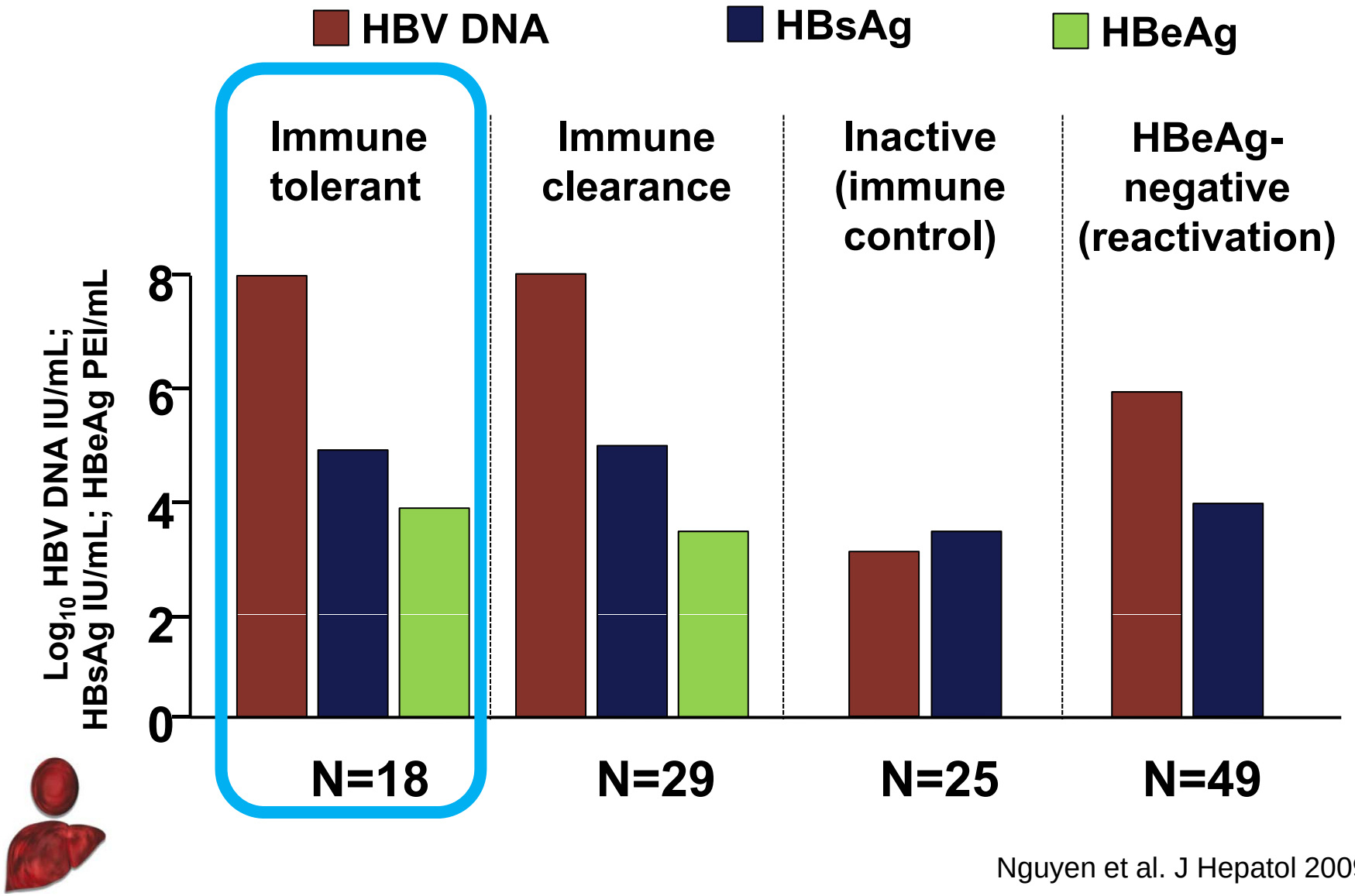
Case 1

- A 20 year-old university student
- Known chronic HBV infection since he was 12 year-old.
- His father died from HCC.
- Two of his 3 brothers also have chronic hepatitis B
- Still asymptomatic with persistent normal ALT of about 20-30 IU/L
- Normal physical examination
- HBsAg 4.96 log IU/ml
- HBeAg positive antiHBe negative
- HBV DNA 9.8 log IU/ml

- **Do and how serum HBV DNA and HBsAg levels during immune tolerance phase predict natural course of chronic hepatitis B?**

Lowest HBsAg and HBV DNA levels found in the inactive (immune control) phase

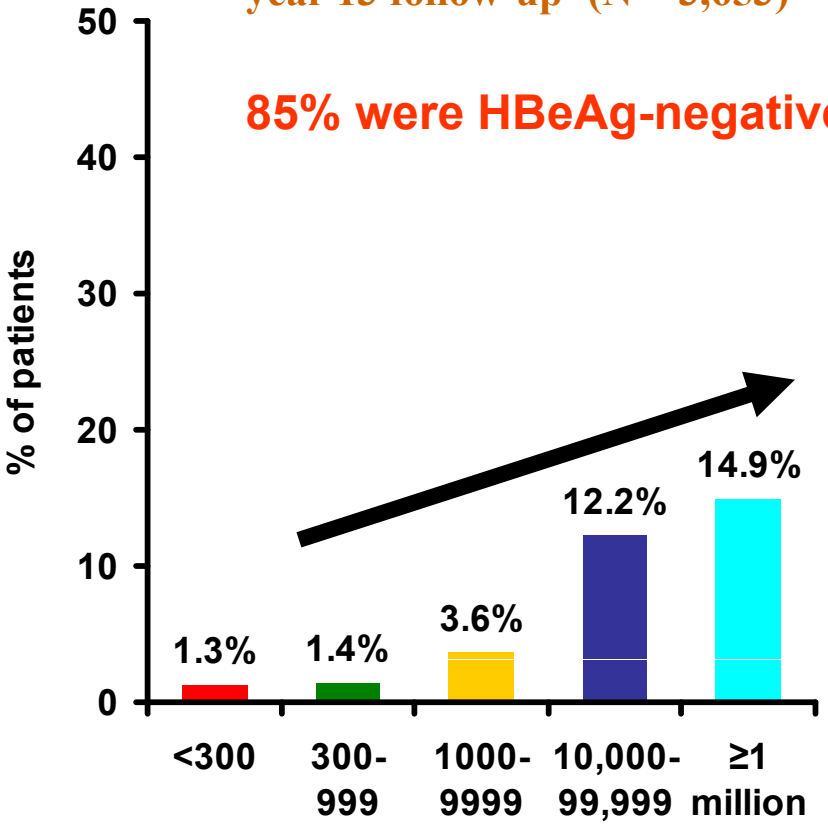


Nguyen et al. J Hepatol 2009 (A370)

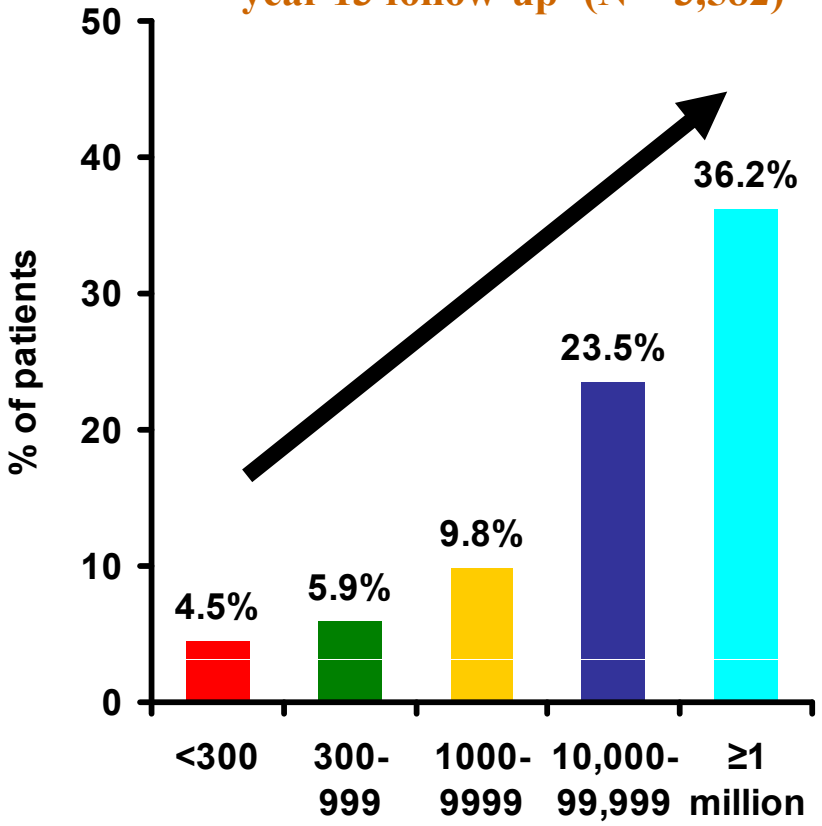
High Baseline HBV DNA Associated With Increased Risk of Cirrhosis and HCC

Cumulative incidence of HCC at year 13 follow-up[1] (N = 3,653)

85% were HBeAg-negative



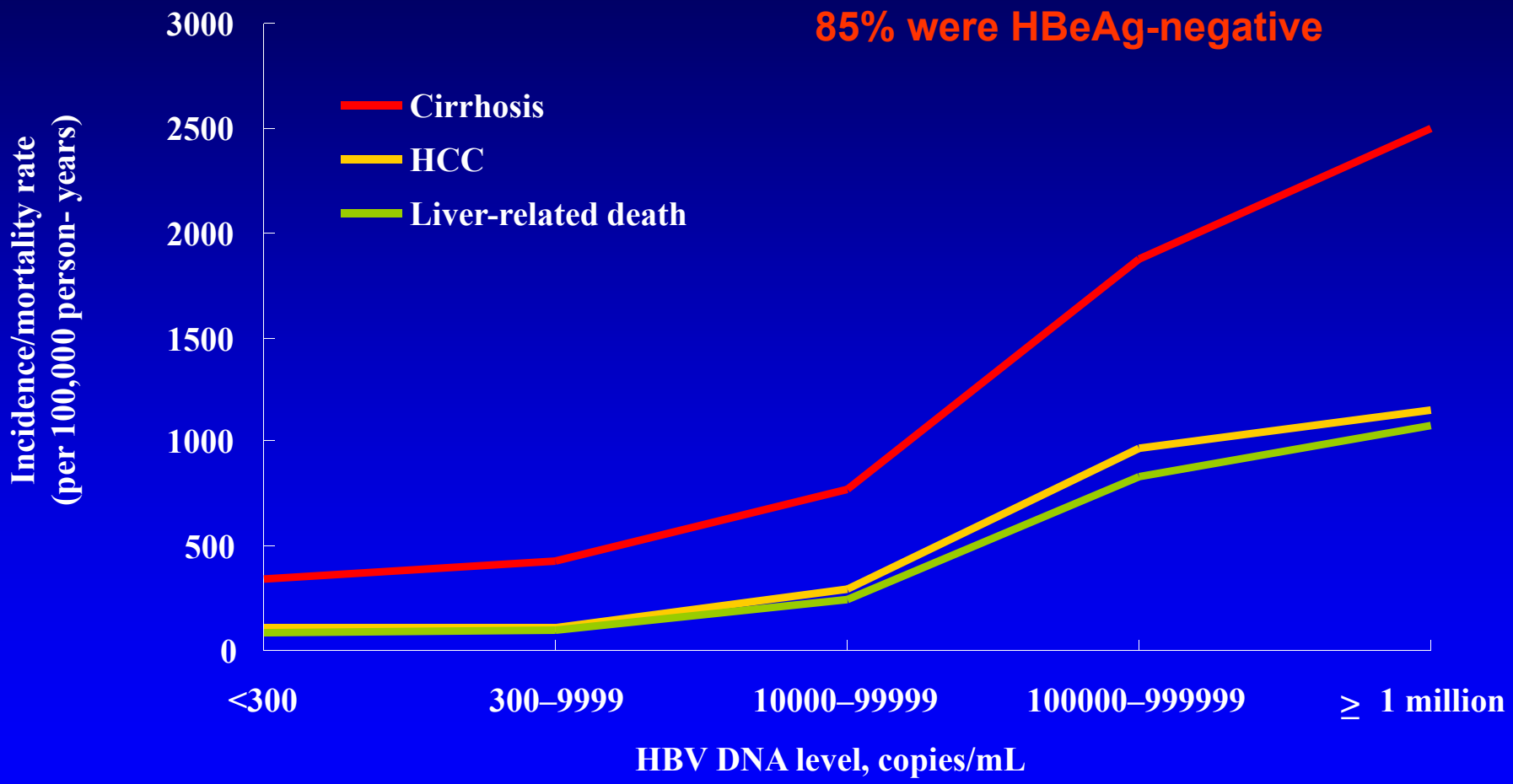
Cumulative incidence of cirrhosis at year 13 follow-up[2] (N = 3,582)



Baseline HBV DNA (copies/mL)

[1]Chen, et al. *JAMA.* 2006;295:65-73.
[2]Iloeje, et al. *Gastroenterology.* 2006;130:678-686.

REVEAL: Incidence of cirrhosis and HCC and liver-related mortality by serum HBV DNA level at study entry

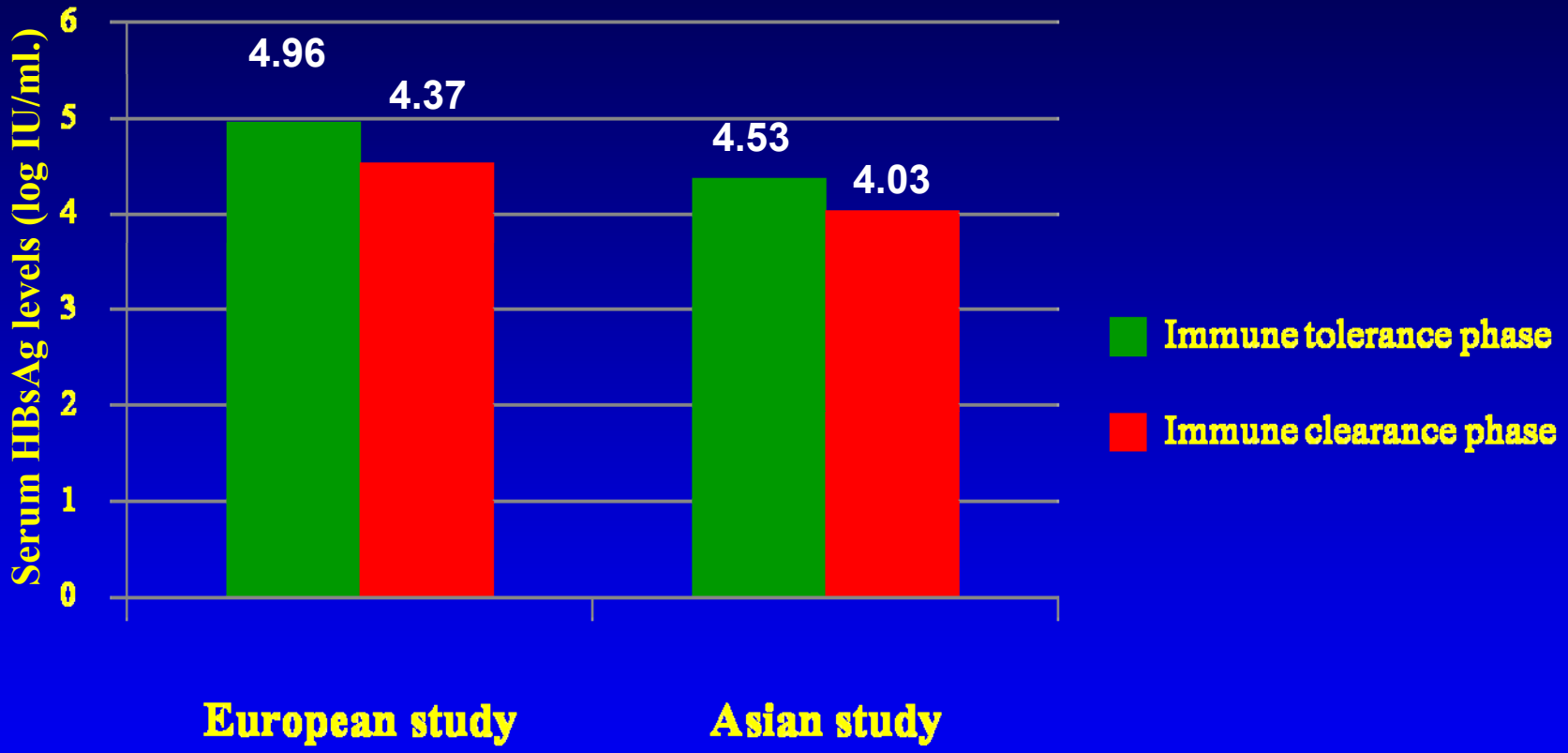


Adapted from Chen CJ et al. JAMA. 2006;295:65–73; Iloeje UH et al. Gastroenterology. 2006;130:378–686; Iloeje UH et al. Clin Gastroenterol Hepatol. 2007;5:921–931.

HBV DNA level has no association with the severity of liver fibrosis in HBeAg positive chronic hepatitis B

Wong GL et al. Clin Gastroenterol Hepatol 2009

Serum HBsAg levels in natural history of chronic HBV infection



A median annual decline 0.006 log IU/ml in immune tolerance VS 0.021log IU/ml in immune clearance phase

Jaroszewicz J. et al. J Hepatol 2010: 52: 514-22
Nguyen T. et al. J Hepatol 2010: 52: 508-13
Chan HL et al. Hepatology 20101: 52: 1232-41

HBsAg among patient in immune tolerance phase

- **HBsAg level is persistently high at approximately 5 log IU/ml**
- **HBsAg level is stable with a median decline of -0.0006 log IU/ml**
- **HBsAg level or HBsAg/HBV DNA can not predict the chance of spontaneous HBeAg seroconversion**

Chan HL. et al. Hepatology 2010.
Nguyen et al. J Hepatol 2009.; Hepatology 2010.

Hepatocellular Carcinoma by Serum HBV DNA Levels at Study Entry and at Last Follow-up

Level of HBV DNA, copies/mL		No. of Participants (N = 3653)*	No. of HCC Cases	Median Time Between the Baseline and Last Follow-up Examination, y	Adjusted HR (95% CI)†	
At Study Entry	At Follow-up				Sex, Age, Cigarette Smoking, and Alcohol Consumpt.	Plus Seropos. for HBeAg, Liver Cirrhosis, and ALT Level
≥ 100 000	< 10 000	146	8	11.1	3.8 (1.7-8.4)	1.9 (0.8-4.4)
≥ 100 000	10 000- 99 999	120	10	10.5	7.3 (3.5-15.3)	4.3 (2.0-9.3)
≥ 100 000	≥ 100 000	537	55	9.9	10.1 (6.3-16.2)	5.3 (2.9-9.7)

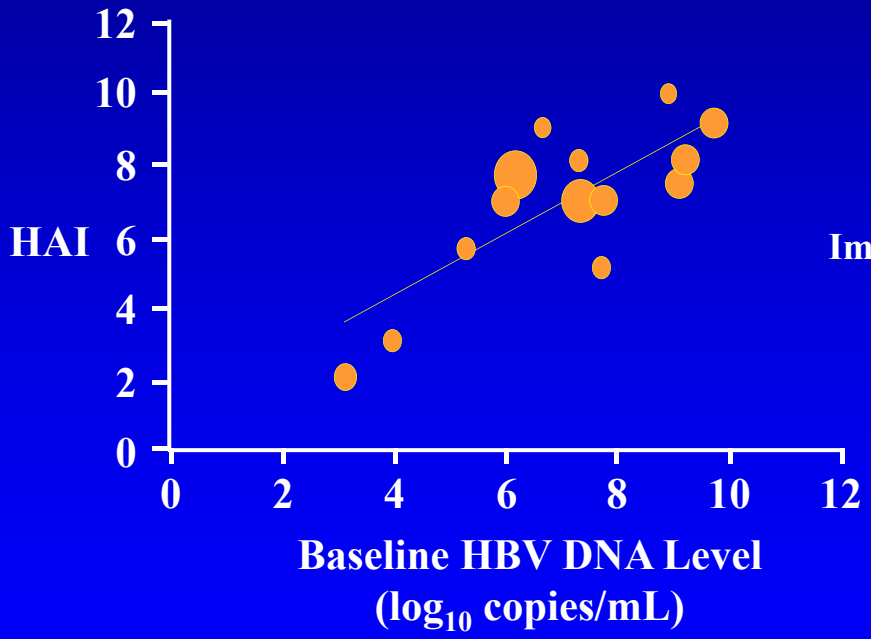
Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HR, hazard ratio.

*There were 289 participants whose last follow-up serum samples were not available.

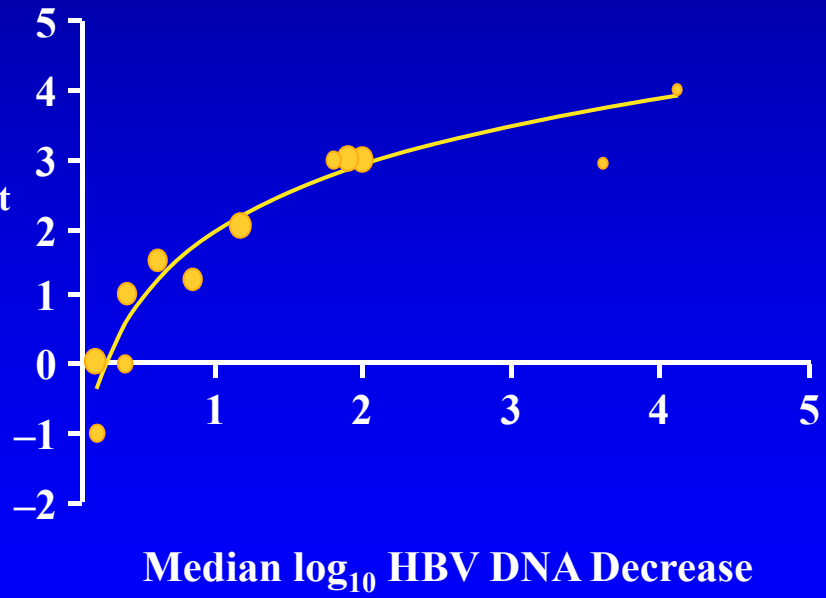
†Cox proportional hazard model was used.

HBV DNA Levels Correlate Quantitatively With Histology

Correlation between HAI and HBV DNA in untreated patients (r=0.78; *P*=0.0001)



Correlation between change in HBV DNA and HAI with treatment (r=0.96; *P*<3x10^{-6})



Mommeja-Marin et al., *Hepatology* 2003;37:1309-1319

- At age of 31 years, he consulted at liver clinic due to persistent ALT elevation for 7 months with ALT of 110-180 IU/L
- Unremarkable physical examination
- CBC : WNL , platelet count 220,000/mm^3 ,PT INR = 1.01
- LFTs: Bilirubin 0.1 / 0.9 mg/dL

  AST 160 IU/L ALT 170 IU/L

  ALP 118 IU/L Alb 4.9 gm/d Glob 2.3 gm/dL
- HBeAg positive anti HBe negative

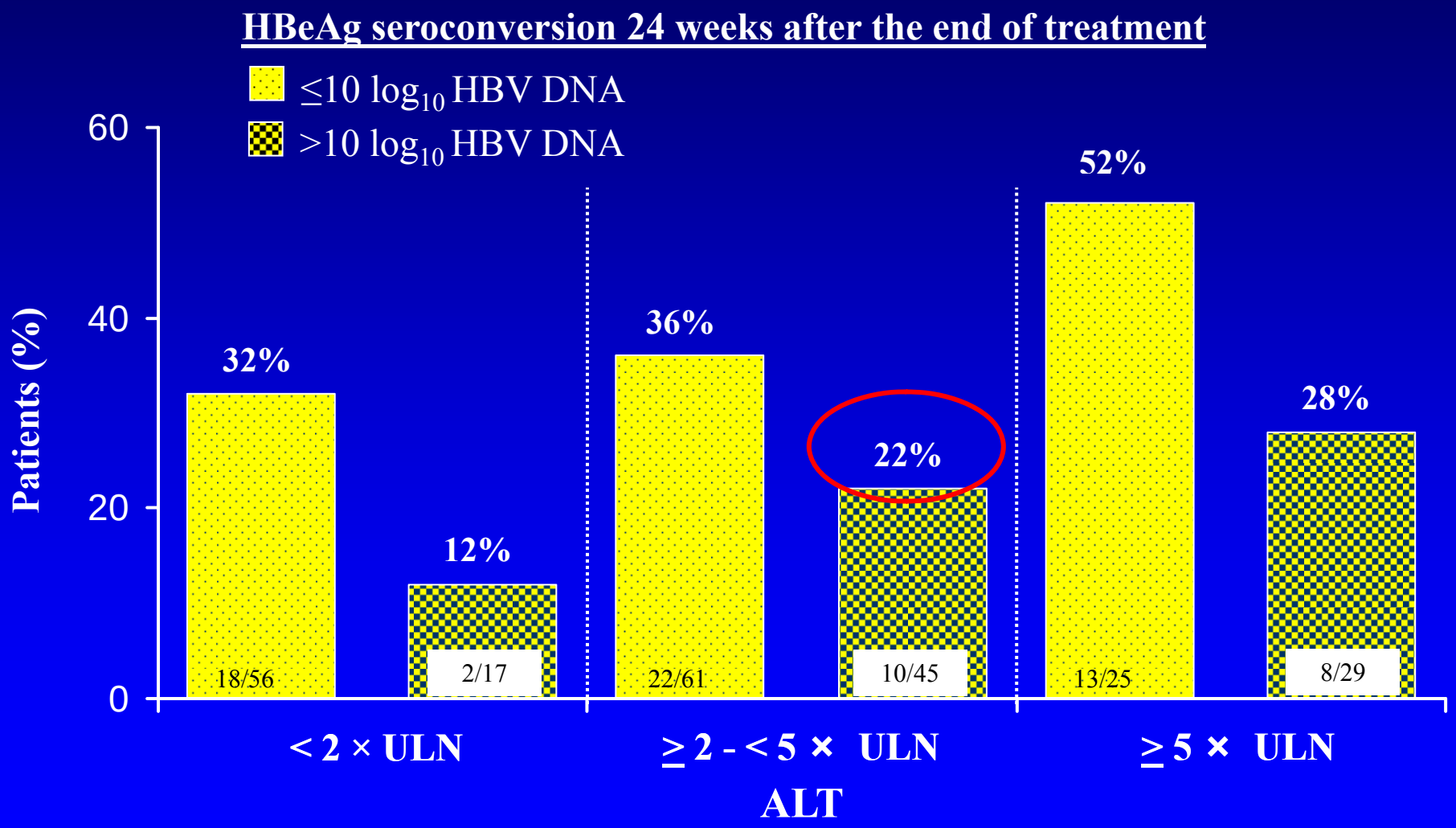
  anti HCV negative HIV : negative
- HBsAg level 4.3 log IU/ml
- HBV DNA 8.0 logs IU/ml
- HBV genotype C
- US revealed normal liver and spleen

- **How can we use baseline serum HBsAg level and HBV DNA in considering HBV treatment?**

- **Baseline serum HBsAg levels tend to be lower in patients achieving sustained response post peginterferon treatment than non-responders, BUT, currently, could not be used to decide treatment strategy due to lack of validated cut-off value and inadequate positive and negative predictive value**

Wong WV. etal. Hepatology 2010;51:1945-1953.
Chan HL. etal. Aliment Pharmacol Ther. 2010;32:1323-315.
Tangkijvanich P, etal. J Clin Virol 2009;46:117-123.

Best response to PegIFN alfa in Asian patients with high baseline ALT and low HBV DNA



Cooksley et al. Shanghai Hong Kong International Liver Congress 2006

Baseline relationship to 5yr response
% patients with 5yr response to Lam

Group	HBV DNA	ALT	HBV DNA <4 logs	HBV DNA PCR -ve	ALT normal	HBeAg serocon
1 (n=17)	< 9 logs cps/ml	≥2xULN	77	41	88	82
2 (n=22)	<9 logs cps/ml	<2xULN	23	18	55	23
3 (n=35)	≥9 logs cps/ml	All	11	6	65	14

Yuen *et al. Antiviral Ther* 2009

- **His physician decided to treat him with peginterferon alfa-2a 180 µg weekly**
- **At week 12 : CBC WNL**

  bilirubin 02/0.8 mg/dL

  AST 170 IU/L ALT 200 IU/L

  ALP 108 IU/L Alb 4.9 gm/dL

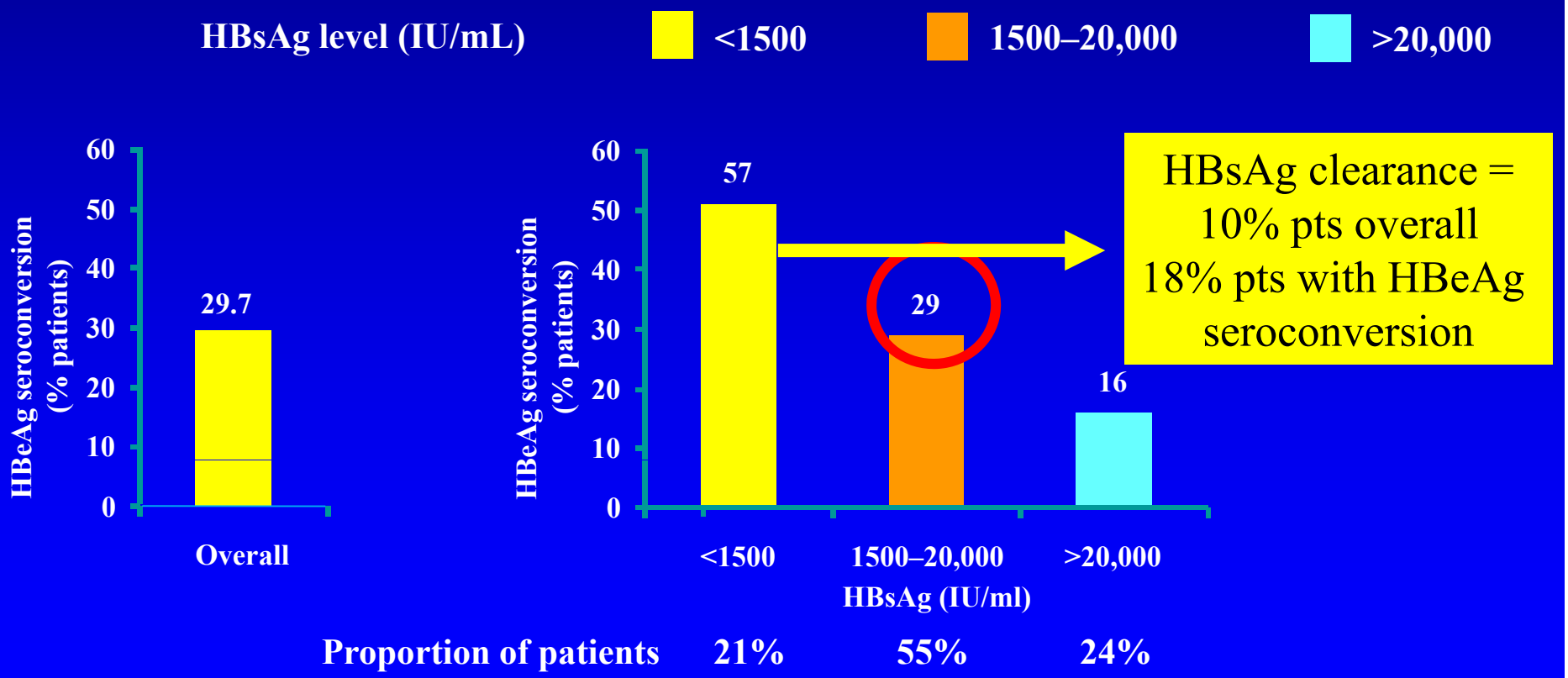
  HBsAg level 3.6 log IU/ml

  HBV DNA 5.1 log IU/ml

How can HBsAg and HBV DNA be used in management of HBeAg-positive CHB?

HBsAg level at week 12 is associated with 6 months post-peginterferon alfa2a treatment response

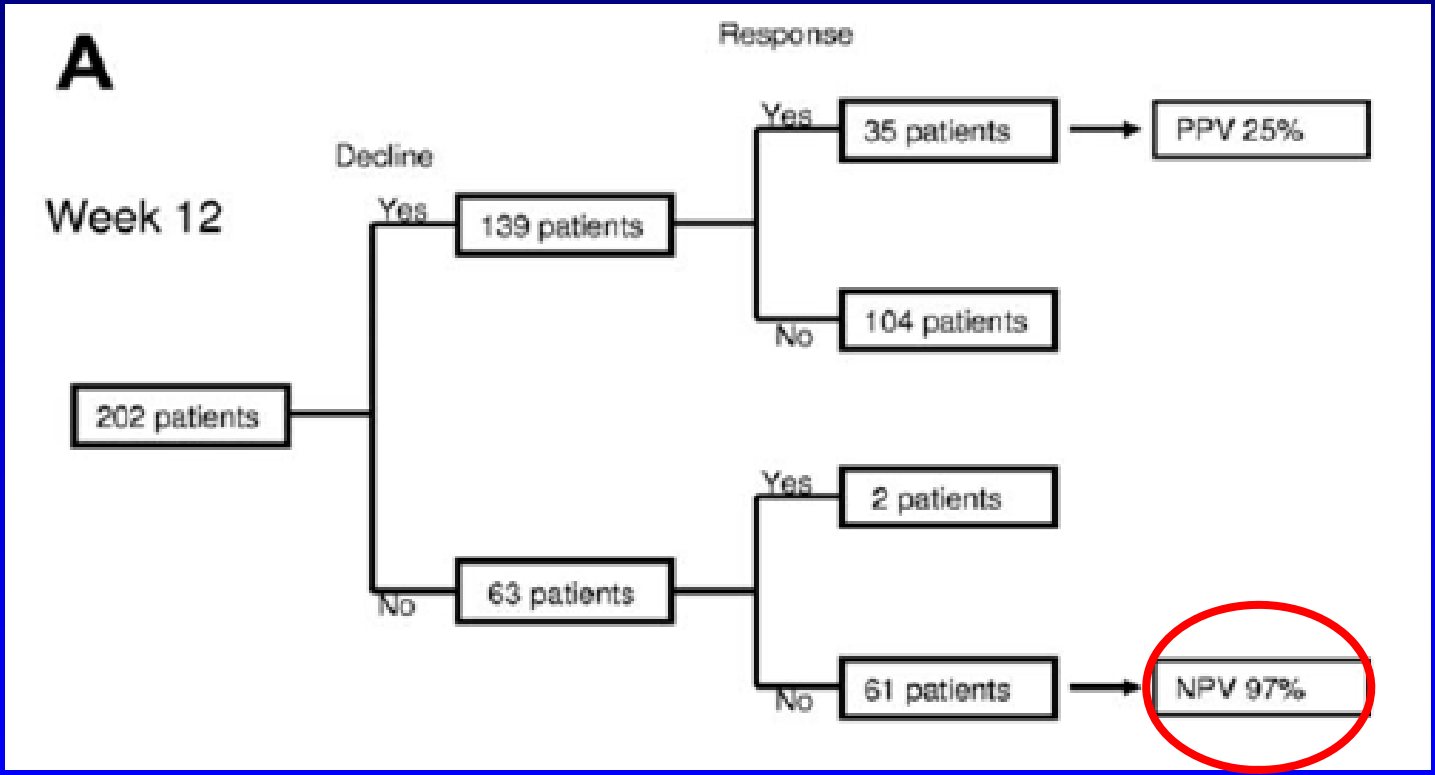
HBsAg < 1,500 IU/ml at week 12 provides PPV 57% , NPV 72% for HBeAg seroconvertion 6 months post therapy



HBeAg-positive patients

Lau et al. AASLD 2008 Piratvisuth et al. APASL 2010

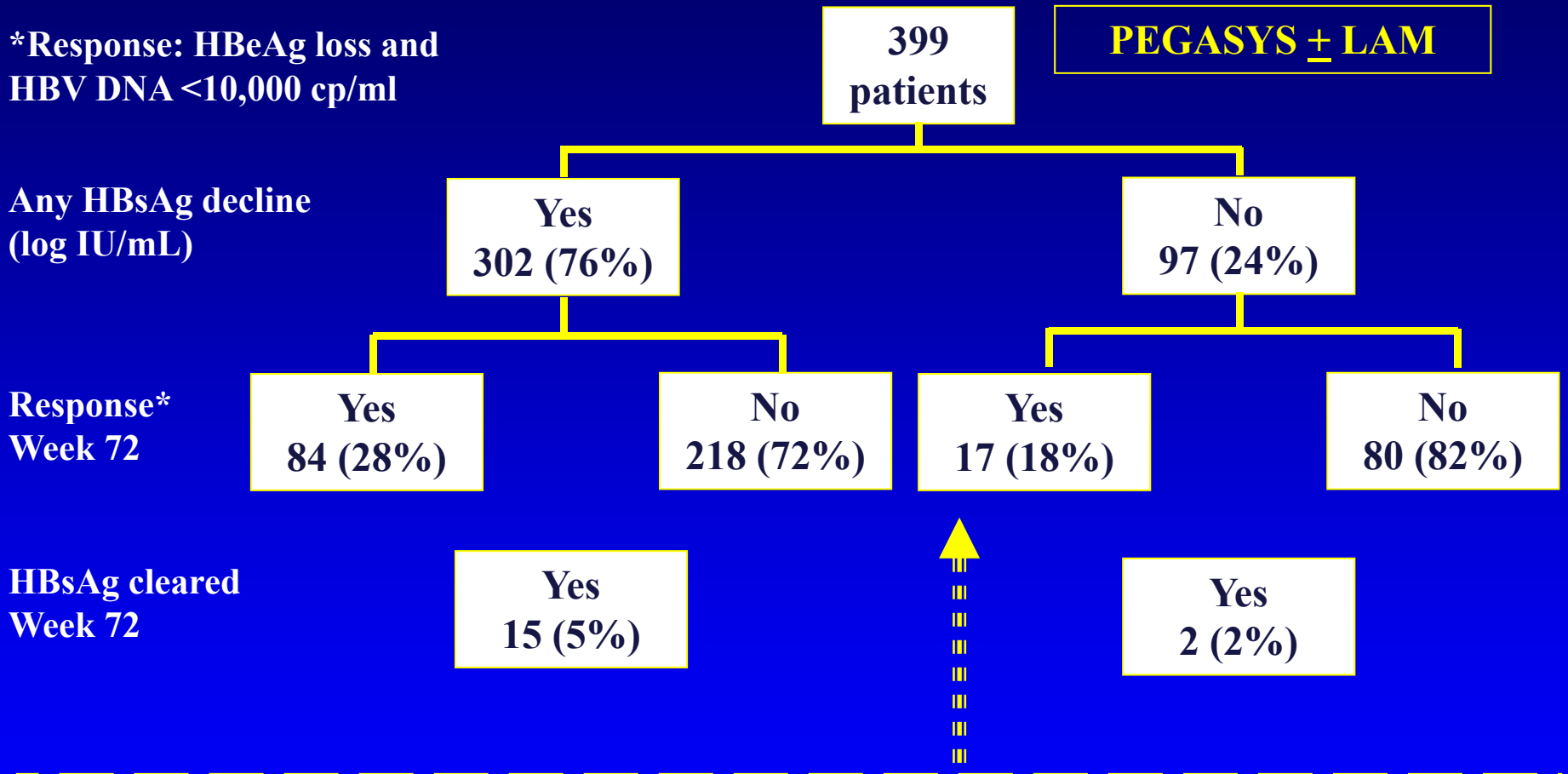
Decline in serum HBsAg levels from baseline at week 12 is associated with sustained response* 26 weeks post PegIFN alfa-2b in HBeAg-positive CH-B



Response* = HBeAg loss and HBV DNA < 2,000 IU/ml

Sonneveld M. et al. Hepatology. 2010;52(4): 1251-1257.

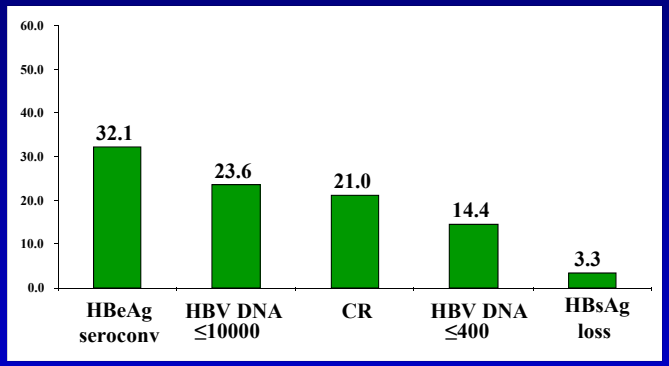
Peginterferon alfa-2a study analysis



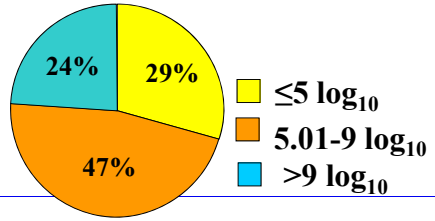
Piratvisuth & Marcellin in press

How good is HBV DNA at week 12 as a decision tool? PEG IFN alfa-2a monotherapy

All patients



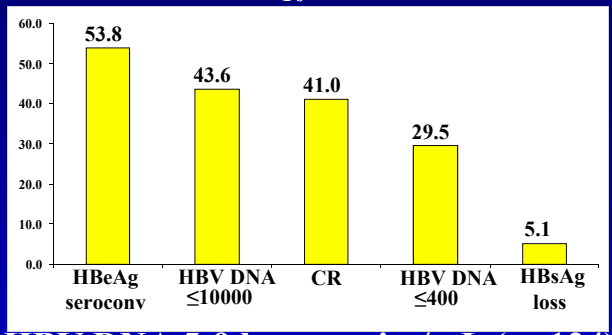
HBV DNA at WEEK 12 (PEG IFN



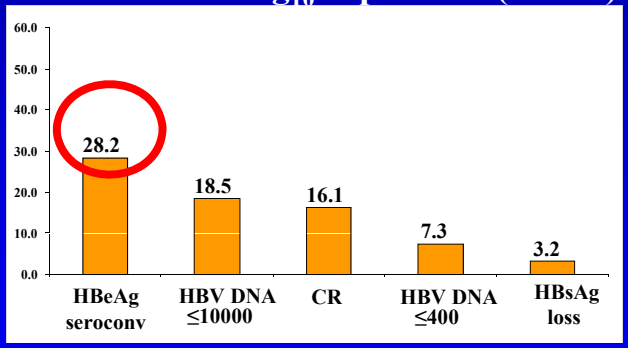
CR=HBeAg seroconversion + HBV DNA ≤ 10,000 copies/mL

Lau,Piratvisuth et al. AASLD 2008

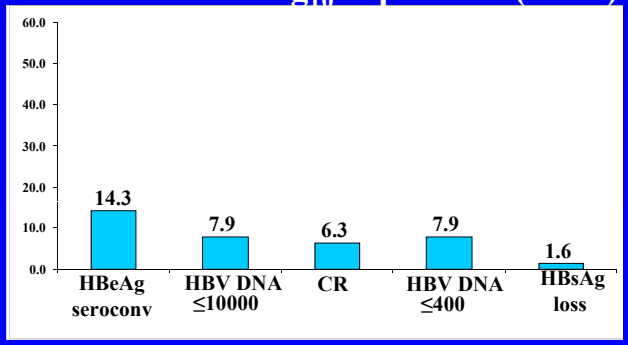
HBV DNA <5 log_{10} copies/mL (n=78)



HBV DNA 5-9 log_{10} copies/mL (n=124)

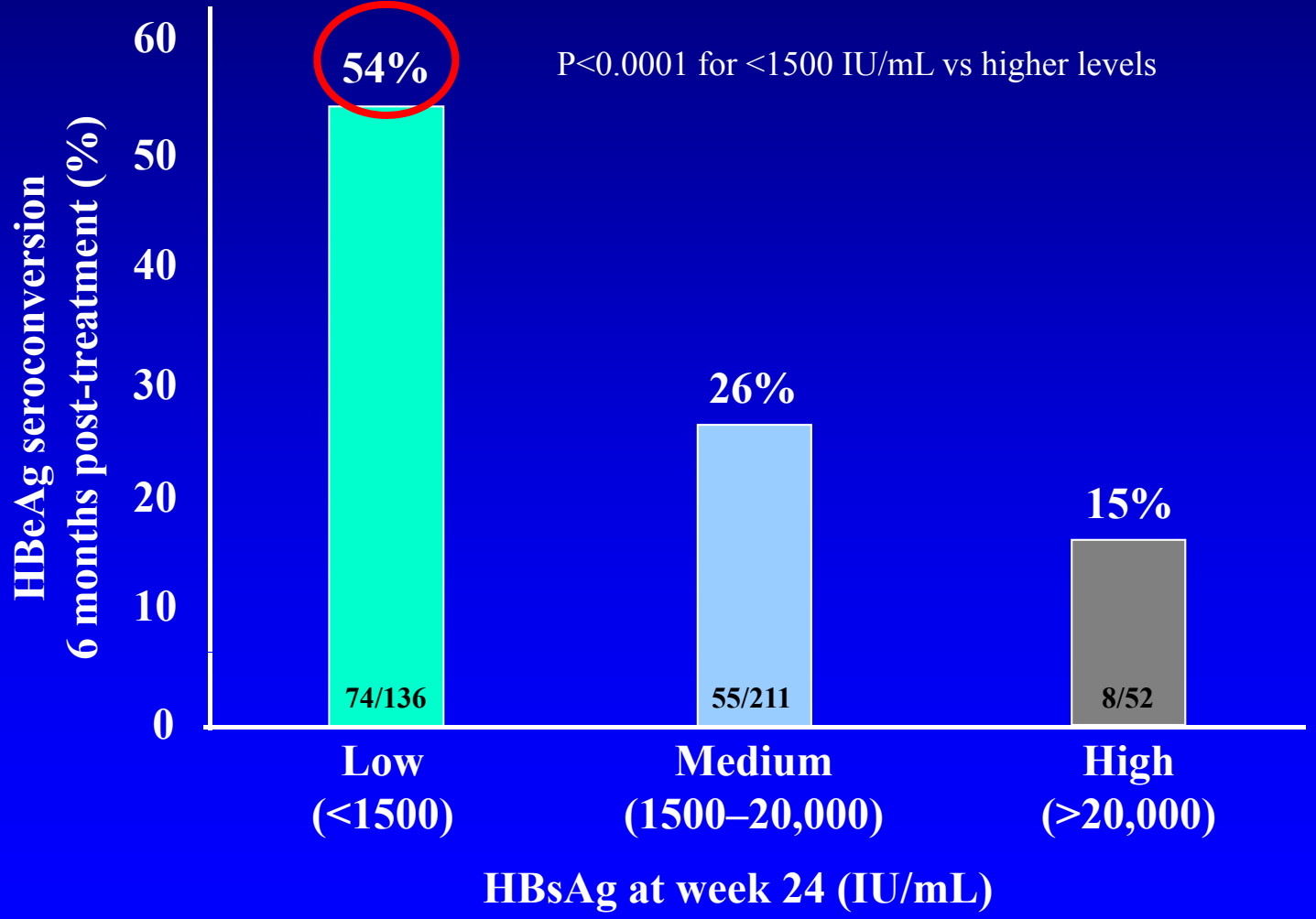


HBV DNA >9 log_{10} copies/mL (n=63)



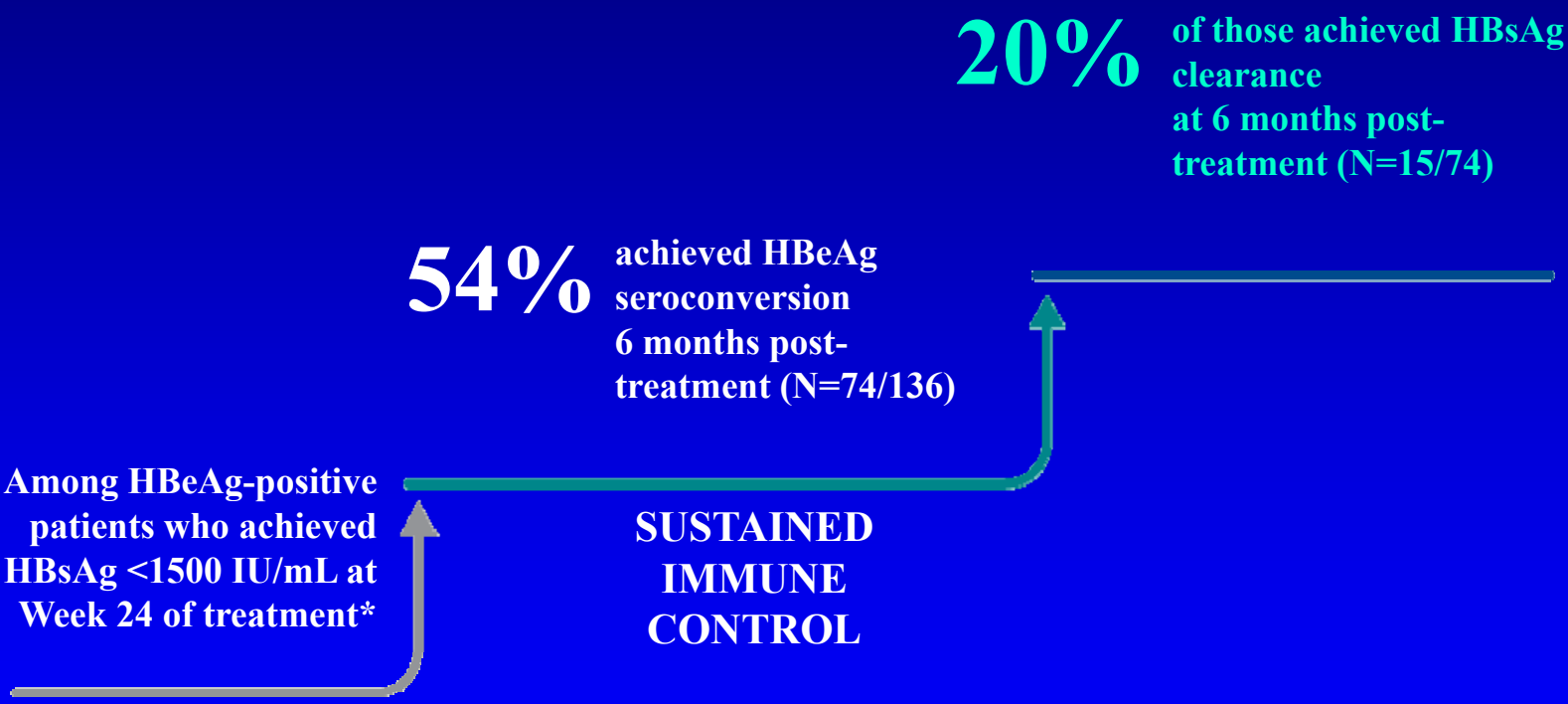
Lowest HBsAg levels at week 24 are associated with highest rate of sustained immune control in HBeAg-positive CHB

HBsAg < 1,500 IU/ml at week 12 provides PPV 54% , NPV 75% for HBeAg seroconvertion 6 months post therapy



Piratvisuth et al. APASL 2010

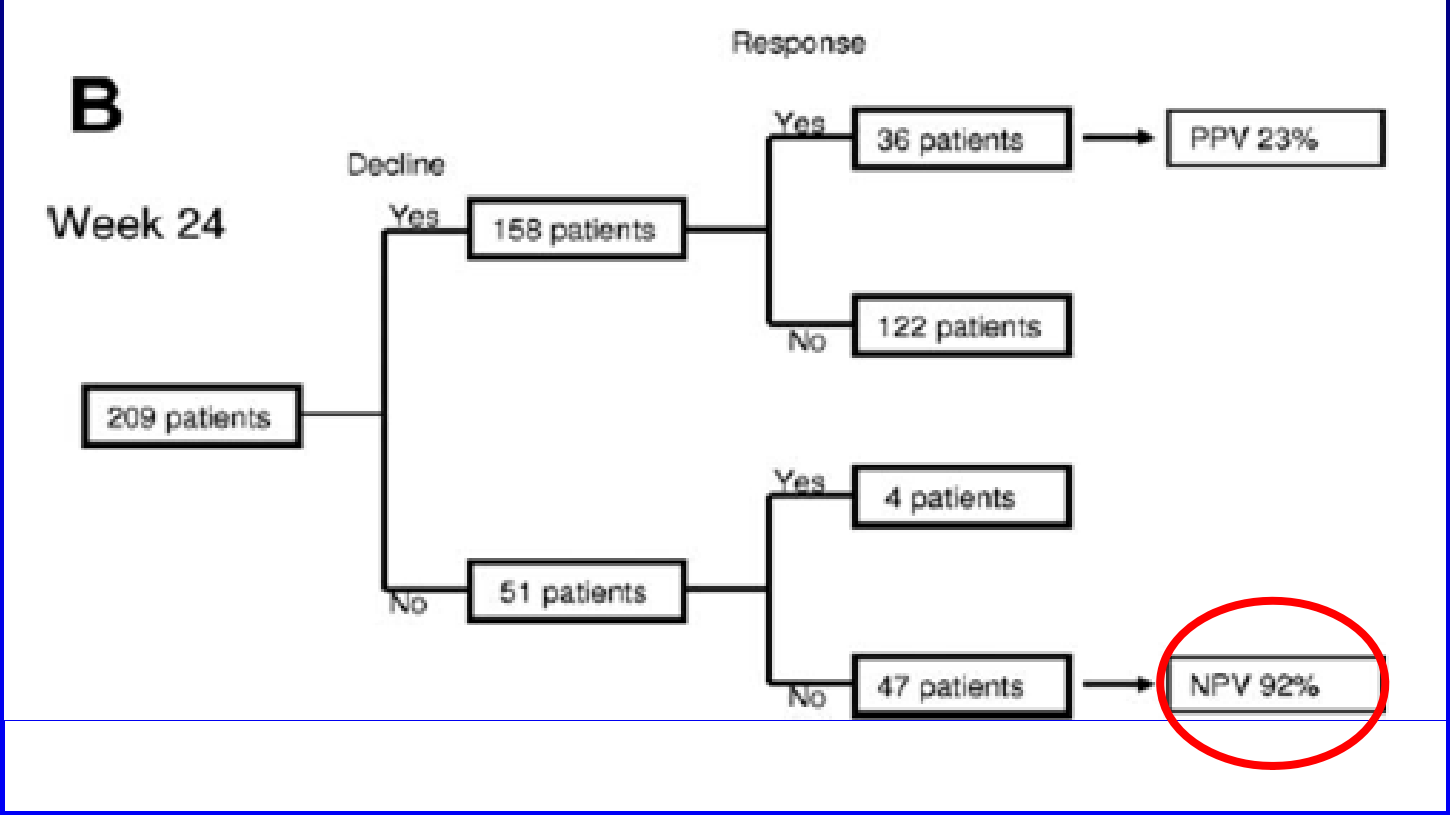
HBsAg reduction at week 24 is an early sign of future HBsAg clearance in HBeAg-positive CHB



*34% of patients (136/399) achieved HBsAg <1500 IU/mL at week 24

Piratvisuth et al. APASL 2010

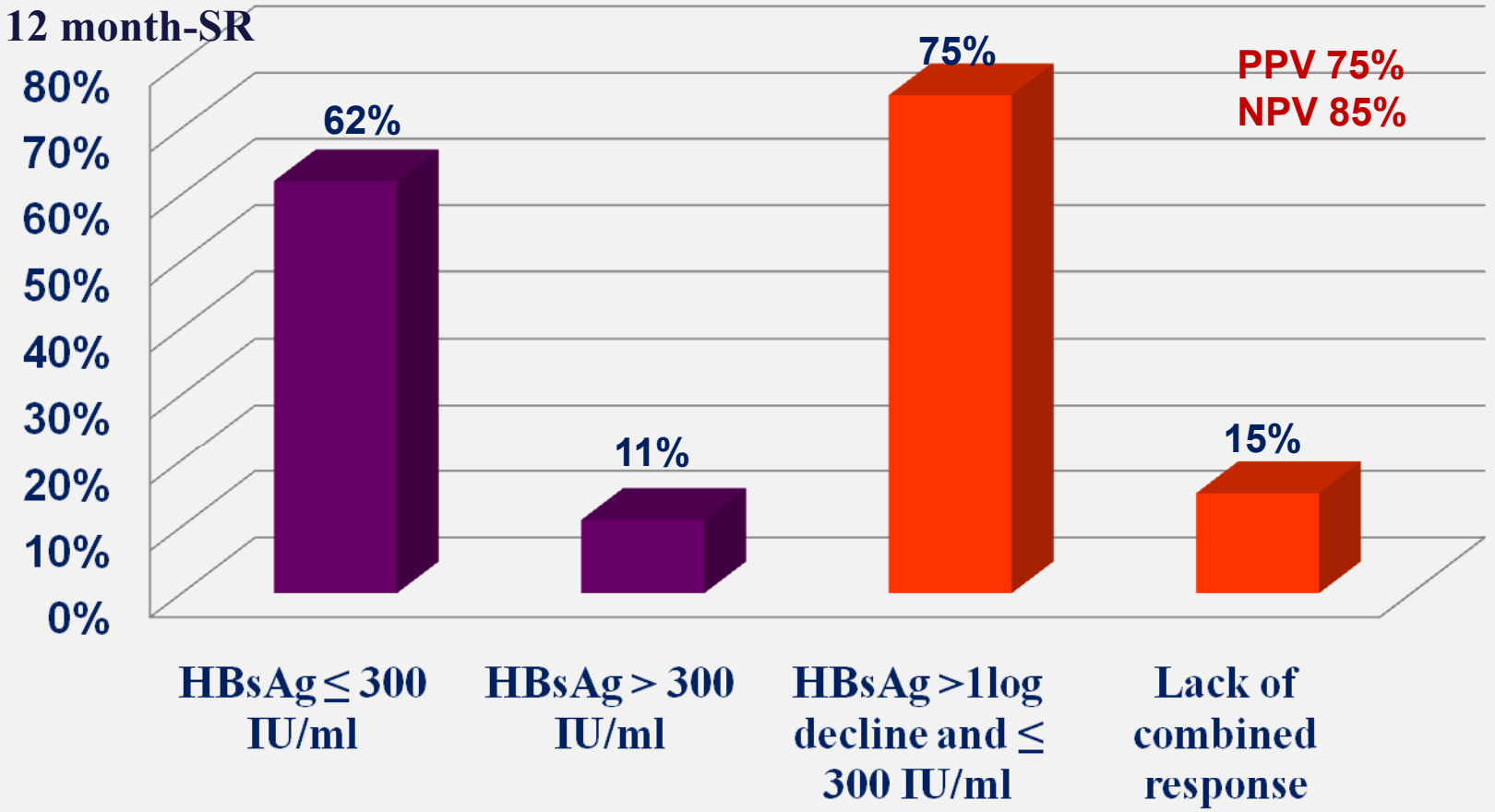
Decline in serum HBsAg levels from baseline at week 24 is associated with sustained response* 26 weeks post PegIFN alfa-2b in HBeAg-positive CH-B



Response* = HBeAg loss and HBV DNA < 2,000 IU/ml

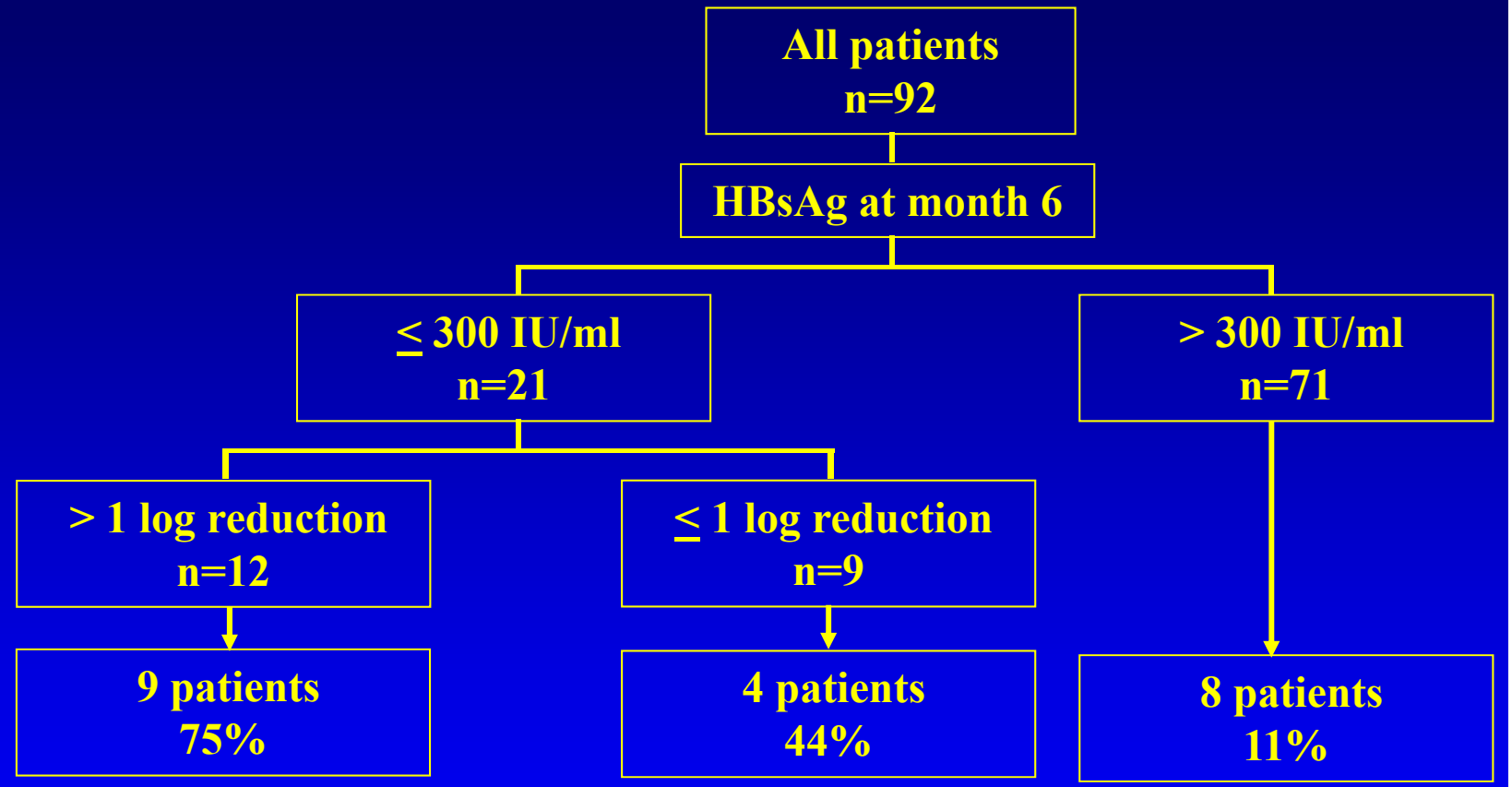
Sonneveld M. et al. Hepatology. 2010;52(4): 1251-1257.

HBsAg at month 6 in prediction of 12 month sustained response post peginterferon and/or lamivudine treatment



Chan HL et al. Aliment Pharmacol Ther 2010; 32: 1323

Combined algorithm using HBsAg level of 250 IU/mL and reduction of HBsAg by greater than 1 log IU/mL at month 6 to predict sustained response (SR)



Recommendation	Continue peginterferon	? Extend duration of peginterferon treatment	? Switch to or combine with nucleos(t)ide analogs

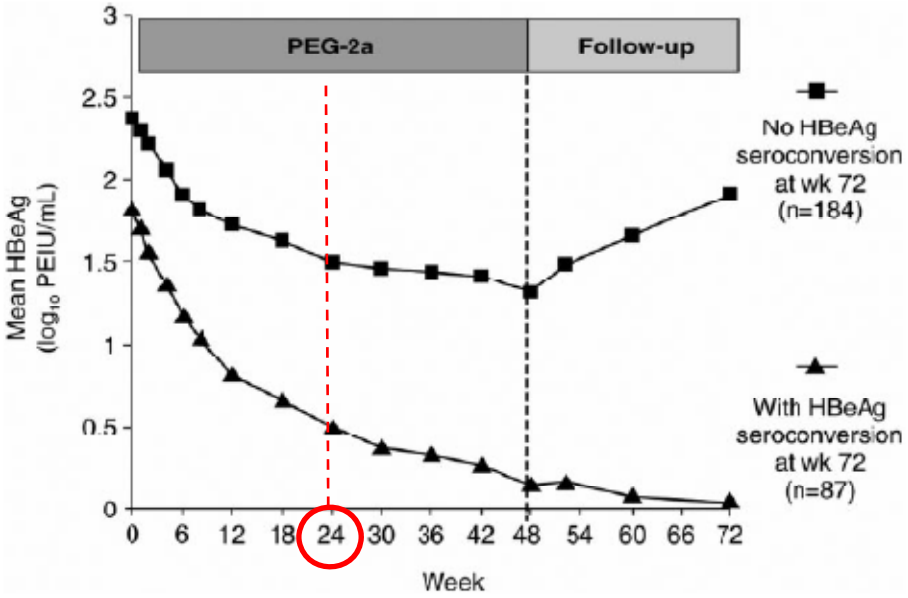
SR: HBeAg seroconversion and HBV DNA < 10,000 cps/ml sustained until 12 months post-treatment

Chan H. L-Y. et al. Aliment Pharmacol Ther. 2010;32:1323-1331.

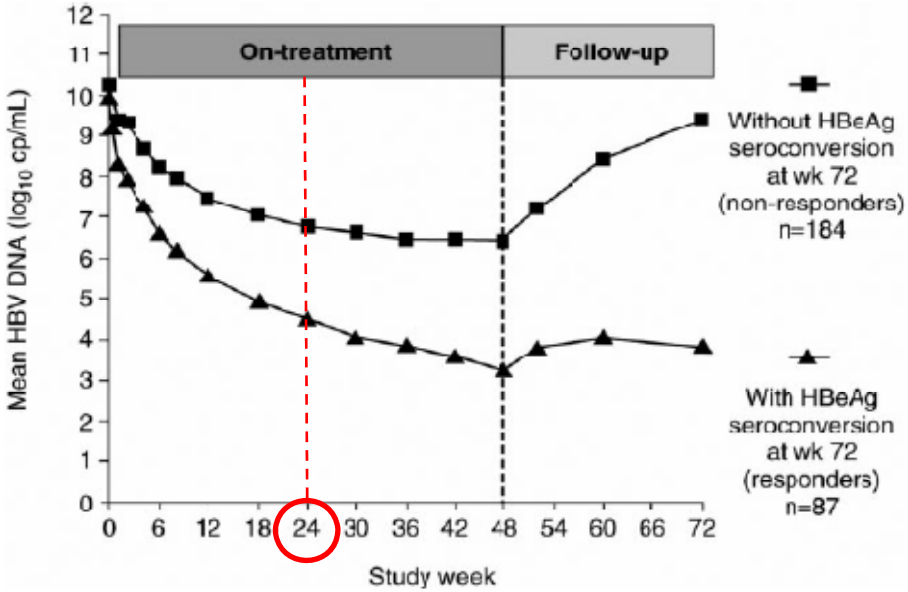
Prediction of response to PEGASYS:

HBeAg vs HBV DNA

Mean HBeAg (PEIU/ml)



Mean HBV DNA (log cp/ml)



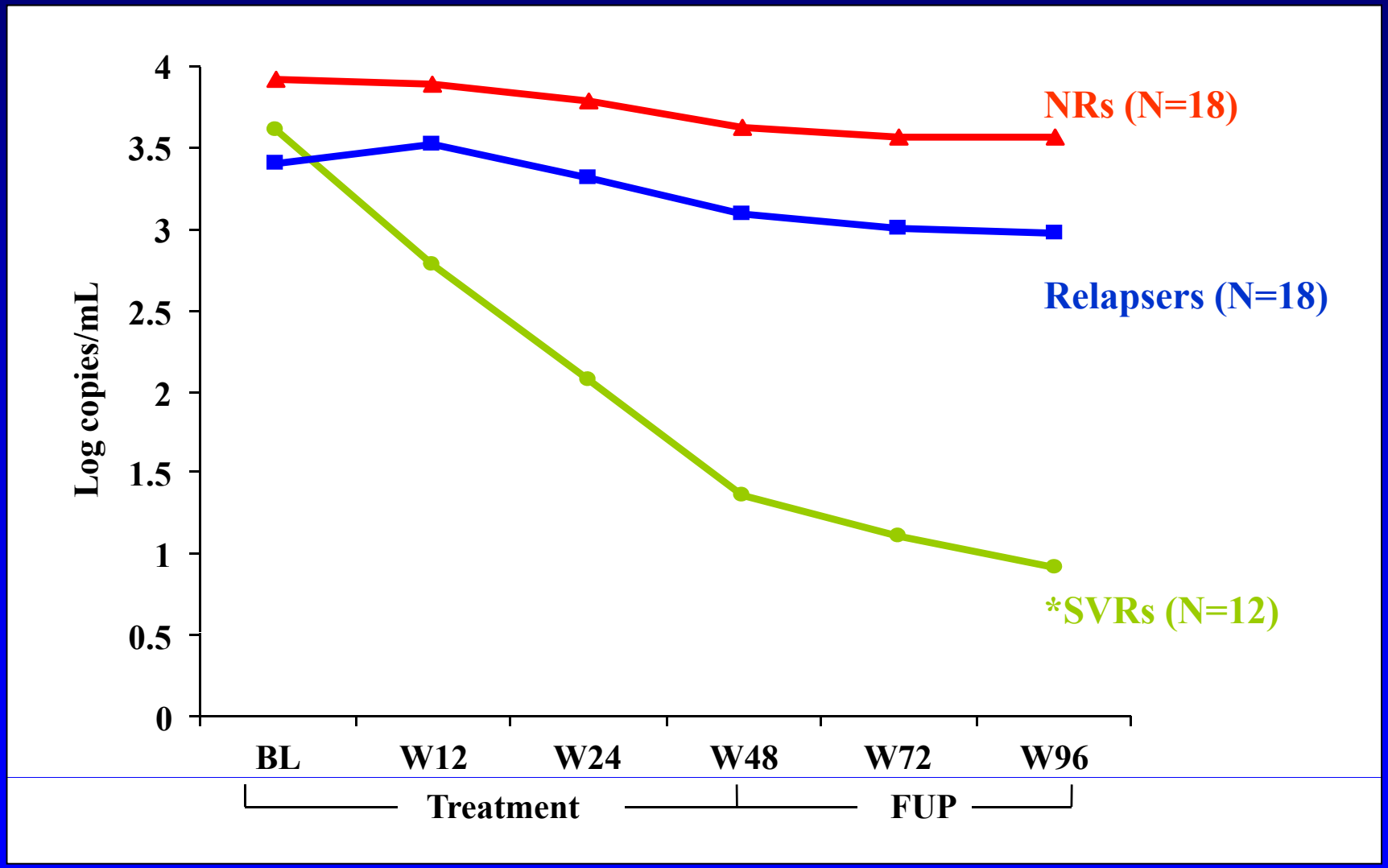
Week 24:

HBeAg >100 U/ml: NPV 96%

HBV DNA > 9 log: NPV 86%

Fried ,Piratvisuth et al, *Hepatology* 2008

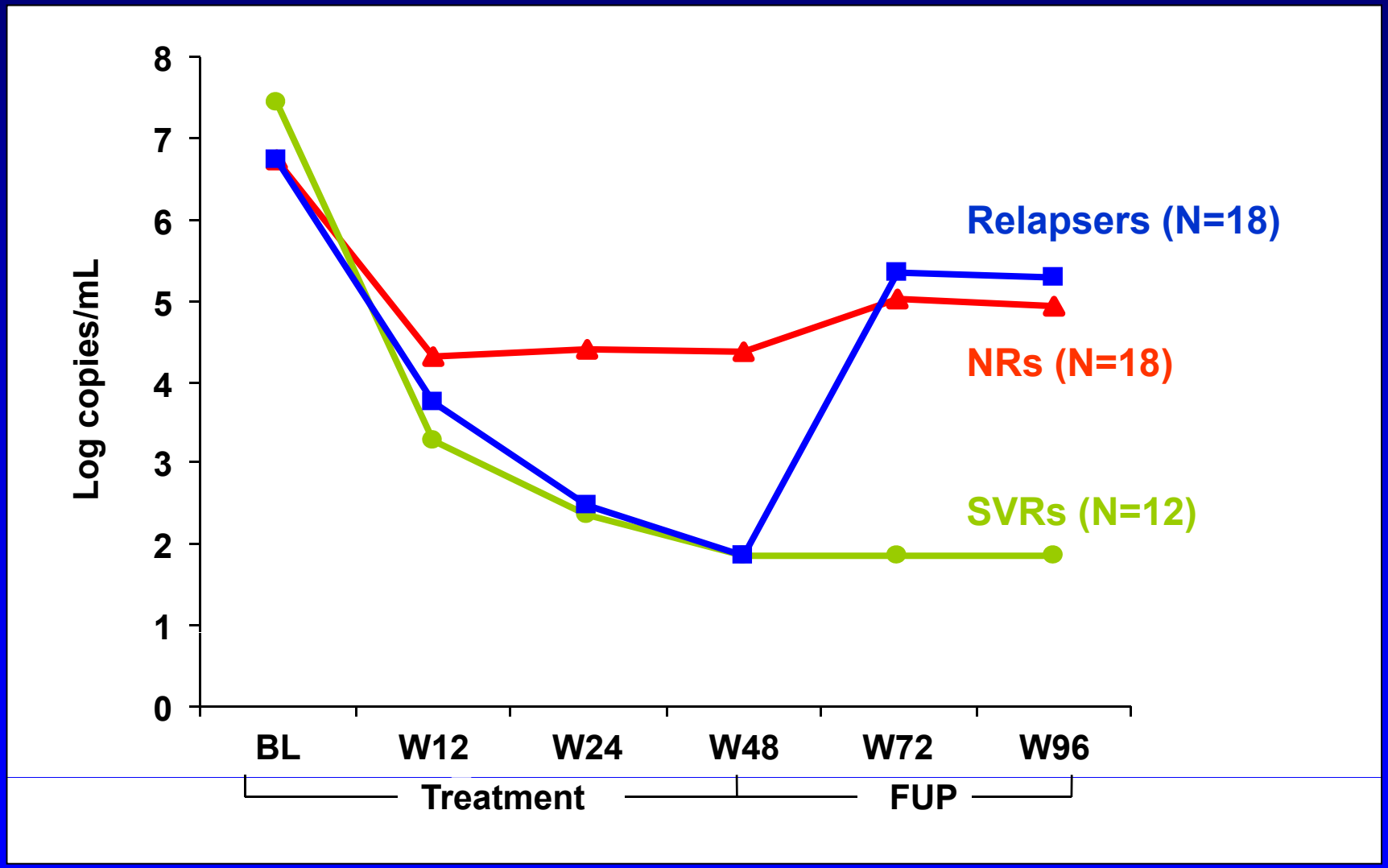
On-treatment HBsAg decline can distinguish between relapsers and responders



*HBV DNA nondetectable by PCR 1 year post-treatment

Moucari R et al. Hepatology 2009

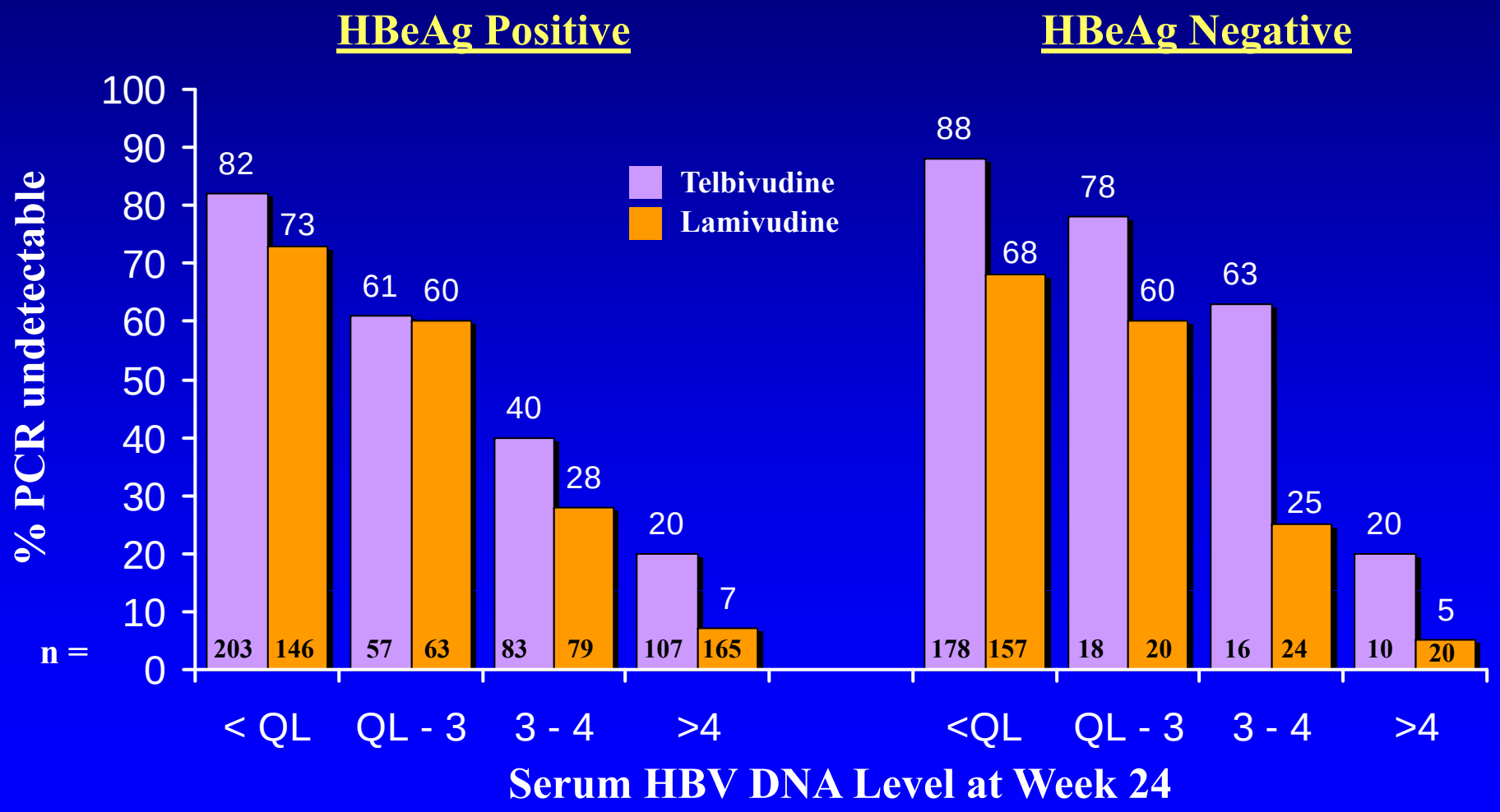
On-treatment HBV DNA decline is similar in sustained responders and relapsers



Moucari R et al. Hepatology 2009

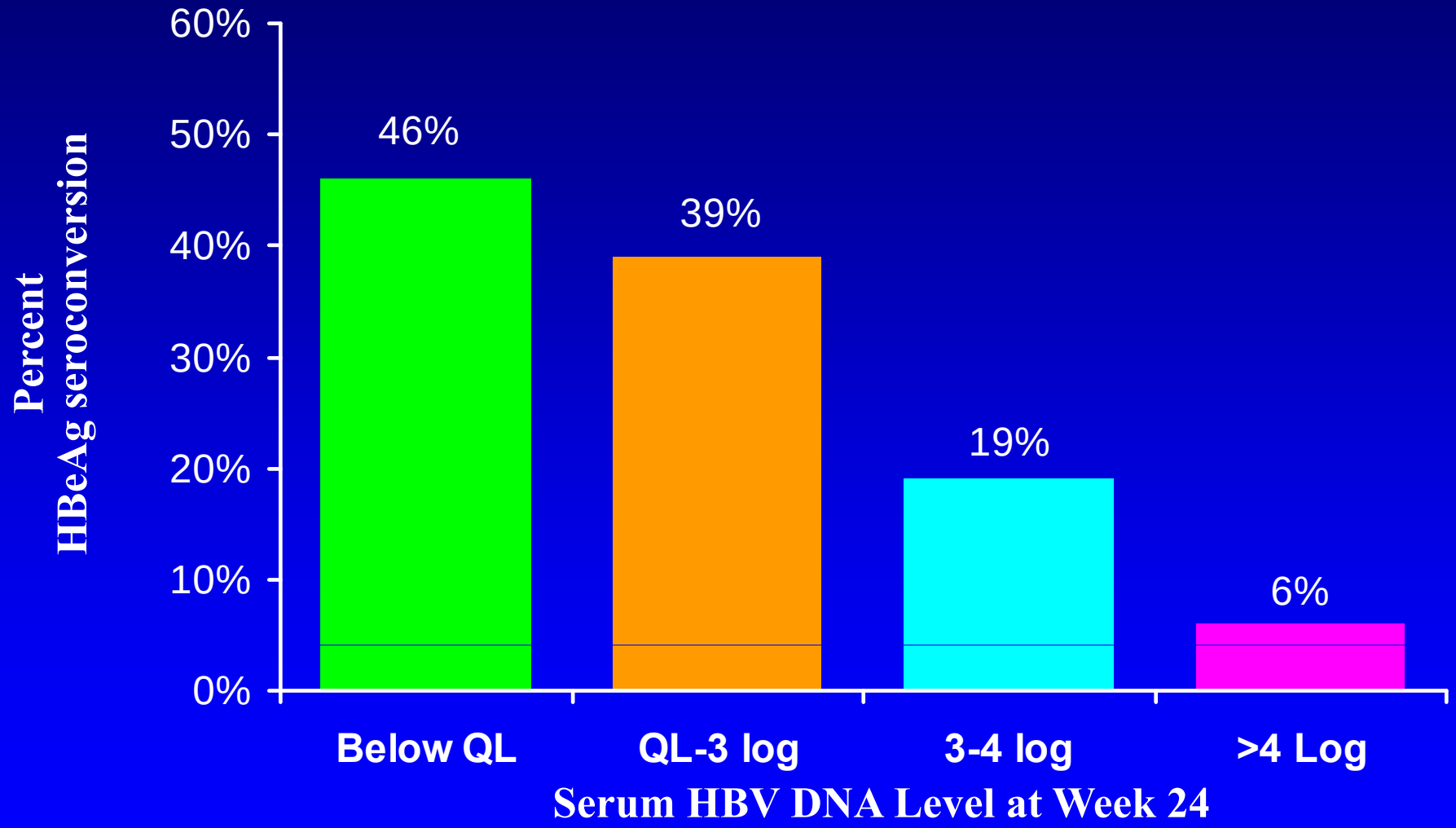
HBV DNA Suppression at 2 Years vs. Antiviral Effect at Week 24

By Treatment Group



Liaw YF. et al. Gastroenterology 2009;136:486-495.

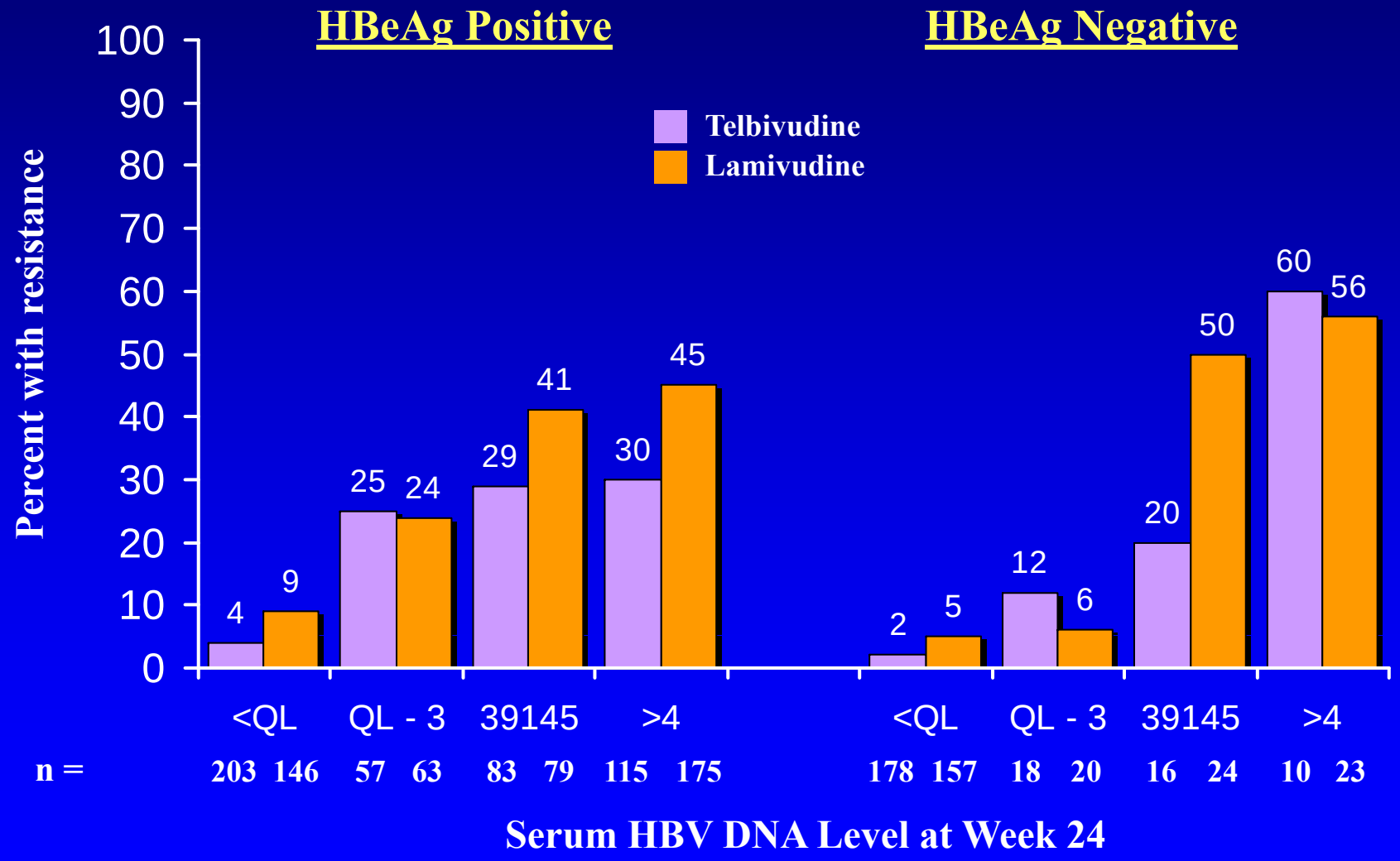
HBeAg Seroconversion at 2 Years vs. Antiviral Effect at Week 24



HBeAg Positive Patients, Combined Treatment Groups (Lam or LdT).

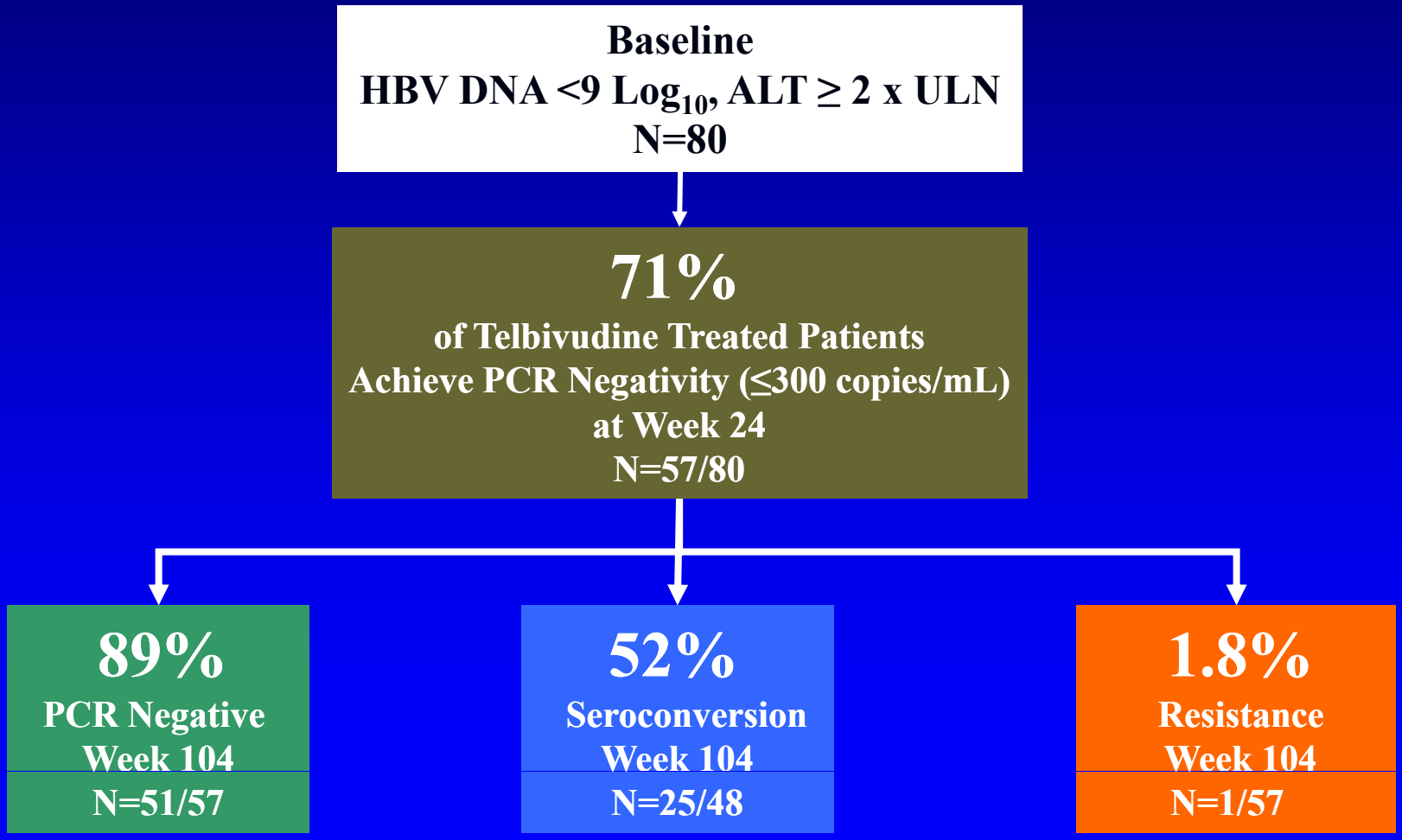
Liaw YF. et al. Gastroenterology 2009;136:486-495.

Viral Resistance at 2 Years vs. Antiviral Effect at Week 24



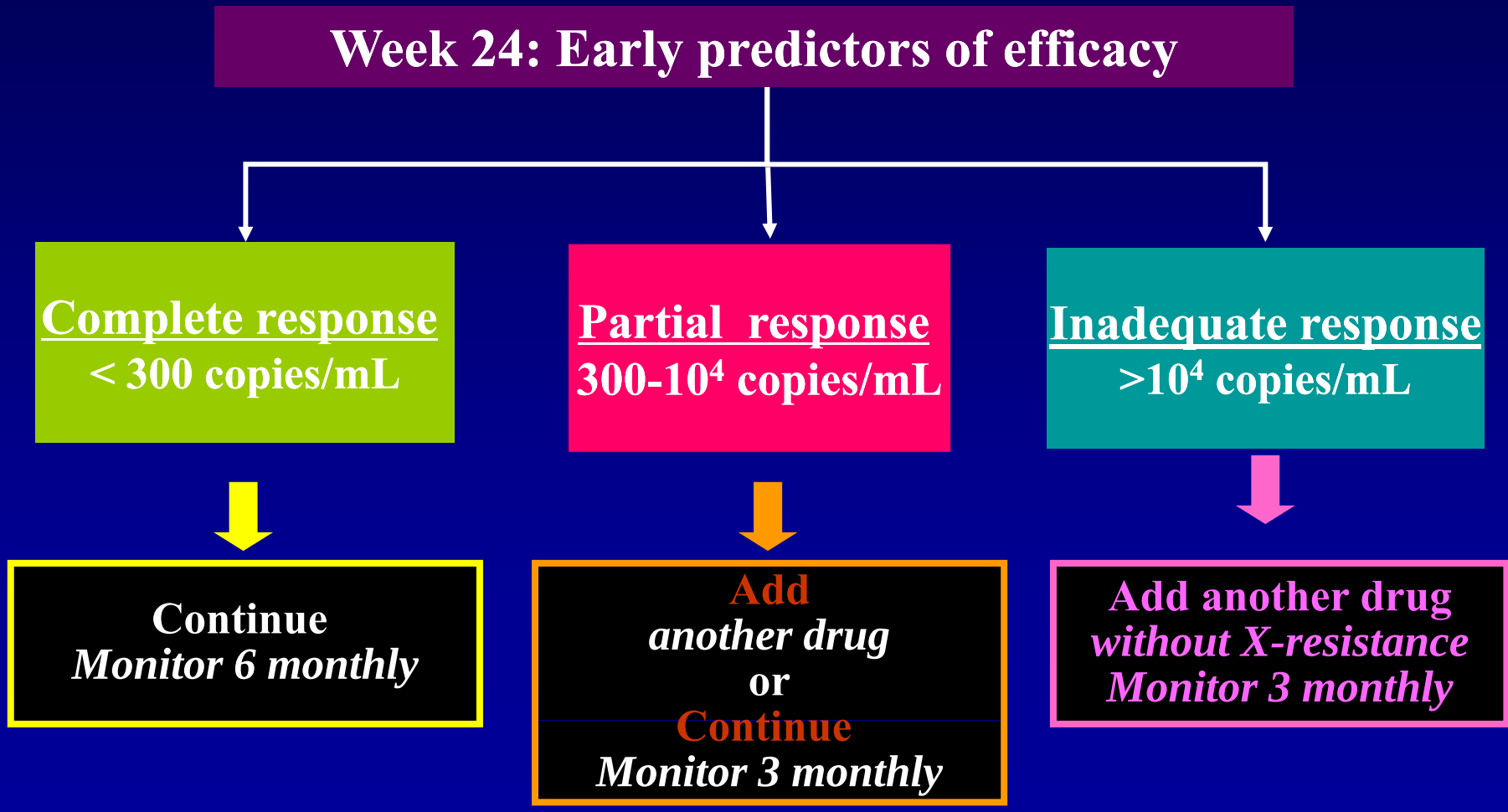
Liaw YF. et al. Gastroenterology 2009;136:486-495.

Telbivudine Is A Good Option for 1st Line Therapy for HBeAg-Positive Patients



Zeuzem S, et al. AASLD 2007 - Poster

Management Algorithm According to 24 Week Virologic Response



Rapid Decline in HBsAg Between Baseline and week 24 Was Predictive for HBsAg Loss at Year 3 With Telbivudine

	HBeAg+ Patients n = 162		HBeAg– Patients n = 143	
	No. of patients	No. of patients with HBsAg loss at year 3	No. of patients	No. of patients with HBsAg loss at year 3
Rapid decline ($\geq$0.5 $\log_{10}$ IU/mL), n/N%	53/162 (33%)	7/53 (13%)	11/143 (8%)	1/11 (9%)
Slow decline (0–0.5 $\log_{10}$ IU/mL), n/N%	48/162 (30%)	2/48 (4%)	59/143 (41%)	1/59 (2%)
Steady levels ($\leq$0 $\log_{10}$ IU/mL), n/N%	61/162 (38%)	0/61 (0%)	73/143 (51%)	0/73 (0%)
Total, n/N%	162/162 (100%)	9/162 (6%)	143/143 (100%)	2/143 (1%)
***P*-value**		0.024		0.036

Wursthorn K, et al. *Hepatology* 2009;50:536A (abstract 487).

Rapid Decline in HBsAg Between Baseline and Year 1 Was Predictive for HBsAg Loss at Year 3 With Telbivudine

	HBeAg+ patients n = 162		HBeAg– patients n = 143	
	No. of patients	No. of patients with HBsAg loss at year 3	No. of patients	No. of patients with HBsAg loss at year 3
Rapid decline (≥1 $\log_{10}$ IU/mL), n/N%	32/162 (20%)	8/32 (25%)	5/143 (4%)	1/5 (20%)
Slow decline (0–1 $\log_{10}$ IU/mL), n/N%	74/162 (46%)	1/74 (1.4%)	70/143 (49%)	1/70 (1.4%)
Steady levels (≤0 $\log_{10}$ IU/mL), n/N%	56/162 (35%)	0/56 (0%)	68/143 (48%)	0/68 (0%)
Total, n/N%	162/162 (100%)	9/162 (6%)	143/143 (100%)	2/143 (1%)
***P*-value**		<0.0001		0.0176

Wursthorn K, et al. *Hepatology* 2009;50:536A (abstract 487).

- **At week 48 : bilirubin 0.1/0.6 mg/Dl**
  AST 28 IU/L ALT 26 IU/L
  ALP 109 IU/L Alb 4.8 gm/dL
  HBsAg level 0.5 log IU/ml
  HBV DNA : undetected
  HBeAg negative antiHBe positive

Conclusion

- Serum HBsAg level or decline can predict sustained response and HBsAg clearance post Peginterferon treatment but currently only insufficient data for NA therapy (telbivudine).

- On-treatment HBsAg level or decline can predict patients with sub-optimal response who will not achieve satisfactory response despite continuing treatment.

- Further study to define the cut-off level and to validate the predictive value across HBV genotype as well as to identify the strategy for management of those who have sub-optimal response is required.

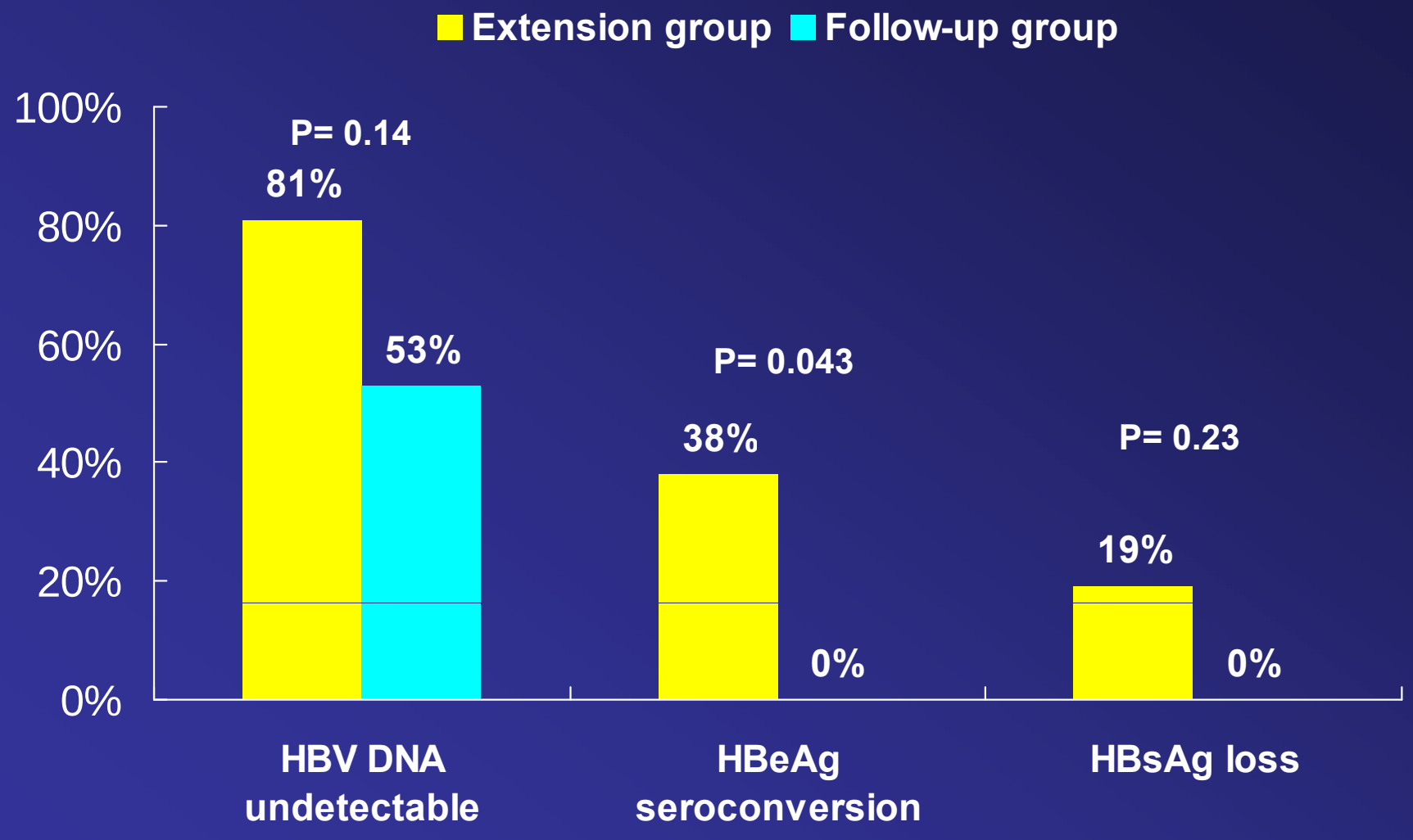
- Serum HBV DNA provides complimentary information to HBsAg level and more important in NA treatment as it can predict virological and serological response as well as drug resistance after long-term NA therapy.

Extending treatment duration with PEGASYS in HBeAg-positive disease

- N=31 patients with partial response to PEGASYS at week 48
  - HBV DNA suppression $<10^5$ copies/mL without HBeAg seroconversion
  - Received either:
    - Further 24 weeks of PEGASYS (= extension group)
    - No further treatment

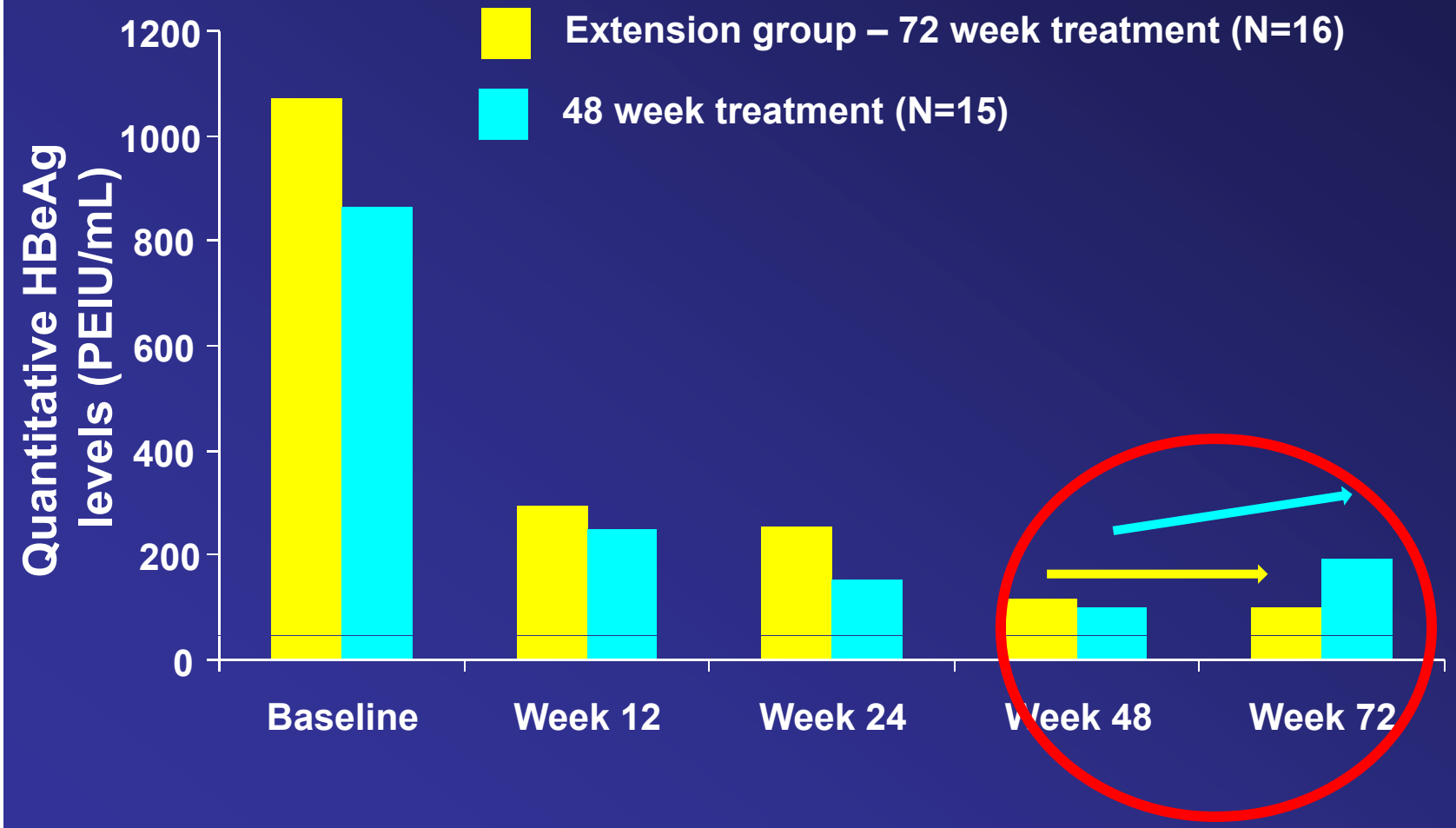
Jiang et al. data on file

Extended treatment is associated with better virological response at week 72



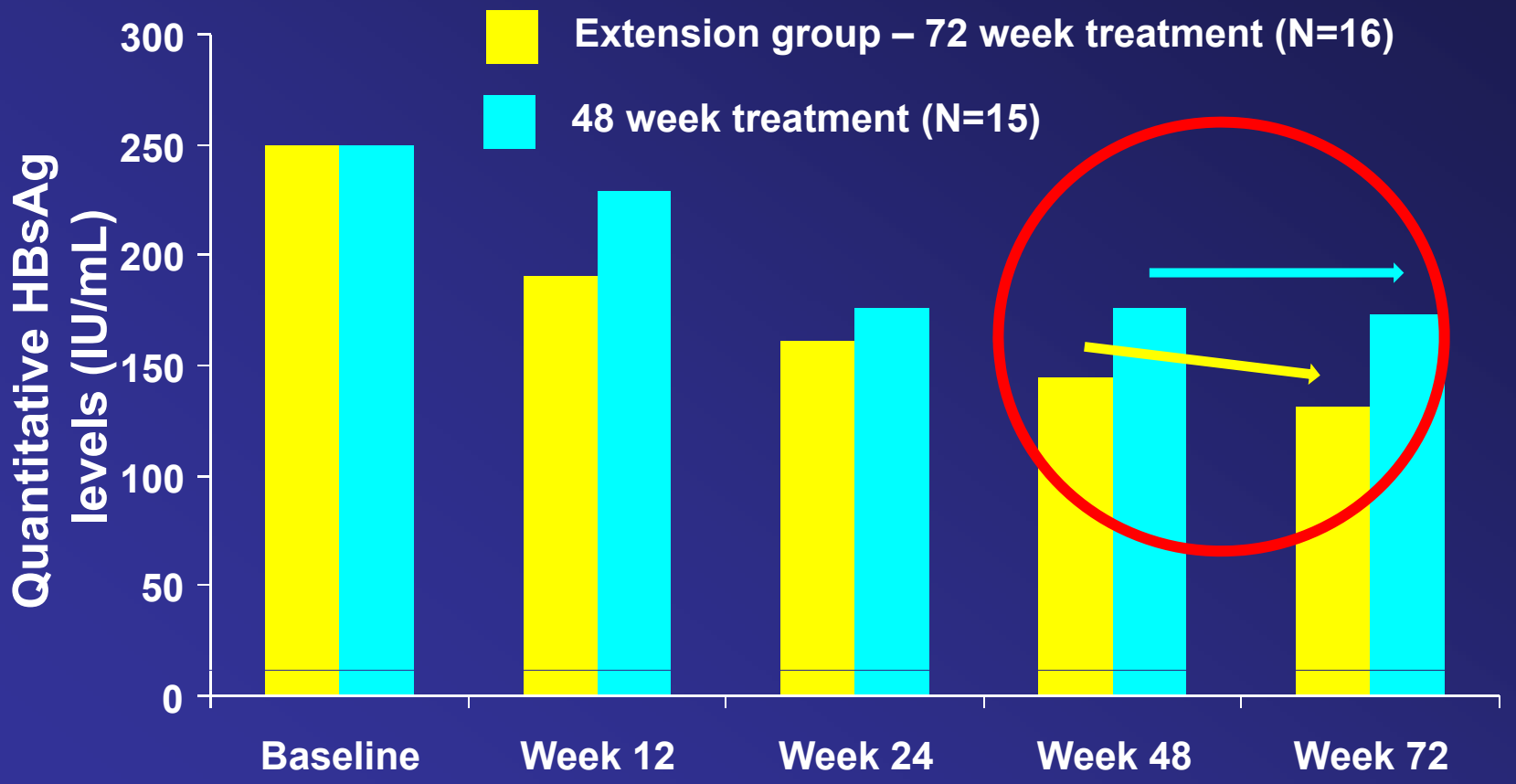
Jiang et al. data on file

Extended treatment keeps HBeAg level down



Jiang et al. data on file

Extended treatment leads to further decline in HBsAg

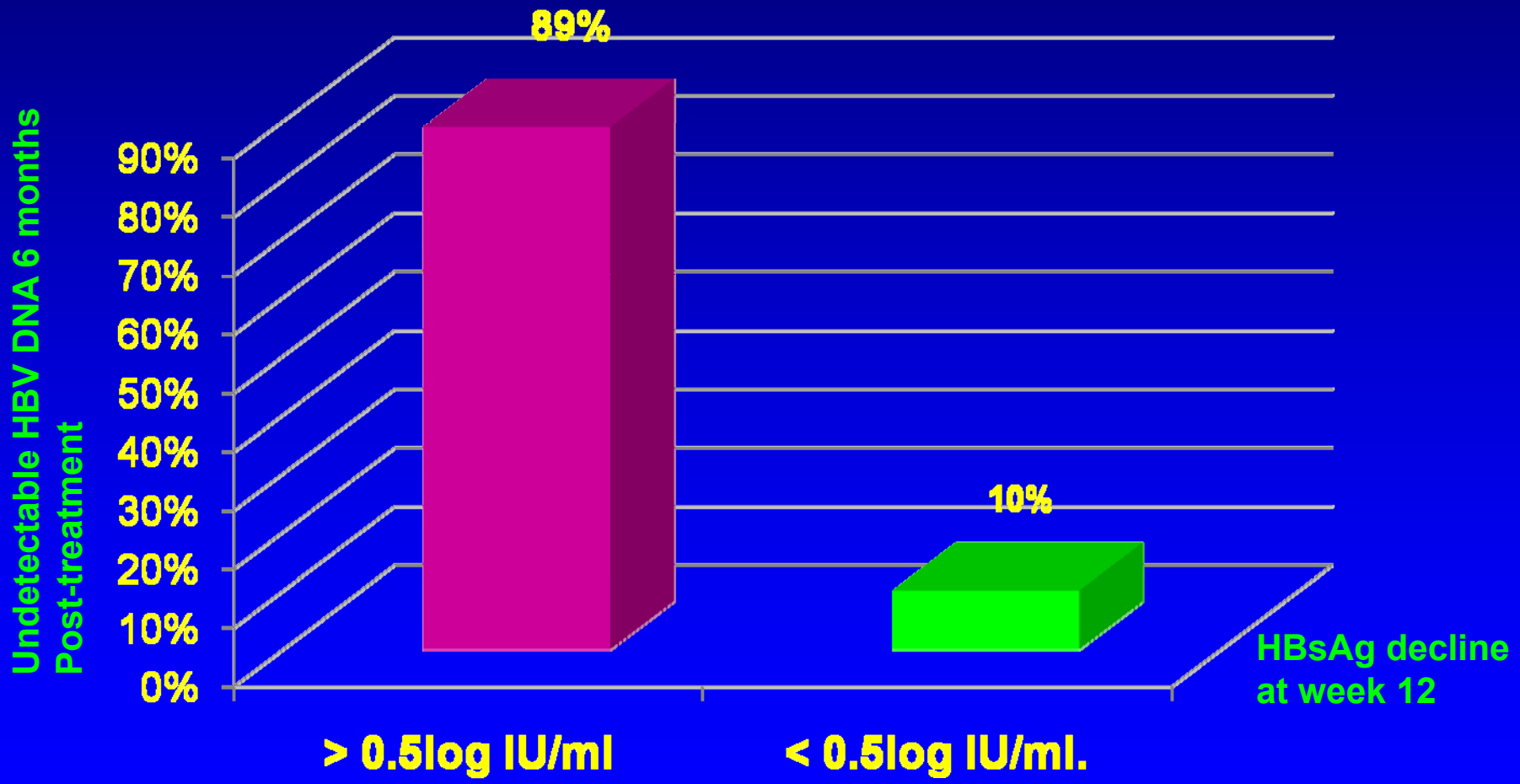


Jiang et al. data on file

HBeAg negative : active CH-B vs. inactive carriers

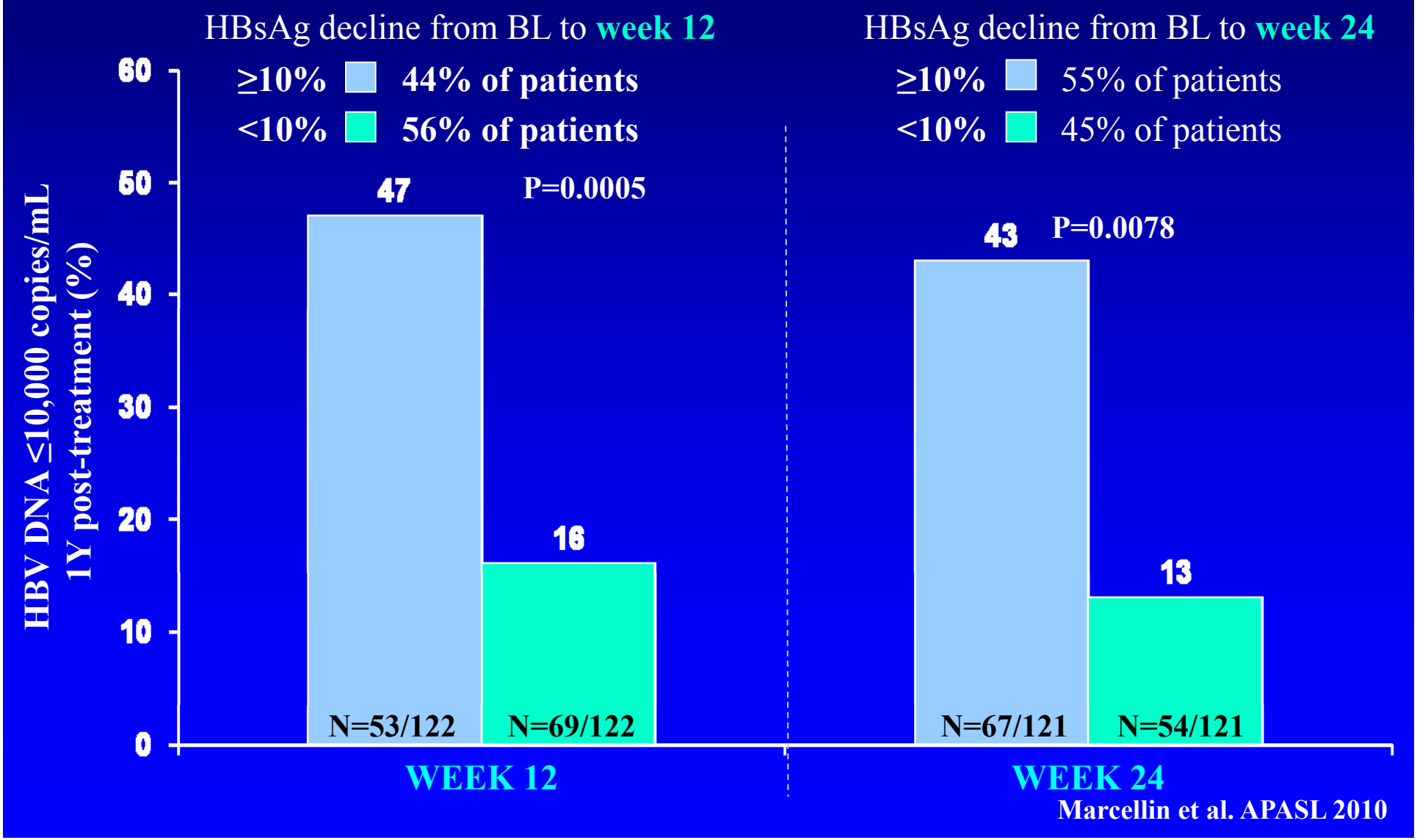
	Prediction of inactive carriers	
	PPV	NPV
HBsAg < 1,000 IU/ml HBV DNA < 2,000 IU/ml (Brunetto 2010)	87.9%	96.7%
HBsAg < 1,000 IU/ml HBV DNA < 400 IU/ml (Matinot-Peignoux 2010)	97%	

HBsAg decline at week 12 pf peginterferon treatment is associated with post-treatment response in HBeAg negative



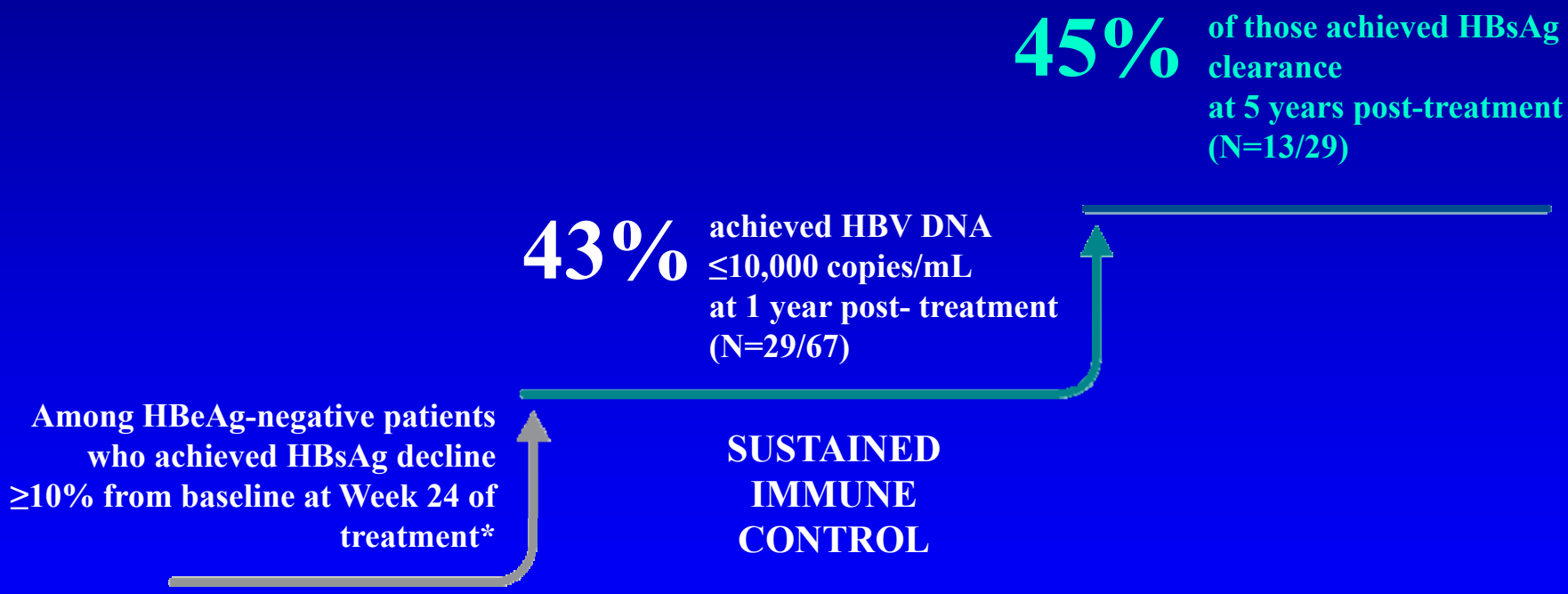
Moucari R et al. Hepatology 2009; 49: 1151-7

HBsAg decline is significantly associated with sustained immune control in HBeAg-negative disease



Marcellin et al. APASL 2010

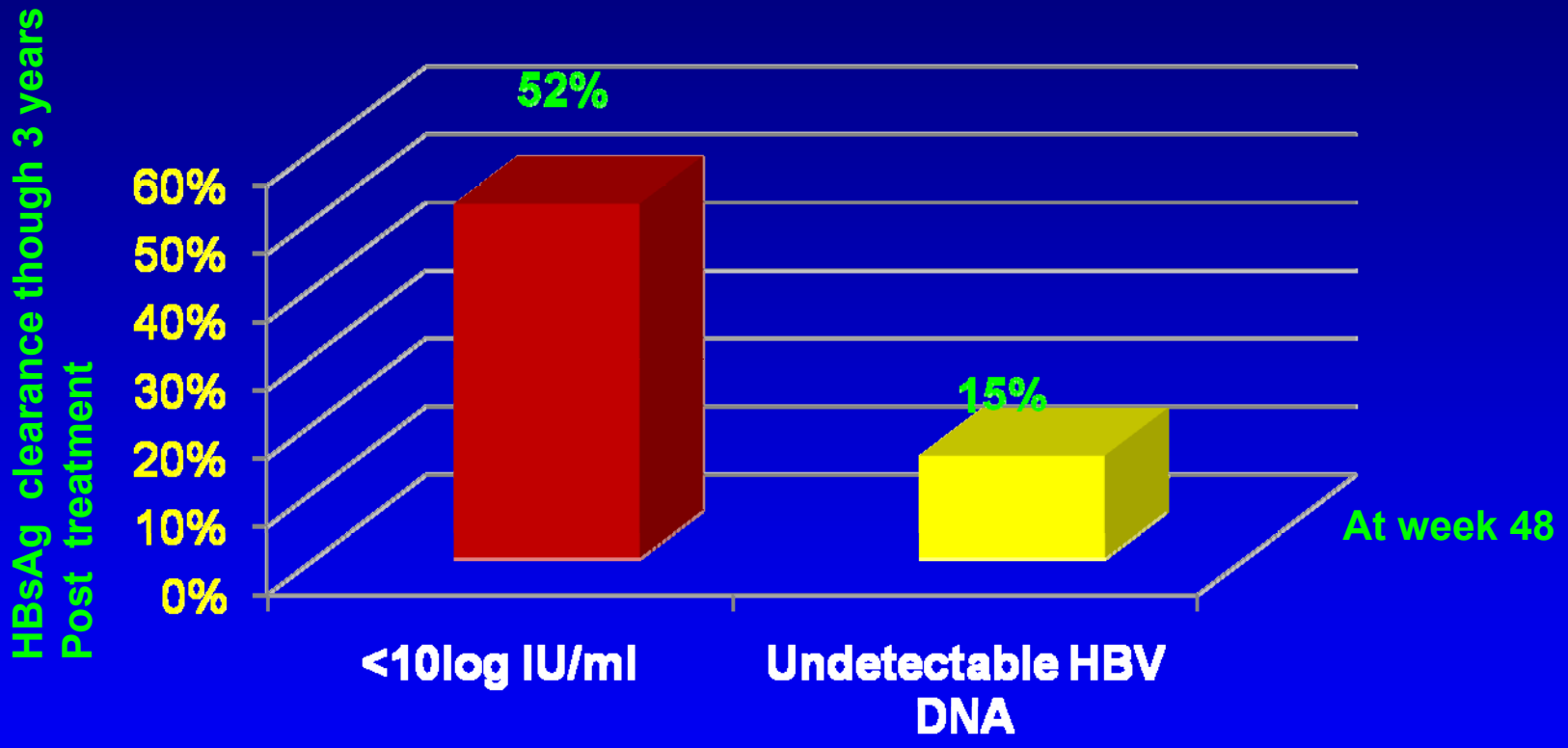
HBsAg reduction at week 24 is an early sign of future HBsAg clearance in HBeAg-negative



*56% of patients achieved HBsAg decline ≥10% at week 24

Marcellin et al. APASL 2010

HBsAg level at the end of 48-week pegIFN alfa-2a treatment provides a better prediction of HBsAg loss than HBV DNA



HBsAg level > 19 IU/ml or a decline from baseline < 0. 46log IU/ml had a low probability of sustained response

Brunetto MR et al. Hepatology 2009: 49: 1141-50
Marcellin, Piratvisuth et al. Hepatology Int 2010; 4: 151