Long-term treatment of HBeAg (-) patients with chronic hepatitis B: What goals can be achieved using current strategies?

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Hôpital Claude Huriez
Lille
Background
Therapeutic indications in patients with obviously active CHB: HBeAg-positive and HBeAg-negative patients

With ALT above 2 times ULN and serum HBV DNA above 20,000 IU/ml may start treatment even without a liver biopsy (B1).

In such patients, liver biopsy may provide additional useful information, but it does not usually change the decision for treatment.

A non-invasive method for the estimation of the extent of fibrosis and most importantly to confirm or rule out cirrhosis is extremely useful in patients who start treatment without liver biopsy (B1).
HBeAg-negative patients with persistently normal ALT levels (ALT determinations at least every 3 months for at least 1 year) and 2000<HBV DNA<20,000 IU/mL, without any evidence of liver disease, do not require immediate liver biopsy or therapy.

Close follow-up with ALT determinations every 3 months and HBV DNA every 6–12 months for at least 3 years is mandatory (C1).
Liver injury in Ag Hbe- patients with DNA < 20 000 UI/ml?

% of patients with necrosis and inflammation ≥ 7 + Fibrosis score ≥ 2
(Histological lesions indicating antiviral therapy)

<table>
<thead>
<tr>
<th>DNA-HBV (UI/ml)</th>
<th>ALT</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 000 - 19 999</td>
<td>Elevated (n = 63)</td>
<td>75%</td>
</tr>
<tr>
<td>80 - 1999</td>
<td>Elevated (n = 42)</td>
<td>62%</td>
</tr>
<tr>
<td>2 000 - 19 999</td>
<td>Normal (n = 35)</td>
<td>17%</td>
</tr>
</tbody>
</table>

Papatheodoridis et al, Hepatology 2009
# Recommendations

<table>
<thead>
<tr>
<th>Treatment guidelines</th>
<th>Recommendation for treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>EASL 2012&lt;sup&gt;1&lt;/sup&gt;</td>
<td>• With ALT above 2 times ULN and serum HBV DNA above 20,000 IU/ml may start treatment even without a liver biopsy (B1).</td>
</tr>
<tr>
<td>EASL 2009&lt;sup&gt;2&lt;/sup&gt;</td>
<td>• At least grade A2 or stage F2 by METAVIR score</td>
</tr>
<tr>
<td>APASL&lt;sup&gt;3&lt;/sup&gt;</td>
<td>• Treat if moderate or greater inflammation, or fibrosis on biopsy</td>
</tr>
<tr>
<td>AASLD&lt;sup&gt;4&lt;/sup&gt; Update 2009</td>
<td>• Treatment may be initiated if there is moderate or severe necroinflammation or significant fibrosis on liver biopsy • Patients HBeAg negative with HBV DNA levels &gt; 20,000 IU/mL after a 3-6 month period of elevated ALT levels &gt; 2 ULN should be considered for treatment (liver biopsy optional)</td>
</tr>
</tbody>
</table>

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ETV : Virological response in HBeAg(-)ve (undetectable HBV DNA)


<table>
<thead>
<tr>
<th>Patients on follow up</th>
<th>6</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>74%</td>
<td>90%</td>
<td>96%</td>
<td>98%</td>
<td>99%</td>
<td>100%</td>
</tr>
</tbody>
</table>

TDF: Virological response in HBeAg(-)ve (undetectable HBV DNA)

Months

<table>
<thead>
<tr>
<th>Months</th>
<th>Patients %</th>
<th>Patients on f-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>74%</td>
<td>217</td>
</tr>
<tr>
<td>12</td>
<td>89%</td>
<td>217</td>
</tr>
<tr>
<td>24</td>
<td>94%</td>
<td>187</td>
</tr>
<tr>
<td>30</td>
<td>96%</td>
<td>130</td>
</tr>
<tr>
<td>36</td>
<td>98%</td>
<td>81</td>
</tr>
</tbody>
</table>

* Undetectable HBV DNA
Sustained Responses and Loss of HBsAg in HBeAg-Negative Patients B Who Stop Long-Term Treatment With Adefovir

Figure 1. Flow chart showing the disposition of patients in the different cohorts of the open-label ADV study.
Sustained Responses and Loss of HBsAg in HBeAg-Negative Patients Who Stop Long-Term Treatment With Adefovir

Figure 2. The number of patients who experienced a relapse and received antiviral therapy (relapsers) or lost HBsAg among the remaining patients during follow-up.
Sustained Responses and Loss of HBsAg in HBeAg-Negative Patients B Who Stop Long-Term Treatment With Adefovir

Graph showing the HBsAg titer at EOT for different groups:
- Relapsers (n=15)
- SR without HBsAg loss (n=5)
- SR with HBsAg loss (n=13)

Hadziyannis SJ, Gastroenterology 2012
Viral suppression Results in the Reversal of Fibrosis/Cirrhosis
Correlation of viral suppression and histological improvement

Meta-analysis of 26 prospective studies

3,428 HBV patients avec HBC (treated or untreated), 73.6% non-asians

Diminution of HBV DNA from day J0 - Median log₁₀

Histological improvement of activity in comparison to baseline - Median

$r = 0.96$
$p < 0.000003$

Disease progression
What can we learn from the Lamividune experience

- Randomized study of lam. vs placebo in 651 patients with HBV-related severe fibrosis (Ishak ≥ 4)

**ITT disease progression**
- Placebo: 21% at 3 years, placebo vs LAM p = 0.001
- LAM: 9% at 3 years

**Hepatocellular carcinoma**
- Placebo: 10% at 3 years, placebo vs LAM p = 0.047
- LAM: 5% at 3 years

Placebo n = 215
YMDD n = 209 (49%)
Wild type n = 221

Long-term entecavir therapy and fibrosis regression

Chang TT, Hepatology 2010
Long-term Tenofovir therapy and fibrosis regression

- 344/348 patients had histological analysis at baseline, 1 and 5 years
- 74% of reversal of Cirrhosis

Marcellin P, Lancet 2012
EASL guidelines: goal of therapy

“The goal of therapy for hepatitis B is to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC and death”

“This goal can be achieved if HBV replication can be suppressed in a sustained manner”

Virological Endpoint of HBV Therapies

• Inhibition of HBV replication:
  • as profound as possible,
  ANTIVIRAL POTENCY
  • as sustained as possible.
  HIGH BARRIER TO RESISTANCE
• The most potent drugs with the optimal resistance profile should be used as first-line monotherapies:

  • Entecavir
  • Tenofovir

J Hepatol  2012
NUCs for HBeAg-negative CHB: Summary and Conclusions

- 1-5 years: undetectable HBV DNA in most patients
- NUC-R: easily identified and rescued with appropriate strategies
- No contraindications, few side effects, excellent tolerability
- Long-term NUC suppressive therapy achieves:
  - Biochemical normalization
  - Histological improvement (reversal of cirrhosis)
  - Prevention of clinical decompensation
  - Improvement of portal hypertension
  - Reduction of HCC

NUCs: best strategy for most HBeAg (-) patients
Nucleosid(t)s analogs improve outcome of patients with advanced disease
Potential Impact of Long-Term Nucleoside Therapy on the Mortality and Morbidity in Hepatitis B: a modeling approach

Table 4. Morbidity and Mortality of Active Chronic Hepatitis B by HBeAg Status in the Natural History Scenario

<table>
<thead>
<tr>
<th>CHB Stage at Entry</th>
<th>n</th>
<th>Cirrhosis (%)</th>
<th>Decompensated Cirrhosis (%)</th>
<th>HCC (%)</th>
<th>Liver Transplant (%)</th>
<th>Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cirrhosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg+</td>
<td>2634</td>
<td>317 (12)</td>
<td>94 (4)</td>
<td>93 (4)</td>
<td>8 (0.3)</td>
<td>248 (9)</td>
</tr>
<tr>
<td>HBeAg−</td>
<td>3051</td>
<td>1354 (44)</td>
<td>266 (9)</td>
<td>388 (13)</td>
<td>22 (0.7)</td>
<td>858 (28)</td>
</tr>
<tr>
<td>All no cirrhosis</td>
<td>5685</td>
<td>1671 (29)</td>
<td>360 (6)</td>
<td>481 (8)</td>
<td>30 (0.5)</td>
<td>1106 (19)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg+</td>
<td>174</td>
<td>174 (100)</td>
<td>55 (32)</td>
<td>17 (10)</td>
<td>2 (1.1)</td>
<td>127 (73)</td>
</tr>
<tr>
<td>HBeAg−</td>
<td>662</td>
<td>662 (100)</td>
<td>160 (24)</td>
<td>172 (26)</td>
<td>6 (0.9)</td>
<td>492 (74)</td>
</tr>
<tr>
<td>All cirrhosis</td>
<td>836</td>
<td>836 (100)</td>
<td>215 (26)</td>
<td>189 (23)</td>
<td>8 (1.0)</td>
<td>619 (74)</td>
</tr>
<tr>
<td>Total</td>
<td>6521</td>
<td>2507 (38)</td>
<td>575 (9)</td>
<td>670 (10)</td>
<td>38 (0.6)</td>
<td>1725 (26)</td>
</tr>
</tbody>
</table>

Abbreviations: CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HCC, hepatocellular carcinoma.
Potential Impact of Long-Term Nucleoside Therapy on the Mortality and Morbidity in Hepatitis B: a modeling approach

NH=Natural History  HPD=High Resistance Profile drug
SRX=Salvage Therapy  LPD=High Resistance Profile drug

Toy M, Hepatology 2009
Potential Impact of Long-Term Nucleoside Therapy on the Mortality and Morbidity in Hepatitis B: a modeling approach

NH = Natural History  HPD = High Resistance Profile drug
SRX = Salvage Therapy  LPD = High Resistance Profile drug

Toy M, Hepatology 2009
Italian ETV cohort: Complication-free survival in patients with compensated cirrhosis

- Prospective real-world study to assess the 5-year efficacy and safety of ETV in a large cohort of NUC-naïve patients with CHB
- 100% VR at Year 5, with 62% of patients achieving HBeAg seroconversion and 33% having HBsAg loss

Selected baseline characteristics (N=418):
- Age, yr †: 58 (18–82)
- Male: 316 (76%)
- HBeAg-ve: 346 (83%)
- ALT, UI †: 92 (11–2,241)
- Cirrhosis: 204 (49%)
- Genotype D: 84/93 (90%)

*Kaplan–Meier estimates.
† Median, (range).

Japanese cohort: ETV reduced HCC incidence, compared with control

PS matched cohort multivariate cox regression analysis:
HR 0.37 (95% CI 0.15–0.91) p=0.030

ETV therapy reduced the 5-year HCC risk, compared with control group

Log-rank test: p<0.001

ETV therapy reduced the 5-year HCC risk, compared with control group

*Adjusted for age, sex, alcohol, smoking, cirrhosis, HBV genotype, HBeAg status, HBV-DNA, ALT, albumin, γGTP, total bilirubin and platelet count.

Patient survival after renal transplantation

Impact of antiviral therapy before renal transplantation


Patients survival rate

Post transplant years

Pre-transplant AgHBs - (n=1988)
Lamivudine used pre Tx AgHBs + (n=27)
Lamivudine not used pre Tx AgHBs + (n=39)

P<0.0001

Viral suppression is associated with survival benefit

Yao FY Hepatology 2001 (Perrillo RP 2001, Schiff E 2007)
ETV in Decompensated cirrhosis

Table 1. Baseline characteristics of the compensated and decompensated groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n = 199)</th>
<th>Compensated group (n = 144)</th>
<th>Decompensated group (n = 55)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>131/68</td>
<td>96/48</td>
<td>35/20</td>
<td>0.687</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.4 ± 10.2</td>
<td>46.8 ± 10.1</td>
<td>52.6 ± 9.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HBV DNA (log10 copies/ml)</td>
<td>7.34 ± 1.43</td>
<td>7.55 ± 1.51</td>
<td>7.18 ± 1.15</td>
<td>0.101</td>
</tr>
<tr>
<td>HBeAg-positive</td>
<td>117 (58.8%)</td>
<td>90 (62.5%)</td>
<td>27 (49.1%)</td>
<td>0.086</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>141.4 ± 150.1</td>
<td>156.5 ± 160.5</td>
<td>101.9 ± 110.7</td>
<td>0.021</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>1.7 ± 1.4</td>
<td>1.2 ± 0.4</td>
<td>3.0 ± 2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.5 ± 0.6</td>
<td>3.7 ± 0.4</td>
<td>2.8 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prothrombin time (s)</td>
<td>14.0 ± 2.3</td>
<td>13.1 ± 1.3</td>
<td>16.2 ± 2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelet count (10^3/µl)</td>
<td>124.8 ± 62.7</td>
<td>143.1 ± 60.8</td>
<td>76.2 ± 36.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Child–Turcotte–Pugh score</td>
<td>6.1 ± 1.6</td>
<td>5.3 ± 0.5</td>
<td>8.1 ± 1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MELD score</td>
<td>8.5 ± 3.3</td>
<td>7.0 ± 1.5</td>
<td>11.5 ± 3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ascites</td>
<td>31 (15.6%)</td>
<td>–</td>
<td>31 (56.4%)</td>
<td></td>
</tr>
<tr>
<td>Episodes of hepatic encephalopathy</td>
<td>7 (3.5%)</td>
<td>–</td>
<td>7 (12.7%)</td>
<td></td>
</tr>
<tr>
<td>Episodes of variceal bleeding</td>
<td>13 (6.5%)</td>
<td>–</td>
<td>13 (23.6%)</td>
<td></td>
</tr>
</tbody>
</table>

Shim JH J Hepatol 2010
ETV in Decompensated cirrhosis

Shim JH J Hepatol 2010
ETV vs ADV in Decompensated Cirrhosis

- Randomized (1:1), open-label, Phase IIIb study in CHB patients with evidence of hepatic decompensation
- ETV (1.0 mg/day) versus ADV (10 mg once daily) treatment until the last randomized patient reaches Week 96

Liaw YF Hepatology 2011
ETV vs ADV in Decompensated cirrhosis

Table 1. Baseline Demographics and Disease Characteristics of Study Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ETV 1.0 mg (n = 100)</th>
<th>ADV 10 mg (n = 91)</th>
<th>Total (n = 191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SE)</td>
<td>51 (1.2)</td>
<td>53 (1.1)</td>
<td>52 (0.8)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>78 (78)</td>
<td>64 (70)</td>
<td>142 (74)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>55 (55)</td>
<td>49 (54)</td>
<td>104 (54)</td>
</tr>
<tr>
<td>White</td>
<td>35 (35)</td>
<td>28 (31)</td>
<td>63 (33)</td>
</tr>
<tr>
<td>Black/African</td>
<td>5 (5)</td>
<td>5 (5)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (5)</td>
<td>9 (10)</td>
<td>14 (7)</td>
</tr>
<tr>
<td>HBV DNA by PCR, log_{10} copies/mL (SE)</td>
<td>7.53 (0.18)</td>
<td>8.16 (0.23)</td>
<td>7.83 (0.15)</td>
</tr>
<tr>
<td>ALT, U/L (SE)</td>
<td>99.2 (11.1)</td>
<td>100 (8.6)</td>
<td>99.6 (7.09)</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL (SE)</td>
<td>2.8 (0.21)</td>
<td>2.5 (0.21)</td>
<td>2.7 (0.15)</td>
</tr>
<tr>
<td>Albumin, g/dL (SE)</td>
<td>3.0 (0.06)</td>
<td>3.1 (0.07)</td>
<td>3.0 (0.04)</td>
</tr>
<tr>
<td>Platelets, x 10^{9} (SE)</td>
<td>87.3 (4.77)</td>
<td>93.3 (4.95)</td>
<td>90.2 (3.43)</td>
</tr>
<tr>
<td>Prothrombin time, seconds (SE)</td>
<td>16.3 (0.23)</td>
<td>15.3 (0.20)</td>
<td>15.8 (0.16)</td>
</tr>
<tr>
<td>Creatinine, mg/dL (SE)</td>
<td>0.9 (0.03)</td>
<td>0.9 (0.03)</td>
<td>0.9 (0.02)</td>
</tr>
<tr>
<td>MELD score (SE)</td>
<td>17.1 (0.50)</td>
<td>15.3 (0.48)</td>
<td>16.23 (0.35)</td>
</tr>
<tr>
<td>CTP score (SE)</td>
<td>8.81 (0.20)</td>
<td>8.35 (0.19)</td>
<td>8.59 (0.14)</td>
</tr>
<tr>
<td>CTP class, n (%)</td>
<td>A 7 (7)*</td>
<td>10 (11)*</td>
<td>17 (9)</td>
</tr>
<tr>
<td></td>
<td>B 63 (63)</td>
<td>61 (67)</td>
<td>124 (65)</td>
</tr>
<tr>
<td></td>
<td>C 30 (30)</td>
<td>20 (22)</td>
<td>50 (26)</td>
</tr>
<tr>
<td>Prior LVD treatment, n (%)</td>
<td>39 (39)</td>
<td>34 (37)</td>
<td>73 (38)</td>
</tr>
<tr>
<td>Prior LVD duration, weeks</td>
<td>Mean (SD)</td>
<td>126 (98.2)</td>
<td>122 (81.8)</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>115 (0.1-459)</td>
<td>121 (0.4-321)</td>
</tr>
<tr>
<td>LVD-resistant, n (%)</td>
<td>36 (36)</td>
<td>30 (33)</td>
<td>66 (35)</td>
</tr>
<tr>
<td>HBeAg-positive, n (%)</td>
<td>54 (54)</td>
<td>50 (55)</td>
<td>104 (54)</td>
</tr>
</tbody>
</table>

All data are mean unless otherwise stated. SE, standard error.
*CTP score at time of eligibility determination was ≥7.

Liaw YF Hepatology 2011
ETV vs ADV in Decompensated Cirrhosis

- Multicenter, comparative open-label study where subjects were randomly assigned 1:1 to receive ETV 1.0 mg/day or ADV 10 mg/day
  - 38% of patients had prior LVD experience; 39% in ETV arm and 37% in ADV arm
- All patients had hepatic decompensation (CTP score ≥7, no upper limit)

The primary efficacy endpoint was the mean reduction in serum hepatitis B virus (HBV) DNA at Week 24

Liaw YF et al., Hepatology 2011;54:91–10
ETV vs ADV in Decompensated cirrhosis

CTP score ≥2 point improvement

Week 24
ETV (N=100) 32
ADV (N=91) 24

Week 48
ETV (N=100) 35
ADV (N=91) 27

Change in MELD score

Week 24
ETV (N=100) -2
ADV (N=91) -0.9

Week 48
ETV (N=100) -2.6
ADV (N=91) -1.8

Liaw YF, Hepatology 2011
Four AEs of grade 1 to 2 decrease in serum bicarbonate were reported (ETV 1/4 2; ADV 1/4 2); no subject had temporally related AEs with an associated risk of metabolic acidosis.

Liaw YF et al., Hepatology 2011
TDF is comparable to ETV in decompensated patients

- All patients had hepatic decompensation (a CTP score of 7–12)
- The primary study objective was to evaluate and compare the safety/tolerability of TDF, FTC/TDF, and ETV in the treatment of CHB patients with decompensated liver disease.

The primary study endpoint was safety.

Liaw YF, Hepatology 2011
Lactic acidosis in patients with high baseline MELD scores receiving NAs

- 5/16 cases of lactic acidosis (LA) reported in patients treated with ETV (MELD scores ≥22) (Lange CM, 2009)
- In 37 patients treated with either LVD, ADV, ETV, TDF or untreated control, lactic acidosis occurred in 2 patients receiving TDF, 2 patients in the control group and 0 patients receiving ETV or LVD (Lange CM, 2010)
- In the ETV-048 study, grade 2 lactic acidosis was reported in one ETV treated patient (baseline MELD score 21), which resolved without treatment modification (Liaw YF 2011)
“Patients with decompensated cirrhosis require urgent antiviral treatment. Rapid and profound viral suppression and efficacious prevention of resistance are particularly needed in this group. Significant clinical improvement can be associated with control of viral replication, but patients with very advanced liver disease may not always benefit if treated at this late stage and should be considered for liver transplantation (A1).”

“Treatment is indicated even if HBV DNA level is low in order to prevent recurrent reactivation. Potent NUCs with good resistance profiles (entecavir or tenofovir) should be used.”

EASL Clinical Practice Guidelines: Management of chronic hepatitis B. *J Hepatol* 2009
Summary

• New nucleosids analogs induce disease regression and fibrosis regression
• Long-term antiviral therapy with nucleosid analogs will have a major preventive effect on liver-related mortality and morbidity in HgHBe negative patients
• Reversal of cirrhosis is observed in patients with viral suppression
• In patients with decompensated cirrhosis, nucleosid analogs need to be urgently initiated