Hepatitis B*

Overview and Update

*B for Boring
Objectives

• Epidemiology
• Treatment decisions and treatment options
• Treatment of special populations
  • Pregnant women
  • Treatment-experienced patients
  • Patients with advanced disease stage, especially decompensated cirrhosis
  • Patients with HIV or HCV coinfection
HBV – A Global Problem

• 2 billion people worldwide have been infected with HBV[1]
• ~ 350 million chronic carriers[2]
• Estimated 1.25 million chronically infected in the U.S.
• Leading cause of cirrhosis and HCC worldwide[2]
• ~ 600,000 deaths annually caused by HBV-related liver disease or HCC
• Causes 80% of all HCC in Asian Americans[3]
• 30% to 50% of HCC associated with HBV in the absence of cirrhosis[4]
• HBV is 50-100 times more infectious than HIV[1]

Estimated Prevalence of HBsAg-Positive Persons in the US by Population Segment

<table>
<thead>
<tr>
<th>Population Group</th>
<th>HBsAg Prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign-born API[^1]</td>
<td>8.90</td>
</tr>
<tr>
<td>Non-Asian Americans[^1]</td>
<td>0.42</td>
</tr>
</tbody>
</table>

*Non-Asian Americans includes blacks, whites, and other ethnicities.

- Prevalence reflects patterns of HBV infection in regions of origin
- Potential for immigration from highly endemic countries to ↑ US HBV prevalence despite ↓ incidence of new infections
  - Age-adjusted prevalence of anti-HBc and HBsAg in the US statistically similar during 1999-2006 vs 1988-1994[^2]
  - ~ 40,000 persons with chronic HBV infection immigrate to US each yr[^3]

Impact of Immigration on HBV Prevalence in the US

Immigration Numbers by Continent: 2002-2011

HBV Screening

- Persons born in high and intermediate endemic areas (≥ 2% prevalence)
- US-born children of immigrants from high endemic areas (≥ 8%; only if not vaccinated as infants in the US)
- Household and sexual contacts of HBV carriers
- Persons who have injected drugs
- Persons with multiple sexual partners or history of STDs

- Men who have sex with men
- Inmates of correctional facilities
- Individuals with chronically elevated ALT/AST
- Individuals infected with HIV or HCV
- Patients undergoing dialysis
- Patients undergoing immunosuppressive therapy
- All pregnant women
- Infants born to HBV carrier mothers
**HBV Screening Algorithm**

Assess HBsAg

Positive

**CHB***

Evaluate for treatment

Negative

Assess anti-HBs

**Negative** (no antibodies)

Vaccinate

**Positive** (antibodies present)

Immune to HBV

*Time from positive HBsAg test to diagnosis of CHB is 6 mos.

Potential Barriers to Screening

• Lack of healthcare coverage
  – Makes screening process too expensive for many people
• For those who may not be staying in the US legally, fear of being caught by authorities
• No time to get screened due to busy work schedules
  – Typically true for immigrants and their families
• HBV is silently transmitted and has a silent progression
  – Many people with chronic HBV infection exhibit no symptoms and feel perfectly healthy
Potential Barriers to Screening

• Lack of education regarding the high rate of HBV in Asian populations
  – Leads to lack of urgency to get screened
• For older populations, it may be more difficult for them to use modern technology to its fullest extent to learn more about HBV (eg, Web sites, videos, etc)
• Language and communication difficulties
To treat or Not to Treat: That is the Question

Benefits

- Likelihood of adverse outcome without treatment
- Long-lasting response

Patient’s age and preference

Risks

- Adverse effects
- Drug resistance

Costs

Likelihood of adverse outcome without treatment

Activity and stage of liver disease at presentation

Risk of cirrhosis/HCC in the next 10-20 yrs

Likelihood of long-term benefit with treatment
4 Phases of Chronic Hepatitis B Infection

Current Understanding of HBV Infection

<table>
<thead>
<tr>
<th>Phase</th>
<th>Immune Tolerant</th>
<th>Immune Clearance</th>
<th>Inactive Carrier State</th>
<th>Reactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Minimal inflammation and fibrosis</td>
<td>Chronic active inflammation</td>
<td>Mild hepatitis and minimal fibrosis</td>
<td>Active inflammation</td>
</tr>
</tbody>
</table>

Optimal treatment times
Goals and Benefits of Treatment

• **Prevention of long-term negative clinical outcomes** (e.g., cirrhosis, liver transplantation, HCC, death) by durable suppression of HBV DNA

• **Primary endpoint**
  – Sustained decrease in serum HBV DNA level to undetectable

• **Secondary endpoints**
  – Decrease or normalize serum ALT
  – Improve liver histology
  – Induce HBeAg loss or seroconversion in HBeAg-positive disease
  – Induce HBsAg loss or seroconversion

• **Treatment is often long term or lifelong**, particularly in HBeAg-negative patients
Information Needed to Make Treatment Decision

- HBeAg
- ALT
- HBV DNA
- Liver histology
- Family history?
Chronic Hepatitis B Disease Types

• HBeAg positive
  – Also known as “wild type”
  – Antibody to HBeAg negative
  – HBV DNA > 20,000 IU/mL (> $10^5$ copies/mL)

• HBeAg negative
  – Also known as “precore mutant”
  – Antibody to HBeAg positive
  – HBV DNA > 2000 IU/mL (> $10^4$ copies/mL)

Liver Biopsy

• Establishes disease baseline before initiation of therapy
• Helps to exclude other causes of liver disease
• More sensitive and accurate than ALT
• May be considered in patients who meet criteria for chronic hepatitis

• Limitations
  • Invasive procedure
  • Sampling error
  • Interobserver variability
HBV DNA Testing

• Indicates chronic hepatitis when still positive 6 mos after diagnosis of acute HBV infection
  – Can differentiate chronic, inactive carrier (< 2000 IU/mL) vs resolved HBV infection (undetectable)
• Change in HBV DNA level used to monitor response to therapy
• Increasing HBV DNA level during antiviral therapy indicates emergence of resistant variants
• HBV DNA level correlates with disease progression

2009 AASLD Guidelines: Treatment Candidacy for HBeAg-Positive Patients

HBsAg positive

HBeAg positive

ALT < 1 x ULN
HBV DNA < 20,000 IU/mL
q3-6 mos ALT
q6-12 mos HBeAg

ALT 1-2 x ULN
HBV DNA > 20,000 IU/mL
q3 mos ALT
q6 mos HBeAg
Consider biopsy if persistent or older than 40 yrs of age
Treat as needed

ALT > 2 x ULN
HBV DNA > 20,000 IU/mL
q1-3 mos ALT, HBeAg
Treat if persistent
Liver biopsy optional
Immediate treatment if jaundice or decompensated

2009 AASLD Guidelines: Treatment Candidacy for HBeAg-Negative Patients

**HBsAg positive**

**HBeAg negative**

**ALT < 1 x ULN**
- HBV DNA < 2000 IU/mL
  - q3 mos ALT x 3, then q6-12 mos if ALT still < 1 x ULN

**ALT 1-2 x ULN**
- HBV DNA 2000-20,000 IU/mL
  - q3 mos ALT and HBV DNA
  - Consider biopsy if persistent
  - Treat as needed

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

## Treatment Criteria for Chronic HBV Infection: Comparison of Guidelines

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>HBeAg Positive</th>
<th>HBeAg Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBV DNA, IU/mL</td>
<td>ALT</td>
</tr>
<tr>
<td>APASL 2008</td>
<td>≥ 20,000</td>
<td>&gt; 2 x ULN</td>
</tr>
<tr>
<td>AASLD 2009</td>
<td>&gt; 20,000</td>
<td>&gt; 2 x ULN</td>
</tr>
<tr>
<td>EASL 2012</td>
<td>&gt; 2000</td>
<td>&gt; ULN</td>
</tr>
</tbody>
</table>

Liaw 2008, Lok 2009, EASL HBV
To treat or Not to Treat: That is the Question

• Question is really **when** to treat: now versus later
• All HBV carriers are potential treatment candidates
• A patient who is not a treatment candidate now can be a treatment candidate in the future
  – Changes in HBV replication status and/or activity/stage of liver disease
  – Availability of new or improved treatments
Treatment of Chronic Hepatitis B in Special Populations

• Treatment-experienced patients
• Patients with advanced disease stage, especially decompensated cirrhosis
• Women contemplating pregnancy soon
• Women who are pregnant
Potential Barriers to HBV Treatments

- Patient resistance or cultural beliefs about treatment
- Potential adverse effects (particularly interferon)
- Challenges with long-term therapy
- Understanding endpoints and monitoring strategies
- Lack of symptoms
- Lack of ability to cure disease with current regimens in most patients
- Adherence
HBV Treatment Options

- Lamivudine
- Adefovir
- Peginterferon alfa-2a
- Entecavir
- Telbivudine
- Tenofovir
Current Guideline Recommendations for First-line Therapy

- Peginterferon alfa-2a
  - Exceptions: pregnancy, chemotherapy prophylaxis, decompensated cirrhosis, acute infection
- Entecavir
- Tenofovir

Not head-to-head trials; different patient populations and trial designs

<table>
<thead>
<tr>
<th>Drug Generation</th>
<th>Yr 1</th>
<th>Yr 2</th>
<th>Yr 3</th>
<th>Yr 4</th>
<th>Yr 5</th>
<th>Yr 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st LAM</td>
<td>24%</td>
<td>38%</td>
<td>49%</td>
<td>67%</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>2nd ADV</td>
<td>0%</td>
<td>3%</td>
<td>11%</td>
<td>18%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>LdT</td>
<td>4%</td>
<td>17%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd ETV</td>
<td>0.2%</td>
<td>0.5%</td>
<td>1.2%</td>
<td>1.2%</td>
<td>1.2%</td>
<td>1.2%</td>
</tr>
<tr>
<td>TDF</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADV, adeovir; ETV, entecavir; LAM, lamivudine; LdT, telbivudine; TDF, tenofovir.
Selection of Entecavir vs Tenofovir: Either Is an Excellent Choice for Most Patients

![Graph showing comparison between Entecavir and Tenofovir in response rates.]

**Response at Wk 48-52 (%)**

- **HBeAg positive**
  - HBeAg seroconversion: 21 Entecavir, 21 Tenofovir
  - HBsAg loss: 2 Entecavir, 3 Tenofovir

- **HBeAg negative**
  - HBsAg loss: <1 Entecavir, 0 Tenofovir
How to Use Entecavir or Tenofovir

• Dosage and administration
  – Entecavir: oral administration
    • Patients naive to lamivudine therapy: 0.5 mg QD
    • Patients who are refractory/resistant to lamivudine: 1.0 mg QD
    • Dose adjustment needed if eGFR < 50 mL/min
  – Tenofovir: oral administration
    • 300 mg QD
    • Dose adjustment needed if eGFR < 50 mL/min

<table>
<thead>
<tr>
<th>Setting</th>
<th>Anti-HBV Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decompensated cirrhosis</td>
<td>• Entecavir preferred</td>
</tr>
<tr>
<td></td>
<td>• Tenofovir may be appropriate</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>• Entecavir preferred (with dose modification)</td>
</tr>
<tr>
<td>Pregnancy, woman of child-bearing age planning pregnancy in the near term</td>
<td>• Tenofovir preferred</td>
</tr>
<tr>
<td>Woman of child-bearing age wishing to eradicate virus prior to pregnancy</td>
<td>• Peginterferon alfa-2a or peginterferon alfa-2b</td>
</tr>
<tr>
<td>HIV coinfection</td>
<td>• Tenofovir plus emtricitabine or lamivudine</td>
</tr>
</tbody>
</table>
## Duration and Endpoints of Therapy for Chronic Hepatitis B Infection

<table>
<thead>
<tr>
<th>Agents</th>
<th>Monitoring Recommendations During Treatment</th>
<th>Duration of Therapy</th>
<th>Treatment Endpoints</th>
</tr>
</thead>
</table>
| Nucleotide analogues| • Liver chemistry every 12 wks  
• HBV DNA every 12-24 wks (less frequent monitoring may be warranted with entecavir and tenofovir)  
• HBeAg/anti-HBe every 24 wks  
• Serum creatinine every 12 wks for patients receiving adefovir or tenofovir  
• HBsAg every 6-12 mos | HBeAg-Positive Patients  
6 mos after HBeAg seroconversion, undetectable serum HBV DNA and appearance of anti-HBe  
Until HBsAg loss | HBeAg-Positive Patients  
HBsAg loss, HBV DNA undetectability, ALT normalization  
HBsAg loss, HBV DNA undetectability, ALT normalization |
| Peginterferon alfa   | • Liver chemistry and CBC every 4 wks  
• HBV DNA and TSH every 12 wks  
• HBeAg/anti-HBe every 24 wks  
• HBsAg every 6 mos | 48 wks | HBeAg loss or seroconversion with concomitant HBV DNA < 2000 IU/mL, HBsAg loss  
Undetectable HBV DNA, HBsAg loss |

## Options for Treatment Modification in the Case of a Suboptimal Response

Based on Known Data on Cross-Resistance

<table>
<thead>
<tr>
<th>Nucleo(s)otide Analogue</th>
<th>AASLD Recommendations[Lok 2009]</th>
<th>EASL Recommendations[EASL HBV]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>• Add <strong>tenofovir</strong> or <strong>adefovir</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Switch to <strong>tenofovir</strong> plus <strong>emtricitabine</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• If <strong>tenofovir</strong> not available, add <strong>adefovir</strong></td>
<td></td>
</tr>
<tr>
<td>Adefovir</td>
<td>• Add <strong>lamivudine</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Switch to <strong>tenofovir</strong> plus <strong>emtricitabine</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• If <strong>tenofovir</strong> not available, switch to or add <strong>entecavir</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• If patient was nucleos(t)ide analogue naive before <strong>adefovir</strong>, switch to <strong>entecavir</strong> or <strong>tenofovir</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• If patient had previous <strong>lamivudine</strong> resistance, switch to or add <strong>tenofovir</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• If <strong>tenofovir</strong> not available, add <strong>adefovir</strong></td>
<td></td>
</tr>
<tr>
<td>Telbivudine</td>
<td>• Add <strong>tenofovir</strong> or <strong>adefovir</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Switch to <strong>tenofovir</strong> plus <strong>emtricitabine</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• If <strong>tenofovir</strong> not available, add <strong>adefovir</strong></td>
<td></td>
</tr>
<tr>
<td>Entecavir</td>
<td>• Switch to <strong>tenofovir</strong> or <strong>tenofovir</strong> plus <strong>emtricitabine</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• If <strong>tenofovir</strong> not available, add <strong>adefovir</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• If <strong>tenofovir</strong> not available, add entecavir, telbivudine, lamivudine, or emtricitabine</td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>• N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If <strong>tenofovir</strong> not available, add entecavir, telbivudine, lamivudine, or emtricitabine</td>
</tr>
</tbody>
</table>
# PegIFN vs Nucleos(t)ide Analogues

<table>
<thead>
<tr>
<th>PegIFN</th>
<th>Con</th>
<th>Nucleos(t)ide Analogues</th>
<th>Pro</th>
<th>Con</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pro</strong></td>
<td></td>
<td></td>
<td><strong>Pro</strong></td>
<td></td>
</tr>
<tr>
<td>- Finite course of therapy</td>
<td>- SQ administration</td>
<td>- PO administration</td>
<td>- Need for long-term or indefinite therapy</td>
<td></td>
</tr>
<tr>
<td>- No resistance</td>
<td>- Frequent AEs</td>
<td>- Infrequent AEs</td>
<td>- Potential for drug resistance</td>
<td></td>
</tr>
<tr>
<td>- Higher rate of HBeAg loss in 1 yr</td>
<td>- Contraindicated in patients with cirrhosis, in pregnancy, with acute hepatitis B, and who are immunosuppressed</td>
<td>- Safe at all stages of disease, including decompensated cirrhosis†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Higher rate of HBsAg loss with short duration therapy*</td>
<td></td>
<td>- Safe in immunocompromised populations</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Selected drugs probably safe in pregnancy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
When to Consider PegIFN

- Favorable predictors of response\(^{(1,2)}\): low HBV DNA levels, high ALT, Geno A or B > C or D\(^{(3-5)}\), minimal disease

- Specific patient demographics\(^{(1,2)}\):
  - young people
  - females considering pregnancy soon
  - absence of comorbidities
  - patient preference\(^{(1,2)}\)
  - concomitant HCV infection

Treatment of Chronic Hepatitis B in Special Populations

- Treatment-experienced patients
- Patients with advanced disease stage, especially decompensated cirrhosis
- Women contemplating pregnancy soon
- Women who are pregnant
Considerations in Women of Childbearing Age

- Timing of plans for pregnancy
- Uncertainty regarding safety of antiviral medications in pregnancy
- Careful discussion with patient and spouse regarding benefits vs risks
- Indications for treatment
  - Start now: advanced fibrosis/cirrhosis, severe flares/persistently high ALT
  - Defer: no/mild fibrosis, normal/minimally elevated ALT
Which Drug to use

• FDA classification: based on in vitro and animal studies
  – Pregnancy class B: telbivudine and tenofovir
  – Pregnancy class C: interferon, adefovir, entecavir, and lamivudine

• Human data:
  – Antiretroviral pregnancy registry: safety established for lamivudine and tenofovir, including exposure in first trimester\(^1\)
  – Clinical studies of antiviral therapy to prevent perinatal transmission: safety established for lamivudine and telbivudine, mainly exposure in third trimester\(^2\)-\(^5\)

Incidence of Birth Defects With in Utero Exposure to HBV Nucleos(t)ide Analogue

• Data derived from Antiretroviral Pregnancy Registry, 1/1989 - 7/2012\textsuperscript{[6]}
  – International, voluntary, prospective, exposure-registration cohort
  – Data on exposure in HBV-monoinfected mothers began in 1/2003

<table>
<thead>
<tr>
<th>Regimen Containing</th>
<th>First Trimester</th>
<th>Second or Third Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exposed, n</td>
<td>Birth Defects, % (95% CI)</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>4185</td>
<td>3.2 (2.7-3.8)</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>1612</td>
<td>2.4 (1.7-3.3)</td>
</tr>
</tbody>
</table>

• Metropolitan Atlanta Congenital Defects Program, a population-based birth defects surveillance program administered by CDC\textsuperscript{[6,7]}
  – Overall birth defects: 2.72% (95% CI: 2.68-2.76)

Antiviral Therapy for Chronic HBV Infection in Women Considering Pregnancy

• Safety to fetus, including exposure during first trimester
  – Lamivudine, tenofovir, telbivudine
• Risk of drug resistance
  – Lamivudine > telbivudine > tenofovir
• Preferred drug: tenofovir
  – Established safety; potent; low risk of drug resistance
• Benefit vs risk discussed with patient and spouse
  – Inform if become pregnant
Women Who Become Pregnant While Receiving Antiviral Therapy

• When continuing treatment, evaluate for safety
  – Tenofovir: continue
  – Lamivudine or telbivudine: continue if HBV DNA is undetectable
    • Consider switching to tenofovir if HBV DNA remains detectable to prevent breakthrough during pregnancy
  – Adefovir, entecavir, or pegIFN: stop and switch to tenofovir

• When stopping or switching, monitor for hepatic flares

• Breastfeeding: existing data suggests tenofovir is safe
Preventing Perinatal HBV Transmission: Why Is It So Important?

- Risk of progression to chronic infection is inversely related to age at time of infection

![Progression to Chronic Infection](chart)

Prevention of Perinatal HBV Transmission

• Cornerstone: HBIG + HBV vaccine
  – HBIG + first dose vaccine within 12 hrs of birth, different sites
• Efficacy: ~ 95%
• Reasons for failure
  – Delay in administration of HBIG and first dose of vaccine
  – Failure to complete vaccine series
  – Mother HBeAg positive and/or high HBV DNA
Perinatal HBV Transmission Is Related to Maternal HBV DNA Level

- Australian study with 100 pregnant woman
- All infants received HBIG + first dose of HBV vaccine within 12 hrs of birth and additional doses of HBV vaccine at 2, 4, and 6 months
- No HBV transmission was observed if the mother’s HBV DNA level was < $10^8$ copies/mL
- HBV transmission occurred in 4/47 infants (8.5% rate) if mother’s HBV DNA was > $10^8$ copies/mL

TDF vs TDF/FTC in Patients With High HBV DNA, Normal ALT

Prospective, randomized, double-blind, phase II trial

 Patients with chronic HBV, normal ALT, HBV DNA $\geq 1.7 \log_{10}$ IU/mL (N = 126)

TDF 300 mg + Placebo (n = 64)

TDF 300 mg + FTC 200 mg (n = 62)

Primary endpoint: HBV DNA $< 69$ IU/mL at Wk 192

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>TDF</th>
<th>TDF/FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yrs (SD)</td>
<td>33 (9.5)</td>
<td>33 (11.2)</td>
</tr>
<tr>
<td>Asian race, %</td>
<td>87.5</td>
<td>90.3</td>
</tr>
<tr>
<td>Mean HBV DNA, log$_{10}$ IU/mL (SD)</td>
<td>9.2 (0.4)</td>
<td>9.2 (0.4)</td>
</tr>
<tr>
<td>HBV genotype, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- B</td>
<td>51.6</td>
<td>51.6</td>
</tr>
<tr>
<td>- C</td>
<td>37.5</td>
<td>45.2</td>
</tr>
<tr>
<td>- Other</td>
<td>10.9</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Efficacy and Safety of TDF vs TDF/FTC in Pts With High HBV DNA, Normal ALT

- Higher rate of HBV DNA suppression with TDF/FTC
  - No significant difference in HBeAg or HBsAg loss
- Both regimens well tolerated; no grade 3/4 AEs
  - No Cr increases > 0.5 mg/dL or CrCL decreases to < 50 mL/min
  - ALT flare in 1 TDF pt (1.6%), no TDF/FTC pts
- No resistance detected in 69 pts who remained viremic

<table>
<thead>
<tr>
<th>Wk 192 Efficacy, %</th>
<th>TDF (n = 64)</th>
<th>TDF/FTC (n = 62)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA &lt; 69 IU/mL</td>
<td>55</td>
<td>76</td>
<td>.016</td>
</tr>
<tr>
<td>HBeAg loss</td>
<td>6</td>
<td>2</td>
<td>.365</td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td>5</td>
<td>0</td>
<td>.244</td>
</tr>
<tr>
<td>HBsAg loss/seroconversion</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

REVEAL-HBV: Clearance of HBV DNA, not HBeAg or HBsAg, Reduces Risk of HCC

- REVEAL-HBV study cohort (N = 2946; aged 30-65 yrs)
- HBV DNA suppression independently associated with significantly reduced risk of HCC
  - Pts with HBeAg suppression (n = 185) still had high HBV DNA levels and still at high risk of HCC
  - HBsAg suppression not associated with reduced incidence of HCC, but study not powered to detect difference
- Greatest reduction in HCC incidence observed among pts with high baseline HBV DNA (≥ 100,000 copies/mL) who cleared HBV DNA during follow-up
  - HCC incidence highest in pts HBeAg seropositive throughout follow-up
Long-Term Tenofovir DF Therapy for Chronic HBV Infection and HCC Risk

Randomization 2:1

Study 103* Hepatitis BeAg positive – treatment naïve
Study 102* Hepatitis BeAg negative – Lamivudine naïve or Treatment experienced

- Current analysis
  - Compare observed HCC incidence with the predicted HCC incidence based on the REACH-B risk calculator
    - Primary analysis: noncirrhotic patients (n = 482)
    - Sensitivity analysis: cirrhotic patients (n = 152)

*Pretreatment liver biopsy. Other eligibility criteria: age 18-69 years, compensated liver disease, HBV DNA >10^6 copies/mL, ALT ≥2 x ULN and <10 x ULN, Knodell necroinflammatory score ≥3, seronegative for HIV, HDV, and HCV.
†If HBV DNA ≥400 copies/mL, option to add emtricitabine to tenofovir DF in a fixed-dose tablet.

Long-Term Tenofovir DF Therapy and HCC Risk: Summary

- Incidence of HCC in Studies 102 and 103
  - Lower than predicted by the REACH-B model
  - Non-cirrhotics
    - Effect of tenofovir DF become noticeable at approximately 2 years, significant at 6 years
  - Cirrhotics
    - Effect of tenofovir DF less pronounced

- Limitations
  - No placebo arms
  - Patients with active liver disease
  - Relatively small number of cirrhotics
  - REACH-B is designed for non-cirrhotics and may underestimate risk in cirrhotics

Histologic Outcomes With Long-term Tenofovir Treatment for Hepatitis B

- 5-yr on-treatment analysis from 2 long-term tenofovir studies (N = 348 with paired biopsies)
  - HBeAg-negative (Study 102) and HBeAg-positive (Study 103) patients
- 96% of patients with paired biopsies showed histologic improvement or no worsening of fibrosis

Conclusions

• Nucleos(t)ide analogues offer safe and effective treatment for chronic hepatitis B
• Long term use may result in regression of fibrosis/cirrhosis in the majority of pts
• Effective on-treatment viral suppression, but viral rebound occurs often observed after stopping therapy
• Must monitor viral level to assess for persistent viral replication and to assess for resistance