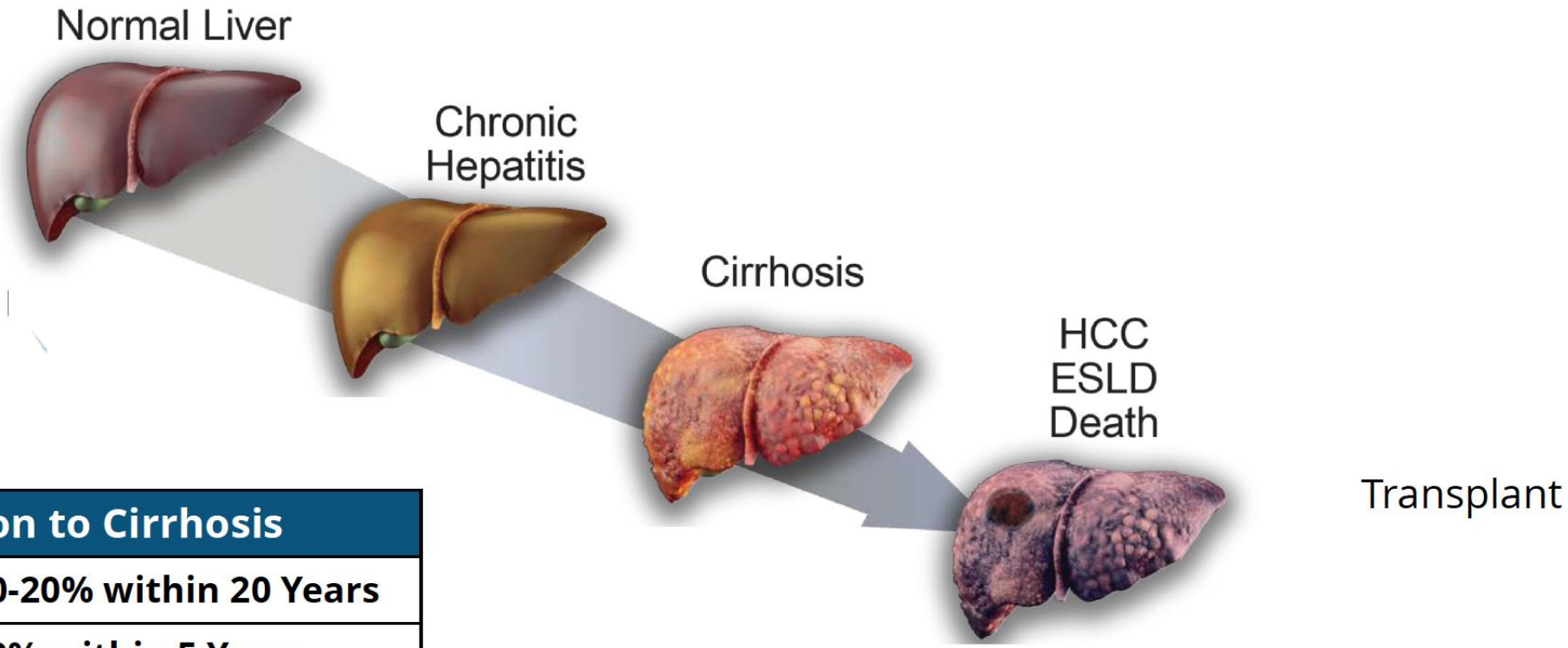
HDV
Most Rapid Progression of Viral Hepatitis

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

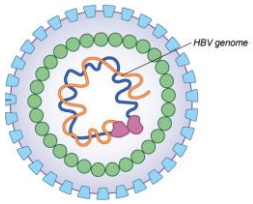
M. RIZZETTO,[1] M. G. CANESE, S. ARICÒ, O. CRIVELLI, C. TREPO, F. BONINO, AND G. VERME

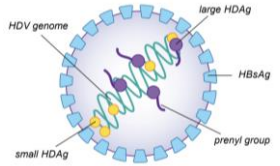
From the Department of Gastroenterology, Ospedale Mauriziano Umberto I, Turin, Italy, the Electron Microscopy Centre of the Faculty of Medicine, University of Turin, Italy, and INSERM U45, and Laboratory of Hygiene, University Claude Bernard, Lyon, France

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



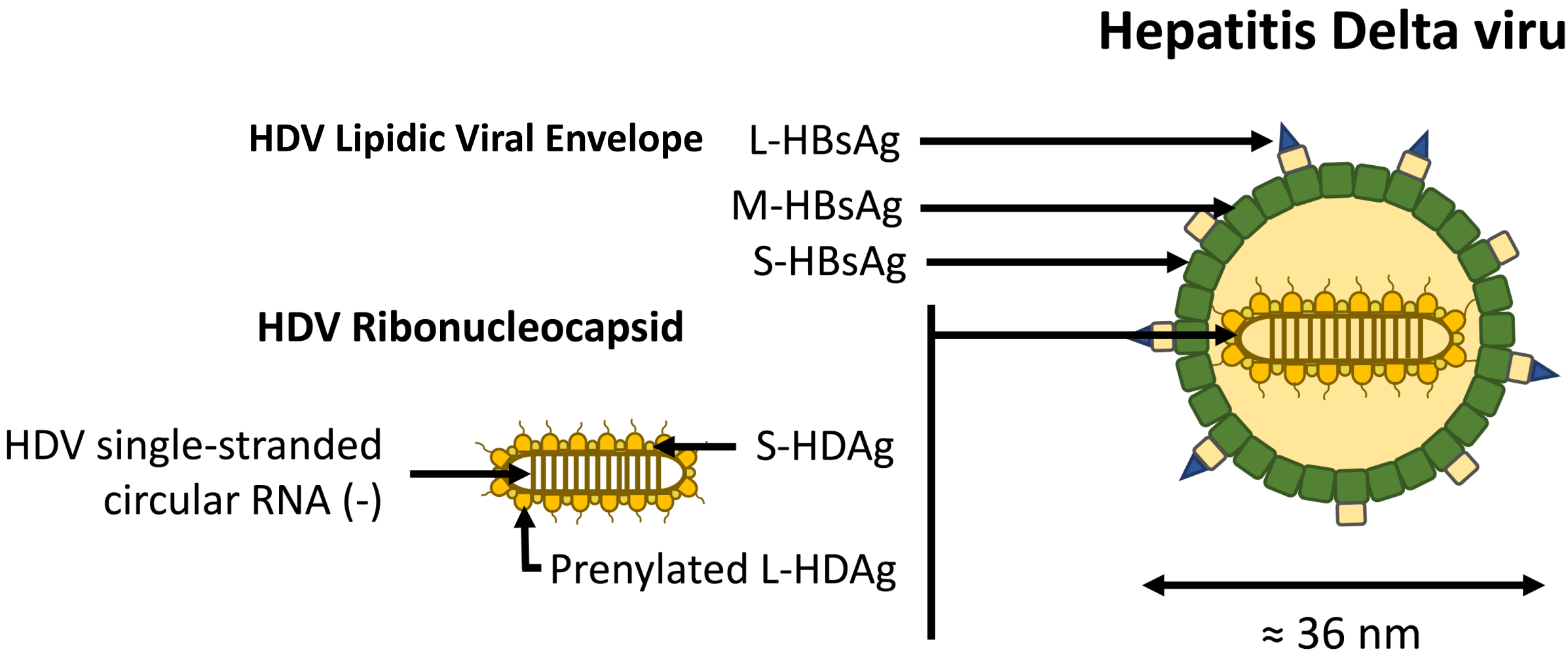


Characteristic	HBV[1]	HDV[1-4]
Family	*Hepadnaviridae*	*Kolmioviridae*
Genus	*Orthohepadnaviruses*	*Deltavirus*
Genome	Relaxed, circular, partially double-stranded DNA 3.2 kbp	Single-stranded (-) RNA 1.7 kbp
Virus-encoded proteins	HBcAg, HBeAg, polymerase, HBx, L-/M-/S-HBsAg	L-/S-HDAg
Cellular receptors	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**

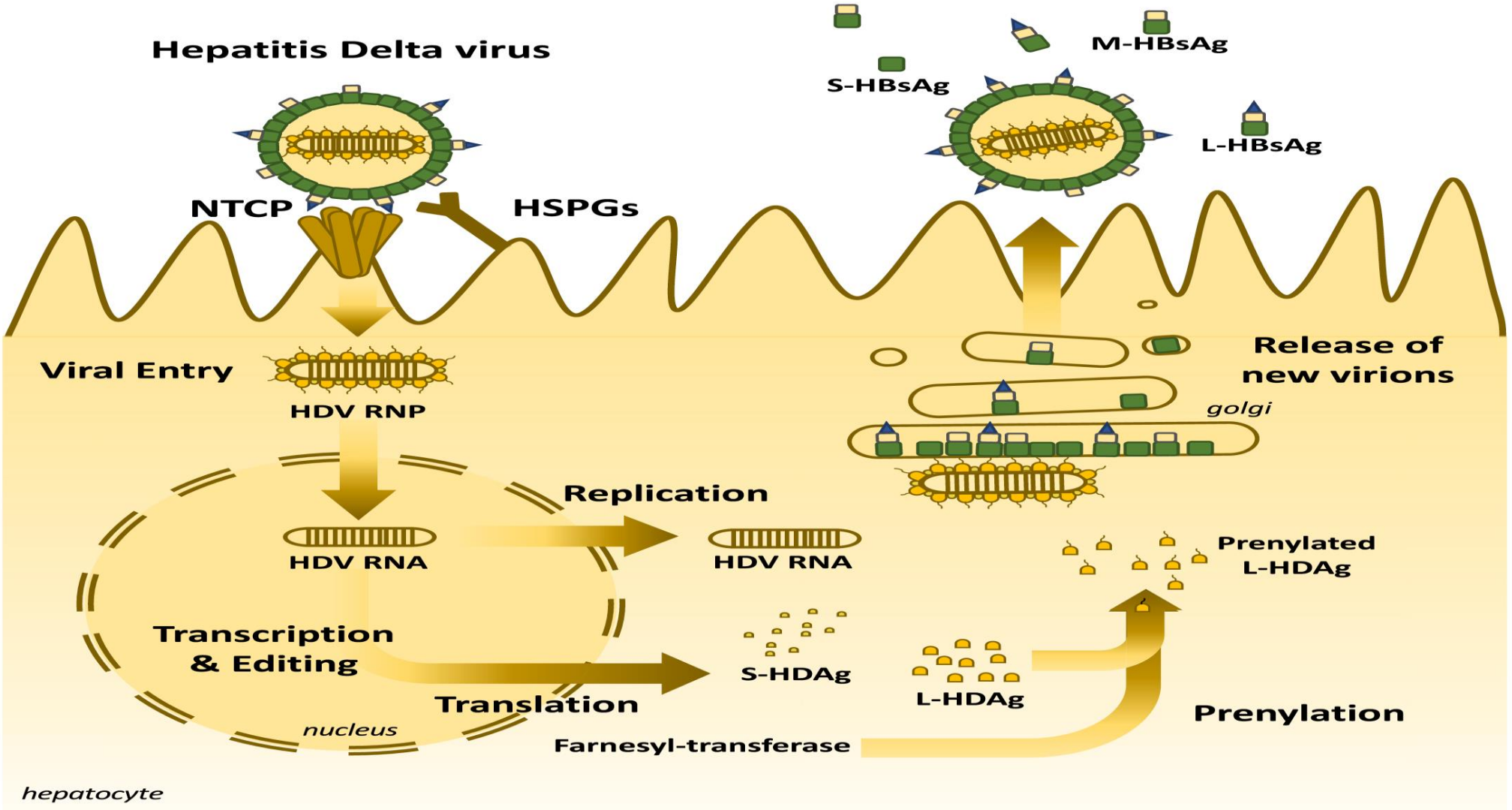
1. Lempp. Viruses. 2017;9:172. 2. Netter. Front Microbiol. 2021;12:652962.
3. Stockdale. J Hepatol. 2020;73:523. 4. Miao. J Infect Dis. 2020;221:1677.

Hepatitis Delta Virus (HDV) Viral Structure



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

Hepatitis Delta Virus (HDV) Viral Structure

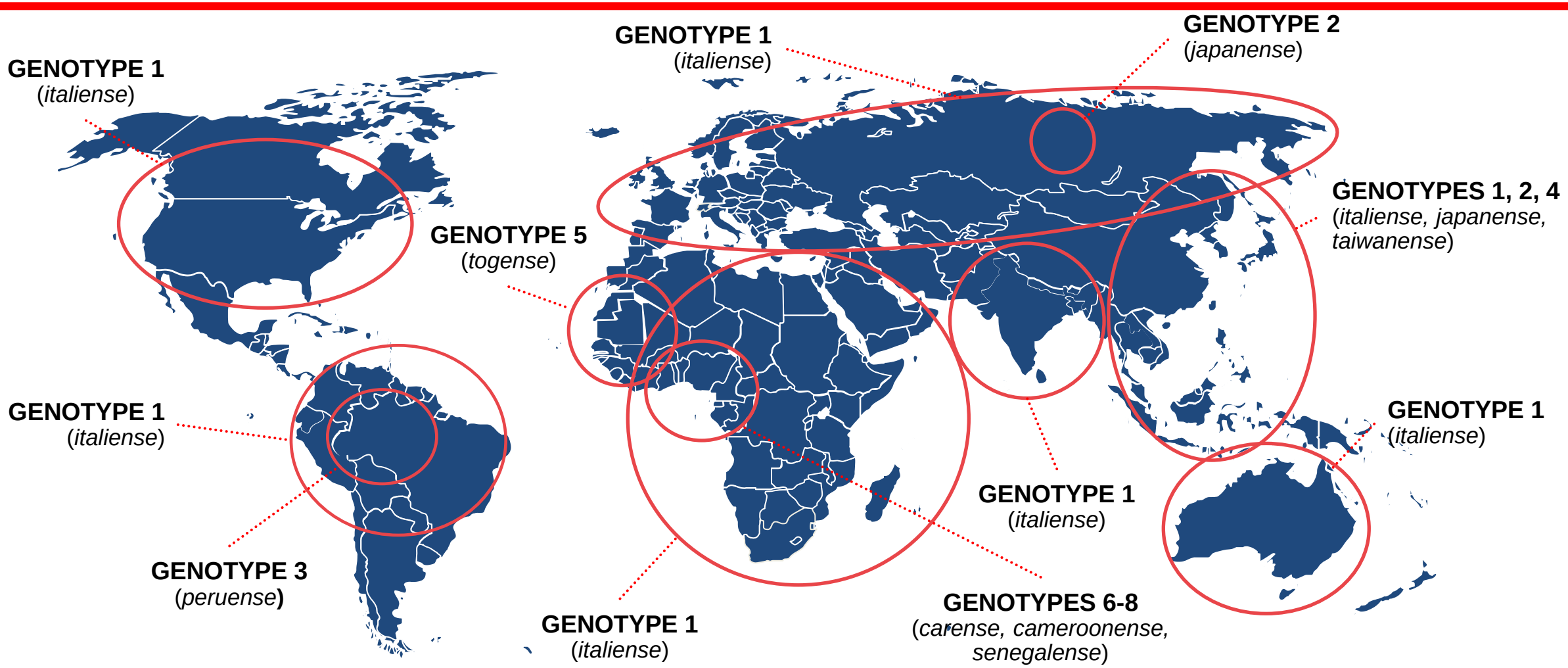


*HSPGs: Heparin Sulfate GlycoProtein

**NTCP: Sodium taurocholate co-transporting polypeptide

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

Eight HDV Genotypes with Varying Geographical Distribution[1-3]

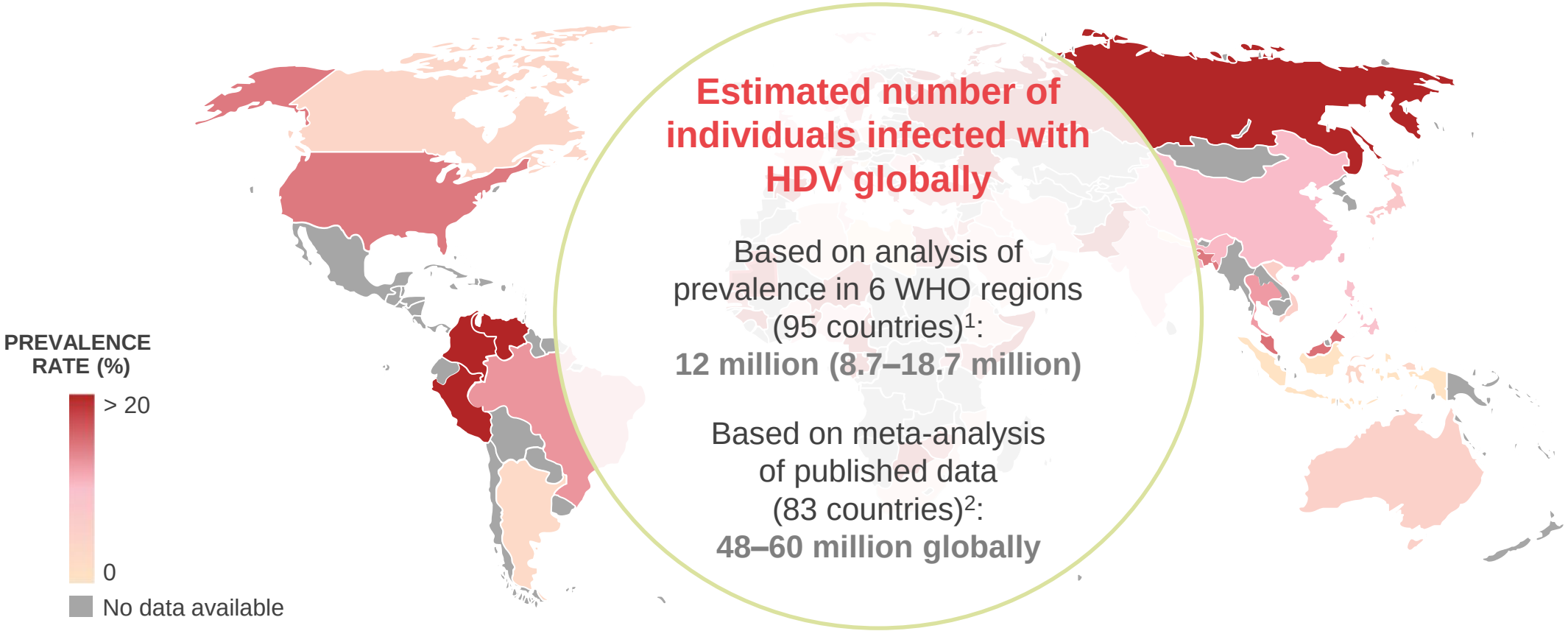


Genotype 1 is the most common HDV genotype

1. Miao Z, et al. *J Infect Dis.* 2020;221(10):1677-1687. 2. Koh C, et al. *Gastroenterology* 2019;156(2):461-476.e1. 3. ICTV. Proposals. March 2020. Accessed September 26, 2021. https://talk.ictvonline.org/ictv/proposals/2020.001G.R.Abolish_type_species.pdf

EPIDEMIOLOGIA
y
FACTORES de RIESGO

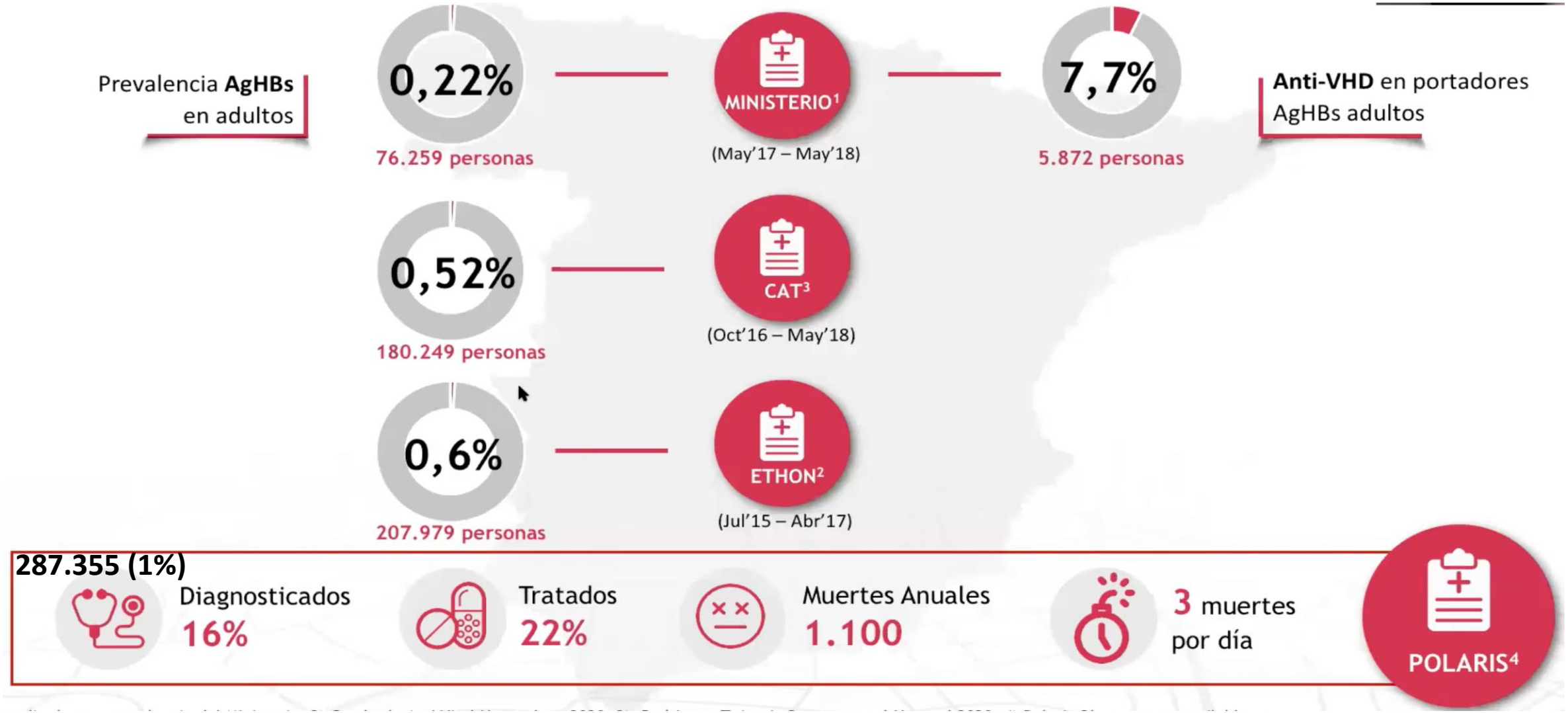
Approximately 4.5%-13% of HBsAg-Positive Carriers Are Coinfected With HDV



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

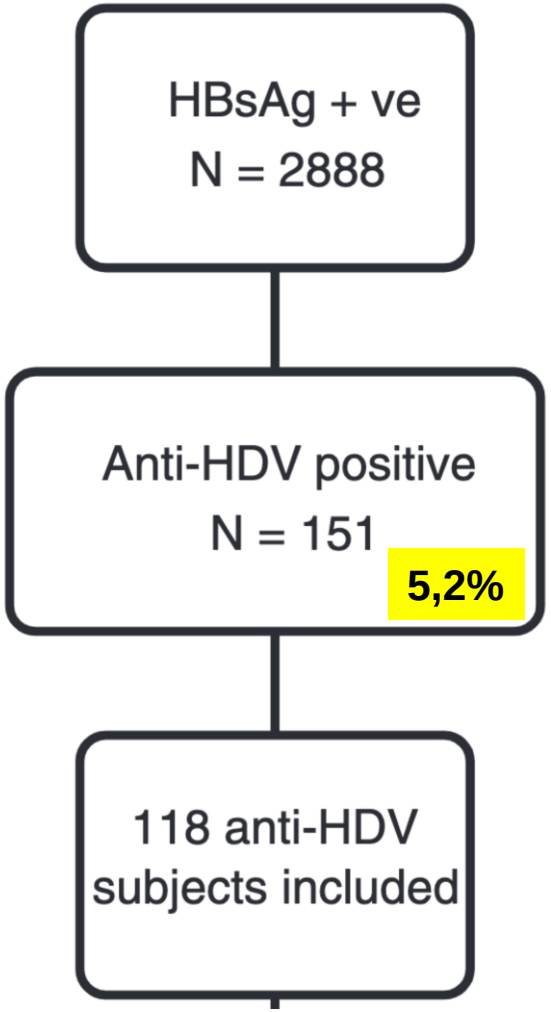
1. Stockdale AJ et al. *J Hepatol*. 2020; 73(3): 523–532; 2. Miao Z, et al. *J Infect Dis*. 2020(10); 221: 1677–1687.

Hepatitis B y D en España



1.-2º Estudio Seroprevalencia en España MSC. https://www.mscbs.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/comoTrabajamos/docs/EstudioSeroprevalencia_EnfermedadesInmunoprevenibles.pdf. 2.-Cuadrado A, et al. J Viral Hepat . 2020 Nov;27(11):1261-1265. 3.-Rodriguez-Tajes S, et al. J Gastroenterol Hepatol 2020 Sep;35(9):1570-1578. 4.-Polaris Observatory. https://cdafound.org/polaris-countries-dashboard/

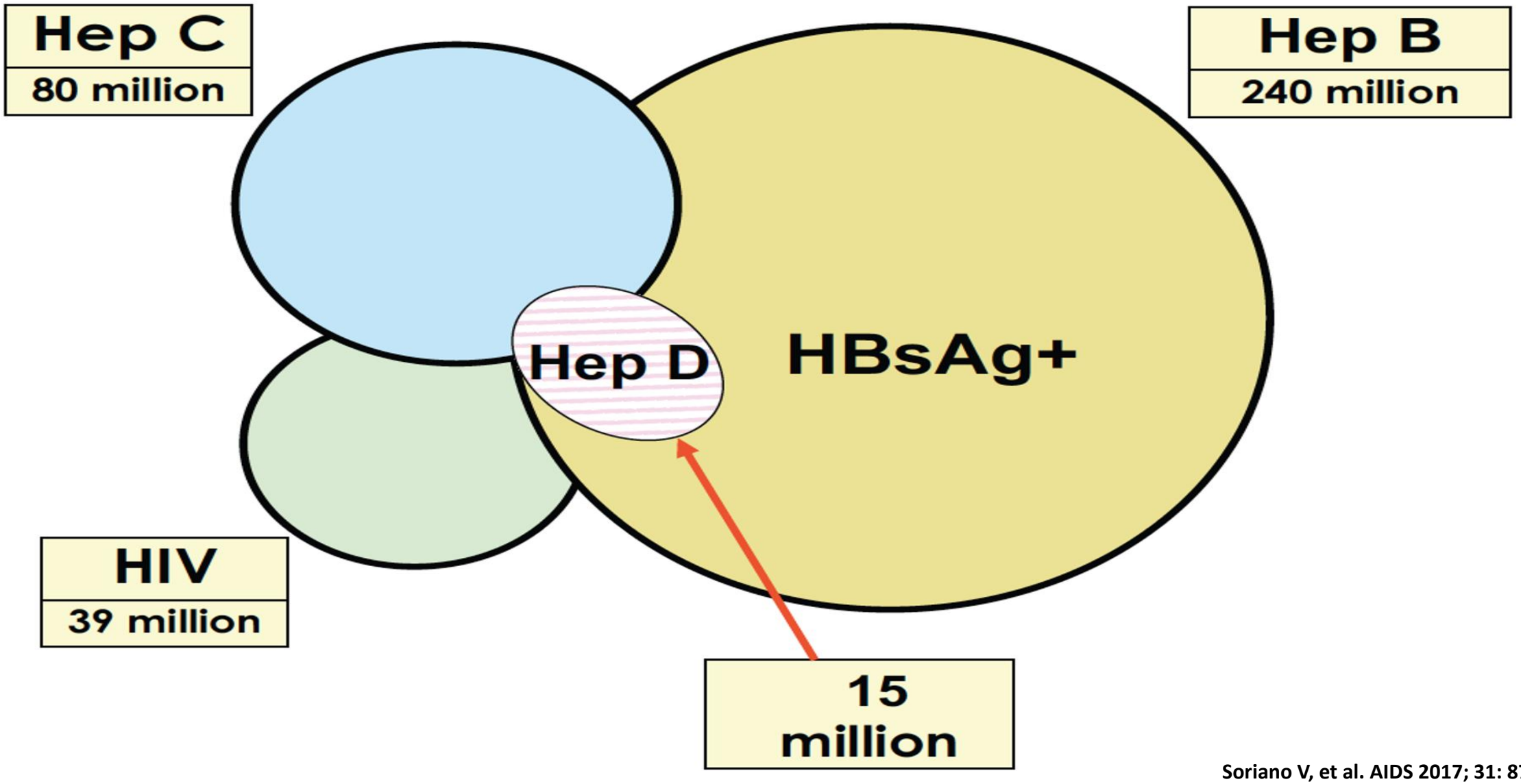
Hepatitis B y D en España



Parameters	All cases (N = 118)	Detectable HDV-RNA (N = 86)	Undetectable HDV-RNA (N = 32)	*P*
Male sex	68 (58%)	51 (59%)	17 (53%)	.676
Age, y	49 (35-54)	47 (36-54)	50 (34-53)	.227
Ethnicity				.151
Caucasian	93 (79%)	71 (83%)	22 (69%)	
Black	23 (19%)	14 (16%)	9 (28%)	
Other	2 (2%)	1 (1%)	1 (3%)	
Risk factors				844
IV drug users	23 (19%)	16 (19%)	7 (22%)	
Vertical	12 (10%)	10 (12%)	2 (6%)	
Sexual	4 (3%)	3 (3%)	1 (3%)	
Unknown	79 (68%)	57 (66%)	22 (69%)	

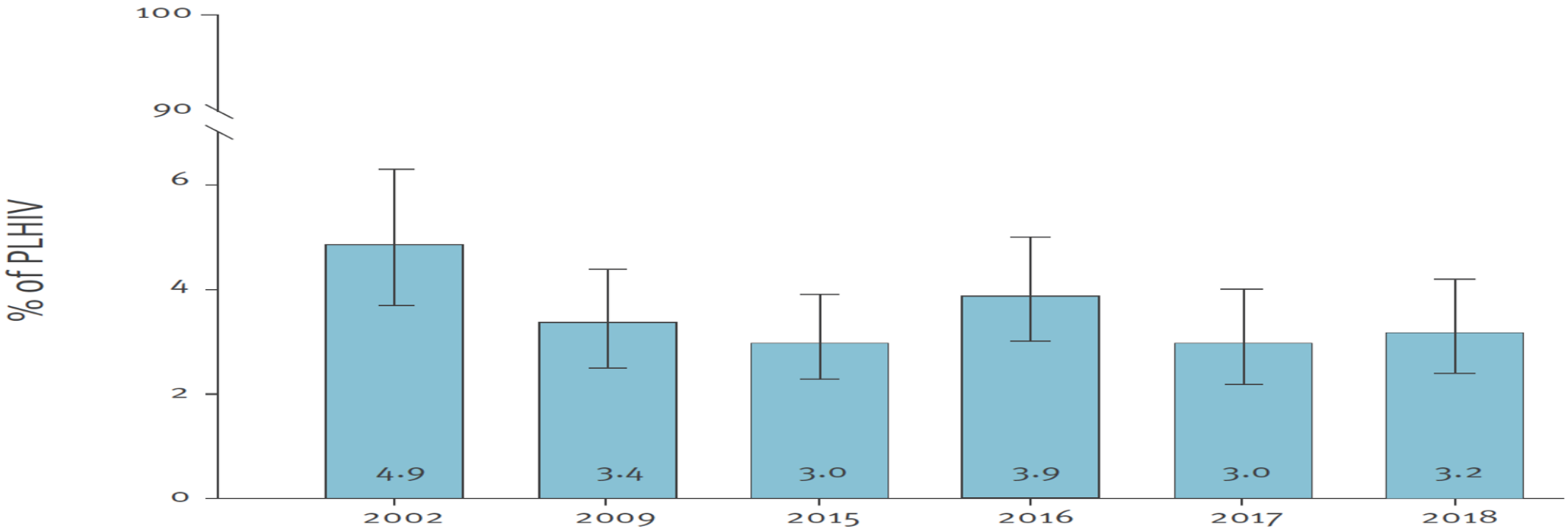
Palom A, et al. Aliment Pharmacol Ther. 2020;51:158–166

Overlapping HBV, HDV&HCV Epidemics



Soriano V, et al. AIDS 2017; 31: 875-884

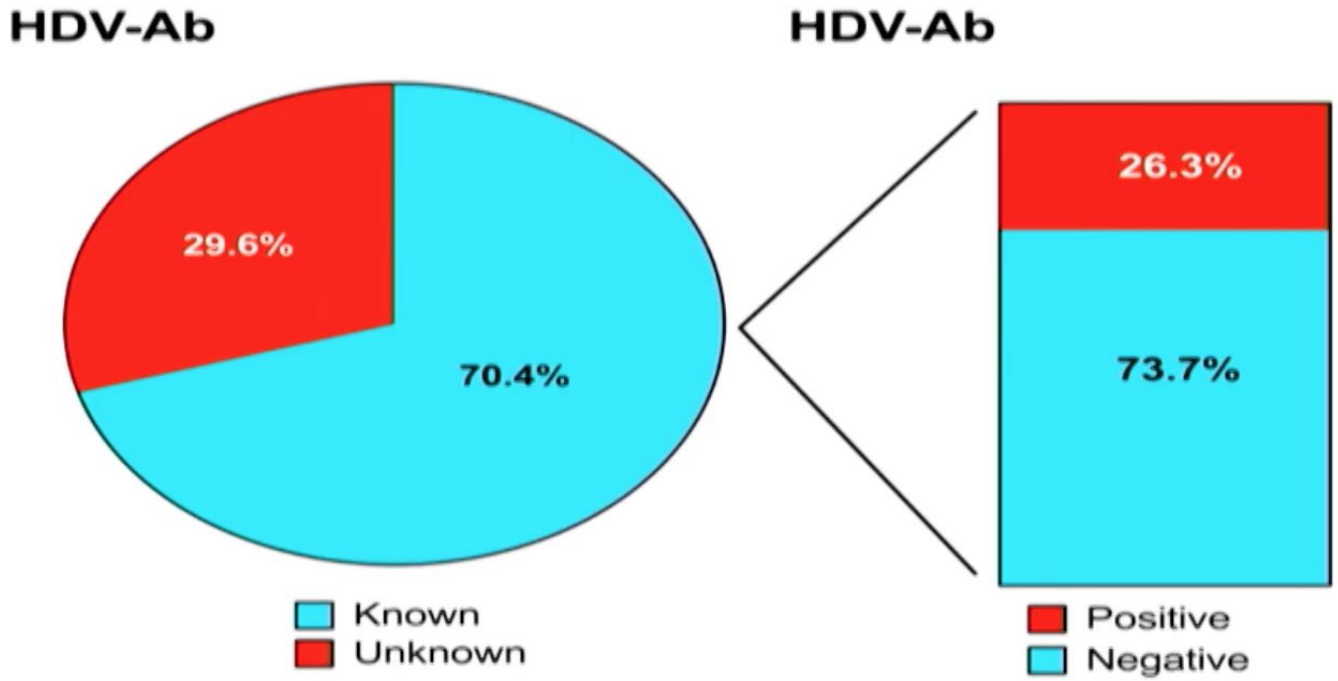
Prevalence of Hepatitis B Virus Infection (HBsAg-positive) among PLHIV, Spain, 2002-2018 (n=9605)

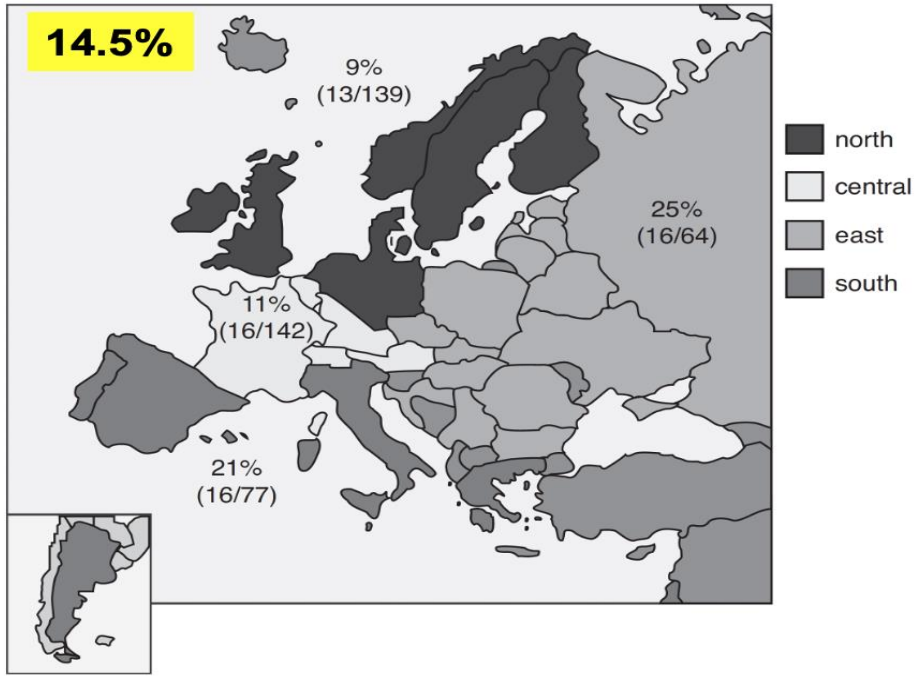


	2002	2009	2015	2016	2017	2018
Participating centres	39	43	41	43	43	43
Reference population	31,800	29,559	35,791	38,904	40,322	40,650
Sample size	1,269	1,458	1,867	1,588	1,690	1,733
Tested for HBsAg	92.7%	97.7%	97.1%	97.5%	96.2%	96.5%
Tested for HCV Ab	99.5%	99.8%	98.7%	99.8%	99.1%	99.3%

Pérez-Latorre L, et al. Euro Surveill 2021 Jun; 26 (25): 20000236. doi: 10.2807/1560-7917.ES.2021.26.25.2000236

HDV in Patients HBsAg Positive among PLHIV, Spain, 2018

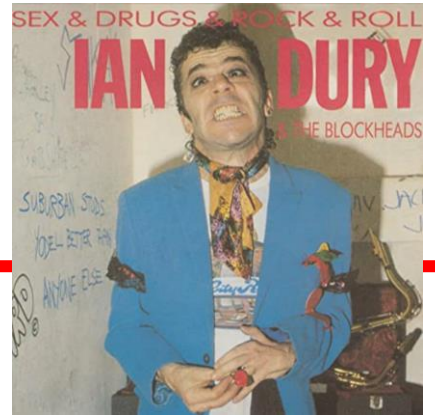




1.-Pérez-Latorre L, et al. Euro Surveill 2021 Jun; 26 (25): 20000236. doi: 10.2807/1560-7917.ES.2021.26.25.2000236. 2.-Soriano V, et al. AIDS 2011; 25: 1987-92

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.

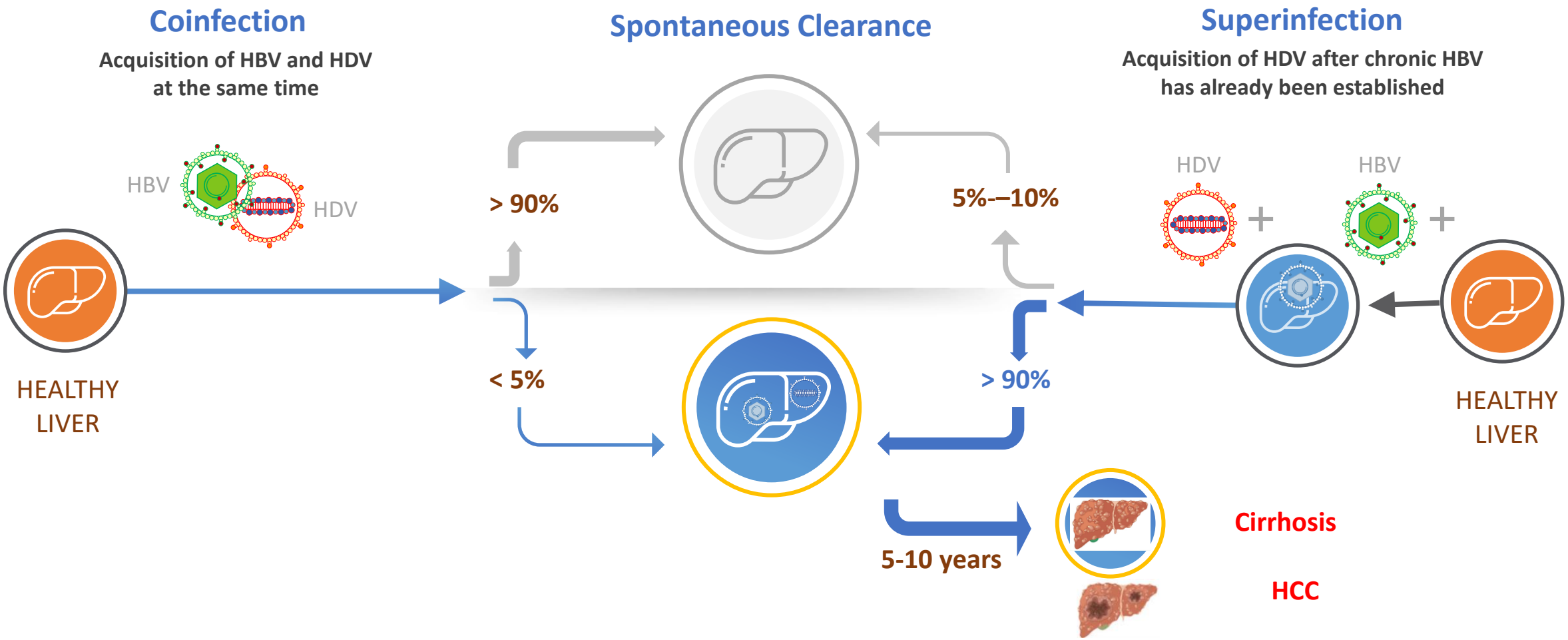
Clínica/Historia Natural

Patrones de Infección

- **Co-Infection:**
  - Both HBV and HDV

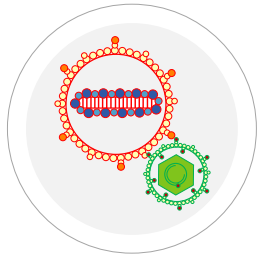
- **Superinfection:**
  - HDV Infection of an individual chronically infected with HBV

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



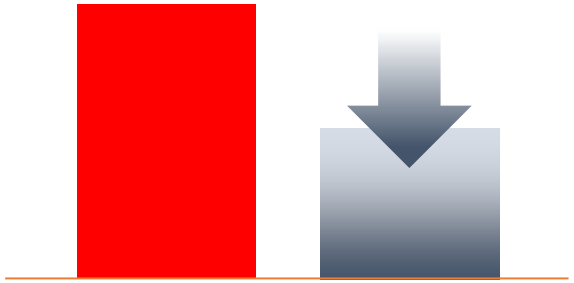
1. Tseligka ED et al. *Viruses*. 2021; 13(5): 778; 2. Jung S et al. *World J Gastroenterol.* 2020; 26(21): 2781–2791; 3. Farci P, Niro GA. *Semin Liver Dis.* 2012; 32(3): 228–236; 4. Buti M et al. *J Viral Hepat.* 2011; 18(6): 434–442; 5. Gilman C et al. *World J Gastroenterol*. 2019; 25(32): 4580–4597;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

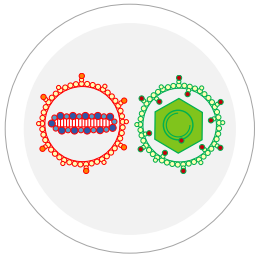
HDV Suppression of HBV: 3 Patterns of Chronic Infection[1,2]



Common

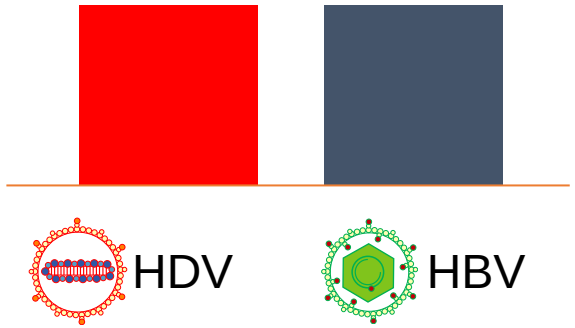
Predominant HDV replication, suppressed HBV replication

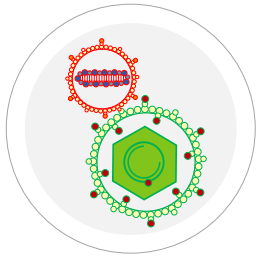




Rare

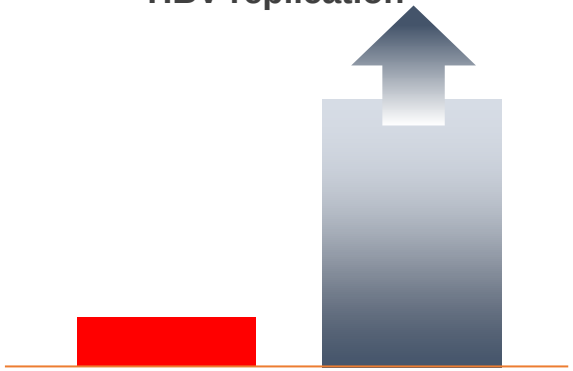
Similar HDV and HBV viral load





Rare

Predominant HBV replication

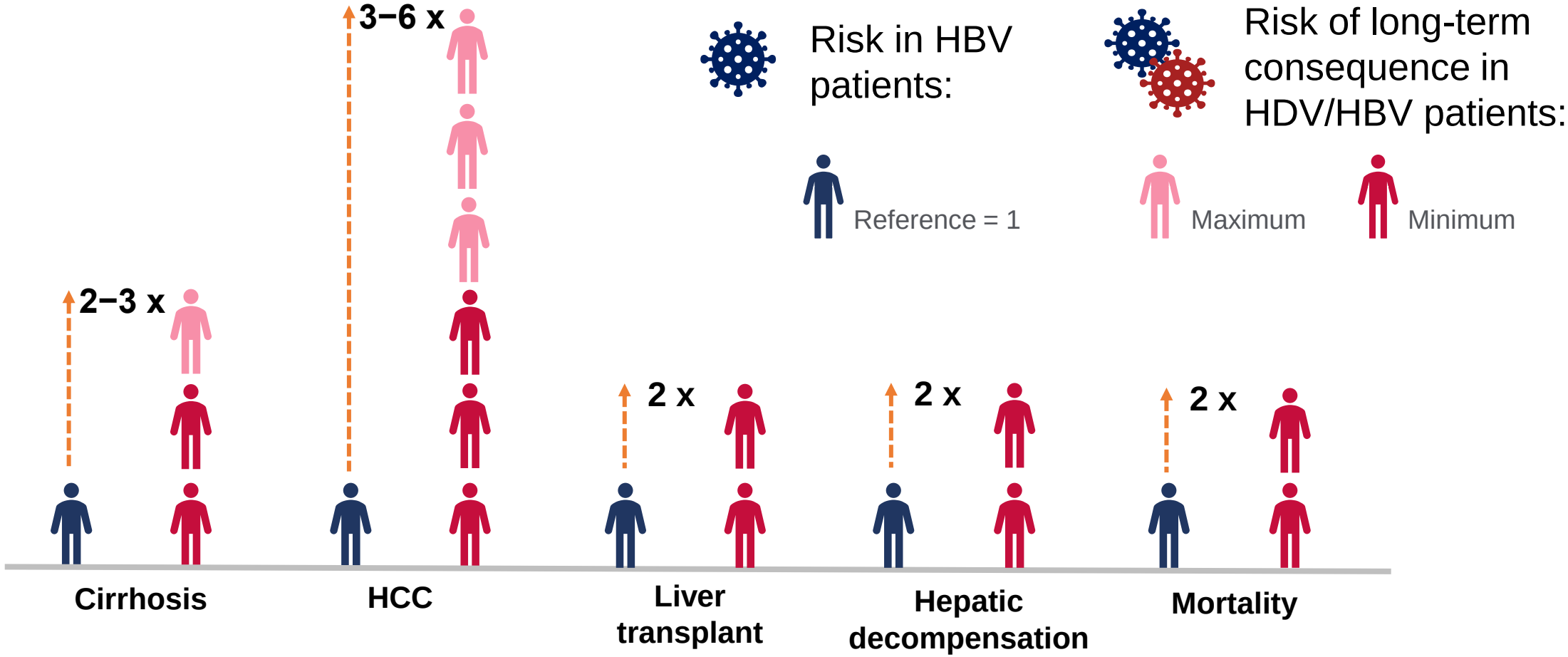


HBV viral load has no impact on HDV viral load and outcomes

1. Da BL et al. *Gastroenterol Rep (Oxf)*. 2019; 7(4): 231–245; 2. Lutterkort GL et al. *J Virol Hepatol*. 2018; 25(11): 1384–1394.

Por qué es Importante Diagnosticarla

Compared with hepatitis B mono-infection



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

Diagnostico

Diagnostico

- Sospecha clínica:
  - Hepatitis B aguda
  - Aparición de Hepatitis Aguda en un paciente con infección crónica por VHB
  - Reactivación y agravamiento de Hepatitis Crónica por VHB
- Descartar en todos los pacientes con HBsAg+

Recomendaciones para el Diagnóstico de la Hepatitis Delta

	Who to test?	How to test?
AASLD[1] (2018)	• HBsAg+ patients with HDV risk factors* • Low/undetectable HBV DNA and high ALT	• Anti-HDV • HDV RNA
APASL[2] (2016)	• Patients with chronic HBV and chronic liver disease	• HDAg or anti-HDV • HDV RNA
EASL[3] (2017)	• All patients infected with HBV	No recommendation
AEEH[4] (2020)	**En todos los pacientes con hepatitis B**	No recomendación

***HIV infection, persons who inject drugs, men who have sex with men and immigrants from areas where HDV is endemic**

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. Documento de Consenso de la AEEH. Gastroentrol Hepatol 2020; 43: 559-87

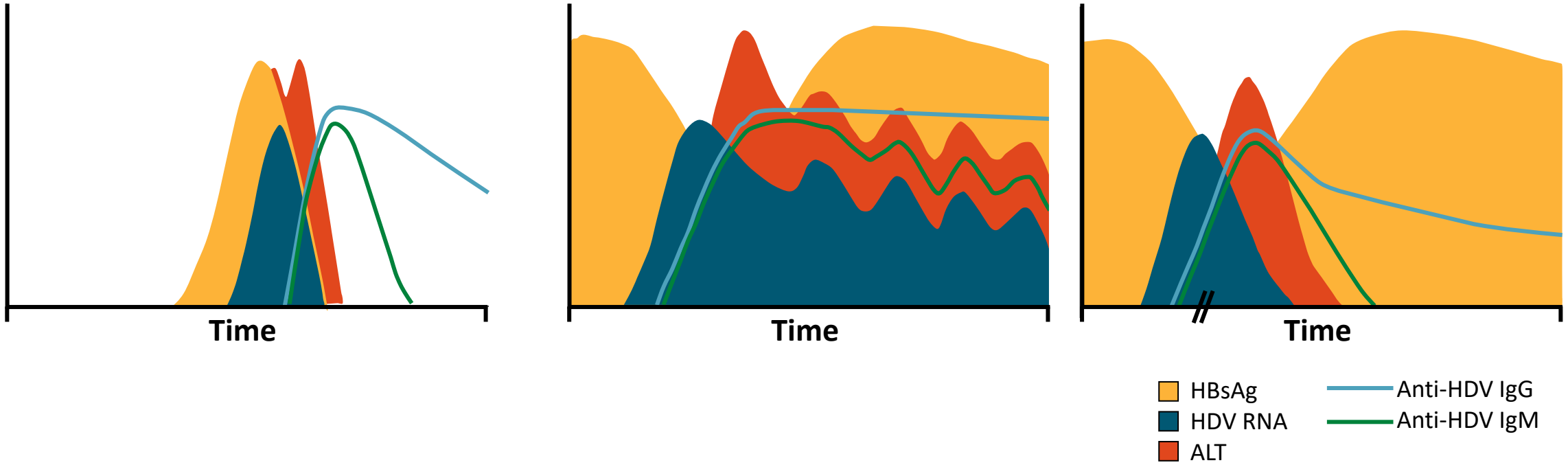
HBV and HDV Serology Varies Depending on Timing of HDV Infection

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.

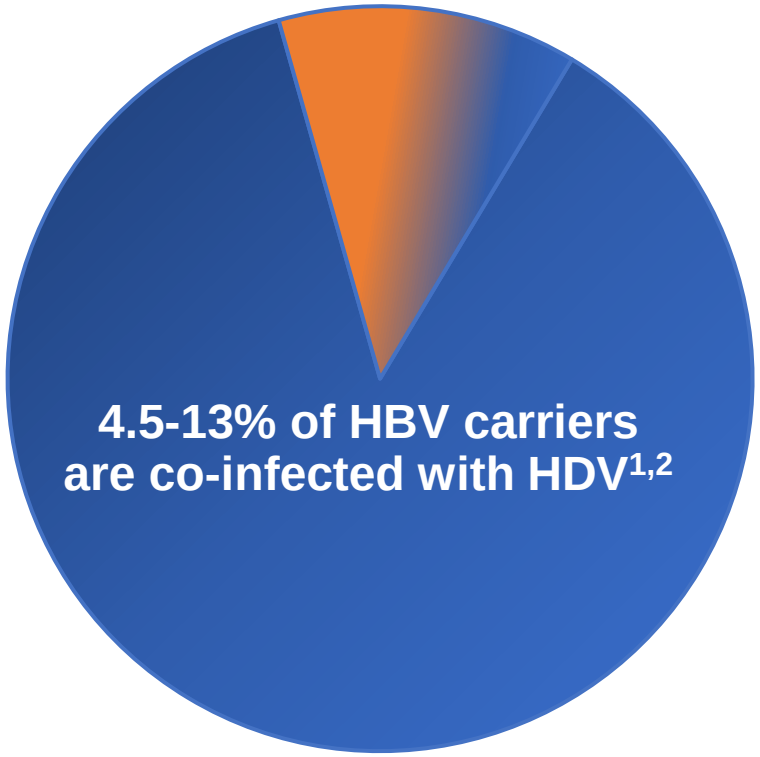
Diagnostic Test for HDV

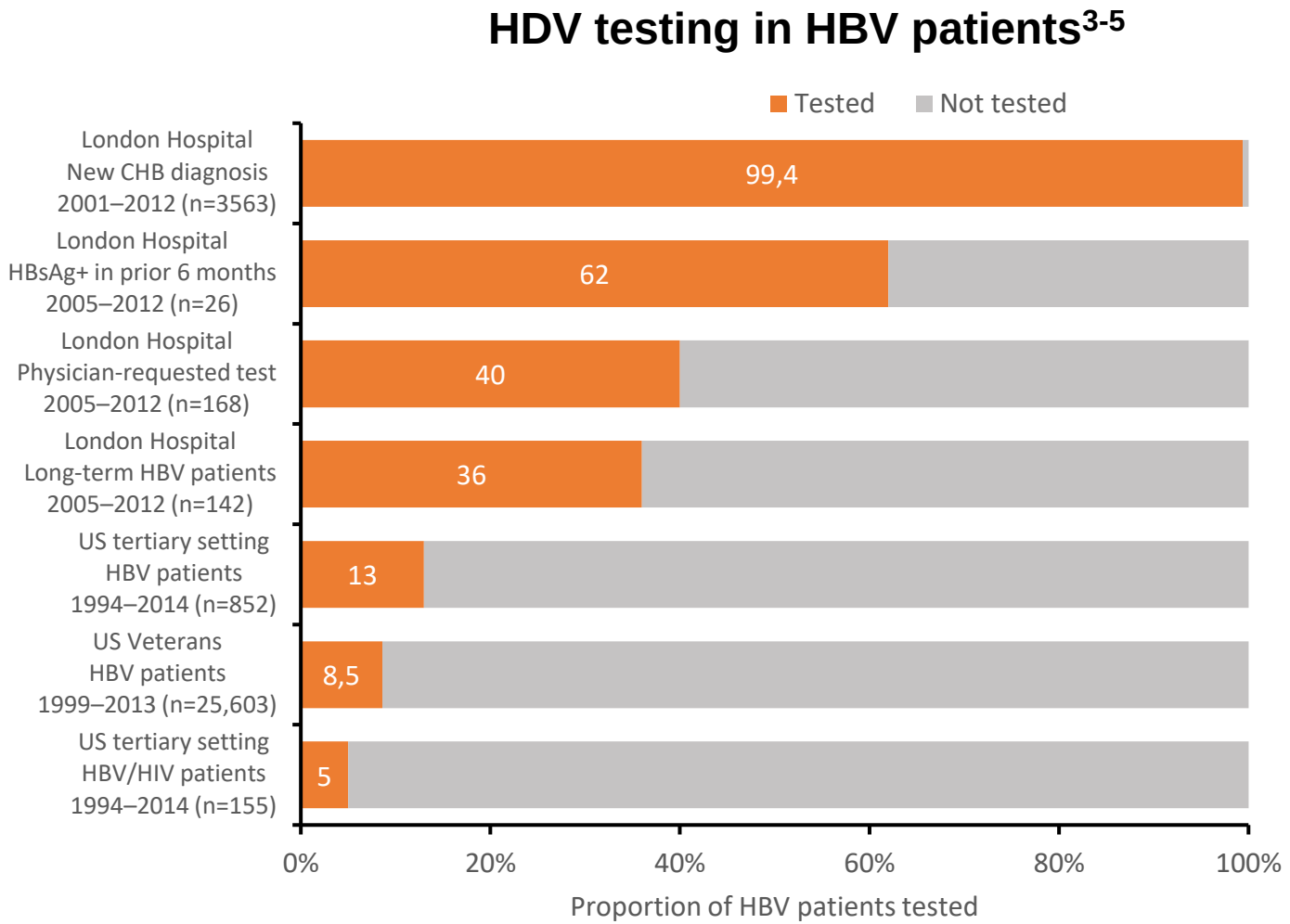
Diagnostic test	Detection	Significance	Comments
Liver HDAg	Detects HDV antigen on liver histology via immunohisto-chemical staining	Indicates active infection	Lack of availability. Poor sensitivity
Serum HDAg	Detects HDV antigen in the serum	Indicates active infection but disappears quickly	Rarely performed. 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

Y en la Práctica … qué Hacemos?





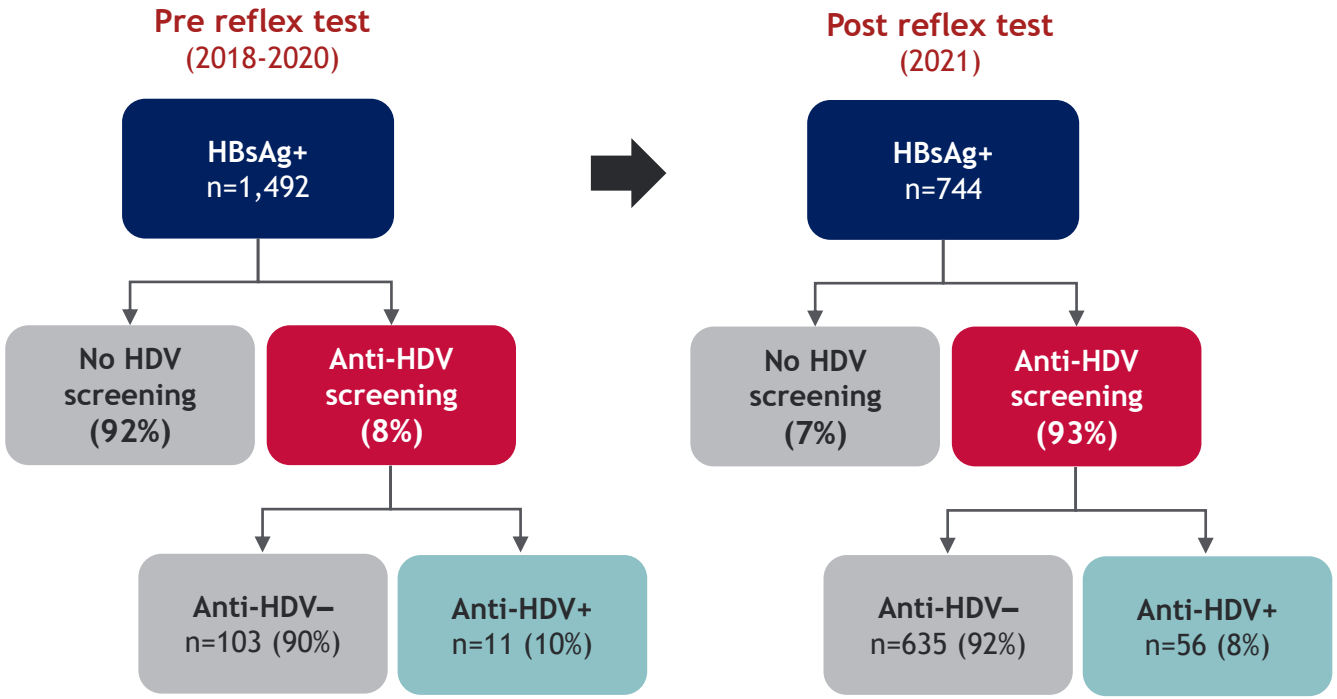
Tenemos margen de mejora!

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.

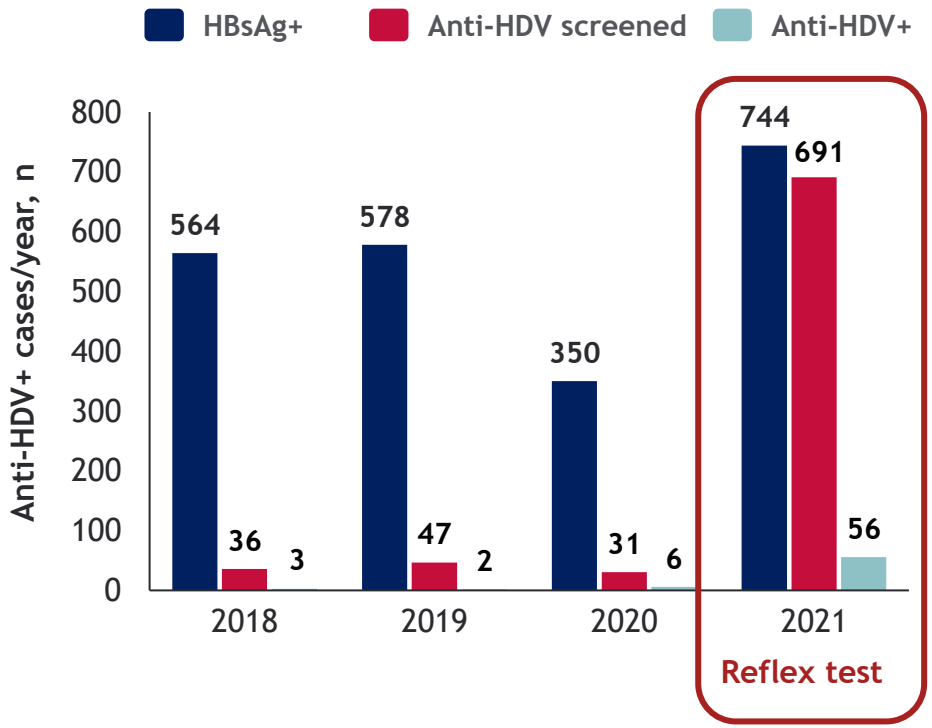
Implementation of HDV Reflex Testing in HBsAg+ Patients

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

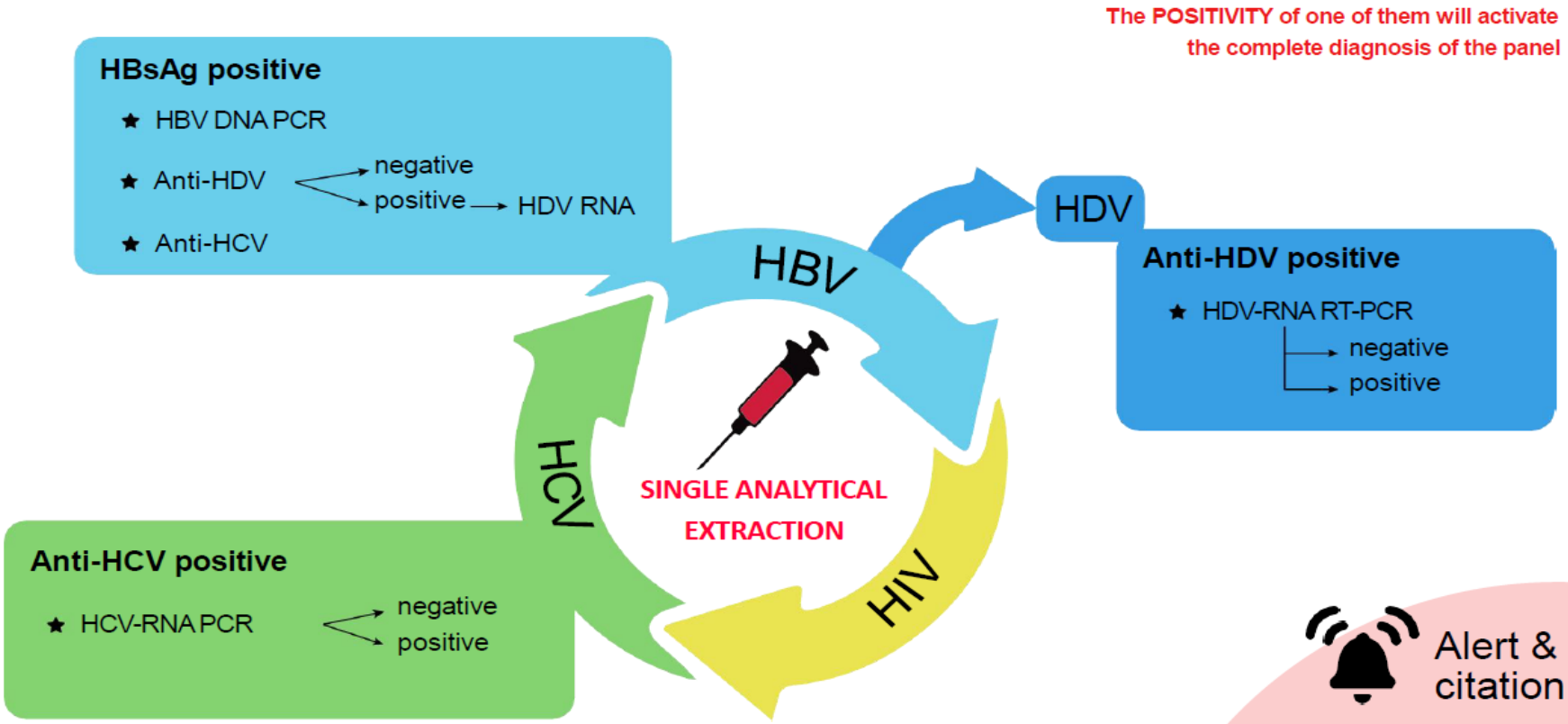


CHD diagnoses increased five-fold following introduction of reflex testing of all HBsAg+ individuals

HBsAg, hepatitis B surface antigen.

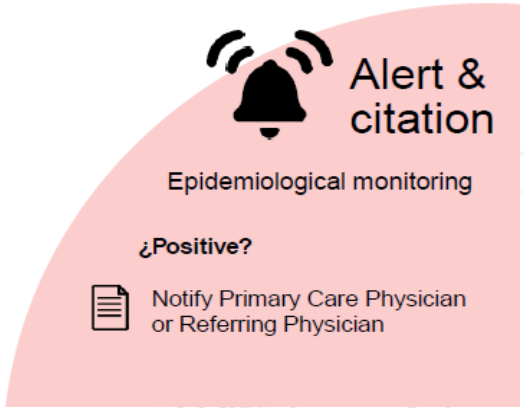
Palom A, et al. EASL 2022. Poster #THU367

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

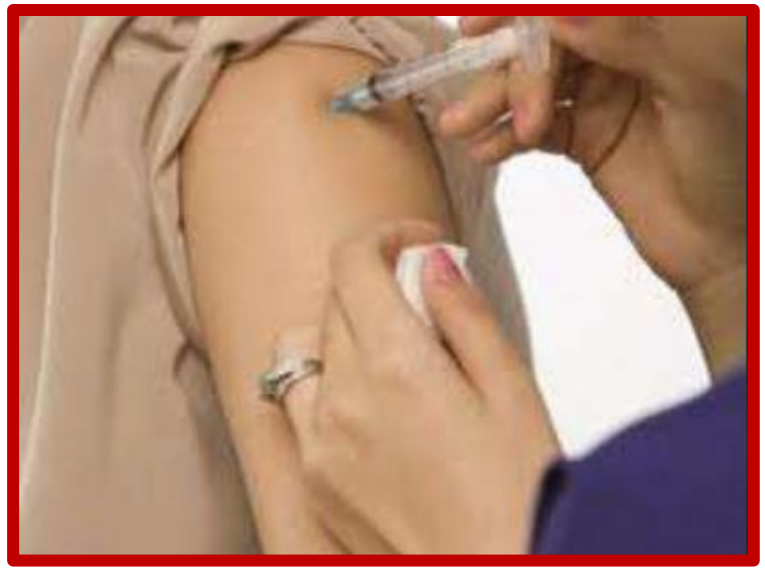


Avalado por:

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

Prevención



1.-La vacuna del VHB protege frente al VHD

2.-Detección de Familiares Asintomáticos

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).

Terapias VHD

- Interferón estándar
- Interferón pegilado
- Lamivudina
- Famciclovir
- Ribavirina ± IFB estándar/PegIFN
- TDF
- Entecavir
- Interferón + Análogo Nucleótido
- **Trasplante Hepático:**
  - Hepatitis fulminante
  - Cirrosis hepática descompensada

1.-Niro GA, et al. Aliment Pharmacol Ther 2005;22:227-32. 2.-Erhardt A, et al. Liver Int 2006;26:805-10. 3.-Lau DT, et al.Hepatology 1999;30:546-9. 4.- Kabaçam G, et al. Clin Infect Dis.2012;55: 645-50.

Clinical Trials on the Use of Pegylated-Interferon-α

Publication	Publication year	Dose and delivery	Study arms and duration	Number of patients	VR	SVR
Erhardt *et al.*	2006	1.5 mcg/kg SC/wk	peg-IFN-α for 48 weeks	12	NR	17%
Niro *et al.*	2006	1.5 mcg/kg SC/wk	peg-IFN-α for 72 weeks ± ribavirin for 48 weeks	38	13%	21%
Castelnau *et al.*	2006	1.5 mcg/kg SC/wk	peg-IFN-α for 48 weeks	14	57%	43%
Wedemeyer *et al.*	2011	180 mcg SC/wk	peg-IFN-α ± adefovir vs placebo for 48 weeks	90	23%	28%
Gheorghe *et al.*	2011	1.5 mcg/kg SC/wk	peg-IFN-α for 52 weeks	49	33%	25%

Peg-IFN-α, pegylated-interferon-α; VR, virological response; SVR, sustained virological response; NR, not reported.

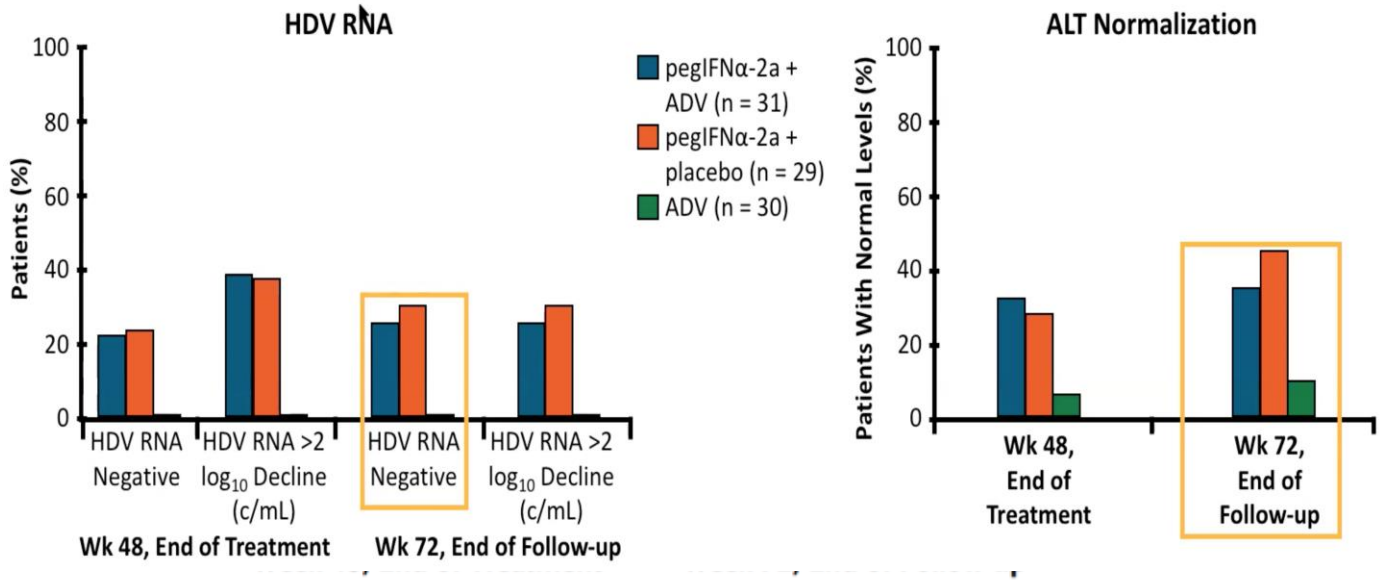
Da BL et al. Gastroenterology Report, 7(4), 2019, 231–245

48 wks Course of PegIFN+ADV vs PegIFN vs ADV in Chronic Hepatitis Delta (HIDIT-1)

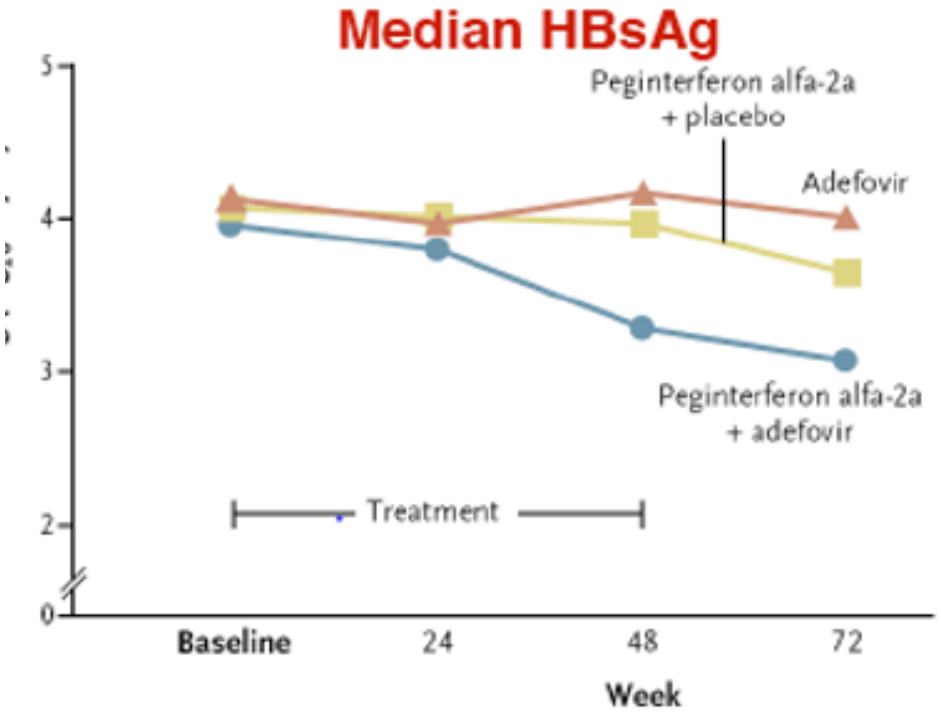
N=90 Chronic Hepatitis Delta

PEG-IFNα-2a (180 µg/wks) + ADV 10 mg/day (n = 31)
PEG-IFNα-2a (180 µg/wks) + placebo (n = 29)
ADV 10 mg/day (n = 30)

- Multicenter, randomized trial of treatment in patients with chronic HDV for 48 wk
  - **Primary endpoint:** undetectable HDV RNA and ALT normalization at Wk 48
  - ADV had **no** beneficial effect on HDV RNA



All HDV GT 1
14-24% cirrhosis



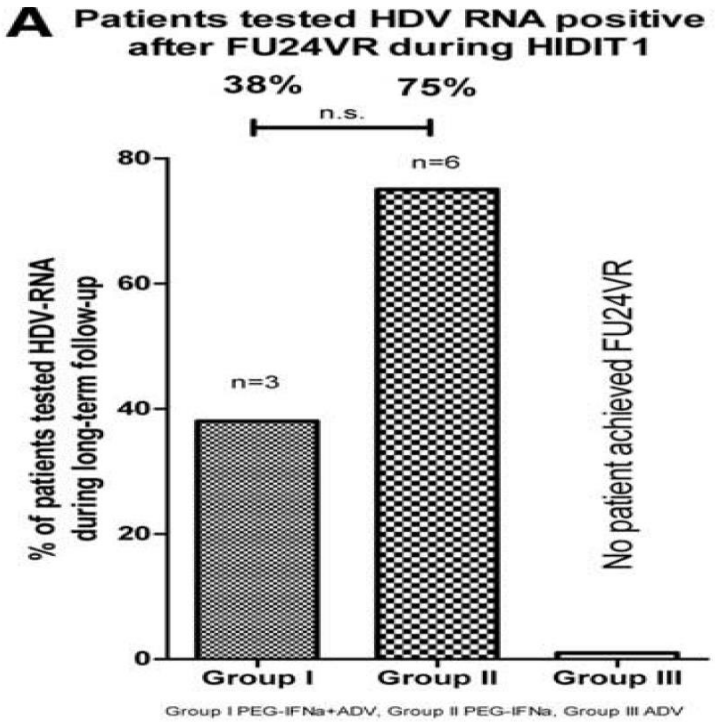
HBsAg loss: 2 patients treated with PegIFN/ADV

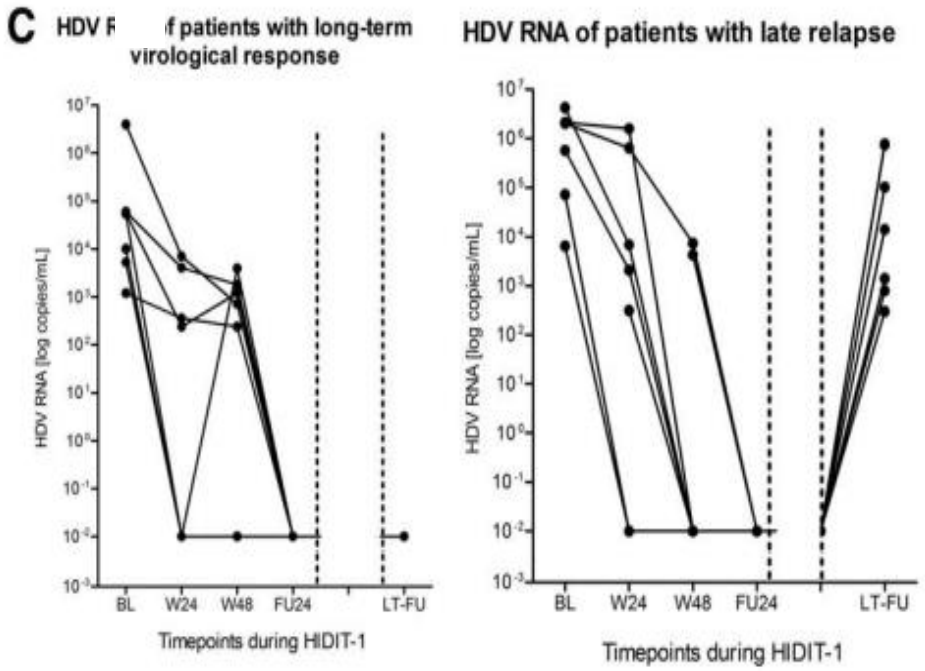
Wedemeyer H. et al, N Eng J Med 2011;364:322-331

Changes in Hepatitis Delta Viremia after Treatment Discontinuation

- Late (5 years follow-up)
  - 9/16 (56%) patients with viral response

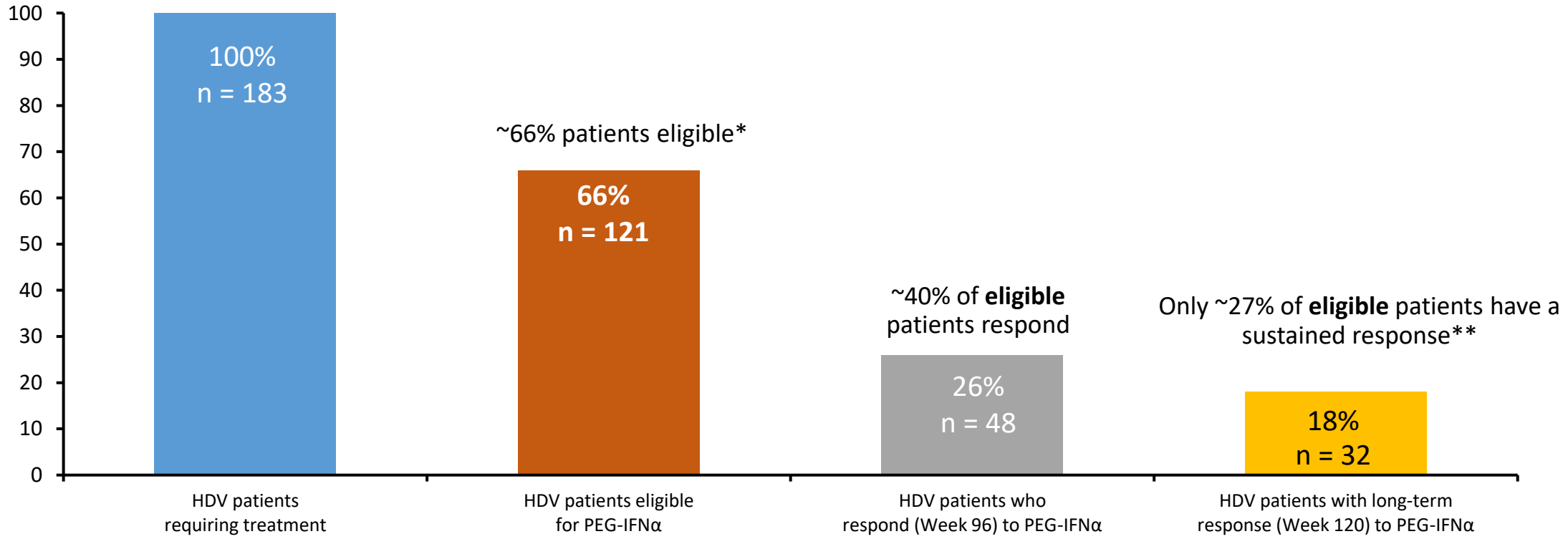
  post-treatment week 24 tested HDV RNA Positive





Heidrich B et al. Hepatology 2014;60:87-97

Response to PEG-IFNα Treatment



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

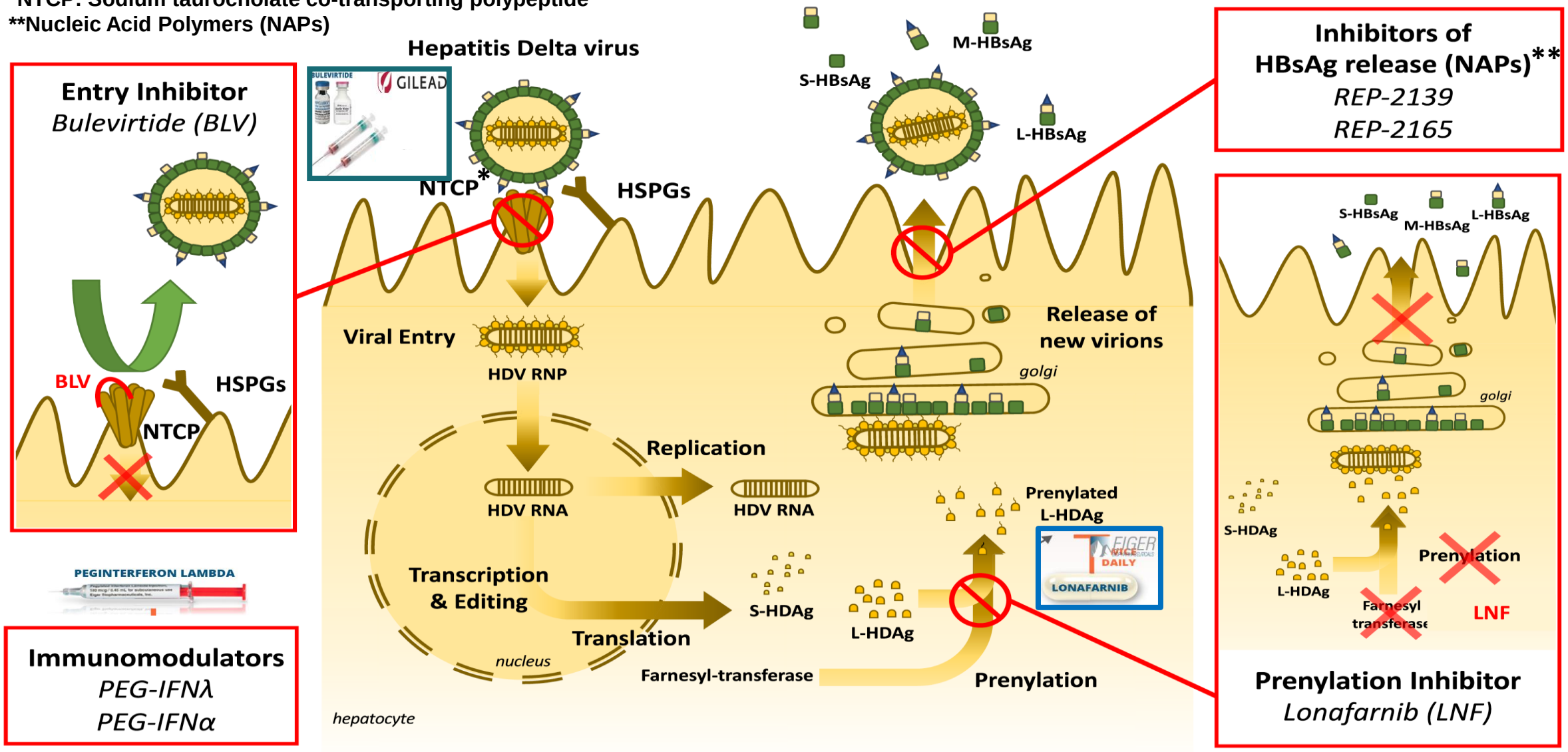
*Ineligibility based on contraindications, intolerance and presence of advanced liver disease in HIDIT-II (62 of 183 screened did not meet inclusion criteria or met exclusion criteria) **Response defined as undetectable HDV RNA after 120 weeks of treatment.
HDV: hepatitis D virus; PEG-IFNα: pegylated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

Regulatory and Guideline Efficacy Endpoints

	Chronic On-Therapy Endpoint	Cure Off-Therapy Endpoint
FDA Draft Guidance November 2019	*"…a **greater than or equal to 2-log$_{10}$ decline in HDV RNA and ALT normalization** on-treatment could be considered an acceptable surrogate endpoint"*	*"The proportion of trial patients with **undetectable serum HDV RNA** (defined as less than the lower limit of quantification (LLOQ), target not detected (TND)) and **ALT normalization**."*
AASLD / EASL 2019 EASL-AASLD HBV Treatment Endpoints Conference October 2019	*"…a **2-log reduction in HDV RNA might suffice**."*	*"…**undetectable serum HDV RNA 6 months after stopping treatment** as the endpoint …Normalisation of ALT is also desired"*

ALT: alanine aminotransferase; HBV: hepatitis B virus; HDV, hepatitis D virus; RNA: ribonucleic acid.

1. **FDA. https://www.fda.gov/media/132137/download. Accessed February 2021;**
2. **2. Cornberg M et al. *J Hepatol*. 2020 Mar; 72: 539–57. doi: 10.1016/j.jhep.2019.11.003. Epub 2019 Nov 12.**

Myrcludex B: First Results of a Phase Ib/IIa Study

24 Patients

Myr cohort

Screening	Myrcludex B 2 mg/day	PegINFα-2a 180 µg/week	Follow-up

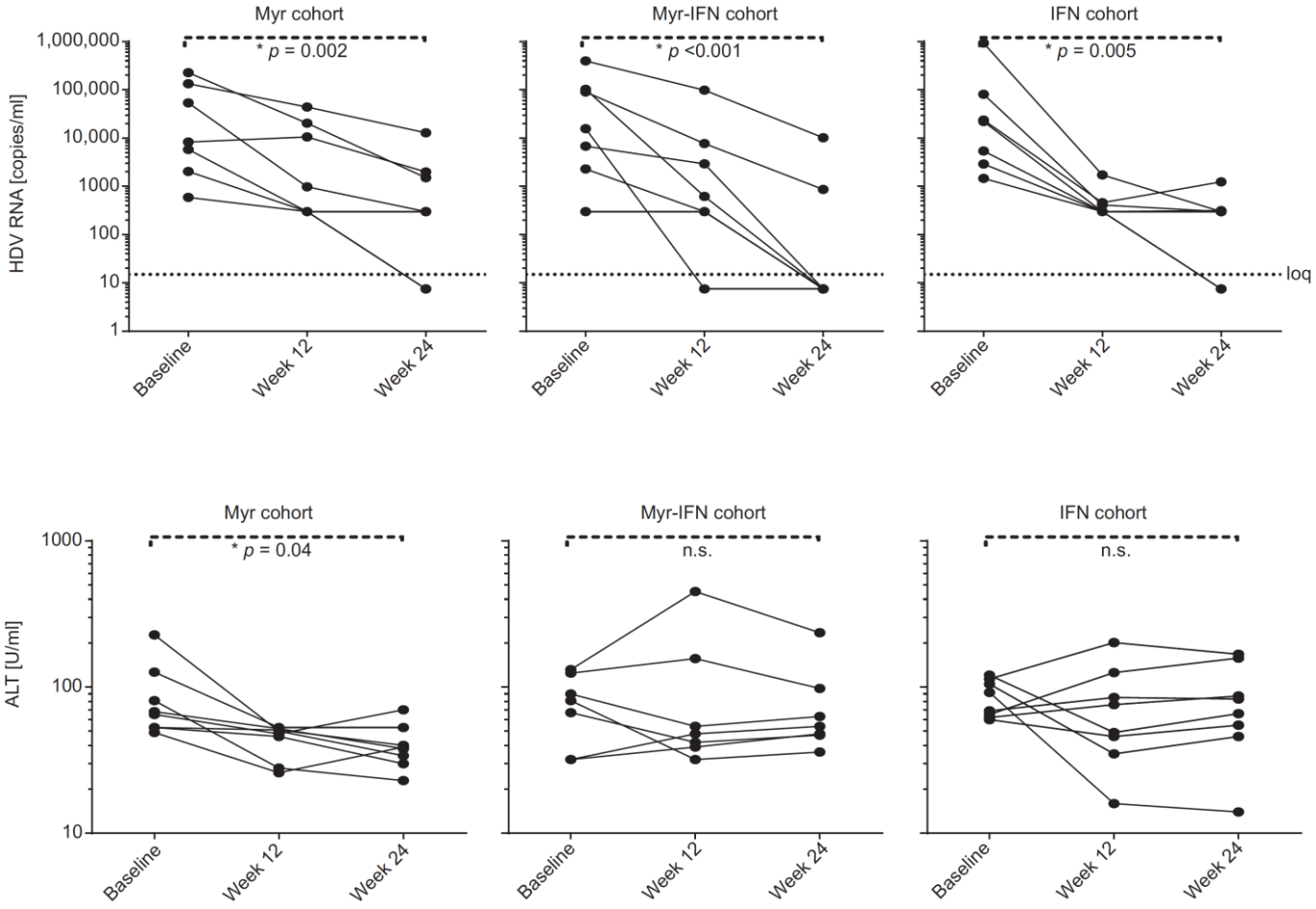
Myr-IFN cohort

Screening	Myrcludex B 2 mg/day PegINFα-2a 180 µg/week	PegINFα-2a 180 µg/week	Follow-up

IFN cohort

Screening	PegINFα-2a 180 µg/week	Follow-up

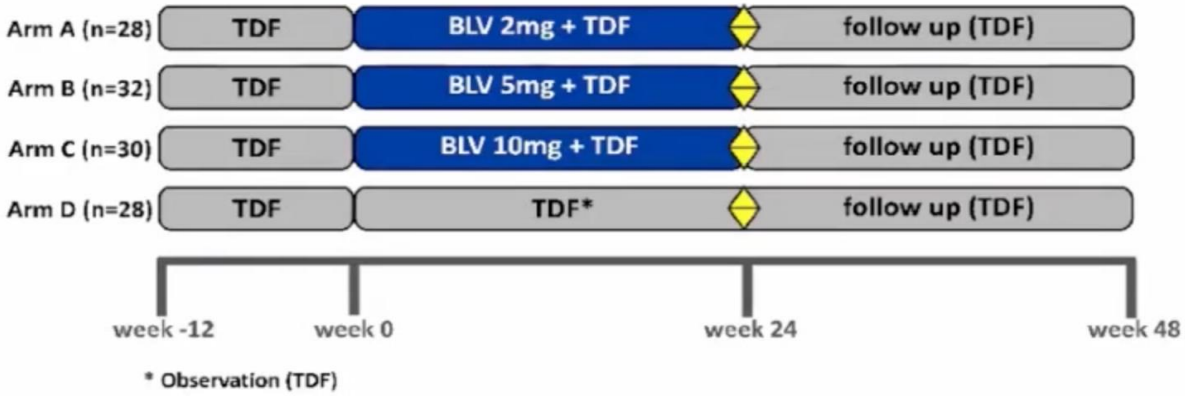
Baseline | Week 12 | Week 24 | Week 36 | Week 48 | Week 60 | Week 72



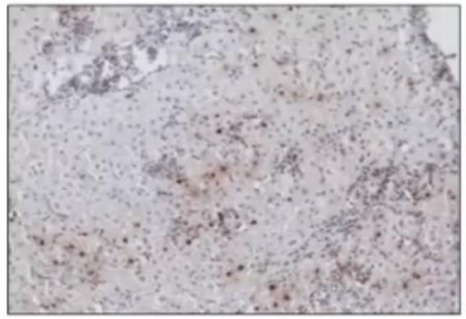
Bogomolov P, et al. Journal of Hepatology 2016 vol. 65 j 490–498

Bulevirtide: Approval Studies MYR202

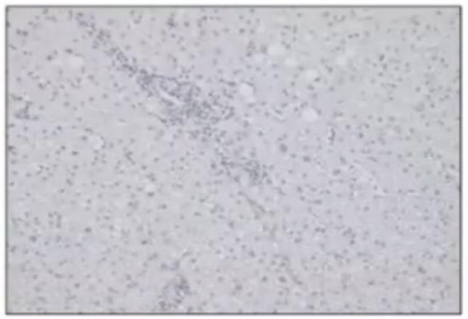
- **120 patients** randomized in 4 groups
- Multicenter, open label, randomized trial with study centers in Germany and Russia
- **Primary endpoint**: HDV RNA undetectable or decrease by ≥2log$_{10}$ IU/mL in week 24



Baseline:



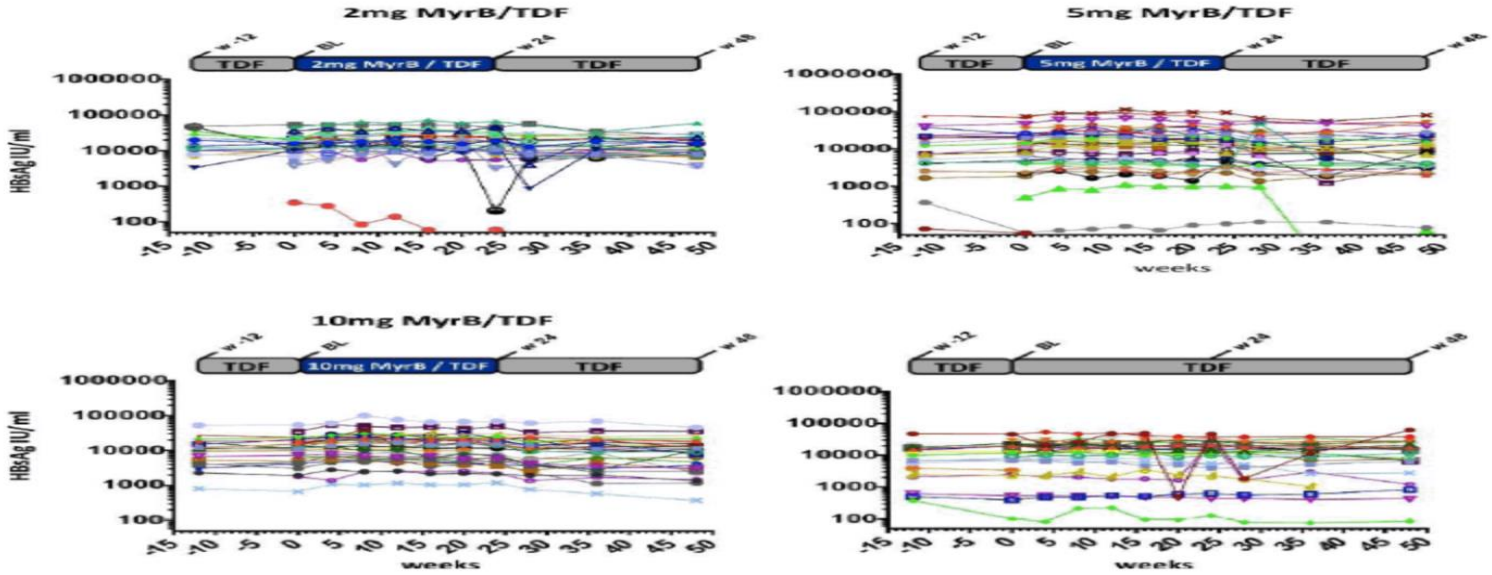
Week 24:



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

→ Decrease of HDAg-positive hepatocytes

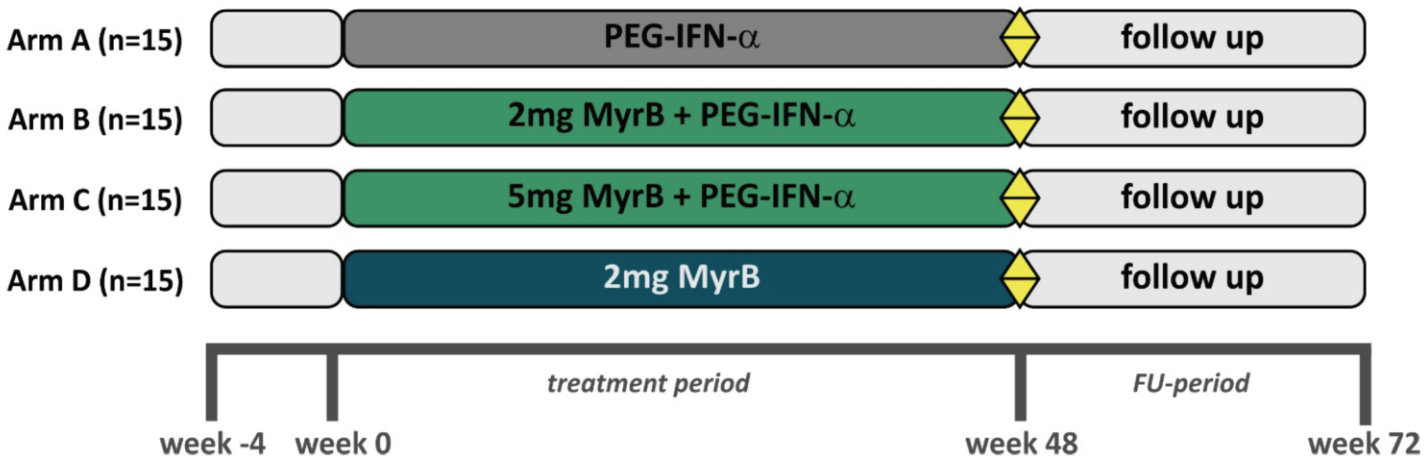
→ I
e



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

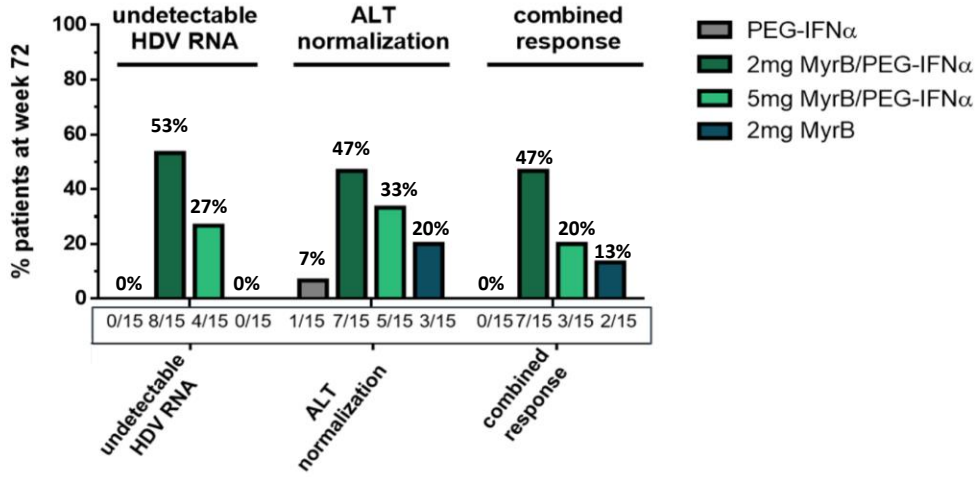
1.- Wedemeyer H, et al. Hepatology 2018;68(Suppl):11. 2.-Wedemeyer H, et al. ILC 2019; GS-13

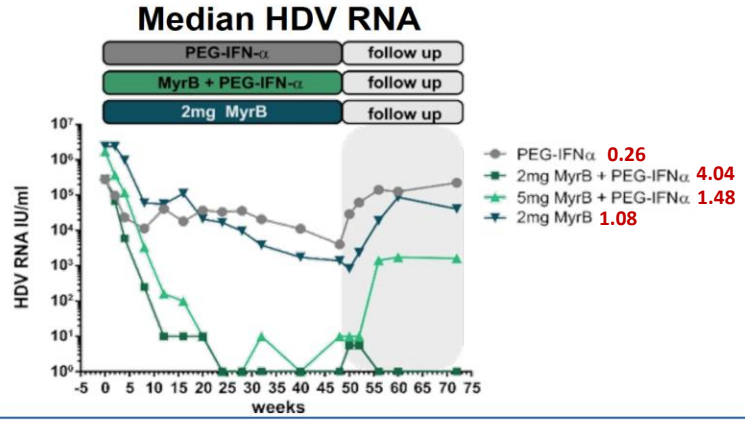
Bulevirtide: Approval Studies MYR203

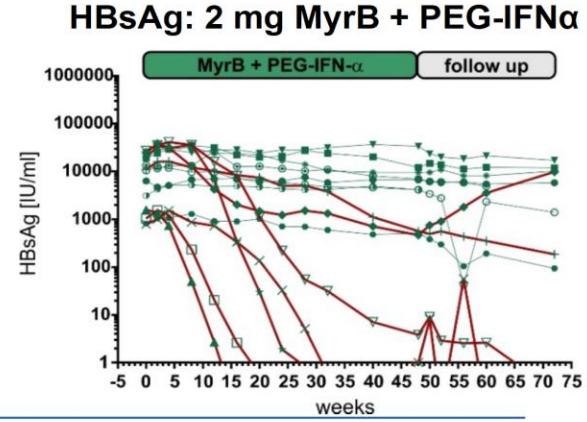
- **Safety:** MyrB was well tolerated, with 155 drug-related AEs up to w72 (mild n=122, moderate n=28, serious n=5), primarily increased total bile salts
  - Most AEs (n=524) related to PegIFNα2a
  - All cases resolved; bile salts returned to baseline by follow-up Week 50
  - Two SAEs (anal fistula and 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





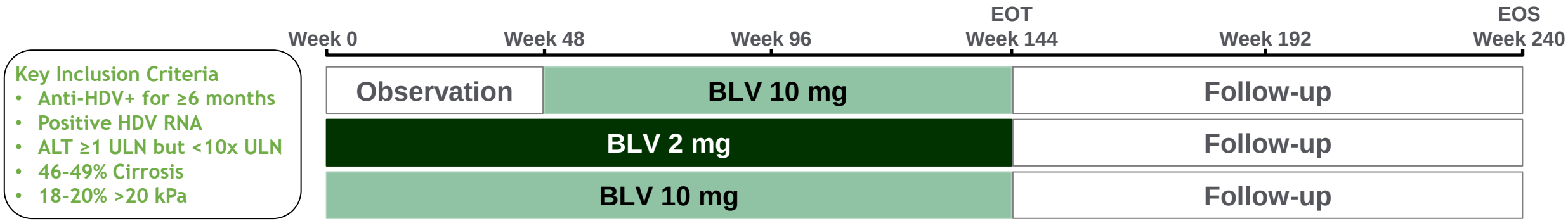


In contrast to PegIFNα2a monotherapy, MyrB + PegIFNα2a demonstrated high rates of HDV RNA suppression. HBsAg loss was achieved in 27% of patients, indicating a potential role for MyrB in future HBV cure regimens

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:

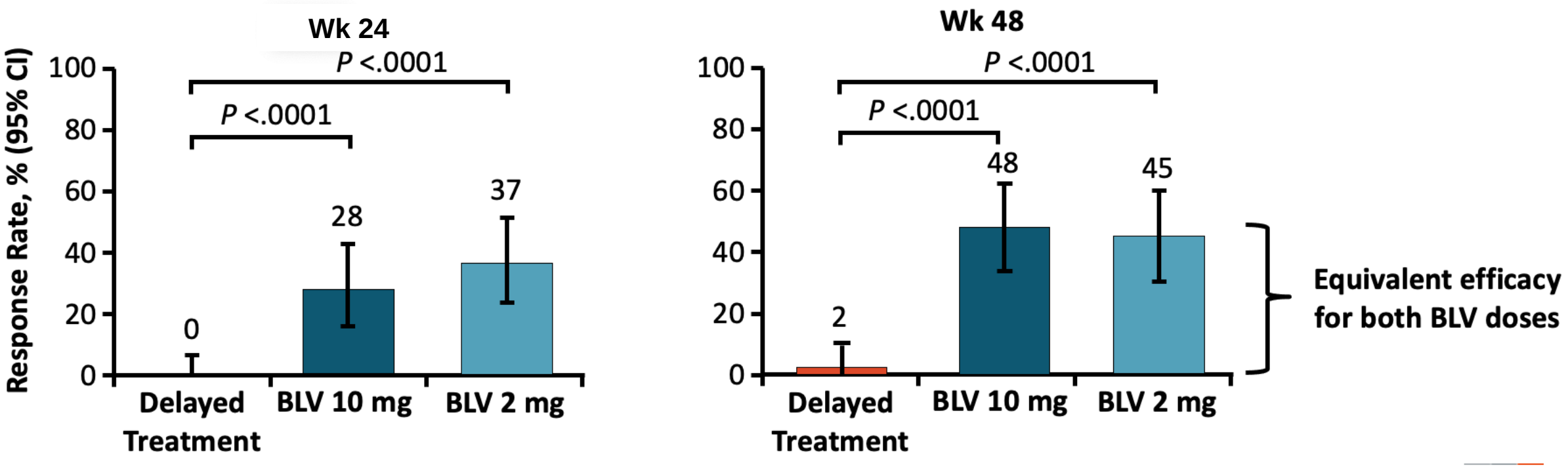
- Undetectable HDV RNA
- ALT normalization
- HDV RNA undetectable 24 weeks after EOT
- HDV RNA undetectable 48 weeks after EOT
- Change in liver stiffness

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

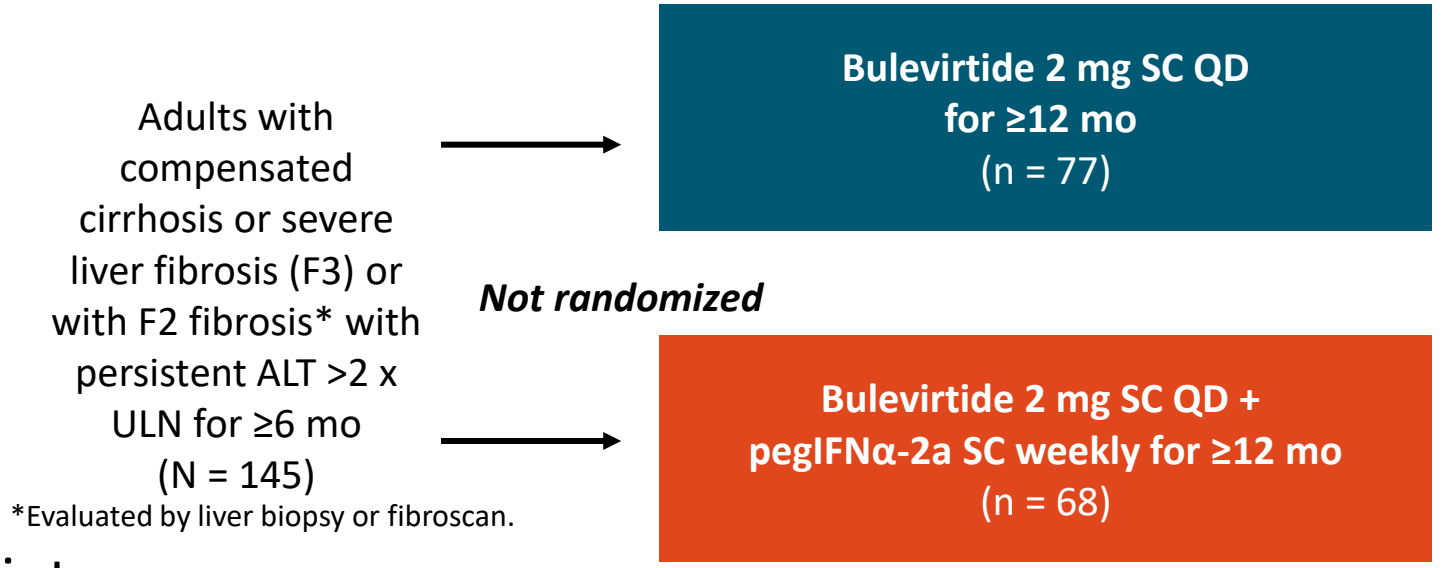
- Multicenter, randomized, phase III trial of BLV 2 mg or 10 mg SC QD for 48 wk vs delayed BLV treatment (10 mg SC QD beginning Wk 48) in patients with chronic HDV (N = 150)
  - Primary endpoint: combined response at Wk 48 (HDV RNA undetectable or ≥2 $\log_{10}$ copies/mL decrease vs baseline with ALT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



Wedermeyer. EASL 2022. Abstr GS006.

French Early Acces Program: Virologic and Biochemical Efficacy

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



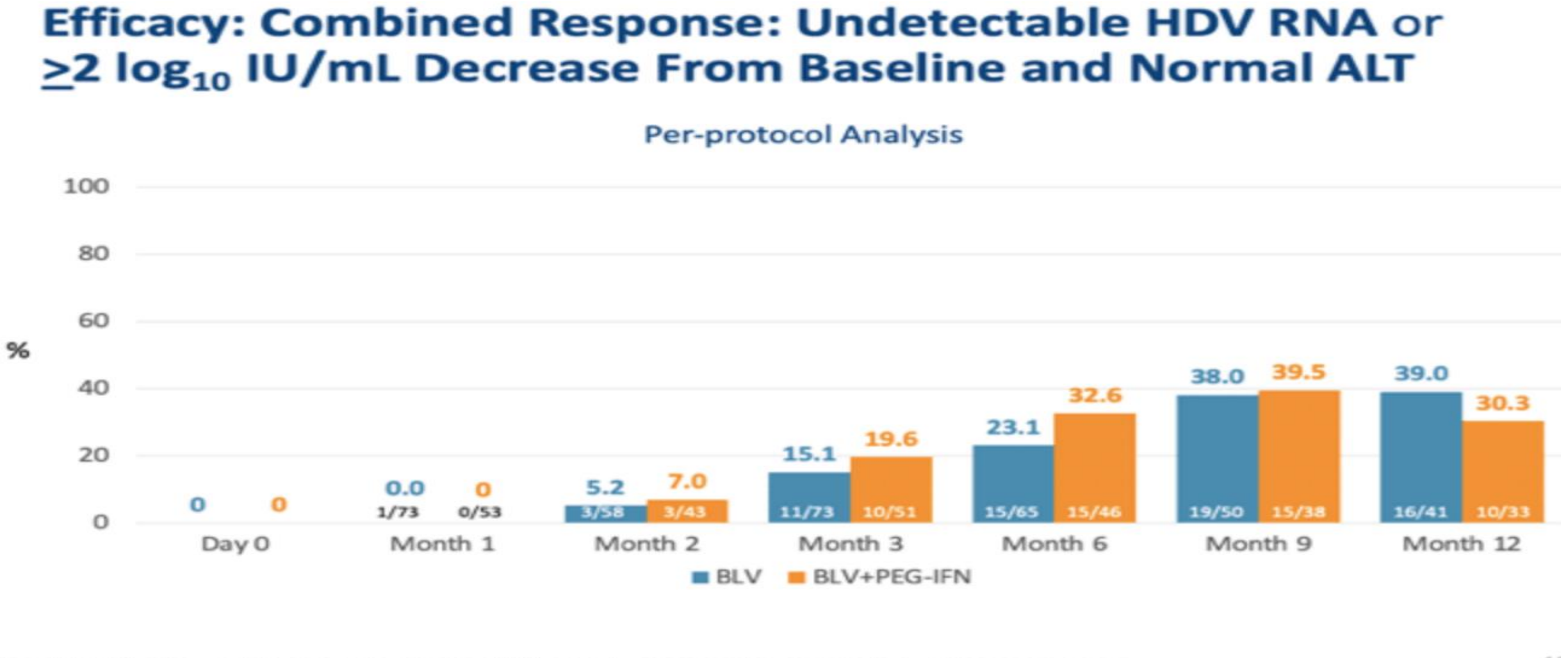
Efficacy endpoints:

- **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



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.

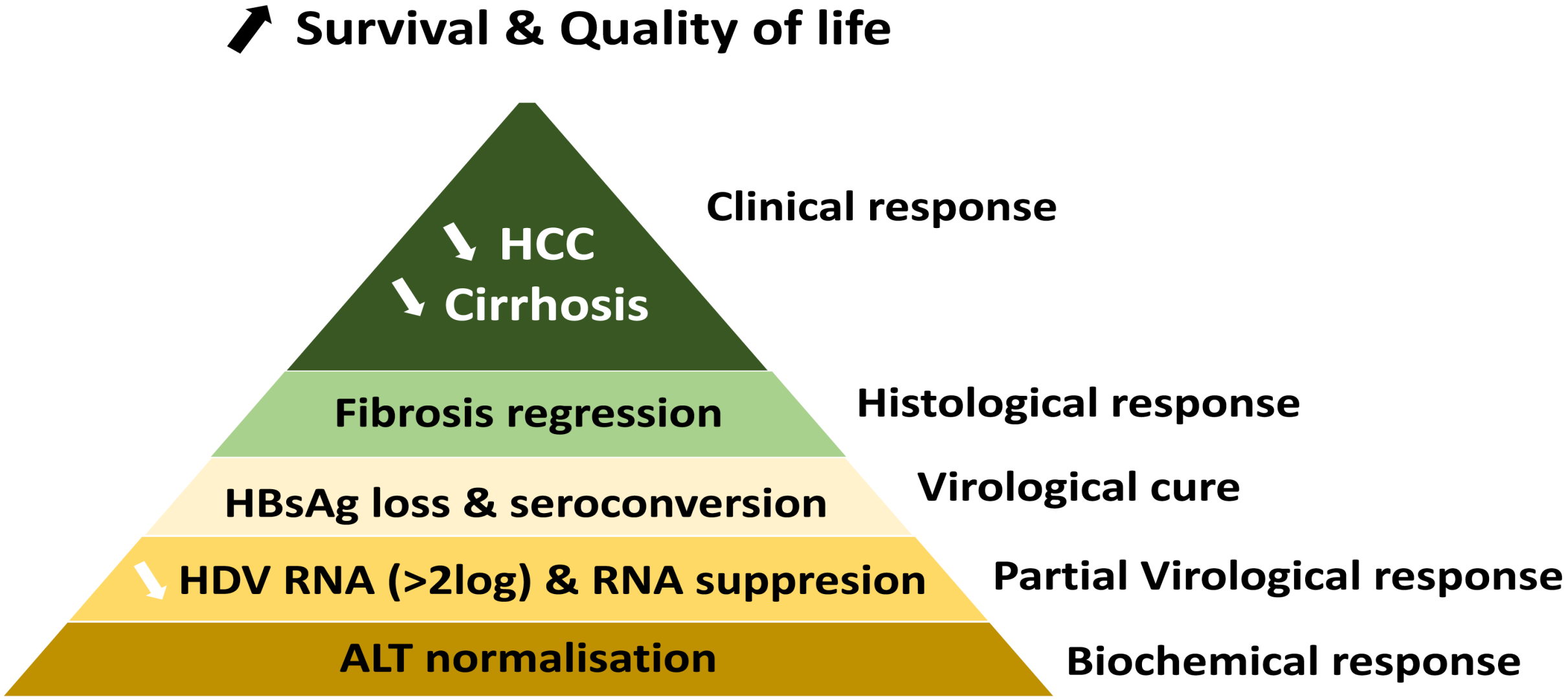
Bulevirtide European Label

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



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


MUCHAS
GRACIAS