Response after End of Treatment with Antivirals in Chronic Hepatitis B
The advent of potent nucleos(t)ide analogues (NAs) has led to effective viral suppression in most chronic hepatitis B (CHB) patients. Nonetheless, functional cure (i.e. HBsAg loss) still very infrequently achieved with NAs, often leading to life-long treatment. Current guidelines for discontinuation of therapy:

- HBeAg-positive patients – HBeAg seroconversion, undetectable HBV DNA + ≥12 months of consolidation therapy
- HBeAg-negative patients - ≥36 months of on-treatment viral suppression
Stop NA Therapy HBeAg negative CHB

Lampertico & Berg Hepatology 2018
Main rationale for stopping NA therapy:
To induce a durable remission of HBV infection (i.e. healthy carrier state with undetectable viremia or functional cure)

HBsAg loss:
- Prospective studies
  - 0-39% in 1-6 years
- Retrospective studies
  - 0.5-47% in 2-9 years
## Summary of studies HBsAg seroclearance after stop NA

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Tx duration</th>
<th>HBsAg loss</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan</td>
<td>53</td>
<td>27 mo</td>
<td>11/53</td>
<td>23% - 5 yrs</td>
</tr>
<tr>
<td>Hadziyannis</td>
<td>33</td>
<td>4-5 yrs</td>
<td>13/33</td>
<td>39% - 3 yrs</td>
</tr>
<tr>
<td>Chen</td>
<td>105</td>
<td>93 wks</td>
<td>?</td>
<td>30% - 6 yrs</td>
</tr>
<tr>
<td>Patwardhan</td>
<td>33</td>
<td>5.3 yrs</td>
<td>?</td>
<td>30% - 6 yrs</td>
</tr>
<tr>
<td>Hung</td>
<td>73</td>
<td>30 mo</td>
<td>20/73</td>
<td>46% - 6 yrs</td>
</tr>
<tr>
<td>Yao</td>
<td>119</td>
<td>151 wks</td>
<td>44/119</td>
<td>55% - 6 yrs</td>
</tr>
<tr>
<td>Berg</td>
<td>21 (42)</td>
<td>&gt;4 yrs</td>
<td>4/21</td>
<td>19% - 144 wks</td>
</tr>
<tr>
<td>Jeng*</td>
<td>691</td>
<td>156 wks</td>
<td>42/691</td>
<td>13% - 6 yrs</td>
</tr>
<tr>
<td>Papatheodoridis</td>
<td>57</td>
<td>5.3 yrs</td>
<td>12/57</td>
<td>25% 1.5 yrs</td>
</tr>
</tbody>
</table>

*Estimated Annual HBsAg loss of 1.78%*

Courtesy F. Zoulim EASL PCG 2018; adapted from Jeng WJ et al. Hepatology 2018;68:425
Relapse & Adverse Events

- Virologic/clinical relapse:
  - 48-75% in 3-8 years

- Stopping treatment almost always leads to virologic relapse, however does not always result in clinical relapse

- Biochemical relapse can range from mild ALT elevation to ALT flares (beneficial/detrimental)

- Adverse clinical events (sometimes flare-associated) do occur in both cirrhotic and non-cirrhotic patients after stopping therapy (decompensation, HCC, death)
• Varying results between studies raise questions as to whether NA cessation can be applied to all patients who meet the current stopping criteria

• Limitations in reaching consensus on stopping:
  – Heterogeneity and geographical area of studies
  – Different criteria for retreatment
  – Small sample size

• Pooled analysis on a global scale is crucial to investigate outcomes following cessation of NA therapy with robust statistical power. This is highly relevant both for current patient care and for drug development aiming at functional cure (HBV Forum).
Aims

To evaluate outcomes following cessation of NA therapy in a large, combined global multi-centre cohort of CHB patients
Types of projects in Retract B

• General Projects: include collection of clinical and biological data generated by the group on the full series of patients, addressing the major goals of the study.

• Specific Projects: these projects can be initiated by any member of the Retract B Study Group and will focus on a specific question in a defined subset of data and/or samples from the Retract B consortium.
General Project:
To study the effect of stopping NA therapy on various viral and biochemical endpoints (e.g. virologic relapse, ALT flares, HBeAg seroreversion, HBsAg loss, HBsAg flares), stratified by on-treatment HBeAg status

Specific Project 1:
To investigate variation in viral and biochemical outcomes according to different NA treatments (e.g. entecavir vs tenofovir) given before cessation

Specific Project 2:
To describe hepatic decompensation and mortality in CHB patients following cessation of NA treatment
General Project: Patients

• Longitudinal observational cohort study (collection of retrospective data)

• Inclusion:
  CHB patients who discontinued NA therapy
  o HBeAg-positive – HBeAg seroconversion and undetectable serum HBV DNA for ≥6 months
  o HBeAg-negative – undetectable serum HBV DNA for ≥12 months

• Exclusion:
  o HCV/HDV/HIV coinfection
  o Interferon treatment within 12 months prior to start of NA treatment
Participating Centres

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

Launch AASLD 2019

Abstract: Overall results AASLD 2020

Manuscript: Overall results 2020

Manuscripts:
- ETV vs TDF
- Adverse Outcomes 2020-2021

Investigators meeting at every AASLD and EASL
Discussion

RETRACT-B
THE GLOBAL STUDY GROUP

Investigators’ Meeting
AASLD The Liver Meeting Nov 9th, 2019