HBV Therapy in Special Populations: Liver Cirrhosis

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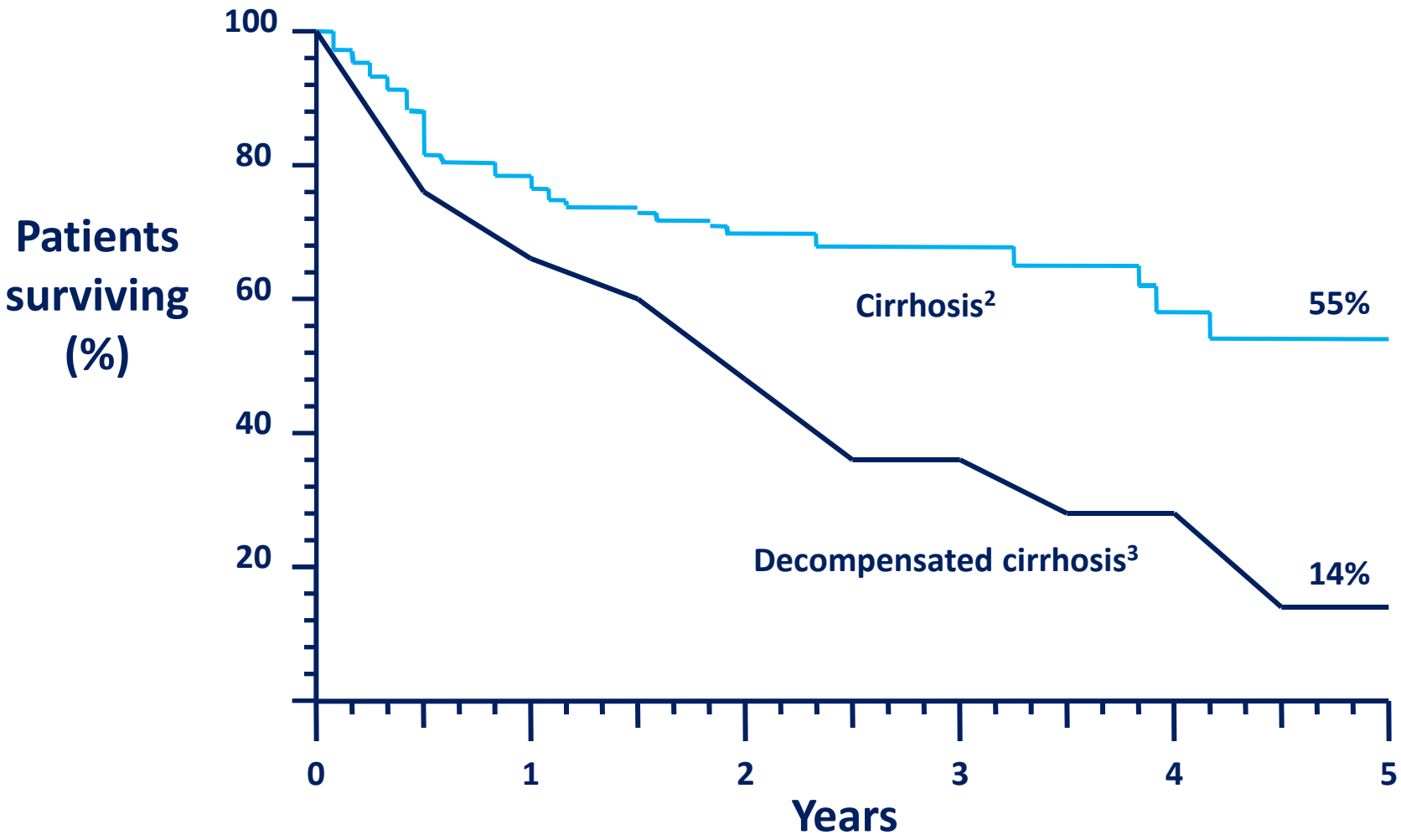
Therapy of HBV cirrhosis
compensated and decompensated disease

1. Who should be treated?
2. How – treatment regimen?
3. Efficacy – effect on long-term prognosis
   - Prevention of decompensation/ liver transplantation?
   - Regression of cirrhosis?
4. Predictors of response?
5. Safety

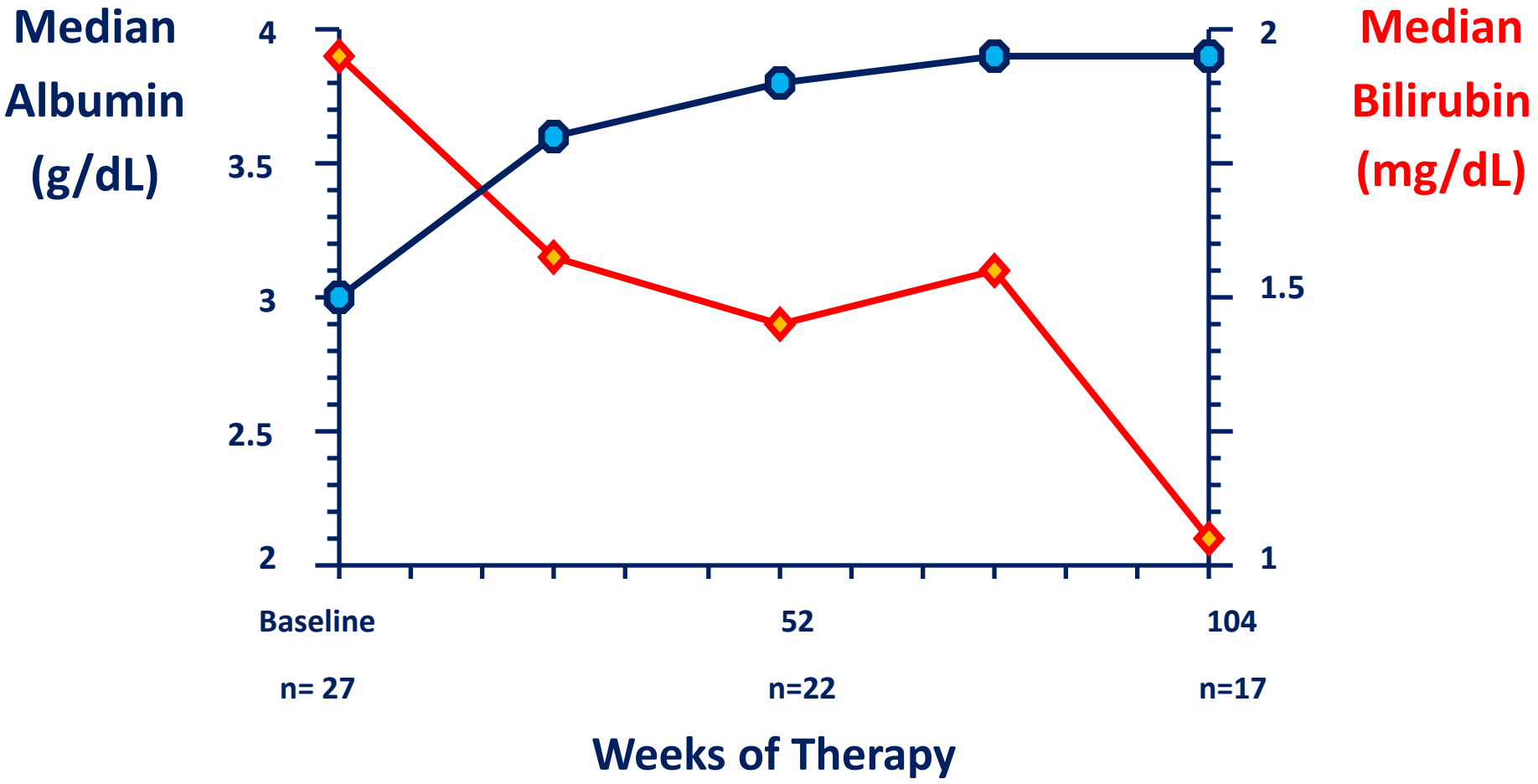
Actuarial Survival in HBV End Stage Liver Disease

Historical Comparisons



Perrillo *et al.*, 2001[1], Weissberg *et al.*, 1984[2], and De Jongh *et al.*, 1992[3]

Patients With End Stage Chronic Hepatitis B Treated with Lamivudine



Perrillo *et al*. Hepatology 2001

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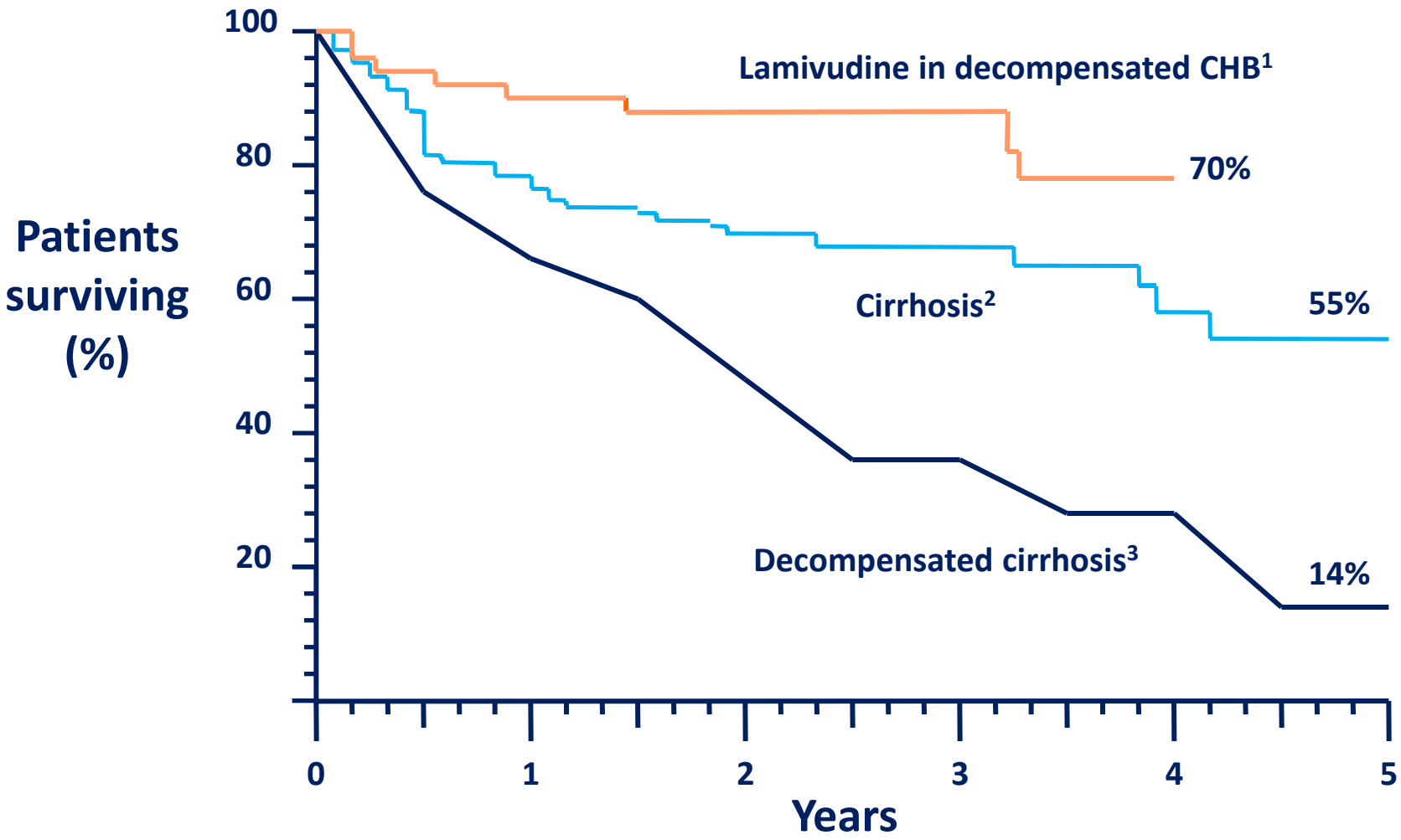
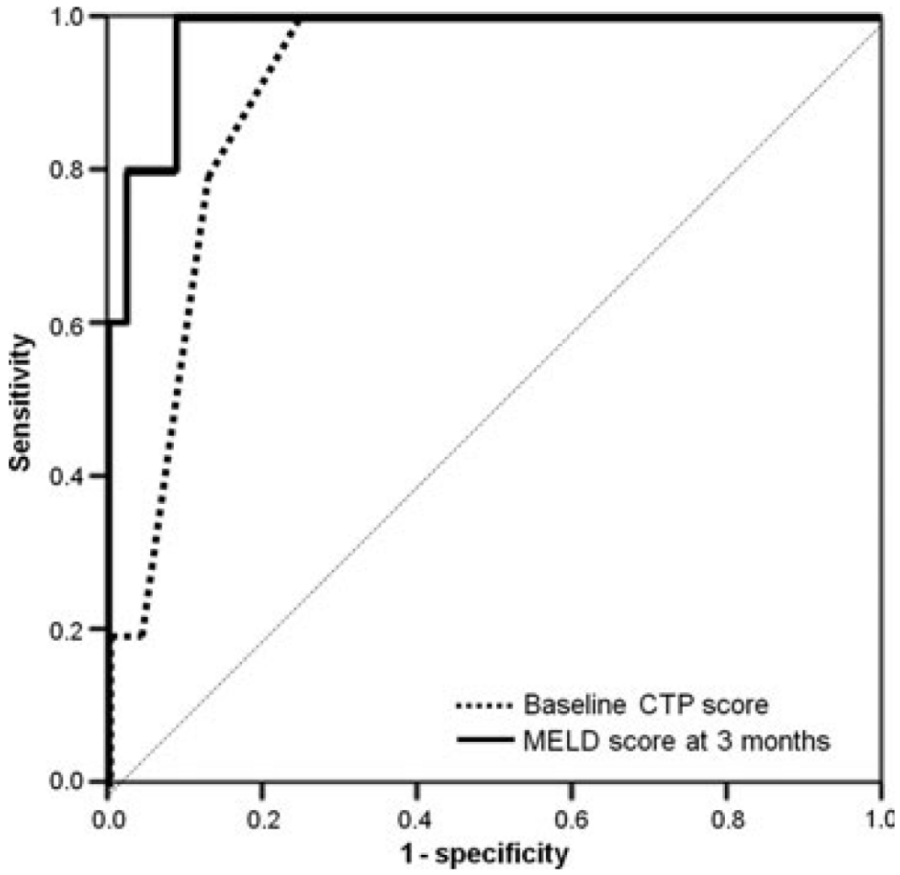


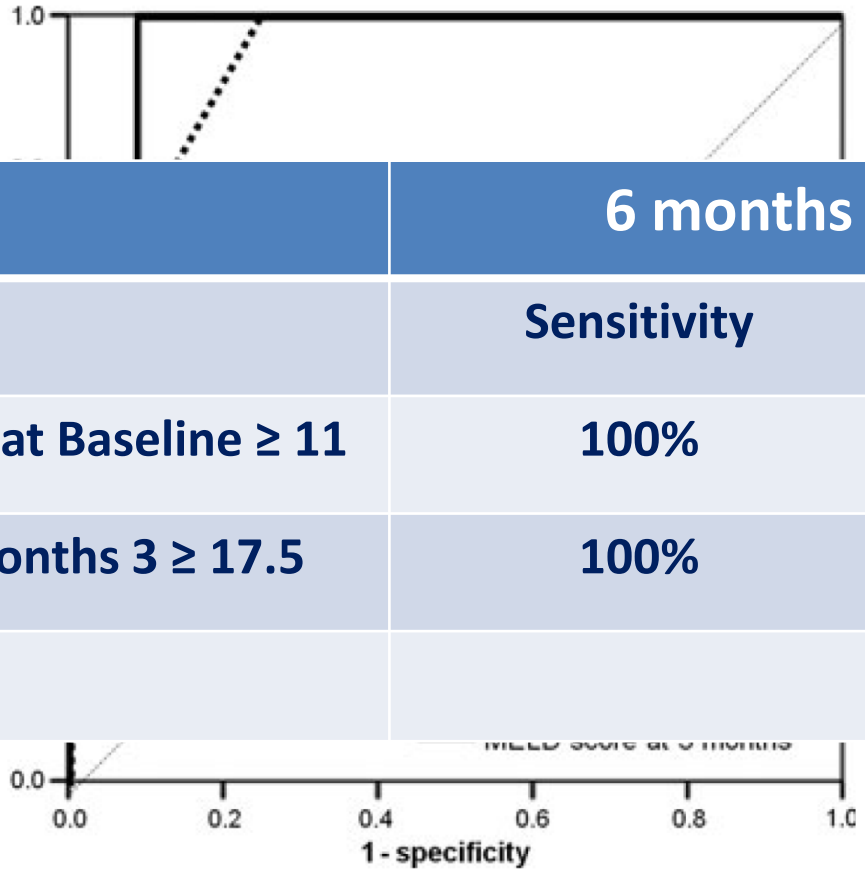
Perrillo *et al.*, 2001[1], Weissberg *et al.*, 1984[2], and De Jongh *et al.*, 1992[3]

NUCs - Lamivudine (LMV) and Entecavir (ETV) – in decompensated HBV cirrhosis: predictors of survival



Hyun JJ et al. Liver Int 2012; 32: 656

NUCs - Lamivudine (LMV) and Entecavir (ETV) – in decompensated HBV cirrhosis: predictors of survival

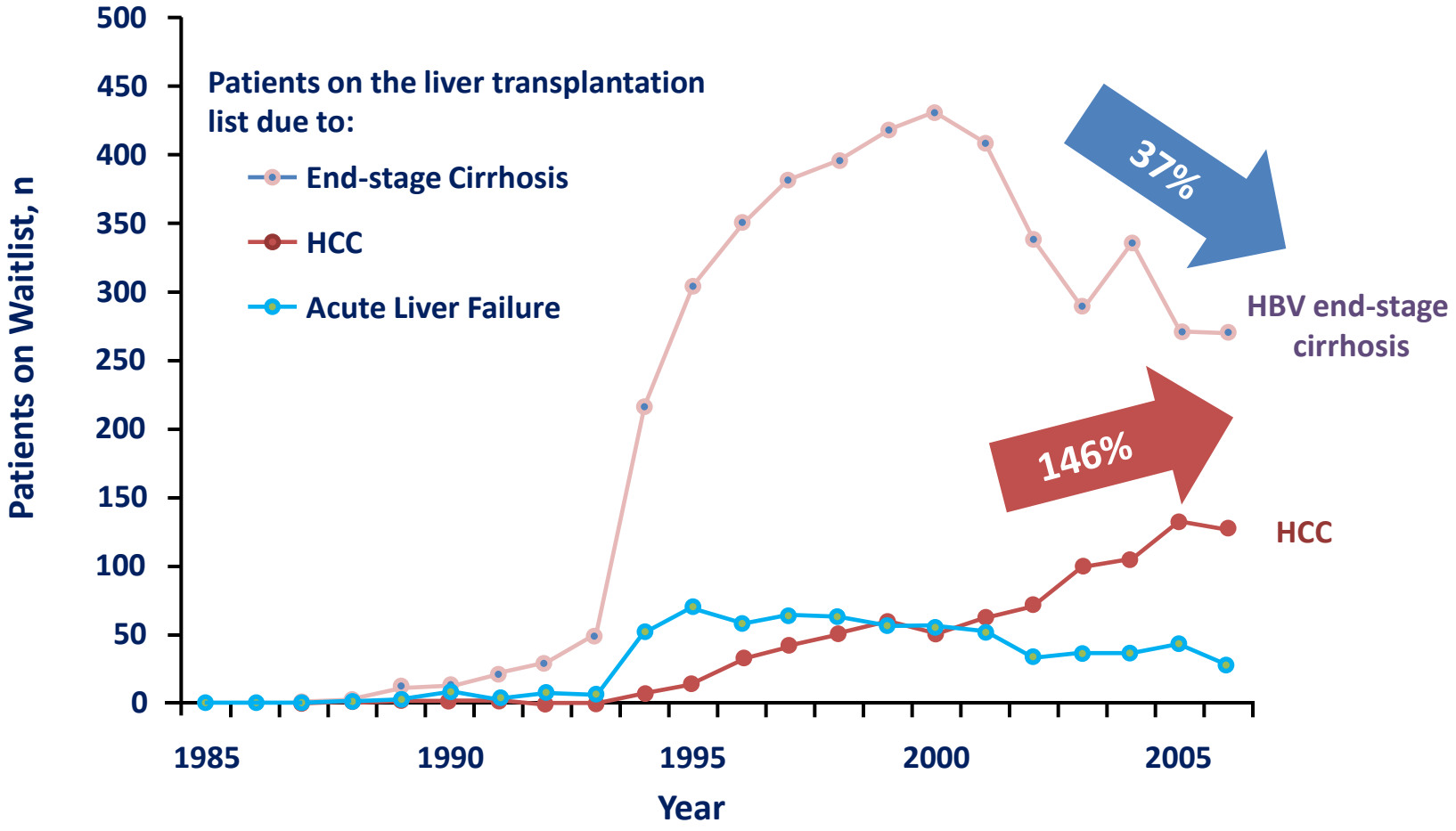


Predictor	6 months mortality	
	Sensitivity	Specificity
Child Pugh Score at Baseline ≥ 11	100%	75.6%
MELD Score at months 3 ≥ 17.5	100%	91%

Hyun JJ et al. Liver Int 2012; 32: 656

Decline in the number of patients placed on the liver transplantation waiting list for hepatitis B-related indications in the US

Kim WR. *Hepatology* 2009;49:S28-S34



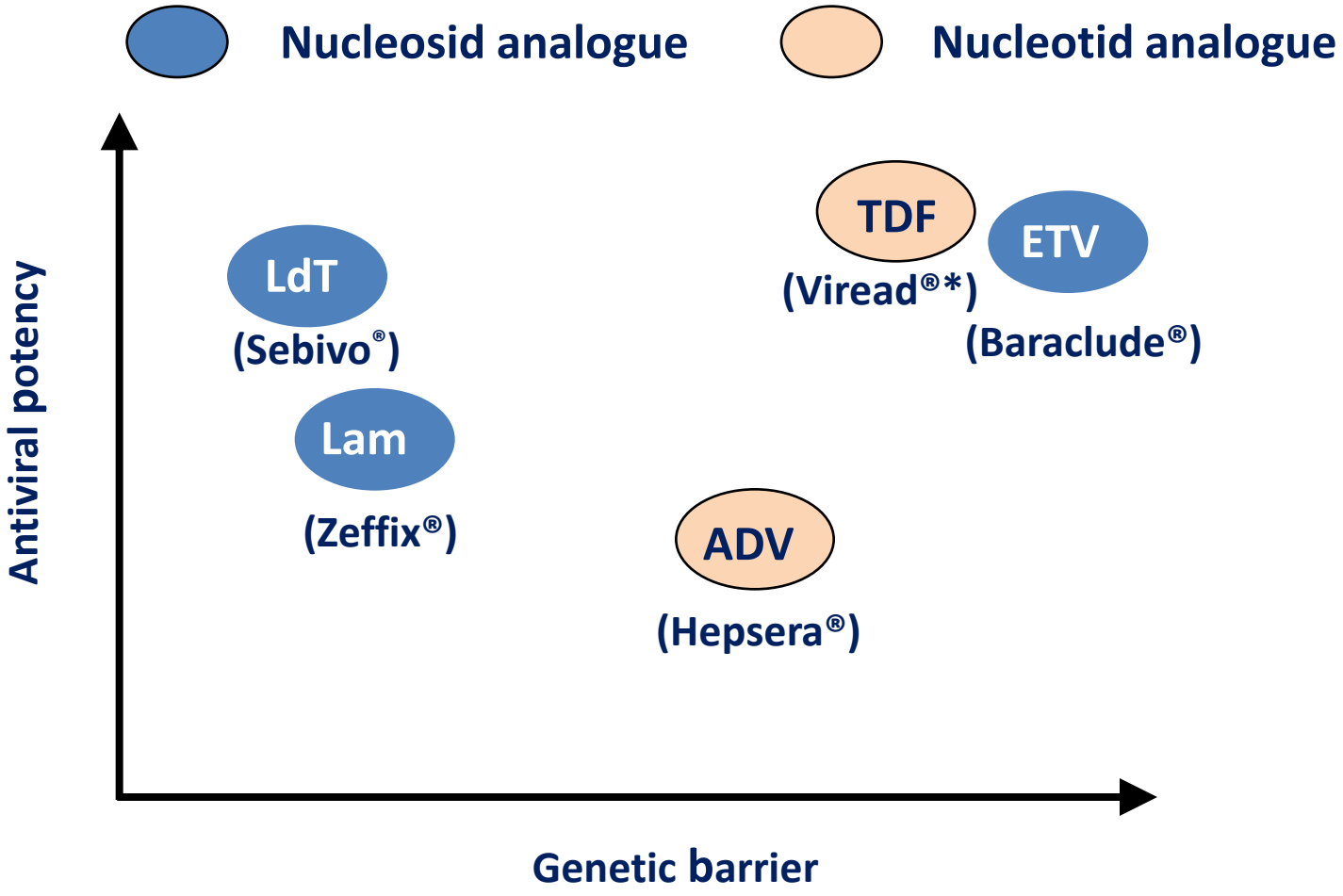
EASL Clinical Practice Guideline Recommendations

- **Patients with compensated cirrhosis and detectable HBV DNA must be considered for treatment even if ALT levels are normal (B1).**
- **Patients with decompensated cirrhosis and detectable HBV DNA require urgent antiviral treatment with NUCs.**
- **Significant clinical improvement can be associated with control of viral replication. However, antiviral therapy may not be sufficient to rescue some patients with very advanced liver disease who should be considered for liver transplantation at the same time (A1).**

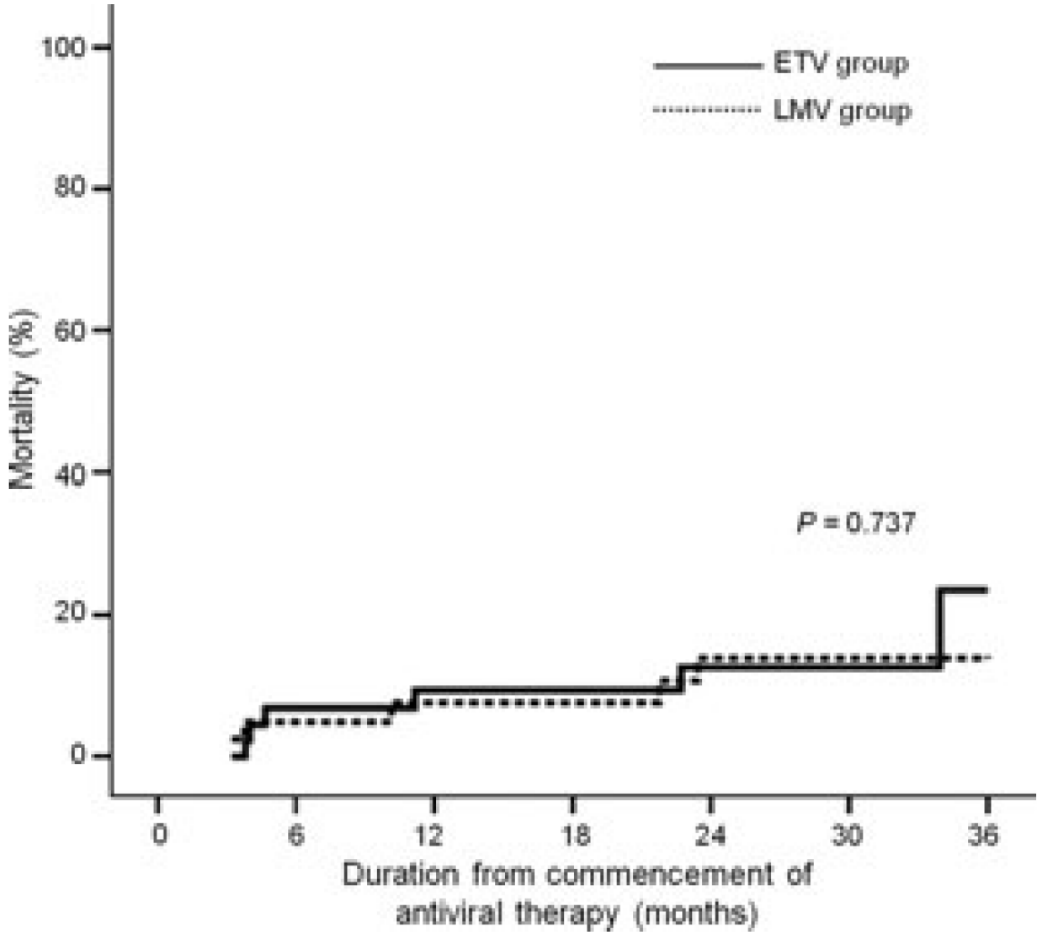
J Hepatol 2012; 57: 167

How to treat?

Charakteristics of different HBV nucleos(t)id analogues



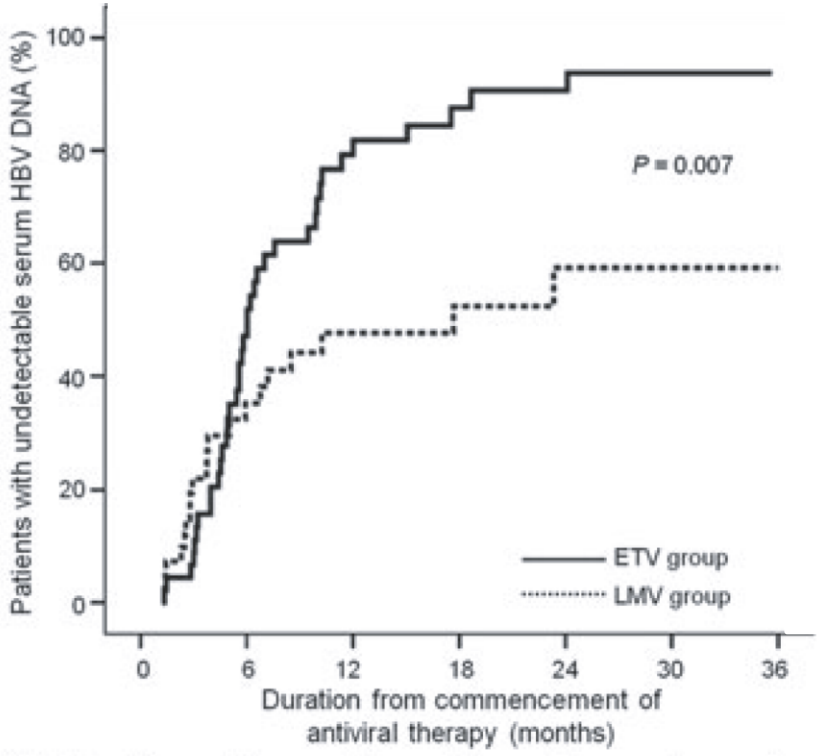
Lamivudine (LMV) vs. Entecavir (ETV) in decompensated HBV cirrhosis: Survival



Hyun JJ et al. Liver Int 2012; 32: 656

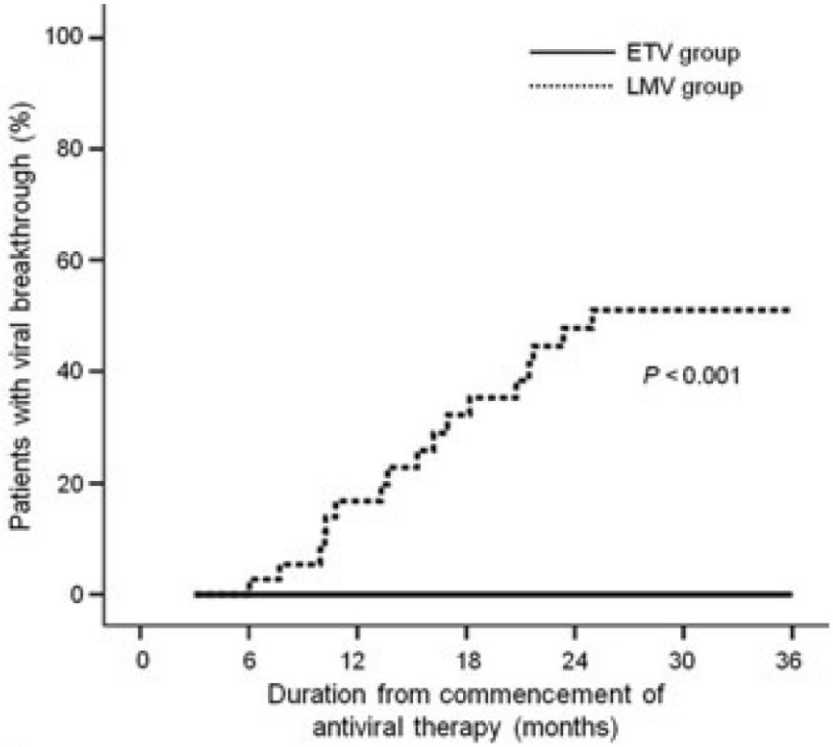
Lamivudine (LMV) vs. Entecavir (ETV) in decompensated HBV cirrhosis

Undetectable HBV DNA



No. Pts.								
	LMV group	41	23	14	10	5	4	3
	ETV group	45	22	8	4	3	1	0

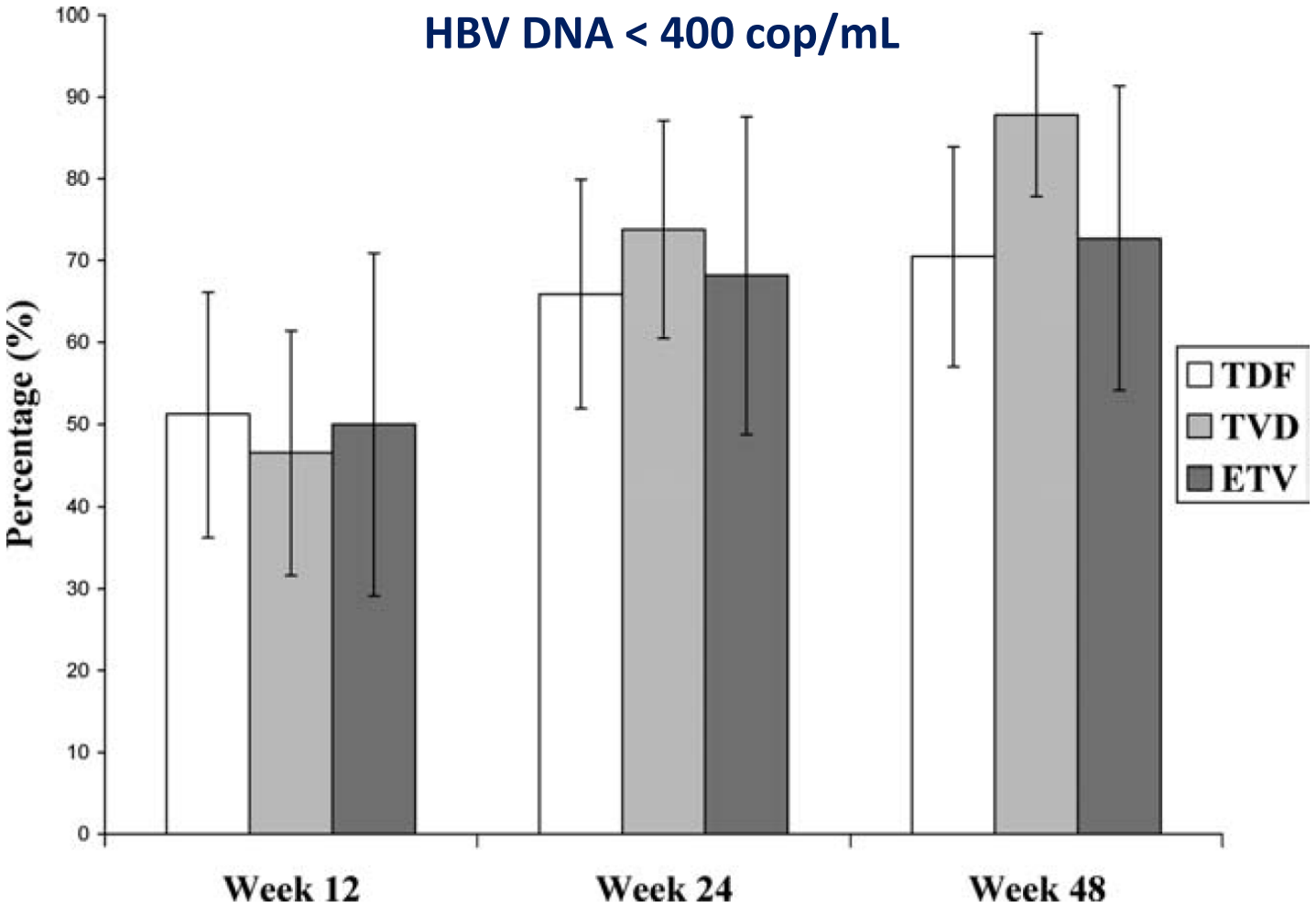
Viral breakthrough



No. Pts.								
	LMV group	41	36	29	22	16	14	10
	ETV group	45	40	35	31	24	14	3

Hyun JJ et al. Liver Int 2012; 32: 656

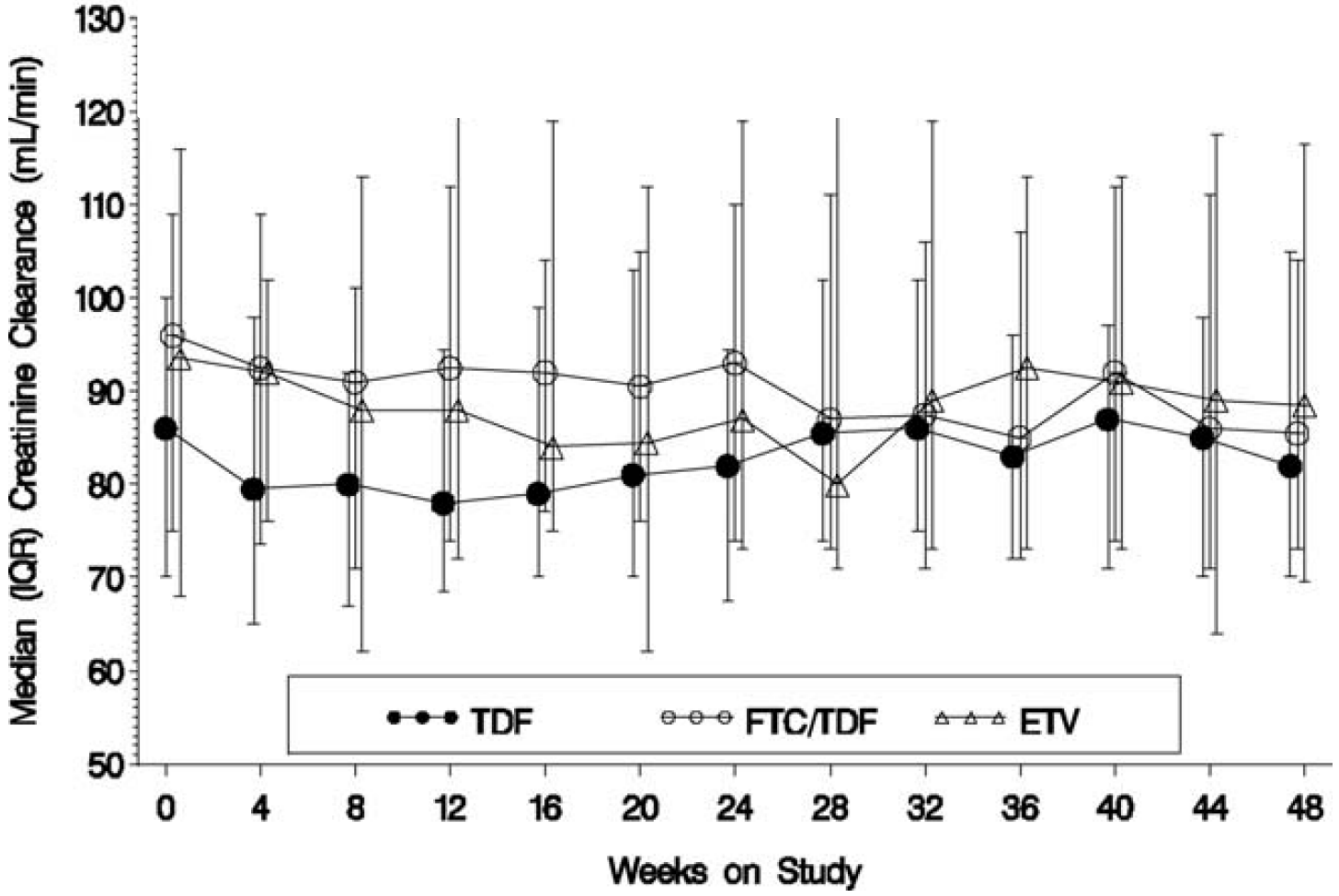
Efficacy of different nucleos(t)ide analogs in patients with decompensated HBV liver cirrhosis



Liaw Y-F et al. Hepatology 2011; 53:62

Safety?

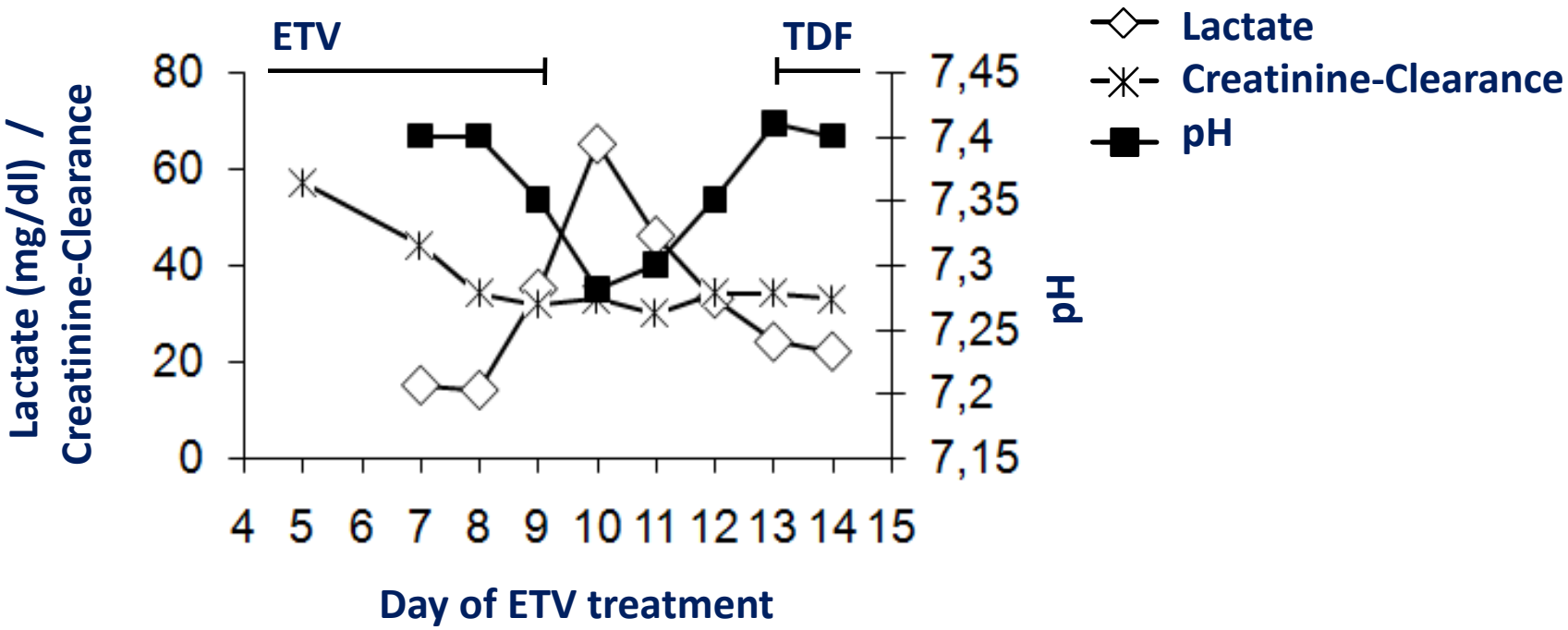
Renal safety of different nucleos(t)ide analog regimens in patients with decompensated liver cirrhosis



Liaw Y-F et al. Hepatology 2011; 53:62

Lactic acidosis during entecavir treatment in patients with decompensated cirrhosis

Lange C et al. Hepatology 2009; 50: 2001

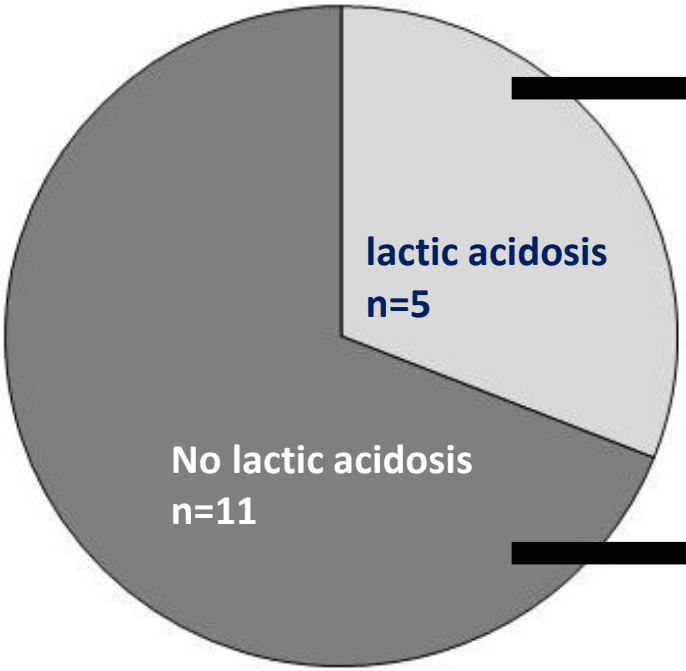


Patient D

ETV, entecavir
TDF, tenofovir disoproxil fumarate

Lactic acidosis during entecavir treatment in patients with decompensated cirrhosis

Lange C et al. Hepatology 2009; 50: 2001



MELD score ≥ 22 (22, 25, 28, 29, 38)

Lactic acidosis reversible after entecavir discontinuation: n=4

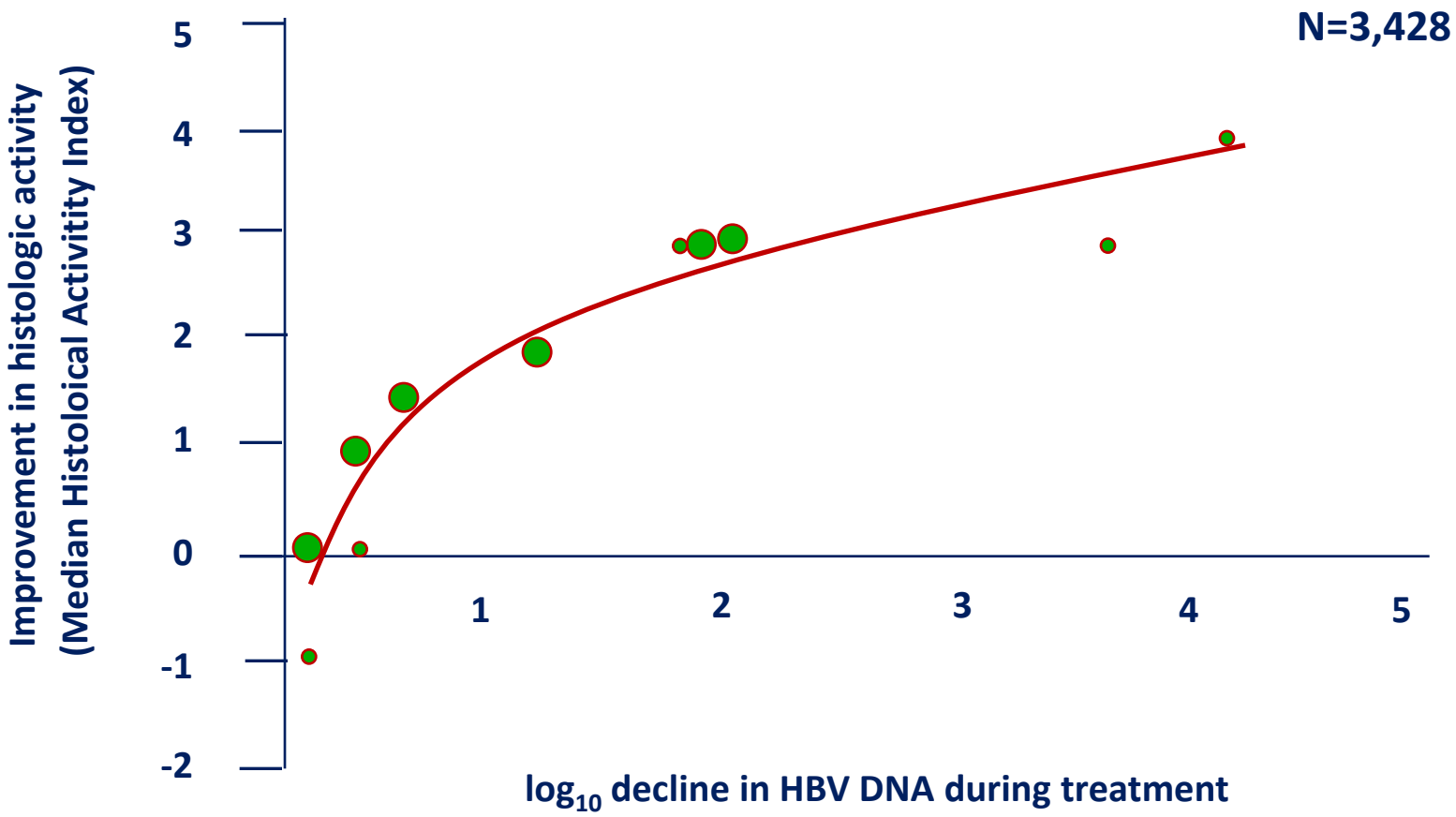
Lethal outcome: n=1
(fulminant liver failure is a differential diagnosis)

MELD score < 22 (6-17)

Development of lactic acidosis correlated with the MELD score and its single parameters INR, bilirubin, creatinine ($p<0.005$ each)

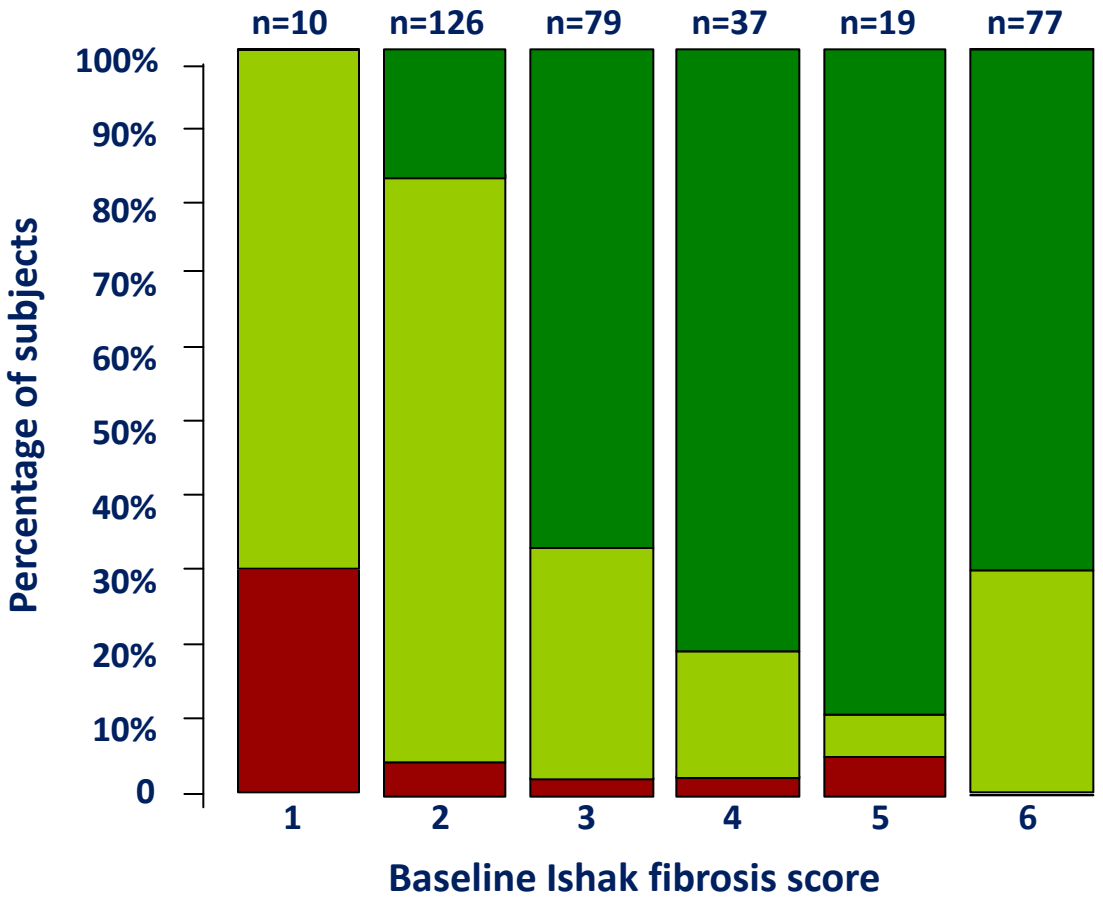
Long-term efficacy?

Correlation between HBV DNA Response during antiviral therapy and histologic response



Mommeja-Marin H et al. Hepatology 2003; 37: 1309

Impact of Tenofovir DF Treatment on Fibrosis Response at Year 5



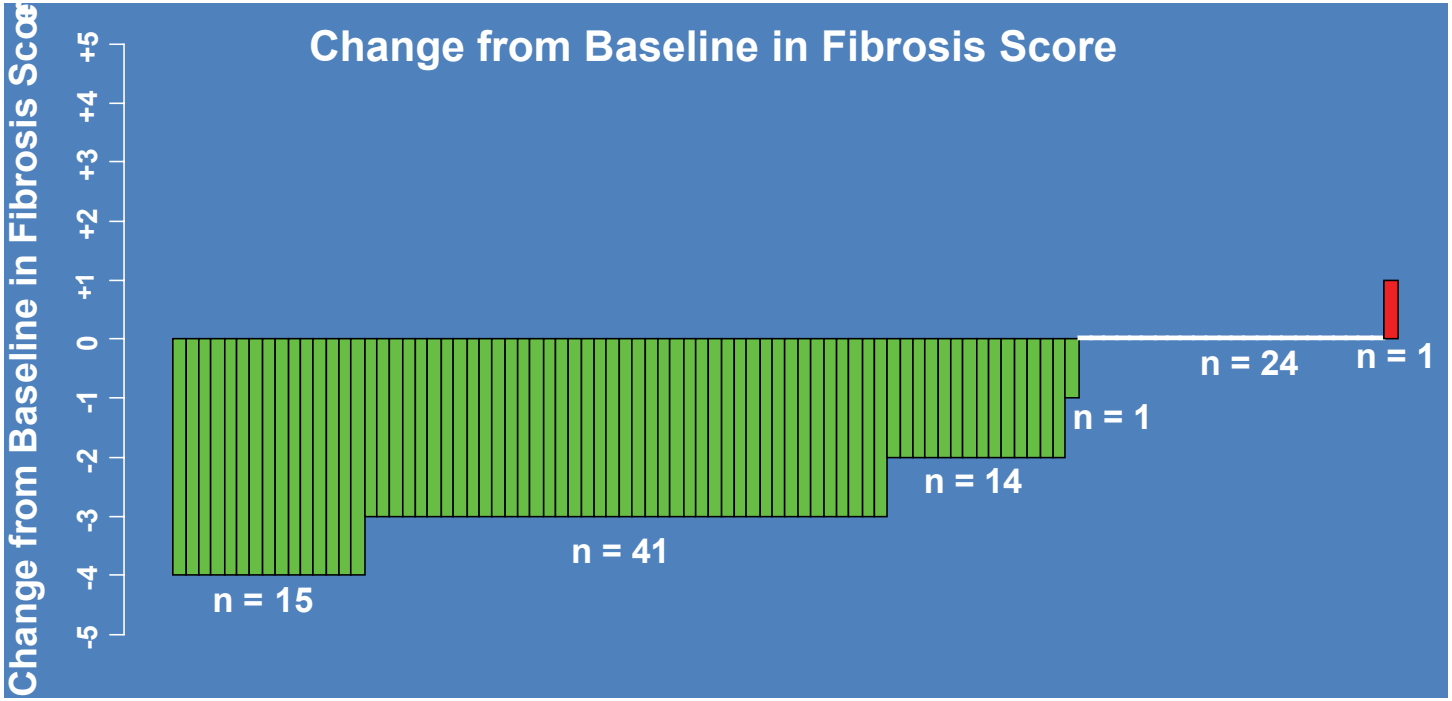
Year 5 Response (348 paired biopsies)

- Improvement
- No Change
- Worsening

71/96 (74%) of cirrhotic patients had cirrhosis reversed (Ishak fibrosis score ≤4) at year 5

Marcellin, P, et al. AASLD 2011; Poster #1375.

Change in Ishak Fibrosis Scores at Year 5 for Patients with Cirrhosis at Baseline



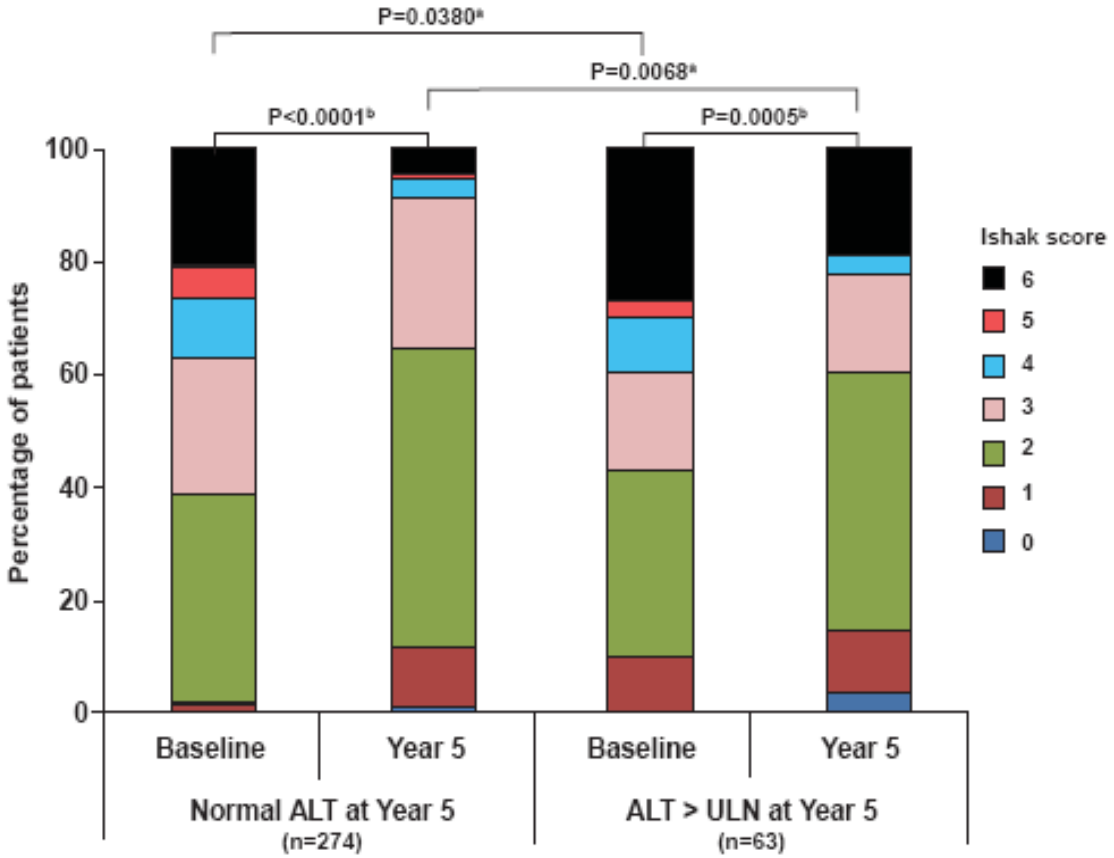
- 96 patients with cirrhosis (Ishak fibrosis score ≥5) had paired BL and Year 5 biopsies
  - 74% (n=71) of patients had cirrhosis reversed (Ishak fibrosis score <5) at Year 5
  - 73% (n= 70) had decreases of ≥2 points at Year 5
  - 25% (n=24) did not change
  - Of 94 patients who did not add FTC, 73% had cirrhosis reversed; 26% showed no change

Marcellin, P, et al. AASLD 2011; Poster #1375.

Studies 102/103

Comparative improvements in Ishak fibrosis scores for patients with normal vs abnormal ALT at Year 5

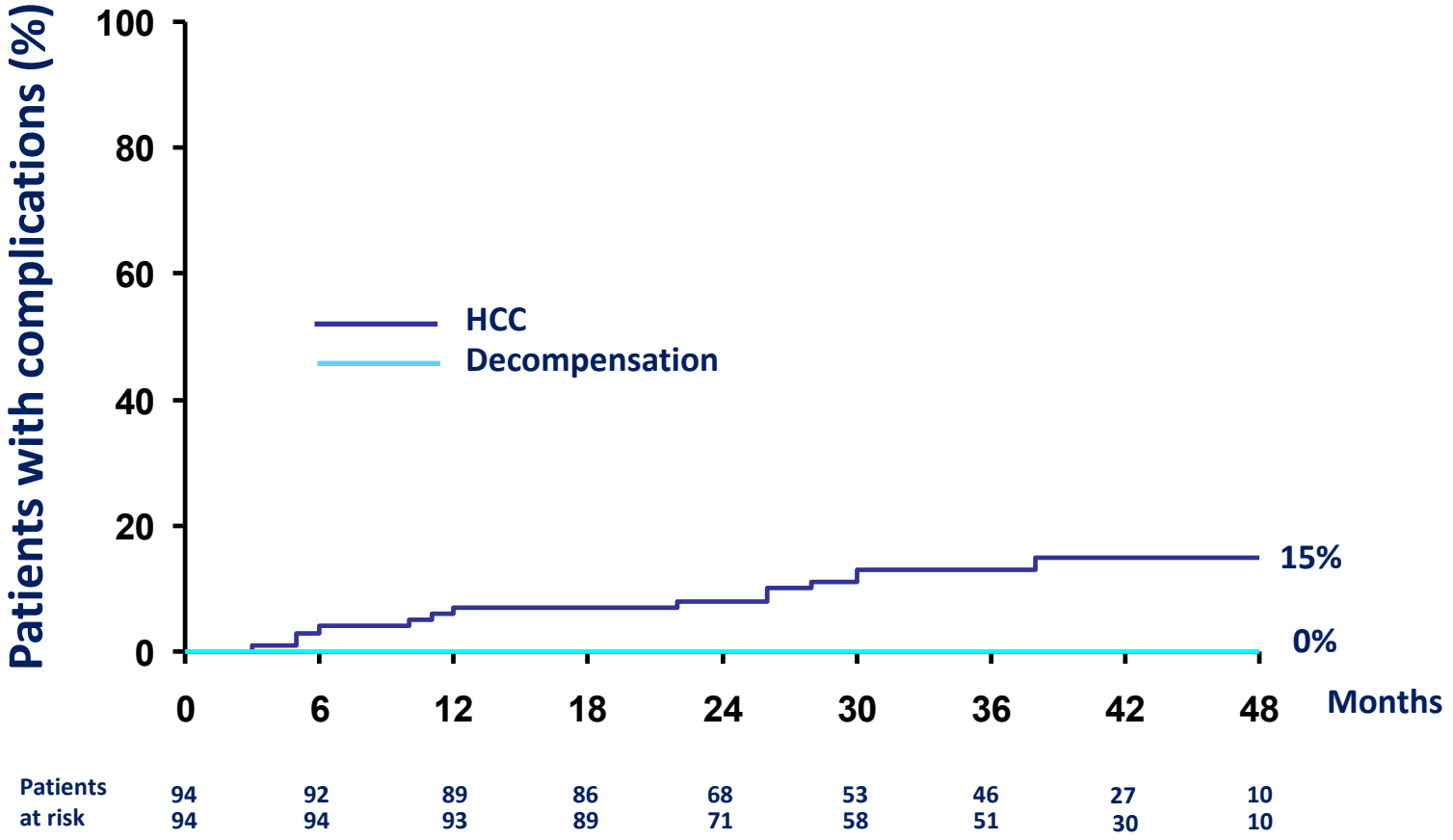
- Both groups showed significant improvements in Ishak scores at Year 5
- A significantly lower percentage of patients in the normal ALT group vs the ALT > ULN group had cirrhosis (Ishak ≥5) at Year 5 (5% vs 19%)



Jacobson I, et al. AASLD 2012; Boston. #411.

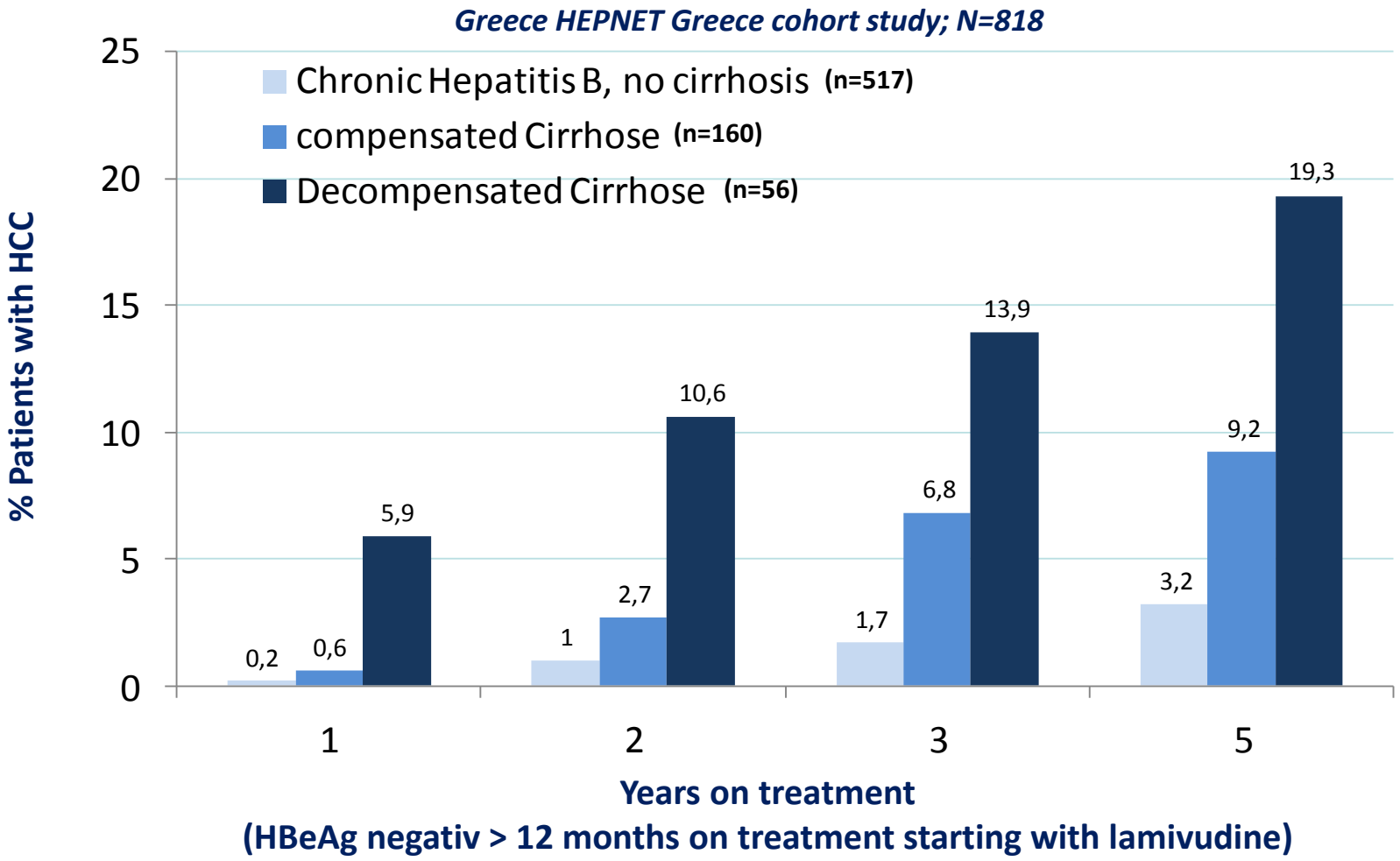
Long-term ADV+LAM therapy in patients with cirrhosis and lamivudine resistance

Lampertico P et al. Gastroenterology 2007; 133: 1445



HCC risk during long-term NUC treatment?

Papatheodoridis G et al. Gut 2011; 60: 1109



(HBeAg negativ > 12 months on treatment starting with lamivudine)

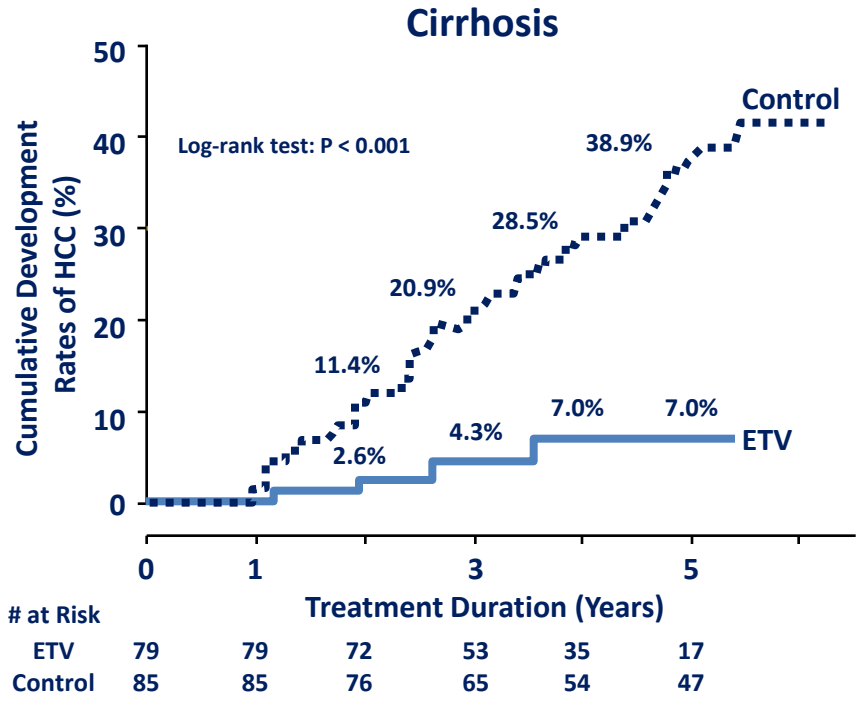
Summary of studies evaluating the HCC risk in NUC naive cirrhotic patients under long-term therapy

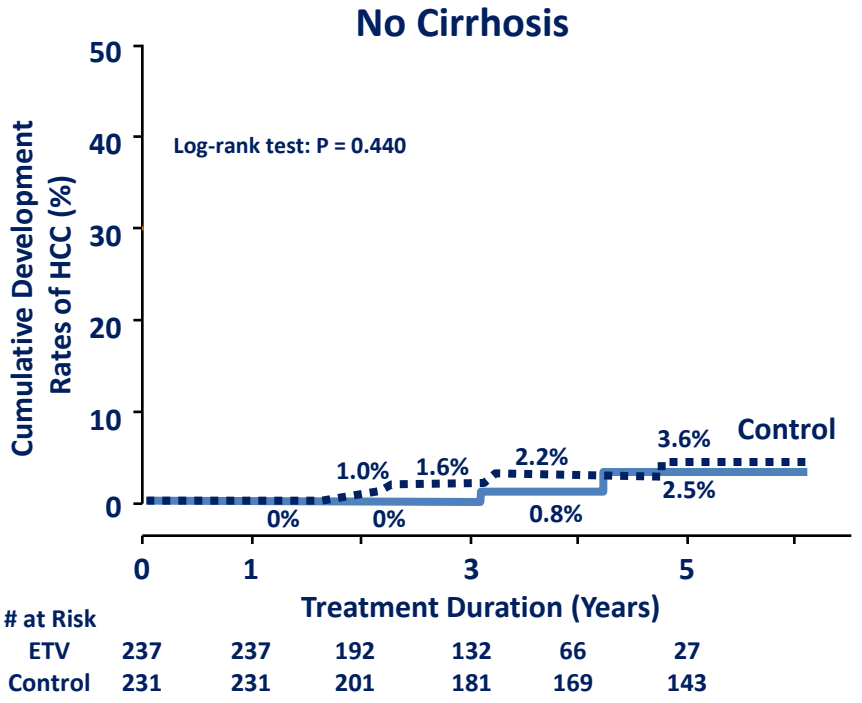
Aghemo A et al. J Hepatol 2012; 57: 1326

Author (year)	HCC/Year %	
Liaw et al. (2004)	LAM	1.5%
Papatheodoridis et al. (2010)	LAM	2.4%
Papatheodoridis et al. (2011)	LAM	2.5%
Kurokawa et al. (2012)	LAM	2.8%
Lampertico et al. (2011)	ETV	2.5%

HCC Incidence in Patients Treated with Long Term ETV

Retrospective cohort study in 472 NA naïve patients who received ETV (2004-2010) vs historical control group of 1143 non-NA-treated HBV patients (1973-1999).
Primary outcome: confirmed HCC diagnosis >1 year after start of therapy



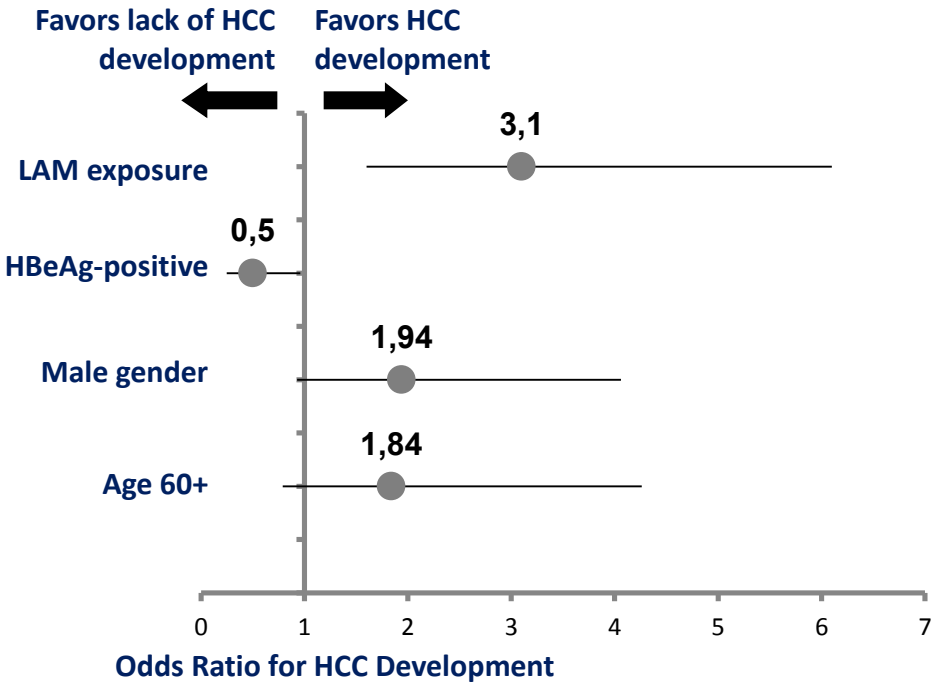


Hosaka T, et al. AASLD 2012; Boston. #357.

Factors associated with HCC Risk in CHB Patients Achieving Viral Suppression with Anti-Virals

Multi-center, retrospective analysis of HCC development in 101 patients who achieved viral suppression on anti-viral therapy compared to 99 matched controls with viral suppression but without HCC development

- Mean duration of therapy (months)
  - 42.25 ± 30.7 in HCC group
  - 44.00 ± 33.14 in control group
- LAM exposure:
  - 79% in HCC group
  - 56% in control group
- Predictors of HCC development
  - Multivariate analysis
    - Lamivudine Exposure
    - HBeAg negative



In this group, despite achieving viral suppression with antiviral therapy, there was still an increased risk of the HCC primarily related to HBeAg negative disease and LAM exposure.

Ghaly S, et al. AASLD 2012; Boston. #332.

EASL Clinical Practice Guideline Treatment of HBV Cirrhosis

J Hepatol 2012; 57: 167

- **Among NUCs, monotherapies with tenofovir or entecavir are preferred. Lamivudine should not be used in such patients.**

- **NUC therapy should usually be continued indefinitely in cirrhotic patients. Treatment might be stopped after confirmed anti-HBe seroconversion (in HBeAg-positive patients) or *ideally* HBsAg loss and anti-HBs seroconversion.**

- **PEG-IFN may increase the risk of bacteraemic infection and hepatic decompensation in patients with advanced cirrhosis However, PEG-IFN in regimens similar to those used in CHB can be used for the treatment of well compensated cirrhosis**

- **Regression of fibrosis and even reversal of cirrhosis have been reported in patients with prolonged suppression of viral replication. Nonetheless, long-term monitoring for HCC is mandatory despite virological remission under NUCs, since there is still a risk of developing HCC**