Present and future treatments of chronic hepatitis B

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Disclosures

Advisory Board/Speaker Bureau for:

- BMS, ROCHE, GILEAD SCIENCES, GSK, ABBVIE, MSD, ARROWHEAD, ALNYLAM, JANSSEN
Main concepts and features of current treatment strategies for HBV

<table>
<thead>
<tr>
<th>Features</th>
<th>PegIFNα</th>
<th>ETV, TDF, TAF</th>
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</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>Subcutaneous injections</td>
<td>Oral</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>48 weeks</td>
<td>Long-term until HBsAg loss (stopping NA after some years might be considered in selected cases)¹</td>
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<tr>
<td>Tolerability</td>
<td>Low</td>
<td>High</td>
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<tr>
<td>Long-term safety concerns</td>
<td>Very rarely persistence of on-treatment adverse events (psychiatric, neurological, endocrinological)</td>
<td>Probably not (uncertainties regarding kidney function, bone diseases for some NA)</td>
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<tr>
<td>Contraindications</td>
<td>Many (i.e., decompensated disease, co-morbidities etc.)</td>
<td>None (dose adjustment according to eGFR²)</td>
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<tr>
<td>Strategy</td>
<td>Induction of a long-term immune control by finite treatment</td>
<td>Stopping hepatitis and disease progression by inhibiting viral replication</td>
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<tr>
<td>Level of viral suppression</td>
<td>Moderate (variable response pattern)</td>
<td>Universally high</td>
</tr>
<tr>
<td>Effect on HBeAg loss</td>
<td>Moderate, depending on baseline characteristics</td>
<td>Low in the first year, increases to moderate during long-term treatment</td>
</tr>
<tr>
<td>Effect on HBsAg levels</td>
<td>Variable, depending on baseline characteristics (overall higher as compared to NA)</td>
<td>Low: slowly increases with treatment time in HBeAg-positive patients³; usually very low in HBeAg-negative patients</td>
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<tr>
<td>Risk of relapse after treatment cessation</td>
<td>Low for those with sustained response 6–12 months after therapy</td>
<td>Moderate if consolidation treatment provided after HBeAg seroconversion. High for HBeAg-negative disease</td>
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<tr>
<td>Early stopping rules</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Risk of viral resistance development</td>
<td>No</td>
<td>Minimal to none⁴</td>
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</table>

1. See section on ‘Treatment strategies’.
2. Dose adjustments in patients with eGFR <50 ml/min are required for all NA, except for TAF (no dose recommendation for TAF in patients with CrCl <15 ml/min who are not receiving haemodialysis).
3. A plateau in serologic responses has been observed beyond treatment year 4.
4. So far no TDF or TAF resistance development has been detected.

Table 2

EASL 2017 CPG HBV, J Hepatol 2017
10 years of ETV or TDF therapy for CHB

Summary

- Viral suppression in >95% patients (ETV, TDF)
- HBeAg seroconversion in 40-50%
- HBsAg clearance in 1% (20% in selected group)
- ALT normalization in ~85%
- No major safety issues
- Histological improvement of fibrosis (cirrhosis?)
- Decompensation reduced, portal hypertension improved, HCC reduced
- Overall, improved survival

EASL 2017 HBV Guidelines, J Hepatol 2017
Unmed medical needs for NUC therapy in 2018

- Safety in selected TDF treated pts (ETV/TAF available)
- HCC risk reduced but not abolished
- Low rates of HBsAg loss (functional cure)
Definition of HBV cure: what do we want to achieve?

- **Partial cure***: detectable HBsAg but persistently undetectable serum HBV DNA
- **Functional cure**: sustained undetectable HBsAg and HBV DNA in serum ± anti-HBs
- **Complete (sterilising) cure**: HBsAg undetectable + eradication of HBV DNA including intrahepatic cccDNA and integrated HBV DNA.

* Inactive carriers with undetectable HBV DNA
** HBsAg loss
How to improve HBsAg decline/loss in long-term NUC treated patients?

- Stop NUC (“stop to flare” strategy)
- New strategies based on “current” drugs
  - “switch” NUC to PEG
  - “add-on” PEG to NUC
- New strategies based on “new” drugs
NUC discontinuation in HBeAg negative CHB before HBsAg loss

Potential outcome predictors

- Age, time to undetectable HBV DNA, and duration of viral suppression under NA, HBsAg levels at NA baseline and NA cessation, type of NA (TDF vs. ETV), HBV DNA levels during reactivation phase, re-treatment strategy, and HBV genotype

Treatment phase (> 3 years)

Lag-phase (<1-12 months)

Reactivation phase (~ 3 months)

Consolidation phase (~ 12 months)

Long-term outcome

D) Chronic hepatitis B requiring re-treatment (~ 40%)

C) Indeterminate state not fulfilling immediate re-treatment criteria (~ 10-20%)

B) Sustained virologic response (true „healthy carrier“ state) ± HBsAg level decline ~ 20-30%

A) HBsAg loss (~ 20% after 2-3 years of follow-up)

Lampertico P and Berg T, Hepatology 2018 in press
How to improve HBsAg decline/loss in long-term NUC treated patients?

• Stop NUC ("stop to flare" strategy)

• New strategies based on "current" drugs
  - "switch" NUC to PEG
  - "add-on" PEG to NUC

• New strategies based on "new" drugs


### “Switch to” PEG long-term ETV treated pts

**Results at week 48* - mITT**

<table>
<thead>
<tr>
<th></th>
<th>PegIFN alfa2a (n=94)</th>
<th>ETV (n=98)</th>
<th>P value</th>
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<tbody>
<tr>
<td><strong>HBeAg loss</strong></td>
<td>16 (38%)</td>
<td>16 (33%)</td>
<td>NS</td>
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<tr>
<td><strong>HBeAg seroconversion</strong></td>
<td>14 (15%)</td>
<td>6 (6%)</td>
<td>0.046</td>
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<tr>
<td><strong>HBsAg &lt;100 IU/ml</strong></td>
<td>22 (27%)</td>
<td>4 (4.4%)</td>
<td>&lt;0.0001</td>
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<tr>
<td><strong>HBsAg &lt;10 IU/ml</strong></td>
<td>13 (16%)</td>
<td>0</td>
<td>&lt;0.0001</td>
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<tr>
<td><strong>HBsAg loss</strong></td>
<td>8 (8.5%)</td>
<td>0</td>
<td>&lt;0.01</td>
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<tr>
<td><strong>HBsAg seroconversion</strong></td>
<td>4 (4.3%)</td>
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<td>NS</td>
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<tr>
<td><strong>HBV DNA &lt;1000 cp/mL</strong></td>
<td>59 (72%)</td>
<td>90 (98%)</td>
<td>&lt;0.0001</td>
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<tr>
<td><strong>ALT normal</strong></td>
<td>48 (58%)</td>
<td>84 (94%)</td>
<td>&lt;0.0001</td>
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</tbody>
</table>

25% HBsAg loss in pts with HBsAg <1500 IU/ml at baseline

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*End of treatment for PEG

Ning Q, et al, J Hepatol 2014
How to improve HBsAg decline/loss in long-term NUC treated patients?

- Stop NUC ("stop to flare" strategy)

- New strategies based on "current" drugs
  - "switch" NUC to PEG
  - "add-on" PEG to NUC

- New strategies based on "new" drugs
The possible future curative regimen for hepatitis B

- **Nucleos(t)ide analogue**: To control viral replication and cccDNA re-amplification.
- **Viral antigen inhibitor**: To inhibit HBV life cycle processes (e.g., entry, mRNA transcription, capsid assembly, viral protein secretion).
- **Immune modulation**: To activate or restore HBV targeting immune responses.
- **cccDNA inhibitor**: To silence or eliminate cccDNA.

**Functional cure**

**Complete Cure?**
The possible future curative regimen for hepatitis B

- Nucleos(t)ide analogue: To control viral replication and cccDNA re-amplification
- Viral antigen inhibitor: To inhibit HBV life cycle processes (e.g. entry, mRNA transcription, capsid assembly, viral protein secretion)
- Immune modulation: To activate or restore HBV targeting immune responses
- cccDNA inhibitor: To silence or eliminate cccDNA

Functional cure

Complete Cure?
Future HBV therapies: new targets, new drugs

Immunomodulation
- Toll-like receptors agonists, e.g. GS-9620
- Anti-PD-1 mAb, e.g. BMS-936559
- CYT107
- GI13000
- Vaccine therapy

Entry inhibitors (HBV/HDV)
- Lipopeptides, e.g. Myrcludex-B

RNA interference, (siRNA)
e.g. ARC-520

Inhibition of HBsAg release, e.g. REP 9AC

Polymerase inhibitors
- Nucleoside analogues, e.g. TAF, amadoxovir, MIV-210
- Non-nucleoside, e.g. LB80380

Inhibition of Nucleocapsid Assembly, e.g. Bay 41-4109, NVR1221

Inhibition of Prenylation (HDV)
- Lonafarnib

RNAi therapeutics vs NUC treatment for HBV
RNA interference and AASLD 2016
Safety issues

▪ **Arrowhead**

  nonclinical toxicology study in non-human primates using EX1, the company’s liver-targeted, intravenously administered delivery vehicle. This study involves higher doses of EX1 than those used clinically in humans and higher than those used in the company’s previous animal toxicology studies. The cause of these animal deaths is unknown and under investigation. The EX1 delivery vehicle is used in the company’s ARC-520, ARC-521, and ARC-AAT programs.

▪ **Alnylam**

  Revusiran, a clinical candidate for transthyretin (TTR) cardiomyopathy using our first generation GalNAc-siRNA chemistry……..the DMC reported an imbalance in cardiac mortality in the drug group, no longer supporting development.

  We also terminated, ALN-AAT, for alpha-1 antitrypsin deficiency-associated liver disease, due to transient, asymptomatic, LFT elevations after single doses in 3/15 healthy volunteers.
Bi-weekly Dosing of ARB-1467 LNP siRNA in HBeAg Negative NUC Suppressed Patients with CHB

**STUDY DESIGN AND METHODS**

**Figure 2: ARB-1467-002 study design**

<table>
<thead>
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<th>Cohort</th>
<th>Duration</th>
<th>Dosing Schedule</th>
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<tr>
<td>1</td>
<td>Wk 0-24</td>
<td>HBeAg&lt;sup&gt;-1&lt;/sup&gt; 0.2 mg/kg Monthly</td>
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<tr>
<td>2</td>
<td>Wk 0-24</td>
<td>HBeAg&lt;sup&gt;-1&lt;/sup&gt; 0.4 mg/kg Monthly</td>
</tr>
<tr>
<td>3</td>
<td>Wk 0-24</td>
<td>HBeAg&lt;sup&gt;-1&lt;/sup&gt; 0.4 mg/kg Monthly</td>
</tr>
<tr>
<td>4</td>
<td>Wk 0-Wk 48</td>
<td>HBeAg&lt;sup&gt;-1&lt;/sup&gt; 0.4 mg/kg Bi-weekly</td>
</tr>
</tbody>
</table>

Randomized 3:1 active:placebo

Data collected pre-dose and throughout Weeks 0–10; Last dose at Week 8 (monthly and bi-weekly)

Cohort 4 subjects continued to monthly dosing up to Treatment Week 48 if they met the following criteria (after 5 bi-weekly doses of ARB-1467):
- **Responder Criteria**: HBsAg ≤1000 IU/mL with ≥1 log10 decline during the first 10 weeks of treatment

- ARB-1467 or placebo given as a 2-hour IV infusion (Cohort 4 open-label)
- Broad inclusion criteria
  - Non-cirrhotic, chronic HBV infection receiving NA therapy with ETV or TDF for ≥12 months
  - HBsAg ≥1000 IU/mL, HBV-DNA negative
  - ALT or AST ≤ 2x ULN
  - Fibroscan ≤ 9 kPa
- **Pre-medications given** the evening prior and 30 minutes prior to each infusion
- Safety monitoring and HBV markers were performed throughout monthly and bi-weekly portions of the study

Agarwal K et al, AASLD 2017, LB #17
Cohort 4:
- 7 of 11 (64%) subjects were "Responders" within week 10
- 5 of 7 (71%) subjects met Responder criteria after only 2 doses
- Maximum individual HBsAg decline was 2.7 log10 IU/ml
- 5 of 7 (71%) Responders reached HBsAg <50 IU/ml
- IL28B genotype CC predictor for HBsAg response
Nucleic Acid Polymers (NAPs)

NAPs block subviral particle release (cccDNA and integration derived) → Efficient HBsAg clearance from the blood

Critical effects of HBsAg clearance:

• Unmasking anti-HBs response
• Elimination of HBsAg mediated immunosuppression
• Improved response to immunotherapy
• Functional control can be established in most patients

M. Bazinet et al., 2016 Hepatology 64: S912A
Al-Mahtab et al., 2016 PLOS One 11: e0156667
Shi et al. 2012 PLOS One 7: e44900
Woltman et al. 2011 PLOS One 6: e15324
Op den Brouw et al., 2009. Immunology, 126: 280-289
Wu et al., 2009. Hepatology, 49: 1132-11
Xu et al., 2009. Molecular immunology, 46: 2640-2646
Functional control of HBeAg negative chronic HBV infection persists after withdrawal of combined therapy with REP 2139 or REP 2165, tenofovir disoproxil fumarate and pegylated interferon α-2a - REP 401 study

Clinicaltrials.org # NCT02565719
Randomized, open label, active comparator controlled
3 trial sites (Chisinau, Moldova)

Patient population:
• Treatment naive
• HBeAg negative
• Fibrotic (not cirrhotic)

Dosing:
• TDF 300mg PO qD
• Pegasys 180ug SC qw
• **NAPs: REP 2139-Mg or REP 2165-Mg 250mg IV qw**
• REP 2165 = REP 2139 variant with improved tissue clearance

Primary efficacy endpoints:
• Serum HBsAg reduction
• Appearance of anti-HBs
• Functional control maintained after treatment withdrawal
• Functional cure: functional control for 24 weeks off treatment
On-treatment efficacy data with REP 2139 (+ PEG and NUC) in HBeAg negative CHB patients

HBV-DNA levels

REP 2139

TDF effect unaltered in triple combination with pegIFN and NAPs

LLOQ = lower limit of quantification (10 IU / ml)
TND = HBV DNA target not detected
On-treatment efficacy data with REP 2139 (+ PEG and NUC) in HBeAg negative CHB patients

HBsAg response > 4 log: 8/10 7/10
HBsAg loss (≤0.01 IU/mL): 7/10 4/10

Elevation in serum anti-HBs correlated with extent of HBsAg reduction

LLOQ = lower limit of quantification (0.05 IU / mL)
TND = HBsAg not detected (0.00 IU/mL)

Red segment indicates off-treatment rebound in a single patient who withdrew from the trial for depression attributed to Pegasys exposure
On-treatment safety data (ALT / AST / GGT)

Elevation in serum ALT correlated with HBsAg reduction (self-resolving with continued therapy)

--- upper limit of normal
## Interim off-treatment efficacy data (REP 2139)

### Functional control of HBV infection persisting in 8/10 patients – all with normal transaminase levels.

### Functional cure achieved in 4/10 patients to date.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Genotype</th>
<th>Parameter</th>
<th>Baseline</th>
<th>EOT</th>
<th>FW4</th>
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<td>55</td>
<td>36</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>AST (U/L)</td>
<td>31</td>
<td>63</td>
<td>37</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>01-077</td>
<td>D2</td>
<td>HBsAg (IU/mL)</td>
<td>1334</td>
<td>TND</td>
<td>TND</td>
<td>TND*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>anti-HBs (mIU/mL)</td>
<td>5.81</td>
<td>38</td>
<td>30</td>
<td>31*</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>HBV DNA (IU/mL)</td>
<td>2183000</td>
<td>TND</td>
<td>TND</td>
<td>TND*</td>
<td></td>
</tr>
<tr>
<td></td>
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<td>ALT (U/L)</td>
<td>263</td>
<td>70</td>
<td>34</td>
<td>24</td>
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<tr>
<td></td>
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<td>AST (U/L)</td>
<td>78</td>
<td>61</td>
<td>33</td>
<td>25</td>
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</tr>
<tr>
<td>03-023</td>
<td>D1</td>
<td>HBsAg (IU/mL)</td>
<td>9595</td>
<td>TND</td>
<td>TND</td>
<td>TND</td>
<td>TND</td>
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<tr>
<td></td>
<td></td>
<td>anti-HBs (mIU/mL)</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBV DNA (IU/mL)</td>
<td>1132000</td>
<td>TND</td>
<td>TND</td>
<td>TND</td>
<td></td>
</tr>
<tr>
<td></td>
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<td>ALT (U/L)</td>
<td>175</td>
<td>39</td>
<td>39</td>
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<tr>
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<td>AST (U/L)</td>
<td>85</td>
<td>34</td>
<td>34</td>
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</tr>
</tbody>
</table>

- HBsAg reduction to <1IU/mL during treatment
- >1log_{10} HBsAg reduction but >1IU/mL
- Functional control after removal of therapy

Oct 23, 2017
The possible future curative regimen for hepatitis B

- **Nucleos(t)ide analogue**: To control viral replication and cccDNA re-amplification.
- **Viral antigen inhibitor**: To inhibit HBV life cycle processes (e.g., entry, mRNA transcription, capsid assembly, viral protein secretion).
- **Immune modulation**: To activate or restore HBV targeting immune responses.
- **cccDNA inhibitor**: To silence or eliminate cccDNA.

**Functional cure** vs. **Complete Cure?**

Seto WK And Yuen MF. Clinical Liver Disease 2016;8,4, 83-88
Future HBV therapies: new targets, new drugs

Immunomodulation
- Toll-like receptors agonists, e.g. GS-9620
- Anti-PD-1 mAb, e.g. BMS-936559
- CYT107
- GI13000
- Vaccine therapy

RNA interference, (siRNA) e.g. ARC-520

Inhibition of HBsAg release, e.g. REP 9AC

Entry inhibitors (HBV/HDV)
- Lipopeptides, e.g. Myrcludex-B

Targeting cccDNA
- HAPs
- Chromatin-modifying enzymes

Polymerase inhibitors
- Nucleoside analogues, e.g. TAF, amadoxovir, MIV-210
- Non-nucleoside, e.g. LB80380

Inhibition of Nucleocapsid Assembly, e.g. Bay 41-4109, NVR1221

Inhibition of Prenylation (HDV)
- Lonafarnib

GS-4774 in NUC-suppressed CHB patients
Changes of HBsAg from Baseline

<table>
<thead>
<tr>
<th>HBsAg IU/ml log_{10}^*</th>
<th>NUC alone (n=27)</th>
<th>NUC + 2 YU GS-4774 (n=51)*</th>
<th>NUC + 10 YU GS-4774 (n=50)</th>
<th>NUC + 40 YU GS-4774 (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 24</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from Baseline</td>
<td>-0.02 (-0.07, 0.03)</td>
<td>-0.02 (-0.06, 0.01)</td>
<td>-0.03 (-0.06, 0.01)</td>
<td>-0.05 (-0.08, 0.01)</td>
</tr>
<tr>
<td>Treatment Difference</td>
<td></td>
<td>0 (-0.06-0.06)</td>
<td>-0.01 (-0.07, 0.06)</td>
<td>-0.03 (-0.09, 0.03)</td>
</tr>
<tr>
<td><strong>Week 48</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from Baseline</td>
<td>-0.04 (-0.18, 0.09)</td>
<td>-0.05 (-0.15, 0.04)</td>
<td>-0.05 (-0.14, 0.04)</td>
<td>-0.17 (-0.26, -0.07)</td>
</tr>
<tr>
<td>Treatment Difference</td>
<td></td>
<td>0.01 (-0.18-0.15)</td>
<td>-0.01 (-0.17, 0.16)</td>
<td>-0.12 (-0.29, 0.04)</td>
</tr>
</tbody>
</table>

*1 subject was randomized to receive 4774 2 YU but received 10 YU. This subject was included in the 10YU group for safety analysis, and in the 2YIU for efficacy analysis

*Results are from repeated measures mixed effect models, mean (95% CI)

*None of the patients cleared HBsAg

Lok AS et al, J Hepatol 2016
GS-9620 in NUC suppressed CHB patients
Changes in HBsAg Up to Week 24

- HBsAg changes were minimal in all cohorts, with no patients having >0.5 log declines in HBsAg at Week 24 in any GS-9620-treated arms
- No patient cleared HBsAg by Week 24
Summary

- Efficacy and safety of long-term NUC therapy excellent
- New definitions of "HBV cure"
- In NUC suppressed patients, functional cure can be achieved by:
  - Continuous administration of ETV/TDF/TAF
  - Stop NUC before HBsAg loss ("stop to flare")
  - "Add-on" or "switch to" Peg-IFN
  - Newer drugs (siRNA, NAP, ...... immunomodulators ??)
- Combination of 3 or more drugs with complementary or synergistic mechanisms of action is likely required
- Efficacy, safety and cost of these new strategies to be determined
Back-up slides
HBsAg kinetics in HBeAg-negative patients treated with TDF for 4 years

• Asians have lower baseline levels of HBsAg than non-Asians
• In both groups, the overall 192 week declines were modest

HBsAg decline: 0.35 - 0.50 log/4 years

Fung S, et al. APASL 2012; Poster #PP09-043.
Standard and New markers for HBV

**Standard markers:**
- qHBsAg
- HBeAg/anti-HBe
- HBV-DNA levels
- Anti-HBc

**New markers:**
- ultra sens qHBsAg
- HBeAg levels
- ultra sens HBV-DNA
- Anti-HBc levels
- HBcrAg
- HBV-RNA levels
- Different HBsAg proteins

* No commercially available assays available