Treatment of hepatitis B

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Hepatitis B Virus

- Nucleic Acid: 3.2 kb DNA
- Classification: Hepadnaviridae
- Multiple serotypes and genotypes A-H
- Enveloped
- In vitro model: primary hepatocyte culture and transfection of cloned HBV DNA
- In vivo replication: in cytoplasm, cccDNA in nucleus; hepatocyte and other tissues, human and other primates
Prevalence of HBV: Global Estimates

350 million With Chronic HBV

<table>
<thead>
<tr>
<th>Country</th>
<th>HBsAg Positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taiwan</td>
<td>10-13.8</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>5.7-10</td>
</tr>
<tr>
<td>China</td>
<td>5.3-12</td>
</tr>
<tr>
<td>Africa</td>
<td>5-19</td>
</tr>
<tr>
<td>Philippines</td>
<td>5-16</td>
</tr>
<tr>
<td>Thailand</td>
<td>4.6-8</td>
</tr>
<tr>
<td>Japan</td>
<td>4.4-13</td>
</tr>
<tr>
<td>Indonesia</td>
<td>4.0</td>
</tr>
<tr>
<td>South Korea</td>
<td>2.6-5.1</td>
</tr>
<tr>
<td>India</td>
<td>2.4-4.7</td>
</tr>
<tr>
<td>Russia</td>
<td>1.4-8</td>
</tr>
<tr>
<td>United States</td>
<td>0.2-0.5</td>
</tr>
</tbody>
</table>

HBsAg Prevalence
- High (>8%)
- Intermediate (2%-7%)
- Low (<2%)


New HBV Infections by Year: United States (1966-2006)

Vaccine Licensed
HBsAg Screening of Pregnant Women Recommended
Infant Immunization Recommended
OSHA Rule Enacted
Adolescent Immunization Recommended

HBV and Hepatocellular cancer (HCC)

- Globally, commonest underlying cause of HCC
- In Asia, up to 40% of HCC in HBV in noncirrhotics
- Western countries show significantly less risk in HBV carriers
- Annual incidence: 0.2% to 2.5%
Hepatitis B: Natural History

- If it is not treated, in 1/3 of patients, hepatitis B can cause liver damage leading to cirrhosis and liver cancer\(^1\)

- Hepatitis B is responsible for 80% of primary liver cancer globally, which is almost always fatal\(^2\)
  - Liver cancer is the 2nd highest cause of death by cancer \(^3\)
  - Without appropriate treatment or monitoring, 1 in 4 persons with chronic hepatitis B will die of liver cancer or liver disease

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1. WHO. Available at: www.who.int/csr/disease/hepatitis/en/;
**Natural History of Chronic HBV Infection**

- **Childhood**
  - >95% Immune Tolerance
- **Adulthood**
  - <5% HBeAg+ CHB
  - HBeAg- CHB
  - Inactive carrier
  - HCC And or cirrhosis

<15-30% of HCC associated with HBV occurs in the absence of cirrhosis or advanced fibrosis

**HBV DNA vs. Liver Cirrhosis : REVEAL data**

- No of patients = 3,482*
- Baseline HBV DNA
  - ≥10⁸ copies/mL
  - 10⁵–<10⁸
  - 10⁴–<10⁵
  - 300–<10⁴
  - <300

Cumulative rate of Liver Cirrhosis

* HBeAg negative n=2960

Aiming for True Inactive Carrier Status

- **Milestone 1:** Start of decline of HBV DNA
- **Milestone 2:** HBeAg/anti-HBe sero-conversion
- **Milestone 3:** HBV DNA decreased to undetectable
- **Milestone 4:** Clearance of HBsAg
- **Milestone 5:** Clearance of cccDNA

**HBeAg(+)**, anti-HBe(-)  HBeAg(-), anti-HBe(+)  Undetectable level of HBV DNA  Low HBV DNA (<2000 IU/mL) for reduced progression risk  **Healthy**  Immune tolerance  Immune clearance  Inactive carrier state  Functional cure/CURE

This is where we would like our patients to be

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**HBV DNA vs. HCC: REVEAL Data**

<table>
<thead>
<tr>
<th>Baseline HBV DNA</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10^9 copies/mL</td>
<td>8.6</td>
</tr>
<tr>
<td>10^9–10^8</td>
<td>6.1</td>
</tr>
<tr>
<td>10^8–10^7</td>
<td>2.3</td>
</tr>
<tr>
<td>&lt;10^7</td>
<td>1.1</td>
</tr>
<tr>
<td>&lt;300</td>
<td>1.0</td>
</tr>
</tbody>
</table>

No of patients = 3,653*  
Cumulative rate of HCC

*HBeAg negative n=3088

Goals of therapy for Hepatitis B

- Liver histology Improves
- Serum HBV DNA declines
- Prevention of Death, Cirrhosis, and HCC
- Seroconversion (loss of HBeAg, production of anti-Hbe, loss of HBsAg)
- ALT normalization

US FDA dates of Approved Therapies for CHB

<table>
<thead>
<tr>
<th>Nucleosides/Nucleotides</th>
<th>Product/Brand</th>
<th>Company</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir*</td>
<td>VIREAD®</td>
<td>Gilead Sciences</td>
<td>2008</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>TYZEKA™</td>
<td>Idenix / Novartis</td>
<td>2006</td>
</tr>
<tr>
<td>Entecavir*</td>
<td>BARACLUE™</td>
<td>Bristol-Myers Squibb</td>
<td>2005</td>
</tr>
<tr>
<td>Adefovir dipivoxil</td>
<td>HEPSERA™</td>
<td>Gilead Sciences</td>
<td>2002</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>EPIVIR-HBV®</td>
<td>GlaxoSmithKline</td>
<td>1998</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interferons</th>
<th>Product/Brand</th>
<th>Company</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peginterferon alfa-2a*</td>
<td>PEGASYS®</td>
<td>Roche Laboratories</td>
<td>2005</td>
</tr>
<tr>
<td>Interferon alfa-2b, recombinant</td>
<td>INTRON® A</td>
<td>Schering / Merck</td>
<td>1992</td>
</tr>
</tbody>
</table>

Preferred therapies – AASLD Guidelines
Candidates for HBV Treatment

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg positive</td>
<td>20,000</td>
<td>2000</td>
<td>20,000</td>
<td>20,000</td>
</tr>
<tr>
<td>HBeAg negative</td>
<td>2000</td>
<td>2000</td>
<td>2000</td>
<td>2000-20,000</td>
</tr>
<tr>
<td>ALT:</td>
<td>-</td>
<td>-</td>
<td>Use revised, lower range (M: 30 U/L; F: 19 U/L)</td>
<td>Use revised, lower range (M: 30 U/L; F: 19 U/L)</td>
</tr>
<tr>
<td>Normal range</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>When to treat:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>key factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy</td>
<td>Consider in certain groups</td>
<td>Consider in certain groups</td>
<td>Consider in certain groups</td>
<td>Consider in certain groups</td>
</tr>
</tbody>
</table>


Treatment Guidelines: Recommendations for First-Line Therapy in Patients Without Cirrhosis

HBeAg Positive or Negative Chronic HBV

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Alternative</th>
<th>Not Preferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir DF</td>
<td>Adefovir</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>Entecavir</td>
<td>Telbivudine*</td>
<td></td>
</tr>
<tr>
<td>Peg-IFN alfa-2a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*HBV DNA must be undetectable at 24 weeks to continue (Keeffe).
AASLD guidelines: lamivudine and telbivudine not preferred due to relatively high rate of resistance. Adefovir not preferred due to weak antiviral activity and relatively high rate of resistance in HBeAg-negative studies.

### Treatment Guidelines: Recommendations for Patients With Cirrhosis

#### Compensated Cirrhosis

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Potential</th>
<th>Not Preferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir DF</td>
<td>Peg-IFN alfa-2a*</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>Entecavir</td>
<td>Adefovir</td>
<td>Telbivudine</td>
</tr>
</tbody>
</table>

#### Decompensated Cirrhosis

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Not Preferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir DF plus lamivudine</td>
<td>Peg-IFN alfa-2a and alfa-2b†</td>
</tr>
<tr>
<td>Tenofovir DF</td>
<td></td>
</tr>
<tr>
<td>Entecavir</td>
<td></td>
</tr>
</tbody>
</table>

Note: therapies are approved for monotherapy only.

*Early cirrhosis only.
†Contraindicated.


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#### ETV 3-year Clinical Trial HBV DNA Suppression HBeAg-negative Patients

<table>
<thead>
<tr>
<th>Proportion of patients with HBV DNA &lt;300 copies/mL (%)</th>
<th>ETV-027</th>
<th>HBeAg(-) ETV Long-term Cohort (ETV-027 → ETV-901)</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of Dosing</td>
<td>94%</td>
<td>90%</td>
</tr>
<tr>
<td>Baseline</td>
<td>4%</td>
<td>95%</td>
</tr>
<tr>
<td>Wk 12</td>
<td>59%</td>
<td>33%</td>
</tr>
<tr>
<td>Wk 24</td>
<td>83%</td>
<td>93%</td>
</tr>
<tr>
<td>Wk 48</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td>Wk 72</td>
<td>91%</td>
<td>91%</td>
</tr>
<tr>
<td>Wk 96</td>
<td>95%</td>
<td>95%</td>
</tr>
</tbody>
</table>

n
- 93/99
- 4/99
- 56/95
- 79/95
- 84/90
- 72/77
- 67/74
- 54/57†

End of Dosing: Baseline: 4% (ETV-027) 59% (HBeAg(-) ETV Long-term Cohort (ETV-027 → ETV-901))

- Off-treatment >80 days
- 94% (ETV-027) 59% (HBeAg(-) ETV Long-term Cohort (ETV-027 → ETV-901))

†In the randomised controlled study (ETV-027), patients received 0.5mg ETV. In the 901 rollover study, patients received 1mg ETV.
‡10 patients who remained on treatment at Week 144 of ETV-901 visit had missing PCR samples.

Shouval D, et al. AASLD 2008; poster 927.
**Studies 102/103: Virologic Suppression With Tenfovir at Year 6**

<table>
<thead>
<tr>
<th>Response</th>
<th>HBeAg- Patients (Study 102)</th>
<th>HBeAg+ Patients (Study 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 5</td>
<td>Year 6</td>
</tr>
<tr>
<td>HBV DNA &lt; 400 copies/mL Intent-to-treat*, % (n/N)</td>
<td>83  (291/350)</td>
<td>81  (281/345)</td>
</tr>
<tr>
<td>HBV DNA &lt; 400 copies/mL On treatment†, % (n/N)</td>
<td>99  (292/295)</td>
<td>99.6  (283/284)</td>
</tr>
</tbody>
</table>

* LTE-TDF (missing = failure/addition of FTC = failure)
† Observed (missing = excluded/addition of FTC = included)

- 80% of 585 patients entering the open-label phase remained on study at Year 6; 73% of enrolled patients remained on study
- HBeAg loss/seroconversion rates of 50% and 37%, respectively, through 6 years
- 11% of HBeAg+ patients had confirmed HBsAg loss (8% with seroconversion)
- No resistance to TDF was detected through 6 years

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**HCC Risk in Caucasian, Chronic HBV Patients Treated With Entecavir or Tenofovir DF**

- Multi-country cohort (Greece, Italy, Turkey, Spain, The Netherlands) (n=1231)
  - Chronic HBV with no co-infection, liver transplantation, or HCC
  - Initiated either entecavir (43%) or tenofovir DF (55%)
- HCC 5-year incidence
  - 4.2% at median of 17 months
  - 13.5 new HCC cases/1000 person-years
- Strongest HCC risk factors
  - Decompensated liver disease (HR: 2.75; P=0.019), lower platelet count (HR: 0.97; P=0.002), older age (HR: 1.05; P=0.12)
- Asian-based HCC risk scores may not be applicable to Caucasians with chronic HBV

![HCC Risk Chart]

**Interferon**

- Short fixed duration therapy (16-48 weeks)
- No Renal toxicity
- Ideal for patients with high ALT and medium to low DNA
- Has stopping rules and “continuation” rules
- Chance of DNA suppression long-term is less than 20%
- HBsAg loss is 10%
  - Same as with Nuc therapy
- HBsAg quant is best stopping (test) rule, but not available in the US

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**HBsAg Reduction at Week 24 of PEG INF can Predict of Future HBsAg Clearance**

45% of those achieved HBsAg clearance at 5 years post-treatment (N=13/29)

43% achieved HBV DNA ≤ 10,000 copies/mL at 1 year post-treatment (N=29/67)

Among HBeAg-negative patients who achieved HBsAg decline ≥10% from baseline at Week 24 of treatment*

*SUSTAINED IMMUNE CONTROL

*56% of patients achieved HBsAg decline ≥10% at week 24

NIDDKD Cohort: HBsAg Loss by Mode of HBeAg Clearance

- Treatment-induced HBeAg clearance (n=51)
  - Interferon related: 86%
- Cumulative incidence of HBeAg loss per year (P=0.02)
  - Spontaneous: 1.6%
  - Nucleoside analog induced: 4.4%
  - Interferon induced: 6.3%
- Most significant predictors of HBsAg loss
  - Mode of HBeAg loss
  - Race

Probability of HBsAg Loss by Mode of HBeAg Clearance

[Graph showing probability of HBsAg loss by mode of HBeAg clearance with data points for interferon-related, nucleoside analog-related, and spontaneous losses.]


HBsAg Loss in HBeAg-Positive and HBeAg-Negative Patients

[Bar chart showing percentage of patients with HBsAg loss for different treatments: Lamivudine 52 weeks (1.5%), Adefovir 96 weeks (3.0%), Entecavir 96 weeks (5%), Tenofovir DF 4 years (10%), Tenofovir DF 52 weeks (1%), PegIFNα + LAM 72 weeks (15%), PegIFNα 72 weeks (8%), PegIFNα 52 weeks (5%), PegIFNα + LAM 96 weeks (3%), PegIFNα + LAM 72 weeks (1%).]

When can treatment be stopped?

- **IFN** defined duration, 12 months for both HBeAg+ and HBeAg- patients

- **Nucleos(t)ide analogues** until treatment endpoint
  - HBeAg+ patients: HBeAg seroconversion + >6 mos consolidation Rx, ~50% after 5 yr Rx
  - HBeAg- patients: endpoint not defined, HBsAg loss ~5% after 5 yr Rx
  - Cirrhotics: life-long Rx?

Cirrhosis Reversal Following Lamivudine Rx in HBV

Courtesy of Ian Wanless, MD.
Types of Virological Response

<table>
<thead>
<tr>
<th>Types of Response</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>On Treatment</td>
<td>HBV DNA (Log 10 IU/ml) decreases below LLOD</td>
</tr>
<tr>
<td>Relapse</td>
<td>HBV DNA (Log 10 IU/ml) increases above LLOD</td>
</tr>
<tr>
<td>Sustained Response</td>
<td>HBV DNA (Log 10 IU/ml) remains below LLOD</td>
</tr>
<tr>
<td>Maintenance</td>
<td>HBV DNA (Log 10 IU/ml) remains below LLOD</td>
</tr>
<tr>
<td>On Continuous Treatment</td>
<td>HBV DNA (Log 10 IU/ml) increases above LLOD</td>
</tr>
</tbody>
</table>

Antiviral Resistance: Nomenclature

- **Genotypic resistance**: Detection of HBV polymerase mutation(s) associated with resistance
- **Phenotypic resistance**: Decreased in vitro susceptibility to an antiviral agent
- **Virologic breakthrough**: Increase in HBV DNA by >1 log10 over nadir on treatment
- **Biochemical breakthrough**: Increase in ALT on treatment

Differences in Development of Resistance with Long-term Treatment in Nuc-naïve Patients

Patients with resistance (%)

Year 1  Year 2  Year 3  Year 4  Year 5  Year 6
Lamivudine1  24  53  65  0.1  3  11
Adefovir2   42  70   29  0.4  1.0  1.2
Entecavir3-6  0.4  0.4  0.4  1.0  1.2  4
Tellebivudine7,8  0  0  0  0  0  22
Tenofovir9,10  0  0  0  0  0  0


Summary: Guidelines for Management of Antiviral-Resistant HBV

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Rescue Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td><strong>Add adefovir or tenofovir DF</strong>&lt;br&gt;Stop lamivudine, switch to emtricitabine/tenofovir DF</td>
</tr>
<tr>
<td>Adefovir</td>
<td><strong>Add lamivudine</strong>&lt;br&gt;Stop adefovir, switch to:&lt;br&gt;Emtricitabine/tenofovir DF&lt;br&gt;Switch to or add entecavir (if no prior lamivudine resistance)</td>
</tr>
<tr>
<td>Entecavir</td>
<td><strong>Switch to tenofovir DF or emtricitabine/tenofovir DF</strong></td>
</tr>
<tr>
<td>Tellebivudine</td>
<td><strong>Add adefovir or tenofovir DF</strong>&lt;br&gt;Stop tellebivudine, switch to emtricitabine/tenofovir DF</td>
</tr>
<tr>
<td>Adefovir/Lamivudine</td>
<td><strong>Consider tenofovir emtricitabine DF, or tenofovir+ entecavir</strong></td>
</tr>
<tr>
<td>Lamivudine Entecavir</td>
<td><strong>Consider tenofovir or tenofovir DF/emtricitabine</strong></td>
</tr>
</tbody>
</table>

Tenofovir + Entecavir for Multidrug resistant HBV infection

- 51/57 (90%) of patients achieving HBV-DNA undetectability (LLoD 80IU/ml)

Peterson Journal of Hepatology 2012 vol. 56 j 520–526

Indications for HBV vaccination

- HBIG and HB vaccine to infants of HBsAg+ mothers
- Routine vaccination of infants and adolescents
- Catch-up vaccination of children
- Vaccination of adults at risk of infection
HBV DNA Level and Perinatal Transmission of HBV

Perinatal Transmission

<table>
<thead>
<tr>
<th>Maternal HBV DNA (copies/mL)</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10⁵</td>
<td>0%</td>
</tr>
<tr>
<td>10⁵-10⁶</td>
<td>0%</td>
</tr>
<tr>
<td>&gt;10⁸</td>
<td>8.5%</td>
</tr>
</tbody>
</table>

No cases of transmission from mothers with HBV DNA <8 log₁₀ copies/mL. One case of escape mutation identified.


Treatment during pregnancy

- **Xu et al**

<table>
<thead>
<tr>
<th>HBsAg(+) pregnant women</th>
<th>Maternal HBV DNA &gt; 1000 mEq/mL (n = 114)</th>
<th>Lamivudine (100 mg/day) from 32 ± 2 weeks of gestation to 4 weeks postpartum (n = 56)</th>
<th>All infants received</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HBV vaccine (10 g/0.5 mL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HB Ig (200 IU, single dose)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo (n = 59)</td>
</tr>
</tbody>
</table>

- **Primary endpoint** HBsAg + infant at 1 yr
- **Secondary endpoint** HBsAb+, HBV DNA+

Treatment during pregnancy

- Xu et al: Improved outcomes for the infants

<table>
<thead>
<tr>
<th>Infant Status at 52 weeks</th>
<th>LAM (n = 56)</th>
<th>Placebo (n = 59)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg(+) %</td>
<td>18</td>
<td>39</td>
<td>.014</td>
</tr>
<tr>
<td>HBV DNA(+) %</td>
<td>20</td>
<td>46</td>
<td>.003</td>
</tr>
</tbody>
</table>

HBsAb positive 84% vs. 61% (p=0.008)

Treatment of HBV: Special Cases

- Prophylactic treatment during chemotherapy to prevent reactivation (Rx from 1 wk before to 3-12 mo after)\(^1\)
  - % with hepatitis: 53% untreated vs. 14% lamivudine-treated
  - Treatment of women during the third trimester of pregnancy to reduce rate of vertical transmission\(^2\)
    - Studies limited; use in women with HBV DNA >10\(^8\) c/mL
  - HBV/HIV coinfection\(^3\)
    - If HAART needed, then tenofovir + emtricitabine or lamivudine
  - Prophylactic treatment after liver transplantation to prevent reinfection\(^3\)

HBV Reactivation Following Rituximab-Containing Chemotherapy

- Single-center cohort with a variety of hematologic diagnoses (n=62) (2011-2013)
  - HBsAg negative, anti-HBc positive
  - HBV DNA <10 IU/mL
  - No concomitant liver disease or prior HBV treatment
  - Reactivation: HBV DNA >10 IU/mL regardless of HBsAg status
  - Follow-up: 36.6 months
- High rate of reactivation
  - Majority occurred within the first 6 months (86.7%)
  - Presence of low anti-HBs levels was not protective against HBV reactivation

Cumulative Rate of HBV Reactivation

9-Month Cumulative Rate: 29.3%

Hepatitis B reactivation recommendationshigh-Risk Patients (Anticipated Incidence of HBV Reactivation, >10% of Cases)

- Tenofovir/Entecavir preferred agents
- Continue antiviral therapy for at least 6 months after discontinuation of immunosuppressive therapy (at least 12 months for B-cell–depleting agents).
  - Hepatitis B surface antigen (HBsAg)-positive/anti-hepatitis B core antibody (HBe)–positive patients treated with B-cell–depleting agents (eg, rituximab, ofatumumab)
  - HBsAg-positive/anti-HBe–positive patients treated with anthracycline derivatives (eg, doxorubicin, epirubicin)
  - HBsAg-positive/anti-HBe–positive patients treated with moderate-dose (10-20 mg prednisone daily or equivalent) or high-dose (>20 mg prednisone daily or equivalent) corticosteroids daily for ≥4 weeks.


Hepatitis B reactivation recommendations

Moderate-Risk Patients (HBV Reactivation, 1%-10% of Cases)

- Tenfovir/Entecavir preferred, continue treatment for 6 months after discontinuation of immunosuppressive therapy
- HBsAg-positive/anti-HBc–positive or HBsAg-negative/anti-HBc–positive patients treated with tumor necrosis factor alpha inhibitors (eg, etanercept, adalimumab, certolizumab, infliximab)
- HBsAg-positive/anti-HBc–positive or HBsAg-negative/anti-HBc–positive patients treated with other cytokine or integrin inhibitors (eg, abatacept, ustekinumab, natalizumab, vedolizumab)
- HBsAg-positive/anti-HBc–positive patients treated with tyrosine kinase inhibitors (eg, imatinib, nilotinib)
- HBsAg-positive/anti-HBc–positive patients treated with low-dose (< 10 mg prednisone daily or equivalent) corticosteroids for ≥ 4 weeks
- HBsAg-negative/anti-HBc–positive patients treated with moderate-dose (10-20 mg prednisone daily or equivalent) or high-dose (> 20 mg prednisone daily or equivalent) corticosteroids daily for ≥ 4 weeks
- HBsAg-negative/anti-HBc–positive patients treated with anthracycline derivatives (eg, doxorubicin, epirubicin).

How do we screen for HCC in HBV

- No studies define unequivocally the best modality for diagnosing HCC
- Ultrasonography (US) every 6 months with alpha-fetoprotein (AFP) every six months is current standard of care for screening high risk patients
  - US has technical limitations (operator dependence, reduced efficacy in those with elevated BMI)
  - US if subject has normal BMI
- AFP alone is not sufficient unless imaging modalities are not available
- Our practice at IU: MRI every 9 months or Dual Phase Spiral CT, or US every 6 months if normal BMI
  - MRI or US preferred due to radiation risk with CT scan
AASLD Guidelines: HBV

- Surveillance recommended in at-risk groups
  - Specific hepatitis B carriers
    - Asian males >40 years
    - Asian females >50 years
    - Africans >20 years
    - All HBV cirrhotic pts
    - Family history of hepatoma
- Patients should be screened at 6-month intervals
  - US and AFP level

Other Clinical Pearls

- Avoid entecavir use in HBV/HIV
  - leads to HIV resistance
  - Check HIV serology prior to initiating entecavir
- Telbivudine /Tenofovir are pregnancy category B
  - Useful in young females trying to conceive
  - Acute HBV in pregnancy
  - Low rate of resistance if HBV undetected by week 24 but must monitor for resistance
• Chronic HBV infection: HBsAg+ > 6 months

• Evidence of virus replication: serum HBV DNA >10^{4-5} \text{ copies/ml (2000-20,000 IU/ml)}

• Evidence of liver damage: elevated ALT and/or chronic hepatitis on biopsy

**Summary**

**Prevention**
- Avoid unnecessary treatment
- Initiate treatment with potent antiviral that has low rate of drug resistance (tenfovir or entecavir) or with combination therapy
- Switch to alternative therapy in patients with primary non-response

**Monitoring**
- Test for serum HBV DNA (PCR assay) every 3-6 months during treatment
- Check for medication compliance in patients with virologic breakthrough
- Confirm antiviral resistance with genotype testing
Summary of Guidelines
Treatment of Hepatitis B

When to start therapy
- Elevated HBV DNA [≥20,000 IU/mL for HBeAg(+) and ≥2,000 IU/mL for HBeAg(-)] plus elevated ALT, and/or significant disease on liver biopsy

When to stop or alter therapy
- HBeAg(+): HBeAg seroconversion and (-) HBV DNA
- HBeA(-): long-term therapy
- Inadequate VR (≥2,000 IU/mL) at week 24
- Development of antiviral drug resistance

Summary

Treatment
- Guided by genotypic assays
- Add on therapy or switch therapy per guidelines
- Rescue therapies for multi-drug resistance
  - tenofovir+entecavir
  - tenofovir DF/emtricitabine