Why Hepatitis B Antiviral Treatment is So Confusing (it doesn’t have to be!)

Camilla S. Graham, MD, MPH
Division of Infectious Disease
Beth Israel Deaconess Medical Center
Disclosure

• None for hepatitis B
• Author, UpToDate, Hepatitis C
WHO Guidelines for the Prevention, Care, and Treatment of Persons with Chronic Hepatitis B Infection

“Ensuring the human rights and ethical principles of fairness, equity, and urgency guide the development of national treatment policies so that barriers in access to testing, prevention, and treatment services, particularly among certain populations, are addressed.”

People Living with HBV Are at High Risk of Not Being Appropriately Treated

- 66% of people with chronic HBV infection have not been diagnosed
  - no diagnosis = no treatment
- 2338 patients enrolled in CHeCS-HBV from 2006 to 2013
  - 37% had ≥1 HBV DNA test annually
  - 14% with cirrhosis had ≥1 annual liver imaging study
  - 56% with cirrhosis were prescribed antiviral therapy

Classic View of Natural History of HBV

Mother-to-child transmission

Immune-tolerant phase

Person-to-person transmission

Immune-active phase

Clearance of HBsAg

Inactive carrier phase

Cirrhosis

Hepatocellular carcinoma

Slide courtesy of Marion Peters, MD
HBsAg (+)

HBeAg (+)
- Usually anti-HBe (-)
- HBV DNA > 20,000 IU/mL
  - ALT normal (Typically children and teens)
  - Immune tolerant
  - Retest HBV DNA and ALT every six months
  - Consider treatment with entecavir or tenofovir (TAF)

HBeAg (-)
- Usually anti-HBe (+)
- HBV DNA > 20,000 IU/mL
  - ALT elevated
  - Immune active
  - HBV DNA > 2,000 IU/mL
    - ALT elevated
    - Usually precore or basal core promoter mutations
    - Retest HBV DNA and ALT every six months
    - Consider treatment with entecavir or tenofovir (TAF)
    - Likelihood of perinatal (lifelong) infection, age, stage of fibrosis, likely adherence to medications

HBV DNA > 2,000 IU/mL
- ALT normal
- Inactive phase
- Retest HBV DNA and ALT every six months

 ellas ete
- HBV DNA < 2,000 IU/mL
  - ALT normal
  - Can reactivate and may have significant fibrosis from lifelong infection

Abnormal ALT
- Females: ALT > 19
- Males: ALT > 30

AASLD Guidelines 2018
## HBV AASLD Guidelines Leave Many People in a “Grey Area”

<table>
<thead>
<tr>
<th>HBeAg</th>
<th>HBV DNA</th>
<th>ALT &lt; ULN M&lt;35, F &lt;25</th>
<th>ULN &lt; ALT &lt; 2x ULN</th>
<th>ALT &gt; 2x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>&gt;20,000</td>
<td>Monitor</td>
<td>Monitor*</td>
<td>Treat</td>
</tr>
<tr>
<td></td>
<td>&lt;20,000</td>
<td>Monitor</td>
<td>Monitor*</td>
<td>Monitor*</td>
</tr>
<tr>
<td>-</td>
<td>&gt;2,000</td>
<td>Monitor*</td>
<td>Monitor*</td>
<td>Treat</td>
</tr>
<tr>
<td></td>
<td>&lt;2,000</td>
<td>Monitor</td>
<td>Monitor*</td>
<td>Monitor*</td>
</tr>
</tbody>
</table>

*Values, alone or in combination, that would shift decision making towards antiviral therapy:*
- Inflammation >A3 (requires liver biopsy)
- Fibrosis >=F2 (elastography, noninvasive serum markers, biopsy)
- Age >40
- Persistent ALT >ULN >6 months
- Other causes elevated ALT excluded (alcohol, fatty liver, autoimmune, etc)

If persistent ALT >ULN > 6 months and HBV DNA >2,000 and age >40, consider antiviral treatment

---

HBV Guidelines AASLD 2018; table adapted from Dr. Hawra Al Lawati
Classic View of Natural History of HBV

Adapted from slide courtesy of Marion Peters, MD
Need for a Simplified Approach to HBV Treatment

• “Grey area” guidelines are confusing and hard to implement
• HBV experts often don’t actually follow these guidelines
• Guidelines should be straightforward enough that community practitioners are able to follow them

Tenofovir reduces HCC Incidence by ~70%

Propensity matched cohort of patients in US and Taiwan (95% Asian) with TDF vs no antiviral treatment.
Cumulative Incidence HCC, Tx or Death in Patients with Immune Tolerant, Immune Active, and Minimally Active HBV

Immune tolerant (ALT <19 for women and <30 for men) and Minimally Active (ALT 1-2 X ULN) patients were not treated with antivirals; Immune Active (ALT 2x ULN) patients were on antivirals (58% lamivudine)

Kim, Gut, 2017
HBV DNA Integrations are Found in All Human Chromosomes

Potential Initiating Event for HCC Development

“Immune tolerant”, Immune active HBeAg+, IA HBeAg-

“A

1 - 249 mbp
2 - 243 mbp
3 - 198 mbp
4 - 190 mbp
5 - 182 mbp
6 - 171 mbp
7 - 159 mbp
8 - 145 mbp
9 - 138 mbp
10 - 134 mbp
11 - 135 mbp
12 - 133 mbp
13 - 114 mbp
14 - 107 mbp
15 - 102 mbp
16 - 90 mbp
17 - 83 mbp
18 - 80 mbp
19 - 59 mbp
20 - 64 mbp
21 - 47 mbp
22 - 51 mbp
y - 57 mbp
x - 156 mbp

Mbps: 0 25 50 75 100 125 150 175 200 225 250

“Immune tolerant” age 15 - 39

B

1 - 249 mbp
2 - 243 mbp
3 - 196 mbp
4 - 190 mbp
5 - 182 mbp
6 - 171 mbp
7 - 159 mbp
8 - 145 mbp
9 - 136 mbp
10 - 134 mbp
11 - 135 mbp
12 - 133 mbp
13 - 114 mbp
14 - 107 mbp
15 - 102 mbp
16 - 90 mbp
17 - 83 mbp
18 - 80 mbp
19 - 59 mbp
20 - 64 mbp
21 - 47 mbp
22 - 51 mbp
y - 57 mbp
x - 156 mbp

Mbps: 0 25 50 75 100 125 150 175 200 225 250

Mason, Gastro 2016
Simplified Approach Eliminates “Grey Area”

<table>
<thead>
<tr>
<th></th>
<th>ALT &lt; ULN</th>
<th>ALT &gt; ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA &gt;2,000</td>
<td>Age ≥ 30</td>
<td>Treat</td>
</tr>
<tr>
<td></td>
<td>Age &lt; 30</td>
<td>Monitor</td>
</tr>
<tr>
<td>HBV DNA &lt;2,000</td>
<td>Age ≥ 30</td>
<td>Monitor</td>
</tr>
<tr>
<td></td>
<td>Age &lt; 30</td>
<td>Monitor</td>
</tr>
</tbody>
</table>

Monitor:
- Age ≥ 30 = If HBV DNA >2,000 then treat
- Age <30 = If HBV DNA >2,000 and ALT > ULN then treat
A Bit of Nuance

<table>
<thead>
<tr>
<th></th>
<th>ALT &lt; ULN</th>
<th>ALT &gt; ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA &gt;2,000</td>
<td>Age ≥ 30</td>
<td>Treat</td>
</tr>
<tr>
<td></td>
<td>Age &lt; 30</td>
<td>Monitor</td>
</tr>
<tr>
<td>HBV DNA &lt;2,000</td>
<td>Age ≥ 30</td>
<td>Monitor*</td>
</tr>
<tr>
<td></td>
<td>Age &lt; 30</td>
<td>Monitor</td>
</tr>
</tbody>
</table>

*Factors that make me lean towards antiviral treatment:
- Preference of person with HBV infection
- HBV DNA levels “near” 2,000
- Liver fibrosis tests that cannot exclude advanced fibrosis
- Family history of HCC
- Genotype with basal core promoter mutation
Reasons to Treat People Living with HBV Infection

- Reduce incidence of HCC
- Reduce the risk of progression to cirrhosis
- Reduce need for liver transplant
- Reduce perinatal transmission in pregnant people
- Allow people in certain professions to return to work
- May better position people for future curative strategies
- Reduce stigma
- Treatment as prevention?
Possible role of prior suppressive therapy in HBV treatment regimens under investigation

<table>
<thead>
<tr>
<th>Company</th>
<th>Investigational Drug (s)</th>
<th>HBV status</th>
<th>Nuc Requirement (stable entecavir, TDF or TAF)</th>
<th>HBV DNA Requirement (duration time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbutus Biopharma</td>
<td>AB-729 (plus Nucleos(t)Ide Analogue and Peg-IFN)</td>
<td>HBeAg-negative</td>
<td>≥12 months</td>
<td>&lt;LLOQ at Screening (no duration)</td>
</tr>
<tr>
<td>NCT04980482</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assembly Biosciences</td>
<td>vebicorvir (ABI-H0731) AB-729 (plus Nuc)</td>
<td>HBeAg negative for &gt; 3 months</td>
<td>&gt;12 months</td>
<td>&lt;LLOQ for ≥6 months</td>
</tr>
<tr>
<td>NCT04820686</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoffmann-La Roche</td>
<td>CpAM (RO7049389); TLR7 (RO7020531); siRNA (RO7445482); PEG-IFN; PD-L1 LNA (RO7191863) (plus Nuc)</td>
<td>No mention</td>
<td>≥12 months</td>
<td>LLOQ or &lt; 20 IU/mL for &gt; 6 months</td>
</tr>
<tr>
<td>NCT04225715</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>GSK3228836; GSK3528869A (vaccine)</td>
<td>HBeAg positive or negative</td>
<td>&gt; 6 months</td>
<td>“suppressed” &lt;90 IU/mL (no duration)</td>
</tr>
<tr>
<td>NCT05276297</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vir Biotech</td>
<td>VIR-2218; VIR-3434; +/- PEG-IFNα</td>
<td>HBeAg positive or negative</td>
<td>≥2 months</td>
<td>No mention</td>
</tr>
<tr>
<td>NCT04856085</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altmimmune Inc.</td>
<td>HepTcell (Adjuvanted FP-02.2)</td>
<td>HBeAg-negative</td>
<td>No mention</td>
<td>≥ 10 IU/mL at screening</td>
</tr>
<tr>
<td>NCT04684914</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Case 1

- 52 yo man from Albania with HBsAg(+) and HBeAg(-) infection diagnosed ten years ago

<table>
<thead>
<tr>
<th>Months from first visit</th>
<th>ALT</th>
<th>AST</th>
<th>Total bilirubin</th>
<th>Platelets</th>
<th>HBV DNA (IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>25</td>
<td>20</td>
<td>0.4</td>
<td>327,000</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>22</td>
<td>0.3</td>
<td>310,000</td>
<td>120</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>24</td>
<td>0.4</td>
<td>280,000</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>22</td>
<td>25</td>
<td>0.4</td>
<td>305,000</td>
<td>60</td>
</tr>
</tbody>
</table>

- Keep checking labs every six months
- 15% chance of developing immune active disease (immune escape) at some point
- Due to age >40, screen for HCC every 6 - 12 months
Case 2

- 34 yo man from Cape Verde with HBsAg(+) infection diagnosed two years ago

<table>
<thead>
<tr>
<th>Months from first visit</th>
<th>ALT</th>
<th>AST</th>
<th>Total bilirubin</th>
<th>Platelets</th>
<th>HBV DNA (IU/mL)</th>
<th>Hepascore</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>35</td>
<td>30</td>
<td>0.4</td>
<td>220,000</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>38</td>
<td>0.3</td>
<td>260,000</td>
<td>60</td>
<td>0.40</td>
</tr>
<tr>
<td>6</td>
<td>48</td>
<td>40</td>
<td>0.4</td>
<td>280,000</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>42</td>
<td>30</td>
<td>0.4</td>
<td>240,000</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

- Keep checking labs every 3 - 4 months
- Look for other causes of elevated liver enzymes – alcohol, HCV, HDV, hemochromatosis, autoimmune, medications, hepatic steatosis/NASH
- Due to birth in West Africa, screen for HCC every six months
Case 3

- 44 yo woman from South Korea with HBsAg(+) and HBeAg(-) infection diagnosed twenty years ago. Mother has chronic HBV.

<table>
<thead>
<tr>
<th>Months from first visit</th>
<th>ALT</th>
<th>AST</th>
<th>Total bilirubin</th>
<th>Platelets</th>
<th>HBV DNA (IU/mL)</th>
<th>Hepascore</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>21</td>
<td>19</td>
<td>0.4</td>
<td>220,000</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>21</td>
<td>0.3</td>
<td>260,000</td>
<td>60</td>
<td>0.40</td>
</tr>
<tr>
<td>6</td>
<td>32</td>
<td>26</td>
<td>0.4</td>
<td>280,000</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>42</td>
<td>36</td>
<td>0.4</td>
<td>240,000</td>
<td>6,000</td>
<td></td>
</tr>
</tbody>
</table>

- Recheck HBV DNA level and if still >2,000 IU/mL, start antiviral treatment
- Most likely developing immune escape
- Screen for HCC every six months
Case 4

• 42 yo man from China with HBsAg(+) infection diagnosed in China years ago. Does not think he has been treated. Mother also with chronic HBV

<table>
<thead>
<tr>
<th>Months from first visit</th>
<th>ALT</th>
<th>AST</th>
<th>Total bilirubin</th>
<th>Platelets</th>
<th>HBV DNA (IU/mL)</th>
<th>Hepascore</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>32</td>
<td>30</td>
<td>0.4</td>
<td>220,000</td>
<td>2,500</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>38</td>
<td>0.3</td>
<td>180,000</td>
<td>6,000</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>40</td>
<td>0.4</td>
<td>200,000</td>
<td>3,000</td>
<td>0.65</td>
</tr>
<tr>
<td>9</td>
<td>38</td>
<td>32</td>
<td>0.4</td>
<td>170,000</td>
<td>10,000</td>
<td></td>
</tr>
</tbody>
</table>

• Most likely has precore or basal core promoter mutations
• Treat with tenofovir (not entecavir) since cannot exclude exposure to lamivudine
• Transient elastography to evaluate for advanced fibrosis
• Screen for HCC every six months