Optimal Therapy for HBeAg-positive Chronic Hepatitis B:

Why Do I Treat My Patient with a NUC?

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Conflict of Interest Disclosure

- **I was on advisory board of, and/or, received speaker fee from pharmaceutical companies including:**

  BMS, GSK, MSD, Novartis and Roche

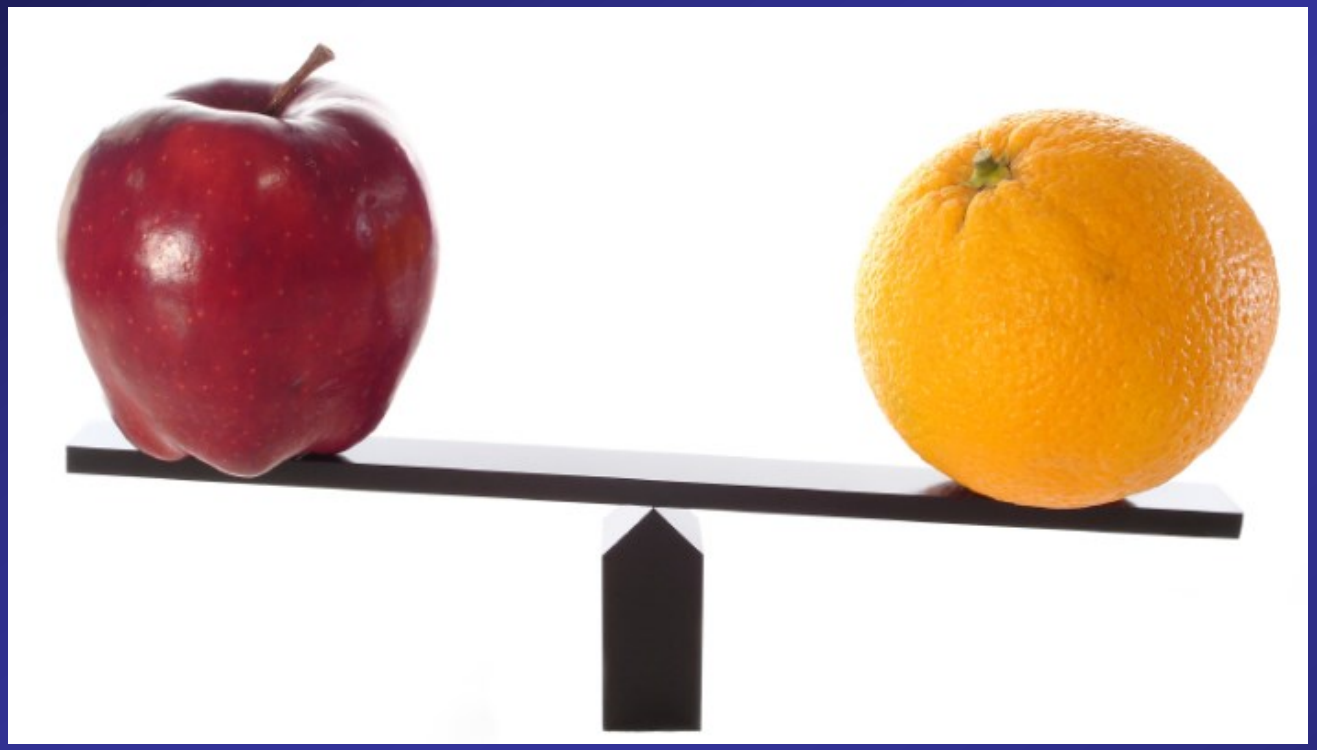
- **I will not talk about off-label use of any drug**

Pros and cons of PEG-IFN vs NAs

PEG-IFN	Nucleos(t)ide analogues
Pros	*Pros*
Finite duration of therapy	Daily oral dosing
Absence of viral resistance	Potent HBV DNA suppression
Response durable post-therapy	Minimal side effects in the short term
Proven effect in general patient population	Proven effect in patients with advanced liver disease
Increase in HBsAg seroconversion rate	Less expensive during first year, possibly equally or more costly after long-term therapy
Cons	*Cons*
Frequent side effects	Risk of resistance
Weekly subcutaneous injection	Limited increase in HBsAg seroconversion rate
Less effective HBV DNA suppression	Response less durable post-therapy
Expensive	Long-term or indefinite therapy may be required

Sonneveld MJ, et al. Curr Hepatitis Rep 2010; 9:91–8

Compare an Apple and an Orange



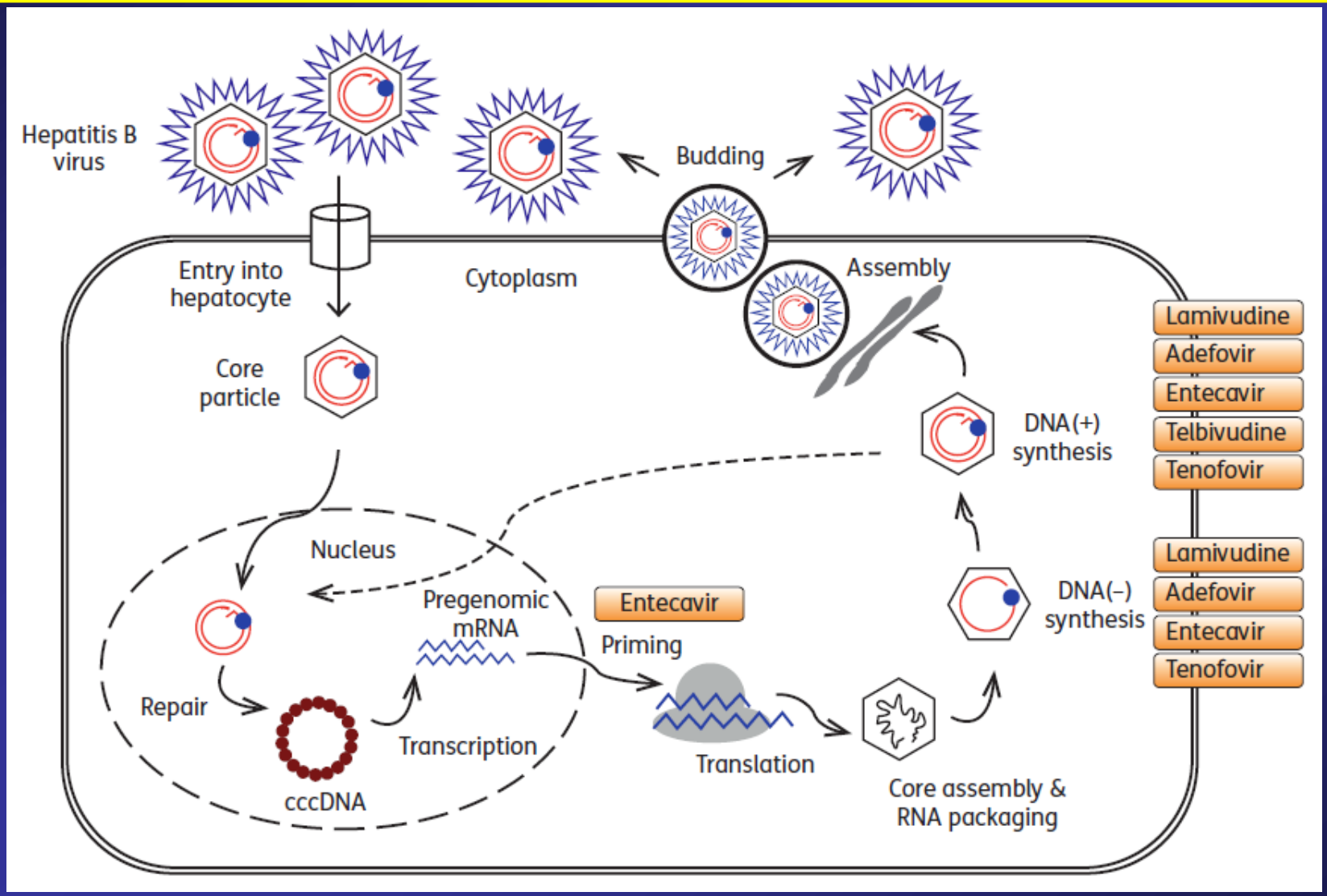
Predicators for IFN therapy :

Ideal	Realityin China
•Virus GT: A>B>C>D	•Virus GT: B & C predominant
•Low viral load	•high viral load
•High ALT	•Low-moderate ALT
•High HAI	•Low-moderate HAI
•Younger age	•Older age
•Female	•Male predominant
•Adult transmission	•Perinatal/early childhood transmission

Wang Y, Jia J. Expert Rev Anti Infect Ther 2011; 9(1):21-5.

•Chan HL, Jia JJ. Gastroenterol Hepatol 2011; 26 (Suppl 1):131-7.

The replication cycle of HBV and sites of action of NAs



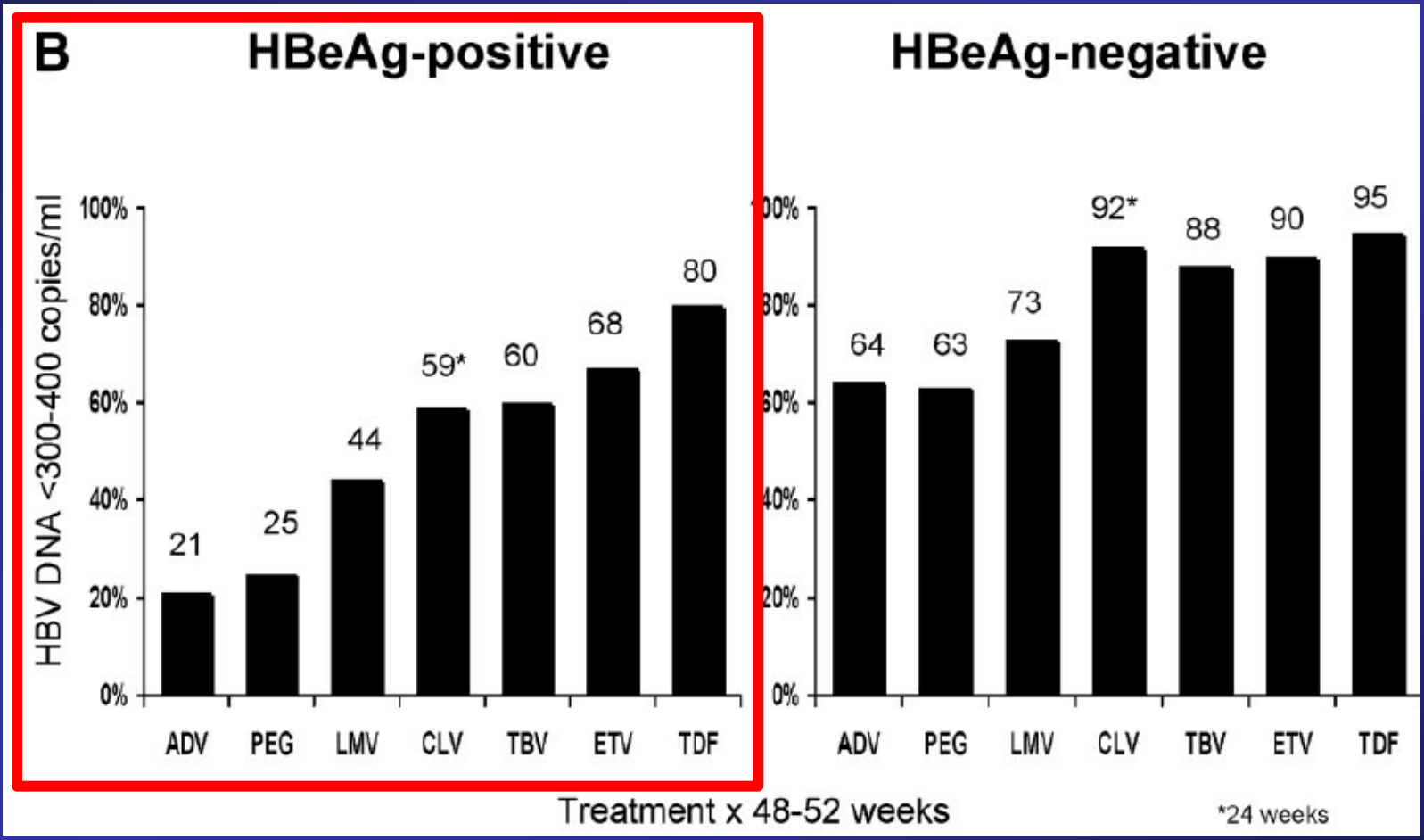
Fung J, et al. J Antimicrob Chemother 2011; 66: 2715–25

Outlines

- Potent viral suppression
- Histology improvement
- Effective for decompensated liver disease
- Resistance is manageable

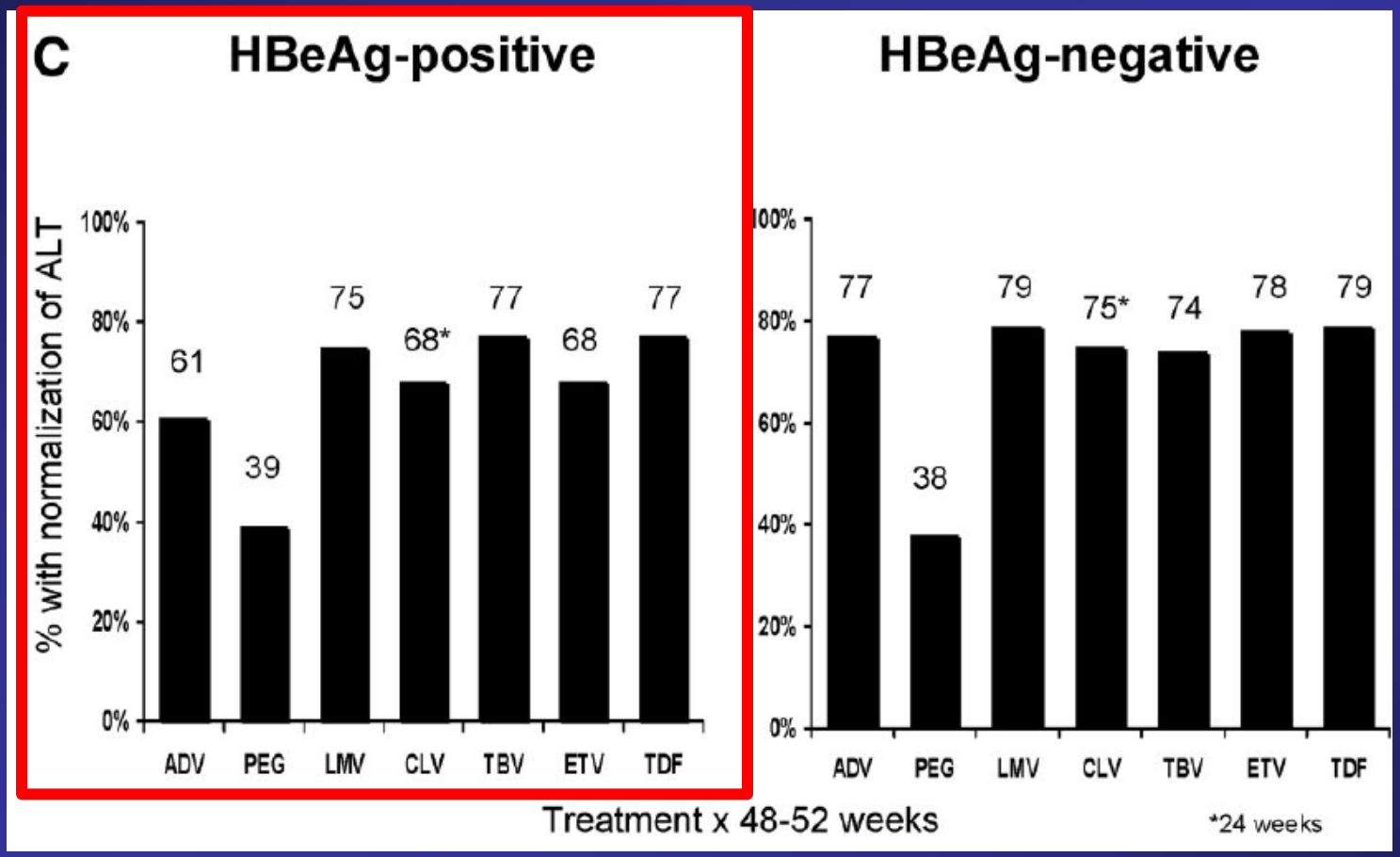
NAs show high anti-HBV potency not only in pivotal clinical trials but also in real-world practice

Comparisons of the virological endpoints achieved during 1 year of antiviral therapy in patients CHB



Dienstag, JL.HEPATOLOGY 2009;49: S112-S121.

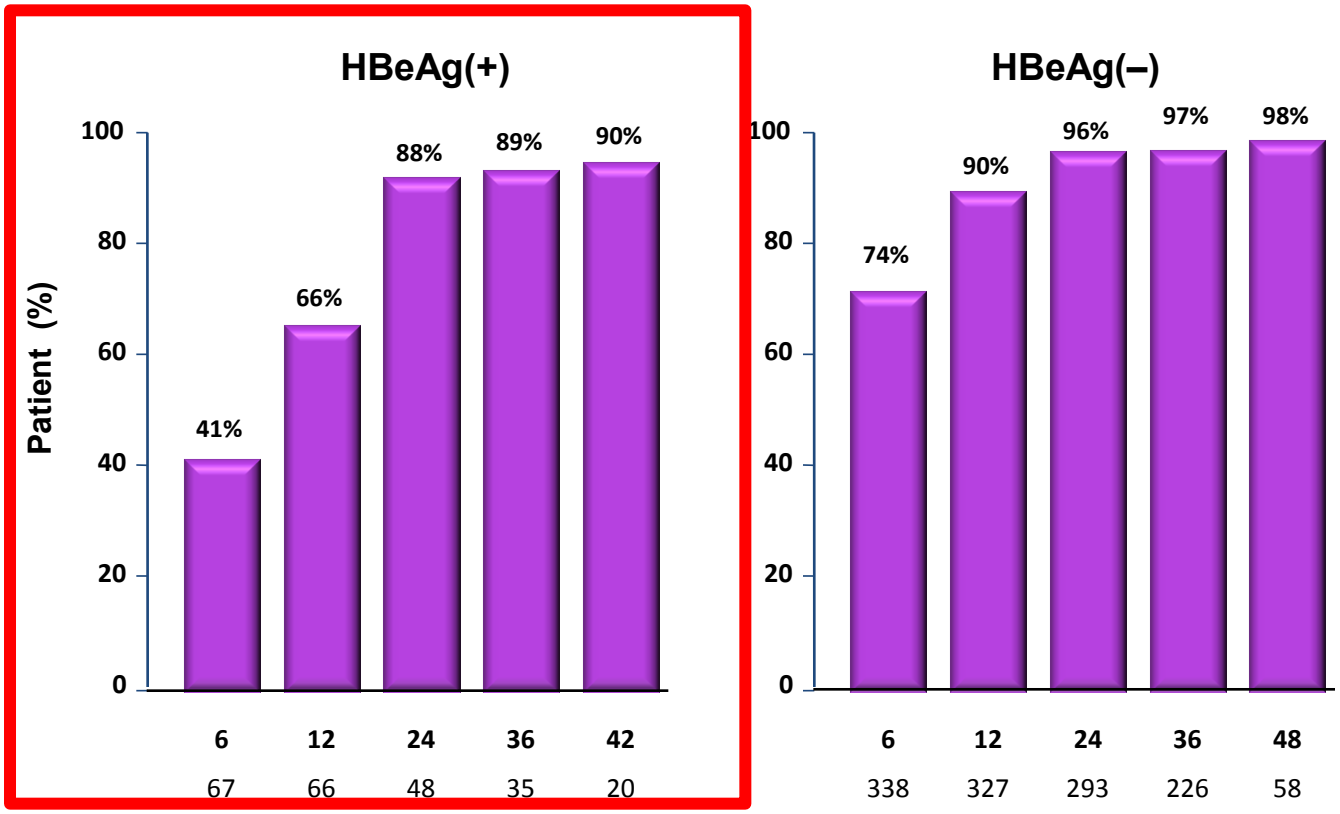
Comparisons of the biochemical endpoints achieved during 1 year of antiviral therapy in patients with CHB



Dienstag, JL.HEPATOLOGY 2009;49: S112-S121.

ETV for NA-naïve CHB in an Italian cohort real-life study: Viralogical response

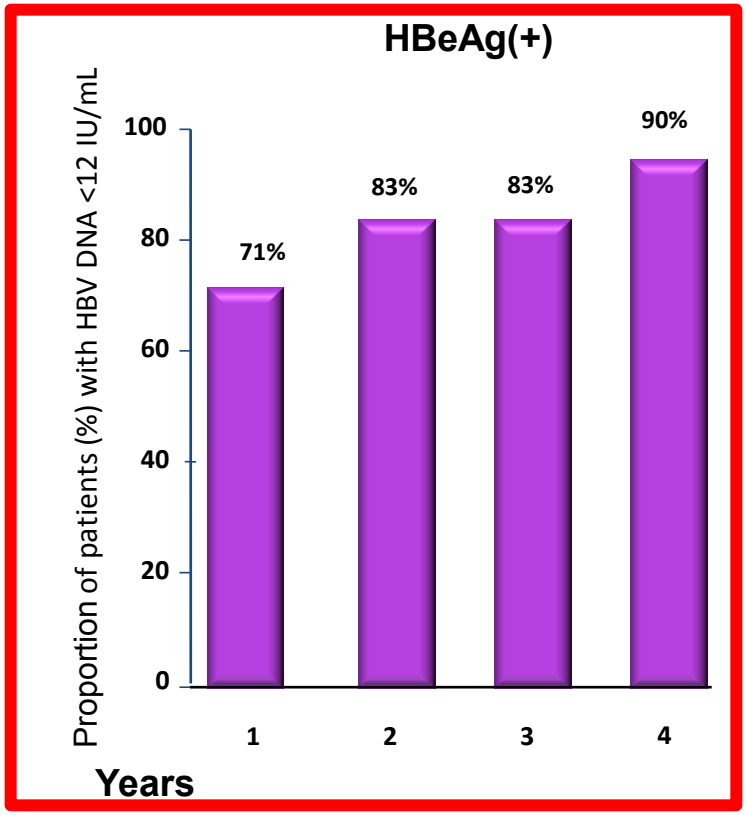
Baseline(n=418): **Median age: 58 (18–82), cirrhosis: 49%,HBeAg(–): 83%**

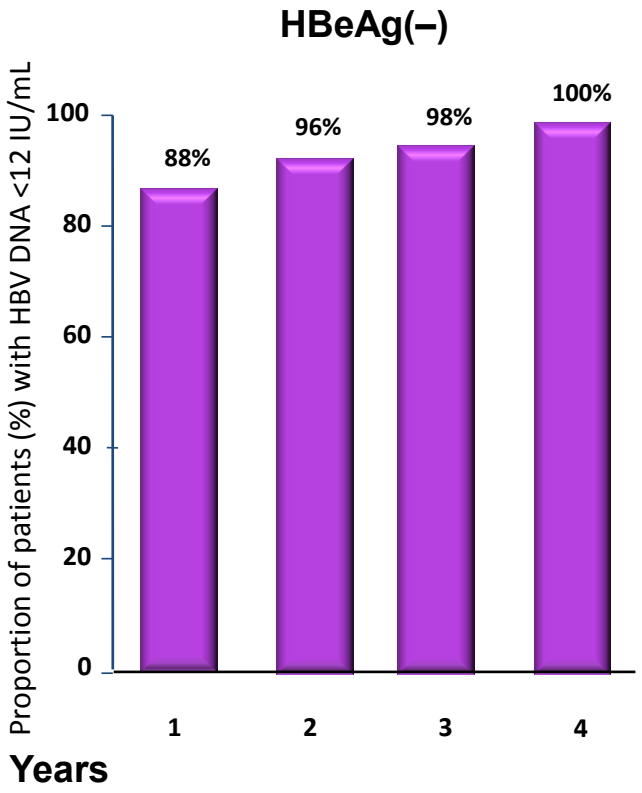


† Kaplan–Meier analysis

Lampertico P, et al. Hepatology 2011; 54(Suppl 1): Abstract 1436.

Hong Kong cohort study: 4-yrs ETV for CHB: Undetectable HBV DNA



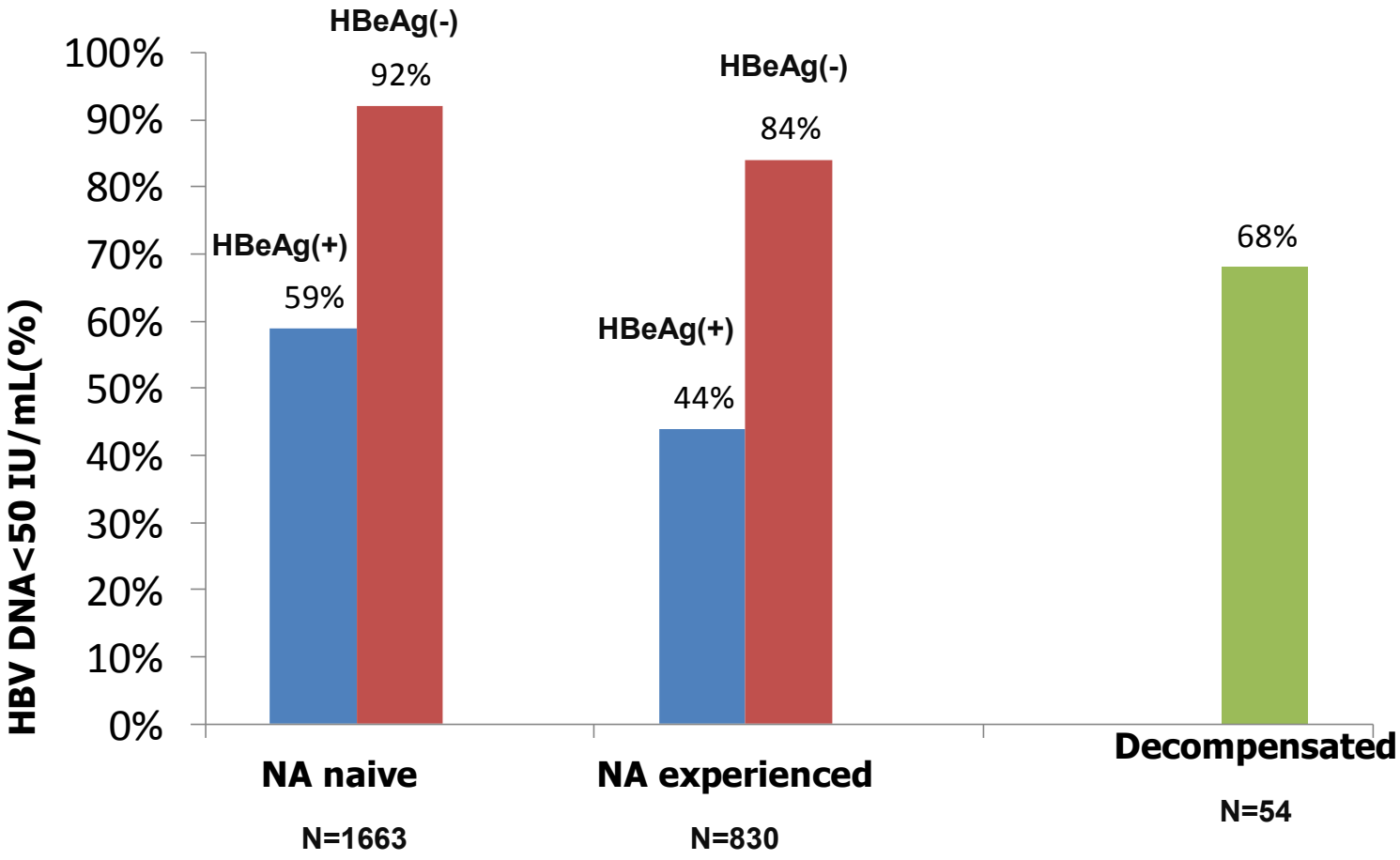


Baseline (n=222):

- **age: 47 (21–77)**
- **HBV DNA: 7.1 (4.0 –>8.8) log copies/mL**
- **HBeAg(–): 59.5%**

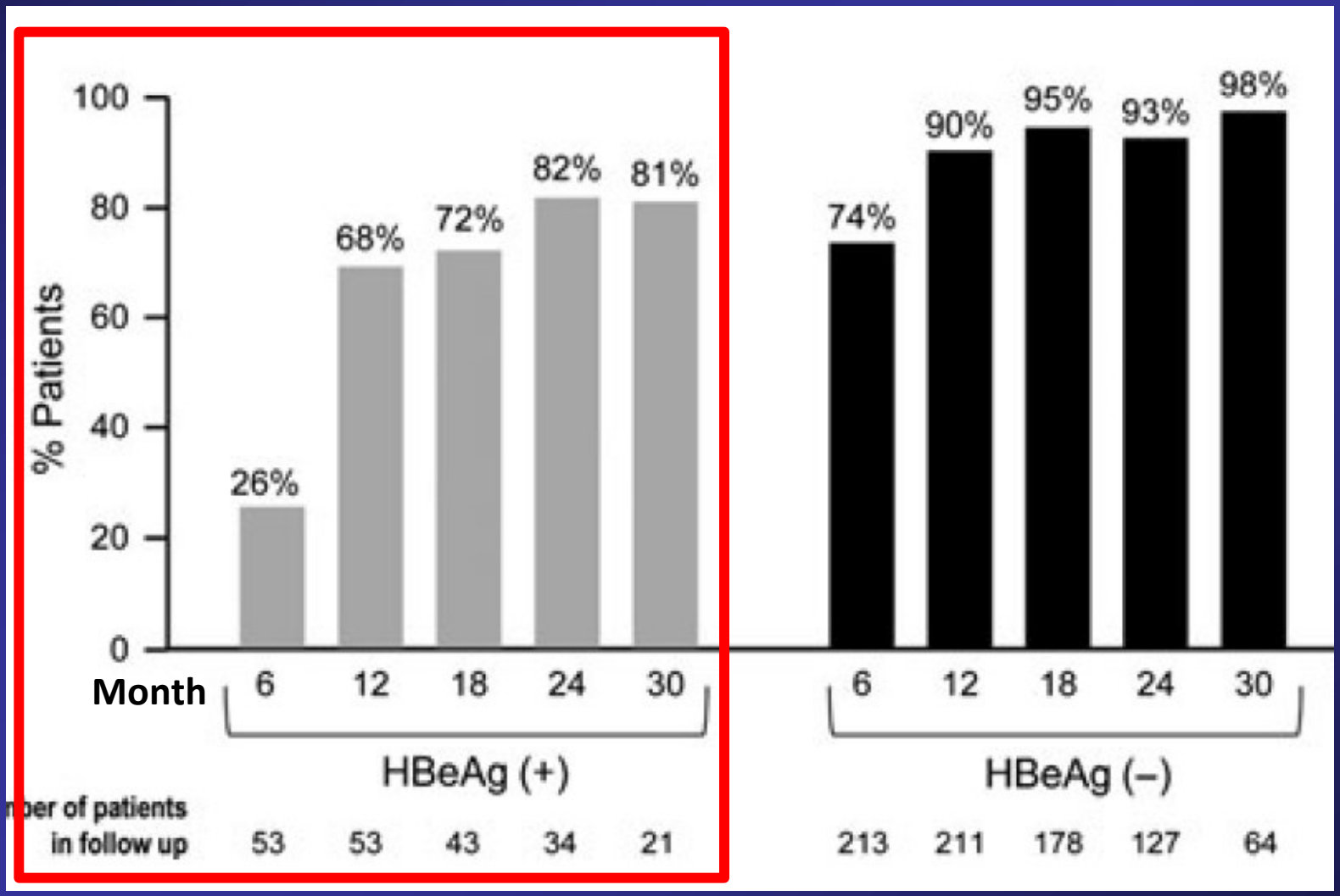
Seto WK, et al. J Hepatol 2011; 54: S301.

REALM China sub-study: ETV decreases HBV DNA in all patients with CHB



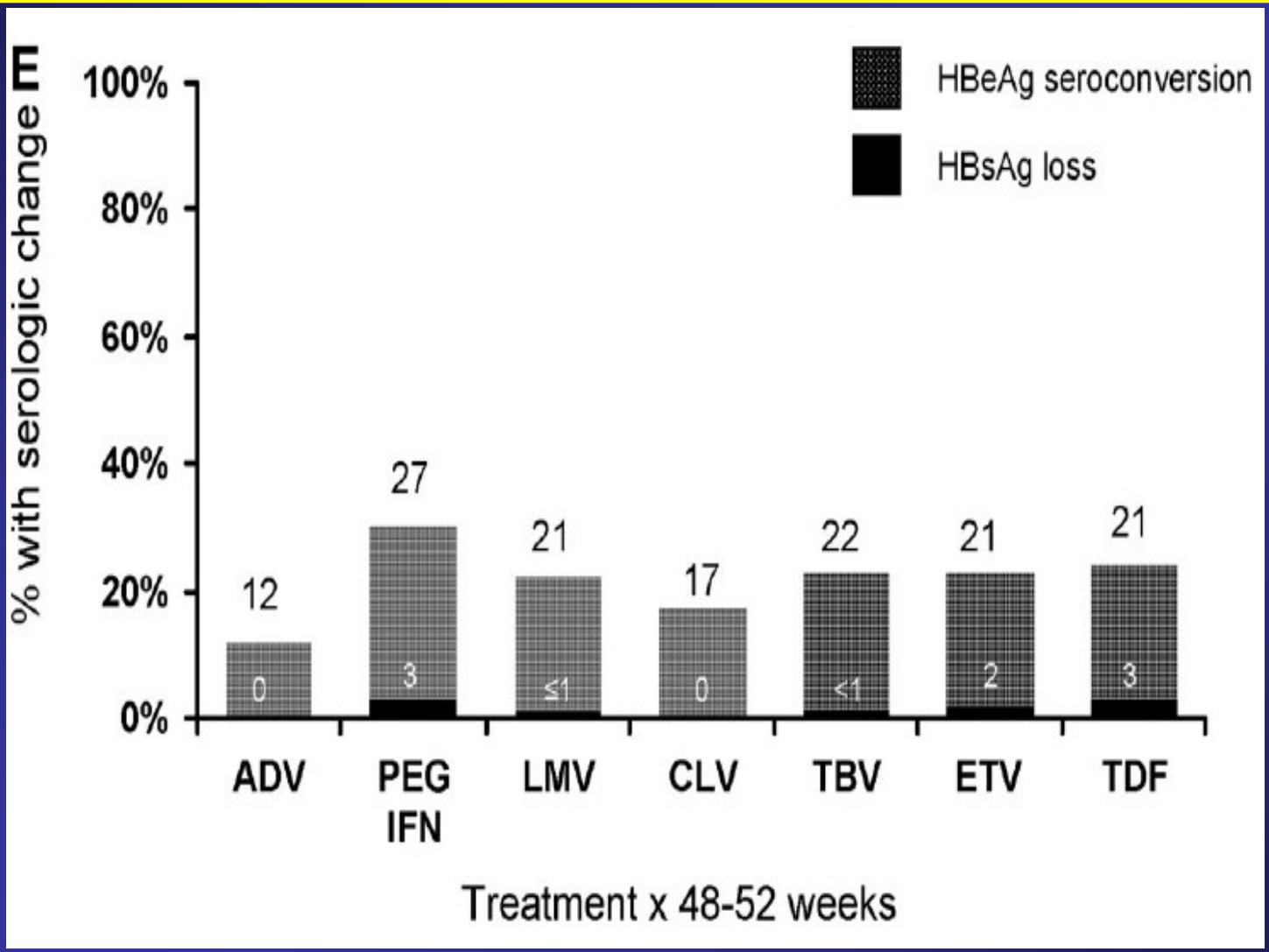
Hou JL et al. APASL 2011, Poster PP05-146.

TDF for NA-naïve CHB in an Europe cohort real-life study: Virologic response



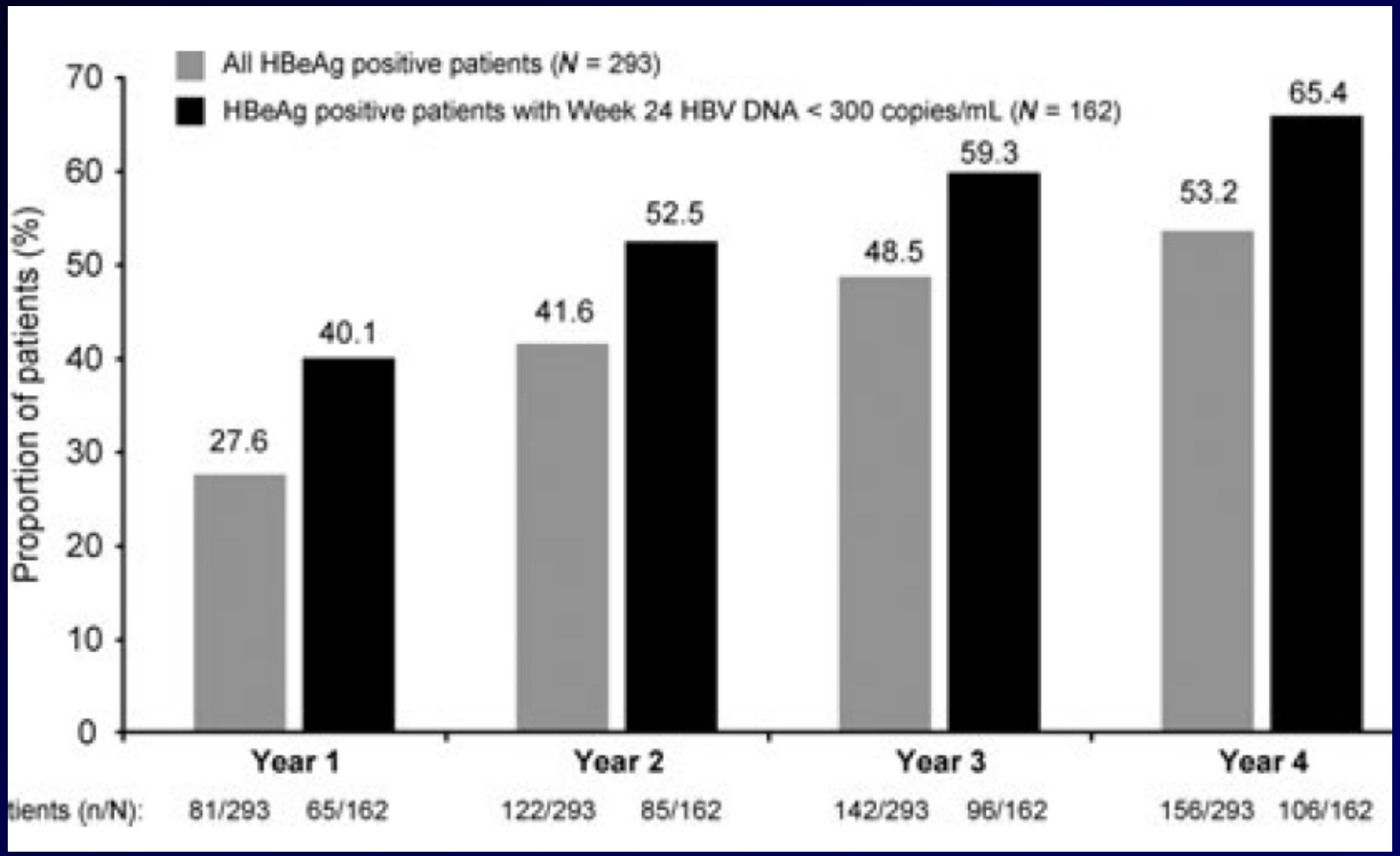
Lampertico P, et al. Hepatology 2011; 54(Suppl 1): Abstract 1433.

Serological response on 1 yr NAs



Dienstag, JL.HEPATOLOGY 2009;49: S112-S121.

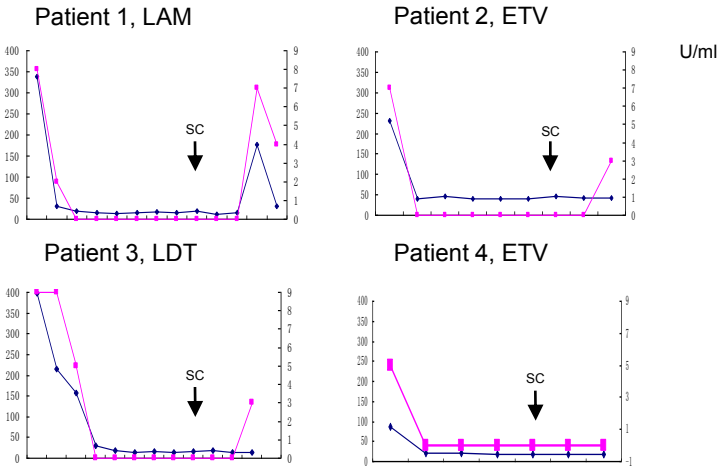
Cumulative HBeAg seroconversion rates over time in telbivudine-treated HBeAg positive patients without genotypic resistance after Year 2

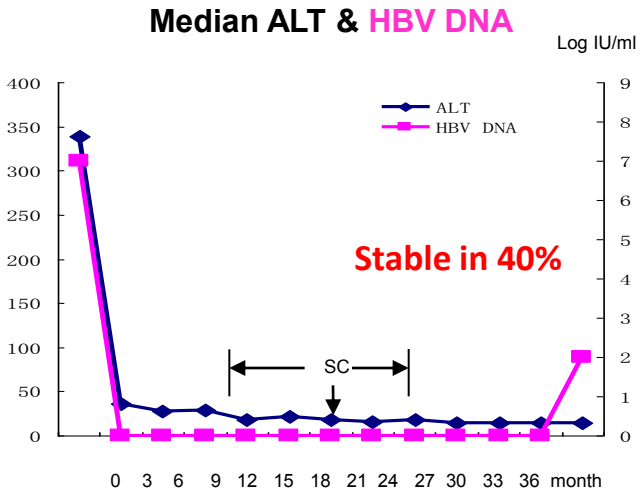


Wang Y, et al. JVH 2012;

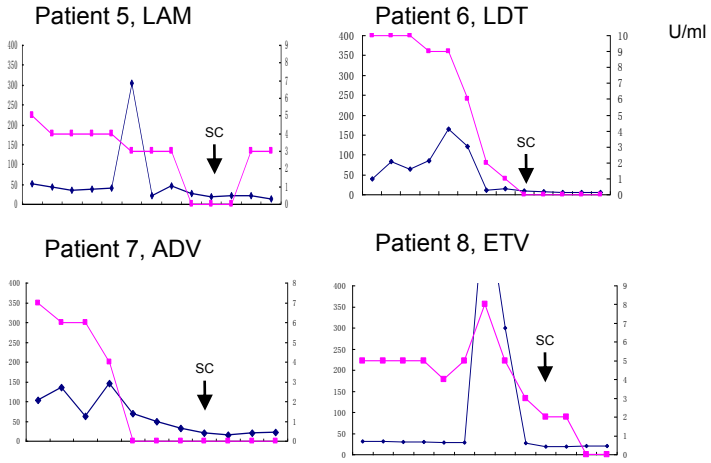
Two patterns of HBeAg seroconversion during NA therapy

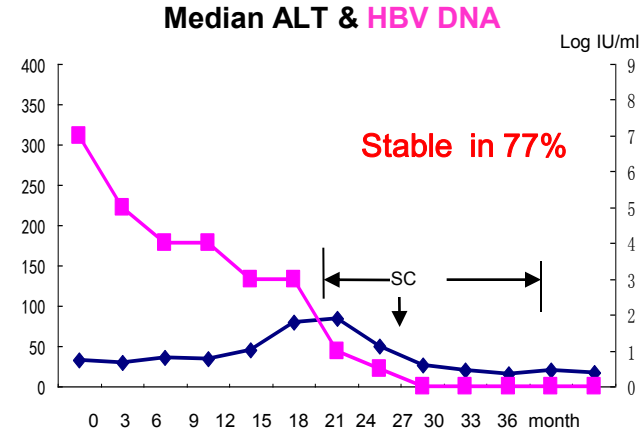
A Seroconversion Type I





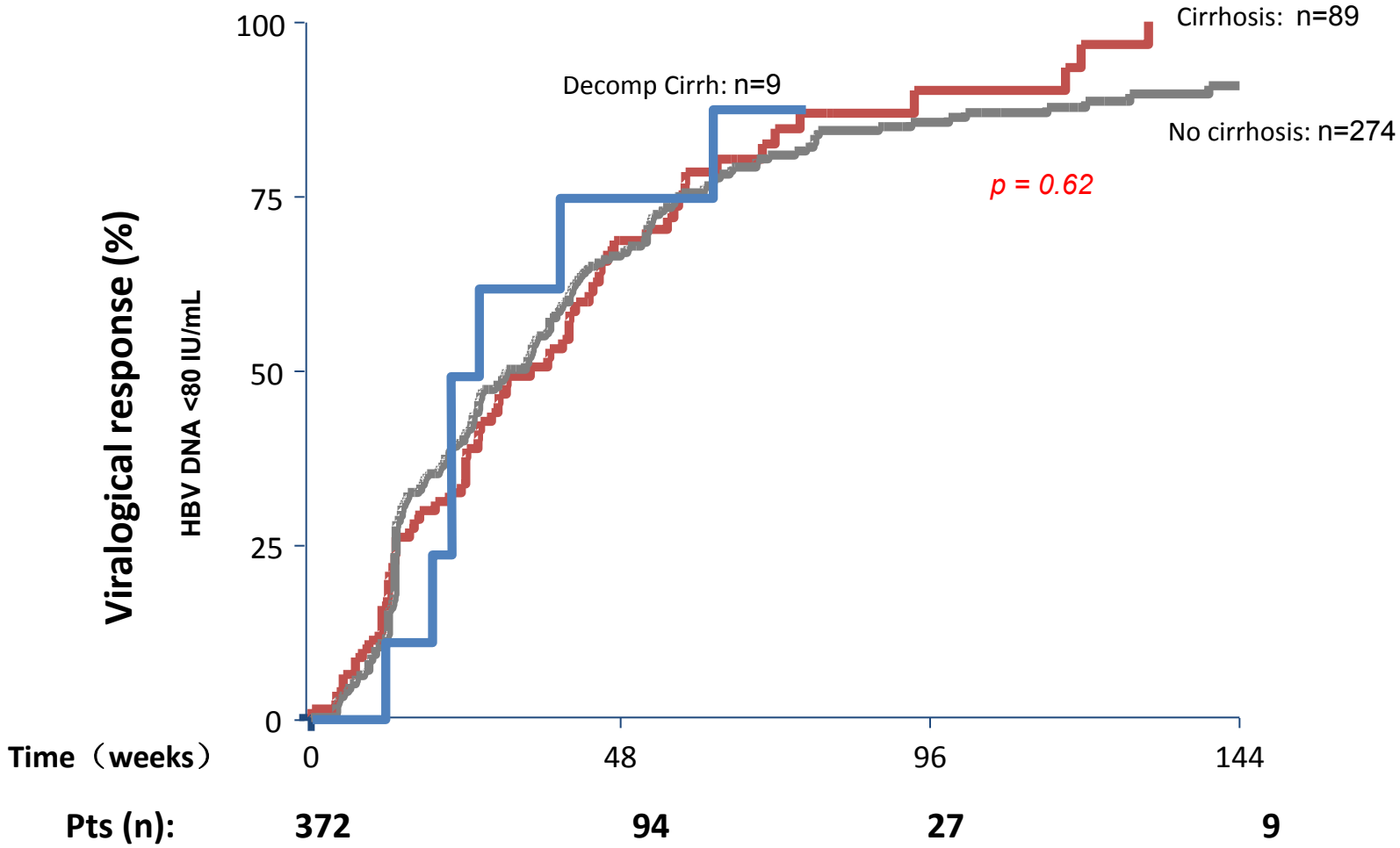
B Seroconversion Type II





You H, et al. J viral Hepat 2009;16:876-82

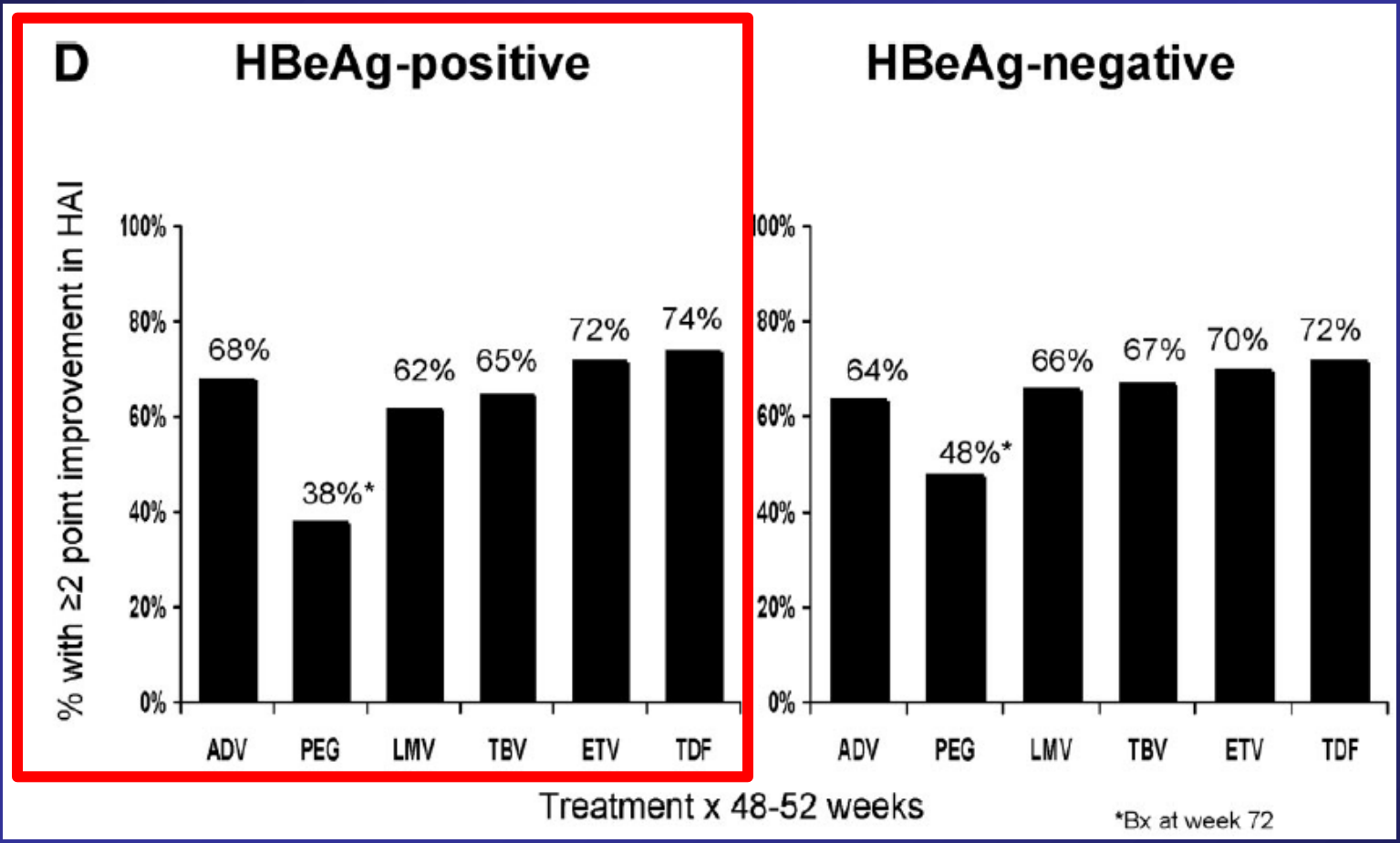
VIRGIL Study：Liver disease severity not influence viralogical response to ETV



Zoutendijk R, et al. Gut 2012 Apr 5. [Epub ahead of print]

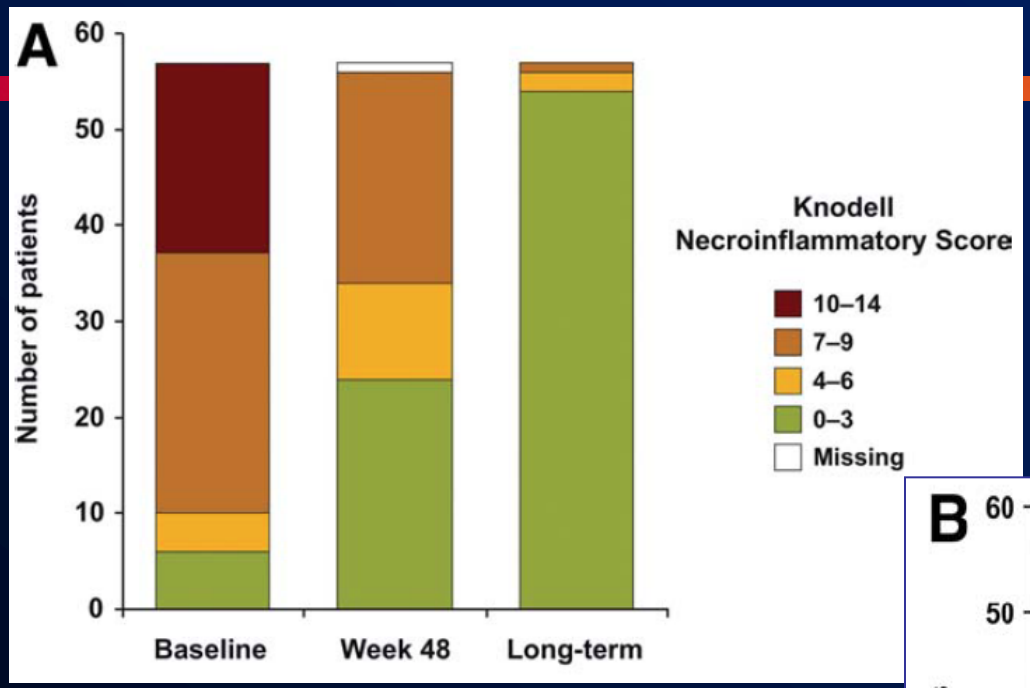
Long-term NA therapy improves liver histology

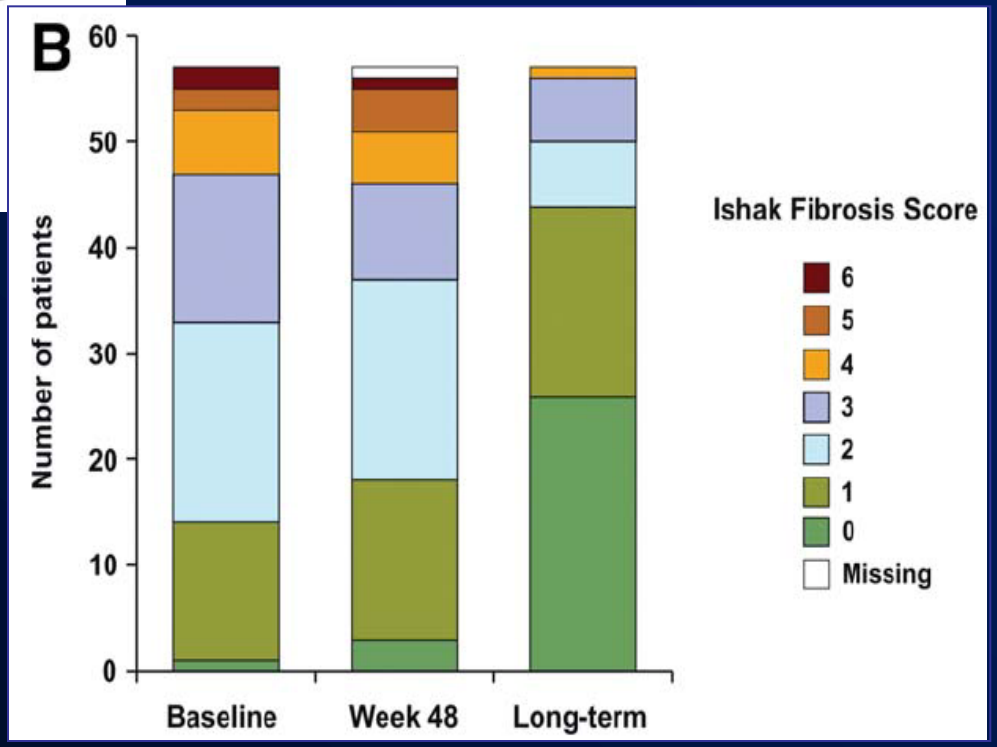
Comparisons of the histological endpoints achieved during 1 year of antiviral therapy in patients with CHB



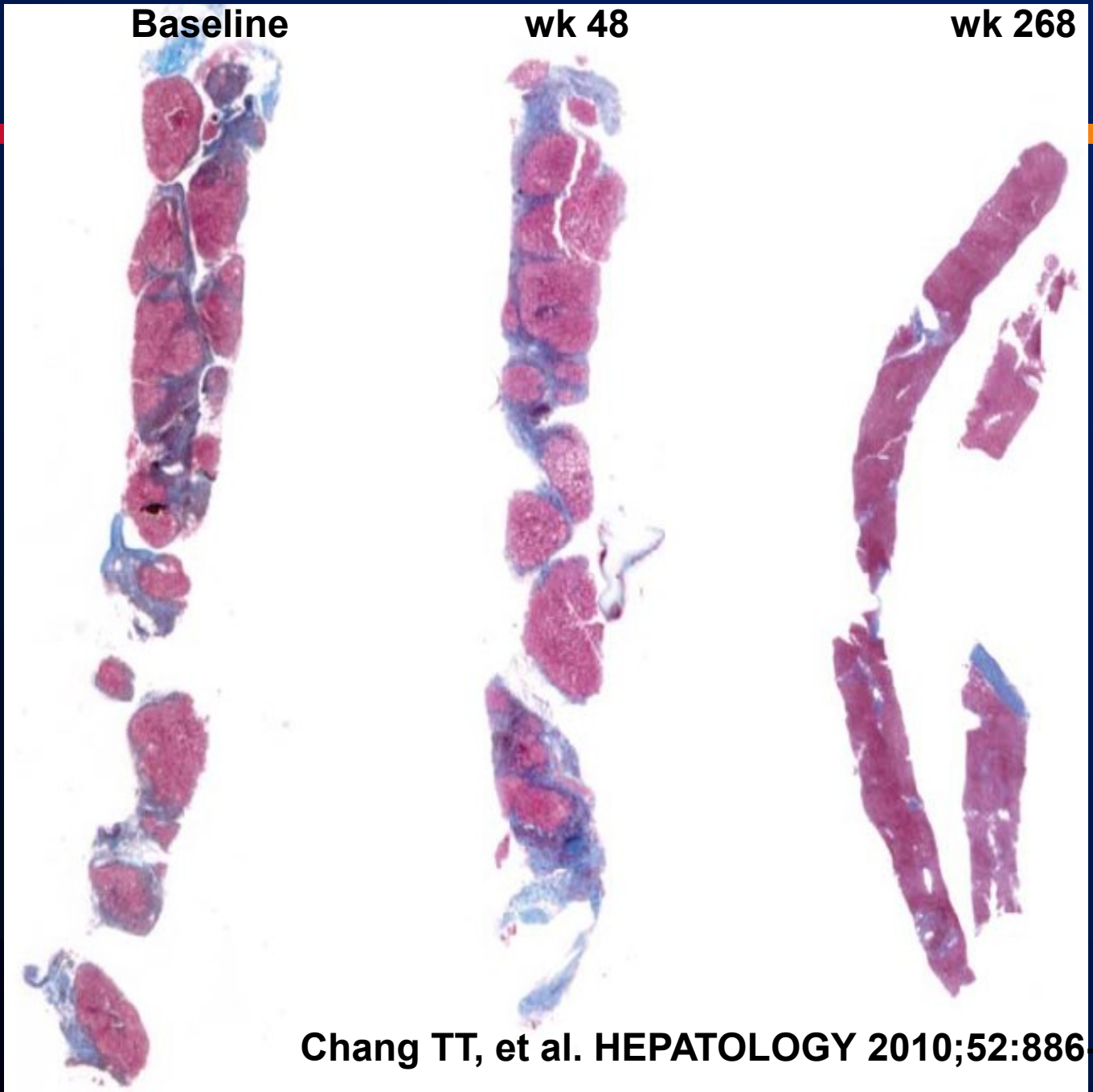
Dienstag JL, et al. HEPATOLOGY 2009;49: S112-S121.

Long-term ETV Improves Liver Histology in CHB
(median: 5.6 yr, n=57)



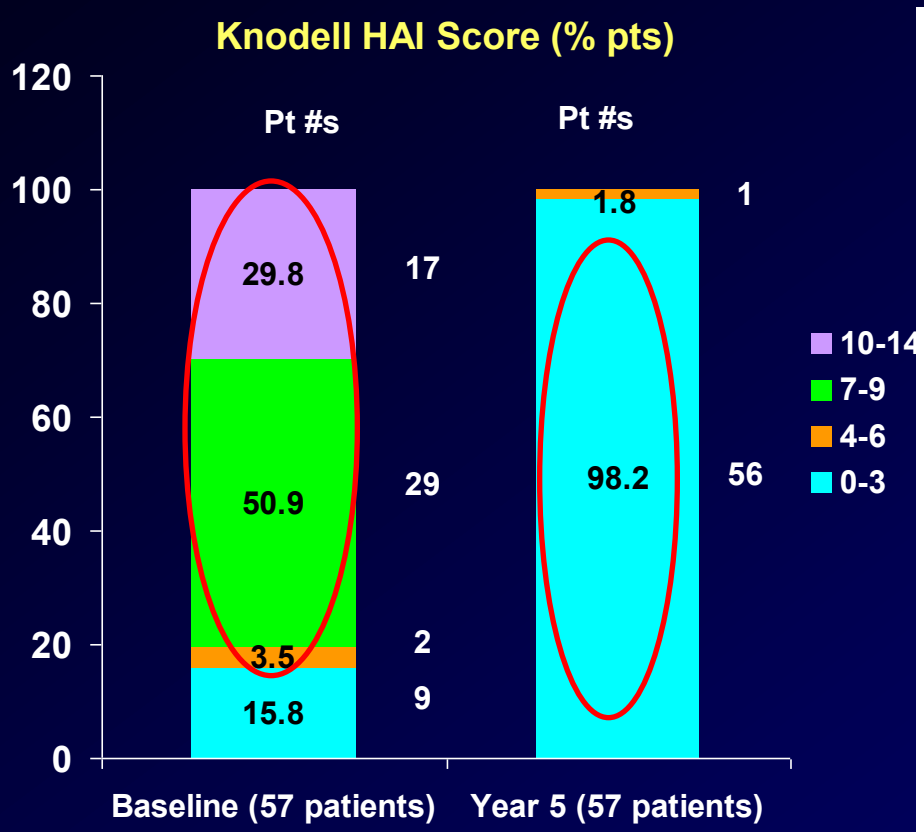


Chang TT, et al. HEPATOLOGY 2010;52:886-93



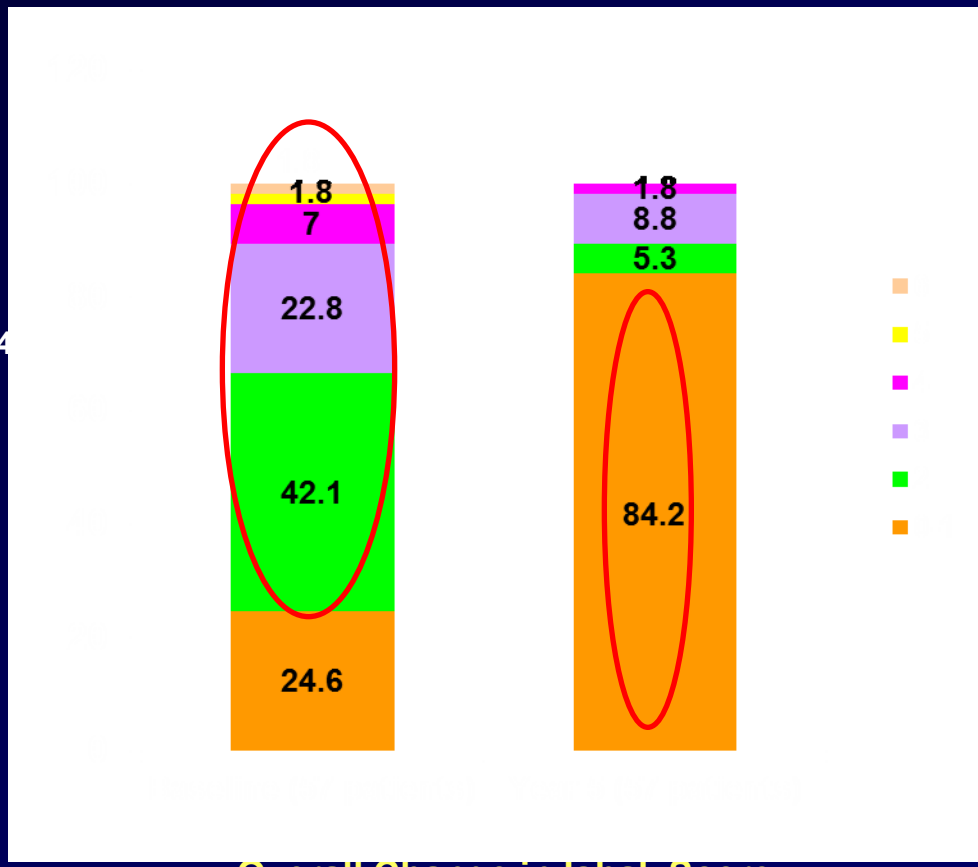
Chang TT, et al. HEPATOLOGY 2010;52:886-893

5 Years of LDT Treatment Results in Profound Regression in Liver Necroinflammation and Fibrosis in CHB Patients



Overall Change in Knodell HAI Score

- Improvement: 94.7% (54/57)
- Unchanged: 3.5% (2/57) (BL score 0 or 1)
- Worsened: 1.8% (1/57) (BL score 1 to 3)



Overall Change in Ishak Score

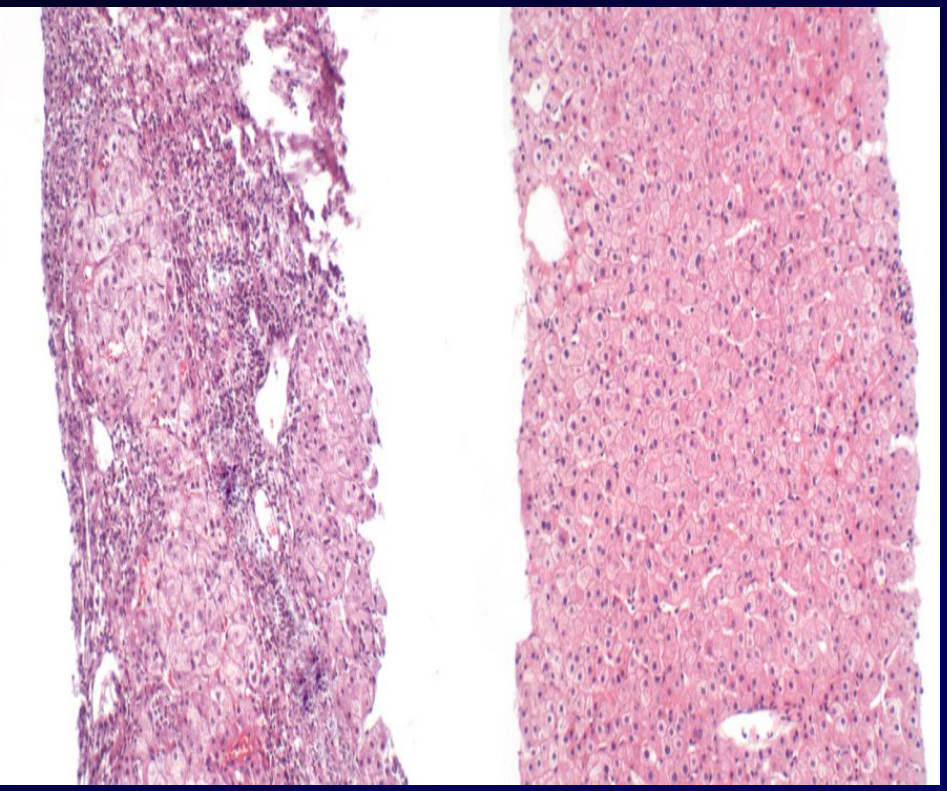
- Improvement: 77.2% (44/57)
- Unchanged: 15.8% (9/57) (BL score ≤ 2)
- Worsened: 7% (4/57) (BL score ≤ 2)

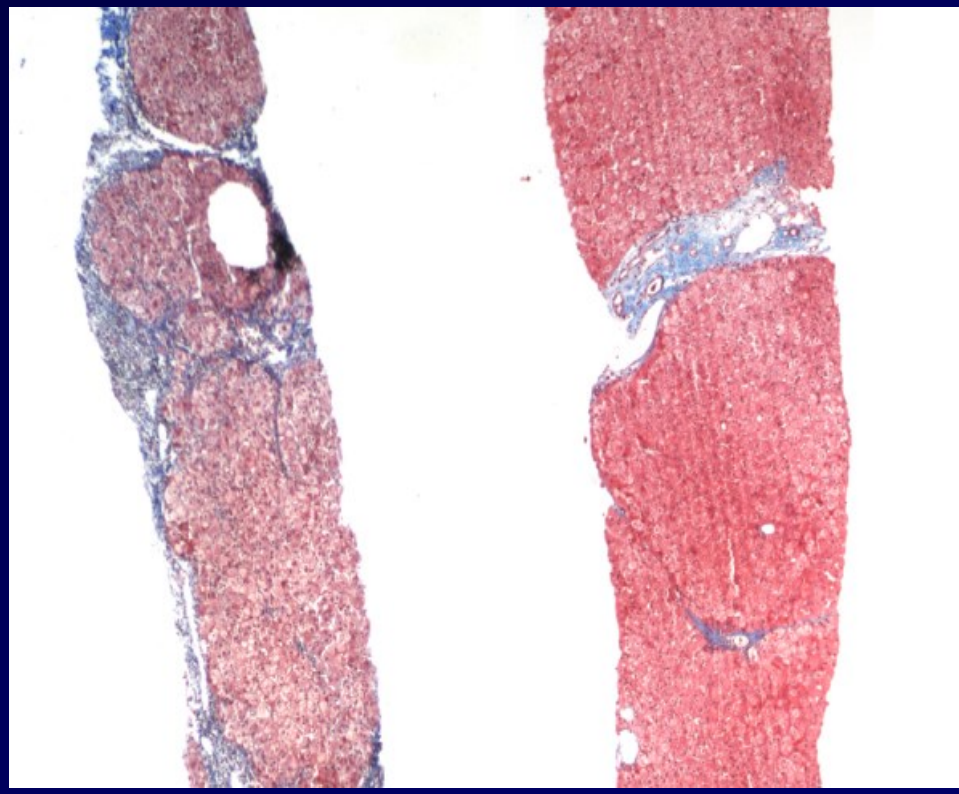
Hou J, et al. EASL 2011 poster presentation.

5 Year LDT Treatment Exerts Significant Effect on Liver Histology

Summary of the available data

- **Profound and durable viral suppression with LDT over 5 years significantly improves liver histology along with a favorable safety and tolerability profile.**
- **Prolonged LDT treatment has the potential to achieve the long-term goals of therapy for chronic hepatitis B.**



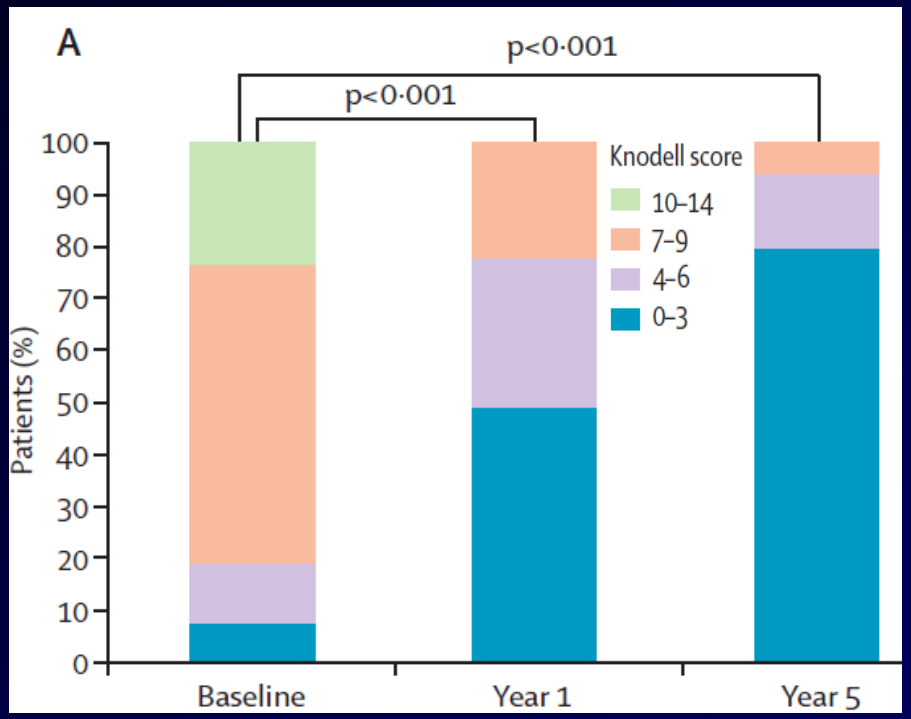


Hou J, et al. EASL Berlin 2011. Poster 716.

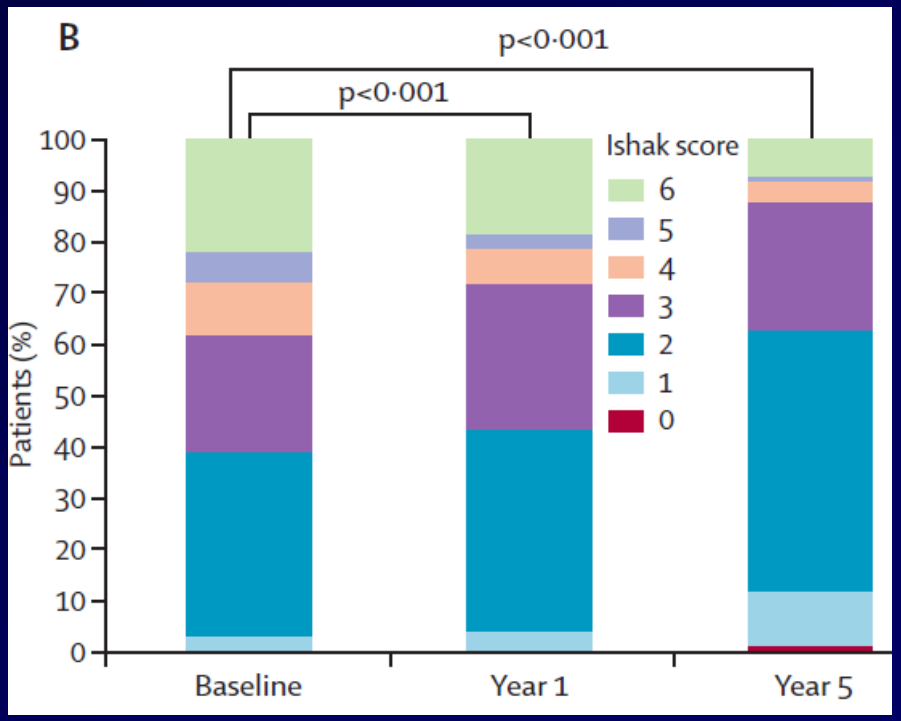
Histology results over 5-year TDF treatment

348/641 (54%) with biopsy samples at year 5

Knodell necroinflammatory scores



Ishak fi brosis scores



Maraellin P, et al. Lancet 2012, December 10 published online

NAs improve clincal outcome of decompensated liver disease

TDF, FTC/TDF or ETV for Decompensated CHB: Efficacy Results at Week 48

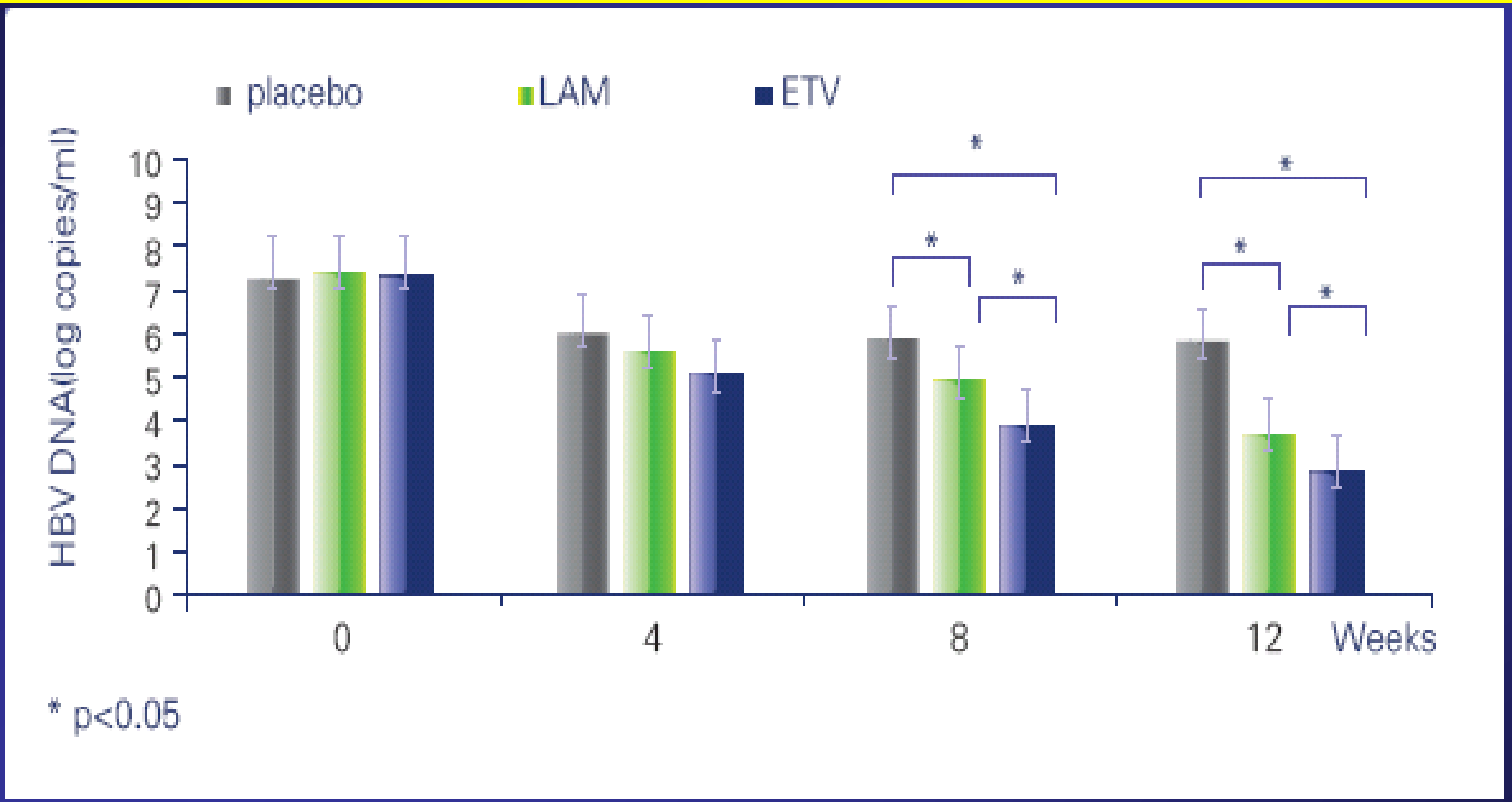
	TDF (*N*=45)	FTC/TDF (*N*=45)	ETV (*N*=22)
HBV DNA < 400 copies/mL,* (69 IU/mL) *n/N* (%)†	31/44 (70.5%)	36/41 (87.8%)	16/22 (72.7%)
95% confidence interval	57.0%, 83.9%	77.8%, 97.8%	54.1%, 91.3%
Median (IQR) change from baseline in HBV DNA (log_{10} copies/mL)*,‡	−3.11 (-4.1, -2.4)	-3.92 (-5.2, -2.2)	-3.40 (-5.0, -1.3)
Normal ALT§, *n/N* (%)†	25/44 (56.8%)	31/41 (75.6%)	12/22 (54.5%)
95% Confidence Interval	42.2%, 71.5%	62.5%, 88.8%	33.7%, 75.4%
Normalized ALT,§ *n/N* (%)†	12/26 (46.2%)	16/25 (64.0%)	7/17 (41.2%)
95% confidence interval	27.0%, 65.3%	45.2%, 82.8%	17.8%, 64.6%
Median (IQR) change from baseline in serum ALT (U/L)‡	−7.0 (−42.0, 1.0)	−16.5 (−64.5, −2.5	−25.5 (−44.5, −5.5)
CTP Score† ≥ 2 point decrease‖ (*n/N*; %)	7/27 (25.9%)	12/25 (48.0%)	5/12 (41.7%)
95% confidence interval	9.4%, 42.5%	28.4%, 67.6%	13.8%, 69.6%
CTP Score† ≥ 2 point increase (*n/N*; %)	0/43	1/38 (2.6%)	0/22
95% confidence interval		0.0%, 7.7%	
Median (IQR) change from baseline in MELD score‡	−2.0 (−12, 3)	−2.0 (−18, 4)	−2.0 (−10, 1)
HBeAg loss,¶ *n/N* (%)†	3/14 (21.4%)	4/15 (26.7%)	0/7
95% confidence interval	(0.0%, 42.9%)	(4.3%, 49.0%)	
HbeAg seroconversion,¶ *n/N* (%)†	3/ 14 (21.4%)	2/ 15 (13.3%)	0/7
95% confidence interval	(0.0%, 42.9%)	(0.0%, 30.5%)	
HBV recurrence after liver transplantation	0/2	0/4	–

Liaw YF, et al. HEPATOLOGY 2011;53:62-72

Lamivudine and entecavir treatment in patients with chronic hepatitis B liver failure: a large, multicenter, placebo controlled, prospective study in China

Yida Yang1, Jianrong Huang1, Jifeng Sheng1, Hongyu Jia1, Dong Yan1, Jun Li1, Qing Xie2, Zhi-liang Gao3, Yuming Wang4, Zhongping Duan5, Huifen Wang6, Linshumei Lan7, Tao Hao8, Jianhe Gan9, Chen Pan10, Lanjun Li

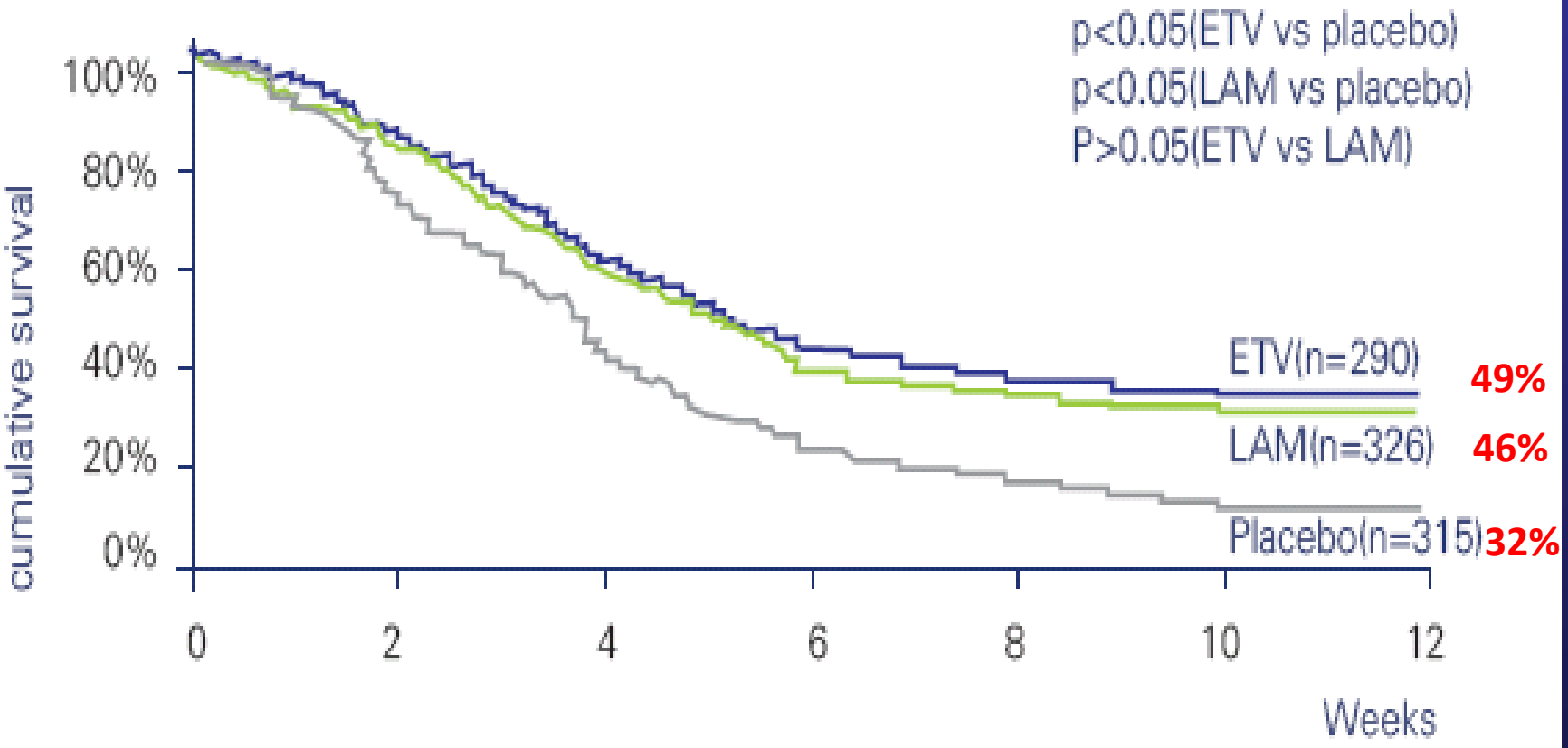
Mean change of HBV DNA from baseline through 12 weeks



Both LAM and ETV treatment vs placebo group from week 8 (P＜0.05).
Also the ETV group vs LAM group from week 8 (P＜0.05)

YD Yang, et al. EASL, 2012, Poster 526

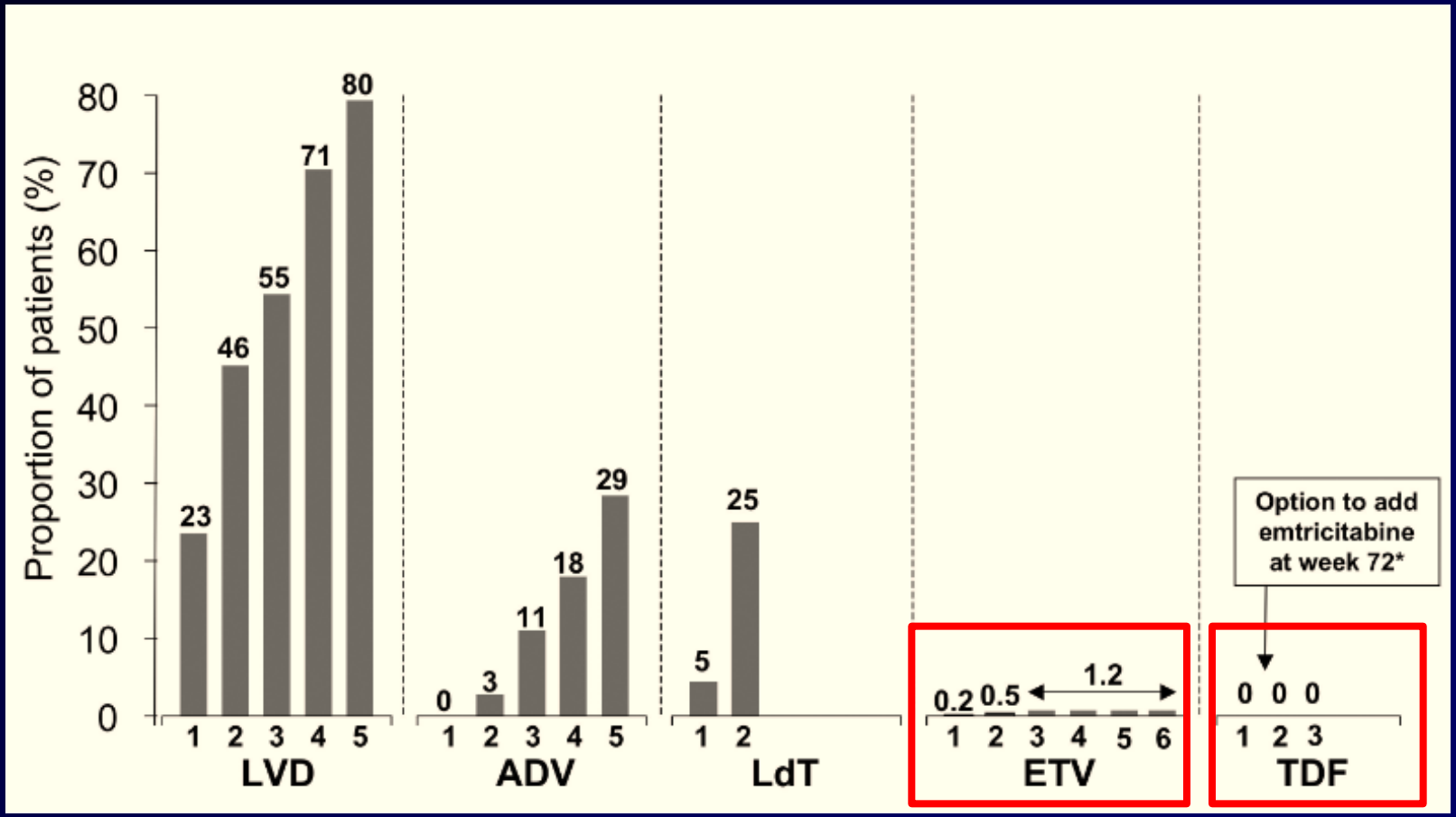
Kaplan-Meier estimate of the cumulative survival rate in the three groups



YD Yang, et al. EASL, 2012, Poster 526

Resistence is preventable and manageble

Cumulative incidence of HBV resistance to LAM, ADV, ETV, LdT and TDF in pivotal trials in NUC-naive patients(not head-to-head comparison)



Gish R, Jia JD, Locarnini S, Zoulim F. Lancet Infect Dis 2012; 12:341-53

Choice of Agents for Naive CHB in US & Europe

AASLD (2009)	• PegIFN-α,TDF,ETV, LdT,LVD （ADV,LVD & LdT not preferred） • Retreat with NA if failed（Peg）IFNα
EASL (2012	• PegIFN-α （mainly for HBeAg[+]）， or ETV/TDF

NA,核苷类似物

No Resistance to Tenofovir Disoproxil Fumarate Detected After up to 144 Weeks of Therapy in Patients Monoinfected With Chronic Hepatitis B Virus

Andrea Snow-Lampart,[1] Brandi Chappell,[1] Maria Curtis,[1] Yuao Zhu,[1] Florence Myrick,[1] James Schawalder,[1] Kathryn Kitrinos,[1] Evguenia S. Svarovskaia,[1] Michael D. Miller,[2] Jeff Sorbel,[1] Jenny Heathcote,[3] Patrick Marcellin,[4] and Katyna Borroto-Esoda[1]

No patient developed amino acid substitutions associated with resistance to TDF.

Virological breakthrough on TDF monotherapy was infrequent over 144 weeks (13/426, 3%) and was attributed to documented nonadherence in most cases (11/13, 85%).

Persistent viremia (400 copies/mL) through week 144 was rare (5/641, 0.8%) and was not associated with virological resistance to TDF by population or clonal analyses.

(HEPATOLOGY 2011;53:763-773)

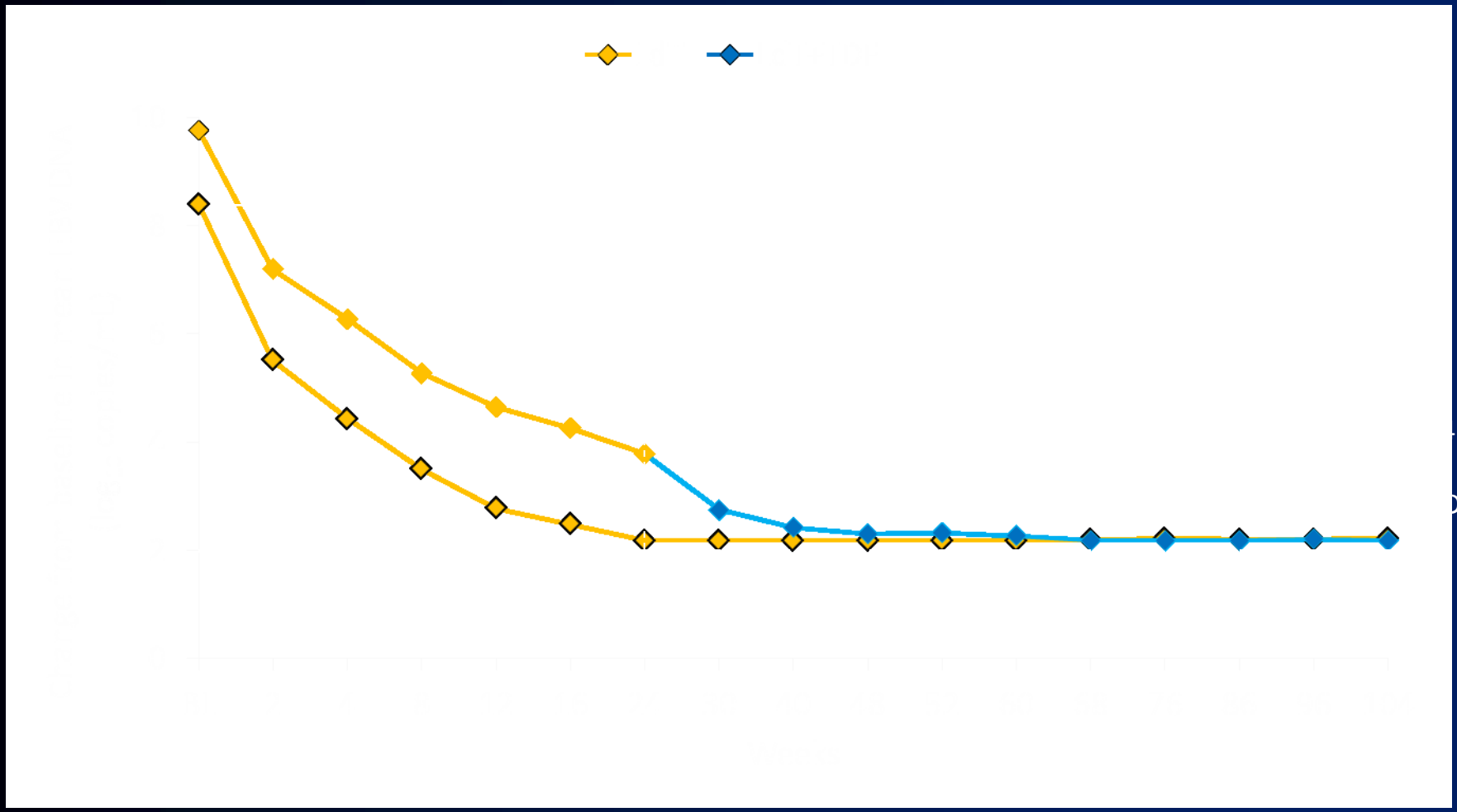
Choice of Agents for Naive CHB in Asia

CSH (2010)	• IFN / PegIFNs, LVD,ADV,ETV, LdT (high potent/low resistant agents are preferred if it is feasible) • Thymosin α-1 may be used
APASL (2012)	• IFN, PEG-IFN-α • ETV & TDF(preferred), ADV, LdT &LVD can also be used • Thymosin α-1 may be used

2-Year Results of Telbivudine (LdT) Roadmap Study Verify Optimal Efficacy and Safety Results in HBeAg-Positive Chronic Hepatitis B Patients

T. Piratvisuth, P. Komolmit, T. Tanwandee, W. Sukeepaisarnjaroen, H.L.-Y. Chan, M. Pessoa, E. Fassio, S. Ono-Nita, F. Bessone, J. Daruich, S. Zeuzem, H. Cheinquer, R. Pathan, Y. Dong, A. Trylesinski

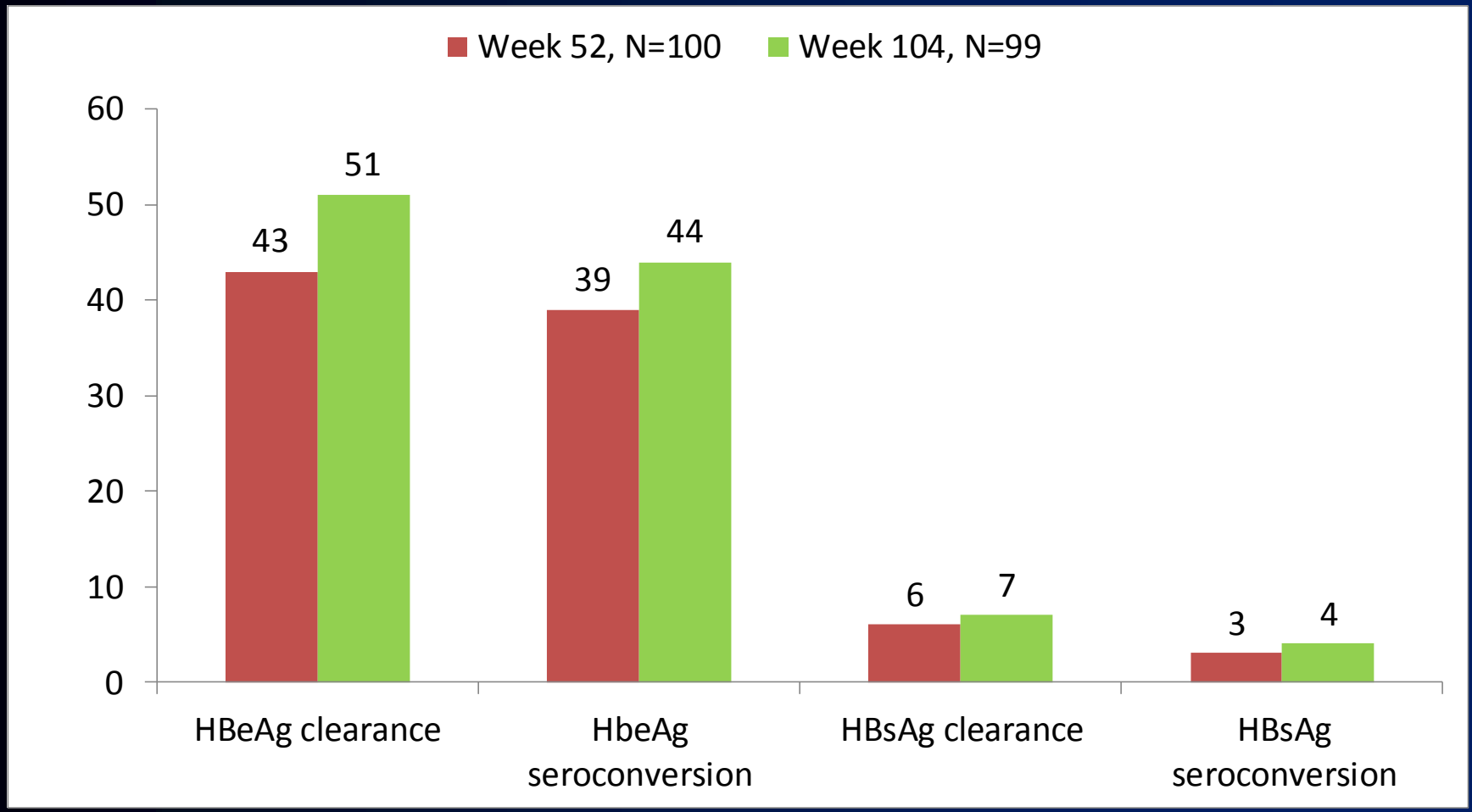
Treatment Modification Based on Week 24 HBV DNA Result Was Prospectively Validated in HBeAg Positive Patients (Study 2410)



HBV DNA reductions at all visits P<0.0001 vs. baseline

Piratvisuth T, et al. APASL 2011.

Impressive HBeAg/HBsAg Response Rates at Weeks 52 and 104 (start with LdT)



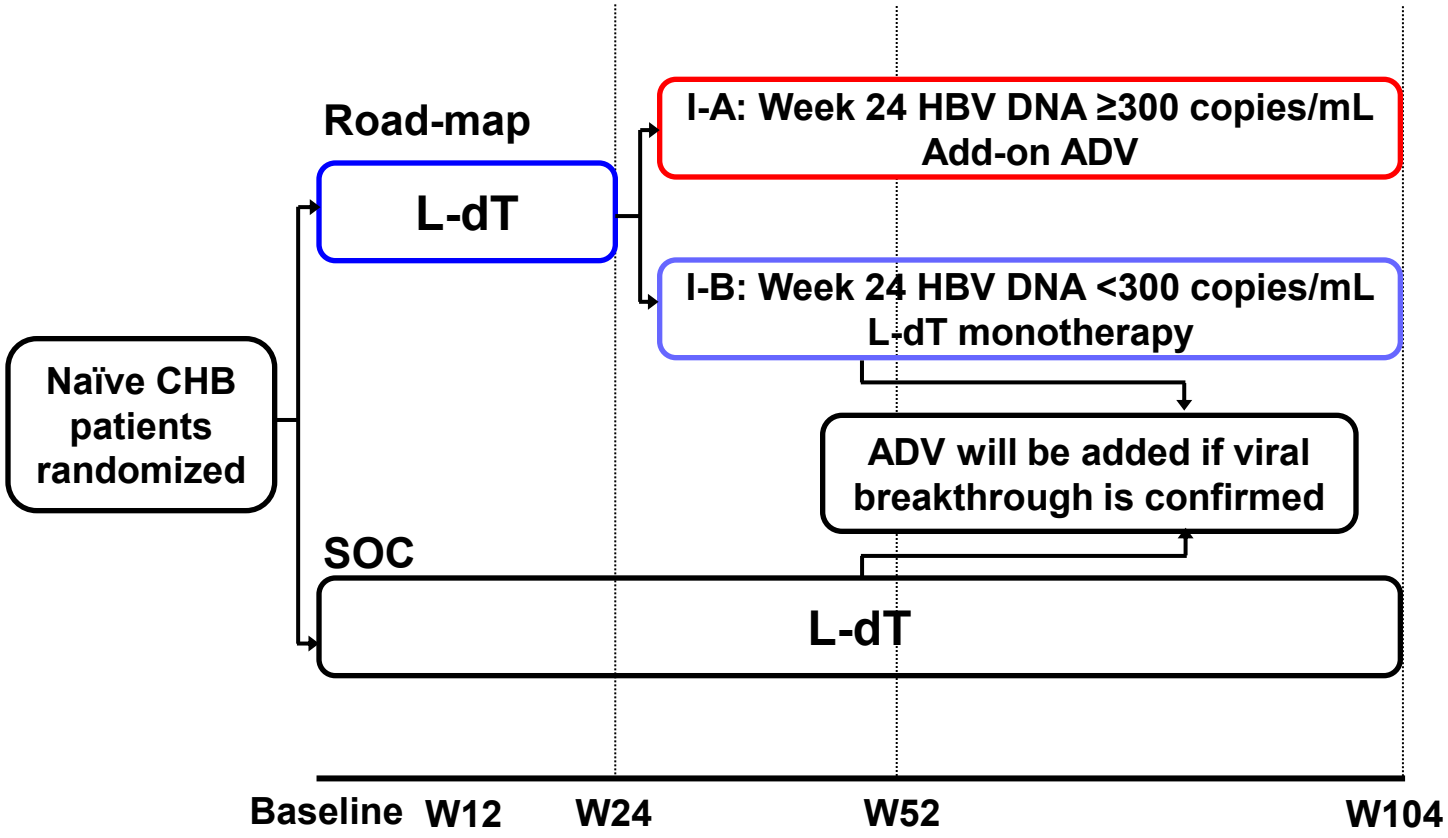
Note:

One patient (251-018) discontinued from the study before Week 52 due to lost to follow-up.

No Week 52 or 104 HBeAg/HBsAg responses data collected.

Piratvisuth T, et al. APASL 2011.

EFFORT STUDY: a multicenter, randomized, controlled, 2-year study in China



Hou J, et al. Data on file , 2013

Efficacy at W104: LdT-based Road-map vs SOC

Variable	Road-map (N=300)	SOC (N=299)	P value
Virological response (%)*	76.7 (230/300)	61.2 (183/299)	<0.001
Serum HBV DNA >4 log_{10} copies/ml (%)	6.0 (18/300)	18.1 (54/299)	<0.001
Serum HBV DNA (median change in log_{10} copies/ml from baseline)	-6.30	-6.10	0.009
ALT normalization (%)†	80.7 (234/290)	79.2 (232/293)	0.680
HBeAg loss (%)	29.0 (87/300)	31.1 (93/299)	0.574
HBeAg seroconversion (%)	23.7 (71/300)	22.1 (66/299)	0.697
HBsAg loss (%)	0.7 (2/300)	0.7 (2/299)	1.000
HBsAg seroconversion (%)	0.3 (1/300)	0.3 (1/299)	1.000
Virological Breakthrough (%)‡	6.0 (18/300)	30.1 (90/299)	<0.001
Genotypic Resistance (%)‡	2.7 (8/300)	25.8% (77/299)	<0.001

Hou J, et al. Data on file , 2013

Summary: the rationale for choosing NAs for CHB

- High anti-HBV potency not only in pivotal clinical trials but also in real-world practice
- Long-term NA therapy improves liver
- Improve clinical outcome of liver decompensation
- Resistance is preventable and manageable
- Prevent HBV reactivation in immune compromised setting
- Prevent mother-infant transmission in pregnancy
- Reduce HCC development
- Decrease HCC recurrence
- Excellent safety profile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