

HEP DART 2005

frontiers in drug development for viral hepatitis

Significant and sustained clinical improvement following long term treatment with adefovir dipivoxil: results after 5 years of therapy

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**Adefovir Dipivoxil (Hepsera®)
Long-Term
Clinical Update**

**HepDART
December 15, 2005**

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Adefovir Dipivoxil (ADV) Clinical Profile

- First of a new class
- Nucleotide analogue of adenosine monophosphate
- Chain terminator of HBV DNA, active against wild-type (WT), pre-core mutant and all patterns of LAM-R HBV
- Increasing efficacy over time
 - In all patient populations and disease stages
- Proven safety and tolerability up to five years
- Best resistance profile at year one in all patient populations and up to 5 years
- Convenient dosing
 - One dose, without regard to food
- Leading prescribed antiviral for chronic hepatitis B (CHB)

ADV Development Program 5 Year Long-Term Studies

- **Treatment-naive**
 - HBeAg- , compensated liver function
 - HBeAg+, compensated liver function
- **Lamivudine-resistant HBV**
 - Waitlisted for liver transplantation
 - Post-liver transplantation
 - HIV Co-infection

Long-term Adefovir Dipivoxil Treatment Induces Regression of Liver Fibrosis in Patients With HBeAg-Negative CHB: Results After 5 Years of Therapy

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AASLD 2005
San Francisco, CA

HBeAg- CHB

Study Design



* Patients in ADV 10mg group re-randomized in a 2:1 fashion at week 48.

** Patients transferred to a general open-label study.

† Optional liver biopsy

HBeAg- CHB Assessments

- HBV DNA (Roche Amplicor Monitor, LLQ = 1000 copies/mL) and ALT every 4 weeks to week 96, then every 12 weeks
- Liver biopsies
 - Required at 0 and 48 weeks
 - Optional at 96, 144, and 240 weeks
- Annual genotyping of all samples with detectable HBV DNA by PCR
- All analyses were of observed data except histology (last observation carried forward [LOCF] for missing data at 96 weeks only)

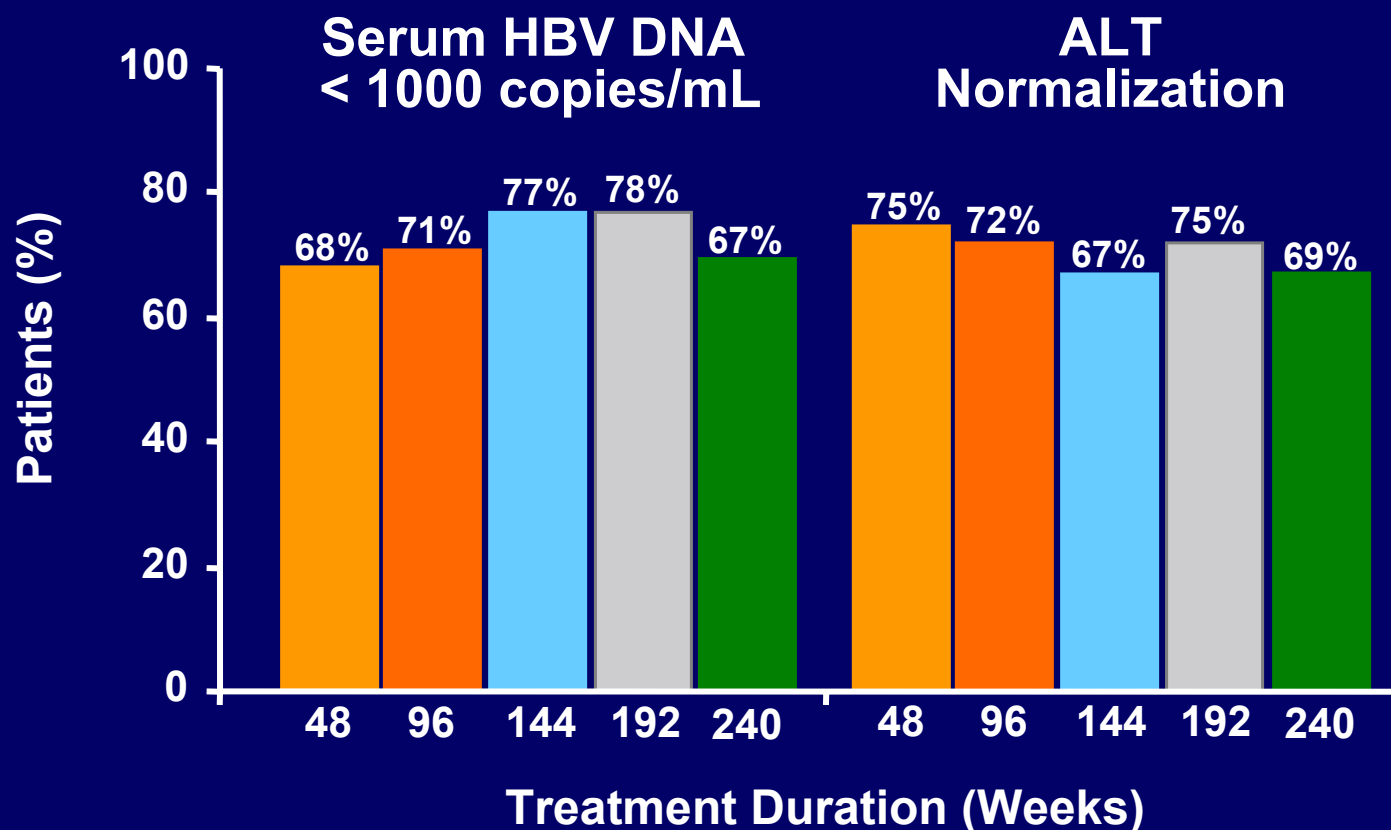
HBeAg- CHB

Pre-Treatment Characteristics

Characteristic	4 Years ADV Treatment n=55	5 Years ADV Treatment n=70
Male	46 (84%)	57 (81%)
Caucasian	38 (69%)	49 (70%)
Asian	16 (29%)	18 (26%)
Median Age (years)	46	47
Median ALT (U/L) (ADV baseline [ADV BL])	62	99
Median HBV DNA (log ₁₀ copies/ml, ADV BL)	5.85	7.08
Number with ADV BL and end-of-treatment biopsy (4 or 5 years of ADV)*	22	24
Median Knodell necroinflammation (ADV BL)	8.0	8.5
Median Ishak fibrosis score (ADV BL)	2.5	2.0

HBeAg- CHB Year 5 Cohort

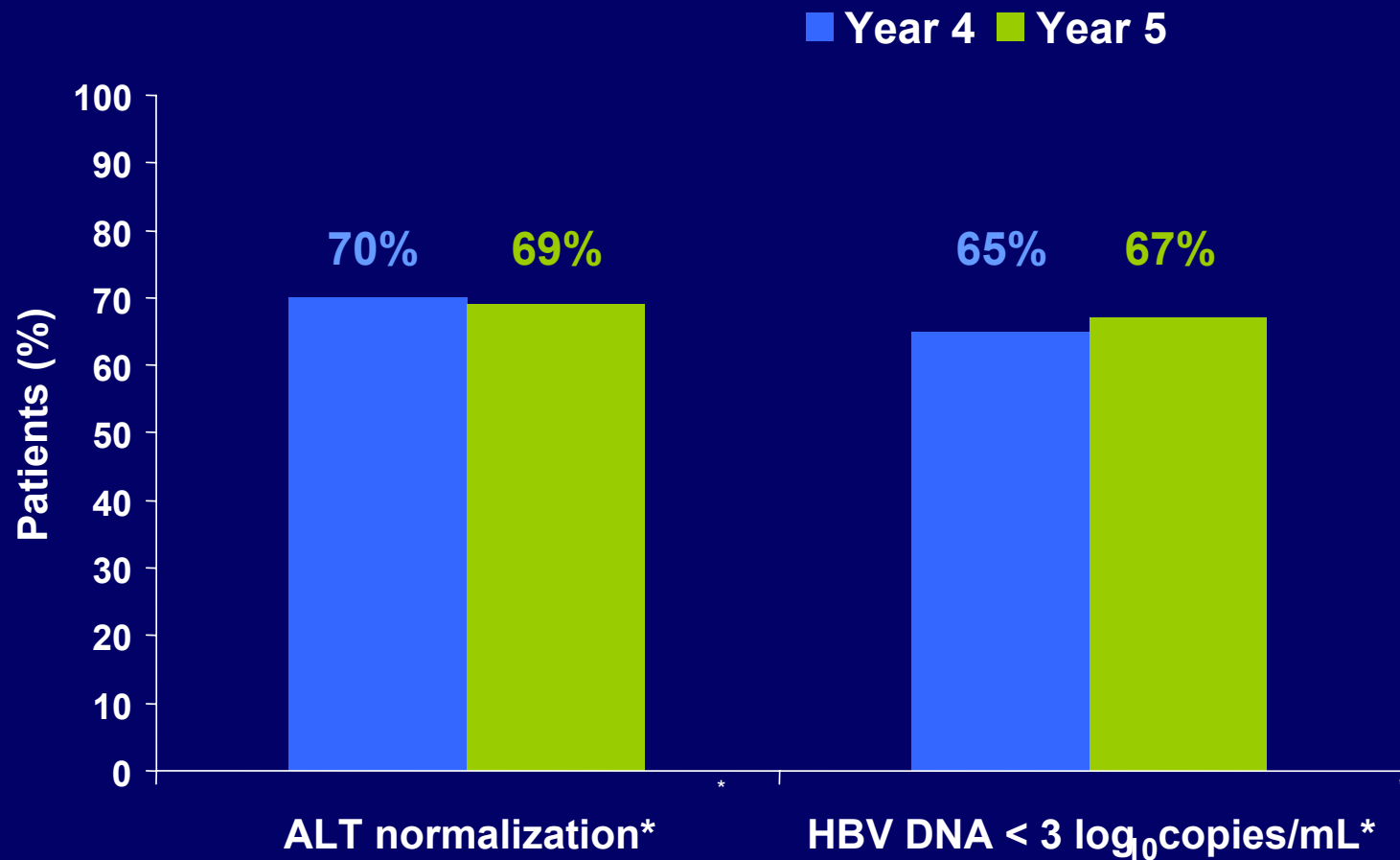
HBV DNA Undetectability and ALT Normalization



Missing=failure for resistance or HCC; Missing=excluded otherwise
Hadziyannis, AASLD 2005

HBeAg- CHB

Virologic and Biochemical Efficacy



- Missing = failure for resistance or hepatocellular carcinoma
- Hadziyannis, AASLD 2005

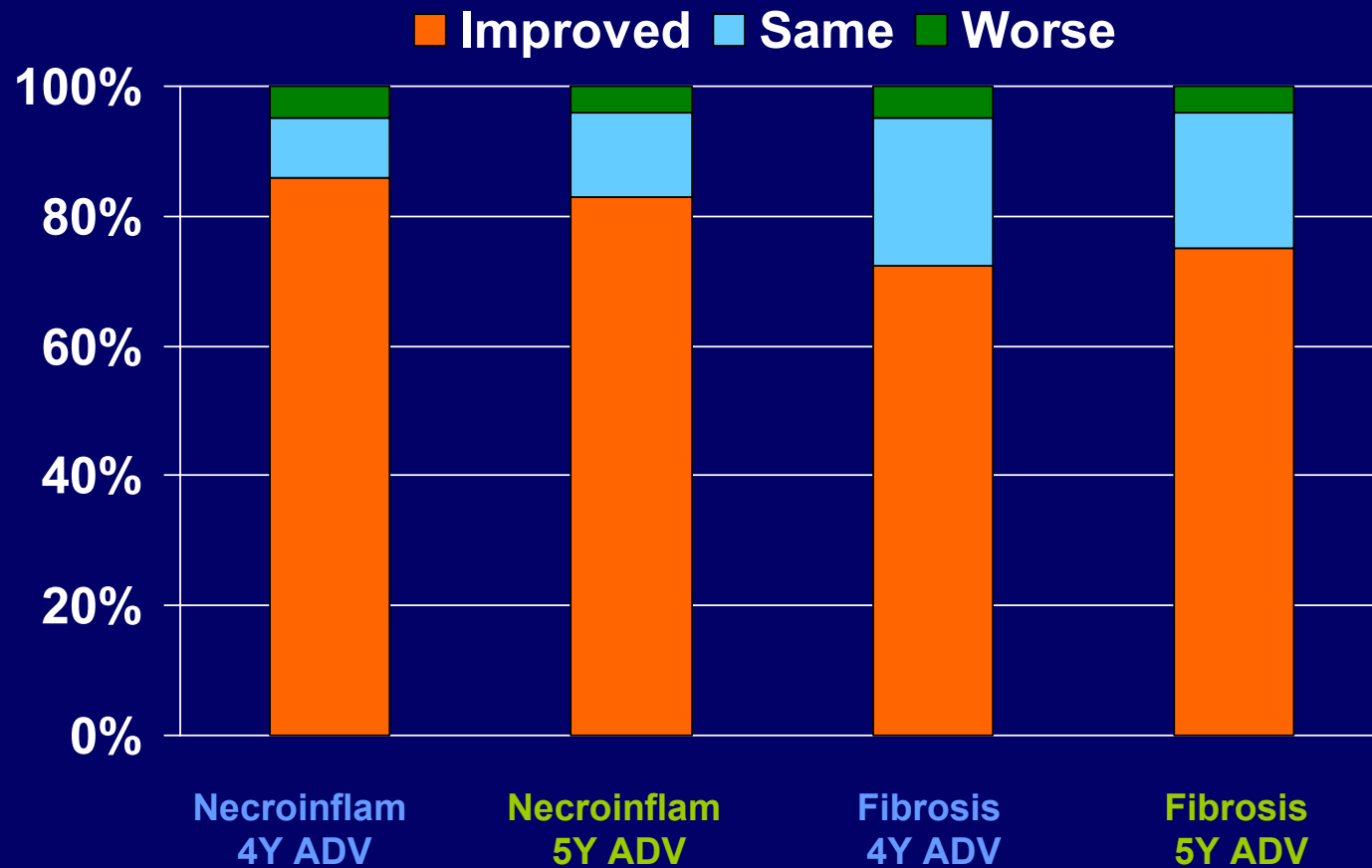
HBeAg- CHB

HBsAg Seroconversion on ADV

- Six patients (5%) had HBsAg loss
- Five of the 6 patients had anti-HBs at the last available time point
- Time to HBsAg loss
 - One patient lost HBsAg in < 0.5 year
 - One patient in < 1.5 years
 - Four patients after > 3.5 years of ADV

HBeAg- CHB

Ranked Histologic Assessments



Median Change in
Knodell Score
From ADV Baseline

- 4.5

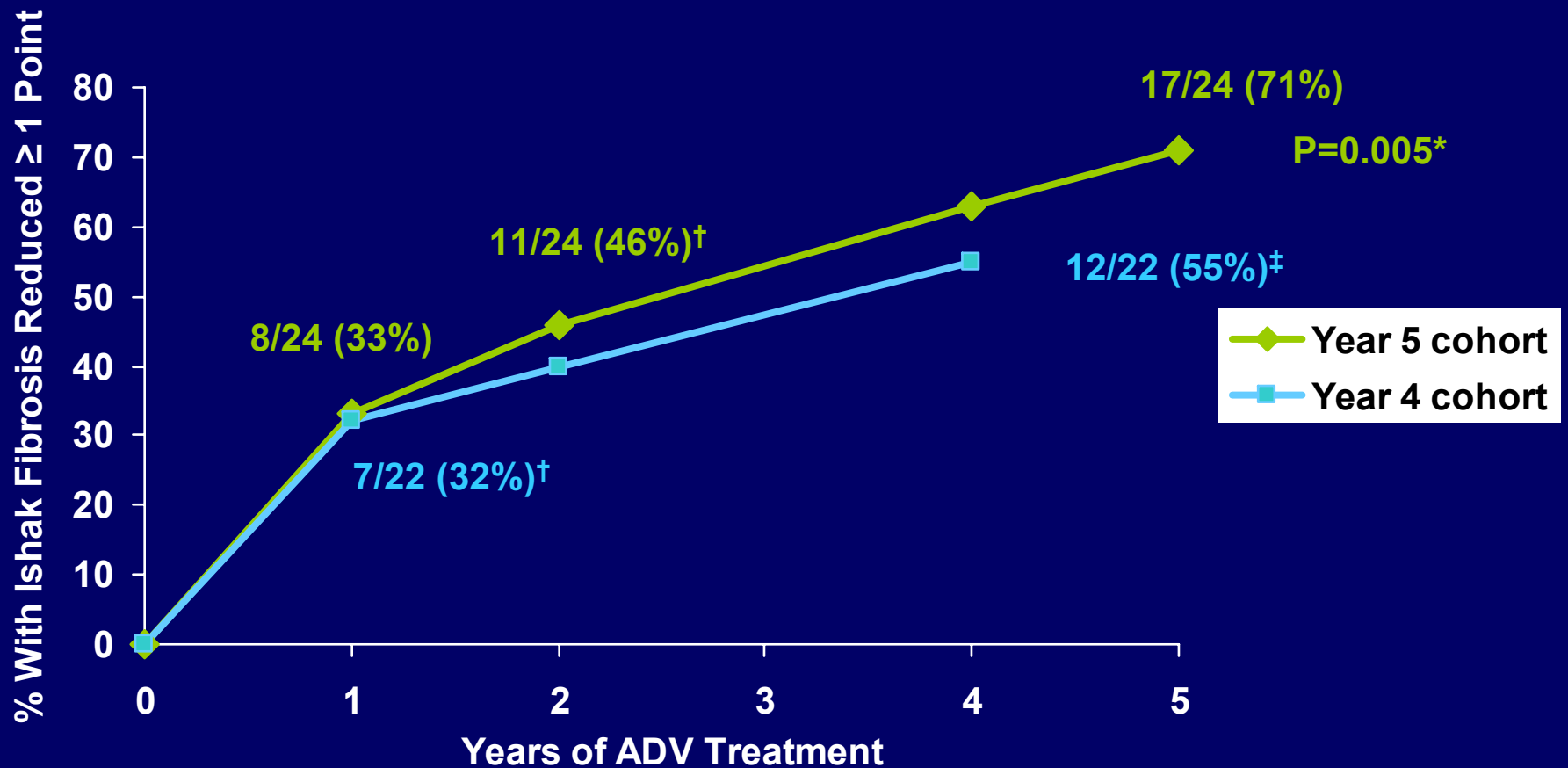
- 5.0

- 1.0

- 1.0

HBeAg- CHB

Improved Ishak Fibrosis Scores Over Time



*Cochran-Armitage exact test of trend over time for 5Y cohort.

[†]LOCF (no improvement) n=9 for 4Y cohort;

n=15 for 5Y cohort. [‡]1 patient received concomitant LAM

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HBeAg- CHB

Improvement in Fibrosis in Patients with Pre-treatment Bridging Fibrosis or Cirrhosis

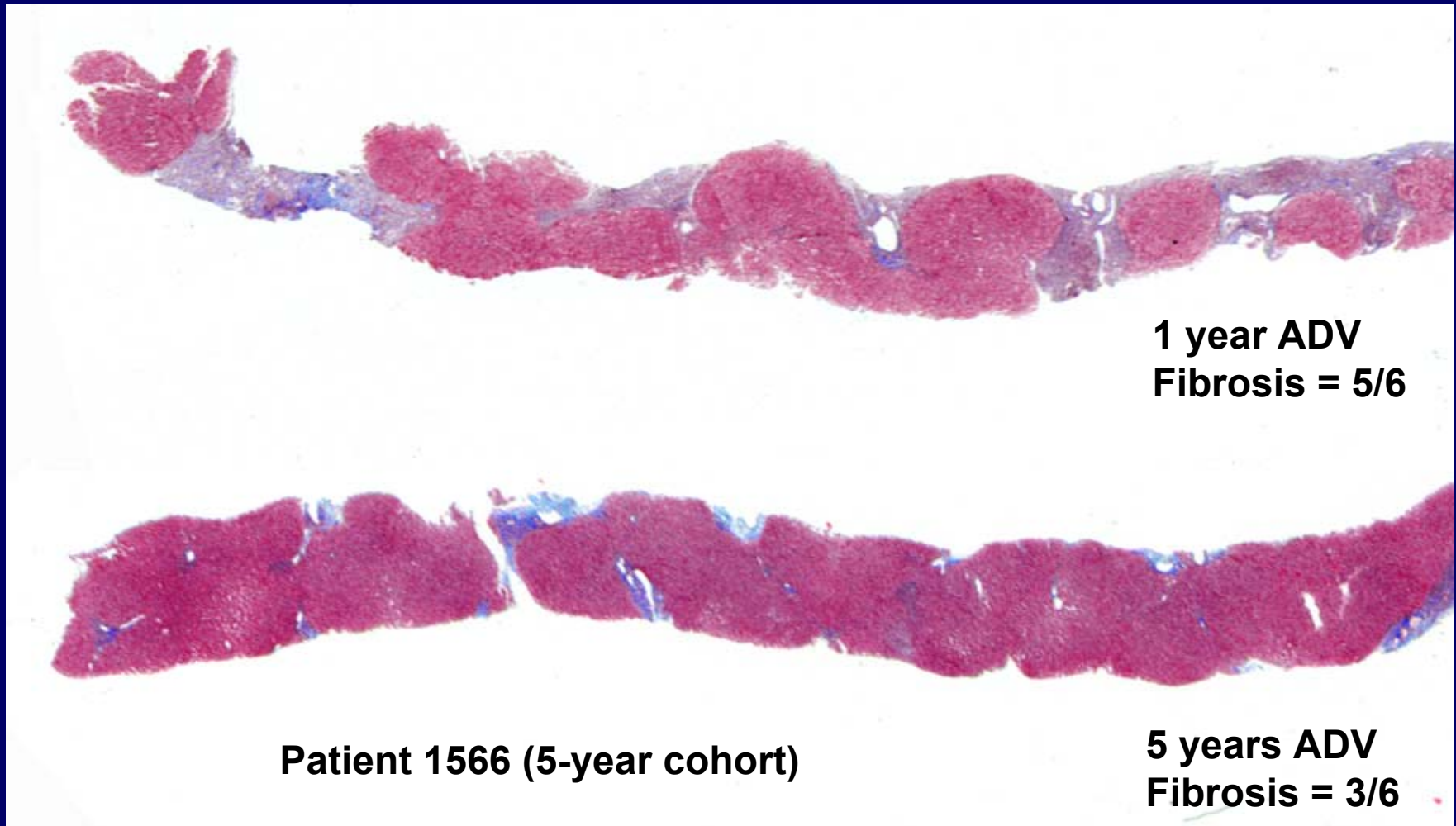
	Pretreatment Ishak Fibrosis Score	Ishak Score 1 year ADV	End-of-Treatment Ishak Fibrosis Score
4-Year Cohort (n=5)	6	3	2
	6	2	2
	4	4	2
	6	6	5
	5	---	6
5-Year Cohort (n=7)	6	6	2
	5	5	3
	5	3	2
	4	1	1
	4	3	3
	4	3	3
	4	4	4

• Among 12 patients with bridging fibrosis or cirrhosis pretreatment, **7 improved ≥ 2 points** after 4 or 5 years of ADV (1 received concomitant lamivudine).

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HBeAg- CHB

Fibrosis Regression on ADV



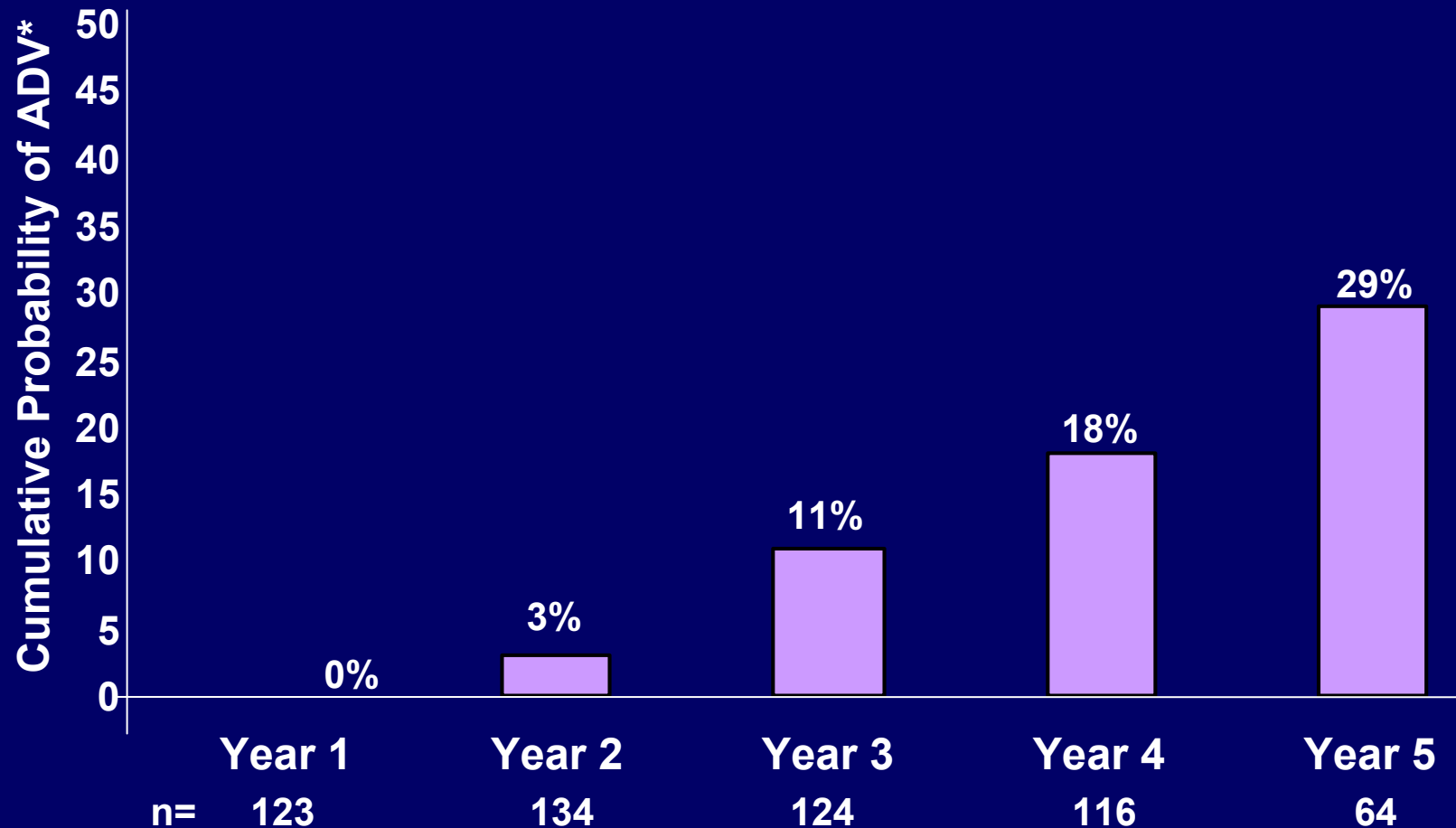
**1 year ADV
Fibrosis = 5/6**

Patient 1566 (5-year cohort)

**5 years ADV
Fibrosis = 3/6**

HBeAg- CHB

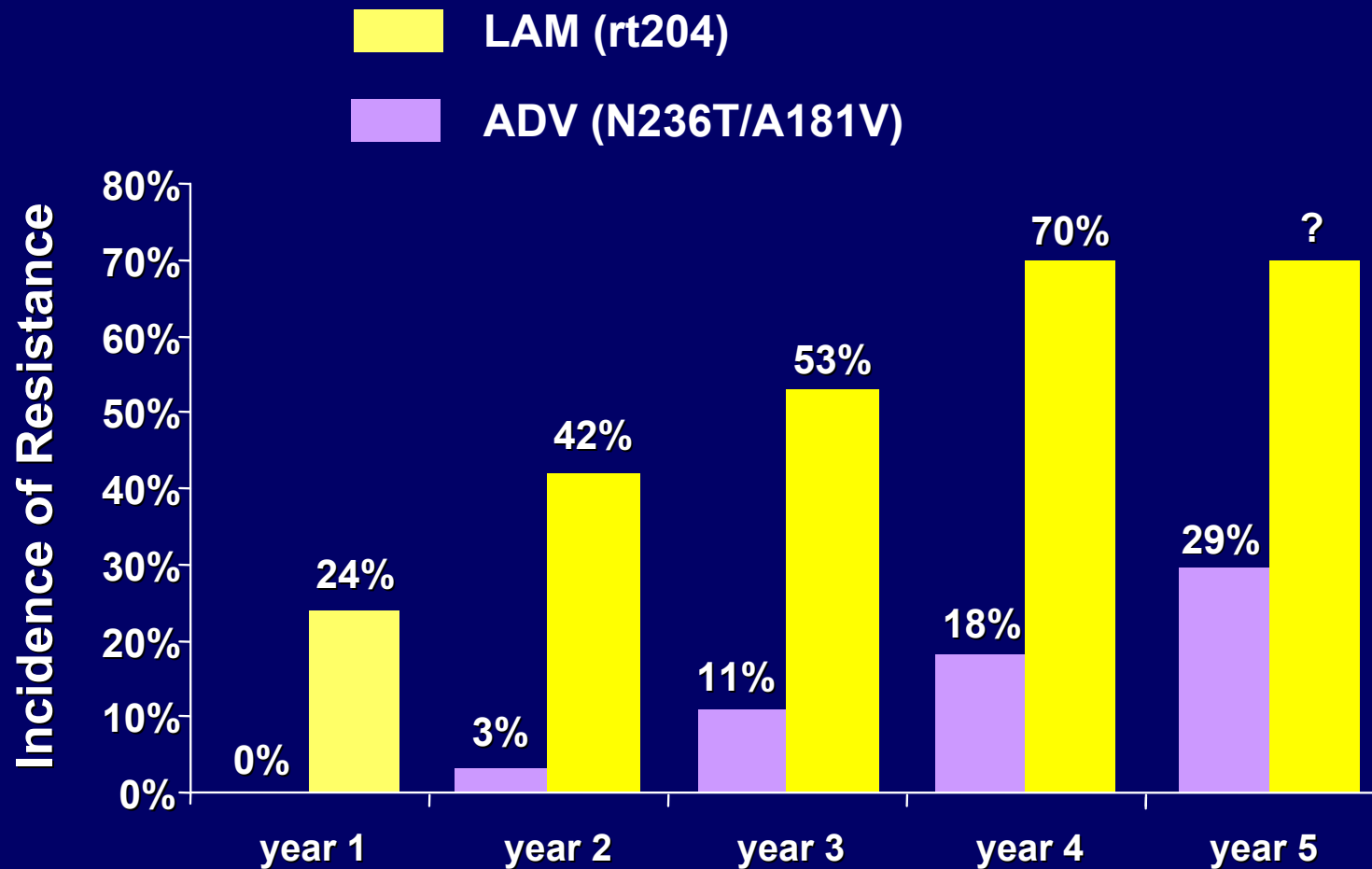
Cumulative Probability of ADV Genotypic Mutations



* Cumulative rate calculations for ADV genotypic mutations (rtN236T or rtA181V) performed using life-table method (illustration depicts \pm 95% confidence interval)

Hadziyannis, AASLD 2005

Incidence of HBV Genotypic Mutations LAM and ADV



Lai CL, *Clin Infect Dis* 2003;36:687.
Locarnini et al., EASL 2005.

HBeAg- CHB

Safety Parameters

- Renal Laboratory Parameters
 - By year 5, no patient had confirmed serum phosphorus <2.0 mg/dL during treatment
 - Four patients (3%) had confirmed increase in serum creatinine ≥ 0.5 mg/dL above baseline
 - All absolute values were \leq grade 1
 - Maximum value 1.5 mg/dL
- Adverse events
 - Three patients permanently discontinued due to an adverse event
 - Serious adverse events occurred in 24 patients (19%)
 - None were related to ADV
 - 3 patients developed hepatocellular carcinoma

HBeAg- CHB

Conclusions

- Long-term treatment with ADV 10 mg QD in the 4- and 5-year cohorts produced significant and increasing improvement in hepatic fibrosis
- The majority of patients normalized ALT, suppressed serum HBV DNA, and 5% lost HBsAg
- Treatment with ADV was generally well-tolerated
- The cumulative probability of developing genotypic mutations (rtN236T or rtA181V) on ADV therapy was 29% after 5 years

ADV Development Program

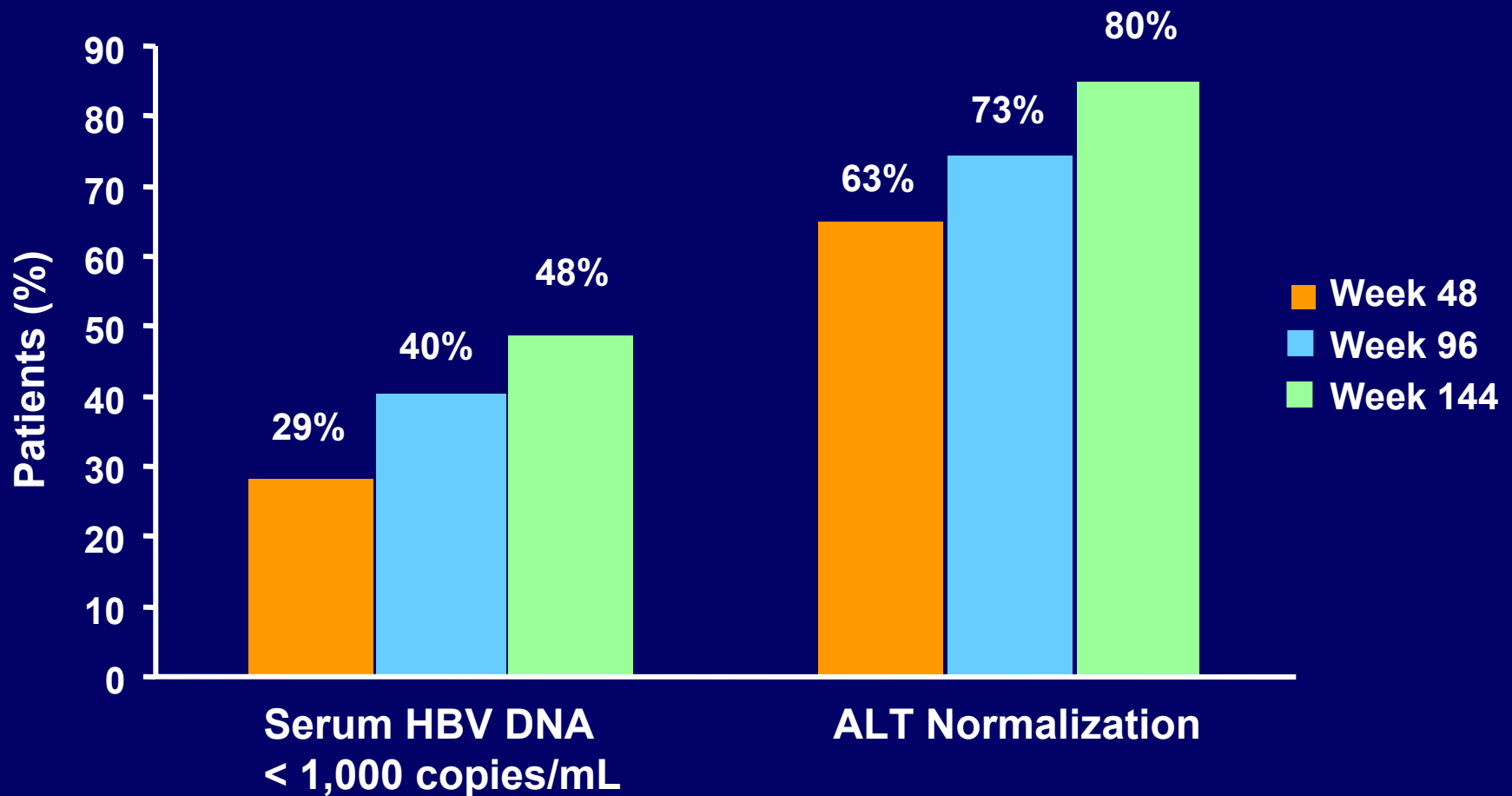
5 Year Long-Term Studies

- **Treatment-naive**
 - HBeAg- , compensated liver function
 - HBeAg+, compensated liver function

- **Lamivudine-resistant HBV**
 - Waitlisted for liver transplantation
 - Post-liver transplantation
 - HIV Co-infection

HBeAg+ CHB

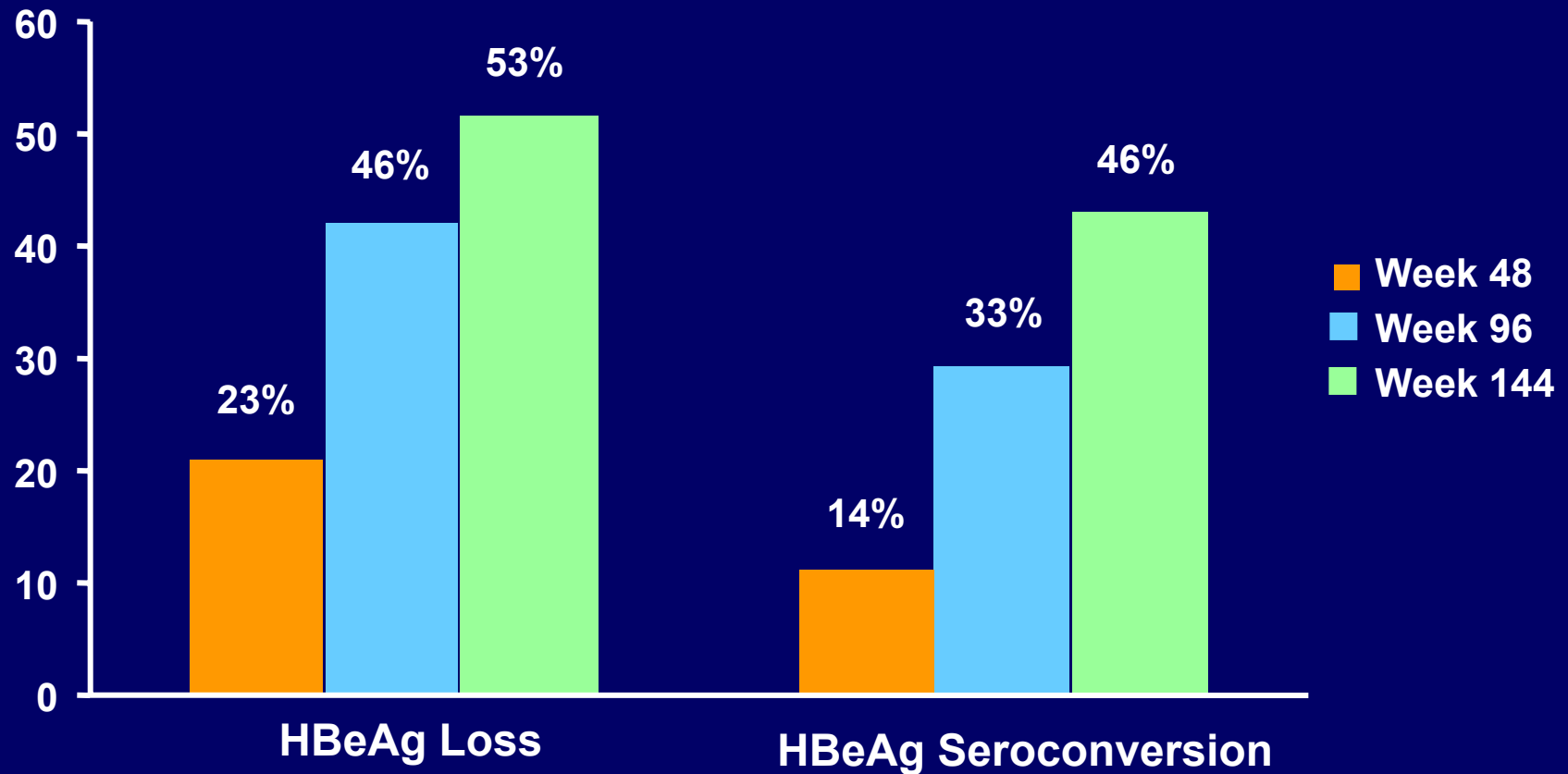
HBV DNA Undetectable and ALT Normalization



Roche Amplicor Monitor™ PCR, LLQ 1000 copies/mL
Kaplan-Meier estimates
Marcellin et al. 40th EASL. April 2005. Oral 73

HBeAg+ CHB

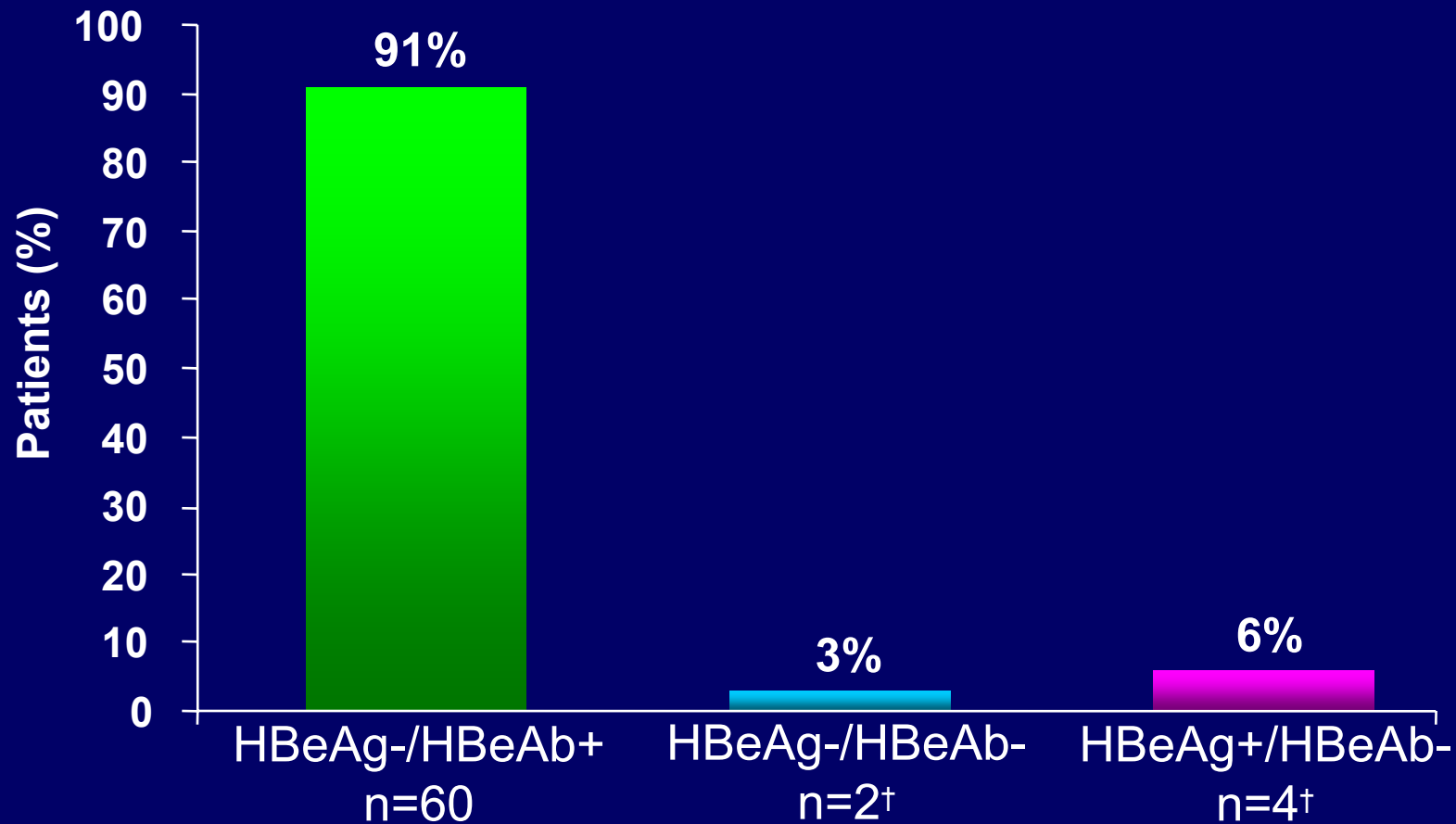
HBeAg Loss and Seroconversion Over Time



Kaplan-Meier estimates

HBeAg+ CHB

Durability of Seroconversion



* Median duration off ADV therapy: 55 weeks (range 5-114)

† All patients who did not maintain seroconversion were genotype C

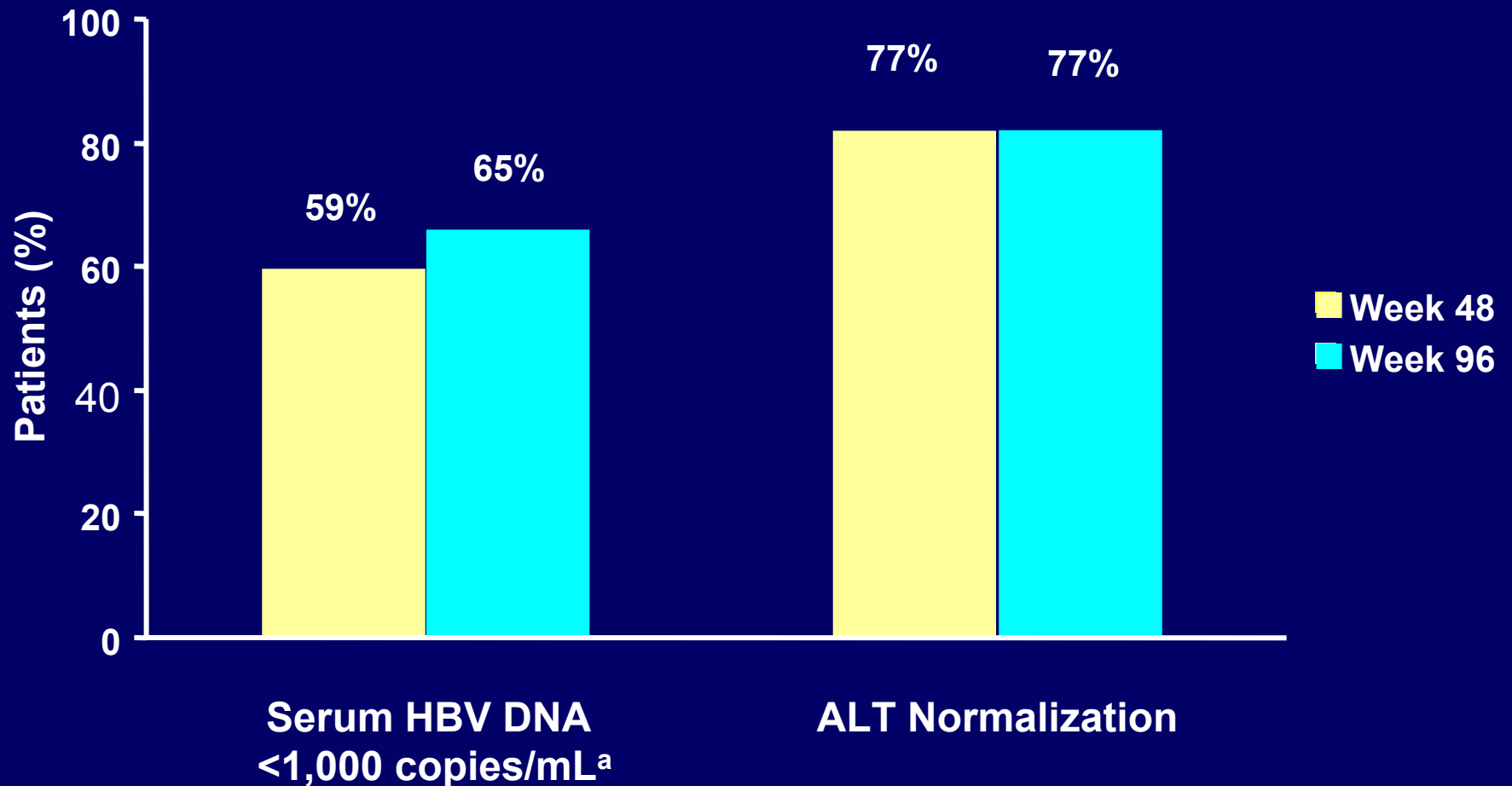
HBeAg+ CHB

Safety

- No patient who continued treatment with adefovir dipivoxil had a serum creatinine elevation (>0.5 mg/dL above baseline) or a serum phosphorus < 2.0 mg/dL
- No patient had an ALT elevation accompanied by signs of worsening liver function

Pre-OLT Failing LAM

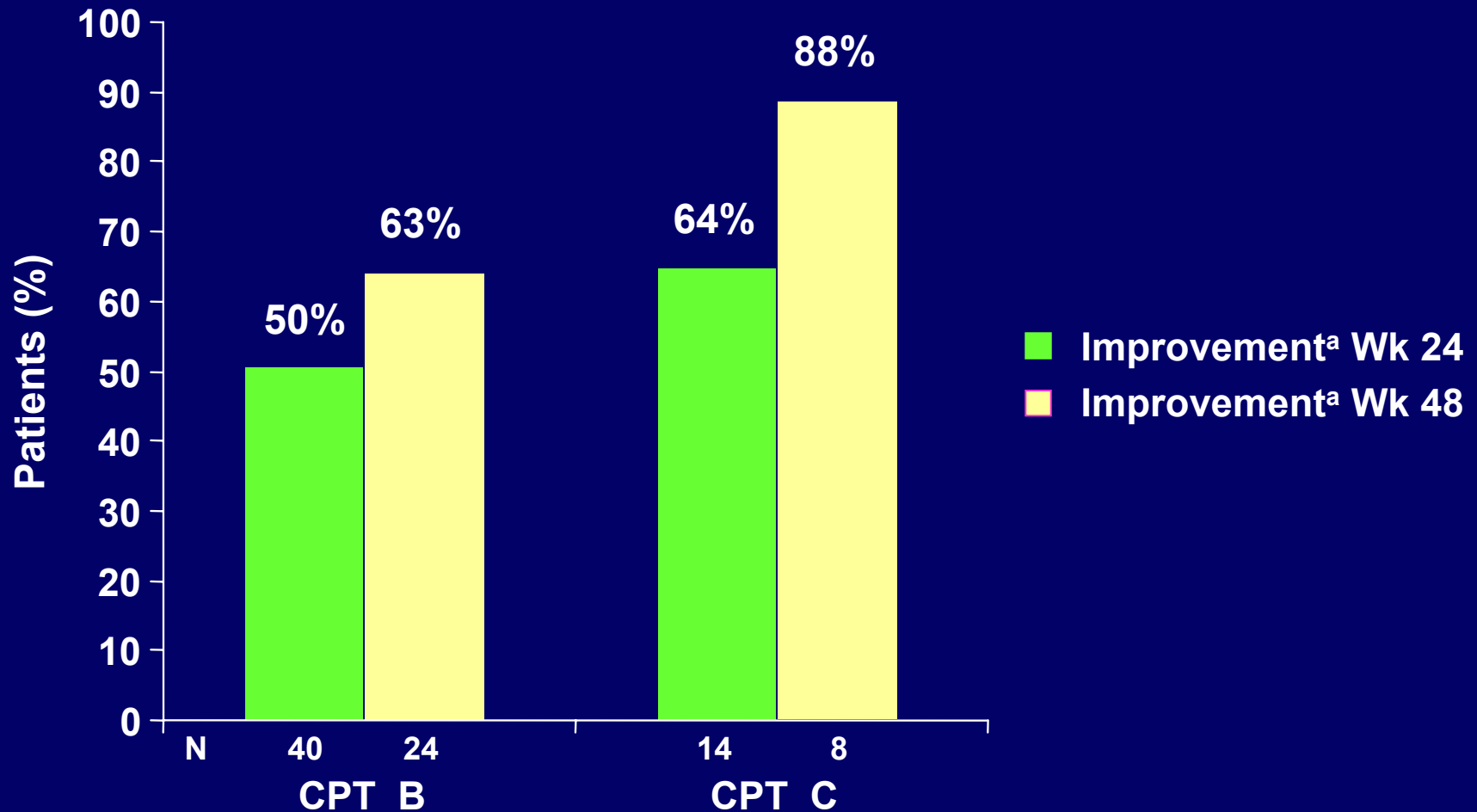
Undetectable HBV DNA and ALT Normalization



a. Roche Amplicor Monitor PCR LLQ < 1,000 copies/mL

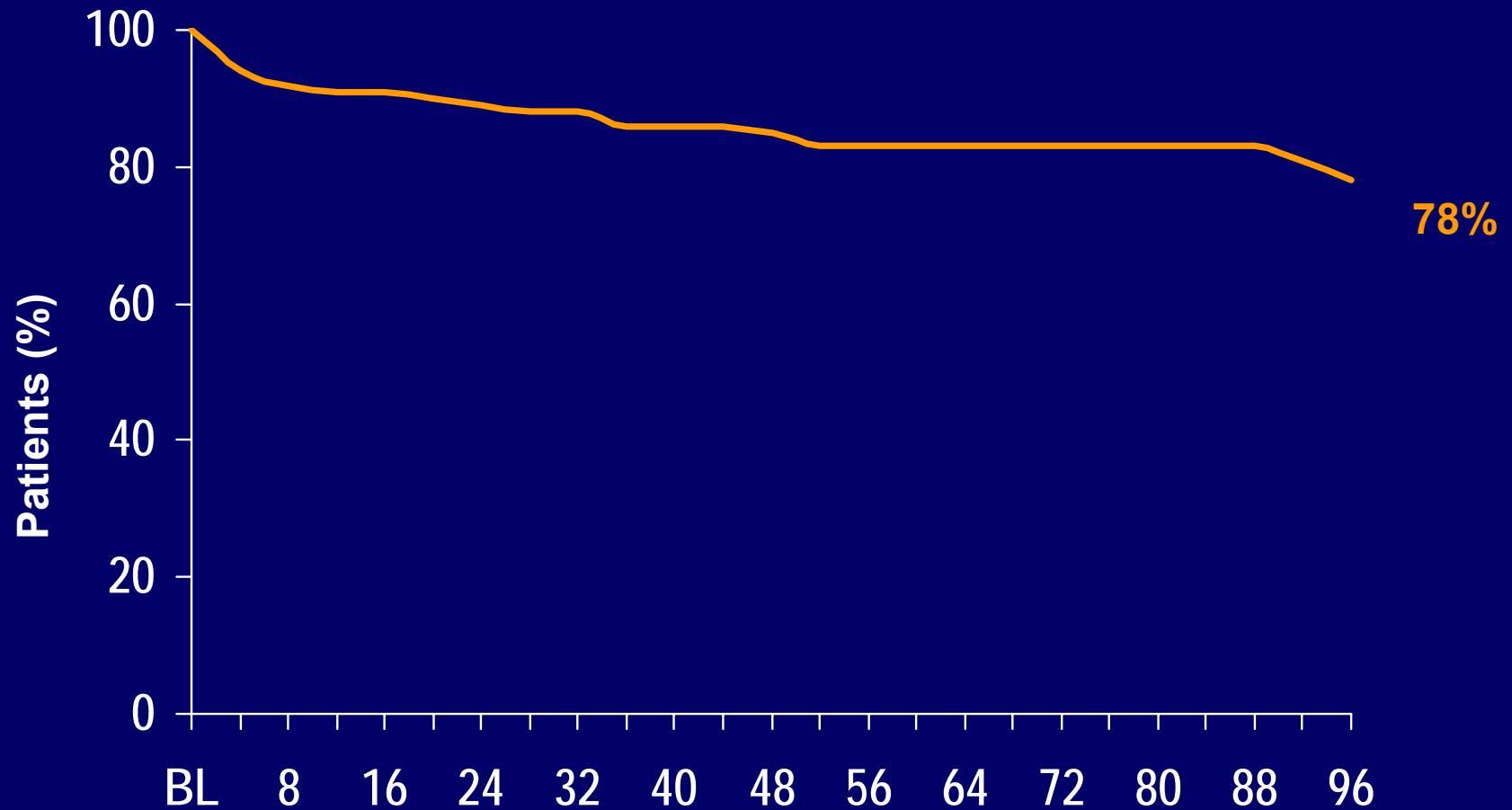
Pre-OLT Failing LAM

Improvement in Child-Pugh-Turcotte (CPT) Score



a. Improvement defined as a 2 point improvement in Child-Pugh-Turcotte (CPT) Score

Pre-OLT Failing LAM Survival

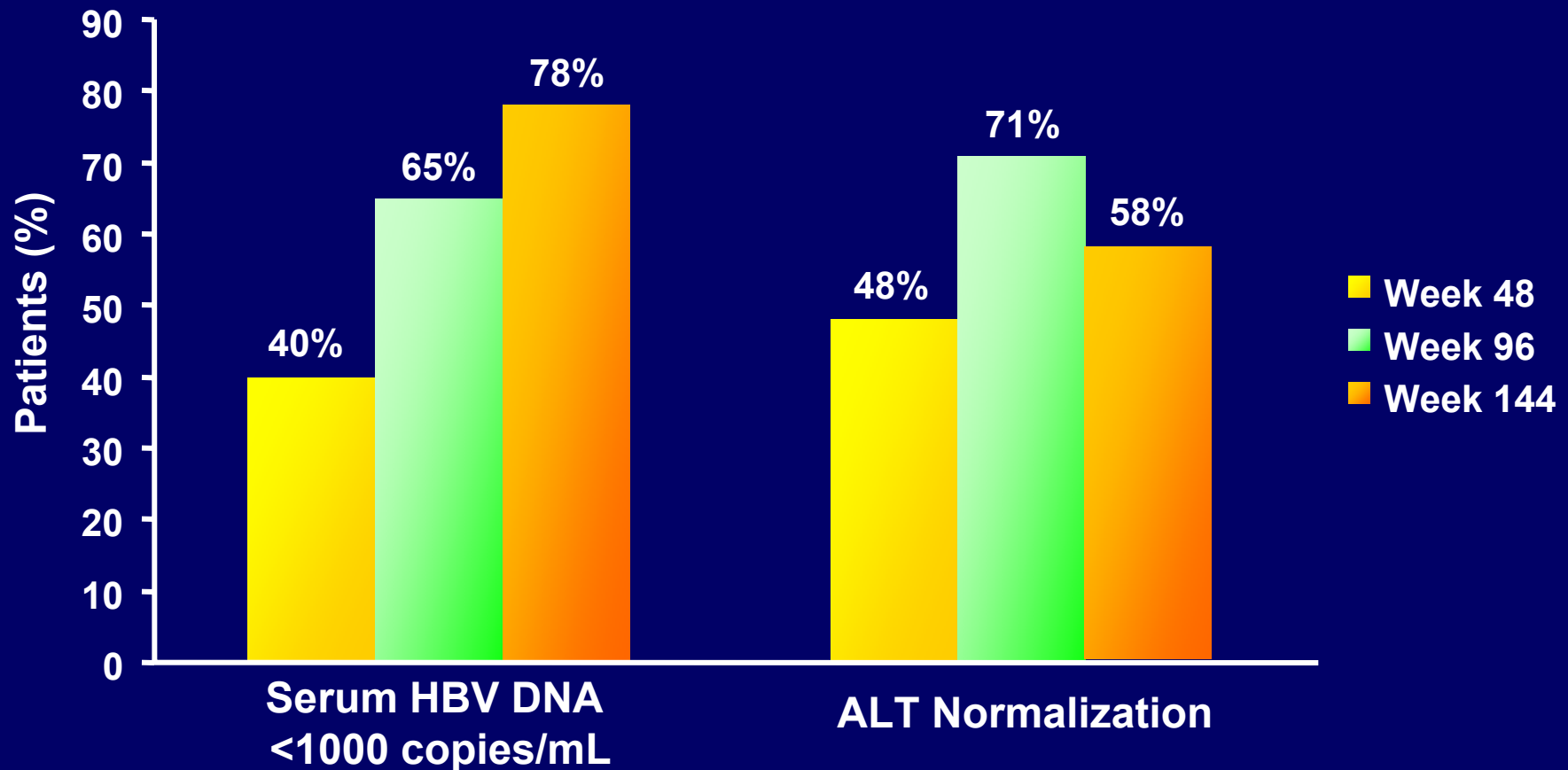


Kaplan-Meier Analysis

Schiff et al. 40th EASL. April 2005. Oral 7

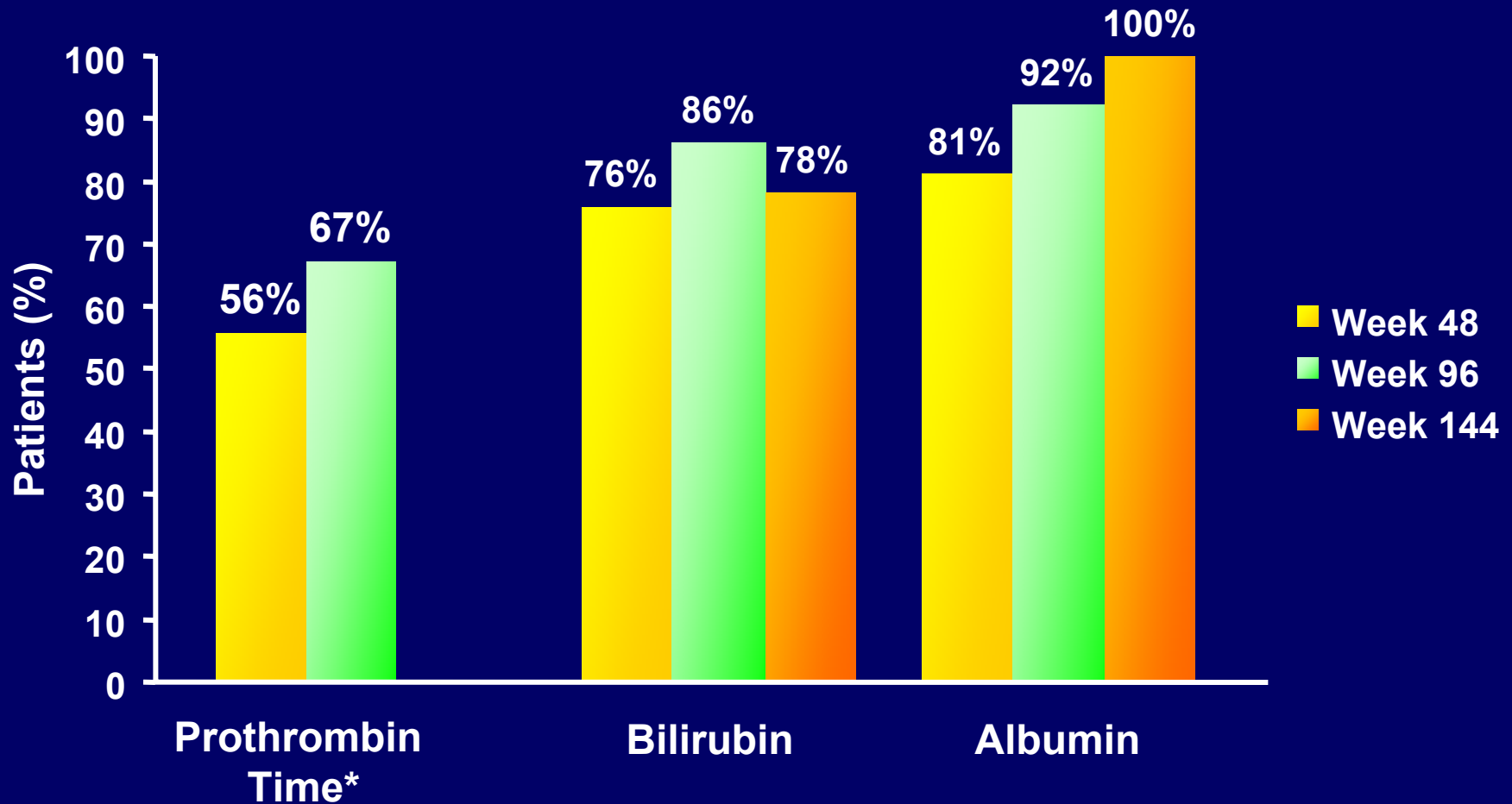
LAM-R HBV Post-OLT

Undetectable HBV DNA and ALT Normalization



LAM-R HBV Post-OLT

Rapid Normalization in Clinical Liver Function

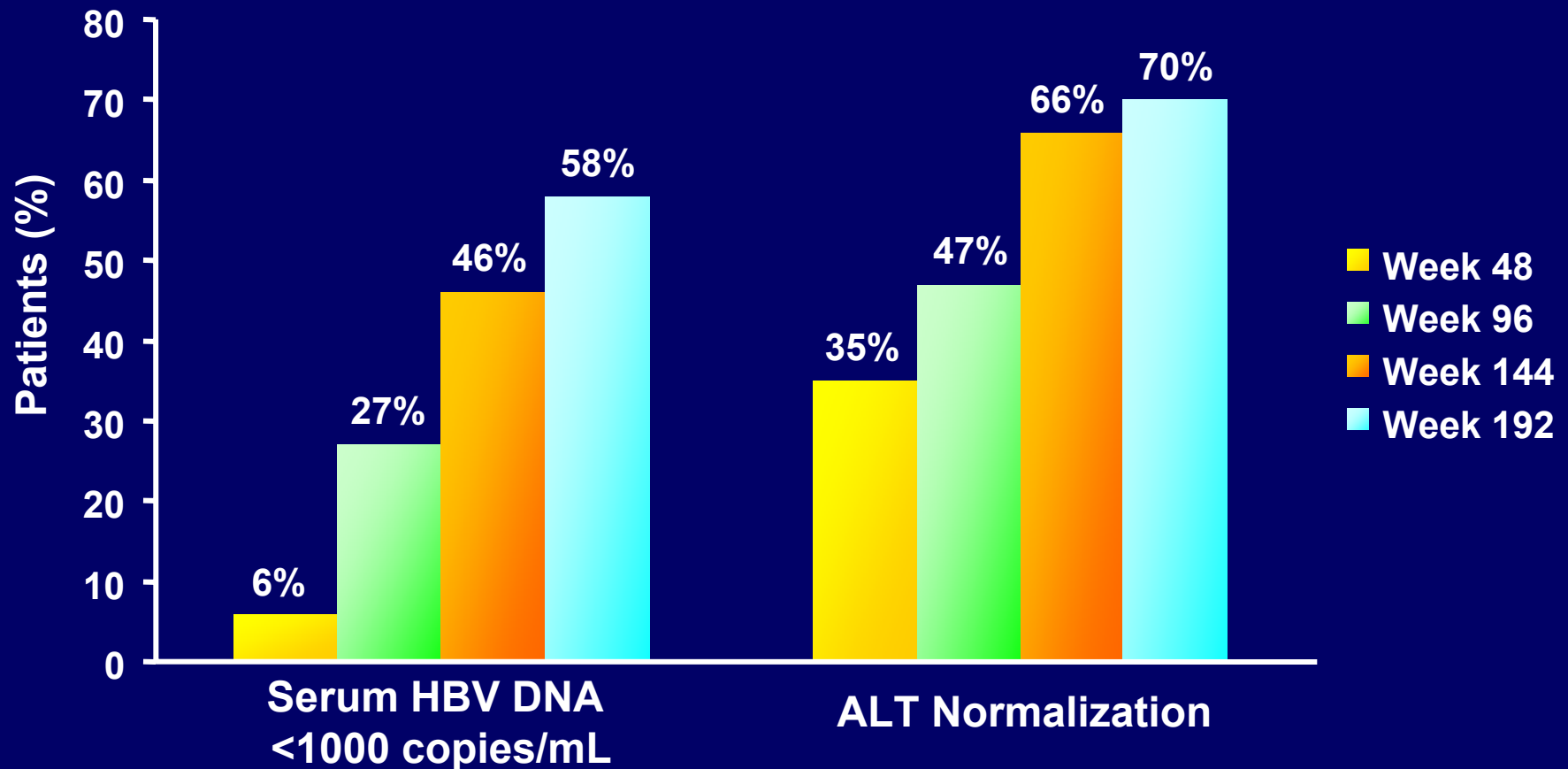


*Insufficient numbers of patients with data at week 144

Schiff et al. *Hepatology*. 2004.

HIV/HBV Co-Infection

Increasing Efficacy Over Four Years



Roche Amplicor Monitor™ PCR, LLQ < 1,000 copies/mL

*Kaplan-Meier estimates

Benhamou et. al, WAIDS 2004; In press J Hepatology

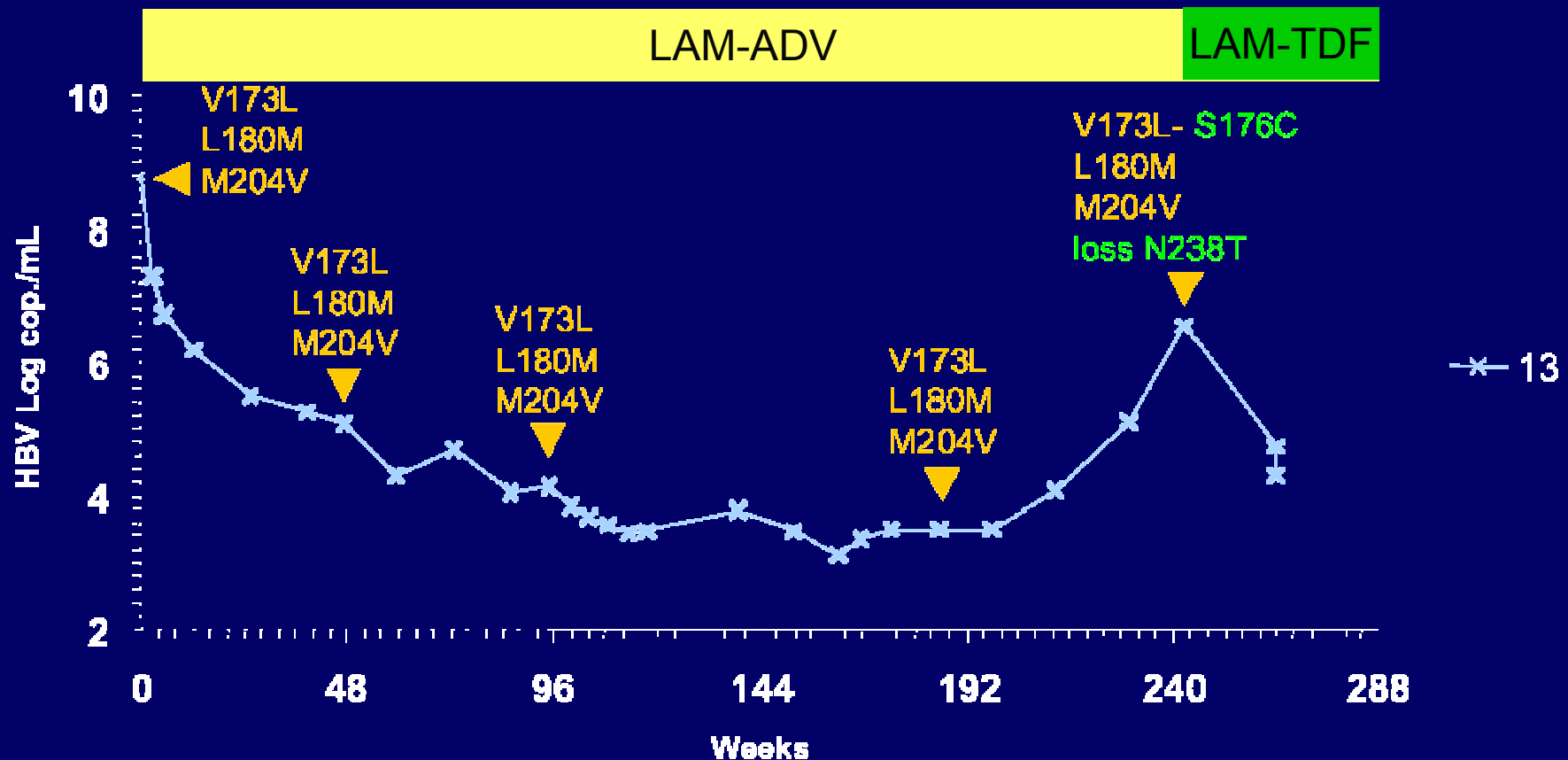
ADV in HBV/HIV Co-infection

Key Findings

- ADV added to ongoing LAM in patients with HIV/HBV co-infection and LAM-R HBV
 - Baseline median serum HBV DNA of 9.8 log₁₀ copies/mL
- Increasing efficacy over 5 years demonstrated
 - 6.4 log₁₀ reduction in serum HBV DNA
 - 60% HBV DNA < 1000 copies/mL
 - ALT normalization 84%
- No ADV mutations (rt236 or rt181) detected
- VL breakthrough in one patient accompanied by a new novel conserved mutation rtS176C
 - confirmation in progress

ADV in HBV/HIV Co-infection

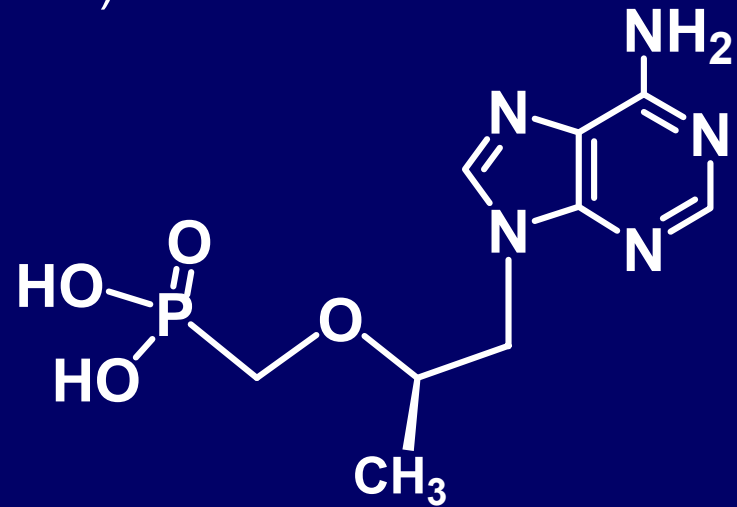
HBV Viral Load Evolution in Patient 13 Treated with LAM-ADV and Switched to LAM-TDF



- The role of the 173 mutation will be confirmed in vitro
- Switch to TDF resulted in a decrease in serum HBV DNA

Tenofovir Disoproxil Fumarate (TDF)

- Orally bioavailable prodrug of tenofovir (PMPA)
- Nucleotide analogue of adenosine
- Chain-terminator
- Approved for treatment of HIV-1 infection
- Active against WT, pre-core mutant and LAM-resistant HBV
- Excellent safety profile in HIV
- Long serum and intracellular half-lives



TDF in HBV/HIV Co-infection Published Data

	n	LAM-R at baseline	Time of Results	HBV DNA reduction (log ₁₀ copies/mL)
Nelson (AIDS 2003)	20	11/15	W24	-4*
Ristig (JID 2002)	6	6/6	W24	-3.6*
Nunez (AIDS 2002)	12	7/11	W24	-3.78*
Benhamou (NEJM 2003)	12	10/12	W24	-3.83**
Gozlan (WAIDS 2004)	29	16/22	1 year	-4.9
Piketty (CROI 2004)	119	73/119	9 months	-3.8*
Dore (JID 2004)				
907(not ARV naive)	10	6/10	W 24	-4.9**
903 (naive)	5	0/5	W 48	-4.7**

* Median reduction

**Mean reduction

**Randomized Phase II Controlled Trial
Comparing the Efficacy of Adefovir
Dipivoxil and Tenofovir Disoproxil
Fumarate for the Treatment of
Lamivudine-Resistant
Hepatitis B Virus in Subjects Who Are
Co-infected With HIV**

Marion Peters, MD

Professor of Medicine

University of California, San Francisco

For the AACTG Study 5127 Team

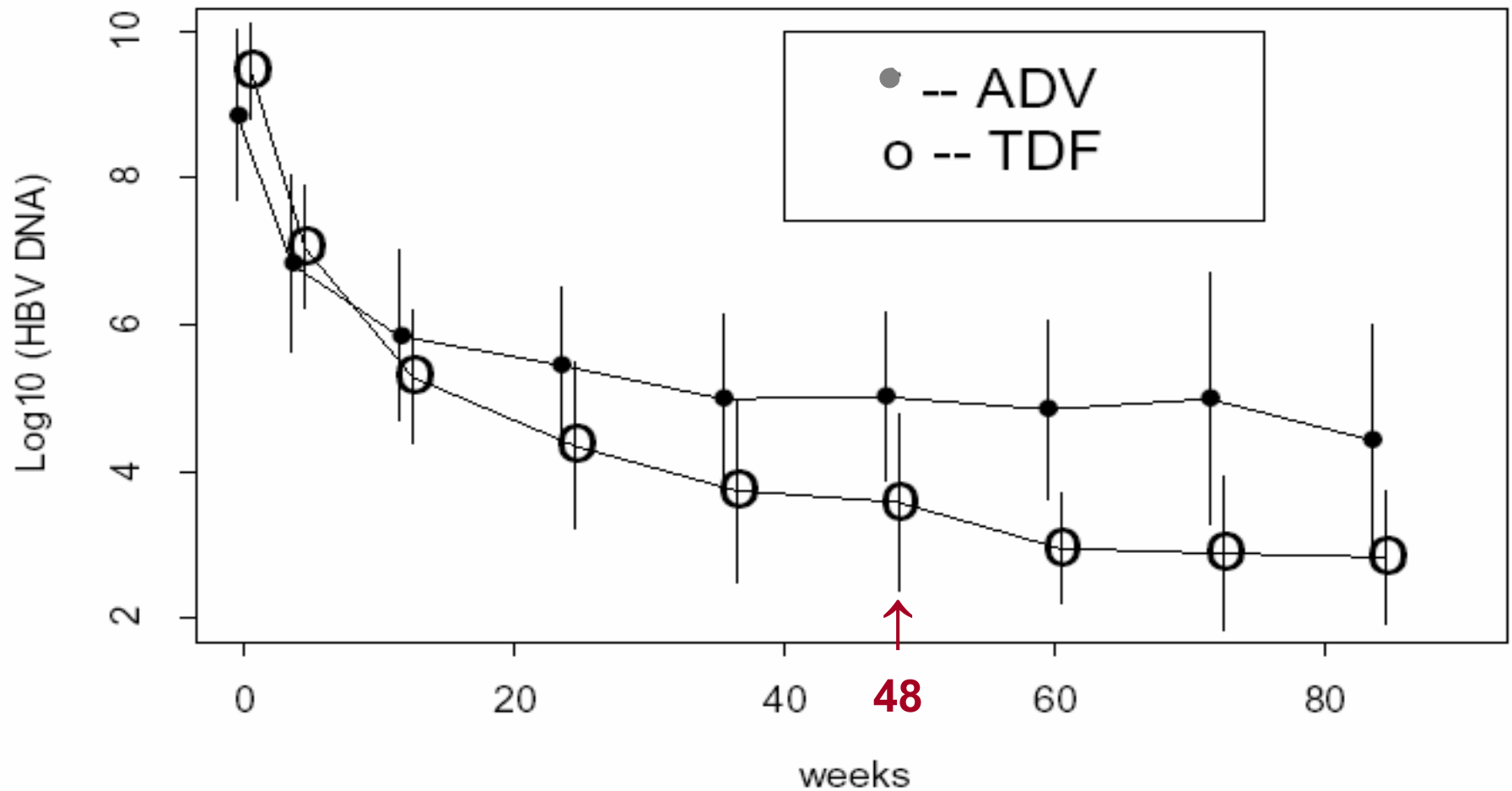
CROI Boston 2005



Submitted, October 2005

ACTG 5127

Mean Change from Baseline in HBV DNA



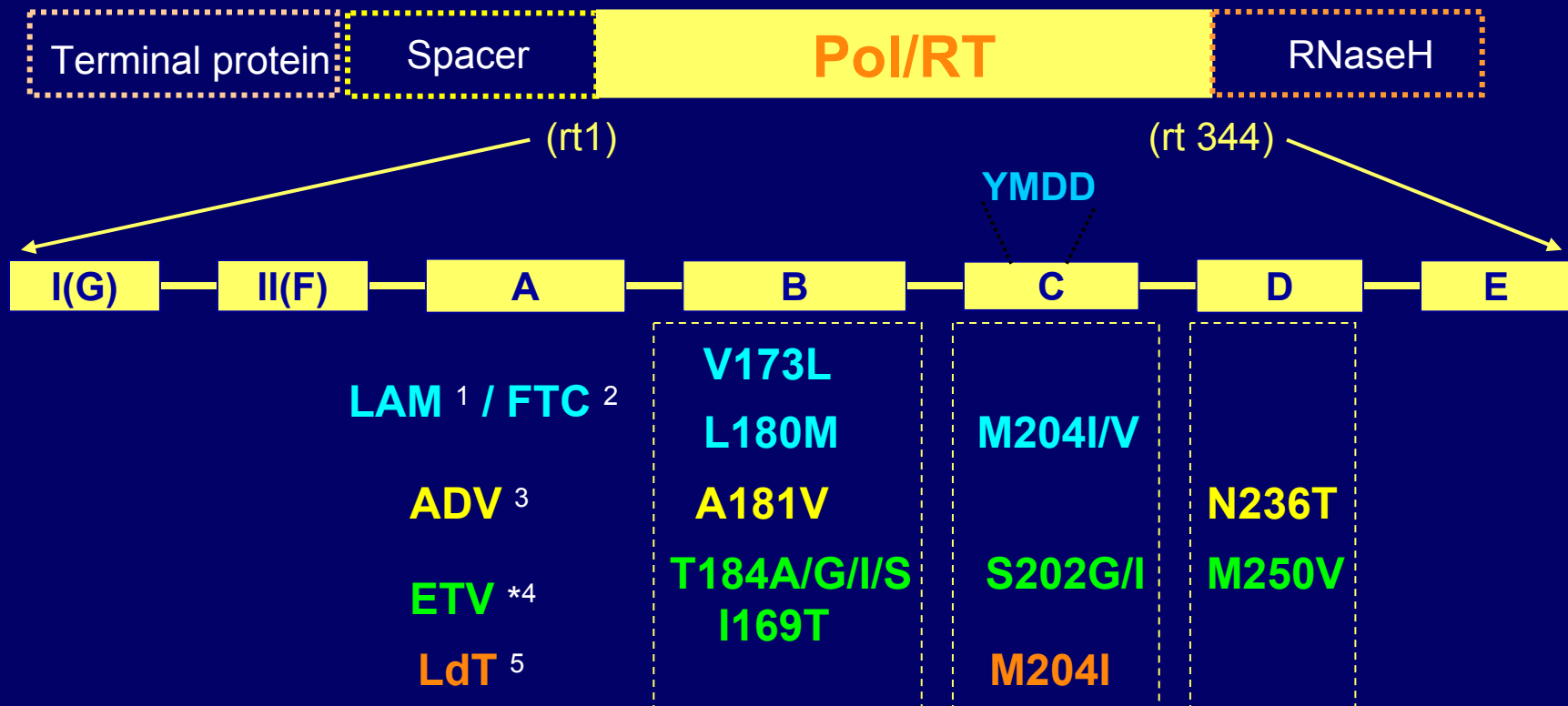
TDF Safety Profile in HIV

- FDA approval for the treatment of HIV October 2001
- HIV clinical trial experience in ~ 14,000 patients
 - > 1500 HIV patients received TDF 300 mg in controlled clinical trials
 - > 11,000 HIV patients received TDF in expanded access studies
- Cumulative exposure ~400,000 patient-years of treatment
- Estimations of exposure derived from published and presented TDF data in CHB (most in HIV/HBV co-infection)
 - 328 CHB patients have received TDF 300 mg for ≥ 24 weeks
 - Of these, 227 received TDF 300 mg for 48 weeks

Rationale for Clinical Development of Tenofovir DF in CHB

- ADV Study 437 (10mg vs 30mg ADV) in HBeAg+ CHB and FTCB-201 (ADV vs ADV + FTC) highlight that ADV 10mg antiviral efficacy can be enhanced
- In ADV phase 3 clinical trials, approximately 10-15% of ADV 10mg patients have < 2 log reduction in serum HBV DNA at 48 weeks
 - ACTG 5127 establishes that TDF was non-inferior to ADV
 - TDF less variability of response compared to ADV
- ADV and TDF both active against wild-type, pre-core mutant and all patterns of LAM-R HBV
- TDF active against the ADV mutant A181V

Mutations Selected and Associated With Resistance to HBV Antivirals *In Vivo*



* All ETV resistance require background YMDD mutations.

1. Allen, et al. *Hepatology*. 1998 27:1670-7.
2. Gilead data on file.
3. Qi, et al. *J Hepatol*. 2004;40(suppl 1):20-1.
4. Tenney, et al. *AAC*. 2004;48:3498-507.
5. Lai, et al. *Hepatology*. 2003 38 262A.

LAM Genotypic Mutations

In Vitro Susceptibility to Acyclic Nucleotides

Fold-Change from Wild-Type

Compound	V173L+			
	L180M + M204V	L180M + M204V	M204I	L180M + M204I
Adefovir	1.1	1.1	1.8	2.1
Tenofovir	0.8	1.8	2.1	0.7

■ Sensitive

■ Reduced susceptibility

■ Resistant

LAM Genotypic Mutations

In Vitro Susceptibility to L-and D- Nucleosides

Compound	Fold-Change from Wild-Type			
	L180M + M204V	V173L+ L180M + M204V	M204I	L180M + M204I
Entecavir	37	164	471	38
Emtricitabine	>2000	898	>2000	845
Lamivudine	>700	>1000	>1000	>1000
Clevudine	>1600	>1600	>1600	>1600
Telbivudine (L-dT)	>322	>322	>322	>322

■ Sensitive
 ■ Reduced susceptibility
 ■ Resistant

ADV Genotypic Mutations

In Vitro Susceptibility to Nucleos(t)ide Analogs

	Fold Change (IC ₅₀)	
	(N236T/ wild-type)*	(A181T/ wild-type)**
Adefovir	7.3	4.2
Tenofovir	4.6	3.0
Lamivudine	2.1	14.0
Telbivudine	2.4	>15.0
Entecavir	0.67	12.0
Clevudine	4.9	>164

■ Sensitive

■ Reduced susceptibility

■ Resistant

* Qi et al, DDW 2004

** Xiong, EASL 2005

TDF for HBV

Clinical Development Program

- Two Phase 3 international studies initiated July 2005 in HBeAg+ and HBeAg- CHB
- ADV as standard of care compared to TDF
- Study results and potential NDA 2007

Conclusions

- ADV demonstrates increasing efficacy over time
 - In all patient populations and disease stages
- Proven safety and tolerability up to five years
- No change in safety profile with extended dosing
- ADV has the best resistance profile at year one and up to 5 years
- No ADV resistance mutations (N236T or A181V) observed in Gilead studies when ADV used in combination with LAM, FTC, or PEG
- TDF potential as an agent for CHB under study