Chronic Hepatitis B: Taming an Old Dog with New Tricks

George M. Abraham, MD, MPH, FACP, FIDSA
Chief of Medicine, Saint Vincent Hospital
Professor of Medicine, University of Massachusetts Medical School
Chair, Board of Governors, and Regent, American College of Physicians (ACP)
Chair, Infectious Disease Board, American Board of Internal Medicine (ABIM)

CHB worldwide
- Approximately 350 million people worldwide have CHB
- High prevalence areas include regions of:
  - Asia
  - Africa
  - Latin America
  - Eastern Europe
  - The Caribbean
- Most people in the US who have CHB were born in regions of the world where the virus is common

Modes of HBV Transmission
- Horizontal transmission
  - Prolonged close contact (eg, household)
  - IV drug use
  - Sexual contact
  - Exposure to blood or bodily fluid
  - Hemodialysis
- Vertical transmission via mother
  - Up to 90% of neonates will develop CHB if their mothers carry the virus

Course of HBV Infection
- Immune tolerant
  - The phase occurs in patients with perinatally acquired infection
  - Minimal or no inflammation
  - May last 1 to 4 decades
  - High or fluctuating HBV DNA levels
  - Persistent or intermittent fluctuation in ALT levels
  - Active inflammation and liver damage
- Immune clearance
  - Low or undetectable HBV DNA levels
  - Normal ALT levels
  - Marked hepatitis, minimal fibrosis, but cirrhosis may be present
  - Fluctuating levels of ALT and HBV DNA
- Inactive carrier
  - Some patients may have reactivation of HBV replication
  - Usually older patients with more advanced liver disease
  - Fluctuating levels of ALT and HBV DNA
- Reactivation
  - After many years, some patients may enter a reactivation phase
  - Not considered a "cure" as intracellular HBV DNA is still present
- Resolution
  - Not considered a "cure" as intra-cellular HBV DNA is still present

HBV, hepatitis B virus.
Natural History of Chronic HBV Infection

**Immunotolerance**
- Low/undetectable HBV DNA
- ALT Normal
- Anti-HBe Positive
- No Yet Exposed (Monitor)

**Immune Clearance**
- HBsAg+ Anti-HBe+
- HBsAg– Anti-HBe–
- Anti-HBc Positive
- Immune from Vaccination

**Immune Control (Nonreplicative)**
- HBsAg+ Anti-HBe–
- HBsAg– Anti-HBe+
- ALT Normal
- Do Not Treat

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**CHB Management Algorithm**

*Patients who obtained immunity through natural exposure may need to be monitored if immunosuppressant therapy is initiated, and treatment may be indicated*

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**Distribution of Viral Genotypes at Baseline by Race**

<table>
<thead>
<tr>
<th>Race</th>
<th>Genotype A</th>
<th>Genotype B</th>
<th>Genotype C</th>
<th>Genotype D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian (n=122)</td>
<td>31%</td>
<td>31%</td>
<td>23%</td>
<td>36%</td>
</tr>
<tr>
<td>Black (n=12)</td>
<td>36%</td>
<td>21%</td>
<td>17%</td>
<td>26%</td>
</tr>
<tr>
<td>Caucasian (n=240)</td>
<td>26%</td>
<td>33%</td>
<td>32%</td>
<td>29%</td>
</tr>
<tr>
<td>Pacific Island (n=16)</td>
<td>23%</td>
<td>32%</td>
<td>33%</td>
<td>32%</td>
</tr>
<tr>
<td>Other (n=15)</td>
<td>28%</td>
<td>31%</td>
<td>29%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Combined data includes both HBsAg+ patients.


Ishak, Knodell, and METAVIR are scales frequently used to characterize the extent of fibrosis. The relationship between Ishak score and extent of fibrosis is not linear.

Staging Liver Fibrosis: Common Scales

- **Ishak**
- **Knodell**
- **METAVIR**

**General Appearance**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Ishak</th>
<th>Knodell</th>
<th>METAVIR</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>No fibrosis (normal)</td>
</tr>
<tr>
<td>F1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Fibrous expansion of some portal areas</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(short fibrous septa)</td>
</tr>
</tbody>
</table>
| F2    | 2     | 2       | 2       | Fibrous expansion of most portal areas | 2
|       |       |         |         | with occasional portal-to-portal (P-P) bridging |
| F3    | 3     | 3       | 3       | Fibrous expansion of most portal areas with occasional portal-to-portal (P-P) bridging |
|       |       |         |         | as well as portal-to-central (P-C) bridging |
| F4    | 4     | 4       | 4       | Cirrhosis, probable or definite |

**Categorical Assignment**

1. **F0**: No fibrosis (normal)
2. **F1**: Fibrous expansion of some portal areas (short fibrous septa)
3. **F2**: Fibrous expansion of most portal areas with occasional portal-to-portal (P-P) bridging
4. **F3**: Fibrous expansion of most portal areas with occasional portal-to-portal (P-P) bridging as well as portal-to-central (P-C) bridging
5. **F4**: Cirrhosis, probable or definite

**Degree of fibrosis as measured by collagen proportionate area:** proportion (%) of area of biopsy sample showing Sirius red staining for collagen

- **F0**: 0%
- **F1**: 1.9%
- **F2**: 4.5%
- **F3**: 24.3%
- **F4**: 31.8%

**Complications Associated With CHB**

- **Healthy liver tissue**
- **Consequence of ongoing liver injury and repair**
- **Risk of progression to cirrhosis is 2%-6% annually**
- **Typically presents 3-5 years after a diagnosis of CHB with cirrhosis**
- **Average survival in patients with HCC is ~8-12 months, often due to late diagnosis**

**Host and Viral Risk Factors for HCC**

- **Host Factors**
  - Male gender
  - Family history of HCC
  - Older age
  - Coinfection with HCV, HDV, or HIV
  - Alcohol consumption
  - Cigarette smoking

- **Viral Factors**
  - HBV DNA levels >2,000 IU/mL (>10,000 copies/mL)
  - HBV genotype C
  - Basal core promoter mutation
  - Precore mutation
  - Presence of HBeAg

**Management of CHB**

Although cirrhosis is a strong risk factor for HCC, 30% to 50% of HCC associated with HBV occurs in the absence of cirrhosis.

- Host and Viral Risk Factors for HCC
- Management of CHB
**CDC Recommendations for Routine CHB Testing**

**Populations at high risk of CHB include:**

- **Foreign-born:** People born in regions of high or intermediate prevalence of HBV infection
- **Children of foreign-born parents:** US-born people not vaccinated as infants, whose parents were born in regions of high prevalence of HBV infection
- **Family and household members:** People whose family or household members have HBV infection
- **Infants born to mothers who have HBV infection**
- **Hemodialysis patients**
- **People with certain medical conditions:** People who need cytotoxic or immunosuppression therapy for a medical condition such as:
  - Cancer that requires chemotherapy
  - Immunosuppression related to organ transplantation
  - Immunosuppression related to rheumatologic and gastrointestinal disorders
- **People with elevated ALT/AST of unknown causes**
- **All pregnant women**

**Serologic Markers in HBV Infection**

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>The HBV surface antigen is used clinically as an index of viral replication and infectivity</td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Antibody to HBsAg</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>Antibody to the HBV core antigen can be used as a marker of infection</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>Indicates ongoing viral replication</td>
</tr>
<tr>
<td>Levels correlate with replication and infectivity</td>
<td></td>
</tr>
</tbody>
</table>

**Hepatitis B Virus**

- Presence in serum >6 months defines CHB

**HBsAg**

- Antibody to HBsAg markers of immunity to HBV
- Levels correlate with replication and infectivity

**Additional Recommended Screening in CHB Patients**

- **Hepatitis C Virus (HCV)**
  - 10% to 15% of patients with CHB are coinfected with HCV

- **Hepatitis D Virus (HDV)**
  - A higher proportion of persons with chronic HBV/HDV coinfection develop cirrhosis, hepatic decomposition, and HCC

- **Human Immunodeficiency Virus (HIV)**
  - Individuals with HBV and HIV coinfection tend to have more severe liver disease and increased rates of liver-related mortality

- **Immunity to Hepatitis A Virus (HAV)**
  - Persons with CHB who are not known to be immune to HAV should be vaccinated

**Vaccination**

- The hepatitis B vaccine provides long-term protection for people who have not been infected with the virus
- The hepatitis B vaccine is a series of 3 shots given over 6 months
- Alternative vaccination schedules given over 4 months demonstrate similar rates of seroprotection
Evaluation of CHB

**Evaluation**

**STEP 2 — EVALUATE**

<table>
<thead>
<tr>
<th>HBeAg</th>
<th>HBV DNA</th>
<th>ALT</th>
<th>Recommended Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>≥20,000 IU/mL</td>
<td>Elevated</td>
<td>Treat Patient</td>
</tr>
<tr>
<td></td>
<td>&lt;20,000 IU/mL</td>
<td>Elevated</td>
<td>Treat Patient</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>Monitor Patient&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>−</td>
<td>≥2000 IU/mL</td>
<td>Elevated</td>
<td>Treat Patient</td>
</tr>
<tr>
<td></td>
<td>&lt;2000 IU/mL</td>
<td>Elevated</td>
<td>Monitor Patient&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>Monitor Patient&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

Patients with signs and symptoms suggestive of advanced liver disease or indication of cirrhosis should be evaluated by a specialist. These patients frequently require ongoing evaluation and management of liver-related complications.

Normal ALT values are defined as ≤30 IU/L for men and ≤19 IU/L for women.

Patients with cirrhosis should be considered for treatment regardless of HBV DNA level.

Consider liver biopsy examination, particularly if patient is 15 to 40 years of age, if disease in the absence of biopsy examination, observe for increase in ALT values.

Consider therapy in patients with known significant histologic disease, even if low-level replication.

**Vibration Controlled Transient Elastography (Fibroscan<sup>®</sup>):**

**HCV Disease Progression in Patients With Normal ALT**

- Randomized, controlled trial of two interferon dosing regimens in patients with elevated (n = 59) or persistently normal (n = 37) serum ALT levels<sup>1</sup>

- Despite persistently normal ALT levels, > 75% have some degree of liver damage on biopsy.<sup>1</sup>

- There are no known factors that predict which patient with persistently normal ALT will have disease progression<sup>1</sup>

Normal ALT<sup>*</sup> (n = 37)

<sup>*</sup>Total value exceeds 100% due to rounding

Diagnostic Performance of FibroScan for Assessing Liver Stiffness in NAFLD

- Multicenter, prospective study evaluating diagnostic performance of FibroScan for liver stiffness measurement in pts undergoing biopsy for suspected NAFLD (N = 374 analyzed)
- Fibrosis (biopsy): F0, 17%; F1, 23%; F2, 23%; F3, 29%; F4, 9%

FibroScan LSM Correlation With Fibrosis Stage

<table>
<thead>
<tr>
<th>Fibrosis Stage</th>
<th>AUROC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 F1</td>
<td>0.77 (0.72-0.82)</td>
</tr>
<tr>
<td>2 F2</td>
<td>0.80 (0.75-0.84)</td>
</tr>
<tr>
<td>2 F4</td>
<td>0.89 (0.84-0.93)</td>
</tr>
</tbody>
</table>

- By multivariate analysis, only factor significantly influencing LSM was fibrosis stage

Monitoring CHB in Patients not Recommended for Treatment

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>HBV DNA</th>
<th>ALT*</th>
<th>Recommended Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>≥20,000 IU/mL</td>
<td>Normal</td>
<td>ALT every 3 to 6 months</td>
</tr>
<tr>
<td>-</td>
<td>≥2000 IU/mL</td>
<td>Normal</td>
<td>Consider liver biopsy or treatment if ALT becomes elevated</td>
</tr>
</tbody>
</table>

Other Monitored Patients

- ALT every 6 to 12 months for inactive carriers
- If ALT levels increase, check HBV DNA levels and rule out other causes of disease

Patients with signs and symptoms suggestive of advanced liver disease or indicative of cirrhosis should be evaluated by a specialist. These patients frequently require ongoing evaluation and management of liver-related complications.

*Normal serum ALT values are defined as ≤30 IU/L for men and ≤19 IU/L for women.
Recommendations for HCC Surveillance in Patients With CHB

Alpha-fetoprotein and abdominal ultrasound every 6 months

Recommended candidates for surveillance

- Asian men >40 years of age
- Asian women >50 years of age
- Africans >20 years of age
- Patients with cirrhosis
- Patients with a family history of HCC
- Patients >40 years of age with ALT elevations and/or high HBV DNA levels (>2000 IU/mL)
- Patients 30 to 35 years of age who were infected at birth or in early childhood


Expert Panel Consensus: US Treatment Algorithm

Treatment

Efficacy in Treatment-naive HBeAg-positive CHB Patients – Year 1 (%)

<table>
<thead>
<tr>
<th>IFNa</th>
<th>PegIFNa</th>
<th>PegIFNa + LAM</th>
<th>Oral Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>LAM</td>
</tr>
<tr>
<td>Loss of Serum HBV DNA</td>
<td>37</td>
<td>25</td>
<td>69</td>
</tr>
<tr>
<td>Loss of HBeAg</td>
<td>33</td>
<td>30 / 34</td>
<td>27 / 28</td>
</tr>
<tr>
<td>HBeAg Seroconversion</td>
<td>&lt;18%</td>
<td>27 / 32</td>
<td>24 / 27</td>
</tr>
<tr>
<td>Loss of HBeAg</td>
<td>7.80</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Normalization of ALT</td>
<td>&gt;23%</td>
<td>38</td>
<td>46</td>
</tr>
<tr>
<td>Histologic Improvement</td>
<td>NA</td>
<td>38 / 41</td>
<td>41</td>
</tr>
<tr>
<td>Durability of Response</td>
<td>53-60</td>
<td>56</td>
<td>59-60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

48 weeks for LAM, ADV, ETV, TDF, PegIFNa, PegIFNa + LAM. 12-24 weeks for IFNa and PegIFNa. 24 weeks for ADV. ADV= Adefovir dipivoxil, LAM= Lamivudine.

† Hybridization or branched chain DNA assays (upper limit of detection 500,000 IU/mL or 6 logs copies/mL) in standard IFN-α studies and some lamivudine studies and PCR assays (lower limit of detection ~50 IU/mL or 250 copies/mL) in other studies. NA= not available.

‡ Responses at week 48 / week 72 (24 weeks after stopping treatment).

§ Post-treatment biopsies obtained at week 72.

© Randomized trial of consolidation treatment; Adefovir and telbivudine: most patients had consolidation treatment.

AASLD Practice Guidelines 2009
Current Options in 2018

Recommended Nucleos(t)ide Analogues for HBV

<table>
<thead>
<tr>
<th>Nucleos(t)ide Analogue</th>
<th>Approval in RNA</th>
<th>Approval in CHB</th>
<th>QD Dose</th>
<th>Lowest CrCl Without Dose Adjustment (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entecavir</td>
<td>2005</td>
<td>2005</td>
<td>0.5 mg</td>
<td>50</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>2001</td>
<td>2006</td>
<td>300 mg</td>
<td>(no dose recommendation at &lt; 10 without dialysis)</td>
</tr>
<tr>
<td>Tenofovir alafenamide</td>
<td>2015 (as part of fixed-dose combination with antiretrovirals)</td>
<td>2016</td>
<td>25 mg</td>
<td>15 (not recommended at &lt; 15 in HBV monoinfection)</td>
</tr>
</tbody>
</table>


TAF vs TDF: Mechanism of Action

- Tenofovir alafenamide: novel prodrug of tenofovir

TAF: no dose adjustment needed in pts with CrCl > 15 mL/min

TAF vs TDF in Chronic HBV Infection: Wk 96 Efficacy

- HBV DNA: TAF noninferior to TDF at Wks 48 and 96 in both studies; no resistance found in any arm (HBeAg negative)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HBV DNA&lt; 29 IU/mL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAF</td>
<td>90</td>
</tr>
<tr>
<td>TDF</td>
<td>91</td>
</tr>
</tbody>
</table>

Treatment difference (95% CI): -0.6% (-7.0, 5.8), P = .84*

- ALT: significantly greater rate of ALT normalization at Wk 96 with TAF vs TDF

- HBeAg-positive pts: higher rate of HBeAg seroconversion at Wk 96 vs Wk 48 with TDF or TAF

- HBeAg-negative pts: minimal decline in HBsAg with TDF or TAF (1 TAF-treated pt with GT A had HBsAg loss and seroconversion)

§ HBV DNA: TAF noninferior to TDF at Wks 48 and 96 in both studies; no resistance found in any arm (HBeAg negative)

- **Treatment difference (95% CI): -2.2% (-8.3, 3.9), P = .47**

- **ALT: significantly greater rate of ALT normalization at Wk 96 with TAF vs TDF**

- **HBeAg-positive pts: higher rate of HBeAg seroconversion at Wk 96 vs Wk 48 with TDF or TAF**

- **HBeAg-negative pts: minimal decline in HBsAg with TDF or TAF (1 TAF-treated pt with GT A had HBsAg loss and seroconversion)**

Significantly smaller effect on spine BMD with TAF at Wk 48 and Wk 96 in HBeAg-negative pts [1]

**TAF vs TDF in Chronic HBV Infection: Renal and Bone Outcomes**

- Significantly smaller effect on renal function with TAF at Wk 48 and Wk 96 in HBeAg-negative pts [1]

**Choosing Among Nucleos(t)ide Analogues**

- If no comorbidities (for most pts)
  - When to prioritize ETV over TAF
    - If less expensive (generic available)
    - Dosing guidelines for CrCl < 15 mL/min

- When to prioritize TAF over ETV
  - Previous nucleoside exposure
    - • Lamivudine with or without adefovir resistance
    - • HIV/HBV coinfection
    - No dose adjustment for CrCl ≥ 15 mL/min
  - If risk of or preexisting bone or renal disease
    - • Age > 60 yrs
    - • Bone disease
    - • Chronic steroids or other meds that affect bone
    - • History of fragility fracture
    - • Osteoporosis
    - • Renal abnormalities
    - • eGFR < 60 mL/min/1.73 m²
    - • Albuminuria > 30 mg or moderate proteinuria
    - • Low phosphate (< 2.5 mg/dL)
    - • Hemodialysis

**Switch to TAF vs Continuing TDF in Chronic HBV Infection: Renal and Bone Outcomes**

- Analysis of open-label extension data from 2 phase III trials in HBV-infected pts switching from TDF to TAF at Wk 96
- 88% of pts achieved virologic suppression at Wk 96 (pre-switch) and maintained to Wk 120 (post-switch)
- Significantly higher proportion of pts achieved ALT normalization after switch to TAF

**Chronic HBV Infection: Management of Pts With NA Resistance**

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Switch Strategy</th>
<th>Add Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adefovir</td>
<td>Entecavir [1]</td>
<td>Entecavir</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Tenofovir* [2]</td>
<td>Tenofovir* or emtricitabine/tenofovir* [3]</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Tenofovir* [1,4]</td>
<td>Tenofovir (or emtricitabine/tenofovir*)</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>Tenofovir* [1,4]</td>
<td>Tenofovir*</td>
</tr>
<tr>
<td>Teltinguine</td>
<td>Tenofovir* [1,4]</td>
<td>Tenofovir* + entecavir [1]</td>
</tr>
</tbody>
</table>

*Includes either TDF or TAF in EASL guidelines; AASLD guidelines not yet updated since approval of TAF [1,2]

Guidelines: When to Start HBV Therapy

Guideline  a  HBeAg Positive  HBeAg Negative

<table>
<thead>
<tr>
<th>Liver Disease</th>
<th>HBV DNA, IU/mL</th>
<th>ALT ≥ 2 x ULN</th>
<th>ALT</th>
<th>Liver Disease</th>
<th>HBV DNA, IU/mL</th>
<th>ALT</th>
<th>Liver Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>&gt; 20,000</td>
<td>N/A</td>
<td>N/A</td>
<td>Cirrhosis</td>
<td>N/A</td>
<td>N/A</td>
<td>Cirrhosis</td>
</tr>
</tbody>
</table>


Guidelines: What to Start as Initial HBV Therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Preferred[1]</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>Yes</td>
<td>High potency, high genetic barrier to resistance</td>
</tr>
<tr>
<td>Entecavir</td>
<td>Yes</td>
<td>High potency, high genetic barrier to resistance</td>
</tr>
<tr>
<td>Peginterferon</td>
<td>Should only be considered as initial therapy for pts with mild/moderate CHB or selected pts with compensated cirrhosis (no portal hypertension)</td>
<td></td>
</tr>
<tr>
<td>TDF</td>
<td>No</td>
<td>Low genetic barrier to resistance</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>No</td>
<td>Low genetic barrier to resistance</td>
</tr>
<tr>
<td>Adefovir</td>
<td>No</td>
<td>Low genetic barrier to resistance</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>No</td>
<td>Low genetic barrier to resistance</td>
</tr>
<tr>
<td>TAF</td>
<td>Yes (EASL only)</td>
<td>High potency, high genetic barrier to resistance</td>
</tr>
</tbody>
</table>

*EASL guidelines not yet updated since approval of TAF.**

**TDF: monitor renal function, consider monitoring BMD in pts at risk.

ETV, TDF, TAF have very favorable safety profiles.[1]

Monitoring Treated Patients

1. Asses HBV DNA and ALT levels every 3 months until complete virologic response is confirmed
2. Monitor HBV DNA and ALT every 6 months thereafter

Assessing Treatment Failure/Resistance

<table>
<thead>
<tr>
<th>Failure</th>
<th>Measures</th>
</tr>
</thead>
</table>
| Primary treatment failure (HBV DNA decline from baseline <1 log_{10} IU/mL) | - If patient is compliant, add more potent drug
- If noncompliant, counsel |
| Complete response (HBV DNA <60 IU/mL) | - Continue therapy
- Monitor every 6 months |
| Partial response (HBV DNA 60 to <2000 IU/mL) | - Depending on drug profile, monitor every 3 months or add 2nd agent |
| Inadequate response (HBV DNA ≥2000 IU/mL) | - Add more potent drug; monitor every 3 months |

When possible, use agents with low risk for resistance as initial therapy

Stopping Treatment

When to Consider Stopping Treatment

HBeAg+ (without cirrhosis)

- Continue to treat after HBeAg seroconversion, until HBV DNA levels are undetectable by PCR; treatment then should be continued for an additional 12 months before considering stopping
- If HBV DNA levels are still detectable but stable, continue treatment for 6 months; if then HBV DNA levels are undetectable by PCR and HBeAg seroconversion is confirmed, treatment should be continued for an additional 12 months before considering stopping
- If no HBeAg seroconversion, treat indefinitely

HBeAg- (without cirrhosis)

- Definitive guidelines have not been established; however, long-term therapy is associated with lower rates of relapse

Cirrhosis

- Treatment should be long term
- Continue until patient becomes HBV DNA--negative and has lost HBeAg

PCR, polymerase chain reaction.


Guideline  a  HBeAg Positive  HBeAg Negative

<table>
<thead>
<tr>
<th>Liver Disease</th>
<th>HBV DNA, IU/mL</th>
<th>ALT ≥ 2 x ULN</th>
<th>ALT</th>
<th>Liver Disease</th>
<th>HBV DNA, IU/mL</th>
<th>ALT</th>
<th>Liver Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>&gt; 20,000</td>
<td>N/A</td>
<td>N/A</td>
<td>Cirrhosis</td>
<td>N/A</td>
<td>N/A</td>
<td>Cirrhosis</td>
</tr>
</tbody>
</table>

Cure as a Goal of Therapy

- **Actual cure**
  - True cure = all traces of HBV gone from the liver (like HCV)
  - VERY difficult (if not impossible) → cccDNA

- **Functional cure**
  - Use the markers of pts who do well:
    1. HBsAg loss (ideally with anti-HBs)
    2. Possibly sustained off-treatment inactive disease without HBsAg loss (HBeAg negative, DNA undetectable, normal ALT, normal histology)

*Cure not so simple . . . reasons lie in the virology*

Why Is Cure Rare With Nucleos(t)ide Therapy?

Is Long-term HBV Therapy Required?

- Systematic review of stopping nucleos(t)ide therapy in HBeAg-negative (n = 967) and HBeAg-positive (n = 733) pts

<table>
<thead>
<tr>
<th>Pct in Virologic Remission (%)</th>
<th>Months After Nucleos(t)ide Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6</td>
</tr>
<tr>
<td>HBeAg-negative</td>
<td>64</td>
</tr>
<tr>
<td>HBeAg-positive</td>
<td>24</td>
</tr>
</tbody>
</table>

HBeAg-positive
Post-markers: 1.7% (58/3560), Duration biochemical remission: 57% (3964/693)

HBV Therapy Reduces Risk of Disease Progression

- Prospective cohort study in pts with HBV and first-onset complications of decompensated cirrhosis (N = 707) treated predominantly with lamivudine (n = 203) or entecavir (n = 198)

*Nonresponders included pts with HBV rebound or genotypic resistance, primary nonresponse, NE due to early event (death, LT, LTFU).

HBV Therapy *Reduces* Risk of Disease Progression

- Antiviral therapy improved transplant-free survival over mean follow-up of 49 mos (P = .0006 vs untreated)

<table>
<thead>
<tr>
<th>LT-Free Survival (%)</th>
<th>Months After Nucleos(t)ide Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Treated, responder</td>
<td>100</td>
</tr>
<tr>
<td>Treated, nonresponder*</td>
<td>77</td>
</tr>
<tr>
<td>Untreated</td>
<td>70</td>
</tr>
</tbody>
</table>

*Bonferroni-adjusted P < .0003

**Long-term Oral HBV Therapy is Highly Effective**

- Suppresses HBV DNA\(^1,^2\)
- Normalizes ALT\(^2,^3\)
- Prevents fibrosis progression\(^3,^4\)
- Promotes fibrosis regression, even in cirrhosis\(^4\)
- Prevents and even reverses hepatic decompensation\(^1\)
- Reduces, but does not eliminate, the risk of HCC\(^1,^5\)
- Long-term therapy is effective . . . but low rates of HBsAg loss\(^6\)


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**Long-term Oral HBV Therapy: Downsides**

- **Toxicity**
  - Potential for renal, bone complications with TDF
- **Resistance**
  - High with lamivudine (not preferred by guidelines)\(^2\)
  - Very low with entecavir—unless already LAM resistant\(^2\)
  - None with TDF in clinical trials (similar expected with TAF)\(^2\)
- **Cost**
- **Adherence**

---

**Do You Ever Really Get Rid of HBV?**

- Immune control—not clearance
- “Resolved HBV” a misnomer—still HBV DNA in liver

---

**HBV Polymerase Primary Resistance Mutations**

- Terminal Protein
  - 183
  - 349 (rt1)
  - 692 (rt 344)
  - 843 a.a.

- Spacer

- POL/RT

- RNaseH

- LAM Resistance
  - rtL180V
  - rtM204V/I

- LdT Resistance
  - rtA181T/V
  - rtM230I

- ADV Resistance
  - rtA181T/V
  - rtD30N/V

- ETV Resistance
  - rtM250V
  - rtS323T

*Secondary mutations.

**HBV primary resistance mutations associated with TDF have not been characterized.**

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**References:**

Do You Ever Really Get Rid of HBV?

- Immune control—not clearance
- "Resolved HBV" a misnomer—still HBV DNA in liver


Along Comes Immune Suppression

- Immune control can be lost
- Immune-mediated liver damage with immune reconstitution

HBV Reactivation

**Definition**
- Loss of HBV immune control in a patient with inactive or "resolved" HBV infection
- Abrupt reappearance or increase in viral replication with liver damage occurring during and/or following immune reconstitution

**Clinically**
- Range from subclinical to severe/fatal hepatitis
- Rise in HBV DNA ± return of HBeAg
- ALT increase (may be mild or very dramatic)
- May progress to liver failure/death despite antiviral therapy

---

**Subset of Agents Reported to Cause HBV Reactivation**

<table>
<thead>
<tr>
<th>Class</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Dexamethasone, methylprednisolone, prednisolone</td>
</tr>
<tr>
<td>Antitumor antibiotics</td>
<td>Actinomycin D, bleomycin, daunorubicin, doxorubicin, epirubicin, mitomycin-C</td>
</tr>
<tr>
<td>Plant alkaloids</td>
<td>Vinblastine, vincristine</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>Carboplatin, chlorambucil, cisplatin, cyclophosphamide, ilosfamide</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Azauridine, cytarabine, fluorouracil, gemcitabine, mercaptopurine, melphalan, thioguanine</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>Alemtuzumab, rituximab</td>
</tr>
<tr>
<td>Others</td>
<td>Colaspase, docetaxel, etoposide, fluorarabine, folinic acid, interferon, procarbazine</td>
</tr>
</tbody>
</table>

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**Steroids Increase Risk of HBV Reactivation**

- 50 patients with NHL who were HBeAg positive randomized to epirubicin, cyclophosphamide and etoposide (ACE) vs prednisolone (P)

---


Who Should Be Screened?

- AASLD recommends screening high-risk individuals\(^1\)
  - Immigrants
    - Pacific Islands, Middle East, Eastern Europe, America, Caribbean, Aboriginal
  - Children
  - Men who have sex with men
  - HIV/HCV positive
  - History of IDU, incarceration
  - Hemodialysis patients

CDC\(^2,3\) & EASL\(^4\) recommend screening ALL patients prior to starting chemotherapy.

Significance of Lone Anti-HBc Positive Marker

- Indicates exposure to HBV
- Usually persists lifelong but may lose after yrs
- May be false positive if truly no HBV risk factors
- No guidelines for management
- Risk for reactivation
  - Low risk for most standard solid tumor regimens
  - Consider preemptive HBV therapy if cirrhosis
  - Consider preemptive HBV therapy if the following treatment strategies are used
    - Rituximab
    - Bone marrow/stem cell transplantation


Rituximab: A Particular Problem

- Monoclonal antibody against CD20 (B-cell marker)
- Reduces B-cell numbers and antibody levels
- Increasingly used as part of CHOP-R, EPOCH-R
- Increased risk of HBV reactivation, including HBsAg-negative patients
- Reverse seroconversion: reappearance of HBsAg in previously HBsAg-negative patient due to loss of immune control


Management of Anti-HBc–Positive Patients Receiving Rituximab

- No consensus, limited data
- Options
  - Start antiviral therapy before chemotherapy
  - Follow HBV DNA closely on chemotherapy → treat if HBV DNA positive
  - Follow HBsAg closely on chemotherapy → treat if HBsAg positive
  - Combination approach: follow HBsAg and HBV DNA
Agents Reported to Cause HBV Reactivation

- Anti-TNF (infliximab, adalimumab, etanercept)
- Anti-metabolite (methotrexate)
- Purine Analogues (azathioprine/6mp)
- Steroids (prednisone, budesonide)
- Other (rituximab, cyclosporine)

Summary of Management Strategies

- No clear consensus on management of lone anti-HBc positive receiving rituximab
- Preemptive treatment if HBV DNA positive may be considered if anti-HBs negative and/or if there is a concern about compliance with follow-up testing
- Close follow-up of HBV DNA likely effective but costly and requires compliance
- Following HBsAg alone may be adequate for most cases but clearly associated with some risk
Phase IIb Study of HBV/HDV Entry Inhibitor, Myrcludex B + TDF in Pts With Chronic HBV/HDV

- Interim results from an open-label, randomized phase IIb study

<table>
<thead>
<tr>
<th>Week</th>
<th>TDF (N=30)</th>
<th>MyrB 2 mg SC QD + TDF (N=30)</th>
<th>MyrB 5 mg SC QD + TDF (N=30)</th>
<th>MyrB 10 mg SC QD + TDF (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HBeAg-negative patients with chronic HDV infection (N=52)

- All patients continued TDF until Week 48

Myrcludex B is synthetic N-acylated preS1 lipopeptide which blocks receptor functions of NTCP and virus entry

Ongoing clinical studies in HBV and HDV infection

Vilchez et al. Gastroenterology 2019, 157: 46-84
Activity of Myrcludex B + TDF in Patients With Chronic HBV/HDV Infection

<table>
<thead>
<tr>
<th>Activity</th>
<th>MyrB 2 mg + TDF (n = 30)</th>
<th>MyrB 5 mg + TDF (n = 30)</th>
<th>MyrB 10 mg + TDF (n = 30)</th>
<th>All MyrB + TDF Arms (n = 90)</th>
<th>TDF (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV pgRNA</td>
<td>0.1</td>
<td>-0.0</td>
<td>-0.6</td>
<td>--</td>
<td>0.1</td>
</tr>
<tr>
<td>Total HBV DNA</td>
<td>0.3</td>
<td>0.1</td>
<td>-0.7</td>
<td>--</td>
<td>0.7</td>
</tr>
<tr>
<td>cccDNA/cell</td>
<td>0.1</td>
<td>0.3</td>
<td>-0.0</td>
<td>--</td>
<td>0.7</td>
</tr>
<tr>
<td>Serum HBsAg</td>
<td>0.1</td>
<td>-0.0</td>
<td>-2.0</td>
<td>--</td>
<td>0.7</td>
</tr>
<tr>
<td>HDV RNA</td>
<td>-0.9</td>
<td>-1.1</td>
<td>-1.4</td>
<td>-1.02 -0.3</td>
<td>--</td>
</tr>
<tr>
<td>HDVAg hepatocytes</td>
<td>-0.7</td>
<td>-0.9</td>
<td>-1.1</td>
<td>-0.84</td>
<td>--</td>
</tr>
<tr>
<td>NTCP</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>0.1</td>
<td>--</td>
</tr>
<tr>
<td>OVP531</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>0.3</td>
<td>--</td>
</tr>
<tr>
<td>CXCL10</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>-0.4</td>
<td>--</td>
</tr>
<tr>
<td>IL-18</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>-0.3</td>
<td>--</td>
</tr>
</tbody>
</table>

MyrB, Myrcludex B; HDV, Hepatitis D virus; HBV, Hepatitis B virus; TDF, tenofovir disoproxil fumarate; NTCP, sodium taurocholate cotransporting polypeptide; CYP7A1, cytochrome P450 7A1; CXCL10, C-X-C motif chemokine 10; IL18, interleukin 18.
Strategies of Immune Modulation for CHB

Adaptive Immunity

HBV T-cell Vaccine

New Targets for HBV “Cure”

Applause!!

QUESTIONS??