Case debates on Chronic Hepatitis B

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First line treatment in an HBe Ag positive patient (1)

- M. A., 37 years old, diagnosed 4 years ago because boyfriend HIV-HBV co-infected.
- No tests done until December 2007
- Biological tests in January 2008:
  - HBs Ag positive, HBe Ag positive and anti-HBe Ac negative
  - AST = 45 UI/mL, ALT = 60 UI/mL

First line treatment in an HBe Ag positive patient (2)

- Would you perform more tests?
- Would you biopsy this patient ?
- Would you treat this patient ?

First line treatment in
an HBe Ag positive patient

- Would you perform more tests ?

YES !

Complete hepatitis tests:
-HCV, HDV, HAV
-HBV-DNA measure
-HBV genotying
-Other causes of hepatitis
(especially if very elevated ALT)

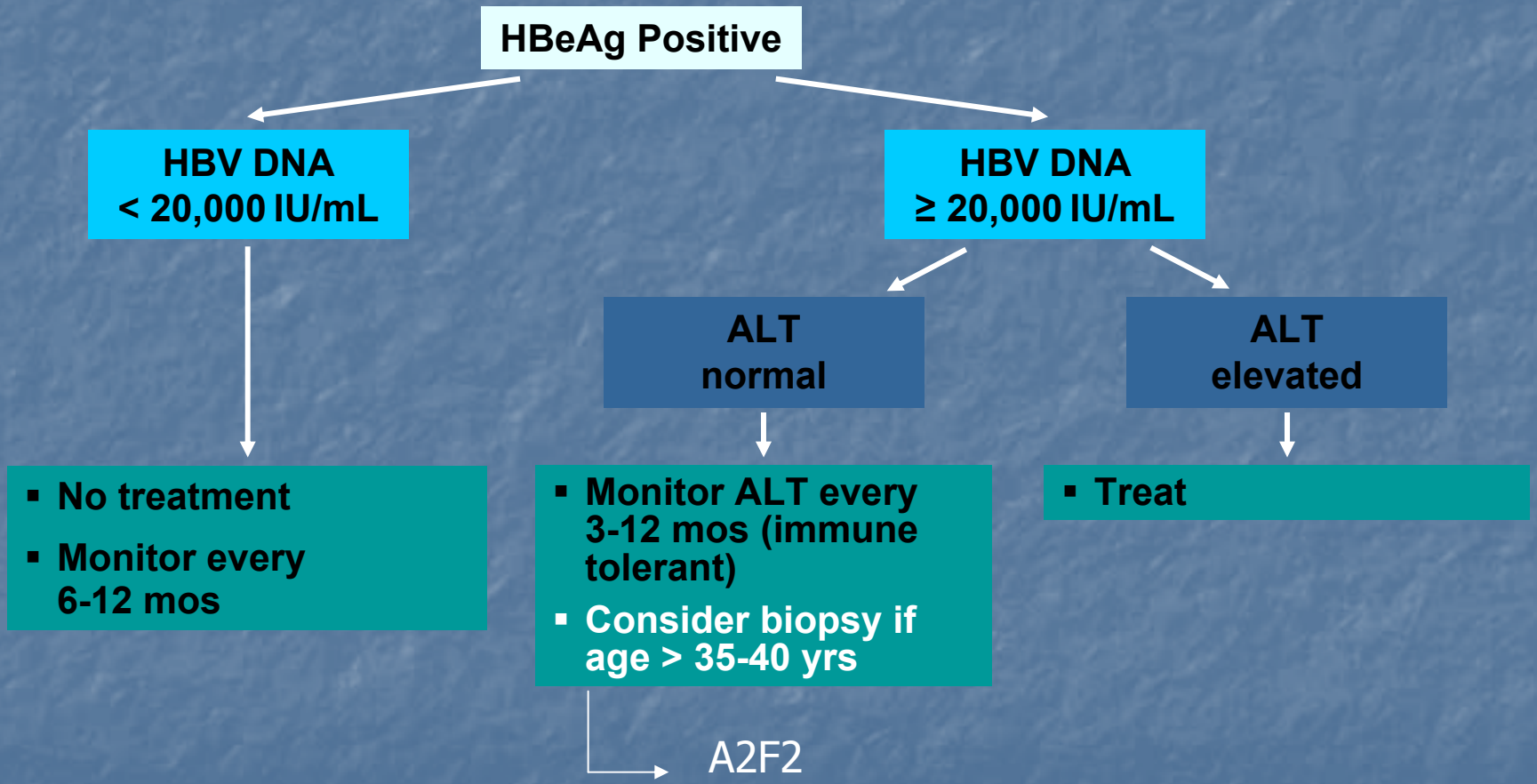
Perform liver ultrasound

Complete biological profile
-ALP, GGT
-Prothrombin, V fact.
-Serum iron, ferritin

-HCV, HAV, HDV negative
-HBV-DNA = 96 000 UI/mL
-genotype A
-No other cause of hepatitis
-No cholestasis
- PT = 98%, V fact. = 100%
-Serum iron normal

First line treatment in an HBe Ag positive patient

- Would you biopsy this patient ?



Updated from Keeffe EB, et al. Clin Gastroenterol Hepatol. 2006;4:936-962.

First line treatment in
an HBe Ag positive patient

- Would you treat this patient ?

2007 AASLD Guidelines

- Who to treat?
  - HBV DNA > 20,000 IU/mL and ALT > 2 x ULN*
  - Consider biopsy if age > 40 yrs, ALT 1-2 x ULN, or family history of HCC; treat as needed
- Preferred drug(s)
  - Entecavir or Tenfovir
  - Adefovir ? Telbivudine ?
  - or peginterferon
- Duration of therapy
  - Continue 6 mo after HBeAg → anti-HBe

First line treatment in an HBe Ag positive patient

Summary

- **Patient with HBeAg-positive chronic hepatitis B recommended to undergo treatment based on:**
  - Serum HBV DNA > 20,000 IU/mL (96,000 IU/mL),
  - Elevated ALT > 30 IU/L (60 IU/L)
  - Inflammation (grade 2) and fibrosis (stage 2) on biopsy

- **Peg-interferon alfa-2a 180 µg/wk can be treatment of choice because:**
  - ALT elevated, HBV-DNA modestly increased, genotype A, HBeAg+, young age.

- **Entecavir 0.5 mg/day, Tenofovir 300mg/day,**
  - Adefovir 10 mg/day, telbivudine 600 mg/day
  - "combination" or "add on" strategy to be debated

First line treatment in an HBe Ag negative patient (1)

- M. W, born in Zaire, 63 years old.
- Parents dead « from the liver »
- Diagnosed HBs Ag positive during an HIV screening in a VCT in September 2006
- Results of tests performed in October 2006:
  - HCV, HDV, HIV negative, HAV IgG positive
  - ALT = 115 UI/mL, AST = 90 UI/ml
  - HBe Ag negative, anti-HBe Ac positive
- New tests performed in March 2007:
  - ALT = 34 UI/mL, AST = 22 UI/ml
  - HBV-DNA = 1200 UI/ml

First line treatment in an HBe Ag negative patient (2)

- In which chronic hepatitis B stage is this patient ?
- Would you offer him treatment ? Why ?

First line treatment in
an HBe Ag negative patient

- In which chronic hepatitis B stage is this patient ?

Phases of Chronic HBV Infection				
	Immune Tolerance	**Immune Clearance/ HBeAg-Positive CHB**	**Nonreplicative (Inactive Carrier)**	**Reactivation/ HBeAg-Negative CHB**
HBV DNA, IU/mL	10^5 - 10^{10}	10^4 - 10^{10}	< 10^4	10^3 - 10^8
HBeAg	HBeAg+	HBeAg+	HBeAg-	HBeAg-
ALT	Normal	High or fluctuating	Normal	High or fluctuating
Other	--	Active inflammation on liver biopsy	HBsAg may become undetectable	Active inflammation on liver biopsy
Candidates for therapy?	No	Yes	No	Yes

➔ Nonreplicative/inactive HBsAg carrier phase after recent HBeAg seroconversion
➔ Reactivation/HBeAg-negative chronic hepatitis B phase currently quiescent with minimal viral replication

First line treatment in an HBe Ag negative patient

- Would you offer him treatment ? Why ?

NO

➔Need to repeat tests and follow up for at least 6 months

➔Will help to make the difference between the two stages

First line treatment in an HBe Ag negative patient

- How would you manage this patient for the next 12 months?

  - Follow-up with repeated ALT and HBV DNA testing to properly classify phase of infection
  - Liver biopsy to assess presence and degree of necroinflammation and fibrosis
  - Noninvasive test for necroinflammation and fibrosis

First line treatment in
an HBe Ag negative patient

- 12 months later (March 2008), next visit with biological tests:
  - AST = 154 UI/mL, ALT = 187 UI/mL
  - HBV-DNA = 76000 UI/mL
  - Same serological markers
  - Liver biopsy : A2F3

First line treatment in an HBe Ag negative patient

- What happened to this patient ?
- Would you treat him ?

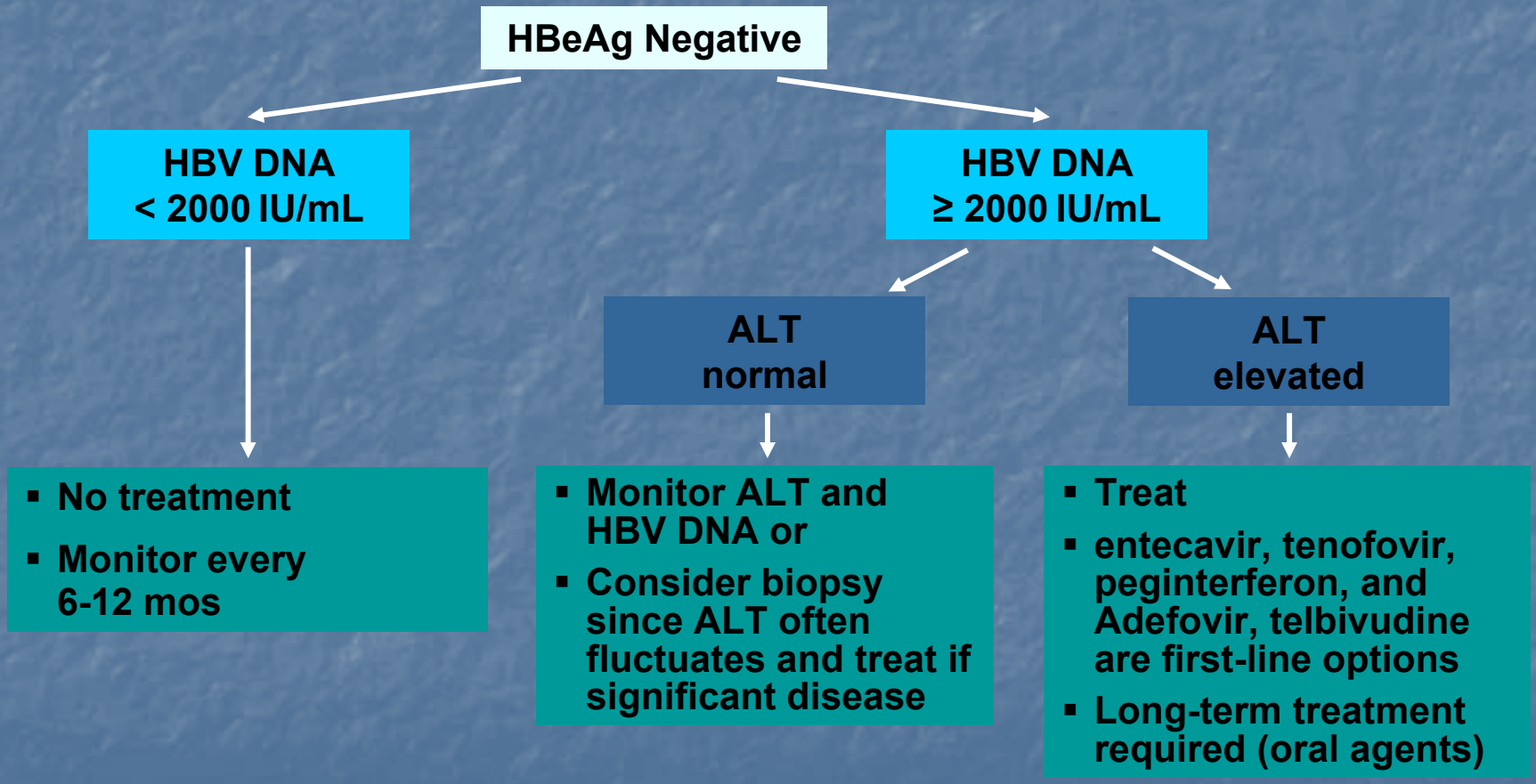
First line treatment in an HBe Ag negative patient

- What happened to this patient ?

➔ Patient has a HBe Ag negative (pre core) chronic hepatitis B, with fluctuating transaminases

First line treatment in an HBe Ag negative patient

- Would you treat him ?



First line treatment in
an HBe Ag negative patient

Summary

- **Patient has HBeAg-negative chronic hepatitis B**
  - often has a fluctuating course
  - advanced necro-inflammatory stage

- **Need exists to treat long term using agent with low resistance rates**
  - Tenofovir or entecavir are preferred oral treatment options over adefovir, lamivudine or telbivudine because of resistance rates
  - Combination therapy might be better option
  - Peginterferon alfa-2a is an alternative option

First line treatment of a cirrhotic patient (1)

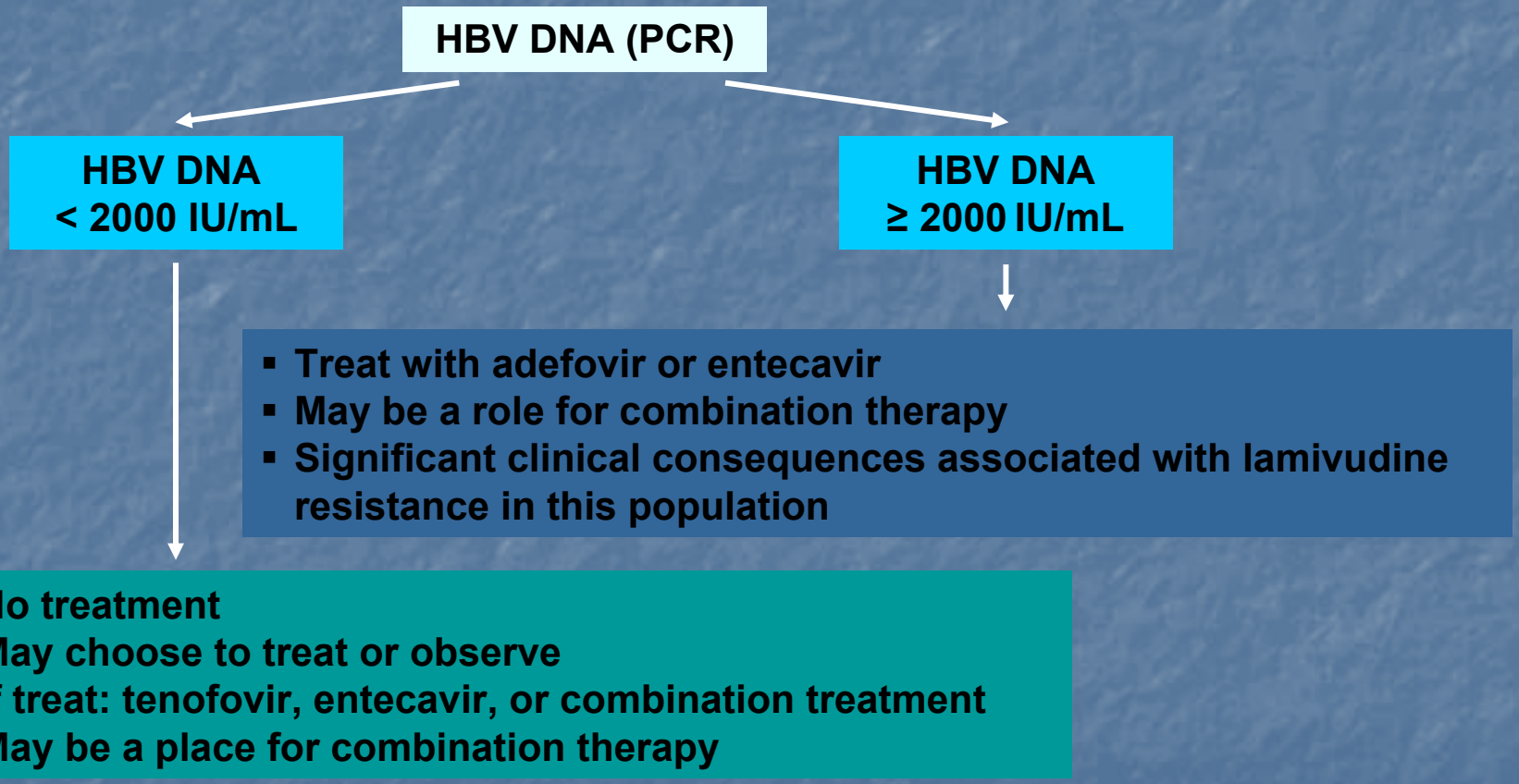
- Ms Y., chinese migrant, diagnosed HBsAg positive after family testing
- Asymptomatic at first visit in November 2007
- Physical exam: hepatosplenomegaly
- Biological assessment:
  - AST = 120 UI/ml, ALT = 87 UI/mL
  - HBeAg neg, anti HBeAb pos, genotype C, pre core
  - HBV-DNA = 110 000 UI/mL
  - Prothrombin time: 65%, V factor = 54%
  - PLT count = 95 000/mm^3, leucocytes = 3100 / mm^3
  - αFP=10ng/mL
  - Abdominal US: Coarse liver with nodular surface
  - Liver biopsy: A1F4

First line treatment of a cirrhotic patient (2)

- Will you treat this patient ?
- If not, on which criteria ?
- If yes:
  - What would the optimal treatment options?
  - How long would you treat for ?

First line treatment
of a cirrhotic patient

Will you treat this patient ?



First line treatment
of a cirrhotic patient

- Will you treat this patient ?

Compensated cirrhosis

2007 AASLD Guidelines

- Who to treat?
  - HBeAg positive or negative
  - HBV DNA > 2000 IU/mL; no ALT specified
  - HBV DNA < 2000 IU/mL; consider treating if ALT elevated
  - HBV DNA negative; observe
- Preferred drug(s)
  - Adefovir or entecavir

Decompensated cirrhosis

2007 AASLD Guidelines

- Who to treat?
  - HBeAg positive or negative
  - Any HBV DNA level
- Preferred drug(s)
  - Lamivudine + adefovir or entecavir monotherapy
- Duration of therapy
  - Long term
- Other recommendations
  - Refer for transplantation

First line treatment
of a cirrhotic patient

- Summary
  - Compensated cirrhosis with precore virus, genotype C
  - HBV-DNA >2000 UI/mL, no matter the level of ALT : Treat !
  - Adefovir or entecavir, add-on therapy?

Managing resistance to nucleoside analogs (1)

- Young MSM, 38 years old, contaminated in 1993.
- No symptoms, non complaint.
- Liver assessment in July 2006 :
  - HBeAg positive, no anti-HBe Ab
  - AST = 135 UI/mL, ALT = 347 UI/mL
  - HBV-DNA = 7.10^6 UI/mL
  - Liver biopsy = A3-F2

Managing resistance to nucleoside analogs (2)

- First line Lamivudine 100mg/day in september 2006, and tests in september 2007:
  - Liver enzyme normalisation after 6 months
  - HBV-DNA undetectability after 12 months
  - No HBe Ag seroconversion
- New liver assessment in March 2008:
  - HBV-DNA = 2.10^5 UI/mL
  - AST = 65 UI/mL, ALT = 95 UI/ml
  - Anti-HCV Ac negative, anti-HDV Ac negative
  - Prothrombin time: 95%, αFP=3ng/mL
  - Plt count normal

Managing resistance to nucleoside analogs (3)

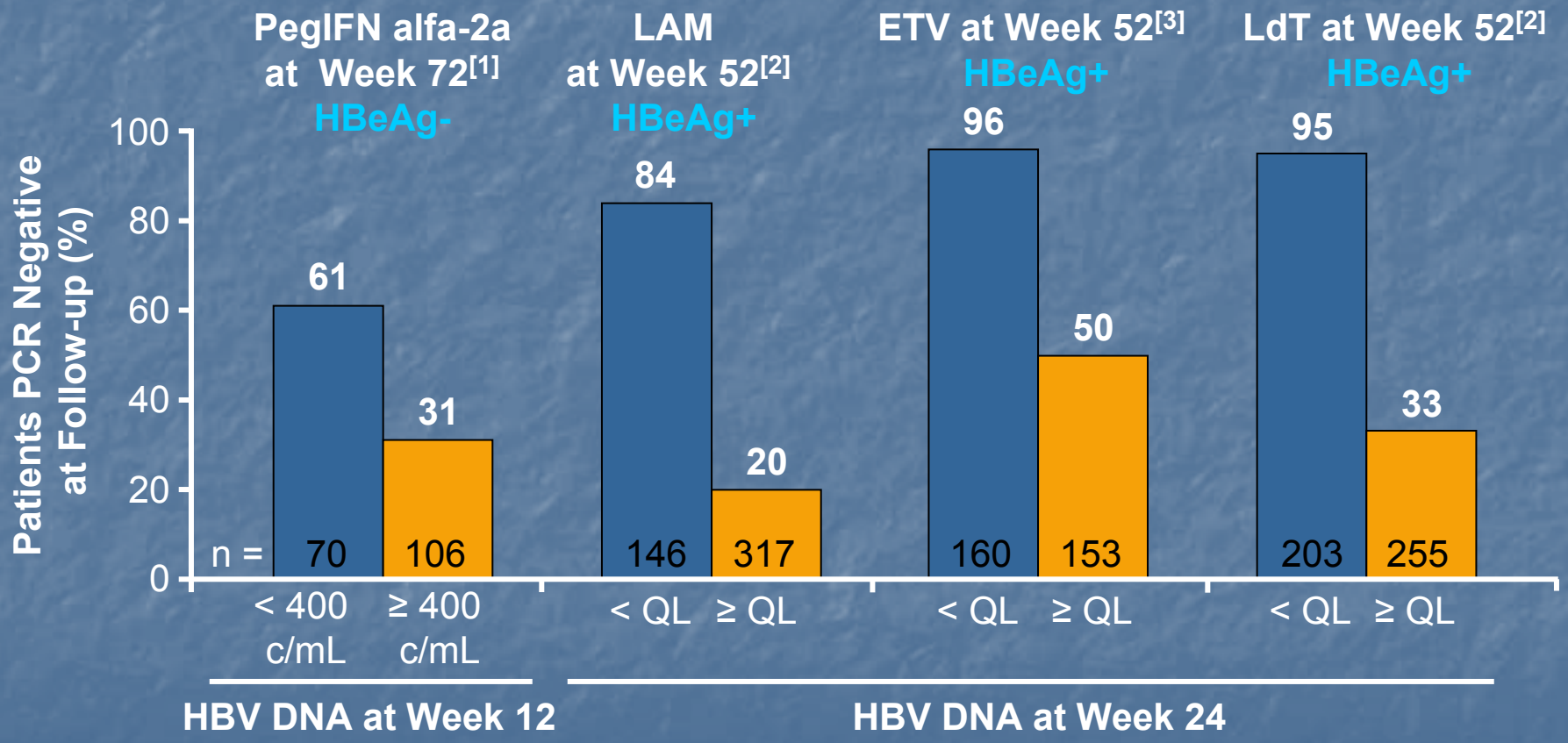
- Will you change treatment ?
- If yes, would you favor a switch or an add-on therapy ?
- Which molecules would you use ?

- Will you change treatment (1) ?

YES → suspicion of LAM resistance acquisition

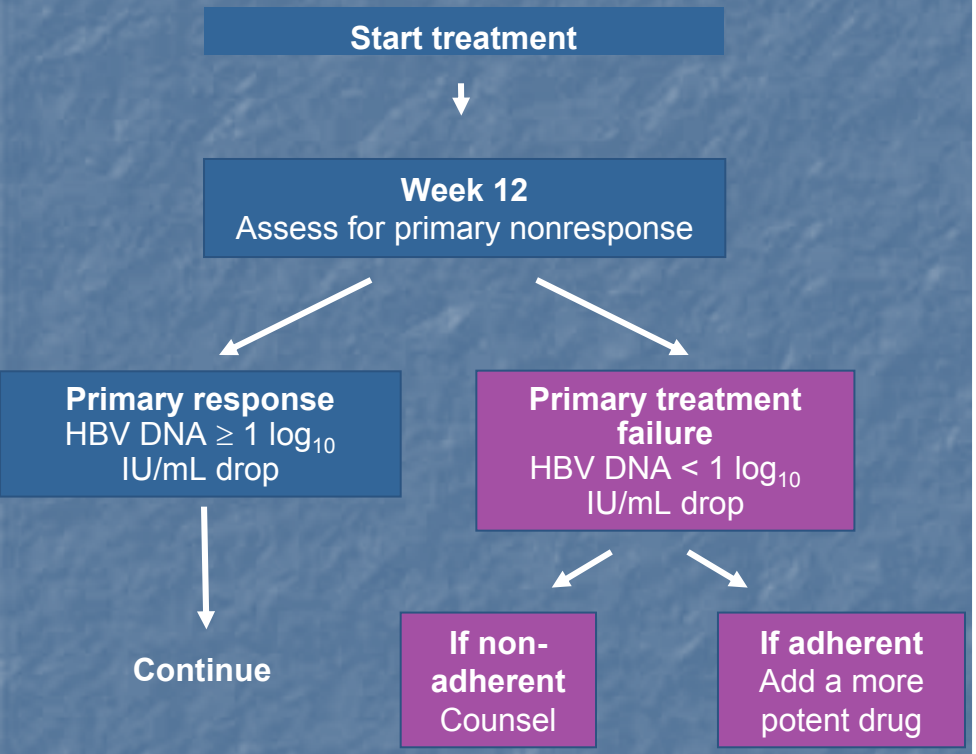
- HBV DNA should be monitored regularly
- Sequencing should be performed when persistent or recurrent viremia
- If residual viremia, but no breakthrough pattern, resistance testing should be performed
  - Whenever resistance suspected
    - According to profile of the drug (determined by barrier to resistance)
      - eg, Week 24 for LAM, LdT; Week 48 or more for ETV, ADV
  - Whenever a change in regimen is contemplated
    - Except for primary nonresponse at Month 3
- If viral breakthrough or rebound, testing should always be performed

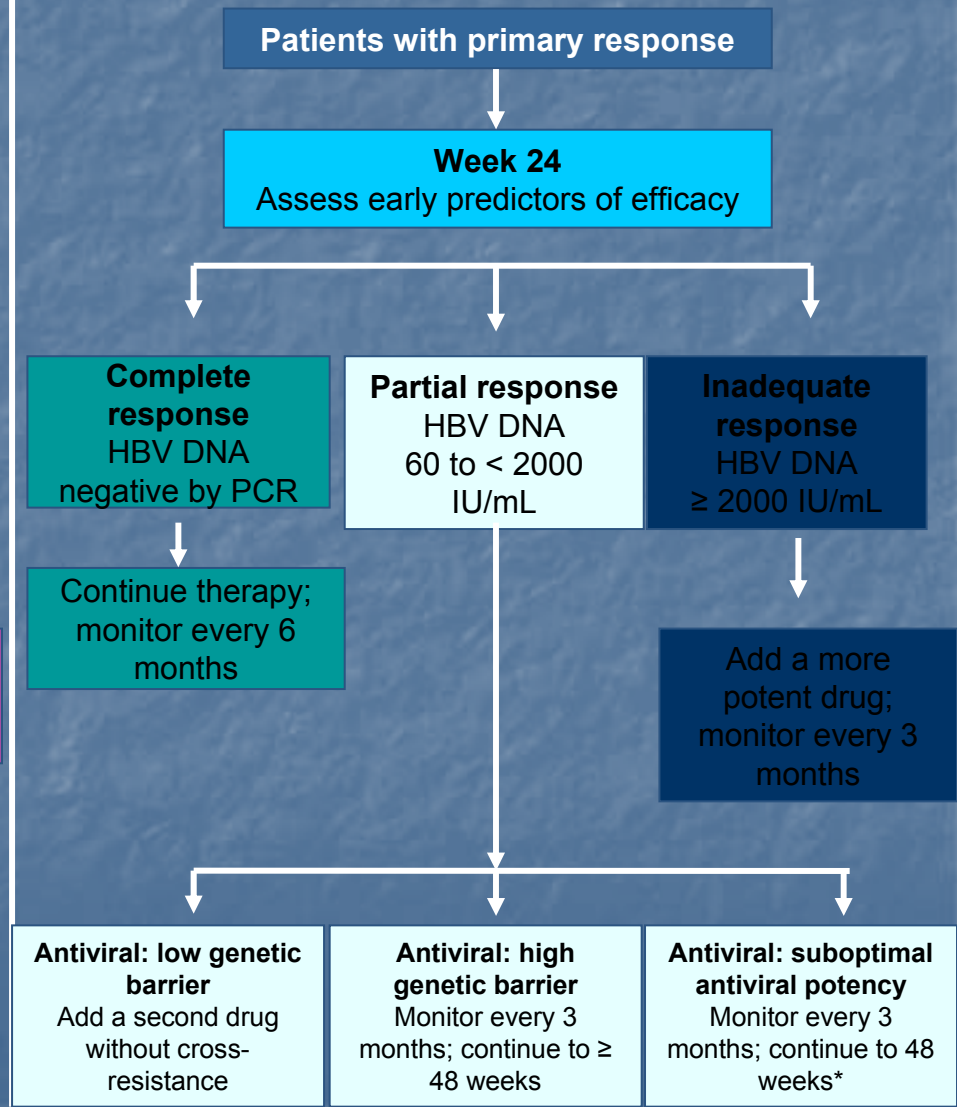
Will you change treatment (2) ?



1. Farci P, et al. EASL 2005 Abstract 484. 2. Zeuzem S. EASL 2006. Abstract 51.
3. Yurdaydin C, et al. EASL 2006. Abstract 80.

Will you change treatment (3) ?





Managing resistance to nucleoside analogs

- If yes, which molecules would you choose and would you favor a switch or an add-on therapy ?

Resistance	Rescue Therapy
LAM	▪ Add ADV (superior to ADV switch) ▪ Switch to ETV (increased risk of ETV resistance development) ▪ Add TDF* or switch to FTC/TDF*
ADV	▪ Add LAM (superior to LAM switch) ▪ Switch to or add ETV (only in the absence of LAM resistance) ▪ Switch to FTC/TDF*
ETV	▪ Add or switch to ADV or TDF*
LdT	▪ Add ADV (superior to ADV switch) ▪ Switch to ETV (increased risk of ETV resistance development) ▪ Add TDF* or switch to FTC/TDF*

AASLD Recommendations for Managing Virologic Breakthrough

Lok A, et al. Hepatology. 2007;45:507-539.

Managing resistance to nucleoside analogs

- Switch or an add-on therapy ?
- 2007 AASLD guidelines
  - "Patients who failed to achieve primary response as evidenced by < 2 log decrease in serum HBV DNA level after at least 6 months of NA therapy should be switched to an alternative treatment"
- NIH Clinical Research Workshop
  - No data show that using 2 nucleos(t)ide analogues results in deeper viral suppression vs single agent
  - Level of suppression equal to most potent agent in regimen
  - Current evidence does not support combination therapy for CHB
- Except potentially with lamivudine-resistant disease
  - Adefovir + lamivudine appears preferable to adefovir alone

Lok AS, et al. Hepatology. 2007;45:507-539.
Hoofnagle J, et al. Hepatology. 2007;45:1056-1075.

- Summary
  - Patients with Hbe Ag pos chronic hepatitis
  - Virologic breakthrough with LAM
  - Treatment options: add ADV or switch FTC/TDF (off label)
  - Follow 12 and 24 weeks algorithm for monitoring

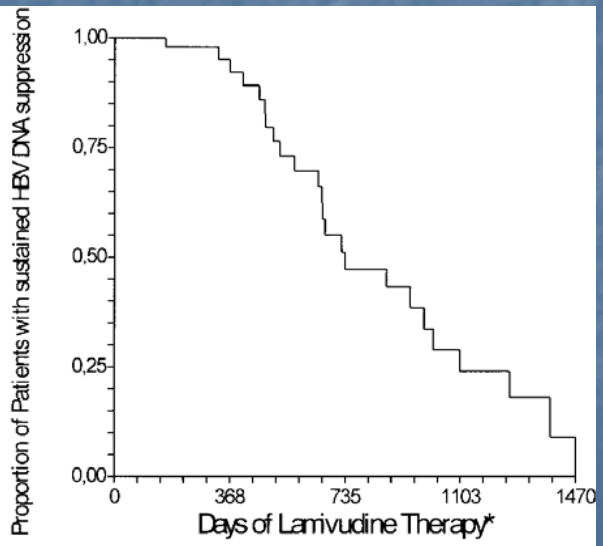
How to deal with HIV co-infection (1) ?

- Ms D., 34 years old, from the Ivory Coast
- Diagnosed 4 years ago during pregancy
- Treated with Combivir® + Efavirenz
- CD4+cell count: 310/$mm^{3,}$ HIV-RNA: 5460 copies/ml
- HIV-1 positive, HCV, HDV negative
- Liver assessment:
  - ALT = 124 UI/mL, AST = 97 UI/mL
  - HBV-DNA = 2.10^5 UI/ml
  - HBs Ag positive, HBe Ag positive, anti-HBe Ac negative
  - Other tests (including liver US and αFP): normal

How to deal with HIV co-infection (2) ?

- How would you explain the results of the liver assessment ?
- Would you perform a liver biopsy ? Why ?
- Would you change treatment ?
- If yes, what would you choose ?
- How will you deal with the HIV co-infection ?

- How would you explain the results of the liver assessment ?
  - Chronic hepatitis B in immune clearance phase
  - Need for evaluation of necro-inflammatory status
  - ProbableVirological breakthrough with a wild-type virus : lamivudine is part of Combivir®!



Long-Term Incidence of Hepatitis B Virus Resistance to Lamivudine in Human Immunodeficiency Virus–Infected Patients
YVES BENHAMOU,1 MARIE BOCHET,2 VINCENT THIBAULT,3 VINCENT DI MARTINO,1 ERIC CAUMES,2 FRANC¸ OIS BRICAIRE,2 PIERRE OPOLON,1 CHRISTINE KATLAMA,2 AND THIERRY POYNARD1
HEPATOLOGY Vol. 30, No. 5, 1999

- Would you perform a liver biopsy ? Why ?
  - No liver biopsy performed to date and thus, no baseline necro-inflammatory status assessed.
  - In HIV infection, many causes for liver fibrosis / elevated transaminases other than HBV infection:
    - Hepatotoxicity of ARVs
    - Mitochondrial cytopathy
    - NASH
    - Iron overload
    - Mycobacteria, parasites
    - Etc.
  - Values of biochemical and fibroscan under assessment.

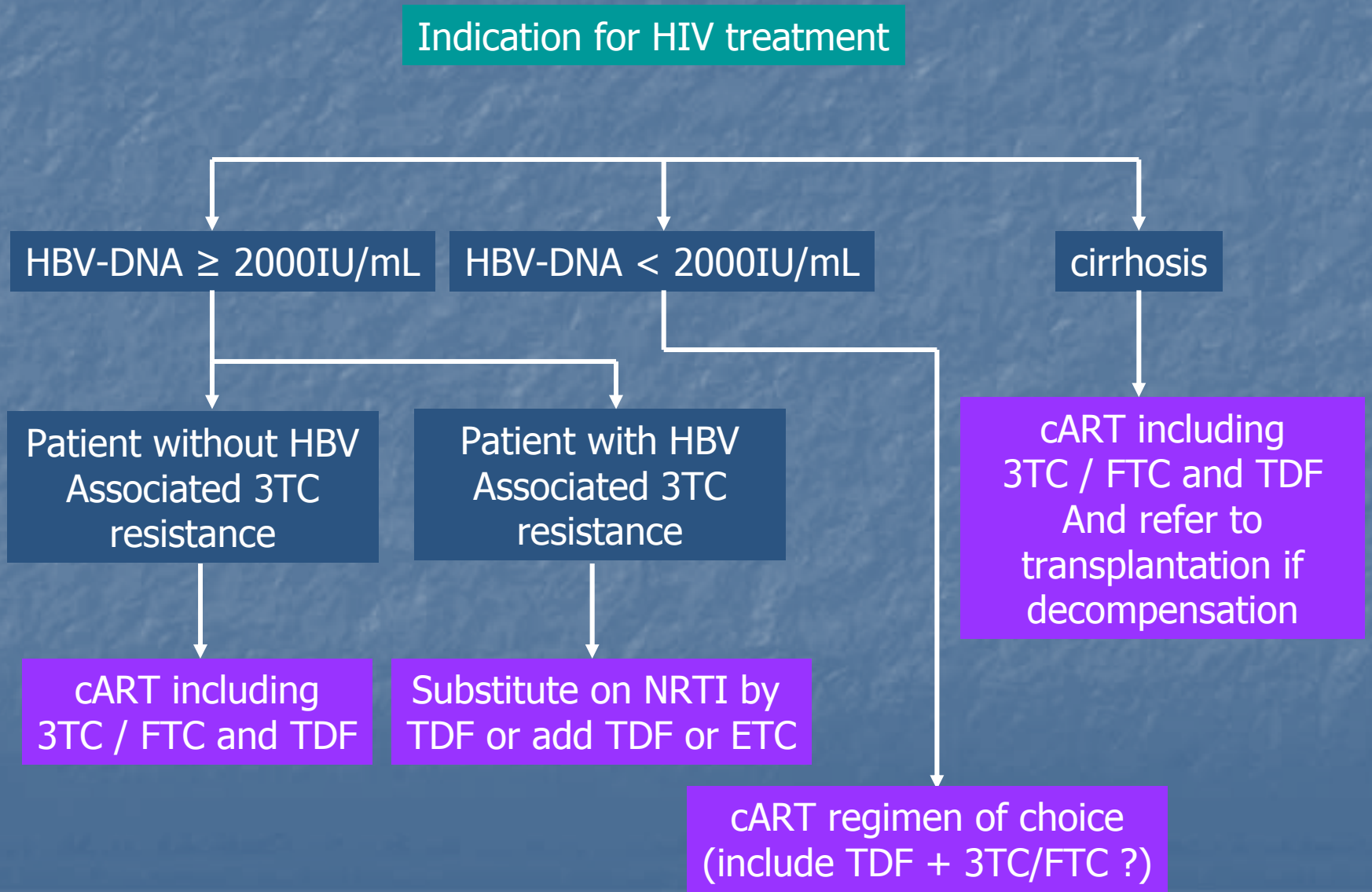
➔ In this case, a liver biopsy is indicated in order to rule out other causes for elevated transaminases and get a 1st evaluation of necro-inflammatory status of patient.

Would you change treatment ?

YES

- Virological breakthrough probably because of YMDD mutation
- Objective of anti-HBV treatment = complete suppression on HBV replication
- Evolution of liver disease increased in the presence of HIV, and associated to the level of HBV replication

- If yes, what would you choose ?



- How will you deal with the HIV co-infection ?
  - Change whole treatment after HIV genotyping, depending of treatment history
  - Switch for protease inhibitor with no or mild potential hepatotoxicity (atazanavir, lopinavir, fosamprenavir)
  - Be carefull with tipranavir, darunavir
  - Monitor transaminases closely (once a week for the 1st month, then monthly for 3 to 6 months)
  - Monitor HIV-RNA at M1 and M3, then every 3 months
  - Monitor HBV-DNA at M3 and M6.
  - Adapt HBV treatment to algorithm