Delta Hepatitis:
An Overview & Update

Outline – Delta Hepatitis (HDV)

- Definition
- Epidemiology
- Risk factors
- Diagnosis and Natural History
- Treatment

Hepatitis Delta

- Caused by the hepatitis delta virus (HDV)
- “Satellite virus”
  - Infects only those with hepatitis B (HBV)
- Can lead to acute or chronic disease
- May be acquired simultaneously with HBV as co-infection OR may be acquired by chronically infected HBV patients as super infection

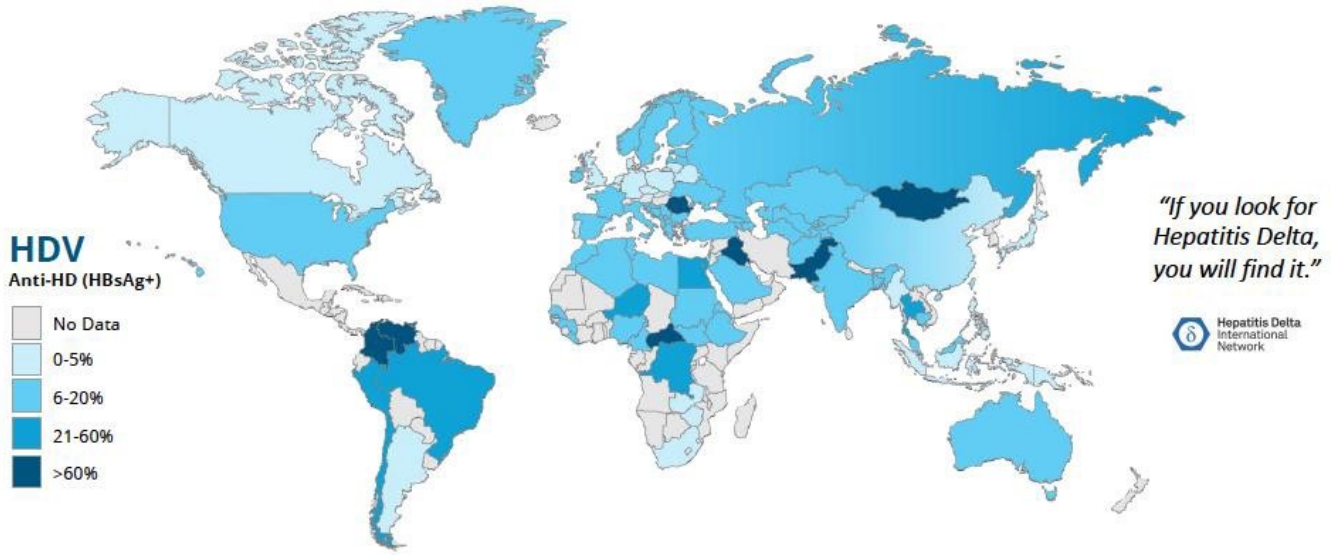
Epidemiology

HDV Worldwide Prevalence: 15 – 20 Million

- Common in Eastern Europe, Southern Europe, Mediterranean region, Middle East, West and Central Africa, East Asia, Amazon Basin
  - > 100K in US
  - > 200K in EU
  - > 2M in China
- In US, at least 4% of HBV infected patients have HDV

HDV Worldwide Prevalence: 15 – 20 Million

4.5% - 15% of HBV population coinfected with HDV



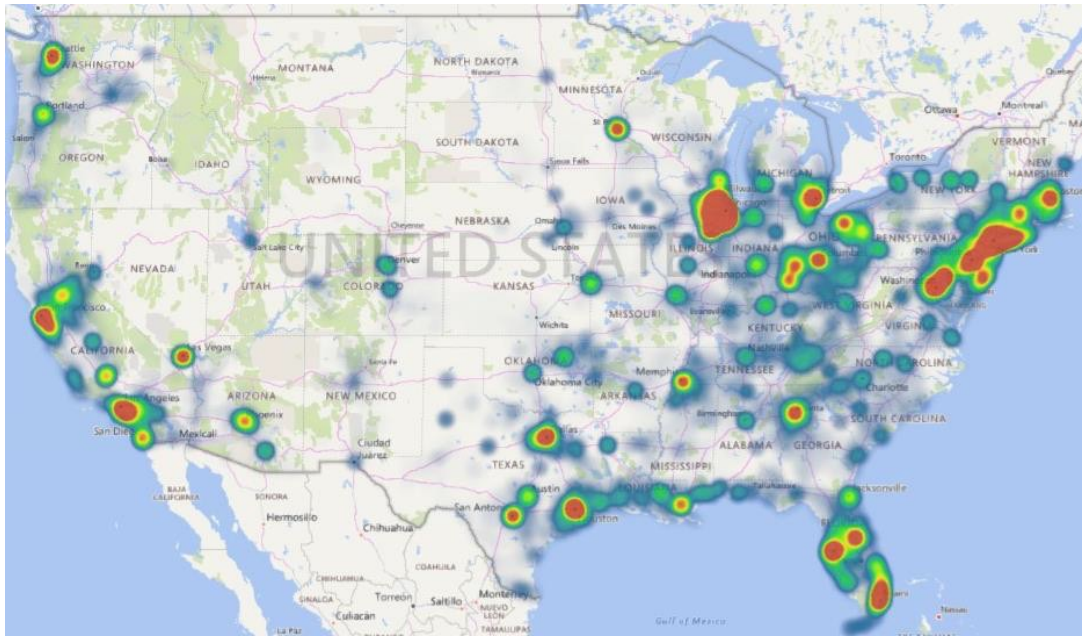
Stockdale AJ, et al. J Hepatol 2020; 73:523-32.
Chen H-Y, et al. Gut 2019; 68:512-21.

HDV Has 8 Genotypes

Genotype	Commonly Found
1	North America, Europe, Middle East, North Africa
2 and 4	East Asia
3	Amazon Basin of South America
5,6,7,8	West and Central Africa

HDV Geographic Footprint Is Growing

U.S. major metro hotspots identified

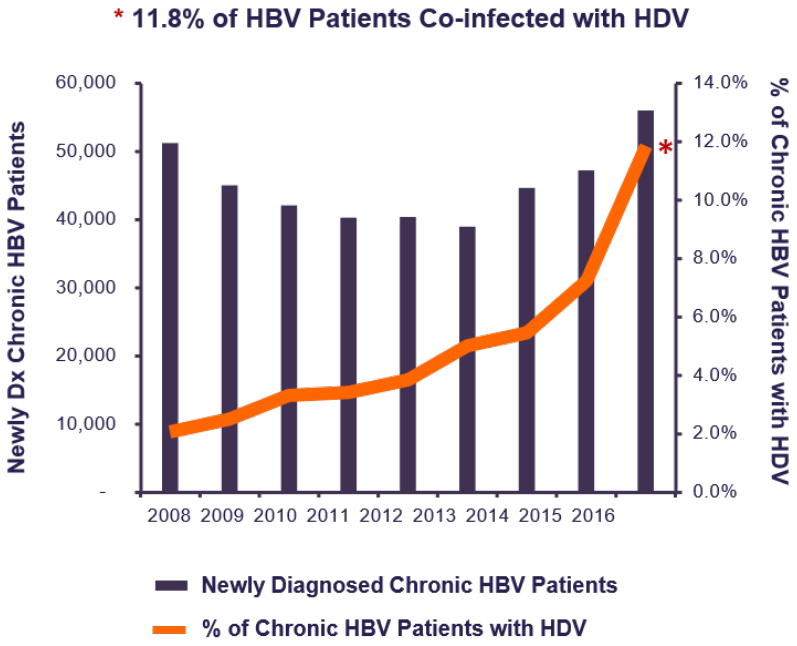


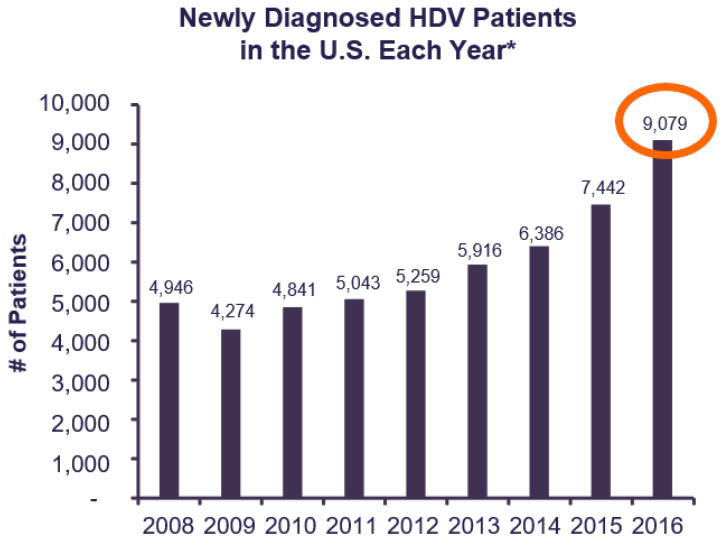
Top 10 U.S. Cities in 2016
1. Chicago, Illinois
2. Berwyn, Illinois
3. Brooklyn, New York
4. Corona, New York
5. Waukegan, Illinois
6. New York, New York
7. Bronx, New York
8. Jamaica, New York
9. Lombard, New York
10. Aurora, Illinois

Martins, et al. DDW. 2017.

U.S. HDV Prevalence in 2018: ~110,000

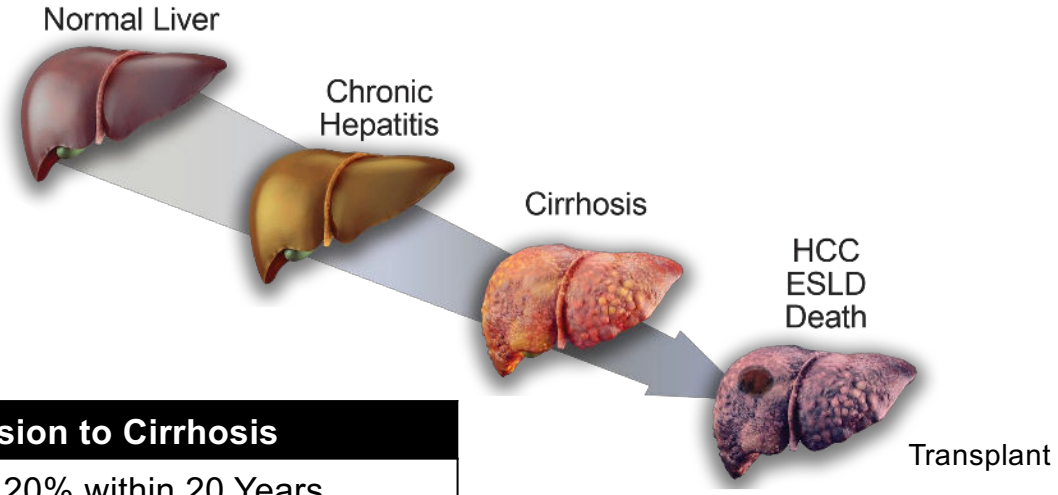
Increased screening leads to increased HBV and HDV diagnosis





Martins, et al. DDW. 2017.

HDV: Most Rapid Progression of Viral Hepatitis



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

Westbrook, et al. *J Hepatology.* 2014; Fattovich, et al, *Seminars in Liver Diseases.* 2003; Nourredin, et al. *Curr Gasterol Rep.* 2013.

Adverse Outcomes More Common With HDV/HBV Than HBV Alone

Table 3. Associated risks of chronic hepatitis D

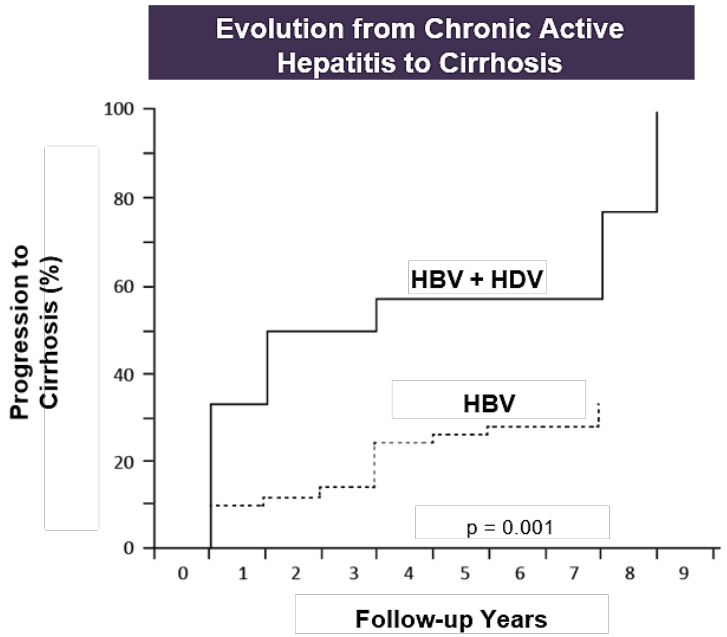
Clinical outcome	Approximate relative risk increase*
Cirrhosis [58, 90, 110]	2- to 3-fold
Hepatocellular carcinoma [58, 61, 78, 90, 111–113]	3- to 6-fold
Liver transplantation [48]	2-fold
Hepatic decompensation [111]	2-fold
Mortality [42, 78, 90, 111]	2-fold

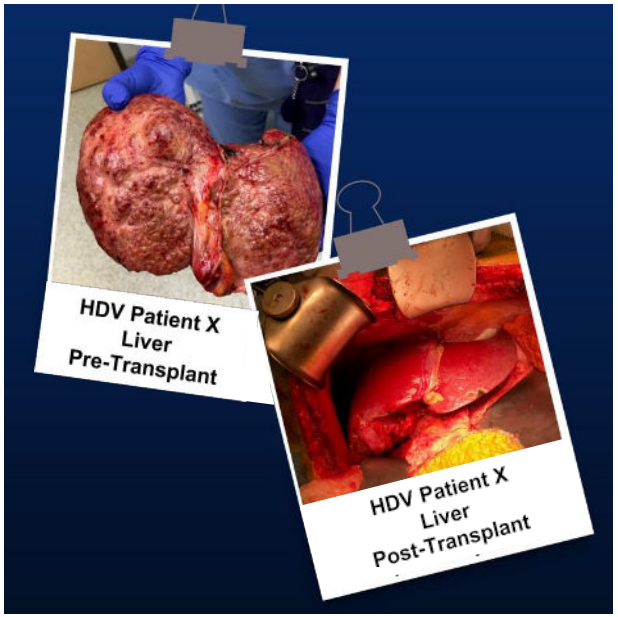
*Compared with hepatitis B mono-infection.

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

HDV Causes Most Rapid Disease Progression

At diagnosis, > 50% of HDV patients are cirrhotic





Fattovich, et al. *J Infect Dis.* 1987; Fattovich, et al. *Gut.* 2000.

Risk Factors

Hepatitis Delta Risk Factors

- Birth to an infected mother
- Intravenous drug use
- Sex with an infected partner
- Contact with blood from or open sores of an infected person
- Needle sticks or exposures to sharp instruments
- Sharing items (razors, toothbrushes, etc.) with an infected person
- HDV endemic country of origin
- Elevated ALT despite suppressed HBV DNA

Populations at Risk For HDV Infection

- People chronically infected with HBV
- Infants born to mothers with HDV
- Sex partners of persons infected with HDV
- MSM
- Injection drug users
- Household contacts of people with HDV
- Health care and public safety workers at risk for occupational exposure to blood or blood-contaminated fluids
- Hemodialysis patients

HDV: Signs/Symptoms

- Fever
- Fatigue
- Loss of appetite
- Nausea
- Vomiting
- Abdominal Pain
- Dark urine
- Clay-colored stools
- Joint pain
- Jaundice

These signs typically appear 3-7 weeks after infection.

Farci, et al. *Semin Liver Dis.* 2012.

Prevention

- Risk factor avoidance
- Hepatitis B vaccine
- No vaccine available for HDV

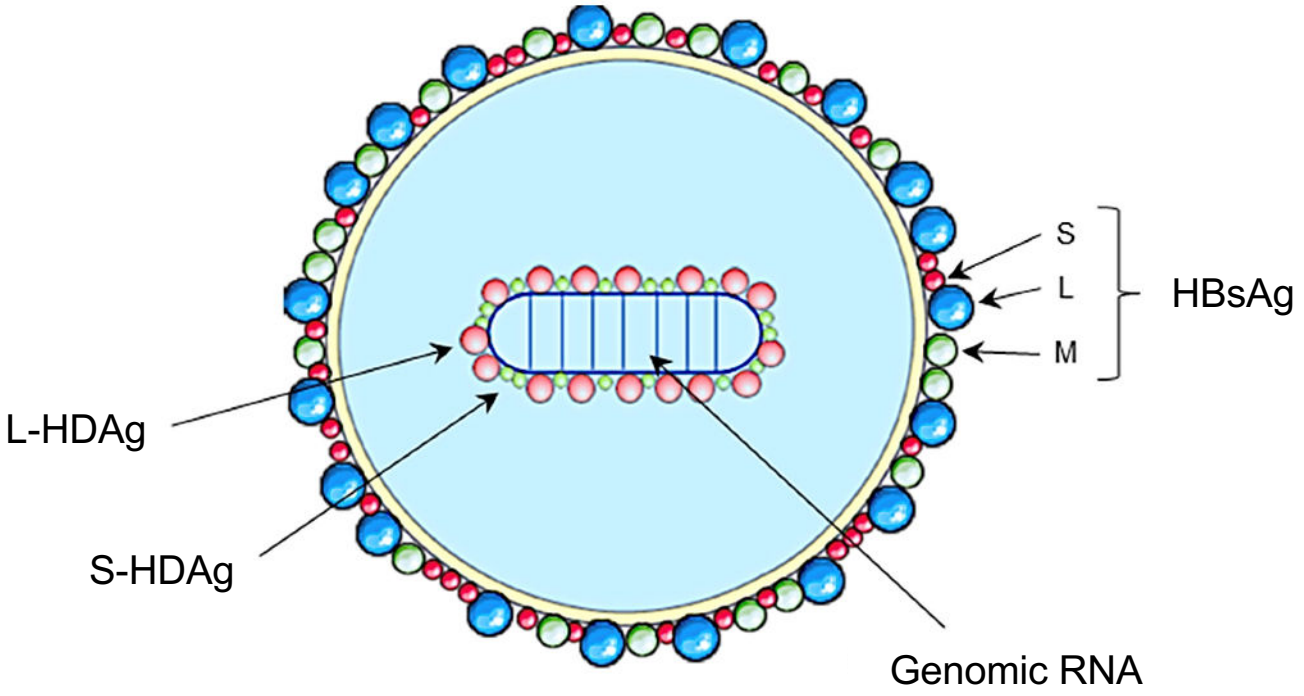
Molecular Biology

HDV Structure

- Positive single stranded circular RNA genome of ~1700 nucleotides
- HDV RNA genome is ~74% of paired bases giving it a rod-like structure
- Encodes HDAg, in 2 forms
  - Small (S-HDAg)
  - Large (L-HDAg)
  - HDAg associated with HDV genome forming a ribonucleoprotein (RNP)
  - RNP is enveloped by HBsAg

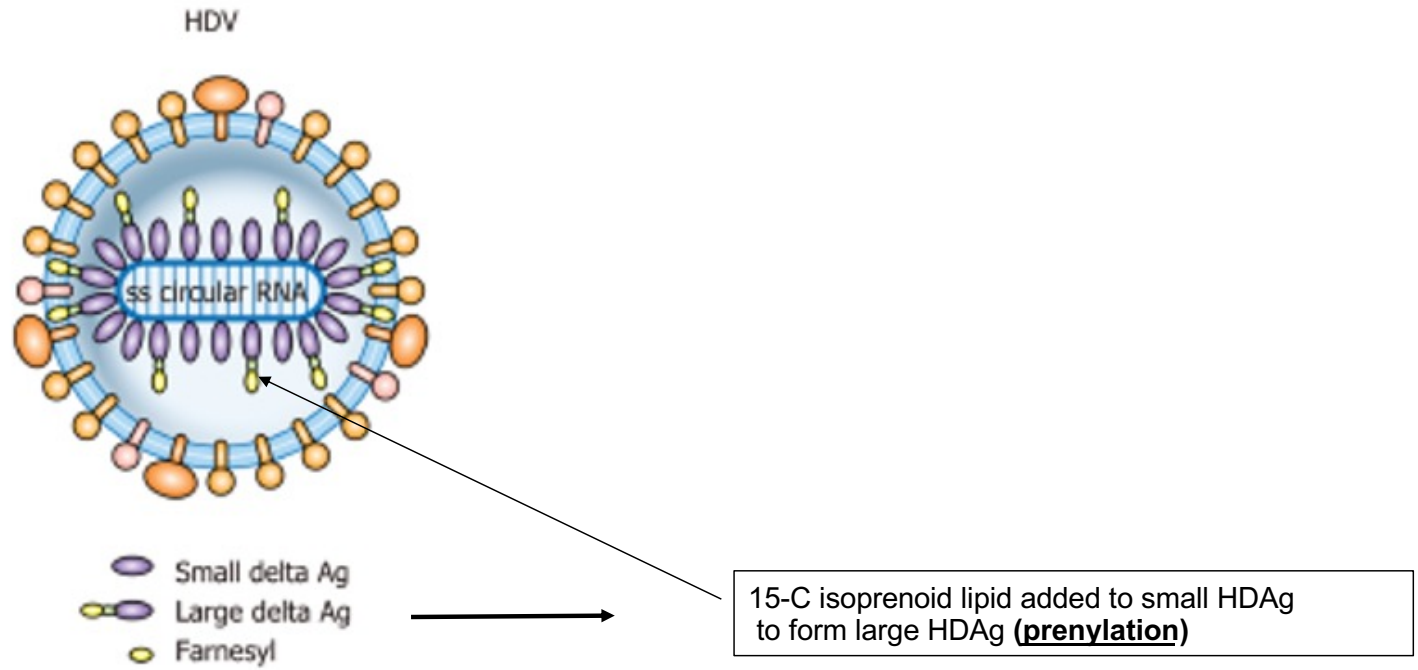
Turon Lagot, et al. *J Clin Med. 2020*

HDV Structure



Turon Lagot, et al. *J Clin Med. 2020*

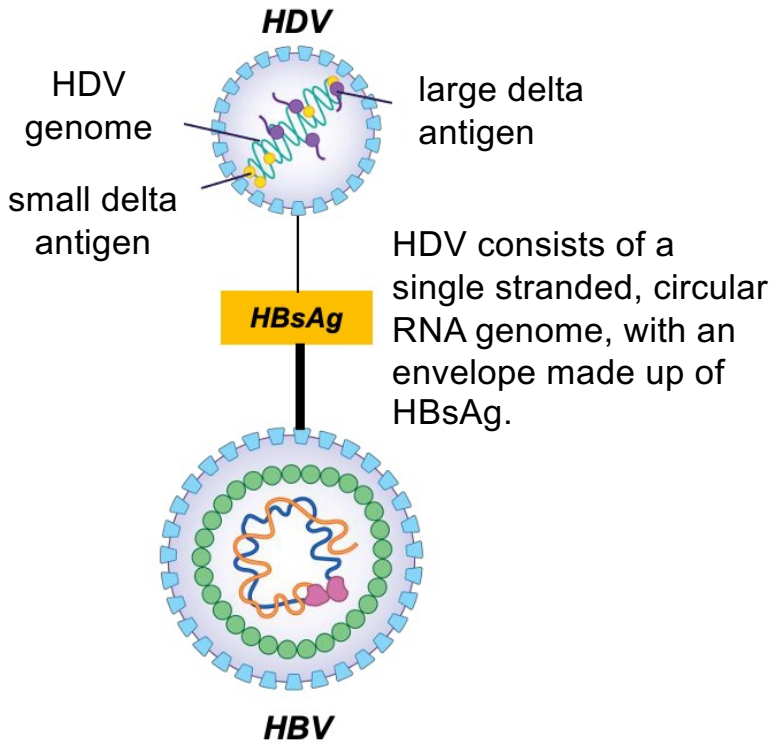
Hepatitis D Virus (Delta): The Most Pathogenic Hepatitis Virus



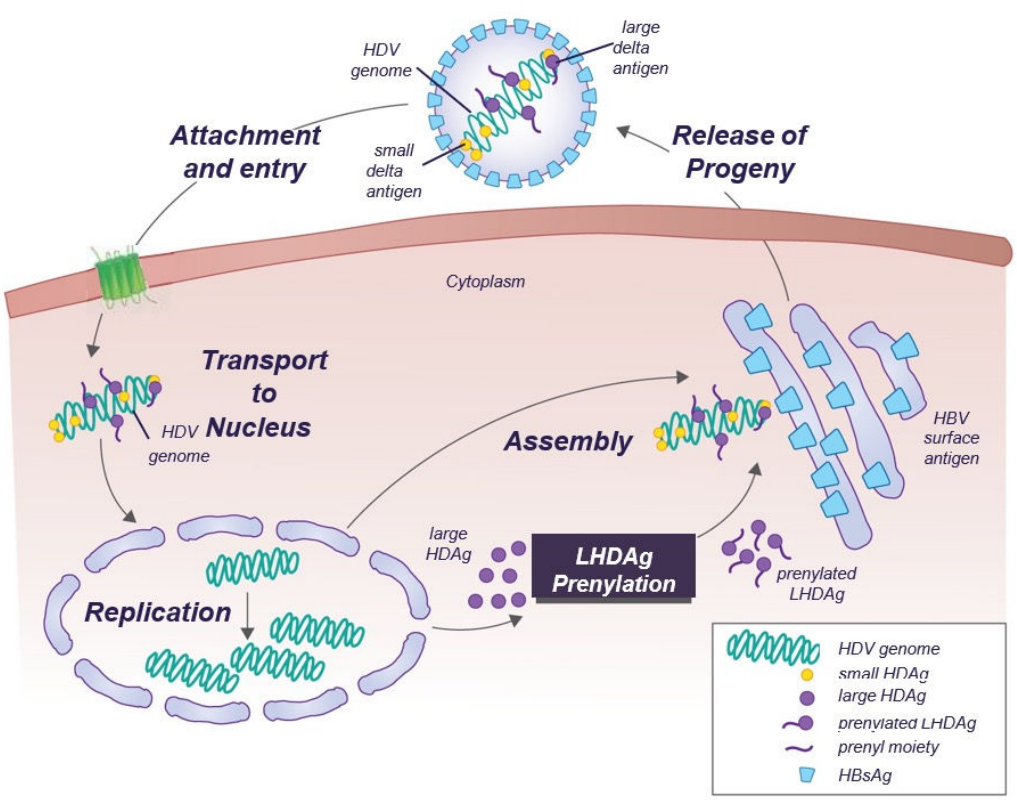
Adapted from Wang M, Casey P. Nat Rev Mol Cell Biol 2016;17:110–122

HDV Requires HBsAg to Complete Virus Assembly

- Assembly with HBsAg is mediated by large delta antigen prenylation



HDV Life Cycle



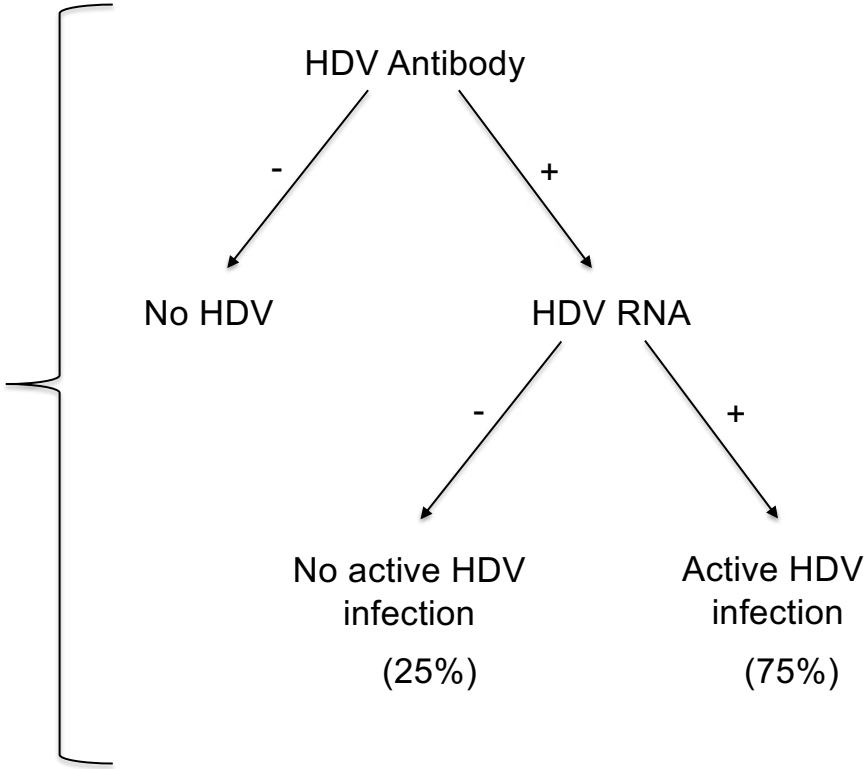
- HDV genome encodes for a single protein, the hepatitis delta antigen.
- HDV relies on host cell machinery for replication.
- New virions can be assembled only in the presence of hepatitis B virus.

Diagnosis & Natural History

HDV: Diagnostic Tests

- HDV antibodies (IgG, IgM)
- HDV RNA
- HBsAg

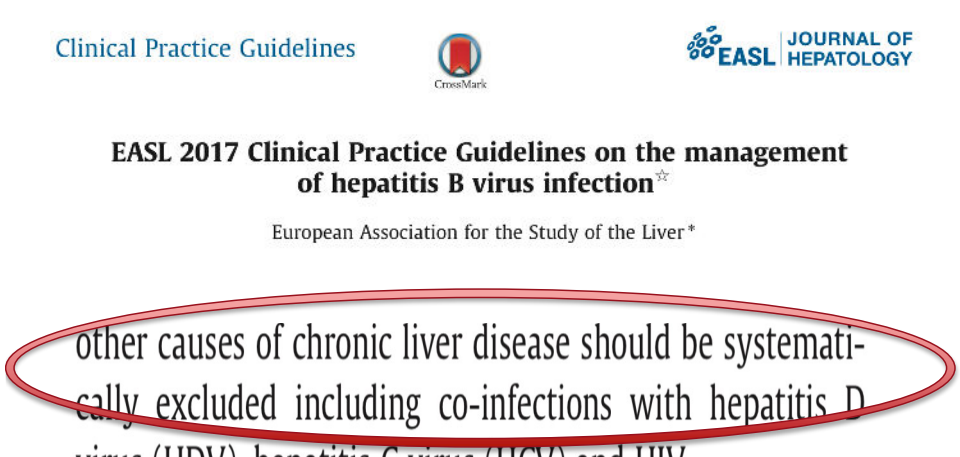
Testing Algorithm



HDV RNA Quantification is the Gold Standard in HDV Diagnosis and Management

- Available in Quest - a leading provider of diagnostic services
  - Over 2,200 patient service centers across the US
  - Highly targeted patient and physician outreach
  - HDV testing program for HBV-positive patients
- HDV RNA quantification
- HBV/HDV reflex testing

What are the guidelines?



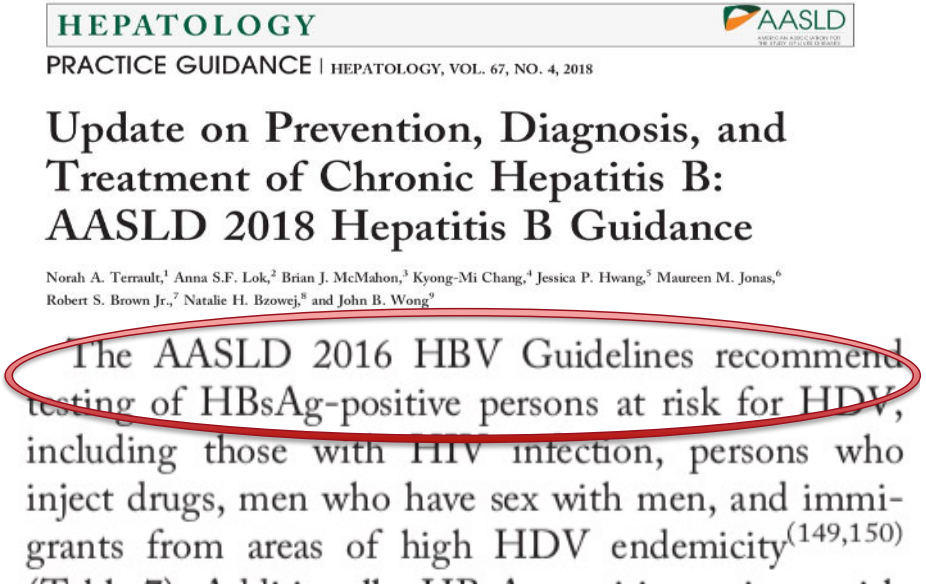
Clinical Practice Guidelines

EASL JOURNAL OF HEPATOLOGY

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection☆

European Association for the Study of the Liver*

other causes of chronic liver disease should be systematically excluded including co-infections with hepatitis D virus (HDV), hepatitis C virus (HCV) and HIV.



HEPATOLOGY AASLD

PRACTICE GUIDANCE | HEPATOLOGY, VOL. 67, NO. 4, 2018

Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance

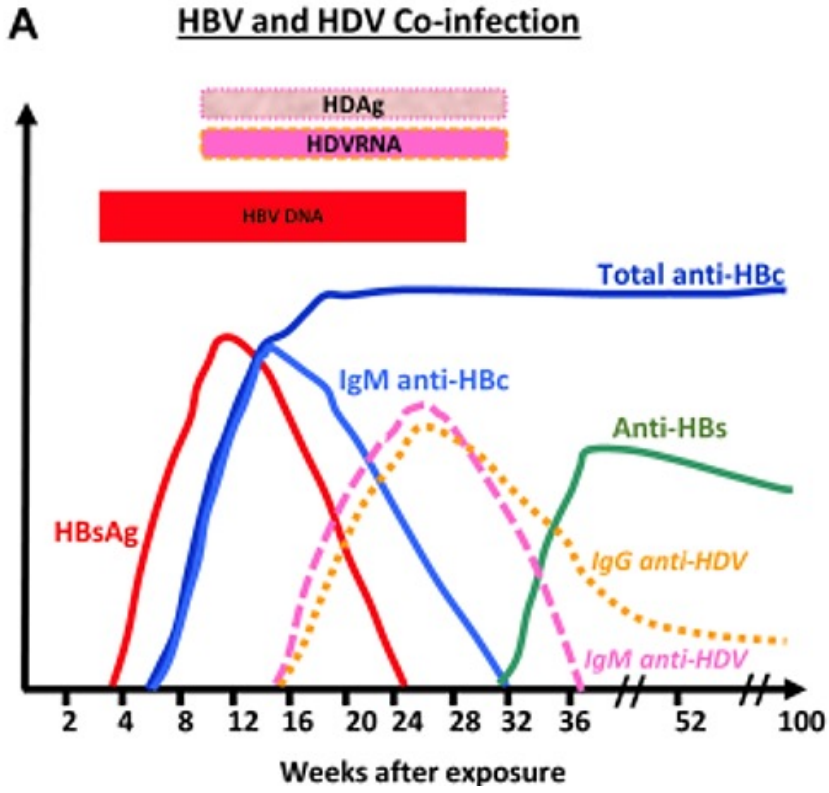
Norah A. Terrault,[1] Anna S.F. Lok,[2] Brian J. McMahon,[3] Kyong-Mi Chang,[4] Jessica P. Hwang,[5] Maureen M. Jonas,[6] Robert S. Brown Jr.,[7] Natalie H. Bzowej,[8] and John B. Wong[9]

The AASLD 2016 HBV Guidelines recommend testing of HBsAg-positive persons at risk for HDV, including those with HIV infection, persons who inject drugs, men who have sex with men, and immigrants from areas of high HDV endemicity[149,150]

Emerging consensus: All HBsAg+ patients should have a one-time test for HDV!

HBV/HDV Coinfection

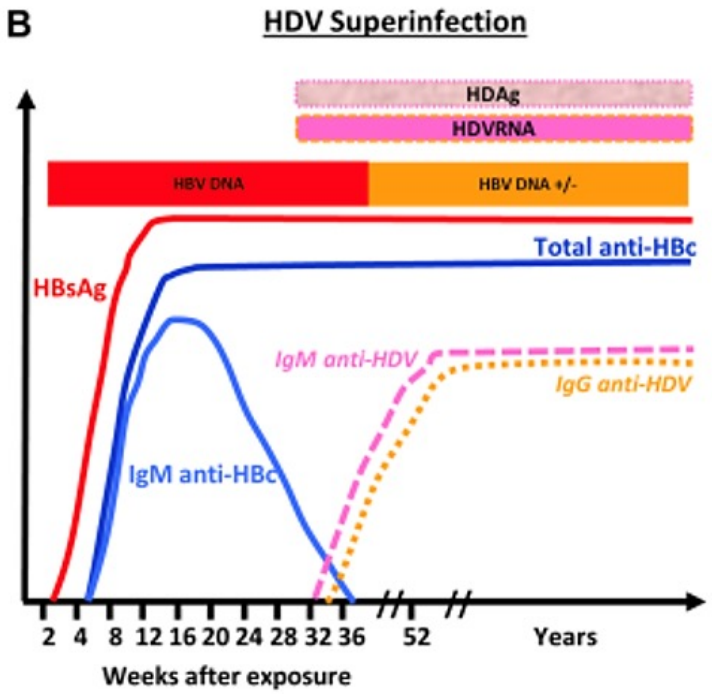
- Simultaneous infection with HBV and HDV
- Usually resolves
- > 5% develop chronic disease
- **Acute Liver Failure** more common with HDV/HBV than HBV alone



WHO 2019
Smedile et al. Lancet 1982.

HDV Superinfection

- Occurs when a person already with chronic HBV acquires HDV
- Results in rapid progression to cirrhosis and liver failure
  - 15% in 1-2 years
  - 70-80% in 5-10 years
- Higher risk of HCC
  - 3-6 fold increase
- Higher risk of mortality
  - 2 fold increase



Da, et al. *Gastro Report. 2019*

National Institute for Health. National Institute of Diabetes and Digestive and Kidney Diseases. United States 2017. Department of Health and Human Services. Available at https://www.niddk.nih.gov/health-information/liver-disease/viral-hepatitis/hepatitis-d#common

HDV Clinical Course and Outcomes

HDV: A devastating disease with no approved treatment

HIGH DISEASE BURDEN	LOW SURVIVAL RATE	HIGH COST TRANSPLANTS
~70% Cirrhotic[1]	**~60% Mortality[2]**	**~$575K Cost[3]**
Within 5-10 years	Within 10 years	>14,000 Waiting List

25% of People on Waiting List Die Each Year Before Receiving a Liver Transplant[1]

[1]Nourredin, et al. *Curr Gasterol Rep*. 2013; [2]Serrano, et al. EASL. 2011; [3]*UPMC Health Beat*. 2018. US liver transplant cost.

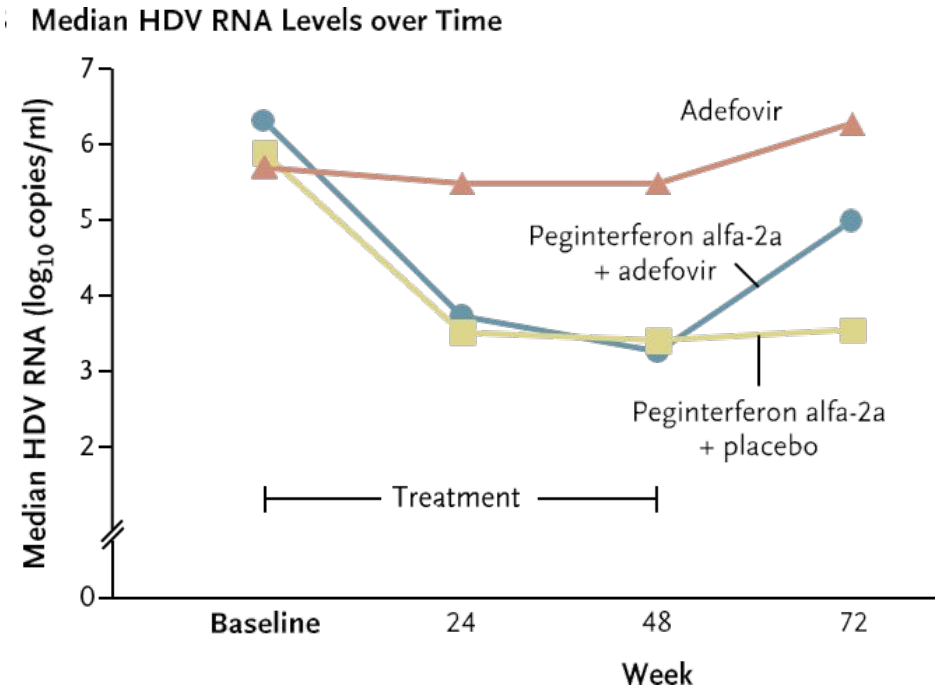
Treatment

HDV Treatment

- No FDA approved therapy for HDV
- PEG IFN alpha is only drug with any demonstrated efficacy
- 20-25% response rate and rarely achieve sustained viral clearance
- Suboptimal due to:
  - Significant side effects (including cytopenias)
  - Limited efficacy
  - High long-term relapse rates

Turon Lagot, et al. *J Clin Med. 2020*

HDV Treatment



- ~2.5 log decline in median HDV RNA at EOT
- 25% neg 24 wks post Rx in patients receiving PEG-IFN
- 0% with nucleoside analog alone (no effect on HBsAg)

HIDIT-1; Wedemeyer, et al. *NEJM*. 2011.

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

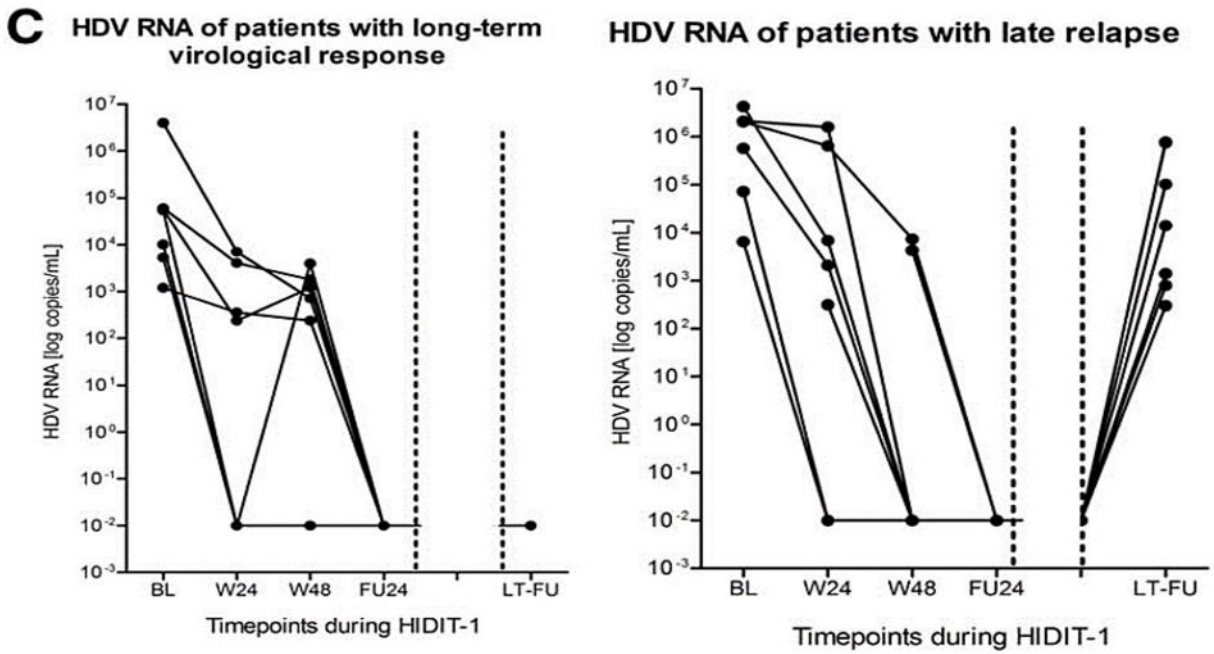
N=120

	EOT	f/u week 24
	Week 96	Week 120
PEG IFN 2a + TDF	28 (48%)	18 (31%)
PEG IFN 2a + PBO	20 (33%)	14 (23%)
CI	1·84 (0.86–3·91),	1·46 (0·64–3·31),
p value	0·1154	0·37

>50% of "24-week SVRs" relapse at 4 years: not like HCV!

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

Late Relapse is Common with PEG IFN alpha



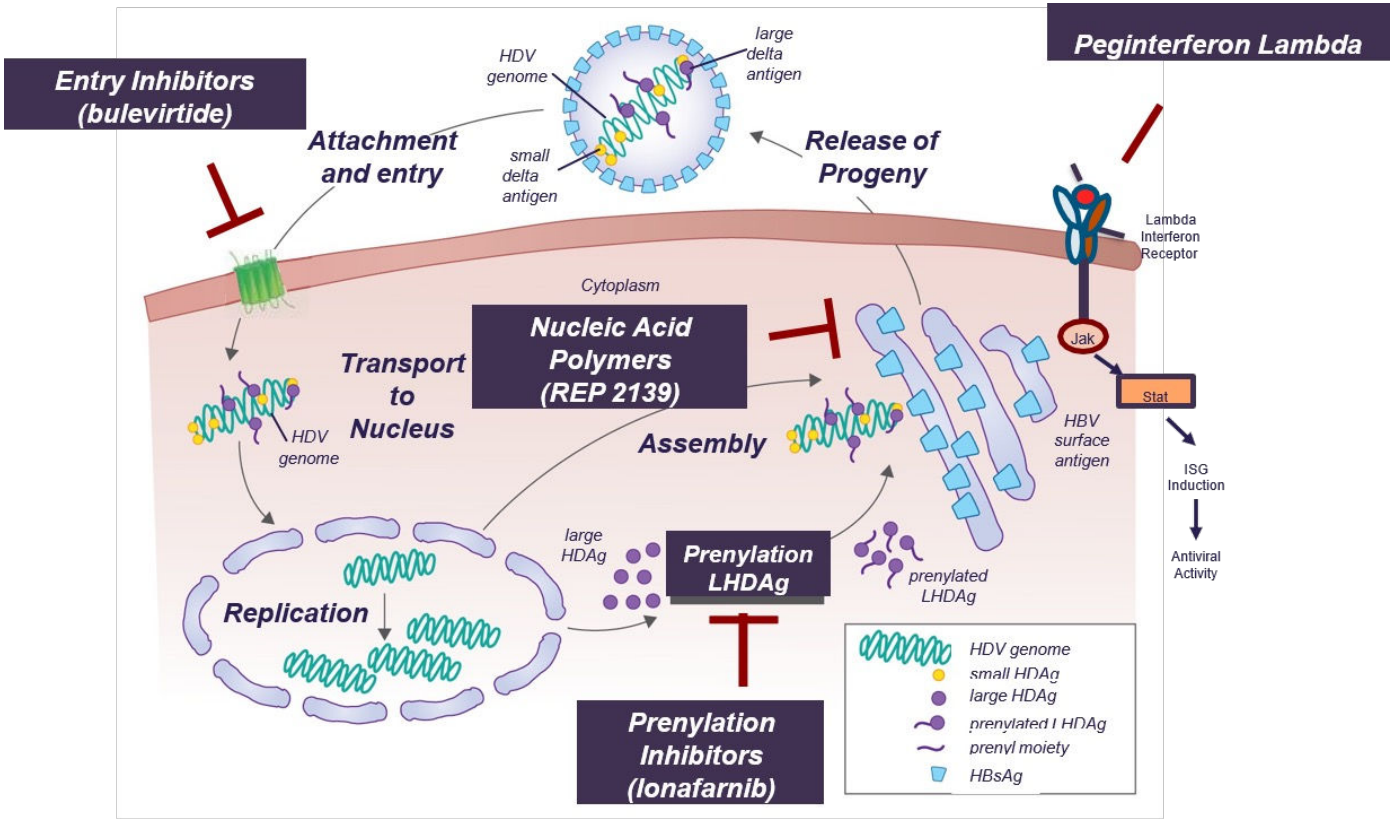
- Long term f/u of HIDIT-1
- Of 16 patients that were negative for HDV RNA at 6 months after therapy ended, 9 will test positive during long term f/u

Heidrich, et al. *Hepatology* 2014.

HBV Functional Cures Will Not Eradicate HDV

- Approved HBV nucleos(t)ide treatments only suppress HBV DNA
  - They do not affect HBsAg and have no effect on HDV
- Investigational HBV treatments target functional cure
  - Not expected to completely eliminate HBsAg needed by HDV

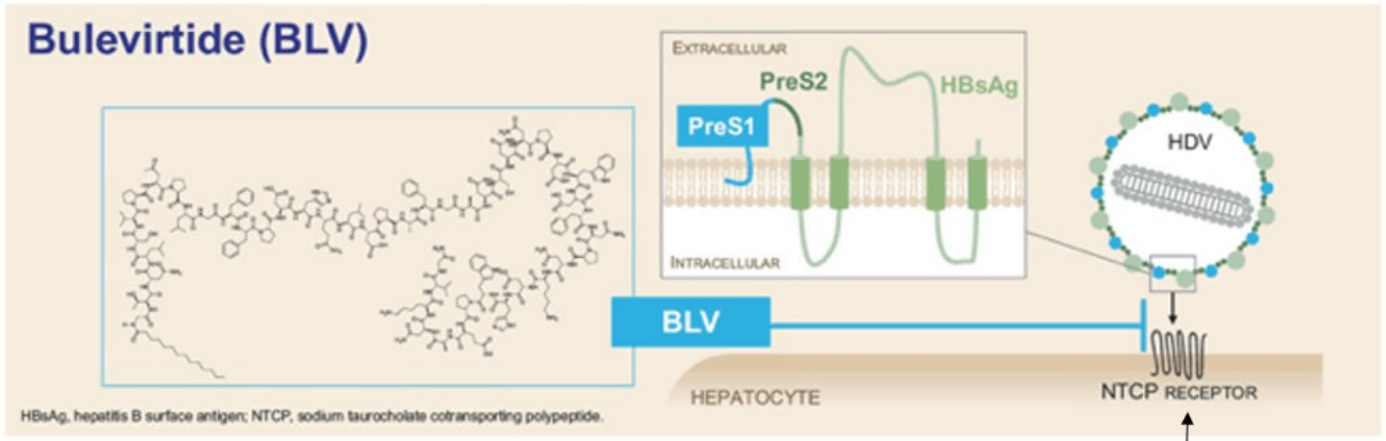
HDV Treatments in Development



HDV Treatments in Development

Treatment	Company	Stage of Development	
		Phase 2	Phase 3
Lonafarnib	EIGER BIOPHARMACEUTICALS	Daily Oral	
Peginterferon Lambda	EIGER BIOPHARMACEUTICALS	Weekly SQ injection	
Bulevirtide	Gilead MYR	Daily SQ injection	
Rep-2139	replicor	Weekly IV infusion	

Bulevirtide (Myrcludex, Hepcludex)
A Novel HBV Entry Inhibitor



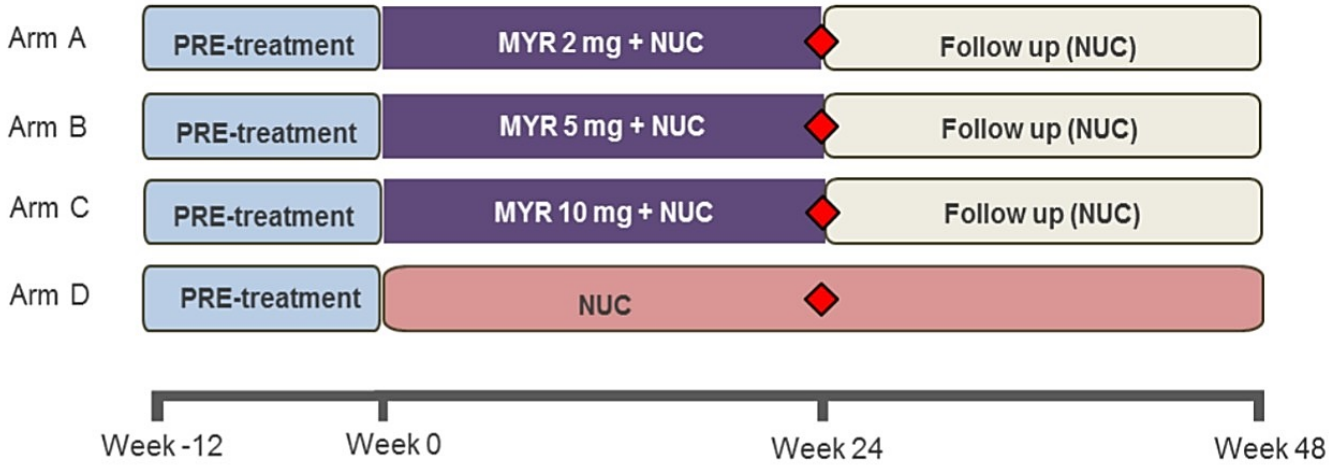
- First-in-class entry inhibitor for treatment of chronic HDV infection

Bile acid receptor

- Synthetic 47 aa lipopeptide resembling pre-S1 portion of HBsAg, binds to bile acid receptor (NTCP), blocking viral entry
- Development program evaluated BLV 2 mg or 10 mg alone, with or w/out PEG IFN and PEG IFN alone
- Targets NTCP (bile acid receptor)
- Subcutaneous dosing
- Approved in Europe mid-2020 at 2 mg dose SQ daily based on early results in ~150 patients

Urban S et al, Recent Adv Clin Prac Gut 2021;0:13

Phase 2b, Open-Label Bulevirtide / TDF Study



Primary Endpoint

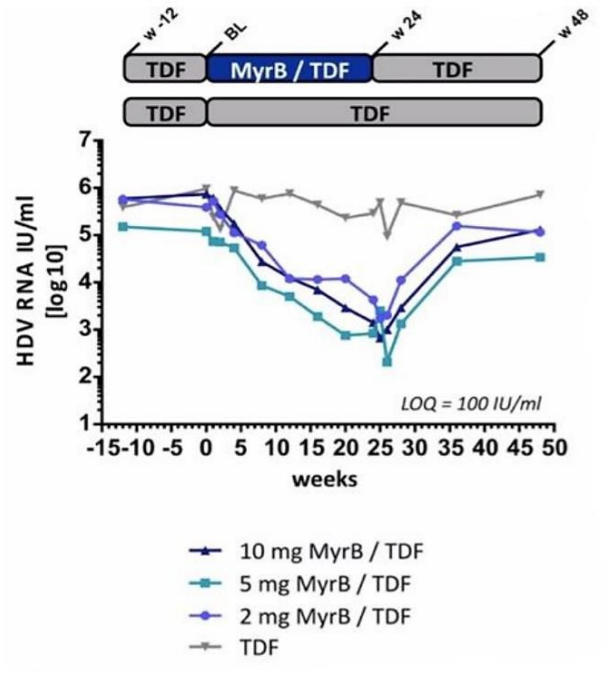
- HDV RNA < LLOD at 24 weeks post-tx (Week 72)

Secondary Endpoint

- HDV RNA < LLOD at Week 48
- ALT nl at Week 48, 72
- HDV RNA > 2 log decline and ALT nl at Week 48, 72
- HBsAg undetectable or > 1 log decline at Week 48, 72

Wedemeyer, et al. EASL. 2018.

Phase 2b, Open-Label Bulevirtide / TDF Study

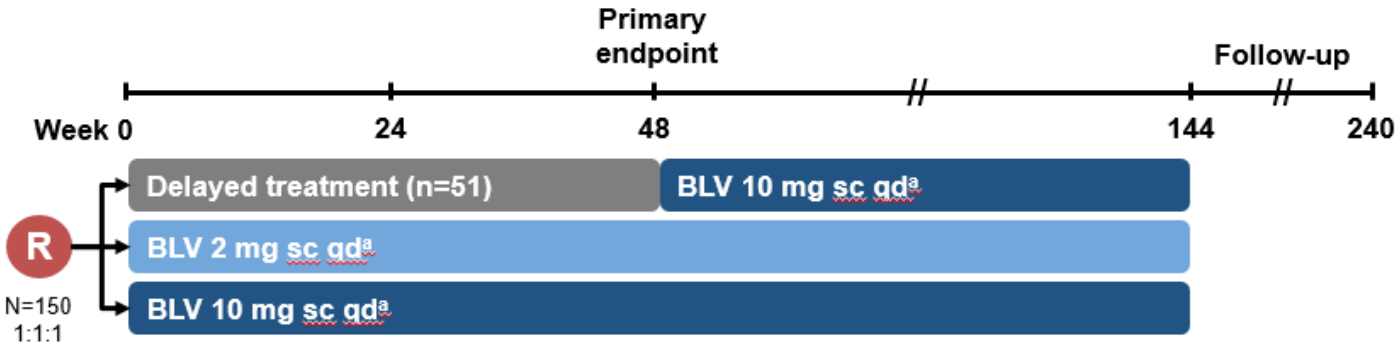


Regimen	Median HDV RNA Change from Baseline at Week 24
2mg MyrB/TDF	-1.75
5mg MyrB/TDF	-1.60
10mg MyrB/TDF	-2.70
TDF	-0.18

Modeling suggested 2-3 years of continuous treatment might be needed to achieve HDV RNA negativity. Wedemeyer, et al. EASL. 2018.

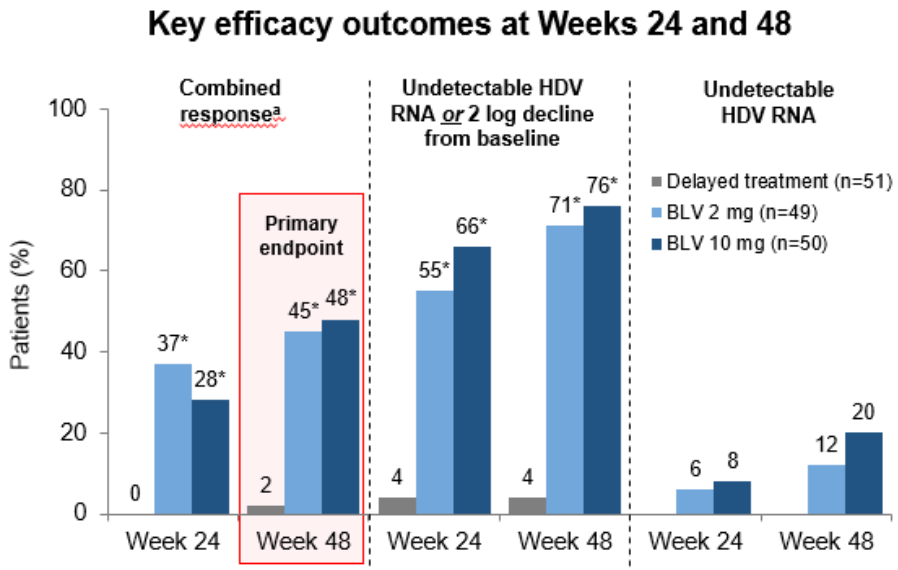
MYR301: Phase 3, Randomized, Open-label Trial of Bulevirtide Monotherapy for Patients with Chronic Hepatitis Delta

Key inclusion criteria:
- CHD with/without cirrhosis and CPT ≥7
- ALT >1x to <10x ULN
- Platelets ≥60,000/mm^3
- Controlled HIV coinfection allowed

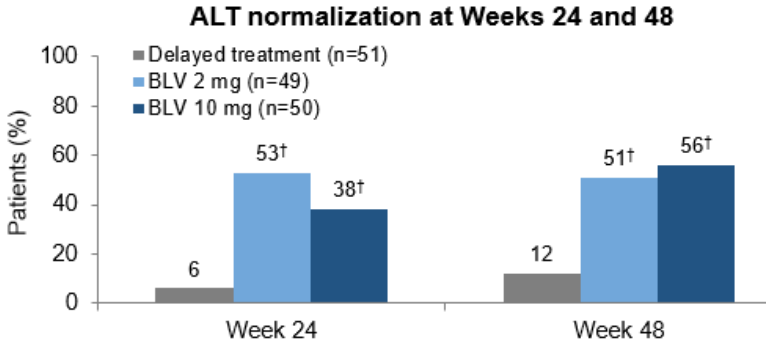


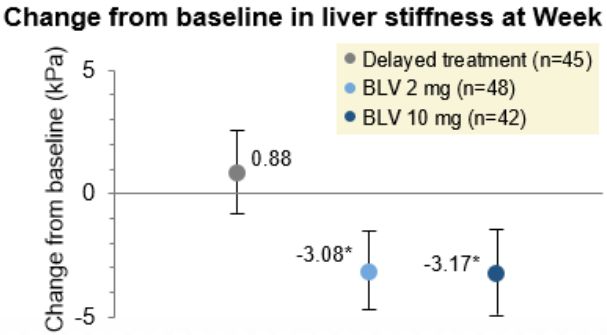
Wedemeyer H, et al. EASL 2022. #GS006
Behrendt et al. Liver International 2022, epub ahead of print

MYR301: Phase 3, Randomized, Open-label Trial of Bulevirtide Monotherapy for Patients with Chronic Hepatitis Delta



*P<0.0001 vs delayed treatment arm; [a]Combined response defined as undetectable HDV RNA or ≥2 log IU/mL decline from baseline and ALT normaliza





*P=0.001; †P<0.0001 vs delayed treatment arm

Wedemeyer H, et al. EASL 2022. #GS006
Behrendt et al. Liver International 2022, epub ahead of print

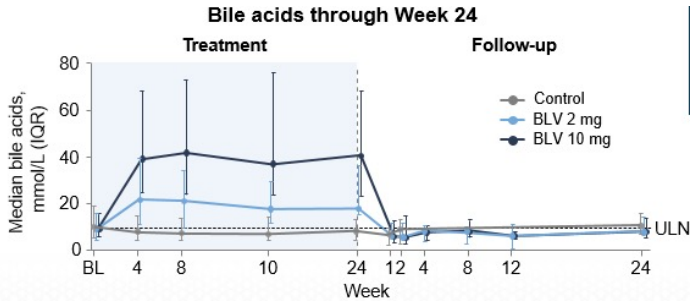
MYR301: Phase 3, Randomized, Open-label Trial of Bulevirtide Monotherapy for Patients with Chronic Hepatitis Delta

Data are n (%)	Delayed treatment (n=51)	BLV 2 mg (n=49)	BLV 10 mg (n=50)
Any AE	39 (77)	40 (82)	44 (88)
Grade 3/4	3 (6)	5 (10)	4 (8)
SAE	1 (2)	2 (4)	1 (2)
AEs leading to discontinuation	0	0	0
TRAEs	0	24 (49)	36 (72)
AEs of interest			
Headache	0	9 (18)	10 (20)
Dizziness	0	2 (4)	2 (4)
Nausea	2 (4)	3 (6)	4 (8)
Pruritus	0	6 (12)	8 (16)
Fatigue	1 (2)	5 (10)	8 (16)
ISRs	0	8 (16)	15 (30)

- No deaths
- ISRs mild to moderate in severity
- Asymptomatic total serum BA and eosinophils elevations in BLV arms

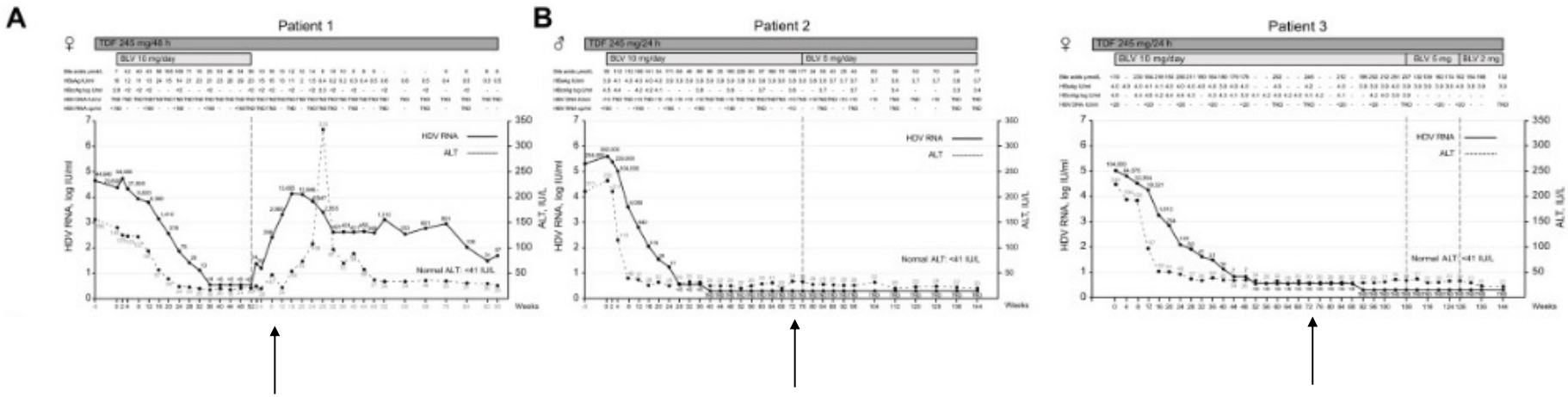
*Injection site reactions

Wedemeyer H, et al. EASL 2022. #GS006



Lampertico P, et al. EASL 2022. #SAT352.

Myrcludex Monotherapy in Compensated Cirrhotics With HDV: Safety and Effectiveness Beyond 2 Years of Treatment



1 patient with recurrent viremia after stopping therapy

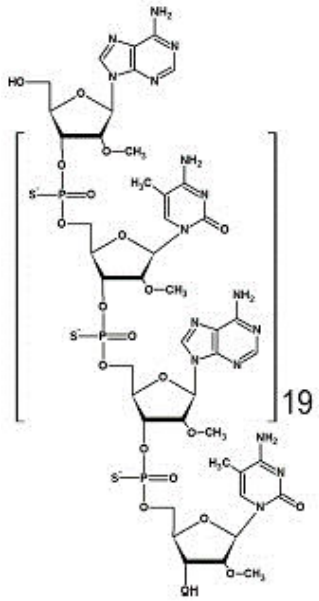
2 patients who remained on therapy had persistent viral suppression with normalization of ALT
Improved clinical outcomes noted (resolution of varices)

- *These data may be a sign of how bulevirtide will be used…as a long-term maintenance therapy*

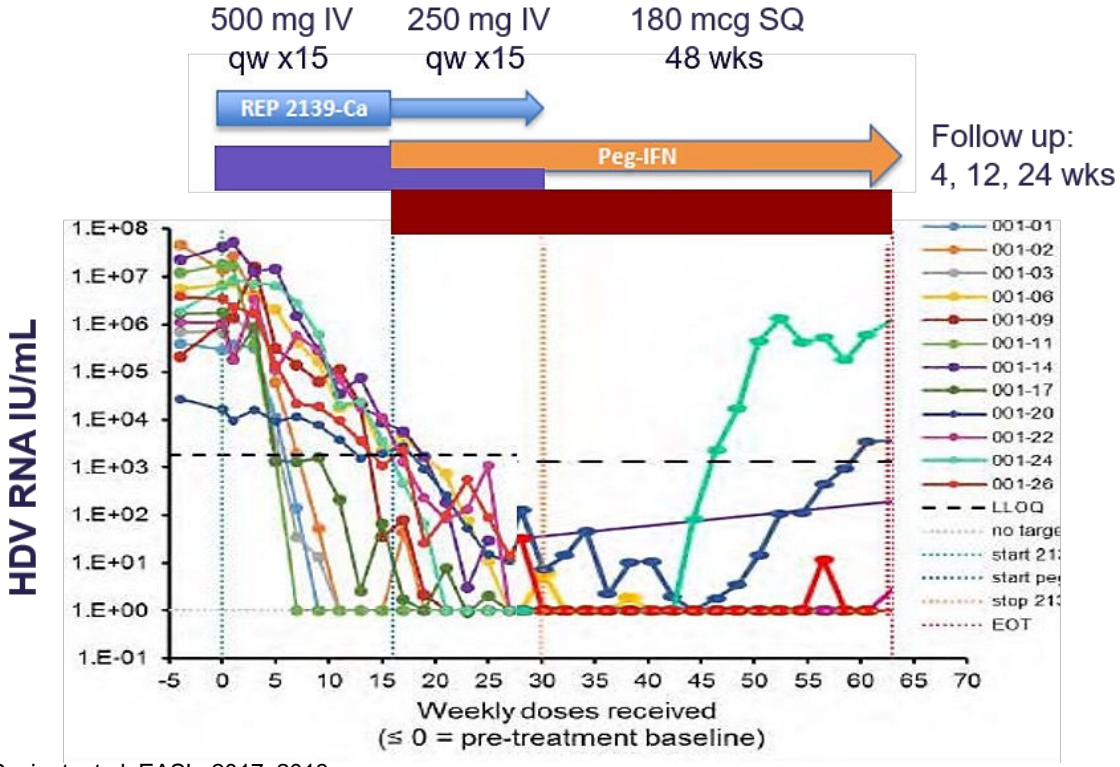
Loglio A et al, J Hepatology 2022;76:464-469

REP 2139

- Nucleic acid polymers (NAPs) are oligonucleotides with broad spectrum in vitro antiviral activities
- Reported to act via entry inhibition in other viruses
- Also proposed to bind to amphipathic protein structures
- These amphipathic protein structures are common in viral proteins, but are also found in key host cell proteins
- REP 2139 inhibits secretion of HBsAg from cells



Phase 2 REP 301 Study



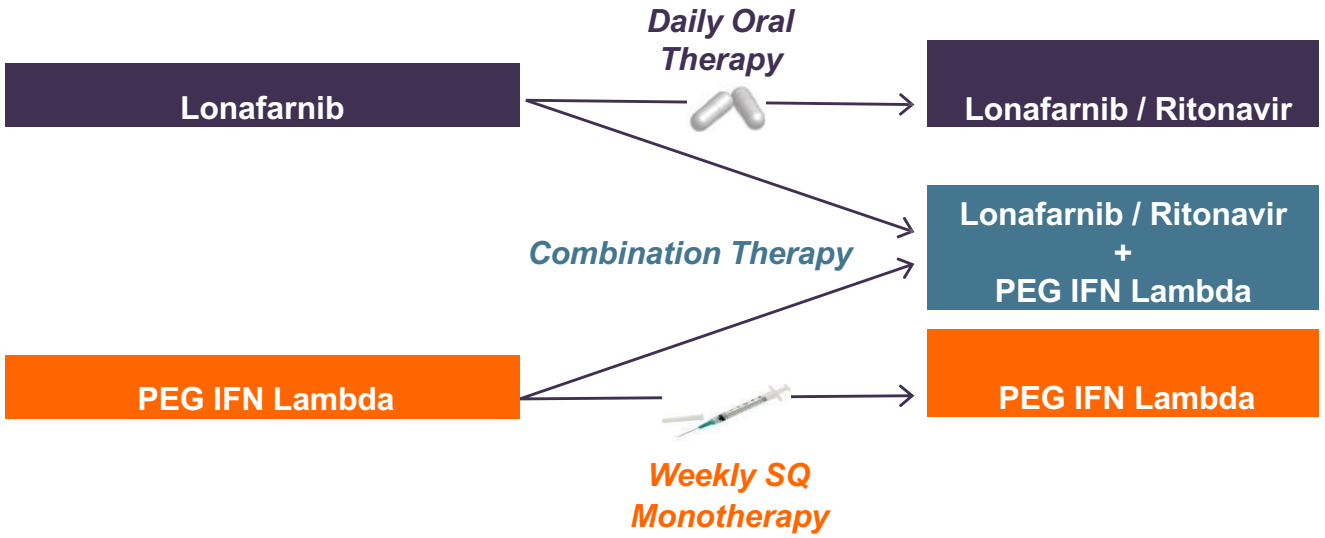
Bazinet, et al. EASL. 2017, 2018;
Vaillant, et al. EASL. 2015.

- 12 HDV pts in Moldova
- Anti-HDV/RNA +
- HBsAg > 1000
- Non-cirrhotic

- Responses mostly maintained on interferon
- 5 patients rebound with cessation of IFN (EASL 2017)
- Responses maintained to date (EASL 2018)

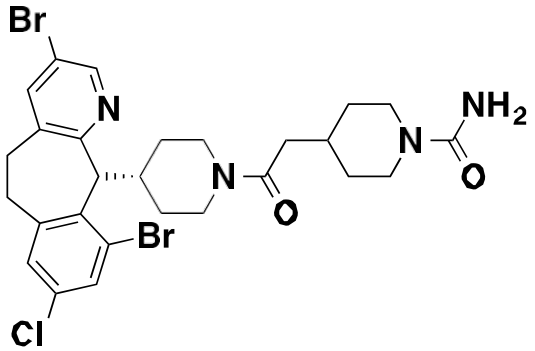
First-in-Class Treatments in Development for HDV

Multiple Options to Treat HDV

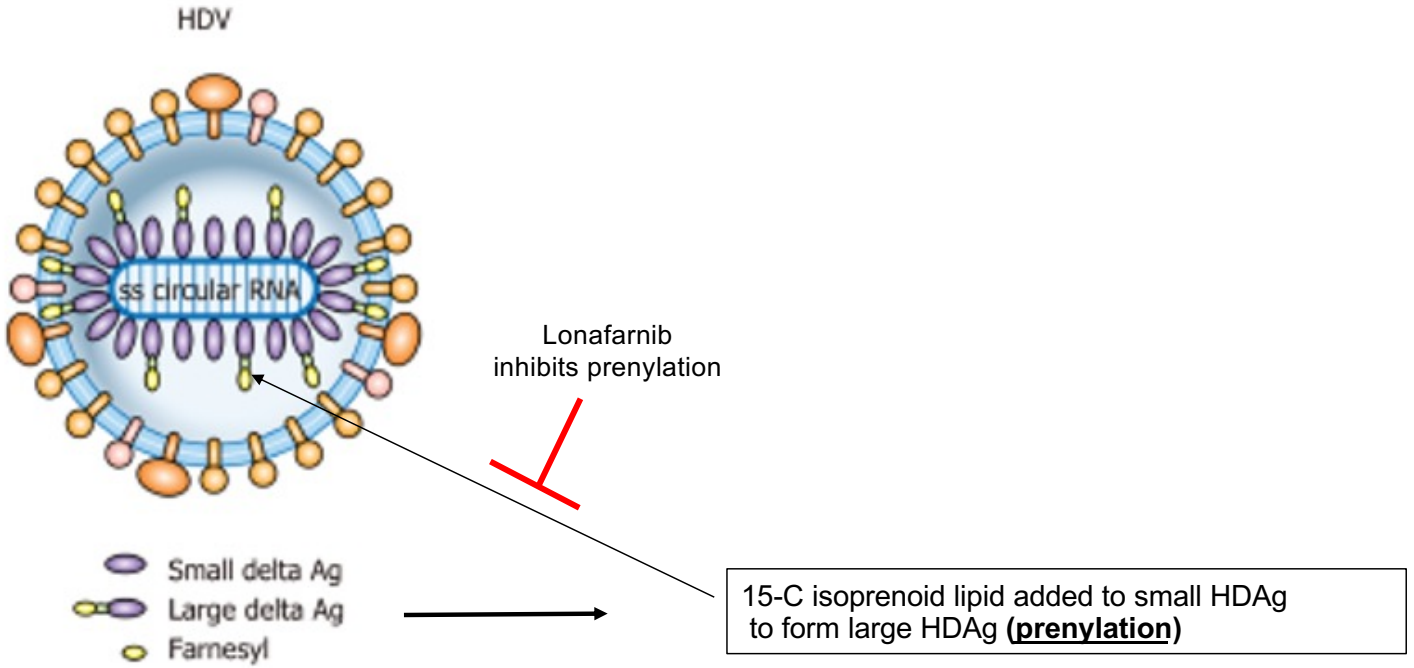


Lonafarnib

- Small molecule, first-in-class, oral prenylation inhibitor
- Well-characterized through Phase 3
  - > 2,000 subjects dosed in oncology program by Merck (Schering)
  - Dose limiting toxicity is GI (class effect)
- Over 120 HDV patients dosed across international sites
- US & EU Orphan Designation, FDA Breakthrough and EMA PRIME Designation
- Broad range of lonafarnib + ritonavir doses and durations studied
- US and multiple international sites



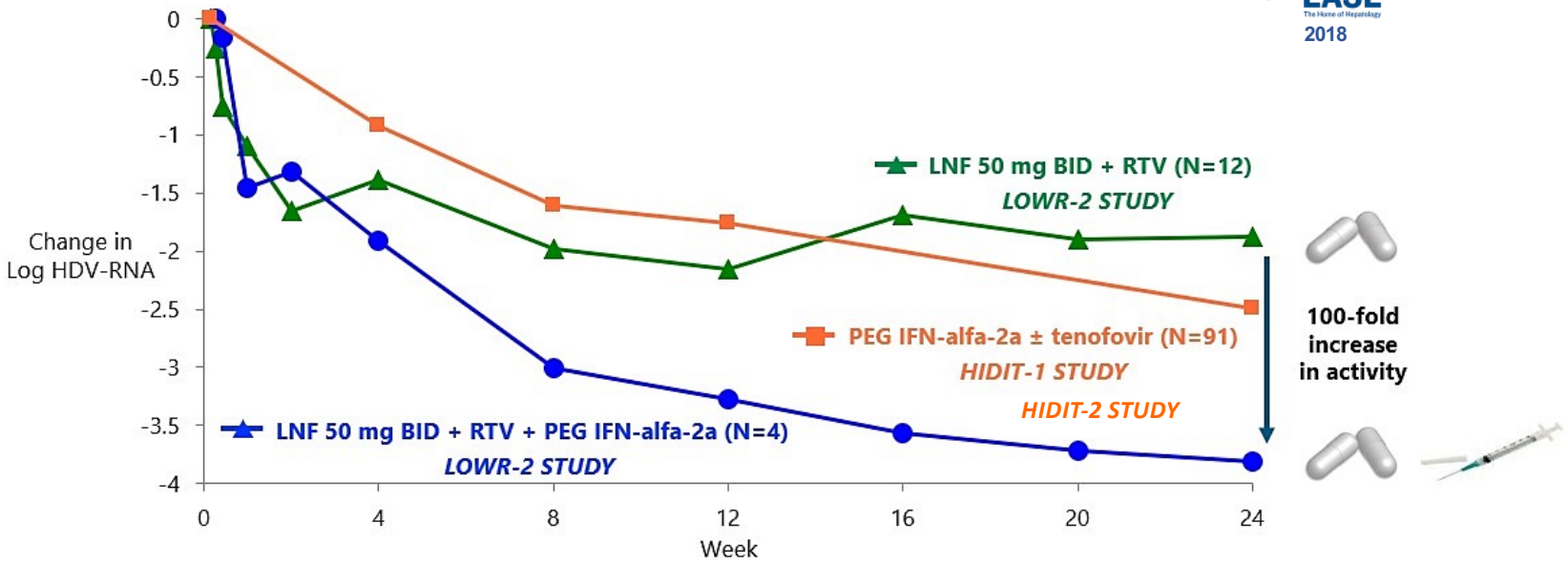
Hepatitis D Virus (Delta): The Most Pathogenic Hepatitis Virus



Adapted from Wang M, Casey P. Nat Rev Mol Cell Biol 2016;17:110–122

LOWR: Phase 2 Lonafarnib Study

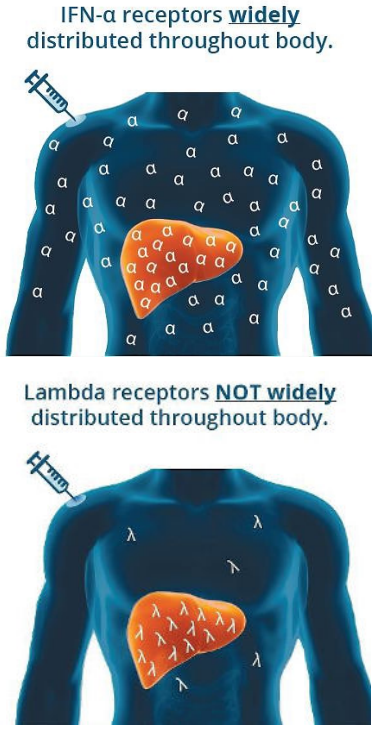
Compared to PEG-IFN-alfa-2a Alone



Yurdaydin, et al. EASL. 2018. LOWR-2; Wedemeyer. et al. 2019. HIDIT-2.

Peg IFN Lambda: A Better Tolerated Interferon

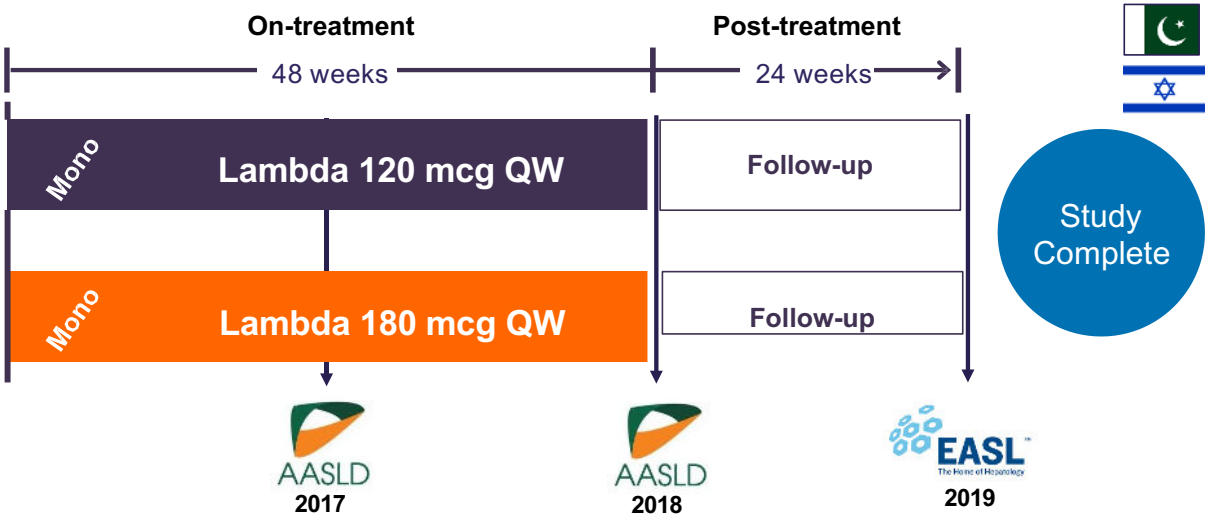
- A novel, first-in-class Type III interferon
- Binds to a unique receptor versus Type I interferons
  - Highly expressed on hepatocytes
  - Limited expression on hematopoietic cells and CNS cells
- Uses similar downstream signaling pathway as Type I interferons
- Studied in > 3,000 subjects across 17 clinical trials (HCV / HBV)
- Comparable antiviral activity with less of the typical IFN alfa related side effects



Chan, et al. *J Hepatol*. 2016 May;64(5):1011-1019.

LIMT: Phase 2 Lambda Study

A Better Tolerated Interferon for HDV Monotherapy



Primary Endpoint:

- Evaluate Safety, Tolerability, Efficacy

Secondary Endpoint:

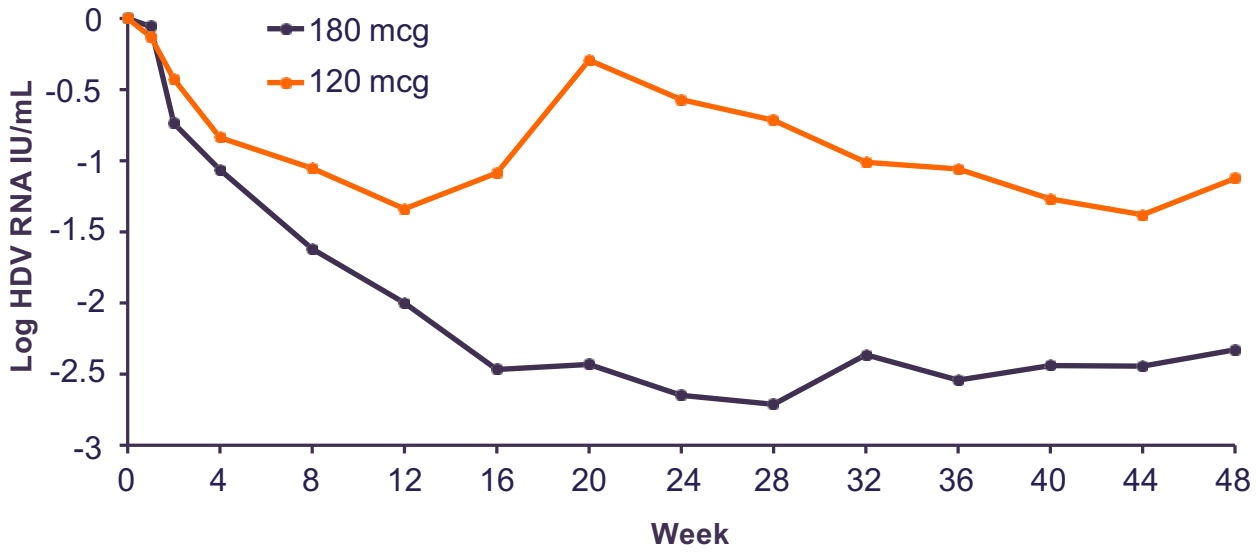
- Proportion of Patients with HDV RNA BLQ 24 weeks after EOT

Etzion O, et al. 2017. Robogene® 2.0 HDV RNA PCR assay. LLOQ = 14 IU/mL.

Peginterferon Lambda Activity Through Week 48

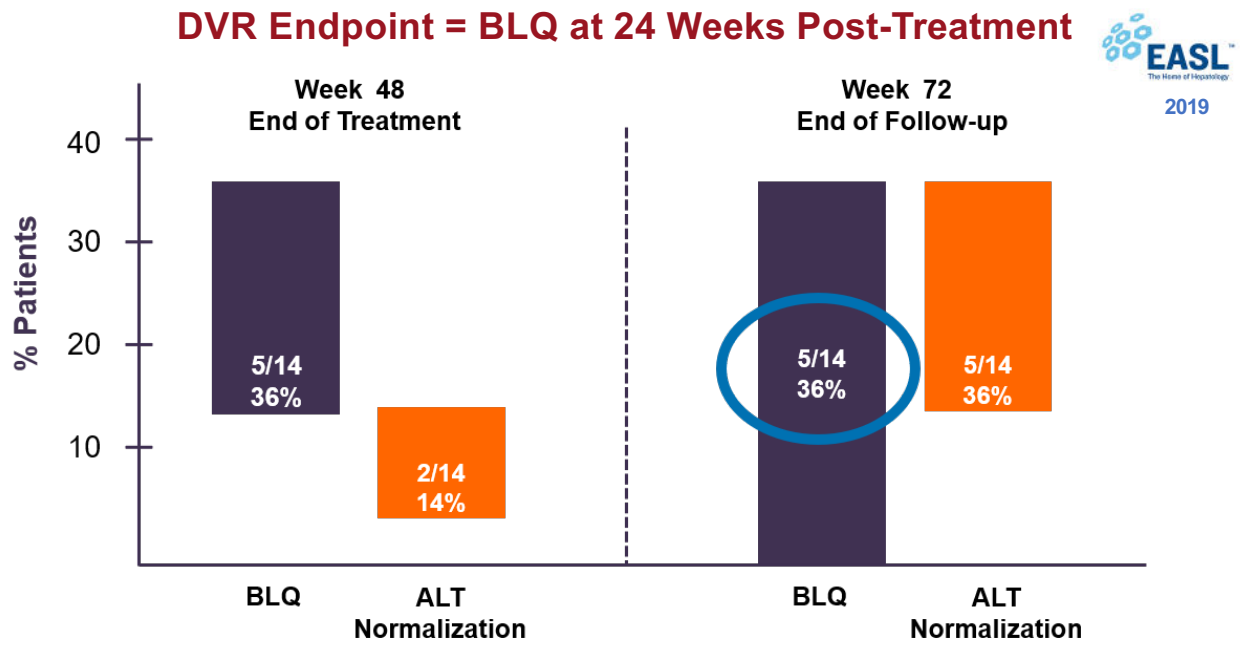
Lambda 180 mcg has Comparable Antiviral Activity to Alfa 180 mcg with Improved Tolerability

EASL 2019



Etzion O, et al. 2017. Robogene® 2.0 HDV RNA PCR assay. LLOQ = 14 IU/mL.

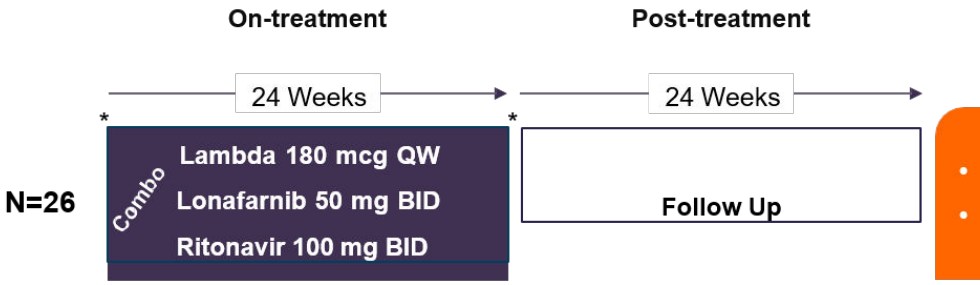
Peginterferon Lambda: 36% Durable Virologic Response



Etzion et al, EASL 2019, LIMT Phase 2 Study; Robogene® 2.0 HDV RNA PCR assay, LLOQ = 14 IU/mL; DVR = BLQ at 24 Weeks Post-Treatment

LIFT: Phase 2 Lambda & Lonafarnib Combination Study

A Better Tolerated Interferon for Combination



Primary Endpoint:
- ≥ 2 Log HDV RNA reduction at EOT

Secondary Endpoint:
- Histological Improvement (biopsy confirmed)

- **Dosing**
- **End of Treatment Data Q4'19**

AASLD THE LIVER MEETING® NOVEMBER 8-12 2019 BOSTON

interim EOT data

- Median Decline of HDV RNA: -3.4 Log at Week 24
- 95% of Patients Achieve > 2 Log Decline in HDV RNA at Week 24
- > 50% of Patients Achieve Undetectable or BLOQ HDV RNA at Week 24

Koh C et al, AASLD 2019

Lonafarnib, Ritonavir, and Lambda Interferon for HDV: Interim End-of-Treatment Results – the LIFT Study

Aims:

Evaluate the safety and antiviral effects of therapy with lonafarnib (LNF), ritonavir (RTV), and lambda interferon (LMD) in patients with chronic hepatitis D

Methods:

Phase 2a, open-label, prospective treatment trial in 26 patients for 24 weeks, with 24 weeks of post-therapy follow-up

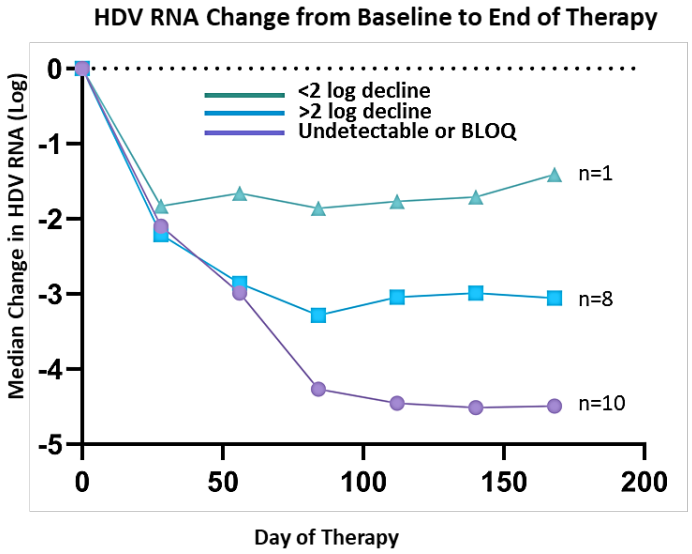
Main Findings:

At the end of therapy (19 of 26 patients), the median HDV RNA decline was 3.4 log IU/ml (p<0.0001) with 10 (53%) patients achieving undetectable or BLOQ HDV RNA in serum.

Conclusions:

Triple combination therapy with LNF/RTV/LMD in chronic HDV patients appears to be safe and tolerable for up to 6 months in most patients.

Koh C, et al., Abstract LO8



58% of patients achieved undetectable or BLOQ* HDV RNA by the end of therapy

Summary

- HDV is the most severe form of viral hepatitis
- HDV remains underdiagnosed
- HBV vaccination is protective against acquiring HDV
- HDV/HBV infection causes more rapid disease progression as compared to HBV monoinfection
- New therapies being developed based upon HDV life cycle
- Several HDV therapies currently in phase 2 and 3 development
  - Bulevirtide and lonafarnib
- Promising future!

The Near Future For HDV Therapy?

- Hoped for new treatments: Bulevirtide, lonafarnib, PEG IFN lambda, nucleic acid polymers (NAPS)
- Bulevirtide approved in Europe, possibly in US soon
- Viral suppression enhanced with addition IFN alpha for bulevirtide, lonafarnib
- Issue is whether rates of sustained response will be significantly enhanced with combination therapy and whether IFN will improve this
- Maintenance therapy with a safe monotherapy not associated with resistance may be preferred by some clinicians and patients