7 June 2017

New therapeutic strategies for HBV

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Disclosures

Advisory Board/Speaker Bureau for:

- BMS, ROCHE, GILEAD SCIENCES, GSK, MSD, ARROWHEAD, ALNYLAM, ARBUTUS
# Natural history of HBV and treatment indications

<table>
<thead>
<tr>
<th>New terminology</th>
<th>HBeAg positive Chronic <em>infection</em></th>
<th>HBeAg positive Chronic hepatitis</th>
<th>HBeAg negative Chronic <em>infection</em></th>
<th>HBeAg negative Chronic hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Old terminology</strong></td>
<td>Immune tolerant</td>
<td><strong>HBeAg-positive CHB</strong></td>
<td>Inactive carrier</td>
<td><strong>HBeAg-negative CHB</strong></td>
</tr>
<tr>
<td>HBsAg</td>
<td>High</td>
<td>High/Intermediate</td>
<td>Low</td>
<td>Intermediate</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>&gt;10E7 IU/mL</td>
<td>10E4-10E7 IU/mL</td>
<td>&lt;2,000 IU/mL*</td>
<td>&gt;2,000 IU/mL</td>
</tr>
<tr>
<td>ALT</td>
<td>Normal</td>
<td>Elevated</td>
<td>Normal</td>
<td>Elevated**</td>
</tr>
<tr>
<td>Liver disease</td>
<td>None/minimal</td>
<td>Moderate/severe</td>
<td>None</td>
<td>Moderate/severe</td>
</tr>
<tr>
<td>Disease progression</td>
<td>Low</td>
<td>Moderate to high</td>
<td>No, very low</td>
<td>Moderate to high</td>
</tr>
<tr>
<td>Treatment</td>
<td>Not indicated***</td>
<td>Indicated</td>
<td>Not indicated</td>
<td>Indicated</td>
</tr>
</tbody>
</table>

* HBV-DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis

** Persistently or intermittently

*** Treatment is indicated in some patients
Current HBV treatments - Summary

- PEG-IFN for few patients, effective in some
- ETV/TDF for most CHB patients, very effective (>95%)
- Prevention of clinical decompensation, improvement of portal hypertension
- HCC is the only complication during ETV/TDF
- Excellent 5-yr overall and liver-related survival
- NUC treatment is easy, effective and inexpensive
ETV or TDF therapy for CHB - Limitations

- Partial response in HVL patients (NUC-R ?)
- Safety issues in selected TDF treated patients
- Low HBeAg/HBsAg seroconversion rates
- Limited stopping rules (HBsAg seroconversion ?)
- Long duration of therapy
- Cost, compliance, resistance, safety >10 years ??
- Residual risk of HCC
Registration studies (8 years) showed minimal renal events on TDF (~2%)

Real-life studies with TDF showed controversial results

8 cases of TDF-induced Fanconi syndrome have been described

Higher risk of TDF renal toxicity in older patients, previously exposed to ADV, with comorbidities

Need for more research with more sensitive markers of tubular damage

The best management of the few cases with renal toxicity unclear (TAF or ETV ?)
UBCR* in HBV patients on long-term TDF
A real life study in 414 patients

Age 62 yr, 94% Caucasian, 81% GT D, 76% males, 92% normal ALT, 90% negative HBV DNA, eGFR 68 mL/min, 45% cirrhotics, 36% HTA, 15% diabetes, TDF therapy for 82 (1-118) months

*urinary B2-microglobulin:crea

*Grossi G et al, EASL 2017
Strategies to manage TDF renal toxicity

- Stop TDF and follow-up
- Proactive reduction of TDF doses (eGFR <65….)
- Add-on LDT
- Switch to ETV
- Switch to TAF

Variables to be considered:
acut vs chronic renal damage, glomerular vs tubular, cofactors, severity of liver disease…….
Mechanism of Action

Tenfovir alafenamide (TAF) – A Novel Prodrug of Tenfovir

- **TFV** (tenofovir)
- **TDF** (tenofovir disoproxil fumarate) 300 mg
- **TAF** (tenofovir alafenamide) 25 mg

**GI TRACT**

- Dianion
- Esters
- Amidate

**RENAL TUBULAR CELL**

- TFV
- OAT 1 & 3

**PLASMA**

- ~90% LOWER PLASMA TFV

**HEPATOCEL**

- TFV→TFV-DP
- HBV

**RÉNAL TUBULAR CELL**

- TFV
- OAT 1 & 3

†T₁/₂ based on *in vitro* plasma data - TDF = 0.4 minutes, TAF = 90 minutes.


**Primary endpoint** (non inferiority margin of 10%):
- HBV DNA <29 IU/mL at Week 48

**Key secondary endpoints**
- HBV DNA <29 IU/mL at Week 96
- ALT normalisation
- Renal and bone mineral density parameters
- Serology (HBsAg loss/seroconversion)

**Inclusion criteria:** HBV DNA ≥20,000 IU/mL; ALT >60 U/L (males), >38 U/L (females), eGFR_{CG} >50 mL/min

**Study 108 and 110: Phase 3 CHB Studies: TAF vs TDF**

Antiviral Efficacy of TAF and TDF at Week 96

Rates of Viral Suppression (ITT; M=F)
HBV DNA <29 IU/mL

- No resistance was detected through 96 weeks
- Similar HBV DNA suppression rates for TAF compared to TDF through Week 96

*Adjusted for baseline HBV DNA level and oral antiviral treatment status strata
M=F: Missing = Failure
Agarwal, EASL 2017, FRI-153;
Brunetto, EASL 2017, PS-042; Gilead, Data on File.
Study 108 and 110: Phase 3 CHB Studies: TAF vs TDF

ALT Normalisation of TAF and TDF at Week 96

Central Laboratory

- HBeAg- patients: 81% TAF vs 71% TDF, P=0.038
- HBeAg+ patients: 75% TAF vs 68% TDF, P=0.017

AASLD Laboratory Criteria

- HBeAg- patients: 50% TAF vs 40% TDF, P=0.035
- HBeAg+ patients: 52% TAF vs 42% TDF, P=0.003

Significantly higher ALT normalisation rate with TAF vs TDF

Central lab upper limit of normal (ULN): males ≤43 U/L and females ≤34 U/L (≥69 y: males ≤35 U/L and females ≤32 U/L); AASLD criteria ULN: males ≤30 U/L and females ≤19 U/L.

Brunetto, EASL 2017, PS-042; Agarwal, EASL 2017, FRI-153
Renal Safety Through Week 96

TAF treatment had significantly less impact on eGFR than TDF at all time points
Changes in Renal Markers During Treatment with TAF or TDF

**Changes in Quantitative Proteinuria at Week 96**

<table>
<thead>
<tr>
<th>Proteinuria Type</th>
<th>Median % Change (Q1, Q3)</th>
<th>Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPCR</td>
<td>TAF</td>
<td>TDF</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>-50</td>
</tr>
<tr>
<td></td>
<td>0-50</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>-50</td>
</tr>
<tr>
<td>Glomerular</td>
<td>TAF</td>
<td>TDF</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>-50</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td>0</td>
<td>-50</td>
</tr>
<tr>
<td>UACR</td>
<td>TAF</td>
<td>TDF</td>
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<td></td>
<td>100</td>
<td>50</td>
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<td></td>
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<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>-50</td>
</tr>
<tr>
<td>RBP:Cr</td>
<td>TAF</td>
<td>TDF</td>
</tr>
<tr>
<td></td>
<td>108.5</td>
<td>126.7</td>
</tr>
<tr>
<td>Tubular</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>0</td>
<td>-50</td>
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<tr>
<td></td>
<td>0-50</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>-50</td>
</tr>
<tr>
<td>β2m:Cr</td>
<td>TAF</td>
<td>TDF</td>
</tr>
<tr>
<td></td>
<td>153.1</td>
<td>221.3</td>
</tr>
<tr>
<td>β2 microglobulin</td>
<td>TAF</td>
<td>TDF</td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>199.6</td>
</tr>
</tbody>
</table>

Significantly smaller changes in renal tubular markers with TAF vs TDF

UPCR, urine protein-to-creatine ratio; UACR, urine albumin-to-creatine ratio; RBP:Cr, retinol binding protein-to-creatine ratio; B2M:Cr, β2 microglobulin-to-creatine ratio

* p-values from 2-sided Wilcoxon rank-sum test

Chuang, EASL 2017, SAT-171
Study 108 and 110: Phase 3 CHB Studies: TAF vs TDF

Mean Change in BMD Through Week 96

TAF treatment resulted in smaller declines* in hip and spine BMD compared with TDF

* All p-values from Week 24-96 are < 0.001; p-values from analysis of variance model including treatment as a fixed effect; † p-values from mixed model repeated measures

Fung, EASL 2017, SAT-162
Change in Diagnosis of Osteopenia or Osteoporosis* through Week 96

Fewer subjects in the TAF group had worsening spine and hip BMD clinical status at Week 96 compared with the TDF group

* Normal, osteopenia and osteoporosis as defined by T-score, where Normal: ≥ −1.0; Osteopenia: -2.5 to -1.0; Osteoporosis: ≤ −2.5

Gilead, Data on File.
Fung, EASL 2017, SAT-162
Multiple Risk Factors and BMD Decline

Known risk factors for osteoporosis assessed included female gender, age ≥50 y, Asian race, and baseline eGFR_{CG} <90 mL/min

Fewer patients had >3% BMD declines on TAF compared to TDF independent of the number of risk factors

*P-values by Fisher’s Exact Test.
Fung, EASL 2017, SAT-162
Study 108 and 110: Phase 3 CHB Studies: TDF to TAF Switch (Interim Analysis)

Study Design

- Two Phase 3, randomised, double-blind, active-controlled trials
  - Study 108 (N=425): HBeAg-negative patients
  - Study 110 (N=873): HBeAg-positive patients
- Key inclusion criteria (both studies)
  - HBV DNA $\geq 20,000$ IU/mL; ALT $>60$ U/L (males) $>38$ U/L (females); eGFR $\geq 50$ mL/min
- 2:1 randomisation
  - Stratified by HBV DNA level and treatment status (naïve/experienced)
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- 2:1 randomisation
  - Stratified by HBV DNA level and treatment status (naïve/experienced)
Switch from TDF to TAF: Efficacy snapshot

Viral suppression was maintained and ALT normalisation rate increased 24 weeks after switching from TDF to TAF.

Graphs adapted from Chan, EASL 2017, PS-041
Renal Laboratory Parameters in CHB Patients Treated with TDF Switched to TAF

Study 108 and 110: Phase 3 CHB Studies: TDF to TAF Switch (Interim Analysis)

Significant improvement in $\text{eGFR}_{CG}$ was observed at 24 Weeks after switching from TDF to TAF

$\text{eGFR}_{CG}$: estimated glomerular filtration rate as measured by the Cockcroft-Gault equation
Chan, EASL 2017, PS-041
Renal Tubular Markers in CHB Patients Treated with TDF Switched to TAF

Study 108 and 110: Phase 3 CHB Studies: TDF to TAF Switch (Interim Analysis)

Significant improvements in renal tubular markers were observed at Week 120 in patients who switched from TDF to TAF at 96 Weeks.

Chan, EASL 2017, PS-041
Significant improvements in hip and spine BMD were observed at Week 120 in patients who switched from TDF to TAF at 96 Weeks.
New TAF HBV Studies

♦ Stable and suppressed switch studies
  – Randomized (1:1), double-blind study in patients suppressed on TDF with eGFR ≥50 mL/min (GS-US-320-4018); N=300
  – Randomized (1:1), open-label study in renally-impaired post-liver transplant patients on TDF (GS-US-320-3912); N=60
  – Open-label, single arm study in patients on OAV(s) including TDF with moderate, severe, or end-stage renal disease on HD (GS-US-320-4035); N=100

♦ Adolescent patients with CHB (GS-US=320-1092)

♦ Patients with decompensated liver disease
  – Safety and efficacy data needed for US label
  – Child-Pugh Class B and C patients

♦ Prevention of mother to child transmission (MTCT)
When to use TAF in clinical practice in 2017

- All NUC-naïve patients
- NUC-naïve patients at risk of bone/kidney toxicity
- All NUC-treated patients
- All TDF-treated patients
- All TDF treated patients at risk of bone/renal dysfunction
- All TDF-treated patients with bone/renal dysfunction
ETV or TDF therapy for CHB - Limitations

- Partial response in HVL patients (NUC-R ?)
- Safety issues in selected TDF treated patients

- Low HBeAg/HBsAg seroconversion rates
- Limited stopping rules (HBsAg seroconversion ?)
- Long duration of therapy

- Cost, compliance, resistance, safety >10 years ??
- Residual risk of HCC
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
Aiming Higher

We should aim to **Cure** HBV infection!

- **“Sterilizing Cure”**
  - Eliminate all copies of virus
  - Likely to be difficult
  - No clear precedent in HBV

- **“Functional Cure”**
  - Establish lasting host immunity
  - Inactivate virus
  - Precedent: natural & nucleoside induced HBsAg seroconversion
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, amdoxovir, MIV-210
- Non-nucleoside, e.g. LB80380

**Targeting cccDNA**
- HAPs
- Chromatin-modifying enzymes

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

**Inhibition of Prenylation (HDV)**
- Lonafarnib

Future HBV therapies: new targets, new drugs

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- Lonafarnib

RNAi therapeutics vs NUC treatment for HBV

**Reduction/Elimination of Reinfection, Contagion**

**Reduced Viral Replication**

**Immune Suppression Unchanged**

**Reduced Viral Protein Production**

**Reduced Viral Antigens HBsAg, HBeAg**

**Reduced Viral Protein Production**

**Reduced Viral Antigens**

**Reversal of Immune Suppression**

**HBsAg seroclearance & functional cure**
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.
A Phase 2a Study Evaluating the Multi-dose Activity of ARB-1467 in HBeAg pos and HBeAg neg NUC suppressed CHB patients - Overall Summary

Adrian Streinu-Cercel et al, EASL 2017
Future HBV therapies: new targets, new drugs

**Immunomodulation**
- Toll-like receptors agonists, e.g. GS-9620
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**Polymerase inhibitors**
- Nucleoside analogues, e.g. TAF, amdoxovir, MIV-210
- Non-nucleoside, e.g. LB80380

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

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

**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>Week 24</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>Week 24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Difference</td>
<td>0 (-0.06-0.06)</td>
<td>-0.01 (-0.07, 0.06)</td>
<td>-0.03 (-0.09, 0.03)</td>
<td></td>
</tr>
<tr>
<td>Week 48</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>Week 48</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Difference</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>
<td></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 patients had HBsAg loss at Week 24
What May a HBV Curative Regimen Look Like?

- **NUC ± Entry inhibitor**
  - Agent to prevent viral spread, cccDNA re-amplification

- **Immune inhibitor**
  - Agents to activate antiviral immunity or perturb cccDNA

- **HBV antigen inhibition**
  - Agents to inhibit other components in the HBV life cycle [entry or cell-spread, capsid, HBX, HBsAg]

Safety, efficacy, cost........

*Adapted from S. Locarnini, 2014*
New biomarkers for HBV

- HBeAg levels (quant)
- Anti-HBc levels (quant)
- HBsAg fractions
- cccDNA
- HBcrAg levels
- HBV-RNA levels
EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection

European Association for the Study of the Liver*

Chair: Pietro Lampertico

Panel members:
Kosh Agarwal, Thomas Berg, Maria Buti, Harry L.A. Janssen, George Papatheodoridis, Fabien Zoulim; EASL Governing Board representative: Frank Tacke

Reviewers:
EASL Governing Board, Maurizia Brunetto, Henry Chan, Markus Cornberg
New therapeutics for HBV - Summary

- Excellent efficacy and safety of current SOC (ETV/TDF)
- Significant long-term clinical benefits of ETV/TDF
- TAF may further improve the safety profile
- New endpoints to be explored (stop NUC, HBsAg levels?)
- New therapeutics failed to significantly reduce HBsAg levels
- 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