NCSCG
8TH ANNUAL LIVER SYMPOSIUM

JANUARY 21, 2023
HOTEL NIA | MENLO PARK, CA

NCSCG 8th Annual Liver Symposium Updates in Management of HBV/HDV

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JANUARY 21, 2023

Disclosures

- I have no relevant conflicts of interest to disclose.

Updates in Management of HBV and HDV

- Objectives:

- Gain familiarity with updated HBV and HDV epidemiologic data and understand current strategies towards elimination
- Understand current guidelines for HBV/HDV management, including treatment indications and monitoring
- Understand limitations of current treatments for HBV/HDV and new definitions of cure
- Become familiar with emerging therapies for HBV/HDV and expected treatment endpoints

HBV Epidemiology Update: What is the current burden of disease?

- Worldwide: 272 million people living with chronic hepatitis B infection in 2020
  - 2.4 million in the U.S.
- 1.5 million new infections annually
  - Rising rates of acute HBV in U.S. due to IDU
- Highest prevalence in Western Pacific (116 million), Africa (81 million), Eastern Mediterranean (18 million) and South East Asia (16 million)
- Represents a substantial public health problem as the leading cause of hepatocellular carcinoma (HCC) worldwide
- Life-time risks of HCC and liver-related mortality estimated to be 40-50% for men, 15% for women without treatment

Robinson, Wong et al. Clin Liver Dis. 2023 Feb;27(1):17-25

HDV Epidemiology Update: What is the current burden of disease?

- Worldwide: estimated 20 million affected globally
- Most common in Eastern and Southern Europe, Mediterranean, Middle East, West and Central Afria, East Asia and Amazon Basin
- US:
  - Recent data showed 8% of CHB patients were coinfected, of which 73% had cirrhosis
  - HDV seroprevalence rising from 29% to 50% among IDUs
- Represents the most severe form of chronic viral hepatitis, conferring a higher risk of morbidity and mortality due to ESLD and HCC

Robinson, Wong et al. Clin Liver Dis. 2023 Feb;27(1):17-25

Epidemiology Update: What is being done to achieve HBV/HDV elimination?

- **HBV Screening and Vaccination**
  - Aggressive campaigns for interruption of mother-to-child transmission
    - CDC/USPSTF: All pregnant women should be screened at first prenatal visit
    - AASLD: Mothers with high HBV VL should receive TDF during pregnancy; newborns should receive HBV vaccine/HBIG
  - CDC now recommends universal one-time screening for HBV for all adults and adults 19-59 should be vaccinated

HBV Treatment

- Renewed efforts to develop better therapeutic strategies for HBV
- Emerging treatments targeting new aspects of viral lifecycle and immune responses
- New therapeutic goal of "functional cure"
  - Loss of detectable HBsAg
  - Appearance of neutralizing anti-HBs

Epidemiology Update: What is being done to achieve HBV/HDV elimination?

- **HDV Screening**
  - AASLD recommends screening for HDV in patients with HIV infection, IDU, MSM, immigrants from areas of high HDV endemicity, and patients with high ALT despite low HBV viral load
  - Experts recommend screening all patients at least once for HDV given higher than expected prevalence, poor outcomes without treatment and the advent of new treatments

HDV Treatment

- Renewed efforts to develop better therapeutic strategies for HDV
- Emerging treatments for HDV targeting new aspects of viral lifecycle and immune responses
- Non-interferon based treatments now showing promising results.

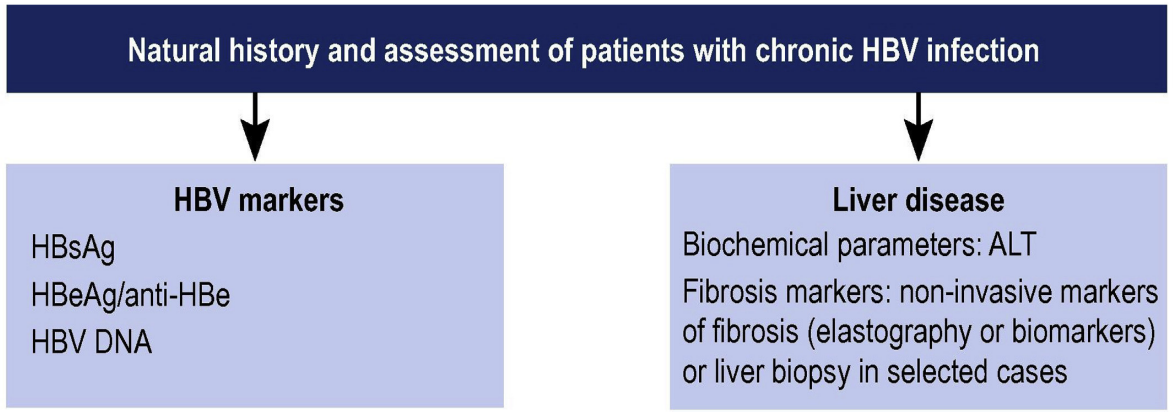
HBV/HDV Treatment Update: Who needs to be treated?

- HBV is a dynamic disease with different phases of infection that do not necessarily follow a linear progression, and HBV antiviral treatment is not indicated for all patients
- To identify patients for treatment, we must distinguish between two main HBV states:
  - **1) Chronic infection**, characterized by detectable HBV viral load, but no hepatic inflammation
    Phase(s): "immune-tolerant", "inactive HBV"
  - **2) Chronic hepatitis,** characterized by detectable HBV viral load accompanied by hepatic inflammation
    Phase(s): "immune-active"
- Monitoring of liver enzymes and HBV viral load every 3-6 months is needed to identify individuals in the "immune-active" phase of HBV infection who require treatment to reduce their risk for progression to cirrhosis, hepatic decompensation, HCC and death.

HBV/HDV Treatment Update: Who needs to be treated?

AASLD	EASL	APASL
ALT >2x ULN or significant histologic disease plus elevated HBV DNA (2,000 IU/ml for HBeAg negative, 20,000 IU/ml for HBeAg positive)	HBV DNA >2000 IU/ml plus ALT >40 IU/ml, moderate liver necroinflammation, moderate liver fibrosis, or age >30 years	Elevated HBV DNA (2,000 IU/ml for HBeAg negative, 20,000 IU/ml for HBeAg positive) plus ALT >2x ULN or moderate-to-severe inflammation or fibrosis
Compensated cirrhosis with HBV DNA >2000 IU/ml or decompensated cirrhosis regardless of ALT level	All compensated and decompensated cirrhosis	Compensated cirrhosis with HBV DNA >2000 IU/ml or decompensated cirrhosis regardless of ALT level
Consider tx for age >40y, family hx of cirrhosis or HCC, extrahepatic manifestations	Consider tx for family hx of cirrhosis or HCC, extrahepatic manifestations	Consider tx for family hx of cirrhosis or HCC, extrahepatic manifestations

HBV/HDV Treatment Update: Who needs to be treated?



	HBeAg positive		HBeAg negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBsAg	High	High/intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10^7 IU/ml	10^4-10^7 IU/ml	<2,000 IU/ml°°	>2,000 IU/ml
ALT	Normal	Elevated	Normal	Elevated*
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis

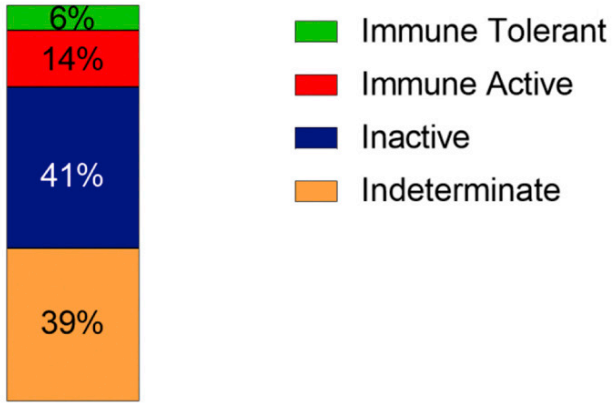
Clinical Gastroenterology and Hepatology 2022 201766-1775DOI: (10.1016/j.cgh.2021.07.036)

HBV/HDV Treatment Update: Who needs to be treated?

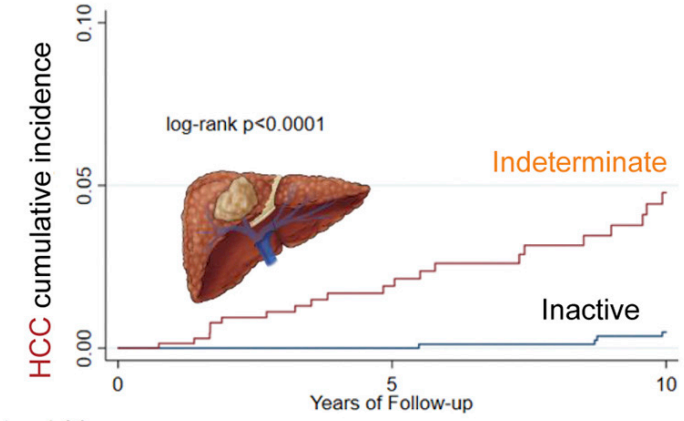
Natural History and HCC Risk in Chronic Hepatitis B Indeterminate Phase

3,366 treatment naïve CHB patients

- ✓ 39% were in the **indeterminate** phase at baseline
- ✓ **HCC** risk among **indeterminate** patients was 14X that of inactive patients



Distribution of clinical phases (%) at baseline



Huang et al.

Clinical Gastroenterology and Hepatology

HBV/HDV Treatment Update: What treatments are currently recommended?

- Current first-line therapies for HBV include entecavir, tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF) and pegylated interferon alfa-2a
- The HBV polymerase inhibitors tenofovir and entecavir are both highly effective at suppressing HBV replication with minimal toxicity and ease of administration, but treatment is generally lifelong for most patients
- Peg-IFN is reasonable for patients preferring finite treatment with 48 weeks, e.g., young patients or women of childbearing potential
- Current treatments offer very limited potential for functional cure (HBsAg loss), but maintained suppression can reverse liver fibrosis and decrease risk s of cirrhosis, HCC and liver-related mortality.

Terrault et al. Hepatology 67(4):p 1560-1599, March 25, 2018.

HBV/HDV Treatment Update: What treatments are currently recommended?

- Combination therapy does not offer any advantage over monotherapy with TDF, TAF, entecavir or Peg-IFN for HBV
- Virologic relapse is common when NAs are discontinued, but can consider for:
  - HBeAg-positive patients after 1 year following HBeAg seroconversion
  - HBeAg-negative patients after HBsAg loss (functional cure, <1% of patients), though some emerging data suggest stopping after 2-3 years of viral suppression
- Limited data suggest TDF may reduce risk for HCC recurrence compared to entecavir

Likhitsup and Lok. Clinics in Liver Disease, 2019-08-01, Vol 23, Issue 3, p401-416.

HBV/HDV Treatment Update: What treatments are currently recommended?

- For HDV: 48 weeks of peg-IFN is the only FDA-approved treatment available
- There are no options for treatment failures and peg-IFN is contraindicated in patients with decompensated cirrhosis
- Unlike HBV, HDV utilizes host RNA polymerase for replication so virus-specific inhibitors were historically difficult to develop
- Functional cure (HBsAg loss) occurs rarely after 1 year of therapy, but sustained HDV virological response (negative HDV RNA) at 6 months after stopping therapy is achievable (up to 23% of patients)

Terrault et al. Hepatology 67(4):p 1560-1599, March 25, 2018.

HBV/HDV Treatment Update: How do we monitor patients on treatment?

- Check liver enzymes and HBV viral load every 6 months
- For TDF:
  - Check renal function every 6-12 months given a low risk of nephrotoxicity
  - Check DEXA scan every 2-3 years given a low risk of bone density loss
- For Peg-IFN: monitor for flu-like sx, fever, fatigue, depression, autoimmune illnesses
- Conduct liver cancer screening with abdominal ultrasound and alpha-fetoprotein measurement in at-risk individuals
  - Asian men >40 years, Asian women >50 years, Africans >20y, family hx of liver cancer, HBV with cirrhosis

Terrault et al. Hepatology 67(4):p 1560-1599, March 25, 2018.

HBV/HDV Treatment Update: Is it helpful to measure HBsAg levels?

- HBsAg level <100 IU/ml in HBeAg-negative patients predicts spontaneous HBsAg loss
- Higher HBsAg levels suggest a lower likelihood of spontaneous clearance
- Declines in HBsAg can help predict response to therapy with Peg-IFN
- HBsAg has been incorporated into scores to predict the risk of HCC, cirrhosis and liver-related outcomes that may guide disease monitoring and inform treatment decisions
- Assay not readily available, but access is increasing

Nguyen et al. Clin Microbiol Rev. 2020 Apr; 33(2): e00046-19.

HBV/HDV Treatment Update: What is our treatment endpoint?

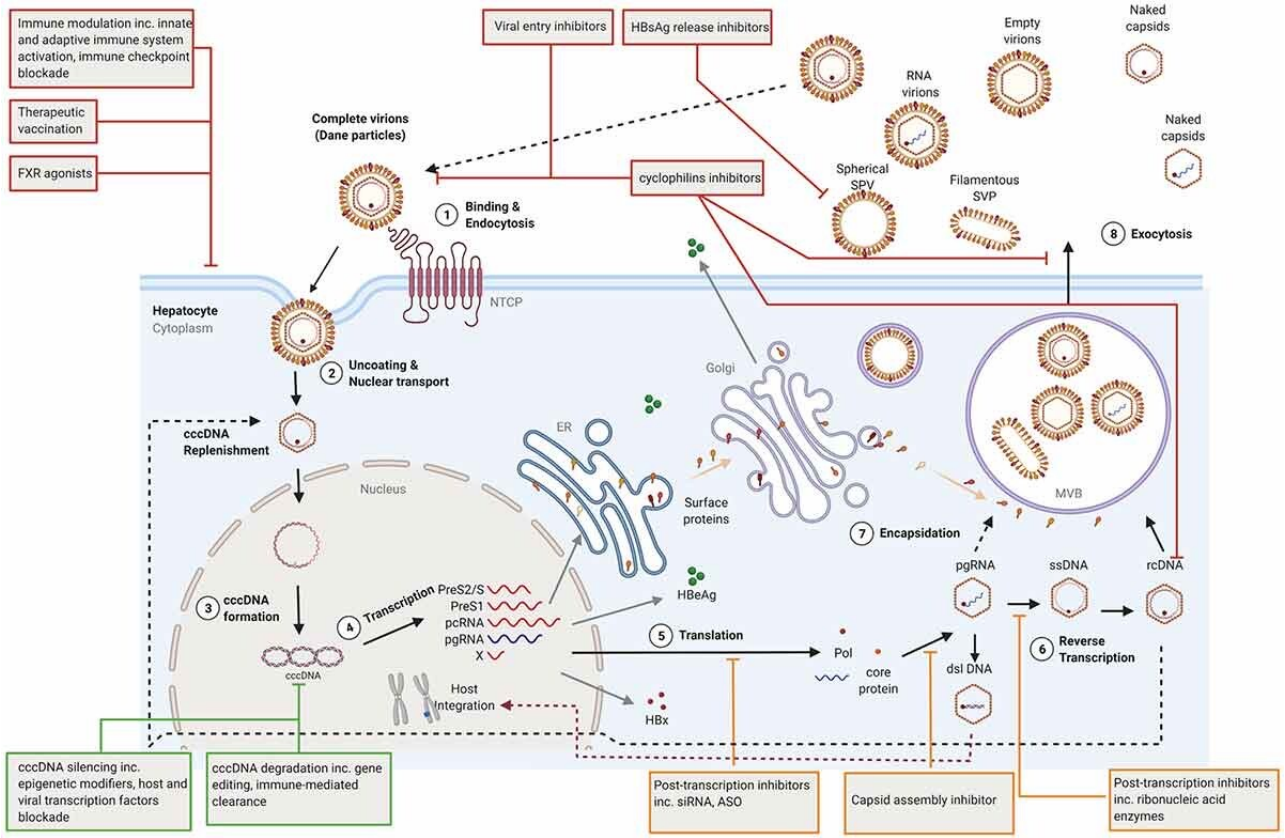
- **Are we able to cure HBV?**

	Complete/Sterilizing Cure	Idealistic Functional Cure	Realistic Functional Cure	Partial "Cure"
Clinical Scenario	Never Infected	Recovery After Acute HBV	Chronic HBV with HBsAg Loss	Inactive Carrier Off Treatment
HBsAg	Negative	Negative	Negative	Positive
Anti-HBs	Negative	Positive	Positive/negative	Negative
HBeAg	Negative	Negative	Negative	Negative
Serum HBV DNA	Not detected	Not detected	Not detected	Low level or not detected
Hepatic cccDNA, transcription	Not detected Not active	Detected Not active	Detected Not active	Detected Low level
Integrated HBV DNA	Not detected	Detected?	Detected	Detected
Liver disease	None	None	Inactive, fibrosis regress over time	Inactive
Risk of HCC	Not increased	Not increased	Declines with time	Risk lower vs active hepatitis

Likhitsup and Lok. Clinics in Liver Disease, 2019-08-01, Vol 23, Issue 3, p401-416.

HBV/HDV Treatment Update: What new drugs are on the horizon?

- **Emerging HBV Treatments**
- Entry inhibitors (Bulevirtide)
- HBsAg secretion inhibitors (REP 2139)
- Core particle assembly modifiers
- Small interfering RNAs
- Genome editing tools (CRISPR/Cas9)
- Immune modulatory therapies
  - Therapeutic vaccines
  - Check-point inhibitors
  - Engineered T cells
  - Activators of innate immune response

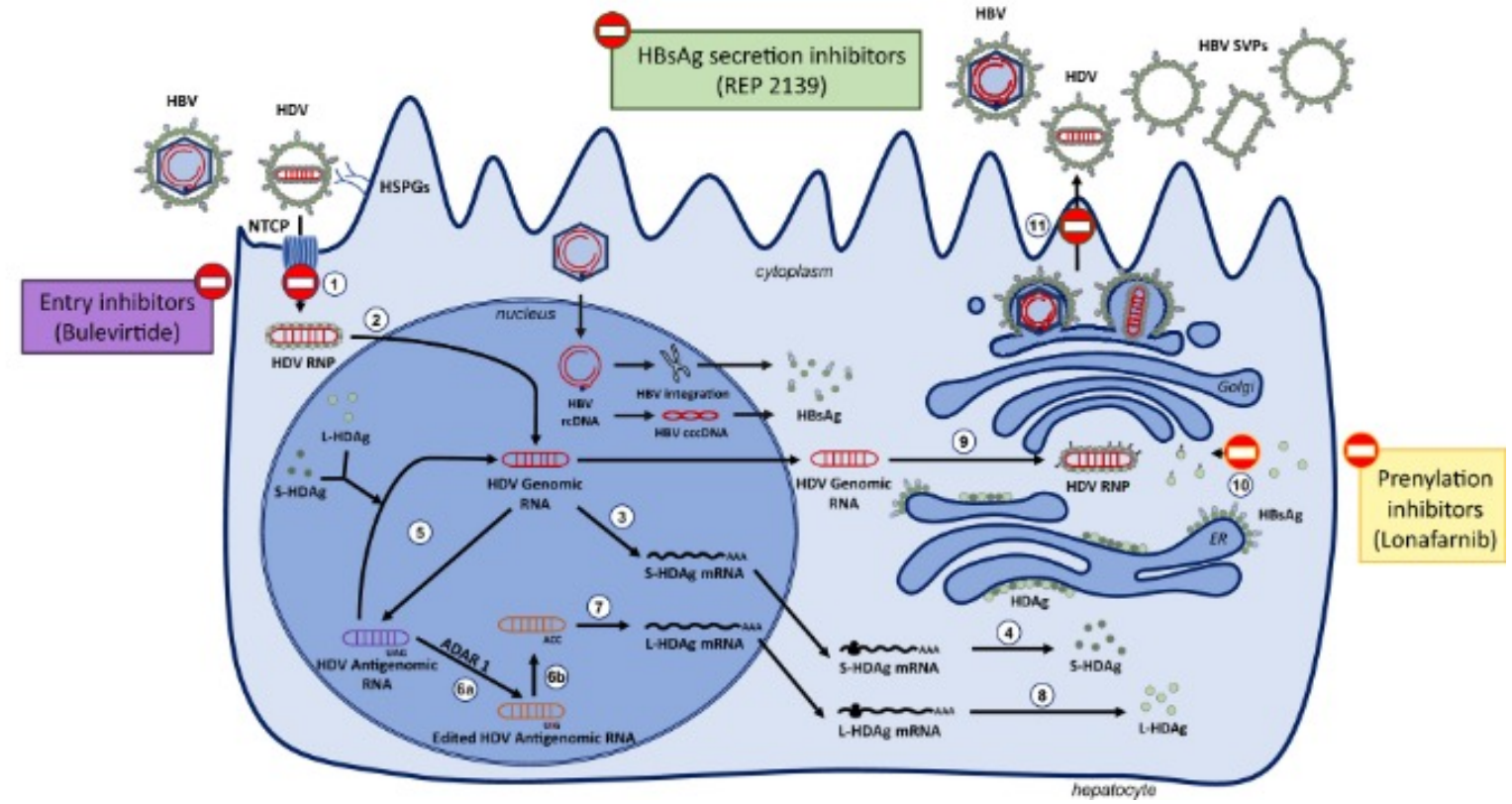


Phillips et al. Virulence. 2022 Dec;13(1):1111-1132.

HBV/HDV Treatment Update: What new drugs are on the horizon?

Emerging HDV Treatments

- Entry Inhibitors (Bulevirtide)
- Prenylation inhibitors (Lonafarnib)
- HBsAg Secretion Inhibitors (REP 2139)



Liver International, Volume: 40, Issue: S1, Pages: 54-60, First published: 20 February 2020, DOI: (10.1111/liv.14356)

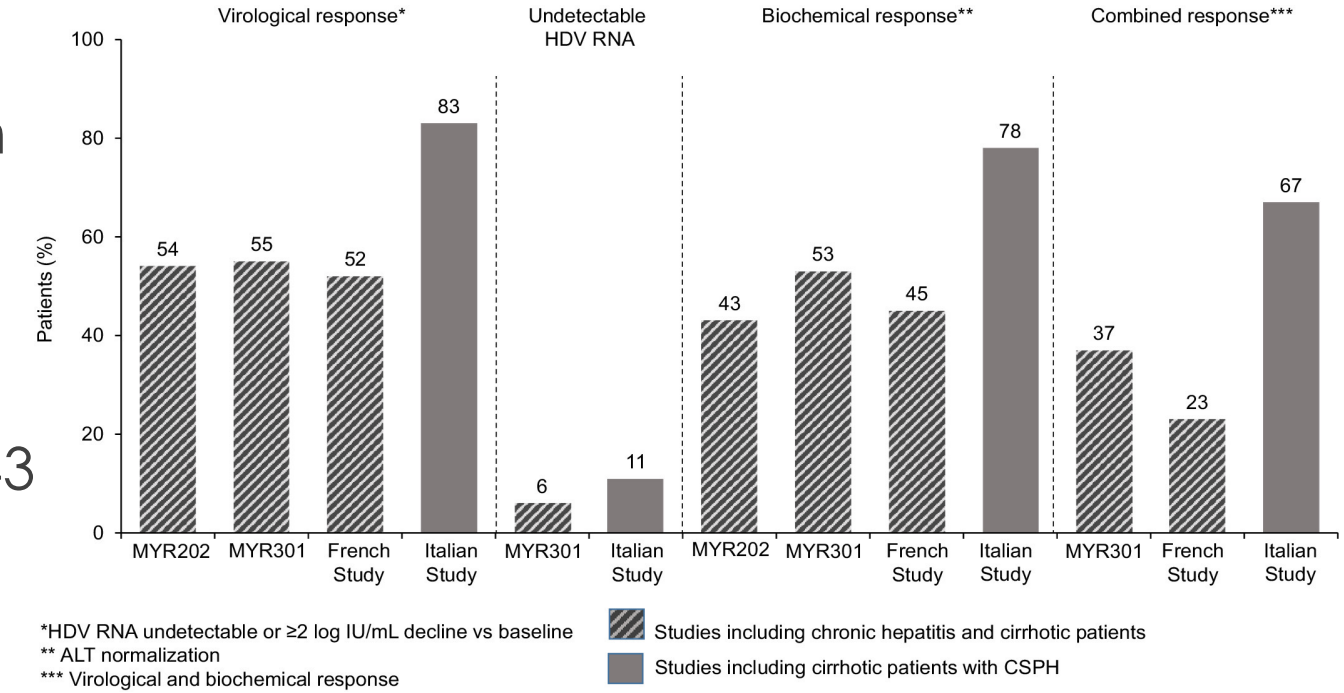
Emerging HBV/HDV Treatments - Bulevirtide

- Peptide entry inhibitor that blocks binding of HBsAg-enveloped particles to NTCP, the cell entry receptor for both HBV and HDV
- Gained provisional EMA approval in 2020 and available in the US through the manufacturer
- Favorable therapeutic potential and safety demonstrated in phase II and III trials and confirmed by real-world studies
- Daily subcutaneous injection used as monotherapy or in combination with pegIFN-alpha and nucleoside analogs

Liver International, Volume: 40, Issue: S1, Pages: 54-60, First published: 20 February 2020, DOI: (10.1111/liv.14356)

Emerging HBV/HDV Treatments – Bulevirtide Monotherapy

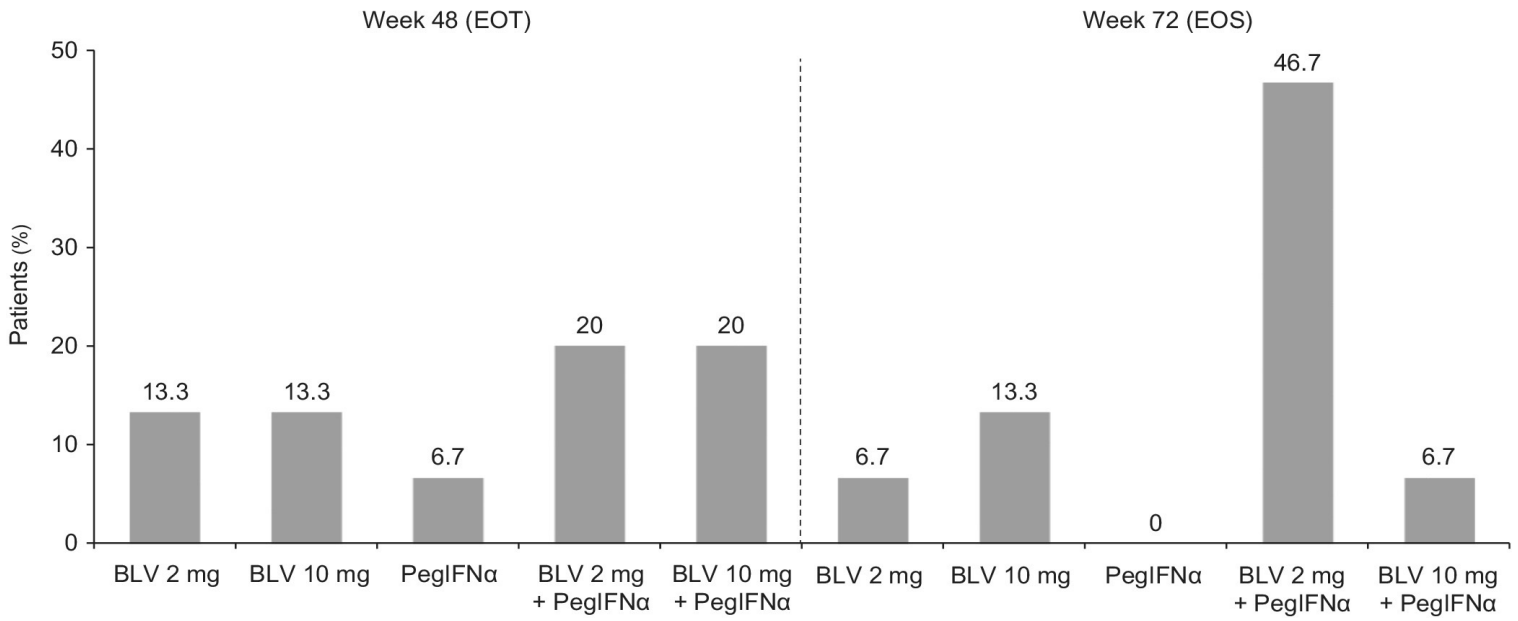
- EOT outcomes after short-term BLV (≤48 weeks):
  - Virologic response: 52-54% (83% in Italian Study of patients with cirrhosis and CSPH)
  - Undetectable HDV RNA: 6-11%
  - Biochemical response (ALT wnl): 43 78%
  - Combined response: 23-67%



Liver International, First published: 09 August 2022, DOI: (10.1111/liv.15389)

Emerging HBV/HDV Treatments – Bulevirtide Monotherapy

- MYR 203 study showed combined response rates 6-months after 48 weeks of BLV:
  - BLV 2mg: 6.7%
  - BLV 10mg: 13.3%
  - No patients achieved functional cure or HBsAg decline >1 log compared to baseline

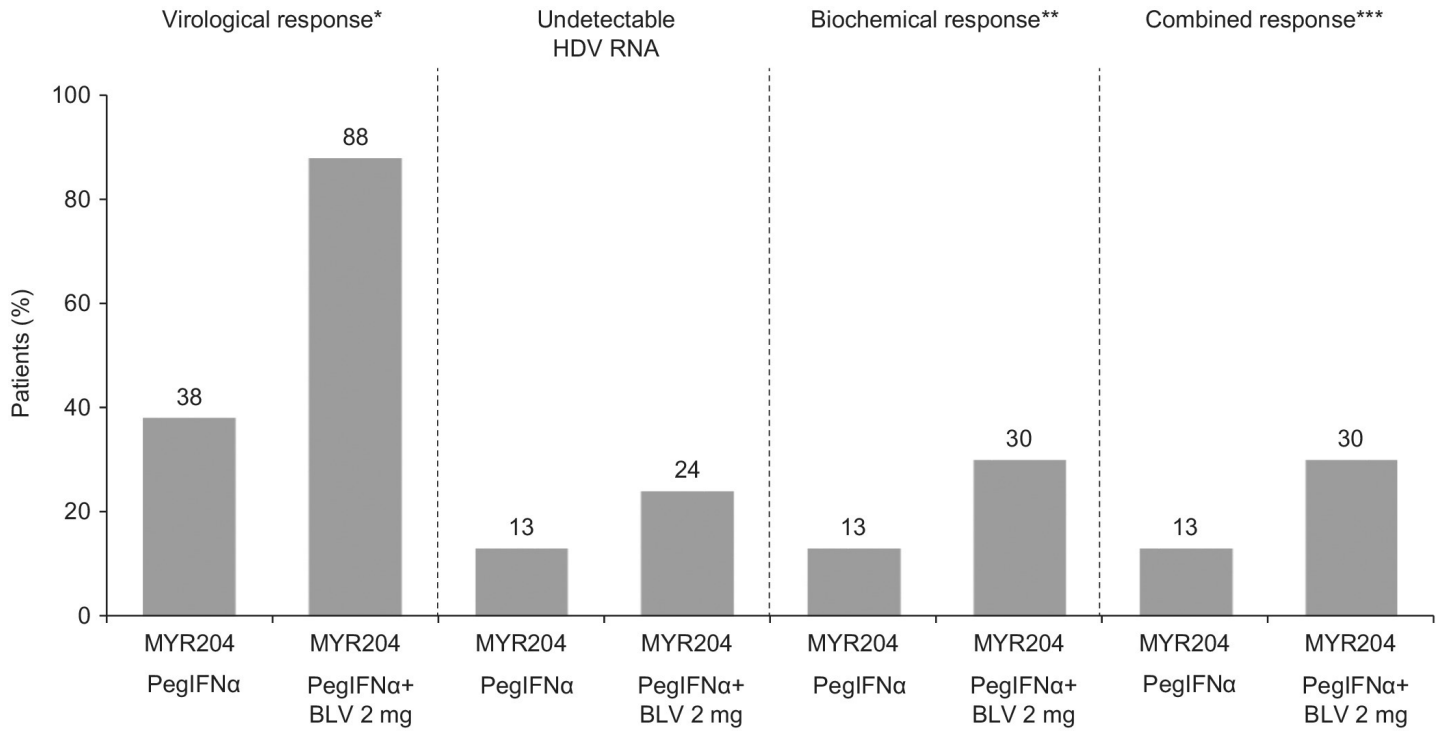


Combined virological and biochemical responses at weeks 48 and 72 in the MYR203 study.

Liver International, First published: 09 August 2022, DOI: (10.1111/liv.15389)

Emerging HBV/HDV Treatments – Bulevirtide + PEGIFN-alpha

- MYR 204 study evaluated BLV 2mg + PEGIFN-alpha vs PegIFN-alpha monotherapy x24w:
- 2x virologic, biochemical and combined response rates
- 24% had undetectable HDV RNA



*HDV RNA undetectable or ≥2 log IU/mL decline vs baseline
** ALT normalization
*** Virological and biochemical response

Liver International, First published: 09 August 2022, DOI: (10.1111/liv.15389)

Emerging HBV/HDV Treatments – Bulevirtide + Peg-IFNa

- French multicenter real-life study extending treatment to 48 weeks showed EOT rates of virologic response of 94% and undetectable HDV RNA of 85%
- MYR 203 study showed 24-week off-therapy combined response of 46.7% for this combination and 40% achieved functional cure (HBsAg loss)
- The combination of pegIFN-alpha and higher BLV doses (10mg) was not superior to low-dose BLV (2mg)
- Importantly, BLV is generally safe and well-tolerated:
  - Clinical and real-world studies even among patients with cirrhosis and CSPH did not demonstrate any major or unexpected adverse events apart from a dose-dependent increase of bile acids

Liver International, First published: 09 August 2022, DOI: (10.1111/liv.15389)

Emerging HBV/HDV Treatments

PLOS ONE

RESEARCH ARTICLE

Treatment of chronic hepatitis B naïve patients with a therapeutic vaccine containing HBs and HBc antigens (a randomized, open and treatment controlled phase III clinical trial)

Mamun Al Mahtab[1☯], Sheikh Mohammad Fazle Akbar[2☯¤*], Julio Cesar Aguilar[3], Gerardo Guillen[3], Euduaro Penton[3], Angela Tuero[3], Osamu Yoshida[4], Yoichi Hiasa[4], Morikazu Onji[5]

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Citation: Al Mahtab M, Akbar SMF, Aguilar JC, Guillen G, Penton E, Tuero A, et al. (2018) Treatment of chronic hepatitis B naïve patients with

Emerging HBV/HDV Treatments

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Gastroenterology 2020;159:521–533

CLINICAL—LIVER

JNJ-56136379, an HBV Capsid Assembly Modulator, Is Well-Tolerated and Has Antiviral Activity in a Phase 1 Study of Patients With Chronic Infection

Fabien Zoulim,[1,2] Oliver Lenz,[3] Joris J. Vandenbossche,[3] Willem Talloen,[3] Thierry Verbinnen,[3] Iurie Moscalu,[4] Adrian Streinu-Cercel,[5] Stefan Bourgeois,[6] Maria Buti,[7] Javier Crespo,[8] Juan Manuel Pascasio,[9] Christoph Sarrazin,[10] Thomas Vanwolleghem,[11,12] Umesh Shukla,[13] John Fry,[14] and Jeysen Z. Yogaratnam[14]

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Emerging HBV/HDV Treatments

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Check for updates

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Citation: Al Mahtab M, Akbar SMF, Aguilar JC, Guillen G, Penton E, Tuero A, et al. (2018) Treatment of chronic hepatitis B naïve patients with

Gastroenterology 2020;158:2180–2194

CLINICAL—LIVER

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CLINICAL LIVER

CLINICAL—LIVER

Safety and Efficacy of 48 Weeks REP 2139 or REP 2165, Tenofovir Disoproxil, and Pegylated Interferon Alfa-2a in Patients With Chronic HBV Infection Naïve to Nucleos(t)ide Therapy

Michel Bazinet,[1] Victor Pântea,[2] Gheorghe Placinta,[2] Iurie Moscalu,[3] Valentin Cebotarescu,[2] Lilia Cojuhari,[2] Pavlina Jimbei,[4] Liviu Iarovoi,[2] Valentina Smesnoi,[4] Tatiana Musteata,[4] Alina Jucov,[2,3] Ulf Dittmer,[5] Adalbert Krawczyk,[5,6] and Andrew Vaillant[1]

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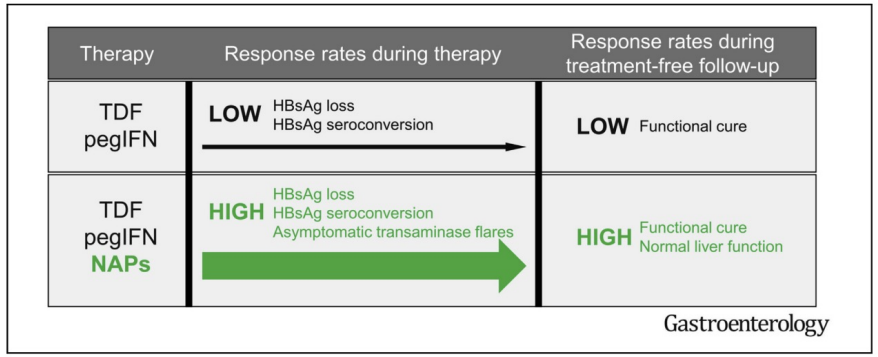

Emerging HBV/HDV Treatments

Assembly inhibitors				
Capsid	**Drug Name**	**Trial NCT**	**Phase**	**Sponsor**
	RO7049389	02952924	2	Hoffmann-La Roche
	GLS4	04147208	2	Sunshine Lake Pharm.
	AB836	04775797	1	Arbutus Biopharm.
	EDP514	04470388	1	Enanta Pharm.
	HRS5091	04480294	1	Jiangsu HengRui Medicine
	ALG-000184	04536337	1	Aligos Therapeutics
	GSTHG141	04868981	1	Fujian Cosunter Pharm.
Post-transcription Inhibitors				
RNAi, Antisense RNA	**Drug Name**	**Trial NCT**	**Phase**	**Sponsor**
	GSK3228836	04449029	2	GlaxoSmithKline
	ALG-020572	05001022	1	Aligos Therapeutics
HBV entry inhibitors				
Peptide	**Drug Name**	**Trial NCT**	**Phase**	**Sponsor**
	Hepalatide	04426968	2	Shanghai HEP Pharm.
NMAb	VIR3434	04423393	1	Vir Biotech
HBsAg release inhibitors				
NAPs	**Drug Name**	**Trial NCT**	**Phase**	**Sponsor**
	ALG010133	04485663	1	Aligos Therapeutics
Modulators of the adaptive immune system				
Therapeutic vaccines	HepTcell	04684914	2	Altimmune
	GSK3528869A	03866187	1	GlaxoSmithKline
	VTP300	04778904	1/ 2	Vaccitech
Modulators of the innate immune system				
TLR9a	**Drug Name**	**Trial NCT**	**Phase**	**Sponsor**
	HEPLISAV-B	04843852	2	University of Maryland

Combination therapies				
CI +NAs	ABIH2158+ETV	04398134	2	Assembly Bioscience
	QL-007+TDF	04157699	2	QILU Pharm.
CI+NAs+PEG	ABIH0731+ETV+PEG	04781647	2	Assembly Bioscience
CI+RNAi	JNJ56136379+JNJ73763989	03982186	2	Janssen Sciences Ireland
CI+/-RNAi+NAs	ABIH0731+/-AB729+NAs	04820686	2	Assembly Bioscience+ Arbutus Biopharm.
CI+RNAi+NAs	JNJ56136379+ JNJ73763989+ETV	04129554	2	Janssen Sciences Ireland
CI+ RNAi +NAs+PEG	JNJ56136379+JNJ73763989+NAs+PEG	04667104	2	Janssen Research & dvp
CI+RNAi+NAs+ PEG	JNJ56136379+JNJ73763989+TDF+PEG	04439539	2	Janssen Research & dvp
RNAi+PEG	JNJ73763989+PEG	05005507	2	Janssen Research & dvp
	VIR2218+PEG	04412863	2	Vir Biotech
RNAi+NAs+PEG-IFN-α	AB729+NAs+ PEG-IFN-α	04980482	2	Arbutus Biopharm.
CI+/-RNAi +/- TLR7a+NAs+/- PEG	RO7049389+/-RO7445482+/-RO7020531+NAs+/-PEG	04225715	2	Hoffmann-La Roche
RNAi +/- TLR8a+Nivo+NAs	VIR2218+/-GS9688+Nivo+TAF	04891770	2	Gilead and Vir Biotech
RNAi+TV+/- IFN-α	VIR2218+BRII179+/-IFN-α	04749368	2	Vir Biotech
RNAi+NMAb	VIR2218+VIR3434	04856085	2	Vir Biotech
TLR7a+NAs	TQA3334+ETV	04180150	2	Chia Tai Tianqing Pharm.
TLR7a + α-PDL-1 mAb	TQA3334+TQB2450	04202653	2	Chia Tai Tianqing Pharm.
TV+NAs	ChAdOx1-HBV+ NAs	04297917	1	Vaccitech
HF Cyp I	CRV431	03596697	1	Hepion
HF PAPD5/ PAPD7 inhibitor + CI	EDP721+EDP514	04971512	1	Enanta Pharma

Phillips et al. Virulence. 2022 Dec;13(1):1111-1132.

Updates in Management of HBV and HDV

- Summary:

- HBV and HDV continue to represent a significant public health burden and greater efforts across the care continuum are needed to achieve elimination
- Patients with chronic hepatitis or "immune active" disease should receive treatment to reduce their risk for liver disease progression and HCC
- Current first-line therapies for HBV offer excellent viral suppression, but rarely result in functional cure
- A growing armamentarium of HBV and HDV therapies are in development and combination therapies represent an attractive treatment strategy.

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