Clinical management and long-term treatment outcomes of hepatitis B

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CHB NATURAL HISTORY

- 4 distinct phases based on:
  - HBeAg status
  - HBV DNA level
  - ALT

- ‘New’ EASL terminology
  - Chronic infection vs chronic hepatitis

- Hepatitis phases: persistent ALT↑
  → Treatment indication

TO TREAT OR NOT TO TREAT?

**General**

- HBeAg+ Chronic Infection
- HBeAg+ Chronic Hepatitis
- HBeAg- Chronic Infection
- HBeAg- Chronic Hepatitis

**Exceptions**

- Family history of HCC or cirrhosis
- Risk for transmission
- Previous treatment history
- Extrahepatic manifestations
- Compensated or decompensated cirrhosis
- Co-infected patients
- Pregnancy
- Patients undergoing immunosuppressive therapy or chemotherapy

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Furquim d’Almeida, UEGJ 2021; EASL CPG 2017 J Hepatol 2017
Real world practice: Gaps in evaluation and treatment

Chronic HBV infection in the United States
2003-2019, N = 12,608

- 72% Patients with adequate evaluation
- 28% Patients without adequate evaluation

Proportion of treatment-eligible patients who received treatment

- Total: 66%
  - By AASLD guideline: 65%
  - By EASL guideline: 60%
- Treated at any time: 60%
  - By AASLD guideline: 60%
  - By EASL guideline: 54%
- Treated within 12 months: 60%
  - By AASLD guideline: 60%
  - By EASL guideline: 54%

Ye Q et al. J Hepatol 2022
GOALS OF CHB TREATMENT

- Improve clinical outcomes:
  - Prolong survival
  - Prevent liver decompensation
  - Prevent progression towards cirrhosis/HCC

- HBV DNA ~ HCC and cirrhosis progression (REVEAL-HBV cohort)

- Virological endpoints (=surrogate):
  - HBV DNA < det limit
  - HBeAg seroconversion
  - HBsAg clearance/seroconversion = “functional cure” → NUC STOP

# SHORT TERM VIROLOGICAL OUTCOMES

Virological outcomes of the registrational trials after 48 weeks of treatment

<table>
<thead>
<tr>
<th></th>
<th>PegIFN-α2a</th>
<th>ETV</th>
<th>TDF</th>
<th>TAF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBeAg+</td>
<td>HBeAg-</td>
<td>HBeAg+</td>
<td>HBeAg-</td>
</tr>
<tr>
<td>Number of patients (n=)</td>
<td>271</td>
<td>177</td>
<td>354</td>
<td>325</td>
</tr>
<tr>
<td>Virologic response*</td>
<td>25</td>
<td>63</td>
<td>67</td>
<td>90</td>
</tr>
<tr>
<td>ALT &lt;ULN (%)</td>
<td>39</td>
<td>38</td>
<td>68</td>
<td>78</td>
</tr>
<tr>
<td>HBsAg loss (%)</td>
<td>+/- 3°</td>
<td>+/- 4°</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>HBeAg seroconversion (%)</td>
<td>27</td>
<td>/</td>
<td>21</td>
<td>/</td>
</tr>
</tbody>
</table>

*HBV DNA<400 copies/mL (PegIFN-α2a), <300 copies/mL (ETV), <69 IU/mL (=400 copies/mL) (TDF); <29 IU/mL (TAF)

° at 6 months after 48 weeks of therapy

## LONG TERM VIROLOGICAL OUTCOMES

<table>
<thead>
<tr>
<th>HBeAg Positive</th>
<th>Peg-IFN*</th>
<th>Entecavir†</th>
<th>Tenofovir Disoproxil Fumarate†</th>
<th>Tenofovir Alafenamide†</th>
</tr>
</thead>
<tbody>
<tr>
<td>% HBV-DNA suppression</td>
<td>30-42 (&lt;2,000-40,000 IU/mL)</td>
<td>61 (&lt;50-60 IU/mL)</td>
<td>76 (&lt;60 IU/mL)</td>
<td>73 (&lt;29 IU/mL)</td>
</tr>
<tr>
<td>(cutoff to define HBV-DNA suppression)</td>
<td>8-14 (&lt;80 IU/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% HBeAg loss</td>
<td>32-36</td>
<td>22-25</td>
<td>—</td>
<td>22</td>
</tr>
<tr>
<td>% HBeAg seroconversion</td>
<td>29-36</td>
<td>21-22</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>% Normalization ALT</td>
<td>34-52</td>
<td>68-81</td>
<td>68</td>
<td>—</td>
</tr>
<tr>
<td>% HBsAg loss</td>
<td>2-7</td>
<td>4-5</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>(at 3 years posttreatment)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>HBeAg Negative</th>
<th>Peg-IFN</th>
<th>Entecavir†</th>
<th>Tenofovir Disoproxil Fumarate†</th>
<th>Tenofovir Alafenamide†</th>
</tr>
</thead>
<tbody>
<tr>
<td>% HBV-DNA suppression</td>
<td>43 (&lt;4,000 IU/mL)</td>
<td>90-91 (&lt;50-60 IU/mL)</td>
<td>93 (&lt;60 U/mL)</td>
<td>90 (&lt;29 IU/mL)</td>
</tr>
<tr>
<td>(cutoff to define HBV-DNA suppression)</td>
<td>19 (&lt;80 IU/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Normalization ALT</td>
<td>59</td>
<td>78-88</td>
<td>76</td>
<td>81</td>
</tr>
<tr>
<td>% HBsAg loss</td>
<td>4</td>
<td>0-1</td>
<td>0</td>
<td>&lt;1</td>
</tr>
<tr>
<td>(at 3 years posttreatment)</td>
<td></td>
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</tbody>
</table>

HBV DNA suppression:
- ↑ NUC treatment vs low after pegIFN

HBsAg loss:
- ↑ after pegIFN with longer FU duration, but low in NUC-treated HBeAg- CHB
NUC induced HBsAg loss: Clinical outcomes

Korea 1999-2011. n= 5409 R/LAM or ETV, median FU 6 yrs
HBsAg loss; n=110 → HBsAg loss: 0.33%/year

Excellent outcomes after HBsAg seroclearance
Only baseline cirrhosis associated with residual risk for adverse outcomes

Kim et al. Gut 2014;63:1325
NUC Treatment outcome: Survival

- Europe. n=1951 R/ TDF or ETV since 2012
- Excellent survival rates
  - 94% after 8 years of NUCs = general population
- Cirrhosis: ↑ overall and liver-related death
- HCC: ↑ transplantation and liver-related mortality
  - HR 169.80; P <0.001

| Table 2. Deaths or liver transplantation in 1,951 Caucasian patients with CHB who received long-term entecavir or TDF therapy. |
|-----------------|-----------------|-----------------|------------------|------------------|
|                 | Total (N = 1,951) | No cirrhosis (n = 1,379) | Cirrhosis (n = 526) | p value* |
| Death from any cause | 84 (4.3%) | 37 (2.7%) | 44 (8.4%) | <0.001 |
| Liver-unrelated death | 50 (2.6%) | 27 (2.0%) | 21 (4.0%) | 0.018 |
| Liver-related death | 34 (1.7%) | 10 (0.7%) | 23 (4.4%) | <0.001 |
| Liver transplantation | 17 (0.9%) | 8 (0.6%) | 9 (1.7%) | 0.027 |

Liver-related death/liver transplantation

- In patients with HCC: 44/118 (37.3%) vs. 17/37 (45.9%) vs. 26/80 (32.5%)
- In patients without HCC: 7/1,833 (0.4%) vs. 1/1,342 (0.01%) vs. 6/446 (1.3%)

CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; TDF, tenofovir disoproxil fumarate.
* For cirrhosis vs. no cirrhosis by chi-square test.

G. Papatheodoridis, JHEP 2018
NUC Treatment outcome: Prevent Transplantation

- Korea 2005-2012. Prospective cohort study; R/ LAM/ETV
- CHB (n=707) with first-onset complications of decompensated cirrhosis

- Treated,* responder (n = 245)
- Treated,* nonresponder (n = 178)
- Untreated (n = 284)

*Treated predominantly with lamivudine (n = 203) or entecavir (n = 198).

- NUC treatment with viral suppression improved transplant-free survival over 5 yrs (P = .0098 vs untreated)

**NUC Treatment outcome: Fibrosis Regression**

**ETV: LBx 3 to 7 yrs after start**

- Baseline
- Week 48
- Long term

**Ishak fibrosis score (n=57)**
- Missing
- 6
- 5
- 4
- 3
- 2
- 1
- 0

**TDF: Lbx 5 yrs after start (cirrhotic patients)**

- 74% of patients had reversal of cirrhosis
- n=41
- n=14
- n=24
- n=1
- n=15

Non-cirrhotic CHB: Persistent low risk of HCC

Cirrhotic CHB: Drop in HCC risk treated for 5 years
→ But > 1.5%: Continuous HCC surveillance

Europe. n=1951 R/ TDF or ETV since 2012
Additional benefit of HBsAg loss over HBV DNA suppression

HCC incidence:
- N= 603 (3.5%) with viral suppression
- N= 121 (4.4%) without complete viral suppression (P<0.001)
- N= 2 (0.5%) with HBsAg seroclearance (P<0.001)

Hepatic events: viral suppression ~ HBsAg loss (P=0.505)
Duration of NUC Treatment

- Very slow HBsAg decline on NUC treatment:
  - Caucasians $0.084 \log_{10} \text{IU/ml/yr}$
  - Asians $0.043 - 0.044 \log_{10} \text{IU/mL/yr}$

- Estimated duration of NUC treatment:
  - Caucasians: 52.2 years (IQR 30.8–142.7 yrs)
  - Asians: 73.5-74.1 years
  - “Lifelong”

Conclusion: Long term benefit of NUC treatment

- **Virological:**
  - HBV DNA suppression almost universal with 2nd generation NUCs
  - HBsAg loss very rare: 0.33%/year
  - Lifelong NUC treatment anticipated

- **Excellent long-term clinical outcomes:**
  - Survival similar to general population, only cirrhosis/HCC impacting survival
  - Prevention of Liver Transplantation/Recompensation
  - Regression of liver fibrosis
  - Additional benefit of HBsAg loss
SAFETY OF CHB TREATMENT

- NUCs generally well tolerated
  - ETV: Lactic acidosis in decompensated cirrhosis
  - TDF:
    - Hypophosphatemia
    - Renal tubulopathy?
    - Osteomalacia?

- IFN: specific side effects
Safety NUCS: Kidney and Bone?

Hong Kong 2000-2012: n=53,500 chronic HBV, n=7,046 NUC-treated

3-year cumulative risk analysis

Nucleotide vs Nucleoside analogues:
Higher risk of hip fracture (HR 5.69, P=0.001)
→ Absolute risk still very low, 0.7% in 3 years vs 0.2% in untreated

Renal Safety of NUCS: Real World ETV vs TDF

- Retrospective analysis; 25 centers, USA, Hong Kong, Korea, Taiwan, Japan, Singapore, Mainland China
- TDF (n=2482) vs ETV (n=3707)
- Adjusted mean eGFRs lower in TDF vs. ETV during 10 years of follow-up (all p < 0.01)
Safety of NUCS: 96 weeks of TDF vs TAF non-inferiority RCT

- **Viral endpoints:**
  - HBV DNA < 29 IU/mL:
    - **HBeAg+**: 73% (423/581) (TAF) vs 75% (218/292) (TDF); P=0.47
    - **HBeAg-**: 90% (257/285) (TAF) vs 91% (127/140) (TDF); P= 0.84
  - HBsAg loss:
    - **HBeAg+**: 7/576 (1%) (TAF) vs 4/288 (1%) (TDF); P=0.88

- **Biochemical changes:**
  - grade 3 fasting LDL levels: 6% TAF vs TDF 1% ("lipid lowering effect of TDF")

- **Bone Mineral Density and Creatininin Clearance**

![Graph showing mean change in hip bone mineral density](image1)

![Graph showing median change in eGFR by Cockcroft-Gault](image2)

**Agarwal K. J Hepatol 2018**
Safety NUCS: Switch TDF to TAF, non-inferiority RCT

- Long term TDF treatment, per protocol switch to TAF or continue TDF
- Viral endpoints:
  - HBV DNA > 20 IU/mL: 1 (<1%) (TAF) vs 1 (<1%) (TDF); P=0.95
  - HBsAg loss: 0/243 (TAF) vs 5/245 (2%) (TDF); P=0.028
- Biochemical changes:
  - Median fasting lipid parameters ↑ after TAF switch
- Bone Mineral Density and Creatinin Clearance
Choice of 2nd generation NUCS?

TAF vs TDF: Non-inferiority ≠ Superiority

- Viral endpoints similar
- HBsAg loss significantly higher on continuous TDF vs switch to TAF
- Lipids higher on TAF vs TDF
- Bone and Kidney parameters significantly better on TAF vs TDF
- Long-term results?

EASL CPG:

- ETV ~ TAF ~ TDF
- Chronic kidney or bone disease: ETV ~ TAF > TDF
Overall long-term outcome of NUC treatment

- Excellent clinical outcomes
- Residual HCC risk in baseline cirrhosis
- Additional benefit after HBsAg loss
- Lifelong NUC treatment anticipated
- Kidney and bone safety good compared to untreated CHB patients
- Long-term side effect profile of different 2nd generation NUCs requires further study
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