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
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- 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>Vietnam</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)

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%
If it is not treated, in 1/3 of patients, hepatitis B can cause liver damage leading to cirrhosis and liver cancer. Hepatitis B is responsible for 80% of primary liver cancer globally, which is almost always fatal.

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

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

HCC And or cirrhosis


HBV DNA vs. Liver Cirrhosis: REVEAL data

No of patients = 3,482*

Baseline HBV DNA RR
≥10^4 copies/mL 16.6
10^3—<10^5 9.7
10^2—<10^3 3.6
300—<10^2 2.0
<300 1.0

* HBeAg negative n=2960

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

HBeAg(+), anti-HBe(-)
HBeAg(-), anti-HBe(+)

Undetectable level of HBV DNA
Low HBV DNA (<2000 IU/mL) for reduced progression risk

Immune tolerance
Immune clearance
Inactive carrier state
Functional cure (CURE)
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

U.S. FDA dates of Approved Therapies for CHB

<table>
<thead>
<tr>
<th>Nucleosides/Nucleotides</th>
<th>Gilead Sciences</th>
<th>Bristol-Myers Squibb</th>
<th>Roche Laboratories</th>
<th>GlaxoSmithKline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir* VIREAD®</td>
<td>2008</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telbivudine TYZEKA™</td>
<td>2006</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Entecavir* BARACLEUDE™</td>
<td>2005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adefovir dipivoxil HEPSERA™</td>
<td>2002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine EPIVIR-HBV®</td>
<td>1998</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Interferons</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Peginterferon alfa-2a*</td>
<td>PEGASYS®</td>
<td>Roche Laboratories</td>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>Interferon alfa-2b, recombinant INTRON® A</td>
<td>Schering / Merck</td>
<td>1992</td>
<td></td>
<td></td>
</tr>
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</table>
**Candidates for HBV Treatment**

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>HBV DNA threshold (IU/L)</strong></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>2000-20,000</td>
</tr>
<tr>
<td><strong>ALT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal range</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><strong>When to treat</strong></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>HBV DNA and ALT</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>
<tr>
<td><strong>Biopsy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></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

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

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

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


A tool to minimize resistance:
HBV Roadmap: Definitions of Virologic Response

- **Primary Non-Response at Week 12**
  (HBV DNA <1 log10 IU/mL decrease from baseline)

  - **Early Predictors of Efficacy at Week 24**
    - **Complete Response** (PCR Negative)
    - **Partial Response** (HBV DNA >60 to <2000 IU/mL)
    - **Inadequate Response** (HBV DNA >2000 IU/mL)

HBV Roadmap: Treatment Response to HBV DNA

Early Predictors of Efficacy at Week 24

- **Complete Response** (PCR Negative)
  - No Change in Treatment
- **Partial Response** (HBV DNA >60 to <2000 IU/mL)
- **Inadequate Response** (HBV DNA >2000 IU/mL)


Low Genetic Barrier Drug
- Switch or add alternative drug
- More frequent monitoring (every 3 months)

High Genetic Barrier Drug
- No change in treatment
- More frequent monitoring (every 3 months)
HBV Roadmap: Treatment Response to HBV DNA

Early Predictors of Efficacy at Week 24

- Complete Response (PCR Negative)
- Partial Response (HBV DNA >60 to <2000 IU/mL)
- Inadequate Response (HBV DNA >2000 IU/mL)

Switch or Add Alternative Therapy
Narrow Monitoring Frequency

Cirrhosis Reversal Following Lamivudine Rx in HBV

Courtesy of Ian Wanless, MD.
Effect of LAM on Incidence of HCC in CHB and Advanced Fibrosis


Types of Virological Response

ACG's Hepatitis School - Las Vegas, NV
Copyright 2015 American College of Gastroenterology
Implications of Resistance to HBV Therapies

- Loss of clinical benefits
  - Loss of initial HBV DNA response with rebound
  - ALT increase and eventual reversion of histologic improvement
  - Progressive liver disease
  - In patients with cirrhosis, decompensation
- Development of multidrug resistance
  - Cross resistance
  - New resistance mutations
- Transmission of resistant virus


Antiviral Resistance: Nomenclature

<table>
<thead>
<tr>
<th>Genotypic resistance</th>
<th>Detection of HBV polymerase mutation(s) associated with resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotypic resistance</td>
<td>Decreased <em>in vitro</em> susceptibility to an antiviral agent</td>
</tr>
<tr>
<td>Virologic breakthrough</td>
<td>Increase in HBV DNA by &gt;1 log₁₀ over nadir on treatment</td>
</tr>
<tr>
<td>Biochemical breakthrough</td>
<td>Increase in ALT on treatment</td>
</tr>
</tbody>
</table>

Factors associated with antiviral resistance

VIRUS
• Daily production
• Replication fidelity
• Pre-existent mutations

DRUG
• Potency
• Genetic barrier to resistance

HOST
• Prior Rx
• Compliance
• Immune Status
• Pharmacogenetics
• Body Size

What causes antiviral-resistant HBV mutants to become dominant?

• Survival of the fittest: selection of virus with survival advantage in the presence of antiviral therapy
Manifestations of Antiviral Resistance

Consequences of Antiviral Resistance

- Loss of initial virologic, biochemical and histological response
- Hepatitis flares, hepatic decompensation and death
- Increased risk of HBV recurrence post-liver transplant
- Limit future treatment options
- Transmission to treatment-naïve persons → public health problem
Differences in Development of Resistance with Long-term Treatment in Nuc-naive Patients

- Not head to head trials
- Different patient populations and trial designs

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>Adefovir</td>
<td>Entecavir</td>
<td>Telbivudine</td>
<td>Tenofovir</td>
<td></td>
</tr>
<tr>
<td>53%</td>
<td>65%</td>
<td>42%</td>
<td>29%</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td>24%</td>
<td>70%</td>
<td>65%</td>
<td>42%</td>
<td>29%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Lamivudine:

Adefovir:

Entecavir:

Telbivudine:

Tenofovir:
- Telbivudine (Tyzeka®) prescribing information; May 2009; Novartis Pharmaceuticals, East Hanover, NJ
- Lai CL, Hepatology 2006;44(Suppl 1):222A

The hepatitis B virus (HBV) polymerase open reading frame

Lok et al Hepatology 2007;46:254-265
In Vitro HBV Cross-resistance

<table>
<thead>
<tr>
<th>Mutations</th>
<th>LAM</th>
<th>ETV</th>
<th>LdT</th>
<th>ADV</th>
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</thead>
<tbody>
<tr>
<td>L180M</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L181I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V173L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S202I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M204I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M204V</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N235T</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M250V</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Selection of mutations in YMDD motif may affect future treatment options
Thus lamivudine should not be first line treatment


Diagnosis of Antiviral Resistance

- **Determination of virologic breakthrough**
  - Increase in serum HBV DNA by $\geq 1.0$ log as compared with nadir
- **Rule out non-HBV-related causes of treatment failure**
  - Adherence
- **Confirm resistance with HBV mutant detection**
  - Characterization of mutations will help guide future therapy (cross-resistance)
- **Note that clinical resistance (biochemical breakthrough) lags behind viral resistance**
  - Rescue therapy should be considered in patients with viral resistance to prevent hepatitis flares
  - Rescue therapy is more effective when initiated at the time of viral resistance, prior to clinical resistance*

Adapted from Lok ASF, McMahon BJ. Hepatology 2007;45:507-539.

### Summary: Guidelines for Management of Antiviral-Resistant HBV

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Rescue Therapy</th>
</tr>
</thead>
</table>
| Lamivudine | Add adefovir or tenofovir DF  
Stop lamivudine, switch to emtricitabine/tenofovir DF |
| Adefovir   | Add lamivudine  
Stop adefovir, switch to:  
Emtricitabine/tenofovir DF  
Switch to or add entecavir (if no prior lamivudine resistance) |
| Entecavir  | Switch to tenofovir DF or emtricitabine/tenofovir DF |
| Telbivudine| Add adefovir or tenofovir DF  
Stop telbivudine, switch to emtricitabine/tenofovir DF |
| Adefovir/ Lamivudine | Consider tenofovir emtricitabine DF, or tenofovir+ entecavir |
| Lamivudine Entecavir | Consider tenofovir or tenofovir DF/emtricitabine |


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### Tenofovir + Entecavir for Multidrug resistant HBV infection

- 57 subjects received ETV 0.5 or 1 mg with TDF 300 mg

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>45 [median, range 21-79]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Female/Male)</td>
<td>6/51</td>
</tr>
<tr>
<td>ALT (ULN)</td>
<td>1.0 [median, range 0.3-22]</td>
</tr>
<tr>
<td>Liver cirrhosis or severe fibrosis</td>
<td>24</td>
</tr>
<tr>
<td>HBsAg positive</td>
<td>37/57</td>
</tr>
<tr>
<td>HBV DNA (\log_2 \text{IU/ml})</td>
<td>4.1 [median, range 1.9-12]</td>
</tr>
<tr>
<td>HBV genotypes</td>
<td>4x A, 3x B, 5x C, 26x D, 3x E, 1x D/G, 15x n.a.</td>
</tr>
<tr>
<td>Lines of antiviral pre-treatment</td>
<td>3 [median, range 1-4]</td>
</tr>
<tr>
<td>Duration of antiviral pre-treatment</td>
<td>49 months [median, range 0-173]</td>
</tr>
<tr>
<td>Last treatment before rescue therapy</td>
<td>6x ADV, 14x ETV, 1x LAM, 7x TDF, 1x LoT, 12x ADV + LAM, 10x ADV + ETV, 6x TDF + LAM</td>
</tr>
<tr>
<td>Antiviral experience</td>
<td>28% IFN (17/57), 86% LAM (44/57), 77% ADV (44/57), 42% ETV (44/57), 23% TDF (13/57), 2% LoT (1/57)</td>
</tr>
</tbody>
</table>

Peterson Journal of Hepatology 2012 vol. 56 j 520–526
Tenofovir + Entecavir for Multidrug resistant HBV infection

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

Summary

Prevention
- Avoid unnecessary treatment
- Initiate treatment with potent antiviral that has low rate of drug resistance (tenofovir 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

Treatment

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