Treatment of Chronic Hepatitis B

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Global Burden of HBV

- >350 million persons worldwide have chronic disease
- 800,000 – 2 million in the U.S. have chronic disease

Burden of Chronic Hepatitis B in the U.S.

- U.S. prevalence: 0.8 – 2 million
- 65% are unaware of their infection status
- Deaths directly related to HBV infection (2006): 3,000
- Incidence of acute HBV infection is declining in the U.S., but number of people living with chronic HBV infection may be increasing as a result of immigration from highly endemic countries
- Asian and Pacific Islander (API) Americans make up only 4.5% of the U.S. population, but account for >50% of Americans with chronic HBV infection


Groups at High Risk for HBV Infection Who Should be Screened

- Individuals born in areas of high (≥8%) or intermediate (2%-7%) prevalence rates for HBV including immigrants and adopted children
- U.S. born persons not vaccinated as infants whose parents were born in regions with high HBV endemicity
- Household and sexual contacts of HBsAg (+) persons
- Persons who have ever injected drugs

Groups at High Risk for HBV Infection Who Should be Screened (con’t.)

- Persons with multiple sexual partners or history of sexually transmitted disease
- Men who have sex with men
- Inmates of correctional facilities
- Individuals with chronically elevated ALT or AST
- Individuals infected with HCV or HIV
- Patients undergoing renal dialysis
- All pregnant women
- Persons needing immunosuppressive therapy


Natural History of HBV Infection

Chronicity>95%

Chronicity<5%

HBeAg+ CHB

HBeAg- CHB

Inactive Carrier

Cirrhosis

HCC

Chen DS. J Gastroenterol Hep 1993;8:470-475.
Adverse Liver Outcomes in Chronic Hepatitis B: Relationship to HBV DNA Levels

Incidence of Cirrhosis

<table>
<thead>
<tr>
<th>HBV DNA Level</th>
<th>Incidence Rate</th>
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<tbody>
<tr>
<td>&lt;300</td>
<td>0.19%</td>
</tr>
<tr>
<td>~1,000</td>
<td>0.48%</td>
</tr>
<tr>
<td>~10,000</td>
<td>0.78%</td>
</tr>
<tr>
<td>~100,000</td>
<td>1.81%</td>
</tr>
<tr>
<td>&gt;1,000,000</td>
<td>2.79%</td>
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Incidence of HCC

<table>
<thead>
<tr>
<th>HBV DNA Level</th>
<th>Incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;300</td>
<td>0.13%</td>
</tr>
<tr>
<td>~1,000</td>
<td>0.11%</td>
</tr>
<tr>
<td>~10,000</td>
<td>0.37%</td>
</tr>
<tr>
<td>~100,000</td>
<td>0.94%</td>
</tr>
<tr>
<td>&gt;1,000,000</td>
<td>1.16%</td>
</tr>
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</table>

1. Iloeje UH et al. Gastroenterology 2006;130:678-686.

Chronic HBV Patients with Normal ALT May Have Significant Liver Disease

- 18% of patients with chronic HBV and persistently normal ALT (n=59) had significant fibrosis (stage 2+); 34% had grade 2 or 3 inflammation

- 42% of chronic HBV patients with normal ALT (n=38) had significant fibrosis, 24% had cirrhosis, and 26% had significant inflammation

HBeAg (+) Hepatitis B: Algorithm for Treatment

HBeAg (+)

ALT < 1 X ULN
Age <40
Q6mo ALT
Q6mo HBeAg

HBV DNA >20,000
Liver biopsy
Significant Inflammation/Fibrosis

ALT 1-2 X ULN
Age >40
Q3-6mo ALT
Q3-6mo HBeAg

ALT > 2 X ULN
Monitor ALT, HBV DNA and HBeAg q3-6mo


HBeAg (+) Hepatitis B: HBV DNA Undetectable During Continued Nucleos(t)ide Treatment

Not Head to Head Trials, Different Patient Populations and Trial Designs

<table>
<thead>
<tr>
<th>Year</th>
<th>Percent of Patients</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Entecavir 55%</td>
</tr>
<tr>
<td></td>
<td>Tenofovir 83%</td>
</tr>
<tr>
<td>2</td>
<td>Entecavir 89%</td>
</tr>
<tr>
<td></td>
<td>Tenofovir 89%</td>
</tr>
<tr>
<td>3</td>
<td>Entecavir 91%</td>
</tr>
<tr>
<td></td>
<td>Tenofovir 91%</td>
</tr>
<tr>
<td>4</td>
<td>Entecavir 94%</td>
</tr>
<tr>
<td></td>
<td>Tenofovir 94%</td>
</tr>
<tr>
<td>5</td>
<td>Entecavir 76%</td>
</tr>
<tr>
<td></td>
<td>Tenofovir 89%</td>
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AASLD guidelines recommend that treatment should be continued for at least 6 months after the patient has achieved both HBeAg seroconversion [HBeAg (-); anti-HBe (+)] and undetectable serum HBV DNA.

Some patients remain viremic after HBeAg seroconversion and reversion to HBeAg positivity occurs in up to 50% of patients when treatment is stopped.

Thus, many patients will enter the inactive carrier phase and remain in that phase for months, years, or decades after HBeAg seroconversion.

Treatment can be discontinued in patients who complete consolidation therapy after HBeAg seroconversion; continued monitoring is required.

Lifelong treatment is recommended for patients who had decompensated cirrhosis.

Lifelong treatment may be considered for patients who had compensated cirrhosis.

Treatment may be stopped in those with documented reversal of cirrhosis and those with confirmed HBsAg loss; continued monitoring is required.
HBeAg (-) Hepatitis B: Algorithm for Treatment

ALT < 2 X ULN
- HBV DNA < 2000
  - Q6mo ALT
  - Q6mo HBV DNA
- Age < 40
- Significant Inflammation/Fibrosis
- Liver biopsy
- Begin Antiviral Therapy

ALT > 2 X ULN
- HBV DNA > 2000
  - Age < 40
  - Investigate for other causes of liver disease (Medications, Hepatitis C, Alcohol)
  - HBV DNA < 2000
- HBV DNA > 2000
- HBV DNA < 2000

References:

Antiviral Therapy for HBeAg (-) CHB: Loss of Serum HBV DNA

Not Head to Head Trials, Different Patient Populations and Trial Designs

Loss of serum HBV DNA (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Loss of HBV DNA (%)</th>
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<tbody>
<tr>
<td>PLB</td>
<td>15%</td>
</tr>
<tr>
<td>LAM</td>
<td>96.6%</td>
</tr>
<tr>
<td>ADV†</td>
<td>81%</td>
</tr>
<tr>
<td>LdT§</td>
<td>90%</td>
</tr>
<tr>
<td>ETV⁺</td>
<td>80%</td>
</tr>
<tr>
<td>TDF⁺</td>
<td>69%</td>
</tr>
</tbody>
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Treatment Duration: *, 48 wks; †, 48-52 wks; §, 52 wks.
PLB = Placebo; LAM = Lamivudine; ADV = Adefovir;
ETV = Entecavir; LdT = Telbivudine; TDF = Tenofovir

Adapted from Lok ASF, McMahon BJ. Hepatology. 2009;50:1-36.
HBeAg (-) Hepatitis B Treatment Duration: Nucleos(t)ide Analogs

- AASLD guidelines recommend that treatment with nucleos(t)ide analogs in HBeAg (-) hepatitis B patients should be continued until the patient has achieved HBsAg clearance.
- Life-long treatment is recommended for patients with decompensated cirrhosis.


AASLD Recommendations for HCC Surveillance of HBV Carriers

- HBV carriers at high risk for HCC should receive an US examination every 6 – 12 months including:
  - Asian men >40 years of age
  - Asian women >50 years of age
  - Persons with cirrhosis
  - Persons with a family history of HCC
  - Africans >20 years of age
  - Any carrier >40 years with persistent or intermittent ALT elevation and/or HBV DNA level >2,000 IU/mL
- Periodic surveillance with serum AFP should be considered for high risk HBV carriers living in areas where U.S. is not readily available.

The Problem of Nucleos(t)ide Resistance in Chronic Hepatitis B

Factors Affecting the Development of Resistance

- Non-compliance
- Pretreatment HBV DNA levels
- Potency of the antiviral agent
- Rapidity of viral suppression
- Prior exposure to oral nucleoside or nucleotide antiviral therapy
- Duration of treatment
- Degree of genetic barriers to resistance to the individual drug
- Pharmacologic barrier: Blood and tissue levels

Consequences of Antiviral Resistance

- Virologic breakthrough; loss of initial virologic, biochemical, and histologic response
  - Can lead to hepatitis flares and hepatic decompensation, death, or urgent transplant
- Cross-resistance limits future treatment options
  - Subsequent requirement for dual therapy
- Transmission to treatment-naïve persons poses a potential public health problem
- Vaccine failure

Adapted from Lok ASF, McMahon BJ. Hepatology. 2009;50:1-36.

Increased Resistance with Long-Term Treatment in Nucleoside-Naïve Patients

**Minimal Resistance with Long-Term Treatment in Nucleoside-Naïve Patients**


**Nucleos(t)ide Resistance Profile: First-Line Treatment Options Have the Lowest Resistance Rates**

Resistance does not appear to emerge during treatment with IFN α-2b or PEG-IFN α-2a

What Is HBV Reactivation?

- HBV reactivation is a well-characterized syndrome marked by the abrupt reappearance or rise of HBV DNA in the serum of a patient with previously inactive or resolved HBV infection
  - Often, but not always, accompanied by reappearance of disease activity or a flare of hepatitis in previously minimal or inactive disease
  - May occur spontaneously or as a result of immunosuppression
- The complex virological and biological features of reactivation often cause confusion and delayed recognition
  - Different studies often use different markers and criteria for diagnosing HBV reactivation
- There is no consensus on the definition in terms of which patients should be considered at high risk for reactivation based on their HBV serologic markers

Colonno et al. Hepatology. 2006;44(suppl 1):S228A.

Overview of HBV Reactivation

- Frequency of HBV reactivation is not well-defined
- Risk for reactivation appears to be high among patients undergoing chemotherapy
  - For patients with lymphoma, incidence of HBV reactivation has been reported between 24%-67%
- Among patients with breast cancer, incidence of reactivation has been reported to be as high as 41% to 56%
- Reactivation is not limited to chemotherapy, and has been described in the treatment of patients with rheumatic, dermatological, and gastroenterological disorders


Risk of HBV Reactivation by Diseases

Bone Marrow Transplantation
Organ Transplantation
Lymphoma
Leukemia
Myeloma
Cancer Patients with systemic infections (HIV, HCV)
Autoimmune diseases
Inflammatory bowel disease

HBV Reactivation in Oncology Patients

- Reactivation may occur during or after chemotherapy
- Without prophylaxis for HBV, reactivation occurs in up to 85% of HBsAg+ patients, Non-Hodgkin’s Lymphomas patients
- Those who received steroid containing chemotherapies had an associated HBV related death of 30 to 50%
- With appropriate antiviral prophylaxis, chemotherapy related reactivation of HBV is significantly decreased

Reactivation has occurred in patients who are HBsAg+ or anti-HBc+ only.


HBV Reactivation in Lymphoma Patients Receiving Chemotherapy Without Antiviral Prophylaxis

- First large prospective study in Hong Kong studied 100 lymphoma patients receiving chemotherapy
- 48% (13/27) of the HBsAg+ patients developed reactivation during or shortly after chemotherapy
- 4% (2/51) of the HBsAg-/HBcAb+ patients, developed an extreme form of HBV reactivation, called “reverse seroconversion”
- 46% (7/15) of the reactivation cases developed jaundice
- 3/7 patients with jaundice developed hepatic failure and 1 was fatal

Immunosuppressive Therapies

- Immunosuppressive therapies used in:
  - Chronic Inflammatory disorders
  - Chemotherapy
- TNF alpha antagonists

Immunosuppressive therapies have been implicated in HBV Reactivation across multiple disease processes.


HBV Reactivation in Dermatologic and Rheumatologic Conditions

- Dermatologic Conditions\(^1\)
  - 41.3% of patients with systemic sclerosis treated with corticosteroid
  - Corticosteroid therapy can cause immunosuppression

- Rheumatologic Conditions\(^2\)
  - 25% of patients are receiving biologic therapies
  - Use of biologic therapies can cause immunosuppression

Patients undergoing treatment with any immunosuppressant agent should be screened for HBV prior to initiation of therapy.


HBV Reactivation in Inflammatory Bowel Disease

- HBV reactivation has been documented in patients being treated with immunosuppressive agents for inflammatory bowel disease¹
- Immunosuppressive side effect of agents can lead to HBV reactivation in chronically infected patients¹

<table>
<thead>
<tr>
<th>HBV Seroprevalence in Patients Treated for IBD²</th>
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<tbody>
<tr>
<td>HBsAg+</td>
</tr>
<tr>
<td>Crohn's</td>
</tr>
<tr>
<td>Ulcerative Colitis</td>
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</tbody>
</table>

Patients undergoing treatment for inflammatory bowel disease should be screened for HBV at diagnosis.


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HBV Reactivation in Hematopoietic Stem Cell Transplantation

- HBV Reactivation is more common in stem cell transplantation than seen with standard cancer chemotherapy

- Incidence of HBsAg seroreversion post-transplantation
  - 2 years: 40%
  - 5 years: 70%

All patients candidates for stem cell transplantation should be screened for HBV prior to conditioning chemotherapy regimen.

HBV Reactivation with Organ Transplantation

- HBV reactivation has been described in patients who have received transplantation with heart, liver and kidneys\(^1,2\)
- Liver transplantation\(^2\)
  - Occurs due to organ donor being HBsAg or anti-HBc positive
  - Most dramatic examples of reverse HBsAg seroconversion occur with anti-HBc\(^+\) / HBsAg\(^-\) donor organs to HBsAg\(^-\) recipients
  - HBV reactivation rate: 70%

Reactivation of HBV in kidney and heart transplant recipients ranges from 50 to 94% without antiviral prophylaxis.\(^2\)

Risk of Reactivation With Rituximab

- Reactivation flares of HBV have been well documented in patients receiving rituximab\(^1,2\)
- Currently, rituximab is commonly used to treat\(^2,3\)
  - Non-Hodgkin’s Lymphoma
  - Chronic Leukocytic Leukemia
  - Rheumatoid Arthritis
  - Lupus Nephritis

\(^1\) Lubel JS, Angus PW. J Gastroenterol Hepatol. 2010;25:864-871.
Conclusions

• HBV is common and most patients are unaware that they are infected
• Guidelines for screening have been developed
• Treatment is safe and highly effective at suppression
• Resistance is not a common problem
• Advanced fibrosis is reversible with successful treatment
• Reactivation can be a devastating problem