MÁSTER EN HEPATOLOGÍA

UNIVERSIDAD AUTONOMA DE MADRID

Universidad de Alcalá

Asignatura: Hepatitis Virales

Hepatitis D (delta)

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Sumario

- Etiología
- Epidemiología/poblaciones de riesgo
- Virología
- Patogénesis
- Genotipos
- Historia natural
- Diagnóstico
- Tratamiento

Hepatitis D: datos básicos

9-60 million people infected with HDV globally

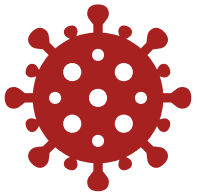
Defective RNA virus, requiring HBV for infection

4.5-13% of HBV carriers co-infected with HDV

Most severe form of viral hepatitis

Increased risk of cirrhosis/HCC and higher mortality vs HBV

Progression to cirrhosis within 5 years and to HCC within 10 years



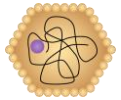
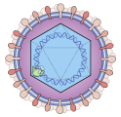
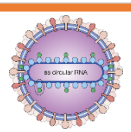
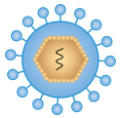
Eight HDV genotypes

Until recently, no approved therapeutic options

Hughes SA, et al. Lancet 2011;378:73-85; Koh C, et al. Gastroenterology 2019;156:461-7; Miao Z, et al. J Infect Dis 2020;221:1677-87; Stockdale AJ, et al. J Hepatol 2020;73:523-3.

HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HDV: hepatitis delta virus; RNA: ribonucleic acid.

El VHD causa la forma más grave de hepatitis vírica

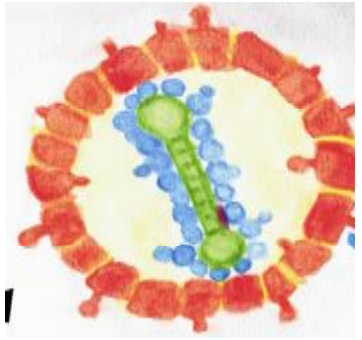
	Risk of progression to chronic hepatitis?		Risk of cirrhosis/HCC?	
 Hepatitis A[2]	✗	No, but can cause fatal fulminant hepatitis in a very small proportion	✗	No as infection is generally short-lived
 Hepatitis B[3]	✓	Adults: 5% Children: 90%	✓	20-30% (lifetime)
 Hepatitis C[4]	✓	55-85%	✓	15-30% (20 years)
 Hepatitis D[1]	✓	76%	✓	Cirrhosis within 5 years; HCC within 10 years
 Hepatitis E[5]	✓	Can occur rarely in immunosuppressed individuals	✗	No, as virus does not result in chronic infection

1. Miao Z, et al. J Infect Dis 2020;221:1677-87; 2-5. Hepatitis: fact sheets - World Health Organization
2. Hepatitis A. Available at: https://www.who.int/news-room/fact-sheets/detail/hepatitis-a; 3. Hepatitis B. Available at: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b; 4. Hepatitis C. Available at: https://www.who.int/news-room/fact-sheets/detail/hepatitis-c; 5. Hepatitis E. Available at: https://www.who.int/news-room/fact-sheets/detail/hepatitis-e. (All WHO fact sheets accessed March 2021).

HCC: hepatocellular carcinoma; HDV: hepatitis D virus; WHO: World Health Organization.

Virus de la hepatitis D (delta)

- Defective virus that needs HBsAg for dissemination
- Smallest animal virus (genome 1,700 nucleotides)
- Similarities with viroids
- More rapid progression to liver cirrhosis and liver cancer



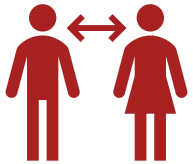
Rizzetto M, et al
Gut 1977

Calle Serrano et al.,
Semin Liver Dis. 2012;

Lempp et al.,
Nature Reviews Gastro. & Hepatol., 2016

Wedemeyer et al., J Hepatology, 2020

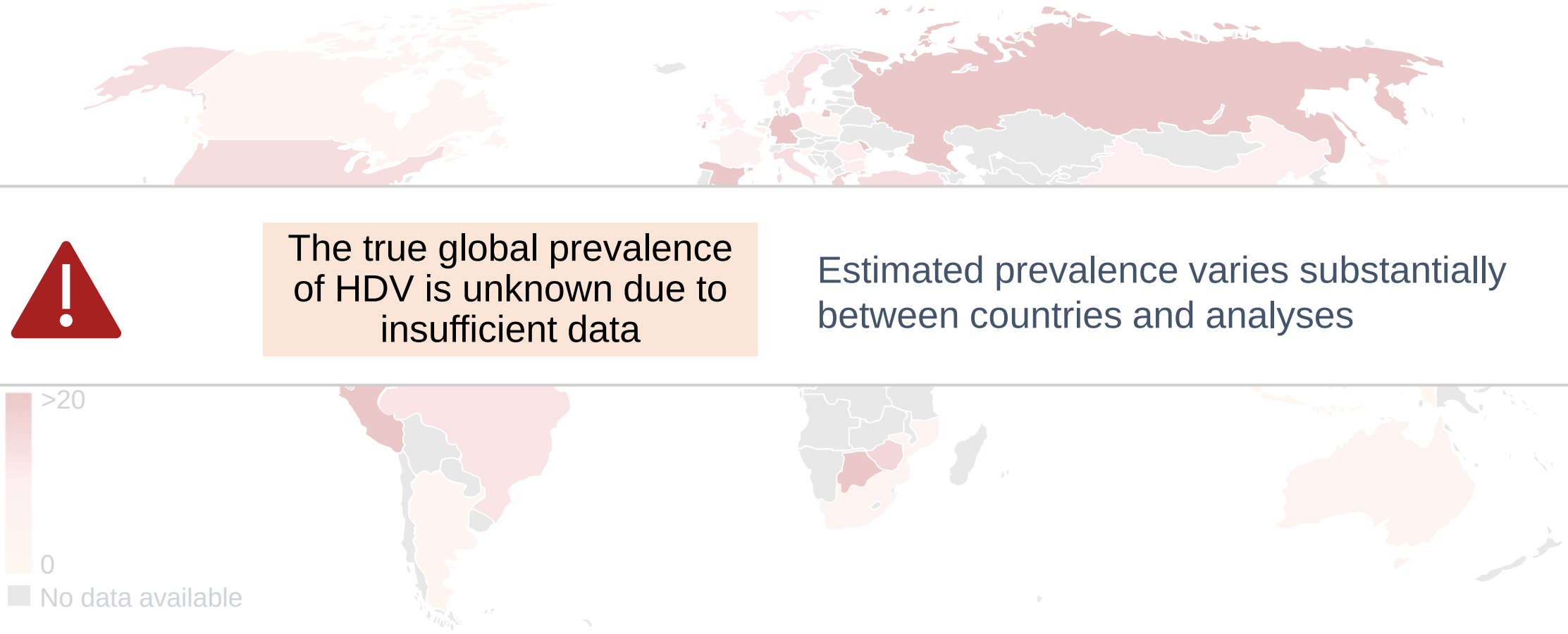
Hepatitis D. Etiología

 Cause	Infection with HDV	Only patients infected with HBV can contract HDV - HDV is acquired simultaneously (co-infection) or as a superinfection in those already infected with HBV
 Transmission	Via direct contact with bodily fluids	Routes of transmission: contaminated needles or transfusion, sexual transmission, mother to baby
 Symptoms	Often asymptomatic	No particular symptoms relate specifically to HDV. Individuals with chronic infection are at high risk of developing severe liver disease, including cirrhosis and HCC
 Course of infection	Acute or chronic	*Acute*: occurs suddenly, may cause severe symptoms, resolves within 6 months. However, can lead to acute liver failure *Chronic*: long-term consequence of infection associated with high risk of liver disease
 Consequences of infection	Increased risk of cirrhosis and HCC than HBV alone	HDV is the most severe form of chronic viral hepatitis due to more rapid progression to liver-related death and HCC than the other viruses

Centers for Disease Control and Prevention. Hepatitis D Questions and Answers for Health Professionals. https://www.cdc.gov/hepatitis/hdv/hdvfaq.htm#section1. Accessed March 2021; World Health Organization. Hepatitis delta fact sheet. July 2020. https://www.who.int/news-room/fact-sheets/detail/hepatitis-d. Accessed March 2021.

HBV: hepatitis B virus;
HCC: hepatocellular carcinoma;
HDV: hepatitis delta virus.

Approximately 4.5-13% of HBsAg-positive carriers are co-infected with hepatitis D



The true global prevalence of HDV is unknown due to insufficient data

Estimated prevalence varies substantially between countries and analyses

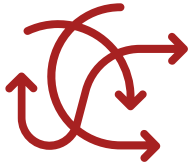
Miao Z, et al. J Infect Dis 2020;221:1677-87; Stockdale AJ, et al. J Hepatol 2020;73:523-3; Da BL, et al. Gastroenterol Rep 2019;7:231-45.

Prevalence of HDV in HBsAg-positive patients.
HBsAg: hepatitis B surface antigen; HDV: hepatitis delta virus.

Concerted efforts are needed to overcome challenges when assessing the global epidemiology of HDV

Insufficient testing

- Variation in screening guidance and lack of effective therapy until recently
- Low proportion of HBsAg-positive individuals are considered for HDV testing



Variable estimates from individual countries

- Potential variability in type of source data between studies
- Some analyses may exclude certain groups at high risk of HDV (ie injecting drug users, HIV patients, patients with liver disease)
- No concerted global effort to look at the epidemiology of HDV as a whole

Lack of accuracy

- Many studies assessing HDV seroprevalence in HBV patients do not use confirmatory PCR tests
- Lack of standardised confirmatory tests

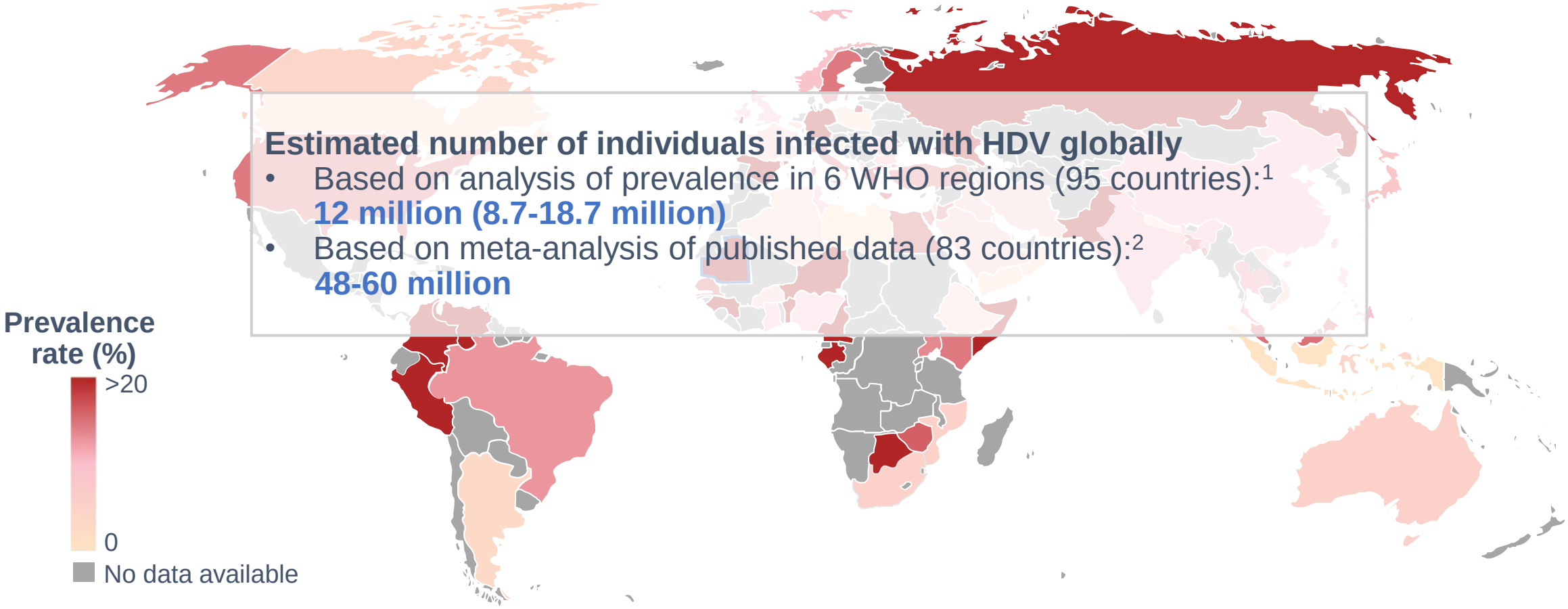
Outdated information

- Inclusion of data from analyses conducted before HBV vaccination programmes were initiated

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

HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HDV: hepatitis delta virus;
HIV: human immunodeficiency virus; PCR: polymerase chain reaction.

Approximately 4.5-13% of HBsAg-positive carriers are co-infected with HDV



Estimated number of individuals infected with HDV globally

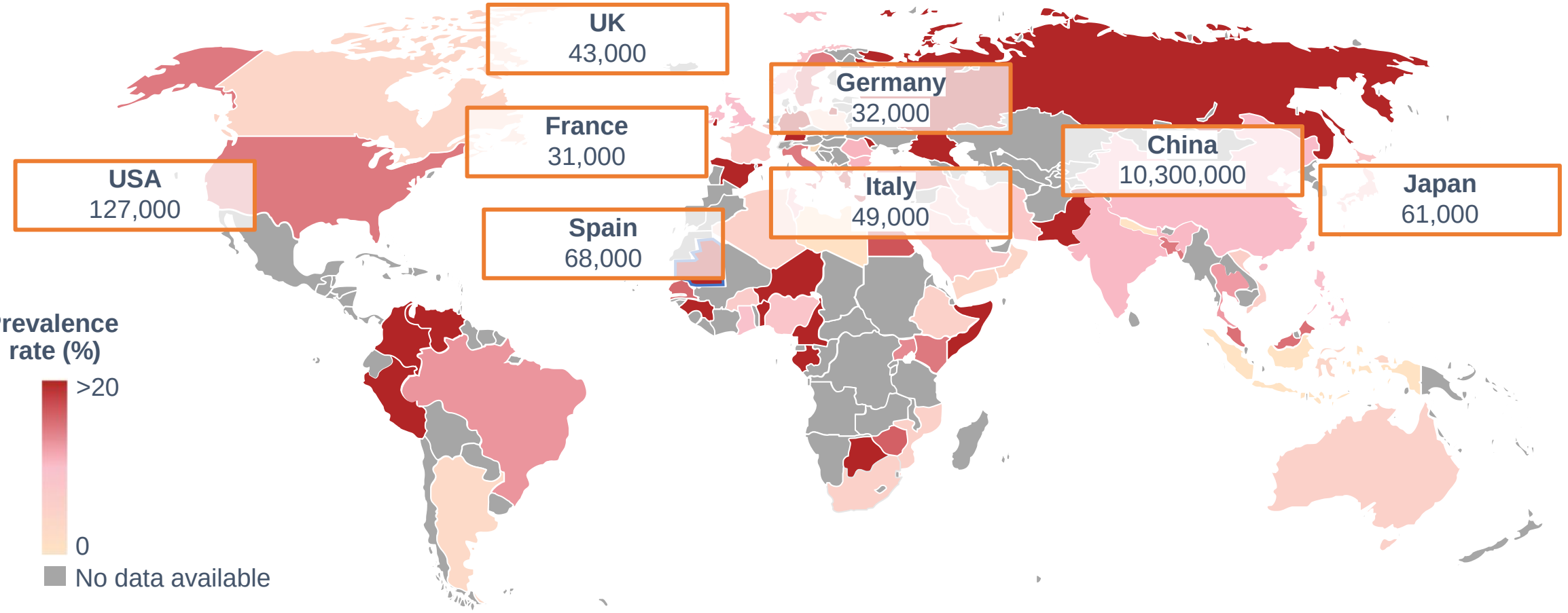
- Based on analysis of prevalence in 6 WHO regions (95 countries):[1]
  12 million (8.7-18.7 million)
- Based on meta-analysis of published data (83 countries):[2]
  48-60 million

1. Stockdale AJ, et al. J Hepatol 2020;73:523-3;
2. Miao Z, et al. J Infect Dis 2020;221:1677-87.

Prevalence of HDV in HBsAg-positive patients from Ref 2.
HBsAg: hepatitis B surface antigen; HDV: hepatitis delta virus; WHO: World Health Organization.

Estimated number of individuals with HDV in selected countries

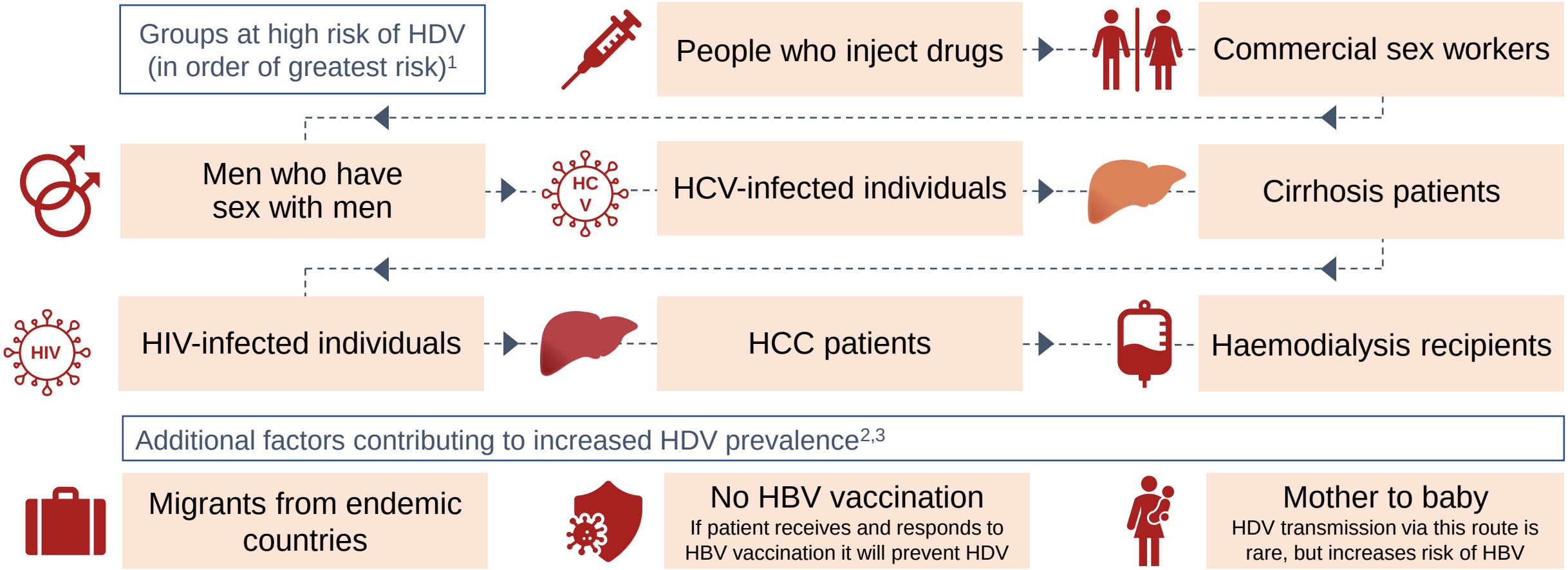
An estimated 48-60 million people are infected with HDV worldwide



Numbers shown are patient numbers, ie prevalence of HDV in HBsAg-positive patients.
HBsAg: hepatitis B surface antigen; HDV: hepatitis delta virus.

Miao Z, et al. J Infect Dis 2020;221:1677-87.

Poblaciones de riesgo de infección por el VHD



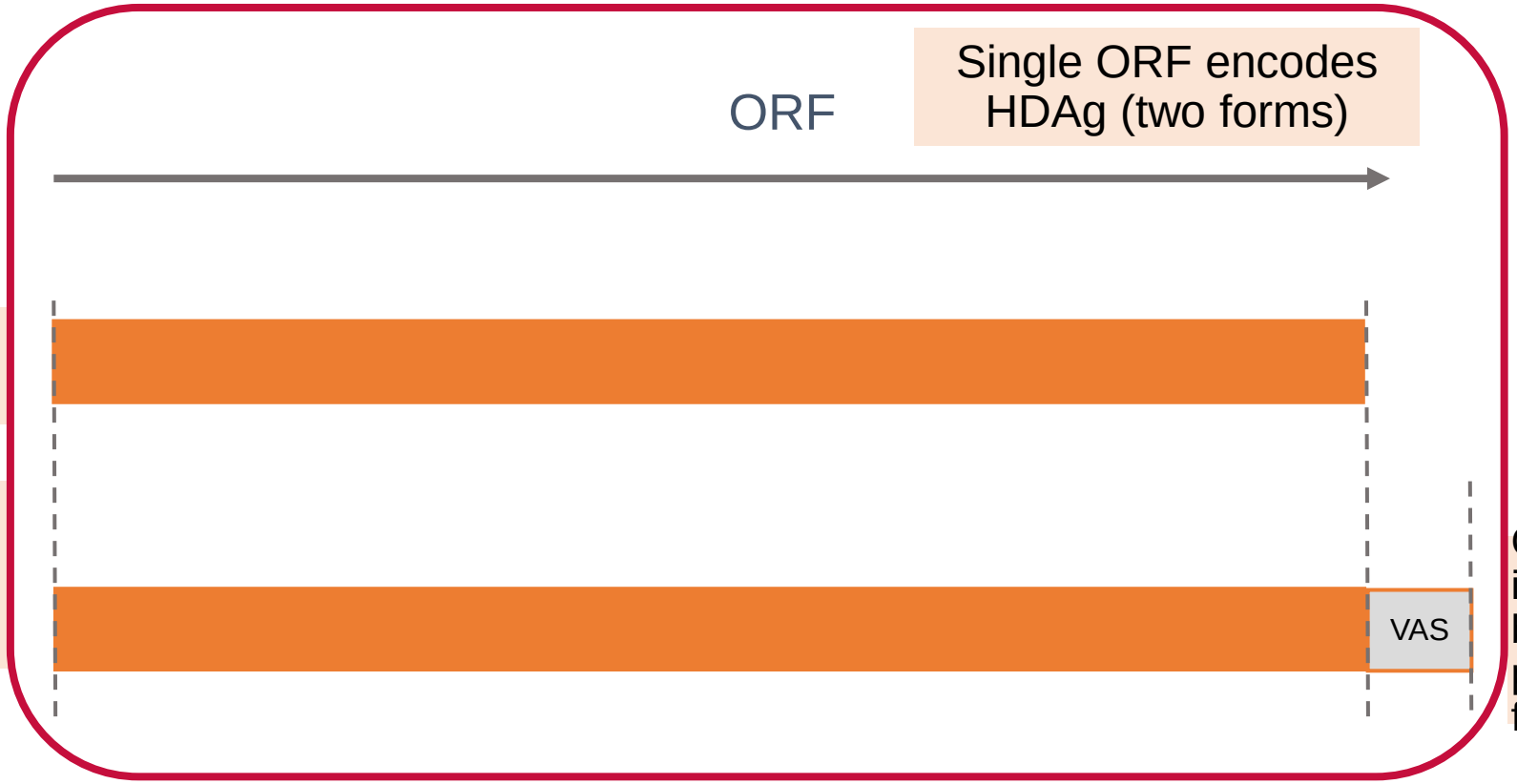
1. Stockdale A, et al. J Hepatol. 2020;73:523-32; 2. World Health Organization. Hepatitis delta fact sheet. July 2020. https://www.who.int/news-room/fact-sheets/detail/hepatitis-d. Accessed March 2021; 3. Centers for Disease Control and Prevention. Hepatitis D Questions and Answers for Health Professionals. https://www.cdc.gov/hepatitis/hdv/hdvfaq.htm#section1. Accessed March 2021.

Risk of developing HDV vs general population or HBsAg-positive population without HDV.

HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HDV: hepatitis delta virus; HIV: human immunodeficiency virus.

Virus de la hepatitis D (delta)

HDV virion contains a single-stranded circular RNA genome (1672-1697 nucleotides, genotype dependent)



S-HDAg:195 aa, 24kD
Required for replication

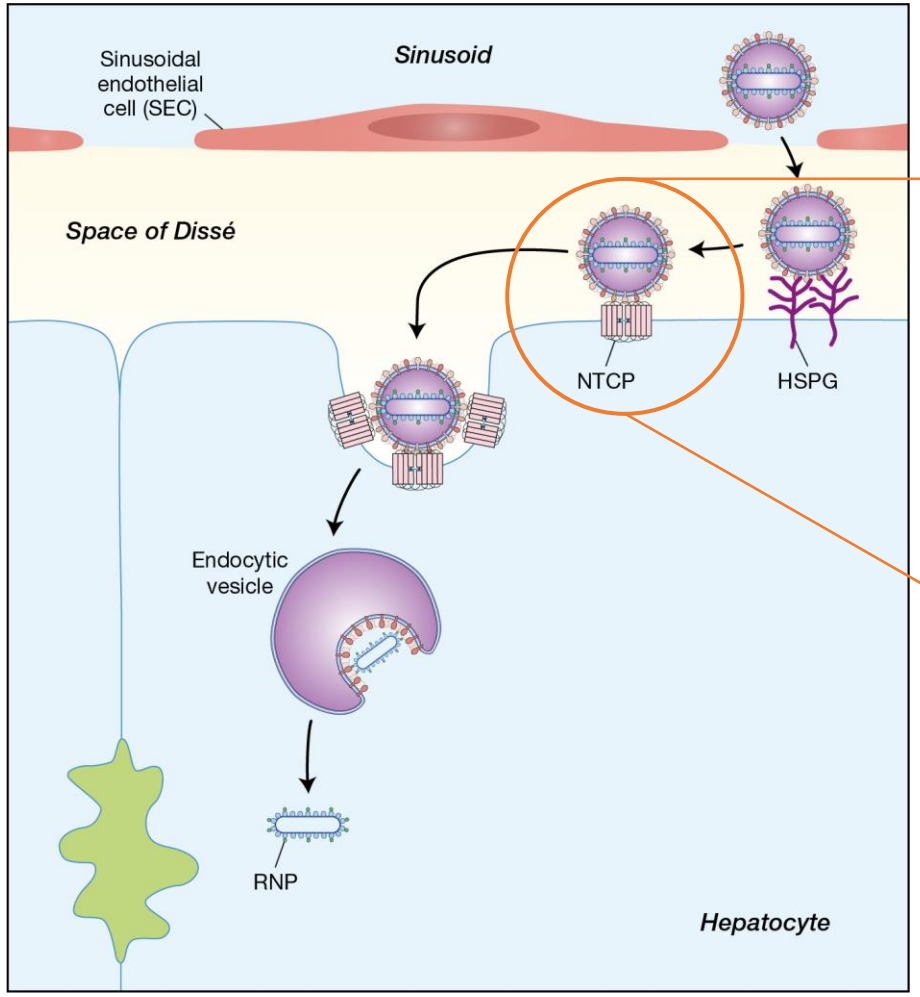
L-HDAg: 214 aa, 27kD
Inhibits replication; required for packaging with HBsAg

Cys residue (C211) in the VAS becomes prenylated by farnesyltransferase

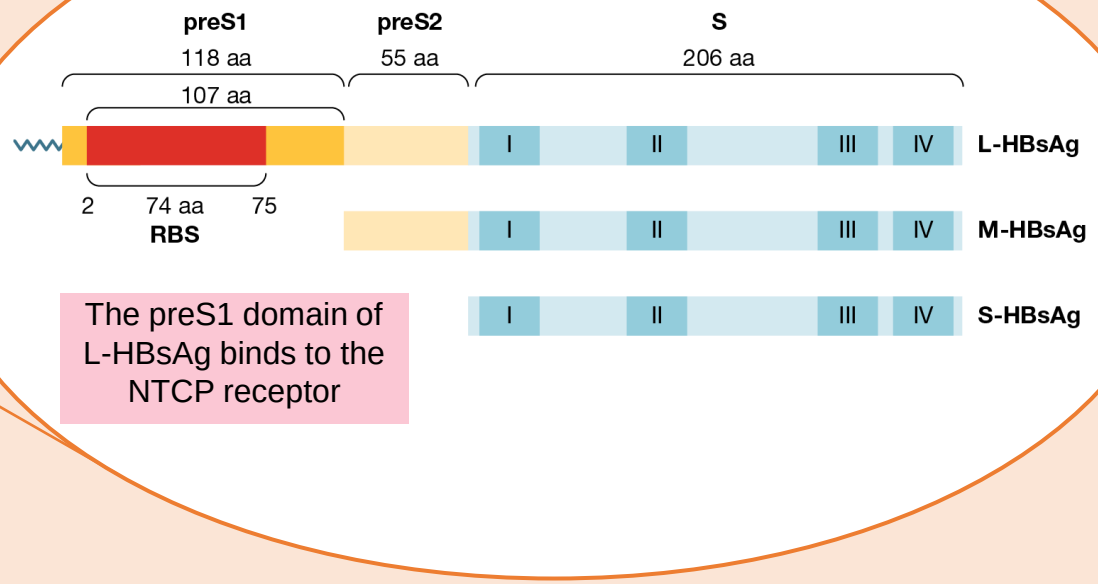
Adapted from Lempp FA, et al. Nature Rev Gastroenterol Hepatol 2016;13:580-9.

Cys: cysteine; HBsAg: hepatitis B surface antigen; HDAg: hepatitis delta antigen; HDV: hepatitis delta virus;
L: large; ORF: open reading frame; RNA: ribonucleic acid; S: small; VAS: virus assembly sequence.

El VHD entra en el hepatocito a través del receptor NTCP



Interaction between HDV and NTCP occurs at a binding site on HBsAg



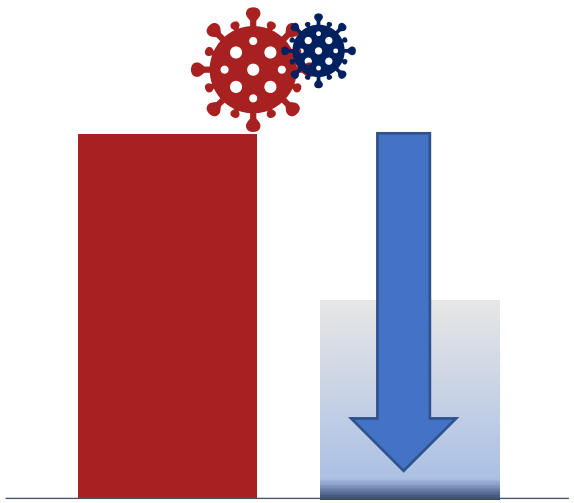
The preS1 domain of L-HBsAg binds to the NTCP receptor

Adapted from Urban S, et al. Gastroenterol 2014;147:48-64;
Lempp FA, et al. Nature Rev Gastroenterol Hepatol 2016;13:580-9.

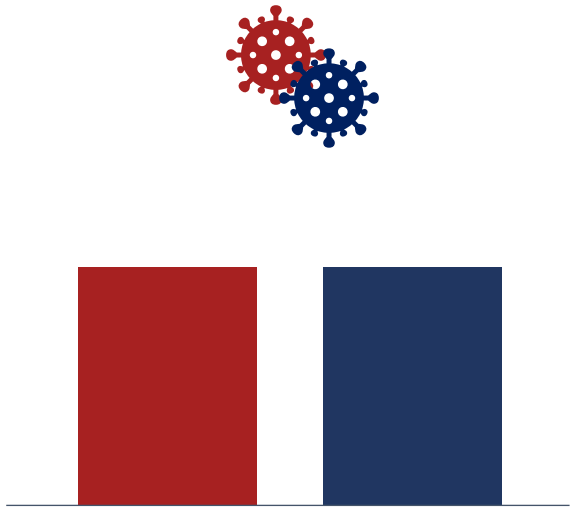
AA: amino acids; HBsAg: hepatitis B antigen; HDV: hepatitis delta virus; HSPG: heparan sulfate proteoglycan; L: large; M: middle; NCTP: human sodium taurocholate cotransporting polypeptide; RBS: receptor binding site; RNP: ribonucleoprotein; S: small; SEC: sinusoidal endothelial cell.

HDV suppression of HBV: three patterns of chronic infection

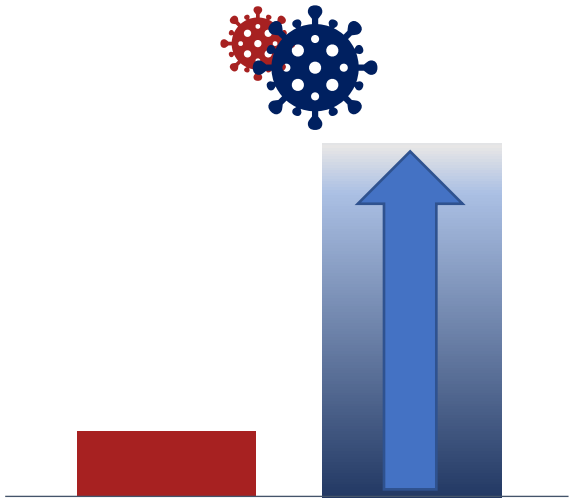
Predominant
HDV replication, suppressed
HBV replication



Similar
HDV and
HBV viral load



Rare
predominant **HBV** replication

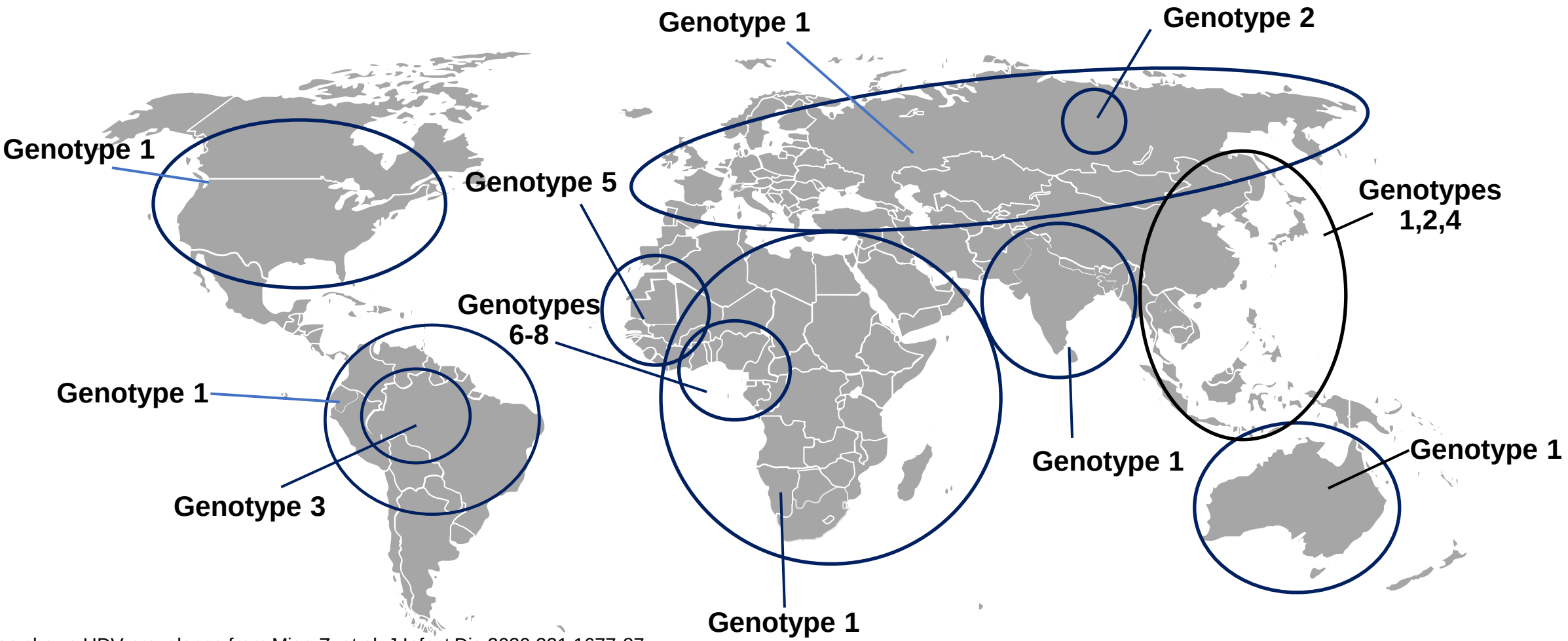


- HBV viral load has no impact on HDV viral load and outcomes
- HDV tends to suppress HBV replication
- Decrease in HDV viral load during treatment can increase HBV viral load as HDV's suppressive effect reduces
- Management of HBV with NAs should be based on guidelines and individual clinical decisions
- Treatment of HBV with NAs has no effect on HDV

1. Wedemeyer H, et al. Liver Int 2011;31(Suppl 1):140-4; 2. Da BL, et al. Gastroenterol Rep 2019;7:231-45;
3. Shah PA, et al. Gastroenterol Rep 2019;7:396-402; 4. Koh C, et al. Clin Liver Dis 2019;23:557-72.

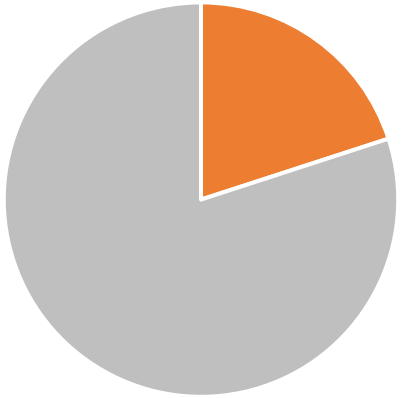
HBV: hepatitis B virus; HDV: hepatitis delta virus; NA; nucleos(t)ide analogue.

Genotipos del VHD

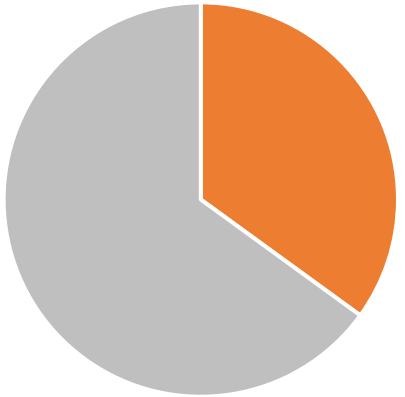


Map shows HDV prevalence from Miao Z, et al. J Infect Dis 2020;221:1677-87; Koh C, et al. Gastroenterology 2019;156:461-76.

Diversidad genética entre los genotipos del VHD



<20% divergence within one genotype[1]



Up to 36% divergence between genotypes[1]

Disease severity[2]		Diversity between genotypes[3]						
		2	3	4	5	6	7	8
Genotype 1	Mild to severe	25.6	35.0	26.5	27.9	28.0	28.6	22.6
Genotype 2	Mild		34.4	24.1	24.1	26.1	26.9	25.3
Genotype 3	Severe, linked to Labrea fever			33.7	35.9	34.2	35.4	35.4
Genotype 4	Usually mild				25.0	26.6	26.2	24.9
Genotype 5	Not characterised					25.5	25.4	25.1
Genotype 6	Not characterised						28.5	26.5
Genotype 7	Not characterised							23.4
Genotype 8	Not characterised							

<25% divergence
25-<30% divergence
30-<35% divergence
>35% divergence

1. Lempp FA, et al. Nature Rep Gastroenterol Hepatol 2016;13:580-9;
2. Hughes SA, et al. Lancet 2011; 378:73-85; 3. Le Gal F, et al. Emerging Infect Dis 2006;12:1447-50.

Similarity calculated from complete nucleotide sequences.
HDV: hepatitis delta virus.

Hepatitis D (delta) aguda y crónica

Aguda

Incubation period: 3-7 weeks

Non-specific flu-like symptoms, high ALT/AST, jaundice

Severity of infection is influenced by timing of HDV infection (co-infection or superinfection)

Can cause hepatic failure (1-5%)

Crónica

HDV persists for >6 months

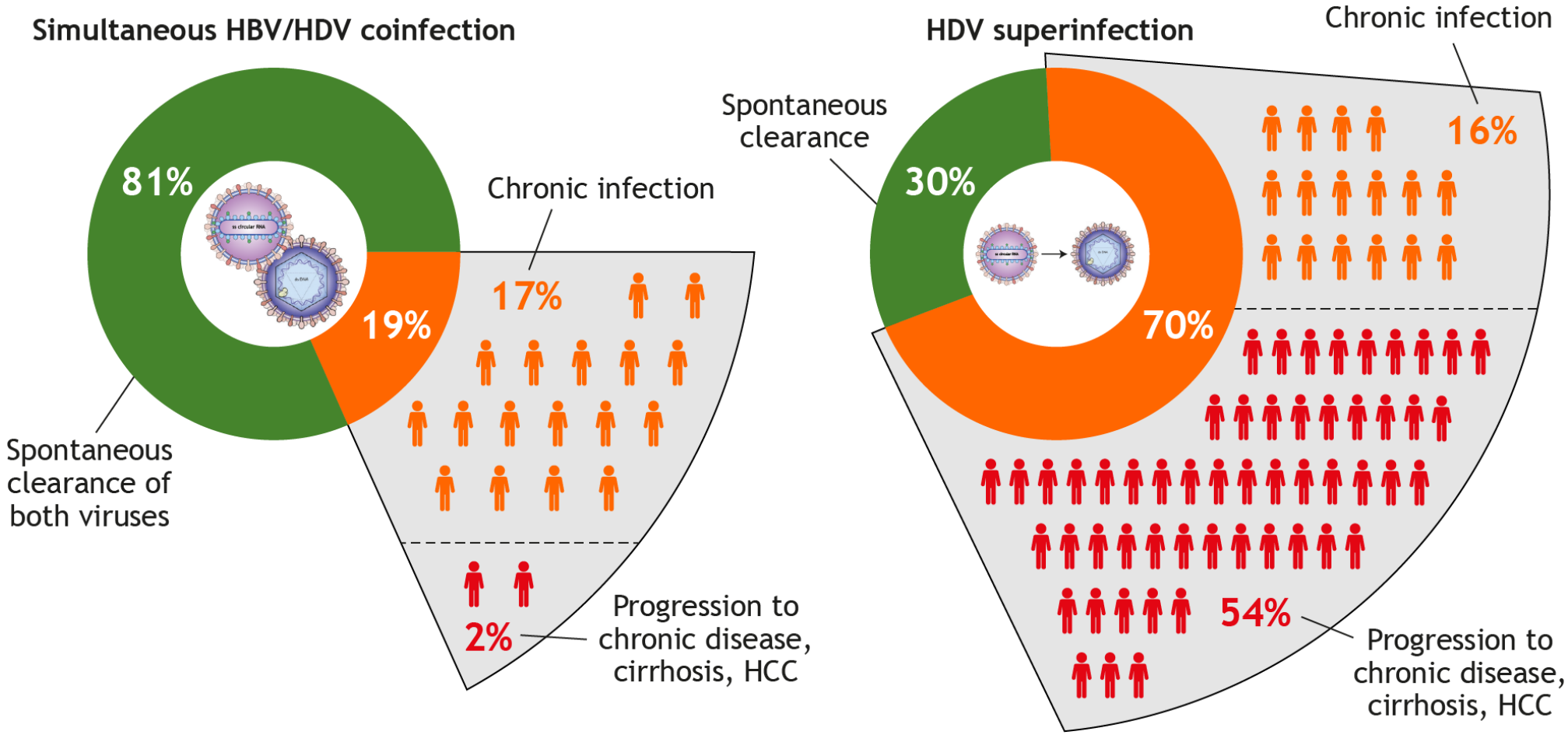
Non-specific symptoms including fatigue, malaise, anorexia

Three patterns of infection
- HDV predominant (frequent)
- HBV and HDV similarly predominant
- HBV predominant (rare)

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

ALT: alanine aminotransferase; AST: aspartate aminotransferase; HBV: hepatitis B virus; HDV: hepatitis delta virus.

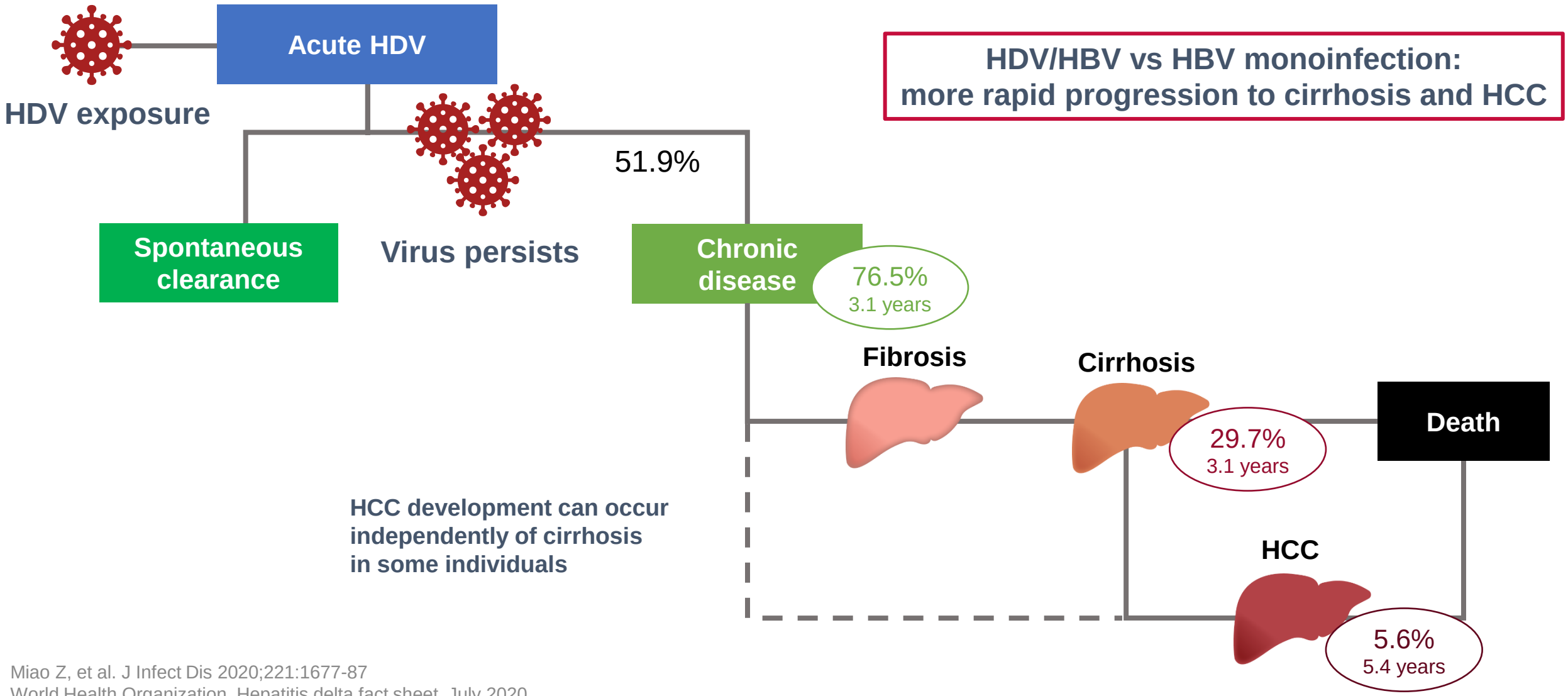
Curso evolutivo de la hepatitis D: coinfección vs superinfección



Miao Z, et al. J Infect Dis 2020;221:1677-87

Data presented are based on estimates of HDV prevalence and disease progression rates determined in a large global epidemiology analysis.
HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HDV: hepatitis delta virus.

Historia natural de la hepatitis D

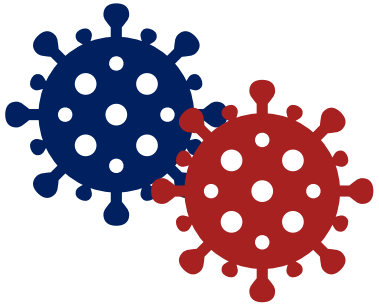


Miao Z, et al. J Infect Dis 2020;221:1677-87
World Health Organization. Hepatitis delta fact sheet. July 2020. https://www.who.int/news-room/fact-sheets/detail/hepatitis-d. Accessed March 2021.

HBV: hepatitis B virus; HCV: hepatitis C virus; HCC: hepatocellular carcinoma; HDV: hepatitis delta virus.

El VHD favorece la progresión a cirrosis y CHC en pacientes con infección por VHB

Chronic HBV/HDV infection



Rapid progression to long-term sequelae of liver disease

Cirrhosis within 5 years

HCC within 10 years

Miao Z, et al. J Infect Dis 2020;221:1677-87.

Disease progression in chronic hepatitis B is not linear and HCC can develop in the absence of cirrhosis.
HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HDV: hepatitis delta virus.

Received: 19 June 2019 | First decision: 14 July 2019 | Accepted: 9 September 2019
DOI: 10.1111/apt.15521

AP&T Alimentary Pharmacology & Therapeutics WILEY

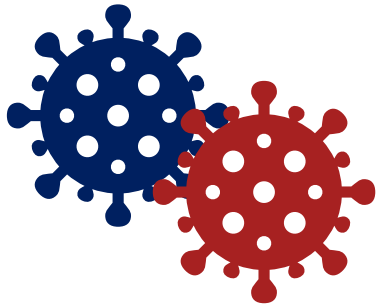
Long-term clinical outcomes in patients with chronic hepatitis delta: the role of persistent viraemia

Adriana Palom[1] | Sergio Rodríguez-Tajes[2,3] | Carmen A. Navascués[4] | Javier García-Samaniego[3,5] | Mar Riveiro-Barciela[1,3] | Sabela Lens[2,3] | Manuel Rodríguez[4] | Rafael Esteban[1,3] | Maria Buti[1,3]

Conclusions: Subjects with persistently positive HDV-RNA had a worse prognosis in terms of clinical events. Baseline-event-anticipation score is useful in predicting the risk of developing liver decompensation and hepatocellular carcinoma. Interferon was beneficial in reducing liver decompensation, even in the absence of virological response.

Mechanisms underlying increased progression to HCC in HBV/HDV patients

HBV/HDV co-infection



HDV **induces** oncogenic mechanisms
- NFkB activation
- JAK-STAT activation
- Down regulation of *GSTP-1*

HDV **enhances** HBV oncogenic properties
- Enhanced TGF-β signalling

HCC

Puigvehi M, et al. JHEP Rep 2019;1:120-30.

GSTP-1: glutathione S-transferase P1; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HDV: hepatitis delta virus; JAK-STAT: Janus-kinase-signal transducer and activator of transcription; NFkB: nuclear factor kappa B; TGF-β: transforming growth factor beta.

Riesgo de descompensación y/o CHC en pacientes con hepatitis D

JOURNAL OF VIRAL HEPATITIS
JVH

Journal of Viral Hepatitis, 2014, **21**, e154–e163 doi:10.1111/jvh.12251

Development and evaluation of a baseline-event-anticipation score for hepatitis delta

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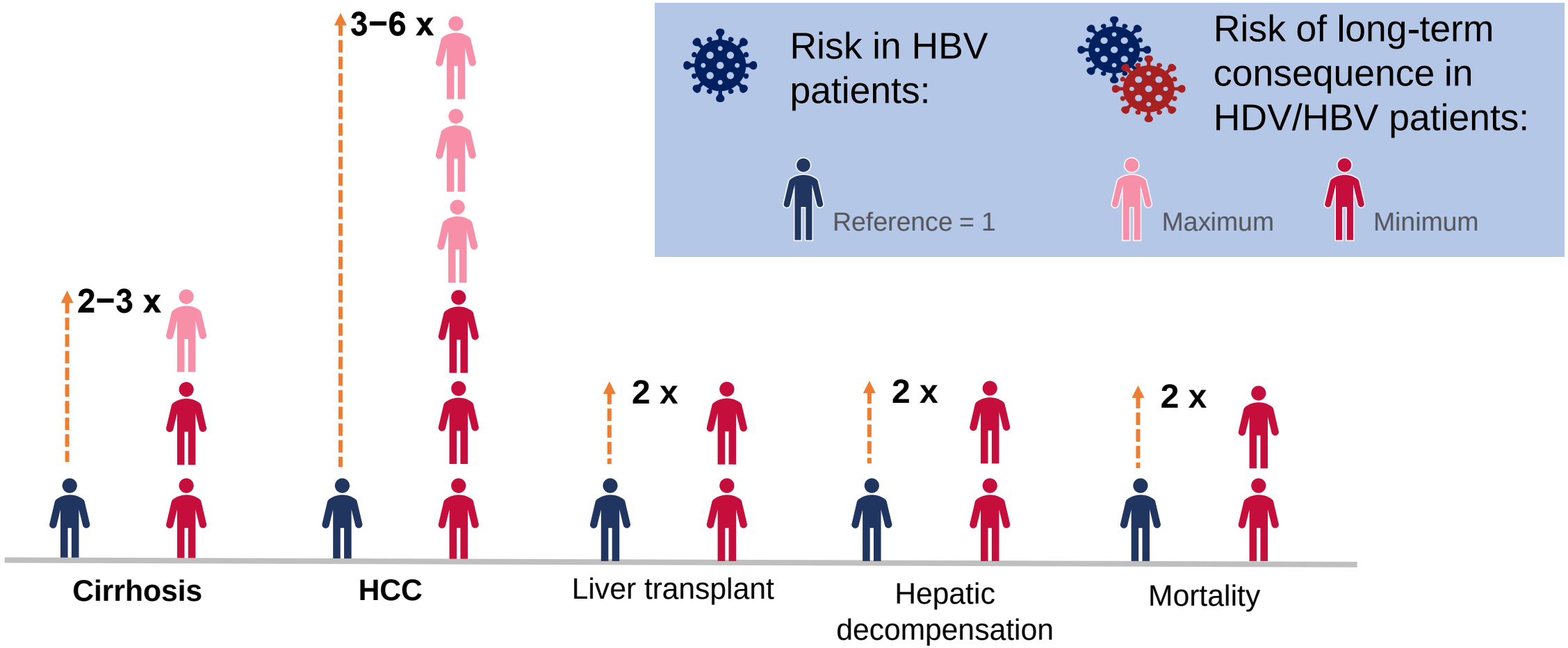
SUMMARY. Hepatitis delta is considered the most severe form of viral hepatitis, but variables associated with disease progression are poorly defined. This study aimed to identify risk factors associated with worse clinical outcome in patients with hepatitis delta and to develop a clinical score to determine their risk of experiencing liver-related morbidity or mortality. We followed 75 HBsAg–anti-HDV-positive patients with hepatitis delta for up to 16 years (median 5 years). The baseline-event-anticipation score (BEA score) was developed based on variables associated with the development of liver-related clinical complications. Age, region of origin, presence of cirrhosis, albumin, INR, hyperbilirubinemia and thrombocytopenia were all associated with the development of an event in the training cohort. The BEA score included age, sex, region of origin, bilirubin, platelets and INR. Points were allocated according to hazard ratios, and three risk groups were defined: BEA-A mild risk, BEA-B moderate risk and BEA-C high risk. Hazard ratios of BEA-B and BEA-C patients for liver-related clinical endpoints were 9.01 and 25.27 vs BEA-A with an area under curve of the receiving operating characteristic curve of 0.88. The accuracy of the BEA score was confirmed in two independent validation cohorts followed in Barcelona ($n = 77$) and Düsseldorf ($n = 62$). Delta hepatitis is associated with a very severe long-term outcome. The BEA score is easy to apply and predicts with a very high accuracy the development of liver-related complications in patients with hepatitis delta.

Keywords: BEA score, clinical score, co-infection, HBV, HDV, hepatitis delta.

Increased risk of long-term consequences of viral hepatitis in HBV/HDV patients versus HBV monoinfection



Disease progression in chronic hepatitis B is not linear and HCC can develop in the absence of cirrhosis.
HBV: hepatitis B virus;
HCC: hepatocellular carcinoma; HDV: hepatitis delta virus

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

Diagnóstico de la infección por VHD: serología y RNA-VHD

Anti-HDV	• First-line screening test	• Generally available globally • Limited availability in developing countries
HDV RNA	• Assessed by NAT/RT-PCR • Qualitative and quantitative • Confirmatory test for active infection	• Broad commercial availability required • Potential for false negatives • High cost burden

Shah PA, et al. Gastroenterol Rep 2019;7:396-402;
Ahn J, Gish RG. Gastroenterol Hepatol 2014;10:647-86;
Cheung A, Kwo P. Clin Liver Dis 2020;24:405-19.

HDV: hepatitis D virus; NAT: nucleic acid amplification testing;
RNA: ribonucleic acid; RT-PCR: reverse transcription polymerase chain reaction.

Marcadores serológicos y diagnóstico de la hepatitis D

	HBV serology				HDV serology			
	HBsAg	Anti-HBc IgM	Anti-HBc IgG	HBV DNA	HDAg	Anti-HDV IgM	Anti-HDV IgG	HDV RNA
Acute HBV/HDV co-infection	+	+	+	+	±	+	+	+
Acute HBV/HDV superinfection	+	-	+	±	±	+	+	+
Chronic HBV/HDV infection	+	-	+	±	±	+	+	+
Resolved HBV and HDV	-	-	+	-	-	-	+	-

HBV and HDV serology markers can indicate the stage of infection

Cheung A, Kwo P. Clin Liver Dis 2020;24:405-19.

HDAg is often present transiently and is often not detected.
Anti-HBc IgG and anti-HDV IgG may not be present in early infection; Anti-HDV IgM remains persistently increased.
HBc: hepatitis B core; HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; HDAg: hepatitis delta antigen; HDV: hepatitis delta virus; IgG: immunoglobulin G; IgM: immunoglobulin M; RNA: ribonucleic acid.

Hepatitis D: recomendaciones de las guías

	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)	All patients infected with HBV	No recommendation

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

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; HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; HDAg: hepatitis D antigen; HDV: hepatitis D virus; RNA: ribonucleic acid; WHO: World Health Organization.

Gastroenterología y Hepatología 2020;43(9):559–587

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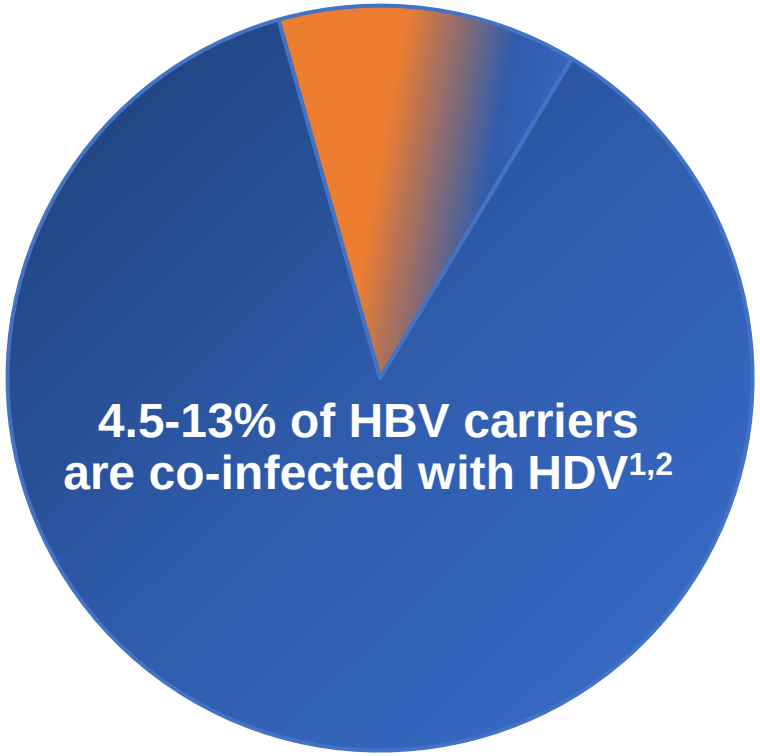
DOCUMENTO DE CONSENSO

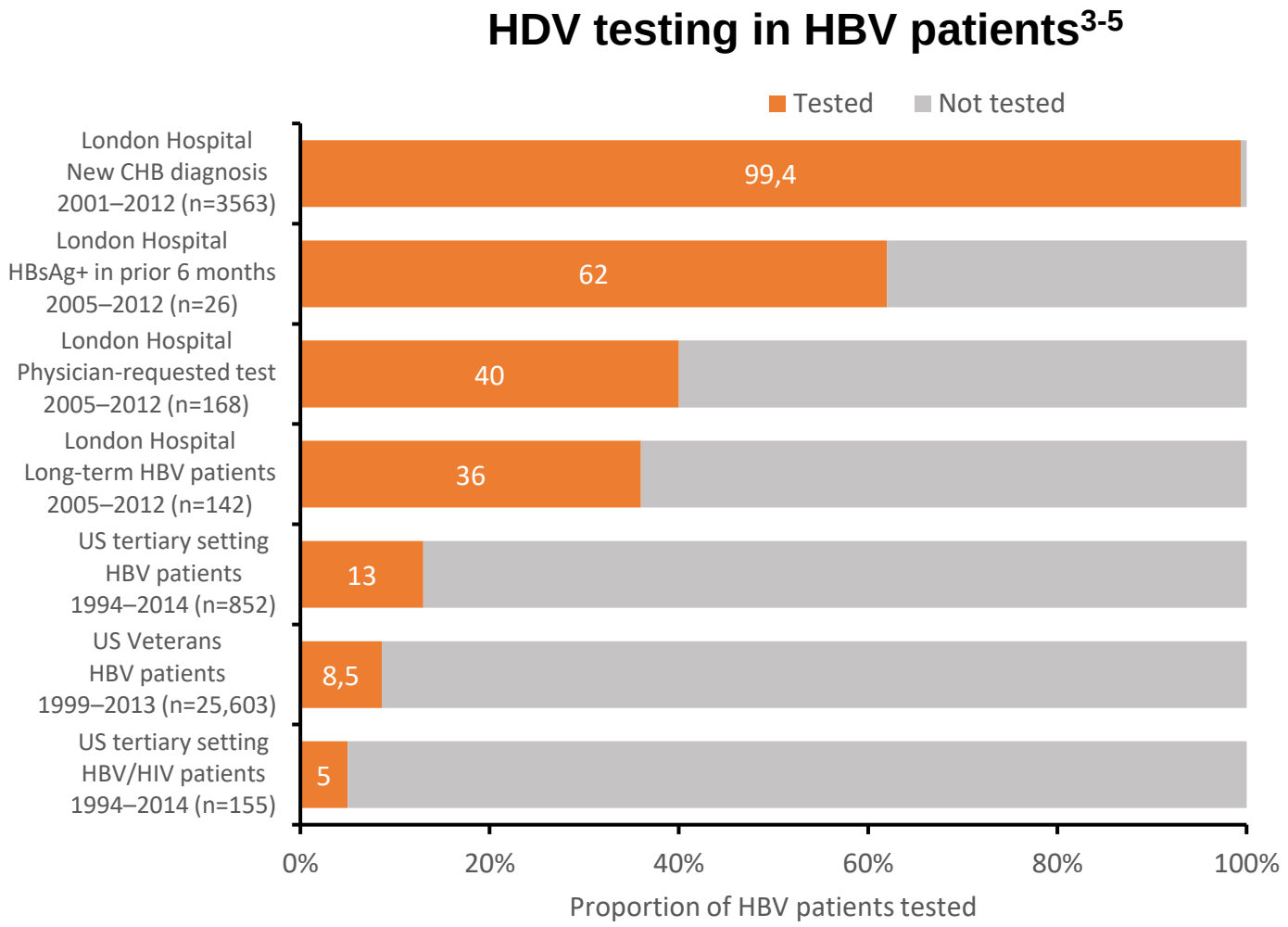
Documento de consenso de la Asociación Española para el Estudio del Hígado sobre el tratamiento de la infección por el virus de la hepatitis B (2020)

Manuel Rodríguez[a,*], María Buti[b], Rafael Esteban[b], Sabela Lens[c], Martín Prieto[d], Emilio Suárez[e] y Javier García-Samaniego[f,*]

"*El VHD infecta únicamente a los pacientes con HBsAg positivo y ello obliga a realizar el cribado de infección por VHD en* ***todos*** *los pacientes con hepatitis B*"

Disparidad en el cribado de la infección por VHD





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.

CHB: chronic hepatitis B virus; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus;
HDV: hepatitis D virus; HIV: human immunodeficiency virus.

Tratamientos basados en interferón para la hepatitis D

Treatment of Hepatitis Delta with PEG-IFNa-2a: ~25% HDV RNA suppression

- **Wedemeyer, Yurdaydin et al. NEJM 2011**

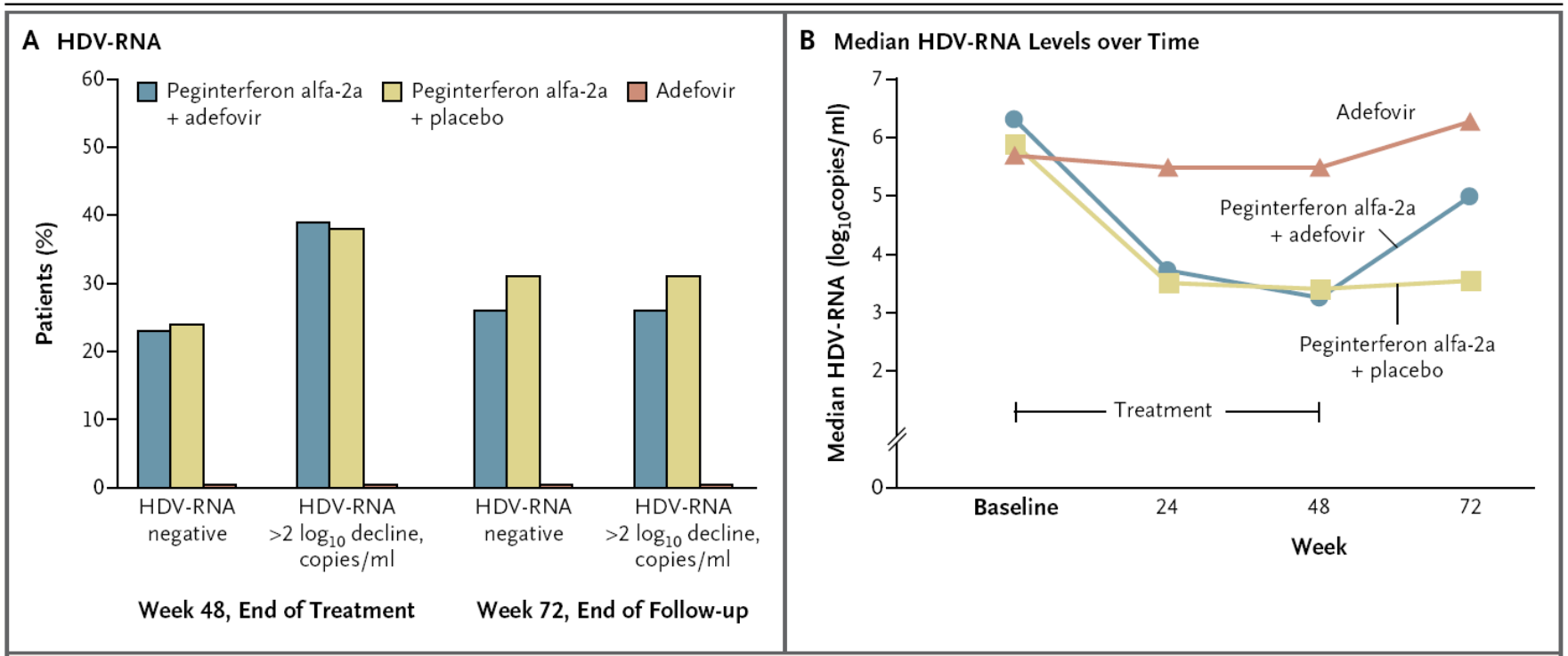
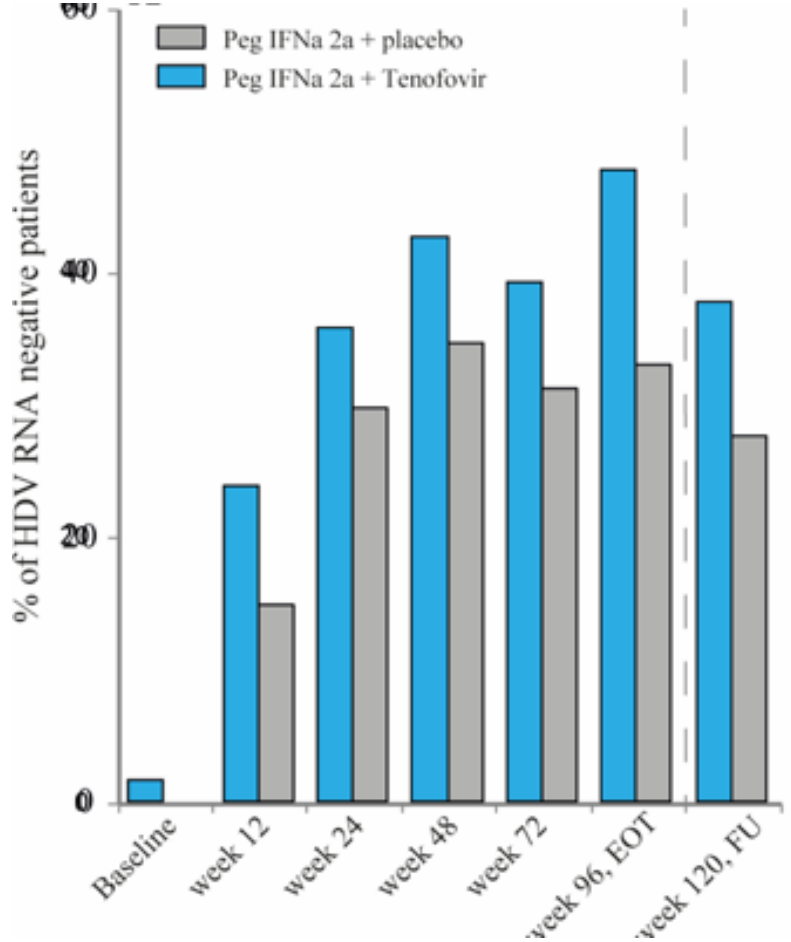
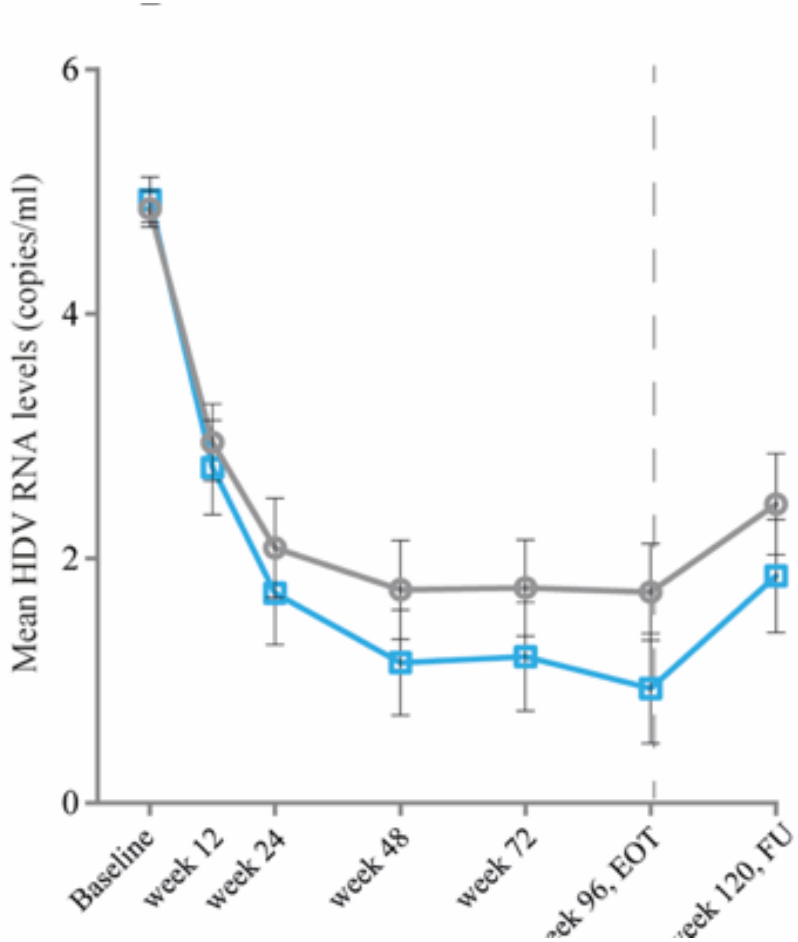


Figure 1. Virologic Response to Treatment as Determined by Serum Level of HDV RNA, According to Treatment Group.

PEG-IFNα-2a plus TDF / Placebo

Wedemeyer et al., Lancet Infect. Dis. 2019; 19:275-286





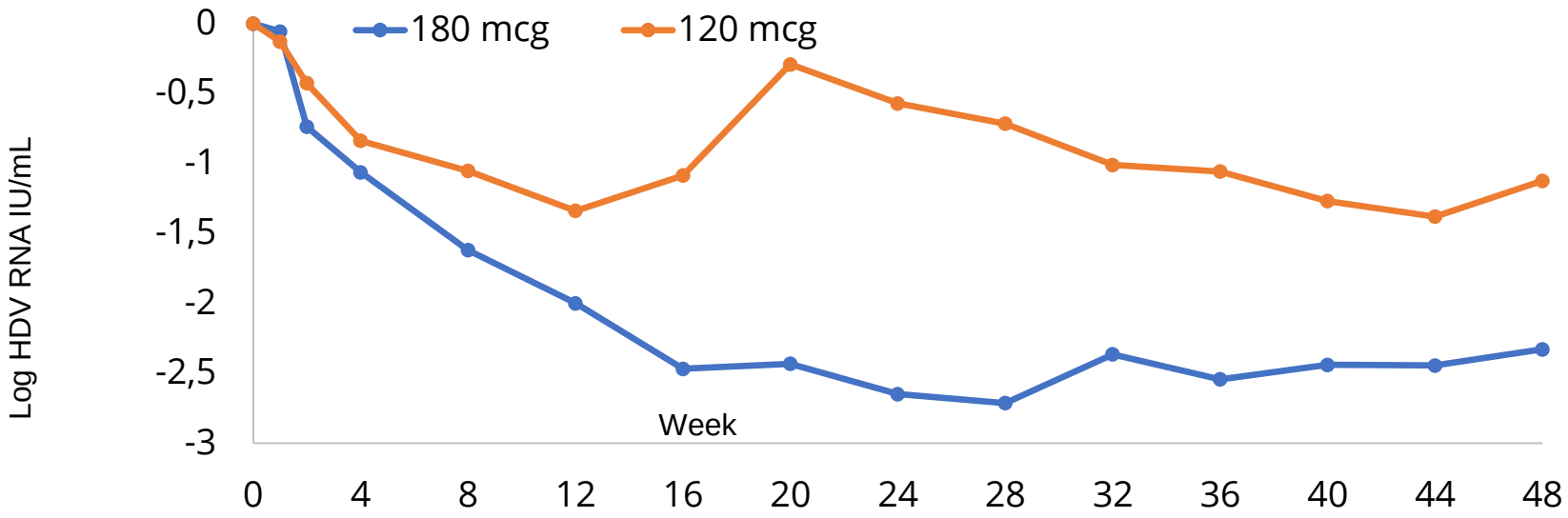
PEG-IFNa treatment of hepatitis D

- PEG-IFNα leads to undetectable HDV RNA 24 weeks after therapy in:
  HIDIT-I: 31% of patients (48 weeks of therapy; n=60) *(Wedemeyer, Yurdaydin et al., NEJM. 2011;364:322-31)*
  HIDIT-II: 23% of patients (96 weeks of therapy; n=120)*(Wedemeyer, Yurdaydin et al., Lancet ID. 2019;19:275-86)*
- Late relapses occur in >50% of patients

(Heidrich et al., Hepatology. 2014;16:87-97)

- HDV RNA reduction/suppression is associated with an improved clinical long-term outcome
  - *Farci Gastroenterology. 2004;126:1740-1749)* *(Heidrich et al., Hepatology. 2014;16:87-97)*
    (Wranke et al., Hepatology. 2017;65:414-425)
    (Yurdaydin et al., J Infect Dis 2018;217:1184-92)
    (Kamal et al., Hepatology 2020) *(Roulot et al., J Hepatology 2020)*

Therapy of HDV with IFN-lambda: Dose Dependent HDV RNA reduction



Etzion O, Hamid S et al. AASLD 2018

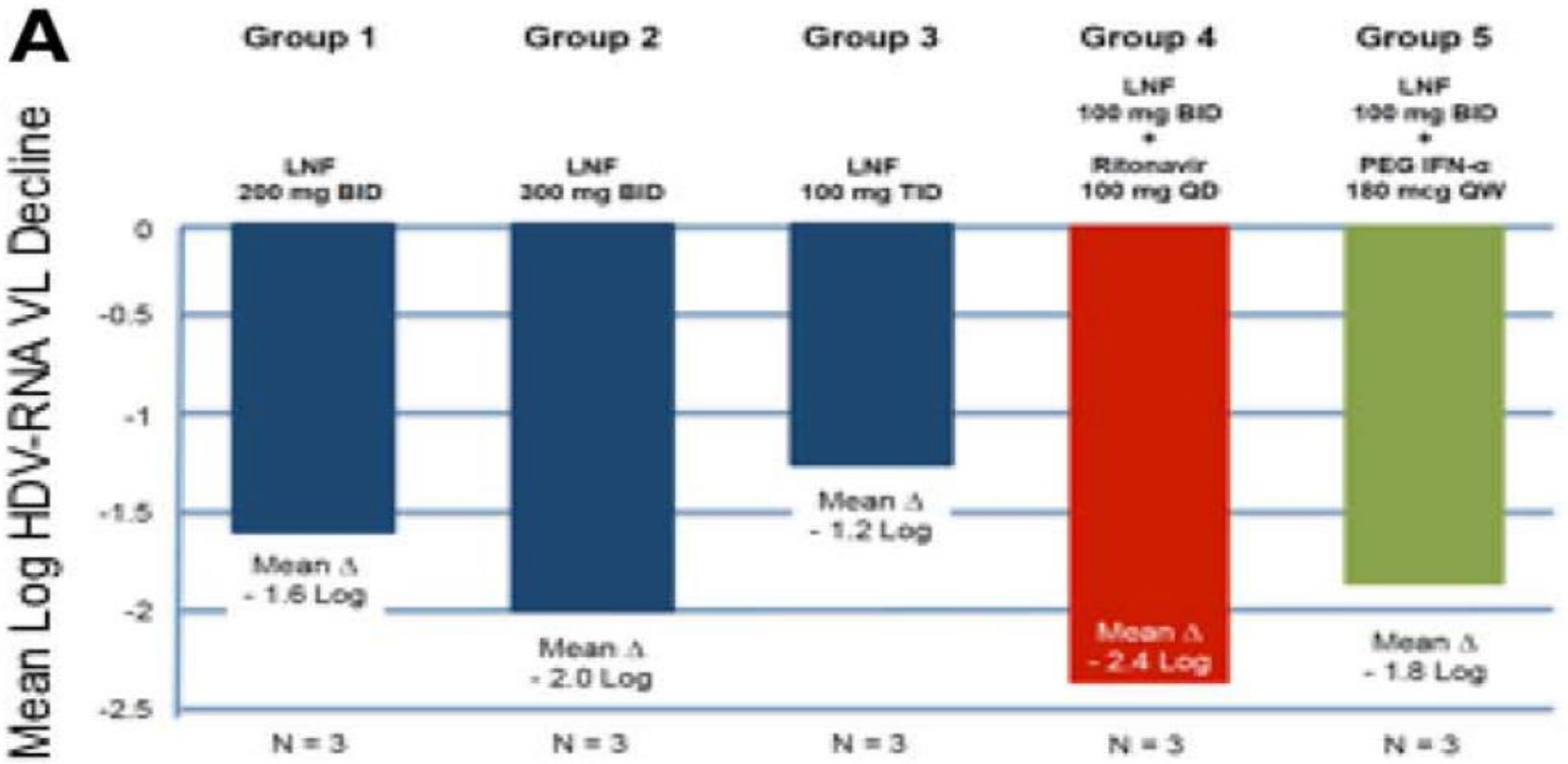
Nuevas opciones terapéuticas frente al VHD

Novel antiviral strategies against HDV in clinical development

	Target	Drug	Structure/function	Clinical Phase
Entry inhibitors	• Sodium taurocholate co-transporting polypeptide (NTCP)	Myrcludex B	• Myristoylated lipopeptide obtaining 47 amino acids of the pre S1 domain of L-HBsAg	Phase II
Prenylation inhibitors	• Farnesyl or geranylgeranyl prenyl lipids	Lonafarnib	• Inhibitor of an essential step in viral propagation and assembly	Phase II
Nucleic acid polymers	• Amphipathic alpha-helices in class I surface glycoproteins	REP 2139-Ca	• Blocks release of HBsAg particles: entry and post-entry antiviral activity	Phase II

Deterding & Wedemeyer; AIDS Rev 2019;21:126-134

Lonafarnib for HDV infection
LOWR-HDV-1



Yurdaydin et al., Hepatology 2018

Bulevirtide (Myrcludex B)

- Specifically binds to sodium taurocholate co-transporting polypeptide (NTCP) at the basolateral membrane of differentiated hepatocytes

  (***Ni et al., Gastroenterology. 2014;146:1070-1083; Urban et al., Gastroenterology. 2014;147:48-64)***

- Shows strong inhibitory potential for HBV/HDV infection (IC_{50} ca 80 pM in PHH)

  (***Schulze et al., J. Virology. 2010;84:1989-2000)***

  - Exclusively targets parenchymal liver cells

    (***Meier et al., Hepatology. 2013;58:31-42)***

➢ Has been dosed to >800 hepatitis B and D patients and healthy subjects

Bulevirtide (Myrcludex B)

EMA/312782/2020 EMEA/H/C/004854

Hepcludex (*bulevirtide*)

An overview of Hepcludex and why it is authorised in the EU

Bulevirtide (Myrcludex B) to treat Hepatitis D

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4.1 Therapeutic indications

Hepcludex is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease.

4.2 Posology and method of administration

Treatment should be initiated only by a physician experienced in the treatment of patients with HDV infection.

Hepatitis D: datos básicos & resumen

9-60 million people infected with HDV globally

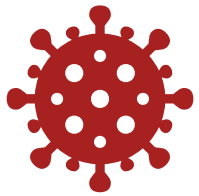
Defective RNA virus, requiring HBV for infection

4.5-13% of HBV carriers co-infected with HDV

Most severe form of viral hepatitis

Increased risk of cirrhosis/HCC and higher mortality vs HBV

Progression to cirrhosis within 5 years and to HCC within 10 years



Eight HDV genotypes

Until recently, no approved therapeutic options

Screening of HDV is mandatory in all HBsAg-pos patients!

Hughes SA, et al. Lancet 2011;378:73-85; Koh C, et al. Gastroenterology 2019;156:461-7; Miao Z, et al. J Infect Dis 2020;221:1677-87; Stockdale AJ, et al. J Hepatol 2020;73:523-3.

HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HDV: hepatitis delta virus; RNA: ribonucleic acid.

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