GHAPP

Gastroenterology & Hepatology
Advanced Practice Providers

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Annenberg Center For Health Sciences at Eisenhower
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HBV Therapeutic Goal

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Disclosures

Jonathan Yeh, PA

No financial relationships to disclose.

Chronic Hepatitis B (CHB) in the World

Key facts

- Hepatitis B is a viral infection that attacks the liver and can cause both acute and chronic disease.
- The virus is most commonly transmitted from mother to child during birth and delivery, as well as through contact with blood or other body fluids during sex with an infected partner, unsafe injections or exposures to sharp instruments.
- WHO estimates that 296 million people were living with chronic hepatitis B infection in 2019, with 1.5 million new infections each year.
- In 2019, hepatitis B resulted in an estimated 820,000 deaths, mostly from cirrhosis and hepatocellular carcinoma (primary liver cancer).
- Hepatitis B can be prevented by vaccines that are safe, available and effective.

World Health Organization Data, July 27, 2021.

Chronic Hepatitis B in the World

Key facts about hepatitis A, hepatitis B, and hepatitis C

Characteristic	Hepatitis A	Hepatitis B	Hepatitis C
Main route(s) of transmission	Fecal-oral	Blood, sexual	Blood
Incubation period	15-50 days (average: 28 days)	60-150 days (average: 90 days)	14-182 days (average range: 14-84 days)
Symptoms of acute infection	Symptoms are similar and can include ≥ 1 of the following: jaundice, fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, joint pain, dark urine, clay-colored stool, diarrhea (hepatitis A only)		
Perinatal transmission	No	Yes	Yes
Vaccine available	Yes	Yes	No
Treatment	Supportive care	Yes, not curative	Yes, curative

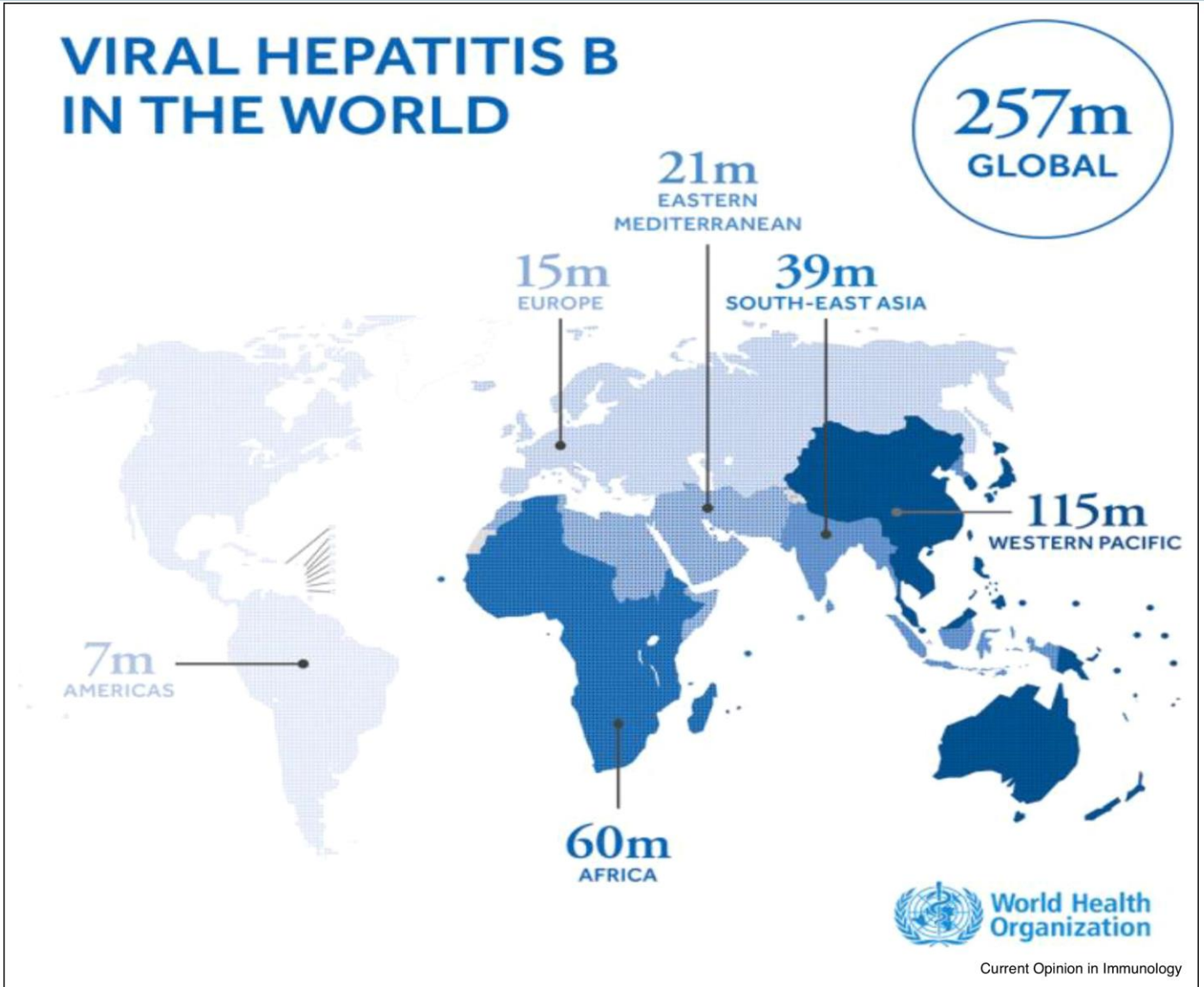
CDC, 2019 Hepatitis Surveillance.

Chronic Hepatitis B in the World
UN Sustainable Development Goals

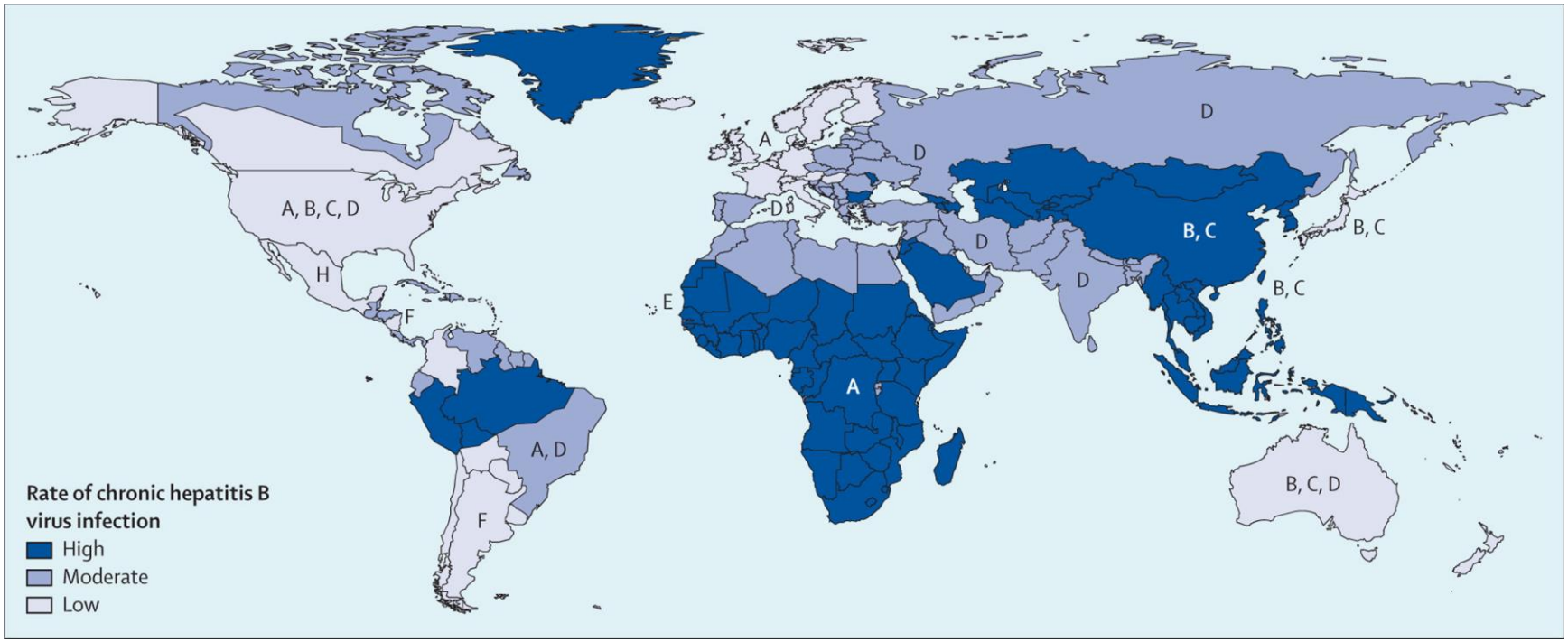
- 17 Goals for People, for Planet The Sustainable Development Goals are a universal call to action to end poverty, protect the planet and improve the lives and prospects of everyone, everywhere. The 17 Goals were adopted by all UN Member States in 2015, as part of the 2030 Agenda for Sustainable Development which set out a 15-year plan
- Under the third goal, the UN would like to see hepatitis, among other illness, epidemic ended by year 2030

Source: un.org 2021; No detail available.

Chronic Hepatitis B in the World



Genotype Distribution



Geographical distribution of major hepatitis B virus genotypes and worldwide frequency of chronic hepatitis B virus infection; Trepo C et al. *Lancet*. 2014; 384: 2053-63.

HBV Routes of Transmission

Chronic Hepatitis B in the United States

CDC Data from 2018 shows:

- About 2 in 3 people do not know being infected.
- 862,000 American living with CHB
- Asian American accounts for 58% of them.
- American Liver Foundation: 1 in 12 Asian Americans and Pacific Islanders infected with CHB.
- 15%-25% of chronically infected people develop chronic liver disease, including cirrhosis, liver failure, or liver cancer

Chronic Hepatitis B Screening

Who should get tested?

- Nationals over 2% prevalence
- IVD Users
- Household members, sexual partners
- Dialysis patients
- Man – sex – Man
- Sexually transmitted Infections, inc. HCV and HIV
- Immunosuppressive therapies, certain cancer treatment
- Pregnant women

Vaccinate if no immunity found – AASLD guideline

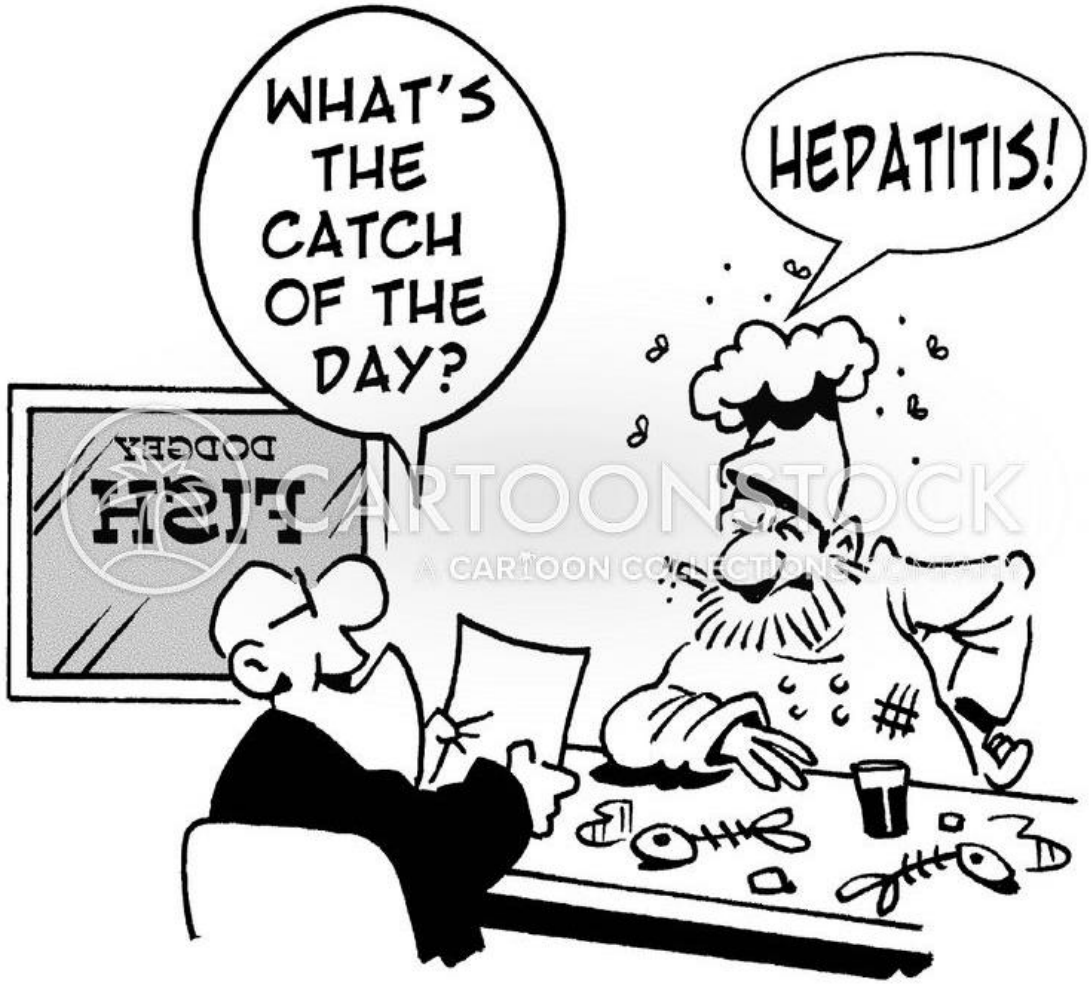
Source: CDC Guideline 2019.

Chronic Hepatitis B Vaccines

- Twinrix, Engerix-B, Heplisav-B
- Over 90% develop protective antibodies
- Other than Heplisav-B (approved 2017) vaccinated patients, response rate dropped to 75% after 60 year of age.

Source: CDC Data 2021.

Light Moment



HBV Prevention

Vaccination

- According to latest WHO estimates, the proportion of children under five years of age chronically infected with HBV dropped to just under 1% in 2019 down from around 5% in the pre-vaccine era ranging from the 1980s to the early 2000s.

Genotype Distribution

- Genotype A is found mainly in Northern Europe, North America, India, and Africa
- Genotype B and C are prevalent in Asia
- Genotype D is more common in Southern Europe, the Middle East, and India
- Genotype E is restricted to West Africa
- Genotype F is found in Central and South America
- Genotype G has been reported in France, Germany, and the United States
- Genotype H has been found in Central America
- Genotype I is found in Vietnam and Laos
- Genotype J was identified in the Ryukyu Islands in Japan

A new genotype of hepatitis B virus: complete genome and phylogenetic relatedness. Stuyver L et al. *J Gen Virol*. 2000; 81 (1): 67.

HBV Genotype and Treatment Efficacy

Response to Interferon treatment – eAg loss

- Prevalence of eAg positivity higher with B than C
- Higher among B vs. C and A vs. D

Kao JH, Wu NH, Chen PJ, Lai MY, Chen DS. Hepatitis B genotypes and the response to interferon therapy. *J Hepatol*. 2000; 33 (6): 998-1002. doi: 10.1016/s0168-8278(00)80135-x. PMID: 11131465; Wai CT, Chu CJ, Hussain M, Lok AS. HBV genotype B is associated with better response to interferon therapy in HBeAg(+) chronic hepatitis than genotype C. *Hepatology*. 2002; 36 (6): 1425-30. doi: 10.1053/jhep.2002.37139. PMID: 12447868; Erhardt A, Blondin D, Hauck K, Sagir A, Kohnle T, Heintges T, Häussinger D. Response to interferon alfa is hepatitis B virus genotype dependent: genotype A is more sensitive to interferon than genotype D. *Gut*. 2005; 54 (7): 1009-13. doi: 10.1136/gut.2004.060327. PMID: 15951551; PMCID: PMC1774609.

It Must Be the Drink

CHB Therapeutical Goal

Current

- Virologic suppression
- Seroconversion
  - Loss HBeAg
  - Loss of HBsAg
  - Development of HBsAb
- early HBeAg seroconversion duringtreatment typically confers a favorable outcome. In contrast, late or absent HBeAg seroconversion leads to early cirrhosis

Lin CL, Kao JH. Hepatitis B viral factors and clinical outcomes of chronic hepatitis B. *J Biomed Sci*. 2008; 15 (2): 137-45. doi: 10.1007/s11373-007-9225-8. Epub 2007 Dec 5. PMID: 18058038.

CHB Therapeutical Goal

Future

- Virologic suppression
- Seroconversion
  - Loss HBeAg
  - Loss of HBsAg
  - Development of HBsAb

Different Definitions of Virological Cure

	Complete Cure	Functional Cure	Partial Cure
cccDNA Eliminated	Yes	No	No
Integrated HBV DNA eliminated	Yes	No	No
cccDNA transcriptionally silent	Yes	Yes	No
HBsAg loss	Yes	Yes	No
HBV DNA Undetectable	Yes	Yes	Yes
Anti-HBs Positive	Yes	No/Yes	No
HBeAg Negative	Yes	Yes	Yes
Anti-Hbe Positive	Yes	Yes	Yes
Achievable Endpoint	Not Yet	Yes	Yes

Lok et al. *Hepatology*. 2017; 66 (4): 1296-1313.

Novel Promising HBV Antivirals

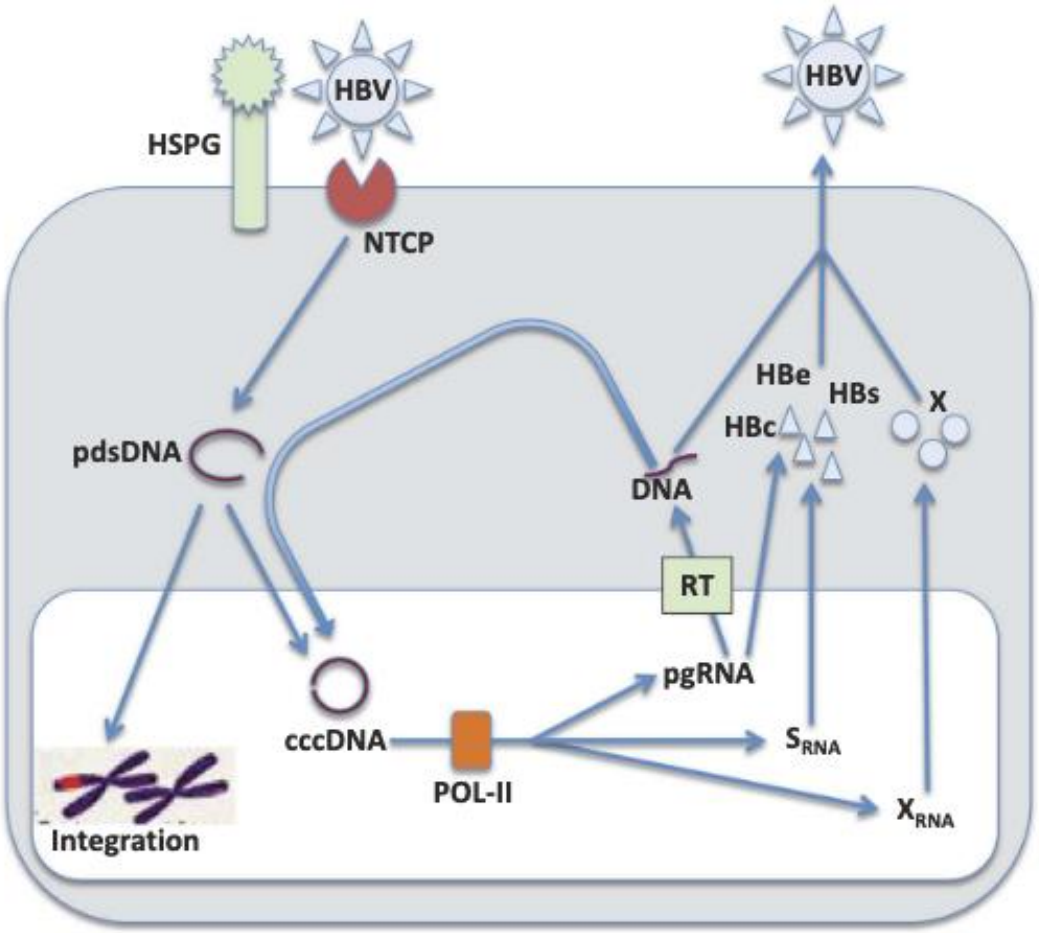
Mechanism of action	Antiviral family	Drugs and delivery
Entry inhibitors	NTCP inhibitors	Myrcludex (Bulevirtide) (sc)
cccDNA disruptors	Gene editing: CRISPR/Cas9	Intravenous administration using vectors
	Epigenetic silencers	GS-5801 (sc)
Translation inhibitors	siRNA	ARC-520, ARB-1467, ARO-B (JNJ-3989), AB-729 (sc)
	ASO	RO-2931, GSK-9404 (sc)
	RNA destabilizers	AAB-452, RG-7834 (sc)
Capsid assembly inhibitors	Assembly disruptors	JNJ-440, JNJ-379, NVR-3778, ABI-H0731, ABI-H2158, AB-506 (oral)
	Core blockers	RO-4389, GLS-4 (oral)
Polymerase inhibitors	RT chain terminators	Tenofovir, entecavir, besifovir (oral)
Secretion inhibitors	NAPs	REP-2139, REP-2165 (sc injection planned)

ASO, anti-sense oligonucleotide; cccDNA, covalently closed circular DNA; HBV, hepatitis B virus; NAPs, nucleic acid polymers; NTCP, sodium taurocholate cotransporting polypeptide; sc, subcutaneous.

Soriano V, Barreiro P, Cachay E, Kottilil S, Fernandez-Montero JV, de Mendoza C. Advances in hepatitis B therapeutics. *Ther Adv Infect Dis*. 2020; 7: 2049936120965027.

HBV Virus Life Cycle

HBV life cycle.
HSPG: heparin sulfate proteoglycan; NTCP: sodium/taurocholate cotransporting polypeptide;
cccDNA: covalently closed circular DNA;
pdsDNA: partially doublestranded DNA;
POL-II: cellular polymerase II; RT: viral reverse transcriptase;
pgRNA: pregenomic RNA;
preS/SRNA: Surface messanger RNA;
XRNA: X messanger RNA;
HBV: hepatitis B virus;
HBc: capsid;
HBs: surface protein.[4]



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Novel Promising HBV Antivirals

Mechanism of Action	Anti-viral Family	
Entry inhibitors	NTCP Inhibitors	Bile acid transporter serving as functional HBV and HDV receptors[1]
cccDNA Disruptors	Gene Editing: CRISPR/CAS9 Epigenetic Silencers	Eliminating cccDNA by gene editing or silencing of epigenetic pathway (vs. mutation) for HBV[2]
Translation inhibitors	siRNA (RNAi)	interfering into RNA transcriptase[3]
	ASO	Antisense oligonucleotide to liver targeted therapy to reduce HBsAg production and viremia[4]
	RNA Destabilizers	Reducing HBsAg load[4]
Capsid Assembly Inhibitors	Assembly Disruptors	stopping the HBV virus from producing new virus before exiting a hepatocyte
	Core Blockers	
Polymerase Inhibitors	RT Chain Terminators	Blocking the enzyme polymerase during the reverse transcriptase phase of HBV virus in the DNA.
Secretion inhibitors	NAPs	Nucleic acid polymers blocks the secretion of HBsAg from HBV infected hepatocytes.

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2. Hong X, Kim ES, & Guo, H. Epigenetic regulation of hepatitis B virus covalently closed circular DNA: Implications for epigenetic therapy against chronic hepatitis B. *Hepatology*. 2017; 66 (6); 2066–2077.

3. van den Berg F, Limani SW, Mnyandu N, Maepa MB, Ely A, & Arbuthnot P. Advances with RNAi-Based Therapy for Hepatitis B Virus Infection. *Viruses*. 2020: 12 (8): 851. https://doi.org/10.3390/v12080851.

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5. Soriano V et al. New antivirals for the treatment of chronic hepatitis B. *Expert Opinion on Investigational Drugs*. 2017; 26 (7): 843-851.

6. Seeger C, Mason WS. Hepatitis B virus biology. *Microbiol Mol Biol Rev*. 2000; 64 (1): 51-68. doi: 10.1128/MMBR.64.1.51-68.2000. PMID: 10704474; PMCID: PMC98986.

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Safe Trip Home