Difficult to treat patients with HBV infection

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Laiko General Hospital,
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Conflicts of interest

• **Advisor/Consultant**: Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novartis, Roche

• **Lectures**: Abbvie, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novartis, Roche

• **Grants**: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Roche

• **Clinical trials**: Abbvie, Astellas, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp & Dohme, Novartis, Regulus, Roche

• **Data Safety Management Board**: Gilead
Current treatment for patients with CHB

**PEG-IFNa**
- Sustained off-therapy response: 30-35% of HBeAg+, 20-25% of HBeAg- pts
- 50% of sustained responders: HBsAg- after 5 years

**ETV/TDF**
- Virological on-therapy remission in practically all compliant patients (95-100%)
- HBeAg seroconversion: 40-50% of HBeAg+ patients
- HBsAg clearance: 10-12% of HBeAg+, 1-2% of HBeAg-
- No major safety issues

- Histological improvement (possible reversion of cirrhosis)
- Decrease (not elimination) of HCC risk
- Improved major outcomes including survival
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Are there any difficult to treat HBV patients?
Difficult to treat patients with HBV infection

- Fulminant/Severe acute hepatitis B or exacerbation of chronic hepatitis B
- Patients with primary no response to NA
- HBeAg+ immunotolerant patients
- HBeAg+ CHB patients with very high viremia
- CHB patients with multidrug resistance
- CHB patients with NA-related AEs
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Acute hepatitis

More than 95–99% of adults with acute HBV infection will recover spontaneously and seroconvert to anti-HBs without anti-viral therapy [195] (A1). Patients with fulminant or severe hepatitis must be evaluated for liver transplantation (A1). These patients may benefit from NA treatment. Support for such a strategy may be found in a small number of reports mainly with lamivudine [196]. As for CHB, entecavir or tenofovir should be used (C1). The duration of treatment is not established. However, continuation of antiviral therapy for at least 3 months after seroconversion to anti-HBs or at least 12 months after anti-HBe seroconversion without HBsAg loss is recommended (C2).

Sometimes, the distinction between true severe acute hepatitis B and reactivation of CHB may be difficult and may require liver biopsy. However, NA treatment is the treatment of choice in both cases [196–198] (B1).
Transplantation-free 3-month survival in LAM treated pts with acute exacerbation of CHB and decompensation

Decompensation: Bil. $>2-3$ mg/dl, PT prolongation $>3$ sec, ascites

### Odds ratio and 95\% CI

<table>
<thead>
<tr>
<th>Study name</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan HL 2002</td>
<td>1.410</td>
<td>0.358</td>
<td>5.553</td>
<td>0.492</td>
<td>0.623</td>
</tr>
<tr>
<td>Chien RN 2003</td>
<td>0.614</td>
<td>0.242</td>
<td>1.558</td>
<td>-1.027</td>
<td>0.304</td>
</tr>
<tr>
<td>Tsubota A 2005</td>
<td>1.833</td>
<td>0.387</td>
<td>8.674</td>
<td>0.764</td>
<td>0.445</td>
</tr>
<tr>
<td>Sheu MJ 2009</td>
<td>1.962</td>
<td>0.120</td>
<td>31.995</td>
<td>0.473</td>
<td>0.636</td>
</tr>
<tr>
<td></td>
<td>0.981</td>
<td>0.502</td>
<td>1.918</td>
<td>-0.055</td>
<td>0.956</td>
</tr>
</tbody>
</table>

Transplantation-free 3-month survival

84\% vs 85\% in 215 LAM treated & 126 untreated patients

Yu W et al. PLoS One 2013;8:e65952
ETV in patients with acute HBV exacerbation

**ETV (vs no treatment):** improved 48-week outcomes (incl. mortality) of acute-on-chronic liver failure due to the acute exacerbation of CHB.


**ETV (vs LAM):** increased 48-week mortality in patients with severe acute exacerbation of CHB but better virological responses.


**ETV (vs LAM):** no different effect on 24-week mortality in CHB patients with severe acute exacerbation and hepatic decompensation.

Chen CH et al. J Hepatol 2014;60:1127-34.

**ETV (vs LAM):** no different effect on 8-week but improved mortality at 52-week in naive patients with spontaneous acute-on-chronic HBV liver failure.

TDF vs ETV for severe acute HBV exacerbation

189 patients with severe acute HBV exacerbation
• HBsAg+ for >6 months & No coinfection or other cause of liver injury
• ALT ≥5xULN & Bil. ≥3 mg/dl, prolonged PT ≥3 sec and/or complication (ascites, encephalopathy)

<table>
<thead>
<tr>
<th>Outcomes within 24 weeks</th>
<th>TDF (N=41)</th>
<th>ETV (N=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>34%</td>
<td>33%</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>17%</td>
<td>18%</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Death/Liver transplantation (LT)</td>
<td>19%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Independent predictors of death/LT: baseline HBV DNA, hypertension, MELD, PLT, ascites within 4 weeks, encephalopathy, hepatorenal syndrome

Severe acute HBV exacerbation in patients undergoing immunosuppressive/chemo-therapy

The best treatment: Prevention of exacerbation = HBV screening

Computerized physician order entry-based system
• Prevention of HBV reactivation in patients treated with biologic agents (PRESHRIB project)

Computerized order entry-based therapeutic control system
• Excellent prechemotherapy HBV screening for cancer patients undergoing chemotherapy
• Effective prevention of severe acute exacerbation of HBV infection in hospitals among HBV endemic areas
Fulminant/Severe acute hepatitis B or exacerbation of chronic hepatitis B - Conclusions

• **Fulminant/Severe acute hepatitis B:** No clear indications for treatment initiation

• **Exacerbation of chronic hepatitis B:** treatment with a NA

• **NA(s):** most probably no effect on short-term mortality

• **Type of NA:** no clear difference on mortality

• **Prompt referral for liver transplantation**
Difficult to treat patients with HBV infection

- Fulminant/Severe acute hepatitis B or exacerbation of chronic hepatitis B
- Patients with primary no response to NA
- HBeAg+ immunotolerant patients
- HBeAg+ CHB patients with very high viremia
- CHB patients with multidrug resistance
- CHB patients with NA-related AEs
## Long-term ETV therapy in patients with primary non-response

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Primary responders (n=1129 – 98.8%)</th>
<th>Primary non-responders (n=14 – 1.2%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>47±10</td>
<td>51±8</td>
<td>0.16</td>
</tr>
<tr>
<td>Males</td>
<td>63%</td>
<td>57%</td>
<td>0.67</td>
</tr>
<tr>
<td>HBV DNA, log IU/ml</td>
<td>7.0±1.4</td>
<td>6.0±1.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>41%</td>
<td>64%</td>
<td>0.08</td>
</tr>
<tr>
<td>HBeAg+</td>
<td>56%</td>
<td>57%</td>
<td>0.94</td>
</tr>
<tr>
<td>ETV duration, months</td>
<td>30 (18-42)</td>
<td>21 (18-26)</td>
<td>0.08</td>
</tr>
<tr>
<td>Virological response</td>
<td>87%</td>
<td>86%</td>
<td>0.70</td>
</tr>
</tbody>
</table>
Primary no response to ETV or TDF

No clinical relevance

No need for testing!
Difficult to treat patients with HBV infection

- Fulminant/Severe acute hepatitis B or exacerbation of chronic hepatitis B
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- HBeAg+ immunotolerant patients
- HBeAg+ CHB patients with very high viremia
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Natural History of Chronic HBV Infection

Replicative/Immune-tolerant phase
HBeAg(+)

Low-replicative phase
HBeAg(-)/anti-HBe(+)

Replicative/reactivating phase*

Serum HBV DNA, log$_{10}$ IU/mL

ALT

ULN

HBeAg(+)-CHB

Inactive carrier state

HBeAg(-)-CHB

*Natural History of Chronic HBV Infection

HBeAg(+) CHB

Inactive

HBeAg(-) CHB

*Immune reactive phases

Types of HBeAg-positive chronic HBV patients

A. Areas with high HBV prevalence – vertical transmission
   (East Asian countries – genotypes B & C)
   Low (5%) mean annual rate of HBeAg seroconversion –
   Substantial proportion of adults: HBeAg+

B. Areas with intermediate HBV prevalence – horizontal transmission
   (Mediterranean & Middle East countries – genotypes D > A)
   High (10-15%) annual rate of HBeAg seroconversion – <10-20% of adults: HBeAg+

C. Areas with low HBV prevalence – transmission among high-risk adults
   (Western countries in the past – genotype A)
   Not many data for HBeAg seroconversion rates (probably high) –
   HBeAg+ adults with short duration of HBV infection

Predictors of HBeAg seroconversion:
   older age, higher ALT, lower HBV DNA, HBV genotypes A (vs D), B (vs C)

TDF vs TDF+FTC x192 wks in HBeAg+ patients with normal ALT and high HBV DNA

Mean age: 33 years; 89% Asians, 93% gen. B/C, mean HBV DNA: $8.4 \log_{10} \text{IU/mL}$

<table>
<thead>
<tr>
<th>Outcome at week-192</th>
<th>TDF (N=64)</th>
<th>TDF+FTC (N=62)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA &lt;69 IU/ml</td>
<td>55%</td>
<td>76%</td>
<td>0.016</td>
</tr>
</tbody>
</table>

HL Chan et al. Gastroenterology 2014;146:1240-8
TDF vs TDF+FTC x192 wks in HBeAg+ patients with normal ALT and high HBV DNA

Mean age: 33 years; 89% Asians, 93% gen. B/C, mean HBV DNA: 8.4 log_{10} IU/mL

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<td>55%</td>
<td>76%</td>
<td>0.016</td>
</tr>
<tr>
<td>HBV resistance</td>
<td>0%</td>
<td>0%</td>
<td>NS</td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td>5%</td>
<td>0%</td>
<td>NS</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>0%</td>
<td>0%</td>
<td>NS</td>
</tr>
</tbody>
</table>
Treatment indications in HBeAg+ CHB patients EASL 2012

ALT >ULN & HBV DNA >2,000 & Biopsy ≥A2/F2

Immunotolerant phase: Persistently ALT ≤ULN

• No Biopsy – No therapy – Follow-up if age ≤30 years
• Biopsy or even therapy if age >30 years and/or family history of HCC, cirrhosis

Potential additional treatment indications

• Immunosuppression/Chemotherapy
• Professional reasons
• Last trimester of pregnancy

Immunotolerant phase: persistently ALT ≤30/19 IU/L for M/F

- No Biopsy – No therapy – Follow-up every 6 months if age ≤40 years
- Therapy if age >40 years and HBV DNA ≥10^6 IU/mL and significant necroinflammation or fibrosis

Do I treat my HBV immunotolerant patients?

No

Except for a few

GV Papatheodoridis. Paris Hepatitis meeting 2016
Difficult to treat patients with HBV infection

- Fulminant/Severe acute acute hepatitis B or exacerbation of chronic hepatitis B
- Patients with primary no response to NA
- HBeAg+ immunotolerant patients
- HBeAg+ CHB patients with very high viremia
- CHB patients with multidrug resistance
- CHB patients with NA-related AEs
ETV vs ETV+TDF x100 wks in HBeAg+ CHB

Open label, randomized study

Baseline HBV DNA <10^8 IU/mL

Patients with HBV DNA <50 IU/ml, %

<table>
<thead>
<tr>
<th></th>
<th>ETV</th>
<th>ETV+TDF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 weeks</td>
<td>78.7</td>
<td>81.1</td>
<td></td>
</tr>
<tr>
<td>96 weeks</td>
<td>83</td>
<td>83</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Baseline HBV DNA ≥10^8 IU/mL

<table>
<thead>
<tr>
<th></th>
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<th>ETV+TDF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 weeks</td>
<td>50.6</td>
<td>70.6</td>
<td></td>
</tr>
<tr>
<td>96 weeks</td>
<td>62</td>
<td>78.8</td>
<td></td>
</tr>
</tbody>
</table>

AS Lok et al. Gastroenterology 2012;143:619-28
Is there a benefit from the combination of ETV+TDF over TDF alone or TDF+LAM?

Is there a benefit from the combination of ETV+TDF over ETV beyond 96 weeks?
Long-term ETV therapy in HBeAg-positive CHB

<table>
<thead>
<tr>
<th>Year</th>
<th>ETV-022 Patients with HBV DNA &lt;300 cp/mL (%)</th>
<th>n/ N</th>
<th>Year</th>
<th>ETV-901 Patients with HBV DNA &lt;300 cp/mL (%)</th>
<th>n/ N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>236/ 354</td>
<td>Year 1</td>
<td>67%</td>
<td>80/ 146</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55%</td>
<td>Year 2</td>
<td>83%</td>
<td>116/ 140</td>
</tr>
<tr>
<td></td>
<td></td>
<td>89%</td>
<td>Year 3</td>
<td>91%</td>
<td>98/ 108</td>
</tr>
<tr>
<td></td>
<td></td>
<td>94%</td>
<td>Year 4</td>
<td>94%</td>
<td>88/ 94</td>
</tr>
</tbody>
</table>

Chang TT et al. Hepatology 2010;51:422-30
HBeAg+ CHB patients with very high viremia

- **Peg-IFNa**: suboptimal efficacy
- **NA+NA (ETV+TDF) combination vs ETV or TDF alone**
  - Higher short-term virological responses
  - Probably similar long-term virological responses
  - No difference in HBeAg seroconversion rates
  - No difference in HBsAg loss rates
Difficult to treat patients with HBV infection

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- HBeAg+ CHB patients with very high viremia
- CHB patients with multidrug resistance
- CHB patients with NA-related AEs
Multidrug resistance (MDR) in HBV patients

- Multiple mutations can be selected leading to MDR
- Impact of Pol gene mutations on the overlapping Surface gene (vaccine escape mutants)
- Treatment adaptation based on the cross-resistance profile
- Complete viral suppression mandatory

Usually associated with (older) sequential therapies (LAM-ADV-ETV)
Virological breakthrough under a NA

- **LAM resistance**: switch to TDF (add ADV if TDF not yet available) (B1)

- **ADV resistance**: in NA naive patients before ADV, switch to ETV or TDF (B1); ETV may be preferred in such patients with high viraemia (C2) in patients with prior LAM-R, switch to TDF and add a nucleoside (C1)

- **TBV resistance**: switch to or add TDF (add ADV if TDF not yet available) (C1)

- **ETV resistance**: switch to or add TDF (add ADV if TDF not yet available) (C1)

- **TDF resistance**: genotyping and phenotyping by an expert laboratory. ETV, TBV, LAM or FTC could be added (C2); switch to ETV may be sufficient if the patient was NA naive before TDF (C2)

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- CHB patients with NA-related AEs
Safety (Renal) monitoring during NAs

- Minimal rates of renal function decline have been reported with all NAs, except perhaps for telbivudine which seems to improve the creatinine clearance (C1)

- The nephrotoxic potential seems to be higher for nucleotide analogues, particularly adefovir (B1)

# TDF trial at year 8
## Safety Summary During the Open-Label Period

<table>
<thead>
<tr>
<th>Adverse Event, n (%)</th>
<th>Total (N=585)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leading to study drug discontinuation</td>
<td>13 (2.2)</td>
</tr>
<tr>
<td>Death</td>
<td>12 (2.1)</td>
</tr>
<tr>
<td>Serious study drug-related adverse events</td>
<td>7 (1.2)</td>
</tr>
<tr>
<td>Grade 3 or 4 drug-related adverse events</td>
<td>6 (1.0)</td>
</tr>
<tr>
<td>Serum creatinine ≥0.5 mg/dL above baseline</td>
<td>13 (2.2)</td>
</tr>
<tr>
<td>$PO_4 &lt;2.0$ mg/dL</td>
<td>10 (1.7) (+1.2%)</td>
</tr>
<tr>
<td>Creatinine clearance &lt;50 mL/min</td>
<td>6 (1.0)</td>
</tr>
<tr>
<td>Dose reduction, treatment interruption, or discontinuation for a renal event†</td>
<td>20 (3.4)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma (HCC) events*</td>
<td>14/641 (2.2)</td>
</tr>
</tbody>
</table>

†Dose reduction (n=18), temporary treatment interruption or drug discontinuation (1 patient each)  
*Cumulative 8 year

Marcellin et al. AASLD 2014, Oral #229
Telbivudine Improves Renal Function in Patients With Chronic Hepatitis B

Edward J. Gane, Gilbert Deray, Yun-Fan Liaw, Seng Gee Lim, Ching-Lung Lai, Jens Rasenack, Yuming Wang, George Papatheodoridis, Adrian Di Bisceglie, Maria Buti, Didier Samuel, Alkaz Uddin, Sophie Bosset, and Aldo Tylesinski

- **GLOBE:** TBV vs LAM for 104 wks – 921 HBeAg+, 446 HBeAg- (Scr_0 ≤ 1.5 mg/dl)
  CKD stage 2 (eGFR 60-89 ml/min/1.73 m²: 37.6% TBV vs 34.1% LAM

- **Long-term extension studies of GLOBE**

- **Switch from LAM to TBV (A2303):** 398 pts without LAM-R (99 HBV DNA+)

- **Off-treatment in A2303:** 66 pts with HBeAg seroconversion & HBV DNA-

- ** Decompensated cirrhosis (A2301):** 228 pts TBV vs LAM for 104 wks
TBV+TDF or LAM+TDF in patients under LAM±ADV: eGFR changes

Figure 2A. Study (1): Mean HBV DNA at Baseline and Weeks 24, 52, and 104

Figure 2B. Study (1): Mean eGFR at Baseline and Week 24, 52, and 104

Gane E et al, EASL 2012
NUCLEOS(T)IDE ANALOGUES FOR HEPATITIS B VIRUS INFECTION IN PATIENTS WITH CHRONIC KIDNEY DISEASES

Creatinine clearance <50-60 ml/min or HBV-related glomerulopathies

**NA naive pts with treatment indications***
- Entecavir regardless of viremia or telbivudine for patients with low viremia#

Patients with resistance to any nucleoside
- Tenofovir

**Patients under immunosuppressive therapy with HBV DNA <2000 IU/ml**
- Entecavir or telbivudine

**NA naive pts with treatment indications***
- Entecavir regardless of viremia and creatinine clearance or telbivudine for patients with low viremia# or tenofovir for cases with creatinine clearance >60 ml/min

Patients with resistance to any nucleoside
- Tenofovir

Renal transplantation

**HBsAg (+) recipients**
- No therapy
- HBV DNA monitoring

**HBsAg (-), anti-HBc (+) recipients or donors**

Hemodialysis patients

**NA naive pts with treatment indications***
- Entecavir or tenofovir
- Entecavir or telbivudine for patients with residual diuresis

Patients with resistance to any nucleoside
- Tenofovir

**HBsAg (+) donors in HBsAg (-), anti-HBs (+) recipients**
- Any NA including lamivudine (plus HBIG in case of donors with HBV viremia)

#Low viremia: HBV DNA <10^6/10^8 IU/mL for HBeAg+/- pts. Pts under TBV: continue TBV if HBV DNA- at 24wks.

C Pipili, E Cholongitas, G Papatheodoridis. APT 2014; 39:35-46
TAF: Tenofovir Alafenamide

Improved stability in plasma:
- Enhanced delivery of active form (TFV-DP) to hepatocytes
- Lower doses are used; systemic exposures of TFV reduced
## Phase III trials with TAF in CHB

<table>
<thead>
<tr>
<th></th>
<th>HBeAg- (Study 108)</th>
<th>HBeAg+ (Study 110)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAF 25 mg (n=285)</td>
<td>TDF (n=140)</td>
</tr>
<tr>
<td></td>
<td>TAF 25 mg (n=581)</td>
<td>TDF (n=292)</td>
</tr>
<tr>
<td>HBV DNA &lt;29 IU/ml at week 48</td>
<td>94.0%</td>
<td>92.9%</td>
</tr>
<tr>
<td></td>
<td>63.9%</td>
<td>66.8%</td>
</tr>
<tr>
<td>Drug discontinuation</td>
<td>0.7%</td>
<td>0.7%</td>
</tr>
<tr>
<td></td>
<td>1.0%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

**TAF & TDF: similar safety and tolerability profile**

**TAF compared to TDF: favorable changes in bone and renal lab parameters**

- Significantly smaller mean percentage decrease from baseline in hip and spine bone mineral density at week 48 (p<0.001).
- Favorable median eGFR from baseline to week 48 (p<0.01).

*Gilead press release, January 6, 2016*

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**12/1/2016: New Drug Application (NDA) to FDA for TAF in CHB**
Thank you for your attention!
Q1. Male patient, 45 years old, is admitted due to jaundice.

ALT 3200 IU/L, AST 2250 IU/L, Bilirubin 25 (direct 16) mg/dl, Total protein 7.1 (albumin 3.8) g/dl, PT 14 sec (control 12), HBsAg+, HBeAg-, anti-HBe+, IgM anti-HBc+, anti-HDV-, anti-HCV-, anti-HIV-, IgM anti-HAV-.

What would you recommend?

1. No antiviral therapy
2. Lamivudine
3. Entecavir/Tenofovir
4. Peg-interferon-alfa
Q1. Male patient, 45 years old, is admitted due to jaundice.
ALT 3200 IU/L, AST 2250 IU/L, Bilirubin 25 (direct 16) mg/dl, Total protein 7.1 (albumin 3.8) g/dl, PT 14 sec (control 12), HBsAg+, HBeAg-, anti-HBe+, IgM anti-HBc+, anti-HDV-, anti-HCV-, anti-HIV-, IgM anti-HAV-.

What would you recommend?

1. **No antiviral therapy**
2. Lamivudine
3. Entecavir/Tenofovir
4. Peg-interferon-alfa
Q2. Female patient, 22 years old, with HBeAg-positive CHB

1\textsuperscript{st} visit: ALT 32 IU/L, AST 22 IU/L, HBeAg+, anti-HBe-, HBV DNA 28,500,000 IU/mL, Fibroscan 6.5 kPa.

2\textsuperscript{nd} visit (3 months later): ALT 48 IU/L, AST 32 IU/L, HBeAg+, anti-HBe-, HBV DNA 400,000 IU/mL.

What would you recommend?

1. Follow-up
2. Lamivudine
3. Entecavir/Tenofovir
4. Peg-interferon-alfa
Q2. Female patient, 22 years old, with HBeAg-positive CHB

1st visit: ALT 32 IU/L, AST 22 IU/L, HBeAg+, anti-HBe-, HBV DNA 28,500,000 IU/mL, Fibroscan 6.5 kPa.

2nd visit (3 months later): ALT 48 IU/L, AST 32 IU/L, HBeAg+, anti-HBe-, HBV DNA 400,000 IU/mL.

What would you recommend?

1. Follow-up
2. Lamivudine
3. Entecavir/Tenofovir
4. Peg-interferon-alfa
Q3. Male patient, 62 years old, with HBeAg-negative CHB, hypertension and diabetes under tenofovir (TDF)

**Before TDF**: ALT 122 IU/L, AST 72 IU/L, HBV DNA 8,500,000 IU/mL, creatinine 1.1 mg/dl, phosphate 3.4 mg/dl, Fibroscan 10.5 kPa.

**2 years under TDF**: ALT 28 IU/L, AST 22 IU/L, HBV DNA undetect., creatinine 1.2 g/dl, phosphate 1.8 mg/dl

What would you recommend?

1. Continue with TDF at the same dose
2. Decrease TDF dose (TDF every other day)
3. Switch to entecavir
4. TDF and telbivudine (both every other day)
Q3. Male patient, 62 years old, with HBeAg-negative CHB, hypertension and diabetes under tenofovir (TDF)

**Before TDF:** ALT 122 IU/L, AST 72 IU/L, HBV DNA 8,500,000 IU/mL, creatinine 1.1 mg/dl, phosphate 3.4 mg/dl, Fibroscan 10.5 kPa.

**2 years under TDF:** ALT 28 IU/L, AST 22 IU/L, HBV DNA undetectable, creatinine 1.2 g/dl, phosphate 1.8 mg/dl

What would you recommend?

1. Continue with TDF at the same dose
2. Decrease TDF dose (TDF every other day)
3. **Switch to entecavir**
4. TDF and telbivudine (both every other day)