Chronic Hepatitis B: Pathophysiology, Diagnosis and Management

Fellows Curriculum
November 29, 2012
David E. Kaplan, MD MSc

Case 1
- 66 yo AAM with history of obesity, HTN and NIDDM. Seen by PCP for c/o fatigue x 1 month.
- No history of liver disease or risk factors for viral hepatitis
- Laboratory studies:
  - TBili = 1.2
  - HAV negative
  - Alk Phos = 130
  - HBsAg reactive
  - AST = 328
  - HCV negative
  - ALT = 300
  - INR = 1.2
  - Plt = 92

Case 1 - continued
- Additional Labs
  - HBcAb IgM equivocal
  - HBeAg reactive
  - HBeAb negative
  - HBV DNA 1,700,000 IU/mL
- Abdominal Ultrasound
  - Liver mildly enlarged with diffuse increased echogenicity. Spleen is "normal".
- After initial consultation with Gastroenterology the patient was seen by cardiology for stable Canadian class 2 angina and underwent a coronary angiogram which showed obstructive 3 vessel coronary artery disease. CABG recommended.

Case 1 - continued
- At this point the most appropriate approach to management is:
  - A) Proceed to CABG, prophylactically transfusing FFP and platelets
  - B) Initiate lamivudine, medically manage CAD with ASA, β-blocker, nitrates
  - C) Initiate tenofovir, medically manage CAD with ASA, β-blocker, nitrates
  - D) Initiate entecavir, proceed with CABG

Case 2
- 32 year old male from Ghana referred to gastroenterology for hepatitis B
- No history of jaundice, encephalopathy, or ascites
- No family history of hepatocellular carcinoma
Case 2 - continued

- Laboratory studies:
  - Tbil = 0.5
  - Alk Phos = 60
  - AST = 21
  - ALT = 23
  - INR = 1.0
  - Plt = 222

- Abdominal US
  - Normal liver and spleen. No ascites.

- HBV DNA 153 million IU/mL
- HBeAg reactive

Case 2 - continued

- At this point the most appropriate approach to management is:
  - A) Initiate pegylated-interferon-α2a
  - B) Initiate lamivudine
  - C) Initiate tenofovir
  - D) Initiate entecavir
  - E) Initiate liver cancer screening with sonography every 6 months

Case 3

- 30 year old Vietnamese female in second trimester of pregnancy, referred to GI by her obstetrician for positive hepatitis B surface antigen
- No history of jaundice, ascites, encephalopathy, or GIB

- Liver Biopsy 1 year prior
  - Grade 1 Stage 1

- Laboratory Studies
  - Tbil = 0.2
  - Alk Phos = 43
  - AST = 23
  - ALT = 33
  - Plt = 220
  - INR = 1.0
  - HBV DNA 8,900,000 IU/mL
  - HBeAg positive

Case 3 - continued

- At this point the most appropriate approach to management is:
  - A) Initiate pegylated-interferon-α2a
  - B) Initiate lamivudine
  - C) Initiate tenofovir
  - D) Initiate entecavir
  - E) Do nothing, but administer HBIG prophylaxis to neonate

Case 4 – second opinion

- 32 year old Chinese female with a history of chronic HBV diagnosed after she had emigrated to the United States.
- No history of ascites/encephalopathy/GIB
- Initial laboratory
  - ALT = 95
  - AST = 99
  - HBeAg negative, HBeAb positive
  - HBV DNA 9,400 IU/mL  Genotype C
Case 4 - continued

- At this point the most appropriate approach to management is:
  - A) Initiate pegylated-interferon-α2a
  - B) Initiate lamivudine
  - C) Initiate entecavir
  - D) Initiate liver cancer screening with sonography every 6 months
  - E) C and D

Case 5

- 70 year old WM admitted for progressive lower extremity weakness and paresthesia.
- Five months before admission he underwent bilateral knee replacements, and he received 6 units of packed red blood cells.
- Three months later he developed malaise, weakness of the right foot dorsiflexors and burning paresthesia of the right foot.
- Over the prior 2 months, he noted intermittent fever, chills, and 35 pounds weight loss

Case 5 - continued

- Temperature were normal.
- Patient unable to walk without support.
- Marked weakness of dorsiflexion of the right foot and of planter flexion of the left foot.
- Unable to stand on the right heel or the left forefoot.
- Upper extremity strength normal.
- DTR absent at the ankles.
- Sensation markedly decreased to vibration and joint position sense in both lower extremities distally with the left worse than the right.
- Livedo reticularis of the feet and knees bilaterally.

Laboratory evaluation at time of leg weakness:
- HBsAg+
- HBsAb-
- HBc IgM+
- HBV DNA 8.4 x 10^6 pg/ml
- AST 489
- ALT 182
- AP 129
- Alk 3.0
- Tdo 0.7
- Cr 0.7
- Plat 252
- INR 1.6. Failed to correct with 1:1 or 4:1 mixture with normal plasma after a 2 hour incubation

Case 5 - continued

- At this point the most appropriate approach to management is:
  - A) Start tenofovir
  - B) Start prednisone 40mg po qd
  - C) Start solumedrol 1000mg IV q24h
  - D) Initiate plasmapheresis
  - E) Start cyclophosphamide

Hepatitis B

- Epidemiology
- Basic Virology
  - Impact on disease management
- Management Options
- Cancer Screening
**Global Impact of Hepatitis B**

- 2 billion with past/present HBV infection
- 350-400 million with chronic hepatitis B

- ~1 million/year die from HBV-associated liver disease

World population 6 billion


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**Geographic Distribution of Chronic HBV Infection**

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**Hepatitis B Virus - Genotypes**

- 8 Genotypes (A-H)
  - A - North America, Western Europe
  - B - Asia
  - C - Asia
  - D - Southern Europe, Middle East, India
  - E - Africa
  - F - South America
  - G - United States, France
  - H - Central America

- Variable rates of progression to cirrhosis and HCC
  - B worse than C

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**Hepatitis B Virus - Genotypes in USA**

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**Epidemiology - Declining Incidence in USA**

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**World population**

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**Hepatitis B Virus - Genotypes in USA**

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**Epidemiology - Declining Incidence in USA**

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Figure 1. The prevalence of HBV genotypes in different regions of the United States. The size of each pie is proportional to the number of patients enrolled.

Hepatitis B virus genotypes in the United States: results of a nationwide study

Chu C, Keeffe EB, Han S, Perrillo RP, Min AD, Soldevila-Pico C, Carey W, Brown RS, Luketic VA, Terrault N, Lok ASF

Gastroenterology 2003

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Reported Acute Hepatitis B Incidence

United States, 1988-2002

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Data from: Annual Epidemiologic Overview Summary (2002)
**HBV Modes of Transmission**

- Sexual
- Parenteral
- Perinatal

**Concentration of HBV in Various Body Fluids**

<table>
<thead>
<tr>
<th>High</th>
<th>Moderate</th>
<th>Low/Not Detectable</th>
</tr>
</thead>
<tbody>
<tr>
<td>blood</td>
<td>semen</td>
<td>urine</td>
</tr>
<tr>
<td>serum</td>
<td>vaginal fluid</td>
<td>feces</td>
</tr>
<tr>
<td>wound exudates</td>
<td>saliva</td>
<td>sweat</td>
</tr>
<tr>
<td>saliva</td>
<td>urine</td>
<td>tears</td>
</tr>
<tr>
<td>urine</td>
<td>feces</td>
<td>breast milk</td>
</tr>
</tbody>
</table>

**Outcome of HBV Infection**

**Outcome of HBV Infection - Adults**

- **Immunocompetent**
  - 95%
  - Asymptomatic
  - Chronic infection
  - Cirrhosis
  - Liver cancer

- **Resolved**
  - Immune

**Outcome of HBV Infection - Children**

- Infant
  - 90%
  - 50%
  - Asymptomatic
  - Chronic infection

- Child <5y
  - 50%
  - Asymptomatic
  - Chronic infection

- **Infection**

**Virology**

- **Hepadnaviridae**
  - Human hepatitis B
  - Woodchuck Hepatitis Virus (groundhogs = WC)
  - Duck hepatitis B
- **Pararetroviridae**
  - Heron hepatitis B
  - Tree Shrew hepatitis virus
- **Caulimoviridae**
  - Badnavirus (Commelina yellow mottle virus)
  - Caulimovirus (Cauliflower mosaic virus)
  - Woolly monkey hepatitis B
  - Ground squirrel hepatitis virus
Hepatitis B Virus - Virion

- Polymerase
- Capsid (HBC)
- DNA
- Surface (HBs)

Hepatitis B Virus - Replication

1. S protein binds to cellular receptor
2. Virus uncoats, DNA shuttled to nucleus
3. Partial dsDNA becomes complete, cccDNA
4. Transcription, translation, replication of genome
5. Packaging, budding with some recycling of DNA

- pgRNA
- S
- C
- P
- X

- (+) strand 2.4 kb
- (-) strand 3.3 kb

- 4 ORFS

Hepatitis B Virus - Replication

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5. Packaging, budding with some recycling of DNA

- pgRNA
- S
- C
- P
- X

- Large
- Sm

- HBsAg
- HBsAb

- cccDNA persist for years, possibly forever
- Some new virion DNA recirculates to the nucleus to maintain pool of 50-100 cccDNA
- Immunosuppression → reactivation

Hepatitis B Virus - Replication

- HBe is an alternative translation of C gene
- Secreted as free form
- F Immunological decoy
- Pre-core mutants lose ability to make HBe

- cccDNA persists for years, possibly forever
- Some new virion DNA recirculates to the nucleus to maintain pool of 50-100 cccDNA
- Immunosuppression → reactivation

- pgRNA
- S
- C
- P
- X

Hepatitis B Virus - Recirculation

- cccDNA persists for years, possibly forever
- Some new virion DNA recirculates to the nucleus to maintain pool of 50-100 cccDNA
- Immunosuppression → reactivation

- pgRNA
- S
- C
- P
- X
Hepatitis B Virus - Integration

- Some nuclear cccDNA integrates randomly into host genome
- Replicates with the host cell and propagated in daughter cells
- Can be partial or complete genome (e.g., may just have S gene or X gene)
- Can lead to destruction of tumor suppressor or expression of oncogene
- Time, faster replication → higher chance of integration

Acute Hepatitis B Virus Infection with Recovery

Typical Serologic Course

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Titers</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>anti-HBs</td>
</tr>
<tr>
<td>IgM anti-HBc</td>
<td></td>
</tr>
<tr>
<td>Total anti-HBc</td>
<td></td>
</tr>
</tbody>
</table>

Natural History of HBV: Development of HBeAg-negative CHB

Phases of HBV infection:
- Replicative or immune tolerance phase
- HBeAg Low-replicative phase
- HBV reactivation

Natural History of Hepatitis B Infection

- Inactive Carrier
- HBeAg+ Chronic Hepatitis B
- HBeAg- Chronic Hepatitis B
- HBeAg loss

Hepadnavirus (C.)


Hepatitis B Disease Progression

Liver Failure

Liver Transplantation

Chronic HBV is the 6th leading indication for liver transplantation in the United States, 5%

Chronic Infection

Active Hepatitis

Resolution

Immune Tolerance

Liver Cancer (HCC)

5%–10%

6% in 5 yr

30%

23% in 5 yr

23% in 5 yr

Liver Transplant

Death

Chronic HBV is the 6th leading indication for liver transplantation in the United States, 5%

Stages of Chronic Hepatitis B

<table>
<thead>
<tr>
<th>Phase</th>
<th>ALT</th>
<th>HBV DNA</th>
<th>HBeAg</th>
<th>HBsAg</th>
<th>HBeAb</th>
<th>HBcAb</th>
<th>HBeAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune Tolerance</td>
<td>Normal</td>
<td>High</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Active Hepatitis</td>
<td>High</td>
<td>VAR</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Resolution</td>
<td>Normal</td>
<td>Low</td>
<td>-</td>
<td>+/−</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Immune Tolerance</td>
<td>Normal</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
HBeAg-negative Chronic Hepatitis B

<table>
<thead>
<tr>
<th>Phase</th>
<th>ALT</th>
<th>HBV DNA</th>
<th>HBeAg</th>
<th>HBsAb</th>
<th>HBeAb</th>
<th>HBcAb</th>
<th>HBsAg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg-</td>
<td>High</td>
<td>Yes</td>
<td>t</td>
<td>t</td>
<td>t</td>
<td>t</td>
<td>t</td>
</tr>
<tr>
<td>HBeAg+</td>
<td>High</td>
<td>High</td>
<td>+/−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

- Pre-Core mutant, unable to make HBe
- More common in Mediterranean, but universal
- More aggressive hepatitis

Basal Core Promoter Mutation of HBV Increases the Risk of Cirrhosis Independent of Hepatitis Activity

- Emergence of PC or BCP mutations may occur
- Study evaluated PC and BCP sequences in 251 patients with viral loads higher than 200 IU/mL at 1 year post HBeAg seroconversion
- Frequency of wild-type PC and BCP mutation was 57.0% and 31.9%, respectively
- BCP mutation was the only independent risk factor for cirrhosis development
- Conclusion: BCP A1762T/G1764A mutation increases the risk of cirrhosis development in spontaneous HBeAg seroconverters with HBV genotype B or C infection

Cumulative incidence of cirrhosis by variants of basal core promoter

<table>
<thead>
<tr>
<th>Years after HBeAg seroconversion</th>
<th>Mutant BCP (n = 80)</th>
<th>Wild-type BCP (n = 169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4.5%</td>
<td>0.7%</td>
</tr>
<tr>
<td>1</td>
<td>11.0%</td>
<td>3.8%</td>
</tr>
<tr>
<td>2</td>
<td>13.0%</td>
<td>8.9%</td>
</tr>
<tr>
<td>3</td>
<td>21.0%</td>
<td>14.6%</td>
</tr>
<tr>
<td>4</td>
<td>27.0%</td>
<td>22.3%</td>
</tr>
<tr>
<td>5</td>
<td>36.2%</td>
<td>34.7%</td>
</tr>
</tbody>
</table>

PC = Precore, BCP = Basal Core Promoter

Tseng T, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011; Abst. 1101.

Actuarial Survival in ESLD:

Historical Studies

Survival with Compensated Cirrhosis

HBeAg Positive vs Negative

Reprinted from Gastroenterology. 103. 1620

Hepatitis B and Risk of Hepatocellular Carcinoma

R.E.V.E.A.L. Study Participants

Prospective cohort study initiated in 1991-1992:
All adult residents of 7 townships in Taiwan aged 30-65
N = 89,293 (47,079 males and 42,214 females)
23,820 enrolled in study (11,973 males and 11,847 females)
4,155 (14.4%) HBsAg positive (2,445 males and 1,710 females)
3,653 had HBV DNA tests and anti-HCV (-)
565 (15%) HBsAg+
3088 (85%) HBeAg-
**REVEAL: Relationship Between HBV DNA Level and All-Cause Mortality**

- Baseline HBV DNA Level
  - <300
  - 10,000-99,999
  - 100,000-999,999
  - ≥1 Million

- Survival

- Year of follow-up

- P=0.001

Viral load presented as copies/mL.

**REVEAL: Cumulative Incidence of Hepatocellular Carcinoma by HBV DNA Level at Study Entry**

- Entire Cohort (N=3653)
- HBeAg- (n=3288)

At end of 13th year of follow-up

Viral load presented as copies/mL.

**Association Between Hepatitis B Genotype and Disease Severity**

- Western patients
  - Frequency of Liver-Related Death
  - Percent of Patients
  - A: 5%, B: 19%, C: 27%

- Asian patients
  - Incidence of Advanced Fibrosis (F3/F4)
  - Percent of Patients
  - A: 1%, B: 10%, C: 209%

P = .02


**Hepatitis B Vaccine**

- Licensed in 1982; currently recombinant (in US)

- 3 dose series, typical schedule 0, 1-2, 4-6 months - no maximum time between doses (no need to repeat missed doses or restart)

- 2 dose series (adult dose) licensed by FDA for 11-15 year olds (Merck)

- Protection ~30-50% dose 1; 75% - 2; 96% - 3; lower in older, immunosuppressive illnesses (e.g., HIV, chronic liver diseases, diabetes), obese, smokers

**Hepatitis B Vaccination: ACIP Recommendations**

- Over 18 – high risk
  - Occupational risk (HCWs)
  - Hemodialysis patients
  - All STD clinic clients
  - Multiple sex partners or prior STD
  - Inmates in correctional settings
  - MSM
  - IDU
  - Institution for developmental disability

- Ages 11-15
  - “catch up”, and through age 18 (VFC eligible)

- Over 18 – high risk
  - Hemodialysis patients
  - All STD clinic clients
  - Multiple sex partners or prior STD
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- Pre-vaccination testing – if cost effective

- Post-vaccination testing – 1-2 months after last shot, if establishing response critical (HCW)

**There are Multiple Treatment Endpoints in Chronic Hepatitis B**

- Normal ALT
- Treatment Endpoints
- HBV DNA Suppression
- HBeAg Seroconversion
- HBeAg Loss
- HbsAg Clearance
Therapeutic Signposts for Chronic Hepatitis B

HBeAg-positive CHB
Start Rx. → Reduce serum HBV DNA → Normal ALT → HBeAg loss → Ant-HBe Seroconversion → PCR Negativity

HBeAg-negative CHB
Start Rx. → Reduce serum HBV DNA → Normal ALT → PCR Negativity → HBsAg loss

Definitions of Virologic Response

Start Treatment
Assess for Primary Nonresponse at Week 12 (HBV DNA <10 IU/mL from Baseline)

Early Predictors of Efficacy at Week 24
- Complete VR (<60 IU/mL)
- Partial VR (≥60 to 2,000 IU/mL)
- Inadequate VR (≥2,000 IU/mL)

Approved Hepatitis B Treatments
- Interferon alpha 2b (Intron)
- Pegylated interferon alpha 2a (Pegasys)
- Lamivudine (Epivir)
- Adefovir (Hepsera)
- Entecavir (Baraclude)
- Telbivudine (Tyzeka)
- Tenofovir (Viread)

Treatments approved for HIV with activity against HBV
- Emtricitabine (Emtriva)
- Tenofovir + Emtricitabine (Truvada)

Which is the Best Initial Treatment?

Long-term Benefits
- Antiviral potency
- Durability of response

Contraindications
- Ease of administration
- Duration of Rx
- Costs of Rx & monitoring
- Patient and provider preference

Side effects
- Drug resistance

How Nucleos(t)ide Analogues Inhibit HBV Replication
- The HBV genome replicates by means of the addition of single nucleos(t)ides
- Nucleos(t)ide analogues are structured to look like nucleos(t)ides
- Nucleos(t)ide analogue binding to the HBV polymerase causes chain termination

FDA Approved Therapies for Chronic HBV

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<th>Trade Name</th>
<th>Company</th>
<th>Year</th>
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<td>Tenofovir</td>
<td>VIREAD®</td>
<td>Gilead Sciences</td>
<td>2008</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>TYZEKA™</td>
<td>Idenix and Novartis</td>
<td>2006</td>
</tr>
<tr>
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</tr>
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Interferons
- Peginterferon alfa-2a | PEGASYS® | Roche Laboratories | 2005 |
- Interferon alfa-2b, recombinant | INTRON®A | Schering Corporation | 1992 |


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### Treatment Criteria for Chronic Hepatitis B

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<th>HBeAg-</th>
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<tr>
<td></td>
<td>HBV DNA</td>
<td>ALT</td>
</tr>
<tr>
<td></td>
<td>&gt;20,000</td>
<td>&gt;2xULN</td>
</tr>
<tr>
<td>EASL 2009</td>
<td>&gt;2,000</td>
<td>&gt;ULN</td>
</tr>
<tr>
<td>US Algorithm 2008</td>
<td>&gt;20,000</td>
<td>&gt;ULN or (+) biopsy</td>
</tr>
<tr>
<td>AASLD 2009</td>
<td>&gt;20,000</td>
<td>&gt;2xULN</td>
</tr>
</tbody>
</table>

*Degertekin B, Lok ASF. Hepatology 2009;49(S5):S129-S137.

### AASLD CHB Treatment Guidelines

#### HBV DNA

<table>
<thead>
<tr>
<th>HBV DNA (IU/mL)</th>
<th>ALT (ULN)</th>
</tr>
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<tbody>
<tr>
<td>&gt;20,000</td>
<td>&gt;2xULN or (+) biopsy</td>
</tr>
</tbody>
</table>


**US Algorithm 2008**

<table>
<thead>
<tr>
<th>HBV DNA (IU/mL)</th>
<th>ALT (ULN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20,000</td>
<td>&gt;2xULN or (+) biopsy</td>
</tr>
</tbody>
</table>

**AASLD 2009**

<table>
<thead>
<tr>
<th>HBV DNA (IU/mL)</th>
<th>ALT (ULN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20,000</td>
<td>&gt;2xULN or (+) biopsy</td>
</tr>
</tbody>
</table>


### HBeAg Positive Patients with Compensated Disease

- **HBV DNA >20,000 IU/mL**
  - No treatment
  - Monitor every 6–12 months

- **HBV DNA >20,000 IU/mL**
  - Monitor ALT every 3-12 months
  - Consider biopsy, if age >35–40, and treat if significant disease

- **HBV DNA <20,000 IU/mL**
  - Monitor every 6–12 months
  - Consider biopsy
  - Treat if persistent

### HBsAg Seroconversion: the ‘champion’ among clinical endpoints

- **HBsAg Seroconversion**
  - HBV DNA Suppression
  - **HBsAg Loss after 2-5 Years of Treatment**

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

- **HBsAg Loss**
  - Peg = peginterferon
  - LMV = lamivudine
  - ADV = adefovir
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- **HBsAg Loss after 2-5 Years of Treatment**
  - Peg = peginterferon
  - LMV = lamivudine
  - ADV = adefovir
  - ETV = entecavir
  - TBV = telbivudine
  - TDF = tenofovir

Distribution of Ishak Fibrosis Scores at Baseline, Year 1, and Year 5 – Tenofovir Phase III Trial

- 348/489 (71%) patients had baseline and year 5 biopsies
- 344 had liver biopsy available at all three time points
- % with cirrhosis (Ishak Score ≥ 5) decreased from 28% at baseline to 8% at Year 5

Marcellin, P, AASLD 2011; Poster #1275

Antiviral Therapy Prevents Disease Progression

Bridging fibrosis or cirrhosis, HBeAg+ / HBV DNA >700,000 GEq/ml

% with disease progression

<table>
<thead>
<tr>
<th>Time to disease progression (months)</th>
<th>Placebo (n=215)</th>
<th>Lamivudine (n=436)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>21%</td>
<td>9%</td>
</tr>
<tr>
<td>1</td>
<td>23%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>&lt;1%</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>&lt;1%</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Liaw YF, NEJM 2004; 351:1521

Clear Cut Cases in Which Treatment Should be Initiated

- Life-threatening disease
- Acute liver failure
- Decompensated cirrhosis
- Severe exacerbations of chronic hepatitis
- High risk of adverse outcome in the near future
- Compensated cirrhosis and high serum HBV DNA
- High risk of progressive liver disease

Should Treatment be Initiated in All Patients with Chronic HBV Infection?

- Progression to cirrhosis and HCC
- Treatment can suppress HBV replication
- Treatment has been shown to improve liver histology and to decrease progression to liver failure and HCC
- Treatment is safe
- Many medical conditions (e.g. hypertension) cannot be cured and require life long treatment

Is Early Treatment Warranted in Everyone with Chronic Hepatitis B Infection?

- Current treatments do not eradicate HBV
- Long-term treatment is associated with
  - risks of drug resistance
  - very high costs
  - potential adverse events
  - non-adherence
- Treatment is less effective in patients who are in the immune tolerant phase

Resistance Rates Through 6 Years of Treatment in Nucleos(t)ide-Naïve Patients

<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>LAM</td>
<td>27%</td>
<td>40%</td>
<td>50%</td>
<td>71%</td>
<td>80%</td>
</tr>
<tr>
<td>ADV</td>
<td>0%</td>
<td>3%</td>
<td>11%</td>
<td>18%</td>
<td>29%</td>
</tr>
<tr>
<td>TBV</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>TDF</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>ETV</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

§ Patients with HBV DNA ≥400 copies/mL at Week 72 could add FTC to TDF
* Cumulative probability of resistance. ETV 1 mg dose used from year 5 onward
Hepatitis B Resistance Mutations

- **845 a.a.**

**T**erminal protein **S**pacer **P**ol/RT **RNase H**

<table>
<thead>
<tr>
<th>I(G)</th>
<th>II(F)</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LAM Resistance</strong></td>
<td>rl(L80V)</td>
<td>rl(L131I)</td>
<td>rl(L188M)</td>
<td>rl(M204V/I)</td>
<td>rl(S202G)</td>
<td>rl(M250V)</td>
</tr>
<tr>
<td><strong>ADV Resistance</strong></td>
<td>rl(A181T)</td>
<td>rl(M230I)</td>
<td>rl(V173L)</td>
<td>rl(V173I)</td>
<td>rl(S229L)</td>
<td></td>
</tr>
<tr>
<td><strong>ETV Resistance</strong></td>
<td>rl(L180M)</td>
<td>rl(M204V/I)</td>
<td>rl(T184S/A/I/L)</td>
<td>rl(S202G/C)</td>
<td>rl(M250I/ V)</td>
<td></td>
</tr>
<tr>
<td><strong>LdT Resistance</strong></td>
<td>rl(L80V/I)</td>
<td>rl(L188M)</td>
<td>rl(M204I)</td>
<td>rl(L229W/V)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Most Common HBV Cross-Resistance Mutations

<table>
<thead>
<tr>
<th></th>
<th>LAM</th>
<th>Telbivudine</th>
<th>Entecavir</th>
<th>Adefovir</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wild-type</strong></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><strong>M204I</strong></td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><strong>L180M + M204V</strong></td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td><strong>A181T/V</strong></td>
<td>I</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td><strong>N236T</strong></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>I</td>
</tr>
<tr>
<td><strong>L180M + M230I + M250V</strong></td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><strong>T184 + S229 + R228</strong></td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

**S**usceptible

**R**esistant

**I**ntermediate

Role of Genotyping prior to Therapy

- Provides prognostic information but does not negate need to screen for complications in "good prognosis" genotypes
- Confirms presence of core and core promoter mutations
- Identifies genotypic resistance, now described in treatment naive patients

A Fundamental Principle of Resistance

- Resistant virions emerge from pool of actively replicating virus
- More residual virus, more opportunity for genotypic resistance to emerge

Adverse Effects of Hepatitis B Treatment

- Interferon
  - Suppression, unmask or exacerbate autoimmune illnesses
- Nucleos(t)ide analogs
  - Lactic acidosis
  - Adefovir and tenofovir – nephrotoxicity
  - Tenofovir – decrease bone mineral density
  - Telbivudine – myopathy, peripheral neuropathy
  - Clevudine – mitochondrial toxicity, myopathy
- Peginterferon + telbivudine
  - Increase incidence of peripheral neuropathy

Is Early Treatment Warranted in Everyone with Chronic Hepatitis B Infection?

- Not all HBV carriers will develop cirrhosis or HCC
- Liver disease is mild during immune tolerant phase
- Host immune response can result in spontaneous remission and in some patients remission can be long-lasting
Hepatocellular carcinoma: Incidence and Risk for CHB patients on Antiviral therapy

• HBV antiviral therapy and HCC relationship was studied using ICD9 codes/liver registry and chart review (240 pts, follow-up 5 years)
• 60 pts developed HCC
• Grade HCC incidence rates (person-years)
  - HBeAg-positive (persistent)
    - No therapy (HR 0.66 [0.34-1.31])
    - HBV antiviral therapy (HR 0.48 [0.23-0.99])
  - Other factors associated with increased risk of HCC included male gender and age 40 at time of CHB diagnosis.

Conclusion: Despite antiviral therapy, HCC can still occur, especially in and older, male CHB population

Hepatocellular Carcinoma: Risk Factors in CHB

• 11-year retrospective analysis of 101 HCC pts and viral suppression compared to matched cohort

Other multivariate analysis: age > 60, male gender, and LM use associated with increased HCC risk

Conclusion: Association of lamivudine exposure with HCC raises the possibility of drug-induced mutations increasing HCC risk

Progression to Cirrhosis and Mortality with CHB

• Study examining the natural history of untreated Caucasian patients in Italy
  - 105 untreated pts
    - 76% male
    - Mean age 45
    - No evidence of cirrhosis
  - 25 year follow-up
  - 47% became inactive carriers
    - 43% of these cleared HBeAg
  - 30% developed cirrhosis (incidence rate 13/1000 personyears which increased risk of liver-related death
  - Older age, male sex, absence of sustained remission and sustained HBV replication predicted cirrhosis occurrence independently.
  - In Caucasian patients with Chronic hepatitis without cirrhosis at presentation, progression to cirrhosis is relatively slow but cirrhosis occurrence strongly predicts liver-related mortality.

When to Treat?

• monitor and treat later when indicated
• All HBV carriers are potential treatment candidates
• A patient who is not a treatment candidate now can be a treatment candidate in the future
  - Changes in HBV replication status and/or activity/stage of liver disease
  - Availability of new and better treatments

When to Start Treatment?

AASLD Practice Guidelines

• Evidence of liver disease — abnormal ALT (>2x ULN) in the presence of high serum HBV DNA (>20,000 IU/ml)
  - Lower threshold if
    - Older age (>40 years)
    - Active inflammation or advanced fibrosis on biopsy
    - Clinical evidence of cirrhosis
  - Borderline ALT or HBV DNA — monitor, if persistent, consider biopsy
  - Others — monitor, treat later when indication arises or more effective treatment available

Lok & McMahon, Hepatology, 2007 and 2008
Reactivation of HBV Among Patients Receiving Chemotherapy

- Reactivation of HBV reported in 20% to 50% of HBsAg carriers undergoing cytotoxic chemotherapy
- Risk of icteric flares, hepatic decompensation and death
  - May be asymptomatic
- Prophylactic antiviral therapy recommended
  - Initiate at time of chemotherapy induction
  - Maintain for 3 months post-chemotherapy

Reactivation of Hepatitis B Infection Among Cancer Patients

Large database from MD Anderson examined to determine HBV screening rates for patients who received chemotherapy

<table>
<thead>
<tr>
<th>HBsAg Status</th>
<th>Number screened</th>
<th>% screened</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg(-)</td>
<td>34</td>
<td>23%</td>
</tr>
<tr>
<td>HBsAg(+)</td>
<td>87</td>
<td>17%</td>
</tr>
<tr>
<td>Total</td>
<td>121</td>
<td>17%</td>
</tr>
</tbody>
</table>

Screening for HBV Before Chemotherapy Is Cost Effective

- the clinical outcomes and costs over a 1-year period of 3 strategies
  1. Screen all patients for HBsAg (All)
  2. Screen all patients identified as being high risk for HBV (HR)
  3. Screen no one (None)
- Screening all patients was both least costly and most effective in increasing the 1-year survival rate
- HBV screening prior to chemotherapy should become standard practice

Results of Prophylaxis or Treatment of 34 Patients with Reactivation

- Conclusion: Persons at risk for HBV are not being adequately screened prior to chemotherapy, resulting in preventable reactivation and mortality

Risk of Hepatitis B Reactivation with Rituximab Treatment

- Retrospective study evaluated 320 patients undergoing RTX
  - and 6.5% for autoimmune disease
- Risk of HBV reactivation increased with RTX dose >3,005 mg/m² and mantle/marginal zone lymphomas
- Conclusion: Marginal and mantle cell lymphomas and higher cumulative RTX dose increase HBV reactivation risk

Screening for HBV Before Chemotherapy

- A decision analytic model was developed for patients with lymphoma to compare the clinical outcomes and costs over a 1-year period of 3 strategies
  1. Screen all patients for HBsAg (All)
  2. Screen all patients identified as being high risk for HBV (HR)
  3. Screen no one (None)
- Screening all patients was both least costly and most effective in increasing the 1-year survival rate
- HBV screening prior to chemotherapy should become standard practice

Risk of Hepatitis B Reactivation

- Cut-off for Cumulative Doses of RTX and HBV Reactivation (n=42)
  - Reactivation in Different Lymphoma Types (n=36)

Hwang JP, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011; Abst. 172.

Gutierrez M, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011; Abst. 507.


Fisher's Exact Test, p<0.05

Results of Prophylaxis or Treatment of 34 Patients with Reactivation

- Conclusion: Persons at risk for HBV are not being adequately screened prior to chemotherapy, resulting in preventable reactivation and mortality

Zurawska U, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011; Abst. 490.

Hwang JP, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011; Abst. 172.

Adherence to HBV Nucleos(t)ide Analogs: Analysis of pharmacy claims database in 3 cohorts of patients treated in the US in 2007, 2008 and 2009

New Patients (n=458)  
Existing Patients (n=10,295)

Adherence (% of days in that year in which patients have medications in their hands) <80% in ~20% patients

BE-LOW Study: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ETV (N=182)</th>
<th>ETV + TDF (N=197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years (SD)</td>
<td>40 (1.1)</td>
<td>39 (1.0)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>84 (46.2)</td>
<td>83 (42.8)</td>
</tr>
<tr>
<td>White</td>
<td>102 (51.8)</td>
<td>97 (49.2)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (2.7)</td>
<td>8 (4.1)</td>
</tr>
<tr>
<td>HBV DNA, mean log_{10} IU/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>7.5 (1.1)</td>
<td>7.5 (1.0)</td>
</tr>
<tr>
<td>HBeAg (+)</td>
<td>8.10 (0.10)</td>
<td>8.15 (0.08)</td>
</tr>
<tr>
<td>HBV genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>38 (20.9)</td>
<td>36 (18.3)</td>
</tr>
<tr>
<td>B</td>
<td>30 (16.5)</td>
<td>35 (17.6)</td>
</tr>
<tr>
<td>C</td>
<td>35 (19.2)</td>
<td>33 (16.9)</td>
</tr>
<tr>
<td>D</td>
<td>93 (50.2)</td>
<td>97 (49.2)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (5.0)</td>
<td>8 (4.1)</td>
</tr>
<tr>
<td>HBV genotypes Other</td>
<td>9 (5.0)</td>
<td>8 (4.1)</td>
</tr>
</tbody>
</table>

BE-LOW Study: HBV DNA <50 IU/mL at Week 96 in HBeAg(+)

Number of patients: 88 vs. 111

Difference: 16.8% (95% CI 2.9, 30.7)

All HBeAg(+)

Baseline HBV DNA <10^8 IU/mL

Baseline HBV DNA ≥10^8 IU/mL

Lok AS, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011; Abst. 223.

BE-LOW Study: Conclusions

- ETV 32.5% vs. ETV/TDF 21.7%
- ETV 2.7% vs. ETV/TDF 3.6%
- No difference in safety including renal function
- No resistance observed in either group
- Conclusion: These data suggest the potential role of combination therapy in HBeAg(+) patients with HBV DNA >10^8 IU/mL
- Caveat: TDF monotherapy was not studied

Lok AS, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011; Abst. 223.
Regression of Hepatic Fibrosis after 5 Years of Tenofovir Therapy

- Naive HBeAg(+) or HBeAg(-) pts treated with TDF 300 mg/day (N=641)
- 348 had paired BL and 5 year biopsies evaluated by Ishak fibrosis score
  - 98% had undetectable HBV DNA at year 5
- 74% of cirrhotic patients no longer had cirrhosis at year 5
- Conclusion: Long-term TDF treatment stabilizes or improves fibrosis in most patients

Marcellin P, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011; Abst. 1375.

ETV and TDF Have Better Adherence as First-line Antiviral Therapy for CHB

- Retrospective study of CHB pts initiating first-line oral antiviral monotherapy for CHB between 7/1/2005-1/31/2010
- 1,741 study samples were divided to recommended (ETV or TDF) vs. not recommended therapies (LAM, ADF or LdT)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Recommended Therapy</th>
<th>Not Recommended Therapy</th>
<th>Rate of Estimated Coefficient (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence (MPR 80%, vs. &lt;80%)</td>
<td>36%</td>
<td>32%</td>
<td>-0.12 (1.00-2.08)</td>
<td>0.001</td>
</tr>
<tr>
<td>Inpatient Admissions</td>
<td>298</td>
<td>381</td>
<td>0.32 (1.05-1.00)</td>
<td>0.037</td>
</tr>
<tr>
<td>Total Health Care Costs</td>
<td>$1,332 PPM*</td>
<td>$1,214 PPM*</td>
<td>0.91 (1.03-1.01)</td>
<td>0.166</td>
</tr>
</tbody>
</table>

Conclusion: Significantly better adherence and persistence with recommended NA therapies associated with fewer admissions and lower cost

Hox HB, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011; Abst. 462.

PEG-IFN vs. ETV for Treatment of HBeAg(+) CHB

- Non-randomized study in which CHB, HBeAg(+) pts treated with one year PEG-IFN±LAM (N=266) or prolonged ETV 0.5 mg (N=91)
  - Groups balanced for HBV genotype, age, sex and previous IFN
  - PEG-IFN pts had higher Baseline HBV DNA (9.1 vs. 8.0 log copies/mL, P=0.001) and ALT (4.3 vs. 3.1 x ULN, P=0.004)
  - Median follow-up 92 weeks for both groups; Follow-up terminated in patients retreated with NA after PEG-IFN
- after 78 weeks
  - Higher rates of HBeAg seroconversion and HBsAg seroclearance with PEG-IFN

Zoutendijk R, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011; Abst. 1398.

Baseline Titer and Decline Predict HBsAg Loss in CHB Patients Who Received PEG-IFN Plus TDF

- HBsAg loss is considered the ultimate therapeutic end point for CHB patients
- Single-arm study to evaluate HBsAg level changes during and after PEG-IFN plus tenofovir treatment and assess predictive value of HBsAg decline for sustained response (N=60)
  - Enrolled patients HBeAg (+) (42%) and HBeAg(-) (58%) and received PEG-IFN alpha 2a (180 µg/week) plus TDF (300 mg/day) for 48 weeks
  - 94% of pts had undetectable HBV DNA at end of therapy
  - 11% of pts had SVR with HBsAg loss

Marcellin P, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011; Abst. 1372.
Baseline Titer and Decline Predict HBsAg Loss in CHB Patients Receiving PEG-IFN plus TDV

Conclusions: High rate of HBsAg loss observed in patients receiving PEG-IFN plus TDF, which was associated with baseline HBsAg titer <3 log_{10} IU/ml and SVR. Absence of >0.5 log_{10} IU/ml HBsAg decline at week 24 has a high negative predictive value (95%) for SVR.

Marcellin P, et al. 62nd AASLD; San Francisco, CA; November 4-8, 2011; Abst. 1372.

Virologic Response by HBeAg Status (Undetectable HBV DNA)

HBeAg Seroconversion Rates*

HBsAg Loss in HBeAg(+) Patients*

HCC Rates in Cirrhotic Patients*

1436. Entecavir Monotherapy in 418 NUC-Naive Patients with Chronic Hepatitis B from Field Practice: High Efficacy and Favorable Safety Profile Over 3 Years of Treatment.
Antiviral Resistance: Nomenclature

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotypic resistance</td>
<td>Detection of HBV polymerase mutation(s) by direct sequencing of PCR products</td>
</tr>
<tr>
<td>Phenotypic resistance</td>
<td>In vitro confirmation by cell culture or enzymatic assays that mutation confers resistance</td>
</tr>
<tr>
<td>Virologic breakthrough</td>
<td>Increase in serum HBV DNA by &gt;1 log₁₀ over nadir while receiving continuous therapy</td>
</tr>
<tr>
<td>Biochemical breakthrough</td>
<td>Increase in ALT while receiving therapy after achieving initial response</td>
</tr>
</tbody>
</table>

Monitoring for Drug Resistance

All patients
- HBV DNA and ALT at baseline and at 3 months after starting therapy (assess antiviral efficacy)

Mild liver disease
- HBV DNA and ALT q 6 mo for first 2 years; thereafter q 3 mo and at any change in therapy

Advanced liver disease/cirrhosis
- HBV DNA and ALT q 3 mo with clinical evaluation

Association Between Viral Suppression and Risk of Genotypic Resistance

<table>
<thead>
<tr>
<th>Drug</th>
<th>Week 24 HBV DNA (log₁₀ copies/mL)</th>
<th>Week 48 HBV DNA (log₁₀ copies/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine[1]</td>
<td>8%</td>
<td>32%</td>
</tr>
<tr>
<td>Adefovir[2]</td>
<td>13%</td>
<td>64%</td>
</tr>
</tbody>
</table>


AASLD Guidelines for Management of Antiviral-Resistant Hepatitis B


Marcellin P, et al. 62nd AASLD: San Francisco, CA; November 4-8, 2011; Abst. 238.