Screening, diagnosis and management of hepatitis B

Fabian V. Rodas, MD
Texas Liver Institute
Associate Professor at UT Health San Antonio
Global Burden of Hepatitis B

- 250 million (3.5%) persons in the world have chronic HBV
  - Born before HBV vaccine was available
  - Acquired during prenatal period or early childhood

- 2.2 million infected in the United States.
  - Foreign born or from endemic regions

- Hepatitis B infections have increased up to 114% from 2006 to 2013 in some states affected by the opioid and heroin epidemics

- Hepatitis B and C could be eliminated as a public health threat (i.e. 90% reduction in new chronic infections, 65% reduction in mortality)

WHO, Global hepatitis report, 2017
Risk of Developing Chronic HBV: Age and Symptoms

Screening for Hepatitis B

- HBsAg and Anti-HBs is recommended
- Screening for Anti-HBc is **not** routinely recommended except if
  - HIV infected
  - Undergoing HCV or immunosuppressive therapy
  - Donating Blood or organs
  - Renal dialysis
- Anti-HBs - negative screened persons should be vaccinated
# HBV Serologies

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>IgG Anti-HBc</th>
<th>IgM Anti-HBc</th>
<th>Anti-HBs</th>
<th>Interpretation</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Never infected and absence of immunity</td>
<td>Vaccinate</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Chronic Infection</td>
<td>Link to HBV directed care</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Acute Infection or disease flare in chronic carrier</td>
<td>Link to HBV directed care</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Recovered from past infection with immunity</td>
<td>Reassurance</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Immunity from vaccination</td>
<td>Vaccinate for HAV if indicated</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>* Isolated HB core Ab</td>
<td>Vaccinate if indicated</td>
</tr>
</tbody>
</table>

* False positive: Repeat testing required
2 Past infection: No action needed
3 Occult HBV infection: Needs to be known if patient ever becomes immunosuppressed or given chemotherapy or treated with antiviral therapy for hepatitis C virus infection. Consider monitoring HBV DNA.
4 Passive transfer to infant born to HBsAg-positive mother No specific action needed
## Vaccines

<table>
<thead>
<tr>
<th></th>
<th>Engerix- B</th>
<th>Recombivax - HB</th>
<th>HEPLisav-B</th>
<th>TwinRix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doses</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>3-4</td>
</tr>
<tr>
<td>Viral antigen mimicked</td>
<td>HBsAg</td>
<td>HBsAg</td>
<td>HBsAg</td>
<td>HBsAg? HAVA g</td>
</tr>
<tr>
<td>Adjuvant Used</td>
<td>Aluminum hydroxide</td>
<td>Aluminum hydroxide</td>
<td>Toll like receptor</td>
<td>Aluminum Hydroxide</td>
</tr>
<tr>
<td>Derivation source</td>
<td>rDNA yeast</td>
<td>rDNA yeast</td>
<td>rDNA yeast. Adjuvant from bacterial DNA</td>
<td>rDNA yeast</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>GSK</td>
<td>Merck</td>
<td>Dynavax</td>
<td>GSK</td>
</tr>
<tr>
<td>Cost</td>
<td>$170</td>
<td>$180</td>
<td>$230</td>
<td>$298</td>
</tr>
</tbody>
</table>
Natural History- *e antigen status*
Goals of Therapy

- HBV DNA undetectable in the serum
- HB e seroconversion, HBsAg loss highly desirable,
- Decrease morbidity and mortality
- Decrease liver inflammation and progression to fibrosis
- Prevention of cirrhosis, hepatic failure and cancer

CURE is not a term typically discussed with patients regarding treatment for Chronic Hepatitis B infection
Why HBV is difficult to eradicate?

cccDNA: replicate intermediate not affected by NA
1-50 cccDNA particles per hepatocyte

Integrated subgenomic HBV DNA fragments into multiple locations within host DNA
DEFINING CURE

• Partial cure
  • HBsAg positive, HBV DNA persistently undetectable off treatment
    • Subgroup of those within inactive carrier

• Functional cure
  • Sustained loss of hepatitis B surface antigen (HBsAg) with or without hepatitis B surface antibody seroconversion

• Sterilizing cure
  • Eradication of detectable HBsAg and all HBV DNA including covalently closed circular (ccc) and integrated DNA
    • No risk for reactivation and elimination of HCC risk

• HBV e antigen seroconversion
  • The loss of serum hepatitis B e antigen (HBeAg) and the development of anti-HBe antibodies (HBeAg seroconversion) mark a transition from the immune-active phase of disease to the inactive carrier state.
Evolution of HBV Therapies

1990: Interferon α
1998: Lamivudine
2002: Adefovir
2005: Telbivudine
2006: PEG-IFN Entecavir
2008: Tenofovir
2016: Tenofovir alafenamide
Who to Treat?

HBsAg+

HBeAg+ without cirrhosis*

ALT ≤ ULN

HBV DNA > 20,000 IU/mL

ALT > ULN but < 2XULN

(26-49 U/L females, 36-69 U/L males)

HBV DNA > 20,000 IU/mL or 2000-20,000 IU/mL

ALT ≥ 2XULN

(≥50 U/L females, ≥70 U/L males)

HBV DNA > 20,000 IU/mL

HBV DNA 2000-20,000 IU/mL

Recommendations

Treat

Don’t treat, monitor only

Assess disease severity using non-invasive tests and/or liver biopsy; consider other causes of liver disease if elevated ALT. If staging indicates ≥F2 or ≥A3, or if other causes of ALT excluded and persistent, treat, especially if ≥40 years of age.

*If cirrhosis, treat regardless of ALT or HBV DNA level.
Chronic Hepatitis HBeAg – **Positive** on NA

**<40 years seroconversion**

- HBeAg → Anti - HBeAb
- Consolidate tx for 12 months
- Monitor for relapse and need of retreatment

**> 40 years seroconversion**

- HBeAg → Anti - HBeAb
- Longer consolidation period ideal
- Monitor for relapse and expect in 50%
- Treating to HBsAg loss may be preferred.

* Treat indefinitely if cirrhosis or advanced fibrosis
* Unclear if therapy withdrawal enhances HBsAg loss
Who to Treat?

HBsAg+

HBeAg-negative without cirrhosis

ALT ≤ ULN

- HBV DNA ≥ 2000 IU/mL
- HBV DNA < 2000 IU/mL

ALT > ULN but < 2XULN

(26-49 U/L females, 36-69 U/L males)

- HBV DNA ≥ 2000 IU/mL
- HBV DNA < 2000 IU/mL

ALT ≥ 2XULN

(≥ 50 U/L females, ≥ 70 U/L males)

- HBV DNA ≥ 2000 IU/mL
- HBV DNA < 2000 IU/mL

Recommendations

- Treat
- Don’t treat, monitor only

If staging indicates ≥ F2 or ≥ A3, or if other causes of ALT excluded and persistent, treat, especially if ≥ 40 years of age.
Chronic Hepatitis HBeAg – **NEGATIVE** on NA

- Treat until HBsAg loss = *functional cure*
  - Unlikely to be achieved with NAs alone
- NA withdrawal strategies _ appear promising
  - Achieves *functional cure* in up to 20% (with 3 years follow up)
  - Achieves *partial cure* (inactive CHB) in additional proportion (at maximum 30%)
  - Close monitoring needed as flare can be severe
  - Predictors: duration of NA therapy: qHBsAg but more studies needed.

* Treat indefinitely if cirrhosis or advanced fibrosis
Indications for selecting ETV or TAF over TDF*

- In some circumstances ETV or TAF may be a more appropriate treatment choice than TDF

**Age**
- >60 years

**Bone disease**
- Chronic steroid use or use of other medications that worsen bone density
- History of fragility fracture
- Osteoporosis

**Renal alteration†**
- eGFR <60 ml/min/1.73 m²
- Albuminuria >30 mg/24 h or moderate dipstick proteinuria
- Low phosphate (<2.5 mg/dl)
- Haemodialysis

<table>
<thead>
<tr>
<th>TAF over ETV</th>
<th>ETV over TAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous nucleoside exposure</td>
<td>Less expensive (generic available)</td>
</tr>
<tr>
<td>Lamivudine with and without adefovir resistance</td>
<td>No prior nucleoside exposure and HIV uninfected</td>
</tr>
<tr>
<td>HIV/HBV coinfection</td>
<td>CrCl &lt;15 mL/min (with dose adjustment)</td>
</tr>
<tr>
<td>No dose adjustment if CrCl &gt; 15 mL/min</td>
<td></td>
</tr>
</tbody>
</table>

*TAF should be preferred to ETV in patients with previous exposure to NAs; †ETV dose needs to be adjusted if eGFR <50 ml/min; no dose adjustment of TAF is required in adults or adolescents (aged ≥12 years and ≥35 kg body weight) with estimated CrCl ≥15 ml/min or in patients with CrCl <15 ml/min who are receiving haemodialysis.

EASL CPG HBV. J Hepatol 2017;67:370–98
## Special Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Entecavir</th>
<th>TDF</th>
<th>TAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis in the setting of immunosuppression</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Acute HBV, with severe protracted course</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Decompensated Cirrhosis</td>
<td>X</td>
<td>X</td>
<td>(X) Good option, Not studied</td>
</tr>
<tr>
<td>Liver transplant patients</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Other Solid organ transplant</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>X</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Children</td>
<td>X (&gt;2 yrs, 30 kg)</td>
<td>X (&gt;12 years)</td>
<td>*</td>
</tr>
</tbody>
</table>

* Insufficient Data to recommend
TAF vs TDF for HBV: Change in eGFR

Median change from baseline in eGFR over 96 weeks
TAF 25 mg (n=866) vs. TDF 300 mg (n=432)

TAF: -1.2
TDF: -4.8

p<0.001

Agarwal K, et al. J Hepatol 2018;68:672–81
TAF vs TDF for HBV: Change in BMD

Median change from baseline in BMD over 96 weeks
TAF 25 mg (n=866) vs. TDF 300 mg (n=432)

Hip
TAF vs TDF: p<0.001

Spine
TAF vs TDF: p=0.80

Agarwal K, et al. J Hepatol 2018;68:672–81
Chronic HBV: Reactivation of Inactive HBV

Risk Factors for Reactivation
- Immune suppression
- Cancer Chemotherapy
- DAA treatment of HCV
FDA BLACK BOX on HCV DAA Therapies

• **Hepatitis B Reactivation**
  • Reported in HCV/HBV co-infected patients on or those who completed HCV DAA therapy who were not on anti-HBV therapy, including cases resulting in fulminant hepatitis, hepatic failure, and death.
Monitoring of HBV During HCV DAA Therapy

- Identify HBV status in all patients prior to DAA therapy
- Monitor for elevations in ALT
- Obtain HBV DNA
- Initiate of suppression if indicated
Hepatitis B: Is it Curable?

- Sterilizing Cure: Remains elusive
- Functional Cure: Yes but rare
  - HBeAg positive > HBsAg negative patients on NAs
  - Peg-IFN offers more rapid route of HBsAg loss
  - Strategies to bolster rates of HBsAg are needed
- Partial Cure: Feasible and current goal
  - Close monitoring after discontinuation essential to monitor for relapse/flares
Case Study

- A 23-year-old, Asian-American male presents for ongoing care.
- History of chronic infection with hepatitis B virus (HBV), which was diagnosed at 21 years of age.
- Positive family history of HBV infection (sister and mother).
- No family history of cirrhosis or liver cancer.
- Findings from his physical examination are normal.
- Never received HBV treatment and takes no medications.
- Imaging: Ultrasound normal; liver stiffness by transient elastography is 3.7 kPa (normal).
# Laboratory Tests

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>6 Months Prior</th>
<th>Current</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT, SGPT</td>
<td>31 U/L</td>
<td>81 U/L</td>
<td>10-40 U/L</td>
</tr>
<tr>
<td>AST, SGOT</td>
<td>-</td>
<td>71 U/L</td>
<td>10-40 U/L</td>
</tr>
<tr>
<td>Bilirubin, Total</td>
<td>-</td>
<td>0.3 mg/dL</td>
<td>0.3-1.0 mg/dL</td>
</tr>
<tr>
<td>CBC</td>
<td>-</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Creatinine, Serum</td>
<td>-</td>
<td>0.9 mg/dL</td>
<td>0.7-1.5 mg/dL</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>20 million IU/mL</td>
<td>2.2 million IU/mL</td>
<td>Negative</td>
</tr>
<tr>
<td>Hepatitis B (HBeAg)</td>
<td>-</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>HCV</td>
<td>-</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HDV</td>
<td>-</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HIV</td>
<td>-</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Case Study (con’t)

- What is the best approach for managing his chronic HBV infection?
  1. Monitor yearly as no treatment is necessary now
  2. Monitor for 2 years before starting treatment
  3. Treat with tenofovir alafenamide now
  4. Treat if ALT and HBV DNA are elevated in 6 months
Thank You