Antiviral treatment of HBV in 2014

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► Advisory Board/Speaker Bureau for

- BMS, ROCHE, GILEAD SCIENCES, GSK, MSD
Outline

- Burden of infection, natural history
- IFN and NUC therapy
- Virological, serological, biochemical results
- Histological data
- Decompensation, portal hypertension (HCC)
- When and how to start antiviral therapy
Global impact of hepatitis B

World population
6 billion

2 billion with evidence of HBV infection

350–400 million with chronic hepatitis B (CHB)

25–40% (75–160 million) die of cirrhosis or liver cancer

• Ninth leading cause of death
• Nearly 75% of HBV chronic carriers are Asian

Conjeevaram HS et al. J Hepatol 2003; 38:S90–S103
Natural History of Hepatitis B Virus Infection

- **Acute Infection**
  - >90% of infected children progress to chronic disease
  - <5% of infected immunocompetent adults progress to chronic disease

- **Chronic Infection**
  - 5%-10% of chronic HBV-infected individuals

- **Cirrhosis**
  - 30% of chronic HBV-infected individuals

- **Liver Failure ( Decomp.)**
  - 23% of patients decompensate within 5 years of developing cirrhosis

- **Liver Cancer (HCC)**
  - ~3%/yr

- **Liver Transplantation**

- **Death**
  - Chronic HBV is the 6th leading cause of liver transplantation in the US

EASL 2012 Clinical Practice Guidelines: What is long-term treatment success in CHB and how do we achieve it?

“...to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, hepatocellular carcinoma (HCC) and death”

“This goal can be achieved if HBV replication can be suppressed in a sustained manner. Then, the accompanying reduction in histological activity of CHB lessens the risk of cirrhosis and decreases the risk of HCC, particularly in non-cirrhotic patients”

Therapeutic strategies for chronic hepatitis B

**Short-term "curative" treatment**

- IFN
  - On treatment response
- Follow-up (mo/yrs)
  - HBV DNA < 2000 IU/ml
  - ALT < UNL (anti-HBe)
- HBsAg loss

**Long-term "suppressive" treatment**

- NUC
  - HBV DNA undetectable by PCR (<10-15 IU)
- HBsAg loss

Years

Follow-up (mo/yrs)
Studies in patients and humanized mice indicate that combination treatments suppressing both HBV replication (NUCs) and cccDNA transcription (IFNα) may trigger significant antigen decline (HBe and HBs) – combination needs to be done in a smart way.

Adapted from Thimme & Dandri, J Hepatol 2012;58:205-9
What can we achieve with Peg-IFN alfa-2a in CHB?

- Treatment aims to enable patients to achieve inactive CHB with sustained immune control

Approximately 30% of patients respond to treatment with Peg-IFN alfa-2a

- Peg-IFN alfa-2a treatment can also result in off-treatment immune control

- Potential long-term clinical benefits of sustained immune control after a finite course of Peg-IFN alfa-2a therapy:
  - Freedom from potentially life-long treatment
  - No long-term safety concerns
  - Decreased risk of cirrhosis and liver cancer
  - HBsAg clearance (clinical cure)

Baseline predictors of response: accurate prediction of response allows more informed treatment decisions

Baseline factors associated with sustained response in patients receiving Peg-IFN alfa-2a

**HBeAg-positive patients**
- Low HBsAg
- High ALT (≥2 × ULN)
- Low viral load (HBV DNA <2 × 10^8 IU/mL)
- HBV genotype (A > B > C > D)
- Female gender
- Wild-type vs precore/core promoter mutants

**HBeAg-negative patients**
- Similar to those observed in HBeAg-positive patients but less well defined

Other biomarkers (including IP10) are under investigation; data from recent studies investigating the relationship between IL28B and response have been controversial and are currently under discussion


IL28B = interleukin 28B
IP10 = interferon gamma-inducible protein-10
ULN = upper limit of normal
Clinical significance of HBsAg level: An additional marker of CHB

Serum HBV DNA: a marker of HBV replication

Serum HBsAg: a marker of transcriptionally active cccDNA*

HBV DNA (virions) → HBV replication

qHBsAg virions + defective particles → HBV replication → cccDNA transcription/mRNA translation

Brunetto. J Hepatol 2010
Response-guided therapy (RGT) using HBsAg levels in Peg-IFN-treated patients: early stopping rules*

**HBeAg-positive**

Week 12:
- No decline of HBsAg (A,D)
- HBsAg $>$ 20,000 IU/mL (B,C)

Week 24:
- HBsAg $>$ 20,000 IU/ml (A,B,C,D)

**HBeAg-negative (geno D)**

Week 12:
- No decline in HBsAg +
  $<$ 2 log decline in HBV DNA

* 97-100% Negative Predictive Values

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Sonneveld et al. Hepatology 2010
Piratvisuth et al. APASL 2010
Liaw et al. Hepatology 2011
Sonneveld et al., Hepatology 2013
Rijckborst et al. Hepatology 2010
Rijckborst / Lampertico et al. J Hepatol 2012
Response-guided therapy (RGT) using HBsAg levels in Peg-IFN-treated patients: early stopping rules*

**HBeAg-positive**

- Week 12:
  - No decline of HBsAg (A,D)
  - HBsAg >20,000 IU/mL (B,C)

- Week 24:

**HBeAg-negative (geno D)**

- Week 12:
  - No decline in HBsAg (B,C)

20-30% of patients can stop Peg-IFN at week 12-24

* 97-100% Negative Predictive Values

Sonneveld et al. Hepatology 2010
Piratvisuth et al. APASL 2010
Liaw et al. Hepatology 2011
Sonneveld et al., Hepatology 2013

Rijckborst et al. Hepatology 2010
Rijckborst / Lampertico et al. J Hepatol 2012
The importance of HBsAg quantification and on-treatment monitoring

- Quantification of HBsAg levels is an accepted clinical tool to determine response to treatment
  - regular monitoring is recommended by both EASL and NICE guidelines\(^1,2\)
  - integral to the stopping rules for Peg-IFN

- HBsAg seroconversion is considered the optimal goal of antiviral treatment\(^1,2\)
  - indicates resolution of chronic HBV infection\(^2\)

\(q\text{HBsAg} = \text{quantitative HBsAg}\)

2. Hepatitis B (chronic): Clinical guideline (June 2013) available at:
NUC
Incidence of Resistance in NUC-naïve Patients

*Collation of currently available data – not from head-to-head studies

adapted from EASL HBV Guidelines, J Hepatol 2012
5 years ETV for real life, naive CHB patients
Virological summary

<table>
<thead>
<tr>
<th>Region</th>
<th>Virological Success</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>97%</td>
<td>n=744</td>
</tr>
<tr>
<td>Italy</td>
<td>99%</td>
<td>n=418</td>
</tr>
<tr>
<td>Hong-Kong</td>
<td>97%</td>
<td>n=222</td>
</tr>
<tr>
<td>Japan</td>
<td>100%</td>
<td>n=252</td>
</tr>
<tr>
<td>China</td>
<td>100%</td>
<td>n=117</td>
</tr>
<tr>
<td>Thailand</td>
<td>96%</td>
<td>n=535</td>
</tr>
</tbody>
</table>

Seven years TDF for naïve CHB patients

Efficacy summary

<table>
<thead>
<tr>
<th>Response</th>
<th>HBeAg- Patients (Study 102)</th>
<th>HBeAg+ Patients (Study 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 6</td>
<td>Year 7</td>
</tr>
<tr>
<td>HBV DNA &lt; 400 copies/mL Intent-to-treat*, (n/N)</td>
<td>81.4% (281/345)</td>
<td>77.3% (269/348)</td>
</tr>
<tr>
<td>HBV DNA &lt; 400 copies/mL On-treatment†, (n/N)</td>
<td>99.6% (283/284)</td>
<td>99.3% (271/273)</td>
</tr>
</tbody>
</table>

* LTE-TDF (missing = failure; addition of FTC = failure)
† Observed (missing = excluded/addition of FTC = included)

♦ No case of TDF resistance
♦ HBeAg loss/seroconversion rates of 55% and 40%, respectively
♦ 12% of HBeAg+ patients had confirmed HBsAg loss (10% with seroconversion)

Neither Truvada (TVD = TDF + FTC) or emtricitabine (FTC) are licensed for use to treat CHB

3-4 years TDF for real life, naive CHB patients

Virological summary

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<tr>
<th>Region</th>
<th>Virological Success</th>
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<tbody>
<tr>
<td>Germany 1</td>
<td>92%</td>
<td>n=184</td>
</tr>
<tr>
<td>France 2</td>
<td>94%</td>
<td>n=440</td>
</tr>
<tr>
<td>Spain 4</td>
<td>100%</td>
<td>n=180</td>
</tr>
<tr>
<td>Europe 4</td>
<td>97%</td>
<td>n=374</td>
</tr>
</tbody>
</table>

Management of NUC resistance
Similar efficacy of TDF vs TDF-FTC in LAM-resistant CHB supports monotherapy

- Randomised, multicentre, international study of TDF and TDF-FTC in LAM-resistant patients. Baseline HBV DNA: 5.7 $\log_{10}$ IU/mL

1. Fung S, et al. Gastroenterology 2014;146:980–8 (NCT00737568);

Neither Truvada (TVD=TDF-FTC) nor emtricitabine (FTC) are licensed for use in CHB; Intent to treat population shown: Missing = Failure analysis
Similar virological response with TDF compared with TDF + ETV in ADV-resistant patients in Korea

- Randomised, multicentre, 36-week open-label study
  - TDF monotherapy (N=50)
  - TDF + ETV (N=52)
- All had ADV resistance mutations
  - ADV resistance mutations only (n=16)
  - ADV and LAM resistance mutations (n=51)
  - ADV, LAM and ETV resistance mutations (n=35)
- Baseline HBV DNA:
  - 3.9 log_{10} IU/mL
- Decline in HBV DNA at Week 36:
  - -2.9 log_{10} IU/mL of TDF group
  - -3.2 log_{10} IU/mL of TDF + ETV group (P=0.42)

TDF rescue therapy after multiple NUC failures in CHB: evidence from the Asia Pacific

TDF rescue monotherapy is effective and well tolerated in CHB patients after multiple NA treatment failures

Retrospective Korean analysis in patients who had prior failure with ≥2 NAs and switched to TDF-containing regimens (N=52)

Open-label, multicentre Australian study in patients who had previously failed LAM and subsequent ADV add-on or switch therapy (N=60)

Progressive decline in HBV DNA
Year 2 = 64% (38/60)
Year 4 = 75% (38/51)
Year 5 = 81% (39/48)

Cumulative virological response (%)

<table>
<thead>
<tr>
<th>Month</th>
<th>3</th>
<th>12</th>
<th>24</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25,0</td>
<td>51,8</td>
<td>74,2</td>
<td>96,7</td>
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Progressive decline in HBV DNA
Year 2 = 64% (38/60)
Year 4 = 75% (38/51)
Year 5 = 81% (39/48)

Median HBV DNA (log10 IU/mL)

1. Kim HJ, et al. AASLD 2013. #906;
TDF-ETV combination therapy in multi-drug resistant patients: European evidence

- Multicentre, EU open-label cohort of 57 patients previously treated with a median of 3 lines of antiviral therapy
- Baseline HBV DNA: $1.5 \times 10^4$ IU/mL
- Median treatment duration with TDF + ETV: 21 months

# Management of HBV Resistance (Early rescue)

<table>
<thead>
<tr>
<th>Resistance Type</th>
<th>Recommended Steps</th>
</tr>
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<tbody>
<tr>
<td>LAM resistance</td>
<td>Switch to TDF (or add ADV)</td>
</tr>
<tr>
<td>LDT resistance</td>
<td>Switch to TDF* (or add ADV)</td>
</tr>
<tr>
<td>ETV resistance</td>
<td>Switch to TDF* (or add ADV)</td>
</tr>
</tbody>
</table>
| ADV resistance   | Switch to ETV or TDF (LAM naive)  
                           Switch to ETV (LAM naive + HVL)  
                           Switch to TDF and add a nucleoside (LAM resist.) |
| TDF resistance**| Switch to ETV (LAM naive)  
                           Add ETV (LAM resistant)* |

*the long-term safety of these combinations is unknown  
**not seen so far; do genotyping and phenotyping in an expert lab to determine the cross-resistance profile

adapted from EASL HBV guidelines, J Hepatol 2012
## Management of HBV Resistance (Early rescue)

<table>
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<th>Action</th>
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<td>ETV resistance</td>
<td>Switch to ETV or TDF (LAM naive)</td>
</tr>
<tr>
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<td>Switch to ETV (LAM naive + HVL)</td>
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<tr>
<td></td>
<td>Switch to TDF and add a nucleoside (LAM resist.)</td>
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<td>ADV resistance</td>
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<tr>
<td></td>
<td>Add ETV (LAM resistant)*</td>
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<tr>
<td>TDF resistance**</td>
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</table>

*the long-term safety of these combinations is unknown

**not seen so far; do genotyping and phenotyping in an expert lab to determine the cross-resistance profile

>95% viral suppression by early add-on ADV or TDF monotherapy

adapted from EASL HBV guidelines, J Hepatol 2012
Histology
5 years ETV monotherapy in NUC naïve HBV Histological outcome

- 69 patients (50 HBeAg-positive and 19 HBeAg-negative) receiving entecavir at least 3 years
- All patients had HBV-DNA level <300 copies/mL (<50 UI/mL)
- 57 patients with paired liver biopsy (median time of biopsy: 6 years)
- A ≥1-point improvement in the Ishak fibrosis score occurred in 88% of patients, including all 10 patients with advanced fibrosis or cirrhosis at baseline

5-year TDF treatment in patients with CHB
Changes of fibrosis in cirrhotics

- 96 patients with cirrhosis (Ishak fibrosis score ≥5) had paired BL and Year 5 biopsies
- 74% (n=71) of patients had cirrhosis reversed (Ishak fibrosis score <5) at Year 5, and 73% (n= 70) had decreases of ≥2 points at Year 5; 25% (n=24) did not change
- Of 94 patients who did not add FTC, 73% had cirrhosis reversed; 26% showed no change

Marcellin P et al, Lancet 2013
5-year TDF treatment in patients with CHB
Changes of fibrosis in cirrhotics

- 96 patients with cirrhosis (Ishak fibrosis score ≥5) had paired BL and Year 5 biopsies
- 74% (n = 71) of patients had cirrhosis reversed (Ishak fibrosis score <5) at Year 5, and 73% (n = 70) had decreases of ≥2 points at Year 5; 25% (n = 24) did not change
  - Of 94 patients who did not add FTC, 73% had cirrhosis reversed; 26% showed no change

Marcellin P et al, Lancet 2013
Decompensation (and HCC)
Does long-term NUC therapy prevent decompensation?

- ETV: 3-5 years real life cohort studies in Europe and Asia (1-4)
- TDF: 3-4 years real life cohort studies in Europe (5-6)

Does long-term NUC therapy prevent decompensation?

- ETV: 3-5 years real life cohort studies in Europe and Asia (1-4)
- TDF: 3-4 years real life cohort studies in Europe (5-6)

Decompensation is fully prevented in ETV or TDF treated compensated cirrhotics

Changes of esophageal varices (EV) in 107 compensated cirrhotics LAM±TDF treated for 12 yrs

> 500 endoscopies over 12 years of NUC treatment

Patients with F1 EV at baseline (n=27)

- EV regression
  - 83%

Patients without EV at baseline (n=80)

- EV development*
  - 10%

* 6 of 7 progressors (86%) had either LMV-R and/or HCC

Invernizzi F. et al, EASL 2014 (poster 1059)
When to stop NUC therapy?
### When to stop NUC therapy?

<table>
<thead>
<tr>
<th>CHB Treatment Guidelines</th>
<th>EASL 2012 guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg positive</strong></td>
<td>A) confirmed anti-HBe seroconversion (and undetectable HBV DNA) after at least 12 months of consolidation*</td>
</tr>
<tr>
<td></td>
<td>B) confirmed HBsAg loss and anti-HBs seroconversion</td>
</tr>
<tr>
<td><strong>HBeAg negative</strong></td>
<td>confirmed HBsAg loss and anti-HBs seroconversion</td>
</tr>
<tr>
<td><strong>Cirrhotics</strong></td>
<td>confirmed HBsAg loss and anti-HBs seroconversion</td>
</tr>
</tbody>
</table>

*A proportion of patients who discontinue NUC therapy after anti-HBe seroconversion may require retreatment, since they fail to sustain their serological and/or virological response*

adapted from EASL HBV Guidelines, J Hepatol 2012
HBsAg kinetics in HBeAg-positive patients treated with TDF for 4 years

1. Adapted from Marcellin P, et al. EASL 2011; Poster #740.
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

Fung S, et al. APASL 2012; Poster #PP09-043.
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

Fung S, et al. APASL 2012; Poster #PP09-043.
When and how to start therapy?
Who should be treated?

Patients with cirrhosis (histol., compensated or decomp.):

- HBsAg pos (any level)
- HBV-DNA detectable (any level >10 IU/ml)

Treat all patients, use NUC (PEG ?)

(Any HBeAg status, any ALT level)

adapted from EASL HBV Guidelines, J Hepatol 2012
Who should be treated?

Patients without cirrhosis:

- HBsAg pos and HBV-DNA >2000 IU/ml and ALT >ULN

Liver disease with:

- Significant fibrosis (Ishak S3-4) (PEG or NUC)
- Moderate fibrosis (S2) but at high risk of disease progression (PEG or NUC)
- Mild or no fibrosis (S0-1) (PEG or no treatment)

adapted from EASL HBV Guidelines, J Hepatol 2012
5-7 years of ETV or TDF therapy for CHB

- Viral suppression in >95% naïve/NUC-R pts (ETV, TDF)
- HBeAg seroconversion in 40-50%
- HBsAg clearance in 1% (10-20% in selected groups)
- ALT normalization in ~85%
- No major safety issues
- Prevention of decompensation, portal hypertension
- Extended survival

Unmet medical needs: HCC, when to stop NUC
General perspective: identify HBV carriers and treat
If ETV and/or TDF not available/reimbursed

- LAM or LDT ± ADV as treatment options
- HBV DNA monitoring not available/reimbursed
- Clinical scenario challenging:
  - High rates of partial virological response (PVR)
  - High rates of drug resistance (NUC-R)
  - High rates of multiple drug resistance (MDR)
  - High risk of ALT flares, decompensation, HCC
  - Safety issues because of long-term ADV use

Unmet medical need: stop viral replication!
Global perspective: high endemic countries!