Nucleos(t)ide analogues for chronic hepatitis B: Cessation of treatment.
Alex Thompson

Gold Coast, 31st September 2016
Acknowledgement to Country

• We recognise the traditional custodians of the land and sea on which we live and work
Disclosures

• Advisory board member - Gilead, Abbvie, Bristol-Myers Squibb (BMS), Merck, and Roche Diagnostics

• Speaker - Gilead, Janssen, Merck, BMS, Abbvie

• PI - Gilead, Merck, Roche, BMS, Janssen, Spring Bank

• Research / grant support – Gilead, Merck, BMS, Abbvie

• My presentation includes discussion of drugs which are not approved for clinical use
### Stopping NAs: Guideline recommendations

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EASL guidelines J Hepatol, 2012; 57:167-85  
Terrault N, Hepatology, 2016; 63(1):261-83  
Sarin, SK. Hepatol Int, 2016; 10:1–98
HBEAG-POSITIVE CHB
## Stopping NAs: Guideline recommendations

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HBeAg S/C is not always durable

- Single centre observational study, $n=132$

<table>
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<tr>
<th>Age, y</th>
<th>38 ± 15</th>
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</thead>
<tbody>
<tr>
<td>Sex (male, %)</td>
<td>100 (76%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>77 (58%)</td>
</tr>
<tr>
<td>Asian</td>
<td>41 (31%)</td>
</tr>
<tr>
<td>Other</td>
<td>14 (11%)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24 ± 4.1</td>
</tr>
<tr>
<td>ALT, × upper limit of normal</td>
<td>2.3 (1.4–4.8)</td>
</tr>
<tr>
<td>HBV-DNA level, $\text{log}_{10}$ copies/mL</td>
<td>8.2 ± 1.6</td>
</tr>
<tr>
<td>Genotype ($N = 127$)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>45 (35%)</td>
</tr>
<tr>
<td>B</td>
<td>25 (20%)</td>
</tr>
<tr>
<td>C</td>
<td>19 (15%)</td>
</tr>
<tr>
<td>D</td>
<td>33 (26%)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>23 (17%)</td>
</tr>
<tr>
<td>Treatment course</td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td>67 (51%)</td>
</tr>
<tr>
<td>Adefovir</td>
<td>33 (25%)</td>
</tr>
<tr>
<td>Entecavir</td>
<td>22 (17%)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (7%)</td>
</tr>
<tr>
<td>Nucleos(t)ide analogue treatment-naive</td>
<td>117 (89%)</td>
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- $42$ patients achieved HBeAg S/C

- $33$ experience SR or VR despite ongoing NA therapy
  = NA resistance

- $9$ patients stopped NA after $> 6$ m consolidation therapy
  - $3/9$ HBeAg SR
  - $7/9$ virological recurrence
Consolidation therapy ≥ 12 months is important for reducing the risk of relapse

Retrospective multi-centre study of Korean patients treated with lamivudine monotherapy

Relapse = HBV DNA > 2800 IU/mL

Lee, Hepatology, 2010
Is 12 months consolidation enough?
Relapse is more common using a more sensitive HBV DNA assay

Durability of consolidation therapy

- Relapse = HBV DNA > 100 IU/mL
- Relapse > 10,000 IU/mL in 25/39
- HBeAg sero-reversion in 3/25

Duration of consolidation therapy

Chaung, J Clin Gastro, 2012
Consolidation > 3 years may reduce relapse rate

Risk of persistent virological relapse significantly reduced at > 2.9 yrs of consolidation therapy vs. 1 yr (Adjusted HR 0.51; 95% CI 0.25–0.99).
Conclusion

• **No cirrhosis**
  – Stopping NA after HBeAg S/C is reasonable
    • HBeAg loss, anti-HBe seroconversion
    • Consolidation ≥ 12m post S/C is important
    • The role of longer consolidation therapy needs to be evaluated
  – People who stop antiviral therapy should be monitored for recurrent viremia, ALT flares, and seroreversion
    • every 3 months for at least 1 year, then 6 monthly

• **Cirrhosis**
  – Stopping NA after HBeAg S/C is controversial
  – AASLD - recommends indefinite antiviral therapy
  – EASL - ...stopping might be considered, but ...NA therapy should usually be continued indefinitely in cirrhotic patients
  – APASL - NA therapy may also be considered in cirrhotic patients with a careful off-therapy monitoring plan
    • Every 1 month for 3 months, every 3 months to 1 year, then 6 monthly
Management of HBeAg-negative CHB

• Nucleoside analogues (NA) are the mainstay of current therapy
  – Potent antiviral activity
  – High genetic barrier to resistance

• But...optimal treatment duration for patients with HBeAg-negative chronic hepatitis B (CHB) remains uncertain
**Stopping NAs: Guideline recommendations**

|----------------|-------------|--------------|--------------|
|                | Confirmed HBsAg loss PLUS anti-HBs seroconversion + ≥ 12m of consolidation | Indefinite treatment is recommended | No cirrhosis:  
i) HBsAg loss PLUS anti-HBs seroconversion OR ≥ 12 months of consolidation  
ii) after treatment for at least 2 years with undetectable HBV DNA documented on three separate occasions, 6 months apart (B1). |
|                | Stopping “MBC” in persons with HBsAg loss | Stopping “MBC” in persons with HBsAg loss |  |
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Stopping “MBC” in cirrhotic patients with a careful off-therapy monitoring plan |

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HBeAg-negative CHB: Virologic relapse occurs when NA stopped

Virological relapse defined as HBV DNA >2000 IU/mL.

Seto 2015
Why STOP?

• Long-term therapy presents challenges
  – adherence can be challenging
  – risk of resistance
  – risk of adverse events (e.g. renal, bone AEs)
  – $$$
Why STOP?

- STOPping long-term NA may have benefit
  - NA deplete cccDNA
  - NA promote restoration of anti-HBV immunity
  - STOPping → virological relapse → therapeutic hepatitis flare:
    - sustained immunological control (phase 3)
    - ± HBsAg loss

Modified from Chan, J Hepatology, 2012
Data from small studies suggest:
- long-term SVR is possible
- HBsAg loss may occur

- Prospective observational study of patients who stopped long-term adefovir
- n = 33, HBeAg-negative CHB, European genotype D disease
- Primary end-point = sustained response
  = HBV DNA persistently ≤ 2000 IU/mL combined with persistently normal ALT values (≤ 40 U/L) following post-treatment month 6 sustained to the end of follow-up.

Hadziyannis, Gastro, 2012
HBsAg levels at EOT may predict for risk of relapse

Hadziyannis, Gastro, 2012
HBsAg levels may also identify patients who achieve HBsAg loss after stopping NA therapy.

MVA – sustained response – low HBsAg levels (EOT), younger age and F gender
MVA – HBsAg loss – low HBsAg, low HBV DNA (PT), longer treatment duration

Chen J Hepatol 2014
HBsAg levels predict for HBsAg decline
(FINITE-CHB study)

TDF-Stop: Week 48 HBsAg Change From Baseline

Lower HBsAg levels – greater reductions in HBsAg / loss

Positive correlation between baseline HBsAg and %change from baseline in HBsAg at Week 48 (corr. = 0.62, p = 0.003)

T Berg et al., 00119 EASL 2015
Long-term consolidation therapy may reduce the risk of relapse in patients with HBeAg-negative CHB.

Consolidation > 64 weeks assoc with lower relapse in pts without cirrhosis and high DNA.

Jeng Hepatology 2013
Long-term consolidation therapy may reduce relapse and increase HBsAg loss

Chi, APT, 2015
Early biochemical flare may predict for HBsAg loss in sustained responders

No HBsAg loss was observed in patients who had NA restarted

Hadziyannis, Gastro, 2012
FINITE-CHB study

HBV DNA < 2,000 at week 48 = 78%

T Berg et al., O0119 EASL 2015
ALT Profiles

- Patients requiring TDF re-initiation (n=3)
- Time TDF was restarted

TDF-Stop (n=21)

- ALT peaked at >2xULN in 12/21 TDF-Stop subjects (57%)

- ALT up to W48
  - Median: 162 U/L
  - Min: 25 U/L
  - Max: 983 U/L

- At W48*
  - 100% (18/18) ALT < 2xULN
  - 83% (15/18) ALT < ULN

* TDF-Restart excluded
FINITE-CHB study

TDF-Stop (n=21)

TDF-Continue (n=21)

HBsAg (log_{10} IU/mL)

Weeks From Baseline

HBsAg loss
Patients requiring TDF re-initiation
Time TDF was restarted

T Berg et al., O0119 EASL 2015
TDF-Stop: HBsAg loss, HBV DNA, ALT, TDF-Restart

- Week 12:
  - HBsAg loss: 52%
  - HBV DNA <2000, ALT <2 x UL: 24%
  - HBV DNA <2000, ALT >2 x UL: 5%
  - HBV DNA >2000, ALT <2 x UL: 10%
  - HBV DNA >2000, ALT >2 x UL: 10%
  - TDF-Restart: 10%

- Week 24:
  - HBsAg loss: 48%
  - HBV DNA <2000, ALT <2 x UL: 38%
  - HBV DNA <2000, ALT >2 x UL: 10%
  - HBV DNA >2000, ALT <2 x UL: 10%
  - HBV DNA >2000, ALT >2 x UL: 10%
  - TDF-Restart: 10%

- Week 48:
  - HBsAg loss: 57%
  - HBV DNA <2000, ALT <2 x UL: 19%
  - HBV DNA <2000, ALT >2 x UL: 10%
  - HBV DNA >2000, ALT <2 x UL: 10%
  - HBV DNA >2000, ALT >2 x UL: 10%
  - TDF-Restart: 14%
Stopping NA therapy is safe*

Systematic review:
- 22 studies, 1732 patients
  - Heterogenous designs, many retrospective case series

Safety:
- Marked ALT flare was rare
- Liver decompensation was observed in 1/1732 patient w cirrhosis, who was salvaged w NA
- Close monitoring is required

Chang, APT, 2015
Why STOP?

- STOPping long-term NA may have benefit
  - NA deplete cccDNA
  - NA promote restoration of anti-HBV immunity
  - STOPping → virological relapse → therapeutic hepatitis flare:
    - sustained immunological control (phase 3) = SVR
    - ± HBsAg loss

Modified from Chan, J Hepatology, 2012
The STOP strategy

• Paradigm shift:
  – Early virological relapse is expected
  – ALT flare is important for achieving SVR and HBsAg loss
    • “therapeutic” flare = immune control
    • close monitoring is necessary

• Prospective studies are needed
  – NHMRC project 1066536
STOPping vs novel immunotherapies?

Adapted from Chan, Thompson et al. J Hepatol, 2011
Novel immunomodulators: “therapeutic flare vs. drug toxicity”

GS-9620 (TLR7 agonist): Chimpanzee studies

The advantage of the STOP strategy:
- Any ALT rise is definitely immune-mediated (not drug toxicity)
- No associated immunosuppression

Lanford, Gastroenterology, 2013
## Conclusion

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Conclusion

• HBeAg-negative CHB?
  – Prospective studies of NA cessation in HBeAg-negative CHB are ongoing
  
  – Goal = HBsAg loss

– Suitable for **non-cirrhotics**

– Close monitoring post-cessation is required