Clinical dilemmas in HBeAg-negative CHB

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Case 2

- 9/2008 - Asymptomatic Greek, 30 year-old, man
- HBsAg+ during blood donation 3 years ago
- ALT: 32-38 IU/L, AST: 12-26 IU/L on 3 occasions over last 3 years
- LFTs, FBC, PT: normal
- HBeAg-, anti-HBe+, anti-HCV-, anti-HDV-, anti-HIV-, anti-HAV+
- No other disease, no family history of liver disease
- Social drinking (<15 g alc/day), Smoker (20 cig./day x14 years)
- Normal physical examination, BMI: 23.5 kg/m2
- Abdominal U/S: normal

ULN for ALT/AST: 40 IU/L

Case 2 - follow-up

- 10/2008 – ALT 42 IU/L, AST 32 IU/L
- HBV DNA 2800 IU/mL
- Fibroscan-stiffness: 7.0 kPa

- 11/2008-03/2009 – ALT 36, 48 and 40 IU/L on 3 occasions
- HBV DNA 4200 IU/mL
- Serum HBsAg 3400 IU/mL

ULN for ALT/AST: 40 IU/L

Case 2 - Summary

- HBeAg- patient

- Normal - Mildly elevated ALT (<1.2xULN)
- Moderate HBV DNA (2000-20000 IU/mL)

- High HBsAg levels (>1000 IU/mL)
- Moderate stiffness

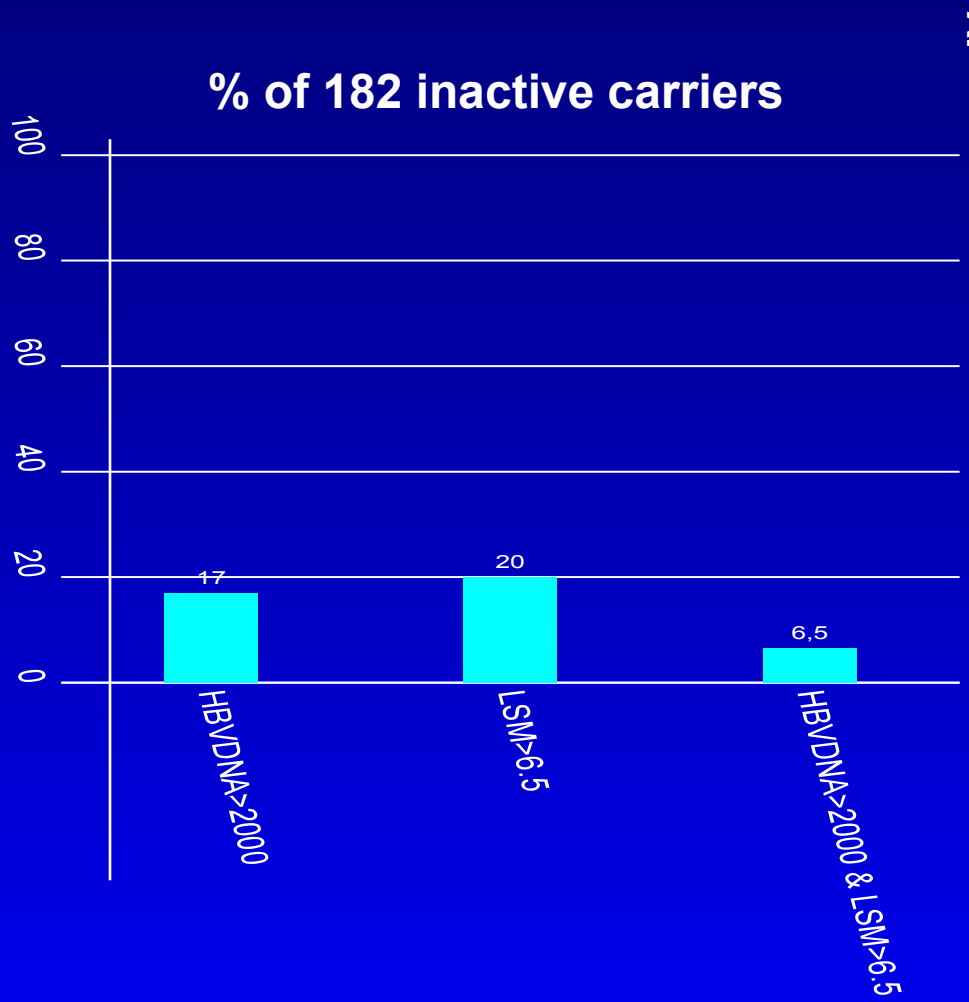
- Reluctant for liver biopsy

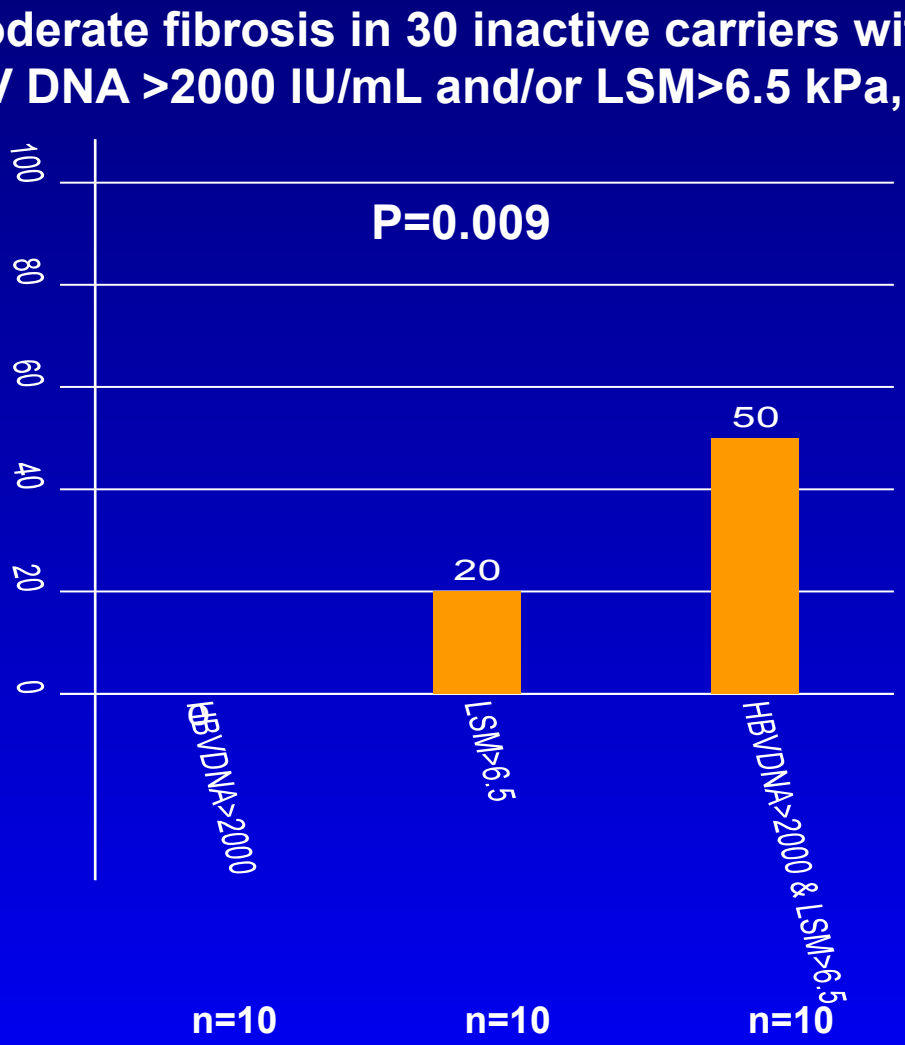
Case 2 – Question

How would you manage this patient?

1. Further follow-up with ALT & HBV DNA
2. Start Peg-IFNa
3. Start LAM
4. Start ETV or TDF

HBV DNA, Elastographic (LSM) and histological findings in 182 HBeAg-negative patients with PNALT & HBV DNA <20000

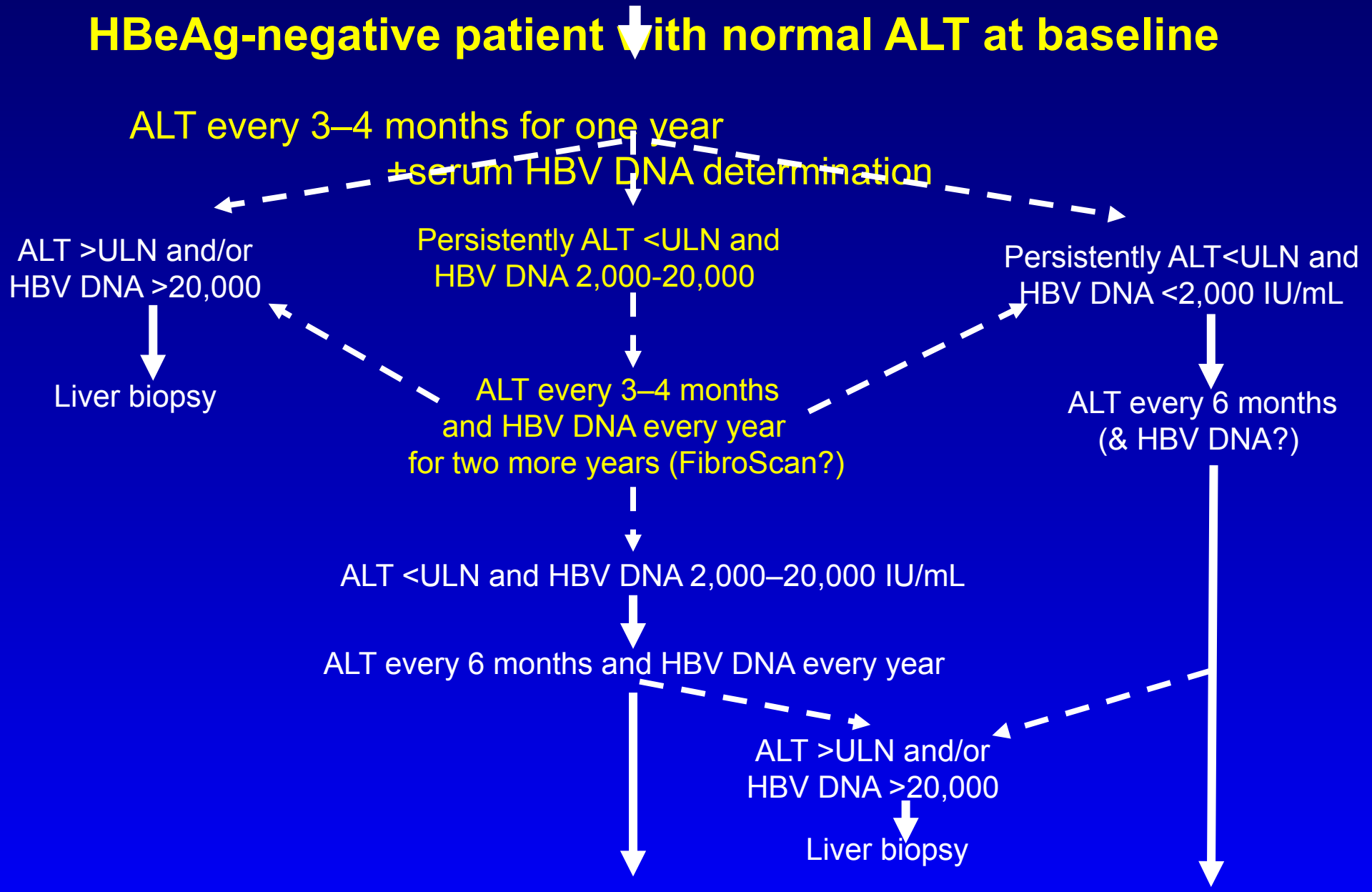




LSM: liver stiffness measurements, PNALT: persistently normal ALT

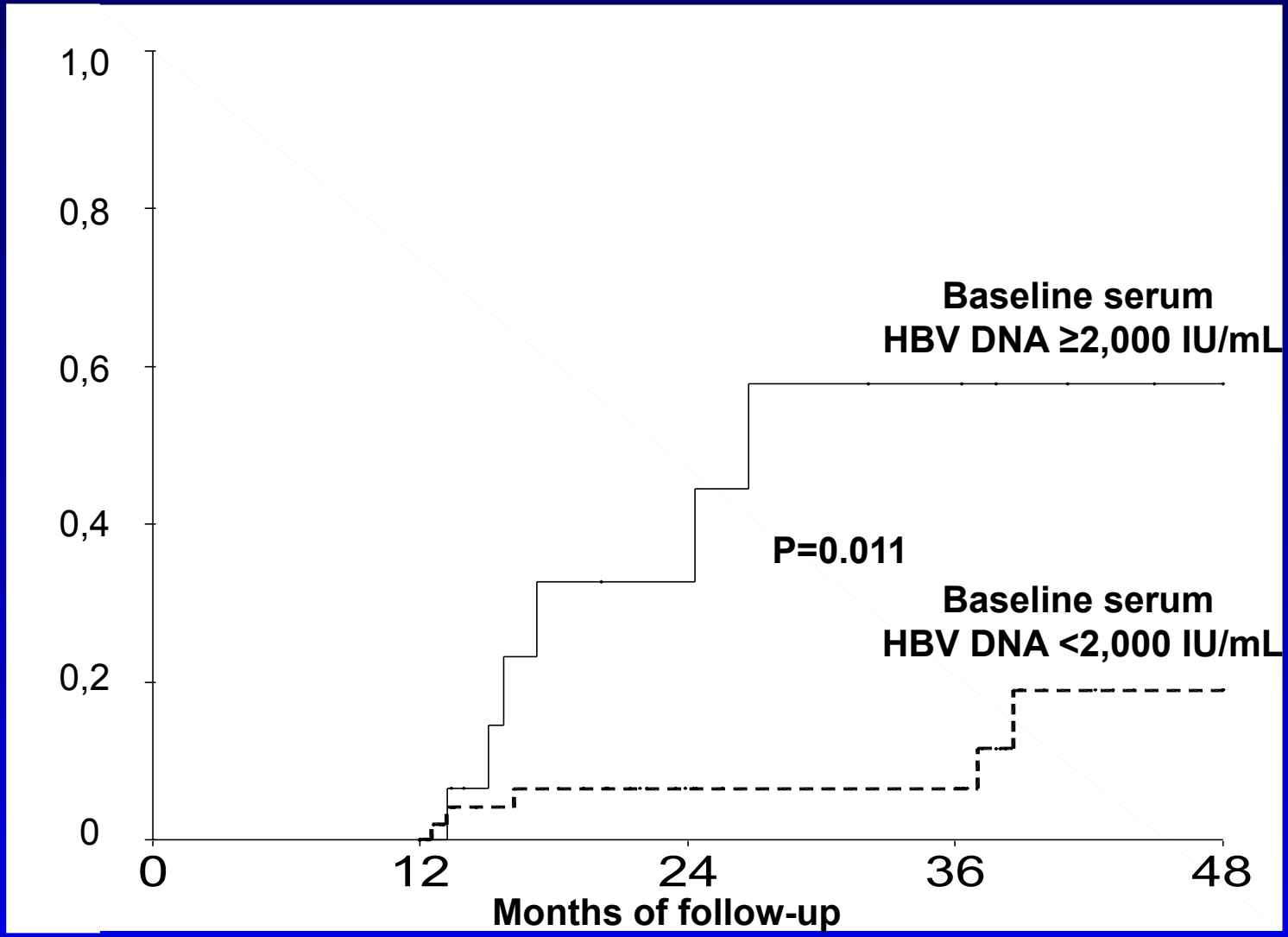
Papatheodoridis GV et al. J Viral Hepat 2014; 21: 517-24

HBeAg-negative patient with normal ALT at baseline



Papatheodoridis GV et al. J Hepatol 2012;57:196–202. EASL HBV CPGs. J Hepatol 2012;57:167–185

Probability of progression from inactive carrier state to HBeAg-negative chronic hepatitis B



Patients at risk

HBV DNA ≥2,000 IU/mL:	*20*	*20*	*9*	*6*	*2*
HBV DNA <2,000 IU/mL:	*65*	*65*	*30*	*26*	*6*

Papatheodoridis GV et al. J Viral Hepat 2008; 15: 434-41

Case 2 – Further follow-up

- 04-10/2009 - ALT 32 and 145 IU/L on two 3-monthly determinations
  - 11/2009 - ALT 220 IU/L

  - 10/2009 - HBV DNA 245,000 IU/mL

    HBsAg 3800 IU/mL

    Fibroscan - stiffness 10.2 kPa

- Treatment initiation (without a liver biopsy) was decided

Possibility for treatment initiation without liver biopsy

- **Patients with obviously active CHB:** HBeAg+ve and HBeAg-ve patients with ALT >2xULN and HBV DNA >20,000 IU/mL (B1).

Liver biopsy additional useful information, but not usually change treatment decision.

A non-invasive method to confirm or rule out cirrhosis is extremely useful in patients who start treatment without liver biopsy (B1).

EASL HBV CPGs, 2012

Case 2 – Question

Which therapeutic agent would you prefer?

1. Peg-IFNa
2. LAM
3. ETV or TDF
4. Other

Optimal first-line therapy in compensated CHB (A1)

Peg-IFNa (IFNa)

- Young (reproductive) age
- Favorable factors of response
  - *HBeAg(+)CHB:*
    low HBV DNA, high ALT,
    genotype A vs D or B vs C
  - *HBeAg(-)CHB: unknown,*
- Patient's preference

ETV/TDF (TBV, ADV, LAM)

- Not candidates for IFNa
- Contraindication for IFNa
- No sustained response with IFNa
- Patient's preference

EASL HBV CPGs, 2012

Case 2 - Question

- 11/2009 – Peg-IFNa-2a 180 µg/week
  Good tolerability

  - At 12 weeks: ALT 65 IU/L
    HBV DNA 650,000 IU/mL
    HBsAg 2800 IU/mL

  - Would you continue Peg-IFNa?
    - Yes
    - No

PegIFN stopping rule

- **HBeAg-ve (genotype D):** no decline in **HBsAg levels** and no **HBV DNA** drop ≥2 log10 IU/mL by month 3 **(B2)**

EASL HBV CPGs, 2012

Case 2 - Question

- Peg-IFNa-2a continued - Good tolerability
  - 11/2010 (48 weeks): ALT 35 IU/L
    HBV DNA 1,200 IU/mL
    HBsAg 1600 IU/mL
  - Would you continue Peg-IFNa?
    - Yes
    - No

Case 2 - Question

- Peg-IFNa-2a stopped
  - 01/2011: ALT 95 IU/L, HBV DNA 125,000 IU/mL
  - 02/2011: ALT 165 IU/L, HBV DNA 825,000 IU/mL

  Retreatment was decided.
  - Which agent would you recommend?
    - Peg-IFNa
    - LAM
    - ETV or TDF
    - Other

Case 2 - Question

- 02/2011: TDF monotherapy started
  - How often would you monitor HBV DNA?
    - At 3 and 6 and then every 6 months
    - Every 6 months
    - At 6, 12 and then every 12 months

      (if HBV DNA undetectable)

HBV monitoring during therapy with NAs

Finite treatment with NAs in HBeAg+ve patients

- HBV DNA every 3 mos
- HBeAg/anti-HBe every 6-12 mos
- NA therapy can be stopped 12 mos after anti-HBe seroconversion (B1)
- HBsAg every 6 mos after anti-HBe seroconversion
- NA treatment may be continued until HBsAg clearance with or without anti-HBs, particularly in patients with severe fibrosis or cirrhosis (C1)

Long-term therapy with NAs

- HBV DNA undetectability by PCR (<10–15 IU/ml) should ideally be achieved to avoid resistance (A1)
- HBV DNA at 3 and then every 3-6 mos
- During ETV or TDF therapy, the frequency of HBV DNA follow-up may be decreased when patient compliance and treatment efficacy have been established (C1)

EASL HBV CPGs, 2012

Case 2 - Question

- 02/2011: TDF monotherapy started
  - How often would you recommend renal safety monitoring?
    - Every month for 1st 3 months and every 3 months thereafter
    - Every 3 months for 1st year and every 6 months thereafter
    - Every 6 months for 1st year and every 12 months

Case 2 - Question

- 02/2011: TDF monotherapy started
  - Which safety monitoring would you recommend?
    - Serum creatinine (eGFR)
    - Serum creatinine (eGFR) & phosphate
    - Serum creatinine (eGFR) & phosphate, urine analysis
    - Serum creatinine (eGFR) & phosphate, urine analysis, bone density

Renal monitoring during NAs

<table>
<tr><th>Renal risk</th><th>Antiviral</th><th>Test (C1)</th><th>Frequency (C2)</th></tr>
<tr><td>Normal</td><td>ADV, TDF</td><td rowspan="2">ClcrSerum phosphate</td><td>0, 3, 6, 9, 12 & then every 6 mos</td></tr>
<tr><td rowspan="2">High</td><td>ADV, TDF</td><td rowspan="2">0, 1, 2, 3, 6, 9, 12 & then every 6 mos</td></tr>
<tr><td>LAM, ETV, TBV</td><td>Clcr</td></tr>
</table>

EASL HBV CPGs, 2012

Case 2 - Question

- 02/2011: TDF monotherapy started
  - Would you recommend HCC surveillance with U/S?
    - Yes
    - No

PAGE-B: a simple HCC risk score for the first 5 years of ETV/TDF therapy in Caucasian CHB patients

Age (years)	Gender	Platelets (/mm3)
16–29: 0	Female: 0	≥200,000: 0
30–39: 2	Male: 6	100,000–199,999: 6
40–49: 4		<100,000: 9

Our case – PAGE-B: 8

Males ≥40 yrs, females ≥70 yrs, PLT <200,000/mm3: moderate to high HCC risk (PAGE-B ≥10)

HCC risk

Low (or no) – PAGE-B<10, Intermediate -PAGE-B=10-17, High –PAGE-B>17

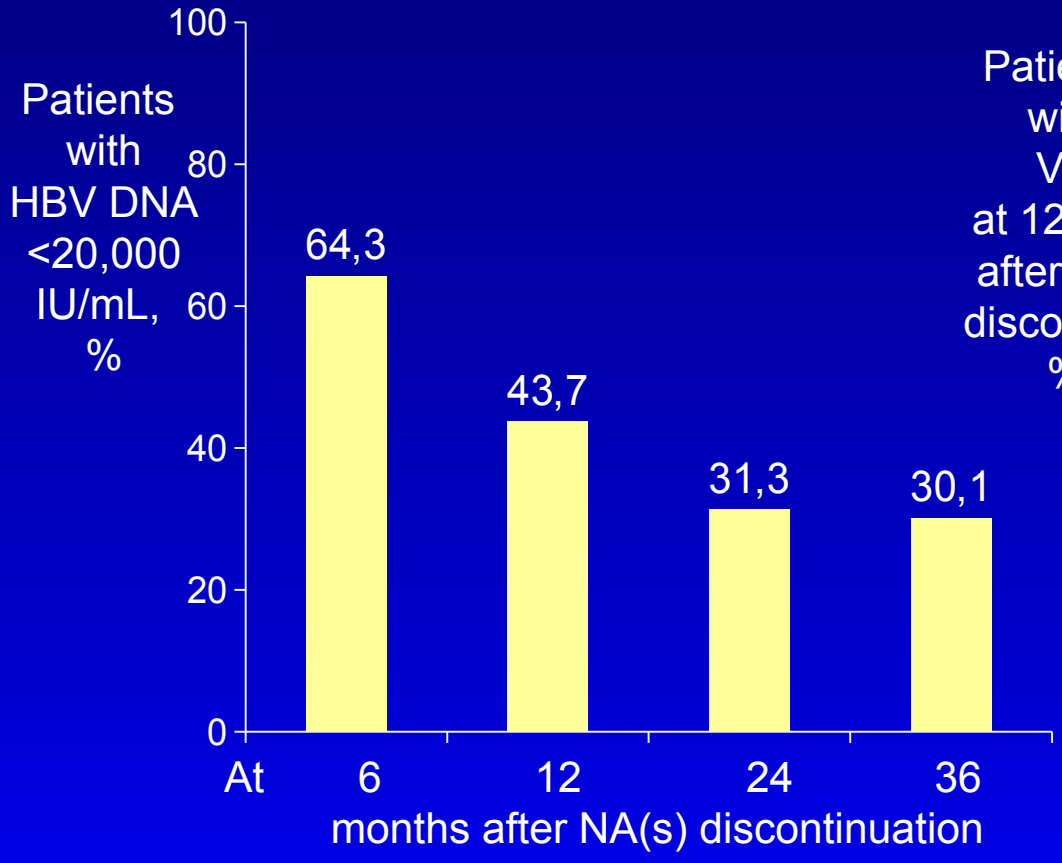
Papatheodoridis GV et al. J Hepatol 2016, in press

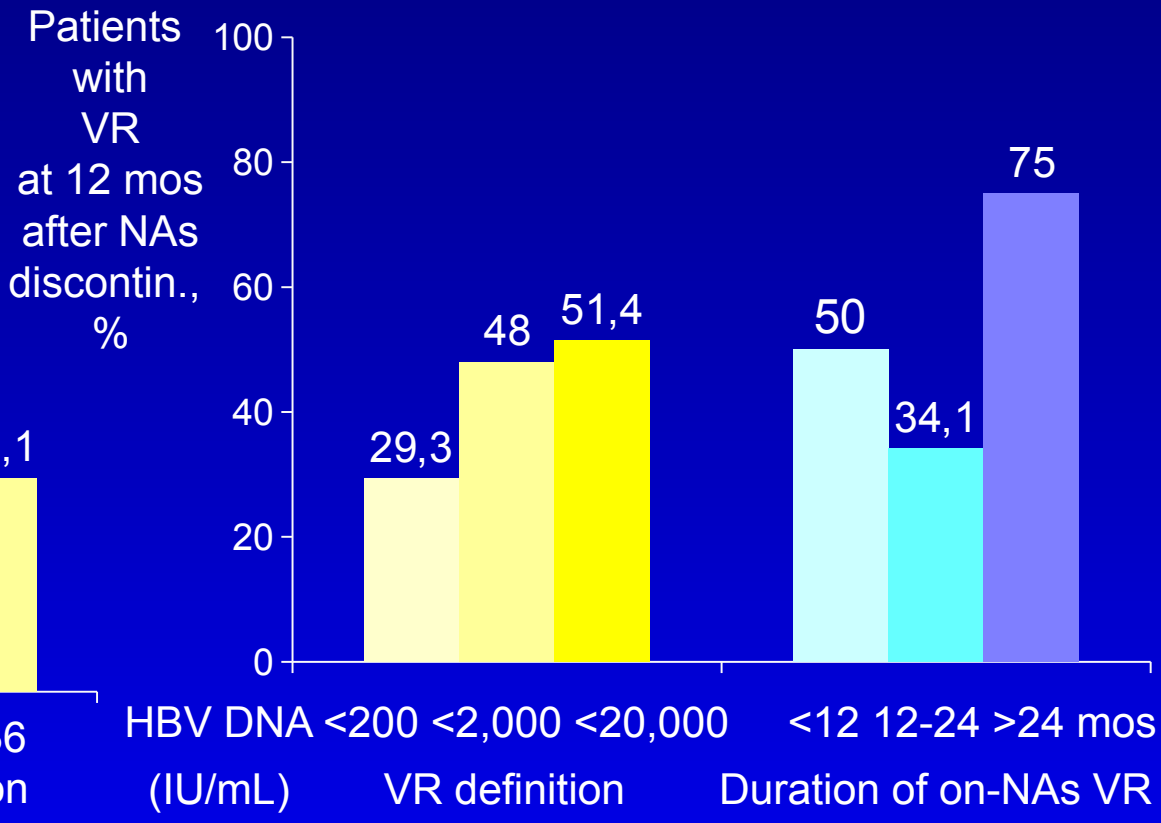
Case 2 - Question

- 01/2016: TDF monotherapy continued
  - ALT<ULN & HBV DNA undetectable since 07/2011
  - HBsAg 3120 IU/mL
  - Would you consider discontinuation of TDF?
    - Yes
    - No

Rates of virological remission after NAs discontinuation

17 studies, 967 HBeAg- patients





Pooled HBsAg loss: 1.7%; Durable biochemical remission: 57%

GV Papatheodoridis et al. Hepatology 2016; accepted manuscript

Case 2 - Questions

If TDF stopped, issues for discussion

- Role of HBsAg levels
- Add-on or switch to Peg-IFNa during the last period of TDF?
- Optimal follow-up after TDF?
- Criteria for retreatment?
- Type of retreatment?

Case 1

- 9/2012 - Asymptomatic Greek, 47 year-old, man
- HBsAg+ diagnosed at blood donation 3 months ago
- ALT: 35 IU/L, AST: 22 IU/L, LFTs, FBC, PT: normal
- HBeAg-, anti-HBe+, anti-HCV-, anti-HIV-, anti-HAV+
- No other disease, no family history of liver disease
- No alcohol, no smoking
- Normal physical examination, BMI: 28.7 kg/m2
- Abdominal U/S: normal

ULN for ALT/AST: 40 IU/L

HBeAg- patients with normal baseline ALT

Inactive chroni HBV carriers

(good long-term outcome)

Patients with HBeAg-negative CHB

(progressive liver disease)

Don’t treat – Follow-

Treat

Case 1 - follow-up

- 10/2012 - ALT 62 IU/L, AST 42 IU/L
- HBV DNA 1,800 IU/mL, anti-HDV-
- Fibroscan-stiffness: 7.2 kPa

  - 11/2012-03/2013 – ALT 68, 98 and 54 IU/L on 3 occasions
  - Negative autoantibodies
  - Ferritin 150 µg/L
  - HBV DNA 980 IU/mL
  - Serum HBsAg 320 IU/mL

ULN for ALT/AST: 40 IU/L

Case 1 – Question

What do you think for this patient?

1. He is an inactive chronic HBV carrier
2. He has HBeAg-negative CHB
3. He needs HBV therapy
4. He needs a liver biopsy

Case 1 - Summary

- HBeAg- patient
- Elevated ALT (occasionally >2xULN)
- Moderate liver stiffness

- Low HBV DNA (<2000 IU/mL)
- Low HBsAg levels (<1000 IU/mL)

Follow-up of HBeAg– patients with persistently normal ALT & HBV DNA <2000 IU/mL

- HBsAg ≥1000 IU/mL: every 6 months
- HBsAg <1000 IU/mL: every 12 months?

Brunetto M et al. Gastroenterology 2010,139:483-90; Tseng TC et al. Hepatology 2013,57:441-50

Case 1 – Elevated ALT: Need for liver biopsy

- 04/2013 -Liver biopsy: lesions of NASH with mild activity, mild fibrosis and mild severity of steatosis

Chronic HBV infection:
HBV is usually but not always the cause of liver injury