Update on Non-HCV Viral Hepatitis

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DISCLOSURES

- **Formal Advisor**: none
- **Research Activities**: Gilead Sciences. Ocera
- **Speaker’s Bureau**: none
- **Full-time/Part-time employment**: none
- **Consultant**: none
- **Ownership Interest (stock options or other)**: none
Outline

- A Few Highlights
  - Hepatitis A, D and E
- Hepatitis B
  - Hepatitis B Treatment Guidelines 2016
  - Towards a “Cure”
  - Tenofovir Alafenamide
## Type of Hepatitis

<table>
<thead>
<tr>
<th>Source of virus</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
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</thead>
<tbody>
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<td>feces</td>
<td></td>
<td>blood/</td>
<td>blood/</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>blood-derived</td>
<td>blood-derived</td>
<td>blood-derived</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>body fluids</td>
<td>body fluids</td>
<td>body fluids</td>
<td></td>
</tr>
<tr>
<td>Route of transmission</td>
<td>fecal-oral</td>
<td>percutaneous permucosal</td>
<td>percutaneous permucosal</td>
<td>percutaneous permucosal</td>
<td>fecal-oral</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Prevention</td>
<td>pre/post-exposure immunization</td>
<td>pre/post-exposure immunization</td>
<td>blood donor screening; risk behavior modification</td>
<td>pre/post-exposure immunization; risk behavior modification</td>
<td>ensure safe drinking water</td>
</tr>
</tbody>
</table>
Hepatitis A Virus
Geographic Distribution of HAV Infection

Anti-HAV Prevalence

- **High**
- **Intermediate**
- **Low**
- **Very Low**
Hepatitis A - Epidemiology

- Incidence has decreased since implementation of vaccination
  - from 6 to 0.4 cases per 100,000 between 1999 and 2014
- Vaccine implementation:
  - 1996 for those at increased risk
  - 1999 for children in states with high incidence
  - 2006 in all infants
Hepatitis A - Clinical Features

- Incubation period: Average 30 days
  Range 15-50 days

- Jaundice by age group:
  <6 yrs, <10%
  6-14 yrs, 40%-50%
  >14 yrs, 70%-80%

- Complications:
  Fulminant hepatitis (<1%)
  Cholestatic hepatitis (<5%)
  Relapsing hepatitis (<10%)
  Autoimmune hepatitis

- Chronic sequelae:
  None
Hepatitis A – Fulminant Hepatic Failure

- Occurs in <1% of cases
- More commonly in those with underlying liver disease, especially HCV
- In one study, 432 with HCV, hepatitis A superinfection occurred in 17
  - 7 developed fulminant liver failure and 6/7 died
- Now recommended to vaccinate patients with chronic liver disease

Hepatitis D (Delta) Virus

- δ antigen
- HBsAg
- RNA
Hepatitis D - Clinical Features

- Individuals with hepatitis D are *always* dually infected with HDV and HBV
Hepatitis D - Clinical Features

- **Coinfection**
  - severe acute disease.
  - low risk of chronic infection

- **Superinfection**
  - usually develop chronic HDV infection.
  - high risk of severe chronic liver disease.
  - may present as an acute hepatitis
Hepatitis D - Prevention

- HBV-HDV Coinfection
  - Pre or post-exposure prophylaxis to prevent HBV infection

- HBV-HDV Superinfection
  - Education to reduce risk behaviors among persons with chronic HBV infection
Hepatitis E - Epidemiologic Features

- Outbreaks associated with faecally contaminated drinking water
- Large epidemics have occurred in the Indian subcontinent, USSR, China, Africa and Mexico
- In US and other nonendemic areas
  - low prevalence of anti-HEV (<2%)
  - outbreaks of hepatitis E have not been documented to occur
  - source of infection for these persons is unknown
Hepatitis E - Clinical Features

- Incubation period: Average 40 days
  Range 15-60 days

- Case-fatality rate: Overall, 1%-3%
  Pregnant women, 15%-25%

- Illness severity: Increased with age

- Chronic sequelae: None identified
Follow general precautions for prevention of travelers' diarrhea

Avoidance of
- water of unknown purity
- food from street vendors
- raw or undercooked seafood, meat or pork products, raw vegetables

Efficacy of immune globulin not established

Vaccine
- Only licensed in China
Hepatitis B Virus
Case 1

- 22 year old Chinese woman born in China
  - c/o fatigue and nausea
- Social History
  - Immigrated to the US at the age of 2
- O/E
  - Normal exam

Would you screen this patient for hepatitis B?
Case 2

- 30 yr old white male comes in for a routine check up
- Reports no problems with his health
- Family History
  - Sister, whom he shares an apartment with, has chronic Hepatitis B
- O/E
  - No stigmata of chronic liver disease
- *Would you screen this patient for hepatitis B?*
Case 3

- 47 year old woman born in the US comes in for annual physical

- Social History
  - Parents immigrated from Korea

- O/E
  - Normal exam

- *Would you screen this patient for hepatitis B?*
PREVALENCE OF HBV: GLOBAL ESTIMATES

HBsAg Prevalence
- High (>8%)
- Intermediate (2%-7%)
- Low (<2%)

HBV Infection in the United States

- Revised HBV prevalence in the United States taking into account recent estimates of foreign-born persons
  - 847,145 to 2,243,757 persons with chronic HBV
  - Average chronic HBV prevalence rate among foreign-born persons living in the United States is 2.0% to 5.4%

Estimated HBV Prevalence Among Foreign-Born Americans (2009)

Foreign-Born Americans: 13.6% of General Population

Candidates for Screening for HBV

- Persons born in high endemic areas (≥2% prevalence)
- Household and sexual contacts of HBsAg-positive persons
- US born children of immigrants from high-risk areas
- Persons who have ever injected drugs
- Persons with multiple sexual partner, or history of STDs
- Men who have sex with men
- Inmates of correctional facilities
- Individuals infected with HIV or HCV
- Patients undergoing dialysis
- All pregnant women
- Individuals with chronically elevated ALT/AST
4 PHASES OF CHRONIC HEPATITIS B (CHB)

1. **Immune-tolerant phase**
   - HBeAg-positive (anti-HBe-negative); very high HBV DNA; normal ALT and histology

2. **HBeAg-positive immune-active phase (anti-HBe negative)**
   - Elevated ALT and HBV DNA in conjunction with liver injury
   - *Wild-type virus*
   - Spontaneous HBeAg seroconversion (HBeAg loss/gain anti-HBe)
     - May occur spontaneously (4% to 12% per year)
     - Associated with a decrease of viral replication and inflammatory activity
     - Currently an endpoint of treatment in this group with prolonged therapy
     - Up to 20% who clear HBeAg have ≥1 HBeAg reversions
     - Marks transition to Inactive CHB phase

3. **Inactive CHB (non/low-replication)**
   - HBeAg negative and anti-HBe positive
   - Undetectable/low HBV DNA
   - Normal ALT
   - Minimal necroinflammation; degree of fibrosis variable

4. **HBeAg-negative immune reactivation phase**
   - HBeAg negative and anti-HBe positive
   - Elevated/fluctuating ALT and HBV DNA
   - Active inflammation on liver biopsy
   - Genetic mutations at *precore or core promoter regions*
   - Treatment endpoint is loss of HBsAg
   - Occurs at a low rate with current therapies

CASES

• Case 1: 22 year old Chinese female
  • HBV DNA: 33,000,000 IU/mL, ALT 12 U/L
  • *Immune-tolerant phase*

• Case 2: 30 yr old white male whose sister has chronic hepatitis B
  • HBeAg+, HBV DNA 1,263,500 IU/mL, ALT 128 U/L
  • *HBeAg-positive immune-active phase*

• Case 3: 47 year old female with Korean born parents
  • HBeAg-, HBV DNA: 800 IU/mL, ALT: 17 U/L
  • *Inactive CHB (non/low-replication)*
HBV Treatment

Hepatitis B Treatment Guidelines 2016
Chronic HBV Treatment: Guidelines Development

- **AASLD**
  - Independent panel of 7 hepatologists (6 US, 1 Canada)
  - Evidence-based recommendations from literature
    - Multiple systematic reviews performed
    - Recommendations graded by weight of evidence

Chronic HBV: Goals of Therapy

- Achieve
  1. Sustained suppression of HBV replication
  2. Remission of hepatic disease
  3. Prevent the development of cirrhosis, hepatic failure, and hepatocellular carcinoma

- HBV is *controlled* by limiting viral replication (not “cured”)

- Control-need prolonged therapy (many years)

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*HBV ccc DNA persists, making HBV incurable with current treatments.*
# Approved Treatments for HBV

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Manufacturer</th>
<th>Year Approved for HBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon alfa-2b</td>
<td>Schering Corporation</td>
<td>1991</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>GlaxoSmithKline</td>
<td>1998</td>
</tr>
<tr>
<td>Adefovir dipivoxil</td>
<td>Gilead Sciences</td>
<td>2002</td>
</tr>
<tr>
<td>Entecavir</td>
<td>Bristol-Myers Squibb</td>
<td>2005</td>
</tr>
<tr>
<td>Peginterferon alfa-2a</td>
<td>Hoffmann La-Roche</td>
<td>2005</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>Idenix</td>
<td>2006</td>
</tr>
<tr>
<td>Tenofovir DF</td>
<td>Gilead Sciences</td>
<td>2008</td>
</tr>
<tr>
<td><strong>Tenofovir Alafenamide (TAF)</strong></td>
<td><strong>Gilead Sciences</strong></td>
<td><strong>2016</strong></td>
</tr>
</tbody>
</table>
AASLD Guidelines (2016): Treatment *Recommendations*: First-Line Therapy

HBeAg Positive or Negative Chronic HBV

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Not Preferred*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir DF</td>
<td>Adefovir</td>
</tr>
<tr>
<td>Entecavir</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>Peg-IFN alfa-2a**</td>
<td>Telbivudine</td>
</tr>
</tbody>
</table>

**Contraindicated in decompensated Cirrhotics; finite therapy**

*Due to high risk of resistance*

AASLD Guidelines (2016):
Immune-Tolerant HBV

- Case 1: 22 year old Chinese female with very high viral load and normal ALT
- In general, antiviral therapy is not recommended
  - Test ALT every 6 months to monitor for potential transition to immune-active or -inactive HBV
- Select patients in whom antiviral therapy is suggested
  - >40 years of age with normal ALT, HBV DNA $\geq$1 million IU/mL, and significant necroinflammation or fibrosis (by liver biopsy)

Case 1: 22 year old Chinese female

- Returns 18 months later and is 28 weeks pregnant
- Repeat labs
  - ALT 14, HBV DNA 33,000,000 IU/mL
- All infants of all HBsAg-positive women should receive immunoprophylaxis
- Should antiviral therapy for chronic HBV infection be recommended during the 3rd trimester to prevent perinatal transmission?


- Antiviral therapy is **suggested** to reduce the risk of perinatal transmission of HBV in HBsAg-positive pregnant women with an HBV DNA level >200,000 IU/mL (limited data)
  - Experience is with lamivudine, telbivudine, and tenofovir
    - Started at 28-32 weeks of gestation in most of the studies

- Antiviral therapy is **not recommended** to reduce the risk of perinatal transmission of HBV in the HBsAg-positive pregnant woman with an HBV DNA ≤200,000 IU/mL

**AASLD Guidelines (2016): Immune-Active Chronic HBV Patients (HBeAg-Positive or -Negative)**

**Case 2: HBeAg+, HBV DNA 1,263,500 IU/mL, ALT 128 U/L**

<table>
<thead>
<tr>
<th>HBV DNA (IU/mL)</th>
<th>ALT (x ULN)</th>
<th>Management Recommendation</th>
<th>Preferred Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20,000 (HBeAg positive)</td>
<td>&lt;2</td>
<td>Observe</td>
<td>Tenofovir DF</td>
</tr>
<tr>
<td>&gt;2000 (HBeAg negative)</td>
<td></td>
<td>Consider biopsy in persons &gt;40 years of age, ALT persistently high normal, or with family history of HCC Consider treatment if biopsy shows moderate or severe inflammation or significant fibrosis</td>
<td>Entecavir, Peginterferon</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment recommended: Presence of extrahepatic manifestations independent of liver disease severity HBV DNA &gt;2000 IU/mL with cirrhosis (regardless of ALT level)</td>
<td></td>
</tr>
<tr>
<td>&gt;2</td>
<td>Observe for 3 to 6 months and treat if no spontaneous HBeAg loss Immediate treatment if icteric or clinical decompensation Consider liver biopsy prior to treatment if compensated Lamivudine and telbivudine not preferred due to high rate of resistance</td>
<td></td>
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</table>

IU/mL to copies/mL conversion:
- Versant HBV DNA 3.0 (bDNA): 1 IU/mL=5.2 copies/mL
- Cobas Amplicor HBV monitor: 1 IU/mL=5.6 copies/mL
- Cobas TaqMan 48 HBV: 1 IU/mL=5.8 copies/mL

Case 2: 30 yr old male whose sister has chronic hepatitis B

- Fibroscan suggests stage 2 fibrosis
- Starts tenofovir treatment
- At 6 months on treatment
  - ALT 25 and HBV DNA undetectable
  - Monitor labs every 6 months
- 4 years later
  - HBeAg is negative and anti-HBe is positive
- Can therapy be stopped?
AASLD Guidelines (2016): **HBeAg-Positive Patients Who Seroconvert to Anti-HBe on NA Therapy**

- **Suggest** discontinuation in non-cirrhotics
  - After a period of treatment consolidation: >12 mos normal ALT levels and undetectable serum HBV DNA
  - If stop therapy: monitor every 3 mos for at least 1 year

- **With cirrhosis** *suggest* indefinite antiviral therapy
  - Risk of decompensation and death
  - Discontinuation may be considered with HBsAg loss (insufficient evidence for definitive guidance)
  - If stop therapy: monitor monthly for 6 mos then every 3 mos

AASLD Guidelines (2016): Inactive CHB (non/low replication)

- Case 3: 47 year old female with very low viral load and normal ALT
- Fibroscan: F1 fibrosis
- Antiviral therapy is *not recommended* for persons without cirrhosis who are HBeAg negative with normal ALT and low-level viremia (<2000 IU/mL)

AASLD Guidelines (2016):  
**Inactive CHB (non/low replication)**

- **Case 3**: 47 year old female with very low viral load and normal ALT
- No treatment
- Should be monitored with ALT and HBV DNA every 6 months
- 5 years later
  - ALT 125, HBV DNA 100,000 IU/mL, HBeAg negative
  - Fibroscan: F2 fibrosis
- Do you treat her now?

# AASLD Guidelines (2016): Immune-Active Chronic HBV Patients (HBeAg-Positive or -Negative)

## Case 2: HBeAg+, HBV DNA 1,263,500 IU/mL, ALT 128 U/L

<table>
<thead>
<tr>
<th>HBV DNA (IU/mL)</th>
<th>ALT (x ULN)</th>
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<th>Preferred Drugs</th>
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<tr>
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<td>Consider biopsy in persons &gt;40 years of age, ALT persistently high normal, or with family history of HCC. Consider treatment if biopsy shows moderate or severe inflammation or significant fibrosis. Treatment recommended: Presence of extrahepatic manifestations independent of liver disease severity. HBV DNA &gt;2000 IU/mL with cirrhosis (regardless of ALT level).</td>
<td></td>
</tr>
<tr>
<td>&gt;2</td>
<td>Observe for 3 to 6 months and treat if no spontaneous HBeAg loss. Immediate treatment if icteric or clinical decompensation. Consider liver biopsy prior to treatment if compensated. Lamivudine and telbivudine not preferred due to high rate of resistance.</td>
<td>Tenofovir DF Entecavir Peginterferon</td>
<td></td>
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IU/mL to copies/mL conversion:
- Versant HBV DNA 3.0 (bDNA): 1 IU/mL=5.2 copies/mL.
- Cobas Amplicor HBV monitor: 1 IU/mL=5.6 copies/mL.
- Cobas TaqMan 48 HBV: 1 IU/mL=5.8 copies/mL.

AASLD Guidelines (2016):
Inactive CHB (non/low replication)

Case 3:
- Starts entecavir
- Within 6 months ALT is normal and DNA is reduced to 2200 IU/mL; at 12 months 1,900 IU/mL
- Monitor every 3 month viral loads:
  - 1,800; 800; 1250; 1100.
- Do you continue this antiviral?

AASLD Guidelines (2016): Management of Patients With Persistent Low-Level Viremia on NA Therapy

- Persistent HBV DNA <2000 IU/mL with entecavir or tenofovir DF
  - *Suggest* to continue monotherapy regardless of ALT
  - Insufficient evidence to advocate for adding a 2nd drug or switching to another drug in lieu of continuing monotherapy

AASLD Guidelines (2016): Duration of Antiviral Therapy for HBeAg-Negative Immune-Active HBV

- Suggest *indefinite* antiviral therapy for adults unless there is a competing rationale for discontinuation
  - **Non-cirrhotics**
    - Decision to discontinue therapy requires careful consideration of risks and benefits for health outcomes
  - **With cirrhosis**
    - Treatment discontinuation is not recommended (concerns for potential clinical decompensation and death)
- Treatment discontinuation may be considered with HBsAg loss (insufficient evidence for definitive guidance)
- If antiviral therapy is stopped, monitor every 3 months for at least 1 year

Future HBV Treatments

Towards Cure
The Current Goal: **Control** rather than cure

Suppression of virus

After prolonged period can stop treatment if:
- HBeAg+ patients if HBeAg seroconversion
- In a minority of HBeAg- patients

Rare loss of HBsAg
No clearance of cccDNA
The New Goal: **Functional Cure**

- **Finite Treatment Duration**
- **Cessation of All Treatment**
- **Absence of HBV DNA and HBsAg**
The New Goal: **Complete Cure**

- **Finite Treatment Duration**
- **Cessation of All Treatment**
- **Absence of HBV DNA and HBsAg**
- **Clearance of cccDNA**
Host Immune responses to chronic HBV offers opportunities for immunomodulation

Direct Immune Stimulation

Antiviral Cytokine

SB-9200

GS-9620

GS-4774 NASVAC

Increase CD8+ cells

Reduce Inhibition

CD8+ T cell

B cell

B-cell Stimulation

GS-9620

SB-9200
HBV Life Cycle offers many targets for Antivirals

- **Entry Inh** (Myrcludex-B)
- **NTCP**
- **cccDNA Inh**
- **Capsid Inh**
- **siRNA**
  - ARC-320
  - TKM-HBV
  - ALN-HBV
- **pgRNA**
- **Pol Inh**
  - TAF/TDF
  - Entecavir, etc
  - NV 3-778 Assembly
- **RT Step**
  - Core
  - HBe
  - HBs
  - HBx
- **HBsAg Secretion**
  - REP-2139
- **α-HBsAg**
New Concepts for HBV Therapy: Towards CURE Combining DAAs and Immune Therapies

![Graph showing changes in HBV DNA, HBsAg, and cccDNA over time with indicated therapy phases.]

Zoulim F (by permission)
Tenofovir Alafenamide

- **Prodrug of tenofovir DF**
  - Tenofovir DF is metabolized in plasma, then undergoes phosphorylation intracellularly to TFV-diphosphate (the active moiety)

- **Tenofovir AF is more stable in plasma/tissues than tenofovir DF**
  - Higher levels of TFV-diphosphate in target cells at lower doses than tenofovir DF

- **Tenofovir DF (but not tenofovir AF) actively enters renal tubular cells**
  - Tenofovir AF has a lesser effect on the proximal renal tubule

90% Lower TFV Levels in Plasma Minimizes Renal and Bone Effects While Maintaining High Potency for Suppressing HIV

Study 108: Tenofovir AF Versus Tenofovir DF in HBeAg-Negative Patients

### Phase 3

- **Double-blind**
- **HBeAg negative**
- **Anti-HBe positive**
- **Treatment-naïve and experienced**
- **HBV DNA >20K IU/mL**
- **ALT**
  - **Males:** >60 U/L
  - **Females:** >38 U/L

**Weekly Endpoint**

- **Primary Endpoint**
  - HBV DNA <29 IU/mL

**Treatment Groups**

- **TAF 25 mg qd (n=285)**
- **TDF 300 mg qd (n=140)**

---

**TAF**: tenofovir alafenamide.

**TDF**: tenofovir disoproxil fumarate.

**Baseline demographics:**
- **Male:** 61%.
- **Asian:** 72%.
- **Mean BMI:** 25 kg/m².
- **Treatment experienced:** 21%.
- **Mean HBV DNA:** 5.7 log₁₀ IU/mL.
- **Mean ALT:** 67 U/L.
- **FibroTest score ≥0.75:** 12%.

**HBV genotype:**
- **A/B/C:** 7%/24%/38%.
- **D/E/H:** 31%/2%/<1%.

Study 108: Treatment Outcomes With Tenofovir AF Versus Tenofovir DF in HBeAg-Negative Patients

- TAF met non-inferiority criteria for the proportion with HBV DNA <29 IU/mL
  - Treatment difference: +1.8% ($P=0.47$)
- TAF arm had higher rates of ALT normalization
- Qualified for resistance sequencing (n=4, 2 in each arm)
  - No resistance detected in either arm

Central laboratory ULN: males/females ($<43/≤34$ U/L) [≥69 years of age: males/females $<35/≤32$ U/L]  
AASLD criteria ULN: $≤30/≤19$ U/L.

Study 110: Treatment Outcomes With Tenofovir AF Versus Tenofovir DF in HBeAg-Positive Patients

Week 48 Outcomes

- **HBV DNA <29 IU/mL**
  - TAF (n=581): 64%
  - TDF (n=292): 67%
  - *Met non-inferiority criteria: treatment difference -3.6% (P=0.25).

- **HBV DNA Central Laboratory ALT Normalization**
  - TAF: 72%
  - TDF: 67%
  - P=NS

- **AASLD Criteria ALT Normalization**
  - TAF: 45%
  - TDF: 36%
  - P<0.01

- **Loss (n=565|285)**
  - TAF: 14%
  - TDF: 12%
  - P=NS

- **Seroconversion (n=565|285)**
  - TAF: 10%
  - TDF: 8%
  - P=NS

*Central laboratory ULN: males/females (≤43/≤34 U/L) [≥69 years of age: males/females ≤35/≤32 U/L]
AASLD criteria ULN: ≤30/≤19 U/L.

Study 108: Safety With Tenofovir AF Versus Tenofovir DF in HBeAg-Negative Patients

<table>
<thead>
<tr>
<th></th>
<th>TAF (n=285)</th>
<th>TDF (n=140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuations due to adverse events (%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Adverse events (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Serious</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>1*</td>
</tr>
<tr>
<td>Grade 3/4 laboratory abnormality (%)</td>
<td></td>
<td></td>
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<tr>
<td>≥1% incidence</td>
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<tr>
<td>ALT/ AST</td>
<td>3/3</td>
<td>3/3</td>
</tr>
<tr>
<td>Amylase</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>GGT</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Glucose (fasting)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total cholesterol/LDL elevation</td>
<td>1/5</td>
<td>0/&lt;1</td>
</tr>
<tr>
<td>Change in eGFR (mL/min)</td>
<td>-1.4†</td>
<td>-4.7</td>
</tr>
</tbody>
</table>

*51-year-old Asian man with cirrhosis died due to HCC at week 56. †P=0.004.

Studies 108: Changes in Spine and Hip BMD With TAF or TDF in HBeAg-Negative Patients

Spine BMD

<table>
<thead>
<tr>
<th>Treatment Week</th>
<th>TAF (n=285)</th>
<th>TDF (n=140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
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</tr>
<tr>
<td>24</td>
<td></td>
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</tr>
<tr>
<td>48</td>
<td></td>
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</tbody>
</table>

Hip BMD

<table>
<thead>
<tr>
<th>Treatment Week</th>
<th>TAF (n=285)</th>
<th>TDF (n=140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
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<tr>
<td>48</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TAF: tenofovir alafenamide.
TDF: tenofovir DF.

Conclusions

- Viral suppression with oral antiviral therapy can prevent disease progression and liver-related complications

- Current duration of antivirals is prolonged with high cost and risk of breakthrough from non-adherence/resistance

- Attempt to increase HBsAg loss and discontinue long-term therapy ⇒ “Functional Cure”

- Ultimate goal will be to develop therapy which can eliminate cccDNA ⇒ “Virological Cure”
Conclusions

- New targets for improved therapy through better understanding of HBV lifecycle and host immunity
- Different strategies may be needed for different phases of HBV infection, HBeAg status, disease severity and treatment status
- HBV Cure will ultimately require combinations which both inactivate cccDNA and restore host immune responses (overcome T-cell exhaustion of chronic HBV)