Chronic Hepatitis B: Who Should You Treat?

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- Speakers Bureau: Gilead Sciences, Clinical Area – Hepatitis B and C
- Speakers Bureau: AbbVie, Clinical Area – Hepatitis C
Chronic Hepatitis B (CHB) Is a Global Health Problem

HBV infection is the most common chronic viral infection in the world\textsuperscript{1,2}

An estimated 257 million people worldwide are living with chronic hepatitis B (CHB)\textsuperscript{1}

Map adapted from Schweitzer A et al.\textsuperscript{3}
HBV=hepatitis B virus; HBsAg=hepatitis B surface antigen.
Prevalence of CHB in the United States

Approximately 2 million persons are living with CHB in the United States\textsuperscript{1,2}

Percentage of foreign-born persons with CHB in the United States who originated from the indicated WHO regions (2001-2010)\textsuperscript{3}

WHO regions
- Africa
- Americas (without US)
- Europe
- Eastern Mediterranean
- Western Pacific and Southeast Asia

Up to 95\% of people with chronic HBV infection in the United States are foreign-born persons from regions of intermediate or high endemicity\textsuperscript{4}

WHO=World Health Organization.
Progression and Complications of CHB

Acute Infection ➔ Chronic Infection

Chronic Infection ➔ Cirrhosis

Cirrhosis ➔ Liver Failure ( Decompensation)

Liver Failure ➔ Death

Liver Transplantation ➔ Death

HCC ➔ Death

0.1%-3% \(^1\)

8%-38% \(^1\)

10%-17% \(^1\)

15% \(^1\)

70%-85% \(^1\)

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\(^a\)Chronic infection is defined as the presence of HBsAg for at least 6 months.\(^2\)
Percentages are 5-year cumulative incidence rates.
HCC=hepatocellular carcinoma.
Antigens and antibodies associated with HBV infection include HBsAg, anti-HBs, anti-HBc, HBeAg, and anti-HBe.

SeroLogic assays are available to test for these markers.

anti-HBe=antibody to HBeAg.

The Natural History of Chronic Hepatitis B

CHB is a dynamic disease – Individuals with CHB can transition through different clinical phases with variable ALT, viral load, and HBV antigens

- HBsAg+ HBeAg+ chronic infection (Immune tolerant)
- HBsAg− HBeAg− chronic infection (Low replication)
- HBsAg− HBeAg− chronic hepatitis (Reactivation)
- HBsAg− HBeAg+ chronic hepatitis (Immune activation)
- HBsAg− Anti-HBe+ HBsAg+ Anti-HBe−

Figure adapted from Tong MJ et al.2
Terminology in parentheses is from Tong MJ et al.2
ALT=alanine aminotransferase; EASL=European Association for the Study of the Liver.
## Populations Recommended for HBV Screening

### Alignment Among AASLD, ACP, CDC, and USPSTF

<table>
<thead>
<tr>
<th>AASLD&lt;sup&gt;1&lt;/sup&gt;</th>
<th>ACP / CDC&lt;sup&gt;2&lt;/sup&gt;</th>
<th>USPSTF&lt;sup&gt;3-5&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons born in regions with prevalence of HBV infection ≥ 2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US-born persons not vaccinated as infants whose parents were born in regions with prevalence of HBV infection ≥ 8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household and sexual contacts of persons with HBV infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All pregnant women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men who have sex with men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection drug users</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persons with elevated liver function tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persons with certain medical conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Needing immunosuppressive therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undergoing hemodialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infected with HCV or HIV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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AASLD=American Association for the Study of Liver Diseases; ACP=American College of Physicians; CDC=Centers for Disease Control and Prevention; HCV=hepatitis C virus; HIV=human immunodeficiency virus; USPSTF=United States Preventive Services Task Force.

This is a list of selected screening recommendations. For a complete list, please see:

## HBV Screening Tests

<table>
<thead>
<tr>
<th>Possible test results&lt;sup&gt;2,3&lt;/sup&gt;</th>
<th>HBsAg</th>
<th>Anti-HBs</th>
<th>Anti-HBc&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Interpretation&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Action&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>−</td>
<td>+/−</td>
<td>+</td>
<td>Acute or chronic infection&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Evaluation and further testing</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>Exposure to HBV At risk for reactivation&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Follow up as appropriate&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>−/−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>Immune due to vaccination</td>
<td>No further action required</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>At risk for HBV infection</td>
<td>Vacinate</td>
</tr>
</tbody>
</table>

<sup>a</sup>Anti-HBc refers to total anti-HBc.<sup>2</sup>
<sup>b</sup>According to the AASLD, ACP, and CDC.<sup>1-3</sup>
<sup>c</sup>Patient is chronically infected if HBsAg+ for ≥6 months. Patients with acute infection will be positive for anti-HBc IgM.<sup>2,3</sup>
<sup>d</sup>Patients undergoing immunosuppressive therapy or treatment with direct-acting antivirals for hepatitis C virus coinfection should be monitored for HBV reactivation.<sup>2</sup>
<sup>e</sup>Patients with cirrhosis should be screened every 6 months for HCC per the AASLD guidelines.<sup>2</sup>

Medical Management of CHB

Pretreatment Evaluation and Initial Follow-up\(^1-3\)

<table>
<thead>
<tr>
<th>History and physical examination</th>
<th>Evaluation tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Symptoms/signs of cirrhosis</td>
<td>• HBV DNA (serial testing)</td>
</tr>
<tr>
<td>• Risk factors for coinfection</td>
<td>• HBeAg and anti-HBe</td>
</tr>
<tr>
<td>• Alcohol and metabolic risk factors</td>
<td>• Liver function tests</td>
</tr>
<tr>
<td>• Presence of comorbid diseases</td>
<td>• Tests for antibodies to HAV, HCV, HDV, and HIV</td>
</tr>
<tr>
<td>• Family history of liver cancer</td>
<td>• HBV genotype</td>
</tr>
<tr>
<td></td>
<td>• HCC screening (ultrasound)</td>
</tr>
<tr>
<td></td>
<td>• Staging of liver disease severity (noninvasive tests or liver biopsy)</td>
</tr>
</tbody>
</table>

Patients should also be counseled on lifestyle modifications, prevention of transmission, and lifelong monitoring\(^1\)

HAV=hepatitis A virus; HDV=hepatitis D virus.
Defining Normal Liver Chemistry Tests

Normal ALT levels in prospectively studied populations without identifiable risk factors for liver disease range from 29-35 IU/L for males and 19-25 IU/L for females – Normal ALT level may not exclude significant liver disease

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>35 U/L</td>
<td>40 IU/L</td>
</tr>
<tr>
<td>Females</td>
<td>25 U/L</td>
<td>40 IU/L</td>
</tr>
</tbody>
</table>

- There is a linear relationship between ALT level and BMI that should be assessed
- AST and ALT ULN ranges can vary between different labs
- Elevated ALT or AST above the ULN in a population without identifiable risk factors is associated with increased liver-related mortality

## Selected Noninvasive Tests to Assess for Stage of Liver Fibrosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Components</th>
<th>Fibrosis Stages Assessed</th>
<th>Requirements</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>APRI</td>
<td>AST, platelets</td>
<td>≥ F2, F4 (cirrhosis)</td>
<td>Basic hematology and clinical chemistry</td>
<td>+</td>
</tr>
<tr>
<td>FIB-4</td>
<td>Age, AST, ALT, platelets</td>
<td>≥ F3</td>
<td>Basic hematology and clinical chemistry</td>
<td>+</td>
</tr>
<tr>
<td><strong>FibroTest</strong></td>
<td>Gamma glutamyl transpeptidase, haptoglobin, bilirubin, A1 apolipoprotein, alpha-2 macroglobulin</td>
<td>≥ F2, ≥ F3, F4 (cirrhosis)</td>
<td>Specialized tests; requires testing at designated laboratories; commercial assay</td>
<td>++</td>
</tr>
<tr>
<td><strong>FibroScan</strong></td>
<td>Transient elastography</td>
<td>≥ F2, ≥ F3, F4 (cirrhosis)</td>
<td>Dedicated equipment</td>
<td>+++</td>
</tr>
</tbody>
</table>

# First-line Treatment Options for CHB

<table>
<thead>
<tr>
<th>Status</th>
<th>Treatment</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred</td>
<td>ETV, TAF*, or TDF†</td>
<td>• High potency, high genetic barrier to resistance</td>
</tr>
<tr>
<td></td>
<td>PegIFN</td>
<td>Less safe with cirrhosis (reserve for mild CHB), contraindicated with decompensated cirrhosis</td>
</tr>
<tr>
<td>Not preferred</td>
<td>LAM, ADV, or TBV</td>
<td>• Low genetic barrier to resistance</td>
</tr>
</tbody>
</table>

*Efficacy and safety of TAF have not been established for CHB in patients with decompensated cirrhosis, pregnant women, or children; recommendations for these populations are subsequently limited. †If TDF is chosen, monitor renal function and BMD in at-risk patients.

ETV, TAF, and TDF have very favorable safety and resistance profiles

AASLD Guidance:
HBeAg-Positive Chronic HBV Infection

Noncirrhotic HBeAg-Positive Patients With CHB

ALT ≤ ULN*

- HBV DNA > 20,000 IU/mL
  - **Monitor** ALT and HBV DNA every 3-6 mos, HBeAg every 6-12 mos

ALT > ULN* but < 2 x ULN*

- HBV DNA > 20,000 IU/mL
  - Note: HBV DNA 2000-20,000 IU/mL may represent seroconversion
    - **Monitor** HBV DNA every 1-3 mos and **treat** if HBV DNA > 2000 IU/mL persists for > 6 mos

ALT ≥ 2 x ULN*

- HBV DNA > 20,000 IU/mL
  - **Treat**

- HBV DNA 2000-20,000 IU/mL may represent seroconversion
  - **Monitor** HBV DNA every 1-3 mos and **treat** if HBV DNA > 2000 IU/mL persists for > 6 mos

• Exclude other causes of ALT elevation: **treat** if ALT elevation persists, especially if > 40 yrs of age
• Evaluate fibrosis/inflammation: **treat** if ≥ F2/A2
**AASLD Guidance: HBeAg-Negative Chronic HBV Infection**

### Noncirrhotic HBeAg-Negative Patients With CHB

#### ALT ≤ ULN*:
- **HBV DNA ≥ 2000 IU/mL**
  - **Monitor** ALT and HBV DNA every 3 mos for 1 yr, then every 6 mos
  - **Monitor** ALT and HBV DNA every 3-6 mos
- **HBV DNA < 2000 IU/mL**
  - **Monitor** ALT and HBV DNA every 3-6 mos
  - **Monitor** HBsAg annually

#### ALT > ULN* but < 2 x ULN*:
- **HBV DNA ≥ 2000 IU/mL**
  - **Treat if ALT elevation persists, especially if > 40 yrs of age**
- **HBV DNA < 2000 IU/mL**
  - **Exclude other causes of ALT elevation**
  - **Evaluate fibrosis/inflammation: treat if ≥ F2/A2**

#### ALT ≥ 2 x ULN*:
- **HBV DNA ≥ 2000 IU/mL**
  - **Treat**
- **HBV DNA < 2000 IU/mL**

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AASLD Guidance: Patients With Cirrhosis

- Persons with compensated cirrhosis and HBV DNA level > 2000 IU/mL are treated per recommendations for immune active CHB → treatment recommended
- Patients with low-level viremia (HBV DNA < 2000 IU/mL) and compensated cirrhosis should be treated, regardless of ALT
- All patients with decompensated cirrhosis who are HBsAg positive should be treated, regardless of HBV DNA, HBeAg status, or ALT

Special Populations: Patients Undergoing Immunosuppressive and Cytotoxic Therapy

- **HBsAg and anti-HBc (total)** = all persons before initiation of any immunosuppressive, cytotoxic, or immunomodulatory therapy.

- **HBsAg-positive, anti-HBc–positive**: initiate anti-HBV prophylaxis before immunosuppressive or cytotoxic and continue during immunosuppressive therapy and for at least 6 months (or for at least 12 months for patients receiving antiCD20 therapies) after completion of immunosuppressive therapy.

- **HBsAg-negative, anti-HBc–positive**: monitor ALT, HBV DNA, and HBsAg with the intent for on demand therapy, except for patients receiving anti-CD20 antibody therapy (e.g., rituximab) or undergoing stem cell transplantation, for whom anti-HBV prophylaxis is recommended.

(Patients should be monitored for up to 12 months after cessation of anti-HBV therapy)
Special Population: Patients With Acute Symptomatic Hepatitis B

- Acute hepatitis B with acute liver failure or who have a protracted, severe course, as indicated by total bilirubin > 3 mg/dL (or direct bilirubin > 1.5 mg/dL), international normalized ratio > 1.5, encephalopathy, or ascites.

- Entecavir, TDF, or TAF are the preferred antiviral drugs.

- Continue treatment until HBsAg clearance is confirmed or indefinitely in those who undergo liver transplantation.
Special Population: Liver Transplant Recipients With Hepatitis B

- All HBsAg-positive should receive prophylactic therapy with or without HBIG post transplantation regardless of HBeAg status or HBV-DNA level pre transplant.

- Combination antiviral therapy and HBIG may be the best strategy for those at highest risk of progressive disease post transplantation, such as HDV- and HIV-coinfected patients.

- HBsAg-negative patients who receive HBsAg-negative but anti-HBc–positive grafts should receive long-term antiviral therapy to prevent viral reactivation. Although lamivudine has been used successfully in this scenario, entecavir, TDF, and TAF are preferred choices.

- Prophylactic therapy should be lifelong.
Special Population: Pregnancy

- **Mother to Child Transmission (MTCT)**
- Extremely low risk when hepatitis B virus (HBV) DNA < 200,000 IU/ml
- Timely neonatal HBIG and vaccine birth dose (as soon as possible within 24 hours of birth), followed by a standard course of vaccine.
- Maternal antiviral prophylaxis with tenofovir disoproxil fumarate starting at 28–32 weeks when risk is substantial.
- Antiviral therapy can be discontinued at birth to 3 months postpartum. With discontinuation of treatment, women should be monitored for ALT flares every 3 months for 6 months.
Key Points: Who Should You Treat

• Assessing treatment candidacy for hepatitis B should include:
  – ALT levels, HBeAg status, HBV DNA level, fibrosis assessment, and family history

• Patients with elevated HBV DNA (> 20,000 IU/mL for HBeAg+ and > 2000 IU/mL for HBeAg-) plus elevated ALT and/or significant disease on elastography or liver biopsy should be considered for treatment
  – ALT ULN for range from 29-35 IU/L for males and 19-25 IU/L for females
  – Incorporate fibrosis assessment into evaluation of patients with hepatitis B

• Consider family history and co morbidities