HBV Update from EASL 2017

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Consultant Hepatologist QE Birmingham
Chairman of the BVHG
BHIVA/BVHG Feedback Meeting
May 2017
**HEPATATOLOGY HIGHLIGHTS**

<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
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<tbody>
<tr>
<td>Ahmed Elsharkawy</td>
<td>Consultancy – Gilead, Chiesi, Abbvie.</td>
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<td>Speaker fees – Gilead, MSD, Abbvie</td>
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<td>Research funding – Gilead.</td>
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<td>Date</td>
<td>May 2017</td>
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Talk Outline

• WHO report and Elimination strategy
• New EASL Clinical Practice Guidelines – significant changes
• Some data on new HBV treatment strategies
• New data on TAF
• Hepatitis delta
It’s very competitive. You are never “done.” Ambition grows as you progress.

It doesn’t get easier. I don’t feel “secure.”

Sometimes I feel like I’m nearly there, other times I feel miles away from my big goal.

Perhaps I will never be “done.” It seems there is always the next step to take.

Universal vaccination in all countries around the world.

Expand access to treatment.

Reduce the barriers to access to treatment.

The closer you think you get to the answer, the more there is to ask...

The ideal therapy would look like this, but not being able to provide it.

Funding, delays in regulatory approval, competing time demands.

I am never bored! The variety is beautifully overwhelming.

The closer you think you get to the answer, the more there is to ask...

You have to look at all the bigger problems.

There is no magic pill that fits all patients. So we try to focus on a more patient specific approach.

Let’s go back in time.

Solution.

Problem. Disease is diagnosed too late.

Preventative methodology to have prognosis of a patient’s health.

Liver cancer.

Pierre Gholam.

If we treat enough people, the reserve of infection will fall and the number of new infections will fall.

Who.

AASLD.

EASL.

APASL.

Governments.

WHO.

PHARMA.

BVHG.

NGO.

Organisations need to talk to each other.

Ahmed Elsharkawy.

BC.

Prisma.

WHOA.
Number of HBV Infected Individuals Worldwide

Table 2 (with graph). Prevalence of HBV infection (HBsAg) in the general population by WHO region, 2015: the WHO African and Western Pacific regions have the highest prevalence and the largest number of persons living with HBV.

Total Numbers of Individuals Infected Worldwide = 257 million
Deaths from Viral Hepatitis

Fig. 1. Deaths from viral hepatitis, by virus and type of sequelae, 2015: most viral hepatitis deaths are due to the late complications of HBV and HCV infection.

HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HEV: hepatitis E virus
# A Shocking Statistic

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Indicator</th>
<th>2015 baseline</th>
<th>2020</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Hepatitis B vaccination</td>
<td>HEPB3 coverage</td>
<td>84%</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>2 HBV PMTCT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>HEP vaccine birth dose coverage</td>
<td>39%</td>
<td>50%</td>
<td>90%</td>
</tr>
<tr>
<td>3 Blood safety</td>
<td>Donations screened with quality assurance</td>
<td>97%</td>
<td>95%</td>
<td>100%</td>
</tr>
<tr>
<td>Injection safety</td>
<td>Proportion of unsafe injections</td>
<td>5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>4 Harm reduction</td>
<td>Syringes &amp; needles distributed/PWID/year</td>
<td>27</td>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>5 Testing services</td>
<td>% HBV-infected diagnosed</td>
<td>9%</td>
<td>30%</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>% HCV-infected diagnosed</td>
<td>20%</td>
<td>30%</td>
<td>90%</td>
</tr>
<tr>
<td>Treatment</td>
<td>% diagnosed with HBV on treatment</td>
<td>8%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>% diagnosed with HCV started on treatment</td>
<td>7%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>80%</td>
<td>80%</td>
</tr>
</tbody>
</table>
And another shocking statistic

Fig. 6. Proportion of health-care injections given with equipment reused without sterilization, by WHO region, 2010: problems persist specifically in the Eastern Mediterranean and South-East Asia regions

Source: Pepin et al. (40)
HBV Cascade of Care

Fig. 7. Cascade of care for HBV infection, by WHO region, 2015: effective treatment is underused in most regions.

Source: WHO estimates, conducted by the Center for Disease Analysis. See Annex 2.

* As the proportion of persons eligible for treatment among those diagnosed is unknown, the treatment gap cannot be calculated.
But Some Good News

Fig. 4. Three-dose hepatitis B vaccine coverage, by WHO region, 2000–2015: a major increase in coverage at the beginning of the 21st century
And Finally the UK Has Caught Up

Public Health England
Protecting and improving the nation’s health

Vaccine update

Issue 261, April 2017

Important

Change of vaccine for routine primary baby immunisation programme

This is the good news that later this year Infanrix hexa® (DTaP/IPV/Hib/HepB) will replace both Pediasert® and Infanrix-IPV+Hib® (DTaP/IPV+Hib) for primary baby immunisations. This change means that as well as providing protection against diphtheria, tetanus, pertussis, polio and Hib, babies will also be given protection against hepatitis B virus.

The planned change only involves the type of vaccine used. There is no change to the immunisation schedule and the current planning assumption is that babies born on or after 1 August will be offered Infanrix hexa® (DTaP/IPV/Hib/HepB) from late September/early October 2017, at the ages of 8, 12 and 16 weeks as part of the routine childhood immunisation schedule.

The exact dates will depend on the remaining availability of pentavalent vaccine.

Contents

- Implications for the national selective immunisation programme for babies at risk of hepatitis B
- Vaccine ordering and stock management
- Shingles immunisation programme 2017/18
- Hepatitis A: preventing infection in men who have sex with men
- MMR vaccines
- Vaccines for the children’s flu programme
- Vaccines not procured and supplied centrally
- Bank Holiday deliveries
- Infanrix RCG vaccine and leaflets
- Change to Rabipur presentation
EASL CPG on Hepatitis B

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection

European Association for the Study of the Liver
Changes in Terminology

• Immunotolerant e antigen positive hepatitis B now HBeAg positive chronic infection
• Immune reactive e antigen positive hepatitis now HBeAg positive chronic hepatitis
• Inactive e antigen negative hepatitis B now HBeAg negative chronic infection
Changes in first line treatments

- TAF, TDF and ETV as monotherapies are preferred first line treatment
- Patients on TDF at risk of development and/or with underlying renal or bone disease should be considered for a switch to TAF or ETV
- TAF preferred to ETV in patients with previous nucleoside exposure

### Indications for selecting TAF or ETV over TDF

<table>
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<tr>
<th>Age &gt;60 years</th>
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### Bone disease

- Chronic steroid use or use of other medications that worsen bone density
- History of fragility fracture
- Osteoporosis

### Renal alteration*

- eGFR <60 mL/min/1.73 m²
- Albuminurina >30mg or moderate dipstick proteinuria
- Low phosphate (<2.5mg/dL)
- Hemodialysis

* ETV dose needs to be adjusted if eGFR <50 mL/min; no dose adjustment of TAF is required in patients with estimated CrCl ≥15 mL/min

Indications for treatment

HBeAg Positive or Negative Chronic Hepatitis
All patients with HBeAg-positive or HBeAg-negative CHB, defined by HBV DNA >2000 IU/mL, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis, should be treated (1-I).

Cirrhosis
Patients with compensated or decompensated cirrhosis need treatment, with any detectable HBV DNA level and regardless of ALT levels (1-I).

Obviously active CHB
Patients with HBV DNA >20,000 IU/mL and ALT >2 x ULN should start treatment regardless of the degree of fibrosis (II-2-1).

HBeAg Positive Chronic Infection >30yrs
Patients with HBeAg-positive chronic HBV infection, defined by persistently normal ALT and high HBV DNA levels, may be treated if they are older than 30 years regardless of the severity of liver histological lesions (III-2).

Family History
Patients with HBeAg-positive or HBeAg-negative chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations can be treated even if typical treatment indications are not fulfilled (III-2).
New Stopping Rules for PEG-IFN

**HBeAg-positive CHB**
- **Genotype**
  - **A**
    - No decline
  - **B**
    - >20,000
  - **C**
    - >20,000
  - **D**
    - No decline

**HBeAg-negative CHB (genotype D)**
- **HBsAg levels**
  - Any decline
    - Continue
- **HBV DNA levels**
  - >2 log decline
    - Continue
  - <2 log decline
    - Stop

**WEEK 12**
- Stop if HBsAg
- >20,000

**WEEK 24**
- Stop if HBsAg
- >20,000

Fig. 4. Week 12 and 24 stopping rules for HBeAg-positive and -negative patients treated with PegIFNα. These rules are based upon viral genotype, HBsAg and HBV levels.
HIV/HBV Co-Infection
Recommendations

- All HIV-positive patients with HBV co-infection should start antiretroviral therapy (ART) irrespective of CD4 cell count (Evidence level II-2, grade of recommendation 1).
- HIV-HBV co-infected patients should be treated with a TDF- or TAF-based ART regimen (Evidence level I for TDF, II-1 for TAF, grade of recommendation 1).
Novel HBV Targets

Entry inhibitors: e.g. Myrcludex, ezetimibe, cyclosporine derivatives...

siRNA: e.g. ALN-HBV, TKM-HBV, ARC-520/521, Isis HBV rx

CpAM: e.g. NVR 3-778, AT-130, BAY41-4119, GLS4...

NUC: e.g. TAF (GS7340), AGX-1009, CMX-157, besifovir...

Entry via NTCP

Translation

Encapsidation

Translation

Encapsulation

Reverse transcription

(-) strand synthesis

(+) strand synthesis

HBx, HBe

HBs, HBe

Recycling of nucleocapsid

Formation of cccDNA

Integration

Regulation of host-gene expression

Inhibitors of HBs release: e.g. Rep2129

Immune modulation:
- PRR agonist or immune-stimulator: e.g. GS9620, TLR9-L, SB9200, CYT107, INO1800
- PD1/PDL1 or CTL4A inhibitors: e.g. Nivolumab, Pidilizumab, MEDI-4736, Lambrolizumab, MPDL3280A, AMP-224
- Therapeutic vaccine: e.g. TG-1050, GS4774, DV601, Altravax HBV, Chimigen

Adaptive immune responses

B cells

CD8+ cells

CD4+ cells

Innate responses

NK cells

MDSC

HBeAg

HBsAg particles

HBeAg

HBsAg

Secretion of HBeAg

Virion assembly

Regulation of host-gene expression

B hepatocytes

Hepatocytes
Nivolumab in Chronic HBV

- Checkpoint inhibitor
- Used increasingly in malignant melanoma
- Phase 1 trial – presented by Ed Gane (PS-044)
- E antigen negative patients
- Single injection of 0.3 mg/kg
- Theory is to increase HBV specific T cell activity to encourage viral clearance
- Trial also included an arm with a therapeutic vaccine (this did not add anything)
Results

The graph illustrates the change in HBsAg from baseline (log10 IU/mL) over study weeks for patients treated with Nivolumab 0.3mg/kg. The orange lines represent individual patient responses, showing variability in the reduction of HBsAg levels over time. The horizontal line at 0.0 indicates the baseline level, and the * symbol indicates a significant change at Week 20.
TAF in HBV Mono-infection
Tenofovir Alafenamide (TAF) – A Novel Prodrug of Tenofovir

Prodrug Pharmacology

TFV

RENAL TUBULAR CELL

OAT 1 & 3

PLASMA

~90% LOWER PLASMA TFV

TFV

RENAL TUBULAR CELL

OAT 1 & 3

TFV → TFV-DP

HBV

GI TRACT

TFV (tenofovir)

DIANION

TDF (tenofovir disoproxil fumarate) 300 mg

ESTER

TAF (tenofovir alafenamid) 25 mg

AMIDATE

short plasma half-life

longer plasma half-life

- greater plasma stability

T1/2 based on in vitro plasma data - TDF = 0.4 minutes, TAF = 30-90 minutes.

TAF HBV Phase 3 Program

Two phase 3, randomized, double-blind studies

- **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 normalization (central lab and AASLD criteria)
  - Serology (HBsAg loss/seroconversion)
- 90% retention rate through Week 96
- Inclusion criteria: HBV DNA ≥20,000 IU/mL; ALT >60 U/L (males), >38 U/L (females), eGFR_{CG} >50 mL/min

Antiviral Efficacy of TAF and TDF at Week 96

Rates of Viral Suppression (ITT)
HBV DNA <29 IU/mL

- No resistance was detected through 96 weeks
- No significant difference between TAF and TDF
- 90% retention rate through Week 96
- Similar rates of mean HBV DNA decline (log10 change) at all time points across both studies

HBV DNA suppression was comparable between TAF and TDF treatment up to Week 96

Agarwal, EASL 2017, FRI-153; Brunetto, EASL 2017, PS-042; Gilead, Data on File.
ALT Normalization at Week 96

Central Laboratory

- 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.

HBeAg−

- Significantly higher ALT normalization rate with TAF vs TDF
- Week 96: 81% (TAF) vs 71% (TDF), *P* = 0.038

HBeAg+

- Week 96: 75% (TAF) vs 68% (TDF), *P* = 0.017

AASLD Laboratory Criteria

- Week 96: 50% (TAF) vs 40% (TDF), *P* = 0.035

Significantly higher ALT normalization 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
## Serologic Response At Week 96

<table>
<thead>
<tr>
<th>Patients, n/n (%)</th>
<th>Study 108 (HBeAg-) (N=425)</th>
<th>Study 110 (HBeAg+) (N=873)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAF n=285</td>
<td>TDF n=140</td>
</tr>
<tr>
<td></td>
<td>TAF n=581</td>
<td>TDF n=292</td>
</tr>
<tr>
<td>HBeAg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Seroconversion</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HBsAg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss</td>
<td>1/281 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Seroconversion</td>
<td>1/281 (&lt;1)</td>
<td>0</td>
</tr>
</tbody>
</table>

Improved serologic responses with higher rates of HBeAg seroconversion with TAF vs TDF – but at limit of statistical significance

Renal Safety Through Week 96

TAF treatment had significantly less impact on eGFR than TDF

*P≤0.001; †P<0.01

Chuang, EASL 2017, SAT-171
**Mean Change in BMD Through Wk 96**

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

* $P<0.001$, p-values from analysis of variance model including treatment as a fixed effect; † $p<0.80$, p-values from mixed model repeated measures

Fung, EASL 2017, SAT-162
Big Proviso

No clinically meaningful outcomes have been presented
Study Design

- Two Phase 3, randomized, 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 ≥20,000 IU/mL; ALT >60 U/L (males) >38 U/L (females); eGFR ≥50 mL/min
- 2:1 randomization
  - Stratified by HBV DNA level and treatment status (naïve/experienced)
Two Phase 3, randomized, double-blind, active-controlled trials
- Study 108 (N=425): HBeAg-negative patients
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2:1 randomization
- Stratified by HBV DNA level and treatment status (naïve/experienced)
Switch from TDF to TAF: Efficacy analysis

**HBV DNA <29 IU/mL**

- 96 weeks: 88/156/177 TDF, 88/148/169 TDF → TAF
- 120 weeks: 88/156/177 TDF, 88/148/169 TDF → TAF

**ALT Normalization**

- 96 weeks: 47/83/176 TDF, 63/106/167 TDF → TAF
- 120 weeks: 63/106/167 TDF, 63/106/167 TDF → TAF

Viral suppression was maintained and ALT normalization rate increased upon switch from TDF to TAF.

Chan, EASL 2017, PS-041
Creatinine Levels in CHB Patients Treated with TDF Switched to TAF

Significant improvement in CrCl was observed at 24 Weeks after switching from TDF to TAF.
Significant improvements in hip and spine BMD were observed at Week 120 in patients who switched from TDF to TAF at 96 Weeks.

Chan, EASL 2017, PS-041
Population Based Study of HBV Co-Morbidities
Age and Comorbidities in CHB Patients

Retrospective, observational study to determine prevalence of comorbidities in 44,026 CHB patients from Commercial, Medicare, and Medicaid databases from 2004–2015

CHB Patients > Age 50

$P < 0.05$ over time between 2006 and 2015

- **Commercial (General population)**: 47% in 2006, 51% in 2015
- **Medicaid (Low-income population)**: 45% in 2006, 52% in 2015
- **Medicare (Older population)**: 71% in 2006, 73% in 2015

Nguyen, EASL 2017, PS-107
The proportion of CHB patients with metabolic comorbidities

Retrospective, observational study to determine prevalence of comorbidities in 44,026 CHB patients from Commercial, Medicare, and Medicaid databases from 2004–2015

The proportion of CHB patients with metabolic comorbidities significantly increased between 2006 and 2015 (Low-income population) (Older population)

Nguyen, EASL 2017, PS-107
Renal Impairment and CKD in CHB Patients

Case-control study of prevalence and incidence of CKD among 44,026 CHB patients and 121,568 non-CHB controls from Commercial, Medicare, and Medicaid databases from 2004–2015.

Prevalence of CKD in CHB patients has increased by 2- to 4-fold from 2006 to 2015, and the prevalence of CKD was significantly higher for CHB patients than matched non-CHB controls ($P<0.05$).

CKD was defined as chronic kidney disease stages I-IV, unspecified chronic kidney disease, end stage renal disease, hypertensive chronic kidney disease stages I-IV, hypertensive heart and chronic kidney disease stages I-IV, or dialysis.

Nguyen, EASL 2017, SAT-132
Osteoporosis and Bone Fracture in CHB Patients

Case-control study of prevalence and incidence of osteoporosis and fracture among 44,026 CHB patients and 121,568 non-CHB controls from Commercial, Medicare, and Medicaid databases from 2004–2015.

Prevalence of bone fracture and osteoporosis increased consistently over the past decade. In addition, the prevalence of bone fracture and osteoporosis was significantly higher for CHB patients than matched non-CHB controls for most payers and years (P<0.05).
Hepatitis Delta

• The final frontier in viral hepatitis
• PEG-IFN therapy sub-optimal in many
• Increasing interest in this
• Prenylation inhibitor Lorafarnib featured strongly at EASL
• 2 oral presentations and one poster
• All phase 2 studies
• Seems to be promising
Limitations

• Triple therapy still requires PEG-IFN
• Need to see significantly bigger number of patients treated
• Delta relapse often occurs late and so need to see 48-96 week post treatment follow up
Summary

• Huge burden of undiagnosed HBV worldwide
• New infections should reduce with better vaccination but prevalent population will continue to die
• EASL CPG has defined new terminology and made some interesting treatment recommendations
• New agents for HBV that are modulatory of the immune system are showing early promise – but you need to pick your target cleverly
• Hepatitis delta remains a problem but there is increasing focus on this
Acknowledgements

• Kate Dorrington from Gilead
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