

THE INFLUENCE OF TREATMENT ON THE NATURAL HISTORY OF CHRONIC HEPATITIS B

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SHORT TERM OBJECTIVES OF THERAPY IN CHRONIC HEPATITIS B

- Inhibit viral replication**
- Induce HBe seroconversion**
- Decrease liver necro-inflammation**
- Stop fibrosis progression**
- Induce fibrosis regression**

LONG TERM OBJECTIVES OF THERAPY IN CHRONIC HEPATITIS B

- Induce HBsAg loss/seroconversion**
 - Prevent cirrhosis**
 - Prevent complications**
 - Prevent HCC**
 - Prevent mortality**
-

SHORT TERM OBJECTIVES

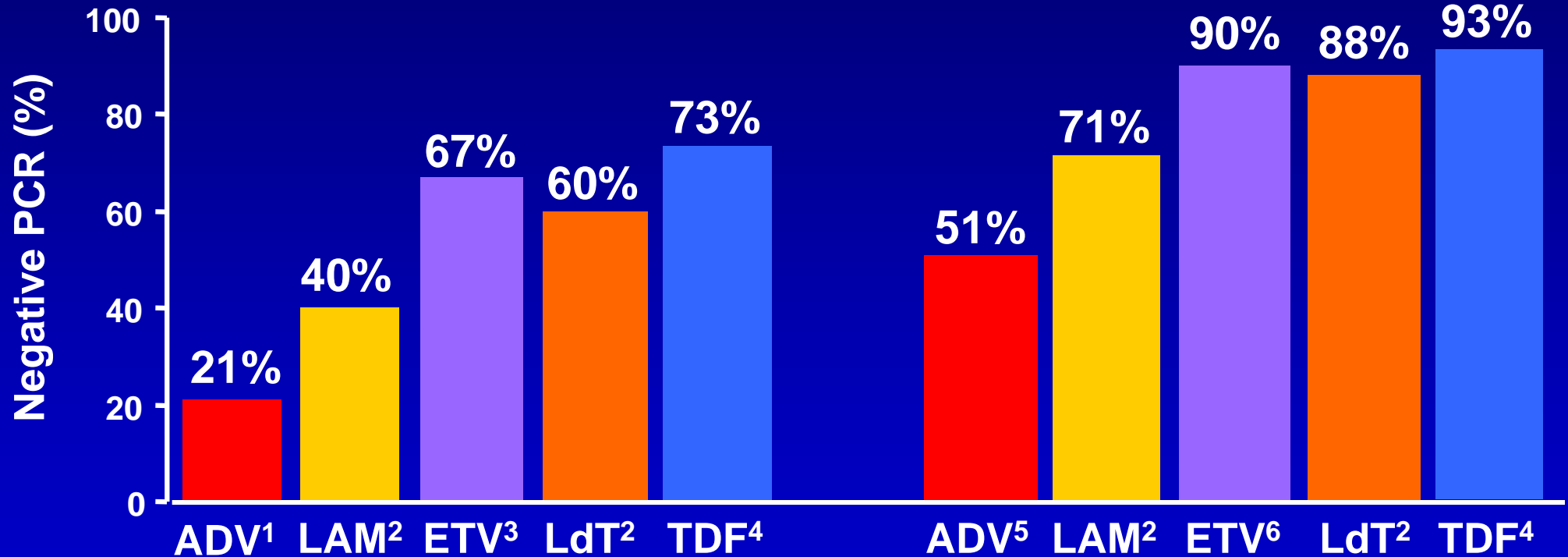
SHORT TERM OBJECTIVES OF THERAPY IN CHRONIC HEPATITIS B

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VIROLOGICAL RESPONSE AT 1 YEAR

HBeAg-positive

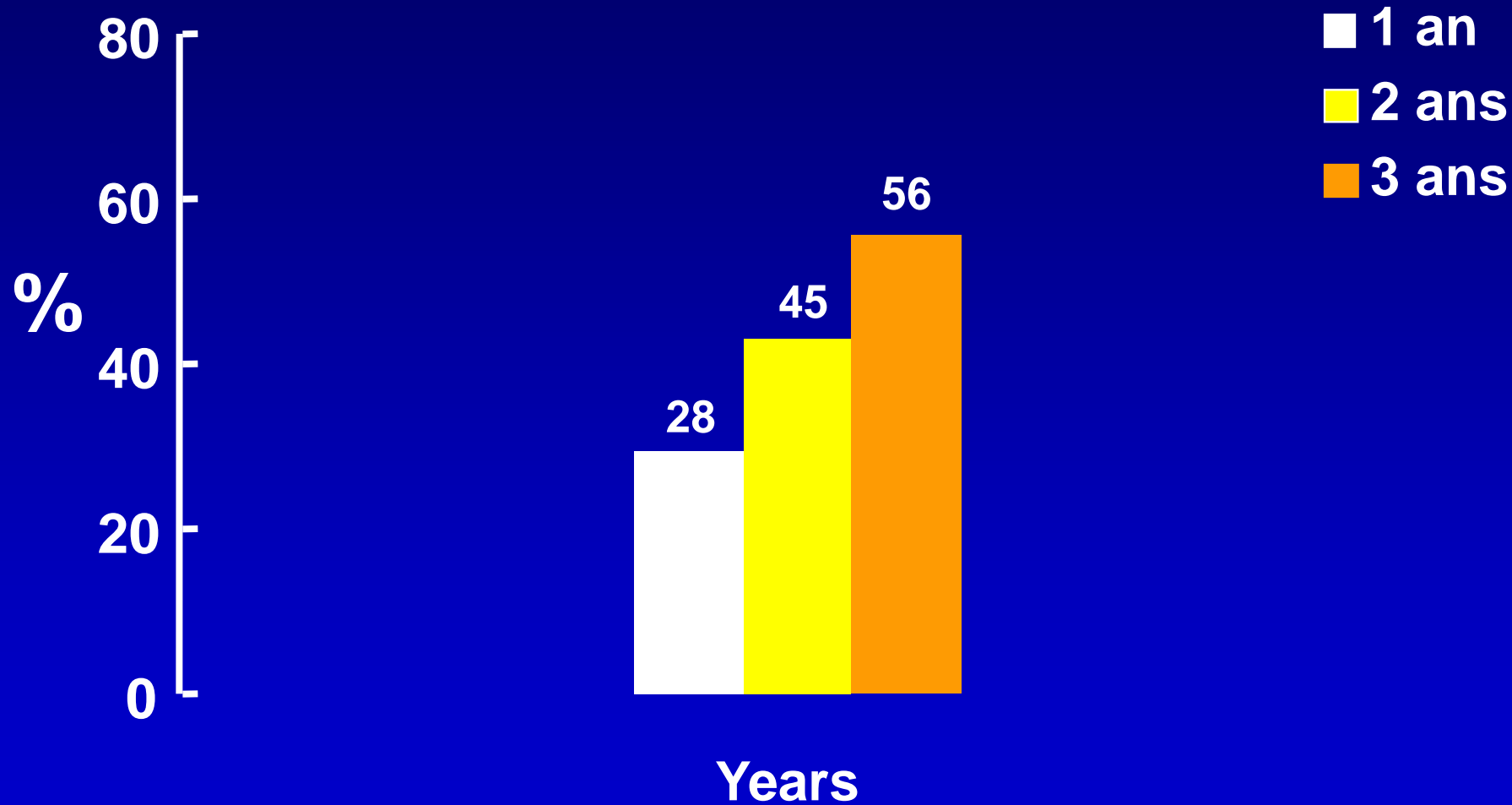
HBeAg-negative



1. Marcellin et al. *N Engl J Med.* 2003
2. Lai et al. *N Engl J Med.* 2007
3. Chang et al. *N Engl J Med.* 2006
4. Marcellin et al. *N Engl J Med.* 2008
5. Hadziyannis et al. *N Engl J Med.* 2003

2. Lai et al. *N Engl J Med.* 2007
6. Lai et al. *N Engl J Med.* 2006

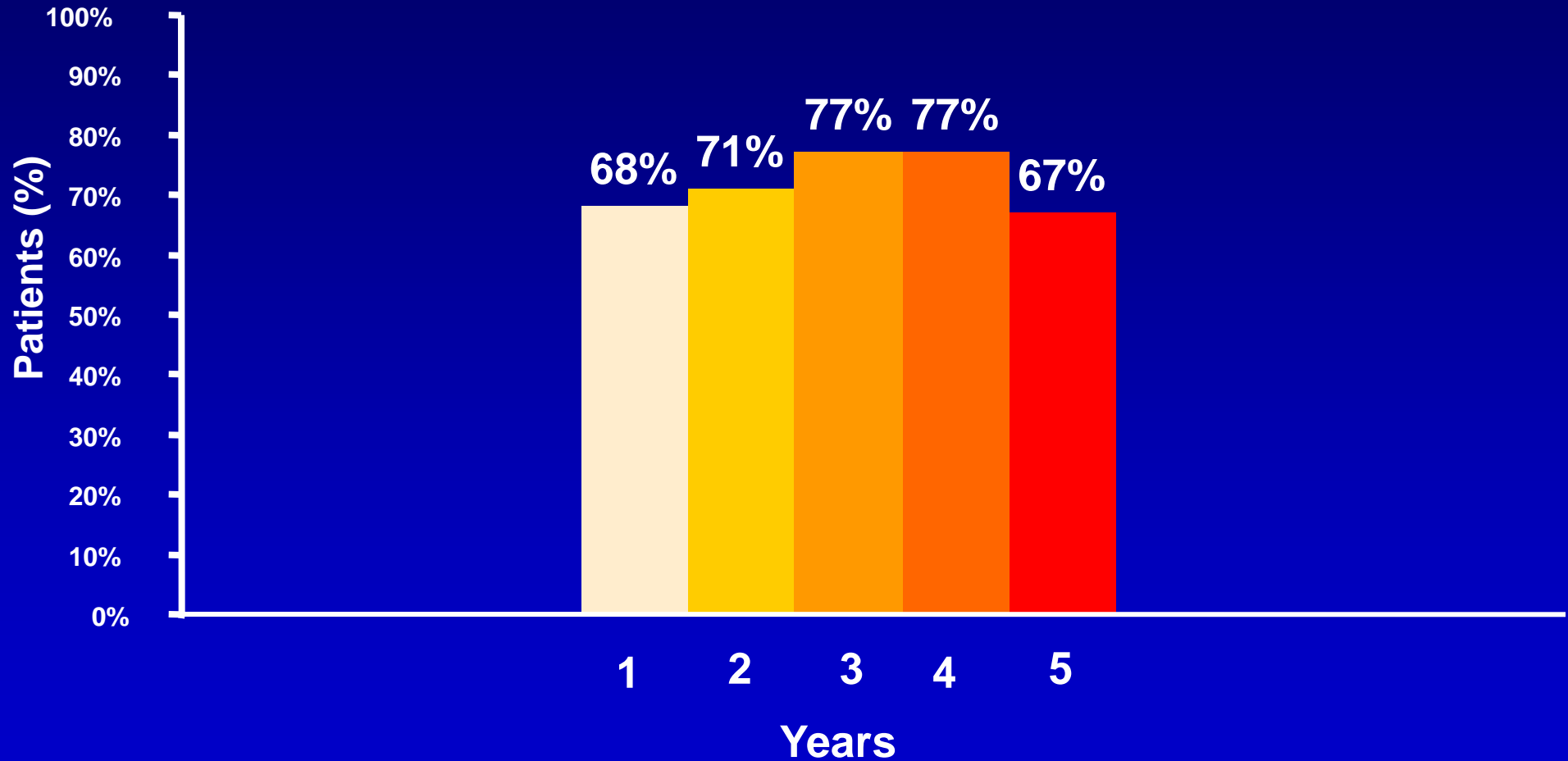
ADEFOVIR IN HBeAg + HBV DNA -



Marcellin et al. NEJM 2003

Marcellin et al. Hepatology 2008

ADEFOVIR IN HBeAg - HBV DNA -

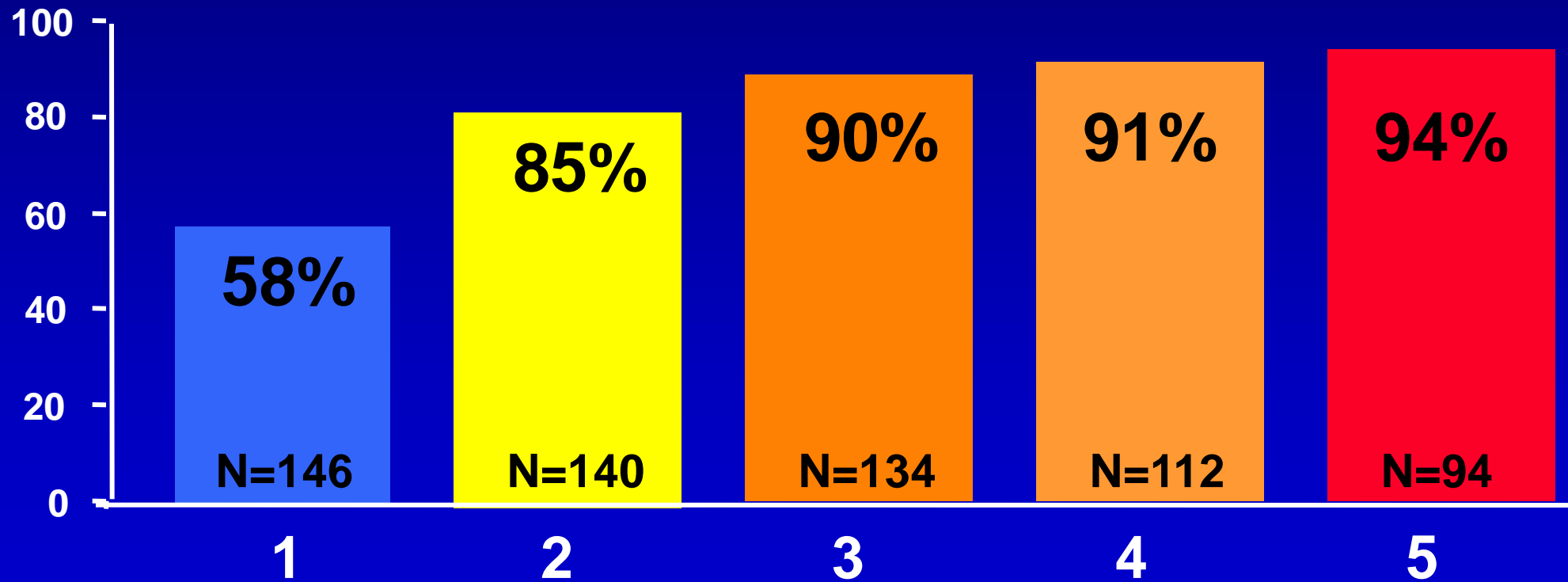


Hadziyannis et al. NEJM 2003

Hadziyannis et al. Gastroenterology

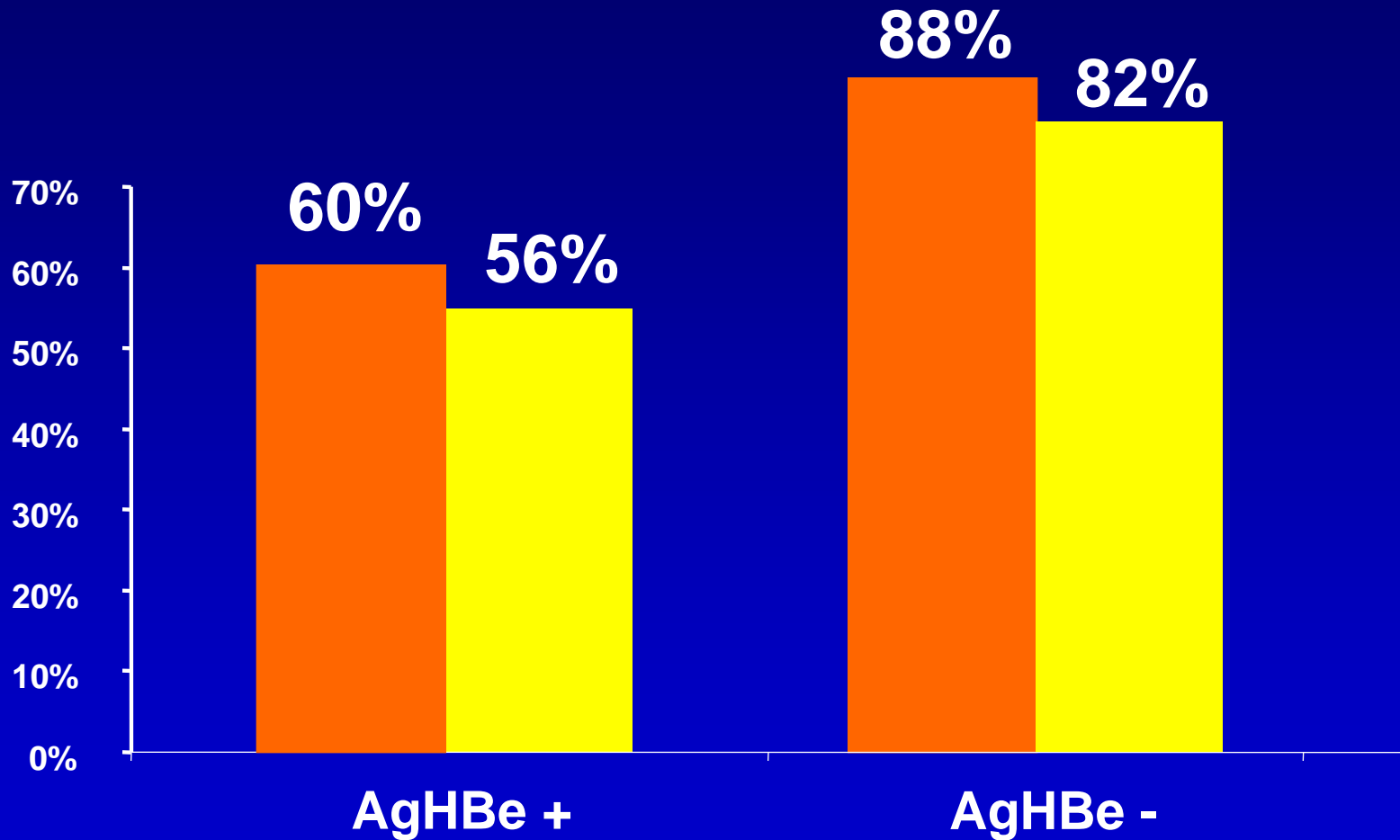
2006

ENTECAVIR IN HBeAg + Efficacy at 5 years



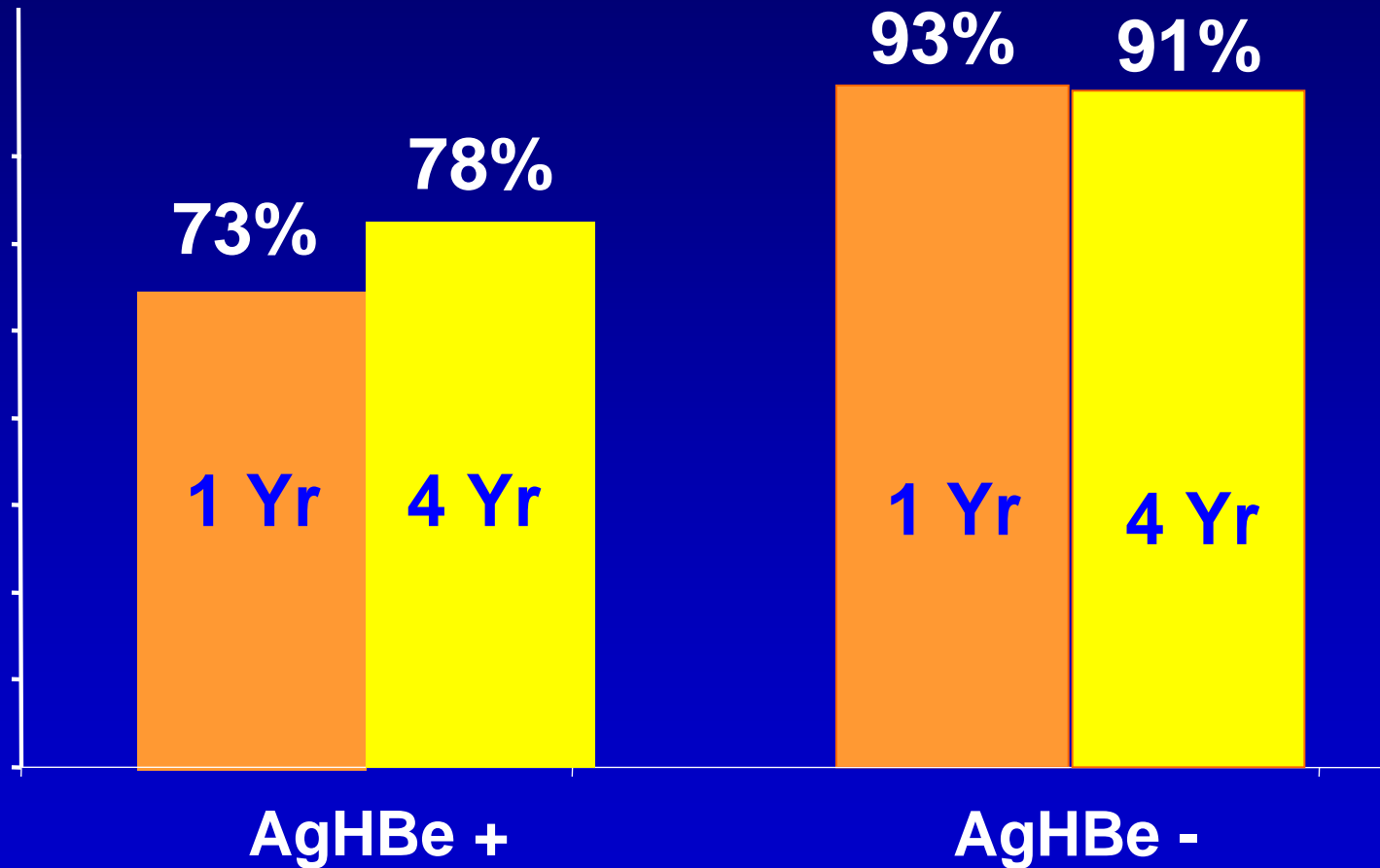
TELBIVUDINE IN HBeAg + AND HBeAg - Efficacy at 2 years

N=1370



Lai et al. NEJM 2007

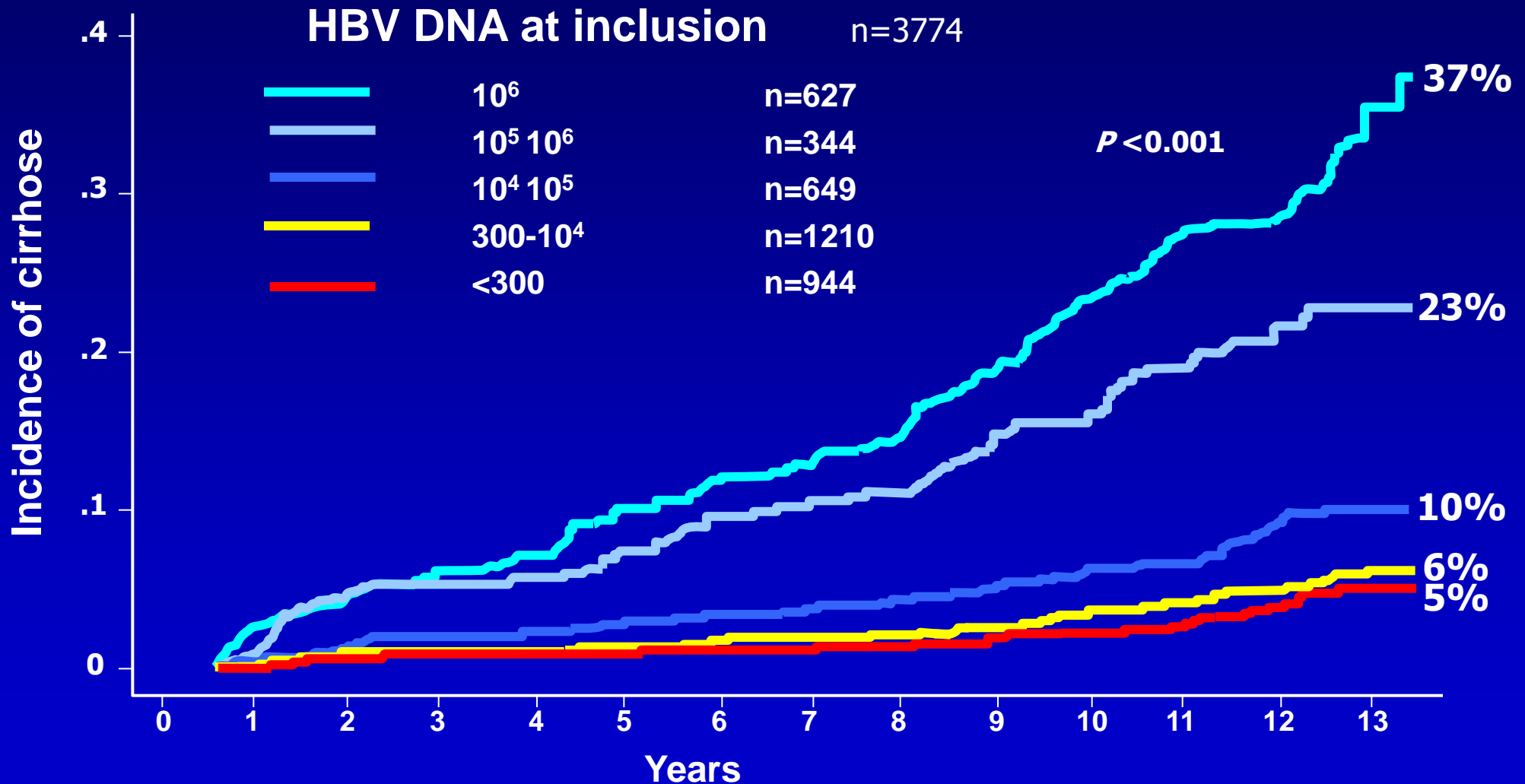
TENOFOVIR IN HBeAg + AND HBeAg -



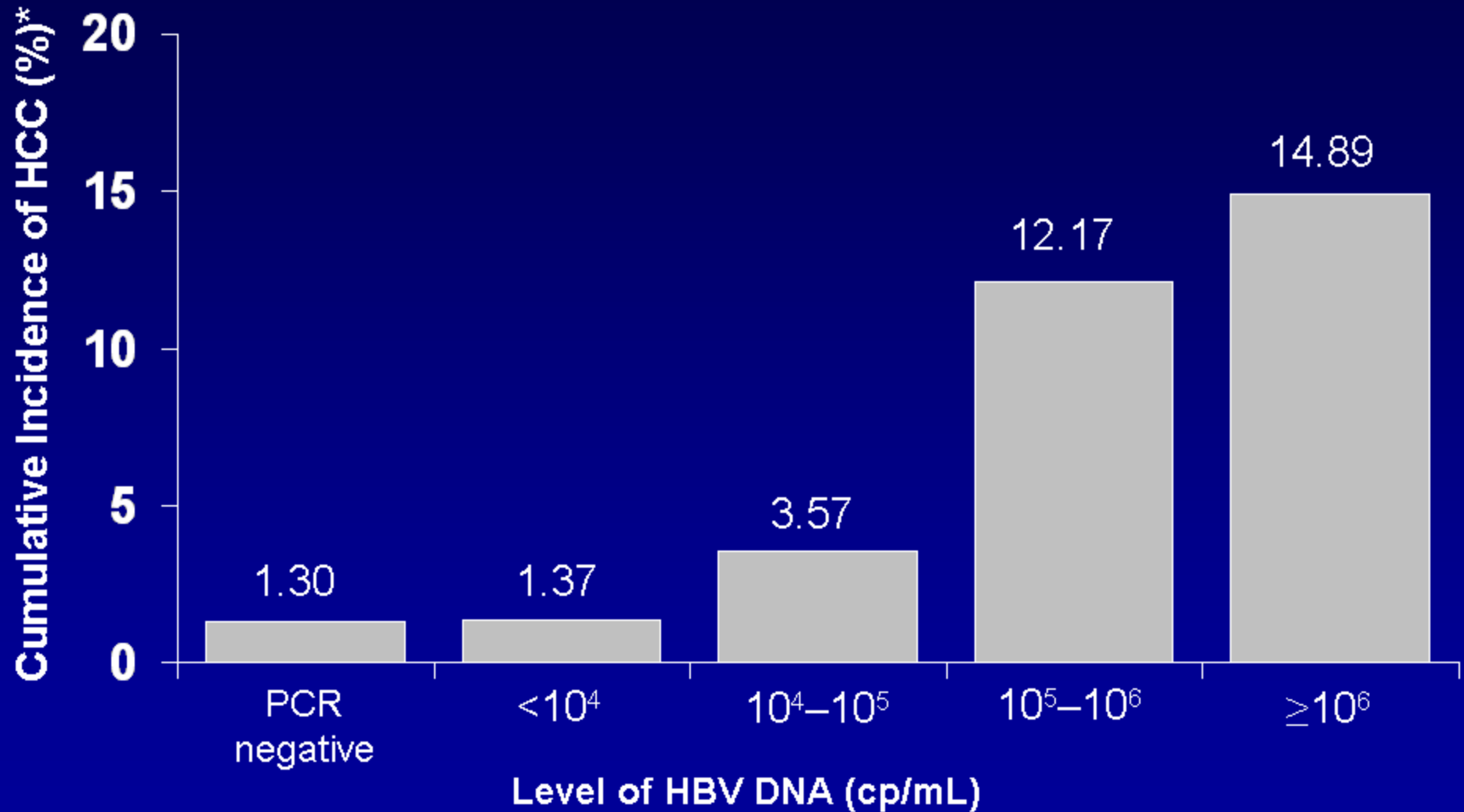
Marcellin et al. NEJM 2008

Marcellin et al. AASLD 2010

HBV DNA LEVEL AND CIRRHOSIS in Untreated Patients



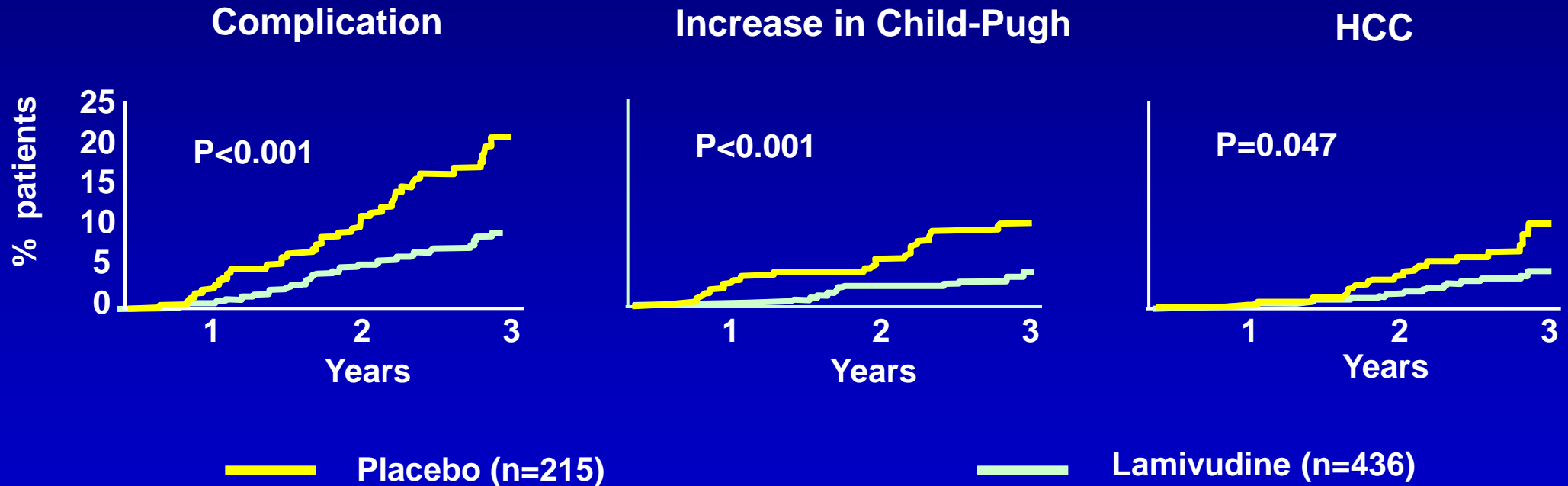
Incidence of Hepatocellular Carcinoma (HCC) by HBV DNA Level



*at the end of the 19th year of follow-up

LAMIVUDINE THERAPY AND OUTCOME OF CHB

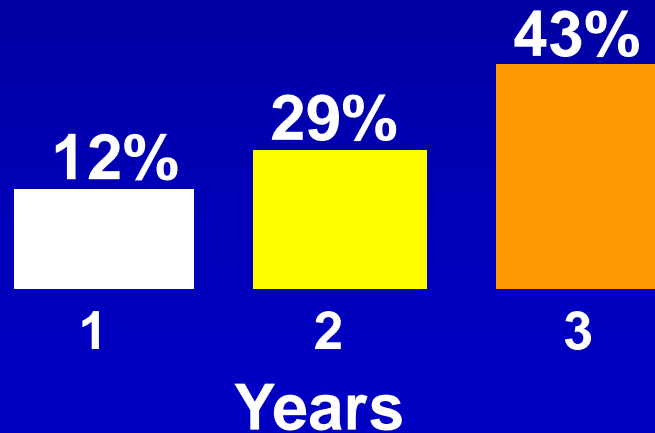
651 patients with severe fibrosis (Ishak>3)



SHORT TERM OBJECTIVES OF THERAPY IN CHRONIC HEPATITIS B

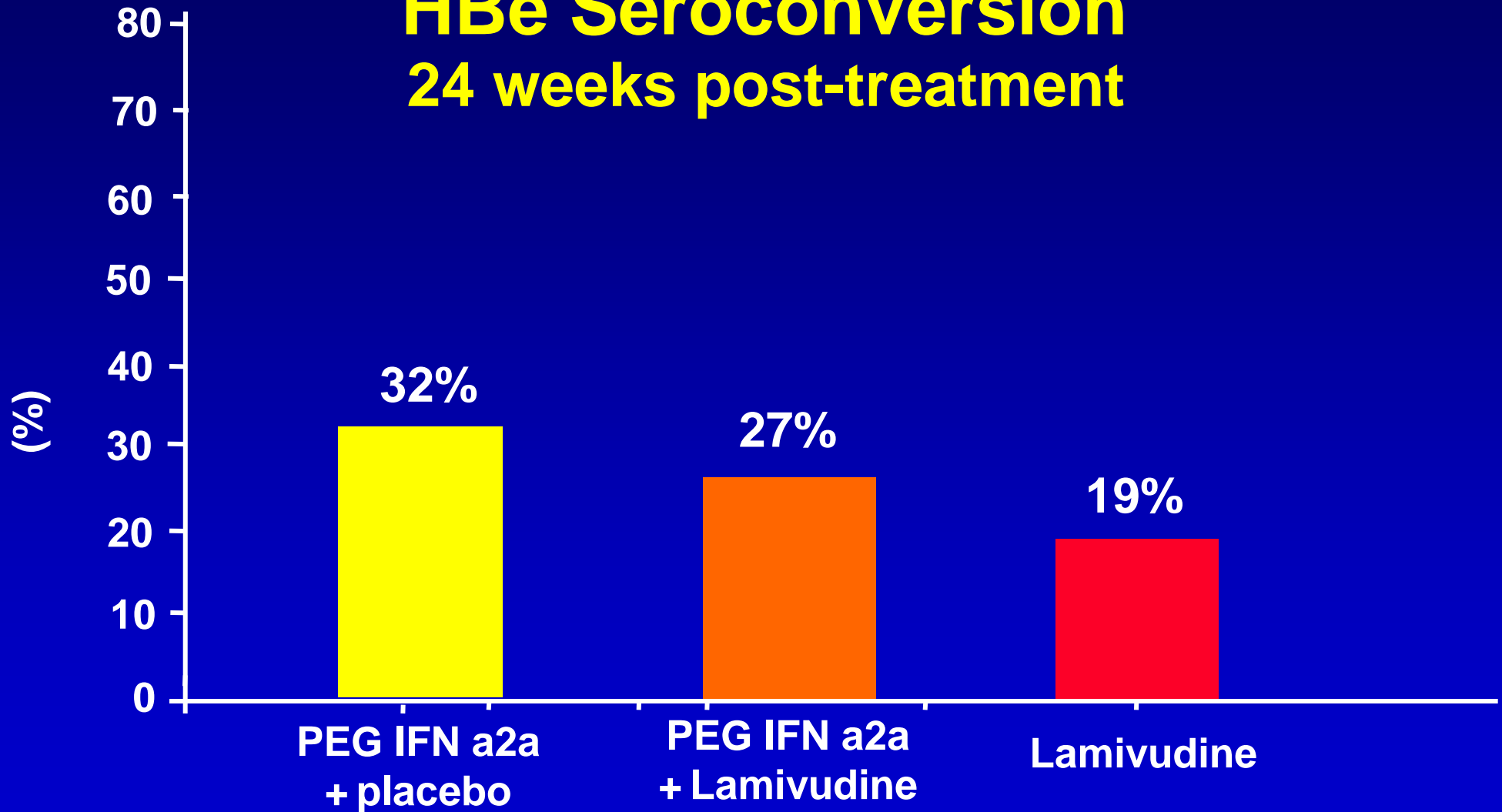
- Inhibit viral replication
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ADEFOVIR IN HBeAg + HBe seroconversion



PEG IFN a2a

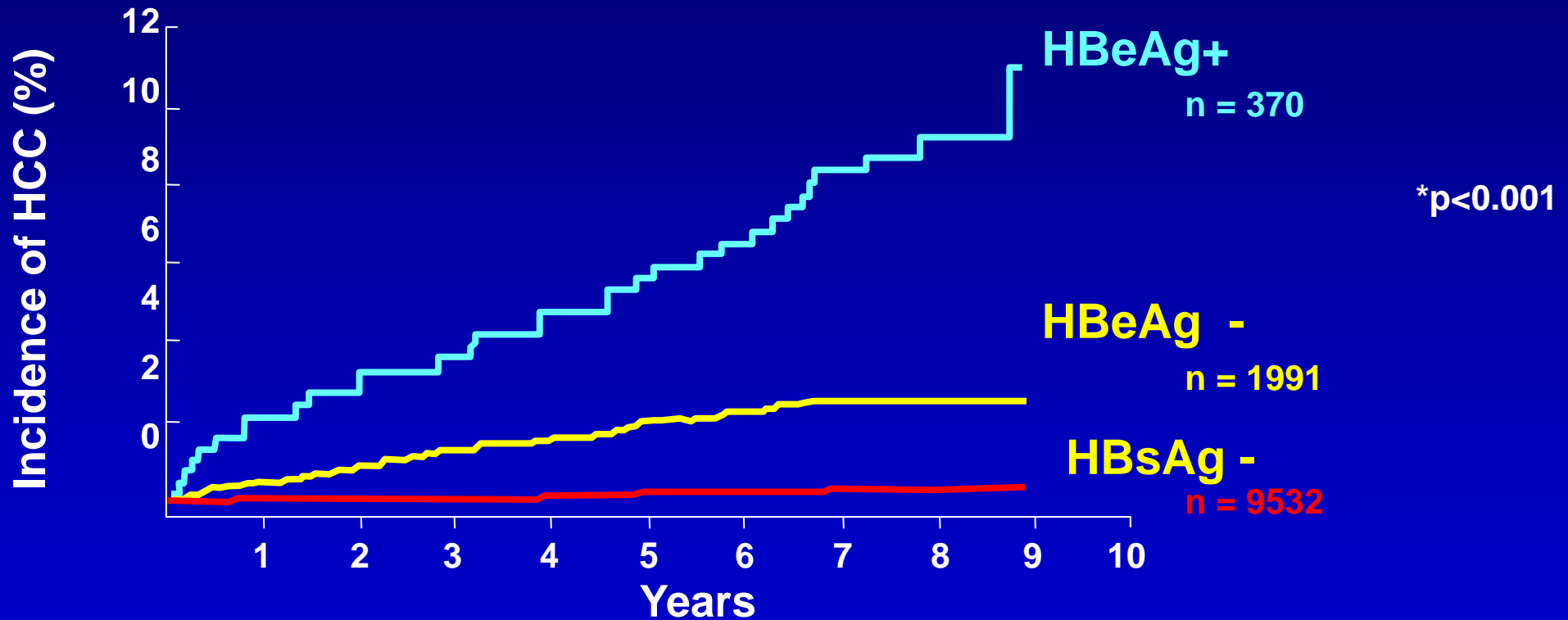
HBe Seroconversion 24 weeks post-treatment



Marcellin et al. NEJM 2004

HBeAg AND HCC

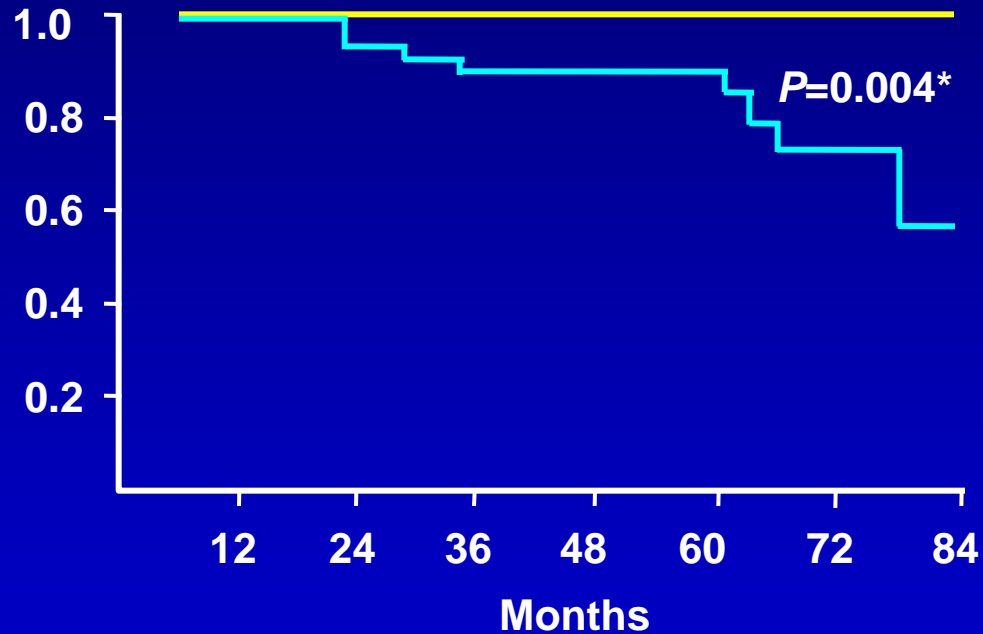
11 893 patients in Taiwan



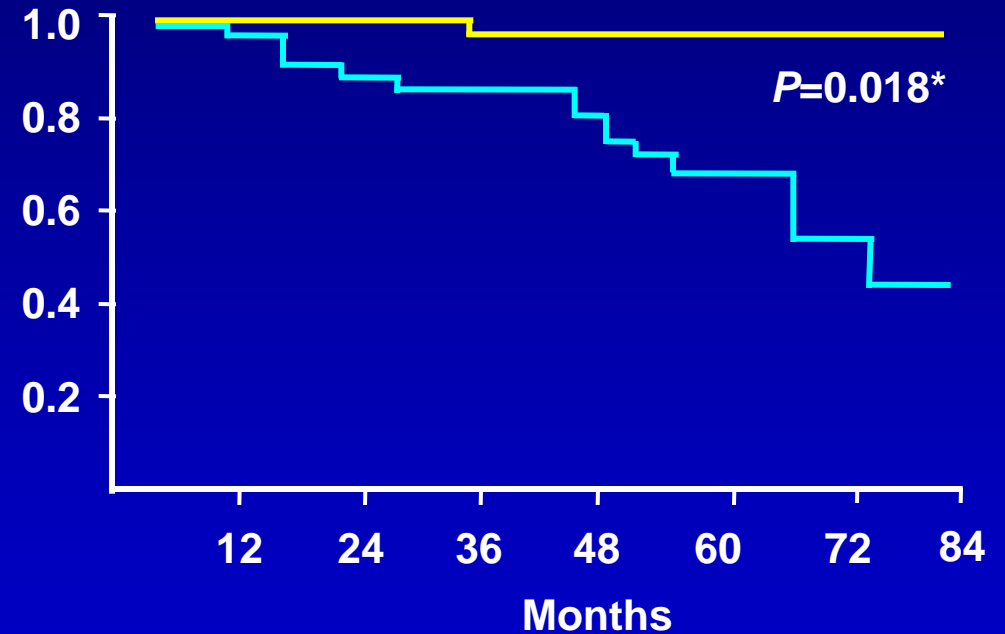
Yang et al. NEJM 2002

COMPLICATIONS AND SURVIVAL ACCORDING TO HBe SEROCONVERSION AFTER IFN

Survival

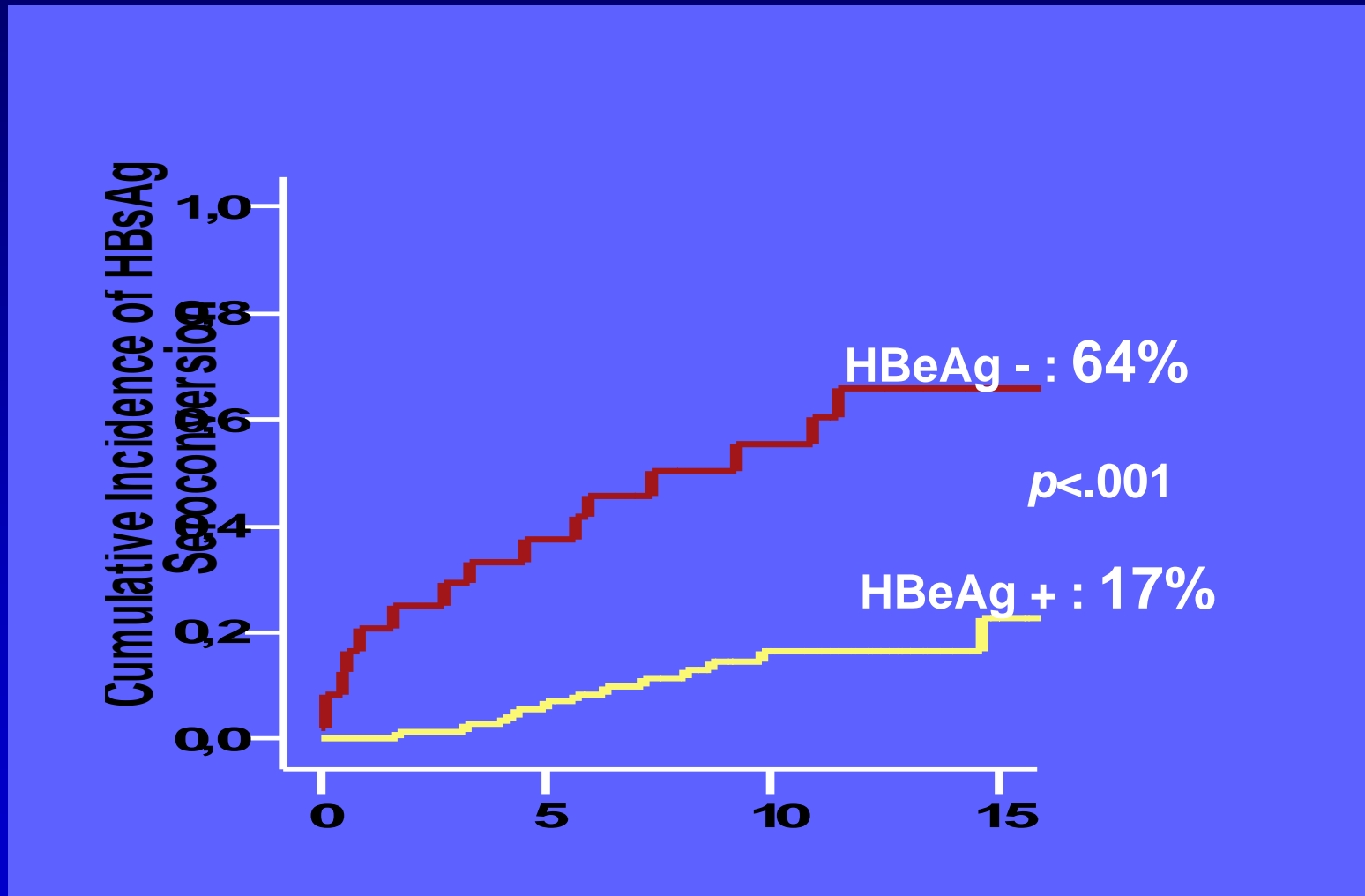


Complications



— Seroconversion
— No seroconversion

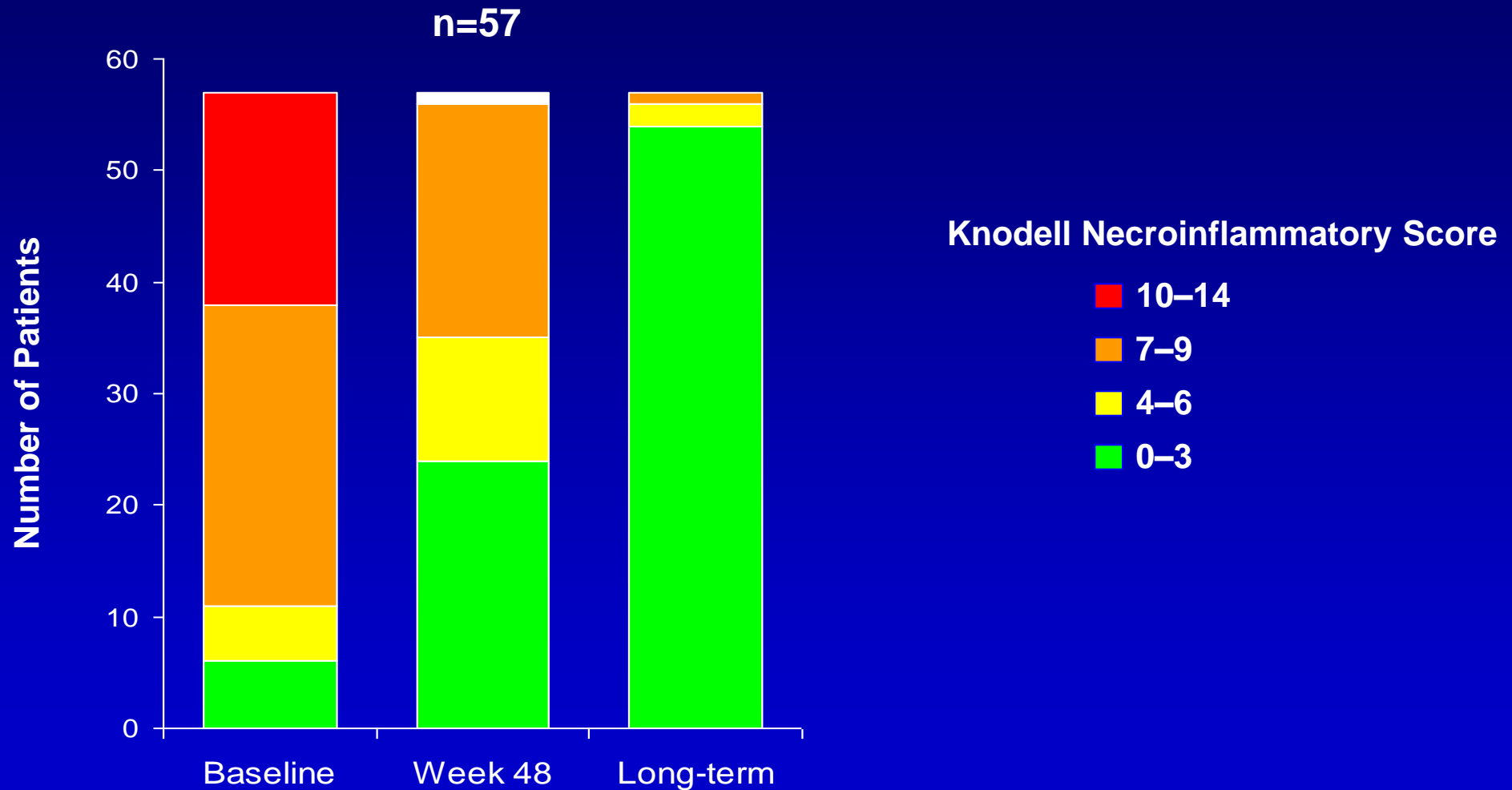
INCIDENCE OF HBsAg LOSS ACCORDING TO RESPONSE TO IFN (HBe seroconversion)



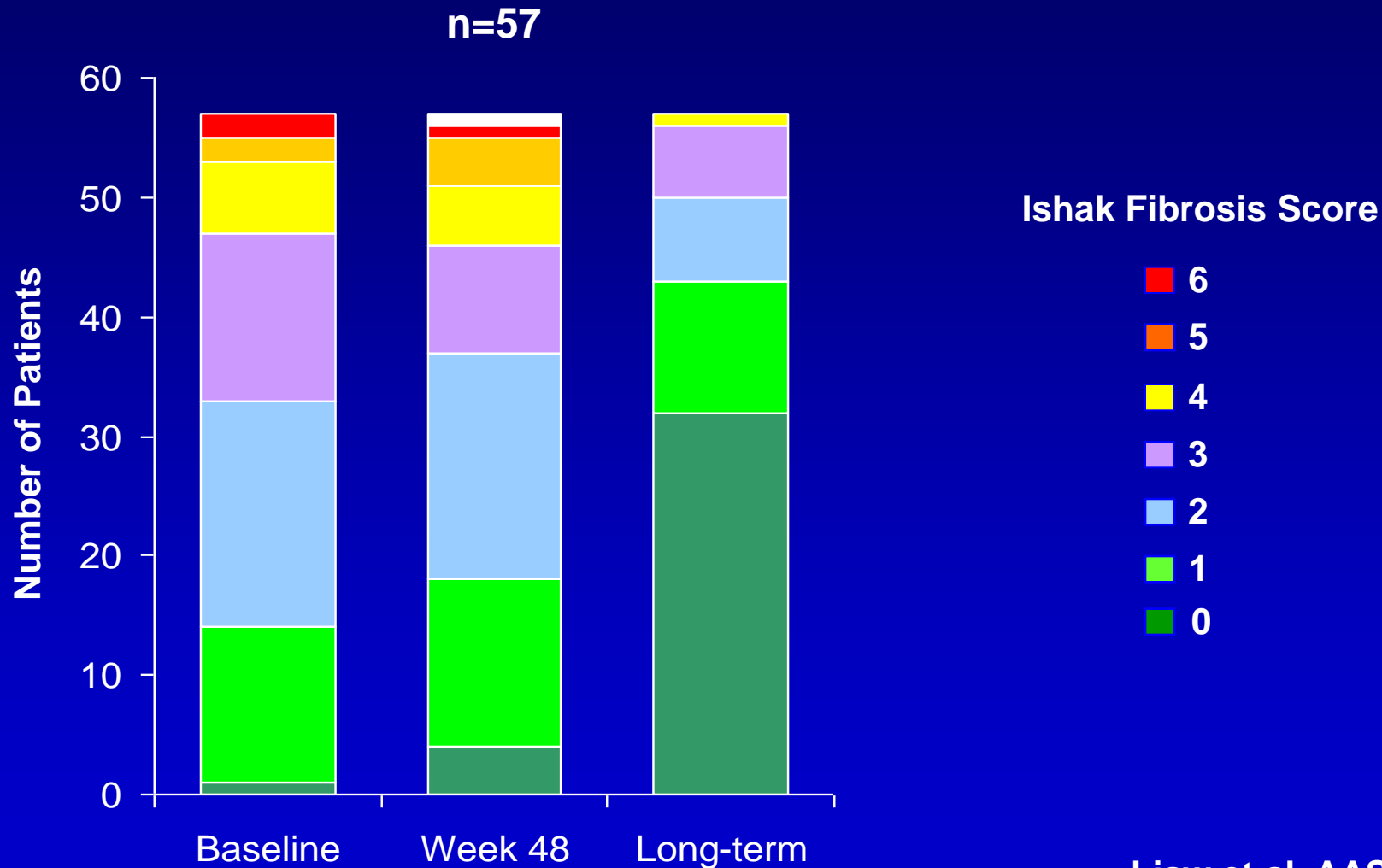
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ETV: Distribution of Knodell Necroinflammatory Scores at Baseline, Year 1, and Years 3–7



ETV: Distribution of Ishak Fibrosis Scores at Baseline, Year 1, and Years 3–7



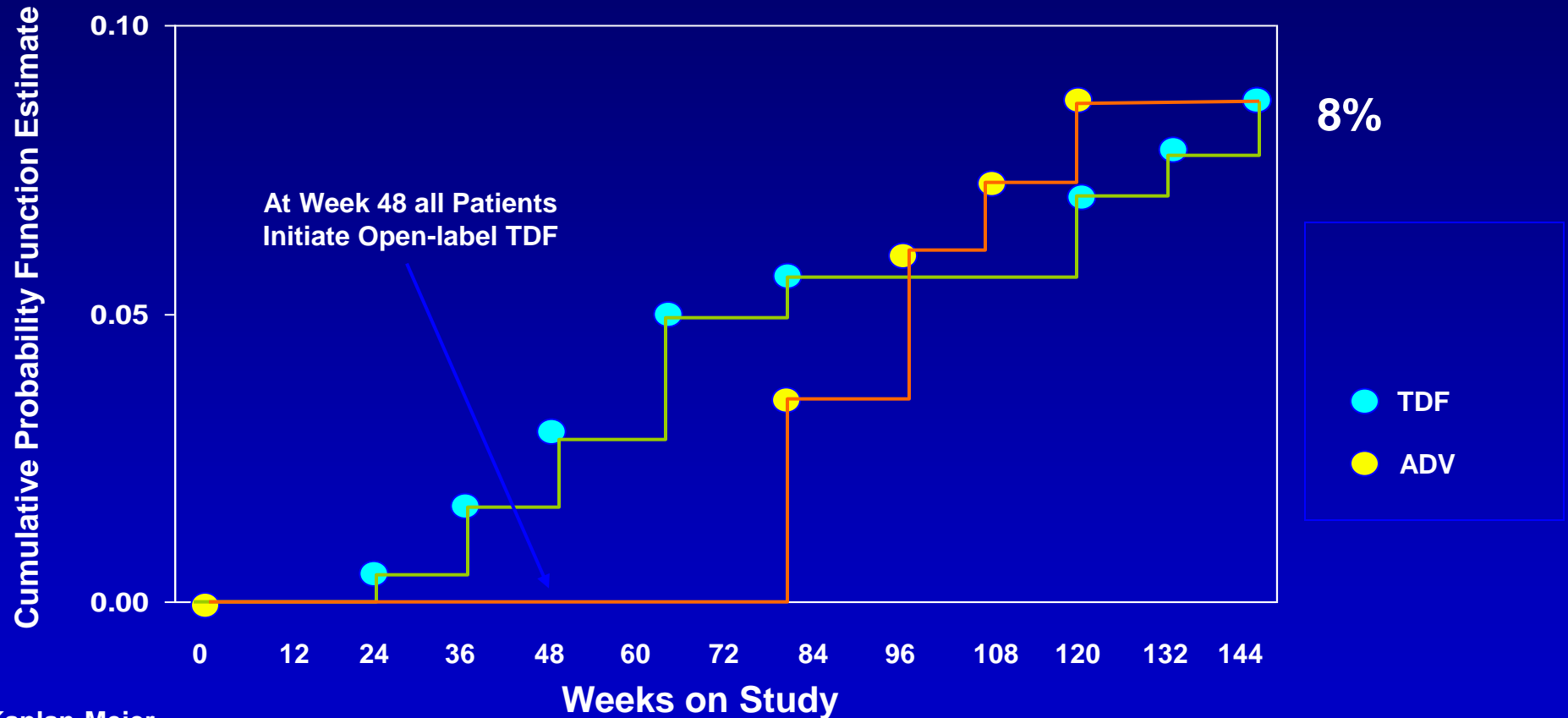
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NO CORRELATION BETWEEN ANTIVIRAL POTENCY AND SEROCONVERSION (1 year)

	<u>HBV DNA decrease (log)</u>	<u>HBeAg seroconv</u>	<u>HBsAg loss</u>
- Lamivudine	5.0	18%	0%
- Adefovir	4.0	12%	0%
- Entecavir	7.0	21%	2%
- Telbivudine	6.5	26%	0%
- Tenofovir	5.5	22%	3%

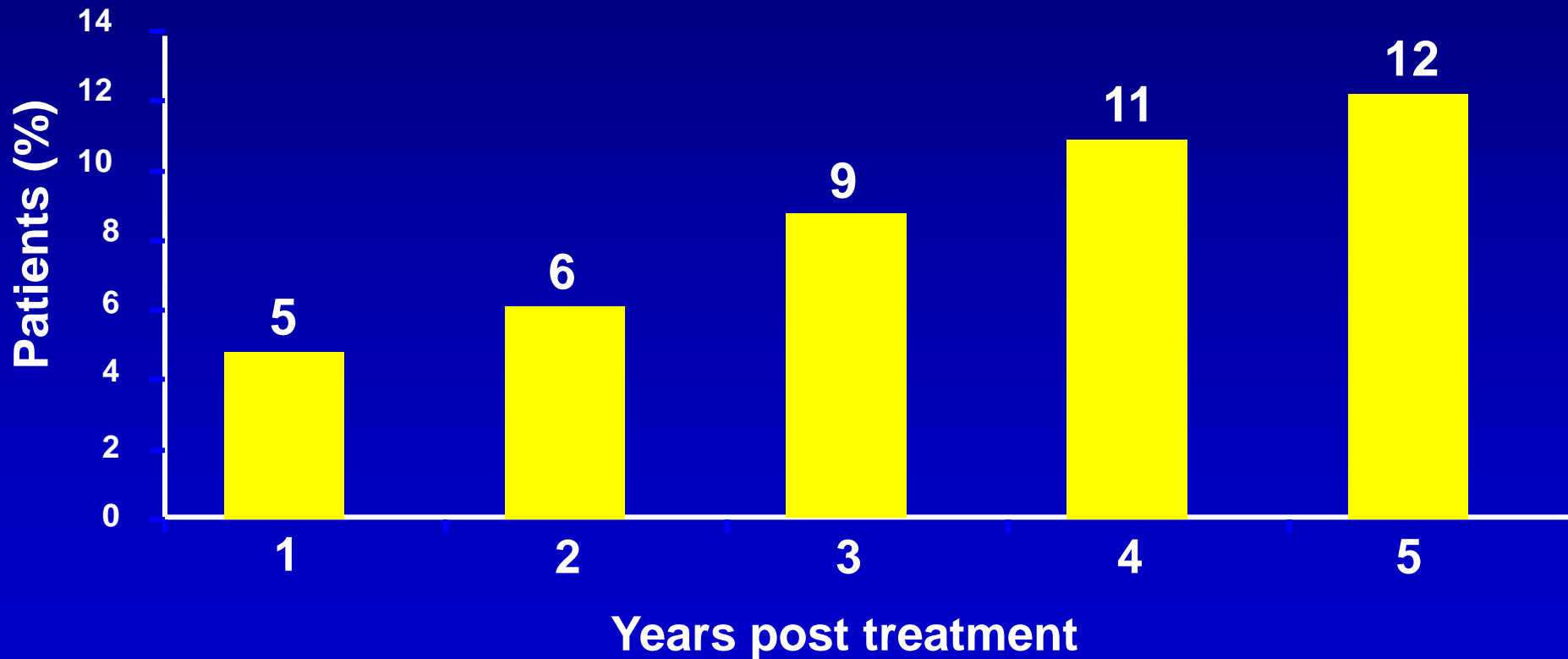
Cumulative probability of HBsAg loss with tenofovir in HBeAg(+) patients



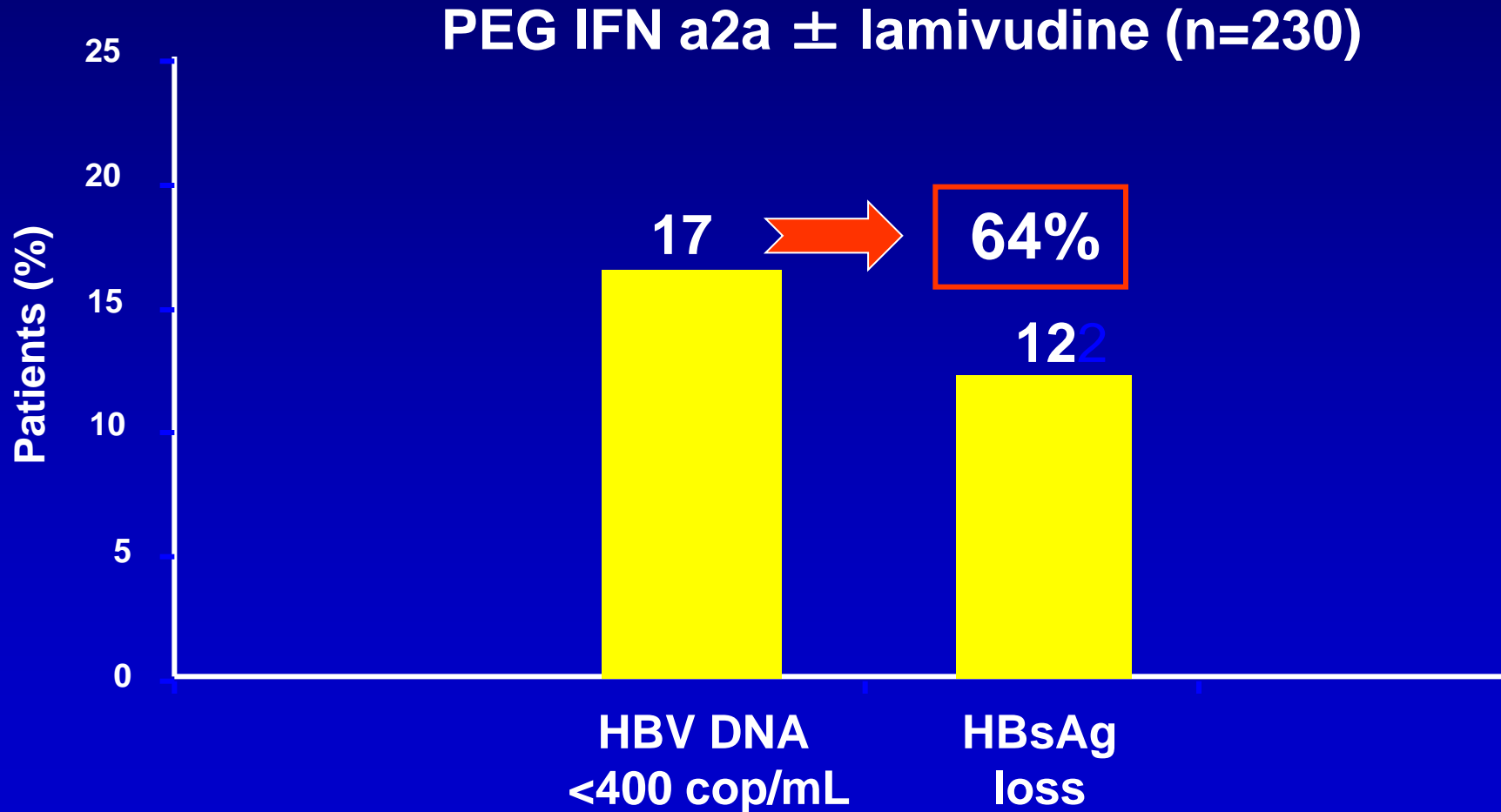
Marcellin et al. NEJM 2008

Marcellin et al. APASL 2009

HBsAg Loss 1–5 years after PEG IFN a2a

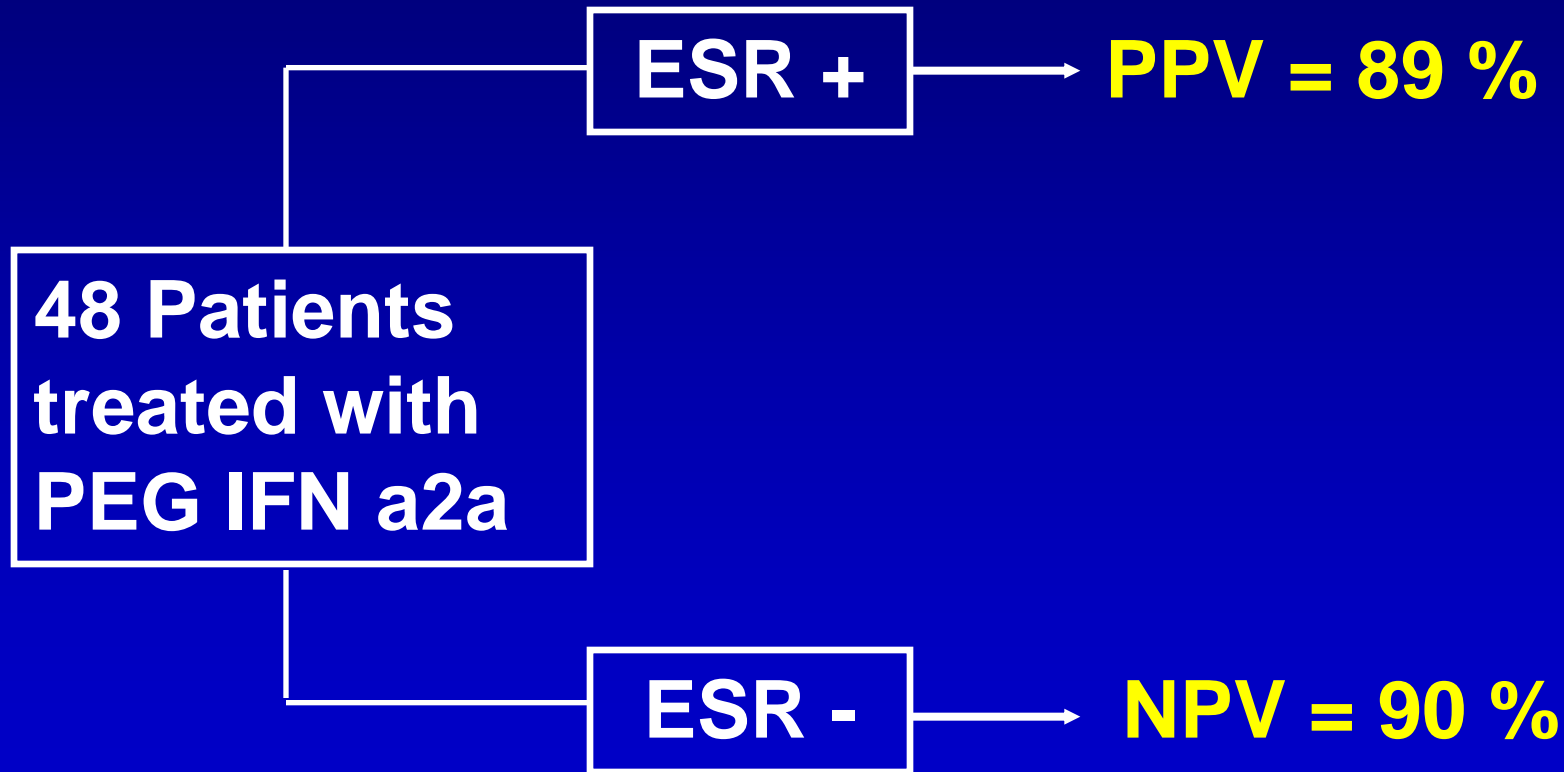


Response to PEG IFN a2a ± lamivudine 5 years post treatment



Quantification of HBsAg: “Stopping Rule”

Early Serological Response = 0.5 log at W12



IMPACT OF HBsAg LOSS

HBsAg AND THE RISK OF HCC

HBV progression and HCC in 11,893 men in Taiwan

HBsAg	HBeAg	ALT	Relative Risk
--	--	normal	1
--	--	elevated	5.4
+	--	normal	10.3
+	--	elevated	29.3
+	+	normal	61.3
+	+	elevated	109

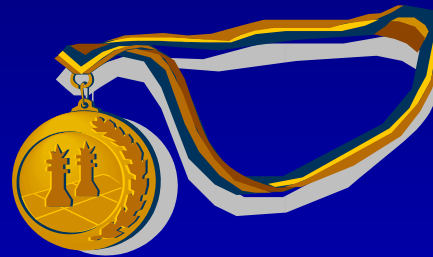
OUTCOME (10 years) AFTER IFN THERAPY ACCORDING TO HBsAg LOSS

n = 97

	HBsAg+	HBsAg-
◆ HCC :	6	0
◆ Ascitis :	5	0
◆ Hemorrhage:	0	0
◆ Mortality (HCC):	4	0

HBsAg SEROCONVERSION: THE CHAMPION AMONG ENDPOINTS

HBsAg
Seroconversion



HBeAg
Seroconversion

HBV DNA
Suppression

1

2

3

CONCLUSION

- **Retrospective and prospective cohort studies of untreated patients** with chronic hepatitis B have shown that HBV DNA level and HBeAg positivity are correlated with the risk of cirrhosis, HCC and mortality
- **Long term follow-up studies of patients treated** with IFN or NUCs have shown durability of undetectable HBV DNA and HBeAg seroconversion

CONCLUSION

- **Long term follow-up studies of patients treated** with IFN or PEG IFN have shown high rates of HBsAg loss/seroconversion associated with an improved outcome (IFN)
- **One single controlled study** has shown the beneficial effect of lamivudine at 3 years in patients with advanced fibrosis

CONCLUSION

- **Large long term follow-up studies of patients treated** with NUCs or PEG IFN are needed to confirm the positive impact of NUCs and PEG IFN on the natural history of chronic hepatitis B
- **HBsAg loss/seroconversion is the ultimate goal of therapy** closest to cure and the best predictor of improved outcome

