Current Therapy of Hepatitis B
Planning for 2014 and beyond

SOTA 2014

Robert Gish
robertgish.com
rgish@robertgish.com
San Diego, CA USA
Medical Director Hepatitis B Foundation

Senior Medical Director St Joseph’s Medical Center, Phoenix Arizona
HBV Relevant Disclosures

• Advisory Board
  – BMS, Gilead, Genentech, Arrowhead, ISIS

• Honorarium, speakers bureau
  – BMS, Gilead,

• Investment (stock options)
  – Arrowhead
HEV Relevant Disclosures

• Advisory Board
  – None

• Honorarium, speakers bureau
  – None
Hepatitis B: The Facts

• Hepatitis B is the world’s most common serious liver infection\(^1\) and is a widespread global health issue
  • HBV is not curable but controllable and suppressible
  • HBsAg clearance is a “functional cure”
    – HBV is 100 times more infectious than HIV (human immunodeficiency virus)\(^2\)
    – 10 times more infectious than hepatitis C\(^3\)
• The virus is transmitted via the blood and bodily fluids\(^1\)
  – Hepatitis B progresses slowly over time
  – Complications generally involve vague symptoms or none at all, and are often undetected for many years

Hepatitis B: By The Numbers

More than 350 million or 1 in 20 people worldwide have chronic hepatitis B infection\(^1\) (Compared with the 33 million living with HIV\(^2\))

1.46-2.2 million people in the United States are chronically infected\(^5\)

14 million in Europe\(^1,4\)

112 million in Asia-Pacific (93 million people in China)\(^1,3\)

---

1. WHO. Available at: www.who.int/csr/disease/hepatitis/en/;
3. Records of the thematic press conference of the Ministry of Health of the PRC at April 21, 2008, from the website of the Ministry of Health of the People's Republic of China;
4. Ulmer T, et al. (2007). European orientation towards the better management of hepatitis B in Europe;
5. CDC. Hepatitis B FAQs for Health Professionals. Available at http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm#overview.
An Unmet Medical Need

- Worldwide, hepatitis B is significantly
  - Under-diagnosed
  - Under-treated\(^1\)

1. BMS Market Research. Information available upon request from Bristol-Myers Squibb;
3. Decision Resources. Hepatitis B virus in China – Emerging markets study #5; 4. BMS Market Research.
New figures from Global Burden of Disease Survey 2010: number of people infected

- Viral Hepatitis: 1,012,873
- Tuberculosis: 827,567
- HIV/AIDS: 304,628
- Malaria: 106,729

Attribution: Seng Gee Lim AASLD 2013
HBV Infection, Diagnosis, and Care in the United States

- Chronic HBV Infection: 1.4-2.2 Million (Low to High Estimate)
- Persons Aware of Their Infection: 400,000-600,000
- Potentially Eligible for Treatment: 350,000-500,000
- Entering Care: 200,000-300,000
- Annual HBV Prescriptions: 50,000
- 2.5% to 5% of the Total HBV-Infected Population

### CDC Recommendations for Routine HBV Testing

<table>
<thead>
<tr>
<th>Populations</th>
<th>Increased HBsAg Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Persons born in regions with high or intermediate prevalence of HBV infection (HBsAg prevalence ≥2%)</td>
</tr>
<tr>
<td></td>
<td>• U.S.-born persons not vaccinated as infants whose parents were born in regions with high prevalence of HBV infection (HBsAg prevalence ≥8%)</td>
</tr>
<tr>
<td></td>
<td>Manage Exposures</td>
</tr>
<tr>
<td></td>
<td>• All pregnant women</td>
</tr>
<tr>
<td></td>
<td>• Infants born to HBsAg+ women</td>
</tr>
<tr>
<td></td>
<td>• Injection drug users</td>
</tr>
<tr>
<td></td>
<td>• Men who have sex with men</td>
</tr>
<tr>
<td></td>
<td>• Household, needle-sharing, or sex contacts of persons known to be HBsAg+ persons</td>
</tr>
<tr>
<td></td>
<td>• Source of blood/body fluid exposures (e.g., needlestick, sexual assault)</td>
</tr>
<tr>
<td></td>
<td>Prevent Nosocomial Infection</td>
</tr>
<tr>
<td></td>
<td>• Donors of blood, plasma, organs, tissue, or semen</td>
</tr>
<tr>
<td></td>
<td>• Hemodialysis patients</td>
</tr>
<tr>
<td></td>
<td>Increased Risk of Medical Consequences</td>
</tr>
<tr>
<td></td>
<td>• HIV+ persons</td>
</tr>
<tr>
<td></td>
<td>• Persons with immunosuppressive therapy</td>
</tr>
<tr>
<td></td>
<td>• Persons with elevated ALT or AST of unknown etiology</td>
</tr>
</tbody>
</table>

2014

What has the USPHSTF changed and going to recommend?

Foreign Born: from endemic regions
   MSM
   IVDU
High risk behavior
HBV: Phase I Tests

• HBsAg = infection
• Anti-HBs = immunity
  – if anti-HBc is negative
• Anti-HBc = exposure
HBV

• Is not curable

• New term: (oxymoron) “functional cure”
  – When HBsAg becomes negative
Outcome of Hepatitis B Virus Infection by Age at Infection

Chronic Infection (%)

Symptomatic Infection (%)
Hepatitis B Disease Progression

- **Acute Infection**
  - >90% of infected children progress to chronic disease
  - <5% of infected adults progress to chronic disease

- **Chronic Infection**
  - 30-40% of chronic HBV-infected individuals

- **Cirrhosis**
  - Liver Cancer (HCC)
  - > 25% Lifetime Risk

- **Liver Failure** ( Decompensation)
  - > 15% Lifetime Risk

- **Liver Transplantation**
  - 35-40% Liver related death

- **Death**

- **Risk for reactivation**

References:
Torresi J. Gastro. 2000;118:S83-103;
Fattovich G. Hepatology. 1995;1:77-82;
# HBV Diagnostic Markers

## Serologic Marker Results

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>Total Anti-HBc</th>
<th>IgM Anti-HBc</th>
<th>Anti-HBs</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Never infected and no evidence of immunization</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Acute infection</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Chronic infection</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>“Recovered” from past infection and not immune, low level carrier</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Immune (immunization)</td>
</tr>
</tbody>
</table>

HBeAg- High infectivity  
HBeAb- Low infectivity

Testing Paradigm

• Always test: anti-HBc

• If anti-HBc + > does not need vaccination
  – >>> risk for reactivation
Hepatitis B: By The Numbers

• If it is not treated, in 1/3 of patients, hepatitis B can cause liver damage leading to cirrhosis and liver cancer\(^1\)

• Hepatitis B is responsible for 80% of primary liver cancer globally, which is almost always fatal\(^2\)
  – Historically: Liver cancer was the 3\(^{\text{rd}}\) highest cause of death by cancer in men\(^3\)
  – Now 2014: Liver cancer is the 2\(^{\text{nd}}\) highest cause of cancer death worldwide\(^3\)
  – Without appropriate treatment or monitoring, 1 in 4 persons with chronic hepatitis B will die of liver cancer or liver disease

1. WHO. Available at: www.who.int/csr/disease/hepatitis/en/;
HBV DNA vs. Liver Cirrhosis: REVEAL data

No of patients = 3,482*

<table>
<thead>
<tr>
<th>Baseline HBV DNA copies/mL</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥10^6</td>
<td>10.6</td>
</tr>
<tr>
<td>10^5–10^6</td>
<td>9.7</td>
</tr>
<tr>
<td>10^4–10^5</td>
<td>3.6</td>
</tr>
<tr>
<td>300–&lt;10^4</td>
<td>2.0</td>
</tr>
<tr>
<td>&lt;300</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* HBeAg negative n=2960

HBV DNA vs. HCC: REVEAL Data

No of patients = 3,653*

Cumulative rate of HCC

Baseline
HBV DNA

≥10^6 copies/mL
6.6

10^5–<10^6
6.1

10^4–<10^5
2.3

300–<10^4
1.1

<300
1.0

*HBeAg negative n=3088

Aiming for True Inactive Carrier Status and CURE

**Milestone 1:** Start of decline of HBV DNA

**Milestone 2:** HBeAg/anti-HBe sero-conversion

**Milestone 3:** HBV DNA decreased to undetectable

**Milestone 4:** Clearance of HBsAg

**Milestone 5:** Clearance of cccDNA

**Milestone 6:** Clearance of cells with integrated HBV DNA sequences

This is where we would like our patients to be

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

Immune tolerance

Immune clearance

Inactive carrier state

Functional cure>>>CURE

Immune control
Why treat early?
Natural History of Chronic HBV Infection

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Acute hepatitis</th>
<th>Chronic hepatitis</th>
<th>Cirrhosis</th>
<th>Liver Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virological</td>
<td></td>
<td>HBeAg: HBV DNA</td>
<td>Anti-HBe</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBsAg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>Replication</td>
<td></td>
<td></td>
<td>Integration</td>
</tr>
<tr>
<td>Time</td>
<td>Months</td>
<td>Years</td>
<td>Decades²³</td>
<td></td>
</tr>
</tbody>
</table>

Next Steps in HBV Management

• Use the right NUC to control HBV for the right patient
  – Personalized medicine
• Help Stop oral (NUC) therapy, current Rx is indefinite
• Choose the correct Nuc for your patient
  – Pregnancy, Drug resistance, Management, Lactic Acidosis
• Safe use of each medicine
• Use combination therapy when appropriate
• Permanent clearance of HBV
  – HBsAg clearance: 10% rate now reported with TDF at 5 years of follow up
    • cccDNA clearance and integrated HBV DNA clearance or prevention
      – CURE?
Endpoints of Antiviral Therapy
Compensated Cirrhosis

• Clinical endpoints similar to those for HBeAg-positive and HBeAg-negative CHB patients

• No liver failure
  – Now
    • Decreased rate of HCC
    • Falling rates of liver transplant
    • Lower death rates due to HBV

  – Future
    • Clear sAg in all patients
    • No ccc DNA remaining in liver cells
    • Cure- Functional >>>> real cure
### US FDA dates of Approved Therapies for CHB

#### Nucleosides/Nucleotides

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Company</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>VIREAD®</td>
<td>Gilead Sciences</td>
<td>2008</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>TYZEKA™</td>
<td>Idenix / Novartis</td>
<td>2006</td>
</tr>
<tr>
<td>Entecavir</td>
<td>BARAACLEDE™</td>
<td>Bristol-Myers Squibb</td>
<td>2005</td>
</tr>
<tr>
<td>Adefovir dipivoxil</td>
<td>HEPSETRA™</td>
<td>Gilead Sciences</td>
<td>2002</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>EPIVIR-HBV®</td>
<td>GlaxoSmithKline</td>
<td>1998</td>
</tr>
</tbody>
</table>

#### Interferons

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Company</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peginterferon alfa-2a</td>
<td>PEGASYS®</td>
<td>Roche Laboratories</td>
<td>2005</td>
</tr>
<tr>
<td>Interferon alfa-2b, recombinant</td>
<td>INTRON® A</td>
<td>Schering / Merck</td>
<td>1992</td>
</tr>
</tbody>
</table>

Preferred therapies – AASLD Guidelines
ETV 3-year Clinical Trial HBV DNA Suppression
HBeAg-negative Patients

ETV-027  HBeAg(-) ETV Long-term Cohort (ETV-027→ETV-901)

Proportion of patients with HBV DNA <300 copies/mL (%)

<table>
<thead>
<tr>
<th>Time</th>
<th>ETV-027</th>
<th>HBeAg(-) ETV Long-term Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of Dosing</td>
<td>94%</td>
<td>4%</td>
</tr>
<tr>
<td>Baseline</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>Wk 12</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>Wk 24</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td>Wk 48</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>Wk 72</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>Wk 96</td>
<td>91%</td>
<td></td>
</tr>
<tr>
<td>Wk 144</td>
<td>95%</td>
<td></td>
</tr>
</tbody>
</table>

n
93/99        4/99        56/95       79/95       84/90       72/77       67/74       54/57†

†In the randomised controlled study (ETV-027), patients received 0.5mg ETV. In the 901 rollover study, patients received 1mg ETV
‡10 patients who remained on treatment at Week 144 of ETV-901 visit had missing PCR samples

Shouval D, et al. AASLD 2008; poster 927.
Korean Cohort: Impact of Entecavir and Lamivudine on Survival in HBV (1999-2011)

- Single-center cohort of chronic HBV (n=9615 treatment-naïve)
  - Entecavir 0.5 mg/day or lamivudine 100 mg/day
  - >20 years of age; no prior HCC, transplant, HCV, HDV, or HIV; HBV DNA ≥2000 IU/mL

- Treatment with entecavir was associated with
  - Minimal risk of drug resistance 1.5% versus 50.8%; P<0.001)
  - Minimal need for rescue therapy (1.8% versus 39.3%; P<0.001)
  - Significantly lower risk of death or transplantation (adjusted hazard ratio 0.42; P<0.001)

HCC Incidence in Patients Treated with Long-term ETV

After propensity score matching, significant difference of treatment effect between groups was seen in patients with cirrhosis ($P<0.001$), but not in patients without cirrhosis ($P=0.440$)

In comparison to a historical untreated control group, long-term ETV treatment reduces the incidence of HCC, especially in cirrhotic CHB patients

Studies 102/103: Virologic Suppression With TDF at Year 6

### Response

<table>
<thead>
<tr>
<th>Response</th>
<th>HBeAg- Patients (Study 102)</th>
<th>HBeAg+ Patients (Study 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 5</td>
<td>Year 6</td>
</tr>
<tr>
<td>HBV DNA &lt; 400 copies/mL Intent-to-treat*, % (n/N)</td>
<td>83 (291/350)</td>
<td>81 (281/345)</td>
</tr>
<tr>
<td>HBV DNA &lt; 400 copies/mL On treatment†, % (n/N)</td>
<td>99 (292/295)</td>
<td>99.6 (283/284)</td>
</tr>
</tbody>
</table>

* LTE-TDF (missing = failure/addition of FTC = failure)
† Observed (missing = excluded/addition of FTC = included)

- 80% of 585 patients entering the open-label phase remained on study at Year 6; 73% of enrolled patients remained on study
- HBeAg loss/seroconversion rates of 50% and 37%, respectively, through 6 years
- 11% of HBeAg+ patients had confirmed HBsAg loss (8% with seroconversion)
- No resistance to TDF was detected through 6 years

Studies TDF 102/103: Observed vs. Predicted HCC Cases

- Incidence of HCC in patients on TDF in studies 102/103 was lower than predicted by the REACH-B model.
- In non-cirrhotic patients, the effect of TDF becomes noticeable between 2-3 years of therapy and became statistically (55% reduction) at 6 years of therapy.

---

*Statistically significant at nominal α-level of 0.05.

Differences in Development of Resistance with Long-term Treatment in Nuc-naïve Patients

Not head to head trials
Different patient populations and trial designs

Patients with resistance (%)

- **Lamivudine**: 24, 53, 70, 65
- **Adefovir**: 11, 18, 29
- **Entecavir**: 1.0, 1.0, 1.2
- **Telbivudine**: 4, 0
- **Tenofovir**: 22, 0

Change in cccDNA Levels After 48-52 Weeks of Antiviral Therapy

TDF has a favourable clinical trial safety profile up to and beyond 192 Weeks*

*On/After week 72, patients with confirmed HBV DNA ≥400 copies/mL were eligible to add FTC in a fixed dose combination tablet

Protocol for Dose Reductions for Oral HBV Medications if Changes in Renal Function

• Recommended GFR >>> dose adjustments, although each hepatologist was free to use their own interpretation of the guidelines in the package insert

  – >70 mL  7 tablets per week
  – 60-69 mL 6 tablets per week
  – 50-59 mL 5 tablets per week
  – 40-49 mL 4 tablets per week
  – 30-39 mL 3 tablets per week
  – 20-29 mL 2 tablets per week
  – 10-19 mL 1 tablet per week

Interferon

• Short fixed duration therapy
• No Renal toxicity
• Ideal for patients with high ALT and medium to low DNA
• Has stopping rules and “continuation” rules
• Chance of DNA suppression long-term is less than 20%
• HBsAg loss is 10%
  – Same as with Nuc therapy
• HBsAg quant is best stopping (test) rule, but not available in the US
NIDDKD Cohort: HBsAg Loss by Mode of HBeAg Clearance

- Treatment-induced HBeAg clearance (n=51)
  - Interferon related: 86%
- Cumulative incidence of HBeAg loss per year (P=0.02)
  - Spontaneous: 1.6%
  - Nucleoside analog induced: 4.4%
  - Interferon induced: 6.3%
- Most significant predictors of HBsAg loss
  - Mode of HBeAg loss
  - Race

**Probability of HBsAg Loss by Mode of HBeAg Clearance**


HBsAg Loss in HBeAg-Positive and HBeAg-Negative Patients

FibroScan: Enhancing Performance to Predict Cirrhosis in HBV Patients using Different Cut-off Values

In this way, liver biopsy can be avoided in approximately 62% of patients with normal ALT and 58% of patients with elevated ALT.

HBV Reactivation Following Rituximab-Containing Chemotherapy

- Single-center cohort with a variety of hematologic diagnoses (n=62) (2011-2013)
  - HBsAg negative, anti-HBc positive
  - HBV DNA <10 IU/mL
  - No concomitant liver disease or prior HBV treatment
  - Reactivation: HBV DNA >10 IU/mL regardless of HBsAg status
  - Follow-up: 36.6 months

- High rate of reactivation
  - Majority occurred within the first 6 months (86.7%)
  - Presence of low anti-HBs levels was not protective against HBV reactivation

Specific Populations: For the Panel

- Immune tolerant patients: NNT is too high with current data to justify treatment
- Occult HBV (defined as anti-HBc (+) and HBsAg(-))
  - Risk of cancer: no intervention yet justified
  - Risk of reactivation: high risk demanding prophylaxis
    - Rituximab, StCTx, BMTx, ablative therapies
- Children
  - Use of INF and approved nucleos(t)ides to treat selected patients
- Pregnancy
  - Use first line, category B drugs (TDF) during 3rd trimester if HBV DNA >10^6
- FHF or AoC: treat HBV with oral therapies while waiting for HBV DNA
- Test all “at risk” patients for delta hepatitis
  - Advanced liver disease
  - IVDU or sexual transmission as risk for HBV
We Need Therapies to Attack: HBV Replication: @ cccDNA Pathway
New therapies en-route

- Anti-Sense: DNA like molecules  ISIS
- iRNA: Modified RNA  Arrowhead
- Uptake inhibitors blocking entry Myclurdex
- Capsid formation inhibitors: block release and cccDNA formation Various
- Block RNAaseH Various
- Block histone modifications Various
VACCINATE !
Concluding Points

• There are currently 7 approved therapies for CHB and determination of which therapy to use includes careful consideration of duration of treatment, stopping rules, drug efficacy, side effects, and potential for antiviral resistance with the nucleos(t)ide analogs

• There is no cure: so what is next?
  – Functional “cure”? S Ag clearance
  – New treatments: clear capsid and cccDNA
    • iRNA
    • Capsid inhibitors
    • Anti-Sense
    • Entry inhibitors
    • RNAase H target

TEST VACCINATE TREAT SURVEILLANCE
Thank you

• Ashley Sandoval
• Drs Paul Pockros and Carrie Frenette
• Our Pharma supporters