Treatment discontinuation:
Asian perspective

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The global and regional burden of CHB

An estimated 296 million subjects chronically infected and 820,000 deaths worldwide by 2019

July 1st 1986 -- nation-wide neonatal HBV vaccination program:
HBV prevalence: decrease from 20% to 7%, with only 0.8% among people younger than 35.

Still, there are 1.9 million CHB patients in Taiwan
The changing phenotype of the CHB patients

*More and more HBeAg negative CHB!*

Increased HBeAg negative proportion of treatment-naïve CHB in CGMH

Current guideline treatment endpoint:

<table>
<thead>
<tr>
<th>Endpoint for HBeAg-Neg CHB</th>
<th>AASLD 2018</th>
<th>EASL 2017</th>
<th>APASL 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg loss</td>
<td></td>
<td>HBsAg loss, finite for selected patients (&gt; 3-year undetectable HBV DNA)</td>
<td>HBsAg loss or finite for patients &gt; 2-year undetectable HBV DNA</td>
</tr>
</tbody>
</table>

HBsAg loss: the ultimate goal

N=20263, ETV and or TDF treated
Mean age: 51.8, 66.8% male, 11% cirrhosis

- No complete viral suppression vs. Complete viral suppression: Gray’s test, p < 0.001
- Complete viral suppression vs. HBsAg seroclearance: Gray’s test, p < 0.001

- 8-yr: 7.8%
- 8-yr: 5.6%
- 8-yr: 0.6%
- 86.4%, N=17499
- 13.6%, N=2764
- 2.1%, N=376

Functional Cure
Why Finite therapy should be considered...

• Willingness/adherence/loss to follow-up in real world

• Long term drug safety > 10 years

• Low HBsAg loss rate during NA treatment

• Cost for life-long, esp. HBV endemic countries
  • (~2200 USD annually per patient, ~2,000,000 CHB patients in Taiwan*)

*estimated in 2018

Functional cure is difficult to reach

HBsAg loss rate by current antiviral treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>E+</th>
<th>E-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg-IFN 3-yr</td>
<td>11%</td>
<td>8-14%</td>
</tr>
<tr>
<td>ETV 7-10 yr</td>
<td>2.50%</td>
<td>2.50%</td>
</tr>
<tr>
<td>TDF 10 yrs</td>
<td>4.90%</td>
<td>3.40%</td>
</tr>
<tr>
<td>TAF 2 yrs</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HBsAg loss rate</th>
<th>No.</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.15% per year</td>
<td>1075</td>
<td>B/C¹</td>
</tr>
<tr>
<td>0.33% per year</td>
<td>5409</td>
<td>C²</td>
</tr>
<tr>
<td>0.3% by 7 year</td>
<td>375</td>
<td>D³</td>
</tr>
</tbody>
</table>

An average HBsAg decline of $0.084 \log_{10}\text{IU/mL/yr}$, estimated time of HBsAg loss: $39-610$ years!⁴, ⁵

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Problem raised during long-term treatment

Human nature: Almost inevitable

**Adherence rate** by meta-analysis: **74.6%**\(^1\) (Optimal: 95%)
- Comparable between high and low income
- Barriers: forgetting, limited understanding of the importance of adherence, change to routine

Liver adverse events hazard ratio increase when adherence < 90%, **greater in those < 70%**\(^2\) (forgot 2 times per week)
- HR: **3.9** for HCC, **4.1** for cirrhotic complication, **22.7** for liver related mortality

Real-world on-treatment lost follow-up cumulative rate
- Prospective, call-back system\(^3\) (N=147): Cumulative 1\(^{st}\): 3%, 3\(^{rd}\): 6%, 5\(^{th}\): 8%, 6\(^{th}\): 13%
- Retrospective, cirrhotic\(^3\) (N=1066): 1\(^{st}\): Cumulative 1\(^{st}\): 6%, 3\(^{rd}\): 8%, 5\(^{th}\):10%, 6\(^{th}\): 11%

Lost to f/u without monitoring may lead to severe flare or hepatic failure\(^4\).

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Poor adherence leads to poor outcome

894 treatment naïve CHB receiving ETV, 10-year longitudinal observational study, overall mean adherence rate: 89%\(^1\)

<table>
<thead>
<tr>
<th>Adherence (%)</th>
<th>HCC</th>
<th>Cirrhotic complication</th>
<th>Liver related mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 90</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>70-90</td>
<td>2.33</td>
<td>2.04</td>
<td>7.55</td>
</tr>
<tr>
<td>&lt; 70</td>
<td>3.9</td>
<td>4.08</td>
<td>22.67</td>
</tr>
</tbody>
</table>

1. Shin JW et al AJG 2018; 113: 998-1008;
A shifting paradigm for HBeAg (-) treatment endpoint

Liaw YF Hepat Int 2019; 13(6):665-673
No increase HCC events in finite therapy among HBeAg negative CHB patients

- The HCC incidence were comparable between finite arm and continued arm in both non-cirrhotic\textsuperscript{1,2} and cirrhotic\textsuperscript{3,4} CHB patients
  - \textbf{Non-cirrhotic:}
    - 5-year: Finite vs. Continued\textsuperscript{1-}:
      - Overall: 2.0\% vs. 4.2\%, \textit{P}=0.494
      - Taiwan (NTUH): 1.3\% vs. 2.2\%, \textit{P}=0.873
  - \textbf{Cirrhotic:}
    - 5-year: Finite vs. Continued
      - LK-CGMH: 7.5\% vs. 12.5\%, \textit{P}=0.182
      - KH-CGMH: Comparable, \textit{P}=0.77

\textsuperscript{1.} Papatheodoridis M/Su TH et al Liver Int. 2022 Mar;42(3):541-550; \textsuperscript{2.} Teng W et al. Hepatol Int. 2021 Dec;15(6):1421-1430 (with Courtesy data from Dr. Teng); \textsuperscript{3.} Chen YC APT 2015 42; 1182-1191; \textsuperscript{4.} Hung CH JVH 2017 24(7):599-607; \textsuperscript{5.} Jeng WJ et al Seminar in liver disease 2021; Jeng WJ et al AASLD 2021 (Left), Jeng WJ et al (submission, right); \textsuperscript{6.} Hsu YC et al CGH 2021 in press
Hepatic decompensation in cirrhotic patients: not higher

After finite Nuc therapy

liver-related mortality:
1% by 5-years

Continuing Nuc therapy

liver-related mortality:
1.1-4.3% by 4-5-years

Untreated natural history

liver-related mortality:
14% by 5-years

HBsAg loss increased in patients off-Nuc

- HBsAg loss in ETV or TDF treated Pts: 2.6-4% by 10 years

<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>Ethiocs</th>
<th>Nuc</th>
<th>No.</th>
<th>Tx (yr)</th>
<th>F/U (mo)</th>
<th>HBsAg loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berg</td>
<td>RCT</td>
<td>Caucasian (88%)</td>
<td>TDF</td>
<td>21</td>
<td>&gt;4</td>
<td>33</td>
<td>30% /3 yrs</td>
</tr>
<tr>
<td>van Bommel</td>
<td>RCT</td>
<td>Caucasian (80%)</td>
<td>Mixed</td>
<td>79</td>
<td>&gt;4</td>
<td>24</td>
<td>10.3% /2 yrs</td>
</tr>
<tr>
<td>Hadziyannis</td>
<td>Pro/Cohort</td>
<td>Caucasian</td>
<td>ADV</td>
<td>33</td>
<td>4-5</td>
<td>66</td>
<td>39% /5 yrs</td>
</tr>
<tr>
<td>Manolakopoulos</td>
<td>Pro/Cohort</td>
<td>Caucasian</td>
<td>ETV/TDF</td>
<td>57</td>
<td>7.5</td>
<td>65</td>
<td>20% /3 yrs</td>
</tr>
<tr>
<td>Garcia-Lopez</td>
<td>Pro/Cohort</td>
<td>Caucasian (93%)</td>
<td>ETV/TDF</td>
<td>27</td>
<td>8</td>
<td>34</td>
<td>30% /3 yrs</td>
</tr>
<tr>
<td>Chan</td>
<td>Cohort</td>
<td>Asian (100%)</td>
<td>LAM</td>
<td>53</td>
<td>3</td>
<td>71</td>
<td>23% /5 yrs</td>
</tr>
<tr>
<td>Chi</td>
<td>Cohort</td>
<td>Asian (80%)</td>
<td>Mixed</td>
<td>59</td>
<td>5</td>
<td>19.4</td>
<td>14% /3 yrs</td>
</tr>
<tr>
<td>Chen</td>
<td>Cohort</td>
<td>Asian (100%)</td>
<td>ETV</td>
<td>250</td>
<td>3.2</td>
<td>&gt;60</td>
<td>20.8% /6 yrs</td>
</tr>
<tr>
<td>Jeng</td>
<td>Cohort</td>
<td>Asian (100%)</td>
<td>ETV</td>
<td>671</td>
<td>3</td>
<td>36</td>
<td>16% /6 yrs (non-LC)</td>
</tr>
<tr>
<td>Hirode (RETRACT)</td>
<td>Global cohort</td>
<td>Asian (88%)</td>
<td>Mixed</td>
<td>1541</td>
<td>3</td>
<td>17</td>
<td>14% /4 yrs</td>
</tr>
</tbody>
</table>
|               |          | Caucasian (N=152) |        |     |         |          | (Asian: 11%, Caucasian: 1%)

HBV specific CD8+ T cell response vs. HBsAg loss

Increase along with follow-up

No increase along with follow-up

Baseline viral markers associated with HBsAg loss

Baseline HBV-specific T cell functionality in patients remaining off-therapy

Rinker F et al JH 2018; García-López M et al J Hepatol 2020
Much increased HBsAg loss rate in finite therapy, with comparable excellent prognosis as spontaneous HBsAg loss patients

- **Cirrhosis** is the only independent factor for HCC: aHR: 8.86 (1.86-42.1), P<0.01
- Clinical or viral relapse prior to HBsAg loss does not increase HCC risk

Chen CH et al JID 2019 219(10):1624-1633; Jeng WJ et al AASLD 2021 (Left), Jeng WJ et al (submission, right)
The cumulative HBsAg seroclearance rate was highest in patients with sustained response and lowest in those retreated

SR > CR untreated > CR treated in two independent cohort

Retreatment decision is crucial: Not too late for safety, not too early to halt HBsAg clearance

Decompensation is rare, mostly reported in cirrhotic patients\(^1\)
5-year: 2.95% in cirrhosis and 0% in non-cirrhosis [HBeAg: (-)]\(^4\)

<table>
<thead>
<tr>
<th>Source</th>
<th>NA</th>
<th>Tx (yrs)</th>
<th>F/U (mos)</th>
<th>HBsAg loss</th>
<th>aOR or aHR, P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hadziyannis(^2)</td>
<td>ADV</td>
<td>4-5</td>
<td>66</td>
<td>1/15 (6%)</td>
<td>13/18 (72.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>No retx</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CR (retx)</td>
<td>0.027 (retx vs. no retx), P=0.002</td>
</tr>
<tr>
<td>Berg(^3)</td>
<td>TDF</td>
<td>&gt; 4</td>
<td>36</td>
<td>0/8 (0%)</td>
<td>4/13 (30.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>No retx</strong></td>
<td></td>
</tr>
<tr>
<td>Jeng(^4)</td>
<td>ETV/TDF</td>
<td>3</td>
<td>36</td>
<td>2/269 (0.7%)</td>
<td>40/410 (9.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>CR (retx)</strong></td>
<td>7.34 (CR+/no-retx vs. CR+/retx), P=0.0124</td>
</tr>
<tr>
<td>Garcia-Lopez(^5)</td>
<td>ETV/TDF</td>
<td>8</td>
<td>34</td>
<td>0/5 (0%)</td>
<td>8/22 (36.4%)</td>
</tr>
<tr>
<td>Manolakopoulos(^6)</td>
<td>ETV/TDF</td>
<td>7.5</td>
<td>65</td>
<td>0/28 (0%)</td>
<td>8/29 (27.5%)</td>
</tr>
</tbody>
</table>

Among 267 no-Rx HBeAg-Neg CHB with 6-year f/u: HBsAg loss in SR: 52.9%, VR: 21.2%, CR: 41.4%
CGMH-LK cohort: 10-year HBsAg loss: **no-CR: 51%, CR: 27%, Rx: 5%**

Current known risk factors for off-Nuc clinical relapse

Host

- Older age
- Host genetic factors: CTLA4 (rs231775); rs3077
- Liver cirrhosis
- Prior Tx history

On-treatment

- HBsAg level (EOT)<100 IU/ml (for ETV), <80 IU/ml for TDF)
- ALT normalization (lower risk if <3 months for TDF)
- EOT HBV RNA
- EOT HBcrAg
- ALT normalization (lower risk if <3 months for TDF)

Host Virus On-treatment

EOT HBsAg level is not the absolute factor for finite therapy decision

Among 691 HBeAg (-) finite therapy, only 16.5% EOT HBsAg <100 IU/mL

• No correlation between EOT HBsAg level and time to relapse
• No correlation between EOT HBsAg level and flare severity
  • Using EOT HBsAg 100IU/mL for prediction of CR or flare: AUROC: 0.66, 0.6, respectively\(^1\)
• Sustained responder by 2-year f/u

<table>
<thead>
<tr>
<th>EOT HBsAg, IU/mL</th>
<th>ETV</th>
<th>TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>71%</td>
<td>47%</td>
</tr>
<tr>
<td>100-999</td>
<td>42%</td>
<td>29%</td>
</tr>
<tr>
<td>&gt;=1000</td>
<td>35%</td>
<td>23%</td>
</tr>
</tbody>
</table>

1. Liu YC/Jeng WJ et al Liver International 2022; Liu YC et al EASL 2021 Oral presentation, submission
## Biochemical marker(s) for retreatment

<table>
<thead>
<tr>
<th>Source</th>
<th>Fu</th>
<th>Criteria to retreat</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Berg T 2017 J Hepatol 2017</td>
<td>2-weekly x 3mo 4-weekly ~</td>
<td>ALT &gt;10X &gt; 2 visit* or 5-10X ≥ 4wk*  Bil ↑ &gt; 1.5 mg or INR ↑ &gt; 0.5</td>
</tr>
<tr>
<td>• Papatheodoridis GV Hepatology 2018</td>
<td>monthly x 3mo 3-monthly~</td>
<td>ALT x 10X# ALT x 5X + Bil &gt; 2 mg ALT &gt; 3X + DNA &gt; 10^5 IU/mL#</td>
</tr>
<tr>
<td>• Liem KS Gut 2019</td>
<td>wk 4 and 6 then/6-8 wk</td>
<td>ALT &gt; 15X ULN (40)# ALT &gt; 5X &gt; 2 visit* ALT 200-600 for 6-8 wks*</td>
</tr>
<tr>
<td>• Garcia-Lopez J Hepatol 2020</td>
<td>monthly x 6 mo then/3 or 4 monthly~24mo</td>
<td>ALT &gt; 10X ULN x 2 visits* ALT &gt; 5-10X ULN + DNA &gt; 2000 IU/mL ≥ 4wk ALT &gt; 2-5X ULN + DNA &gt; 2000 IU/mL ≥ 6 mos</td>
</tr>
</tbody>
</table>

* follow-up > 4-weekly: may be too late
# data at one time point may be too early
Off-Nuc follow-up strategy: APASL guideline *(modified)*

- Monitoring is mandatory!
  - **Off-NUC**: ALT/m x 3m; ALT+HBV DNA/3m for 1yr; then ALT/HBV per 3-6m
  - Once virological relapse (HBV DNA>2000IU/mL) $\rightarrow$ q1-1.5m ALT check up
  - If ALT increasing or > 5X ULN: ALT, bilirubin, INR/1-2 wk for retreatment decision

Retreatment in patients with host-dominating flare halts the decline of HBsAg

Virus dominating flare (Ineffective flare)  Host dominating flare (Effective flare)

1-yr ↓: -1.0 log\textsubscript{10} IU/mL  1-yr ↓: -0.01 log\textsubscript{10} IU/mL

Rapid HBsAg decline (69.8 vs. 8.3%, P<0.001)  HBsAg rebound (33%)

Rapid HBsAg decline: >0.5 log/6m or >1 log/1yr

HBsAg < 100 IU/mL and HBsAg loss by 3 year:
- No retx: 20% and 6%
- Retx: 32% and 2%

HBsAg < 100 IU/mL and HBsAg loss by 3 year:
- No retx: 25% and 21%
- Retx: 12% and 0%

Distinct different relapse pattern between ETV and TDF
Valid in all subgroups

Off-therapy relapse and flare occurs simultaneously in off-TDF patients

Factors for off-therapy flare | aHR (95%CI) | P value
--- | --- | ---
Age >=55 | 1.37 (1.14-1.64) | <0.001
Cirrhosis | 1.49 (1.24-1.79) | <0.001
Prior Tx | 1.37 (1.14-1.64) | <0.001
HBV Genotype C vs. B | 0.69 (0.53-0.88) | 0.004
PreTx HBV DNA >6 log_{10} IU/mL | 1.28 (1.05-1.57) | 0.001
PreTx HBsAg >3 6 log_{10} IU/mL | 1.45 (1.12-1.81) | <0.001
TDF vs. ETV | 2.35 (1.91-2.89) | <0.001
EOT HBsAg<100 | 0.49 (0.35-0.67) | <0.001

Liu YC/Jeng WJ et al Liver Int . 2022 Mar;42(3):551-560
Although severe flare or hepatic decompensation is rare in non-cirrhotic patients, it happens.

- During 1999-2020, 13 of the 1234 patients (1%) encountered hepatic decompensation after stopping Nuc [12/495 (2.4%): cirrhosis, 1/739 (0.1%): non-cirrhosis → the non-LC Pt successfully recovered]¹
  - 7 of 13 not adhered to follow-up protocol
  - Off-Nuc hepatic decompensation risk factor: **Cirrhosis** [aHR: 20.5 (2.65-159.37), P=0.004], **Off-TDF** [vs. ETV, aHR: 5.53 (1.73-17.69), P=0.004]
- 5 of 411 (1.2%) non-LC hepatic decompensation, 8-year: 3%²
  - LAM or ETV, 3/148 (2%) HBe+ -> one mortality, 2/263 HBe- (0.76%)
- 4 of 375 (1%) HBeAg Neg non-LC hepatic decompensation (T.Bil>2 or INR prolonged 3 sec)
  - 2 ETV, 2TDF

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Summary

• Finite therapy in HBeAg negative non-cirrhotic patients is considerable if stringent follow-up being provided and with well mutual communication between physicians and patients, about the risk and benefit.

• Retreatment criteria is still await to be explored: how to be safe but not too early to halt the chance toward functional cure
Thank you for your attention!