OVERVIEW OF STOPPING NUCS IN CURRENT CLINICAL PRACTICE

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Disclosures

No conflicts of interest to disclose
Main goals of nucleos(t)ide analogue (NUC) therapy for chronic hepatitis B (CHB) patients:
- Long-term HBV DNA suppression
- HBeAg loss, with or without anti-HBe seroconversion, in HBeAg positive CHB patients
- ALT normalization
- HBsAg loss, with or without anti-HBs seroconversion → optimal endpoint!
- Improve survival and quality of life by preventing disease progression and HCC

Current guidelines:
- The Asian Pacific Association for the Study of the Liver (APASL) 2016
- The European Association for the Study of the Liver (EASL) 2017
- The American Association for the Study of Liver Diseases (AASLD) 2018
Stopping NUC therapy

**PRO**

- Life-long therapy not required
  - Financial benefits?
  - Adherence/compliance?

- No NUC-related long-term side-effects or safety concerns

- Higher rates of HBsAg loss
  - On-therapy (annual incidence) ~1%\(^1,2\)
  - Off-therapy (cumulative incidence) 0-55% over follow-up durations of 0.5-8 years\(^3,4\)

**CON**

- NUCs are cheap in most regions, safe and effective, improve long-term outcomes, and monitoring is simple

- Prediction of response after stopping unclear:
  - Strict and frequent monitoring required
  - Non-compliance can result in severe or fatal flares
  - Costs?

- While for those who remain HBsAg positive, disease remission may be achieved, long-term HBV DNA undetectability may not be achieved
  - Risk of progression of fibrosis

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**Stopping guidelines: HBeAg positive patients**

<table>
<thead>
<tr>
<th>APASL 2016¹</th>
<th>EASL 2017²</th>
<th>AASLD 2018³</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg loss</td>
<td>HBsAg loss</td>
<td>HBsAg loss</td>
</tr>
<tr>
<td>OR</td>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td>HBeAg seroconversion +</td>
<td>HBeAg seroconversion +</td>
<td>HBeAg seroconversion +</td>
</tr>
<tr>
<td>Consolidation ≥12 months +</td>
<td>Consolidation ≥12 months +</td>
<td>Consolidation ≥12 months +</td>
</tr>
<tr>
<td>Undetectable HBV DNA +</td>
<td>Undetectable HBV DNA +</td>
<td>Undetectable HBV DNA +</td>
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</tbody>
</table>

### Stopping guidelines: HBeAg negative patients

<table>
<thead>
<tr>
<th>APASL 2016&lt;sup&gt;1&lt;/sup&gt;</th>
<th>EASL 2017&lt;sup&gt;2&lt;/sup&gt;</th>
<th>AASLD 2018&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg loss</td>
<td>HBsAg loss</td>
<td>HBsAg loss</td>
</tr>
<tr>
<td>+ Consolidation ≥12 months</td>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td>or anti-HBs+</td>
<td>May be considered in selected patients given the following:</td>
<td>Compelling rationale</td>
</tr>
<tr>
<td>OR</td>
<td>Viral suppression ≥36 months</td>
<td></td>
</tr>
<tr>
<td>NUC therapy ≥24 months +</td>
<td>No cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Undetectable HBV DNA on three occasions 6 months apart +</td>
<td>Guaranteed post-NUC monitoring</td>
<td></td>
</tr>
<tr>
<td>No cirrhosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RCT: FINITE study

- **42 virally suppressed HBeAg negative patients (21 stop, 21 continue):**
  - 88% Caucasian
  - 100% TDF
  - Mean Fibroscan 5.6 kPa

- **Primary endpoint:**
  - HBsAg loss at 144 weeks

- **Conclusions:**
  - Higher HBsAg loss in stop arm at 144 weeks
  - No serious adverse events
  - Highly controlled cohort under strict observation!

- **Retreatment criteria:**
  - ALT flares
  - Clinical relapse
  - Decompensation

*For patients who fulfilled any of these criteria, TDF was restarted at the discretion of the investigator*

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RCT: TORONTO STOP study

• 67 virally suppressed HBeAg-patients (45 stop, 22 continue):
  – 97% Asian
  – 7% ETV, 93% TDF
  – Mean Fibroscan 5 kPa

• Primary endpoint:
  – Sustained response (HBV DNA <2000 IU/mL) at 48 weeks

• Conclusions:
  – NUC withdrawal has marginal benefits in Asians
  – No serious adverse events

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Response at 72 weeks:

<table>
<thead>
<tr>
<th></th>
<th>Stop vs. Continue</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg loss</td>
<td>2.2% vs. 4.5%</td>
<td>1.00</td>
</tr>
<tr>
<td>HBV DNA &lt;20 IU/mL</td>
<td>2.2% vs. 91%</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>ALT ≤ULN</td>
<td>47% vs. 82%</td>
<td>0.01</td>
</tr>
<tr>
<td>ALT ≤ULN + HBV DNA &lt;2000 IU/mL</td>
<td>29% vs. 82%</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Retreated</td>
<td>38% vs. N/A</td>
<td></td>
</tr>
</tbody>
</table>

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• Retreatment criteria:
  – HBeAg seroreversion
  – Clinical relapse

Final decision was at the discretion of the treating physician

RCT: Stop-NUC trial

- **158 HBeAg negative patients** (79 stop, 79 continue):
  - 80% Caucasian
  - 39% ETV, 51% TDF
  - Mean Fibroscan 5.7 kPa

- **Primary endpoint:**
  - HBsAg loss at 96 weeks

- **Conclusions:**
  - Higher HBsAg loss in stop arm at 96 weeks
  - End of therapy HBsAg <1000 U/mL predictive of HBsAg loss
  - No serious adverse events
  - ALT flares respond well to retreatment
  - Long-term monitoring is crucial

### HBsAg loss

<table>
<thead>
<tr>
<th>HBsAg loss</th>
<th>Baseline HBsAg &lt;1000 U/mL</th>
<th>Baseline HBsAg ≥1000 U/mL</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>18 (72%)</td>
<td>53 (98.1%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>7 (28%)</td>
<td>1 (1.9%)</td>
<td></td>
</tr>
</tbody>
</table>

### Results at Week 96: NUC stopping arm

<table>
<thead>
<tr>
<th>Event</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg loss</td>
<td>8 (10.3)</td>
</tr>
<tr>
<td>No retreatment indicated</td>
<td>53 (67.9)</td>
</tr>
<tr>
<td>Retreatment indicated</td>
<td>6 (7.7)</td>
</tr>
<tr>
<td>Retreatment initiated</td>
<td>11 (14.1)</td>
</tr>
<tr>
<td>Total</td>
<td>78 (100)</td>
</tr>
</tbody>
</table>

- **There were six main retreatment criteria:**
  - ALT flares (3)
  - Decompensation (1)
  - **Physician discretion** (2)
# Cohort studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Number of patients</th>
<th>Race/ ethnicity</th>
<th>Pre-therapy HBeAg</th>
<th>HBsAg loss incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan</td>
<td>53</td>
<td>Asian</td>
<td>Neg</td>
<td>23% at 5 years</td>
</tr>
<tr>
<td>Hadziyannis*</td>
<td>33</td>
<td>Caucasian</td>
<td>Neg</td>
<td>39% at 5.5 years</td>
</tr>
<tr>
<td>Chen</td>
<td>188</td>
<td>Asian</td>
<td>Pos / Neg</td>
<td>24% at 6 years</td>
</tr>
<tr>
<td>Patwardhan*</td>
<td>33</td>
<td>N/A</td>
<td>Neg</td>
<td>N/A</td>
</tr>
<tr>
<td>Chi*</td>
<td>94</td>
<td>Mixed</td>
<td>Pos / Neg</td>
<td>3.1% annual rate</td>
</tr>
<tr>
<td>Hung*</td>
<td>73</td>
<td>Asian</td>
<td>Neg</td>
<td>47% at 6 years</td>
</tr>
<tr>
<td>Yao</td>
<td>119</td>
<td>Asian</td>
<td>Neg</td>
<td>55% at 6 years</td>
</tr>
<tr>
<td>Cao</td>
<td>82</td>
<td>Asian</td>
<td>Pos / Neg</td>
<td>10% at 2 years</td>
</tr>
<tr>
<td>Van Hees*</td>
<td>62</td>
<td>Mixed</td>
<td>Pos</td>
<td>N/A</td>
</tr>
<tr>
<td>Jeng*</td>
<td>691</td>
<td>Asian</td>
<td>Neg</td>
<td>13% at 6 years</td>
</tr>
<tr>
<td>Papatheodoridis*</td>
<td>57</td>
<td>Caucasian</td>
<td>Neg</td>
<td>25% at 1.5 years</td>
</tr>
<tr>
<td>Su*</td>
<td>100</td>
<td>Asian</td>
<td>Neg</td>
<td>0% at 2 years</td>
</tr>
<tr>
<td>Chen*</td>
<td>411</td>
<td>Asian</td>
<td>Pos / Neg</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* Reports number of complications off-therapy

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RETRACT-B study

Update on the RETRACT-B study design and protocol presented at the HBV forum in 2019

• **Study design**: Retrospective cohort study (N = 1,556)

• **Study population**: CHB patients who discontinued NUC therapy from participating centers across North America, Europe, and Asia

  • **Inclusion**:
    – Virally suppressed at NUC withdrawal
    – HBeAg negative at NUC withdrawal: both HBeAg positive and negative at start of therapy

  • **Exclusion**:
    – Coinfection: HCV, HDV, and/or HIV
    – HCC diagnosis prior to stopping NUCs
    – Pegylated interferon therapy within 12 months prior to stopping NUCs
RETRACT-B study: Global, multi-center cohort

- Toronto Centre for Liver Disease
- Erasmus Medical Center
- Antwerp University Hospital
- Hospital Clinic of Barcelona
- Hannover Medical School
- Medical School of National and Kapodistrian University of Athens

Additional locations include:
- University of Hong Kong
- The Chinese University of Hong Kong
- Chang Gung Memorial Hospital
- National Taiwan University Hospital
- Kaohsiung Chang Gung Memorial Hospital
- E-DA Hospital/Fu-Jen Catholic University Hospital

(Toronto Centre for Liver Disease logo on the left)
# RETRACT-B study: Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Cohort (N = 1,556)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at NUC withdrawal:</strong> &lt; 50 years / ≥ 50 years, %</td>
<td>37 / 63</td>
</tr>
<tr>
<td><strong>Sex:</strong> Male / Female, %</td>
<td>72 / 28</td>
</tr>
<tr>
<td><strong>Race/ethnicity:</strong> Caucasian / Asian / Other, %</td>
<td>11 / 88 / 1</td>
</tr>
<tr>
<td><strong>NUC prior to withdrawal:</strong> ETV / TDF, %</td>
<td>63 / 29</td>
</tr>
<tr>
<td><strong>Total NUC duration, years, median (IQR)</strong></td>
<td>3.0 (3.0 – 4.0)</td>
</tr>
<tr>
<td><strong>Start of therapy HBeAg status:</strong> Negative / Positive, %</td>
<td>84 / 15</td>
</tr>
</tbody>
</table>

**At NUC withdrawal**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cirrhosis status:</strong> Non-cirrhotic / Cirrhotic, %</td>
<td>88 / 12</td>
</tr>
<tr>
<td><strong>HBsAg, ( \log_{10} ) IU/mL, mean ± SD</strong></td>
<td>2.6 ± 0.8</td>
</tr>
<tr>
<td><strong>ALT x ULN, median (IQR)</strong></td>
<td>0.6 (0.4 – 0.8)</td>
</tr>
</tbody>
</table>

**During off-therapy follow-up**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of follow-up visits, median (IQR)</strong></td>
<td>6 (3 – 9)</td>
</tr>
<tr>
<td><strong>Time between visits, months, median (IQR)</strong></td>
<td>2.8 (2.0 – 5.0)</td>
</tr>
<tr>
<td><strong>Total follow-up time, months, median (IQR)</strong></td>
<td>19.4 (8.0 – 39.8)</td>
</tr>
</tbody>
</table>
RETRACT-B study: HBsAg loss

- Cumulative incidence of HBsAg loss:
  - 3% at 1 year
  - 7% at 2 years
  - 10% at 3 years
  - 13% at 4 years

- Adjusted HBsAg loss ~6 times higher among Caucasians vs. Asians (p <0.001)

- Adjusted HBsAg loss ~22 times higher among patients with end of therapy HBsAg ≤100 IU/mL vs. >100 IU/mL (p <0.001)
RETRACT-B study: Results

- Cumulative incidence of retreatment was 30% at 1 year and 56% at 4 years off-therapy

- 19 patients developed hepatic decompensation:
  - Cumulative incidence of hepatic decompensation was 1% at 1 year and 2% at 4 years off-therapy
  - Higher among patients diagnosed with cirrhosis at any time point prior to NUC withdrawal
  - Higher among start of therapy HBeAg positive patients

- 16 patients developed HCC:
  - Cumulative incidence of HCC was 0.4% at 1 year and 1% at 4 years off-therapy

- 14 (1%) patients died among the total cohort
What we know: Flares

- Risk of severe ALT flares after NUC withdrawal may be associated with severity of virological relapse\(^1\)
- An ALT flare may not be a prerequisite for HBsAg loss,\(^2\) and may result in complications if not retreated

Host-dominating or “effective” flare\(^3\)  
Virus-dominating or “ineffective” flare\(^3\)

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1. Papatheodoridis GV et al. 2018;68(2):415-424  
What we know: Complications

• Case reports of patients who developed off-NUC complications, or descriptive information within a larger study

• Few studies comparing incidence of liver-related complications on- and off-NUC therapy
  – Most with small sample sizes
  – Most show no difference in HCC incidence

• However, rates of hepatic decompensation and HCC cannot be compared across studies due to differences in baseline criteria
  – Need a well-designed large and long-term RCT to answer this question!
What we know: Retreatment

• Current decisions on when to retreat largely based on physician discretion

• Virological relapse after stopping is universal → poor criterion

• No retreatment criteria outlined in any of the three guidelines!

• Decision on when to retreat is crucial:
  – Not to early → to potentially achieve HBsAg loss
  – Not too late → to prevent liver-related complications
Conclusion

• Most existing studies are small, single-site studies that did not correct for selection or measurement bias

• Larger studies on stopping NUCs are from Asia which are not seldom driven by local policies and reimbursement criteria

Future direction:

– Better understanding of viral and host factors involved in the pathogenesis of CHB
– Identification of novel biomarkers and predictors of response after NUC withdrawal
– Off-NUC flare management strategies
– Standardization of stopping and retreatment criteria, and monitoring frequencies
– New antivirals and therapeutic strategies, including combination therapies → more RCTs!