TREATMENT OF HEPATITIS B 2017: ONGOING PROGRESS

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HOW OLD IS HBV?

- HBV associated with humans for >1,000 years but no definitive evidence
- Recent evidence establishes ≥500 years
- Naturally mummified body of a Korean child found virtually intact
- Laparoscopy: Large organ in RUQ and biopsies sent for pathology and HBV DNA testing
  - HBV DNA genotype C isolated from the liver
  - Pathology: Appeared to be normal liver

MORE THAN 2 BILLION PEOPLE SHOW EVIDENCE OF HEPATITIS B (HBV) INFECTION


HBV GENOME AND REPLICATION

- The HBV genome has 4 overlapping reading frames leading to 4 mRNA species
- 4 RNA species translate into the following proteins:
  - Envelope S, M, and L
  - Nucleocapsid core protein
  - Secretory Hep B e protein
  - Viral reverse transcriptase/polymerase
  - X protein

These antigens and corresponding antibodies are useful markers of past, current, or chronic infection

VIRAL CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>HBV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus</td>
<td>DNA Hepatitisvirus</td>
<td>RNA Flavivirus</td>
</tr>
<tr>
<td>Eradication possible with therapy?</td>
<td>No—Lateness of response</td>
<td>No—cccDNA</td>
</tr>
<tr>
<td>Viral targets</td>
<td>Mainly CD4+ cells</td>
<td>Hepatocytes</td>
</tr>
<tr>
<td>Variants</td>
<td>6 genotypes A-H</td>
<td>6 genotypes 1-6</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>Damage to host immune system</td>
<td>Host immune response</td>
</tr>
</tbody>
</table>

Hepatitis B is 50 to 100 times more infectious than HIV
Unlike HIV, it can live outside the body in dried blood for longer than a week

DISCLOSURES

- Advisory Boards: Merck, Abbvie, Intercept, Gilead
- Speakers Bureau: Gilead, Abbvie, Intercept
- Research Grants: Gilead, Genfit, FruitStreet Health, Nicholson Foundation

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OUTCOME OF HEPATITIS B VIRUS INFECTION BY AGE OF TRANSMISSION

- Predominantly neonatal infection in Asia
- Predominantly adult infection in Western countries
- Chronic infection
- Symptomatic infection

GEOGRAPHIC PREVALENCE OF CHRONIC HEPATITIS B MAY BE IMPACTED BY MIGRATION From 1996–2002

- ~350,000 Africans
- ~400,000 South Americans
- ~2 million Asians

WORLDWIDE DISTRIBUTION OF HCC CASES

- Annual Incidence (cases per 100,000):
  - 10-15
  - 3-10
  - <3
  - Undefined

- Globally, 75% to 80% of cases of primary liver cancer are attributable to persistent viral infections with either HBV (50%–55%) or HCV (25%–30%)²

USPSTF SCREENING RECOMMENDATIONS FOR HBV INFECTION IN PREGNANT WOMEN AND HIGH-RISK INDIVIDUALS

- Grade A Recommendation
  - HBV screening in pregnant women at first prenatal visit¹

- Grade B Recommendation
  - HBV screening in individuals at high risk for HBV infection

Under PPACA, preventive services rated Grade A or B by the USPSTF must be covered with no patient cost sharing by:
- Most private insurers and all Medicaid programs
- Medicare programs that cover these services

USPSTF SCREENING RECOMMENDATIONS FOR HBV INFECTION IN HIGH-RISK INDIVIDUALS

- HBsAg prevalence
- ≥8%
- ≥2%
- <2%

- People born in regions with prevalence of HBV infection of ≥8%
- US-born people not vaccinated as infants whose parents were born in regions with prevalence of HBV infection of ≥2%

Note: Figures adapted from Table 1 in LeFevre ML ¹ and Figure 3 in CDC ²
HEPATITIS B BY THE NUMBERS

- Prevalence in non-Asian US population, 0.1%1
- Prevalence in Asian Americans, approximately 10%1
- 1 out of 8 Vietnamese Americans, 1 out of 10 Chinese Americans, and 1 out of 12 Korean Americans are chronically infected with HBV2


COMPARISON OF INITIATION THRESHOLDS AMONG EXISTING CHB TREATMENT GUIDELINES/ALGORITHMS

<table>
<thead>
<tr>
<th>Guidelines/Algorithm</th>
<th>HBV DNA (IU/mL)</th>
<th>ALT (U/L)</th>
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<th>ALT (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AASLD 20091</td>
<td>&gt;20,000</td>
<td>&gt;2x ULN or (+) biopsy</td>
<td>&gt;20,000 if &gt;2000 or (+) biopsy</td>
<td></td>
</tr>
<tr>
<td>US Treatment</td>
<td>2000</td>
<td>&gt;ULN or (+) biopsy</td>
<td>&gt;2000</td>
<td>&gt;ULN or (+) biopsy</td>
</tr>
<tr>
<td>Algorithm 20082</td>
<td>2000</td>
<td>&gt;ULN or (+) biopsy</td>
<td>&gt;2000</td>
<td>&gt;ULN or (+) biopsy</td>
</tr>
<tr>
<td>EASL 20093</td>
<td>2000</td>
<td>&gt;ULN or (+) biopsy</td>
<td>&gt;2000</td>
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<tr>
<td>APASL 20084</td>
<td>2000</td>
<td>&gt;ULN or (+) biopsy</td>
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1. AASLD, American Association for the Study of Liver Diseases; APASL, Asian Pacific Association for the Study of the Liver; EASL, European Association for the Study of the Liver; ULN, upper limit of normal.


1991-1992

June 2004: 43,993 PYs follow-up

Cohort study: 4808 chronic HBV carriers
- Cumulative risk of HCC greater for HBsAg+ carriers with a family history of HCC (P = .0001)

Adjusted Rate Ratio of HCC (RR)ab

<table>
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<tr>
<th>HBV DNA Level</th>
<th>Adjusted Rate Ratio of HCC of Cirrhosisb</th>
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<tbody>
<tr>
<td>&lt;60 IU/mL</td>
<td>1.0</td>
</tr>
<tr>
<td>60-&lt;2,000 IU/mL</td>
<td>1.4</td>
</tr>
<tr>
<td>2,000-&lt;20,000 IU/mL</td>
<td>2.5ab</td>
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<tr>
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<td>9.8ab</td>
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5% CI: 1.47-3.95 95% CI: 1.21-3.62 95% CI: 2.02-15.26

aAdjusted for age at recruitment (continuous variable), the total number of siblings in the family, educational levels (senior high school and above, junior high school, or primary school and below), cigarette smoking, and alcohol drinking.
bCompared with male HBV carriers without a first-degree family history of HCC.

VIRAL LOAD PREDICTS DISEASE PROGRESSION: THE REVEAL STUDY

Prospective, multicenter, observational cohort study

Risk Evaluation of Viremia Elevation & Associated Liver Disease

Previously Untreated Taiwanese Patients with CHB (N=3582)

Adjusted Relative Risk (RR) of Cirrhosisab

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aAdjusted for age, sex, cigarette smoking and alcohol consumption; risk of cirrhosis is independent of HBeAg status and ALT levels.

REVEAL STUDY: HIGHER HBV DNA LEVELS ARE ASSOCIATED WITH INCREASED INCIDENCE OF CIRRHOSIS

Previously Untreated Taiwanese Patients with CHB (N=3582)
HEPATIC STEATOSIS ASSOCIATED WITH SEVERE FIBROSIS IN CHB

- Comparison of steatosis and insulin resistance (IR) in CHB and chronic hepatitis C (CHC) and effect on fibrosis (N=340)
  - Steatosis prevalence similar
  - IR rate higher in CHC
    - For CHB, severe fibrosis (F3-F4) independently associated with:
      - Older age (OR 1.054, p=0.02)
      - Low platelet levels (OR 0.984, p=0.003)
      - High YGT (OR 1.010, p=0.04)
      - Steatosis >10% (OR 3.601, p=0.01)
      - Moderate-severe necroinflammatory activity (OR 8.111, p=0.005)
    - Conclusion: CHB has high rate of steatosis, which is associated with fibrosis

Comparison of patients with CHB and CHC

GOALS OF TREATMENT FOR CHRONIC HBV

- Prevent adverse clinical outcomes
- Durable suppress HBV

Markers of Treatment Response

- Decrease of serum HBV DNA to low or undetectable levels
- Improvements in liver histology
- Clinical trial endpoint
- Decrease or normalization of serum ALT
- Induction of HBeAg loss or seroconversion
- Not a goal for HBeAg- patients at diagnosis
- Induction of HBsAg loss or seroconversion
- "Complete response" endpoint in some clinical trials

6 ENDPOINTS IN HBV TREATMENT
HBV IS INCURABLE

- **Eradication**: Equates to driving the virus to extinction from the earth. eg: small pox (vaccination)
- Elimination: reduce to a rare disease

VERSUS

- **Functional Cure**: equates to eliminating the virus from the blood of the infected host. (NH vs treatment)

FOR HEPATITIS B: Yes, it can be eliminated only if we have a cure and vaccine application

TO DEFINE ENDPOINTS: WE NEED TO KNOW THE "TERMS" IN PLAY:

- **Natural Cure**
  - Clearance of HBsAg without therapy and serum HBV DNA is undetectable
- **Functional Cure**
  - Based on the clinical outcome, in which the patient’s life expectancy becomes the same as that of an individual who has resolved HBV infection without therapy
- **Apparent Virologic Cure**
  - Based on the stable off-drug suppression of HBV viremia and antigenemia and the normalization of ALTs and other laboratory tests
- **Absolute Cure**
  - In which an individual with chronic hepatitis B completely resolves the infection, and is then at the same risk of death from liver disease as someone the same age who has never been infected

ABSOLUTE OR ULTIMATE: CURE WILL INCLUDE

- Clearance of all cells with cccDNA
- Elimination of cells with integrated HBV DNA
  - Remove integrated HBV DNA to complete stop risk of HCC
  - Prevent risk of HBV reactivation in anti-HBc(+) patients

WHAT WOULD A TRUE CURE = HBV ELIMINATION LOOK LIKE?

**In the blood**: HBV DNA/HBsAg negative
- anti-HBs positive
- anti-HBc positive
- No HBV RNA
- HBcAg negative
- HBeAg negative

**In the liver**: no HBV cccDNA
- no HBV RC/DSL DNA
- HBcAg staining negative
- No HBsAg
- No integrated HBV DNA

CURRENT TREATMENT CHALLENGES

- if use low genetic barrier NAs, drug resistance a serious problem
- long term therapy with NAs (> 3 years) affects patient compliance and typically has little effect on HBsAg levels
- Lack of qHBsAg in many countries
- Peg-IFN has substantial toxicity
  [RGT Rules Developed]
DRUGS WITH ANTI-HBV ACTIVITY – 2017

Nucleoside Analogs:
- Lamivudine¹ Epivir HBV
- Entecavir² Baraclude
- Telbivudine Tyzeka
- Emtricitabine¹³ Emtriva

Nucleotide Analogs
- Adefovir Dipivoxil Hepsera
- Tenofovir Disoproxil Fumarate¹³ Viread
- Tenofovir Alafenamide Vemlidy

Immune Modulator/Antiviral
- Interferon alfa Intron-A
- Pegylated Interferon alfa Pegasys

¹. Active against and approved for HIV
². Possible activity against HIV
³. FDA-approved for treatment of HBV August 2008

Tenofovir Alafenamide (TAF)

- In comparison with tenofovir, TAF enables enhanced delivery of the parent nucleotide and its active diphosphate metabolite into lymphoid cells and hepatocytes.
- This is attributed to an improved plasma stability and differential intracellular activation mechanism for TAF relative to TDF

LIVER TRANSPLANT WAIT-LISTING TRENDS BY INDICATION (2003-2013)

HOW TO ACHIEVE A CURE?

- HBV DNA suppresses immune response by
  - "Shock and Awe" Overwhelming antigens
  - Control viral replication
  - Cripple the virus
  - Reactivate the host immune response
  - Release immune tolerance
  - Clear cccDNA

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LIVER TRANSPLANT WAIT-LISTING TRENDS BY INDICATION (2003-2013)

- HBV*
  - Dramatic decrease in the rate of wait listing for ESLD with stabilization of the rate for HCC
  - Likely reflects the success of effective all-oral antiviral therapy

- HCV
  - Slight decrease in wait listing for ESLD
  - Rate of wait listing for HCC continues to rise

- NASH*
  - Rates of wait listing continue to increase for ESLD and HCC

STRATEGIES USED BY HBV TO ENSURE PERSISTENCE

- HBeAg
  - Soluble and secreted protein
  - "Toleragen" now called trained immunity at [perinatal transmission] and is essential for PERSISTENT infection
  - Possible immune regulatory function both INNATE and ADAPTIVE
    - [dampens host’s immune response to virus-infected hepatocytes]
  - Pre-core protein regulates level of HBV replication
  - Excess empty virus particles (decoy: anti-Pre-S1)
STRATEGIES USED BY HBV TO ENSURE PERSISTENCE

2. HBsAg
   - Excess production (decoy: anti-HBs) of 22 nm particles and filaments
   - Diverts anti-HBs neutralization of virions (42nm forms)

3. HBV cccDNA
   - Major transcriptional template
   - Heterogeneous topoisomerase species
   - Variable half-life
   - Resistant to nucleoside analogue therapy
   - Histone acylation and other modifications

After S Locarnini

HBV CURE: EMERGING STRATEGIES

Viral Replication Inhibition

- Small Molecule Capsid Assembly Inhibitors
- Cyclophilin Inhibitors

Inhibit HBsAg Production or Secretion

- RNAi Approach
  - Nucleic Acid Polymers
  - Small Molecules

Reducing or Eliminating cccDNA

Restoration of Antiviral Immunity

HBV CURE: EMERGING STRATEGIES

HBV TREATMENT STRATEGIES

Therapeutic targets

Vaccines
Remove or inhibit HBV-specific T cell responses
Neutralize anti-HBs neutralization of virions

Humoral responses
Neutralize HBV-specific T cell responses
Remove cccDNA

Innate immunity
Seroconversion through cytokine- and APC-mediated mechanisms

HBV CURE: EMERGING STRATEGIES

Viral Replication Inhibition

- Small Molecule Capsid Assembly Inhibitors
  - Preclinical proof of concept achieved
  - Awaiting clinical POC
- Cyclophilin Inhibitors
  - Nucleotides
  - Clinical
  - CMX157
  - Preclinical

Inhibit HBsAg Production or Secretion

- RNAi Approach
  - Nucleic Acid Polymers
  - Small Molecules

Reducing or Eliminating cccDNA

Step 1: DP-rcDNA
Step 2: DP-rcDNA (cccDNA precursor)

Restoration of Antiviral Immunity

- Blocking inhibitory cytokines
- Vaccine therapy
- Engineering HLA-t cells

HBV CURE: EMERGING STRATEGIES

HBV CURE: THE DRUG DISCOVERY LANDSCAPE

Immune modulation
- Toll-like receptors agonists, Gilead, Roche
- Anti-TLR-3 mAb, BMS, Merck
- Vaccine therapy, Transgene, Gilead, Roche
- Immune modulation, Alnylam, GSK

Antiviral therapies
- Nucleoside analogues, e.g. Gilead, BMS
- Non-nucleoside, e.g. LB80380
- Transgene, Gilead, teeGen, Alnylam, ITS
- Replicor, Novira, AssemblyPharma, Gilead, Roche, Tekmira

HBV cure: The drug discovery landscape

NEW THERAPEUTIC AGENTS FOR HBV

Nucleoside analogues
- NUC-212: inhibits viral DNA polymerase
- Adenosine 3'-monophosphate
- Gilead, Medimmune, ITS

Non-nucleoside analogues
- GS-4774
- Therapeutic vaccine
- Gilead Sciences

Non-interferon immune enhancers
- GS-5752
- Therapeutic vaccine
- Gilead Sciences

COMBINATION THERAPY

- No single approach will be sufficient to deliver a cure
- As in HCV and HIV combinations of drugs with different MOA's will be the solution
- Which combination will deliver the ultimate "cure" is yet to be determined
- But it will require a combination of antiviral and immunomodulatory approaches

WHAT MIGHT A HBV CURATIVE REGIMEN LOOK LIKE?

- DAA: Blue
- Indirect: Green

Polio NA ➔ agent to prevent viral spread and cccDNA re-amplification
cccDNA inhibitor ➔ safe and selective agent to reduce or silence cccDNA
Immune Activator ➔ agent(s) to activate specific antiviral immune responses or relieve repression/exhaustion of the system
HBV Antigen Inhibitor ➔ agent(s) to block/inhibit the HBV life-cycle [entry, cell-spread, capsid assembly, HBx, HBeAg, HBsAg]
CONCLUSIONS

- HBV is a growing and insidious threat to world health
- Vaccination is key to prevention
- Treatment by permanently suppressing viral load is the key to preventing the long term complications of cirrhosis and HCC
- The new treatment paradigm is closely paralleling the treatment of HIV: suppressing viral replication prevents long term morbidity
- Cure of HBV is an achievable goal in the next 5 years