HBV Diagnosis and Treatment

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• Intellectual property rights
  – UpToDate
Outline

• Diagnosis of HBV
  – HBV markers: old and new

• Treatment
  – Efficacy and limitations of available therapies
  – Indications: when to start
  – Which drug
  – When to stop
### Serological Markers of HBV Infection

<table>
<thead>
<tr>
<th>Marker</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Acute/chronic infection</td>
</tr>
<tr>
<td>Anti-HBc IgM</td>
<td>Recent infection</td>
</tr>
<tr>
<td>HBeAg</td>
<td>High infectivity</td>
</tr>
<tr>
<td>Anti-HBe</td>
<td>Low infectivity</td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Immunity</td>
</tr>
<tr>
<td>Anti-HBc IgG + HBsAg</td>
<td>Chronic infection</td>
</tr>
<tr>
<td>Anti-HBc IgG + anti-HBs</td>
<td>Resolved infection</td>
</tr>
</tbody>
</table>

**Screening for HBV infection:** HBsAg and anti-HBs +/- anti-HBc IgG
# Interpretation of HBV Serology

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>Total anti-HBc</th>
<th>IgM anti-HBc</th>
<th>Anti-HBs</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Not been exposed</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Chronic infection</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Acute Infection</td>
</tr>
<tr>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>Immunity from past infection</td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>Immunity after vaccination</td>
</tr>
<tr>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Occult / past HBV infection</td>
</tr>
</tbody>
</table>
Concurrent HBsAg and Anti-HBs

• Prevalence
  – 5%-60%
  – 6.6% in NIH-funded Hepatitis B Research Network (HBRN)

• Clinical characteristics
  – No differences in country of birth, modes of transmission, AST, ALT, HBeAg, HBV DNA, HBV genotype; but lower HBsAg level
  – Anti-HBs not neutralizing, management as for other chronic HBV patients who are anti-HBs-
Isolated Anti-HBc+ (HBsAg-, anti-HBs-)

- Most common scenario: past HBV with spontaneous loss of HBsAg, particularly in
  - Persons from endemic areas
  - Persons with risk factors for HBV
    - Risk behaviors
    - HCV or HIV infection
- HBV DNA
  - Usually not detected in serum except for those who are HIV+
  - Often detected in liver
Isolated Anti-HBc+ / Occult HBV

• Potential clinical implications
  – Antiviral treatment not indicated
  – HBV vaccine not necessary
  – Underlying liver damage may be present if chronically infected for decades before HBsAg loss
  – Risk of hepatocellular carcinoma may be increased compared to anti-HBc- persons
  – HBV reactivation with reappearance of HBsAg may occur during potent immunosuppressive therapy
Phases of Chronic HBV Infection

- **HBeAg**
- **Anti-HBe**

- **HBV DNA**
- **ALT**

- Immune tolerant
- Immune clearance HBeAg-positive chronic hepatitis
- Inactive carrier state
- Reactivation HBeAg-negative chronic hepatitis

Years
HBsAg Levels during Different Phases of Chronic HBV Infection

- HBV produces excess S proteins; subviral particles outnumber complete virions >1000:1
- HBsAg levels lowest in inactive carriers, correlate with cccDNA and immune control of HBV

220 patients
IT = immune tolerance, IC = immune clearance
LR = inactive carrier, ENH = HBeAg- chronic hepatitis

Nguyen T, J Hepatol 2010; 52: 508
HBsAg Levels Predict Disease Progression in HBeAg- Patients with Low HBV-DNA Levels

1068 Taiwanese HBeAg- persons with HBV DNA <2000 IU/mL followed for a mean of 13.0 years

Tseng T, Hepatology 2013;57:441
HBV Genotypes

- A-J, difference in geographical distribution
- B/C most common in the US followed by A, D, & E
- Genotype C associated with delayed spontaneous HBeAg seroconversion
- Genotype C (F) associated with increased risk of HCC
- Genotype A associated with highest rate of interferon-related HBeAg and HBsAg loss
- No impact on response to nucleos(t)ide analogue therapy
- Testing not clinically indicated except for patients in whom treatment is indicated and are potential candidates for interferon therapy
HBV Precore and Core Promoter Variants

- Abolish or decrease HBeAg production, but HBV replication and HBcAg expression not affected
- Present in most patients with HBeAg- chronic hepatitis
- Geographical distribution related to HBV genotype
- Precore variant most common in genotypes D, B, C, rarely A
- Core promoter variant less genotype-specific, most common in genotype C
- Testing not indicated in most clinical settings
AASLD Guidelines for HCC Surveillance

• 2017 guidelines
  – Who: adults with cirrhosis but not Child C unless on liver transplant waiting list
  – How: Ultrasound ± alpha-fetoprotein (AFP) q 6 months

• 2005 guidelines for HBsAg+ patients
  – Who
    • Asian males ≥40, Asian females ≥50, Africans >20
    • All patients with cirrhosis
    • For noncirrhotics, consider screening if high HBV DNA and ongoing hepatic necroinflammation
    • Family history of HCC
  – How (2011 update)
    • US q 6 months

Approved HBV Treatments

- **Interferons (IFN)**
  - Standard IFN alfa - 1992
  - Pegylated IFN alfa - 2005

- **Nucleos(t)ide analogues**
  - Lamivudine - 1998
  - Adefovir - 2002
  - Entecavir - 2005
  - Telbivudine - 2006
  - Tenofovir disoproxil fumarate - 2008
  - Tenofovir alafenamide - 2016
### Tenofovir Alafenamide (TAF) vs Tenofovir Disoproxil Fumarate (TDF) in HBeAg+ and in HBeAg- Patients

<table>
<thead>
<tr>
<th></th>
<th>HBeAg+ patients</th>
<th>HBeAg- patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA &lt;29 IU/mL, %</td>
<td>64/581</td>
<td>67/292</td>
</tr>
<tr>
<td>P</td>
<td>0.25</td>
<td>0.47</td>
</tr>
</tbody>
</table>

- **Response at Week 48**

  - **HBeAg+ patients**
    - TAF: 64/581
    - TDF: 67/292
    - P = 0.25
  - **HBeAg- patients**
    - TAF: 268/285
    - TDF: 130/140
    - P = 0.47

TAF Associated with Less Decrease in Spine and Hip Bone Mineral Density Than TDF

 Fewer TAF patients had >3% decreases in BMD at Week 48
  - Spine: 18% TAF; 38% TDF (p <0.001)
  - Hip: 8% TAF; 24% TDF (p <0.001)
Decrease in Serum HBV DNA after 1 Year of Treatment

Log$_{10}$ decrease in HBV DNA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Log$_{10}$ Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAM</td>
<td>-5.5</td>
</tr>
<tr>
<td>ADV</td>
<td>-3.5</td>
</tr>
<tr>
<td>ETV</td>
<td>-6.9</td>
</tr>
<tr>
<td>TBV</td>
<td>-6.5</td>
</tr>
<tr>
<td>TDF</td>
<td>-6.2</td>
</tr>
<tr>
<td>PEG-IFN</td>
<td>-3.0</td>
</tr>
</tbody>
</table>

Not head-to-head comparison, results from various trials combined

LAM=lamivudine, ADV=adefovir, ETV=entecavir, TBV=telbivudine, TDF=tenofovir, PEG-IFN=peginterferon
HBsAg Loss after 2-5 Years of Treatment

HBeAg+ Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HBsAg Loss (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg ^</td>
<td>11</td>
</tr>
<tr>
<td>LMV#</td>
<td>3</td>
</tr>
<tr>
<td>ADV #</td>
<td>2</td>
</tr>
<tr>
<td>ETV #</td>
<td>5</td>
</tr>
<tr>
<td>TBV *</td>
<td>1.3</td>
</tr>
<tr>
<td>TDF#</td>
<td>10</td>
</tr>
</tbody>
</table>

HBeAg- Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HBsAg Loss (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg ^</td>
<td>8</td>
</tr>
<tr>
<td>LMV#</td>
<td>1</td>
</tr>
<tr>
<td>ADV #</td>
<td>5</td>
</tr>
<tr>
<td>ETV</td>
<td>0.5</td>
</tr>
<tr>
<td>TBV *</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Peg = peginterferon
LMV = lamivudine
ADV = adeovir
ETV = entecavir
TBV = telbivudine
TDF = tenofovir

^ 3 years off Rx
# 4-5 years on Rx
* 2 years on Rx
348/641 (54%) had liver biopsy at baseline and Year 5
71/96 (74%) with cirrhosis (Ishak Score ≥5) at baseline no longer had cirrhosis at Year 5

Marcellin, P, Lancet 2013; 381: 468
Antiviral Therapy Prevents Disease Progression

Bridging fibrosis or cirrhosis, HBeAg+ / HBV DNA >700,000 GEq/ml

% with disease progression

Increase CTP score, liver failure or HCC

Liaw YF, NEJM 2004; 351:1521
Antiviral Therapy Decreases Incidence of HCC

651 pts, bridging fibrosis or cirrhosis, HBeAg+ and/or HBV DNA >140,000 IU/mL

Time to diagnosis (months)

P=0.047

After exclusion of cases in yr 1: HR = 0.47; P = 0.052

Liaw YF, NEJM 2004; 351:1521
Risk of HCC Remains after Five Years of ETV or TDF Therapy in Caucasian CHB Patients

794 adult Caucasian CHB patients

Cumulative HCC Incidence in Relation to Presence of Cirrhosis

HCC risk seems to be decreasing after the first 5 years of ETV/TDF therapy in CHB patients, especially in those with compensated cirrhosis at baseline. Older age (≥55 yrs) at treatment initiation appears to represent the main risk factor associated with late HCC development.

Papatheodoridis G, AASLD 2015, abs 2012
Efficacy of Currently Available HBV Therapies

- Potent viral suppression
- Reverse hepatic fibrosis / cirrhosis
- Prevent progression to liver failure

BUT

- Low rate of HBsAg loss
- Decrease but not eliminate incidence of HCC
HBV Treatment: for Whom and When?

- Treat Now
- Treat Now or Monitor?
- Monitor & Deferred Treatment Until Indicated

Risk of Cirrhosis, Liver Failure and HCC

Likelihood of response
Clear-Cut Cases in Which Treatment Should Be Initiated Now

- Life-threatening liver disease (regardless of HBV DNA and ALT level)
  - Fulminant hepatitis B
  - Severe exacerbations of chronic hepatitis B
  - Decompensated HBV cirrhosis
- High risk of liver failure/HCC in the near future
  - Compensated cirrhosis (any HBV DNA level?)
- HBsAg+ patients who will be starting immunosuppressive therapy
- HBsAg+ pregnant women with HBV DNA >200,000 IU/mL
- Noncirrhotics at high risk of progressive liver disease
When to Initiate Treatment in Noncirrhotics?
### AASLD Guideline Recommendations Regarding When to Start Treatment

<table>
<thead>
<tr>
<th>Status</th>
<th>AASLD 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg+</strong></td>
<td></td>
</tr>
<tr>
<td>Immune tolerant</td>
<td>No treatment except age $&gt;40$, 3rd trimester pregnancy</td>
</tr>
<tr>
<td>Immune active</td>
<td>Treat, HBV DNA $&gt;20,000$ IU/mL, ALT elevated, moderate-severe inflammation / fibrosis</td>
</tr>
<tr>
<td><strong>HBeAg-</strong></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td>No treatment if truly inactive</td>
</tr>
<tr>
<td>Immune active</td>
<td>Treat, HBV DNA $&gt;2,000$ IU/mL, ALT elevated, moderate-severe inflammation / fibrosis</td>
</tr>
<tr>
<td><strong>Cirrhosis</strong></td>
<td></td>
</tr>
<tr>
<td>Compensated</td>
<td>Treat regardless of ALT, especially if HBV DNA $&gt;2000$ IU/mL</td>
</tr>
<tr>
<td>Decompensated</td>
<td>Treat regardless of ALT and HBV DNA</td>
</tr>
</tbody>
</table>

Terrault N, Hepatology 2016; 63: 261
High Viral Load is Associated with Increased Incidence of HCC

REVEAL Study (n = 3,653), mean age 43

Baseline HBV DNA level, copies/mL

- $\geq 10^6$ (n = 627)
- $10^5$–$<10^6$ (n = 349)
- $10^4$–$<10^5$ (n = 643)
- 300–$<10^4$ (n = 1,161)
- $<300$ (n = 873)

Cumulative incidence of HCC (% subjects)

Year of follow-up

Log rank test of trend

P < 0.001

Outcome of Patients in the Immune-tolerant Phase is Favorable after 10-Year Follow-up

- 240 patients (130 M: 110 F), mean age 27.6 yr
- Mean FU 10.5 yr (3-20)
- Spontaneous HBeAg seroconversion: 85%
- Reactivation of hepatitis after HBeAg seroconversion: 2.2%/yr
- Cirrhosis: ~1.5% after 10 yr
- HCC: none

Tenofovir vs Emtricitabine + Tenofovir x 4 Years Immune Tolerance Phase
HBeAg+, HBV DNA ≥8 log_{10} c/mL, ALT ≤ULN

Universal relapse when treatment stopped

% of patients

<table>
<thead>
<tr>
<th>Response at Week 192</th>
<th>TDF (n=64)</th>
<th>FTC/TDF (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA &lt;400 c/mL</td>
<td>55%</td>
<td>75%</td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Chan H, J Hepatol 2013; 58: S45
Can HBeAg+ Patients in Immune Tolerance Phase Phase Wait?

- Minimal inflammation / fibrosis
- No to low risk of cirrhosis and HCC during 10-year follow-up
- Possibility of spontaneous HBeAg seroconversion and durable remission
- Response to both IFN and nucleos(t)ide analogue poor
Persistence of HBeAg after Age 40 Associated with Increased Risk of Cirrhosis

Chu & Liaw J Viral Hepat 2007; 14: 147
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Interferon</th>
<th>Nucleos(t)ide Analogue</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route</strong></td>
<td>Parenteral</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Duration of treatment</strong></td>
<td>Finite duration ~12 mos</td>
<td>Long duration, yrs to life-long</td>
</tr>
<tr>
<td><strong>Antiviral activity</strong></td>
<td>Modest, also immunomodulatory effects</td>
<td>Potent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ETV/TDF/TAF/TBV &gt;LAM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;ADV</td>
</tr>
<tr>
<td><strong>HBsAg loss</strong></td>
<td>1%-3% after 1 yr</td>
<td>Rare, 0%-1% after 1 yr</td>
</tr>
<tr>
<td><strong>Resistance mutations</strong></td>
<td>None</td>
<td>0%-25% after 1 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LAM&gt;TBV&gt;ADV&gt;ETV/TDF/TAF</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Frequent</td>
<td>Rare</td>
</tr>
</tbody>
</table>

ADV: adefovir; ETV: entecavir; LAM: lamivudine, TBV: telbivudine; TDF: tenofovir
Combination of Tenofovir and Peg-IFN Increases Rate of HBsAg Loss Compared with Monotherapy

7 patients had HBsAg seroreversion on or after Week 48 (4 [TDF + PEG 48 wk], 3 [TDF + PEG 16 wk → TDF 32 wk])

- 5/7 had ≤ 1 week of therapy after HBsAg loss

Marcellin P, Gastroenterol 2016; 150: 134
Combination of Tenofovir and Peg-IFN Increases HBsAg Loss Only in Genotype A

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>TDF + PEG x 48 wk</td>
</tr>
<tr>
<td>B</td>
<td>TDF + PEG x 16 wk + TDF x 32 wk</td>
</tr>
<tr>
<td>C</td>
<td>TDF x 120 wk</td>
</tr>
<tr>
<td>D</td>
<td>PEG x 48 wk</td>
</tr>
</tbody>
</table>

Marcellin P, Gastroenterol 2016; 150: 134
## Tailoring Treatment to Patient

<table>
<thead>
<tr>
<th>IFN</th>
<th>Nucleos(t)ide analogues</th>
</tr>
</thead>
<tbody>
<tr>
<td>- No contraindications</td>
<td>- Cirrhosis</td>
</tr>
<tr>
<td>- Willing to try</td>
<td>- Severe flares of chronic hepatitis</td>
</tr>
<tr>
<td>- Genotype A</td>
<td>- Contraindications to IFN</td>
</tr>
<tr>
<td>- High ALT</td>
<td>- Unwilling to try IFN</td>
</tr>
<tr>
<td></td>
<td>- Willing to accept long-term treatment</td>
</tr>
</tbody>
</table>

Entecavir, tenofovir: potent antiviral activity, high barrier to resistance. Tenofovir alafenamide: less renal and bone toxicity vs tenofovir disoproxil fumarate
When to Stop Interferon Treatment?

Finite duration

- Immunomodulatory effects may persist after cessation of treatment
- Need for parenteral administration, side effects, and high costs
- 48-52 weeks for both HBeAg+ and HBeAg- patients
  - Week-12 stop rule for futility, genotype-specific, not validated?
### Guideline Recommendations Regarding When to Stop Nucleos(t)ide Analogues

<table>
<thead>
<tr>
<th></th>
<th>AASLD 2015</th>
<th>APASL 2016</th>
<th>EASL 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg+</strong></td>
<td>HBeAg seroconversion and undetectable HBV DNA plus ≥12 mo consolidation</td>
<td>HBeAg seroconversion and undetectable HBV DNA plus preferably 3-yr consolidation</td>
<td>HBeAg seroconversion plus ≥12-mo consolidation</td>
</tr>
<tr>
<td><strong>HBeAg-</strong></td>
<td>HBsAg loss?</td>
<td>HBsAg loss + anti-HBs seroconversion or ≥12-mo consolidation</td>
<td>HBsAg loss or after ≥ 3 years of undetectable HBV DNA if close FU possible</td>
</tr>
<tr>
<td><strong>Cirrhosis</strong></td>
<td>DO NOT STOP</td>
<td>May be considered with careful off-therapy monitoring plan</td>
<td>DO NOT STOP</td>
</tr>
</tbody>
</table>

Risks of Stopping Nucleos(t)ide Analogues

- Risk of relapse
  - HBeAg+ patients who completed ≥12 mos consolidation therapy after HBeAg seroconversion: 10%-50% viral relapse
  - HBeAg- patients who completed >2 yr treatment: 100% viral relapse, ~40% sustained clinical relapse

- Risk of hepatic decompensation
  - Limited data, ~3% among cirrhotics
  - Depends on vigilance of post-treatment monitoring