HBV Treatment
Past, Present and the Future

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Dept Microbiology
Monash University, VIC
## HBV Treatment – Past and Present

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Date Approved for Hepatitis B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon alfa-2b</td>
<td>INTRON® A</td>
<td>Schering Corporation</td>
<td>1991</td>
</tr>
<tr>
<td>Peginterferon alfa-2a</td>
<td>PEGASYS®</td>
<td>Hoffman La-Roche</td>
<td>2005</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>EPIVIR-HBV®</td>
<td>GlaxoSmithKline</td>
<td>1998</td>
</tr>
<tr>
<td>Adefovir dipivoxil</td>
<td>HEPSERA™</td>
<td>Gilead Sciences</td>
<td>2002</td>
</tr>
<tr>
<td>Entecavir</td>
<td>BARACLUDE™</td>
<td>Bristol-Myers Squibb</td>
<td>2005</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>TYZEKA™</td>
<td>Idenix/Novartis</td>
<td>2006</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>VIREAD™</td>
<td>Gilead Sciences</td>
<td>2008</td>
</tr>
</tbody>
</table>
Treatment Endpoints

• Long-term suppression of HBV DNA
  – Ideally by achievement of HBsAg seroconversion

• HBeAg-positive
  – Sustained HBeAg seroconversion
  – If no HBeAg serconversion--> suppression of HBV DNA to low levels

• HBeAg-negative
  – Sustained low level HBV DNA
    • On treatment if nucleosides
    • Off treatment if peg-IFN

AASLD Guidelines
EASL Guidelines
APASL Guidelines
The Past and the Present - Intereron

Immunomodulatory

The Past - Conventional interferon – alpha (IFN-α)
- First compound licensed for treatment of chronic hepatitis B in 1991
- Only effective in a small sub-group of patients

The Present - Pegylated interferon
- More beneficial but still low efficacy
- Renewed interest with introduction of qHBsAg
# Role of Quantitative HBsAg

## Treatment with PEG IFN +/- LMV

<table>
<thead>
<tr>
<th>HBeAg-negative</th>
<th>Week 12 HBsAg on PEG IFN alfa 2a ± LMV</th>
<th>HBV DNA ≤ 10000 copies/ml</th>
<th>HBV DNA ≤ 400 copies/ml</th>
<th>HBsAg loss</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6 months</td>
<td>4 years</td>
<td>6 months</td>
</tr>
<tr>
<td>≤ 1500 IU/mL</td>
<td></td>
<td>59%</td>
<td>39%</td>
<td>39%</td>
</tr>
<tr>
<td>&gt; 1500 IU/mL</td>
<td></td>
<td>34%</td>
<td>12%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Marcellin, P. et al 2008. AASLD
# Role of Quantitative HBsAg

## Treatment with PEG IFN +/- LMV

<table>
<thead>
<tr>
<th>HBeAg-positive</th>
<th>Week 12 HBsAg on PEG IFN alfa 2a ± Lamivudine therapy</th>
<th>End of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1500 IU/mL</td>
<td>HBV DNA ≤ 10,000 copies/ml 46.8%</td>
<td>HBV DNA ≤ 400 copies/ml 31.2%</td>
</tr>
<tr>
<td>1501 – 20,000 IU/mL</td>
<td>22.6%</td>
<td>11.1%</td>
</tr>
<tr>
<td>&gt; 20,000 IU/mL</td>
<td>8.2%</td>
<td>4.1%</td>
</tr>
</tbody>
</table>

Lau, G. et al 2008. AASLD
Update – IFN – HBeAg-positive CHB

• qHBsAg < 300 IU/mL at W24 correlates with SVR
  – Chan et al 2010 Aliment Pharmacol Ther 32: 1323

• qHBsAg < 1500 IU/mL at W12 corresponds to 57% PPV for HBeAg seroconversion
  – Lau & Marcellin 2009 J Hepatol 50: 333

• qHBsAg > 20,000 IU/mL at W12 100% NPV for anti-HBs seroconversion
  – Liaw et al 2011 Hepatology 54:1591
Update – IFN – HBeAg-negative CHB

• qHBsAg >0.5 log at W12 leads to ETR in 90%
  – Moucari et al 2009 Hepatol 49: 1151

• No or little decline in qHBsAg and <2 log decline of HBV DNA shows a NPV of 100%
  – Rijckborst et al 2010 Hepatol 52: 454
The Past and the Present: Nucleos(t)ide Analogues

- Lamivudine  Telbivudine
- Adefovir  Tenofovir
- Entecavir

>> Paucity of virus-specific targets – all target HBV RT
>> Long term treatment limited by antiviral resistance
High Baseline HBV DNA Associated With Increased Risk of HCC and Cirrhosis

REVEAL: Long-term follow-up of untreated HBsAg +ve individuals in Taiwan

Cumulative Incidence of HCC at Year 13 Follow-up[^1] (N = 3653)

Cumulative Incidence of Cirrhosis at Year 13 Follow-up[^2] (N = 3582)

Baseline HBV DNA (copies/mL)

Dot-Blot Hybridisation for HBV DNA in Serum from Patient Co-infected with HIV

Samples A1 to A5 are, respectively, from March 12, March 26, May 7, May 15, and May 26, 1987. Samples B1 to B5 are from June 26, July 2, and July 6, 1987, and Jan 23 and Dec 28, 1988. Samples C1 to C3 are cloned HBV DNA standards of 1000, 100, and 10 pg/ml.

Resistance Rates Through 6 Years Among Nucleos(t)ide-Naïve Patients

Patients with HBV DNA ≥400 copies/mL at Week 72 could add FTC to TDF; 5% were switched by Week 96.\(^5,6\)

\(\frac{1}{5}\) Cumulative probabilities of resistance taken; \(\frac{1}{6}\) Naïve HBeAg (+); \(\frac{1}{1}\) Naïve HBeAg(-); N/A not available.


<table>
<thead>
<tr>
<th>Year</th>
<th>LVD(^1)</th>
<th>ADV(^2,3)</th>
<th>LdT(^2,3)</th>
<th>TDF(^4)</th>
<th>ETV(^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23%</td>
<td>0%</td>
<td>5%</td>
<td>0%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>2</td>
<td>46%</td>
<td>3%</td>
<td>25%</td>
<td>0%(^6)</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>3</td>
<td>55%</td>
<td>11%</td>
<td>—</td>
<td>—</td>
<td>1.2%</td>
</tr>
<tr>
<td>4</td>
<td>71%</td>
<td>18%</td>
<td>—</td>
<td>—</td>
<td>1.2%</td>
</tr>
<tr>
<td>5</td>
<td>80%</td>
<td>29%</td>
<td>—</td>
<td>—</td>
<td>1.2%</td>
</tr>
<tr>
<td>6</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.2%(^6)</td>
</tr>
</tbody>
</table>

\(\frac{1}{5}\) Patients with HBV DNA ≥400 copies/mL at Week 72 could add FTC to TDF; 5% were switched by Week 96.\(^5,6\)

* Cumulative probabilities of resistance taken; \(\frac{1}{6}\) Naïve HBeAg (+); \(\frac{1}{1}\) Naïve HBeAg(-); N/A not available.
Current Antivirals Have Different Genetic Barriers to Resistance

- **LdT**
  - M204I
- **LVD**
  - M204I/V ± L180M
- **ADV**
  - N236T and/or A181T/V
- **TDF**
  - N236T ± A181T/V
- **ETV**
  - T184 or S202 or M250
  - M204I/V
  - ± L180M

* Based on blunted responses to TDF in patients with genotypic ADV resistance.

Cross Resistance – Treatment Adaptation

• LMV resistance >> Add TDF (ADV if not available)

• ADV resistance >> Add ETV (LMV if not available)
  >> switch to TDF plus 2nd drug

• ETV resistance >> Add TDF (ADV if not available)

• TFV resistance?? >> Add ETV (LMV if not available)

Key: Avoid drugs from the same structural group
Avoid the accumulation of mutations
# Treatment Options

## Advantages and Disadvantages

<table>
<thead>
<tr>
<th>Nucleos(t)ide Analogues</th>
<th>Immunomodulatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral administration</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Potent HBV DNA suppression</td>
<td>Less potent HBV DNA suppression</td>
</tr>
<tr>
<td>Antiviral</td>
<td>Antiviral and immunomodulatory</td>
</tr>
<tr>
<td>Few side effects</td>
<td>Frequent side effects</td>
</tr>
<tr>
<td>Risk of resistance development</td>
<td>No resistance</td>
</tr>
<tr>
<td>HBsAg seroconversion rare</td>
<td>HBsAg seroconversion uncommon</td>
</tr>
<tr>
<td>Long-term therapy</td>
<td>Finite therapy duration</td>
</tr>
</tbody>
</table>
Stopping Treatment

APASL Recommendation to Stop Antiviral Treatment

In HBeAg-positive patients: when HBeAg seroconversion has developed > 6 months

In HBeAg-negative patients: when HBV DNA remaining undetectable for three separate occasions 6 months apart

- **Outcomes**
  - 25-50% develop viral relapse with hepatitis
  - up to 40% remain virus free (SVR)
  - half of these lose HBsAg

- **Factors**
  - HBV DNA undetectable at stop
  - HBsAg < 100 IU/ml [low]
  - duration of AV therapy (4-5 years)


Alex Thompson Saturday 10am
HBV Lifecycle Showing Novel Approaches for Viral Targets

# New Agents – The Future

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Target</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV life cycle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV Pol</td>
<td>TAF</td>
<td></td>
</tr>
<tr>
<td>Viral entry</td>
<td>Myrcludex-B</td>
<td></td>
</tr>
<tr>
<td>cccDNA</td>
<td>Zinc finger nucleases</td>
<td>cccDNA conversion inhibitors</td>
</tr>
<tr>
<td>mRNA transcription/ stability</td>
<td>Zinc finger proteins</td>
<td>Epigenetic silencers</td>
</tr>
<tr>
<td>Viral assembly</td>
<td>HAPs</td>
<td>Phenylpropenamides</td>
</tr>
<tr>
<td>HBV antigen secretion</td>
<td>REP 9AC'</td>
<td>Small molecule inhibitors of HBsAg secretion e.g. glucovir e.g. triazolo-pyrimidines</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immuno-therapeutic</td>
<td>PegIFN-λ1a (IL29)</td>
<td></td>
</tr>
<tr>
<td>Cytokines</td>
<td>rIL-7</td>
<td>rIL-21</td>
</tr>
<tr>
<td>TLR agonists</td>
<td>TLR7 (GS-9620)</td>
<td></td>
</tr>
<tr>
<td>Therapeutic vaccines</td>
<td>Adeno-virus approaches (TG1050)</td>
<td>Tarmogen (GI-13020)</td>
</tr>
<tr>
<td>Blocking T cell inhibitory receptors</td>
<td>Anti-PD-1 moAB (BMS936558)</td>
<td>Anti-PD-L1 moAb (BMS936559)</td>
</tr>
</tbody>
</table>
| Intrahepatic blocking of suppressive cytokines / regulatory T cells | TGF-β inhibitors | T reg depletion (e.g. α-CD25, daclizumab) }

*Peter Revill  Saturday 9:30*
Inhibitors of HBV Attachment and Entry

Sodium taurocholate cotransporting polypeptide (NTCP) identified as HBV and HDV receptor in 2012

Myrcludex in phase 2 trials in chronic HBV and chronic HDV decrease in HBV DNA and HDV RNA

Yan H, Elife 2012; 1:e00049
Lempp RA, Urban S. Intervirology 2014’; 57: 151
Reverse Transcription: Improved Potency of NA Tenofovir
Alafenamide (TAF)

- TAF = orally bioavailable phosphonoamidate prodrug of tenofovir (TDF)
- In comparison with tenofovir, TAF enables enhanced delivery of the parent nucleotide and its active diphosphate metabolite into lymphoid cells and hepatocytes.
- This is attributed to an improved plasma stability and differential intracellular activation mechanism for TAF relative to TDF

![Chemical structures of Tenofovir, Tenofovir Disoproxil, and TAF](images/structures.png)

<table>
<thead>
<tr>
<th>Compound</th>
<th>EC&lt;sub&gt;50&lt;/sub&gt; HIV-1 (PBMCs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>1.2 µM</td>
</tr>
<tr>
<td>Tenofovir Disoproxil</td>
<td>0.015 µM</td>
</tr>
<tr>
<td>TAF</td>
<td>0.003 µM</td>
</tr>
</tbody>
</table>
Action for Hepatitis B

• 2nd National Hepatitis B Strategy 2014 - 2017
• National Hepatitis B Testing Policy 2015
• WHO Global Network for Viral Hepatitis 2012
• ICE – HBV 2015