Update on Chronic Hepatitis B Management

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HBV: A Global Problem

- 2 billion people worldwide infected with HBV[^1]
- ~ 350 million chronic carriers[^2]
- Leading cause of cirrhosis and HCC worldwide[^2]
- Causes 80% of all HCC in Asian Americans[^3]
- In the absence of cirrhosis, 30% to 50% of HCC associated with HBV[^4]
- Second only to tobacco as cause of cancer deaths[^5]
- HBV 50-100 times more infectious than HIV[^1]

[^1]: World Health Organization. HBV fact sheet.
[^3]: Stanford Asian Liver Center. For hepatitis B and liver cancer patients.
Chronic Hepatitis Cirrhosis Hepatocellular Carcinoma

Inactive Carriers

Cirrhosis

Liver Related Death

Liver Related Death

70-85%

5-Year Rates of Chronic Hepatitis B Progression

-8% to 17% for HBeAg +
-13% to 38% for HBeAg -

-17% in East Asian
-10% in Europe and US

-14% to 15%

-1% in East Asian
-0.1% in European/US

-3% in East Asian
-1% in Europe and US

-15%

-15%
Natural History of Untreated CHB

Kaiser Permanente Cohort Study from 3/1/96-12/31/05
N = 3,445 Males, 3,244 Females

- HCC deaths represented 70% of cancer death in males and 37% in females
- HBV related deaths were 2X as common from HCC as from decompensated cirrhosis
- Mortality increased markedly in men >40 and women >50
- Lifetime risk of dying from HBV related causes was 42.2%, with 27.6% risk for women and 48.7% risk for men

REVEAL: Relationship Between Baseline HBV DNA and Cirrhosis

- Baseline HBV DNA predicted progression to cirrhosis
  - Relationship independent of HBeAg status


*With 42,115 patient-yrs of follow-up and adjusted for sex, age, anti-HCV levels, smoking, and alcohol use.

1 IU/mL equals approximately 5.6 genomes/mL.

Cumulative Incidence of HCC by Serum HBV DNA Level at Study Entry

N = 3653 Taiwanese patients

Baseline HBV DNA Level, copies/mL
- ≥ 1 million: 13.5%
- 100,000-999,999: 7.96%
- 10,000-99,999: 3.15%
- 300-9999: 0.89%
- < 300: 0.74%

Parameters Used to Determine Candidates for Treatment of HBV

- **ALT**
  - “New” normal or “healthy” ALT: < 30 U/L for men and < 19 U/L for women\(^1\)
  - Presence of 1 normal value does not exclude significant disease or subsequent complications

- **HBV DNA**
  - Predicts development of cirrhosis and HCC\(^2,3\)
  - Interpret in conjunction with ALT and/or histology

- **Liver biopsy**
  - Useful in situations where ALT or HBV DNA do not provide clear guidelines for treatment\(^1\)

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Goals of Response to Therapy in Chronic Hepatitis B

• Biochemical Response: Normalization of ALT
• Virologic Response: Undetectable HBV DNA and loss of HB E Ag in HBeAg (+) with sero-conversion to anti HB E Ab
• Histologic Response: Decrease in histology activity index by at least 2 points and no worsening of fibrosis
• Oncologic Response: Prevent HCC
• Complete response: BR + VR + (HCC) + HBsAg loss

Emmet B. Keeffe et al. Clinical Gastroenterology and Hepatology 2008;6:1315-1341
Phases of Chronic HBV Infection

- **Immune tolerance**
  - HBV DNA \( \uparrow \uparrow \uparrow \uparrow \geq 10^7 \) IU/ml
  - Persistently normal ALT

- **Immune clearance**
  - HBV DNA \( \uparrow \uparrow \geq 20,000 \) IU/ml
  - Elevated ALT

- **Inactive carrier state**
  - HBV DNA = low, < 2000 IU/ml
  - Persistently normal ALT

- **Reactivation**
  - HBV DNA = Fluctuating, > 2000 IU/ml
  - Fluctuating ALT Elevations

Significance of Precore/BCP Mutation

- Most patients with HBeAg (-) chronic hepatitis B harbor precore or basal core promoter (BCP) mutations\(^1\).
- Precore and BCP along with genotype C are associated with risk of HCC\(^2\).
- BCP mutations are associated with increased risk for disease progression in genotype B and C patients\(^3\).
- Precore mutations are associated with ALT elevations, increased HBV DNA levels and persistent necroinflammatory activity in CHB\(^3\).

1- Lok As, McMahon BJ. AASLD Practice Guidelines. Hepatology 2009
AASLD Recommendations

Treatment Initiation

**HBeAg(+)**

- **HBV DNA >20,000 IU/mL**
  - ALT <1 x ULN
  - Q 3-6 mo ALT
  - Q 6-12 mo HBeAg

- **HBV DNA >20,000 IU/mL**
  - ALT 1-2 x ULN
  - Q 3 mo ALT
  - Q 6 mo HBeAg
  - Consider biopsy if persistent or age >40
  - Treat as needed

- **HBV DNA >20,000 IU/mL**
  - ALT >2 x ULN
  - Q 1-3 mo ALT, HBeAg
  - Treat if persistent
  - Liver biopsy optional

**HBeAg(-)**

- **HBV DNA < 2,000 IU/mL**
  - ALT <1 x ULN
  - Q 3 mo ALT x 3
  - Q 6-12 mo if ALT still <1 x ULN

- **HBV DNA 2,000-20,000 IU/mL**
  - ALT 1-2 x ULN
  - Q 3 mo ALT & HBV DNA
  - Consider biopsy if persistent
  - Treat as needed

- **HBV DNA >20,000 IU/mL**
  - ALT >2 x ULN
  - Treat if persistent
  - Liver biopsy optional

# Expert Consensus: Asian American Treatment Algorithm
Assessing Patients for Monitoring and Treatment

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>HBeAg</th>
<th>HBV DNA</th>
<th>ALT</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune Tolerant</td>
<td>+</td>
<td>&gt;2000 IU/ml</td>
<td>≤ ULN</td>
<td>Monitor</td>
</tr>
<tr>
<td>Chronic Hepatitis (based on biopsy or ALT)</td>
<td>+</td>
<td>&gt;2000 IU/ml</td>
<td>&gt; ULN</td>
<td>Treat</td>
</tr>
<tr>
<td>Chronic Hepatitis (based on biopsy or ALT)</td>
<td>-</td>
<td>&gt;2000 IU/ml</td>
<td>&gt; ULN</td>
<td>Treat</td>
</tr>
<tr>
<td>CHB</td>
<td>-</td>
<td>&gt;2000 IU/ml</td>
<td>≤ ULN</td>
<td>Risk Score Assessment</td>
</tr>
<tr>
<td>CHB</td>
<td>±</td>
<td>≤ 2000 IU/ml</td>
<td>&gt; ULN</td>
<td>Risk Score Assessment</td>
</tr>
<tr>
<td>Inactive Carrier</td>
<td>-</td>
<td>≤ 2000 IU/ml</td>
<td>≤ ULN</td>
<td>Monitor</td>
</tr>
</tbody>
</table>

Expert Consensus: Asian American Treatment Algorithm
Assessing Patients for Monitoring and Treatment

**Risk Factors** | **Impact score**
--- | ---
Age ≥ 40 | 1
Male Gender | 1
Male ALT > 30 U/L
Female ALT > 19 U/L | 1
Basal Core Promoter Mutation (BCP) | 2
HCC in First Degree Relative | 3
Albumin ≤ 3.5 g/dl or Platelet ≤ 130,000 mm³ | 3

Total Score

- <3: Monitor w/o treatment
- ≥3: HBV DNA ≤2000 IU/ml
- HBV DNA >2000 IU/ml: Recommend Treatment

## Differentiating HBeAg-Negative CHB From Inactive Carrier State

<table>
<thead>
<tr>
<th>Status</th>
<th>HBeAg-Negative Disease</th>
<th>Inactive Carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg positive</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Anti-HBe positive</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Anti-HBc positive</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>Moderate, often fluctuating levels; serum HBV DNA &gt; 2000 IU/mL</td>
<td>Low or undetectable; serum HBV DNA negative or &lt; 2000 IU/mL</td>
</tr>
<tr>
<td>ALT</td>
<td>Elevated, often fluctuating levels</td>
<td>Normal</td>
</tr>
<tr>
<td>Precore/BCP</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>HBsAg level in genotype B/C</td>
<td>&lt;100 IU/ml and HBV DNA &lt; 2000 IU/ml</td>
<td>&lt;100 IU/ml and HBV DNA &lt; 2000 IU/ml</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>+ + +</td>
<td></td>
</tr>
<tr>
<td>Serologic tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibroscan</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Serial laboratory monitoring is recommended!
### Risk Factors for HCC in CHB

#### Host factors
- Male gender
- Older age > 40
- FH of HCC in first degree relative
- Co-infection HDV, HCV
- Aflatoxin, ETOH, Tobacco
- NAFLD, Hypothyroidism
- A-1-AT def, Hemochromatosis, Porphyria (AIP, PCT)

#### Viral Factors
- Genotype C
- BCP/Precore mutation

#### Viral/Host interactions
- Cirrhosis
- High HBV DNA
- High level of HBsAg
- Persistently (+) HBs or eAg

Dragani TA. J Hepatol 2010;52:252-257
Guerrieri F et al. Semi Liver Dis 2013;33:147-156
Risk of HCC and HBeAg Positive Patients

Relative Risk for HCC

Prospective Study:
N = 11,893 men in Taiwan
Age = 30-65
HCC = 111, follow up = 92,359 person-years

Incidence rate for HCC/100,000 person-yr
HBsAg(-) + HBeAg(-) = 39.1
HBsAg(+) + HBeAg(-) = 324.3
HBsAg(+) + HBeAg(+) = 1169.4

Antiviral Therapies in CHB

**Agents**
- IFN-alpha
- Lamivudine
- Adefovir
- Pegylated IFN
- Entecavir
- Tenofovir

**Preferred First Line Agents**

**Endpoints Therapy**
- Tenofovir
- Entecavir

**Finite Injection Therapy**
- Pegylated IFN
- Exceptions: pregnancy, chemotherapy prophylaxis, decompensated cirrhosis, acute infection

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1- Emmet B. Keeffe et al. Clinical Gastroenterology and Hepatology 2008;6:1315-1341
Definitions Related to Antiviral Resistance to Nucleos(t)ide Analogues

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic breakthrough</td>
<td>↑ HBV DNA by 1 log_{10} (10-fold) above nadir after achieving virologic response, during continued tx</td>
</tr>
<tr>
<td>Viral rebound</td>
<td>↑ HBV DNA to &gt; 20,000 IU/mL or above pre-tx level after achieving virologic response, during continued tx</td>
</tr>
<tr>
<td>Biochemical breakthrough</td>
<td>↑ ALT to above ULN after achieving normalization, during continued tx</td>
</tr>
<tr>
<td>Genotypic resistance</td>
<td>Detection of mutations shown by in vitro studies to confer resistance to the NA administered</td>
</tr>
<tr>
<td>Phenotypic resistance</td>
<td>In vitro confirmation that mutation detected decreases susceptibility (as demonstrated by increase in inhibitory concentrations) to the NA administered</td>
</tr>
</tbody>
</table>

**Manifestations of Antiviral Resistance**

**Antiviral Treatment**

- **Virologic rebound**
- **Virologic breakthrough**
- **Genotypic resistance**
- **Hepatitis flare**
- **Biochemical breakthrough ULN**

5-Yr Rates of Resistance With Oral Agents in Nucleos(t)ide-Naive Patients

*Telbivudine rate determined at Yr 2.

### Response Rate to First Line Therapies

**HBeAg (+) CHB**

<table>
<thead>
<tr>
<th>Response Parameters</th>
<th>Entecavir</th>
<th>Tenofovir</th>
<th>PEG IFN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response at weeks 48-52</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log reduction in HBV DNA, c/ml</td>
<td>6.9</td>
<td>6.2</td>
<td>2-4.5</td>
</tr>
<tr>
<td>Undetectable HBV DNA %</td>
<td>67</td>
<td>76</td>
<td>25</td>
</tr>
<tr>
<td>ALT normalization %</td>
<td>68</td>
<td>77</td>
<td>34-39</td>
</tr>
<tr>
<td>Loss of HBE Ag %</td>
<td>22</td>
<td>21</td>
<td>~30</td>
</tr>
<tr>
<td>HBeAg seroconversion %</td>
<td>21</td>
<td>21</td>
<td>27</td>
</tr>
<tr>
<td>Loss of HBS Ag %</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Histologic improvement %</td>
<td>72</td>
<td>74</td>
<td>38</td>
</tr>
<tr>
<td>Genotypic Resistance %</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Responses during extended treatment % (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetectable HBV DNA %</td>
<td>94 (5)</td>
<td>65 (5)</td>
<td>19 (3.5)</td>
</tr>
<tr>
<td>HBeAg seroconversion %</td>
<td>41 (5)</td>
<td>40 (5)</td>
<td>37 (3.5)</td>
</tr>
<tr>
<td>Loss of HBS Ag %</td>
<td>5 (5)n</td>
<td>10 (5)</td>
<td>11 (3.5)</td>
</tr>
<tr>
<td>Genotypic resistance %</td>
<td>1.2 (6)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

## Response Rates to Approved Therapies
### HBeAg (-) CHB

<table>
<thead>
<tr>
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<th>Entecavir</th>
<th>Tenofovir</th>
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<tr>
<td><strong>Responses week 48-52</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histologic improvement %</td>
<td>70</td>
<td>72</td>
<td>48</td>
</tr>
<tr>
<td>Undetectable HBV DNA %</td>
<td>90</td>
<td>93</td>
<td>63</td>
</tr>
<tr>
<td>HBS Ag loss %</td>
<td>&lt;1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Genotypic resistance</td>
<td>0.2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Responses: Extended Treatment % (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetectable HBV DNA %</td>
<td>NA</td>
<td>83 (5)</td>
<td>18 (3)</td>
</tr>
<tr>
<td>HBS Ag loss %</td>
<td>NA</td>
<td>0.3 (5)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Genotypic resistance %</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Scaglione S, Lok A. Gastroenterology 2012;142:1360-1368
Marcellin, P, et al. AASLD 2011; Poster #1375.
Improvement in Necroinflammation
Tenofovir Therapy

Percentage of patient with Knodell = 0-3 increased over time

Improvement in Fibrosis Score
Tenofovir Therapy

Incidence of HCC in CHB on Nucleo(t)ide Therapy

Systematic review 21 studies of CHB (RCT or observational cohort), 3881 treated patients, 534 untreated, during 46 (32-108) month period
Antiviral therapy = LAM in 14 studies, FTC in one and ADV in one
5 studies with LAM-R treated with ADV or LAM+ADV

Incidence of HCC in CHB on Nucleo(t)ide Therapy

Rate of HCC was higher in LAM-R than Nuc naïve
Even among cirrhotics, HCC rate was higher in LAM-R than Nuc naïve
Achievement of virological response did not seem to significantly reduce the risk of HCC in LAM-R

ETV-Therapy and HCC Risks in CHB

Comparison of hepatocellular carcinoma cumulative incidence rates between the ETV-treated group and the non-treated control group after propensity score matching.

Greatest risk reduction is seen in cirrhotic patients.

Retrospective cohort study
N = 472 NA-naïve pts treated with ETV 0.5mg from 2004-2010
N = 1143 non NA treated pts from 1973-1999
Primary outcome: HCC diagnosis 1 year after start of observation.

Log-rank test: P < 0.001

When to Consider PegIFN

- Favorable predictors of response\textsuperscript{[1,2]}
  - HBeAg (+)
    - Low HBV DNA* $< 2 \times 10^8$ IU/ml\textsuperscript{(6)}
    - High ALT* $\geq 2 \times$ ULN \textsuperscript{(6)}
    - Genotype A $>$ B $>$ C or D\textsuperscript{[3-5]}
    - No advanced disease
  - HBeAg (-)
    - No reliable predictor

- Specific patient demographics\textsuperscript{[1,2]}
  - Generally young people
    - Young women wanting pregnancy in near future
  - Absence of comorbidities
- Patient preference\textsuperscript{[1,2]}
- Concomitant HCV/HDV infection

*Also predictive of response to nucleos(t)ide analogues.

PEG IFN-α2a in HBeAg(-) CHB

Results at 1 & 3 Year Follow Up

PEG IFN n = 116/177  LAM n = 85/181
Patients were treated for 48 wks then follow up
44% of PEG IFN treated group with undetectable HBV DNA cleared HG S Ag

IFN Therapy in HBeAg (+) Reduces Progression to Cirrhosis and HCC

N = 233 IFN α VS 233 matched untreated control
Significant reduction in HCC was seen in those with preexisting cirrhosis
HB E Ag seroconverters in untreated and IFN treated group had lower incidence of cirrhosis and HCC
Heterogenous IFN regimens for 11-28 weeks
Cumulative incidence at 15 years follow up. Median = 6.8 years (1.1-16.5)

Lin SM et al. J Hepatol 2007;46:45-52
<table>
<thead>
<tr>
<th>AASLD Guidelines</th>
<th>US Algorithm</th>
<th>Recommendations for Asian American Patients</th>
</tr>
</thead>
</table>
| **Seroconversion** from HBeAg(+) to HBeAb(+) | **Seroconversion** from HBeAg(+) to Anti-HBe(+)  
  - Treat until HBV DNA is undetectable, then continue treatment for additional 12 months | **Seroconversion** from HBeAg(+) to HBeAb(+)  
  - Continue treatment for additional 12-24 months |
| Duration of therapy: minimum 1 year; continue until at least 6 months after HBeAg seroconversion | **Seroconversion** from HBeAg(+) to Anti-HBe(+)  
  - If HBV DNA is steady and detectable, patients should continue treatment for 6 months, redocument seroconversion, and consider stopping treatment in patients without cirrhosis | **Seroconversion** from HBeAg(+) to HBeAb(+)  
  - After treatment cessation, patients should be monitored closely for relapse |
| **Patients who fail to lose HBeAg** should be treated long-term |

## Treatment Endpoints in HBeAg(-) Patients for Oral Nucleos(t)ide Agents

<table>
<thead>
<tr>
<th>AASLD Guidelines</th>
<th>US Algorithm</th>
<th>Recommendations for Asian American Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Undefined endpoint</td>
<td>• Long-term therapy using entecavir or tenofovir</td>
<td>• Treatment should be considered indefinitely</td>
</tr>
<tr>
<td>• Duration of therapy: &gt;1 year</td>
<td></td>
<td>• If HBsAg is undetectable, treatment may be discontinued</td>
</tr>
<tr>
<td>• Treatment should be continued until the patient has achieved HBsAg clearance</td>
<td></td>
<td>• After treatment discontinuation, close follow-up is mandatory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Retreat patients promptly if HBV DNA or ALT levels increase</td>
</tr>
</tbody>
</table>

# AASLD Guideline Recommendations for Treatment of Patients With HBV Cirrhosis

<table>
<thead>
<tr>
<th>HBeAg</th>
<th>HBV DNA (PCR), IU/mL</th>
<th>ALT</th>
<th>Treatment Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/-</td>
<td>Detectable</td>
<td>Cirrhosis</td>
<td><strong>Compensated</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- HBV DNA &gt; 2000 IU/mL: treat</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- HBV DNA &lt; 2000 IU/mL: consider</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>treatment if ALT elevated</td>
</tr>
<tr>
<td></td>
<td>Undetectable</td>
<td>Cirrhosis</td>
<td><strong>Decompensated</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Coordinate treatment with transplant center; refer for</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>liver transplant</td>
</tr>
</tbody>
</table>

Management of Patients With Compensated Cirrhosis

Preferred therapies

• ETV or TDF
  – NAs should be used; IFN can be associated with hepatitis flare

Treatment duration

• Long-term treatment
  – Can discontinue in HBeAg-positive patients with confirmed HBeAg seroconversion and ≥ 6 mos consolidation therapy
  – Can discontinue in HBeAg-negative patients with confirmed HBsAg clearance

• Treatment discontinuation requires close monitoring for flare or relapse

Management of Patients With Decompensated Cirrhosis

Preferred therapies

- TDF or ETV monotherapy
- (LAM or LdT) + (ADV or TDF)
- Treatment should be coordinated with transplantation center
  - IFNs should not be used in decompensated cirrhosis

Treatment duration

- Lifelong treatment recommended

Summary

• Treatment indicated in patients with evidence of inflammation and fibrosis
• Effective treatments available, safe and well tolerated
• First line agents: TDF, ETV and Peg-IFN
• Avoid LAM
• Inadequate data supporting treatment of immune tolerant patients