10TH ANNUAL

DIGESTIVE DISEASES: NEW ADVANCES

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Hyatt Regency Jersey City On The Hudson

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Hepatitis D

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Disclosures

Abbvie: Consultant; Aligos: Consultant; Altimmune: Research Grant; Antios: Consultant; Arrowhead:Research Grant; Bristol-Myers Squibb: Research Grant; Drug Farm: Consultant; Durect: Consultant, Stockholder; Eiger: Research Grant Consultant; Enanta:; Gilead: Consultant, Research Grant; HepQuant: Consultant; Inventiva: Consultant; Mallinckrodt: Novo Nordisk: Research Grant; Ultragenyx: Research Grant

Off lablel use: Lonafarnib, PEG Lambda, Bulivertide

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

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.

HBsAg = hepatitis B surface antigen.

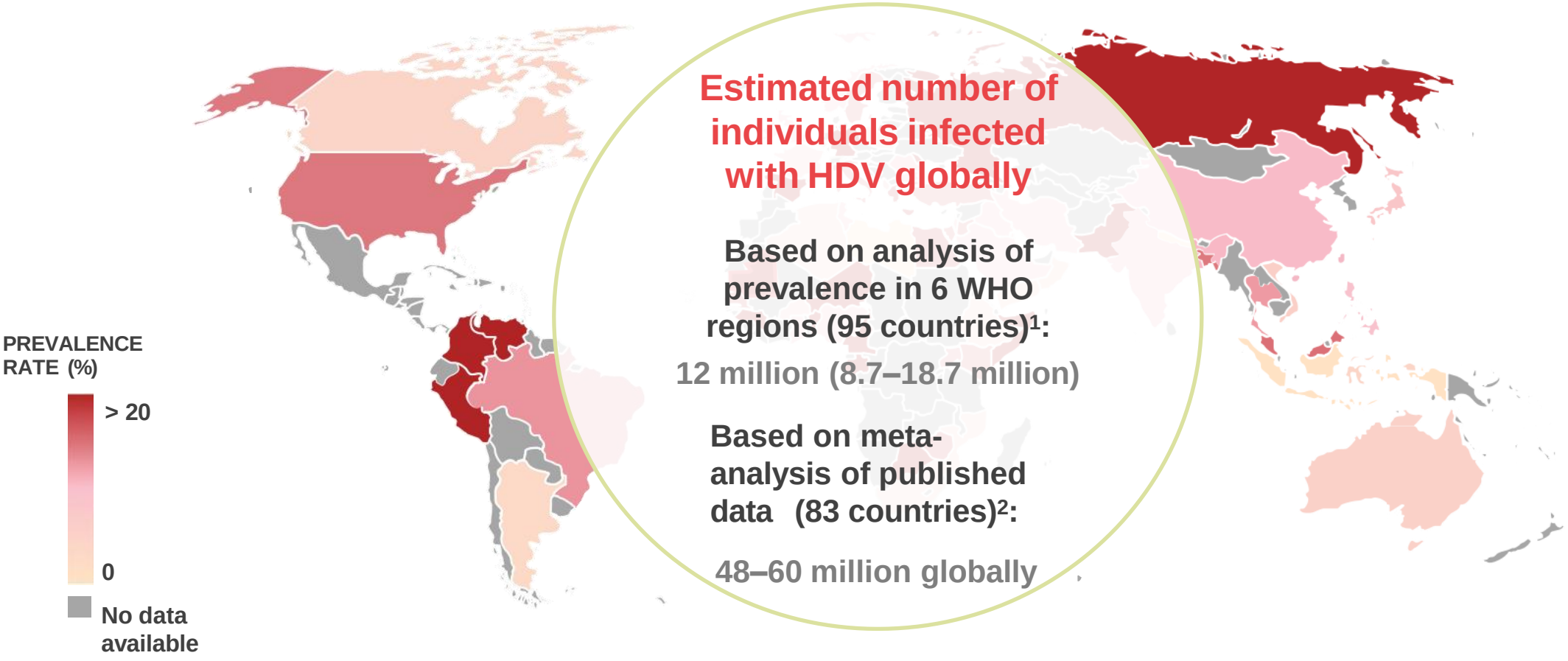
Noureddin M, Gish R. *Curr Gastroenterol Rep.* 2014(1); 16: 365.

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.

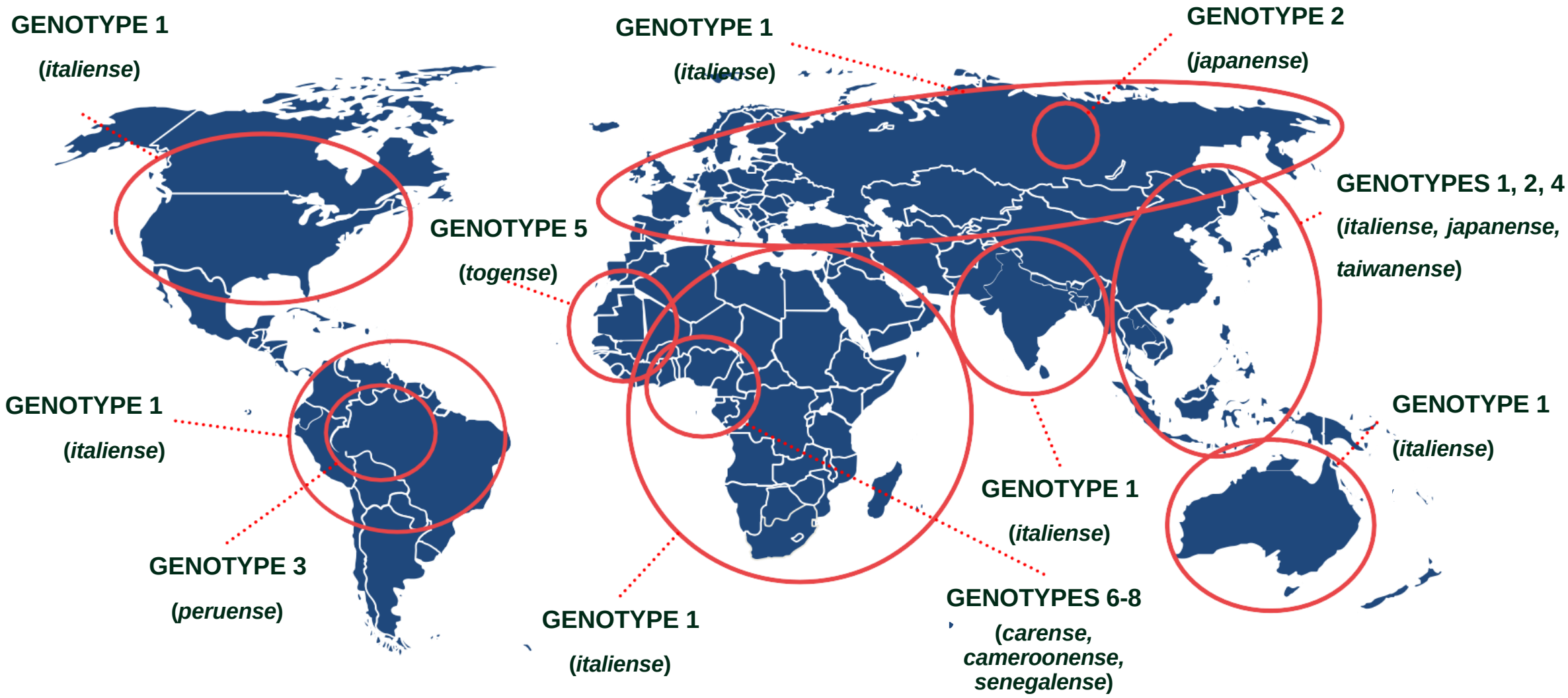
Approximately 4.5%–13% of HBsAg-Positive Carriers Are Coinfected With HDV



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.

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

How About HDV Seroprevalence in the United States?

Population	Years	No. HBsAg+	Prevalence
Northern California[1]	1989–2007	1191	8%
Veterans Affairs[2]	1999–2013	2175	3.4%
Midwest[3]	2012–2016	1007	3.3%
Baltimore IDU[4]	2005–2006	86	11%
NHANES[5]	2011–2016	113	42%

Anti-HDV prevalence range:

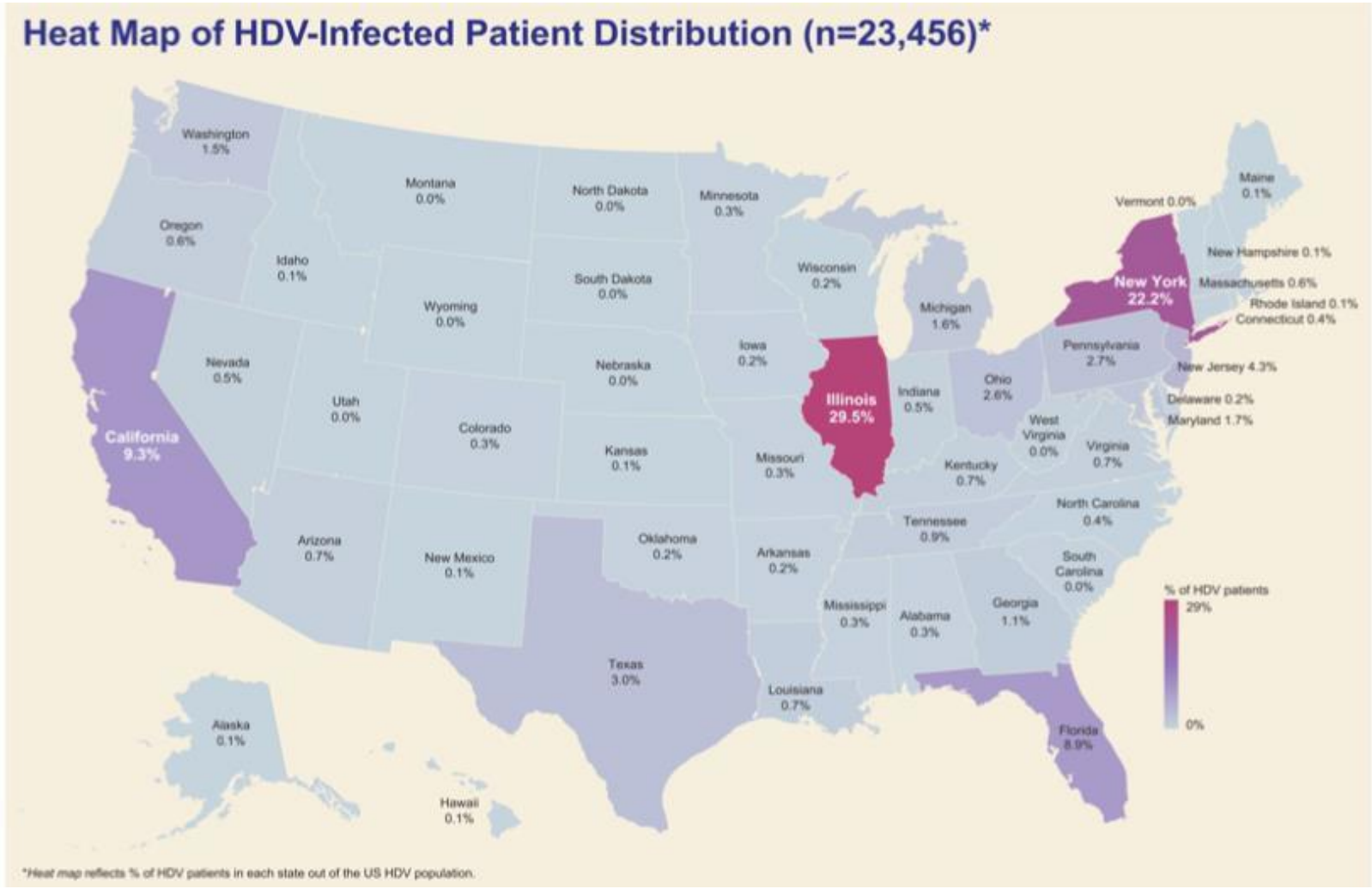
3%–8% of HBsAg-positive persons

Testing for HDV is low among patients with HBV in the United States

Approximately 1 in 12 patients with chronic HBV were screened for HDV

[1]Gish et al. *J Gastroenterol Hepatol*. 2013; [2]Kushner T et al. *J Hepatology* 2015; [3]Safaie et al. *Virus Research* 2018; [4]Kucirka L, *JID*. 2010; [5]Patel E, *CID*. 2019

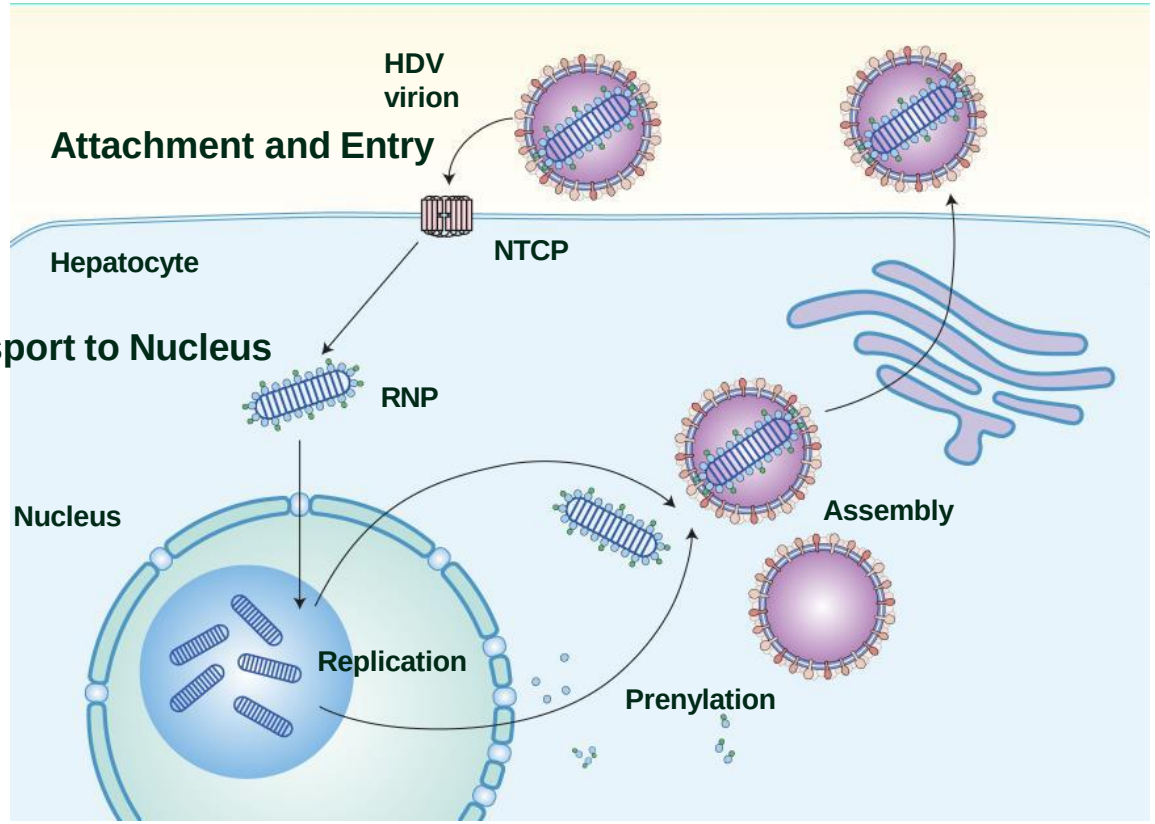
Prevalence of HDV in the US Based on All-Payer Claims Databases



- ***At the state level, the greatest proportion of HDV-infected patients was identified in Illinois (29.5%), followed by New York (22.2%) and California (9.3%), among 23,456 HDV-infected adults**
- **Gish R et al. The Liver Meeting 2021, Abstract 698.**

The HDV Life Cycle

HDV replication cycle[1]



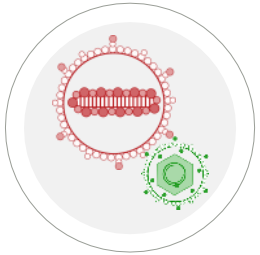
Unlike other RNA viruses, HDV does not encode its own polymerase, but uses the host RNA polymerase II for replication, which normally copies double-stranded DNA templates

HDV has the unique ability to redirect this cellular enzyme to transcribe the HDV RNA genome

NTCP = human sodium taurocholate cotransporting polypeptide; RNA= ribonucleic acid; RNP = ribonucleoprotein; RT = reverse transcriptase.

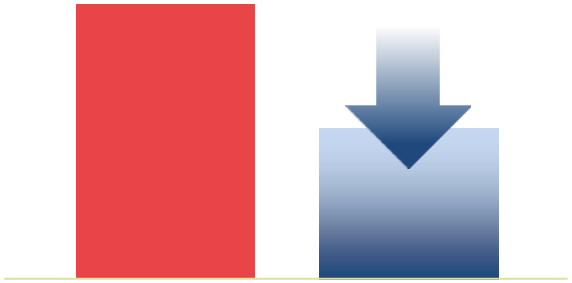
1. Adapted from Gilman C et al. *World J Gastroenterol*. 2019; 25(32): 4580–4597.

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



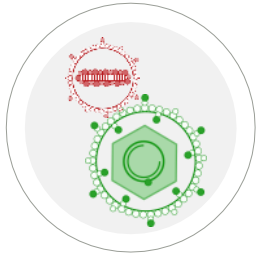
Common

Predominant HDV replication, suppressed HBV replication



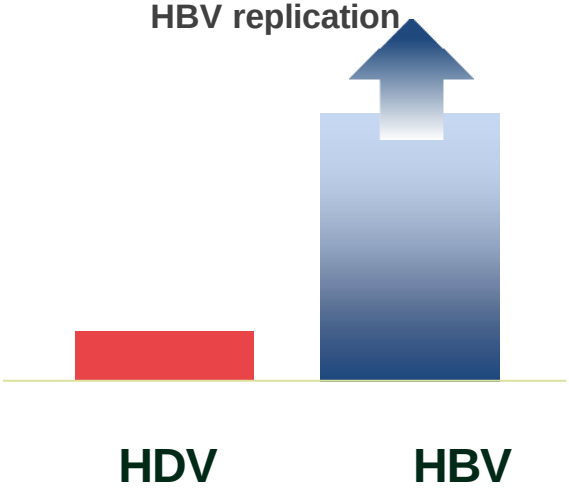
Rare

Similar HDV and HBV viral load



Rare

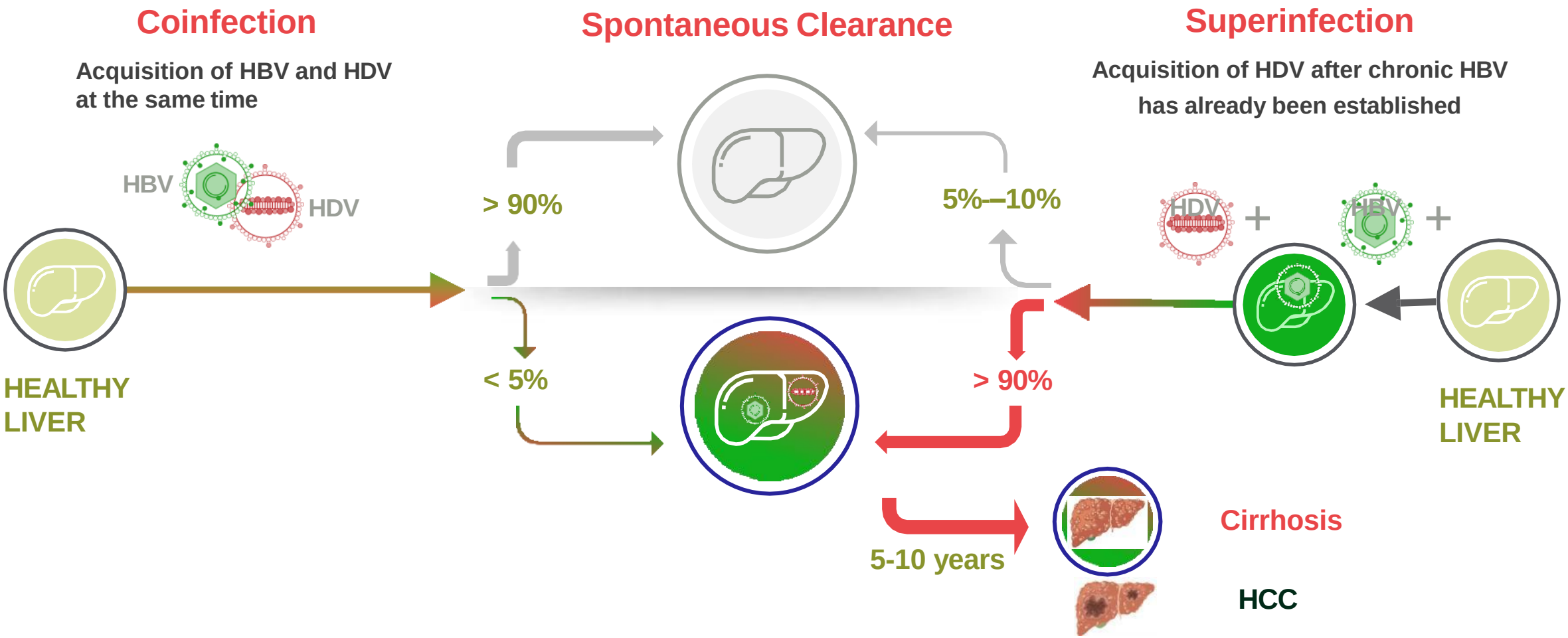
Predominant HBV replication



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.

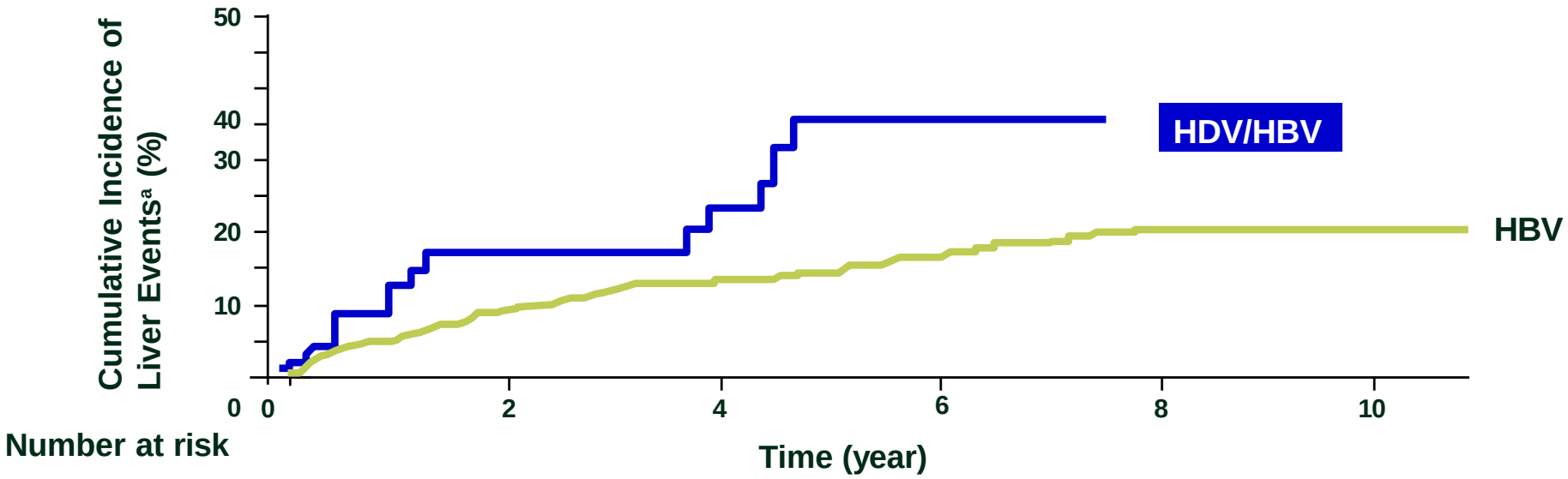
Differences in Major Clinical Outcomes for Adults Based on Coinfection vs Superinfection[1-6]



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 Chronic Infection Has a More Severe Long-Term Course vs HBV Monoinfection

Prospective analysis of adult Greek cohort who tested positive for HBsAG from 1997–2010 (N = 4527)

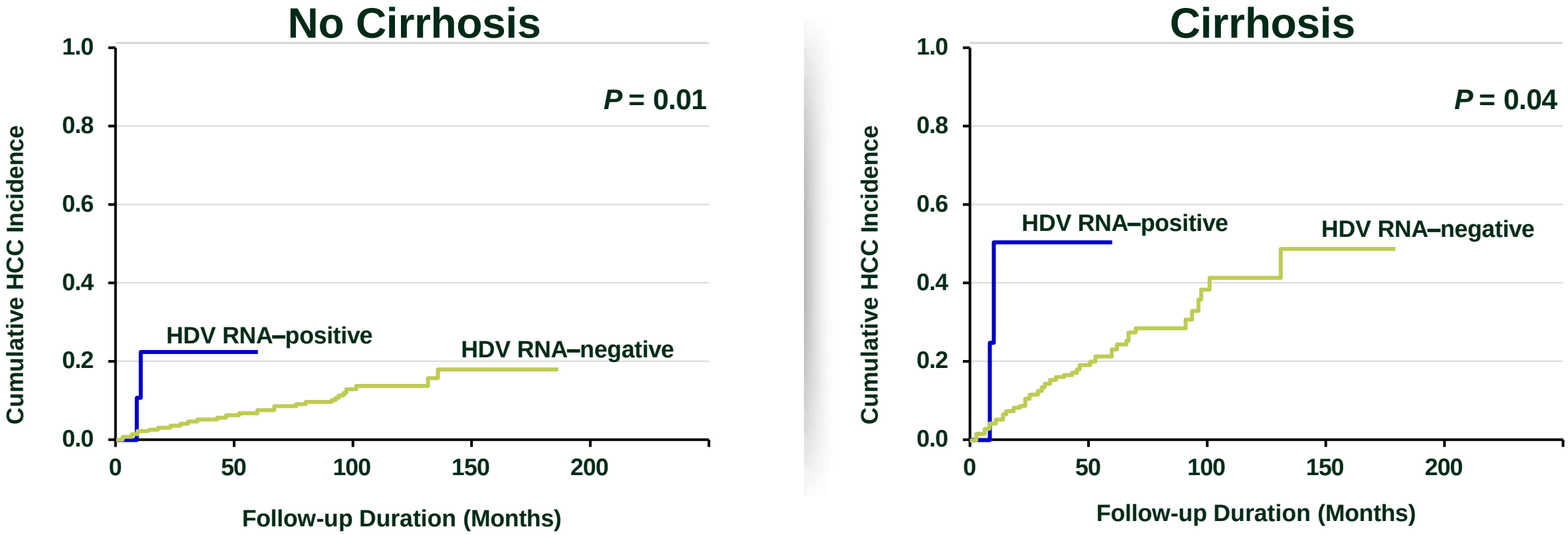


Cirrhosis was more prevalent in HDV-coinfected patients 13/65 (20%) than in HBV-monoinfected patients 159/1836 (8.7%) with higher prevalence of cirrhosis at younger age ($p < 0.001$)

LT = liver transplantation. [a]Development of cirrhosis, liver decompensation, liver failure, HCC, LT, or liver-related death, whichever came first. The most frequent liver-related event was cirrhosis. Manesis EK et al. *J Hepatol*. 2013; 59(5): 949–956.

Cumulative Incidence of HCC in Patients With Chronic HBV With or Without HDV

Retrospective analysis of treated patients with chronic HBV in Taiwan from 2000–2018 (N = 1349)



HDV viremia played a crucial role in HCC development in treated patients with chronic HBV

Jang TY et al. *Sci Rep*. 2021; 11(1): 8184.

Current Screening Recommendations for HDV

	WHOM TO TEST?	HOW TO TEST?
AASLD	HBsAg+ patients with HDV risk factors Low/undetectable HBV DNA and high ALT	Anti-HDV HDV RNA
EASL	All patients infected with HBV	NO RECOMMENDATION
The Asian Pacific Association For The Study of Liver	Patients with chronic HBV and chronic liver disease	HDAg or Anti-HDV HDV RNA
World Health Organization	NO RECOMMENDATION	Anti-HDV HDV RNA

1. Terrault NA et al. *Hepatology*. 2018; 67(4): 1560–1599; 2. EASL. *J Hepatol*. 2017; 67(2): 370–398; 3. Sarin SK et al. *Hepatol Int.* 2016; 10(1): 1–98; 4.

WHO. March 2015. Accessed March 30, 2021. https://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf?sequence=1

AASLD Recommendations for HDV Testing in Clinical Practice: Risk based screening

HBsAg-positive persons at high risk of HDV infection who should be screened

- **Persons born in regions with reported high HDV endemically**
  - Africa (West Africa, horn of Africa)
  - Asia (Central and Northern Asia, Vietnam, Mongolia, Pakistan, Japan, Taiwan)
  - Middle East (all countries)
  - Eastern Europe (Eastern Mediterranean regions, Turkey)
  - South America (Amazonian basin)
  - Other (Greenland)
- **Persons who have ever injected drugs**
- **MSM**
- **Individuals infected with HCV or HIV**
- **Persons with multiple sexual partners or any history of sexually transmitted disease**
- **Individuals with elevated ALT or AST with low or undetectable HBV DNA**

Given the challenges of using risk-based screening, universal screening of all HBsAg-positive persons may be a reasonable alternative.

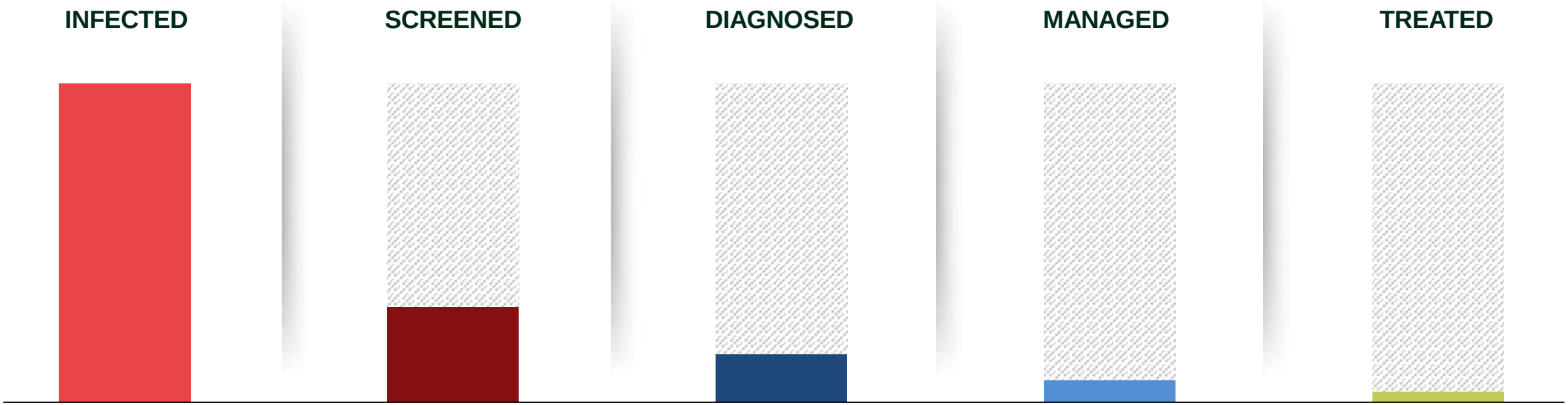
NORAH TERRAULT AND MARC GHANY[2]

AST = aspartate aminotransferase; MSM = men who have sex with men.

[a]This list is incomplete, because many countries do not report HDV rates.

1. Terrault NA et al. *Hepatology*. 2018; 67(4): 1560–1599; 2. Terrault NA, Ghany MG. *Dig Dis Sci*. 2021; 66(8): 2483–2485.

There Are Unmet Needs Across the HDV Cascade of Care[1-3]



Lack of robust data

Number of patients with HDV unknown

Test availability

Standardized screening tests needed

Standardized screening policies needed

Protocol for testing HDV in HBsAg-positive patients needed

Protocol for HDV confirmation in HBsAg-positive patients needed

Surveillance protocols to detect rapid disease progression needed

Lack of effective and specific treatment options

Clarity on which stage of disease to treat patients needed

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

(Oxf). 2019; 7(6): 396–402.

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).

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 The Home of Hepatology 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. Cornberg M et al. *J Hepatol*. 2020 Mar; 72: 539–57. doi:

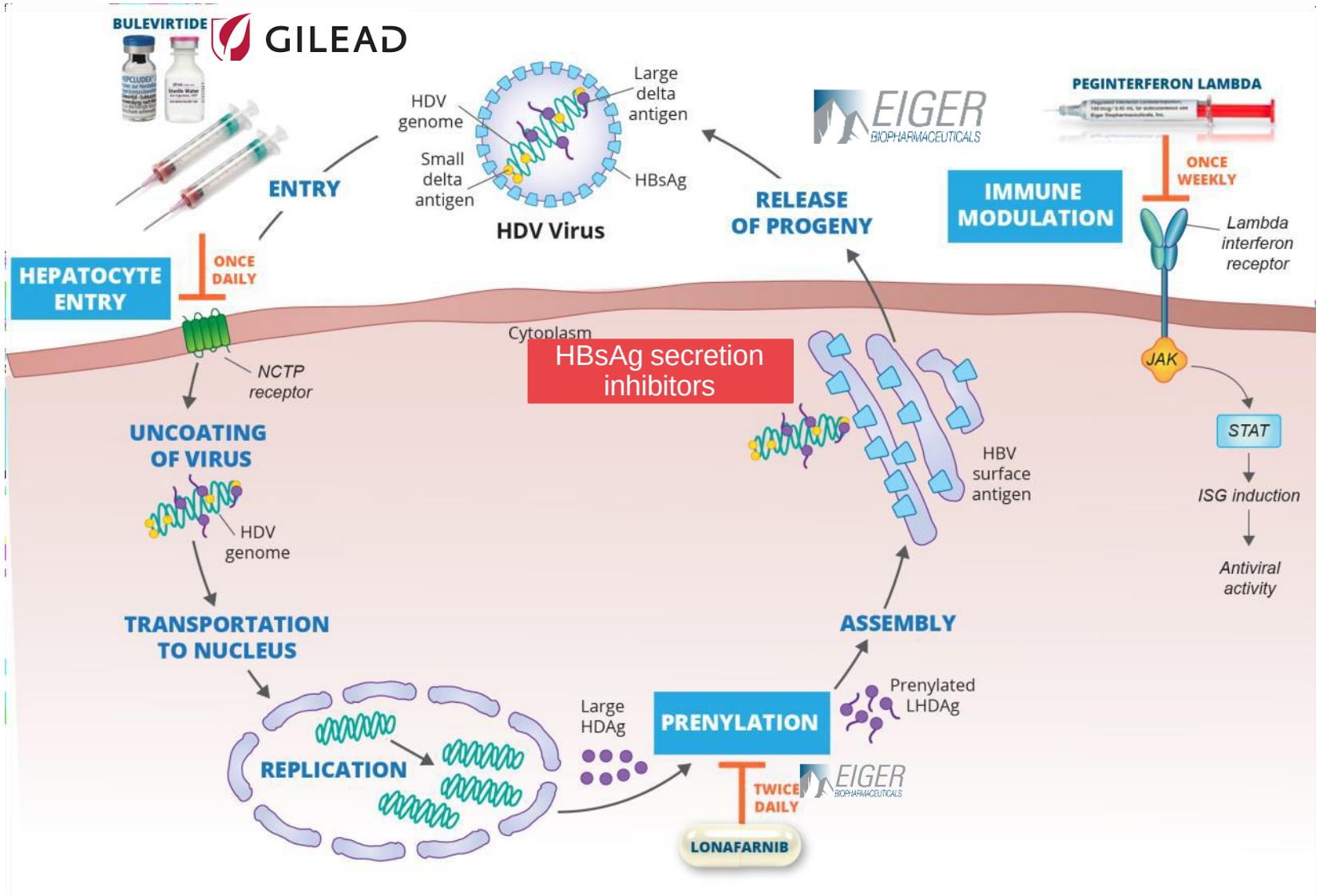
10.1016/j.jhep.2019.11.003. Epub 2019 Nov 12.

Hepatitis D AASLD/EASL Endpoints from 2022

- For Finite Strategies
  - The preferred endpoint for novel anti-HDV therapies is HBsAg loss + anti-HBs seroconversion and HDV RNA below the lower limit of quantification
  - In the absence of HBsAg loss, an alternate endpoint is HDV RNA below the lower limit of quantification at 24 weeks off-treatment
    - There should be a commitment to long-term follow-up (minimum 5 years) to assess durability of this endpoint
- For Maintenance Strategies
  - The preferred endpoint of a maintenance strategy is HDV RNA below the lower limit of quantification at 48 weeks on-treatment that is maintained on-treatment.
    - The optimal duration of maintenance therapy is currently unknown
- If this is not achievable, an alternate endpoint is combined response defined as HDV RNA>2 log decrease from baseline and normal ALT level at 48 weeks on-treatment and during the follow-up on treatment.
- The optimal duration of maintenance therapy is currently unknown

Hepatology Publish Ahead of Print
DOI:10.1097/HEP.0000000000000431

Different Mechanisms of Action to Treat HDV



Current Treatment Options for HDV

In EU in some countries: Bulevirtide[1,2]

- HDV entry inhibitor
- Daily subcutaneous injections
- EMA approved (commercially available in Germany and Russia; early access availability in France, Greece, Austria and Italy)

Global: PEG-IFNα[3,4]

- Immune modulator
- Weekly injections
- 12–18 months' treatment duration
- Off-label use

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

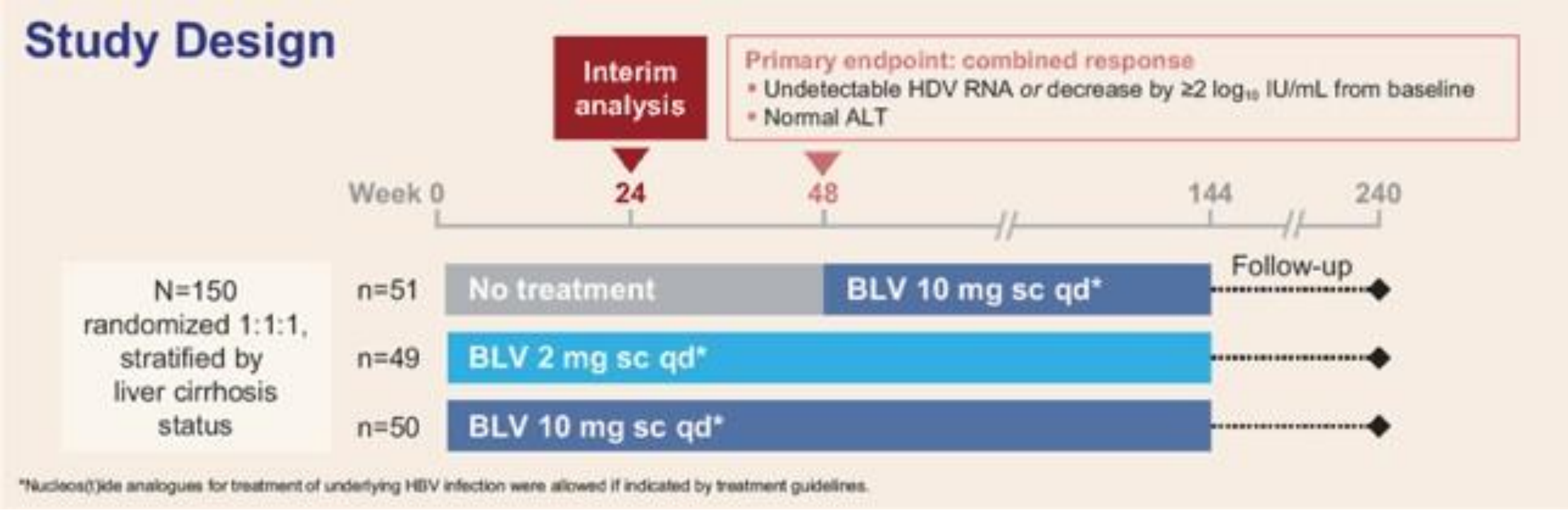
1. EMA. Hepcludex. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/hepcludex#authorisation-details-section. Accessed March 2021; 2. MYR GmbH. HEPCLUDEX▼ (bulevirtide), Summary of Product Characteristics. October 2020; 3. Terrault N et al. *Hepatology*. 2018; 67: 1560–99; 4. Wedemeyer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

Interferon Trials for HDV

Trial	Treatment	Patient Number	SVR 6 Months
Farci et al. *NEJM*. 1994	IFN 9 MIU vs 3 MIU vs No Therapy 12 months	41	0%
Gunsar et al. *Antivir Ther*. 2005	IFN vs IFN+RBV x 24 months	31	20 vs 24%
Castelnau et al. *Hepatology*. 2006	PEGIFN x 12 months	14	43%
Niro et al. *Hepatology*. 2006	PEGIFN vs PEGIFN+RBV x 18 months	38	25 vs 18%
Heller et al. *Aliment Pharmacol Ther*. 2014	PEGIFN at escalating doses to 360 ug/wk for 5 years	13	23%

- **MIU = million international unit**

Bulevirtide: Phase 3 Study Design



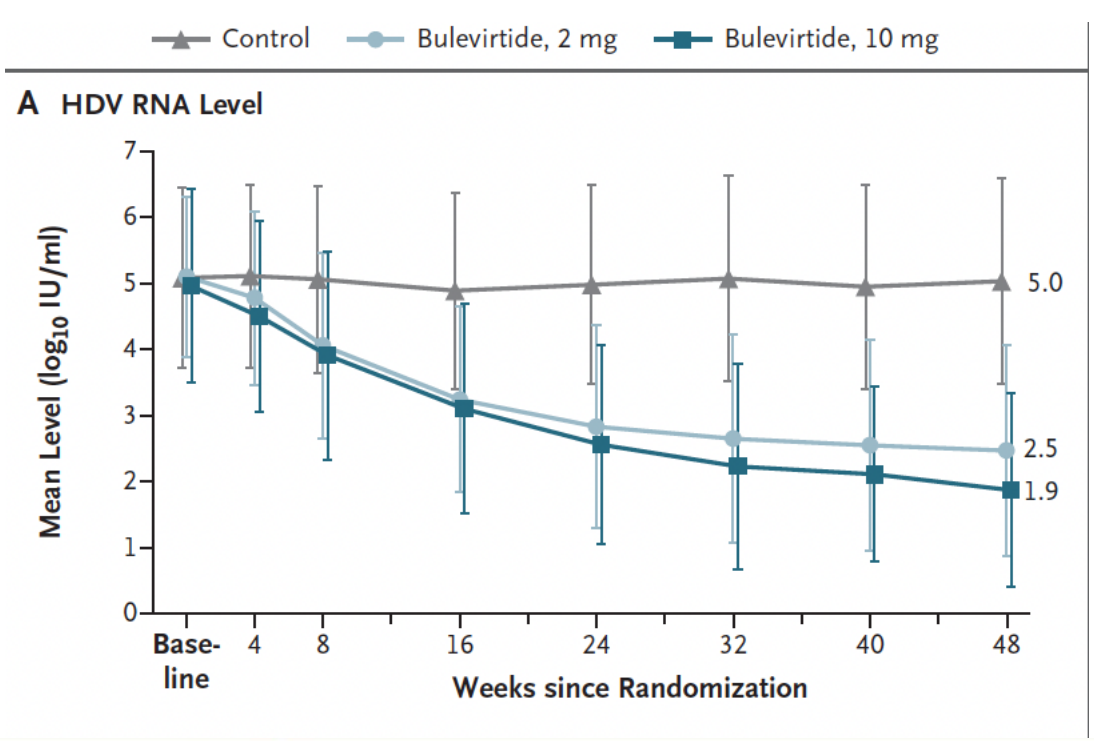
Wedemeyer H et al., EASL 2021

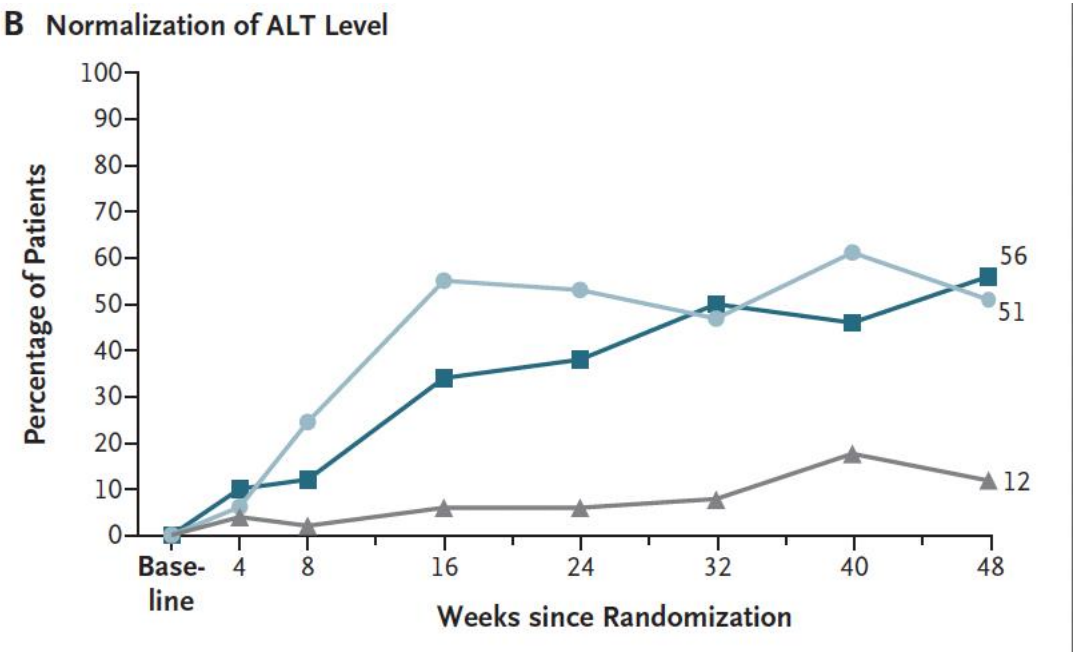
Bulevirtide: Phase 3 Results

Response	Control	Bulevirtide, 2 mg	Bulevirtide, 10 mg
Combined response			
Overall			
No./total no. (%)	1/51 (2)	22/49 (45)†	24/50 (48)†
95% CI — %	0–10	31–60	34–63
Undetectable or ≥2 $\log_{10}$ IU/ml decrease in HDV RNA level			
Overall			
No./total no. (%)	2/51 (4)	35/49 (71)	38/50 (76)
Difference from placebo (95% CI) — percentage points	—	68 (52–80)	72 (56–84)
Normalized ALT level			
Overall			
No./total no. (%)	6/51 (12)	25/49 (51)	28/50 (56)
Difference from placebo (95% CI) — percentage points	—	39 (20–56)	44 (26–60)

Wedemeyer H et al., EASL 2021

Bulevirtide: Phase 3 Results





Undetectable HDV RNA level			
Overall			
No./total no. (%)	0/51 (0)	6/49 (12)‡	10/50 (20)
95% CI — %	—	5–25	10–34
According to cirrhosis status — no./total no. (%)			
Present	—	5/23 (22)	6/24 (25)
Absent	—	1/26 (4)	4/26 (15)

‡

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.

FDA Accelerated Approval Paths for Lonafarnib and Peg IFN Lambda

COMPLEMENTARY TREATMENTS FOR HDV

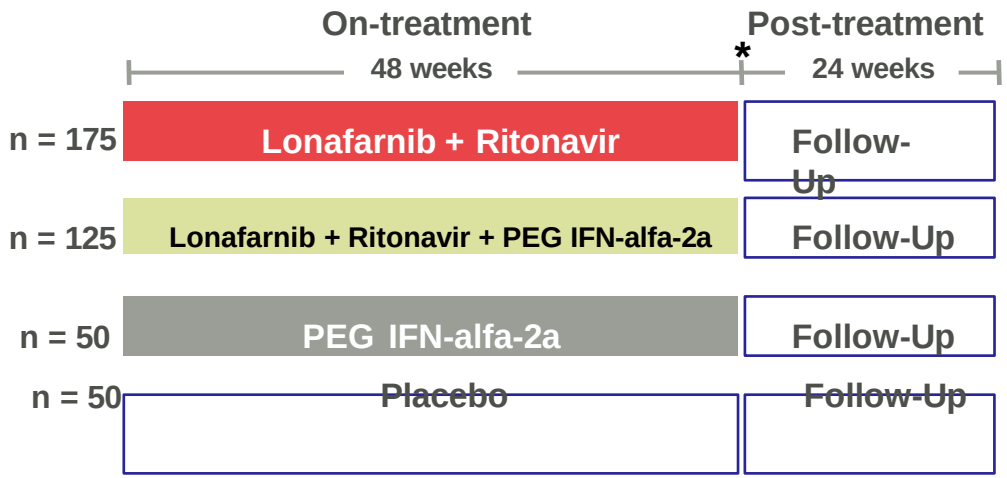
Phase 3 *D-LIVR* (Lonafarnib) Study for CHRONIC Therapy

FDA guidance

on CHRONIC, ON-TREATMENT

endpoint:

"…≥ 2 log decline in HDV RNA and ALT normalization on-treatment could be considered an acceptable surrogate endpoint…"

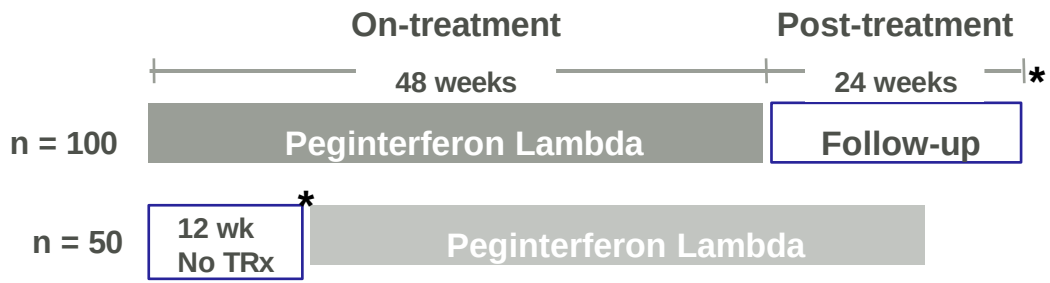


Phase 3 *LIMT-2* (Peginterferon Lambda) Study for FINITE Therapy (Cure)

FDA guidance

on FINITE, OFF-TREATMENT endpoint:

"…the proportion of trial patients with undetectable HDV RNA (defined as less than the lower limit of quantitation (LLOQ) and ALT normalization…"



First Patient Dosed

Dec 2021

***Primary Endpoint**

Chronic Hepatitis D Virus Infection: Developing Drugs for Treatment; FDA Draft Guidance for Industry October 2019.

HDV: Lonafarnib

D-LIVR Phase 3 Clinical trial

Objective

To evaluate the safety, tolerability, and efficacy of LNF boosted with RTV with or without pegIFN Alfa for treatment of chronic HDV infection compared to placebo

Primary Endpoint at Week 48

≥ 2 log decline in HDV RNA
+
Normalization of ALT

Secondary Endpoint at Week 48

No worsening in fibrosis
+
≥ 2-point in Ishak HAI Score

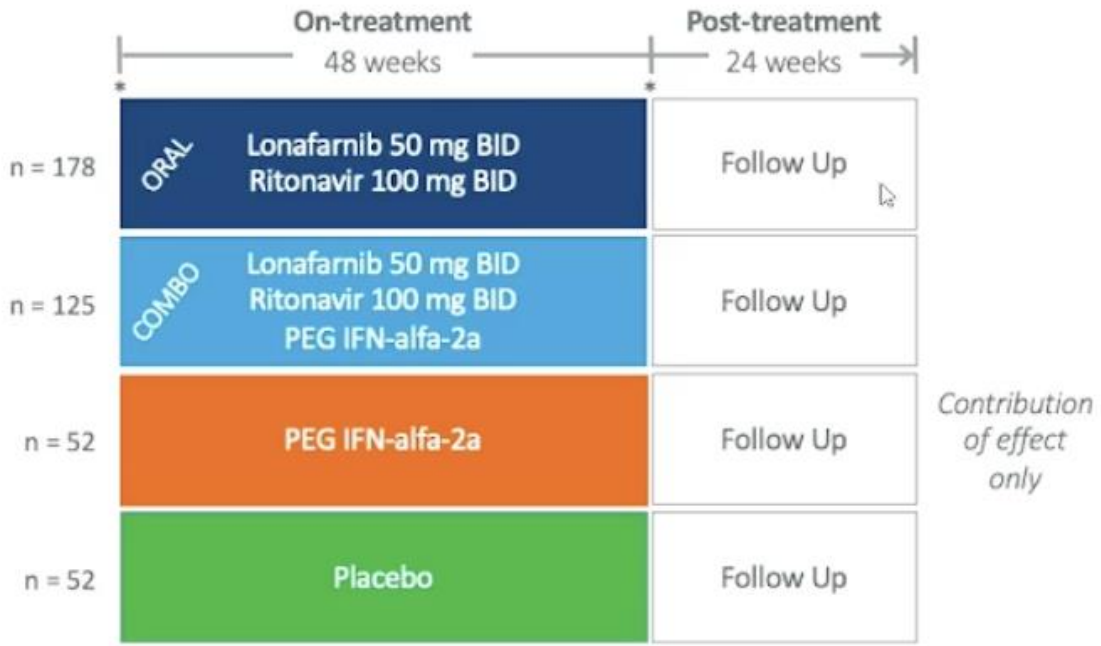
Key Inclusion criteria

CHD with compensated liver disease

HDV RNA > 500 IU/mL

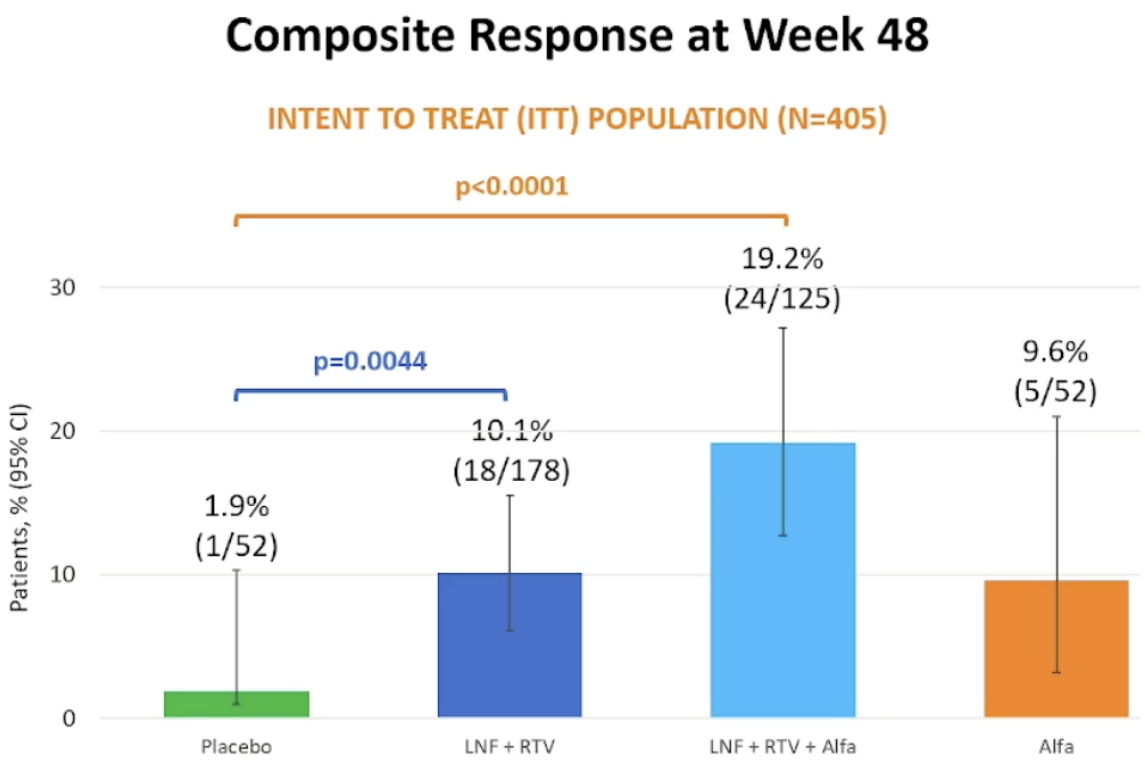
ALT > 1.3X < 10X ULN

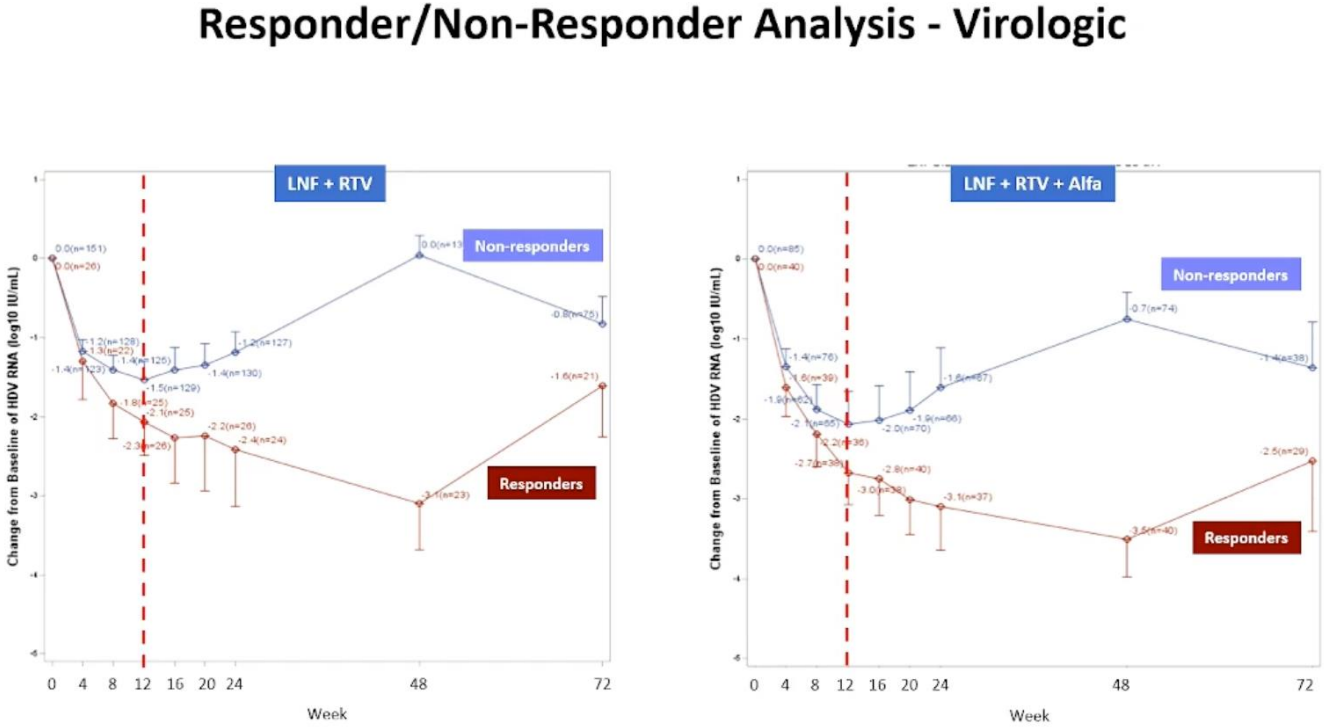
HBV DNA < 20 IU/mL



Etzion, Ohad, et al. Journal of Hepatology 78 (2023): S10. **DOI: 10.1056/NEJMoa2213429**

HDV: Lonafarnib



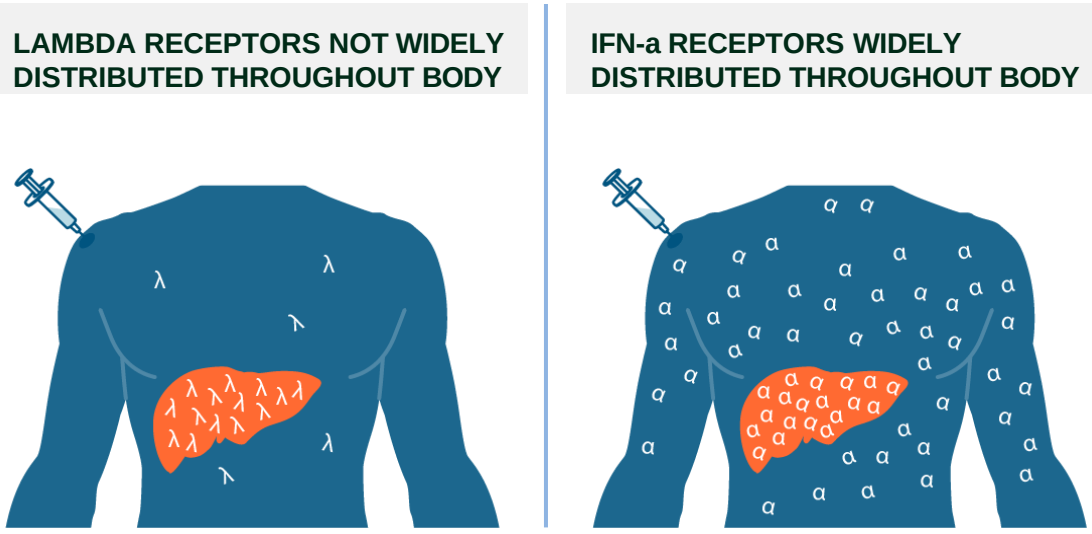


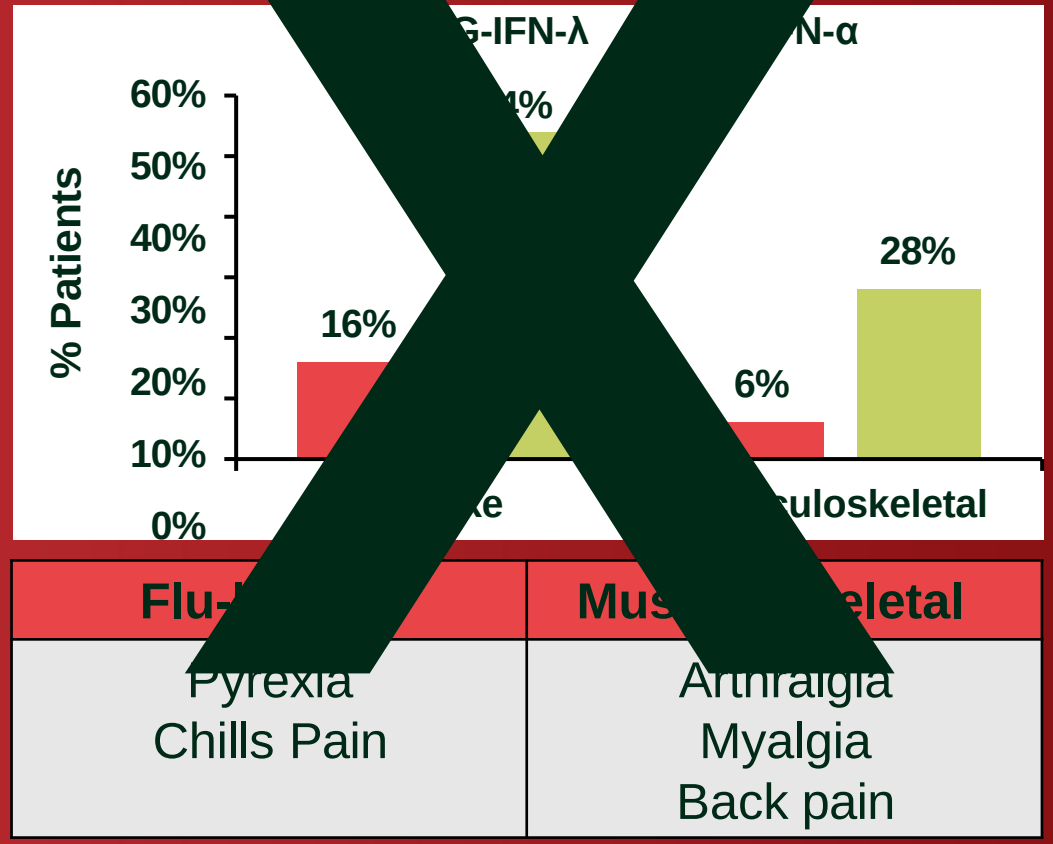
Etzion, Ohad, et al. Journal of Hepatology 78 (2023): S10.

Peginterferon Lambda for HDV: Development halted due to DILI

A WELL TOLERATED INTERFERON

Lambda Receptors Highly Expressed in the Liver

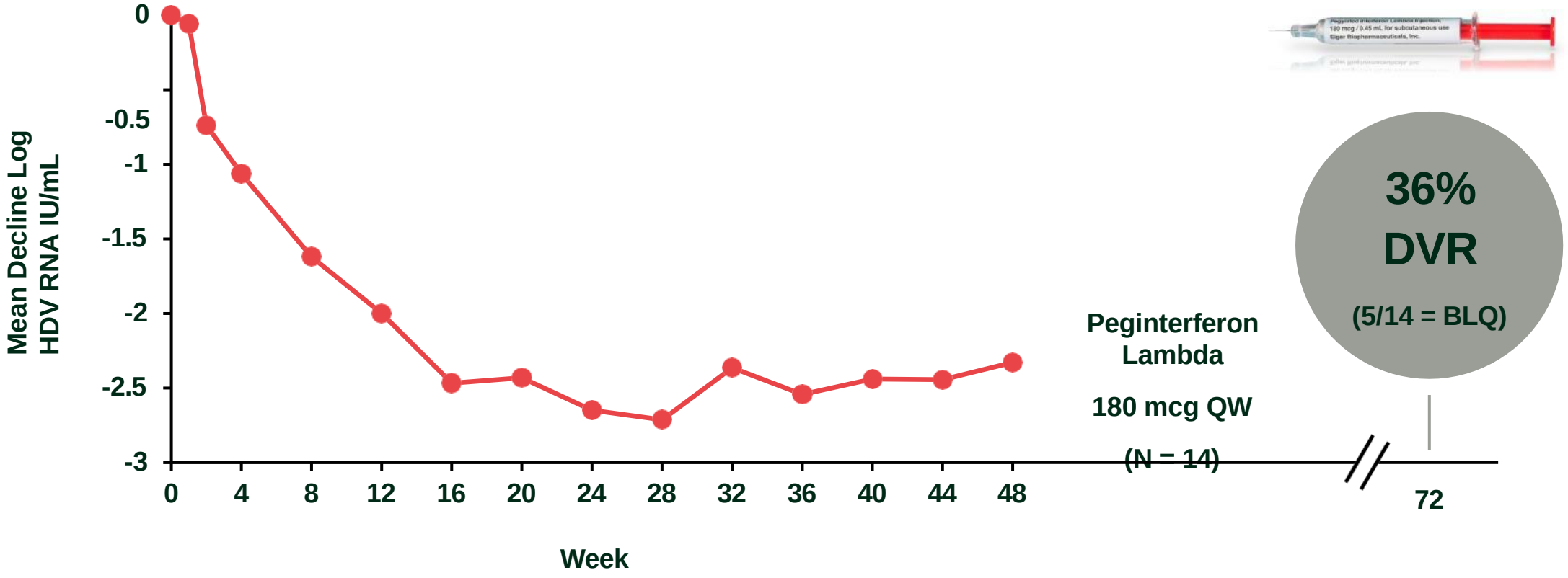




Chan HLY et al. *J Hepatology*. 2016.

Phase 2 Peginterferon Lambda Study Results

36% DURABLE VIROLOGIC RESPONSE (DVR) WITH PEGINTERFERON LAMBDA



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

HDV Tests and Treatments Summary

- HDV is the most severe form of hepatitis
- Risk based testing has failed for HIV, HCV, HBV and has failed for HDV
- Move to test all HBsAg+ for HDV is advised with reflex from anti-HDV to HDV qPCR is best path forward
- HDV treatment approval within the next year with maintenance bulevirtide possible
    - Phase 3 results show suppression of HDV RNA at week 48

HDV Treatments Summary

- Lonafarib/ritonavir/PEG interferon phase 3 results presented
- – Lonafarnib has significant GI side effects, ritonavir with significant drug/drug interaction
  - Current pathway to approval is not clear
- Lambda-interferon phase 3 trial now halted due to high rate of DILI
- Will not replace PEG IFN alfa for HDV as immune modulator