Overview of the Epidemiology and Natural History of Hepatitis B

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Massachusetts General Hospital
Harvard Medical School
Disclosures related to my presentation today

During previous two years

- Consulting (Scientific Advisory Boards)
  - BMS, Gilead, Arrowhead Research
- Data monitoring committees
  - Ikaria, Genzyme—unrelated to my presentation
- Equity
  - Exercised options (Achillion)
Burden of HBV Infection in the US

- >13 million (~1 out of 22) persons in the US have been infected\(^1\)
- >2.2 million are chronically infected in the US\(^2\)
- ~4% of newly diagnosed cases of chronic liver disease

**New Acute Infections per Year\[^{[3]}\]**
- 3,000-20,000

**Chronic Infections\[^{[2]}\]**
- 2,200,000

**Deaths per Year\[^{[3]}\]**
- 2,000-4,000

**Diagnosed HCC per Year\[^{[4]}\]**
- 3,100

**Liver Transplants per Year\[^{[5]}\]**
- 230

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US Incidence/Prevalence
Reported New HBV Infections by Year: United States (1980-2013)

Vaccine Licensed 1981

HBsAg Screening of Pregnant Women Recommended 1988

Universal Infant Immunization Recommended 1991

OSHA Rule* Enacted 1991

Adolescent Immunization Recommended 1995

Decline in MSM and HCW

Decline in IDU

>80% decline in incidence during 1990s

*Occupational Exposure to Bloodborne Pathogens standard

CDC. http://www.cdc.gov/hepatitis/hbv/hbvfaq.htm#overview.

*estimated 19,764 based on underreporting
# Prevalence of Chronic HBV Infection in US Households (age ≥6 yrs, noninstitutionalized)

National Health and Nutrition Examination Survey (NHANES) 1988-2012

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<tbody>
<tr>
<td><strong>Anti-HBc</strong></td>
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<tr>
<td>Past or present</td>
<td>5.3%</td>
<td>4.8%</td>
<td>3.9%</td>
<td>$P &lt; 0.0001$</td>
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<tr>
<td></td>
<td>12.1 million</td>
<td>12.5 million</td>
<td>10.8 million</td>
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<td><strong>HBsAg</strong></td>
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<tr>
<td>Current</td>
<td>0.4%</td>
<td>0.3%</td>
<td>0.3%</td>
<td>$P = 0.1753$</td>
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<tr>
<td></td>
<td>730,000</td>
<td>847,000</td>
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<tr>
<td><strong>Anti-HBs</strong></td>
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<tr>
<td>Vaccine immunity</td>
<td>21.7%</td>
<td>25.1%</td>
<td></td>
<td>PR* 1.16 (1.09-1.23)</td>
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<tr>
<td></td>
<td>57.8 million</td>
<td>68.5 million</td>
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*Prevalence Ratio, CI excludes 1.0 = significant

16% increase
### Prevalence of Chronic HBV Infection in US Households

National Health and Nutrition Examination Survey (NHANES) 1988-2012

**HBsAg Current HBV Infection**

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<tr>
<td><strong>Age (yrs)</strong></td>
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<tr>
<td>6-19</td>
<td>0.2%</td>
<td>0.05%</td>
<td>0.03%‡</td>
<td>PR* 9.4 (0.9-2.0)</td>
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<tr>
<td>20-49</td>
<td>0.4%</td>
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<td>0.4%</td>
<td>NS</td>
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<tr>
<td>&gt;50</td>
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<td>NS</td>
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<tr>
<td><strong>Race/ethnicity</strong></td>
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</tr>
<tr>
<td>White NH §</td>
<td>0.2%</td>
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</tr>
<tr>
<td>Black NH</td>
<td>1.0%</td>
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<td>NS</td>
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<tr>
<td>Asians NH</td>
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<td></td>
<td>3.1%</td>
<td></td>
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<tr>
<td><strong>Place of birth</strong></td>
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<td>0.14%</td>
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<tr>
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*Prevalence Ratio

31-fold higher

8-fold higher

‡ Following universal vaccination in 1991, in 6-19 age group, prevalence of chronic hepatitis B decreased by 79.2% in 1999-2006 and by 87.5% in 2007-2012.

"Nonhispanic"

# Prevalence of Chronic HBV Infection in US Households

**National Health and Nutrition Examination Survey (NHANES) 1988-2012**

**HBsAg Current HBV Infection**

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*Prevalence Ratio

§ Nonhispanic

¶ 2-fold > gen. population (0.3%)  
* n = 199,000  
2.5% in foreign-born vs 0.4% in US-born

‡ 10-fold > gen. population (0.3%)  
* n = 427,000, 93.1% foreign-born  
50% HBV disease burden (5% of population)  
<<12.3% prevalence suggested in other studies

### Prevalence of Chronic HBV Infection in US Households (age ≥6 yrs, noninstitutionalized)

National Health and Nutrition Examination Survey (NHANES) 1988-2012

+ Hepatitis B Among Non-Hispanic Asian Adults in the US, NHANES 2011-2014

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Estimated 1.3 million new persons with chronic hepatitis B were imported to the US, 1974–2008 (4.6% of all new immigrants)

Prevalence of Chronic Hepatitis B (CHB) among Foreign-born (FB) Persons Living in the US by Country of Origin

• Migration of persons with CHB from HBV-endemic regions has increased substantially x past 40 years, contributing to maintenance of constant prevalence rates since 1999.
  • 3.9 million FB persons from endemic areas reside in the US (13.6% of population)
  • Persons with CHB in the US are largely FB, account for 70% of US HBV infections (95% of new infections).
• Weighted average CHB prevalence for all FB living in the US = 3.45% (95% CI: 2.72-4.19) = 1.32 million.
• Based on the assumption that 300,000-600,000 US-native-born (NB) persons have chronic hepatitis B, the total prevalence (FB + NB) = 2.2 million – 2.4 million.

Support for Updating Estimates of US Prevalence of HBV Infection

- NHANES 2007-2012 focused on noninstitutionalized population, does not include...
  - Homeless and incarcerated; multiple high-risk racial/ethnic groups; low capture of foreign-born Americans (1.32 million, 3.45% prevalence)
- Per NHANES estimate, 2.2 million persons are in US jails/prisons, prevalence of HBV infection 2% (range 0.9-3.1%), yielding an additional 44,000 infected.
  - May be an underestimate: 0.9-8.7% of US population are incarcerated, 13-20% are IDU.
- Per NHANES estimate, 0.5% of homeless are infected, may be an underestimate.
  - 24% in homeless shelters are IDUs.
  - 33% of homeless persons with mental illness and substance-use disorders are anti-HBc+.
- Estimate taking foreign-born, institutionalized, homeless, etc. into account: prevalence should be adjusted upwards to >2.2 million.
Modes of Transmission

Sex
- IDU 16%
- MSM 15%
- Heterosexual 33.1%
- Multiple sex partners 34%
- MSM or bisexual male 55%
- Surgery 10%
- Percutaneous injury 5%
- Household contact with hepatitis B pt 1.3%
- Blood transfusion 0.6%
- Occupational blood contact 0.5%
- Hemodialysis 0.2%
- Unknown 57%

Risk factors do not total 100% because of multiple risk factors in some patients.
Persons at Risk of Hepatitis B

- Infants born to infected mothers
- Sex partners of HBV-infected persons
- People with multiple different sex partners
- Persons with a sexually transmitted disease
- Men who have sex with men
- Injection drug users
- Household contacts of HBV-infected persons
- Healthcare and public safety worker exposed to blood on the job
- Hemodialysis patients
- Residents and staff of facilities for developmentally disabled persons
- Travelers to regions with intermediate or high rates of hepatitis B (HBsAg prevalence ≥2%)
- Persons with end-stage renal disease
- Persons with diabetes mellitus
- Children of immigrants from a country with a high HBV prevalence
- Persons with HIV infection

Heterosexual Transmission of Hepatitis C

Relative Efficiency of Heterosexual Transmission

HCV < HIV < HBV

~ 3% < ~ 15% < ~ 30%

Perinatal Transmission of Hepatitis C

Relative Efficiency of Perinatal Transmission

- HCV: ~5%
- HIV: ~25-30%
- HBV: ~90%

Needlestick Transmission of Hepatitis C

Relative Efficiency of Needlestick Transmission

HIV < HCV < HBV

~ 0.3% < ~ 3% < ~ 30%
Natural History/Progression
## HBV: CLINICAL-EPIDEMIOLOGIC CORRELATIONS

<table>
<thead>
<tr>
<th>Endemicity</th>
<th>Location</th>
<th>Age of Infection</th>
<th>Mode of Transmission</th>
<th>Chronicity</th>
<th>HCC Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>N. America</td>
<td>Early</td>
<td>Percutaneous</td>
<td>Rare</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>W. Europe</td>
<td>Adulthood</td>
<td>Sexual</td>
<td></td>
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<tr>
<td>High</td>
<td>Subsahara</td>
<td>Birth</td>
<td>Perinatal</td>
<td>Likely</td>
<td>High</td>
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<td></td>
<td>Far East</td>
<td>Toddler</td>
<td>Horizontal</td>
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The table above outlines the endemicity of HBV infection across different locations and the associated mode of transmission, age of infection, chronicity, and risk of HCC.
Geographic Prevalence of Chronic Hepatitis B: Impact of Migration 1996-2002

HBsAg Prevalence

- ≥8% - High (ever infected 70-90%, 45% of population)
- 2-7% - Intermediate (ever infected 20-50%, 43% of population)
- <2% - Low (ever infected 4-6%, 12% of population)
Overall Risk of Progression to Cirrhosis

105 Italian patients with chronic hepatitis B, mean f/u 5.5 yrs

Cumulative incidence

5.9% annual incidence

Cumulative incidence
20% at 5 yrs

Years after clinical presentation

Cumulative % with progression to cirrhosis

No. of patients

105  90  56  48  30  23  13  10  7  4  2  2  2  3

Incidence of Cirrhosis by Serum HBV DNA at Entry, Stratified by HBeAg Status

HBV - Natural History

Probability of Decompenasation in 349 HBsAg+ Patients with Cirrhosis

Mean f/u 73 months, decompensation in 28% (non-HCC)

No. of patients: 317, 283, 255, 221, 198, 167, 148, 115, 86, 64, 30

Probability of Decompensation:
- 23% at 5 yrs
- 37% at 10 yrs

3-Year Progression in Patients with Cirrhosis (Advanced Fibrosis) in the Placebo Arm of a Prospective RCT

Cases with disease progression (%)

Time to disease progression (mo)

<table>
<thead>
<tr>
<th>Time (mo)</th>
<th>Placebo (n = 215)</th>
<th>LAM (n = 436)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7.8%</td>
<td>17.7%</td>
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<tr>
<td>6</td>
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<td>12</td>
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<td>36</td>
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Effect of Decompensation on Survival of Patients with Hepatitis B Cirrhosis (EUROHEP)

349 cirrhotic patients mean f/u x 73 mo

- Compensated: 84% 5-yr survival, 68% overall survival
- Decompensated: ~28% survival

<table>
<thead>
<tr>
<th>Years</th>
<th>Comp patients</th>
<th>Decomp patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>366</td>
<td>88</td>
</tr>
<tr>
<td>1</td>
<td>310</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>247</td>
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<td>10</td>
<td>36</td>
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</tbody>
</table>

Baseline HBV DNA Level and Future Incidence of HCC

6% at 5 yrs

12% at 10 yrs

Hepatitis B Disease Progression occurs in 15-40% of patients

- Chronic Infection
- Cirrhosis: 30%
- Liver Failure: 23% in 5 yr
- Acute flare
- HCC: 10%-15% in 10 years
- Death
- Liver Transplantation*

*Chronic hep B is the 6th leading indication for liver transplantation in the US.

References:
Impact of Preventive-Therapeutic Interventions on Natural History
30-year Outcomes of the National Hepatitis B Immunization Program in Taiwan Implemented July 1984

Figure. Age- and Sex-Specific Mortality and Incidence Rates of Chronic Liver Disease and Hepatocellular Carcinoma for Birth Cohorts Born Before and After the Launch of the Hepatitis B Immunization Program in 1984 in Taiwan

Declined >90%
Declined >80%
Declined >90%

Regression of cirrhosis during tenofovir Rx for chronic hepatitis B: a 5-year open-label follow-up study in 348 patients

Histologic improvement in 87%

Fibrosis regression in 51%

Of 96 with baseline cirrhosis; 74% no longer had cirrhosis
Retrospective analysis, propensity-matched 21,595 treated patients (≥90 days) vs 21,595 untreated control patients.

Taiwan National Health Insurance Research Database 1997-2010

HR 0.37, CI 0.34-0.39 (adjusted for competing mortality and confounders)

P <0.001

HBV DNA Suppression Reduces Cirrhosis Progression With Lamivudine (LAM)

Cases with disease progression (%)

Time to disease progression (mo)

Placebo (n = 215)

Lamivudine (n = 436)

ITT population

Long-term effect of antiviral therapy on disease course after decompensation in patients with HBV-related cirrhosis

707 Chinese patients with decompensated cirrhosis
284 untreated, 423 treated (58 previously Rxd, 253 early Rx, 112 delayed Rx)

5-Year OLT-free survival

60% treated
46% untreated

“Rescue”

40% delisted for OLT

Decline in the Need for Liver Transplantation for ESLD 2° to HBV in the US

Widespread use of HBV antiviral therapy

Hepatitis B: Take-Away Points

• US prevalence, updated estimate >2.2 million, concentrated in foreign-born immigrants from high-prevalence regions
• Blood-born agent—modes of transmission: perinatal, percutaneous, sexual
• Self-limited or chronic (active disease vs inactive carriage)
• Clinical expression a function of prevalence in population and timing in life of onset of infection
• Natural history: progression to cirrhosis, decompensated liver disease, HCC, death/transplantation
• Preventive/therapeutic interventions improve the natural history of hepatitis B.