CURRENT TREATMENT OF HBV

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Bon Secours Health System
Richmond and Newport News, Virginia

CHRONIC HBV INFECTION DEMOGRAPHICS IN THE USA

- Estimated 1.25 million persons in USA infected
- Vast majority are immigrants or first generation Americans:
  - Southeast Asia, China
  - Sub-Saharan Africa
  - Eastern Europe
  - Likely acquired HBV via vertical transmission
- African Americans account for 20% of persons with chronic infection
**IMMUNE STATES OF HBV ALT, SEROLOGY AND HBV DNA**

- **Acute**: Immune Tolerant
- **Active**: eAg+
- **Inactive**: eAg-
- **Resolved**: Immune Tolerant

**HBV DNA**
- sAg
- Anti-s
- eAg
- Anti-E

**ALT**


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**CHRONIC HBV WHAT IS E-NEGATIVE HBV**

- E-gene located in the pre-core region of HBV
- Not necessary for replication
- Target of the immune response to inactivate HBV

**E-gene**

**Core gene**

- Mutation of the E-gene
- No detectable E-antigen
- Does not prevent replication
- Prevents the immune response from inactivating HBV

**E**

**E**

**Core antigen**

E-ANTIGEN NEGATIVE CHRONIC HBV EVOLUTION

Chronic HBV sAg (+)

E-Antigen (+)

Seroconversion of E-Antigen (+) Strain:

E-antigen (-)  
Anti-E (+)  
Inactive HBV

JH Hoofnagle et al.  
Hepatology 2007;45:1056-1075.
E-ANTIGEN NEGATIVE CHRONIC HBV EVOLUTION

Chronic HBV sAg (+)

E-Antigen (+)

E-Antigen (+) E**Antigen (-)

Seroconversion of E-Antigen (+) Strain:

E-antigen (-) Anti-E (+) Inactive HBV

E**antigen (-) Anti-E (+) Active E**negative HBV

E antigen (-) Anti-E (-) Active E-negative HBV


HCC IN PATIENTS WITH CHRONIC HBV IMPACT OF IMMUNE STATUS

**CHRONIC HBV – REVEAL STUDY**

**HBV DNA CIRRHOSIS AND HCC**

- **RISK of CIRRHOSIS OR HCC**
  - At what level of HBV DNA is the risk of progression and HCC significantly increased?

<table>
<thead>
<tr>
<th>HBV DNA (copies or IU x1000/ml)</th>
<th>Risk of CIRRHOSIS OR HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10⁴</td>
<td>UD</td>
</tr>
<tr>
<td>10⁴-10⁵</td>
<td>&lt;2</td>
</tr>
<tr>
<td>10⁶-10⁷</td>
<td>2-20</td>
</tr>
<tr>
<td>&gt;10⁸</td>
<td>&gt;200</td>
</tr>
</tbody>
</table>

CJ Chen, et al.  
*JAMA 2006;295:65-73.*

**CHRONIC HBV IMMUNE TOLERANT HBV**

- Normal ALT
- Very high HBV DNA
- Absence of inflammation
- None–minimal fibrosis
- No treatment indicated
- Likely to be ineffective
- Monitor
- 50% active over 5 years

Patients in Immune Tolerate State (%)

CK Hui et al.  
IMMUNE TOLERANT HBV
NATURAL HISTORY

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (IU/l)</td>
<td>17 (6-24)</td>
<td>14 (4-23)</td>
</tr>
<tr>
<td>Log HBV DNA (IU/ml)</td>
<td>9.74</td>
<td>9.81</td>
</tr>
<tr>
<td>Inflammation Score</td>
<td>3 (1-6)</td>
<td>3 (1-5)</td>
</tr>
<tr>
<td>Fibrosis:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F0</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>F1</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td>F2</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

CK Hui et al.

IMMUNE TOLERANT HBV
LACK OF AN IMMUNE RESPONSE
Mitchell L. Shiffman, MD, FACG

IMMUNE SYSTEM AND HBV
BALANCING THE IMMUNE RESPONSE

CHRONIC HBV
LOSS OF IMMUNE TOLERANCE

3 log decline in HBV DNA

ACG Governors/ASGE Best Practices Course
January 24-26, 2014 Las Vegas, Nevada

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### HEPATITIS B VIRUS

#### DISEASE STATUS AND TREATMENT

<table>
<thead>
<tr>
<th></th>
<th>Immune Tolerant</th>
<th>Active</th>
<th>Gray Zone</th>
<th>Inactive</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (IU/l)</td>
<td>Normal</td>
<td>Elevated</td>
<td>High/Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>HBsAg</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>HBeAg</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Anti-HBe</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>HBV DNA (IU/ml)</td>
<td>&gt;1 Million</td>
<td>&gt;20,000</td>
<td>&lt;2,000</td>
<td>&lt;2,000</td>
</tr>
<tr>
<td>Histology</td>
<td>Normal</td>
<td>Active</td>
<td>Variable</td>
<td>Normal</td>
</tr>
<tr>
<td>Treatment</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
<td></td>
</tr>
</tbody>
</table>


### CHRONIC HBV MONITORING

**Serum ALT Liver function**

- Every 3-6 months

**HBV DNA**

**E-antigen status**

- Every 6-12 months?
- Depending upon changes in:
  - Serum ALT
  - HBV DNA

**AFP Ultrasound**

- Every 6-12 months

AS Lok, BJ McMahon
TREATMENT OF CHRONIC HBV

GOALS OF THERAPY

E-antigen (+)  E-antigen (-)

• Loss of E-antigen
• Appearance of anti-E
• Conversion to inactive status

• Normalization in serum liver aminotransferases
• Loss of detectable HBV DNA
• Improvement in liver histology
• Reduce the risk of hepatocellular carcinoma
• Loss of S-antigen

E-ANTIGEN SERCONVERSION

EFFECT OF GENOTYPE

PegIFN-2a
Lamivudine

GENOTYPE

GKK Lau et al.
CHRONIC HBV GENOTYPES DISTRIBUTION IN U.S. POPULATION

- A - Non-Asian: 27%
- B: 19%
- C: 31%
- D: 10%
- Other: 13%

GKK Lau et al.

TREATMENT OF CHRONIC HBV PEGINTERFERON

- HBV DNA < 2000IU
- E Antigen Loss
- Normal ALT

YF Liaw et al.
### Anti-Viral Therapy for HBV Study Designs

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Treatment 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>Placebo</td>
<td>Lamivudine 100 QD</td>
<td>Adefovir 10 mg/day</td>
</tr>
<tr>
<td>RCT</td>
<td>Entecovir 0.5 mg/day</td>
<td>Telbivudine 600 mg/day</td>
<td>Adefovir 10 mg/day</td>
</tr>
<tr>
<td>RCT</td>
<td>Telbivudine 600 mg/day</td>
<td>Adefovir 10 mg/day</td>
<td>Tenofovir 300 mg QD</td>
</tr>
</tbody>
</table>

### Treatment of Chronic HBV eAg(+) Virologic Response

![Graph showing virologic response to treatment](chart.png)

TREATMENT OF CHRONIC HBV eAg(+) E-ANTIGEN SEROCONVERSION

Can stop treatment 6 months after seroconversion eAg+ → eAg- and anti-E+


TREATMENT OF CHRONIC HBV eAg(-) VIROLOGIC RESPONSE

Adefovir stopped

Change in Log
HBV DNA (copies/ml)

Adefovir
ADV stopped

SJ Hadjiyannis et al

TREATMENT OF CHRONIC HBV eAg (-)
FLAIR WHEN TREATMENT STOPS

Lamivudine – 70% after 5 years
Adefovir – 30% after 5 years
Telbivudine – 25% after 3 years
Entecovir – 1% after 5 years
Tenofovir – 0% after 5 years

Treat utilizing agents with the lowest rate of resistance unless cost is the primary issue

Use whatever available
Monitor response
Change therapy if resistance develops
**CHRONIC HBV MONITORING TREATMENT**

- **Serum ALT**
  - Liver function
  - Every 3-6 months

- **E-antigen status**
  - Every 6 months in E-Antigen (+)
  - Patients once HBV DNA undetectable

- **Anti-E status**
  - Every 3 months after E-Antigen lost
  - Stop treatment 6-12 months after appearance of Anti-E

- **AFP**
  - Ultrasound
  - Every 6-12 months

**TREATMENT OF CHRONIC HBV WHEN TO SWITCH TREATMENT**

- **Suboptimal Response**
  - Switch to better agent

- **Loss of Response**
  - Exclude Non-compliance

AS Lok, BJ McMahon
**TREATMENT OF CHRONIC HBV HEPATIC DECOMPENSATION**

- **Wild Type**
- **YMDD mutation**
- **Placebo**

YF Liaw et al.

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**TREATMENT OF HBV WITH TENOFOVIR**

**RESOLUTION OF FIBROSIS**

<table>
<thead>
<tr>
<th></th>
<th>E-Ag (+)</th>
<th>E-Ag (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>266</td>
<td>375</td>
</tr>
<tr>
<td>Normalized ALT</td>
<td>73%</td>
<td>85%</td>
</tr>
<tr>
<td>HBV DNA &lt;80 IU/ml ITT On treatment</td>
<td>65% 97%</td>
<td>83% 99%</td>
</tr>
<tr>
<td>HBeAg loss</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>HBsAg seroconversion</td>
<td>8%</td>
<td></td>
</tr>
</tbody>
</table>

P Macellin et al.
**PREVENTING VERTICAL TRANSMISSION PROPHYLAXIS WITH HIGH DNA**

<table>
<thead>
<tr>
<th></th>
<th>Telbivudine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Mother Log HBV DNA (IU/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At Randomization (Start of 3rd trimester)</td>
<td>7.38</td>
<td>7.38</td>
</tr>
<tr>
<td>At birth</td>
<td>1.98</td>
<td>6.90</td>
</tr>
<tr>
<td>Infant at Birth:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sAg (+)</td>
<td>2 (4%)</td>
<td>8 (23%)</td>
</tr>
<tr>
<td>HBV DNA (+)</td>
<td>0 (0%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Infant at day 28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sAg (+)</td>
<td>0 (0%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>HBV DNA (+)</td>
<td>0 (0%)</td>
<td>3 (9%)</td>
</tr>
</tbody>
</table>

CQ Pan et al

**HBV REACTIVATION CANCER CHEMOTHERAPY**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>626 patients</td>
</tr>
<tr>
<td>Elevation in ALT</td>
<td>44%</td>
</tr>
<tr>
<td>Hepatotoxicity from chemotherapy drugs</td>
<td>32%</td>
</tr>
<tr>
<td>Malignant infiltration of liver</td>
<td>6%</td>
</tr>
<tr>
<td>Risk of reactivation:</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
</tr>
<tr>
<td>E-Antigen positive</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
</tr>
</tbody>
</table>

W Yeo et al
HBV REACTIVATION CANCER CHEMOTHERAPY

W Yeo et al

CHRONIC HBV PROPHYLAXIS FOR REACTIVATION

Serologic status:
sAg (+)
E-antigen (-)

Tenofovir
**CHRONIC HBV SUMMARY**

- All patients with surface antigen have chronic HBV
- All patients with chronic HBV are at risk for HCC
- There is no such thing as a “healthy” carrier
- The risk of HCC is related to HBV DNA
- Although the immune tolerant state of HBV is associated with very high HBV DNA the vast majority of these patients should be observed
- Peginterferon is best utilized in patients without cirrhosis and HBV genotype A
- Treatment reduces disease progression, HCC and leads to fibrosis regression

**CHRONIC HBV ANTI-VIRAL THERAPY**

- Treat:
  - Active HBV: HBV DNA >2,000 - 20,000 IU/ml
  - Prior to starting cancer chemotherapy
  - Pregnancy with HBV DNA > 200,000 IU/ml
  - Use anti-viral agents with low resistance
    - Tenofovir or Entecovir
  - If use inferior therapy convert when resistance starts to emerge
- No treatment – Just monitor:
  - Immune tolerant HBV
  - Inactive HBV: HBV DNA < 2,000 – 20,000 IU/ml