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Red Rock Hotel – Las Vegas, NV

Jointly provided by the Annenberg Center for Health Sciences at Eisenhower and Gastroenterology and Hepatology Advanced Practice Providers.
HBV Therapeutic Goal

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Disclosures

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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.

Chronic Hepatitis B in the World

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main route(s) of transmission</td>
<td>Fecal-oral</td>
<td>Blood, sexual</td>
<td>Blood</td>
</tr>
<tr>
<td>Incubation period</td>
<td>15-50 days (average: 28 days)</td>
<td>60-150 days (average: 90 days)</td>
<td>14-182 days (average range: 14-84 days)</td>
</tr>
<tr>
<td>Symptoms of acute infection</td>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinatal transmission</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Vaccine available</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Treatment</td>
<td>Supportive care</td>
<td>Yes, not curative</td>
<td>Yes, curative</td>
</tr>
</tbody>
</table>
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

VIRAL HEPATITIS B IN THE WORLD

257m GLOBAL

21m EASTERN MEDITERRANEAN

15m EUROPE

39m SOUTH-EAST ASIA

115m WESTERN PACIFIC

60m AFRICA

7m AMERICAS

World Health Organization

Current Opinion in Immunology
HBV Routes of Transmission

**Blood And Lymphatic**

**Tattoos**

**Body Piercing**

**Health Care Worker**

- Mother to Newborn
- Sexual Activity
- Sharing Toothbrush, Razor
- Homosexual
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

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

What's the catch of the day?

Hepatitis!
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

Response to Interferon treatment – eAg loss

- Prevalence of eAg positivity higher with B than C
- Higher among B vs. C and A vs. D
It Must Be the Drink

I can't find anything wrong with you - it must be the drink.

Ok - come back when you're sober.
CHB Therapeutical Goal

**Current**

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

CHB Therapeutical Goal

Future

• Virologic suppression
• Seroconversion
  – Loss HBeAg
  – Loss of HBsAg
  – Development of HBsAb
## Different Definitions of Virological Cure

<table>
<thead>
<tr>
<th></th>
<th>Complete Cure</th>
<th>Functional Cure</th>
<th>Partial Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>cccDNA Eliminated</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Integrated HBV DNA eliminated</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>cccDNA transcriptionally silent</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>HBV DNA Undetectable</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Anti-HBs Positive</td>
<td>Yes</td>
<td>No/Yes</td>
<td>No</td>
</tr>
<tr>
<td>HBeAg Negative</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Anti-Hbe Positive</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Achievable Endpoint</td>
<td>Not Yet</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

# Novel Promising HBV Antivirals

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

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

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

# Novel Promising HBV Antivirals

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


Safe Trip Home