Treatment of chronic hepatitis B: EASL guidelines and after

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4.1. Pre-therapeutic assessment of liver disease

4.6. Indications for treatment
Liver biopsy – Histological severity

- **Liver biopsy** is often recommended for determining the degree of necroinflammation and fibrosis since hepatic histology can assist the decision to start treatment (A1).

- Liver biopsy is usually not required in patients with clinical evidence of cirrhosis or in those in whom treatment is indicated irrespective of the grade of activity or the stage of fibrosis (A1).

- **Transient elastography**, which is a non-invasive method widely used in Europe, offers high diagnostic accuracy for the detection of cirrhosis, although the results may be confounded by severe inflammation associated with high ALT levels and the optimal cutoff of liver stiffness measurements vary among studies.

More data about the optimal cut-off points of elastography and for other non-invasive markers are required
Indications for treatment

• Patients should be considered for treatment if
  – HBV DNA >2,000 IU/ml and
  – ALT >ULN and
  – At least moderate necroinflammation and/or at least moderate fibrosis by liver biopsy (or non-invasive markers once validated in HBV-infected patients) (A1)

• If the criteria for HBV DNA and histological severity are fulfilled, treatment may be initiated even if ALT levels are normal (A1)

• Indications for treatment may also take into account age, health status, family history of HCC or cirrhosis and extrahepatic manifestations
No treatment indication –
No need for (immediate) liver biopsy

- **Immunotolerant patients**: HBeAg+ve pts <30 years with PNALT and high HBV DNA, without any evidence of liver disease and without a family history of HCC or cirrhosis. **F-up with ALT at least every 3-6 mos mandatory (B1).**

- **HBeAg-ve patients with PNALT and HBV DNA 2,000-20,000 IU/mL**, without any evidence of liver disease (B1). **F-up with ALT every 3 mos & HBV DNA every 6-12 mos for ≥3 yrs-mandatory (C1).**
**TDF vs TDF+FTC x192 wks in HBeAg+ patients with normal ALT and high HBV DNA**

Mean age: 33 years; 89% Asians, 93% gen. B/C, mean HBV DNA: $8.4 \log_{10} \text{IU/mL}$

<table>
<thead>
<tr>
<th>Outcome at week-192</th>
<th>TDF (N=64)</th>
<th>TDF+FTC (N=62)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA &lt;69 IU/ml</td>
<td>55%</td>
<td>76%</td>
<td>0.016</td>
</tr>
</tbody>
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HL Chan et al. Gastroenterology 2014;146:1240-8
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<td>55%</td>
<td>76%</td>
<td>0.016</td>
</tr>
<tr>
<td>HBV resistance</td>
<td>0%</td>
<td>0%</td>
<td>NS</td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td>5%</td>
<td>0%</td>
<td>NS</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>0%</td>
<td>0%</td>
<td>NS</td>
</tr>
</tbody>
</table>
4.3. End-points of therapy
End-points of therapy

• **Sustained HBsAg loss (± seroconversion to anti-HBs).**
  Ideal - Associated with a complete and definitive remission of the activity of CHB and an improved long-term outcome (A1).

• **Sustained off-treatment virological response (HBV DNA <2,000 IU/mL) for both HBeAg+ve/-ve patients combined with durable anti-HBe seroconversion in HBeAg+ve patients.**
  Associated with improved prognosis (A1).

• **Maintained undetectable HBV DNA by a sensitive PCR assay on treatment with NAs in HBeAg+ve patients who do not achieve anti-HBe seroconversion and in HBeAg-ve patients.**
  Next most desirable end-point (A1).
4.5. Results of current therapies
48 weeks of PegIFNa for CHB

Sustained off-treatment responses

- 30-35% of HBeAg+ patients
- 20-25% of HBeAg- patients
- 50% chance of HBsAg loss after 4-5 years
- histological improvement
- improved major outcomes including survival
96-week PegIFNa therapy increases SVR rates in HBeAg-neg. CHB

PegIFNa-2a
- x48 wks (180µg/wk x48 wks), n=51
- x96 wks (180µg/wk x48 wks–135µg/wk x48 wks), n=52

Patients with HBV DNA <2000 IU/mL, %

<table>
<thead>
<tr>
<th>PegIFNa-2a</th>
<th>End-of-therapy</th>
<th>SR (48-wks post-therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>x48 wks</td>
<td>59</td>
<td>12</td>
</tr>
<tr>
<td>x96 wks</td>
<td>67</td>
<td>29</td>
</tr>
</tbody>
</table>

P=0.37

P=0.03

5 years of ETV or TDF for CHB

- Virological responses in practically all patients (HBV DNA undetectable: 95-100%)

- HBeAg seroconversion: 40-50% of HBeAg+

- HBsAg clearance: 10-12% of HBeAg+, 1-2% of HBeAg-

- ALT normalization: ~85%

- No major safety issues
**Fibrosis Is Reversible**

Liver Fibrosis Regression over 5 Yrs of TDF Therapy

- Patients with cirrhosis (Ishak score ≥5): 28% at baseline, 8% at year 5

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Marcellin P et al. Lancet 2013
### Studies 102/103

#### Virologic Suppression at Year 7

<table>
<thead>
<tr>
<th>Response</th>
<th>HBeAg- Patients (Study 102)</th>
<th>HBeAg+ Patients (Study 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 6</td>
<td>Year 7</td>
</tr>
<tr>
<td>HBV DNA &lt; 400 copies/mL</td>
<td>81.4 (281/345)</td>
<td>77.3 (269/348)</td>
</tr>
<tr>
<td>Intent-to-treat*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV DNA &lt; 400 copies/mL On-treatment†, % (n/N)</td>
<td>99.6 (283/284)</td>
<td>99.3 (271/273)</td>
</tr>
<tr>
<td>HBV Resistance</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* LTE-TDF (missing = failure; addition of FTC = failure)
† Observed (missing = excluded/addition of FTC = included)

♦ HBeAg loss/seroconversion rates of 55% and 40%, respectively, through 7 years

♦ 12% of HBeAg+ patients had confirmed HBsAg loss (10% with seroconversion)

Marcellin P et al. AASLD 2013, Abstr. 926

Neither Truvada (TVD = TDF + FTC) or emtricitabine (FTC) are licensed for use to treat CHB
<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>HCC Rate (%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong</td>
<td>Hong Kong</td>
<td>2.7</td>
<td>247</td>
</tr>
<tr>
<td>Hosaka</td>
<td>Japan</td>
<td>1.4</td>
<td>79</td>
</tr>
<tr>
<td>Yang</td>
<td>Taiwan</td>
<td>5.4</td>
<td>121</td>
</tr>
<tr>
<td>Chen</td>
<td>Taiwan</td>
<td>2.0</td>
<td>100</td>
</tr>
<tr>
<td>Cho</td>
<td>Korea</td>
<td>3.5</td>
<td>378</td>
</tr>
<tr>
<td>Lim</td>
<td>Korea</td>
<td>4.1</td>
<td>860</td>
</tr>
<tr>
<td>Lampertico</td>
<td>Italy</td>
<td>2.6</td>
<td>155</td>
</tr>
<tr>
<td>Papatheodoridis</td>
<td>Greece</td>
<td>0.9</td>
<td>37</td>
</tr>
<tr>
<td>Papatheodoridis</td>
<td>Europe</td>
<td>2.7</td>
<td>111</td>
</tr>
<tr>
<td>Papatheodoridis</td>
<td>Europe</td>
<td>3.7</td>
<td>118</td>
</tr>
</tbody>
</table>

Duration of therapy: 4-6 years

ETV/TDF for NA-naive CHB pts without cirrhosis

HCC rates per year

Duration of therapy: 4-6 years


CHB under NA(s) & HCC

- Heterogeneous data – Difficult to compare
- HCC incidence: most probably reduced in NA(s) treated compared to no treatment (best data in Asian patients) – no clear difference among different NA(s)
- HCC risk remains - patients (cirrhotics) live longer – increasing age = increasing HCC risk

Clinical relevance: patient subgroups who need continued HCC surveillance
# Cumulative Risk Scores for HCC

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Sex</th>
<th>Albumin (g/l)</th>
<th>Bil (µmol/l)</th>
<th>ALT (U/l)</th>
<th>HBe Ag</th>
<th>HBV DNA (cp/ml)</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GAG-HCC¹</strong></td>
<td>In years</td>
<td>M:16 F: 0</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>3 × log</td>
<td>Yes:33 No: 0</td>
</tr>
<tr>
<td><strong>CU-HCC²</strong></td>
<td>≤50: 0 &gt;50: 3</td>
<td>N.A.</td>
<td>≤35: 20 &gt;35: 0</td>
<td>≤18: 0 &gt;18: 1.5</td>
<td>N.A.</td>
<td>N.A.</td>
<td>&lt;4 log: 0 4-6 log: 1 &gt;6 log: 4</td>
<td>Yes:15 No: 0</td>
</tr>
</tbody>
</table>


N.A.: not applicable
HCC risk factors in 1231 Caucasian pts with CHB±cirrhosis treated with ETV/TDF

<table>
<thead>
<tr>
<th></th>
<th>AUROC for HCC development</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAG-HCC</td>
<td>0.58</td>
</tr>
<tr>
<td>CU-HCC</td>
<td>0.62</td>
</tr>
<tr>
<td>REACH-B</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Papatheodoridis GV et al. AASLD 2013; Oral #190
PAGE-B: HCC risk score in Caucasian CHB patients receiving ETV/TDF

- 1619 adult Caucasians with CHB±compensated cirrhosis under ETV/TDF for ≥12 months

<table>
<thead>
<tr>
<th>PAGE-B risk score (Platelets, Age, Gender)</th>
<th>Derivation dataset (N=1,094)</th>
<th>Validation dataset (N=487)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>6-10</td>
<td>7%</td>
<td>7.5%</td>
</tr>
<tr>
<td>&gt;10</td>
<td>15%</td>
<td>11%</td>
</tr>
</tbody>
</table>

PAGE-B: 0.83 AUROC for HCC development

Papatheodoridis GV et al. EASL 2014
4.8. Treatment strategies: how-to-treat
Optimal first-line therapy in compensated CHB (A1)

**HBeAg+ve/HBeAg-ve CHB**

- **Peg-IFNa** *(good predictors#)* (therapy for 48 wks)
  - *If not*, ETV or TDF
    - (finite duration for HBeAg+ve with HBe seroconversion or long-term therapy)

# Peg-IFNa preferred in young (reproductive) age & favorable factors of response:
- **HBeAg+ve CHB**: low HBV DNA, high ALT, genotype A vs D or B vs C
- **HBeAg-ve CHB**: unknown, but IFNa the main option for sustained off-therapy response

*IFNa*: contraindicated, side effects, not patient's preference or ineffective
4.9. Treatment failure

4.10. How to monitor treatment
HBV Monitoring during PegIFN

- **HBeAg/anti-HBe**: at 6 & 12 mos of therapy and at 6 & 12 mos post-treatment (only in HBeAg+ve)
- **HBV DNA**: at 3 (perhaps only in HBeAg-ve), 6 & 12 mos of therapy and at 6 & 12 mos post-treatment
- **HBsAg levels**: at 3 mos of therapy
- **HBsAg**: every 12 mos post-treatment if anti-HBe+ve & HBV DNA-ve
- **Anti-HBs**: if HBsAg-ve
- **F-UP continues after 12 months post-treatment (risk of future reactivation)** (A1)
PegIFN stopping rules

- **HBeAg+ve**: \( \text{HBsAg levels} \geq 20,000 \text{ IU/mL} \) or no decline in HBsAg levels by month 3 (C2)

- **HBeAg-ve (genotype D)**: no decline in \( \text{HBsAg levels} \) and no \( \text{HBV DNA} \) drop \( \geq 2 \log_{10} \text{ IU/mL} \) by month 3 (B2)
**PegBeLiver rule (week 24)**

47 pts treated for 48 wks – 8 pts excluded due to PARC stopping rule at week 12

**Week 24**

<table>
<thead>
<tr>
<th>HBsAg ≤ 7500 IU/mL</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>15/39 (38%)</td>
<td>24/39 (62%)</td>
<td></td>
</tr>
</tbody>
</table>

**SR***

| 1/15 (7%) | 4/24 (17%) |

NPV: 93%

8 + 15 = 22/47 (47%)

*SR: HBV DNA < 2,000 IU/mL at 48 wks post-therapy

Lampertico et al. EASL 2012
PERSEAS rule (week 24)

47 pts treated for 48 wks – 8 pts excluded due to PARC stopping rule at week 12

Week 24

<table>
<thead>
<tr>
<th>HBsAg decline &gt;10%</th>
<th>39 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>15/39 (38%)</td>
</tr>
<tr>
<td>Yes</td>
<td>24/39 (62%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SR*</th>
</tr>
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<tbody>
<tr>
<td>1/15 (7%)</td>
</tr>
<tr>
<td>12/24 (50%)</td>
</tr>
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</table>

NPV: 93%

8+15=22/47 (47%)

*SR: HBV DNA <2,000 IU/mL at 48 wks post-therapy

Goulis et al. AASLD 2013
Primary non-response

• Check for compliance

• Rare with LAM, ETV, TBV, TDF

• In a compliant patient with a primary non-response: genotyping of HBV strains (B1)

• 10–20% under ADV

• In NA(s) naive pts with primary non-response to ADV: rapid switch to TDF or ETV (B1)
### Primary non-response under ETV

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Primary responders (n=1129 – 98.8%)</th>
<th>Primary non-responders (n=14 – 1.2%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>47±10</td>
<td>51±8</td>
<td>0.16</td>
</tr>
<tr>
<td>Males</td>
<td>63%</td>
<td>57%</td>
<td>0.67</td>
</tr>
<tr>
<td>HBV DNA, log IU/ml</td>
<td>7.0±1.4</td>
<td>6.0±1.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>41%</td>
<td>64%</td>
<td>0.08</td>
</tr>
<tr>
<td>HBeAg+</td>
<td>56%</td>
<td>57%</td>
<td>0.94</td>
</tr>
<tr>
<td>ETV duration, months</td>
<td>30 (18-42)</td>
<td>21 (18-26)</td>
<td>0.08</td>
</tr>
<tr>
<td>Virological response</td>
<td>87%</td>
<td>86%</td>
<td>0.70</td>
</tr>
</tbody>
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Partial virological response under a NA

Check for compliance

In compliant patients with partial virological response under

• LAM or TBV at wk 24 or ADV at wk 48, change to a more potent drug (ETV or TDF) preferentially without cross-resistance (A1)

• ETV or TDF at wk 48
  – If HBV DNA levels are declining, continue with the same agent (B1)
  – If HBV DNA levels are not declining, add the other drug in order to prevent resistance in the long term (C2)
Virological breakthrough under a NA

- **LAM resistance**: switch to TDF (add ADV if TDF not yet available) (B1)

- **ADV resistance**: in NA naive patients before ADV, switch to ETV or TDF (B1); ETV may be preferred in such patients with high viraemia (C2)
  - in patients with prior LAM-R, switch to TDF and add a nucleoside (C1)

- **TBV resistance**: switch to or add TDF (add ADV if TDF not yet available) (C1)

- **ETV resistance**: switch to or add TDF (add ADV if TDF not yet available) (C1)

- **TDF resistance**: genotyping and phenotyping by an expert laboratory.
  - ETV, TBV, LAM or FTC could be added (C2);
  - switch to ETV may be sufficient if the patient was NA naive before TDF (C2)
HBV monitoring during NAs

Finite treatment with NAs in HBeAg+ve patients

- **HBV DNA** every 3 mos
- **HBeAg/anti-HBe** every 6-12 mos
- NA therapy can be stopped 12 mos after anti-HBe seroconversion (B1)
- **HBsAg** every 6 mos after anti-HBe seroconversion
- NA treatment may be continued until HBsAg clearance with or without anti-HBs, particularly in patients with severe fibrosis or cirrhosis (C1)

Long-term therapy with NAs

- HBV DNA undetectability by PCR (<10–15 IU/ml) should ideally be achieved to avoid resistance (A1)
- **HBV DNA** at 3 and then every 3-6 mos
- During ETV or TDF therapy, the frequency of HBV DNA follow-up may be decreased when patient compliance and treatment efficacy have been established (C1)
Safety (Renal) monitoring during NAs

- Minimal rates of renal function decline have been reported with all NAs, except perhaps for telbivudine which seems to improve the creatinine clearance (C1)

- The nephrotoxic potential seems to be higher for nucleotide analogues, particularly adefovir (B1)
- **GLOBE**: TBV vs LAM for 104 wks – 921 HBeAg+, 446 HBeAg- (SCr_0 ≤1.5 mg/dl) CKD stage 2 (eGFR 60-89 ml/min/1.73 m^2: 37.6% TBV vs 34.1% LAM

- **Long-term extension studies of GLOBE**

- **Switch from LAM to TBV (A2303)**: 398 pts without LAM-R (99 HBV DNA+)

- **Off-treatment in A2303**: 66 pts with HBeAg seroconversion & HBV DNA-

- **Decompensated cirrhosis (A2301)**: 228 pts TBV vs LAM for 104 wks
NUCLEOS(T)IDE ANALOGUES FOR HEPATITIS B VIRUS INFECTION IN PATIENTS WITH CHRONIC KIDNEY DISEASES

**Creatinine clearance <50-60 ml/min or HBV–related glomerulopathies**

- **NA naive pts with treatment indications**
  - Entecavir regardless of viremia or telbivudine for patients with low viremia#

  Patients with resistance to any nucleoside
  - Tenofovir

- **Patients under immunosuppressive therapy with HBV DNA <2000 IU/ml**
  - Entecavir or telbivudine

**Renal transplantation**

- **HBsAg (+) recipients**
  - No therapy
  - HBV DNA monitoring

- **HBsAg (-), anti-HBc (+) recipients or donors**
  - Any NA including lamivudine (plus HBIG in case of donors with HBV viremia)

- **HBsAg (+) donors in HBsAg (-), anti-HBs (+) recipients**
  - Any NA

**Hemodialysis patients**

- **NA naive pts with treatment indications**
  - Entecavir or tenofovir
  - Entecavir or telbivudine for patients with residual diuresis

  Patients with resistance to any nucleoside
  - Tenofovir

**Low viremia:** HBV DNA <10^8/10^6 IU/mL for HBeAg+/- pts.

Pts under TBV: continue TBV if HBV DNA- at 24wks.

When can we consider stopping NA therapy?

- Recommendations on when NAs can be stopped vary among clinical guidelines:

**HBeAg positive**
- All international guidelines: stop NAs after HBeAg seroconversion & undetectable HBV DNA & 6–12 months consolidation
- EASL: perhaps continue until HBsAg loss (i.e. potentially indefinitely) particularly in severe fibrosis/cirrhosis due to high risk of relapse

**HBeAg negative**
- All international guidelines: continue NAs until HBsAg clearance
- APASL: consider withdrawal after 2 years if HBV DNA undetectable on three occasions 6 months apart (mainly based on cost)

Long-term NA therapy in HBeAg-negative CHB

- Safe discontinuation: HBsAg loss
  - HBsAg loss: 0-1% at 4-5 years

- NA discontinuation in non-cirrhotic HBeAg(-)CHB patients in virological remission under 4-5 years ADV therapy

Perhaps in a proportion (~35%) of patients

Hadziyannis SJ et al. Gastroenterology 2012;143:629-636
HBsAg loss in patients with HBeAg(-) CHB who remained in virological remission under ADV for 4-5 years

**HBsAg levels at EOT**: independent predictor of sustained off-treatment response and HBsAg loss

Hadziyannis SJ et al. Gastroenterology 2012;143:629-636
HBsAg levels as a marker for safe discontinuation of NA therapy in CHB

- HBsAg at end of NAs <100 IU/mL
- 81 (50 e+, 31 e-) pts with post-NAs f-up 32±24 months
  HBsAg at end of NAs <100 IU/mL - AUROC for SVR: 99%
  (sens: 100%, spec: 93%, PPV: 69%, NPV: 100%)
  Suh SJ et al. EASL 2012

- 77 (38 e+, 39 e-) pts with post-NAs f-up ≥6 months
  12-month relapse rates in relation to HBsAg at end of NAs -
  <100 IU/mL: 0%, 100-1000 IU/mL: 50%, >1000 IU/mL: 78%
  Jiang JN et al. EASL 2012
Proportion of HBeAg(-)CHB patients who achieve HBsAg levels <100 IU/mL under ETV or TDF

Cumulative probability of HBsAg <100 IU/mL

<table>
<thead>
<tr>
<th>Years under ETV</th>
<th>ETV</th>
<th>TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

Papatheodoridis et al. AASLD 2013
NAs discontinuation in HBeAg-negative CHB

- 184 HBeAg- compensated CHB pts treated with ETV for 3 (2-6) years who were HBVDNA- on 3 separate determinations at 6 months apart before stopping ETV

- **Virological relapse: HBV DNA >2000 IU/mL**

  virological remission 26% at 24 & 9% at 48 wks

- Virological remission was NOT associated with
  - HBsAg levels at ETV onset or cessation
  - HBsAg reduction following ETV cessation

Seto WK et al. Gut 2014
Approximately 30 studies in the literature

Heterogeneous patient populations

Heterogeneous criteria for NA discontinuation

Heterogeneous duration of therapy/remission

Heterogeneous off-therapy response definitions

Heterogeneous criteria for re-treatment
Towards finite treatment duration

- NA(s) discontinuation after a certain duration
- NA(s) discontinuation in patients with favorable markers of sustained off-therapy remission (e.g., low HBsAg levels)
- Peg-IFNα/λ + ETV or Peg-IFNa + TDF
- Peg-IFN after some years of NA therapy

Early stages of development

- Agents that enhance innate immunity [probably for combination with NA(s)]
- Agents that enhance adaptive immunity [probably for combination with NA(s)]
Treatment of patients with severe liver disease

- **Compensated cirrhosis**: Peg-IFN, ETV or TDF (A1)
- ** Decompensated cirrhosis**: ETV or TDF (A1)
- **Compensated/Decompensated cirrhosis**: close monitoring & HCC surveillance regardless of response (B1/A1)

- **Liver transplantation**: HBIG+NA
  ETV or TDF with shorter courses & lower HBIG doses or HBIG free courses under evaluation

More data about efficacy of safe HBIG early discontinuation in patients under ETV/TDF prophylaxis
Treatment in special patient groups

- HIV co-infected patients
- HDV co-infected patients
- HCV co-infected patients
- Acute hepatitis
- Children
- Healthcare workers
- Pregnancy
- Pre-emptive therapy before immunosuppressive or chemo-therapy
- Dialysis and renal transplant patients
- Extrahepatic manifestations
**TDF for prevention of vertical transmission from immunotolerant mothers**

<table>
<thead>
<tr>
<th></th>
<th>TDF (N=58)</th>
<th>LAM (N=52)</th>
<th>Controls (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy before birth, days</td>
<td>58±19</td>
<td>53±14</td>
<td>0</td>
</tr>
<tr>
<td>Viral load decline, logs</td>
<td>3.6±0.9</td>
<td>2.8±1.3</td>
<td>-</td>
</tr>
<tr>
<td>HBV DNA &gt;7 IU/ml at birth</td>
<td>3%</td>
<td>18%</td>
<td>100%</td>
</tr>
<tr>
<td>Perinatal transmission</td>
<td>2%</td>
<td>0%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Greenup AJ et al. J Hepatol 2014
Prevention of HBV perinatal transmission

- **HBIg & HBV vaccination** for the newborn (A1)

- *(HBeAg+ve) Mothers with HBV DNA >10^{6-7} IU/mL:* 
  LAM, TBV or TDF during the last trimester (B1) 
  plus HBIg & HBV vaccination for the newborn

- If **NA therapy only for prevention of perinatal transmission:** may be discontinued within the first 3 mos after delivery (C1)

- Safety of **NA therapy during lactation** uncertain 
  (Tenofovir but not TDF concentrations in breast milk – Tenofovir: limited oral bioavailability)
HBsAg-/anti-HBc+ patients & chemo-/immunosuppressive therapy

• HBV DNA testing
  – HBV DNA+: treatment similar to HBsAg+ (C1)
  – HBV DNA-: f-up ALT & HBV DNA every 1-3 mos depending on type of immunosuppressive therapy and comorbidities – NA if HBV DNA+ (C1)

• LAM prophylaxis
  – Recipients of liver grafts from anti-HBc+ donors (B1)
  – Bone marrow or stem cell transplantation (C2)
  – Rituximab and/or combined regimens for hematological malignancies, particularly if anti-HBs- and/or close HBV DNA monitoring not guaranteed (C2)
## HBV exacerbation in HBsAg(-)/anti-HBc(+) patients under immunosuppression

<table>
<thead>
<tr>
<th></th>
<th>Hematological</th>
<th>Non hematological</th>
<th>Rituximab</th>
<th>No rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts, n/N</td>
<td>50/266</td>
<td>39/783</td>
<td>5/134</td>
<td>1/433</td>
</tr>
<tr>
<td>Patients with HBV reactivation, %</td>
<td>18.8</td>
<td>4.9</td>
<td>3.7</td>
<td>0.2</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>6.6</td>
<td>0.35</td>
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</tbody>
</table>

- Anti-HBs negative: p<0.001
- Anti-HBs positive: P=0.0034

E Chongolitas, GV Papatheodoridis, Systematic review submitted
### Summary EASL-HEPAMAP clinical/translational research goals in Viral Hepatitis

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>§ Evaluation of cost-effectiveness of screening - improvement of screening implementation</td>
<td>§ Development of new HBV drugs/approaches that can achieve HBsAg loss</td>
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<tr>
<td>§ Assessment of the best cost-effective strategy for case-finding</td>
<td>§ Development of effective approaches than can prevent HCV reinfection after liver transplantation</td>
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<tr>
<td>§ Decrease of the barriers to treatment among diagnosed patients</td>
<td>§ Development of effective agent(s) against HDV</td>
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<td>§ Identification of better predictors of HCC before and after successful therapy</td>
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<td>§ Identification of markers that can predict successful discontinuation of NAs</td>
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<tr>
<td>§ Assessment of safety and efficacy of combination of peg-IFNa with entecavir or tenofovir</td>
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<td>§ Assessment of long-term impact of therapy on the prevention of HCC</td>
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<td>§ Assessment of the integrated efficacy of a multimodal approach on survival in the general population outside referral Centers</td>
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<tr>
<td>§ Establishment of safety and efficacy of the new HCV agents/regimens in all subgroups of patients, especially those with most urgent needs for treatment</td>
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<tr>
<td>§ Continuous assessment of the more cost-effective approach for HCV therapy</td>
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<tr>
<td>§ Research for optimal rescue strategies in patients failing IFNa-free regimens</td>
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