Updates in Treatment of Hepatitis B

Paul Y. Kwo, MD, FACG
Professor of Medicine
Gastroenterology/Hepatology Division
Medical Director, Liver Transplantation
Indiana University Health
Indiana University School of Medicine
975 W. Walnut, IB 327
Indianapolis, IN 46202-5121
phone 317-274-3090
fax 317-274-3106
e-mail pkwo@iu.edu

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

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

<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>


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

Global, 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%
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.
Natural History of Chronic HBV Infection

- Childhood: >95% Immune Tolerance
- Adulthood: <5% HBeAg+ CHB

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

HBV DNA vs. Liver Cirrhosis: REVEAL data

Baseline HBV DNA

No of patients = 3,482*

<table>
<thead>
<tr>
<th>HBsAg negative</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥10^6 copies/mL</td>
<td>10.6</td>
</tr>
<tr>
<td>10^4-&lt;10^6</td>
<td>9.7</td>
</tr>
<tr>
<td>10^4-&lt;10^5</td>
<td>3.6</td>
</tr>
<tr>
<td>300-&lt;10^4</td>
<td>2.0</td>
</tr>
<tr>
<td>&lt;300</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* HBeAg negative n=2060

Aiming for True Inactive Carrier Status

**Milestone 1:** Start of decline of HBV DNA

**Milestone 2:** HBeAg/anti-HBe seroconversion

**Milestone 3:** HBV DNA decreased to undetectable

**Milestone 4:** Clearance of HBsAg

**Milestone 5:** Clearance of cccDNA

This is where we would like our patients to be.

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

- No of patients = 3,653
- Baseline HBV DNA
  - $\geq 10^8$ copies/mL: RR 6.6
  - $10^6-10^7$: RR 6.1
  - $10^4-10^5$: RR 2.3
  - $300-10^4$: RR 1.1
  - $<300$: RR 1.0

*HBeAg negative n=3086

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>Brand Name</th>
<th>Company</th>
<th>Year</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>BARACLUDE™</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>Brand Name</th>
<th>Company</th>
<th>Year</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>
Candidates for HBV Treatment

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA threshold (IU/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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</td>
</tr>
<tr>
<td>ALT: Normal range</td>
<td>-</td>
<td>-</td>
<td>(M: 30 U/L; F: 19 U/L)</td>
<td>2X ULN (M: 30 U/L; F: 19 U/L)</td>
</tr>
<tr>
<td>When to treat: 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>

Other Caveats From Recent AASLD Guideline Update

- The decision to treat persons with ALT above the ULNs, but <2 ULN, requires consideration of severity of liver disease (defined by biopsy or noninvasive testing).
- Therapy is recommended for persons with immune-active CHB and cirrhosis if HBV DNA >2,000 IU/mL, regardless of ALT level.
- The AASLD suggests antiviral therapy in the select group of adults >40 years of age with normal ALT and elevated HBV DNA (1,000,000 IU/mL) and liver biopsy showing significant necroinflammation or fibrosis.

### 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></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</td>
<td></td>
</tr>
<tr>
<td>Entecavir</td>
<td></td>
</tr>
</tbody>
</table>

Note: therapies are approved for monotherapy only.  
*Early cirrhosis only.  
†Contraindicated.

Decrease in Serum HBV DNA after 1 Year of Treatment

<table>
<thead>
<tr>
<th>Medication</th>
<th>Log10 Decrease in HBV DNA</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>-6.6</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

HBeAg Seroconversion after 1-5 Years of Treatment

At 1 Year

<table>
<thead>
<tr>
<th>Medication</th>
<th>HBeAg Seroconversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg IFN</td>
<td>32</td>
</tr>
<tr>
<td>LMV</td>
<td>16-21</td>
</tr>
<tr>
<td>ADV</td>
<td>12-18</td>
</tr>
<tr>
<td>ETV</td>
<td>21</td>
</tr>
<tr>
<td>TBV</td>
<td>21</td>
</tr>
<tr>
<td>TDF</td>
<td>21</td>
</tr>
</tbody>
</table>

> 1 Year

<table>
<thead>
<tr>
<th>Medication</th>
<th>HBeAg Seroconversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg IFN</td>
<td>~35</td>
</tr>
<tr>
<td>LMV #</td>
<td>~50</td>
</tr>
<tr>
<td>ADV #</td>
<td>48</td>
</tr>
<tr>
<td>ETV #</td>
<td>41</td>
</tr>
<tr>
<td>TBV #</td>
<td>42</td>
</tr>
<tr>
<td>TDF#</td>
<td>40</td>
</tr>
</tbody>
</table>

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

@ 6 months off Rx
^ 3 years off Rx
# 5 years on Rx
* 4 years on Rx
HBsAg Loss after 2-5 Years of Treatment

**HBeAg+ Patients**

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

^ 3 years off Rx
# 4-5 years on Rx
* 2 years on Rx

**HBeAg- Patients**

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

Reversal of Fibrosis and Cirrhosis

Tenofovir Phase III Trial: Biopsies at Year 0, 1 & 5

- 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 >140,000 IU/mL

<table>
<thead>
<tr>
<th>% with disease progression</th>
<th>Placebo (n=215) ITT population</th>
<th>Lamivudine (n=436)</th>
<th>p=0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase CTP score, liver failure or HCC</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Time to disease progression (months)

- Placebo (n=215)
- Lamivudine (n=436) p=0.001

Liaw YF, NEJM 2004; 351:1521

Efficacy and Limitations 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
- Long duration / lifelong treatment required to maintain benefit
  - High costs, risks of drug resistance and side effects
**Resistance Rates Through 6 Years Among Nucleos(t)ide-Naïve Patients**

- **LAM**
  - Year 1: 23%
  - Year 2: 46%
  - Year 3: 55%
  - Year 4: 71%
  - Year 5: 80%
  - Year 6: 1.2%

- **ADV**
  - Year 1: 0%
  - Year 2: 3%
  - Year 3: 11%
  - Year 4: 18%
  - Year 5: 29%
  - Year 6: 0%

- **TBV**
  - Year 1: 5%
  - Year 2: 25%
  - Year 3: 25%
  - Year 4: 18%
  - Year 5: 71%
  - Year 6: 55%

- **TDF**
  - Year 1: 0%
  - Year 2: 0%
  - Year 3: 0%
  - Year 4: 0%
  - Year 5: 0%
  - Year 6: 0%

- **ETV**
  - Year 1: <1%
  - Year 2: 1.2%
  - Year 3: 1.2%
  - Year 4: 1.2%
  - Year 5: 1.2%
  - Year 6: 1.2%

---

**Study ETV-901: 5-Year Durable Efficacy of Entecavir in HBeAg-Positive Patients**

- Long-term observational roll-over study
- Previously treatment-naïve patients (n=146)
- Long-term entecavir
  - 94% undetectable through 5 years
  - Maintained ALT normalization
  - Entecavir resistance in 1 patient (1%)
  - Experienced virologic breakthrough at year 3

---

Studies 102/103: Virologic Suppression With Tenofovir at Year 8

<table>
<thead>
<tr>
<th></th>
<th>HBeAg-</th>
<th>HBeAg+</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA &lt;29 IU/mL (ITT)* %</td>
<td>74</td>
<td>58</td>
</tr>
<tr>
<td>HBV DNA &lt;29 IU/mL (Observed), %</td>
<td>99.6</td>
<td>97</td>
</tr>
<tr>
<td>HBeAg loss / seroconversion†, %</td>
<td>NA</td>
<td>47/31</td>
</tr>
<tr>
<td>HBsAg loss/seroconversion (KM%)‡</td>
<td>1.1/0.7</td>
<td>12.9/10.3</td>
</tr>
</tbody>
</table>

*Missing = failure; add FTC = failure (LT-TDF)
†Missing = excluded; add FTC = included
‡KM% = Kaplan-Meier % (KM-ITT)
NA, not applicable

Marcellin, AASLD, 2014, Oral #229

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: 2.78; 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

Interferon

- Fixed duration therapy (48 weeks PEG IFN Alfa 2a)
- 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


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

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

NIDDKD: National Institute of Diabetes and Digestive and Kidney Diseases


HBsAg Loss in HBeAg-Positive and HBeAg-Negative Patients

When can treatment be stopped?

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

Nucleos(t)ide analogues until treatment endpoint

- HBeAg+ patients  HBeAg seroconversion + ≥12 mos consolidation Rx, ~50% after 5 yr Rx
  An alternative approach is to treat until HBsAg loss.

- HBeAg- patients  Indefinite therapy
  HBsAg loss ~5% after 5 yr Rx

- Cirrhotics  life-long Rx


New Polymerase inhibitor Coming

- Tenofovir alafenamide (TAF)
  - New tenofovir (TFV) produg; greater plasma stability than TDF1-3
  - Enhances delivery of active drug (TFV-DP) to hepatocytes1-3
  - Reduces circulating levels of TFV relative to TDF4,5
  - Improved bone and renal safety demonstrated in HIV patients5,6

- Study aim
  - To evaluate efficacy and safety of TAF compared with TDF in HBeAg+ patients with chronic hepatitis B

Tenofovir alafenamide versus tenofovir disoproxil

- Double-blind, active-controlled, Phase 3 study
- Key inclusion criteria
  - HBeAg-positive at screening
  - HBV DNA ≥20,000 IU/mL; ALT >60 U/L (males), >38 U/L (females)
- 2:1 randomization
  - Stratified by HBV DNA level and treatment status (naive vs experienced)

Chan et al EASL 2016

Similar efficacy, better safety profile

Improved renal safety profile
Improved bone turnover parameters
Cirrhosis Reversal Following Lamivudine Rx in HBV

Types of Virological Response

- On Treatment
- Continuous Treatment
- Primary non-response
- Breakthrough

On Continuous Treatment

- Maintained Response
- LLOD

HBV DNA (Log10 IU/ml)

Months

Sustained Response
Relapse

Courtesy of Ian Wanless, MD.
Antiviral Resistance: Nomenclature

- **Genotypic resistance**: Detection of HBV polymerase mutation(s) associated with resistance
- **Phenotypic resistance**: Decreased \textit{in vitro} susceptibility to an antiviral agent
- **Virologic breakthrough**: Increase in HBV DNA by \(>1 \log_{10}\) over nadir on treatment
- **Biochemical breakthrough**: Increase in ALT on treatment


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

Not head to head trials
Different patient populations and trial designs

### 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>Add tenofovir DF</td>
</tr>
<tr>
<td></td>
<td>Stop lamivudine, switch to tenofovir DF</td>
</tr>
<tr>
<td>Adefovir</td>
<td>Add lamivudine</td>
</tr>
<tr>
<td></td>
<td>Stop adefovir, switch to:</td>
</tr>
<tr>
<td></td>
<td>Emtricitabine/tenofovir DF</td>
</tr>
<tr>
<td></td>
<td>Switch to or add entecavir (if no prior lamivudine resistance)</td>
</tr>
<tr>
<td>Entecavir</td>
<td>Switch to tenofovir DF or add tenofovir DF</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>Add tenofovir DF</td>
</tr>
<tr>
<td></td>
<td>Stop telbivudine, switch to tenofovir DF</td>
</tr>
<tr>
<td>Multi Drug</td>
<td>tenofovir DF + entecavir</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 | 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

No cases of transmission from mothers with HBV DNA <3 log10 copies/mL. One case of escape mutation identified.

Treatment during pregnancy

AASLD suggests antiviral therapy to reduce the risk of perinatal transmission of hepatitis B in HBsAg-positive pregnant women with an HBV DNA level >200,000 IU/mL.

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


- Lamivudine (100 mg/day) from 32 ± 2 weeks of gestation to 4 weeks postpartum (n = 56)
- Placebo (n = 59)
- All infants received
  - HBV vaccine (10 g/0.5 mL)
  - HBIG (200 IU, single dose)

- Improved outcomes for the infants
  - HBsAb positive 84% vs. 61% (p=0.008)
  - Lamivudine, telbivudine, and tenofovir may be used, started at 28-32 weeks of gestation
  - Antiviral therapy was discontinued at birth to 3 months postpartum, monitor for flares
  - Breastfeeding is not contraindicated.

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

<table>
<thead>
<tr>
<th>Hepatitis B reactivation recommendations</th>
<th>Moderate-Risk Patients (HBV Reactivation, 1%-10% of Cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tenofovir/Entecavir preferred, continue treatment for 6 months after discontinuation of immunosuppressive therapy</td>
<td></td>
</tr>
<tr>
<td>• HBsAg-positive/anti-HBc–positive or HBsAg-negative/anti-HBc–positive patients treated with tumor necrosis factor alpha inhibitors (eg, etanercept, adalimumab, certolizumab, infliximab)</td>
<td></td>
</tr>
<tr>
<td>• HBsAg-positive/anti-HBc–positive or HBsAg-negative/anti-HBc–positive patients treated with other cytokine or integrin inhibitors (eg, abatacept, ustekinumab, natalizumab, vedolizumab)</td>
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<td>• HBsAg-positive/anti-HBc–positive patients treated with low-dose (&lt;10 mg prednisone daily or equivalent) corticosteroids for ≥4 weeks</td>
<td></td>
</tr>
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<td>• HBsAg-negative/anti-HBc–positive patients treated with anthracycline derivatives (eg, doxorubicin, epirubicin).</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Hepatitis B reactivation recommendations</th>
<th>High-Risk Patients (Anticipated Incidence of HBV Reactivation, &gt;10% of Cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tenofovir/Entecavir preferred agents</td>
<td></td>
</tr>
<tr>
<td>• Continue antiviral therapy for at least 6 months after discontinuation of immunosuppressive therapy (at least 12 months for B-cell–depleting agents).</td>
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<tr>
<td>• Hepatitis B surface antigen (HBsAg)-positive/anti-hepatitis B core antibody (HBc)–positive patients treated with B-cell–depleting agents (eg, rituximab, ofatumumab)</td>
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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

Indications for treatment of chronic hepatitis B
Who Should be Treated?

- Chronic HBV infection: HBsAg+ >6 months
- Evidence of virus replication: serum HBV DNA >10^4-5 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
- HBeAg(-): ?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