Conflicts of interest

- **Advisor**: Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Glaxo-Smith Kleine, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisc, Roche

- **Lecturer**: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp & Dohme, Novartis, Roche

- **Research grants**: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Roche

- **Clinical trials**: Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Janssen, Idenix, Merck Sharp & Dohme, Novartis, Novo Nordisc, Regulus, Roche

- **Data Safety Management Board**: Gilead
CHRONIC HBV INFECTION

• To treat or not to treat?

• To treat the right patient at the right time (who and when to treat)
Who and when to treat (indications for treatment) in patients with chronic HBV infection

Depend on
• Natural history of disease
• Goals of therapy
• Available drugs
  • efficacy
  • safety, tolerability
  • contraindications
  • cost
Inhibition of CHB progression

Change of CHB to chronic infection

Prevention of cirrhosis

Virological & biochemical remission

HBsAg (-), HBV eradication

Reduction of HCC risk

Improvement of survival

Feasible practically in all compliant patients

Ideal but not realistic
Endpoints of therapy

Recommendations:

1) The induction of **long-term suppression of HBV DNA** levels represents the **main endpoint** of all current treatment strategies
   *(Evidence level I, grade of recommendation 1)*

2) The induction of **HBeAg loss**, with or without anti-HBe seroconversion, in HBeAg-positive CHB patients is a **valuable endpoint**, …. 
   *(Evidence level II-1, grade of recommendation 1)*

3) A biochemical response defined as **ALT normalization** should be considered as an **additional endpoint**, …..
   *(Evidence level II-1, grade of recommendation 1)*

4) **HBsAg loss**, with or without anti-HBs seroconversion, is an **optimal endpoint**, ….. *(Evidence level II-1, grade of recommendation 1)*
Natural History of Chronic HBV Infection

Replicative/Immune tolerant phase | HBeAg clearance phase* | Low-replicative phase | Replicative/reactivating phase*

HBeAg(+) | | HBeAg(-)/anti-HBe(+)

Serum HBV DNA, \(\log_{10}\) IU/mL

Immunotolerant phase

HBeAg(+)CHB

Inactive carrier state

HBeAg(-)CHB

ALT ULN

*Immune reactive phases

Natural History of Chronic HBV Infection

Replicative phase | Replicative phase | Low replicative phase | Replicative phase

HBeAg(+)  | HBeAg(+)CHB  | HBeAg(-)CHB

Serum HBV DNA, log_{10} IU/mL

ALT  | ULN

# Treatment indications in CHB

<table>
<thead>
<tr>
<th>EASL¹ (2017) HBeAg (+/-)</th>
<th>AASLD² (2015) HBeAg (+/-)</th>
<th>APASL³ (2015) HBeAg (+/-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT &gt;2xULN (40 IU/L) and HBV DNA &gt;20,000 or Cirrhosis and HBV DNA+:</td>
<td>ALT ≥2xULN (30/19 IU/L for M/F) and HBV DNA &gt;20,000/2,000 for HBeAg+/-: Therapy</td>
<td>ALT ≥2xULN (40 IU/L) and HBV DNA &gt;20,000/2,000 for HBeAg+/-: Therapy</td>
</tr>
<tr>
<td>EASL/APASL - ALT traditional ULN: ~40 IU/L</td>
<td>EASL - Liver stiffness &gt;9 or 12 kPa if ALT ≤ULN or &gt;ULN (&lt;5xULN): severe fibrosis or cirrhosis</td>
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<tr>
<td>ALT &gt;1-2xULN and/or HBV DNA ≤20,000 Elastography* or Biopsy*</td>
<td>ALT &lt;2xULN and HBV DNA &gt;2,000: Therapy if significant histology</td>
<td>ALT &lt;2xULN and /or HBV DNA ≤20,000/2,000 for HBeAg+/-: Follow-up &amp; noninvasive fibrosis test – Biopsy if significant fibrosis, age&gt;35, family history of HCC/Ci</td>
</tr>
<tr>
<td>Follow-up &amp; noninvasive fibrosis test – Biopsy if significant fibrosis, age&gt;35, family history of HCC/Ci</td>
<td>specific indications (perhaps age&gt;40, HCC family history, immunos. etc)</td>
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</tbody>
</table>

*Therapy if stiffness >9/12 kPa for ALT≤/>ULN or biopsy shows ≥ moderate histol. lesions


HBV DNA in IU/mL
Indications for treatment

Recommendations:

1) All patients with HBeAg-positive or -negative chronic hepatitis B, defined by HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis, should be treated. (Evidence level I, grade of recommendation 1)

2) Patients with compensated or decompensated cirrhosis need treatment, with any detectable HBV DNA level and regardless of ALT levels. (Evidence level I, grade of recommendation 1)

3) Patients with HBV DNA >20,000 IU/ml and ALT >2xULN should start treatment regardless of the degree of fibrosis. (Evidence level II-2, grade of recommendation 1)

4) Patients with HBeAg-positive or HBeAg-negative chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations can be treated even if typical treatment indications are not fulfilled. (Evidence level III, grade of recommendation 2)

Chronic HBV cases with grey-zone treatment indications

- Female, 28 years old, HBeAg+
  - HBV DNA 35,000,000 IU/ml
  - ALT 28, 50, 33 IU/L on 3 occasions within last year
  - Liver stiffness 6 kPa

Should we treat without a liver biopsy? Most probably no.

- Male, 45 years old, HBeAg-/anti-HBe+
  - HBV DNA 6,500 IU/ml
  - ALT 45, 34, 38 IU/L on 3 occasions within last year
  - Liver stiffness 8.2 kPa

Should we recommend a liver biopsy?

Which is the probability of ≥moderate histological lesions?
Antiviral therapy in HBeAg(+) patients with PNALT?

- Maintenance of high HBV replication: increasing numbers of infected hepatocytes, risk of progression of liver lesions, increasing HCC risk
- High risk of HBV transmission
- Usually minimal histological lesions
- Low probability of anti-HBe seroconversion after Peg-IFN/NAs
- (Peg-)IFNa: not effective - NAs: inhibition of HBV replication
- Probably life-long therapy in young patients: long-term safety, family planning?
Do I treat my HBV immunotolerant patients?

No

Except for a few

GV Papatheodoridis, 9th Paris Hepatitis Conference 2016
Management of HBeAg-positive patients with high HBV DNA (>20,000 IU/mL) and PNALT

- Age >40 years: treatment
- Age 30-40 years: decisions individualised - liver biopsy
- Age <30 years: follow-up (ALT /3-6 mos, HBeAg/anti-HBe /6-12 mos)
- Positive family history for HCC: reduce the age limit for treatment initiation
- Clinical or laboratory indications of advanced liver lesions
  (eg low PLT, high g-globulins, splenomegaly, spiders, palmar erythema, high stiffness on Fibroscan etc): liver biopsy even in patients <30 years

Potential additional treatment indications
- Professional reasons
- Last trimester of pregnancy
Management of HBeAg-positive patients with high HBV DNA (>20,000 IU/mL) and PNALT

- Age ≥30 years: may be treatment
- Age <30 years: follow-up (ALT /3-6 mos, HBeAg/anti-HBe /6-12 mos)
- Liver stiffness >9 kPa: can be treated
- Positive family history for HCC: can be treated
- Clinical or laboratory indications of advanced liver lesions
  
  (eg low PLT, high g-globulins, splenomegaly, spiders, palmar erythema): can be treated

Potential additional treatment indications

- Professional reasons
- Last trimester of pregnancy

HBeAg(-) chronic HBV

HBeAg-negative chronic infection (inactive carriers)

(good long-term outcome – variable risk of progression to HBeAg-neg. CHB)

Differential diagnosis and follow-up based on ALT, HBV DNA, liver biopsy – emerging role of elastography and HBsAg levels

Don’t treat – Follow-up for life

Patients with HBeAg-negative CHB

(progressive liver disease)
HBV DNA, Elastographic (LSM) and histological findings in 182 HBeAg-negative patients with PNALT & HBV DNA <20,000

% of 182 HBeAg-neg cases with PNALT ≥moderate fibrosis in 30 cases with HBV DNA >2000 IU/mL and/or LSM>6.5 kPa, %

<table>
<thead>
<tr>
<th>Condition</th>
<th>% of Cases</th>
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<tbody>
<tr>
<td>HBVDNA&gt;2000</td>
<td>17</td>
</tr>
<tr>
<td>LSM&gt;6.5</td>
<td>20</td>
</tr>
<tr>
<td>HBVDNA&gt;2000 &amp; LSM&gt;6.5</td>
<td>6.5</td>
</tr>
<tr>
<td>HBVDNA&gt;2000 &amp; LSM&gt;6.5</td>
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</tr>
</tbody>
</table>

P=0.009

LSM: liver stiffness measurements, PNALT: persistently normal ALT

Disease progression in HBeAg-ve patients with HBV DNA<2000 IU/mL

HBeAg-ve CHB

Cirrhosis

Tseng TC et al. Hepatology 2013;57:441-50
Chronic HBV patient with ALT>ULN at baseline

ALT every month for **up to 3 months**

If signs of advanced disease:
Treat if detectable HBV DNA

Vlachogiannakos & Papatheodoridis. Liver Intern 2018
Chronic HBV patient with ALT>ULN at baseline

- ALT >2xULN and HBV DNA >20,000
- [HBeAg (+) or (-)]

ALT every month for up to 3 months

If signs of advanced disease: Treat if detectable HBV DNA

Treatment

Vlachogiannakos & Papatheodoridis. Liver Intern 2018
Chronic HBV patient with ALT>ULN at baseline

ALT every month for **up to 3 months**

If signs of advanced disease: Treat if detectable HBV DNA

ALT >2xULN and HBeAg (+) & ALT 1-2xULN and/or HBV DNA 2,000-20,000

ALT every 3 mos HBeAg, HBV DNA every 6-12 mos

ALT 1-2xULN and HBV DNA decreasing

ALT every 3 mos HBeAg, HBV DNA every 6-12 mos

ALT 1-2xULN and HBV DNA stable or increasing

Vlachogiannakos & Papatheodoridis. Liver Intern 2018
Chronic HBV patient with ALT>ULN at baseline

ALT every month for up to 3 months

If signs of advanced disease: Treat if detectable HBV DNA

ALT >2xULN and HBeAg (+) & ALT 1-2xULN and/or HBV DNA 2,000-20,000

HBeAg, HBV DNA every 6-12 mos

Elastography or Liver biopsy

ALT 1-2xULN and HBV DNA decreasing

ALT every 3 mos HBeAg, HBV DNA every 6-12 mos

ALT 1-2xULN and HBV DNA stable or increasing

Liver stiffness ≤12
Minimal-mild lesions
Follow-up like cases with persistently ALT<ULN

Stiffness >12 kPa
≥Moderate lesions
Treatment

ALT 1-2xULN and HBV DNA >20,000 [HBeAg (+) or (-)]

Treatment

ALT >2xULN and HBV DNA >20,000

Vlachogiannakos & Papatheodoridis. Liver Intern 2018
Chronic HBV patient with ALT>ULN at baseline

ALT every month for up to 3 months

If signs of advanced disease: Treat if detectable HBV DNA

ALT >2xULN and HBeAg (+) & ALT 1-2xULN and/or HBV DNA 2,000-20,000

HBeAg (-) & ALT 1-2xULN and/or HBV DNA 2,000-20,000 IU/mL

Treatment

If signs of advanced disease:

ALT 1-2xULN and HBV DNA decreasing

ALT 1-2xULN and HBV DNA stable or increasing

Liver stiffness ≤12 kPa

Stiffness >12 kPa

Minimal-mild lesions

Moderate lesions

Follow-up like cases with persistently ALT<ULN

Elastography or Liver biopsy

Vlachogiannakos & Papatheodoridis. Liver Intern 2018
HBeAg-positive patient with normal ALT at baseline

ALT every month for 3 months

ALT >ULN or signs of advanced disease

Follow-up and/or Elastography and/or Liver biopsy and/or Treatment
HBeAg-positive patient with normal ALT at baseline

ALT every month for 3 months

- ALT >ULN or signs of advanced disease
- Persistently ALT<ULN and HBV DNA >20,000
- Persistently ALT<ULN and HBV DNA ≤20,000 IU/mL

Follow-up and/or Elastography and/or Liver biopsy and/or Treatment

ALT every 3 mos

- HBeAg, HBV DNA every 6-12 mos
- Stable ALT, HBeAg, HBV DNA status

- Age >30 years
  - Treatment
- Age ≤30 years
  - Elastography
    - Liver stiffness >9
    - Stiffness ≤9 kPa

Vlachogiannakos & Papatheodoridis. Liver Intern 2018
HBeAg-positive patient with normal ALT at baseline

ALT every month for 3 months

- ALT > ULN or signs of advanced disease

Follow-up and/or Elastography and/or Liver biopsy and/or Treatment

- Persistently ALT < ULN and HBV DNA > 20,000
  - ALT every 3 mos
  - HBeAg, HBV DNA every 6-12 mos
  - Stable ALT, HBeAg, HBV DNA status

- Persistently ALT < ULN and HBV DNA ≤ 20,000 IU/mL
  - ALT, HBeAg every 6 mos (periodical HBV DNA)

- Liver stiffness > 9
  - Treatment

- Stiffness ≤ 9 kPa
  - Elastography
HBeAg-negative patient with normal ALT at baseline

ALT every 3-4 months for one year

ALT >ULN and/or HBV DNA >20,000 or signs of advanced disease

Elastography and/or Liver biopsy and/or, Treatment

Vlachogiannakos & Papatheodoridis. Liver Intern 2018
HBeAg-negative patient with normal ALT at baseline

- ALT every 3-4 months for one year

- Persistently ALT < ULN and HBV DNA 2,000-20,000

-Persistently ALT < ULN and HBV DNA < 2,000 IU/mL

- Signs of advanced disease

- Elastography

  - Liver stiffness > 9

  - Stiffness ≤ 9 kPa,

  - ALT every 3-4 mos, HBV DNA every 12 mos for two years

- ALT < ULN and HBV DNA 2,000-20,000 IU/mL

- ALT every 6 mos, periodical HBV DNA

- ALT > ULN and/or HBV DNA > 20,000

- Liver biopsy or Elastography
HBeAg-negative patient with normal ALT at baseline

ALT every 3-4 months for one year

Persistently ALT<ULN and
HBV DNA 2,000-20,000

Persistently ALT<ULN and
HBV DNA <2,000 IU/mL

Elastography

Liver stiffness >9

ALT every 6 mos, periodical HBV DNA

HBsAg<1000

ALT every 12 mos

Liver biopsy or Elastography

ALT >ULN and/or
HBV DNA >20,000

ALT every 6 mos, periodical HBV DNA

ALT >ULN and/or
HBV DNA >20,000

ALT every 6 mos, periodical HBV DNA

ALT every 3-4 mos,
HBV DNA every 12 mos for two years
Additional indications of treatment/prophylaxis for chronic HBV patients

- Liver transplantation (NA ±HBIG)
- HBV-HIV co-infection
- HDV-HBV co-infection with ongoing HBV replication
- HBV-HCV co-infection during and for 12 weeks after DAAs
- Last trimester of pregnancy and up to 12 weeks after delivery if HBV DNA >200,000 IU/ml or HBsAg >4 log_{10} IU/ml
- During and for 12 months after immunosuppressive therapy or chemotherapy
- Healthcare workers performing exposure prone procedures with serum HBV DNA >200 IU/ml
- Extrahepatic manifestations and replicative HBV infection