APASL HBV Guideline Debrief

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Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update

Yun-Fan Liaw, Jia-Horng Kao, Teerha Piratvisuth, Henry Lik Yuen Chan, Rong-Nan Chien, Chun-Jen Liu, Ed Gane, Stephen Locarnini, Seng-Gee Lim,

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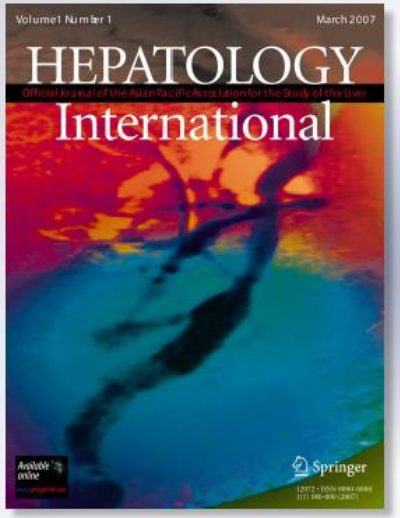


Springer

Grade of evidence/ recommendation

* Grade I	at least 1 well-designed, randomized, control trial
Grade II	well-designed cohort or case-controlled studies
Grade III	case series, case reports or flawed clinical trials
Grade IV	opinions of respected authorities, descriptive studies or reports of expert committees
* Recommendation	A: Strong; B: weak

Recommendations 3

- *Assessment of liver fibrosis is recommended in viremic patients with high normal or minimally raised ALT levels and older than 40 except patients with clinical evidence of cirrhosis(IIA).*

- *Biopsy to grade, stage and exclude other causes as a guide to the indication; assessment by non-invasive method(s) is an alternative*

Liver biopsy recommended to detect advanced liver fibrosis for antiviral therapy

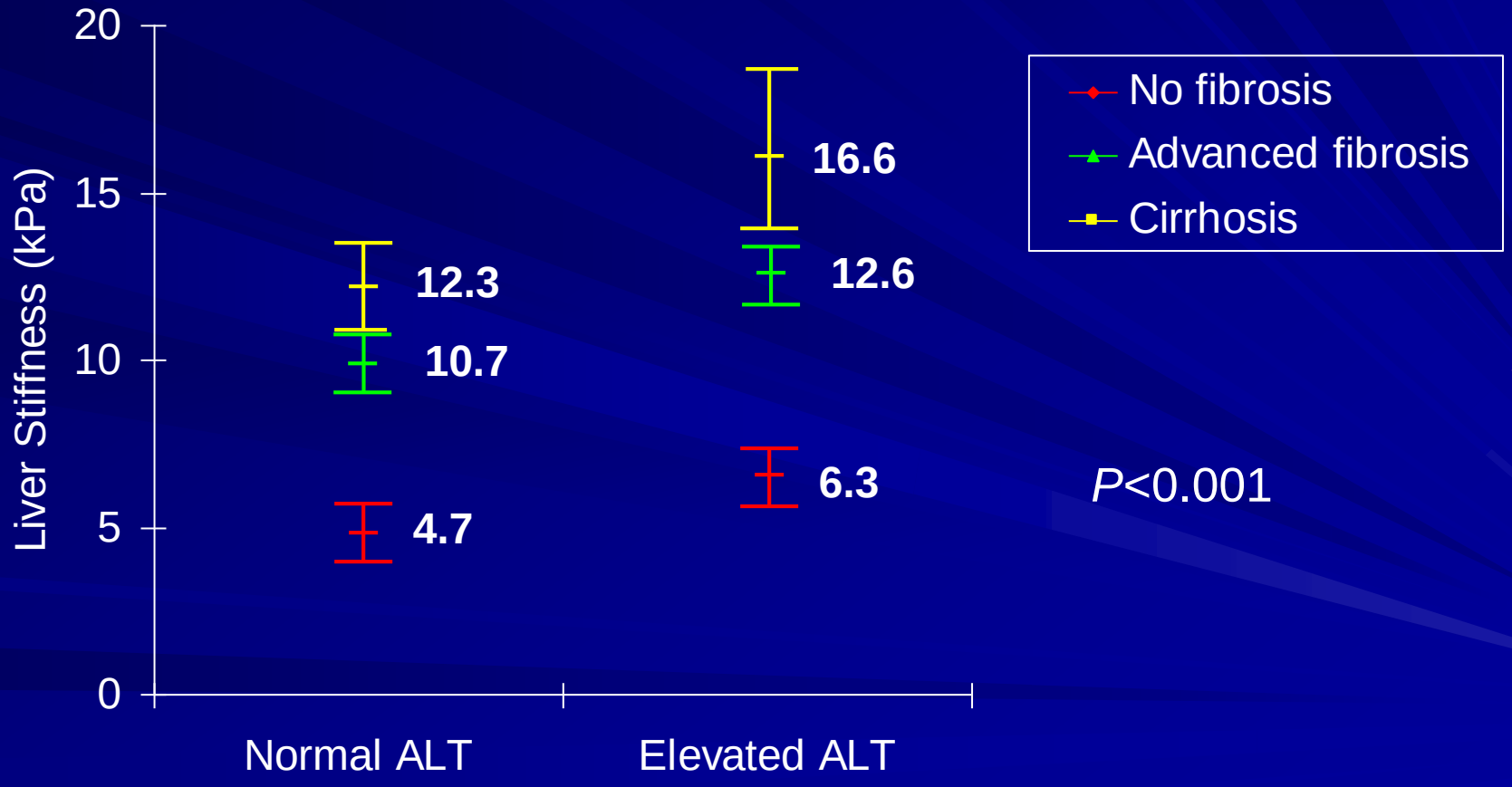
	AASLD 2009	APASL 2012	EASL 2012
HBeAg positive	ALT 1-2x ULN Age > 40	ALT normal or 1-2x ULN HBV DNA > 5 logs Age > 40	ALT normal Age > 30 FH of HCC
HBeAg negative	ALT 1-2x ULN HBV DNA >4 logs	ALT normal or 1-2x ULN HBV DNA > 4 logs Age > 40	ALT > 1x ULN HBV DNA > 4 logs

Lok ASF and McMahon BJ. Hepatology 2009
Liaw YF et al., Hepatol Int 2012
EASL. J Hepatol 2012

Modern Approach to CHB

Assessment of ALT level	Measurement of HBV DNA
Measurement of HBV DNA	Assessment of Liver Fibrosis
Assessment of Liver Fibrosis	Assessment of ALT level
Decision on treatment	Decision on treatment

Liver stiffness was higher in patients with elevated ALT at the same stage of liver fibrosis

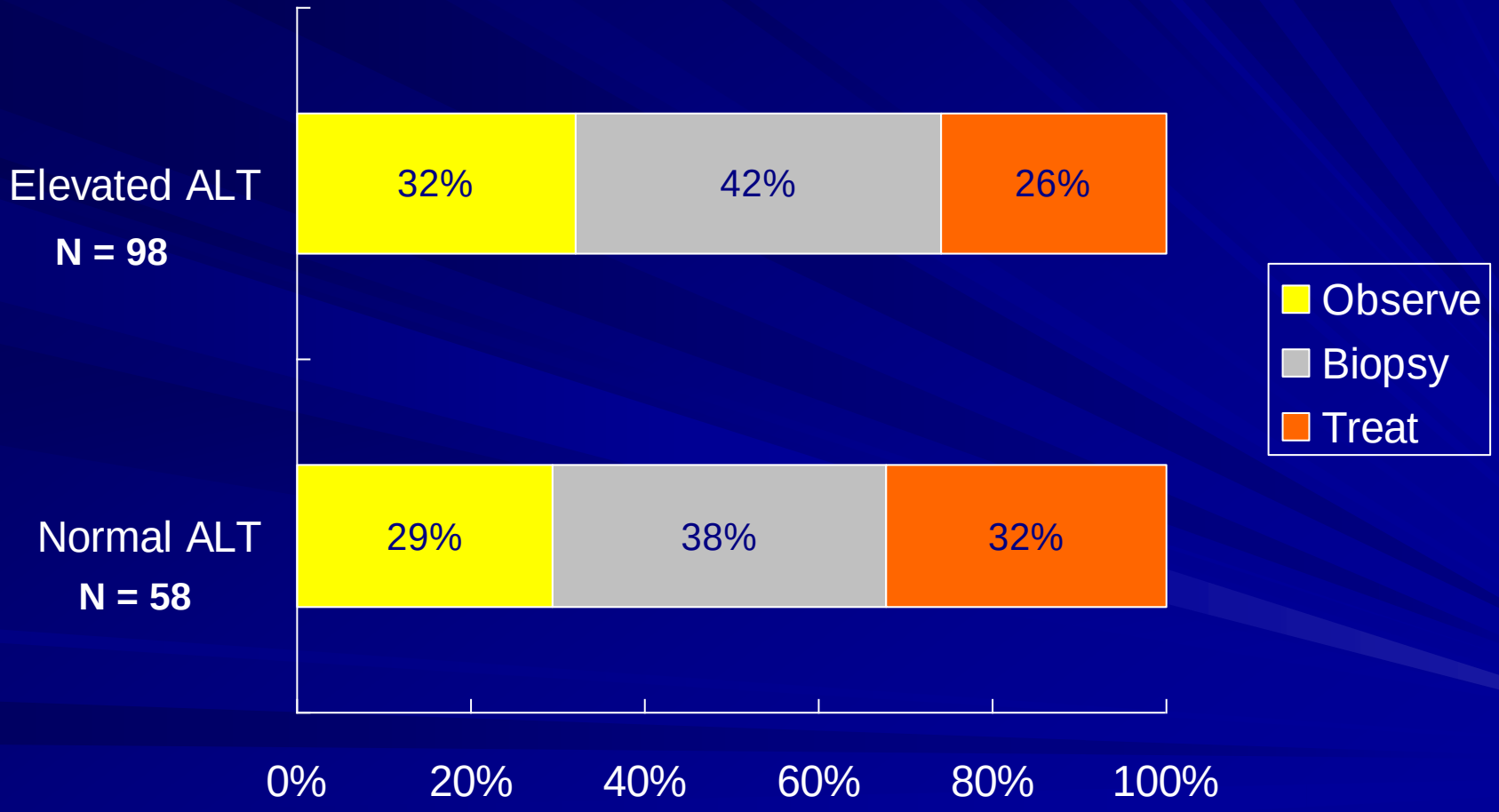


P<0.001

Chan HLY, et al. J Viral Hepat 2009;16:36-44


Normal ALT
≤5.0 kPa
No fibrosis
>5.0 - 6.0 kPa
Insignificant fibrosis
>6.0 kPa – 9.0 kPa
Gray zone
>9.0 – 12.0 kPa
Advanced fibrosis
>12.0 kPa
Cirrhosis
Reassurance
Observe
Liver biopsy
Consider treatment
Consider treatment
Elevated ALT
≤5.0 kPa
No fibrosis
>5.0 – 7.5 kPa
Insignificant fibrosis
>7.5 kPa – 12.0 kPa
Gray zone
>12.0 – 13.4 kPa
Advanced fibrosis
>13.4 kPa
Cirrhosis
Reassurance
Observe
Liver biopsy
Consider treatment
Consider treatment

60% of liver biopsy can be avoided using Fibroscan



Chan HLY, et al. J Viral Hepat 2009;16:36-44

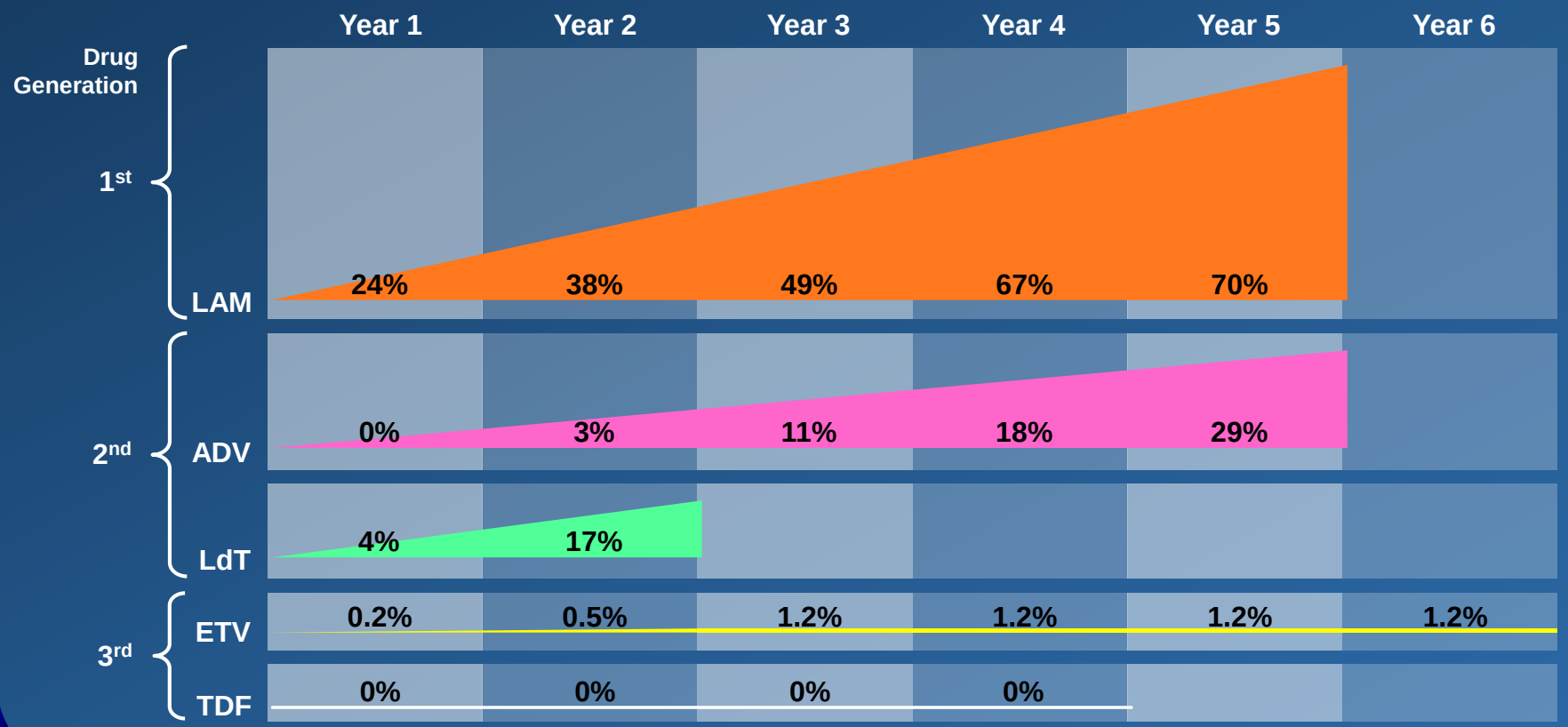
Recommendation 5

- *Treatment naïve patients can be treated with conventional IFN 5-10 MU 3 times per week (IB) or Peg IFN-a2a 180 mg weekly or Peg IFN-a2b 1-1.5ug/Kg weekly (IA), ETV 0.5 mg daily (IA), TDF 300mg daily (IA), ADV 10 mg daily (IB), LdT 600 mg daily (IB), or LAM 100 mg daily (IB). ETV or TDF is the preferred Nuc.*

Liaw YF, et al. Hepatol Int 2012

The choice of first line Nuc is based on the low risk of drug resistance

Not head-to-head trials; different patient populations and trial designs



Adapted from 1. EASL. J *Hepatol*. 2009;**50**:227-42. 2. Tenney DJ, *et al*. *EASL* 2009. Oral presentation #20. 3. Marcellin P, *et al*. *Hepatology* 2009;**50(4, Suppl.)**:532A-3A. 4. Heathcote EJ, *et al*. *Hepatology* 2009;**50(4, Suppl.)**:533A-4A 5. Snow-Lampart A, *et al. AASLD* 2010; Poster #1365.

Problems of drug resistance

- Virological and biochemical relapse
- Histological deterioration
- Increase risk of HCC
- Cross-resistance – reduce the benefit of other antiviral drugs
- Increase drug cost for rescue therapy

Debate

- Drug cost needs to be considered in Asia
- Cost-effectiveness studies need to be performed in different countries

Country	Nuc (USD)	PegIFN (USD)	GNI/capita (USD)
China	704-1935	7968	470
Thailand	913-2774	16464	3400
Taiwan	1095-2665	5760	17930
South Korea	1314-3285	9600	19690

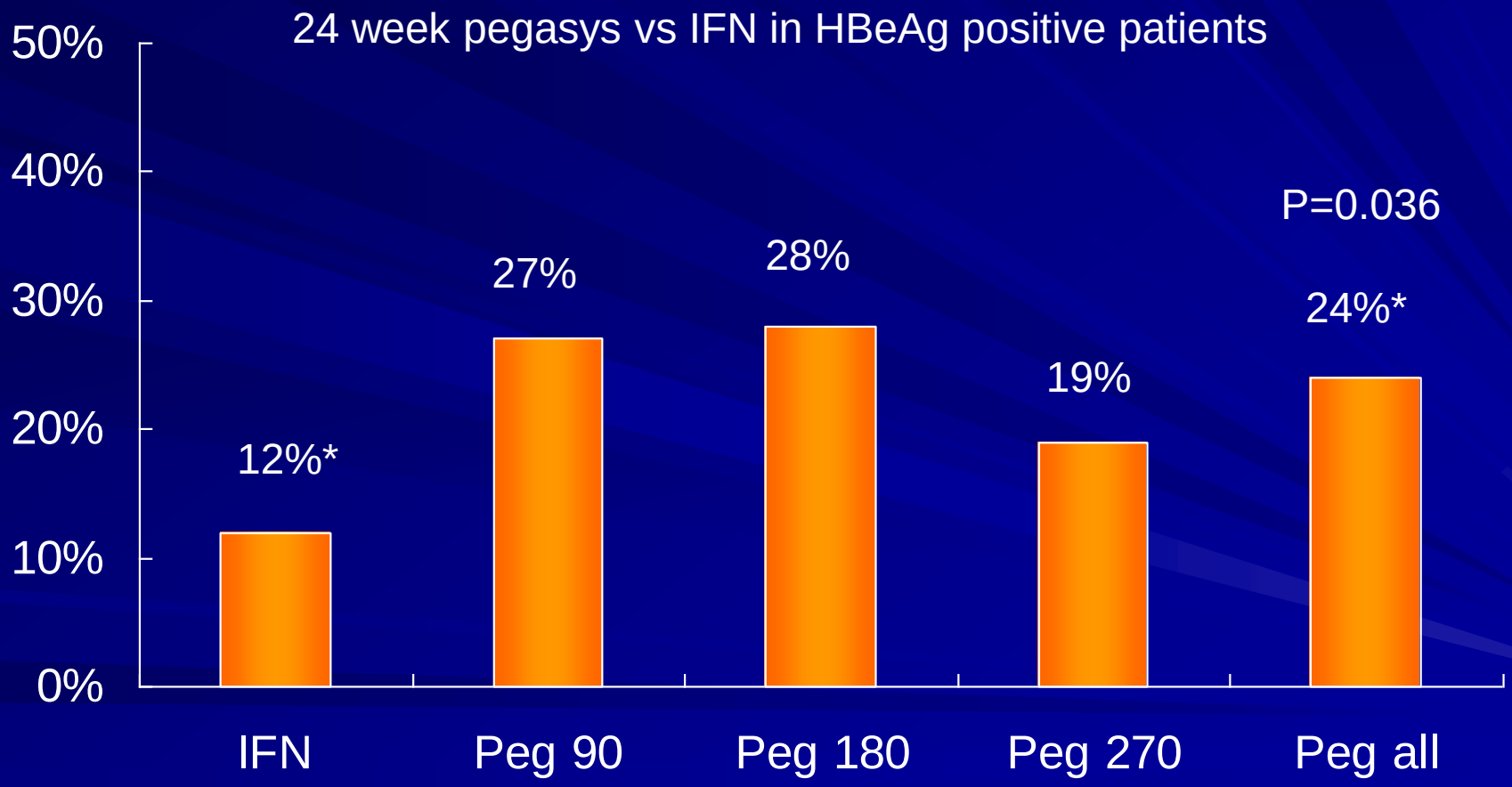
Liaw YF, et al. J Hepatol 2009

Recommendation 8

- *For conventional IFN, the current recommended duration of therapy is 4-6 months for HBeAg positive patients (IA) and at least a year for HBeAg negative patients (IA). For Peg IFN, the recommended duration is 12 months (IA).*

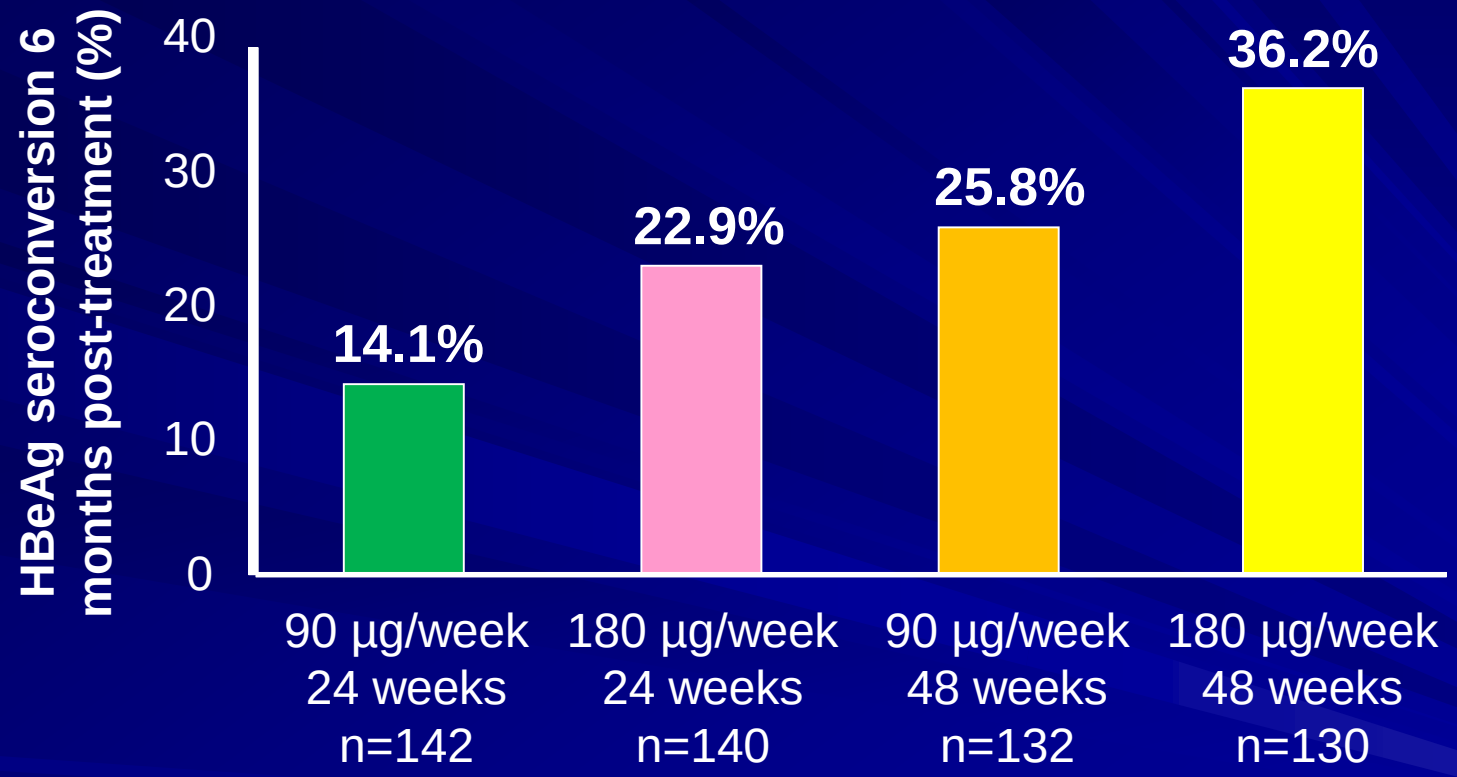
Liaw YF, et al. Hepatol Int 2012

Peginterferon (Pegasys) better than conventional interferon



Cooksley et al J Viral Hepat 2002

NEPTUNE: Highest HBeAg seroconversion rate in the 180 µg/week for 48 weeks group



Confirmed the findings of the Phase 3 PEGASYS study

Liaw YF, Jia JD, Chan HL, et al. Hepatology 2011

To improve response to peginterferon

- Combination therapy can only increase on-treatment HBV DNA suppression but not sustained off-treatment response
- Combination of pegasys and teblivudine results in severe peripheral neuropathy – contraindicated
- Currently, combination therapy of peginterferon and NA cannot be recommended

Liaw YF, et al. Hepatol Int 2012

Recommendation 9

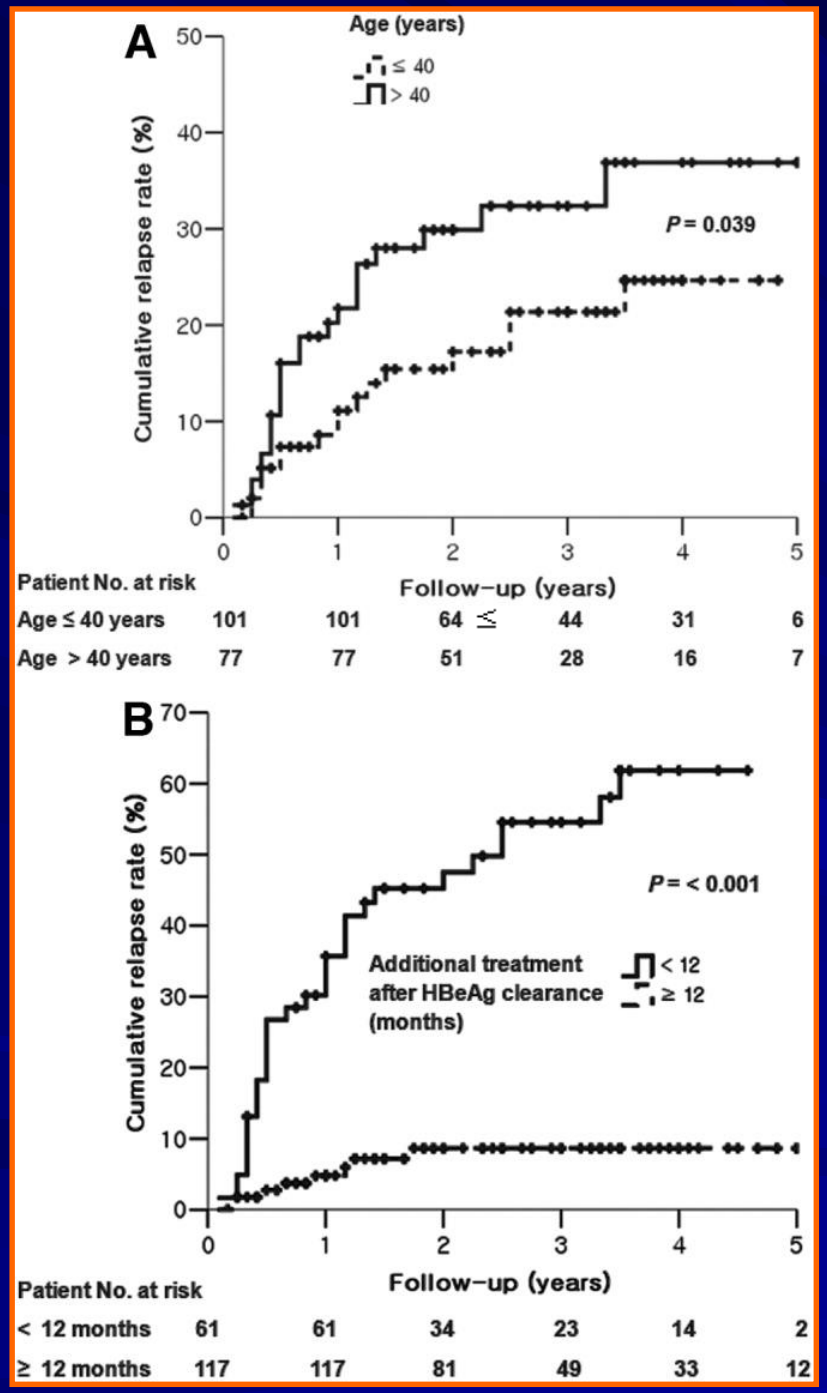
- *Stopping rules for Nucs:*
- *In HBeAg positive patients, treatment can be stopped when HBeAg seroconversion with undetectable HBV-DNA has been maintained for at least 12 months (IIA).*
- *In HBeAg negative patients, it is not clear how long this treatment should be continued if HBsAg remains positive, but treatment discontinuation can be considered if patients have been treated for at least 2 years with undetectable HBV DNA documented on three separate occasions 6 months apart. (IIA).*

Liaw YF, et al. Hepatol Int 2012

Stopping rules with NUCs for HBV therapy

CHB Treatment Guidelines	EASL[1] (April 2012)	AASLD*[2] (Nov 2009)	APASL[3] (Feb 2012)
HBeAg+ve	HBeAg seroconversion with 12 months of consolidation	HBeAg seroconversion with 6 months of consolidation + undetectable DNA	HBeAg seroconversion + undetectable DNA for 12 months
HBeAg-ve	HBsAg clearance	HBsAg clearance	Treatment for at least 2 years + DNA undetectable 3 times 6 months apart

1. EASL *Clinical Practice Guidelines*. *J Hepatol* 2012 (in press). 2. Lok A, *et al*. *Hepatology* 2009;**50(3)**:1-36. 3. Liaw YF, *et al*. *Hepatol Int* 2012 (in press).



36.9%

24.6%

61.9%

8.7%

1999 – 2004

748 Korean patients HBeAg-positive CHB infection were treated with lamivudine

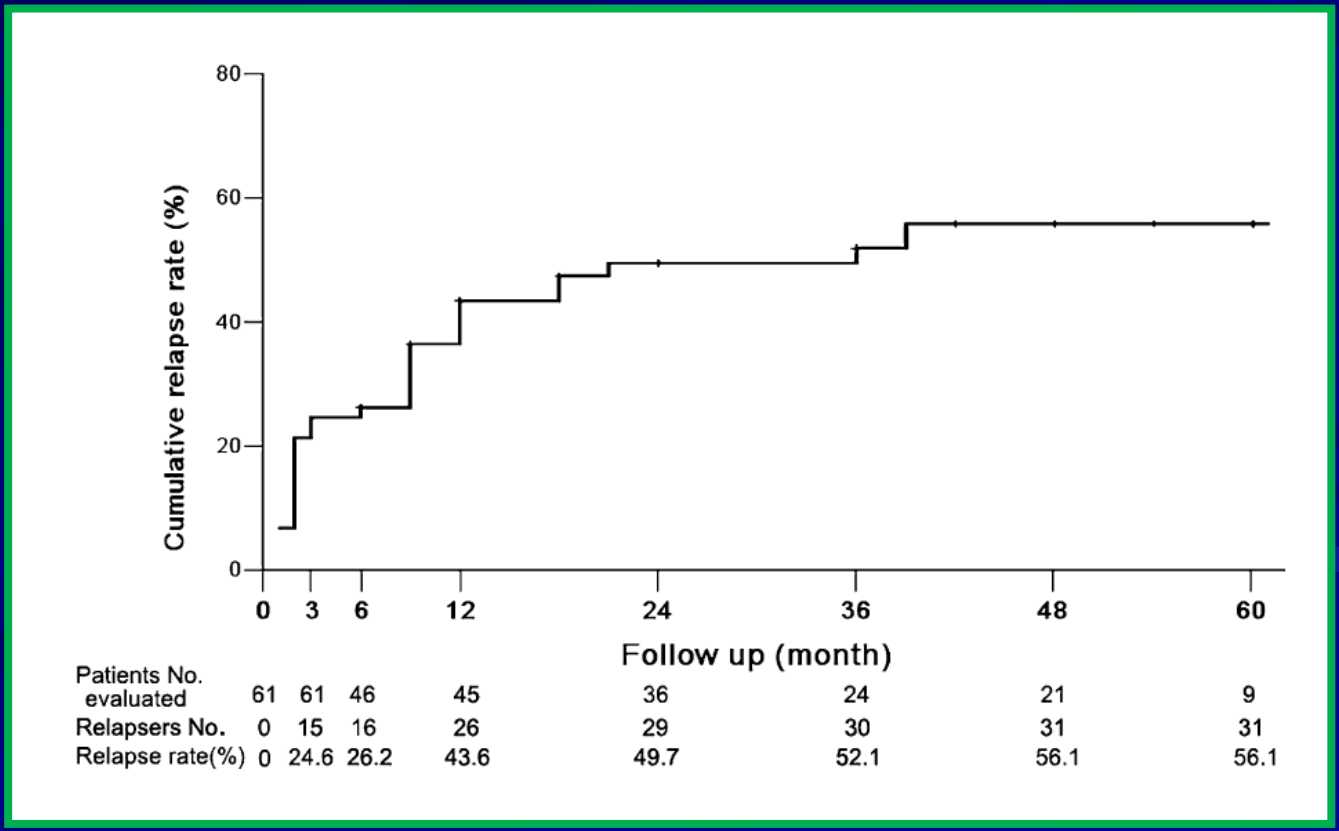
Complete response (CR) normalization of ALT; loss of serum HBV DNA by Digene II assay; and HBeAg clearance

178 patients followed for at least 6 months and discontinued lamivudine treatment after CR

Lee et al., Hepatology 2010

56% of HBeAg-negative CHB patients relapsed after stopping lamivudine in 5 years

61 HBeAg-negative patients on lamivudine x 27 (24-66) months
HBV DNA undetectable x at least 18 months before stopping treatment
FU x 15 (1-84) months



Patients No. evaluated	61	61	46	45	36	24	21	9
Relapsers No.	0	15	16	26	29	30	31	31
Relapse rate(%)	0	24.6	26.2	43.6	49.7	52.1	56.1	56.1

Liu F, et al. J Gastroenterol Hepatol 2011

HBV relapse after adefovir

- ADV in HBeAg negative CHB x 5 years
- 33 patients with undetectable HBV DNA x 4-5 years stopped treatment
- All patients had transient HBV DNA elevation

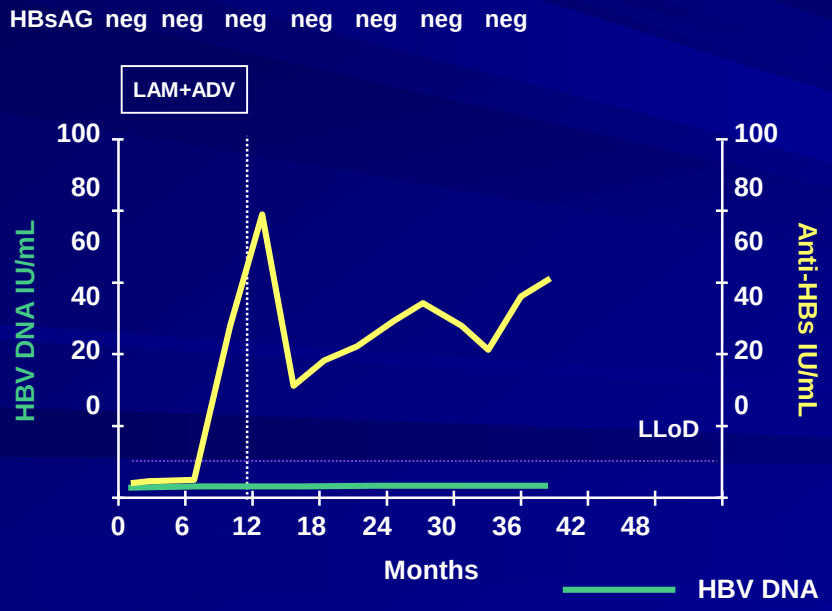
- HBV DNA relapse (> 4 logs)
  - Year 2: 7 (33%)
  - Year 4: 11 (42%)
  - Year 5: 15 (46%)

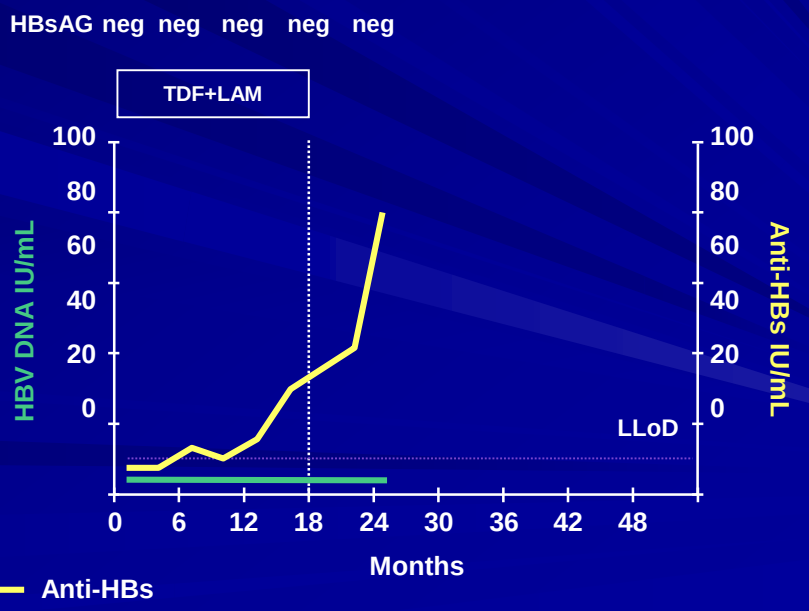
- No relapse: 18
  - PCR undetectable 12 (36%), HBsAg loss 10 (33%)

Hadziyannis et al., AASLD 2006

Nucleos(t)Ide analogues can be safely discontinued after achieving HBsAg seroclearance with 12 month consolidation

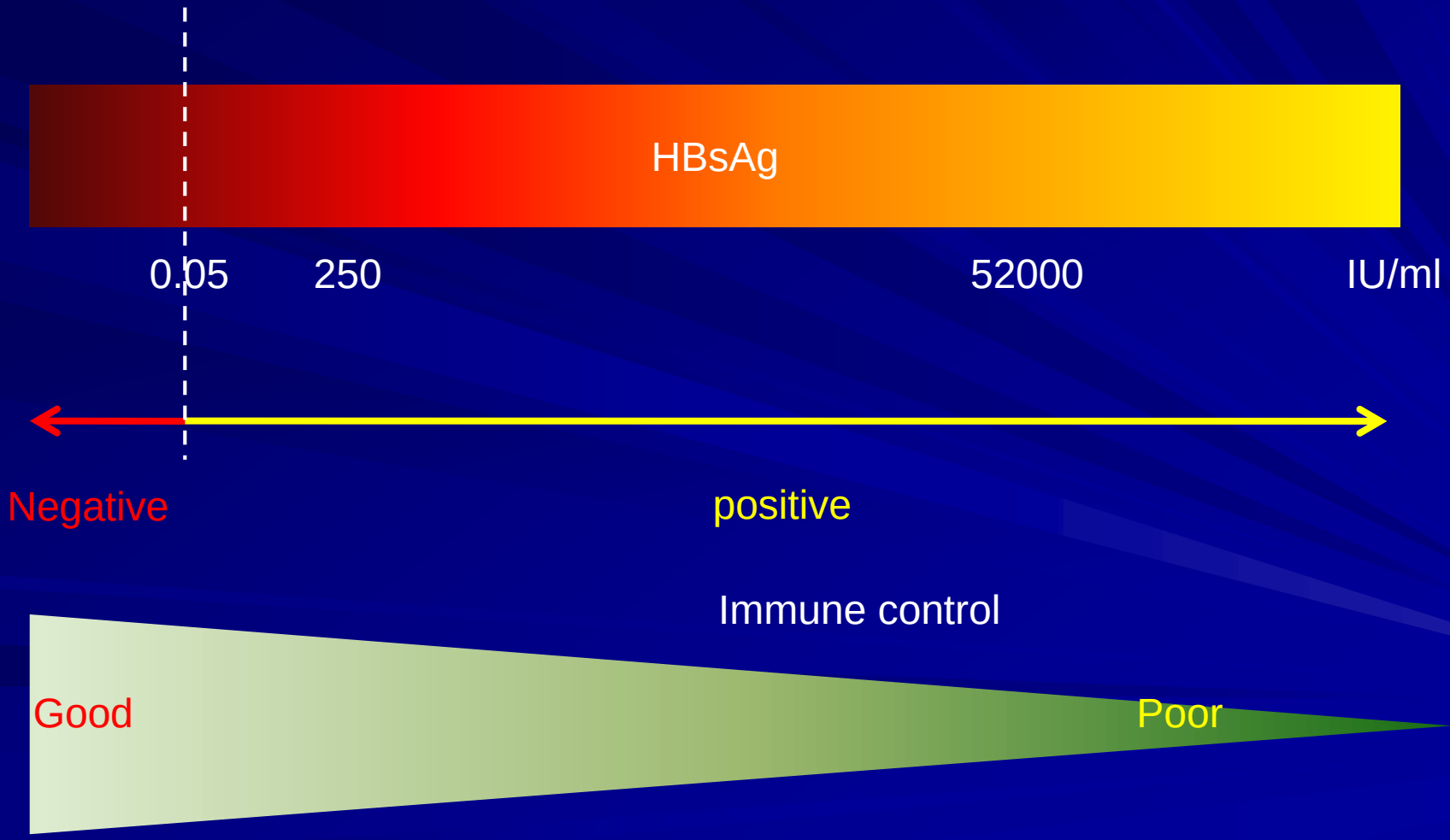
- 25 patients cleared HBsAg (NUC mono, n=17; combo, n=8)
- 21 patients (84%) discontinued NUC therapy after 1 year of consolidation
- All 21 patients remained HBsAg negative during 10 (1-63) months of post-treatment follow-up





Vezali E, *et al.*, *EASL* 2011; Poster # 753.

Meaning of qHBsAg



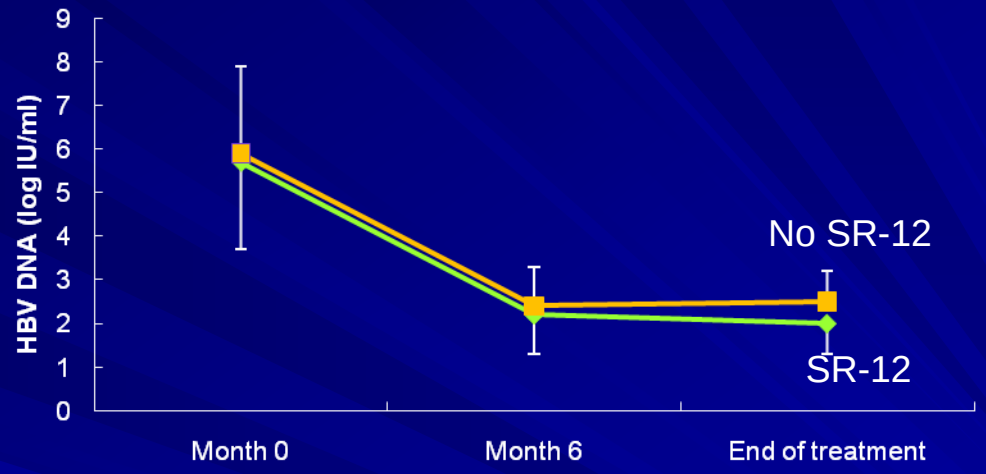
HBsAg but not HBV DNA can differentiate sustained responders vs non-responders in lamivudine treated patients

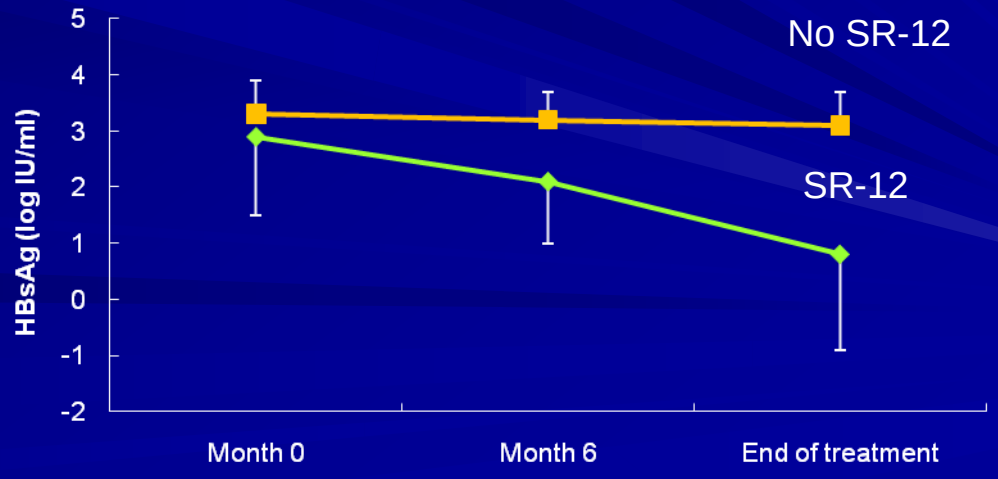
53 HBeAg-negative CHB patients

On lamivudine for 34±23 (12-76) months

Stopped LMV for 47±35 (1-116) months

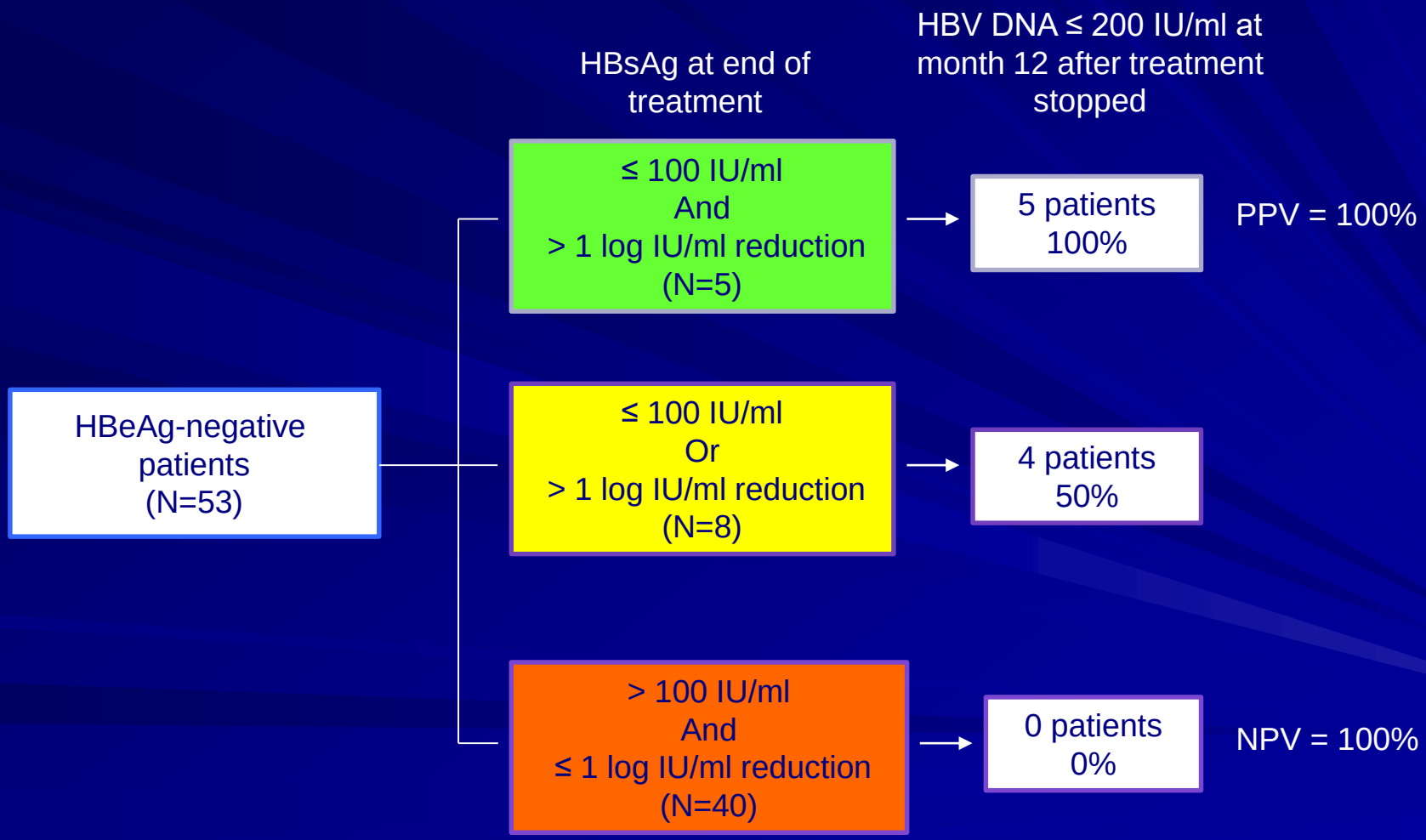
Sustained response at month 12 (SR-12) = HBV DNA ≤ 200 IU/ml at 12 months after stopping lamivudine





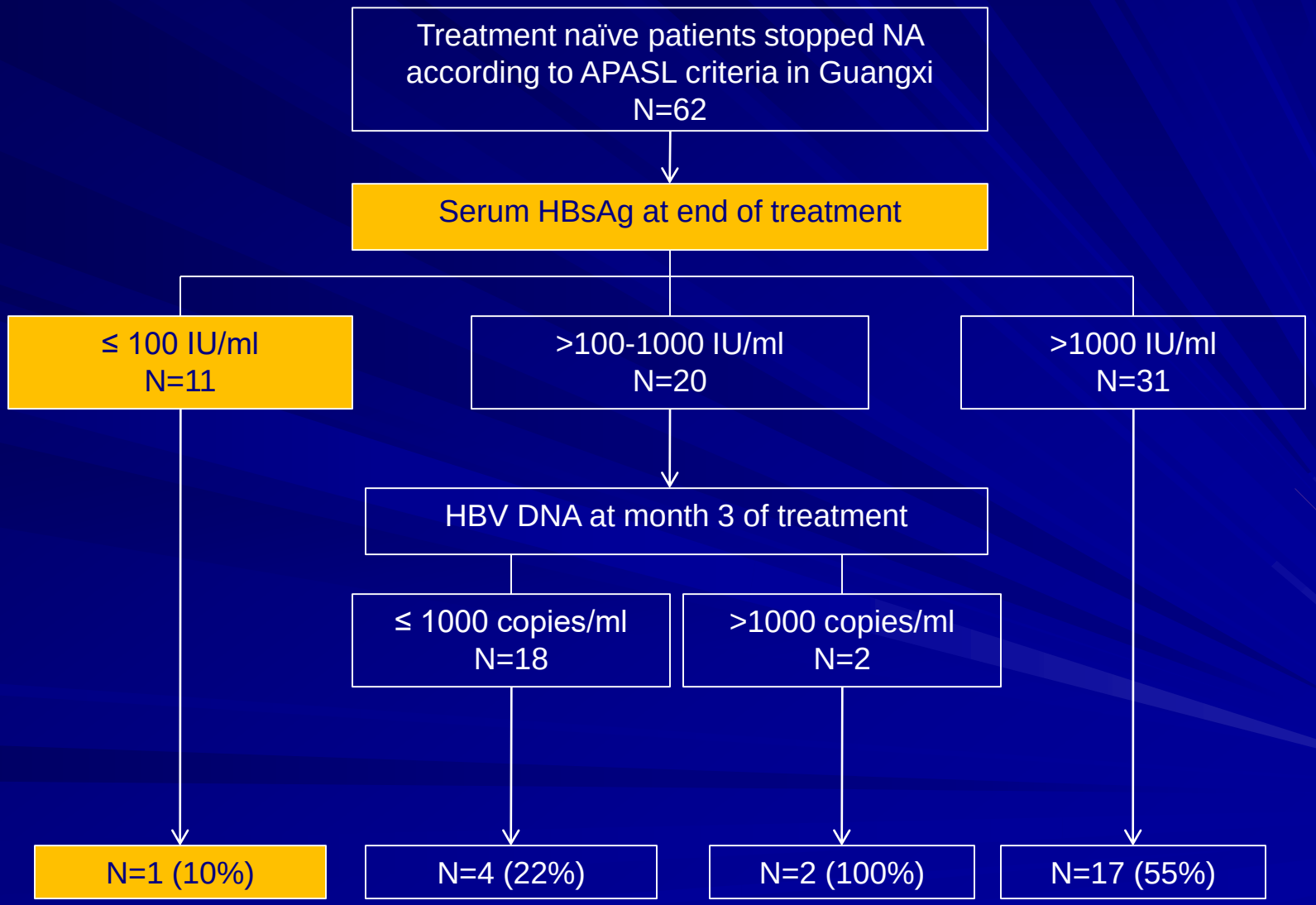
Chan HL, et al. Antivir Ther 2012

Serum HBsAg at end of treatment can predict response at 12 months post-treatment



Chan HL, et al. Antivir Ther 2012

Serum HBsAg at the end of treatment can predict risk of relapse after stopping treatment



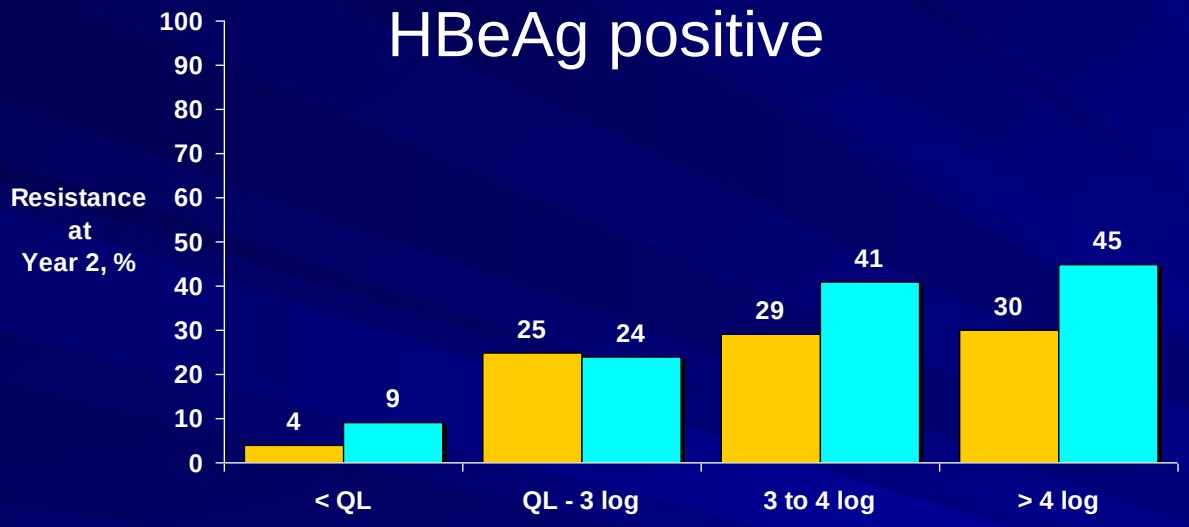
Liang Y, et al. Aliment Pharmacol Ther 2011;34:344-52.

Recommendation 9

- *In compliant patients with primary treatment failure at month 3 or suboptimal viral response at month 6, switch to a more potent or add on a drug without cross resistance if LAM, LdT or ADV was used (IIIA).*

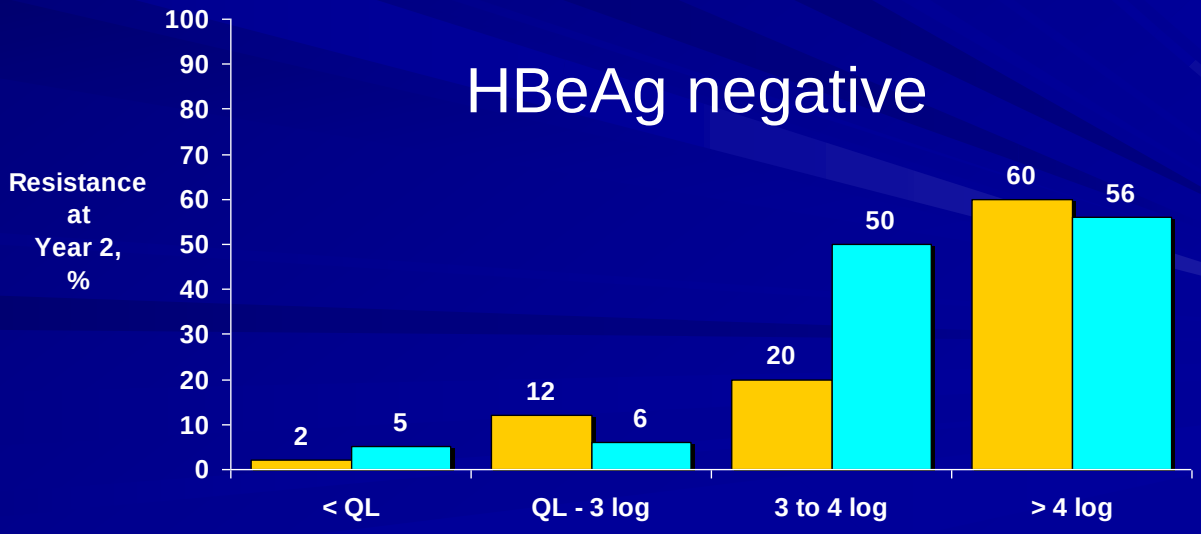
Liaw YF, et al. Hepatol Int 2012

Week 24 HBV DNA can predict drug resistance at year 2 (GLOBE study)



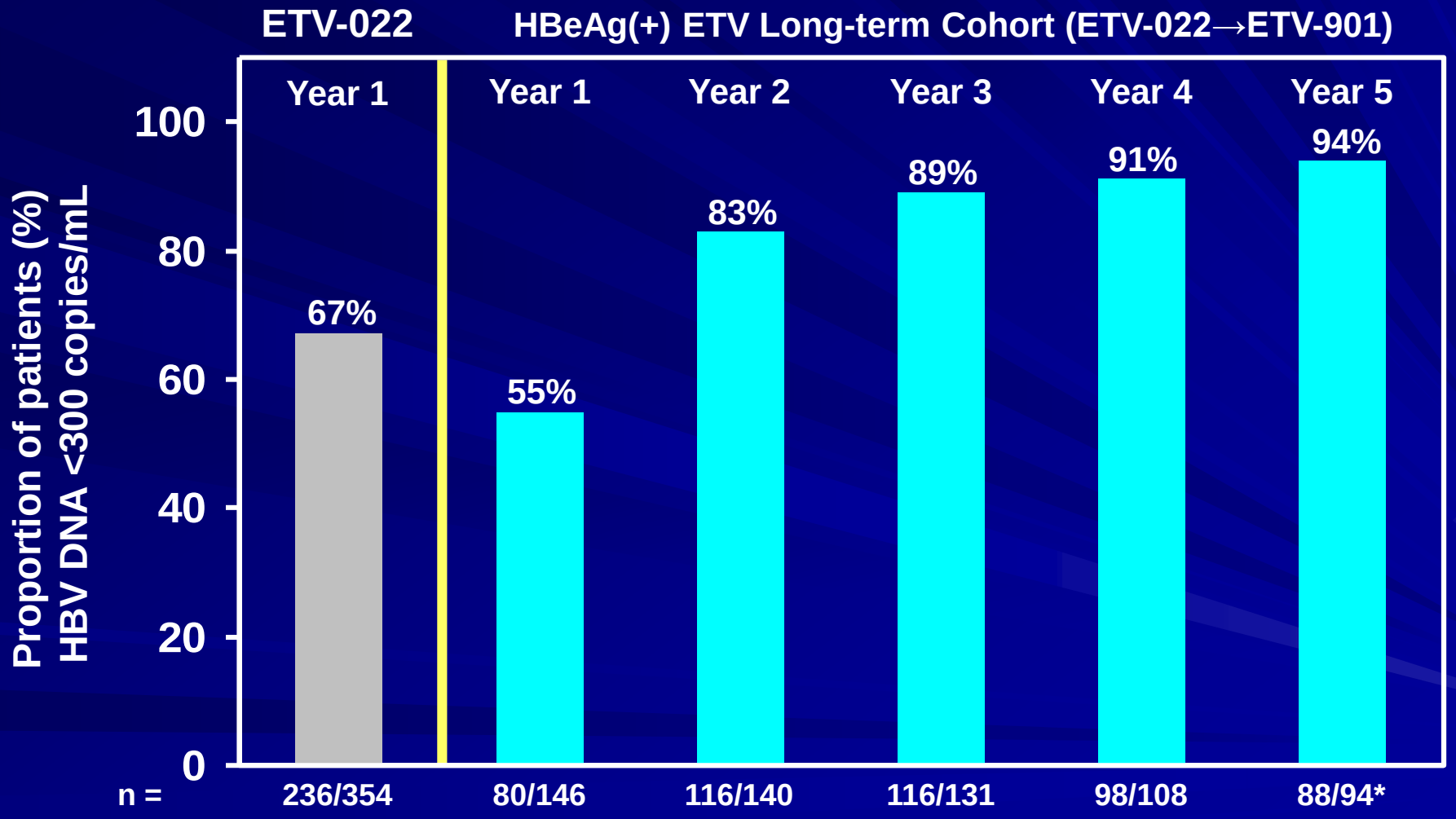
Telbivudine

Lamivudine



Lai et al AASLD 2005

Is on-treatment prediction necessasry for entecavir?



* 5 patients who remained on treatment at the Year 5 visit had missing PCR values (NC=M)

Han et al., AASLD 2008

Prediction of year 3 response by on-treatment HBV DNA suppression with ETV

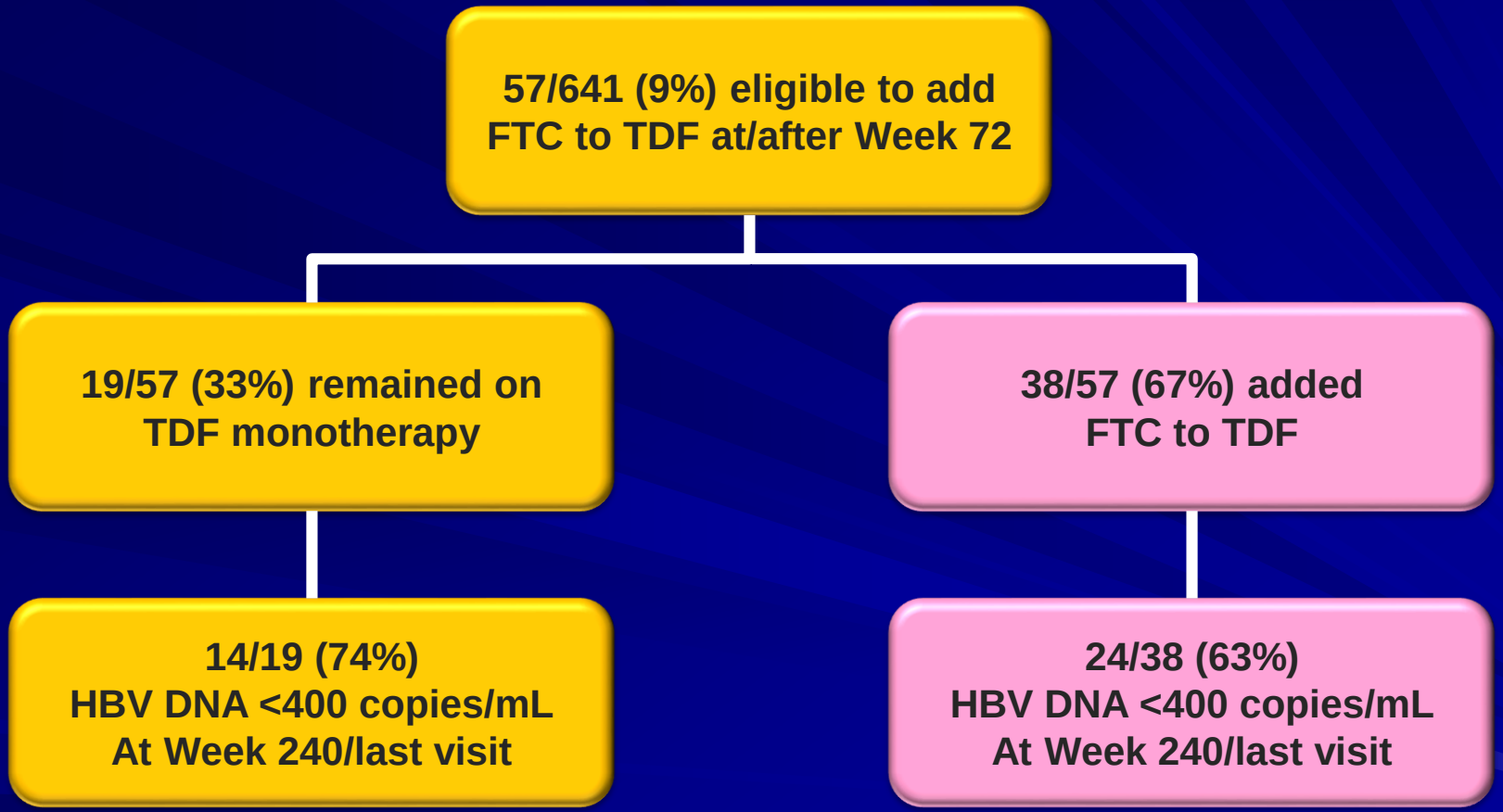
440 treatment-naïve CHB patients on ETV 0.5mg daily FU for 34±9 months
160 (36%) patients with positive HBeAg

Month 12	Undetectable HBV DNA	HBeAg seroconversion	Virological breakthrough	Drug resistant mutation
Responder (74%)	100%	43.2%	2.4%	0%
Partial responder (26%)	57.5%	19.0%	5.1%	1.7%
P value	<0.001	0.003	0.11	0.004

?? Combination therapy can improve HBV DNA and HBeAg seroconversion

Wong GL, … Chan HL, et al. Aliment Pharmacol Ther 2012

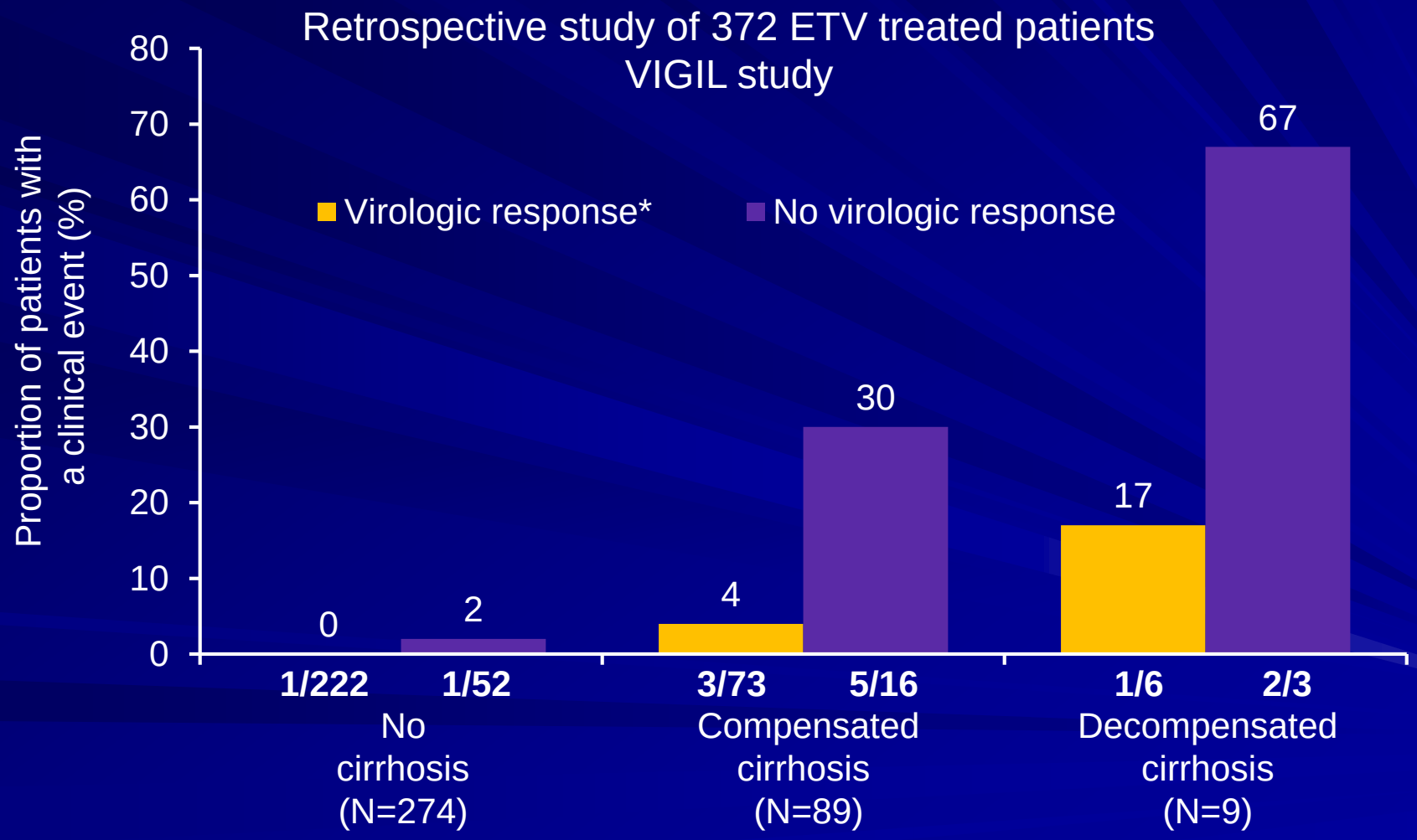
Studies 102/103: Adding FTC vs Maintaining TDF Monotherapy



All subjects analyzed with >400 copies/mL had no TDF resistance detected.

Marcellin P, et al. AASLD 2011. Oral 238.

Complete virologic suppression is associated with reduced hepatic events



*Virologic response (HBV DNA <80 IU/mL) at time of event or censoring

Zoutendijk R, et al. Gut 2012

Questions remain unanswered after APASL guideline 2012

- What is the most cost-effective treatment strategy in different Asian countries?
- How to improve sustained response to peginterferon therapy?
- Any better markers to predict sustained response after stopping Nuc therapy; qHBsAg?
- How to manage suboptimal responders to ETV and TDF?