First line therapy: interferon or analogues?

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When IFN?

No contraindikationen against IFN / (HBV-Genotype A, B)
HBV-DNA < 10^8 IU/ml
ALT > 3 times ULN

Yes

Limited duration with PEG-IFN (48 weeks)
qHBSAg after 12 Wochen
no significant reduction of HBsAg: switch to NUC

No

Long-term therapy with Nucleos(t)idanaloga (Entecavir or Tenofovir)
HBV-DNA all 3 months
qHBsAg ?!

Stopp therapy if anti-HBs > 100 IU/l or S/C (?)
Commerically available quantitative HBsAg tests

Abbott linear range 0.05–125.000 IU/mL
Elecsys linear range 0.05-52.000 IU/ml

Linear Range of tests sufficient for most clinical situations

Bonino et al. APASL 2011; Package insert: Architect HBsAg assay; Package insert: Elecsys HBsAg II quant
Where is the demand for an immunmodulatory therapy?

Long-term therapy with NUCs without reduction of qHBsAg

Long-term therapy with NUCs

PEG-IFN

Off-label!

Off-label?

PEG-IFN

STOPP

Long-term therapy with NUCs

Long-term therapy with NUCs

Long-term therapy with NUCs
When IFN? When NUCs?

- No contraindikationen against IFN / (HBV-Genotype A, B)
- HBV-DNA < 10^8 IU/ml
- ALT > 3 times ULN

Long-term therapy with Nucleos(t)idanaloga (Entecavir or Tenofovir)

- HBV-DNA all 3 months
- qHBsAg

- Stopp therapy if anti-HBs > 100 IU/l or SIC

Limited duration with PEG-IFN (48 weeks)

- qHBSAg

- no significant reduction of HBsAg: switch to NUC

No dogma to use one or the other – start thinking on an individual patient basis – switch might be the right choice for an individual patient
Useful testing of qHBsAg during therapy

Switch instead of add-on sufficient?
Add-on off label
Case 4a
32 yo male German patient, teacher

HBV was probably vertically transmitted

2008: HBeAg negative
   Genotype D (no routine clinical test)
   HBV DNA 34500 IU/ml
   ALT 218 IU/ml
   Histology 2008: Grading 2, Staging 2 (Metavir)

May 2008: NUC or PEG-IFN ?? (all drugs available)

What would you have suggested in 2008 for this patient?
Case 4a
32 yo male German patient, teacher

HBV was probably vertically transmitted

2008: HBeAg negative,
Genotype D
HBV DNA 34500 IU/ml
ALT 218 IU/ml
Histology 2008: Grading 2, Staging 2 (Metavir)

Tenofovir 245 mg since May 2008, didn’t like the idea of PEG-IFN

Since 06/2009 HBV DNA <11 IU/ml, HBsAg stable of about 8000-10.000 IU/ml

Starting discussions about duration of therapy…..becoming intense over time

….adherence over time <100% with reappearance of viremia on and off
Case 4a
32 yo male German patient, teacher

02/2012: wants to switch to PEG-IFN, didn’t like the idea to pause therapy (FINITE study not wanted)

Fibroscan redone: no signs for advanced fibrosis/cirrhosis

2 weeks overlapping tenofovir

Are we within the label for switching and starting PEG-IFN?
### Case - 32a male patient

<table>
<thead>
<tr>
<th>Date</th>
<th>ALT U/l</th>
<th>HBV-DNA IU/l</th>
<th>qHBsAg IU/l</th>
<th>Notes</th>
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<tr>
<td>02.2012</td>
<td>19</td>
<td>56</td>
<td>10.487</td>
<td>Start PEG-IFN</td>
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<td>03.2012</td>
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<td>128</td>
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<tr>
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<td>218</td>
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<td>65</td>
<td>225</td>
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<td>06.2012</td>
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<td>28</td>
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<td>10.2012</td>
<td>33</td>
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<td>12</td>
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<td>06.2013</td>
<td>15</td>
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<td>AntiHBs-</td>
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<tr>
<td>12.2013</td>
<td>19</td>
<td>&lt;11</td>
<td>negative</td>
<td>AntiHBs-</td>
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</table>
Case - 32a male German patient, teacher

12/2013: Is the patient happy?

No, starts discussing about „missing“ anti HBs,

wants therapeutic vaccination to induce antiHBs, comes in with a lot of study results from scientific meetings…. 
Case 4b
25 yo female medical student from Korea

HBV was probably vertically transmitted

HBeAg negative
Genotype B
HBV-DNA 62 298 000 IU/ml
ALT 78 IU/ml

Fibroscan 6,2 kPa

Entecavir 0,5 mg since January 2009

December 2009: HBV DNA <11 IU/ml, HBsAg titer stable of about 7000 IU/ml

Wishes to be switched to PEG-IFN
Case - 25 female patient

<table>
<thead>
<tr>
<th>Date</th>
<th>ALT U/I</th>
<th>HBV-DNA</th>
<th>qHBsAg IU/I</th>
<th>Action</th>
</tr>
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<tbody>
<tr>
<td>01.2013</td>
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<td>&lt;11</td>
<td>7.250</td>
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<td>02.2013</td>
<td>78</td>
<td>36</td>
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<td>04.2013</td>
<td>141</td>
<td>78</td>
<td>3.455</td>
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<td>07.2013</td>
<td>168</td>
<td>65</td>
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<td>10.2013</td>
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<td>1.050</td>
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<td>12.2013</td>
<td>121</td>
<td>&lt;11</td>
<td>850</td>
<td>Stopp PEG-IFN ?</td>
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</tbody>
</table>

Good tolerability, some hair loss, patient wants extension (Italian data)
Stopping rules for PEG-IFN therapy in HBeAg negative patients

12 weeks:
- IF HBV-DNA <2 log reduction and no significant reduction of HBsAg: Stop PEG-IFN
- IF HBV-DNA >2 log reduction and significant reduction of HBsAg (Genotype D): proceed with therapy

Data valid only for naive HBV patients, not for switch pre-treated

Adopted from Rijckborst et al., J Hepatol. 2012 May;56:1006-11
Switch from Entecavir to PEG-IFN (HBeAg+)

- HBV DNA <10³ copies/ml
- qHBeAg <100 PEIU/ml
- ETV 0.5 mg qd 9-36 months

Switch to Pegasys 180 µg qw 48W (n = 97)

ETV 0.5 mg qd 8W

48 W

10.3%

p=0.0014*

ETV 0.5 mg qd 48W (n = 100)

0%

Baseline HBsAg <3000 IU/ml was associated with response

Ning Q, et al. AASLD 2012; A 216
AASLD 2013, Abstract 1006: Higher HBsAg clearance rate achieved in NUC experienced CHB patients treated with pegylated IFN alpha 2a

Yao Xie et al

Figure 1: satisfied responders achieved higher rates of HBeAg clearance, HBsAg loss and obvious qHBsAg decline

<table>
<thead>
<tr>
<th>Condition</th>
<th>Satisfied Responders (n=83)</th>
<th>Poor Responders (n=80)</th>
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<tbody>
<tr>
<td>HBeAg Clearance</td>
<td>38.6</td>
<td>32.5</td>
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<tr>
<td>HBsAg Loss</td>
<td>13.3</td>
<td>11.3</td>
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<tr>
<td>Obvious qHBsAg Decline</td>
<td>26.5</td>
<td>18.8</td>
</tr>
</tbody>
</table>
AASLD 2013, Abstract 1006: Higher HBsAg clearance rate achieved in NUC experienced CHB patients treated with pegylated IFN alpha 2a

AASLD 2013, Abstract 954: Sustained immune control in HBeAg pos. CHB patients who switched from long-term entecavir therapy to PEG IFN alfa 2a: 1 year follow-up pf the OSST study. Meifang Han et al
Stopping of NUCs before HBsAg loss – course after stopping in a real life cohort

14/60 patients without relapse (23%) = 77% relapse

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Previous therapy / months</th>
<th>qHBsAg at therapy stop</th>
<th>qHBsAg IU/ml</th>
<th>qHBsAg IU/ml</th>
<th>qHBsAg IU/ml</th>
<th>qHBsAg IU/ml</th>
<th>qHBsAg IU/ml</th>
<th>HBV-DNA IU/ml and ALT month 48</th>
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<tbody>
<tr>
<td>1</td>
<td>Lamivudine / 74</td>
<td>890</td>
<td>654</td>
<td>726</td>
<td>788</td>
<td>946</td>
<td>6900 / ALT nl</td>
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<tr>
<td>2</td>
<td>Lamivudine / 62</td>
<td>140</td>
<td>HBsAg+Anti-HBs-</td>
<td>HBsAg+Anti-HBs- + (19)</td>
<td>HBsAg+Anti-HBs- + (45)</td>
<td>HBsAg+Anti-HBs- + (105)</td>
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<tr>
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<td>653</td>
<td>300</td>
<td>479</td>
<td>486</td>
<td>536</td>
<td>&lt;200ALT 68 U</td>
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<tr>
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<td>2350</td>
<td>2050</td>
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<td>20,000/ALT nl</td>
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<td>6</td>
<td>Lamivudine / 62</td>
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<td>3400</td>
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<td>1460</td>
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<td>3990</td>
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<td>2350</td>
<td>880 / ALT 64</td>
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<tr>
<td>8</td>
<td>Adefovir / 64</td>
<td>49</td>
<td>HBsAg&lt;0.05/Anti-HBs-</td>
<td>n.a.</td>
<td>HBsAg+Anti-HBs-</td>
<td>HBsAg+Anti-HBs- + (129)</td>
<td>&lt;20 / ALT nl</td>
<td></td>
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<tr>
<td>9</td>
<td>Adefovir / 52</td>
<td>49</td>
<td>HBsAg&lt;0.05/Anti-HBs-</td>
<td>n.a.</td>
<td>HBsAg+Anti-HBs-</td>
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<td>&lt;20 / ALT 73U/NASH</td>
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<tr>
<td>10</td>
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<td>290</td>
<td>450</td>
<td>438</td>
<td>&lt;20 / ALT 53</td>
<td>&lt;20 / ALT nl</td>
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<tr>
<td>11</td>
<td>Telbivudine / 54</td>
<td>379</td>
<td>12</td>
<td>438</td>
<td>438</td>
<td>&lt;20 / ALT nl</td>
<td>&lt;20 / ALT nl</td>
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<td>12</td>
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<td>458</td>
<td>876</td>
<td>398</td>
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<tr>
<td>13</td>
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<td>432</td>
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<td>HBsAg+Anti-HBs- + (105)</td>
<td>HBsAg+Anti-HBs- + (187)</td>
<td>HBsAg+Anti-HBs- + (78)</td>
<td>&lt;20 / ALT nl</td>
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<tr>
<td>14</td>
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<td>HBsAg+Anti-HBs-</td>
<td>HBsAg+Anti-HBs-</td>
<td>HBsAg+Anti-HBs-</td>
<td>HBsAg+Anti-HBs-</td>
<td>&lt;20 / ALT nl</td>
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</tr>
</tbody>
</table>

High relapse rates >200 IU/ml HBsAg

AASLD 2013, Abstract #982: Petersen, Hansen, Buggisch, Hinrichsen, Berg, Wedemeyer, Stoehr, Chan, Arends, Wiegand, Brunetto, Cornberg, Janssen
HBV relapse after stopping NUC therapy: Importance of qHBsAg

HBeAg negative patients

Chen et al., AASLD 2013 (A937)
When IFN? When NUC?

No contraindikationen against IFN / (HBV-Genotype A, B)
HBV-DNA<10^8 IU/ml
ALT >3 times ULN

Long-term therapy with Nucleos(t)idanaloga (Entecavir or Tenofovir)
HBV-DNA all 3 months
qHBsAg ?!

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no significant reduction of HBsAg: switch to NUC

Stopp therapy if anti-HBs >100 IU/l or S/C (?)
Take home messages

• Most HBV treated patients (>90%) receive NUCs in many countries of the EU

• qHBsAg is an important marker to determine the transcriptional activity of HBV replication (for cccDNA)

• Limitation of treatment duration is becoming more important

• There is a need for prospective „switch“ trials

• Stopping rules for qHBsAg need to be evaluated for patients pretreated