Do I treat my HBV immunotolerant patients?

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Do I treat my HBV immunotolerant patients?

No

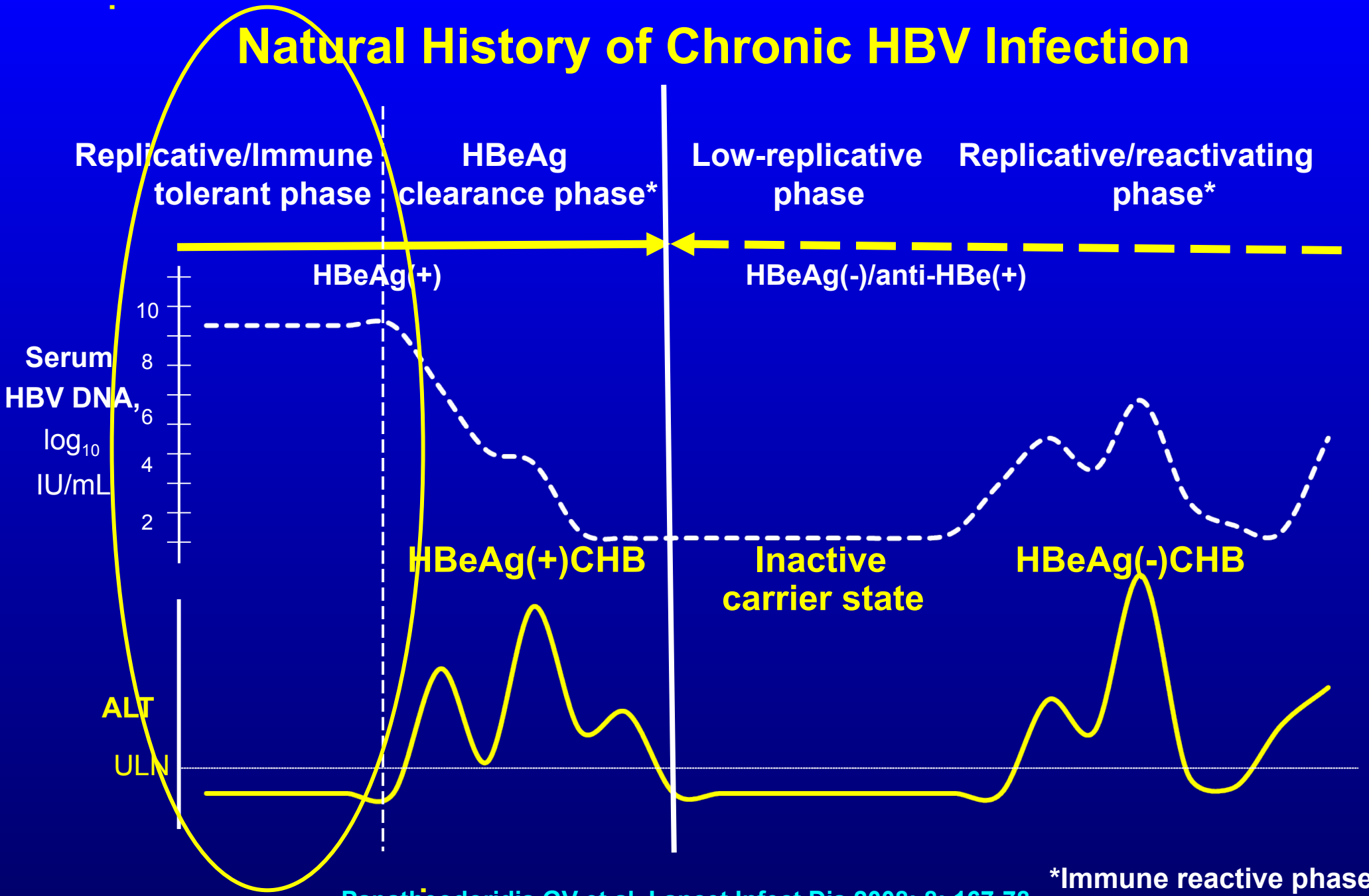
Except for a few

Who are the "HBV immunotolerant patients"?

- Patients with chronic HBV infection and immune tolerance specifically to HBV
- Hyporesponsive HBV specific T cells: anergy, deletion, altered maturation of HBV specific effector cells & expansion of regulatory T cells (Park JJ et al. GE 2015, Dec 9, Epud ahead of print)

- HBeAg positive
- High serum HBV DNA levels (usually >10^7 IU/mL)
- Persistently normal ALT

Natural History of Chronic HBV Infection

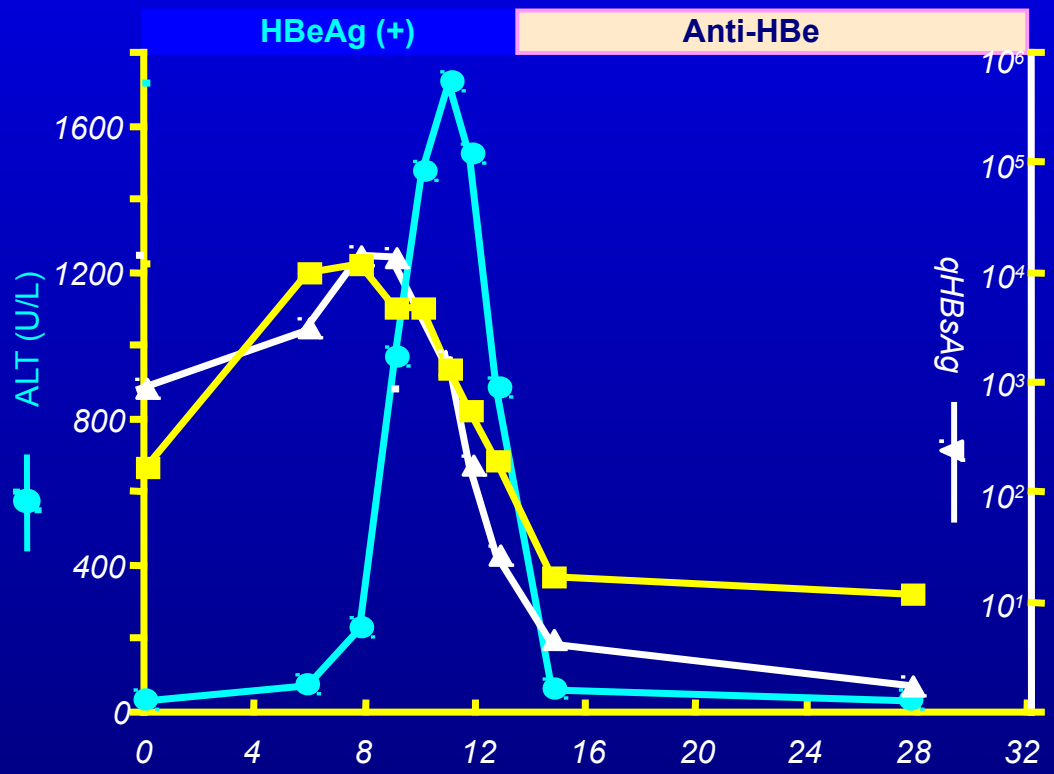


*Immune reactive phases

Papatheodoridis GV et al. Lancet Infect Dis 2008; 8: 167-78.

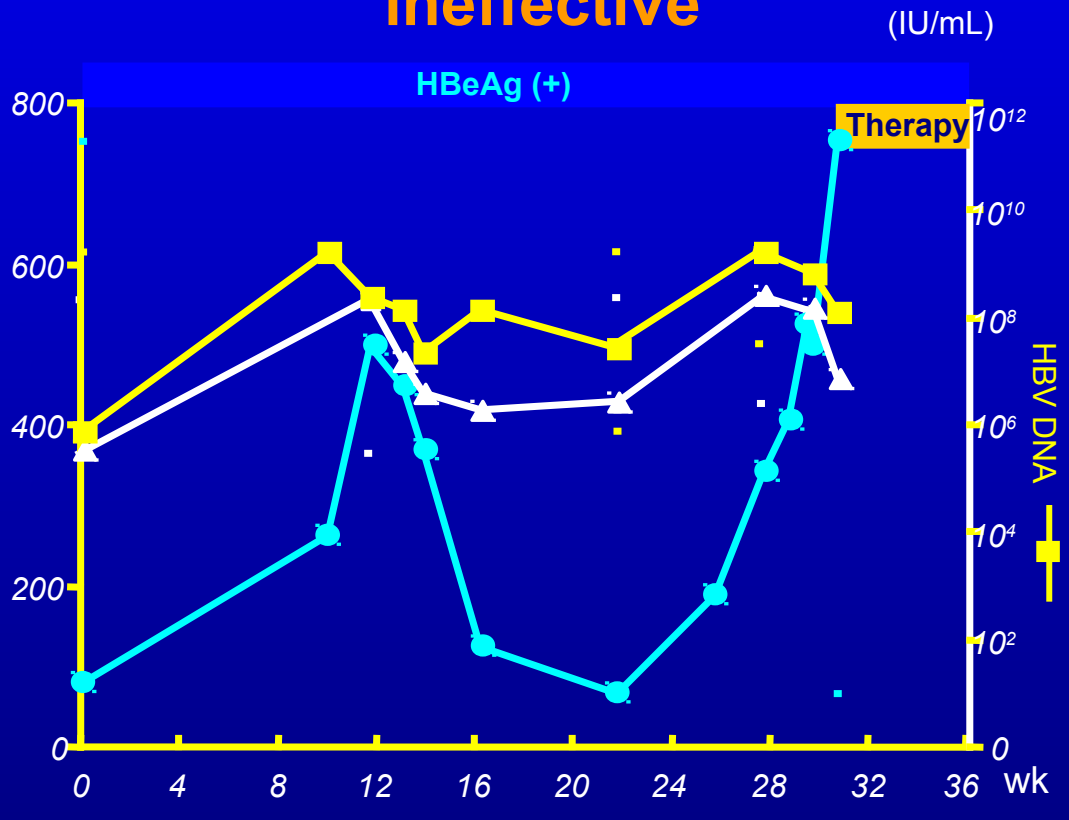
HBeAg clearance phase is not always effective

effective



HBV DNA/HBsAg declining prior to the peak of ALT

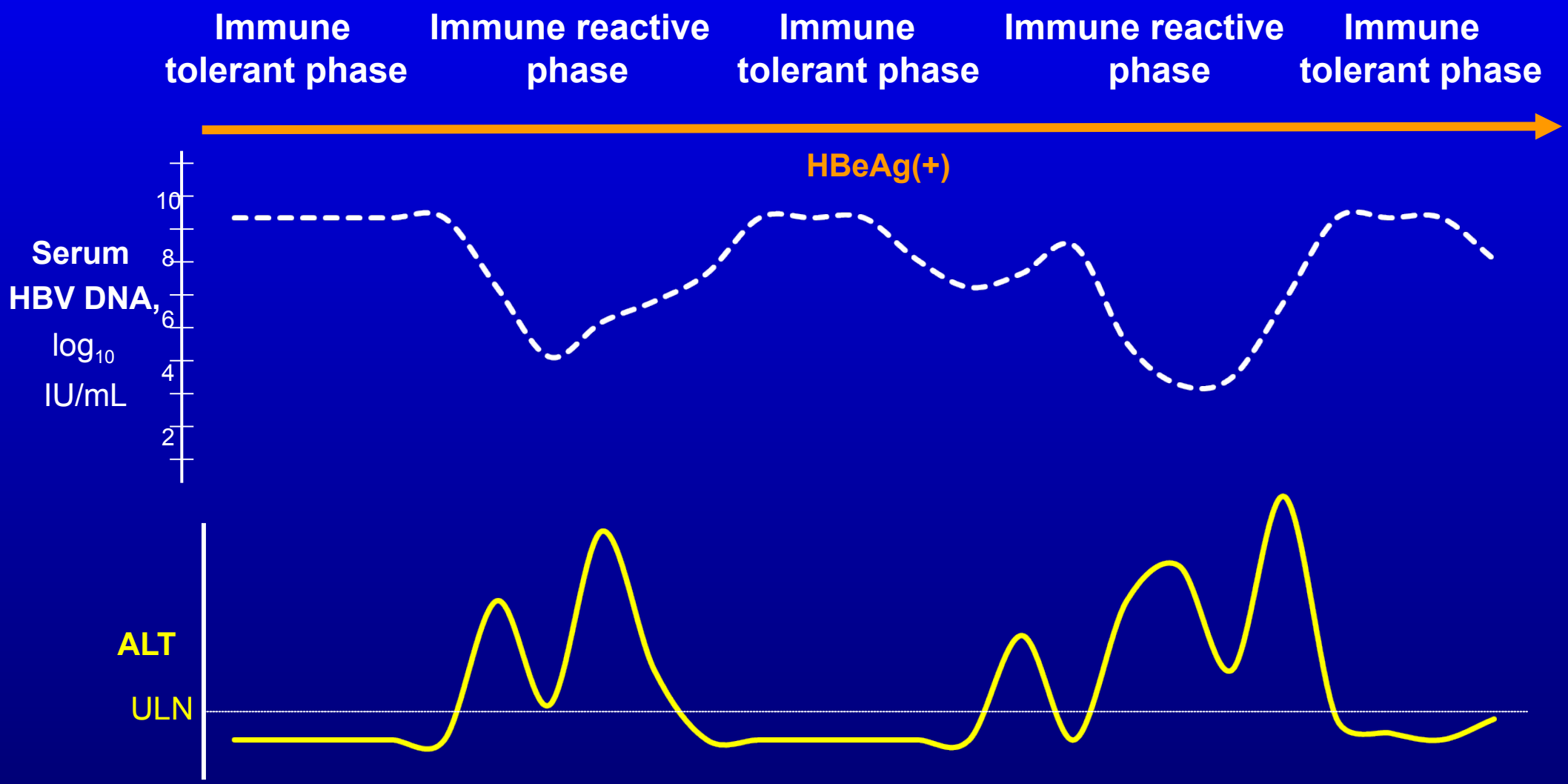
ineffective



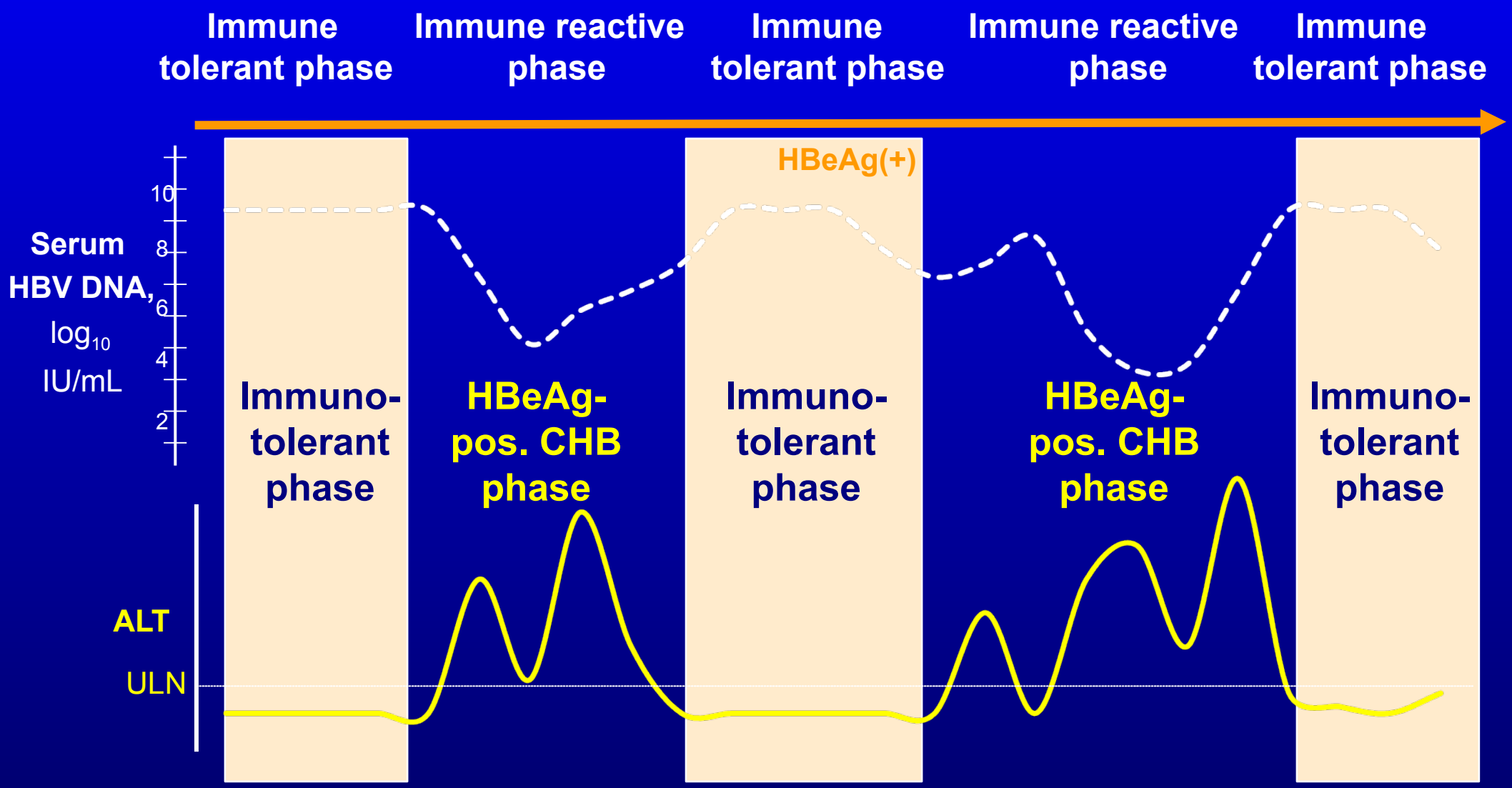
HBV DNA/HBsAg increasing or stable

Chang & Liaw. J Hepatol 2014;61:1407-17.

Natural History of HBeAg(+) Chronic HBV Infection



Natural History of HBeAg(+) Chronic HBV Infection



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)

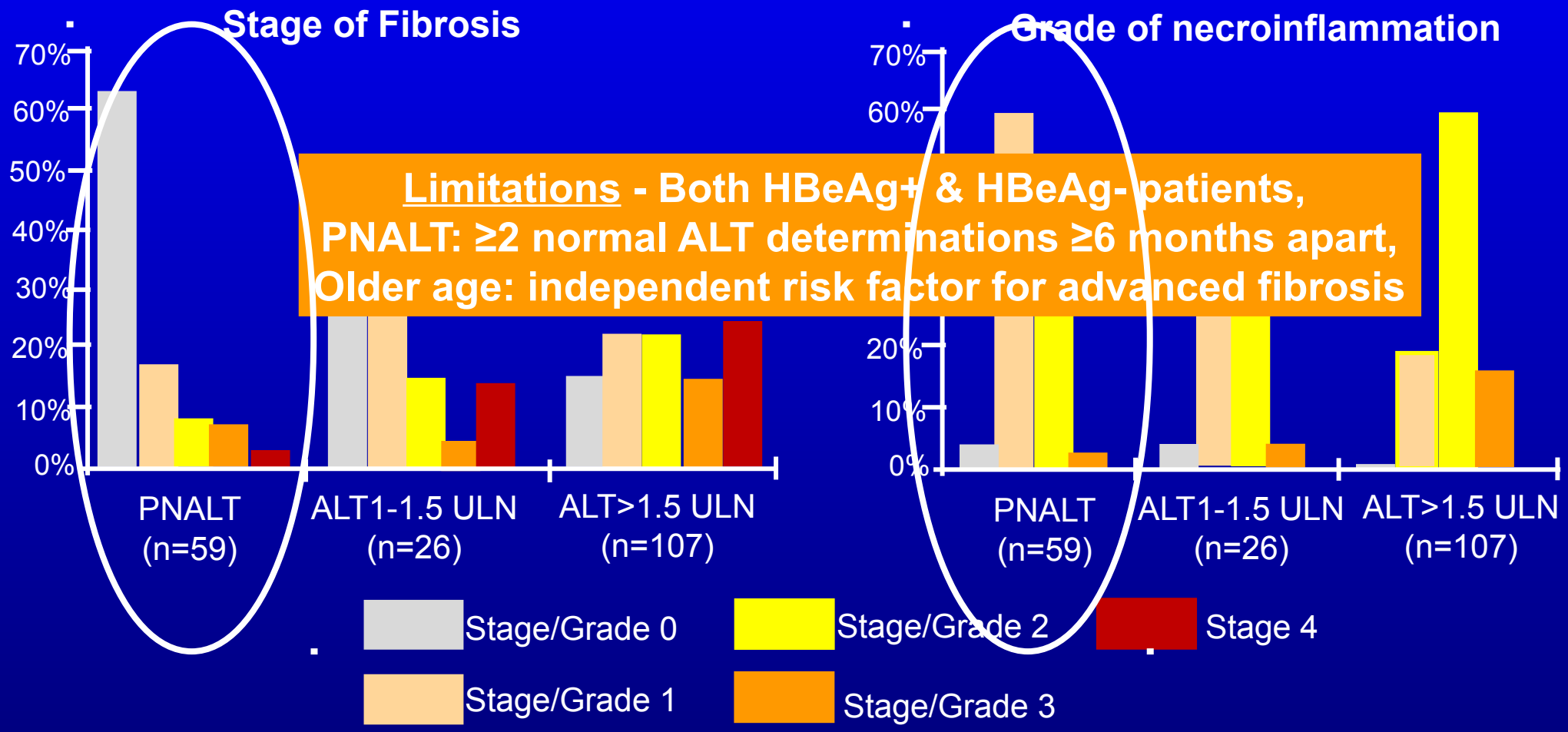
Yang et al. Clin Gastroenterol Hepatol 2012;10:527-534. Liu et al Hepatology 2014;60:77-86.
Fattovich et al, Gut 2008; 57: 84-90. Hadziyannis & Papatheodoridis. Semin Liver Dis 2006;26:130-41.

Main arguments favoring treatment initiation in HBV immunotolerant patients

- **Maintenance of high HBV replication:**
  increasing numbers of infected hepatocytes
  - **Risk of progression of liver lesions**
  - **Increasing HCC risk**

- **High risk of HBV transmission**
  (NAs may be required in the third trimester of pregnancy of HBV immunotolerant women, not any more in infancy/ childhood due to universal vaccination programs)

Liver histological lesions in chronic HBV patients by ALT levels

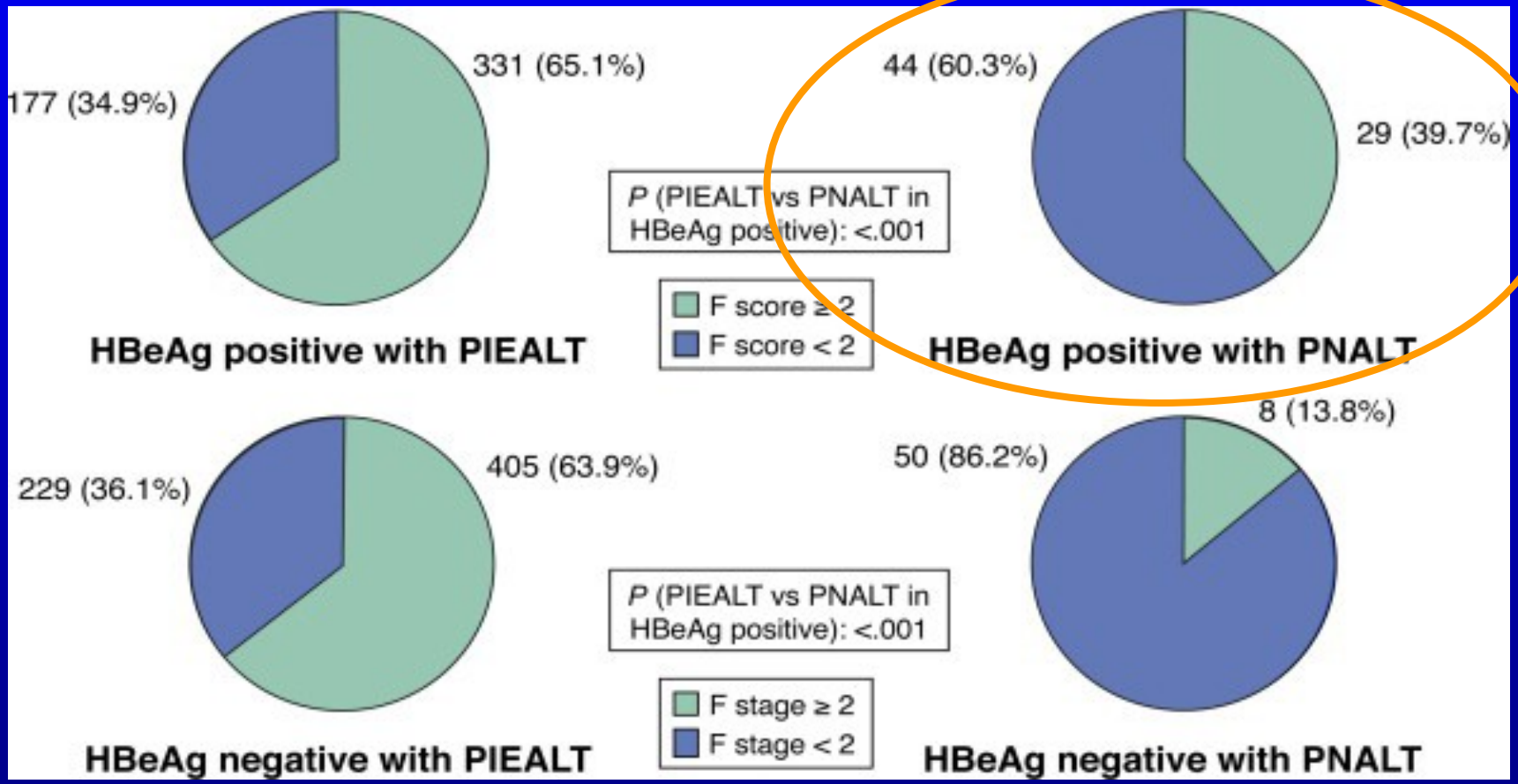


Limitations - Both HBeAg+ & HBeAg- patients,
PNALT: ≥2 normal ALT determinations ≥6 months apart,
Older age: independent risk factor for advanced fibrosis

Overall 37% of patients in the normal ALT group had significant necroinflammation or fibrosis.

Lai M et al. J Hepatol 2007;47:760-7.

Severity of liver fibrosis according to HBeAg status and ALT



PNALT: persistently normal ALT, PIEALT: persistently or intermittently elevated ALT

Limitations – Representative sample? (PNALT/PIEALT: 73/530 for HBeAg+, 116/686 for HBeAg- patients); PNALT: 3 normal values within 12 months

Kumar M et al. Gastroenterolgy 2008;134:1376-84.

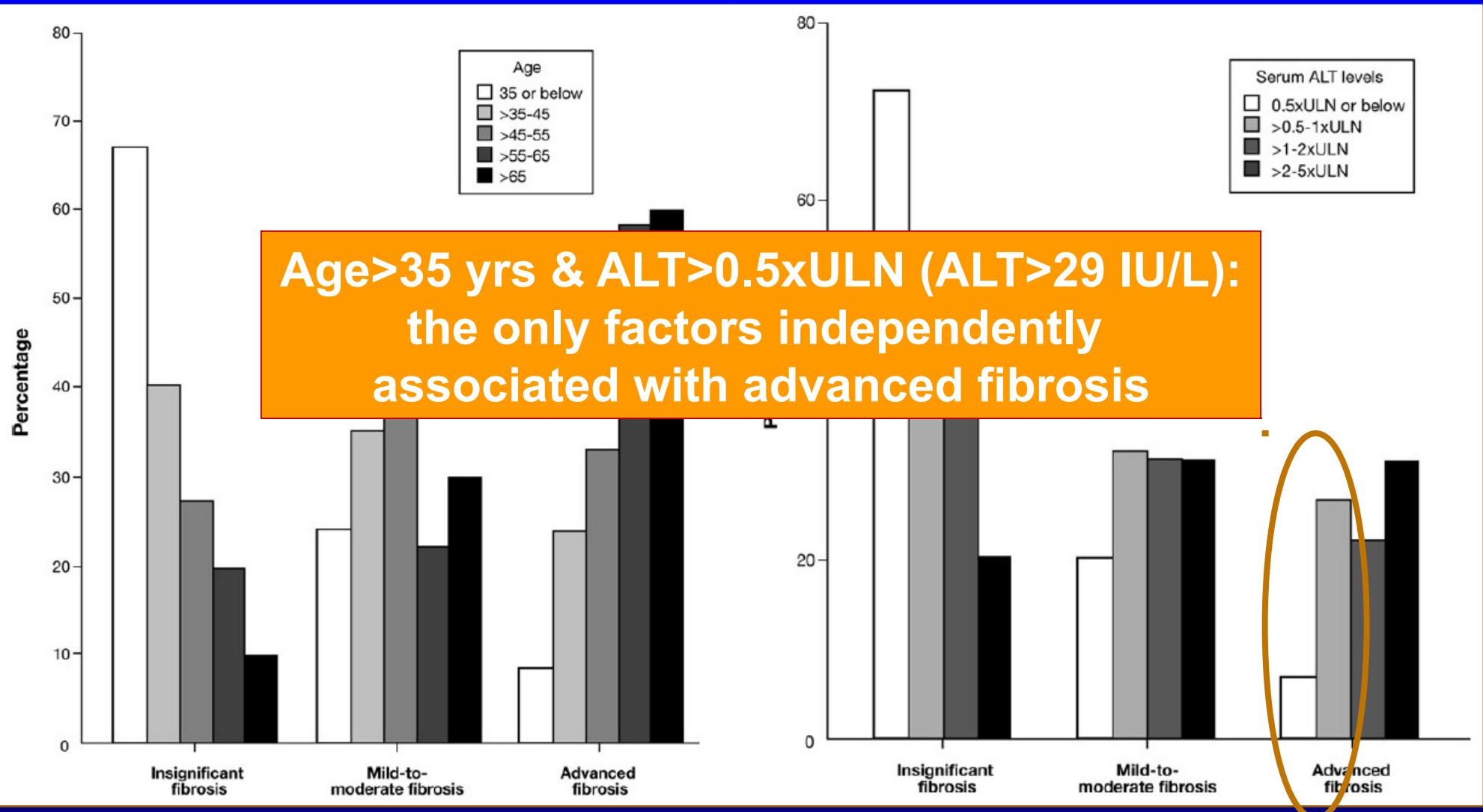
Multiple Logistic Regression for Prediction of Significant Fibrosis (≥F2)

	OR	95% CI	P
Baseline HBV DNA, cp/mL			
<4 log	1		
≥4 log	1.859	1.184-2.917	0.007
ALT status			
PNALT	1		
PIEALT	4.304	2.870-6.452	<0.001
Age, years			
<30	1		
30-39	0.933	0.698-1.247	0.640
40-49	1.134	0.919-1.570	0.447
≥50	1.663	1.131-2.446	0.010

PNALT: persistently normal ALT, PIEALT: persistently or intermittently elevated ALT

Kumar M et al. Gastroenterolgy 2008;134:1376-84.

Liver stiffness in Chinese HBeAg-positive chronic HBV patients



Age>35 yrs & ALT>0.5xULN (ALT>29 IU/L): the only factors independently associated with advanced fibrosis

Insignificant fibrosis: LSM ≤6/7.5 kPa for patients with normal/elevated ALT
Advanced fibrosis: LSM >9/12 kPa for patients with normal/elevated ALT

All pts=453;
Pts with normal ALT=245

Wong GL et al. Clin Gastroenterol Hepatol 2009;7:227-33.

Histological findings in immune tolerant chronic HBV adult patients in France

40 patients with 2 consecutive normal ALT determinations within 6 months & HBV DNA >10^7 cp/ml - median age: 29 years (range: 17-59)

Born in – Asia: 87%, sub-Saharan Africa: 7%, France: 5% (1/2 Asian mother)

Table 2. Results of Liver Biopsy Examination According to Alanine Aminotransferase Level and Age

	All patients (n = 40)	Alanine aminotransferase level <0.5 ULN (n = 12)	Alanine aminotransferase level 0.5–1 ULN (n = 28)	Age <40 y (n = 36)	Age >40 y (n = 4)
Histologic stage of fibrosis[a]					
F0	20	4	16	19	1
F1	20	8	12	17	3
Histologic grade of activity[a]					
A0	9	3	6	8	1
A1	29	9	20	27	2
A2	2	0	2	1	1

[a]Metavir score.

Loss of tolerance [ALT>ULN or HBeAg(-) or HBV DNA<10^5 cp/ml]: 12/31 (38%) during 38 months follow-up

Andreani T et al. Clin Gastroenterol Hepatol 2007;5:636-41.

Natural history of immune tolerant chronic HBV in Chinese adult patients – Histological follow-up

9/5

Histological findings in the 48 patients who remained immunotolerant

Stage of fibrosis		psy	P value
F0			0.58
F1		31	
F2	0	1	
Median Modified HAI score	3 (1-6)	3 (1-5)	

Hui CK et al. Hepatology 2007;46:395-401.

Main arguments favoring treatment initiation in HBV immunotolerant patients

- **Maintenance of high HBV replication:**
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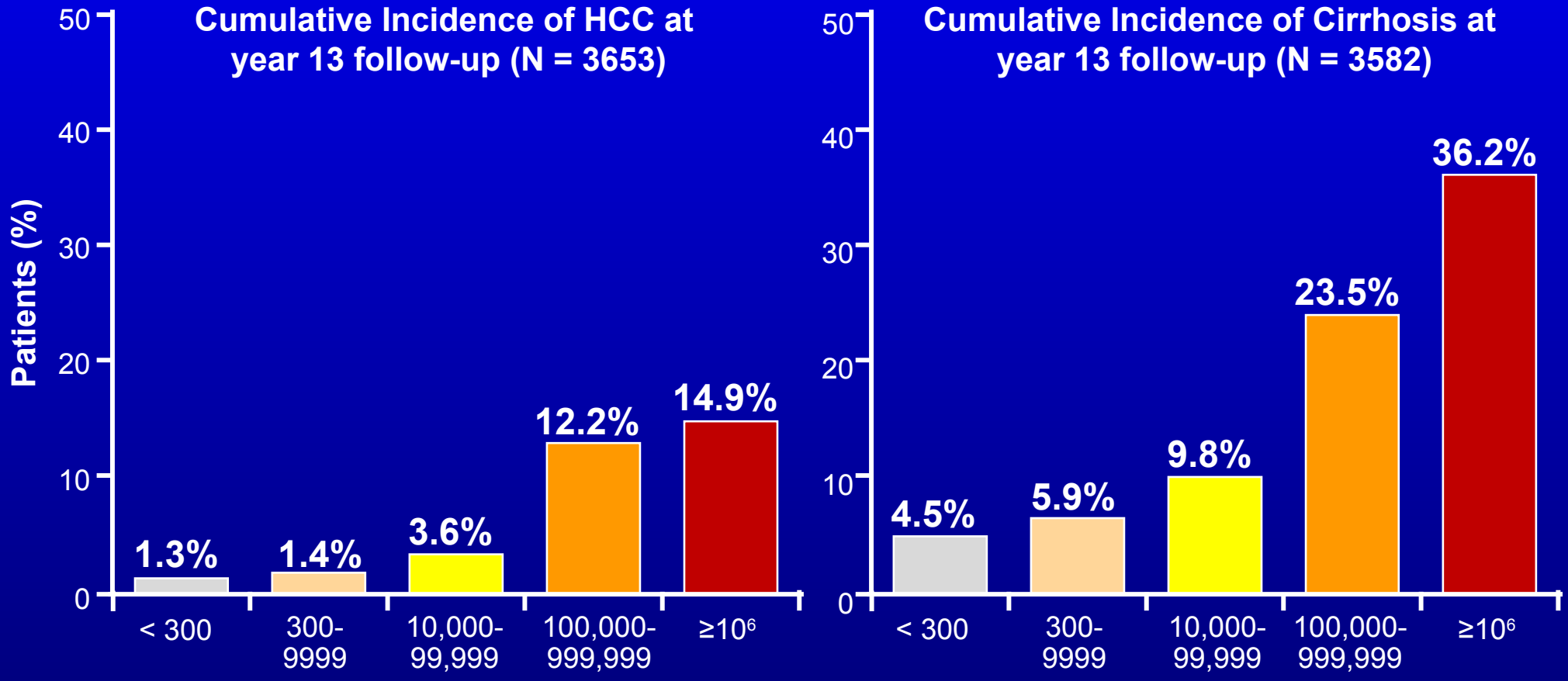
  - **Risk of progression of liver lesions**
  - **Increasing HCC risk**

- **High risk of HBV transmission**
  (NAs may be required in the third trimester of pregnancy of HBV immunotolerant women, not any more in infancy/ childhood due to universal vaccination programs)

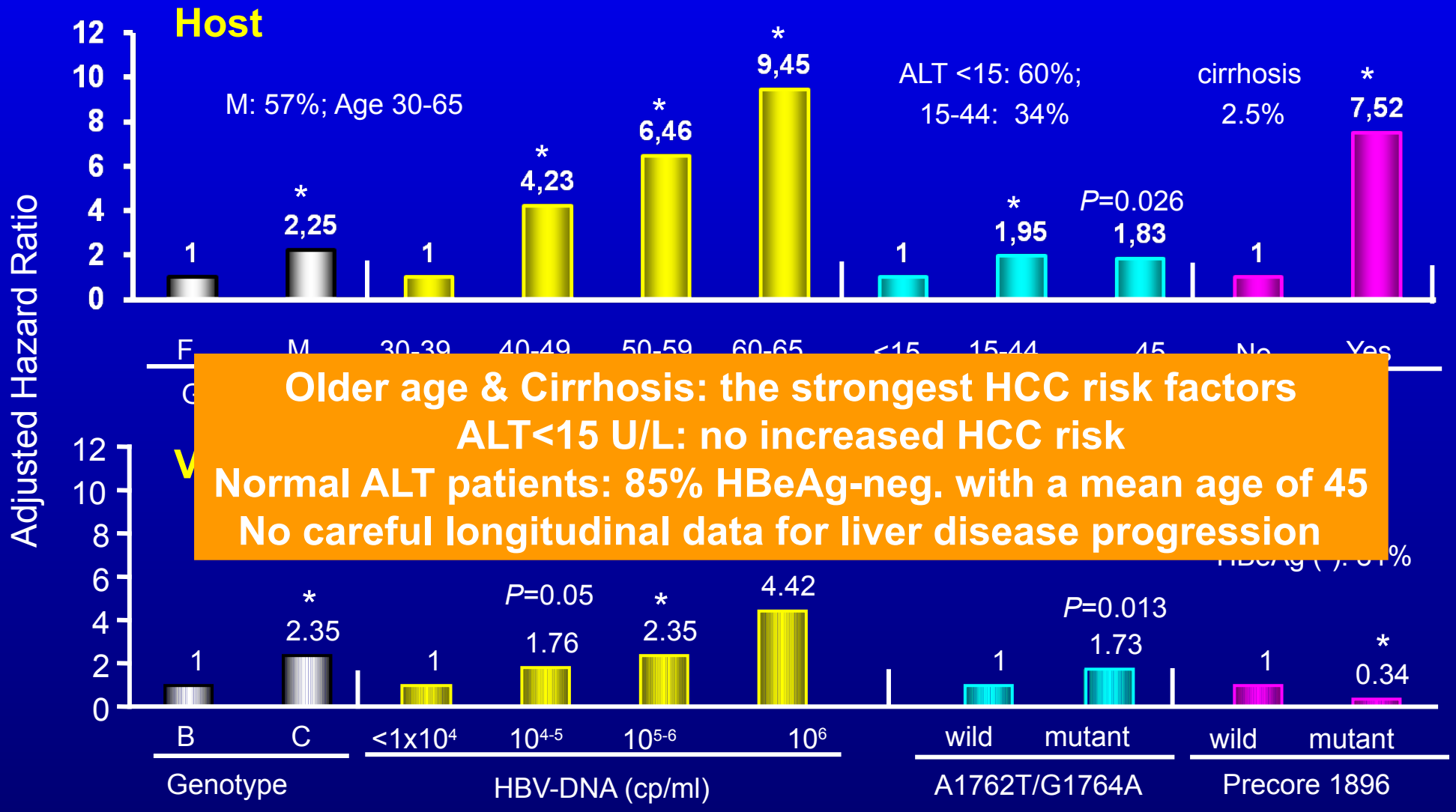
REVEAL cohort: the role of serum HBV DNA levels on HCC and cirrhosis development



Baseline HBV DNA (cp/mL) measured using the Roche COBAS assay

Chen et al. JAMA 2006;295:65-73. Iloeje et al. Gastroenterology 2006;130:678-86.

REVEAL-HBV study: Baseline factors for HCC development (2762 HBsAg carriers/33,847 person-years)



* *P*<0.001

Yang HI et al. JNCI 2008;100:1134-42.

5 year cumulative HCC in HBeAg-negative patients: complete responders under NA(s) vs inactive cases

		N	5-year cumulative HCC incidence	P
No cirrhosis	Complete responder under NA(s)	316	6.9%	<0.001
	Inactive cases	884	0.8%	
Cirrhosis	Complete responder under NA(s)	223	15.3%	<0.001
	Inactive cases	130	6.0%	

Complete responders under NA(s): HBV DNA <2000 IU/ml on therapy

Inactive cases: persistently HBV DNA<2000 IU/ml without treatment

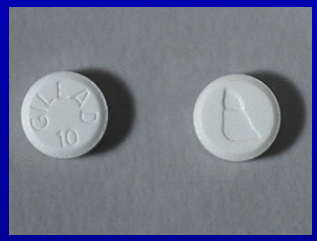
Cho JY et al. Gut 2014;63:1943-50.

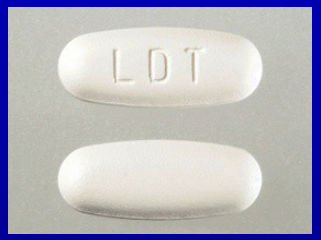
Efficacy of current treatment options in HBV immunotolerant patients

(Peg)-IFNα

ETV, TDF

TBV, LAM, ADV





Very limited data, usually from subgroup analyses of HBeAg-positive CHB patients with normal or slightly increased ALT levels at baseline

(Peg-)IFNa therapy in HBeAg-positive CHB

Higher HBeAg seroconversion rates in patients with

- **Higher ALT levels** (usually >2xULN)
- **Lower HBV DNA levels**

Brook MG et al. Hepatology 1989;10:761-3.
Buster EH et al. Gastroenterology 2009;137:2002–9.
Liaw YF et al. Hepatology 2011;54:1591–9.

Prednisone Withdrawal Followed by Recombinant Alpha Interferon in the Treatment of Chronic Type B Hepatitis: A Randomized, Controlled Trial.

Perrillo PR et al. Ann Intern Med 1988;109:95-100.

ETV or TDF therapy in HBeAg-positive CHB

1 year: HBV DNA undetectability 65-75%

HBeAg seroconversion: 20%

(Higher baseline ALT = higher HBeAg seroconversion rate)

≥4 years: HBV DNA undetectability >90-95%

HBeAg seroconversion: >30-35%

0-1% HBV resistance

Chang TT et al. N Engl J Med 2006;354:1001-10. Chang TT et al. Hepatology 2010;51:422-30.
Marcellin P et al. N Engl J Med 2008;359:2442-55. Heathcote EJ et al. Gastroenterology 2011;140:132-43.
Marcellin P et al. Lancet 2013;381:468-75.

TDF vs TDF+FTC x192 weeks 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

Outcome at week-192	TDF (N=64)	TDF+FTC (N=62)	P
HBV DNA <69 IU/ml	55%	76%	0.016
HBV resistance	0%	0%	NS
HBeAg seroconversion	5%	0%	NS
HBsAg loss	0%	0%	NS

Chan HL et al. Gastroenterology 2014;146:1240-8.

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

EASL. J Hepatol 2012;57:167–185.

Management of immunotolerant patients

HBeAg+ patients with high HBV DNA (>20,000 IU/mL) and PNALT

- **Age >40 years**: treatment
- **Age 30-40 years**: decisions individualised - liver biopsy
- **Age <30 years**: follow-up (ALT /3-6 months, HBeAg/anti-HBe /6-12 months)
- **Positive family history for HCC**: reduce the age limit for treatment initiation
- **Clinical or laboratory indications of advanced liver lesions** *(eg low PLT, high gamma-globulins, splenomegaly, spiders, palmar erythema, advanced fibrosis by noninvasive markers etc):* liver biopsy even in patients <30 years

Potential additional treatment indications

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

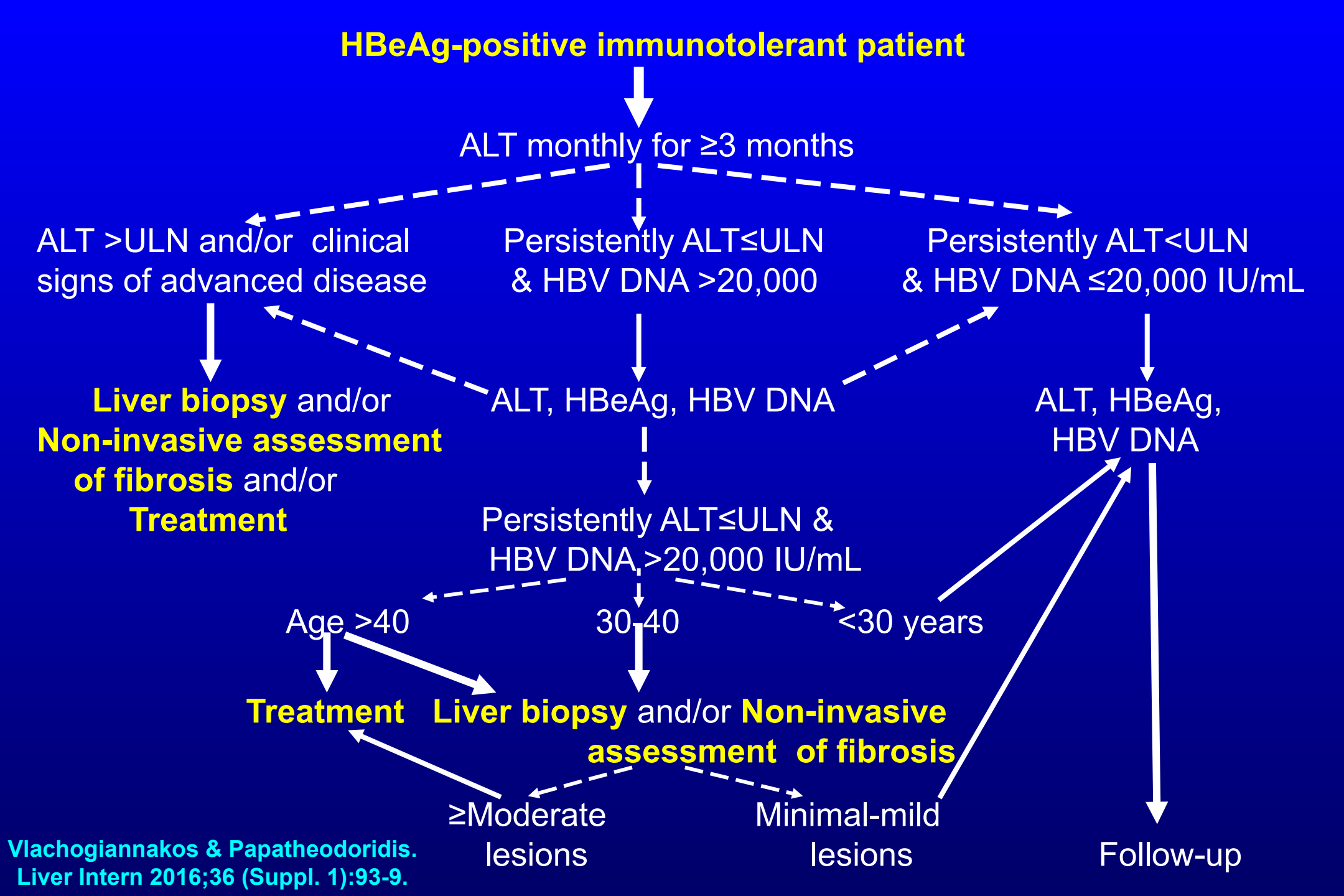
Vlachogiannakos & Papatheodoridis. Liver Intern 2016;36 (Suppl. 1):93-9.

Treatment indications in HBeAg+ immunotolerant chronic HBV patients
AASLD 2015

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

Terrault NA et al. Hepatology 2016;63:261–83.



Vlachogiannakos & Papatheodoridis. Liver Intern 2016;36 (Suppl. 1):93-9.

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Except for a few

Thank you!