Hepatitis D Virus

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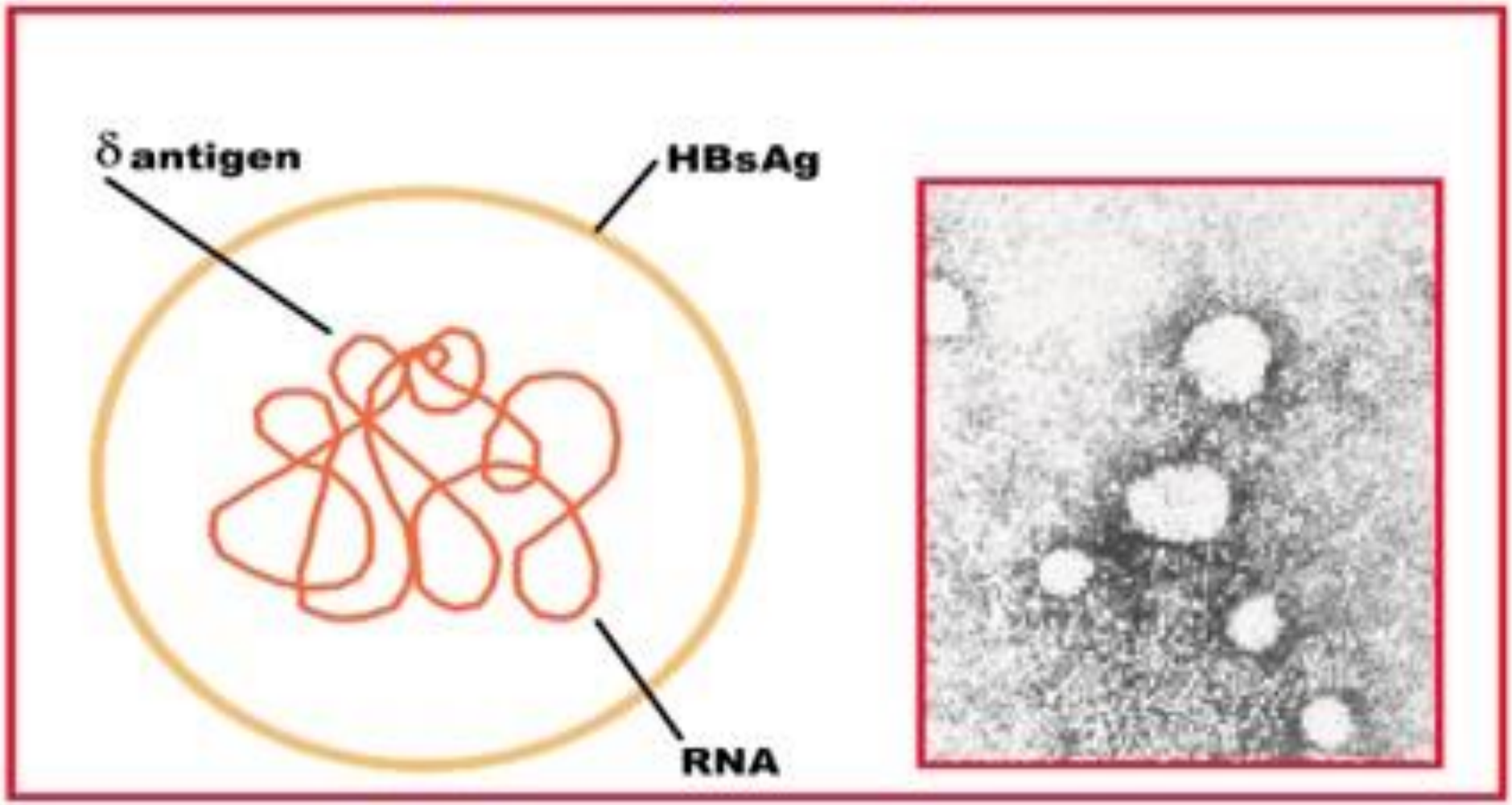
Disclosures

- Consulting: Abbvie, Aligos, Arbutus, Arrowhead, Assembly, BMS, Galmed, Gilead, Glaxo, Intercept, Janssen, Poptest, Redhill
- Research funding: Assembly, BMS, Eli Lilly, Janssen, Enanta, Genfit, Gilead, Janssen, Myr

Hepatitis D Virus

- A unique virus – similar to “satellite viroids” in plants
- 15-60 million infected people worldwide
- 5-10% infection rate in people with chronic hepatitis B
- Single stranded RNA genome
- Codes for only one protein (HDV antigen)
- “Defective” – needs HBV to express its coat protein (HBsAg)
- Can coinfect with HBV de novo or superinfect chronic HBV carriers
- Most patients with chronic HDV are HBeAg-negative and have low HBV DNA levels
- Highly pathogenic – high risk of progressive fibrosis, cirrhosis and hepatocellular carcinoma
- Interferon has been only treatment for many years: limited efficacy
- New drugs offer promise

Hepatitis D (Delta) Virus



Dr. Mario Rizzetto – The Discoverer of HDV

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

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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.

THE LANCET
Volume 314, Issue 8150, 10 November 1979, Pages 986-990

INCIDENCE AND SIGNIFICANCE OF ANTIBODIES TO DELTA ANTIGEN IN HEPATITIS B VIRUS INFECTION

Mario Rizzetto [a, b, c, d], DavidJ. Gocke [a, b, c, d], Giorgio Verme [a, b, c, d], JamesW.-K. Shih [a, b, c, d], RobertH. Purcell [a, b, c, d], JohnL. Gerin [a, b, c, d]

https://doi.org/10.1016/S0140-6736(79)92561-3

Abstract

A microtitre solid-phase blocking radioimmunoassay (RIA) for antibody to the hepatitis B virus (HBV)-associated δ antigen was specific and detected anti-δ antibody at dilutions of serum of up to 10^6. Analysis of sera from HBsAg-negative subjects and different categories of HBsAg carriers from different regions confirmed the association of anti-δ antibody with HBV infection. Anti-δ antibody was detected in persistently high titres in 19·1% and 2·6% of sera from patients with chronic hepatitis and symptomatic chronic carriers, respectively, and was not detected in the sera of HBsAg-negative controls. Anti-δ antibody appeared transiently and in low titres (<1:500) in 4·8% of sera from patients with acute type B hepatitis. The presence and persistence of anti-δ antibody seem to be associated with chronic HBV infection and the development of progressive liver damage.

Proc Natl Acad Sci U S A. 1980 Oct; 77(10): 6124–6128.
doi: 10.1073/pnas.77.10.6124
PMCID: PMC350226
PMID: 6934539

delta Agent: association of delta antigen with hepatitis B surface antigen and RNA in serum of delta-infected chimpanzees.

M Rizzetto, B Hoyer, M G Canese, J W Shih, R H Purcell, and J L Gerin

Abstract

The hepatitis B virus-associated beta antigen was found in the serum of experimentally infected chimpanzee as an internal component of a discrete subpopulation of hepatitis B surface antigen (HBsAg) particles. The 35- to 37-nm particles banded in CsCl at 1.24-1.25 g/cm3 and sedimented with a mobility intermediate between that of the hepatitis B virion and that of the 22-nm form of HBsAg. The particles contained only indistinct internal structure by electron microscopy and were not unique to delta agent infection, similar particles without delta-antigen activity being observed in the preinfection serum of HBsAg carrier chimpanzees. A small RNA (Mr, 5 X 10(5)) was temporally associated with delta antigen in the serum of infected chimpanzees and copurified with the delta-antigen-associated particles. This RNA is smaller than the genomes of known RNA viruses but larger than the viroids of higher plants.

THE LANCET
Volume 315, Issue 8180, 7 June 1980, Pages 1215-1219

EPIDEMIOLOGY OF HBV-ASSOCIATED DELTA AGENT: GEOGRAPHICAL DISTRIBUTION OF ANTI-DELTA AND PREVALENCE IN POLYTRANSFUSED HBsAg CARRIERS

Mario Rizzetto [a, b], RobertH. Purcell [a, b], JohnL. Gerin [a, b]

Show more

https://doi.org/10.1016/S0140-6736(80)91678-5

Abstract

The epidemiology of infection with the hepatis-B-virus (HBV)-associated δ agent was assessed from the prevalence of antibody to δ in 1206 HBsAg-seropositive subjects from various parts of the world. Anti-δ was prevalent in unselected HBsAg-positive Italians, whether residents in Italy or elsewhere, and in drug addicts and polytransfused HBsAg carriers throughout the world, suggesting that δ-associated infection is spread through contact in Italy and parenterally in other countries. Parenteral transmission of the δ agent was confirmed by a separate survey of the prevalence of anti-δ in 648 polytransfused patients with chronic blood disorders, which showed a higher prevalence of anti-δ in HBsAg-positive hæmophiliacs than in the general HBsAg-positive population of Italy, Germany, and the U.S.A. In view of the failure to detect δ in the absence of markers of HBV, the prevalence of anti-δ among polytransfused HBsAg carriers suggests that the δ-associated agent is transmitted by superinfection or coinfection of HBsAg carriers, the HBsAg carrier state possibly providing a rescue function to the superinfecting agent.

Global Distribution of HDV Infection Among HBsAg Carriers

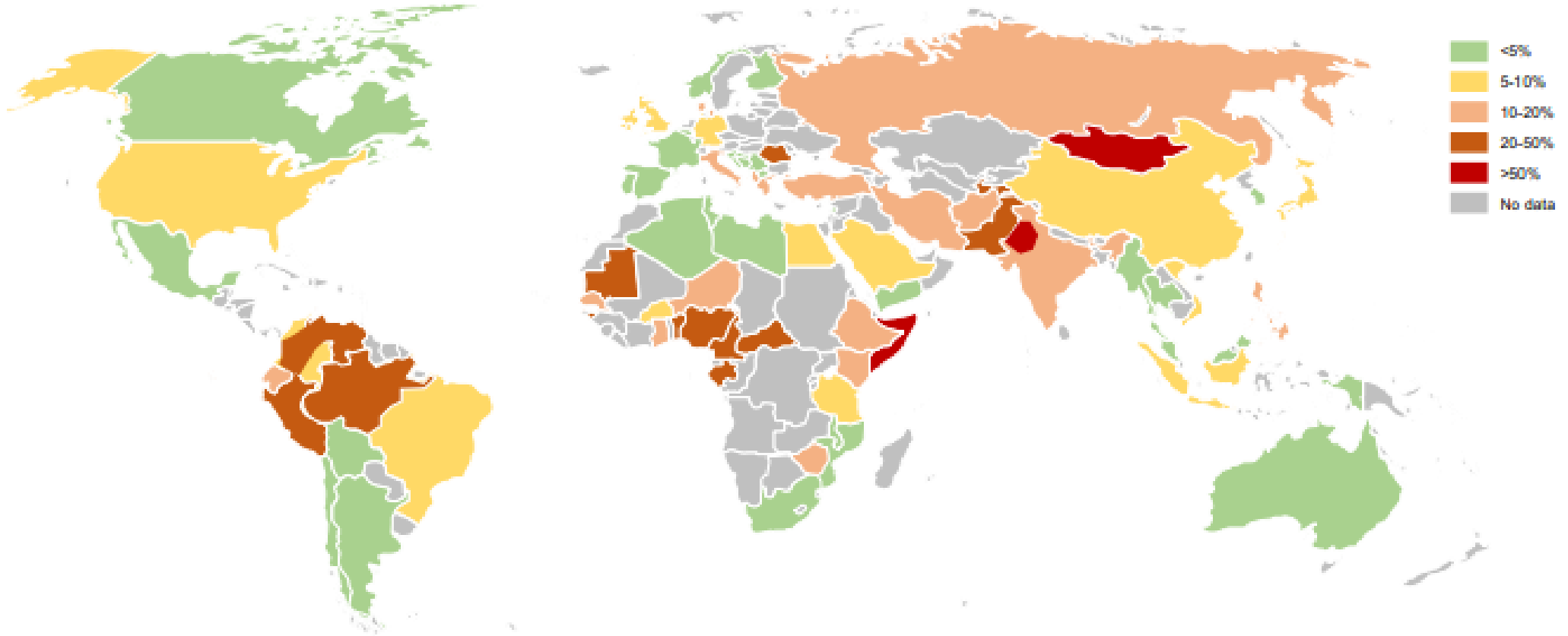
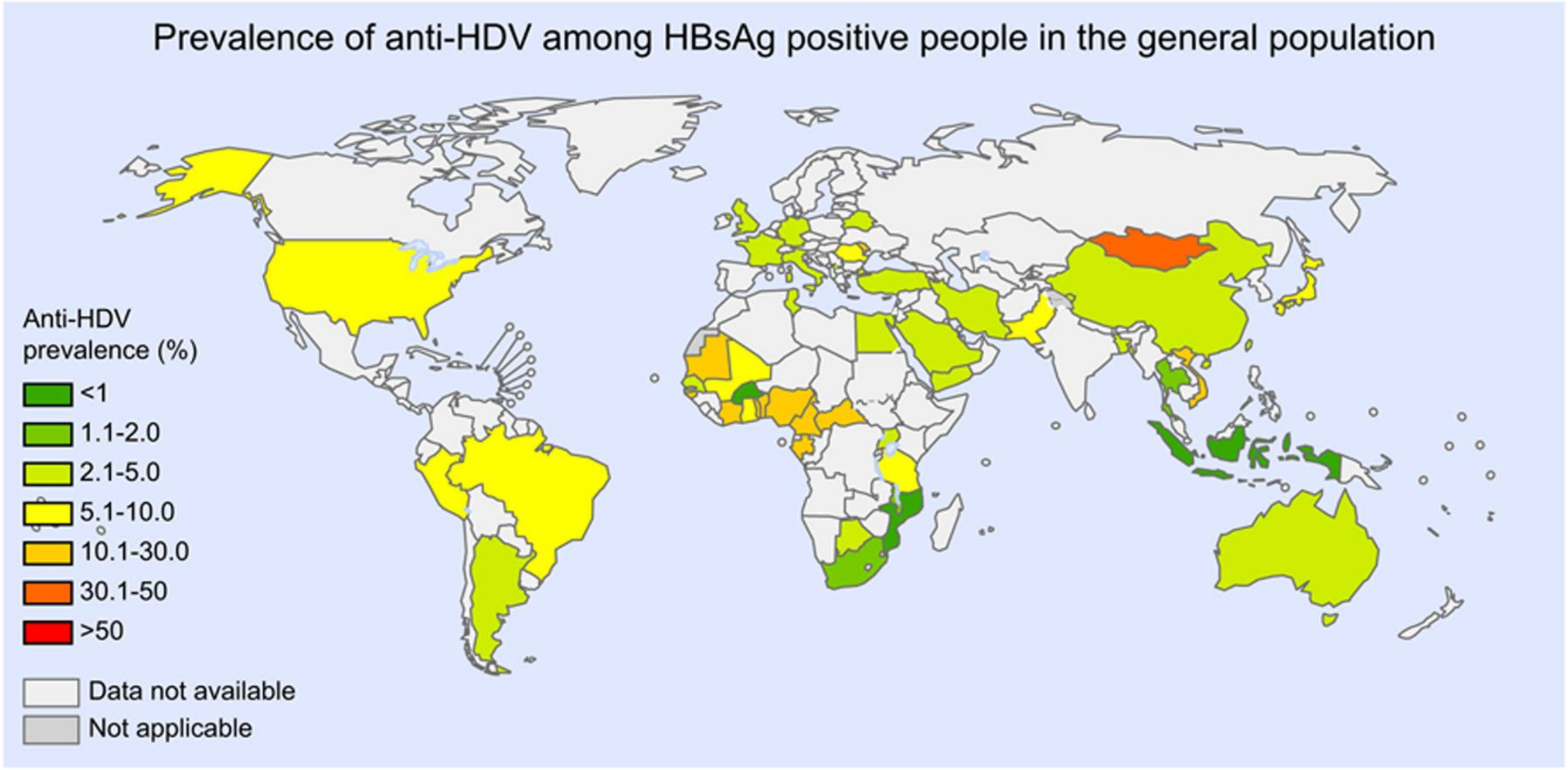


Fig. 1. Global distribution of HDV infection among HBsAg carriers. HDV prevalence is highly different among different countries. The most prevalent areas are Punjab, the Amazon basin, Somalia, and Mongolia. In European countries, the highest prevalences are seen in Romania and Albania. HBsAg, hepatitis B virus surface antigen; HDV, hepatitis delta virus.

Hepatitis D Virus: Global Prevalence
Not All Estimates Agree



Stockdale AJ et al, J Hepatology 2020;73:523-32

Prevalence and Burden of Hepatitis D Virus Infection in the Global Population: A Systematic Review and Meta-Analysis

- Search of PubMed, Embase, Cochrane Library and China Knowledge Resource Integrated databases from 1 January 1977 to 31 December 2016.
- Analysis of 40 million individuals to estimate the prevalence of HDV by using Der-Simonian Laird random-effects model.
- 182 articles from 61 countries and regions met the final inclusion criteria
- Overall prevalence of HDV was 0.98% (95% CI 0.61 to 1.42).
- In HBsAg-positive population, HDV pooled prevalence was 14.6% (95% CI 12.93 to 16.27)
- Seroprevalence 10.6% in mixed population without risk factors of intravenous drug use (IVDU) and high-risk sexual behaviour (HRSB)
- 38% in the IVDU population
- 17% in HRSB population.

Chen HY et al, Hepatology 2019

Risk Factors for Delta Hepatitis in a North American Cohort: Who Should be Screened?

Countries considered endemic	Countries considered endemic
Benin	Pakistan
Cameroon	Romania
Chad	Russia
Congo	Senegal
Egypt	Sierra Leone
Gambia	Somalia
Ghana	Togo
Guinea	Turkey
India	Zimbabwe
Italy	
Ivory Coast	
Liberia	
Mongolia	
Nigeria	
Pakistan	
Romania	
Russia	

Da B et al, American J Gastroenterology 2021;116:206-209

Risk Factors for Delta Hepatitis in a North American Cohort NIH Study

- 3,373 patients tested for HBsAg
- 652 HBsAg+
- 588(90%) patients were tested for HDAb.
- 113(19%) were HDAb+
- 91(80.5%) confirmed to have chronic HDV infection by HDV RNA
- Among those with HDAb
  - 9.8% HBeAg+
  - 79.5% anti-HBe+
  - 65.5% from an endemic country 10.6% IVDU, and 12.4% were on nucleo(s) tides
  - HDV“exposed” patients were more likely to be from a HEC or be IVDU (P , 0.0001) compared with “unexposed” patients.

Da B et al, American Journal of Gastroenterology. 116(1):206-209, January 2021.

Risk Factors for Delta Hepatitis in a North American Cohort: Who Should be Screened?

- Authors recommended screening for HDV with any of the following:
  - History of IVDU
  - Baseline serum HBV-DNA < 2,000 IU/mL
  - ALT >40 U/L
  - Origins from an endemic country

Alternative view (including speaker): Screen all HBsAg-positive persons

Da B et al, American Journal of Gastroenterology. 116(1):206-209, January 2021.

HBV and HDV

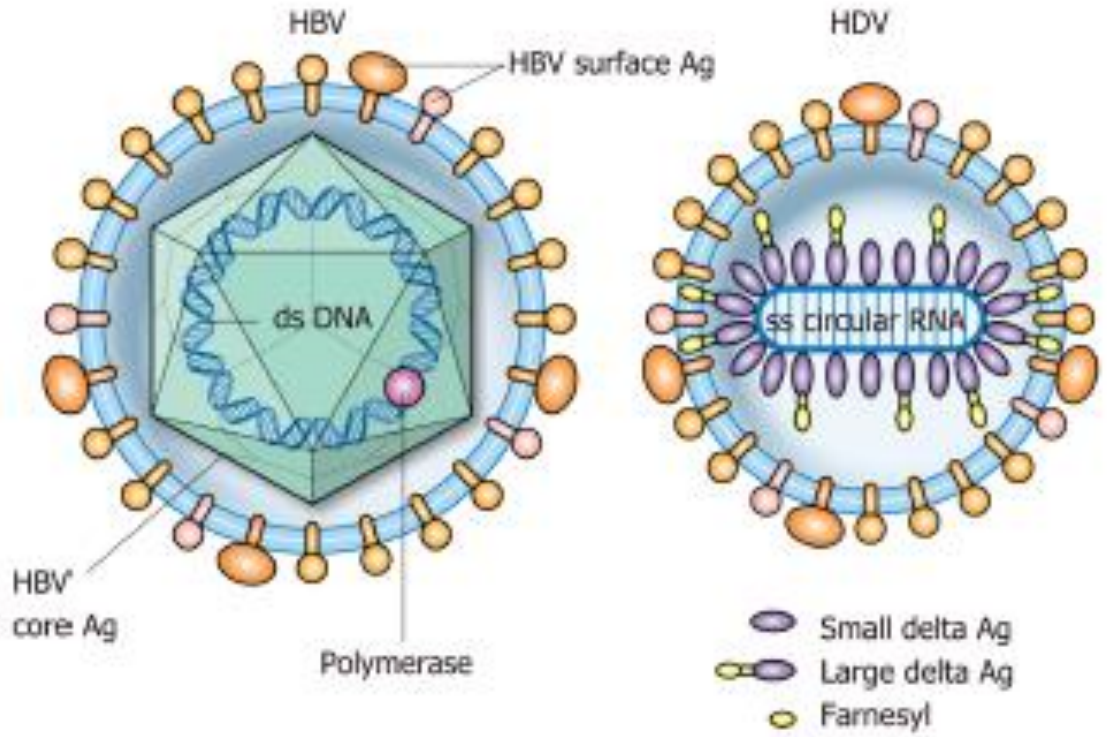


Figure 2 Structural representation of hepatitis B and delta viruses.

Gilman C et al. World J Gastroenterol 2019;25:4580-97

HDV Life Cycle

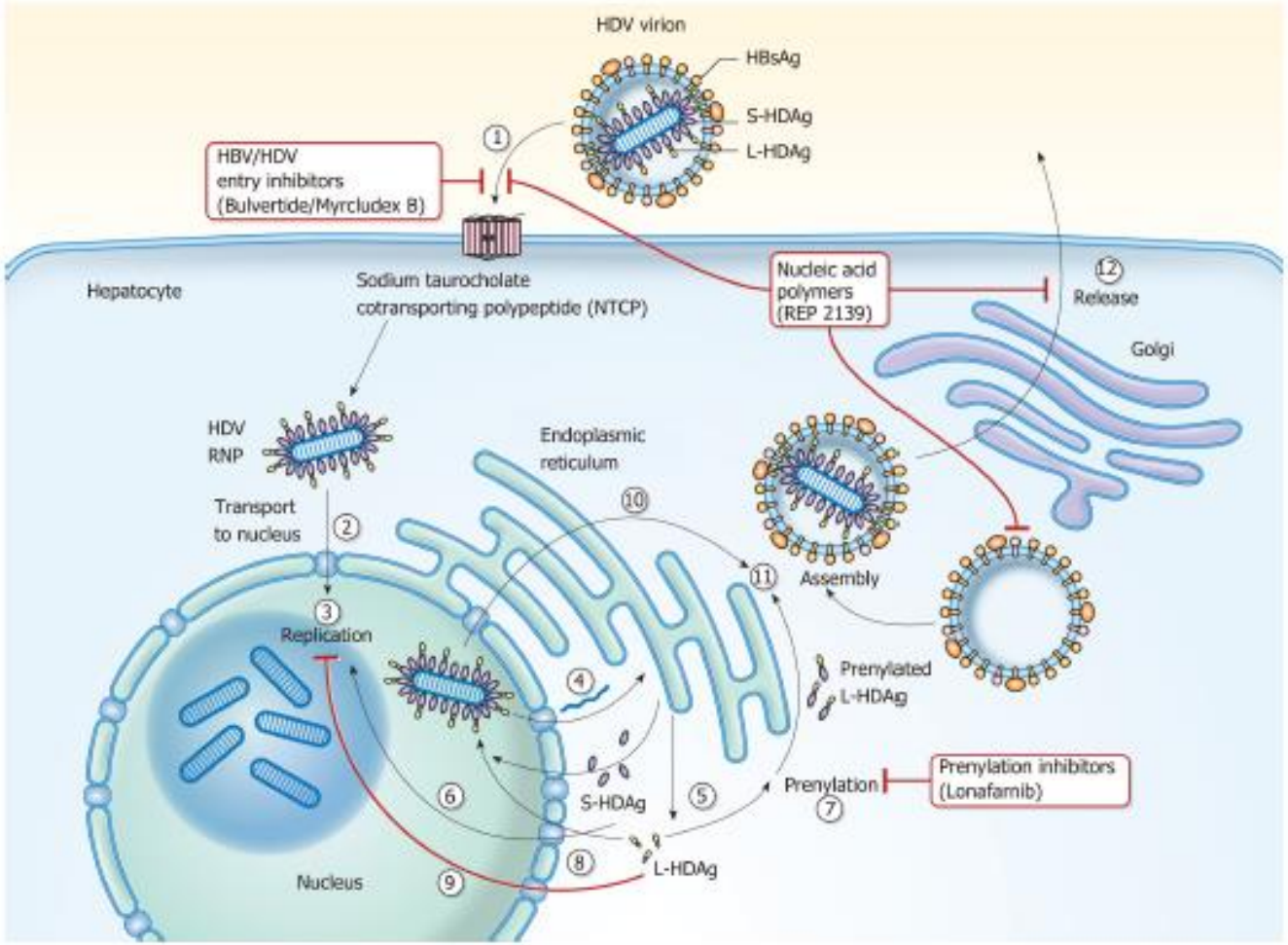


Figure 3 Hepatitis D virus viral life cycle and sites of investigative therapies. (1) Hepatitis D virus (HDV) virion attaches to the hepatocyte through interaction between HBsAg and NTCP; (2) HDV RNP is translocated to nucleus facilitated by HDAg; (3) HDV genome replication occurs via a "rolling cycle" mechanism; (4) HDV antigenome is transported out of the nucleus to the endoplasmic reticulum (ER); (5) HDV antigenome is translated in the ER into SHDAg and LHDAg; (6) SHDAg is transported into the nucleus; (7) SHDAg promotes HDV replication in the nucleus; (8) LHDAg undergoes prenylation prior to assembly; (9) LHDAg inhibits HDV replication in the nucleus; (10) New HDAg molecules are associated with new transcripts of genomic RNA to form new RNPs that are exported to the cytoplasm; (11) New HDV RNPs associate with HBsAg and assemble into HDV virions; and (12) Completed HDV virions are released from the hepatocyte via the trans-Golgi network.

Gilman C et al. World J Gastroenterol 2019;25:4580-97

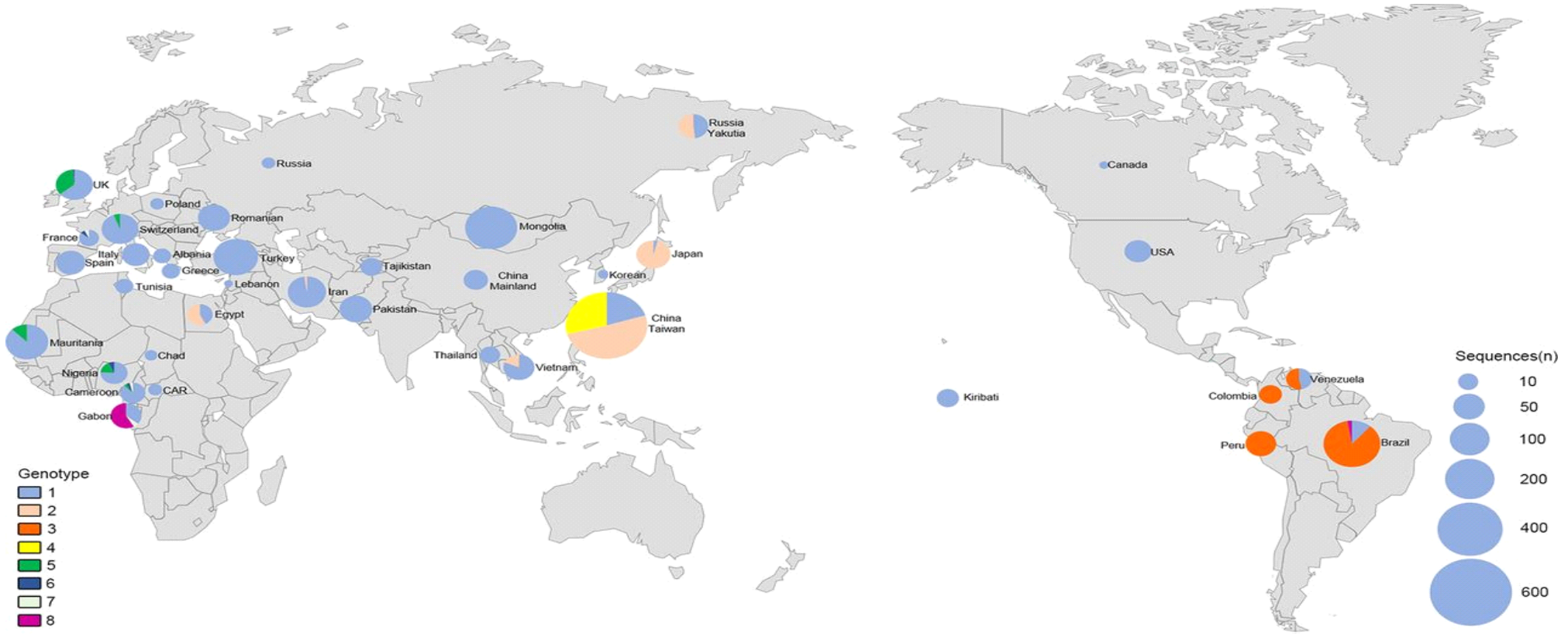
Hepatitis D Virus Genotypes

- 8 distinct genotypes, each with 2-4 subtypes
- Genotype 1 most prevalent worldwide, predominant in Europe and North America
  - In comparative studies vs genotype 2, higher risk of adverse outcomes, lower rates of remission
- Genotype 2: Asia, Middle East
- Genotype 3: Amazon Basin, most divergent from others
  - Most pathogenic
- Genotype 4: Taiwan, China, Japan
- Genotypes 5-8: Africa, genotypes 5-7 also now in Europe

Note: Genotype testing not approved in US, rarely done

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

Global distribution of hepatitis D virus genotypes.



Hai-Yan Chen et al. Gut 2019;68:512-521

Diagnostic Tests for Hepatitis D

Table 2. Diagnostic tests for hepatitis D

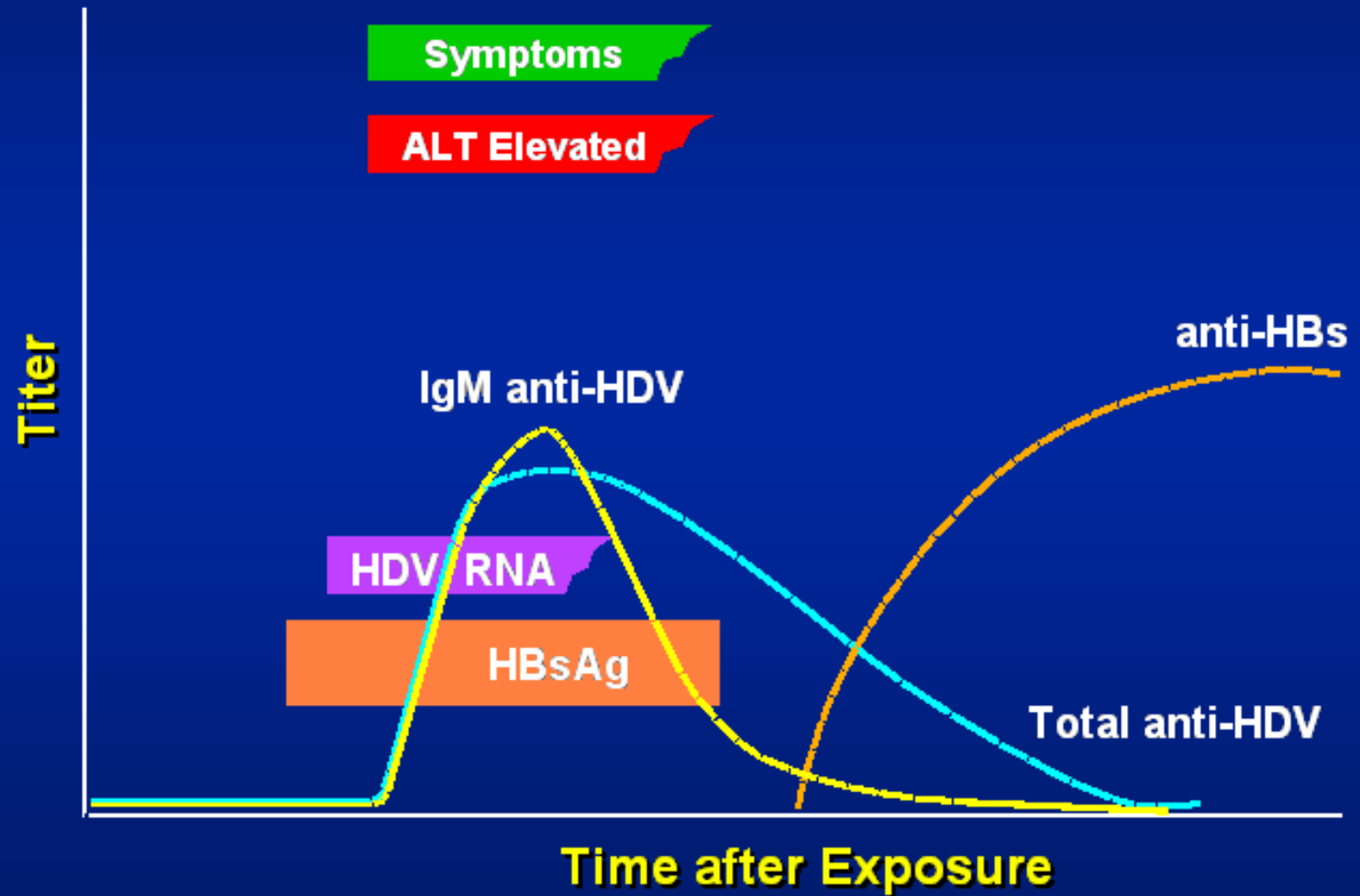
Diagnostic test	Detection	Significance	Comments
Liver HDAg	Detects HDV antigen on liver histology via immunohisto-chemical staining	Indicates active infection	Lack of availability. Poor sensitivity
Serum HDAg	Detects HDV antigen in the serum	Indicates active infection but disappears quickly	Rarely performed. 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 B et al. Gastroenterology Report, 7(4), 2019, 231–245

HBV - HDV Coinfection

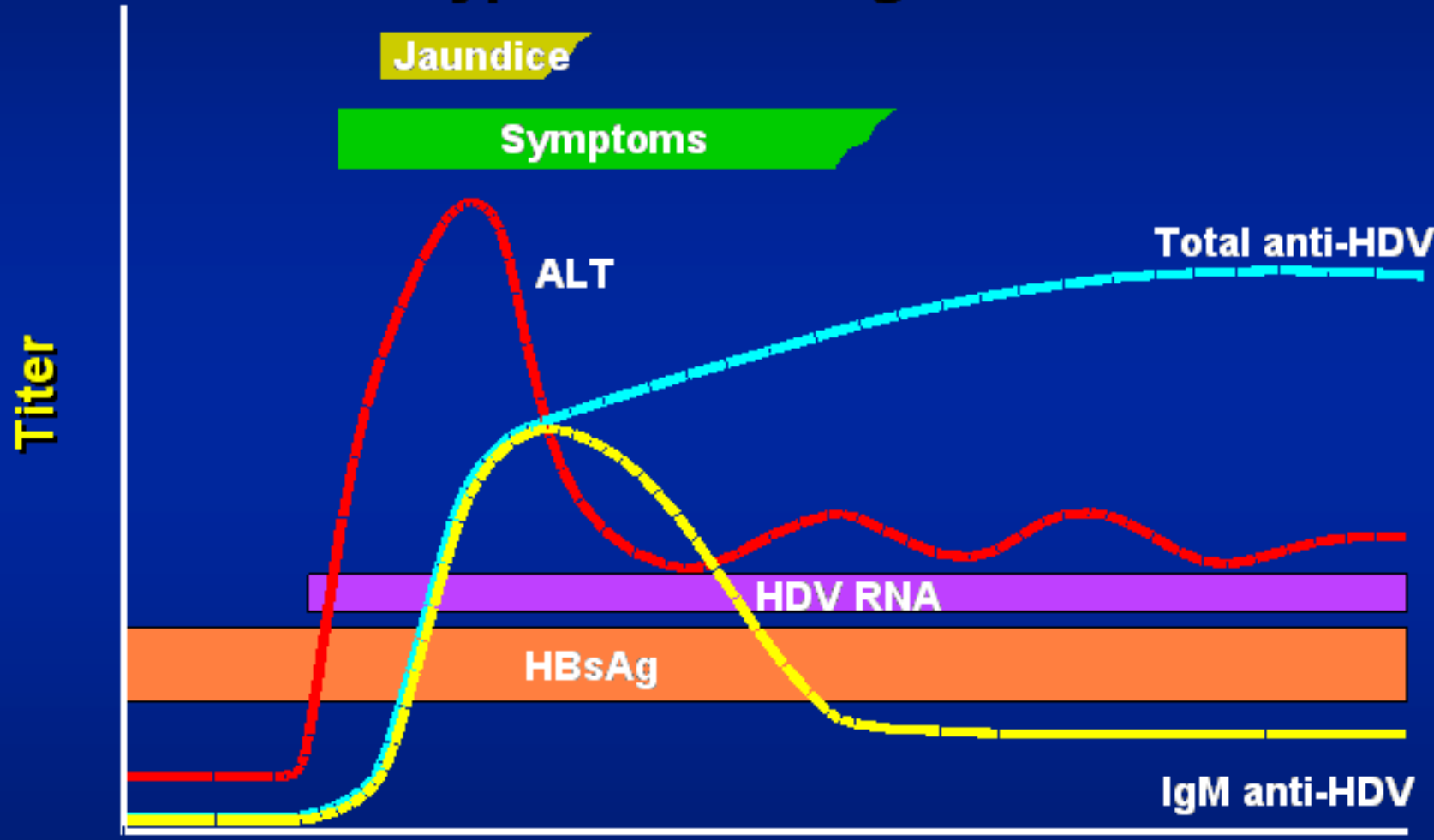
Typical Serologic Course



CDC

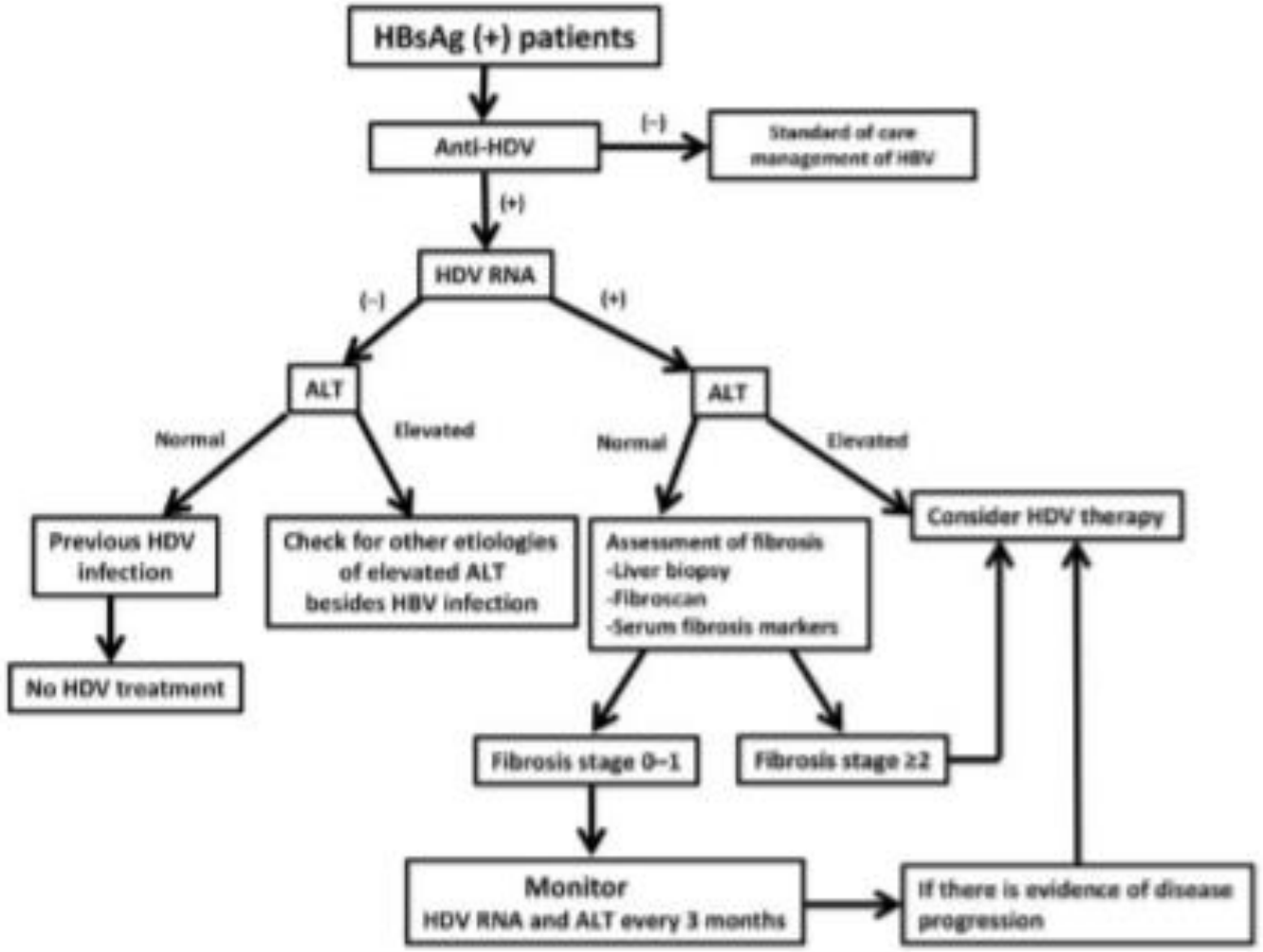
HBV - HDV Superinfection

Typical Serologic Course



CDC

Algorithm for the Evaluation of Hepatitis D



Shah PA et al, Gastroenterology Rep 2019 Oct 19;7(6):396-402

Natural History of HDV Infection

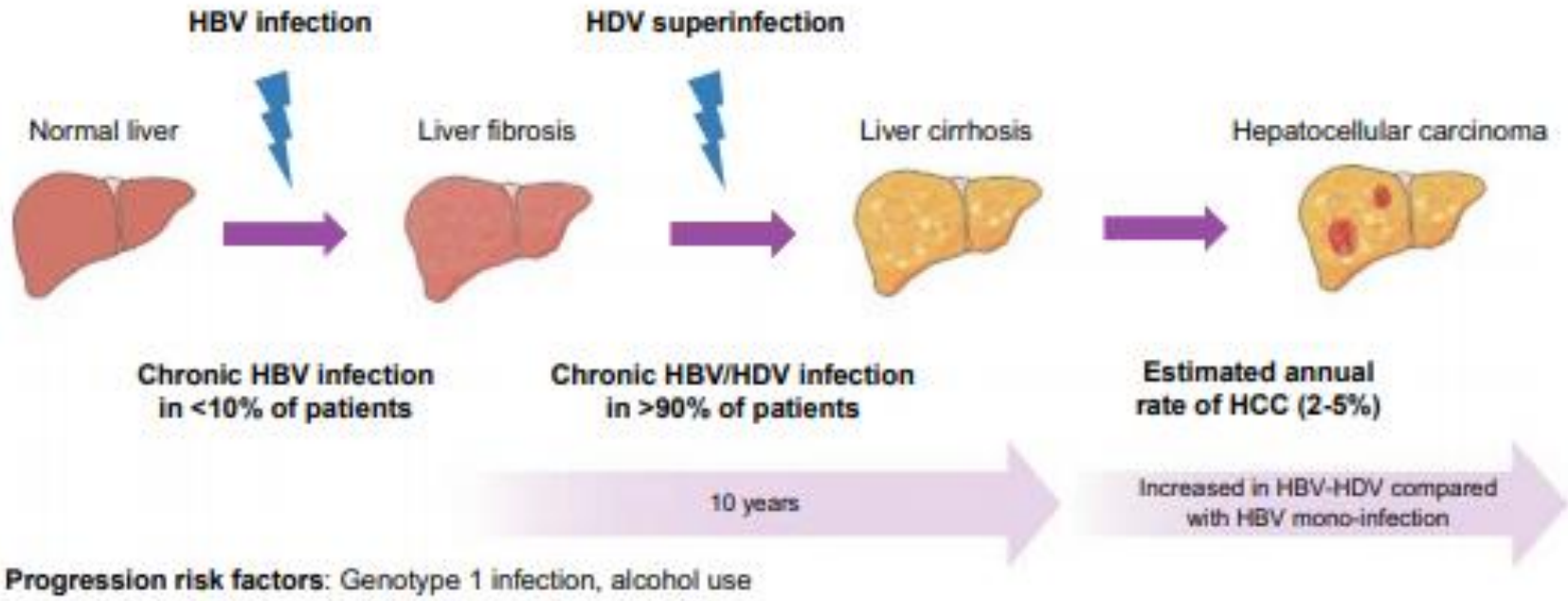


Fig. 3. Natural history of HDV infection. Commonly, HDV infects hepatocytes already infected by HBV (*i.e.* superinfection). After that, 90% of patients will develop a chronic HBV/HDV infection with a faster evolution to cirrhosis in 10 years. Some risk factors, such as alcohol consumption or genotype 1 infection may accelerate liver disease development. HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis delta virus.

JHEP Reports **2019** vol. 1 | 120–130

Adverse Outcomes Increased With Hepatitis D

Table 3. Associated risks of chronic hepatitis D

Clinical outcome	Approximate relative risk increase*
Cirrhosis [58, 90, 110]	2- to 3-fold
Hepatocellular carcinoma [58, 61, 78, 90, 111–113]	3- to 6-fold
Liver transplantation [48]	2-fold
Hepatic decompensation [111]	2-fold
Mortality [42, 78, 90, 111]	2-fold

*Compared with hepatitis B mono-infection.

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

Long-Term Clinical Outcomes in Patients With Chronic Hepatitis Delta: the Role of Persistent Viraemia

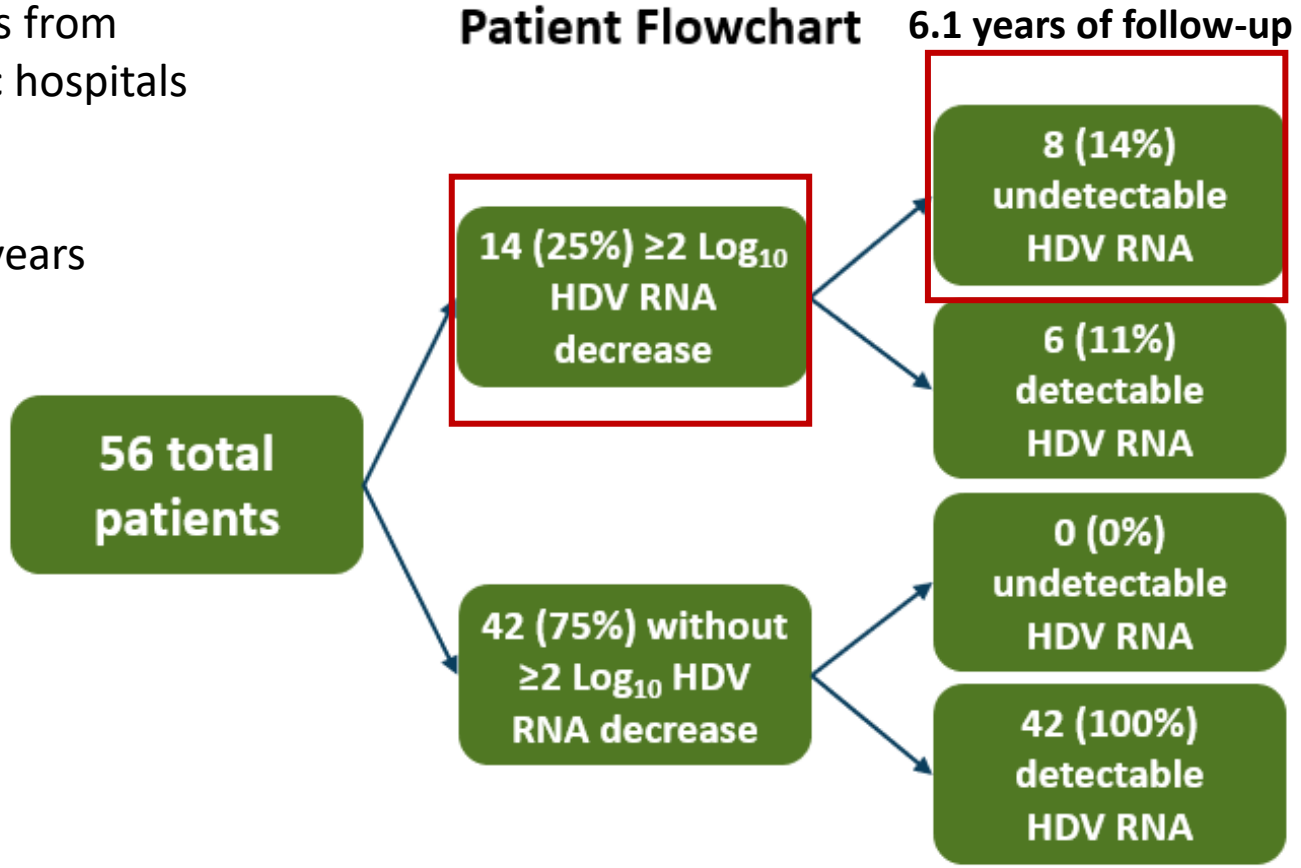
- 2888 HBsAg-positive subjects
- 151 (5.2%) tested positive for anti-HDV
- 118 were included (58% men; median age, 49 years;
- 73% detectable HDV-RNA and 30% cirrhosis, most often in subjects with HDV-RNA

Note: The discordance between anti-HDV and HDV RNA has resulted in screen failures in clinical trials

Palom A et al, Alimentary Pharmacology & Therapeutics. 2020;51:158-166

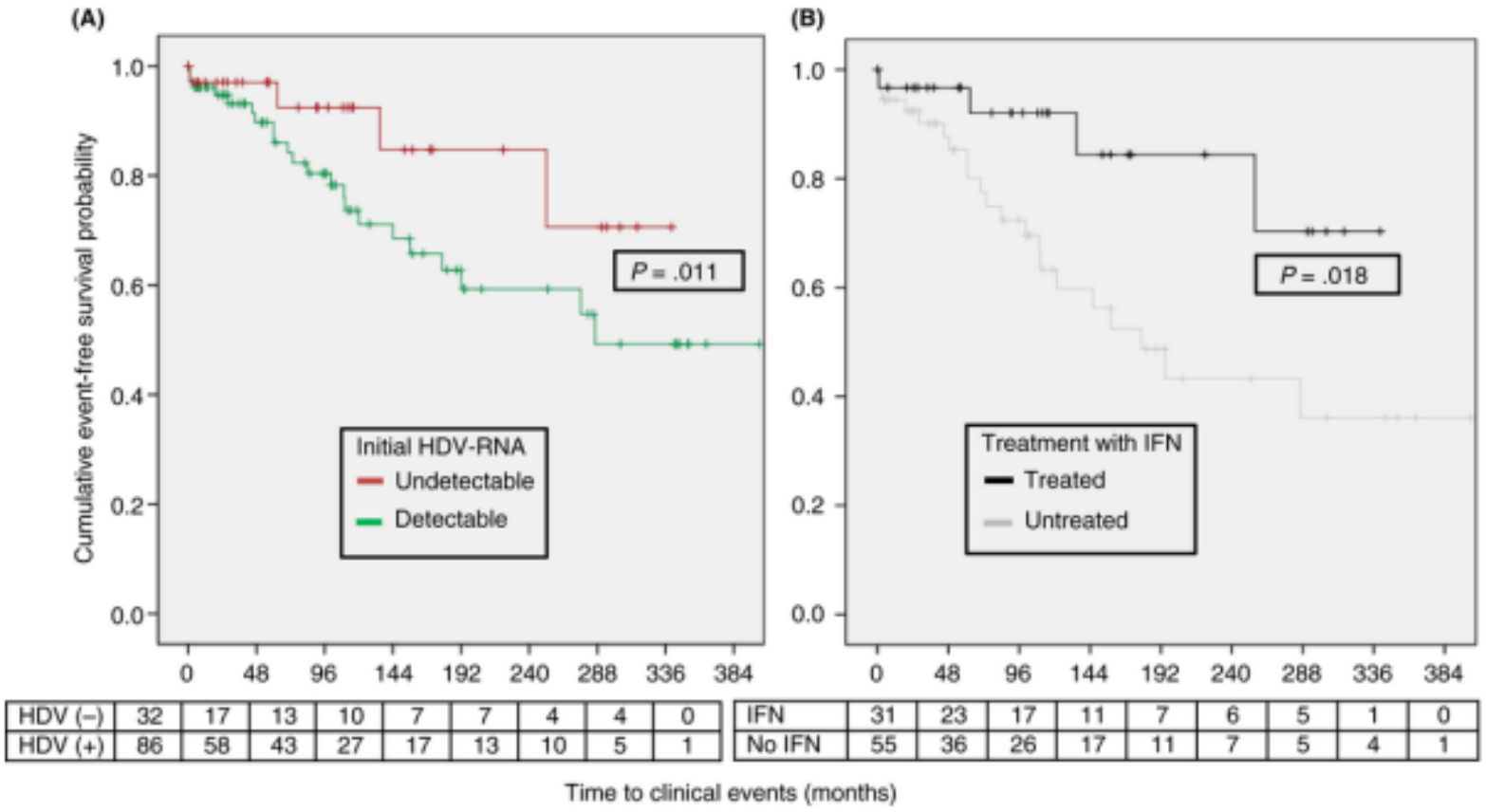
Spontaneous Reduction or Clearance of HCV RNA Over Time

- 331 stored annual consecutive serum samples from 56 CHD patients were collected in 4 academic hospitals
- Inclusion criteria:
  - CHD with detectable HDV-RNA
  - No interferon therapy in the previous 3 years
  - No HCV or HIV coinfection



Palom A, et al. AASLD TLMdX2020. #1023

Long-Term Clinical Outcomes in Patients With Chronic Hepatitis Delta: The Role of Persistent Viraemia



Palom A et al, Alimentary Pharmacology & Therapeutics. 2020;51:158-166

New Data From French National Reference Center for HDV n = 1112

- 659/748 (88%) HDV RNA positive
- Most were immigrants (Sub-Saharan Africa 53%), Southern and Eastern Europe (21%), Northern Africa and Middle East (6%), Asia (6%), South America (0.3%)
- HDV-1 76%, then HDV-5, 7, 6, and 8
- 28% cirrhosis, half with at least 1 episode hepatic decompensation
- At end of follow-up (median 3 yrs), 48% cirrhosis half decompensated
- 9% HCC
- Persistent HDV replication associated with more adverse outcomes
- African patients better response to IFN than non-African (46% vs 29%)
- HDV viral load lower at baseline in subsequent responders to IFN

Roulot D et al, J Hepatology 2020;1046-62

Approved and Investigational HDV Drugs

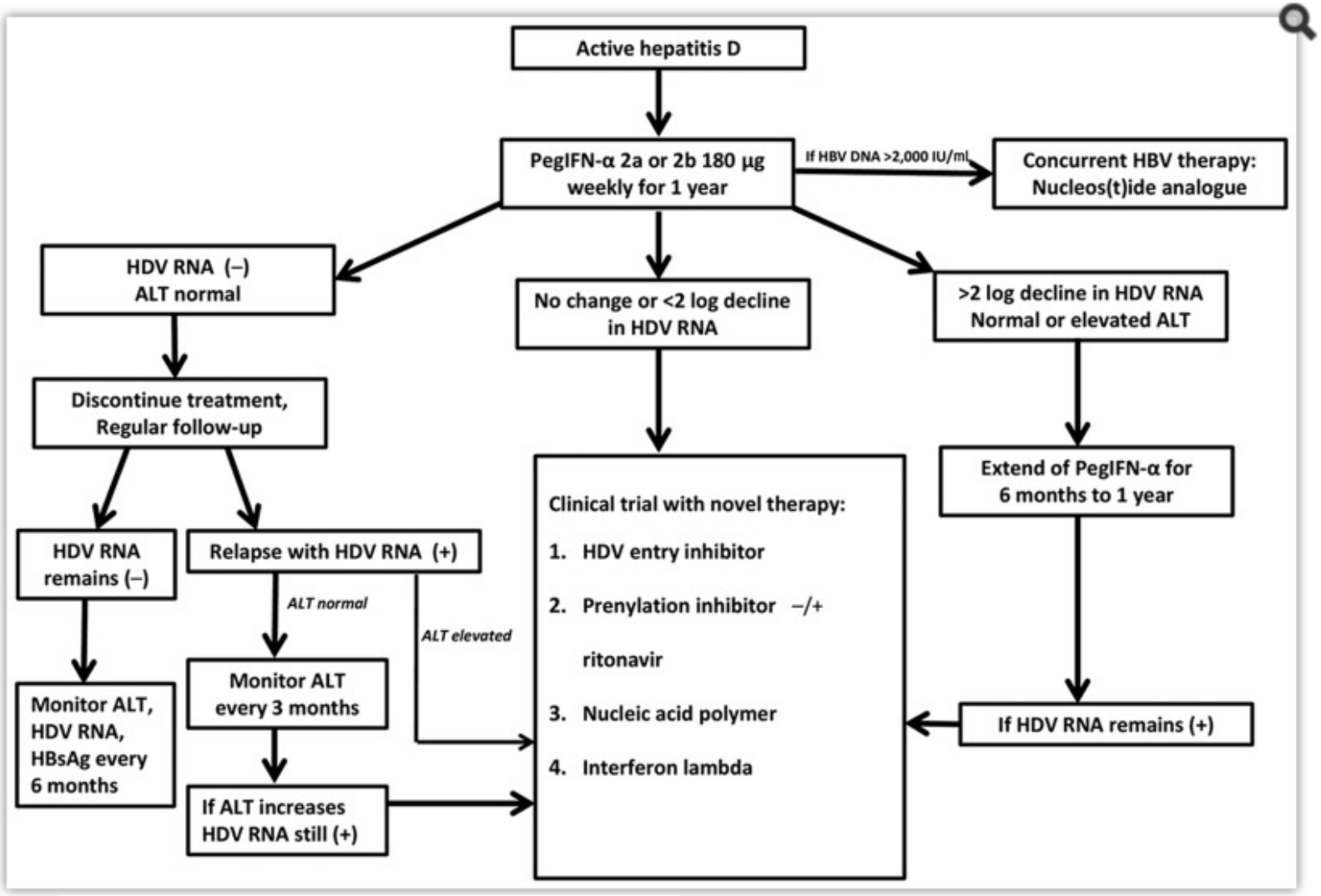
Table 1. Approved and investigational HDV drugs.

Drug	Substance	Mode of action	Availability
Peg-IFN-α	Protein	Cytokine, activating innate immune system	Approved for HBV, off-label use for HDV
Peg-IFN-λ1	Protein	Cytokine, activating innate immune system	Phase II
Bulevirtide	PreS1 peptide	NTCP binding, blocking HBV/HDV entry	Phase III, CMA by EMA in July 2020
Lonafarnib	Small molecule	Inhibiting L-HDAg prenylation and HDV secretion	Phase III
REP 2139	Nucleic acid polymer	Inhibiting HBsAg/HBV /HDV secretion, possibly also HBV/HDV entry	Phase II

CMA, conditional marketing authorisation; L-HDAg, large hepatitis delta antigen; Peg-IFN, pegylated interferon; NTCP, human sodium taurocholate co-transporting polypeptide.

Zhang Z, Urban S. J Hepatology 2020

Algorithm for the Current Management of Hepatitis D



Shah PA et al, Gastroenterology Rep 2019 Oct 19;7(6):396-402

Clinical Trials of PEG IFN alpha

Table 4. 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.* [123]	2006	1.5 mcg/kg SC/wk	peg-IFN-α for 48 weeks	12	NR	17%
Niro *et al.* [131]	2006	1.5 mcg/kg SC/wk	peg-IFN-α for 72 weeks ± ribavirin for 48 weeks	38	13%	21%
Castelnau *et al.* [132]	2006	1.5 mcg/kg SC/wk	peg-IFN-α for 48 weeks	14	57%	43%
Wedemeyer *et al.* [122]	2011	180 mcg SC/wk	peg-IFN-α ± adefovir vs placebo for 48 weeks	90	23%	28%
Gheorghe *et al.* [133]	2011	1.5 mcg/kg SC/wk	peg-IFN-α for 52 weeks	49	33%	25%

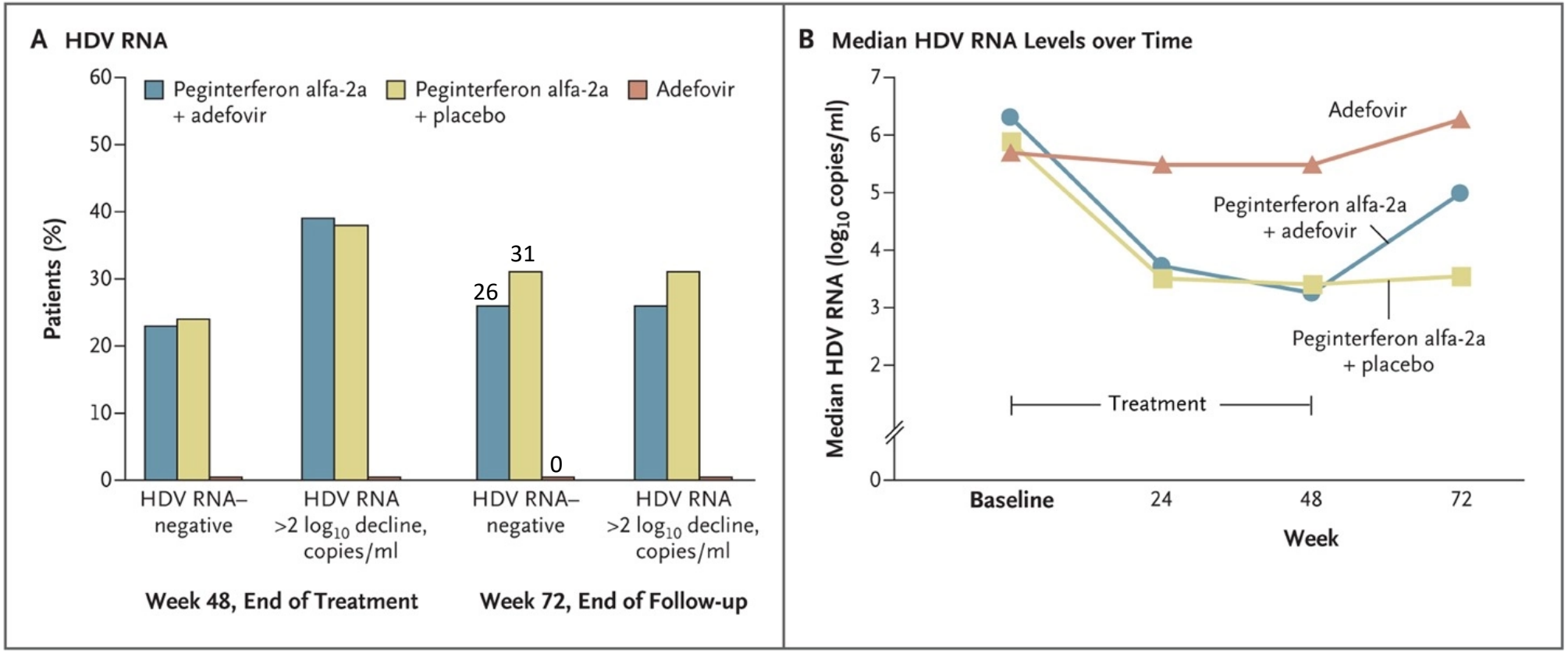
Peg-IFN-α, pegylated-interferon-α; VR, virological response; SVR, sustained virological response; NR, not reported.

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

HIDIT-1: Virologic Response to Treatment as Determined by Serum Level of HDV RNA, According to Treatment Group

PEG IFN + ADV vs PEG IFN vs ADV (n=90)

48 Weeks Treatment, 24 Weeks Followup



Wedemeyer H et al, N Engl J Med 2011;354:322-331

HIDIT-II: PEG IFN + Tenofovir/Placebo for HDV Infection
96 Weeks of Treatment, 24 Weeks Followup

N=120

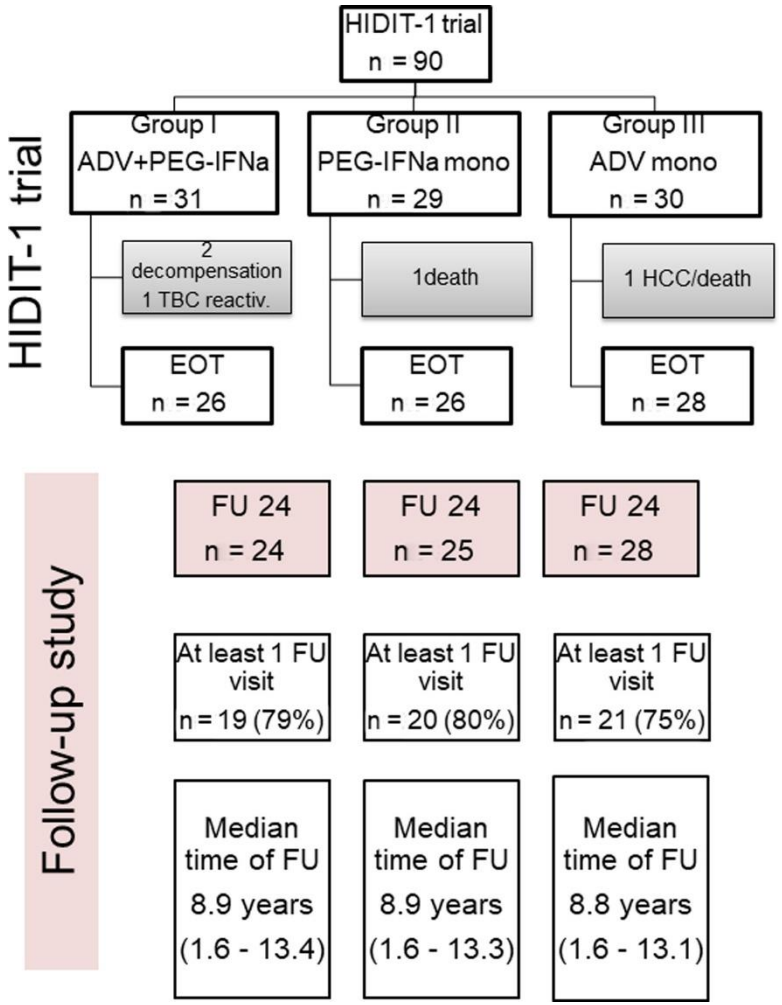
	Baseline	Week 12	Week 24	Week 48	Week 72	Week 96	Week 120
HDV RNA negative							
Peginterferon alfa-2a plus TDF (n=59)	1 (2%)	14 (24%)	21 (36%)	25 (42%)	23 (39%)	28 (48%)	18 (31%)
Peginterferon alfa-2a plus placebo (n=61)	1 (2%)	9 (15%)	18 (30%)	21 (34%)	19 (31%)	20 (33%)	14 (23%)
OR (95% CI), p value	..	1·71 (0·67–4·41), 0·26	1·32 (0·60–2·89), 0·49	1·60 (0·73–3·48), 0·24	1·66 (0·74–3·71) 0·22	1·84 (0.86–3·91), 0·1154	1·46 (0·64–3·31), 0·37
HBsAg decline ≥0·5% from baseline							
Peginterferon alfa-2a plus TDF (n=59)	..	4 (6·8%)	10 (16·9%)	14 (23·7%)	11 (18·6%)	17 (28·8%)	12 (20·3%)
Peginterferon alfa-2a plus placebo (n=61)	..	4 (6·6)	18 (29·5)	15 (24·6)	9 (14·8)	12 (19·7)	14 (23·0%)
OR (95% CI), p value	..	0·90 (0·21–3·90), 0·89	0·40 (0·15–1·03), 0·057	1·08 (0·41–2·86), 0·88	1·60 (0·54–4·67), 0·40	1·74 (0·67–4·51), 0·25	0·85 (0·32–2·26), 0·75
Normal ALT values							
Peginterferon alfa-2a plus TDF (n=59)	8 (14%)	12 (20%)	12 (20%)	18 (31%)	21 (36%)	26 (44%)	27 (46%)
Peginterferon alfa-2a plus placebo (n=61)	3 (5%)	10 (16%)	15 (25%)	16 (26%)	23 (38%)	23 (38%)	16 (26%)
OR (95% CI), p value	3·18 (0·79–12·82), 0·10	1·30 (0·51–3·34), 0·58	0·76 (0·30–1·94), 0·56	1·44 (0·61–3·37), 0·40	1·12 (0·49–2·57), 0·79	1·58 (0·72–3·48), 0·26	3·42 (1·38–8·47), 0·008

HDV=hepatitis D virus. TDF=tenofovir disoproxil fumarate. OR=odds ratio. ALT=alanine aminotransferase.

Table 2: Virological and biochemical treatment response

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

Ten-year follow-up of a randomized controlled clinical trial in chronic hepatitis delta



Wranke A et al. Journal of Viral Hepatitis, Volume: 27, Issue: 12, Pages: 1359-1368, First published: 24 July 2020, DOI: (10.1111/jvh.13366)

Ten-Year Follow-up of a Randomized Controlled Clinical Trial in Chronic Hepatitis Delta

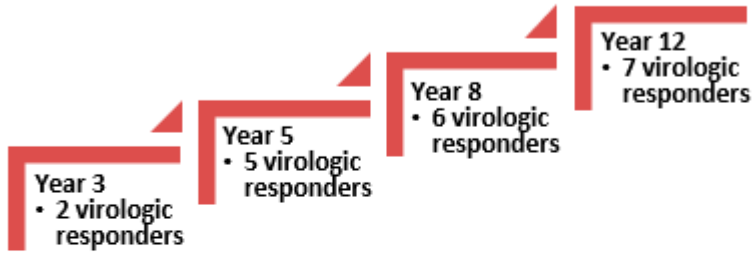
- Analysis of virological response was carried out in 60 patients with long-term follow-up.
- Undetectable HDV RNA at follow-up week 24 was described in 14 patients (seven each of groups I and II, respectively).
- Of the 14 patients, 6 had a maintained virological response. In the remaining 8 patients, late-HDV RNA relapses occurred between years 2 and 9
- Of these 8 patients, five were retreated with IFN-based therapy but this led to HDV RNA negativity during the entire follow-up in only one patient.

Wranke A et al. Journal of Viral Hepatitis, Volume: 27, Issue: 12, Pages: 1359-1368, First published: 24 July 2020, DOI: (10.1111/jvh.13366)

Ten-Year Follow-up of Long-Term Peginterferon-α Treatment for Chronic Delta Hepatitis

- 13 patients
- Mean treatment duration: 75 months (2–397)
- Extension past 5 years in 5 cases
- FU duration: 104 months (2–211)

Cumulative virologic response



- 7/13 patients responded at last follow-up; 4 lost HBsAg
- 2/13 patients responded past 5 years of treatment
- Only responders had normalized transaminases at follow-up

Responses and outcomes

Viral response and outcome at last follow-up (N=13)	
Undetectable serum HDV RNA	7 (54)
Serum HBsAg clearance	4 (31)
Serum anti-HBs antibody development	4 (31)[a]

Data are n (%); [a]1 case not sustained

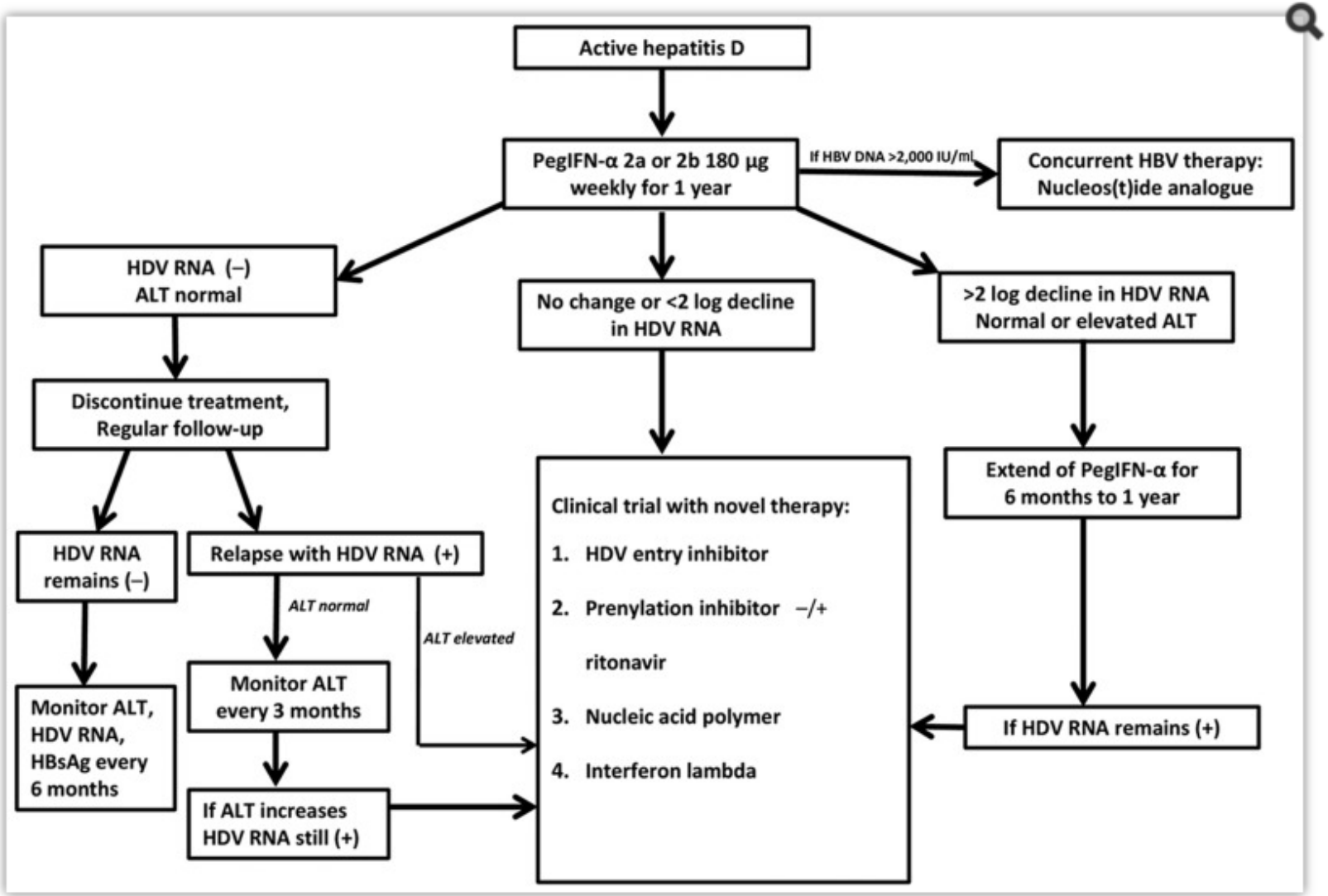
	Responders (n=7)	Non-responders (n=6)
Liver-related outcome	0 (0)	2 (33)
Death[a]	1 (14)	5 (83)

Data are n (%); [a]unrelated to liver disease

Implication: Long term therapy, or repeated courses of therapy, may be necessary to optimize outcomes of patients with HDV

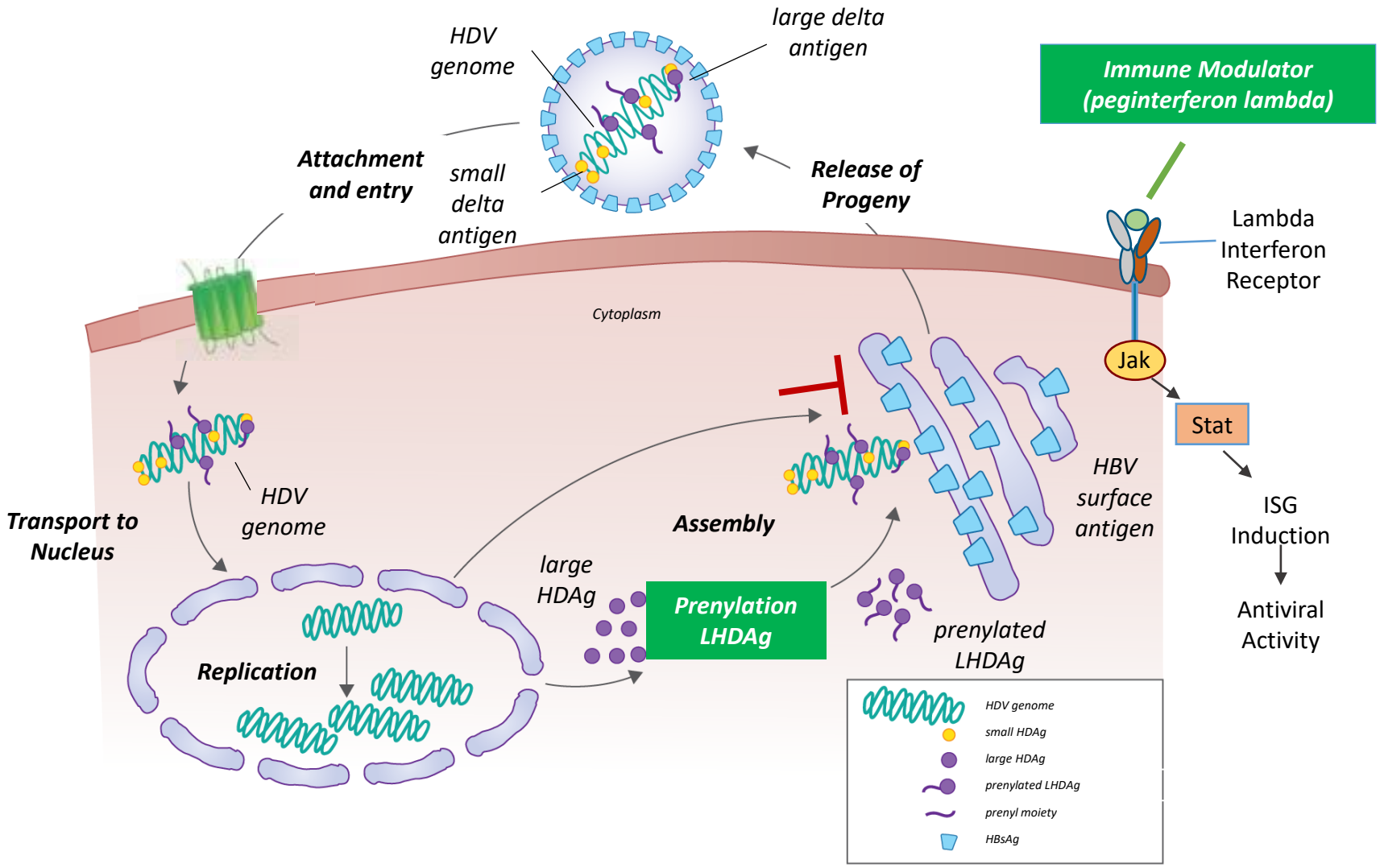
Kim GE, et al. AASLD TLMdX2020. #1028

Algorithm for the Treatment of Hepatitis D in January 2021



Shah PA et al, Gastroenterology Rep 2019 Oct 19;7(6):396-402

HDV Treatments in Development



Courtesy of Dr R Gish

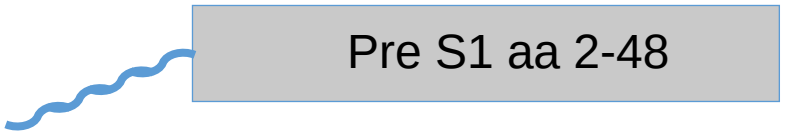
Clinical Trials on Investigative Treatments for Hepatitis D

Therapeutic agents	Publication	Trial phase	Dose and delivery	Study arms and duration	Number of patients	HDV change (log_{10} IU/L)	HDV negative
Pegylated-interferon-λ†	Hamid *et al.* [149]	2	peg-IFN-λ 120/180 mcg SC/wk	peg-IFNλ for 48 weeks	33	NR	3 of 11
Lonafarnib	Koh *et al.* [150]	2	LNF 100/200 mg PO/BID	Lonafarnib for 4 weeks vs placebo	14	100 mg (–0.73) 200 mg (–1.54)	NR
Lonafarnib ritonavir (LOWR-1)	Yurdaydin *et al.* [151]	2	LNF 100/200/300 mg PO/BIDRTV 100 mg PO/BID	LNF ± RTV ± peg-IFN-α for 5-12 weeks	15	LNF 100 mg BID + RTV (–3.2) LNF 100 mg BID + peg-IFN-α (–3.0)	LNF monotherapy (2 of 6)*
Lonafarnib ritonavir pegylated-interferon-α (LOWR-2)†	Yurdaydin *et al.* [152]	2	LNF 25/50/75/100 mg PO/BIDRTV 100 mg PO/BIDpeg-IFN-α 180 mcg SC/wk	LNF + RTV ± peg-IFN-α for 12–24 weeks	58	LNF 25 mg BID + RTV + peg-IFN-α (–5.57)	LNF 25 mg BID + RTV + peg-IFN-α (3 of 5)
Lonafarnib ritonavir (LOWR-3)†	Koh *et al.* [153]	2	LNF 50/75/100 mg PO/dailyRTV 100 mg PO/daily	LNF + RTV for 12–24 weeks	21	LNF 50 mg (–1.93) LNF 75 mg (–1.3) LNF 100 mg (–0.29)	NR
Lonafarnib ritonavir (LOWR-4)†	Wedemeyer *et al.* [154]	2	LNF 50/75/100 mg PO/BID	LNF + RTV for 24 weeks	15	–1.87	NR
Myrcludex B	Bogomolov *et al.* [155]	1b/2a	MB 2 mg SC/daypeg-IFN-α 180 mcg SC/wk	peg-IFN-α for 48 weeks or Myrcludex B ± peg-IFN-α for 24 weeks followed by peg-IFN-α for 24–48 weeks	24	Myrcludex B (–1.67) Myrcludex B + peg-IFN-α (-2.6)	Myrcludex B (2 of 8) Myrcludex B + peg-IFN-α (5 of 7)
Myrcludex B	Wedemeyer *et al.* [156]	2b	MB 2/5/10 mg SC/dayTDF 245 mg PO/day	TDF ± Myrcludex B	120	Myrcludex B 2 mg (–1.7) Myrcludex B 5 mg (–1.6) Myrcludex B 10 mg (–2.7)	NR
Nucleic acid polymer (REP2139)	Bazinet *et al.* [157]	2	REP 500/250 mg IV/weekpeg-IFN-α 180 mcg SC/wk	REP 2139 for 15 weeks followed by peg-IFN-α + REP2139 for 15 weeks followed by peg-IFN-α for 33 weeks	12	–5.34	9 of 12

*Post-treatment result.
†Interim results; peg-IFN-λ, pegylated-interferon-λ; HDV, hepatitis D virus; LNF, lonafarnib; TDF, tenofovir disoproxil fumarate; NR, not reported; RTV, ritonavir; LOWR, LOnfarnib With and without Ritonavir; MB, Myrcludex B; pegylated-interferon-α, peg-IFN-α.

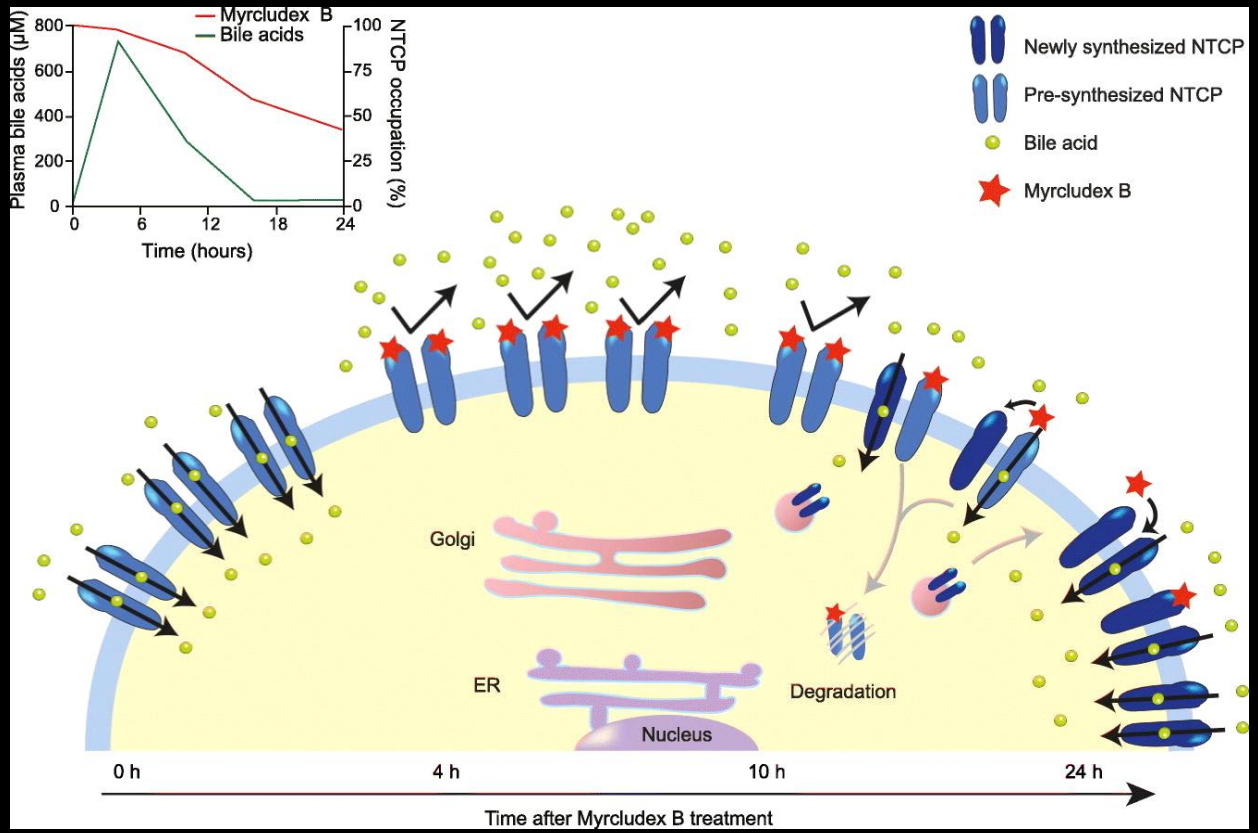
Da B et al. Gastroenterology Report, 7(4), 2019, 231–245

Myrcludex B



- Synthetic 47 amino acid, N-acylated preS1 lipopeptide
- Targets Na-taurocholate cotransporting polypeptide (NTCP)
  - Bile acid receptor on the surface of hepatocytes that acts as the HBV receptor via attachment of preS1 surface protein (discovered 2012)
- Blocks receptor functions of NTCP and HBV/HDV virus entry
- Administered subcutaneously once daily

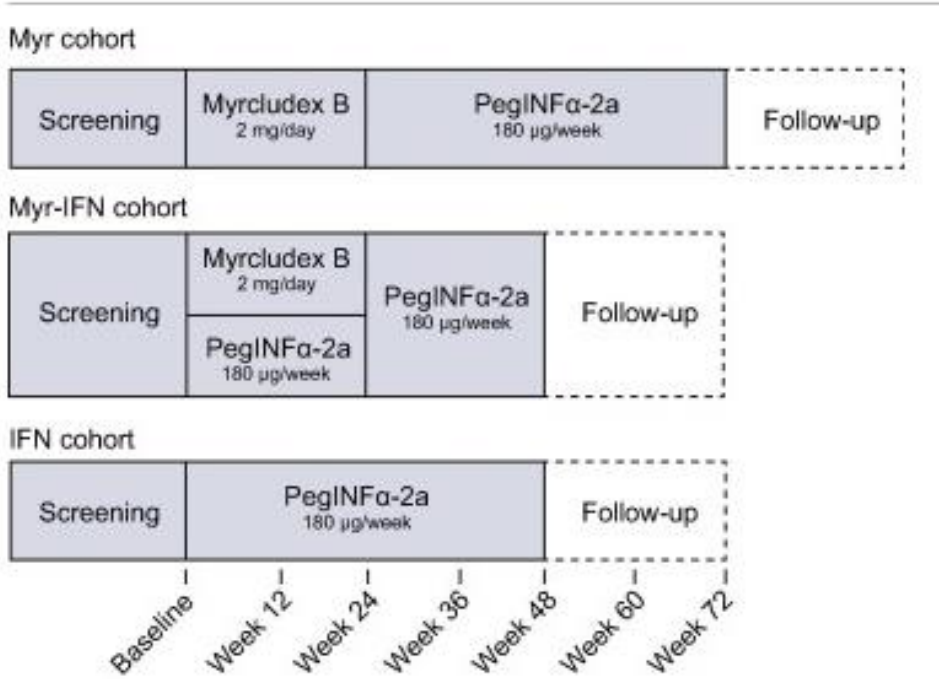
Courtesy of Dr Robert Gish

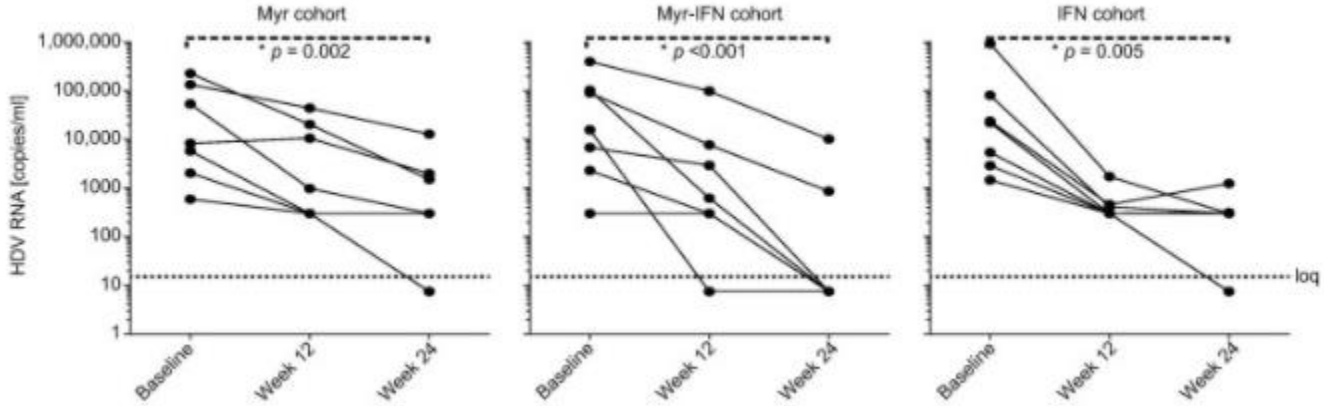


Donkers JM et al

JHEPReport 2019 1278-285DOI: (10.1016/j.jhepr.2019.07.006)

Phase Ib/IIa Study of Myrcludex



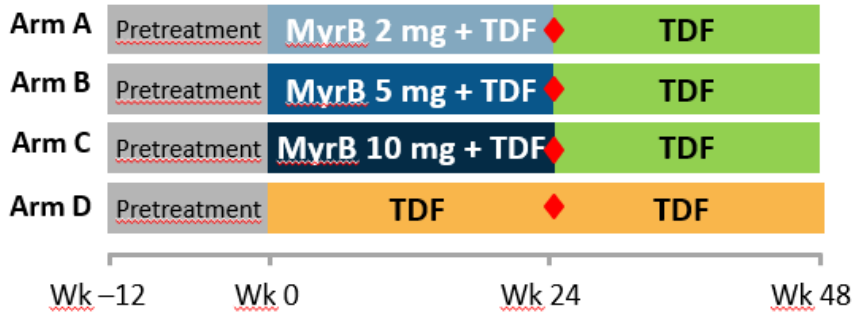


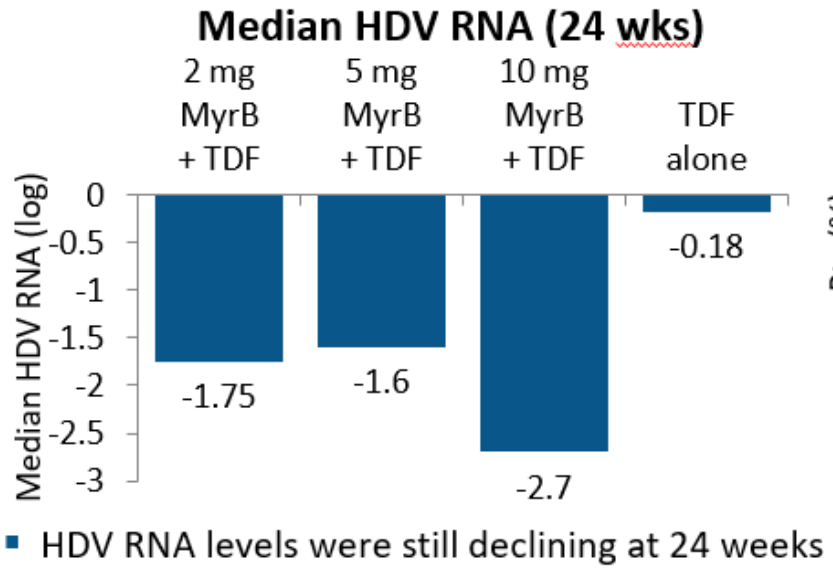
Mean reduction
1.67 log at wk 24
with Myrcludex 2 mg/d

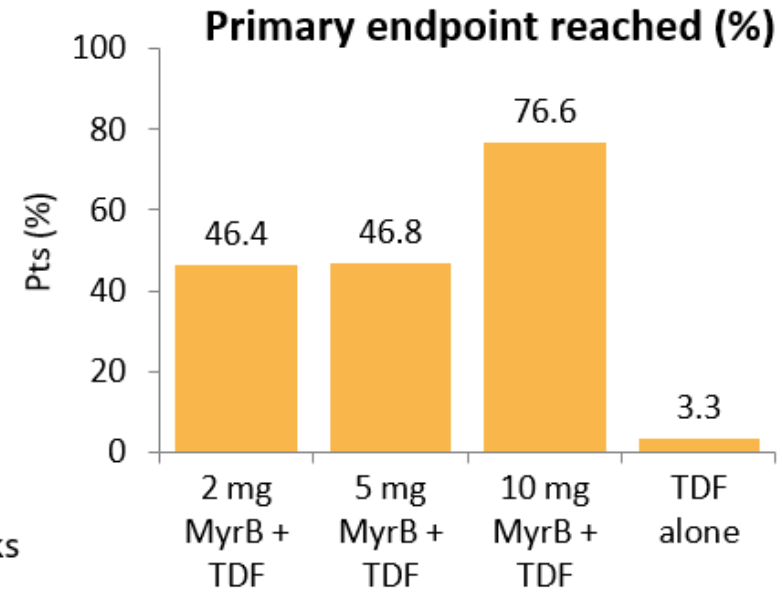
HDV RNA decreased at week 24 ⩾1 log in six of seven patients of the Myr cohort, and became undetectable in two patients during treatment with Myrcludex B alone

Bogomolov P et al, J Hepatology 2016;65:490-498

Final results of a multicenter, open-label Phase 2b trial to assess safety and efficacy of Myrcludex B + TDF in patients with chronic HBV/HDV co-infection

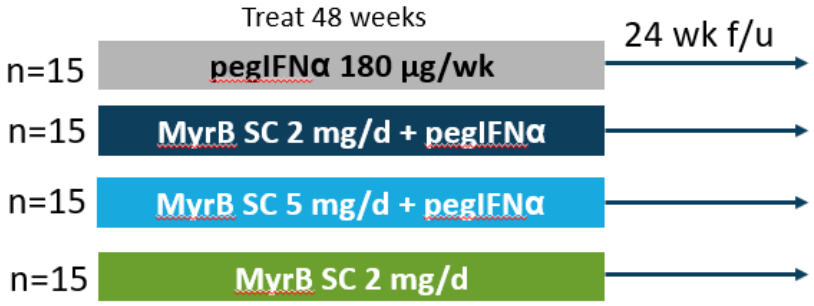




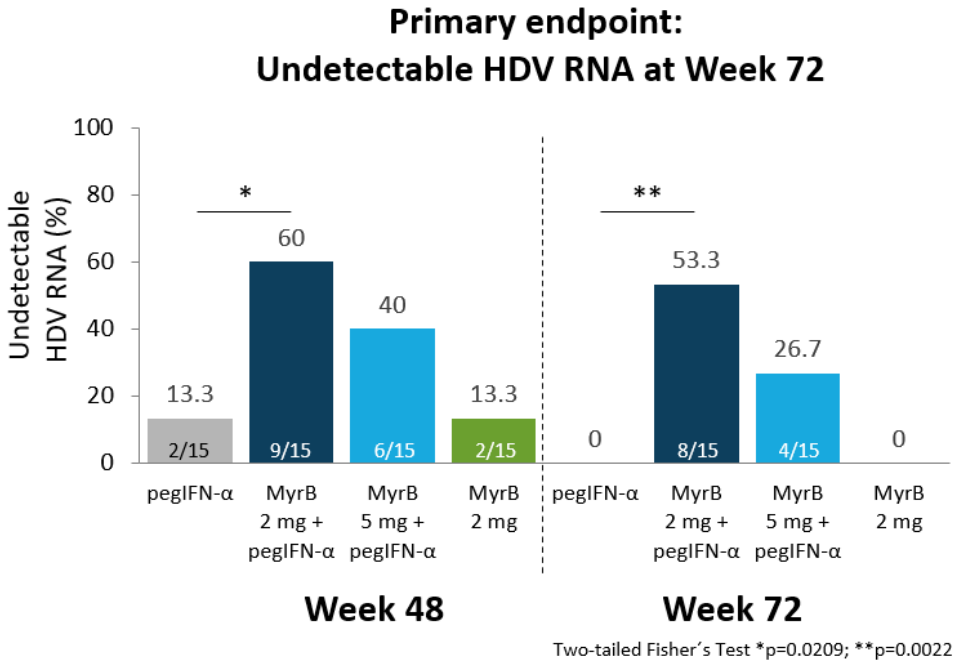


Wedemeyer H, et al. EASL 2018, Paris. #GS-005

Multicenter, open-label Phase 2 clinical trial (MYR203) to assess safety and efficacy of bulevirtide (myrcludex B) with pegIFN-α2a in patients with chronic HBV/HDV co-infection

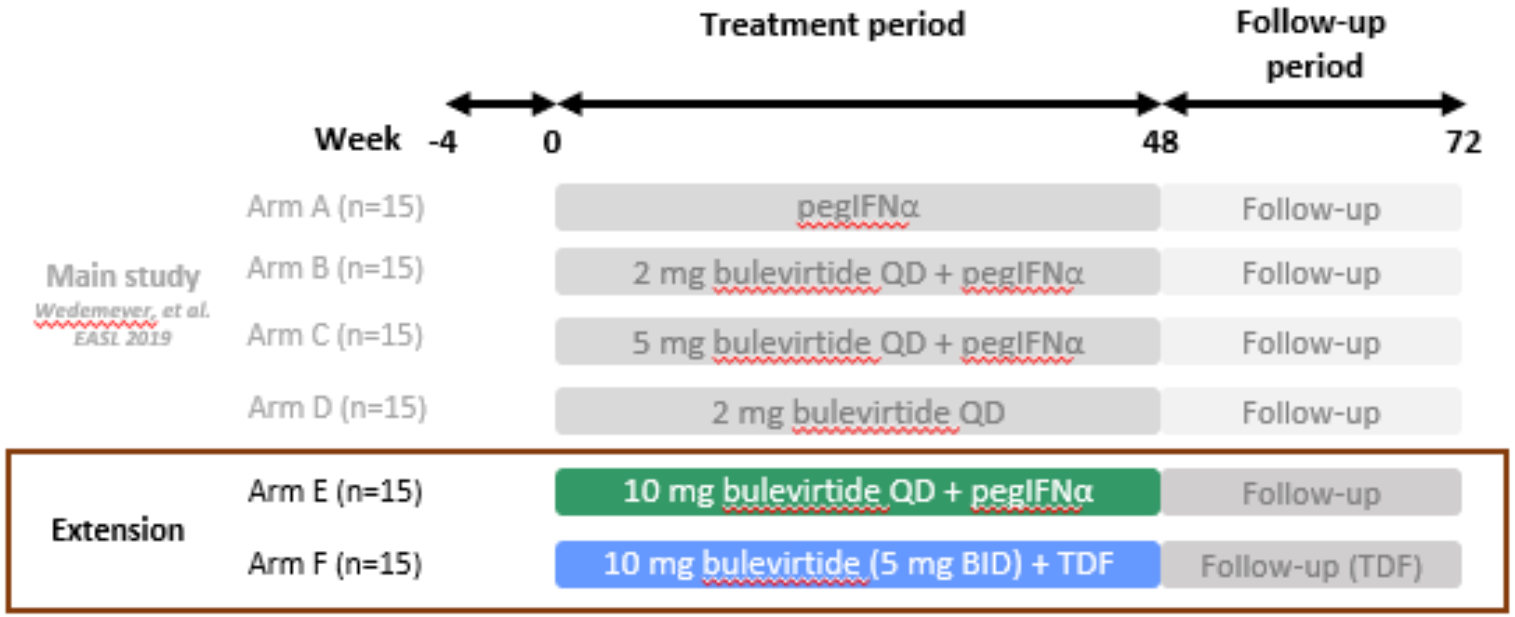


Median serum HDV RNA log reduction	Week 48	Week 72
pegIFN-α	-1.30	-0.26
MyrB 2 mg + pegIFN-α	-4.81	-4.04
MyrB 5 mg + pegIFN-α	-5.59	-1.48
MyrB 2 mg	-2.84	-1.08



Wedemeyer H, et al. EASL 2019, Vienna, Austria. #GS-13

48 Weeks of High Dose (10 mg) Bulevirtide With Nuc or With Peginterferon alfa-2a in Patients With Chronic HBV/HDV Co-infection (MYR203 Extension Study)



Key inclusion criteria

- HBsAg+
- Anti-HDAg+ for ≥6 months
- Positive HDV serum RNA
- HBeAg+ or HBeAg-
- ALT ≥1 ULN but ≤10 ULN

Primary Endpoint

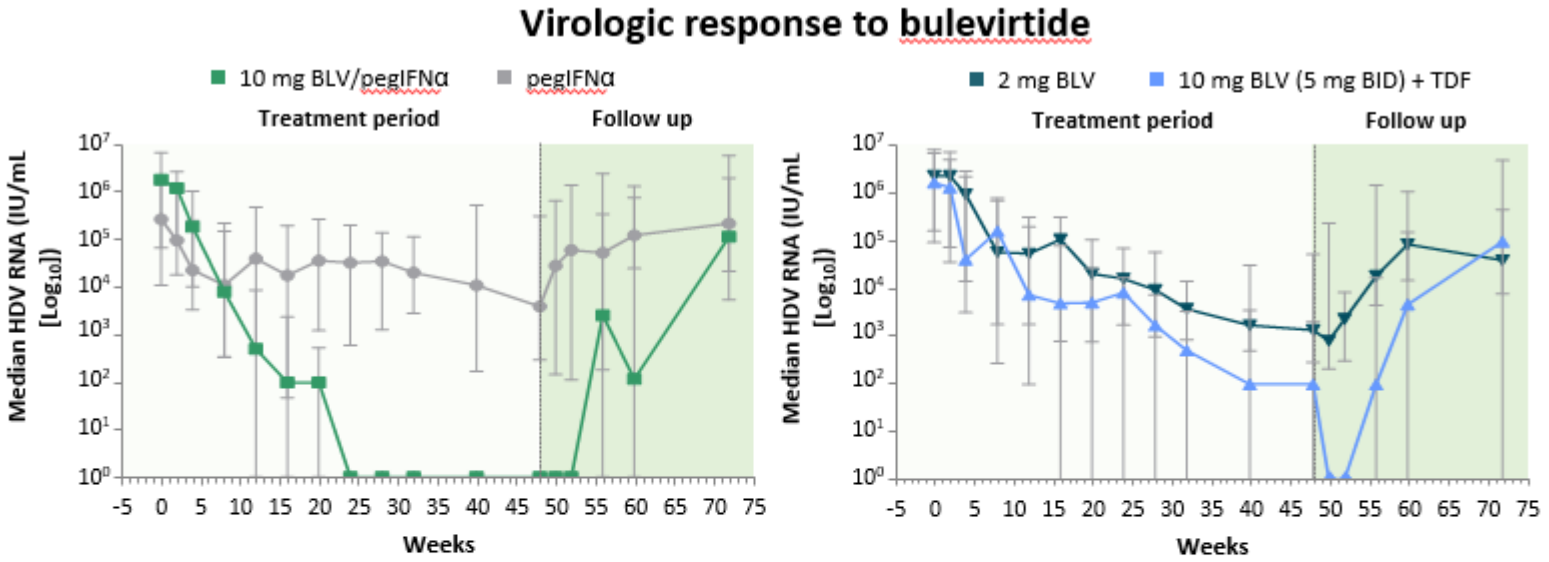
- Undetectable HDV serum RNA at Week 72 (24 weeks after secession of therapy)

Secondary Endpoints

- Undetectable HDV serum RNA Week 48
- ALT normalization at Week 48 and Week 72
- HBsAg decline (>1 Log_{10} IU/mL reduction)

Wedemeyer H, et al. EASL dILC2020. #AS072

48 Weeks of High Dose (10 mg) Bulevirtide With Nuc or With Peginterferon alfa-2a in Patients With Chronic HBV/HDV Co-infection (MYR203 Extension Study)



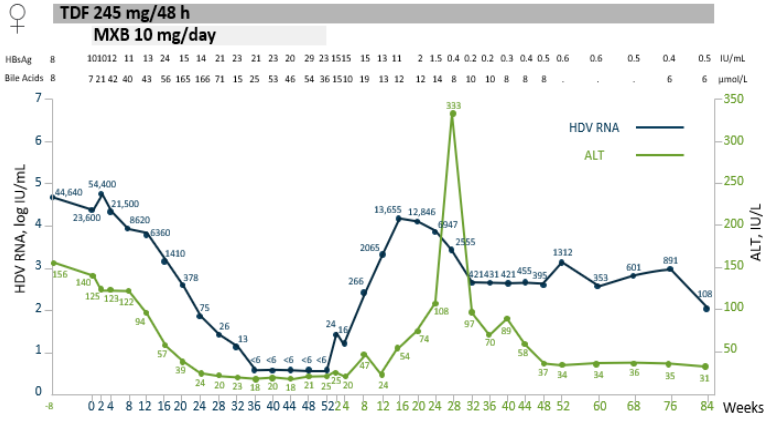
Virological response at Week 72	Primary endpoint: Undetectable HDV RNA	>2Log$_{10}$ reduction or undetectable HDV RNA
pegIFNα	0.0%	0.0%
2 mg BLV + pegIFNα	53.3%	73.3%
5 mg BLV + pegIFNα	26.7%	46.7%
10 mg BLV + pegIFNα	6.7%	33.3%

Virological response at Week 72	Primary endpoint: Undetectable HDV RNA	>2Log$_{10}$ reduction or undetectable HDV RNA
2 mg BLV	6.7%	33.3%
10 mg BLV + TDF	33.3%	46.7%

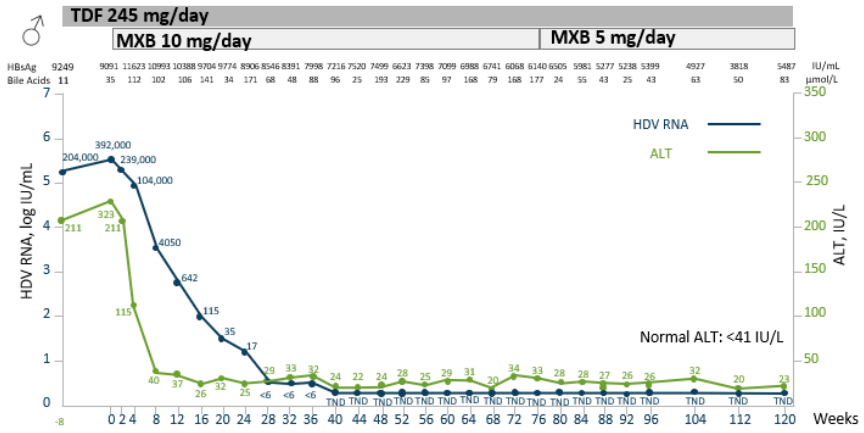
HBsAg response (>1 Log$_{10}$ decline or negativation)	Week 48	Week 72
PEG-IFNα	0.0%	0.0%
2 mg BLV + PEG-IFNα	46.7%	40.0%
5 mg BLV + PEG-IFNα	20.0%	13.3%
10 mg BLV + PEG-IFNα	6.7%	13.3%

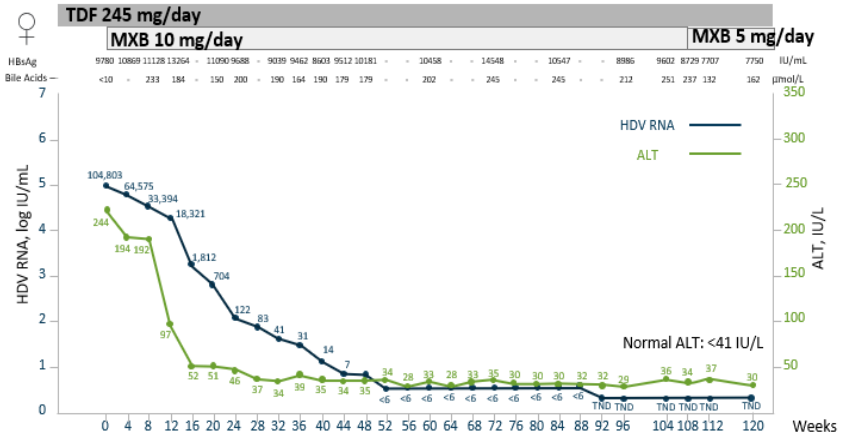
Wedemeyer H et al. EASL dILC2020. #AS072

Myrcludex Monotherapy in Compensated Cirrhotics With Hepatitis Delta: Safety and Effectiveness Beyond 2 Years of Treatment in a Real-Life Setting



1 patient with recurrent viremia after stopping therapy





2 patients with recurrent viremia who remained on therapy with
Persistent viral suppression and normalization of ALT
Improved clinical outcomes noted

Loglio A, et al. AASLD TLMdX2020. #1024

HEPATITIS B FOUNDATION

HEP B BLOG

HDV, Hepatitis B Research, Hepatitis Delta (HDV), News

New Hepatitis Delta Treatment Approved by European Commission

September 2, 2020 | hepbtalk

New Drug Approved for Treatment of Hepatitis Delta in Europe

A new drug to treat hepatitis delta has now been approved by the European Commission! The drug is called bulevirtide and will be marketed under the brand name Hepcludex. It was previously known at Myrcludex B. This approval follows a quarter century of research and development and is the first drug specifically for hepatitis delta approved in Europe. Due to the high prevalence of the hepatitis delta virus in Russia and the former Soviet Union, it has been approved for use there since the end of 2019, under the name Myrcludex. The European Medicines Agency recommended the drug for approval by the Commission at the end of May 2020 (German Center for Infection Research, 2020).

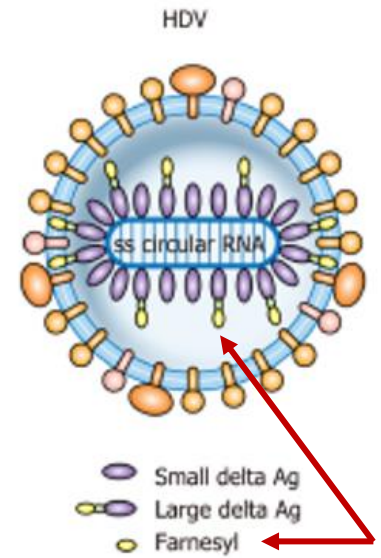
How Does It Work?

Hepcludex, developed by university researchers in Heidelberg, Germany, works as an entry inhibitor – that is, it prevents hepatitis delta virus (HDV) cells, and the hepatitis B virus (HBV) cells upon which HDV depends, from entering healthy liver cells. Both HDV and HBV cells are able to replicate and thrive exclusively in the liver because they need the bile acid transporter NTCP in order to do so. This transporter is the avenue through which HDV is received into the liver cell. Hepcludex works by blocking this reception process, so that the virus does not continue to infect healthy liver cells (German Center for Infection Research, 2020). The currently infected cells either die or are destroyed by the immune system.

Lonafarnib for HDV

FIRST ORAL AGENT IN DEVELOPMENT FOR HDV

- Prenylation inhibitor – prenylation is embedded in the HDV life cycle
- Well-characterized in patients
  - > 2,000 patients dosed in oncology program by Merck (Schering)
  - > 90 children dosed in Progeria program by Boston Children's Hospital
  - > 170 patients dosed in HDV program
  - Longest duration of dosing > 10 years
- Most common experienced AEs are GI related (class effect)
- Orphan Designation U.S. and EU
- FDA Breakthrough Therapy Designation
- EMA PRIME Designation

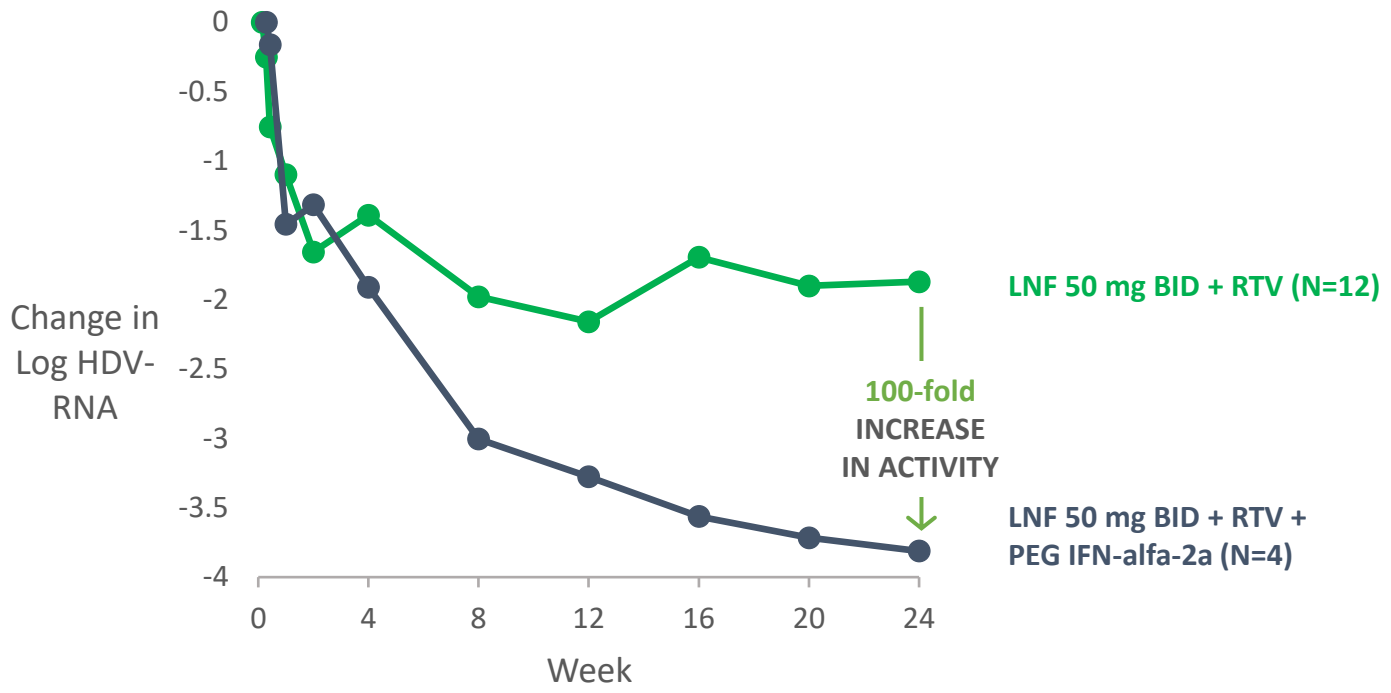


Most prenylated proteins are CAAX proteins, for which prenylation is initiated by the attachment of a 15-carbon (farnesyl) or a 20-carbon (geranylgeranyl) isoprenoid lipid to the Cys residue by protein farnesyltransferase (FTase) or protein geranlygeranyltransferase I (GGTase I), respectively. The enzymatic reaction is termed farnesylation if it involves the farnesyl isoprenoid, or geranylgeranylation if it involves the geranylgeranyl isoprenoid.

*Mei Wang & Patrick J. Casey
Nature Reviews Molecular Cell Biology **volume 17**, pages110–122(2016)

Adapted from Dr Robert Gish

Lonafarnib Phase 2 Data



COMPOSITE ENDPOINT

≥ 2 log Decline
HDV-RNA
+
ALT Normalization

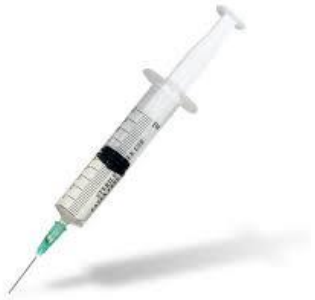
29%

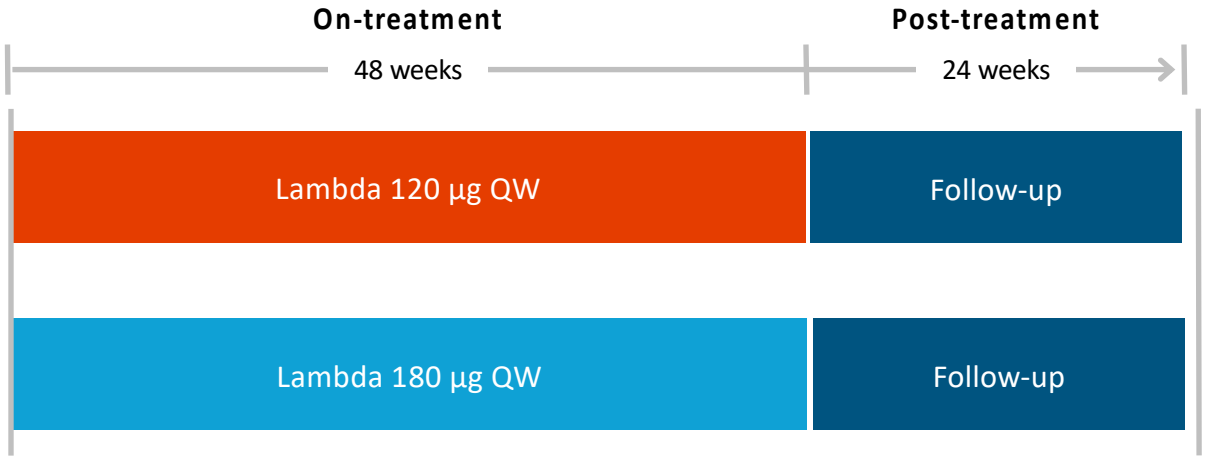
63%

Yurdaydin et al, *J Hepatology* 2018, Phase 2 LOWR 2 Study, Abstract #PS-161

LIMT HDV “MONO”: Phase 2 Study

Lambda Interferon MonoTherapy Study in HDV



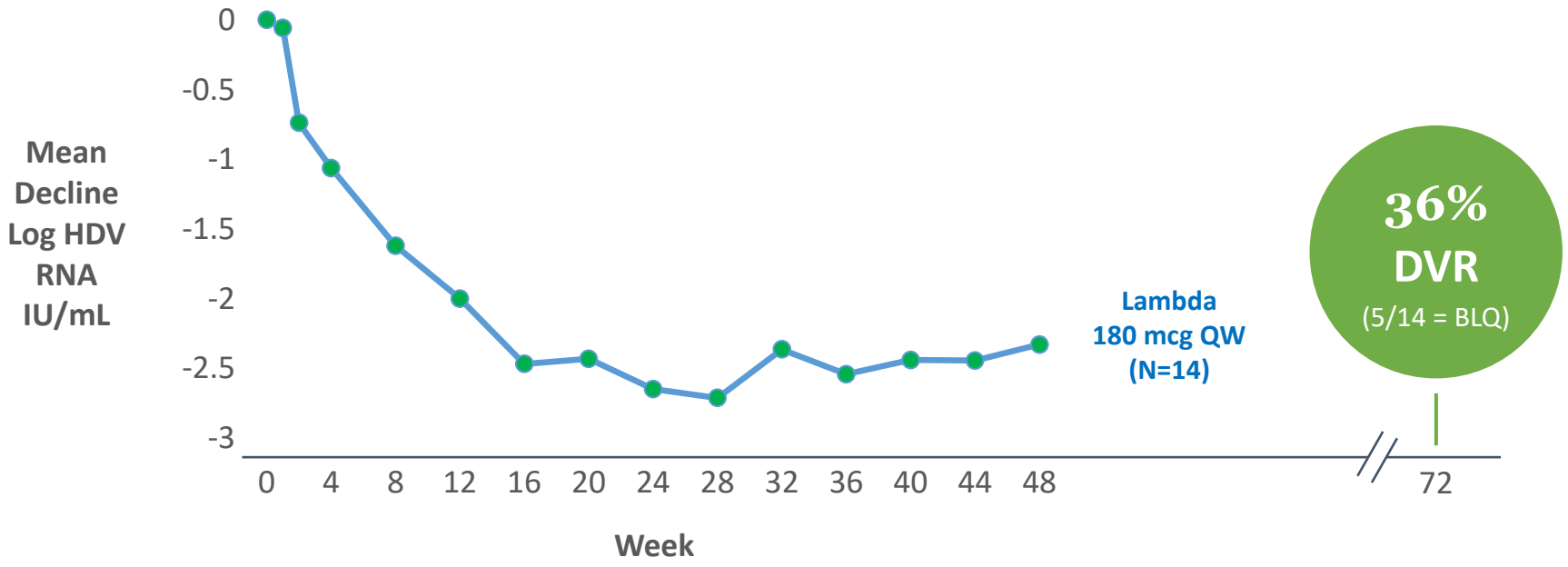


- Randomized, open-label study of Lambda 120 and 180 µg, weekly SC injections for 48 weeks in HDV patients
- Dose reductions permitted
- Major inclusion criteria: HDV RNA (+) by qPCR (BLQ 14 IU/mL)*, ULN<ALT<10×ULN, compensated liver disease
- Tenofovir or entecavir were started at baseline (BL)

*Robogene® 2.0, BLQ = below limit of quantification

LIMT: Phase 2 Lambda Monotherapy Study

36% DURABLE VIROLOGIC RESPONSE (DVR) ("MVR") WITH LAMBDA

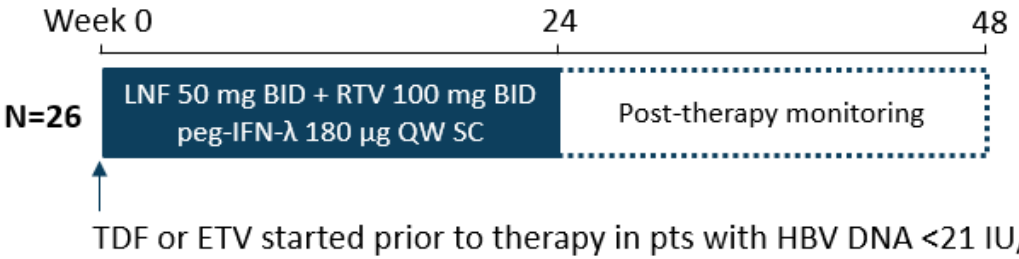


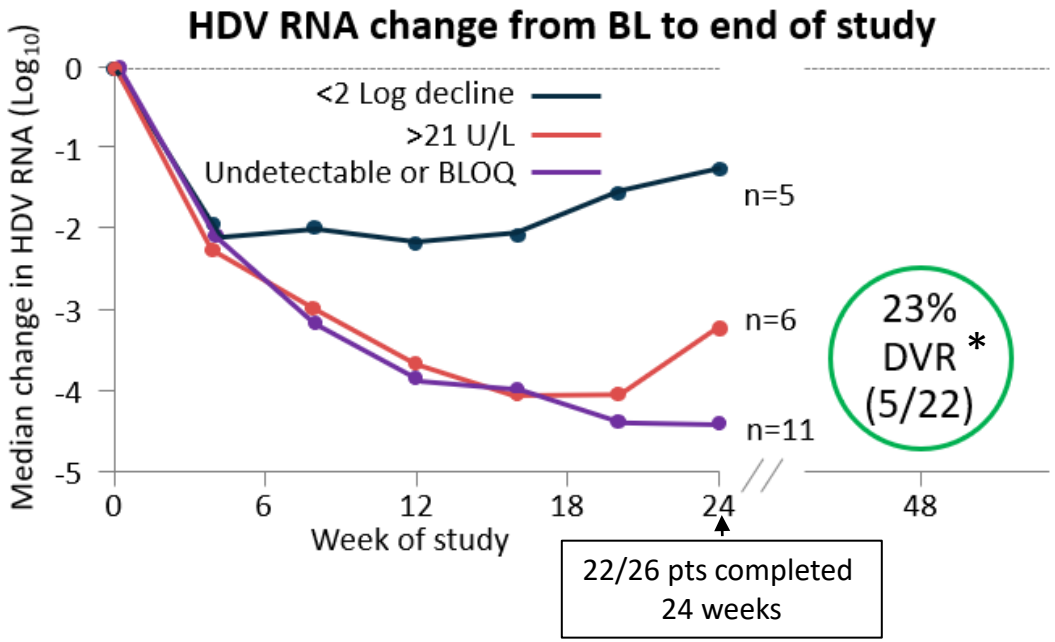
DVR = below the limit of quantification (BLQ) at 24 weeks post-treatment

Robogene® 2.0 HDV RNA PCR assay, LOQ = 14 IU/mL; LOD = 6 IU/mL

Etzion et al, EASL 2019; dose reductions allowed

A Phase 2 study of Peginterferon Lambda, Lonafarnib, and Ritonavir for 24 Weeks: End-of-Treatment Results From the LIFT HDV Study





End of therapy:

- 77% of patients achieved >2 Log HDV RNA decline after 24 weeks of therapy
- 50% had undetectable or BLOQ HDV RNA after 24 weeks of therapy

End of follow-up:

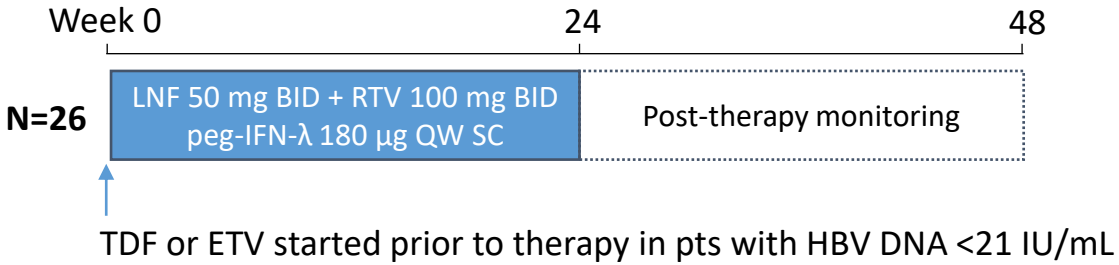
- 5 (23%) maintained undetectable or BLOQ HDV RNA
- 3 (14%) maintained undetectable HDV RNA
- 11/20 (55%) patients demonstrated improvement in HAI

- GI side effects common

*DVR = Durable Virologic Response

Koh C, et al. AASLD TLMdX2020. #LO8

A Phase 2 study of peginterferon lambda, lonafarnib, and ritonavir for 24 weeks: End-of-treatment results from the LIFT HDV study



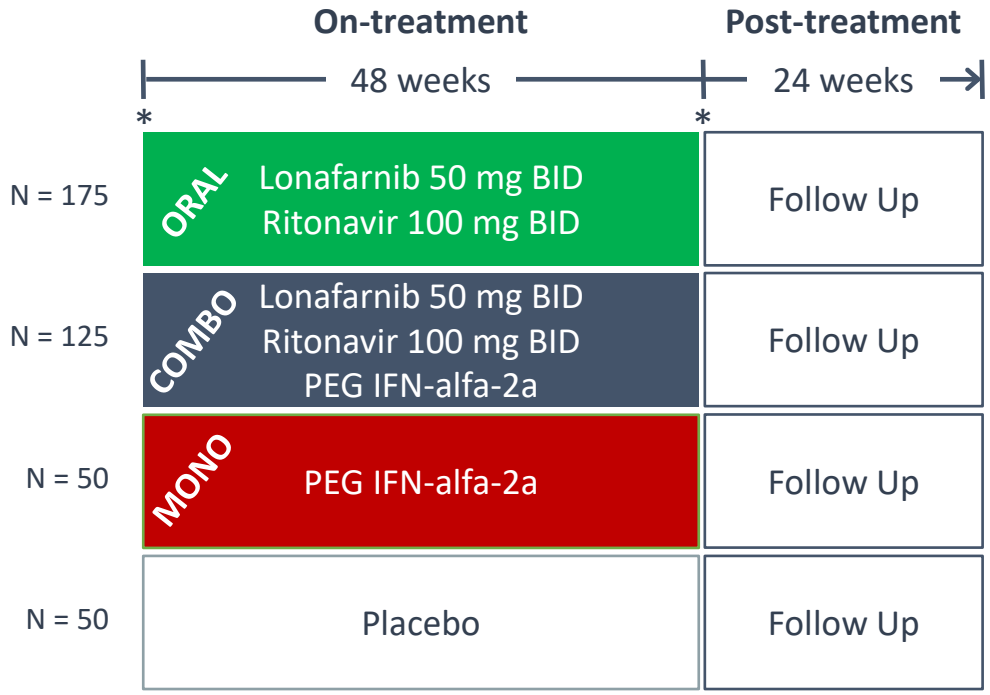
Treatment response at 12 and 24 weeks

Treatment duration	n	Mean change in Log_{10} HDV RNA (IU/mL)	95% CI	p-value
12 weeks	26	3.36	(2.86–3.85)	<0.0001
24 weeks	22	3.23	(2.94–4.49)	<0.0001

- **Most common AEs**
  - Diarrhea – 100%
  - Nausea – 69%
  - GERD – 65%
  - Abdominal bloating – 63%
  - Anorexia – 46%
  - Fatigue – 42%
  - Weight loss – 31%
  - Anemia – 23%
  - Hyperbilirubinemia – 19%
- **2 dose reductions** (1 x anemia, 1 x hyperbilirubinemia)
- **5 discontinuations** (4 x hyperbilirubinemia, 1 x ascites)

Koh C, et al. AASLD TLMdX2020. #LO8

D-LIVR Phase 3 Global Study



Primary Endpoint at Week 48

≥ 2 log decline in HDV RNA

+

Normalization of ALT

Secondary Endpoint at Week 48

Histologic improvement

Improvement of fibrosis

* biopsy

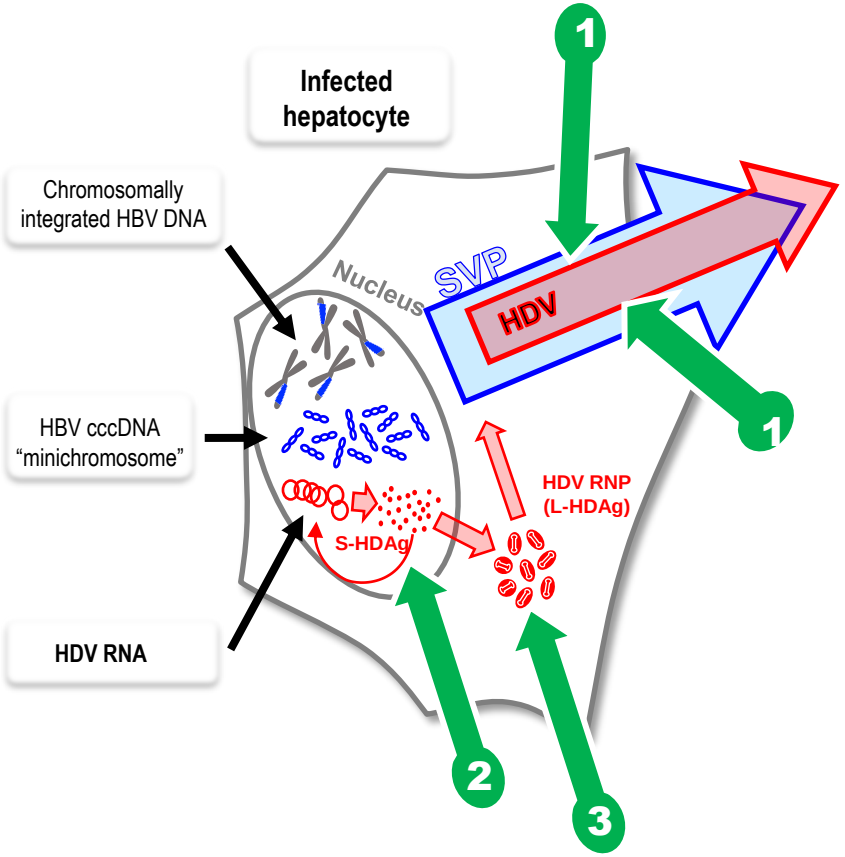
All patients will be maintained on background HBV nucleoside therapy.

Superiority over PEG IFN-alfa-2a not required.

Courtesy of Dr. Robert Gish

Anti-HDV Effects of REP 2139

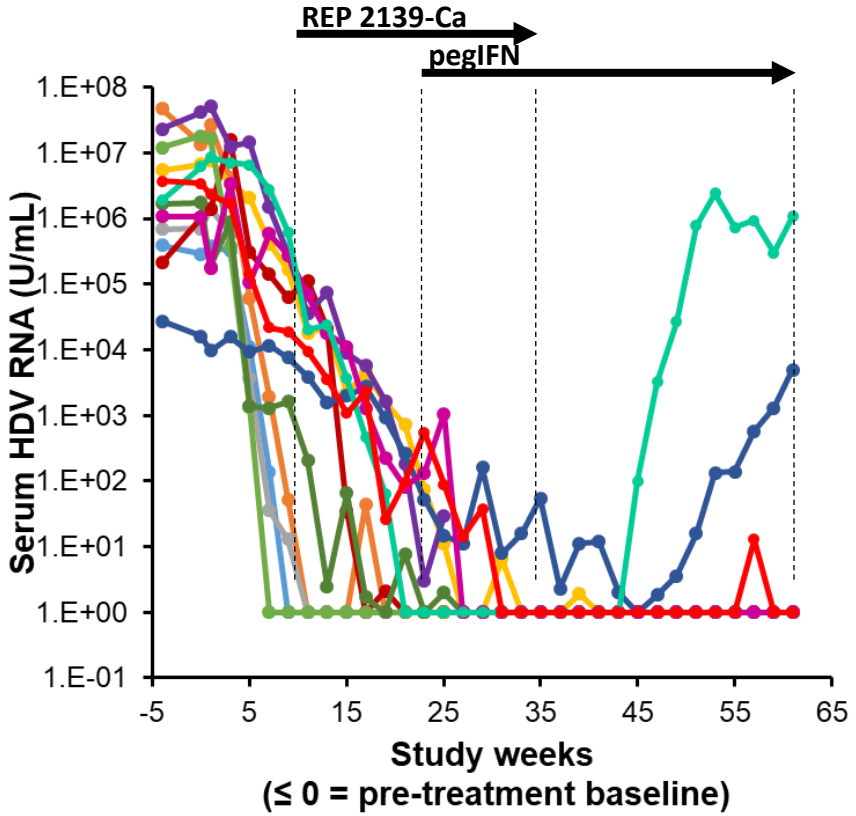
1. **Inhibition of HBV SVP assembly / secretion and HDV envelopment**
   - Allows host mediated clearance of HBsAg / HDV
   - Blocks release of HDV
2. **Interaction with S-HDAg**
   - Potential upstream inhibition of HDV RNA synthesis
3. **Interaction with L-HDAg**
   - Potential upstream inhibition of HDV RNP assembly



Courtesy of Dr Robert Gish

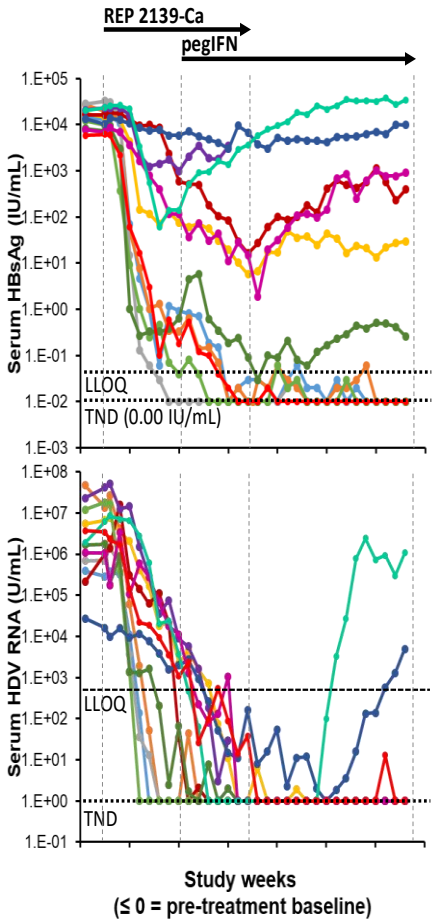
REP 301: REP 2139-Ca + pegIFN in HBV / HDV co-infection

Universal clearance of HDV RNA during therapy driven by multiple antiviral mechanisms



Bazinet et al., Lancet Gastro Hepatol 2017; 2: 877-889

Antiviral effects during REP 2139-Ca / pegIFN



HBsAg clearance prior to pegIFN

Universal HDV RNA response

Target not detected in 11/12 participants during therapy

Even in participants with moderate HBsAg response

Likely due to direct effects against HDV replication

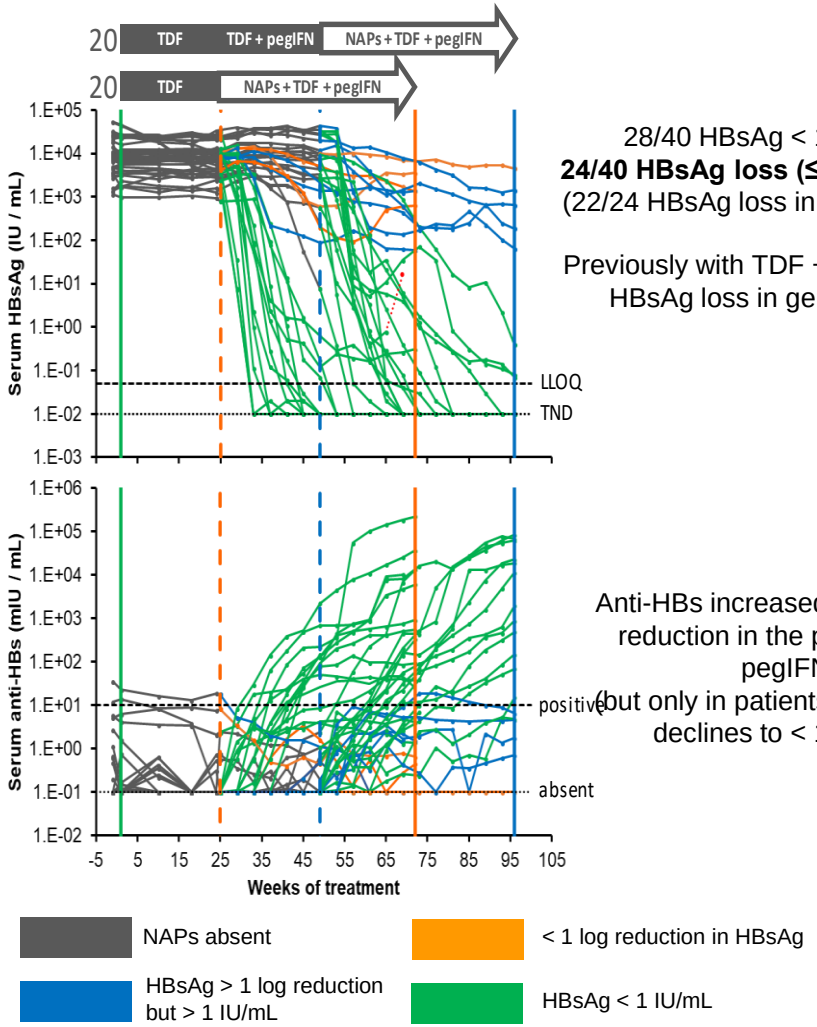
Completed treatment and 3.5 years of follow-up		**11**
Clinical response	Normal ALT	8/11 (73%)
	Normal / declining liver median stiffness	7/11 (64%)
HBsAg response	< 1 IU/ml	6/11 (55%)
	≤ LLOQ (0.05 IU/mL)	5/11 (42%)
	Seroconversion	4/11 (36%)
HDV RNA response	> 2 log_{10} reduction from baseline	9/11 (82%)*
	TND	7/11 (64%)

***2 participants maintaining 2.67 and 2.12 log_{10} HDV RNA reduction from baseline at 3.5 years follow-up did not maintain normal liver function during follow-up.**

Functional cure of HDV at 3.5 years of follow-up (HDV RNA TND, ALT normal)		**7**
HBV DNA response	≤ 2000 IU/mL	7/7 (100%)
	Target not detected (TND)	5/7 (71%)
HBV virologic response	Virologic control HBV (HBV DNA ≤ 2000 IU/mL, normal ALT)	3/7 (43%)
	Functional cure HBV (HBsAg < LLOQ, HBV DNA TND, normal ALT)	4/7 (57%)
	HBV clinical benefit, no therapy required (Low risk of progression, reduced risk of HCC)	7/7 (100%)
On-therapy flare	Asymptomatic transaminase flare while HBsAg ≤ 1IU/mL	7/7 (100%)

Bazinet et al., Lancet Gastro & Hepatol 2017
Bazinet et al., Hepatology 2019

Antiviral effects during TDF / REP 2139/ pegIFN



28/40 HBsAg < 1 IU/mL
24/40 HBsAg loss (≤ 0.05 IU/mL)
(22/24 HBsAg loss in genotype D)

Previously with TDF + pegIFN: no HBsAg loss in genotype D

Anti-HBs increased with HBsAg reduction in the presence of pegIFN
(but only in patients with HBsAg declines to < 1 IU/mL)

Completed treatment and ≥ 24 weeks of follow-up		**36 (32 completed 48 weeks of follow-up)**
Clinical response	Normal ALT	89%
	Normal liver median stiffness	56%
HBsAg response	< 1000 IU/mL	72%
	< 1 IU/ml	50%
	≤ LLOQ (0.05 IU/mL)	42%
	Seroconversion	53%
HBV DNA response	≤ 2000 IU/mL	78%
	Target not detected (TND)	47%
Virologic response	Virologic control (Inactive HBV) (HBV DNA ≤ 2000 IU/mL, normal ALT)	39%
	Functional cure (HBsAg < LLOQ, HBV DNA TND, normal ALT)	39%
	Clinical benefit, no therapy required (Low risk of progression, reduced risk of HCC)	78%

Bazinet et al., Gastroenterology 2020
Marcellin et al., Gastroenterology 2016

REP 301-LTF: Long Term Outcomes from REP 301 Study

11 REP 301 participants completed therapy

↓

3.5 year follow-up in the REP 301-LTF study

↓

7/11 with functional cure of HDV
(HDV RNA target not detected, normal ALT)

3/7 with virologic control of HBV

4/7 with functional cure of HBV
All with associated with transaminase flares while HBsAg < 1 IU/mL

↓

- HBsAg < 0.005 IU/mL maintained in the absence of HBsAg immunocomplexes
- HBV pgRNA target not detected
- HBcrAg < LLOQ

Bazinet et al., Hepatol Comm. 2020 epub Nov 13

Conclusions

- HDV is a major worldwide pathogen
- High risk of liver-related morbidity and mortality
- HBsAg carriers, especially those at high risk, should be screened
- Anti-HDV (HDAb) is the screening test of choice; must confirm with HCV RNA assay
- Treatment with PEG IFN for 1 year yields about 25% SVR; late relapse can occur
- EU action on Myrcludex B (now Hepcludex) is a major development in the field
- Evidence suggests that long term therapy may be needed – maintenance?
- Lonafarnib (oral agent) in phase 3 with PEG IFN
- Results with NAPS warrant further study