6th PARIS HEPATITIS CONFERENCE

HBeAg-negative chronic hepatitis B
Why do I treat my patient with a nucleos(t)ide analogue?

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GP – Paris, 15/1/2013

Conflict of Interest Statement

I use PegIFNα-2a in CHB

Estimated proportions of 1st line therapy in CHB patients in European countries

70-90% vs 10-30%

HBV-RELATED CHRONIC LIVER DISEASE THERAPEUTIC INDICATIONS

NA(s) or (Peg-)IFNa

- Chronic hepatitis B

Only NA(s)

- Decompensated HBV cirrhosis
- Prophylaxis in HBV transplant cases
- Pre-emptive therapy in inactive HBV carriers receiving immunosuppressive/chemo-therapy
- Pregnant women with high HBV viremia
- Health care workers in the HBV immunotolerant phase

TREATMENT OPTIONS IN HBeAg(-) CHB
NA(s) vs Peg-IFNa

Patients prefer pills than injections

One pill per day!

NAs: much better tolerability and safety compared to (Peg-)IFNa

Safety (Renal) monitoring during NA therapy

- Assess baseline creatinine clearance (Clcr) regardless of NA

Renal risk	Antiviral	Test (C1)	Frequency (C2)
Normal	ADV, TDF	Clcr, phosphate	0, 3, 6, 9, 12 & then every 6 months
High	ADV, TDF	Clcr, phosphate	0, 1, 2, 3, 6, 9, 12 & then every 6 months
High	LAM, ETV, TBV	Clcr	0, 1, 2, 3, 6, 9, 12 & then every 6 months

Peg-IFNa therapy: FBC, ALT monthly & TSH every 3 months

EASL HBV CPGs. J Hepatol 2012;57:167-85

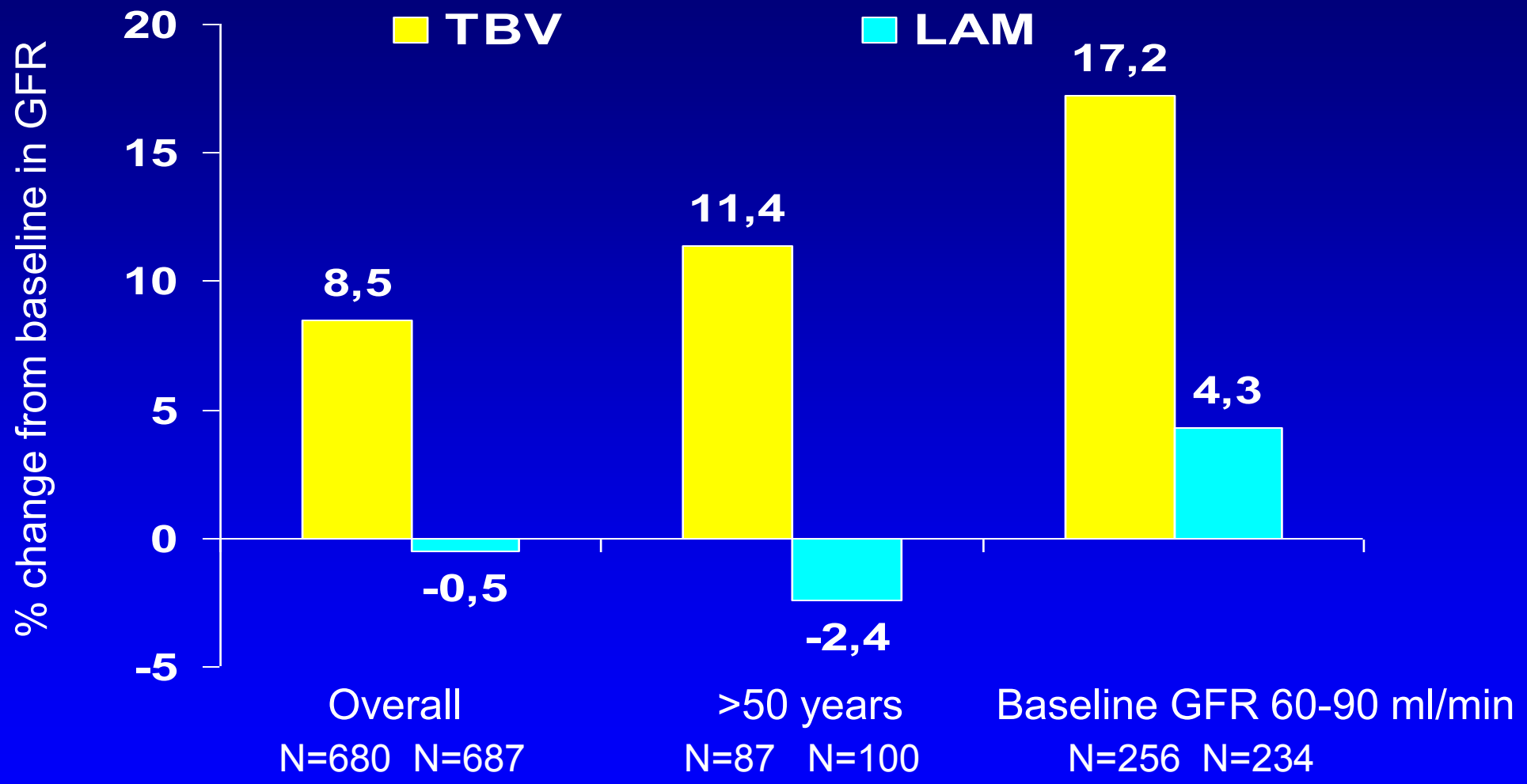
Safety during 288 weeks of TDF therapy
Studies 0102 & 0103

	Total TDF (OL Period) (N=585)
Adverse events leading to drug discontinuation	11 (1.9%)
Deaths	9 (1.5%)
Serious adverse events*	7 (1.2%)
Grade 3 or 4 adverse events*	6 (1.0%)
Confirmed Scr ≥0.5 mg/dL above baseline	9 (1.5%)
Confirmed PO_4 <2 mg/dL	8 (1.4%)
Confirmed CrCL <50 mL/min (Cockcroft–Gault method)	6 (1.0%)

*Study drug-related adverse events only

Marcellin P et al. AASLD 2012

eGFR changes in CHB pts under TBV or LAM for 2 yrs

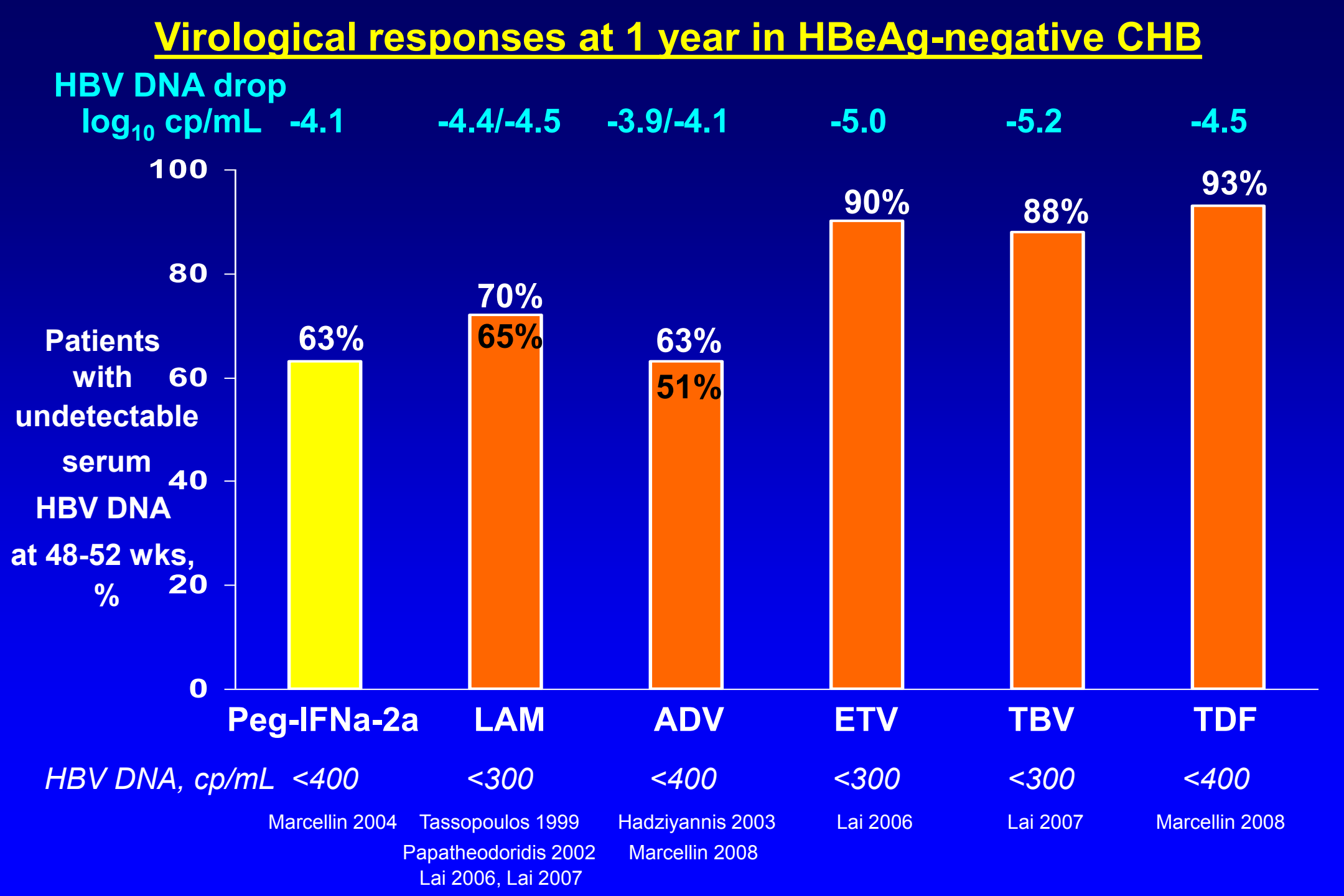


Gane E et al. EASL 2012

TREATMENT OPTIONS IN HBeAg(-) CHB
NA(s) vs (Peg-)IFNa

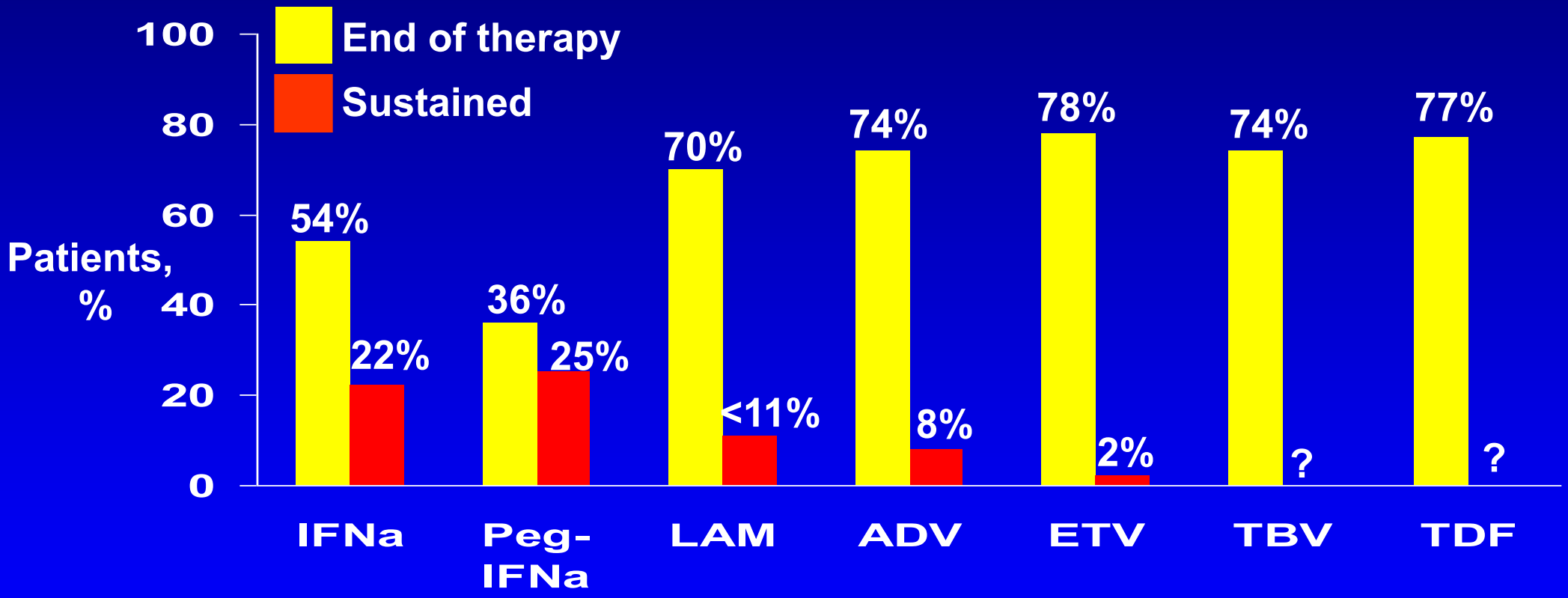
Efficacy

Virological responses at 1 year in HBeAg-negative CHB



EFFICACY OF 12-MONTH COURSES IN HBeAg(-) CHB: Sustained off-therapy responses

Biochemical & virological responses (different definitions among studies)



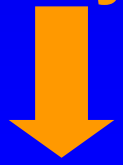
Efficacy of current treatment options in HBeAg(-) CHB

- 12-month courses of Peg-IFNa

better sustained off-treatment response rates than

12-month courses of NA(s)

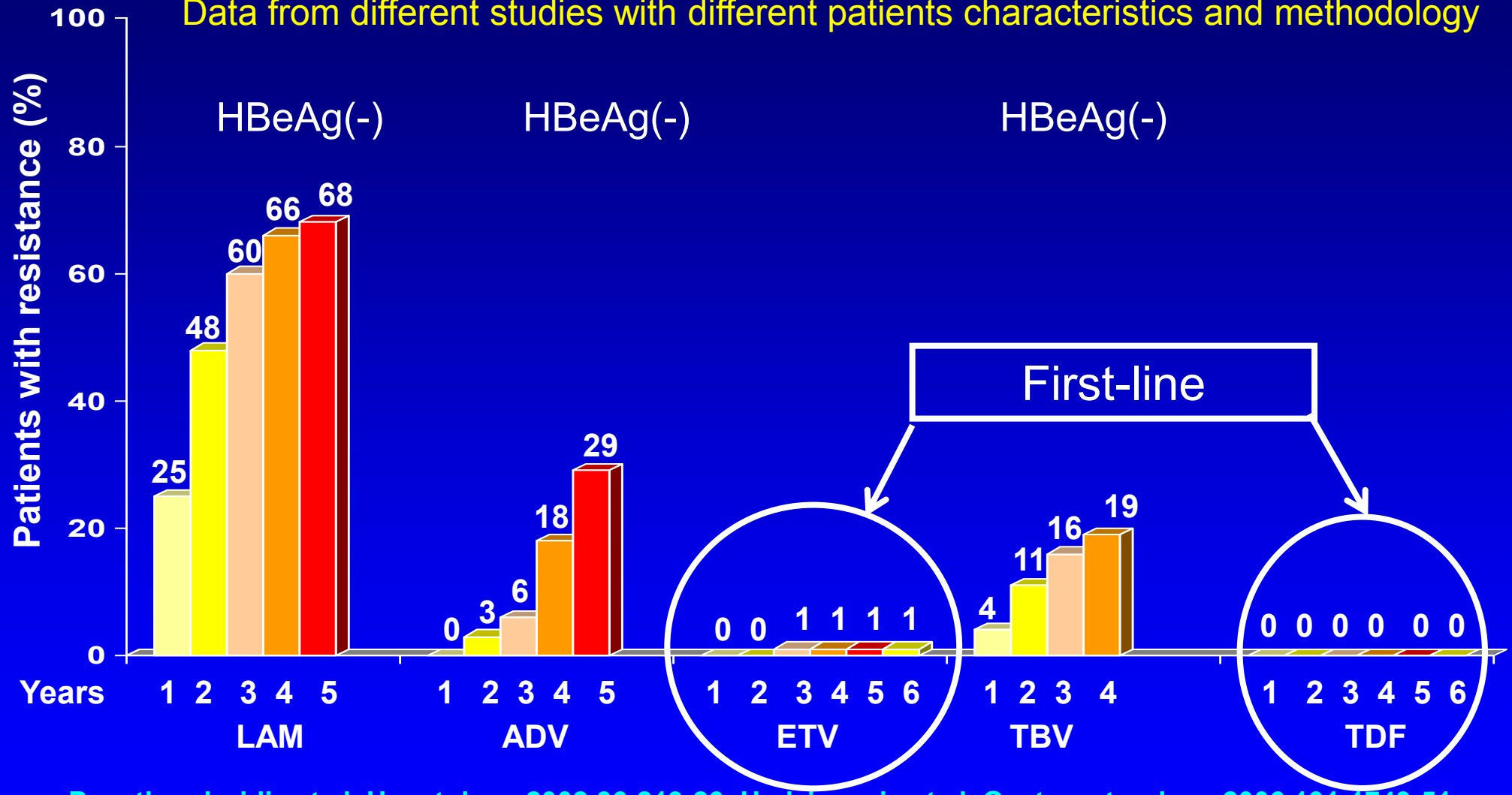
- **Peg-IFNa: responses in a minority of patients**
- **NA(s): high on-treatment remission rates**
- **NA(s) duration: >4-5 years, indefinitely?**



- **Viral resistance?**

Resistance to oral antiviral agents in naive CHB patients

Data from different studies with different patients characteristics and methodology



Papatheodoridis et al. Hepatology 2002,36:219-26; Hadziyannis et al. Gastroenterology 2006,131:1743-51;
Liaw YF et al. Gastroenterology 2009,136:486-95; Wang Y et al. AASLD 2009, Abstr. 482;
Tenney D et al. APASL 2008, Abstr. PL02; Marcellin P et al. AASLD 2012

Long-term therapy with ETV/TDF in HBeAg(-) CHB

- **Viral resistance:**

  not an issue in clinical practice in 2013

- **Virological response rates:**

  >90% at year-1, >98% after year-2

- **Absence of virological response under ETV or TDF: check for drug compliance**

Partial virological response under ETV/TDF

Check for compliance

In compliant patients with partial virological response under

- **ETV or TDF** at wk 48
  - If **HBV DNA levels are declining, continue with the same agent (B1)**
  - If HBV DNA levels are not declining, **add the other** drug in order to prevent resistance in the long term **(C2)**

EASL HBV CPGs. J Hepatol 2012;57:167-85

HBV monitoring during long-term therapy with ETV/TDF

- **Serum HBV DNA at 3 and then every 3-6 months**
- **During ETV or TDF therapy, the frequency of HBV DNA follow-up may be decreased when patient compliance and treatment efficacy have been established (C1)**

EASL HBV CPGs. J Hepatol 2012;57:167-85

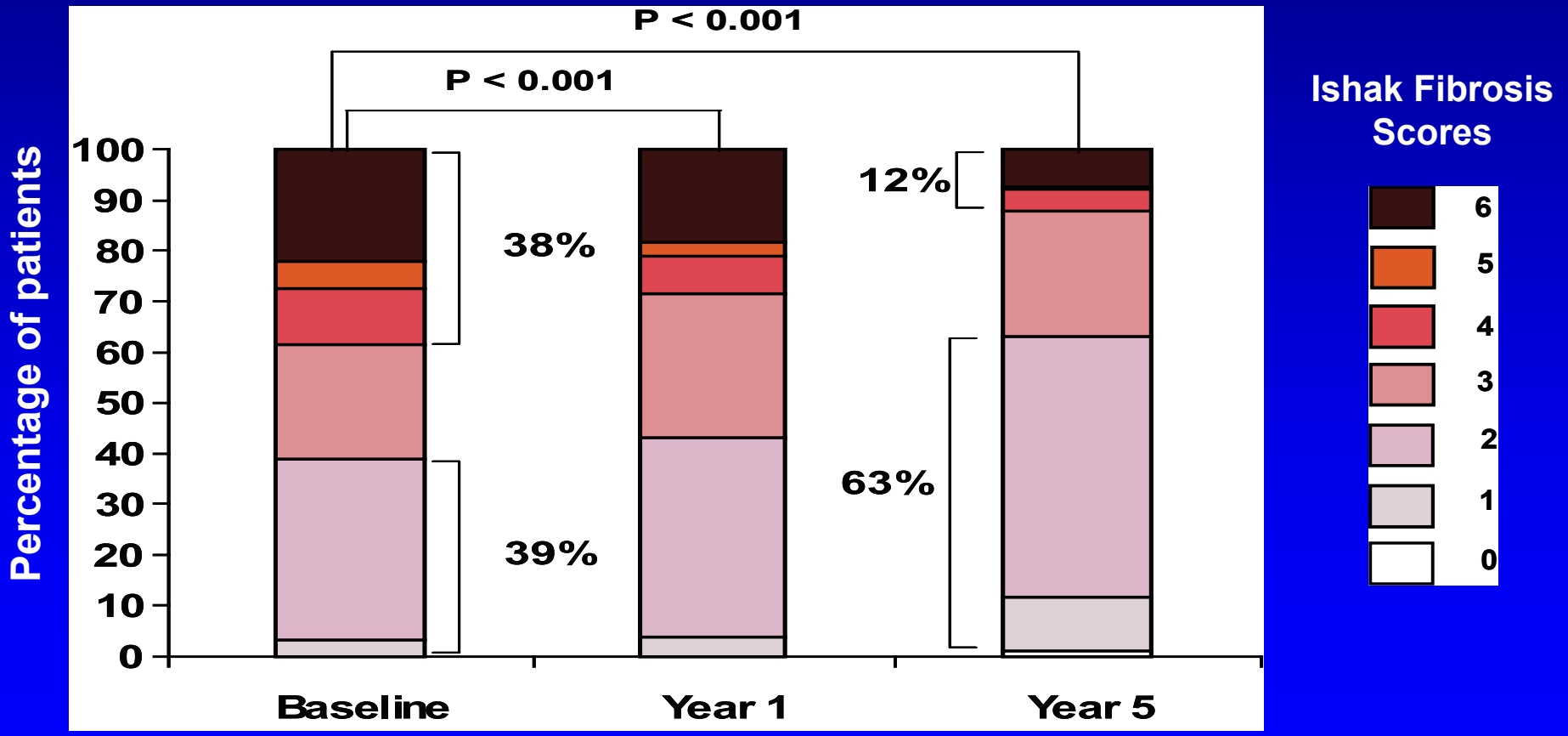
Long-term therapy with NA(s) in HBeAg(-) CHB

Effects on major outcomes including survival

Fibrosis Is Reversible
Liver Fibrosis Regression over 5 Years of TDF Therapy

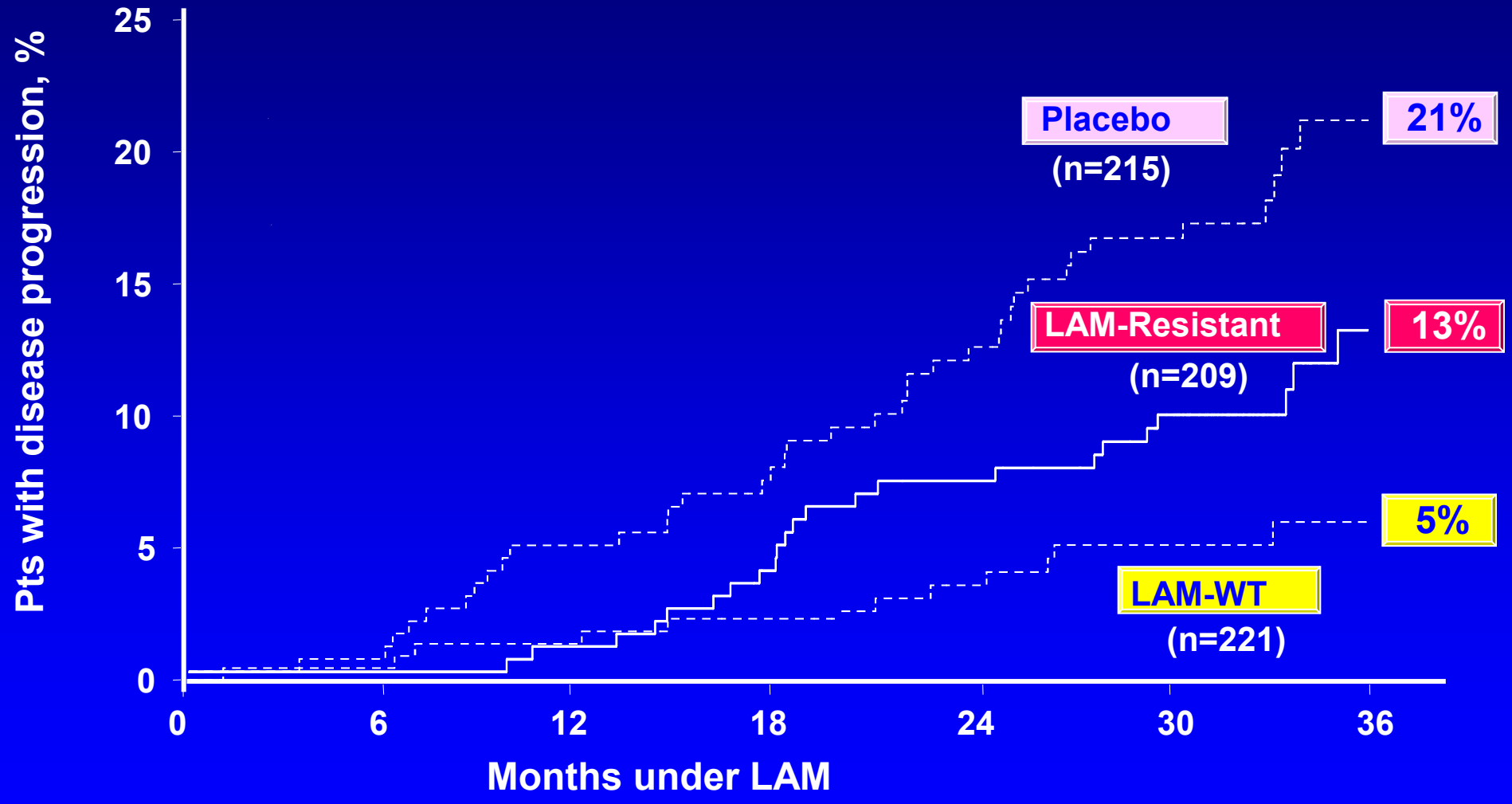
348 patients with paired biopsies at baseline & year 5

- Patients with cirrhosis (Ishak score ≥5): 28% at baseline, 8% at year 5



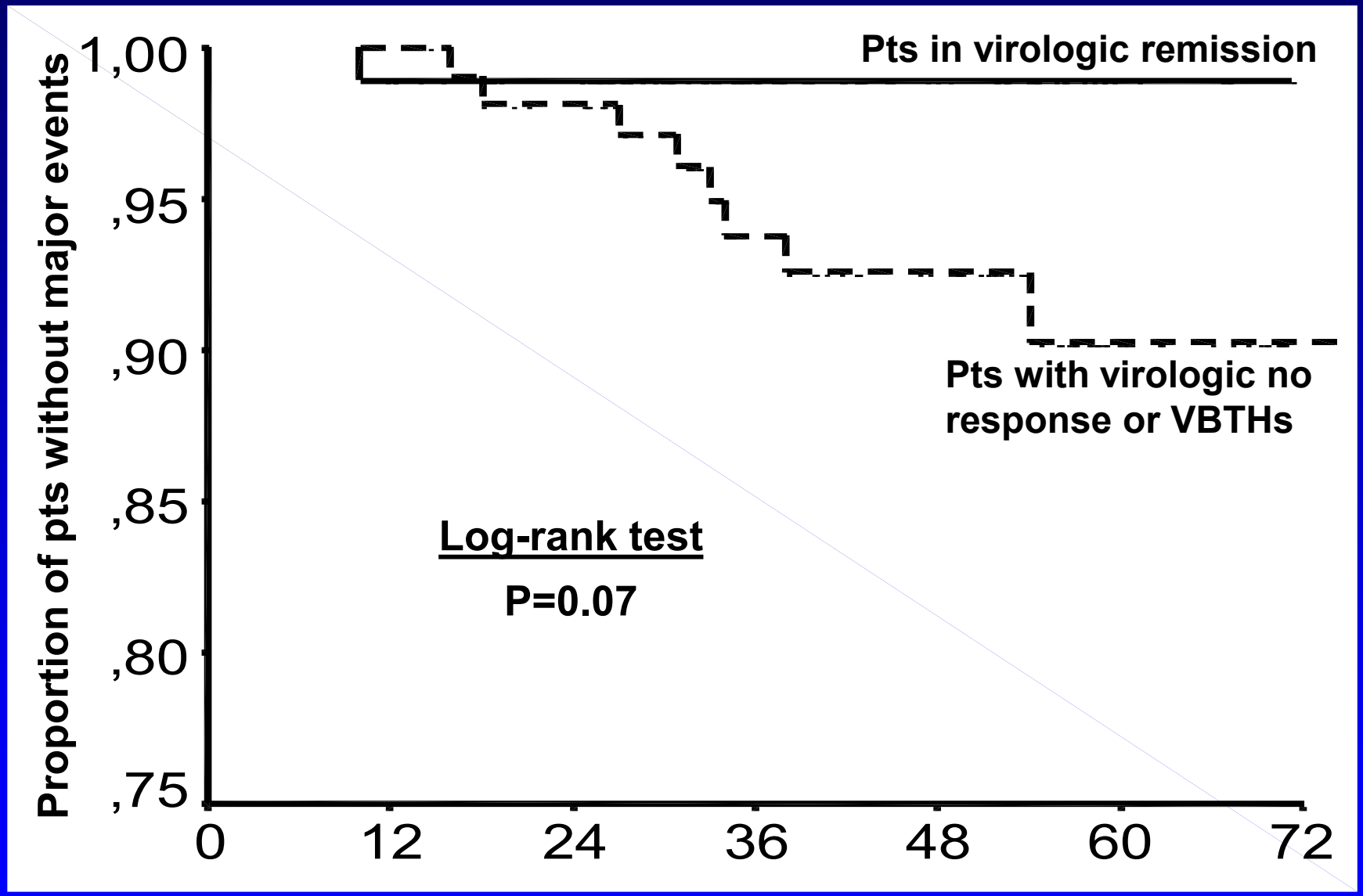
Marcellin P et al. Lancet 2013; in press.

Disease progression in patients with HBeAg(+)/(-) HBV cirrhosis under long-term LAM monotherapy



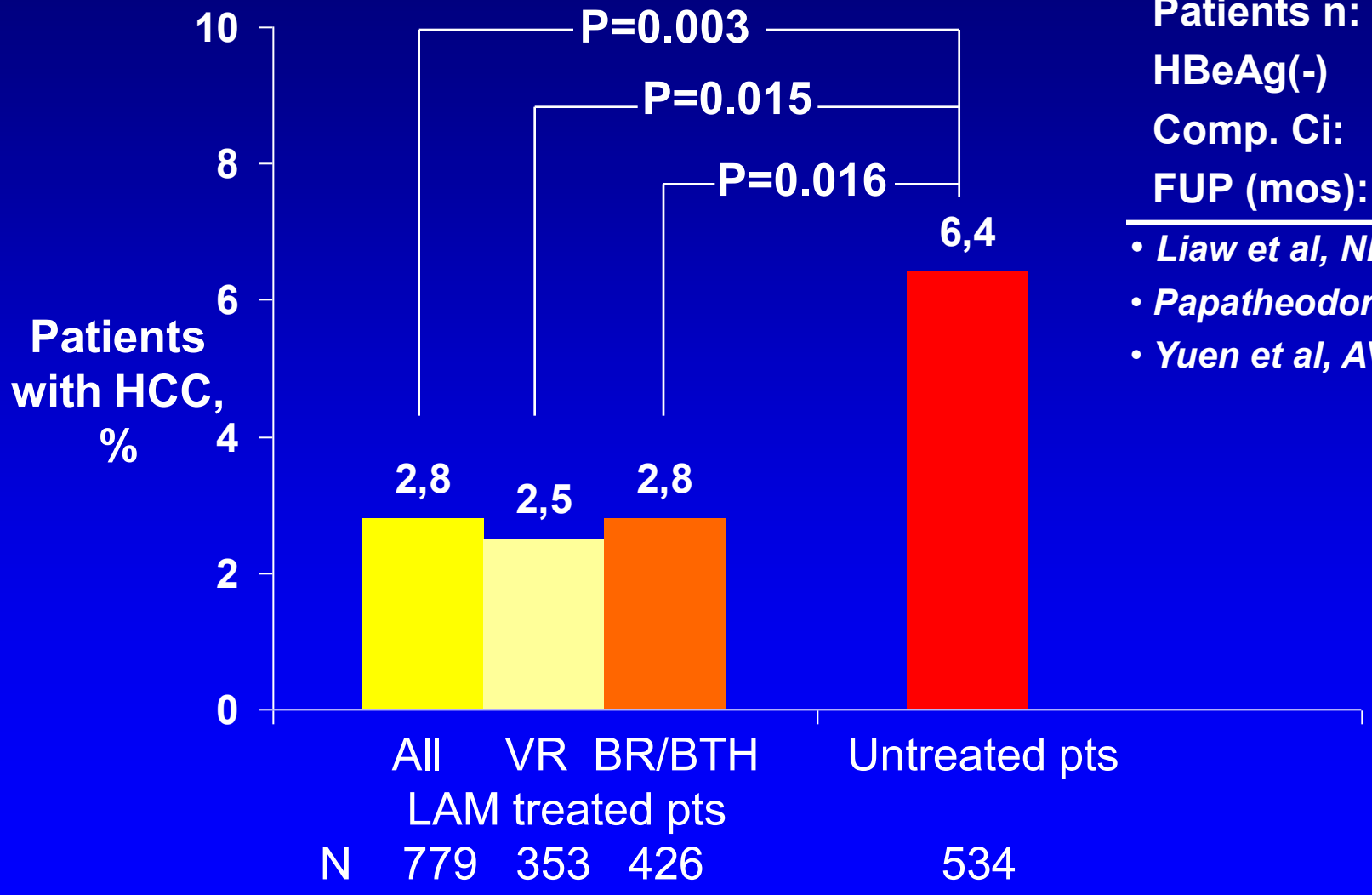
Liaw YF et al. NEJM 2004

Major event free survival under LAM ± salvage ADV



Papatheodoridis et al, Hepatology 2005; 42: 121-9

HCC in CHB patients under LAM

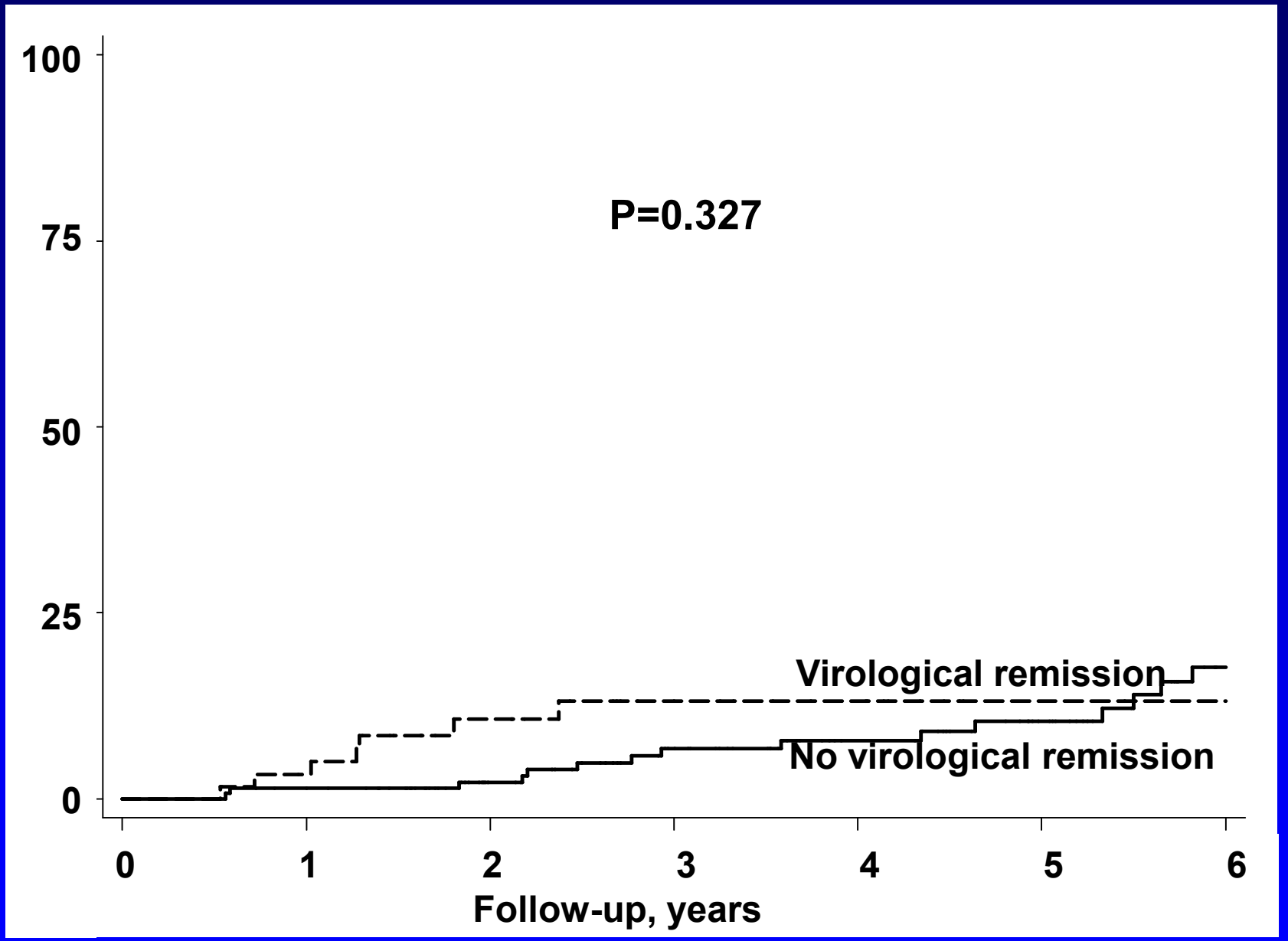


	LAM	Untreated
Patients n:	779	534
HBeAg(-)	49%	54%
Comp. Ci:	29%	39%
FUP (mos):	32-90	32-108

- *Liaw et al, NEJM 2004*
- *Papatheodoridis et al, HEP 2005*
- *Yuen et al, AVT 2007*

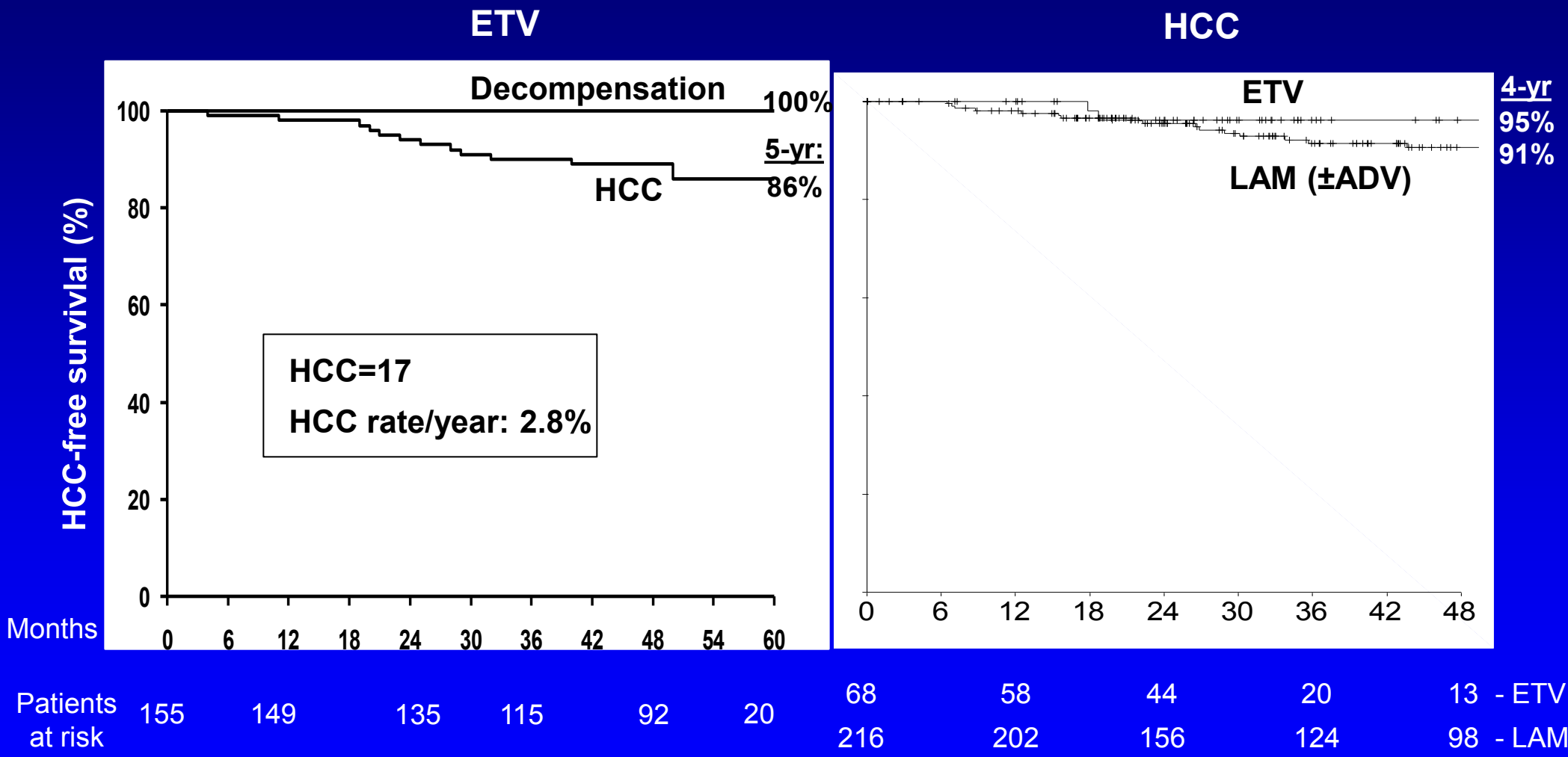
Papatheodoridis, Lampertico, Manolakopoulos, Lok. J Hepatol 2010;53:348-56

HCC in patients with HBV cirrhosis under NA(s) starting with LAM



Papatheodoridis GV et al. Gut 2011, 60: 1109-16

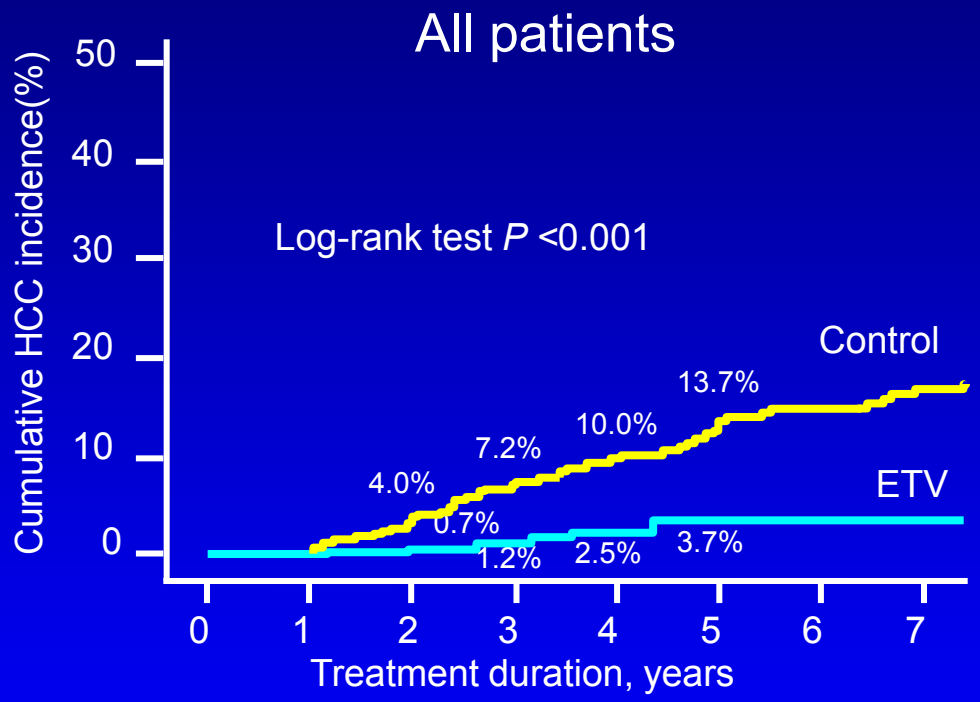
HCC incidence in patients with HBV cirrhosis treated with entecavir



Lampertico P et al. AASLD 2012

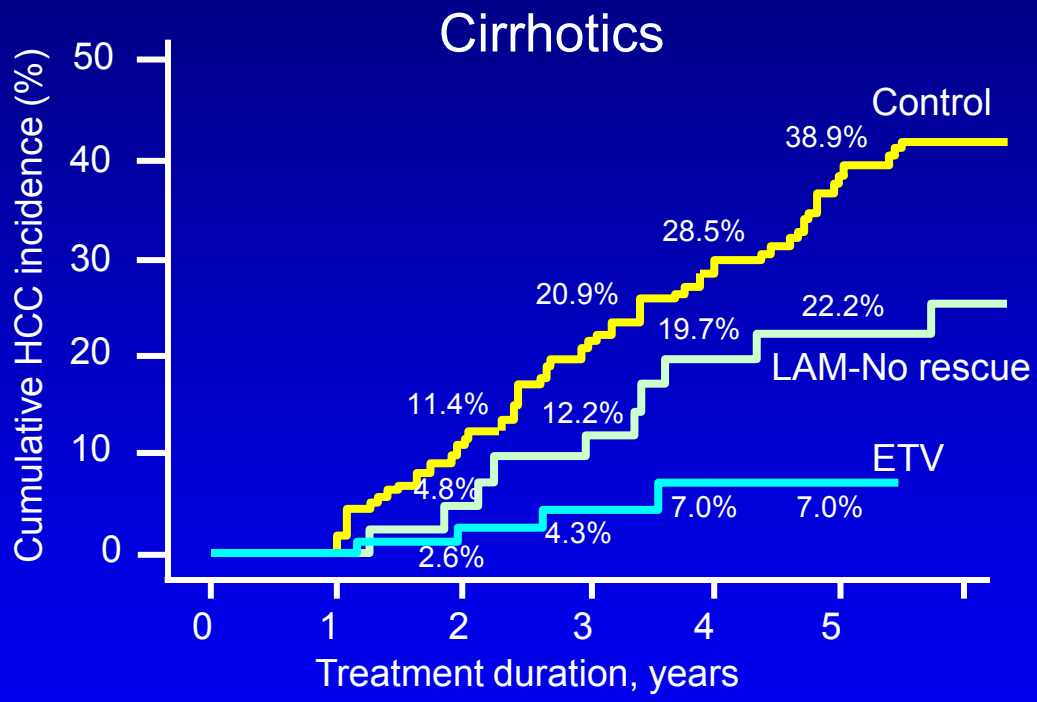
Papatheodoridis G et al. HepNet.Greece cohort 2012

HCC incidence in patients with CHB treated with entecavir



No. at risk

ETV	316	316	264	185	101	44	2	2
Control	316	316	277	246	232	200	187	170



No. at risk

ETV	79	79	72	63	36	17
LAM	49	49	41	35	32	23
Control	85	85	76	66	64	47

Hosaka T et al. Hepatology 2012 Dec 5 [Epub ahead of print]

LONG-TERM ORAL ANTIVIRAL THERAPY IN HBeAg(-) CHB

- Can we ever stop?

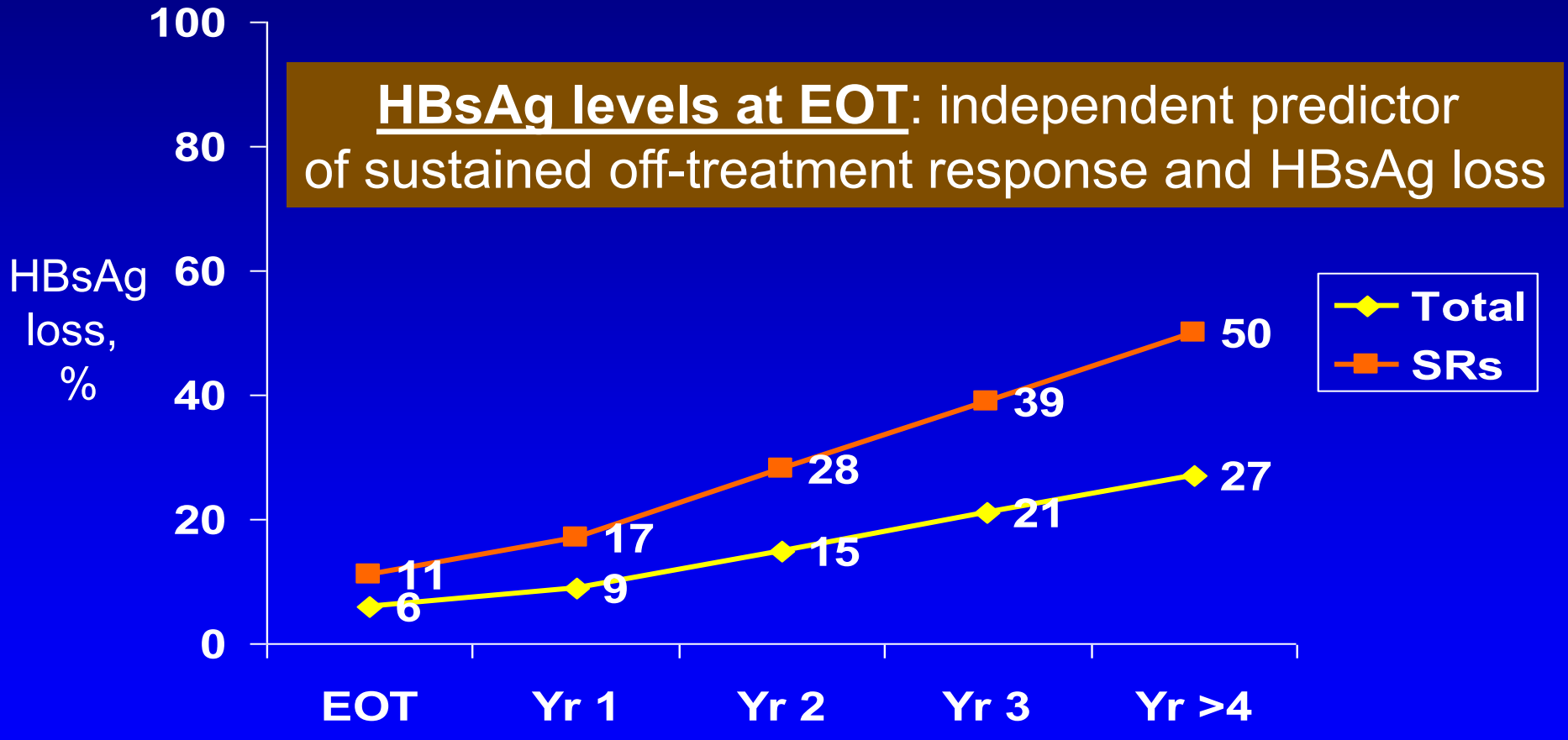
Long-term NA therapy in HBeAg-negative CHB

- **Safe discontinuation: HBsAg loss**
  - **HBsAg loss: 0-1% at 4-5 years**
  - **APASL**: stop NA if HBV DNA (-) on 3 6-monthly occasions
  - **NA discontinuation in non-cirrhotic HBeAg(-)CHB patients in virological remission under 4-5 years ADV therapy**

    Sustained off-therapy response: ~35% (f-up ≥5 yrs)

    Hadziyannis SJ et al. Gastroenterology 2012;143:629-636

HBsAg loss in patients with HBeAg(-) CHB who remained in virological remission under ADV for 4-5 years



Hadziyannis SJ et al. Gastroenterology 2012;143:629-636

HBsAg levels as a marker for safe discontinuation of NA therapy in CHB

- **HBsAg at end of NAs <100 IU/mL**
- 81 (50 e+, 31 e-) pts with post-NAs f-up 32±24 months

  HBsAg at end of NAs <100 IU/mL - AUROC for SVR: 99%

  (sens: 100%, spec: 93%, PPV: 69%, NPV: 100%)

  Suh SJ et al. EASL 2012

- 77 (38 e+, 39 e-) pts with post-NAs f-up ≥6 months

  12-month relapse rates in relation to HBsAg at end of NAs -

  <100 IU/mL: 0%, 100-1000 IU/mL: 50%, >1000 IU/mL: 78%

  Jiang JN et al. EASL 2012

Designs of ongoing trials in CHB

Towards finite treatment duration

- NA(s) discontinuation after a certain duration
- NA(s) discontinuation in patients wih favorable markers of sustained off-therapy remission (eg low HBsAg levels)
- Peg-IFN after some years of NA therapy
- Peg-IFNa/λ + ETV or Peg-IFNa + TDF
- TLR7 agonists + ?

HBeAg-negative chronic hepatitis B

Why do and shall I treat my patients with a NA?

- No contraindication
- Excellent tolerability & good safety
- On-treatment responses in almost all patients
- Minimal safety & efficacy monitoring
- Improved histology & long-term outcomes
- Patients' preference (one pill per day)
- Even in majority of PeglFNa treated patients–PegFNa failures
- Cost reduction in the future
  (already very cheap in some developing countries)
- Probably part of any future combination


Thank you