Management of Chronic Hepatitis B

M. J. Sonneveld, MD PhD
Resident Gastroenterology and Hepatology
Epidemiologist

Erasmus MC University Medical Center Rotterdam
The Netherlands
Disclosures

- Speakers fees: Roche, BMS, Gilead
- Advisory boards: Roche, BMS, Gilead, Fujirebio
- Research support: Roche, BMS, Gilead, Fujirebio
HBV – A Global Health Problem

• One-third of the world’s population has evidence of HBV infection
• Chronic hepatitis B affects 350-400 million people

World population 6 billion
2 billion people with evidence of HBV
Approximately 350 million with Chronic HBV (75% in Asia)
25–40% die of cirrhosis or liver cancer

McMahon, Semin Liver Dis 2005
Case 1

• 38 year old Chinese man

• HBeAg +, HBV DNA 200,000,000 IU/mL
• ALT 35 (<40)
• Fibroscan: F1

• Indication for therapy?
Case 2

- 58 year old Italian woman
- HBeAg -, anti-HBe +, HBV DNA 200 IU/mL
- ALT 35 (<40)
- Fibroscan: F4; ultrasound no sign of HCC
- Indication for therapy?
Who to treat?

- Goal of treatment is to prevent progression of liver inflammation to fibrosis/cirrhosis and HCC
Who to treat?

- Goal of treatment is to prevent progression of liver inflammation to fibrosis/cirrhosis and HCC.

- Risk of progression is determined by:
  - Viremia (HBV DNA / HBsAg levels)
  - Degree of liver inflammation (ALT, histology)
  - Degree of pre-existing fibrosis (liver biopsy, elastography)
### When to consider treatment?

<table>
<thead>
<tr>
<th>HBV Richtsnoer</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>Detectable</td>
<td>N/A</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>&gt; 2000</td>
<td>&gt; ULN</td>
<td>Moderate inflammation or fibrosis</td>
</tr>
<tr>
<td>&gt; 20,000</td>
<td>&gt; 2 x ULN</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Special groups:**
- HBeAg-positive chronic infection with HBV DNA $>10^7$ aged $>30$
- Chronic HBV infection with family history of HCC or extra-hepatic manifestations
- Pregnant women

Nederlands HBV richtsnoer 2018; EASL CPGs 2017
Case 1

• 38 year old Chinese man

• HBeAg +, HBV DNA 200,000,000 IU/mL
• ALT 35 (<40)
• Fibroscan: F1

• Indication for therapy?
Case 1

- 38 year old Chinese man
- HBeAg +, HBV DNA 200,000,000 IU/mL
- ALT 35 (<40)
- Fibroscan: F1
- Indication for therapy?
- Possibly
Case 2

- 58 year old Italian woman
- HBeAg -, anti-HBe +, HBV DNA 200 IU/mL
- ALT 35 (<40)
- Fibroscan: F4; ultrasound no sign of HCC
- Indication for therapy?
Case 2

- 58 year old Italian woman
- HBeAg -, anti-HBe +, HBV DNA 200 IU/mL
- ALT 35 (<40)
- Fibroscan: F4; ultrasound no sign of HCC
- Indication for therapy?
- Yes
Chronic Hepatitis B

How to treat?
Hepatitis B: treatment options

Peginterferon

Nucleos(t)ide analogues
Treatment options

Off-treatment sustained response: peginterferon

- **PEG-IFN**
  - HBeAg seroconversion
  - Low HBV DNA
  - Undetectable HBV DNA
  - HBsAg loss

Treatment maintained response: direct antivirals

- **Nucleos(t)ide analogue**
  - Undetectable HBV DNA during therapy
  - HBsAg loss

(years)
Mechanism of Action of Antivirals

Nucleos(t)ide analogues cause chain termination

Options:
- Lamivudine
- Adefovir
- Telbivudine
- Entecavir
- Tenofovir

Ganem, NEJM 2004
HBV cccDNA persists in hepatocytes despite antiviral therapy

Ganem, NEJM 2004
Case 1

- 38 year old Chinese man
- No relevant comorbidities
- HBeAg +, HBV DNA 200,000,000 IU/mL
- ALT 84
- Fibroscan: F1

- What NUC to start?
Case 2

- 58 year old Italian woman
- History: CKD (eGFR 39), hypertension
- HBeAg -, anti-HBe +, HBV DNA 200 IU/mL
- ALT 35 (<40)
- Fibroscan: F4; ultrasound no sign of HCC
- What NUC to start?
Hepatitis B: treatment options

Nucleo(s)tide analogues

- Lamivudine
- Adefovir
- Telbivudine
- Entecavir
- Tenofovir DF
- Tenofovir AF
Hepatitis B: treatment options

Nucleo(s) tide analogues

- Lamivudine
- Adefovir
- Telbivudine
  - Entecavir
  - Tenofovir DF
  - Tenofovir AF

Nucleos(t)ide analogues
Potent HBV DNA Suppression With Nucleos(t)ide Therapy

Long-term therapy with potent nucleos(t)ides leads to suppression in almost all pts.

Nearly all patients achieve undetectable HBV DNA during entecavir or tenofovir therapy in real-world setting.

Zoutendijk et al. Hepatology 2011; Arends & Sonneveld, Gut 2015
Tenofovir Alafenamide vs Disoproxil

## Antiviral efficacy of TAF vs TDF in HBV

### Study 108: HBeAg-Negative Pts\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Wk 48</th>
<th></th>
<th>Wk 96</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAF</td>
<td>94(\pm)268/285</td>
<td>93(\pm)130/140</td>
<td>90(\pm)257/285</td>
</tr>
<tr>
<td>TDF</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(P = .47^*\)

### Study 110: HBeAg-Positive Pts\(^2\)

<table>
<thead>
<tr>
<th></th>
<th>Wk 48</th>
<th></th>
<th>Wk 96</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAF</td>
<td>64(\pm)371/581</td>
<td>67(\pm)195/292</td>
<td>73(\pm)423/581</td>
</tr>
<tr>
<td>TDF</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(P = .25^*\)

---


*Adjusted for BL HBV DNA and PO antiviral treatment status.
Decline in renal function and bone mineral density with TDF and TAF

- Significantly smaller effect on renal function with TAF at Wk 48 and Wk 96 in HBeAg-negative pts\textsuperscript{[1]}

- Significantly smaller effect on spine BMD with TAF at Wk 48 and Wk 96 HBeAg-negative pts\textsuperscript{[1]}

Similar results seen with HBeAg-positive pts\textsuperscript{[2]}
So what to choose?

- The antiviral efficacy is comparable for ETV, TDF and TAF

- Issues that should be considered:
  - Risk of resistance with ETV (~1.2% @ 6yrs)
  - TDF is nephrotoxic and reduces bone mineral density
  - TAF has a favourable safety profile vs TDF (in HIV)
  - Cost

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost per month</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETV 0.5mg</td>
<td>€ 31,80</td>
</tr>
<tr>
<td>TDF 300mg</td>
<td>€ 37,35</td>
</tr>
<tr>
<td>TAF 25mg</td>
<td>€ 341,56</td>
</tr>
</tbody>
</table>

- Based on price and experience ETV and TDF are preferred options for naive patients without renal or bone disease
The choice of NUC for naive patients depends on comorbidity

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>1st choice</th>
<th>2nd choice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal Disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR 50 – 60 ml/min</td>
<td>ETV(^1)</td>
<td>TAF(^1)</td>
</tr>
<tr>
<td>eGFR &lt; 50 ml/min or hemodialysis</td>
<td>TAF(^2)</td>
<td>ETV(^2)</td>
</tr>
<tr>
<td>albuminuria / hypofosfatemia</td>
<td>ETV(^1)</td>
<td>TAF(^1)</td>
</tr>
<tr>
<td><strong>(at risk for) Bone disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of medicamention that impacts BMD</td>
<td>ETV(^1)</td>
<td>TAF(^1)</td>
</tr>
<tr>
<td>Osteoposis / history of osteoporotic fracture</td>
<td>ETV(^1)</td>
<td>TAF(^1)</td>
</tr>
</tbody>
</table>

1. Based on price and experience. 2. Because no dose-adjustment is required.

Case 1

- 38 year old Chinese man
- No relevant comorbidities
- HBeAg +, HBV DNA 200,000,000 IU/mL
- ALT 84
- Fibroscan: F1

- What NUC to start?
Case 1

- 38 year old Chinese man
- No relevant comorbidities
- HBeAg +, HBV DNA 200,000,000 IU/mL
- ALT 84
- Fibroscan: F1

- What NUC to start?

- ETV or TDF
Case 2

- 58 year old Italian woman
- History: CKD (eGFR 39), hypertension
- HBeAg -, anti-HBe +, HBV DNA 200 IU/mL
- ALT 35 (<40)
- Fibroscan: F4; ultrasound no sign of HCC
- What NUC to start?
Case 2

- 58 year old Italian woman
- History: CKD (eGFR 39), hypertension
- HBeAg -, anti-HBe +, HBV DNA 200 IU/mL
- ALT 35 (<40)
- Fibroscan: F4; ultrasound no sign of HCC

- What NUC to start?

- TAF
Disease Progression during LAM treatment of advanced HBV related liver disease

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Disease Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment (n=215)</td>
<td>21%</td>
</tr>
<tr>
<td>Resistant (n=209)</td>
<td>13%</td>
</tr>
<tr>
<td>No resistance (n=221)</td>
<td>5%</td>
</tr>
</tbody>
</table>

Liaw, NEJM 2004
Regression of cirrhosis during long-term tenofovir
HBV DNA suppression alone does not annihilate the risk of HCC

Years since NUC initiation

Cumulative probability of HCC

Log rank test: P<0.001

Annual HCC rate
- No cirrhosis: 0.5%
- Cirrhosis: 4%
- Dec. cirrhosis: 6%

High risk of HCC in cirrhosis with ETV or LAM

Log rank test: $P=0.999$

Cumulative probability of HCC

Years since NUC initiation

ETV

LAM

24%
HBsAg clearance remains essential despite HBV DNA suppression in NUC treated patients

Kim, Gut 2013
Clearance of HBsAg is rare in patients treated with nucleo(s)tide analogues

Pivotal international studies (integrated data)
HBsAg decline during long-term NUC therapy

<table>
<thead>
<tr>
<th></th>
<th>HBeAg-positive</th>
<th>HBeAg-negative</th>
<th>HBeAg-positive High ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years to HBsAg loss*</td>
<td>36.4 [9.6; 98.3]</td>
<td>38.9 [1.3; 80.5]</td>
<td><strong>19.5 [7.3; 99.9]</strong></td>
</tr>
</tbody>
</table>

Zoutendijk et al. AASLD 2010; Zoutendijk et al. JID 2011
40 years gone by...
Resistance rates through up to 8 years among nucleos(t)ide-naïve patients

Year 1  Year 2  Year 3  Year 4  Year 5  Year 8
LAM¹  23%  46%  55%  71%  80%  
ADV‡¹  0%  3%  11%  18%  29%  
LdT†²,³  5%  25%  -  -  -  
TDF⁴  0%  0% §  0% §  0% §  0% §  0% §  
ETV*⁵,⁶  <1%  <1%  1.2%  1.2%  1.2%  1.2%  

These trials used different populations, exclusion criteria, follow-up end points, and they were not head-to-head comparisons for all the drugs * Cumulative probabilities of resistance taken; † Naïve HBeAg (+) ; ‡ Naïve HBeAg(-); N/A not available

Pegylated Interferon Alfa for CHB
Case 1

- 38 year old Dutch man
- No relevant comorbidities
- HBeAg +, HBV DNA 1,000,000 IU/mL, genotype A
- ALT 110 (<40)
- Fibroscan: F1

Is he a good candidate for PEG-IFN?
One year of PEG-IFN induces HBeAg clearance in one third of patients

On-therapy HBV DNA suppression

Week

Mean log HBV DNA (geq/mL)

56 64 72 80

0 8 16 24 32 40 48

Janssen et al. Lancet 2005

HBeAg Seroconversion Rates at End of Follow-up

29% 29%

n=136 n=130

PEG-IFN α-2b + LAM (n=130)

PEG-IFN α-2b (n=136)

PEG-IFN α-2b
Peg-interferon has significant side-effects

<table>
<thead>
<tr>
<th>Frequency</th>
<th>SAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30%</td>
<td>Flu-like symptoms</td>
</tr>
<tr>
<td></td>
<td>headache</td>
</tr>
<tr>
<td></td>
<td>fatigue</td>
</tr>
<tr>
<td></td>
<td>fever</td>
</tr>
<tr>
<td></td>
<td>myalgia</td>
</tr>
<tr>
<td></td>
<td>trombocytopenia</td>
</tr>
<tr>
<td>1-30%</td>
<td>Anorexia</td>
</tr>
<tr>
<td></td>
<td>Erythema</td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
</tr>
<tr>
<td></td>
<td>Alopecia</td>
</tr>
<tr>
<td></td>
<td>Passivity</td>
</tr>
<tr>
<td></td>
<td>Diffucily focussing</td>
</tr>
<tr>
<td></td>
<td>agitation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency</th>
<th>SAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-30%</td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>diarrhea</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td>Smaakveranderingen</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>Polyneuropathy</td>
</tr>
<tr>
<td></td>
<td>Paranoia</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Retinopathy</td>
</tr>
<tr>
<td></td>
<td>Neuritis optica</td>
</tr>
<tr>
<td></td>
<td>Insults</td>
</tr>
<tr>
<td></td>
<td>Hearing loss</td>
</tr>
<tr>
<td></td>
<td>Libido decrease</td>
</tr>
<tr>
<td></td>
<td>Cardiototoxicity</td>
</tr>
</tbody>
</table>
Response to peginterferon confers an excellent prognosis

van Zonneveld, Hepatology 2004
Factors associated with response to PEG-IFN

<table>
<thead>
<tr>
<th>HBeAg positive*</th>
<th>HBeAg negative**</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV genotype A/B&gt;C/D*</td>
<td></td>
</tr>
<tr>
<td>HBV DNA &lt; 9 log copies/mL*</td>
<td>≤10⁹ copies/mL(200,000,000 IU/mL)</td>
</tr>
<tr>
<td>ALT &gt;2x ULN*</td>
<td>ALT &gt;2 x ULN</td>
</tr>
<tr>
<td>Older*</td>
<td>Younger</td>
</tr>
<tr>
<td>Female gender*</td>
<td>Female gender</td>
</tr>
</tbody>
</table>
## Rapid Evaluation for PEG-IFN Therapy

<table>
<thead>
<tr>
<th>HBV genotype</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALT</strong></td>
<td>≥2 x ULN and &lt;2 x ULN or ≥2 x ULN and &lt;2 x ULN</td>
<td>≥2 x ULN and &lt;2 x ULN or ≥2 x ULN and ≥9log</td>
</tr>
<tr>
<td><strong>HBV DNA (copies/ml)</strong></td>
<td>&lt;9log</td>
<td>≥9log</td>
</tr>
<tr>
<td><strong>Average chance of SVR</strong></td>
<td>57%</td>
<td>31%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HBV genotype</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALT</strong></td>
<td>≥2 x ULN and &lt;2 x ULN or ≥2 x ULN and &lt;2 x ULN</td>
<td>≥2 x ULN and &lt;2 x ULN or ≥2 x ULN and ≥9log</td>
</tr>
<tr>
<td><strong>HBV DNA (copies/ml)</strong></td>
<td>&lt;9log</td>
<td>≥9log</td>
</tr>
<tr>
<td><strong>Average chance of SVR</strong></td>
<td>36%</td>
<td>22%</td>
</tr>
</tbody>
</table>

Buster, Gastroenterology 2009
Rapid Evaluation for PEG-IFN Therapy

<table>
<thead>
<tr>
<th>HBV genotype</th>
<th>HBV DNA (copies/ml)</th>
<th>ALT</th>
<th>Average chance of SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>≥9log</td>
<td>&lt;2 x ULN and ≥9log or ≥2 x ULN and &lt;2 x ULN or &lt;2 x ULN and &lt;2 x ULN</td>
<td>36% 22% 16%</td>
</tr>
<tr>
<td>D</td>
<td>≥9log</td>
<td>≥2 x ULN and &lt;9log or ≥2 x ULN and ≥2 x ULN or &lt;2 x ULN and &lt;2 x ULN</td>
<td>17% 9% 6%</td>
</tr>
</tbody>
</table>

Buster, Gastroenterology 2009
Rapid Evaluation for PEG-IFN Therapy

HBV genotype

ALT
≥2 x ULN and <2 x ULN or <2 x ULN and ≥9log or ≥2 x ULN and <9log

HBV DNA (copies/ml)
<9log ≥9log ≥9log <9log ≥9log ≥9log

Average chance of SVR
57% 31% 23% 30% 28% 21%

HBV genotype

ALT
≥2 x ULN and <2 x ULN or <2 x ULN and ≥9log or ≥2 x ULN and <9log

HBV DNA (copies/ml)
<9log ≥9log ≥9log <9log ≥9log ≥9log

Average chance of SVR
36% 22% 16% 17% 9% 6%

Buster, Gastroenterology 2009
### Rapid Evaluation for PEG-IFN Therapy

#### HBV genotype

<table>
<thead>
<tr>
<th>ALT</th>
<th>HBV DNA (copies/ml)</th>
<th>Average chance of SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 x ULN and/or &lt;2 x ULN</td>
<td>&lt;9log</td>
<td>57%</td>
</tr>
<tr>
<td>≥2 x ULN</td>
<td>≥9log</td>
<td>31%</td>
</tr>
<tr>
<td>&lt;2 x ULN</td>
<td>≥9log</td>
<td>23%</td>
</tr>
<tr>
<td>&lt;2 x ULN</td>
<td>&lt;9log</td>
<td>30%</td>
</tr>
<tr>
<td>&lt;2 x ULN</td>
<td>≥9log</td>
<td>28%</td>
</tr>
<tr>
<td>&lt;2 x ULN</td>
<td>≥9log</td>
<td>21%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ALT</th>
<th>HBV DNA (copies/ml)</th>
<th>Average chance of SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 x ULN and/or &lt;2 x ULN</td>
<td>&lt;9log</td>
<td>36%</td>
</tr>
<tr>
<td>≥2 x ULN</td>
<td>≥9log</td>
<td>22%</td>
</tr>
<tr>
<td>&lt;2 x ULN</td>
<td>≥9log</td>
<td>16%</td>
</tr>
<tr>
<td>&lt;2 x ULN</td>
<td>&lt;9log</td>
<td>17%</td>
</tr>
<tr>
<td>&lt;2 x ULN</td>
<td>≥9log</td>
<td>9%</td>
</tr>
<tr>
<td>&lt;2 x ULN</td>
<td>≥9log</td>
<td>6%</td>
</tr>
</tbody>
</table>

*Buster, Gastroenterology 2009*
Case 1

- 38 year old Dutch man
- No relevant comorbidities
- HBeAg +, HBV DNA 1,000,000 IU/mL, genotype A
- ALT 110 (<40)
- Fibroscan: F1

- Is he a good candidate for PEG IFN?
Case 1

- 38 year old Dutch man
- No relevant comorbidities
- HBeAg +, HBV DNA 1,000,000 IU/mL, genotype A
- ALT 110 (<40)
- Fibroscan: F1

- Is he a good candidate for PEG IFN?
- Yes
HBsAg decline, more than HBV DNA, can distinguish between relapsers & responders to PEG-IFN

* HBV DNA undetectable by PCR 1 year post-treatment
** HBV DNA undetectable at EOT but detected in following 24 weeks

Moucari, Hepatology 2009
HBsAg based management algorithm for HBeAg-positive patients on PEG-IFN therapy

Sonneveld, Hepatology 2013
HBsAg based management algorithm for HBeAg-positive patients on PEG-IFN therapy

HBeAg-positive patient

- Geno A: No decline, NPV: 100%
- Geno B: >20,000 IU/mL, NPV: 92%
- Geno C: >20,000 IU/mL, NPV: 98%
- Geno D: No decline, NPV: 97%

WEEK 12

Sonneveld, Hepatology 2013
HBsAg based management algorithm for HBeAg-positive patients on PEG-IFN therapy

Sonneveld, Hepatology 2013
Chronic Hepatitis B

HCC surveillance
Case 1

- 46 year old Chinese man
- No relevant comorbidities
- Negative family history for HCC
- HBeAg positive CHB, Rx/ TDF
- HBV DNA <LLOD, ALT 30 (<40)
- Fibroscan: F1

- Is there an indication for HCC surveillance?
Persistent risk for HCC: indications for surveillance in HBV

- Cirrhosis
- Asian males > 40
- Asian females > 50
- Subsaharan africans > 20
- Family history of HCC
- Screening is NOT discontinued in patients undergoing antiviral therapy

- Mode of screening: liver US every 6 months
  - Addition of AFP may increase sensitivity; not specificity
Chronic Hepatitis B

NUC discontinuation
Life-long nucleo(s)tide analogue therapy is not ideal

- Compliance is a major issue
  - 70% after 16 weeks, with young age the main risk factor\(^1\)
  - Probably <50% with prolonged therapy\(^2\)
  - Chronic medication use reduced QoL\(^3\)

- One pill a day does not keep HCC away\(^4,5\)

- Renal safety may be a concern\(^6\)

HBV DNA became detectable in 21/21 (100%) of TDF-Stop subjects

HBV DNA up to W48:
- Median: 5.32 log_{10} IU/mL
- Min: 4.41 log_{10} IU/mL
- Max: 8.50 log_{10} IU/mL

At W48*
- 89% (16/18) HBV DNA < 20,000 IU/mL
- 78% (14/18) HBV DNA < 2,000 IU/mL

* TDF-Restart excluded
Outcomes after therapy discontinuation in HBsAg positive patients

- Systematic review of stopping nucleos(t)ide therapy in HBeAg-negative (n = 967) and HBeAg-positive (n = 733) pts

**HBeAg-negative**

- Pooled HBsAg Loss: 1.7% (50/693)
- Durable biochemical remission: 57% (394/687)

**HBeAg-positive**

- Pooled HBsAg Loss: 1.0% (17/341)
- Durable biochemical remission: 76% (268/403)

Subsequent studies have suggested higher rates of HBsAg loss in Caucasians
**FINITE CHB: Stopping TDF after long-term viral suppression in HBeAg-negative CHB: week 48 interim results**

<table>
<thead>
<tr>
<th></th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>52</td>
<td>48</td>
<td>57</td>
</tr>
<tr>
<td>HBV DNA &lt;2000, ALT &lt;2 x ULN</td>
<td>24</td>
<td>38</td>
<td>19</td>
</tr>
<tr>
<td>HBV DNA &lt;2000, ALT &gt;2 x ULN</td>
<td>10</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>HBV DNA &gt;2000, ALT &lt;2 x ULN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV DNA &gt;2000, ALT &gt;2 x ULN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF-Restart</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Berg JHEP 2017
Predictors of Relapse After NUC Cessation

- Studies have yielded discrepant results regarding
  - Probability of sustained response (depends on definition and timing)
  - Probability of HBsAg loss (varies according to ethnicity and follow-up)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of therapy</td>
<td>Possibly higher relapse rates with TDF than with ETV</td>
</tr>
<tr>
<td>Duration of (consolidation) therapy</td>
<td>Longer is probably better</td>
</tr>
<tr>
<td>HBeAg status at baseline</td>
<td>Discrepant results</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Lower HBsAg (&lt;200 IU/ml) associated with higher sustained response and HBsAg loss rates</td>
</tr>
<tr>
<td>HBcrAg</td>
<td>Lower HBcrAg levels (e.g. &lt; 4.90 log U/mL in HBeAg+) predict sustained response</td>
</tr>
<tr>
<td>Combinations</td>
<td>Model based prediction seems promising (e.g. SCALE-B)</td>
</tr>
</tbody>
</table>

Huhner zu Siederdissen, JID 2018; Hsu, AP&T 2019; Sonneveld JVH 2019; Chen, J Hepatol 2014
Chronic Hepatitis B

HBV reactivation
Case

• 36 year old woman
• History: rheumatoid arthritis (Rx/ prednisone, plaquenil)
• HBeAg -, anti-HBe +, HBV DNA 88 IU/mL
• ALT 35 (<40)
• Fibroscan: F1

• Rheumatologist want to start tocilizumab

• Indication for prophylaxis?
Before TOC
HBsAg positive
HBV DNA 88 IU/mL
Normal LFTs

ALT and Bilirubin (IU/L)

ALT
Bilirubin
INR
HBV DNA

Sonneveld, submitted
Before TOC
HBsAg positive
HBV DNA 88 IU/mL
Normal LFTs

Start TOC

ALT
Bilirubin
INR


ALT and Bilirubin (IU/L)

HBV DNA (log IU/mL) and INR

Sonneveld, submitted
ALT - Plaq - Pred

**Before TOC**
HBsAg positive
HBV DNA 88 IU/mL
Normal LFTs

TOC - Plaq - Pred

ALT 2125
Bilirubin 46
INR 1.0

Sonneveld, submitted
Before TOC
HBsAg positive
HBV DNA 88 IU/mL
Normal LFTs

ALT - Plaq - Pred

TOC - Plaq - Pred

HBV DNA \(10^8\)
ALT 2125
Bilirubin 46
INR 1.0

Sonneveld, submitted
Before TOC
HBsAg positive
HBV DNA 88 IU/mL
Normal LFTs

Sonneveld, submitted
**Before TOC**

HBsAg positive
HBV DNA 88 IU/mL
Normal LFTs
Before TOC
HBsAg positive
HBV DNA 88 IU/mL
Normal LFTs

ALT and Bilirubin (IU/L)

HBV DNA (log IU/mL) and INR


ALT
Bilirubin
INR

Sonneveld, submitted
Risk of HBV reactivation

- Risk is determined by
  - HBsAg status
  - Type of immune suppression
  - Duration of immune suppression

- High risk: pre-emptive therapy

- Low – intermediate risk: follow-up or pre-emptive therapy
A 28 year old Chinese woman is referred by her midwife

She has a singleton pregnancy

HBsAg positive, HBeAg positive, HBV DNA 300,000 IU/mL

Normal ALT, no signs of cirrhosis on ultrasound

Is there an indication for antiviral therapy to reduce the risk of transmission?
Risk of progression to chronic infection is inversely related to age at infection.
Prevention of perinatal HBV transmission

- Treatment comprises HBIG and active vaccination <12hrs of delivery

- Failure is predominantly observed in mothers with HBV DNA levels >200,000 IU/mL
  - Prophylactic NUC therapy is indicated in this subgroup
  - Options: lamivudine, telbivudine and TDF
TDF for prevention of perinatal HBV transmission: meta-analysis for efficacy

- 9 studies, 1046 patients
- 75% reduction of perinatal transmission
Incidence of Birth Defects With in Utero Exposure to Lamivudine or TDF

- No significant safety signals in randomized trials

- Data derived from Antiretroviral Pregnancy Registry, 1/1989 - 7/2012[^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, population-based

Overall birth defects: 2.72% (95% CI: 2.68-2.76)
A 28 year old Chinese woman is referred by her midwife

She has a singleton pregnancy

HBsAg positive, HBeAg positive, HBV DNA 300,000 IU/mL

Normal ALT, no signs of cirrhosis on ultrasound

Is there an indication for antiviral therapy to reduce the risk of transmission?
Case

- A 28 year old Chinese woman is referred by her midwife
- She has a singleton pregnancy
- HBsAg positive, HBeAg positive, HBV DNA 300,000 IU/mL
- Normal ALT, no signs of cirrhosis on ultrasound
- Is there an indication for antiviral therapy to reduce the risk of transmission?
- Yes
Case

- A 28 year old Chinese woman is referred by her midwife
- She has a singleton pregnancy
- HBsAg positive, HBeAg positive, HBV DNA 300,000 IU/mL
- Normal ALT, no signs of cirrhosis on ultrasound
- You start TDF
- She contacts you the week before planned delivery: can I breastfeed my child?
Nucleo(s)tide analogues and breastfeeding

- Nucleo(s)tide analogues may transfer to breast milk in low concentrations.

- Older guidelines suggest advise against breastfeeding when on nucleo(s)tide analogue therapy:
  - Predisposes mother to post-partum flares
  - Discourages breastfeeding

- TFV readily crosses the placenta at a concentration ~33% of plasma with no apparent safety signals in randomized trials.
Tenofovir DF and lactation

- Study of 45 Ugandan/Nigerian mothers with HIV on TDF based ART
- Upper limit of breast-milk to plasma concentration ratio was 0.02
- No TFV detected in infants

Waitt, JAC 2018
Tenofovir DF and lactaction

- Study of 49 breastfeeding HIV-negative women taking TDF as PreP
- TFV concentration in breast milk extremely low
- Estimated daily dose for infant 0.47 μg/kg, or <0.01% of therapeutic dose for HIV (6mg/kg)
- TFV undetectable in 94% of infants during lactation

Mugwanya, PLOS 2016
Tenofovir DF and lactation

- Infant TFV exposure during lactation appears to be minimal

- There is no evidence to consider use of TDF an absolute contraindication for lactation
  - The uncertainty regarding long-term safety must be discussed with the patient

Erhardt CID 2015; EASL CPGs; HBV Richtsnoer 2018
Conclusions

- Treatment indications are based on
  - Severity of liver fibrosis
  - Viremia (HBV DNA / HBsAg)
  - Presence of hepatitis (ALT, biopsy)

- ETV, TDF and TAF achieve sustained virological suppression in nearly all patients
  - Choice depends on previous exposure and comorbidities

- PEG-IFN may be useful for some
  - Use of baseline selection and stopping-rules is essential

- Viral suppression does not annihilate the risk of HCC

- Studies are focussing on improving the rates of sustained off-treatment response

- HBV reactivation due to immune suppression may be lethal

- Treatment may be indicated to reduce perinatal HBV transmission
Actueel Nederlands Richtsnoer
- Samenwerking van beroepsverenigingen
- Altijd een actuele versie
- Online beschikbaar

www.HBVrichtsnoer.nl
www.HCVrichtsnoer.nl