Viral hepatitis in reproductive health

Training in reproductive health research - Geneva 2007

20.03.2007

HBV and HCV treatment

Pierre-Jean Malè MD

Background

- Epidemiology and natural history
  - 400 million people with HBV world wide
  - 1.25-2.00 million infected persons in the United States
  - 25% mortality in perinatal acquired disease
  - 7% mortality in adult acquired disease
- The role of on-treatment virologic suppression in achieving treatment goals and improving of treatment outcomes
  - Long-term data on the relationship between viral suppression and outcomes
  - Relationships between early virologic suppression and future outcomes

Gish RG and AC Gadano. J Vir Hep. 2006. In press.

Effect of Timing of Infection

Patients infected during adolescence/adulthood

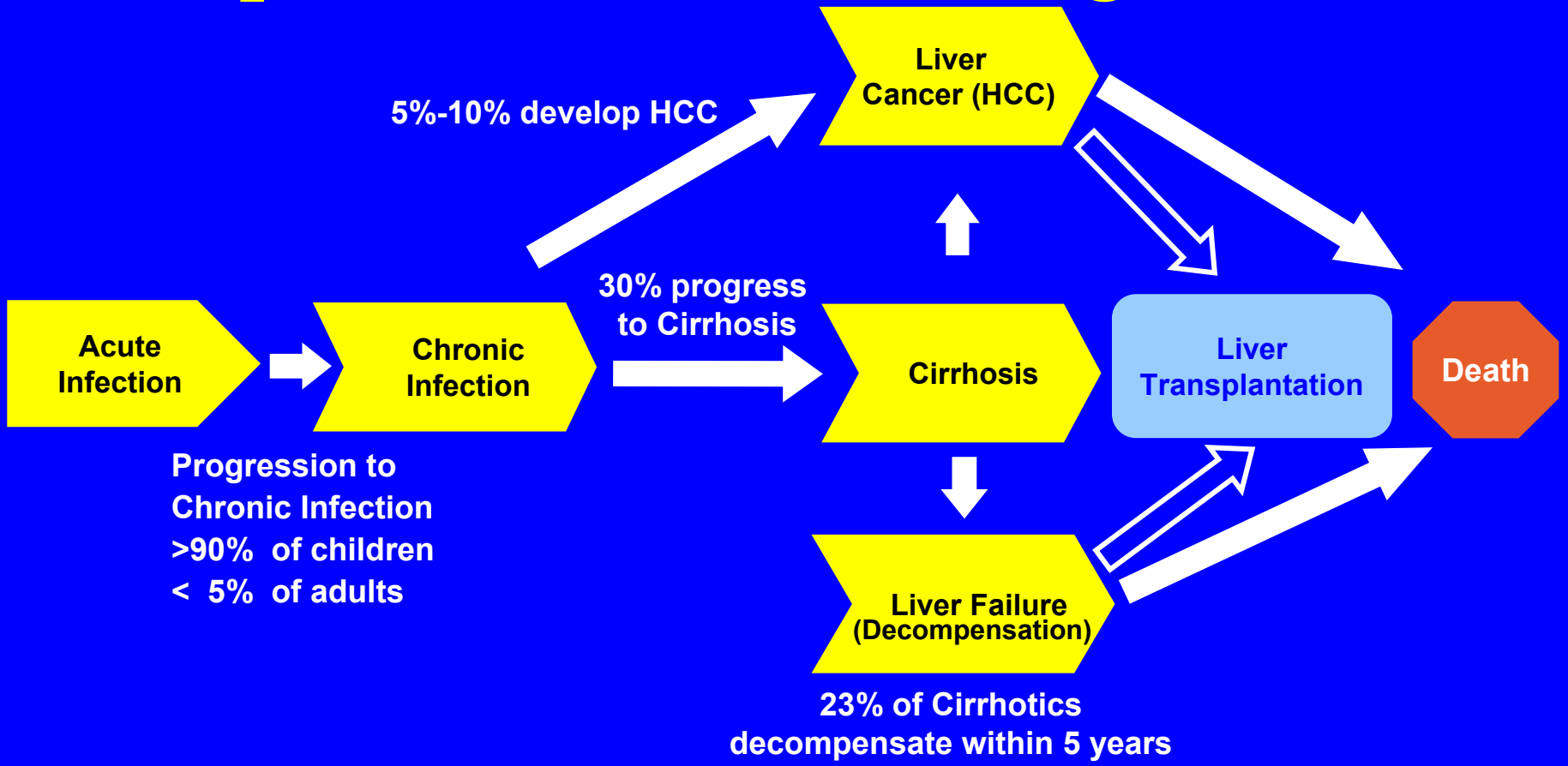
- Majority of white patients
- No immune tolerance phase; disease of relatively short duration
- Good response to immunomodulatory therapy
- Disease nonprogressive after HBeAg seroconversion; HBV DNA levels undetectable by hybridization assays—"healthy carriers"

Patients infected during early childhood

- Asian, African, some Mediterranean patients
- Prolonged immune tolerance and immune clearance phases
- Poorer response to immunomodulatory therapy
- Disease continues to progress in a proportion of anti-HBe patients

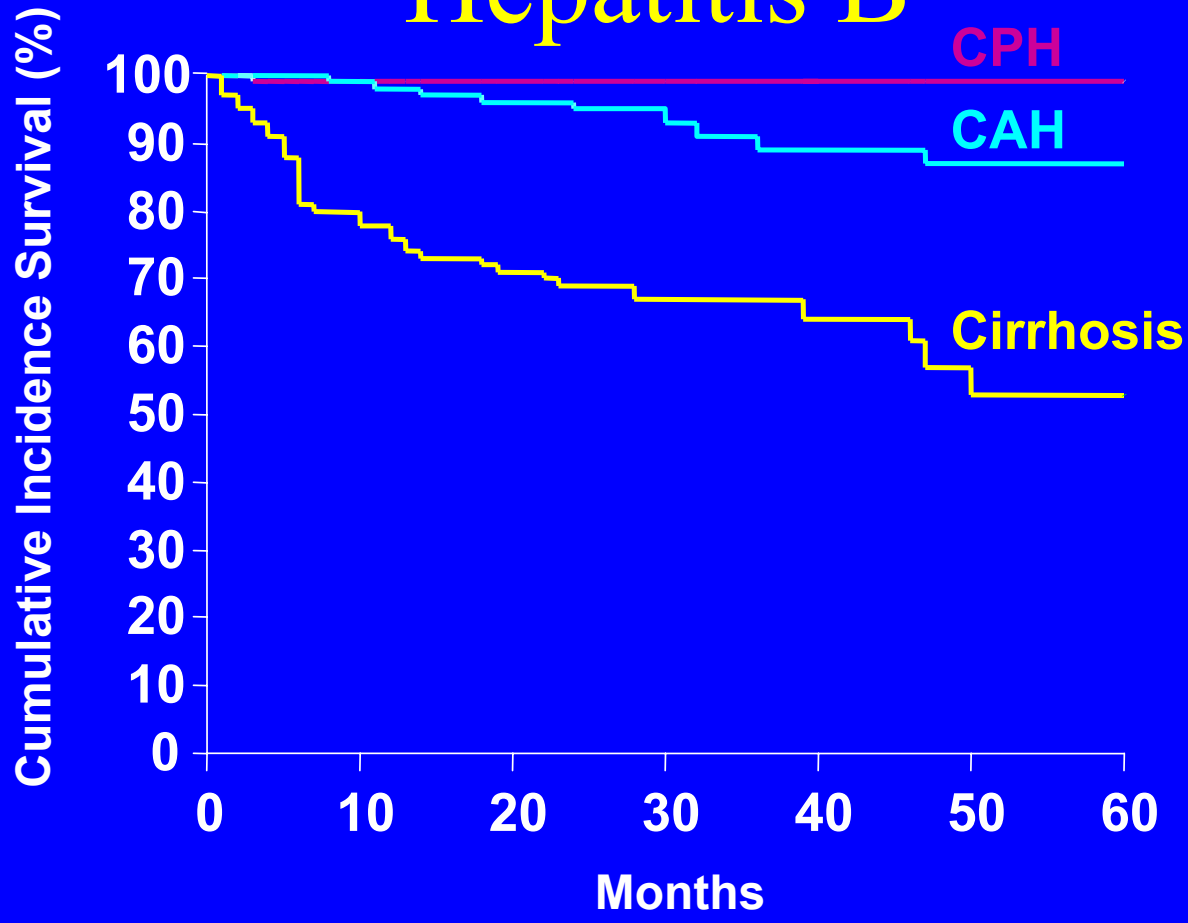
Hoofnagle J, et al. Hepatology. 1987;7:758-763. Lai CL, et al. Lancet. 2003;362:2089-2094.

Hepatitis B Disease Progression



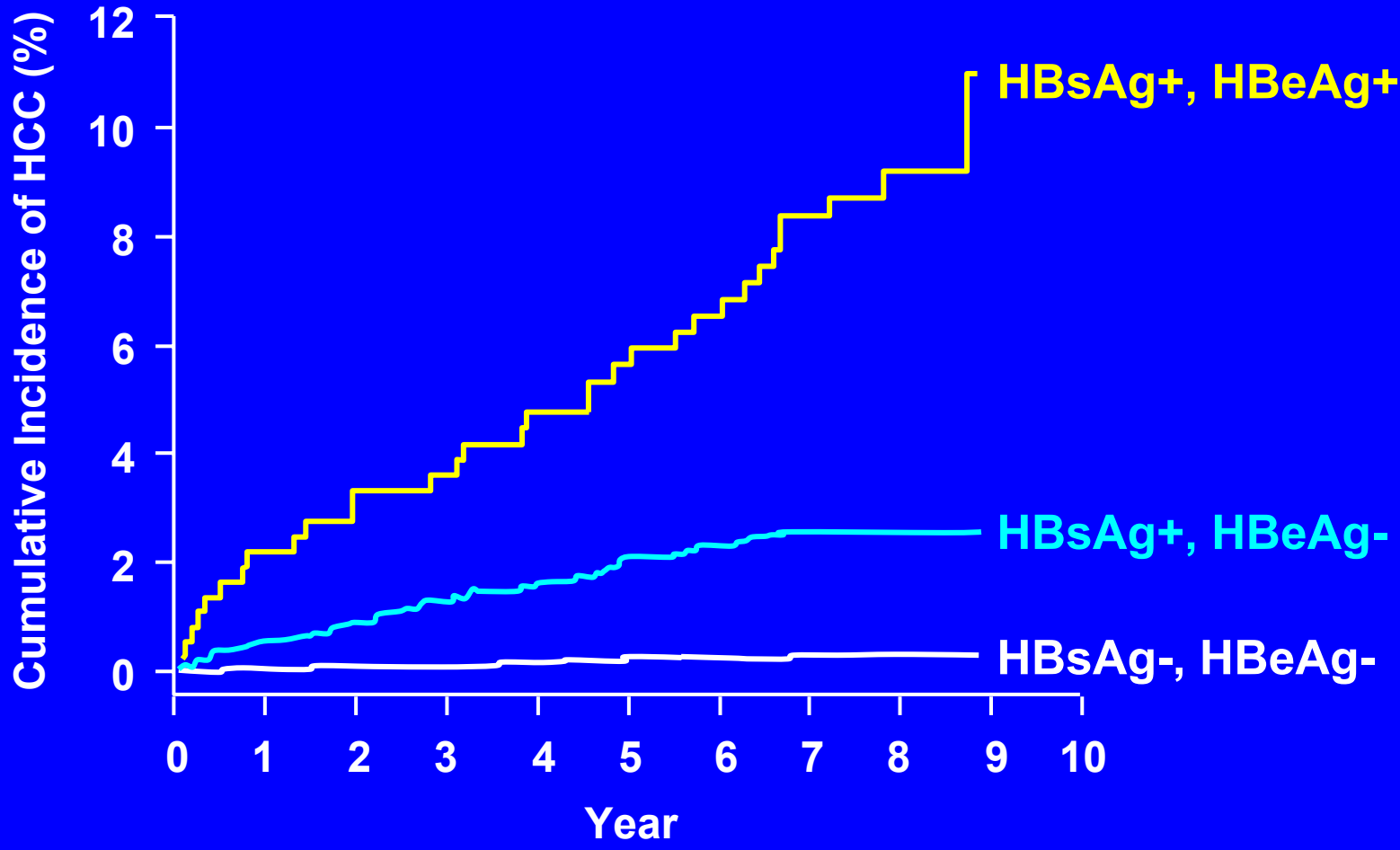
Torresi, J, Locarnini, S. Gastroenterology. 2000.
Fattovich, G, Giustina, G, Schalm, SW, et al. Hepatology. 1995. ; Moyer, LA, Mast, EE. Am J Prev Med. 1994.

5 Year Survival in Chronic Hepatitis B



Weissberg, JI, et al. Ann Intern Med. 1984;101:613-616.

Hepatitis B and Risk of HCC



Yang, HI, et al. N Engl J Med. 2002;347:168-174.

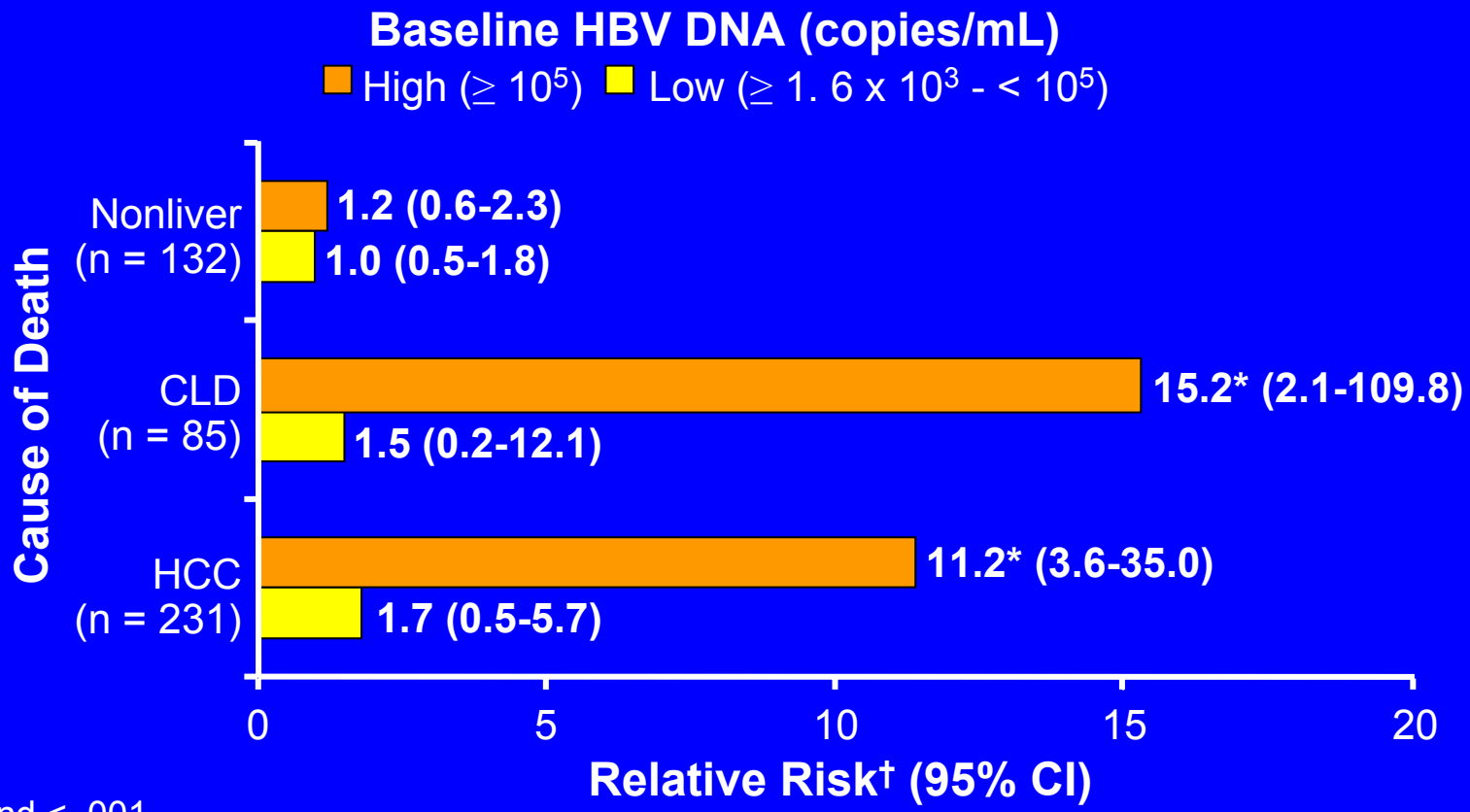
Haimen City Cohort: Viral Load and Mortality From Liver Disease

- 10-year prospective cohort study in Haimen City
- Permanent cohort of 83,794 subjects established 1992-1993
- 2354 subjects included in HBV mortality analysis
  - Serum HBV DNA tested on baseline samples
  - Mortality information from death certificate records
  - 448 deaths (231 HCC, 85 CLD, and 132 nonliver deaths)

CLD, chronic liver disease; HCC, hepatocellular carcinoma.

Chen G, et al. Am J Gastroenterol. 2006;101:1797-1803.

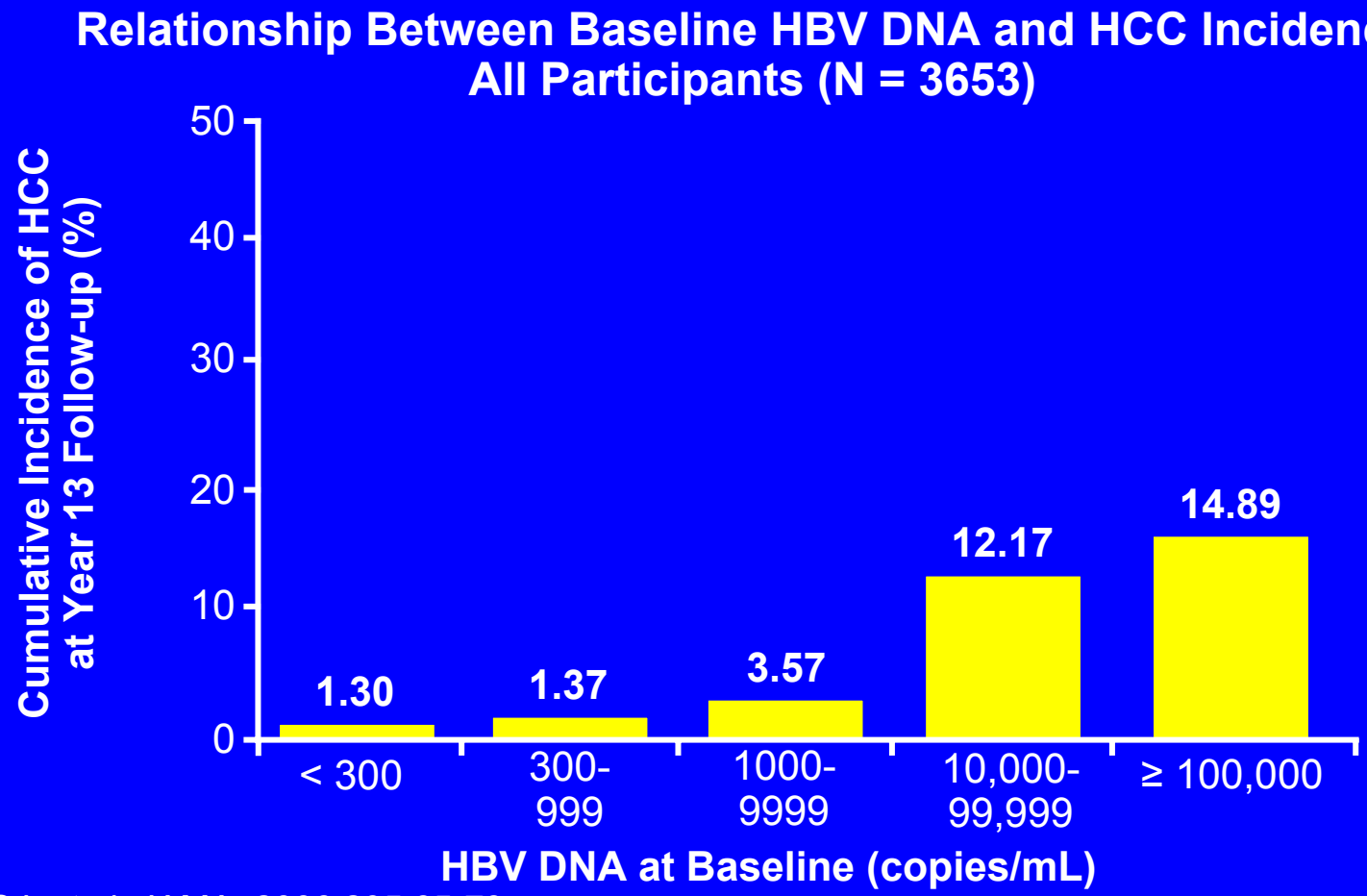
Haimen City: Increased RR of HCC and CLD Mortality With High Viral Load



**P* trend < .001
†Reference HBV DNA: < 1.6 x 10^3 copies/mL, adjusted for age and sex

Chen G, et al. Am J Gastroenterol. 2006;101:1797-1803.

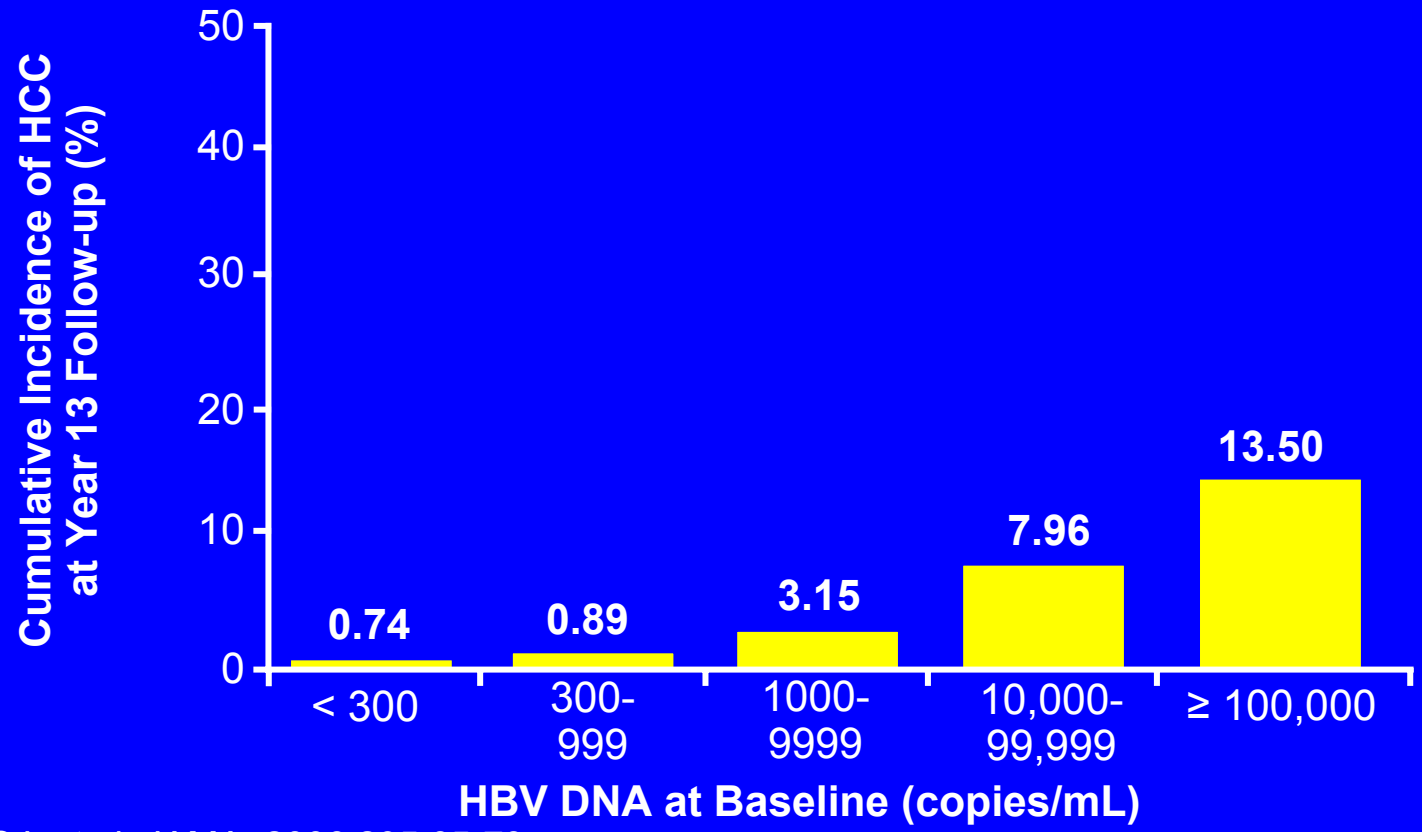
REVEAL: High HBV DNA Associated With Increased HCC Incidence



Chen CJ, et al. JAMA. 2006;295:65-73.

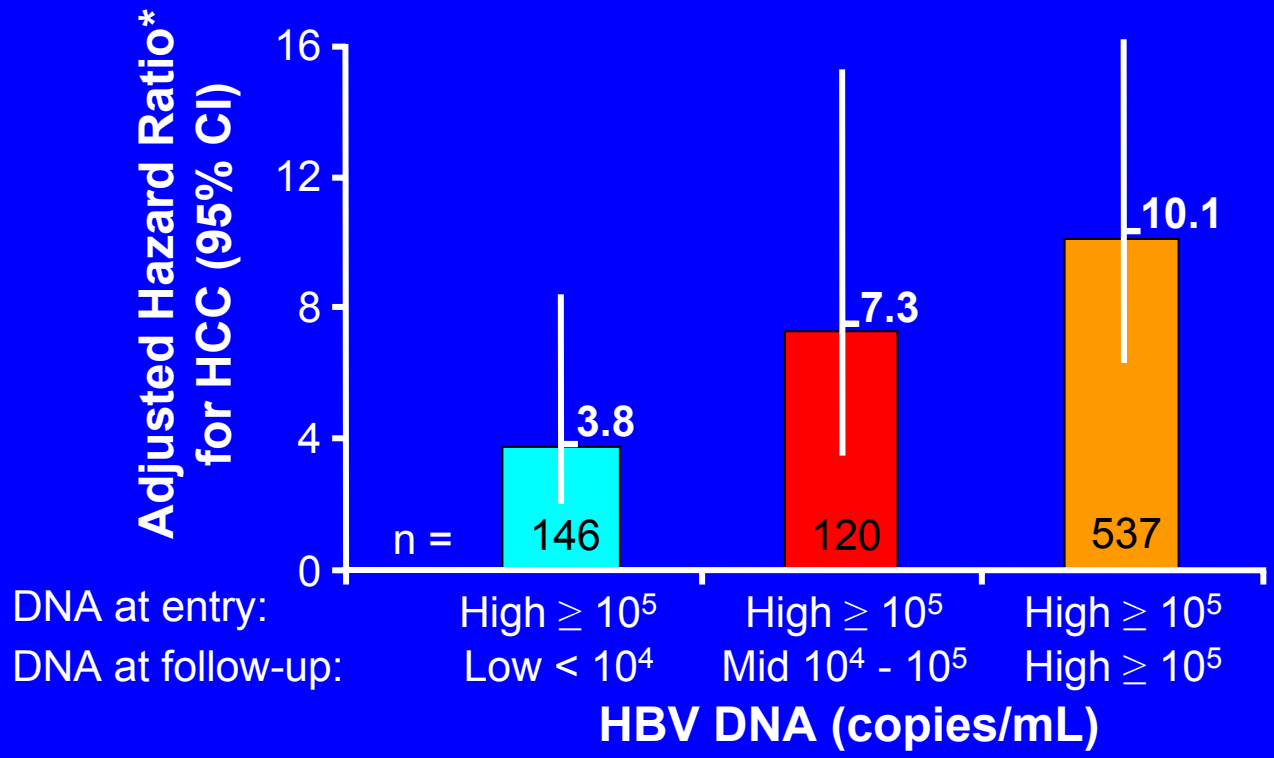
REVEAL: High HBV DNA Associated With Increased HCC Incidence (cont'd)

Relationship Between Baseline HBV DNA and HCC Incidence:
HBeAg Negative, Normal ALT, No Liver Cirrhosis at Entry (n = 2925)



Chen CJ, et al. JAMA. 2006;295:65-73.

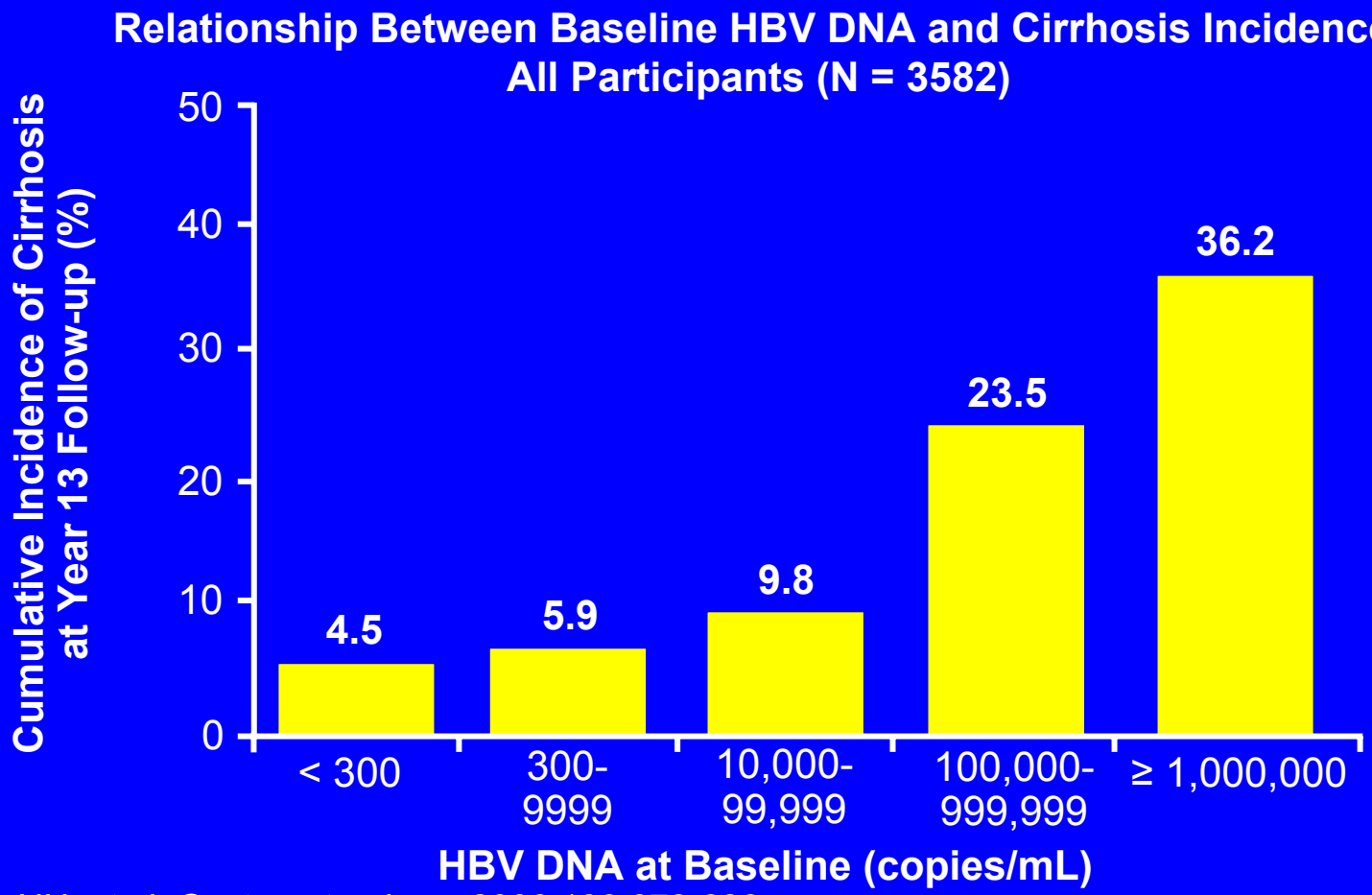
REVEAL: Persistent HBV DNA Associated With Increased HCC Risk



*Cox proportional hazards models. Risk is relative to < 10^4 copies/mL at entry/not tested at follow-up. Data adjusted for sex, age, cigarette smoking, and alcohol consumption.

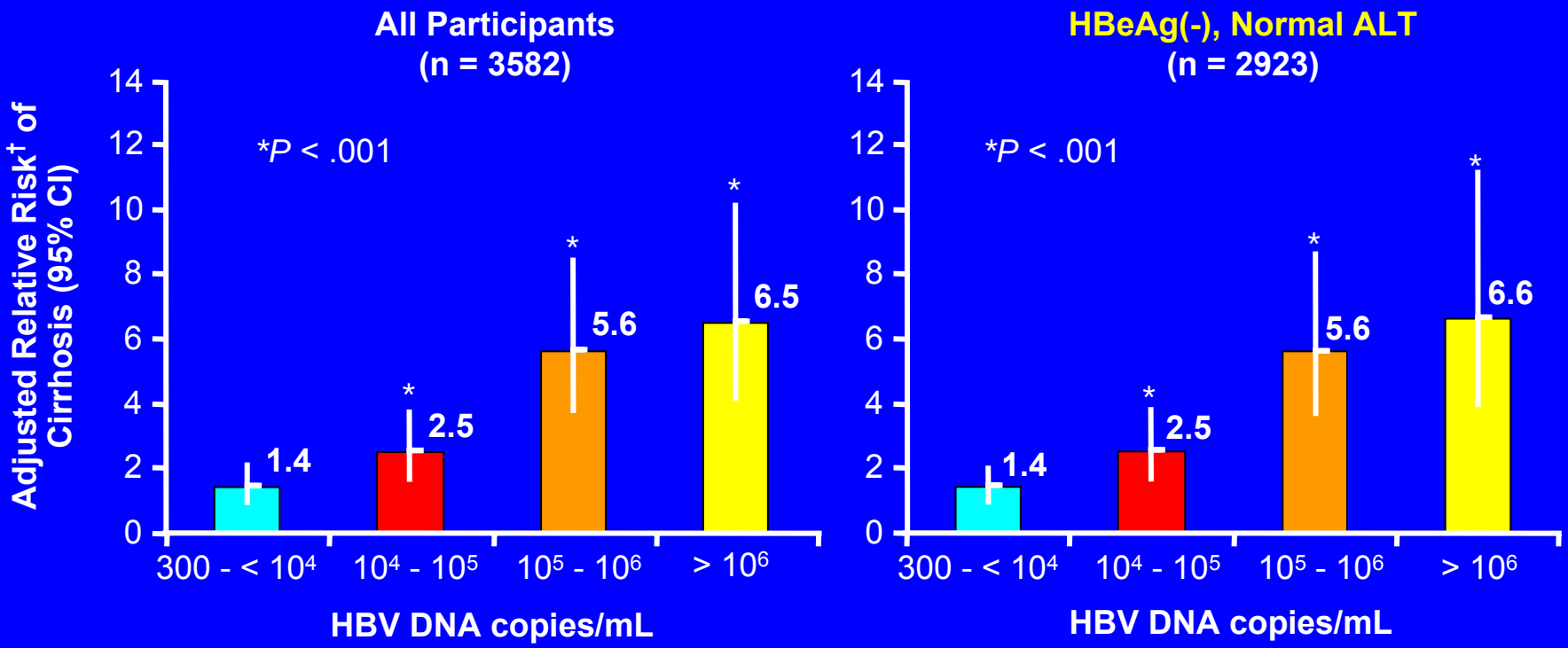
Chen CJ, et al. JAMA. 2006;295:65-73.

REVEAL: High HBV DNA Associated With Increased Incidence of Cirrhosis



Iloeje UH, et al. Gastroenterology. 2006;130:678-686.

REVEAL: HBV DNA Level Is an Independent Risk Factor for Cirrhosis



†Cox proportional hazards regression analysis. Relative to HBV DNA < 300 copies/mL. Relative risk adjusted for age, sex, cigarette smoking, and alcohol consumption.

Iloeje UH, et al. Gastroenterology. 2006;130:678-686.

REVEAL: Conclusion

- Elevated HBV DNA level (> 10^4 copies/mL [~ 2000 IU/mL]) is a strong risk factor for HCC and cirrhosis
  - Relationship is *independent* of HBeAg status and ALT level

Chen CJ, et al. JAMA. 2006;295:65-73. Iloeje UH, et al. Gastroenterology. 2006;130:678-686.

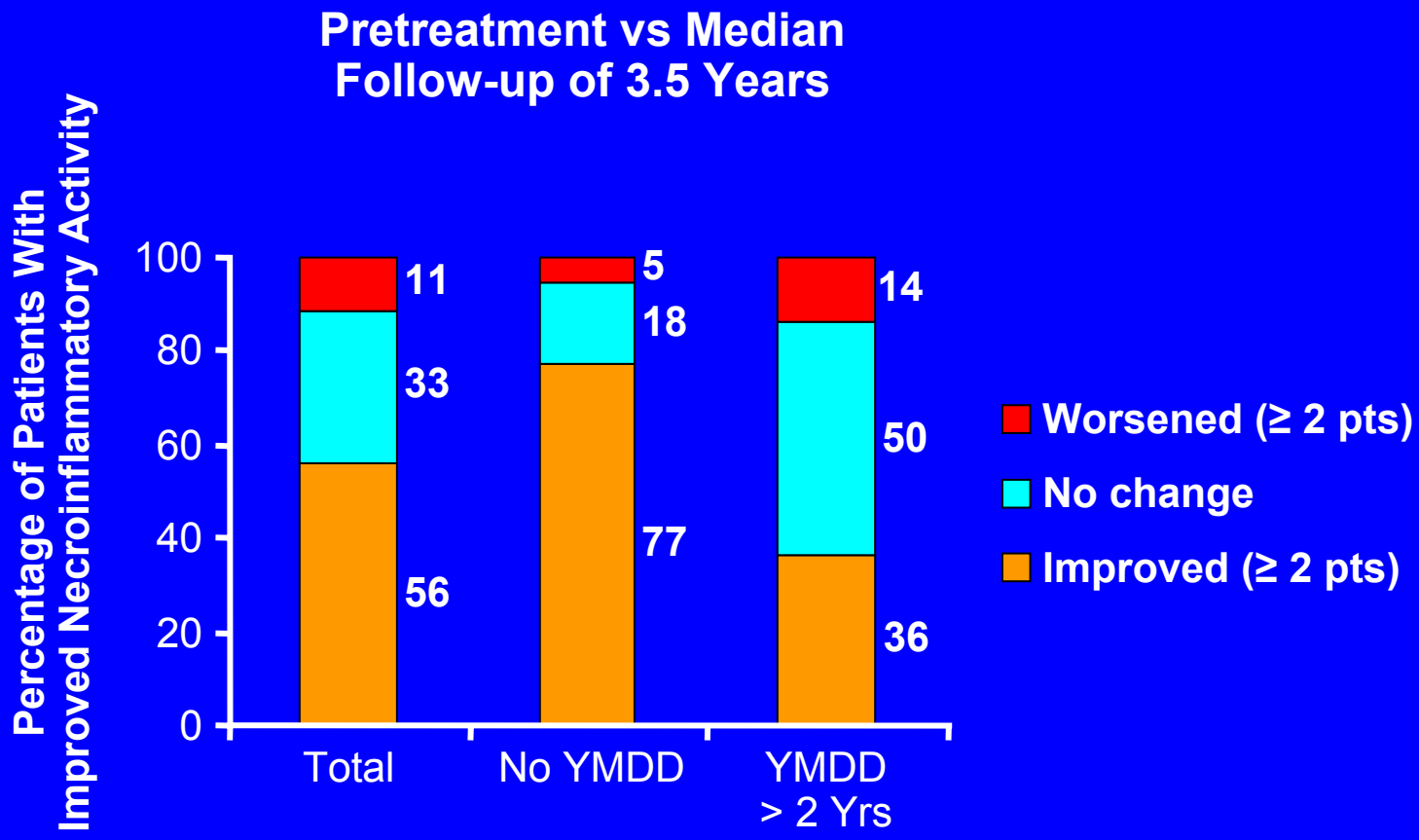
Goals of Hepatitis B Therapy

- Primary goal: suppress HBV DNA to the lowest possible level to achieve
  - Prevention of liver disease progression to cirrhosis
  - Prevention of liver failure and HCC
  - Prevention of liver disease–related transplantation or death
- HBV DNA suppression leads to
  - Histologic improvement
  - ALT normalization
  - HBeAg loss and seroconversion
  - HBsAg loss and seroconversion

Goals of Therapy: 2 Distinct Patient Populations

- HBeAg positive (wild type)
  - HBeAg loss ± seroconversion
  - Durable suppression of HBV DNA to lowest possible levels
  - Therapy discontinued after seroconversion; durability of response ~ 80%
- HBeAg negative (precore and core promoter mutants)
  - HBeAg seroconversion not an endpoint
  - Durable suppression of HBV DNA to lowest possible levels
  - Relapse common after stopping oral therapy; therapy usually administered long term

Improvements in Necroinflammatory Activity on Lamivudine Therapy



Dienstag J, et al. Gastroenterology. 2003;124:105-117.

Reduction of HCC During Maintenance Lamivudine Therapy

Lamivudine-Treated Patients Compared With Matched Controls*
(52% HBeAg(-); F4: 17%, F3: 28%)

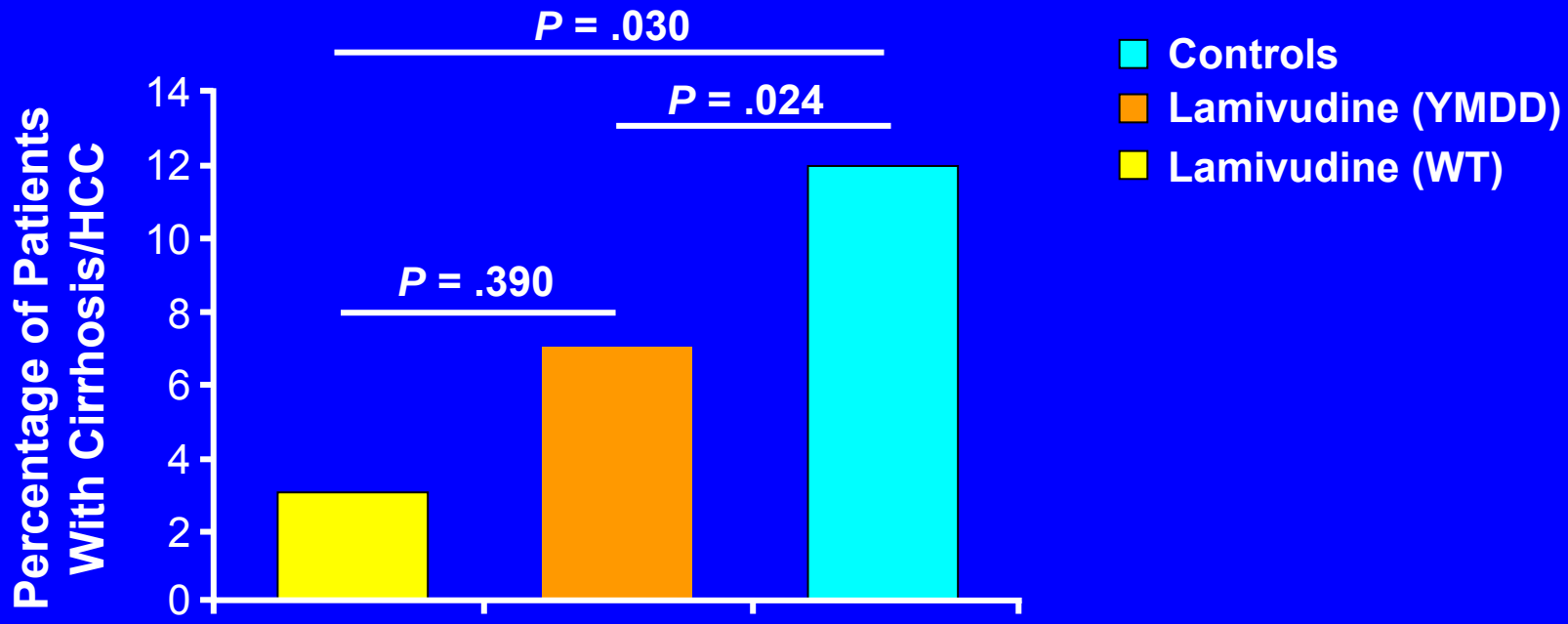
Outcome	Control (n = 377)	Lamivudine (n = 377)	*P* Value
Mean follow-up, yrs	5.3	2.7	--
Cumulative HCC incidence, %/yr	2.5	0.4	.001
F4 fibrosis in patients who developed HCC, %	0	17.4	--

***Age, sex, fibrosis stage, albumin, and platelet matched.**

Matsumoto A, et al. Hepatol Res. 2005;32:173-184.

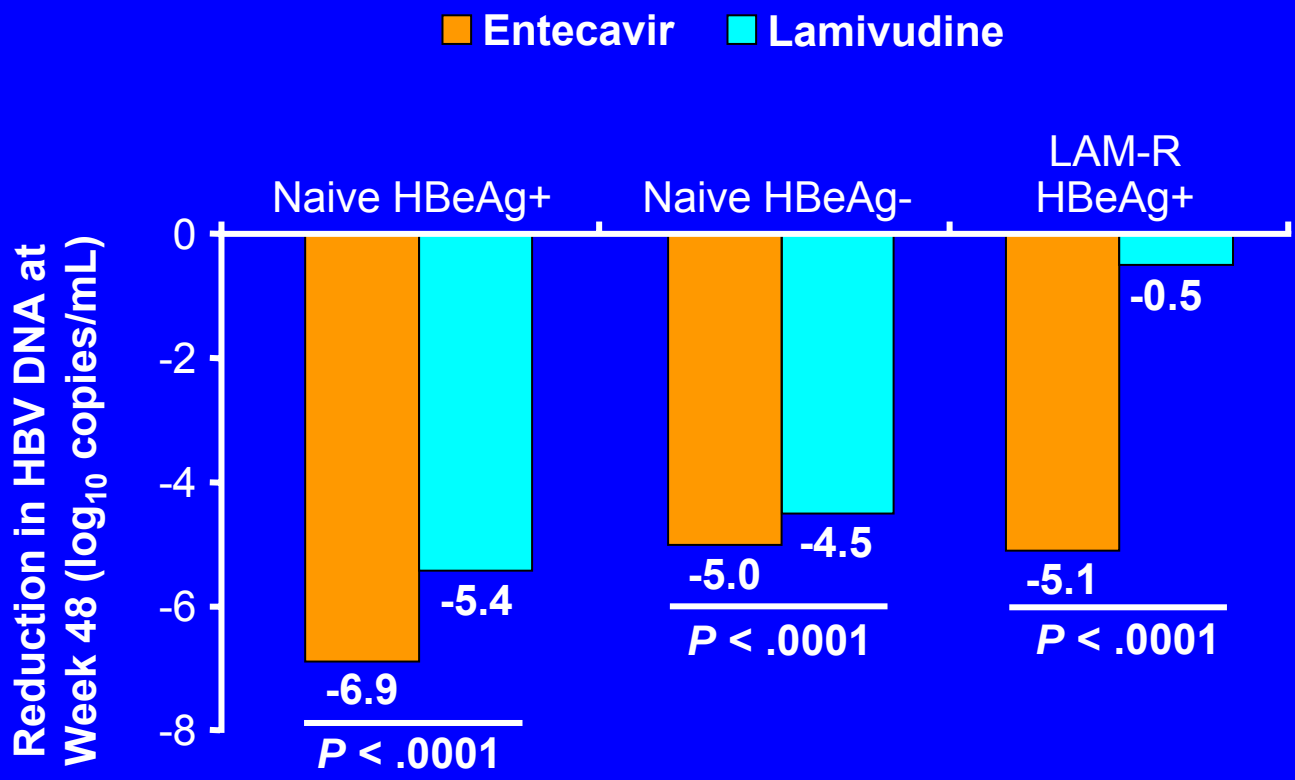
Delayed Disease Progression With Continued Suppression: Noncirrhotics

- 76.3% had YMDD mutations at Year 6, with no new mutations thereafter
  - Benefits of treatment reduced for those with YMDD mutations



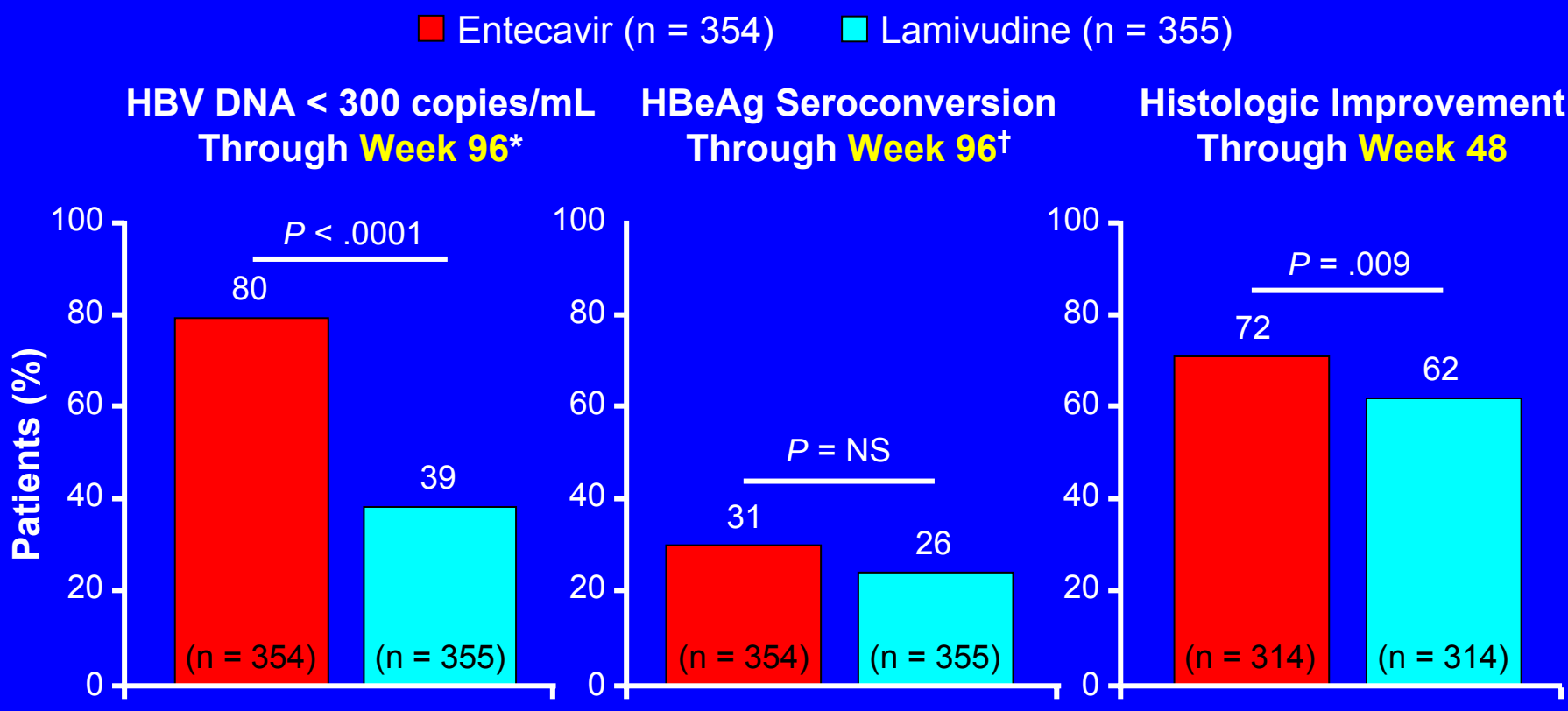
Yuen MF, et al. AASLD 2005. Abstract 985.

Entecavir vs *Lamivudine*



Chang T, et al. N Engl J Med. 2006;354:1001-1010. Lai C, et al. N Engl J Med. 2006;354: 1011-1020. Colonno R, et al. AASLD 2006. Abstract 110. Sherman M, et al. Gastroenterology. 2006;130:2039-2049.

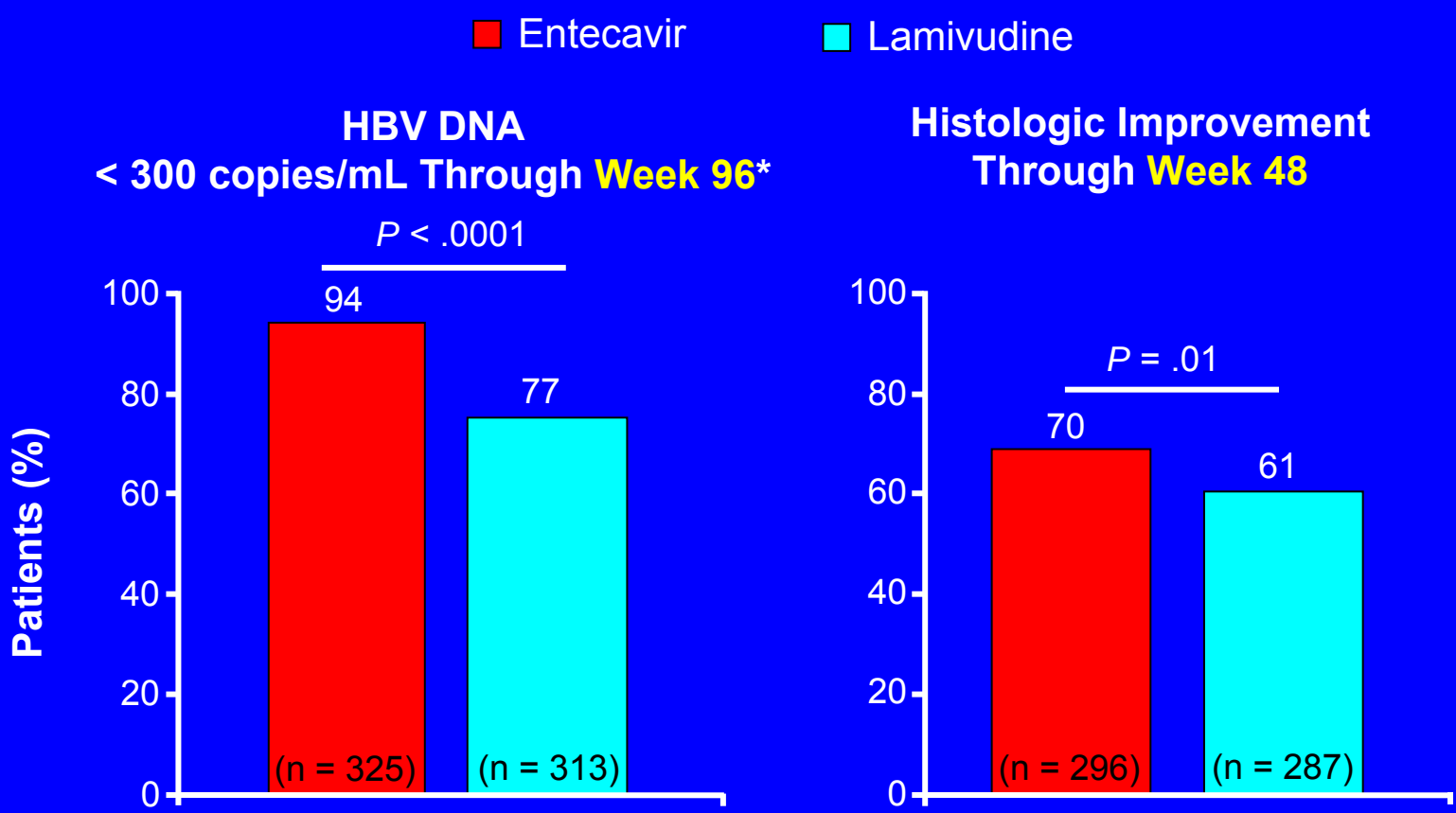
Entecavir Superior to Lamivudine in HBeAg-Positive Patients



*Cumulative confirmed data: 2 data points or last observation on therapy.
†Cumulative confirmed data through last observation and 6 months off treatment.

Gish RG, et al. Hepatology. 2005;42:267A.

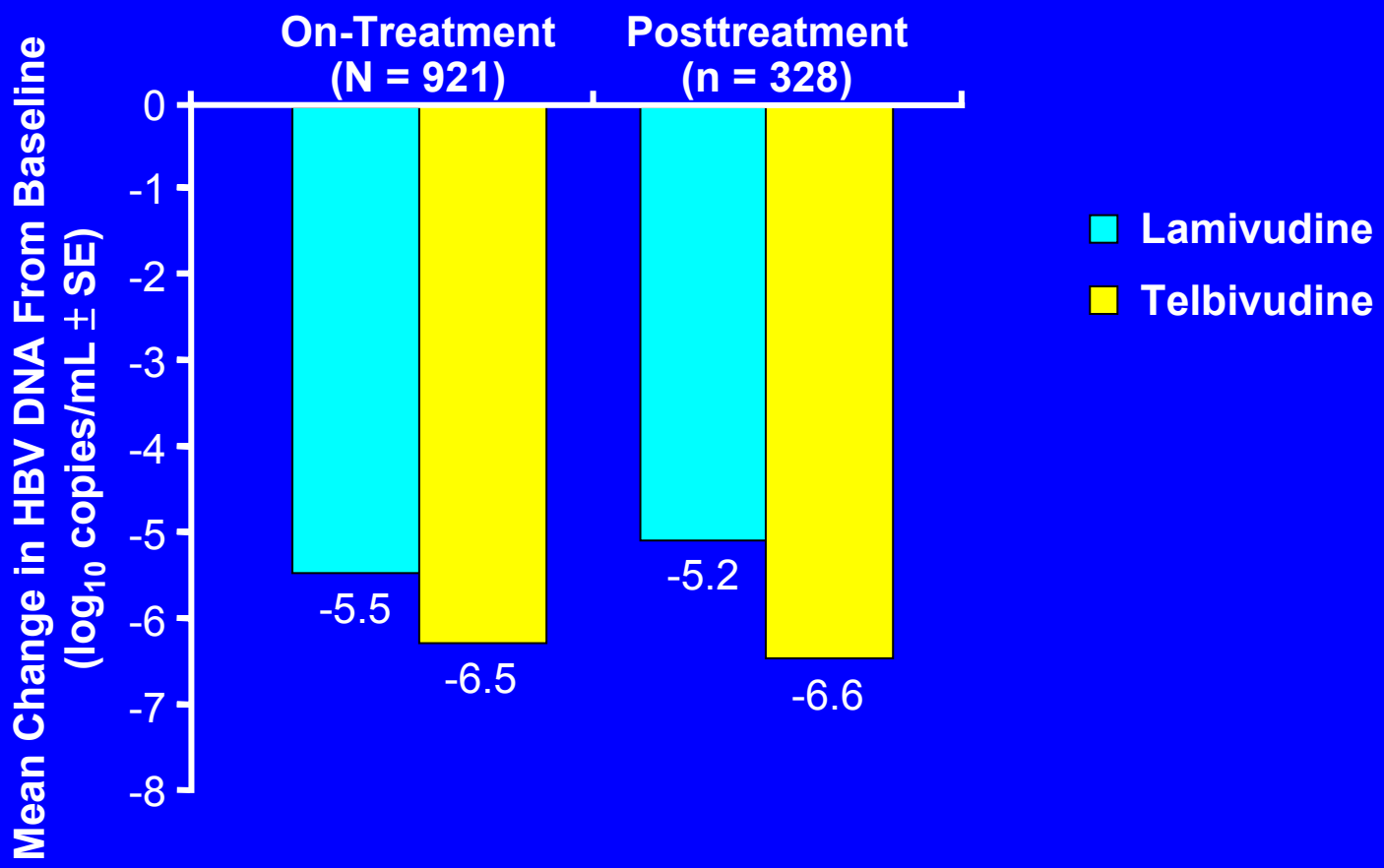
Long-term Entecavir in HBeAg-Negative Patients



*Cumulative confirmed data: 2 data points or last observation on therapy.

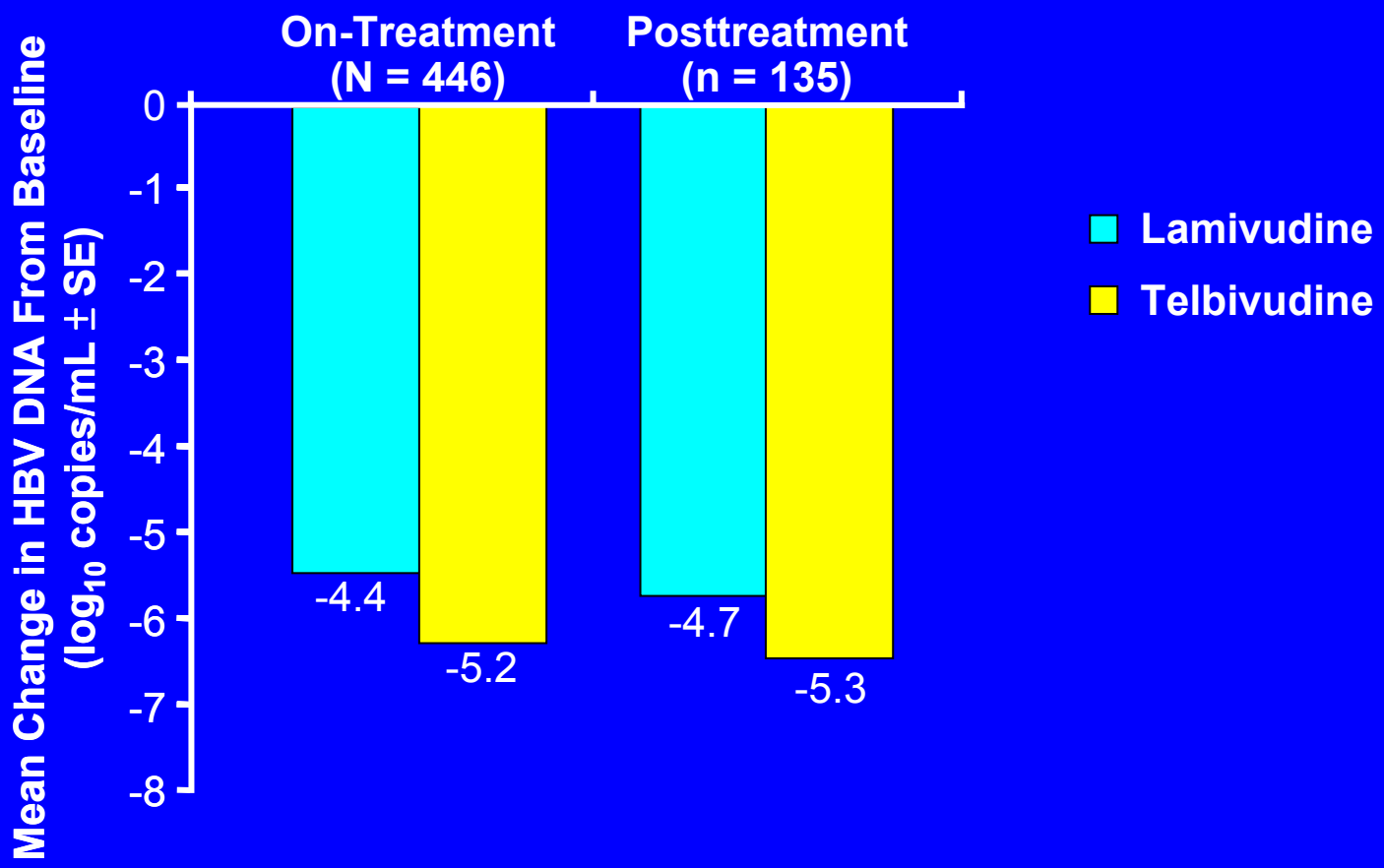
Shouval D, et al. EASL 2006. Abstract 45. Lai C, et al. N Engl J Med. 2006;354:1011-1020.

Telbivudine vs Lamivudine: HBeAg-Positive Patients



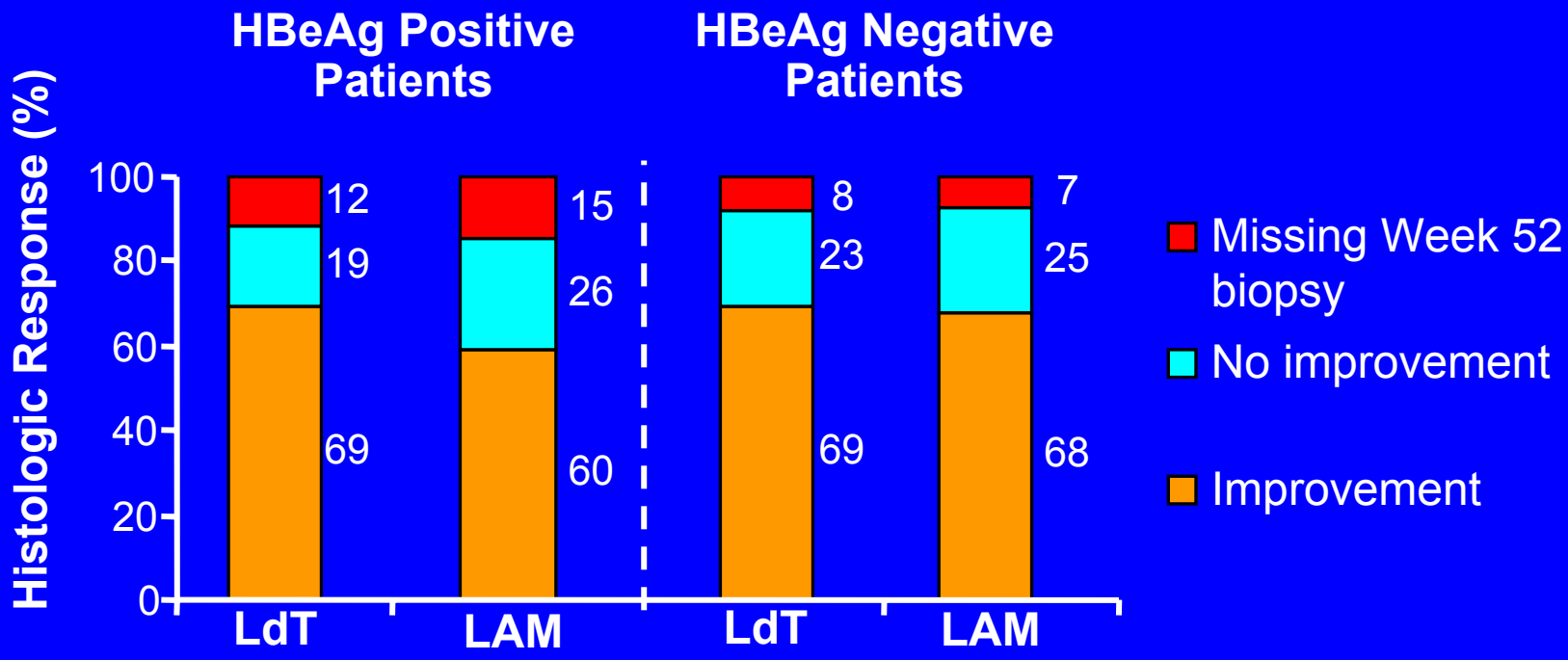
Lai C, et al. HepDart 2005. Abstract 95.

Telbivudine vs Lamivudine: HBeAg-Negative Patients



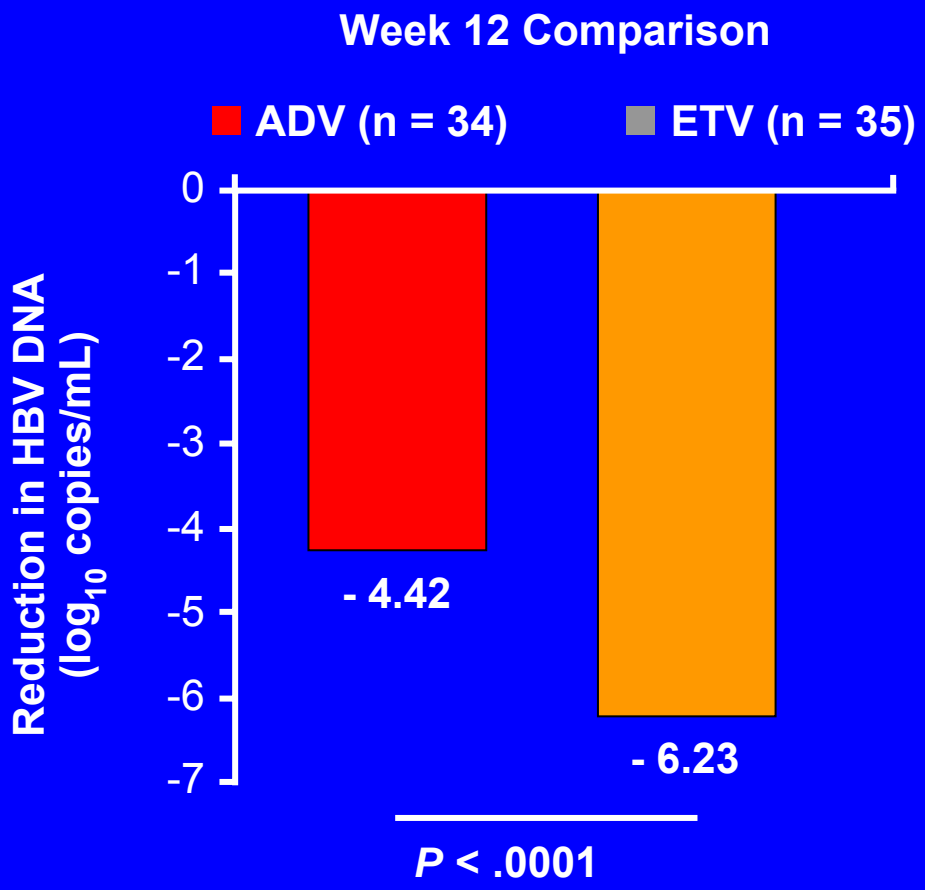
Lai C, et al. HepDart 2005. Abstract 95.

Week 52 Histologic Outcomes: Telbivudine vs Lamivudine



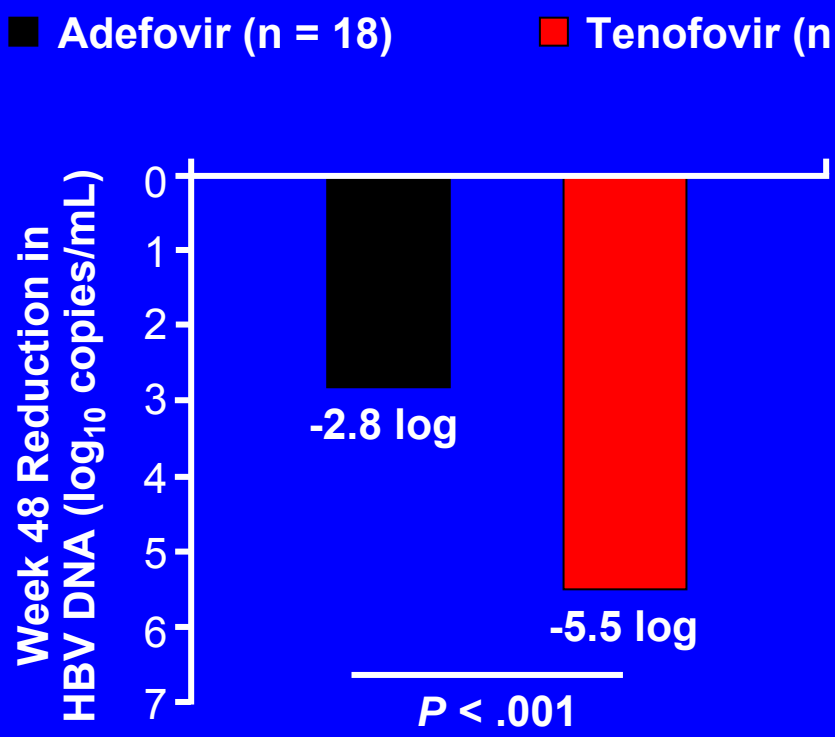
Lai C, et al. AASLD 2006. Abstract 91.

Entecavir vs *Adefovir*



Wilber R, et al. NIH HBV 2006. Abstract 14.

Tenofovir vs Adefovir in LAM-R Patients



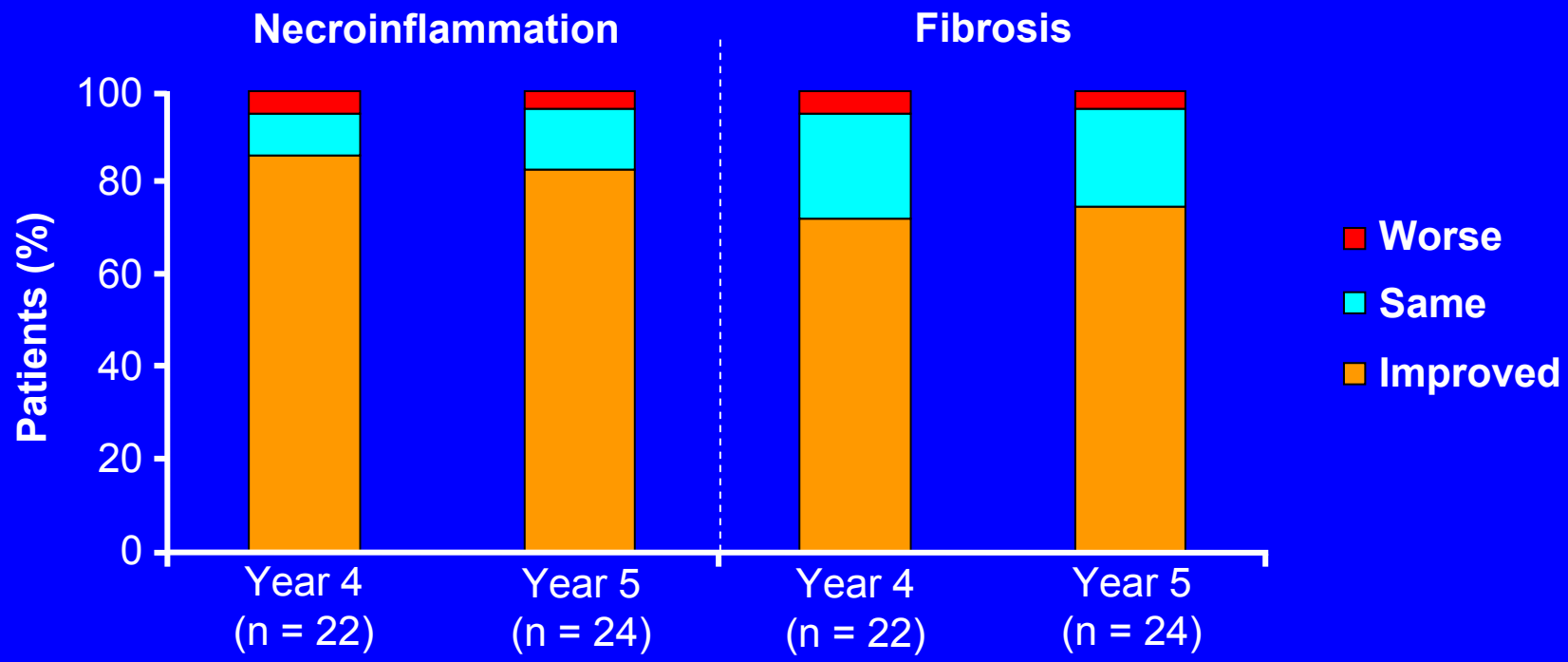
HBV DNA
< 400 copies/mL at
Week 48

Adefovir: 44%
Tenofovir: 100%

van Bommel F, et al. Hepatology. 2004;40:1421-1425.

Histology in 4- and 5-Year HBeAg-Adefovir-Treated Cohorts vs Baseline

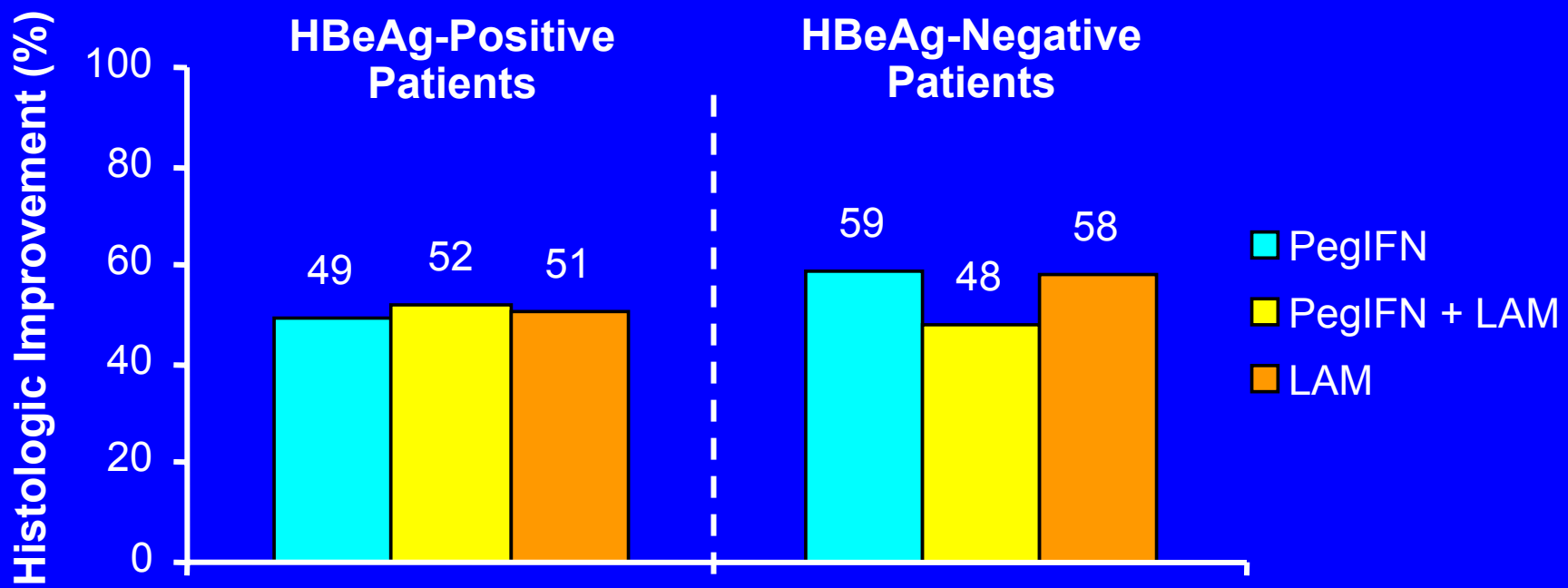
- > 50% had regression of bridging fibrosis or cirrhosis by Yr 5



Median change from ADV Baseline in Knodell necroinflammatory score -4.5 and -5.0 at 4 and 5 yrs; median change in Ishak fibrosis score was -1.0 in both cohorts.

Hadziyannis et al. AASLD 2005. Abstract LB14.

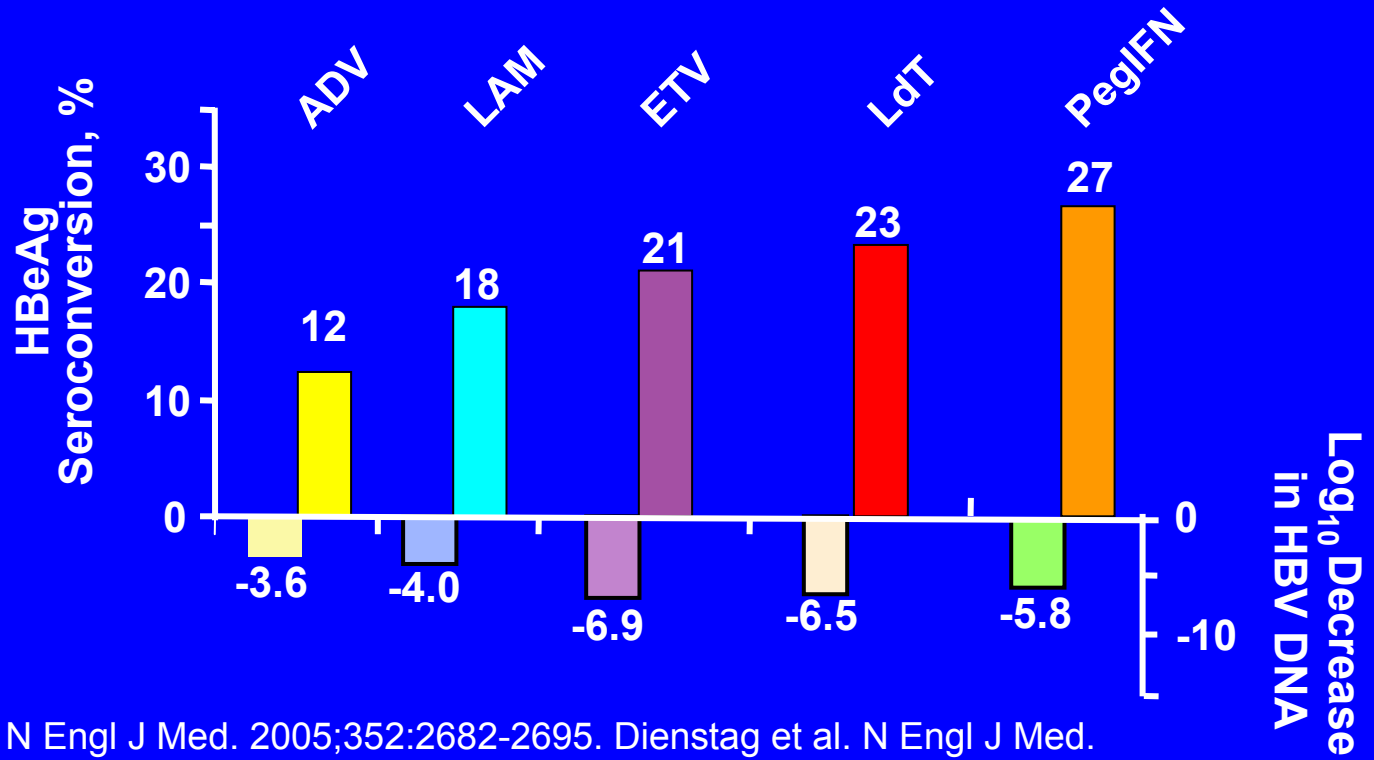
Histologic Improvement With Peginterferon Therapy



Lau GK, Piratvisuth T, Luo KX, et al. N Engl J Med. 2005. 30;352:2682-2695.
Marcellin P, Lau GK, Bonino F, et al. N Engl J Med. 2004. 16;351:1206-1217.

HBV DNA and HBeAg Seroconversion at Year 1 in HBeAg(+) Patients

Data from individual studies, not direct comparisons (different populations, baseline values, HBV DNA assays)



Lau et al. N Engl J Med. 2005;352:2682-2695. Dienstag et al. N Engl J Med. 1999;341:1256-1263. Marcellin et al. EASL 2005. Abstract 73. Lai et al. AASLD 2005. Abstract 72404. Chang et al. AASLD 2004. Abstract 70. Entecavir package insert. Telbivudine package insert.

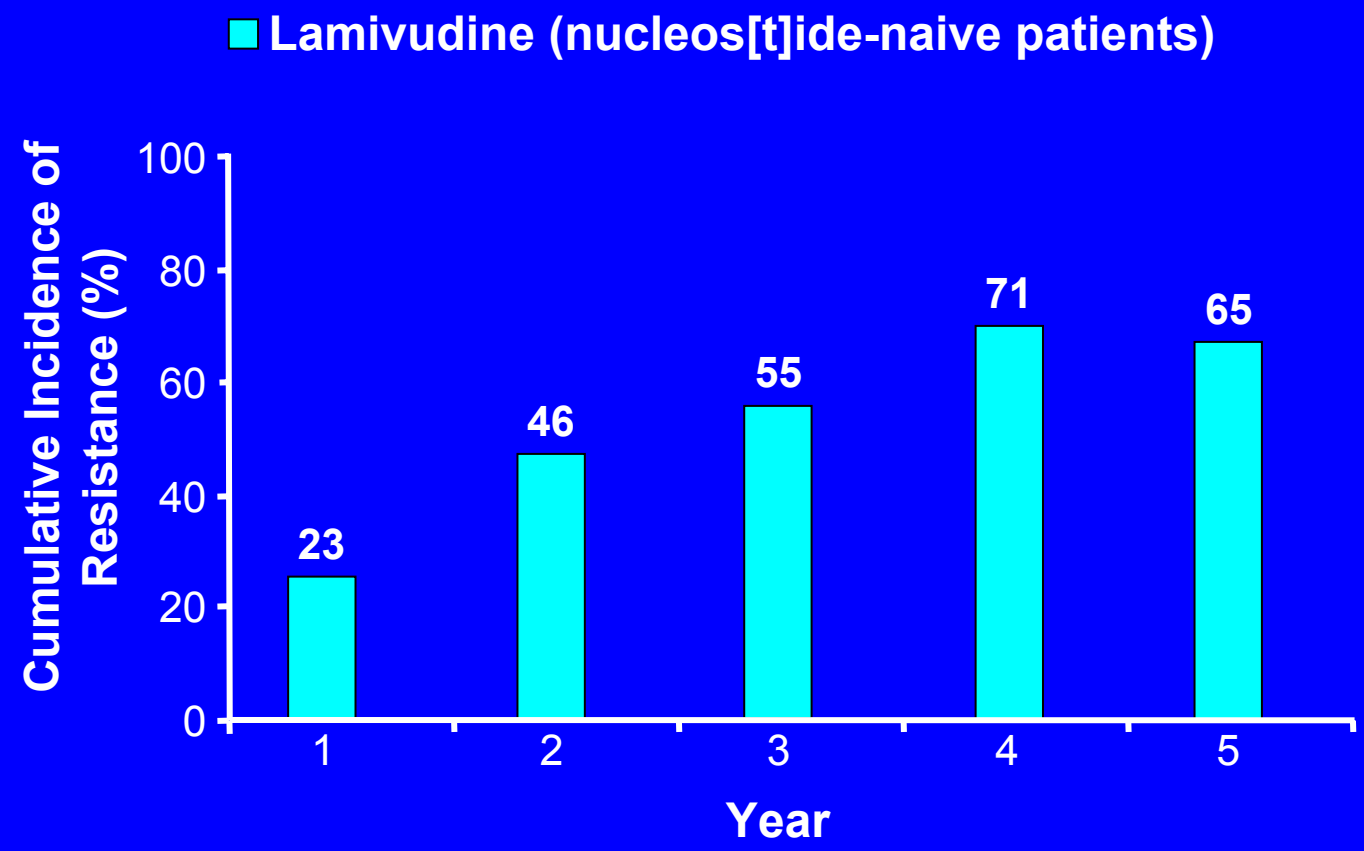
Endpoint of Therapy With HBV Oral Antiviral Drugs

- Inhibition of HBV replication
  - As profound as possible

    ANTIVIRAL POTENCY
  - As sustained as possible

    NO RESISTANCE

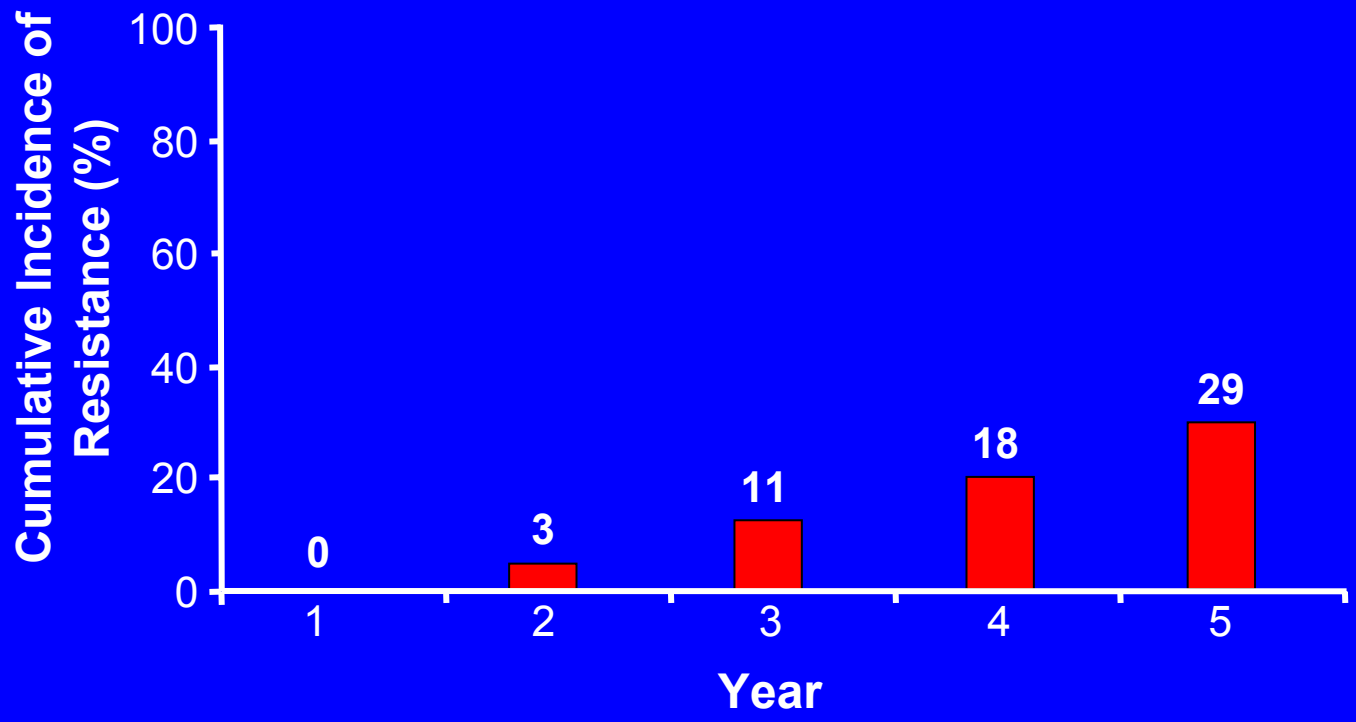
Incidence of HBV Resistance



Lai CL, et al. Clin Infect Dis. 2003;36:687-696.
Lok AS, et al. Gastroenterology. 2003;125:1714-1722.

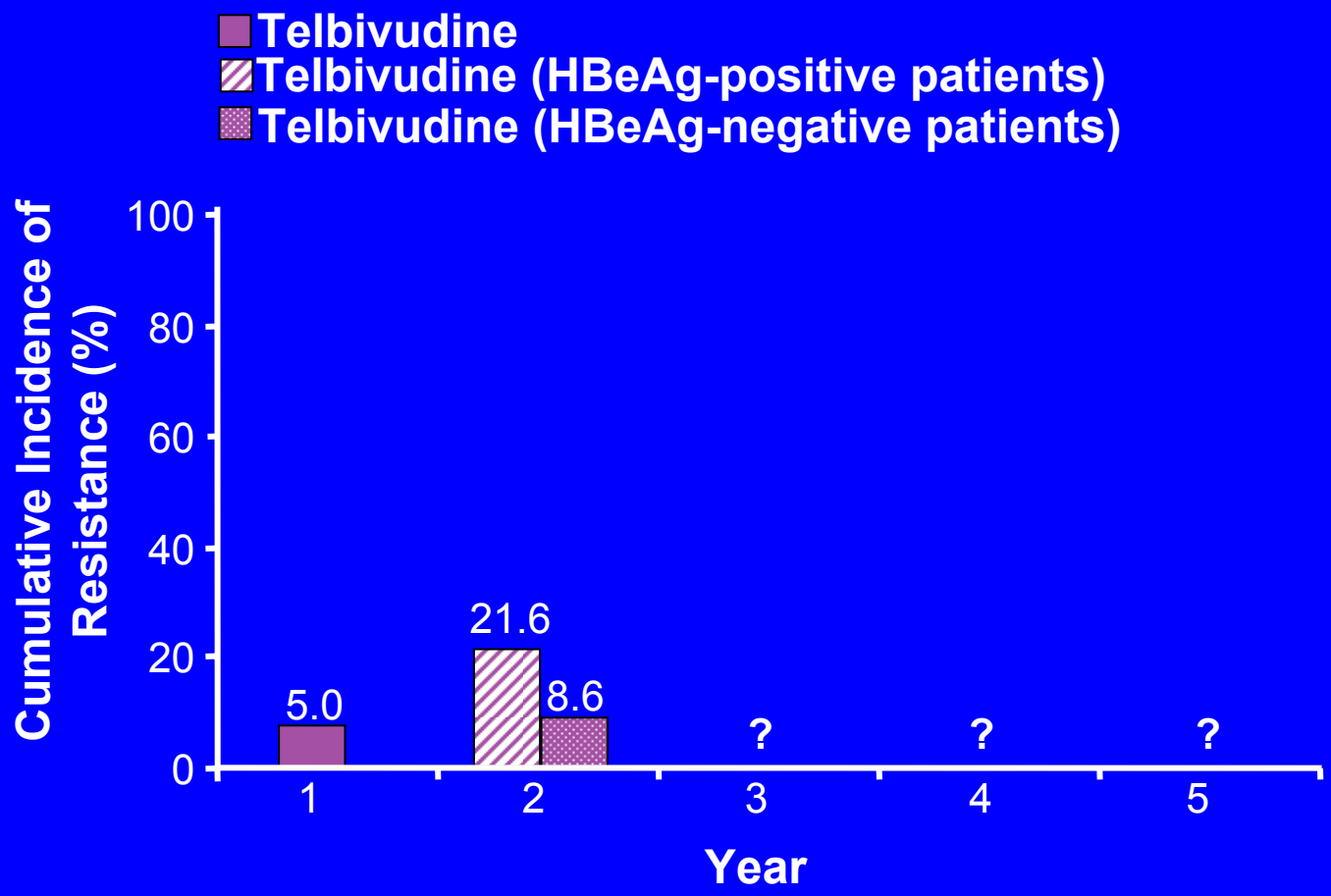
Incidence of HBV Resistance (cont'd)

Adefovir (nucleos[t]ide-naive, HBeAg-negative patients); selection of resistance mutations with or without breakthrough



Borroto-Esoda K, et al. EASL 2006. Abstract 483.

Incidence of HBV Resistance



Lai CL, et al. Gastroenterology. 2005;129:528-536. Lai CL, et al. AASLD 2006. Abstract 91.

Conclusions

- HBV DNA suppression with anti-HBV therapy improves patient outcomes
- Continued benefits are observed with long-term HBV therapy
  - Resistance diminishes the benefits of treatment
- More potent viral suppression can lead to greater patient outcomes
  - HBeAg seroconversion
  - Long-term virologic response
  - ALT normalization
  - Lower risk of resistance

Delaying Viral Resistance

1. Maximally reduce virus replication
   - Use highly potent antivirals

Add-on Adefovir in Lamivudine-Resistant Patients

Endpoints at Year 2	ADV Switch (n = 277)	ADV + LAM (n = 294)	*P* Value
Virologic rebound, n (%)	41 (15)	11 (4)	< .001
ADV genotypic resistance, n (%)	21 (8)	0 (0)	< .001

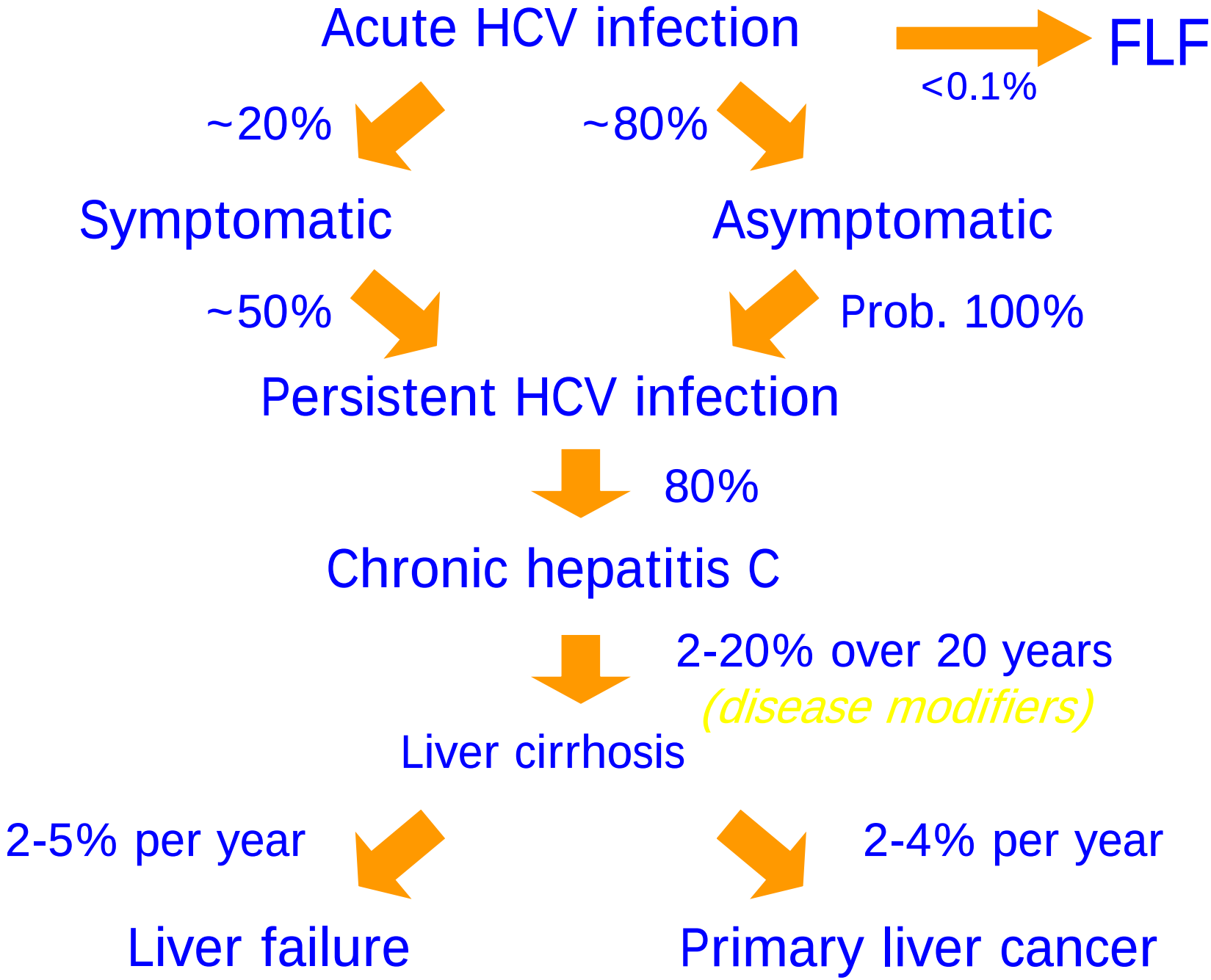
Lampertico P, et al. EASL 2006. Abstract 116.

Summary

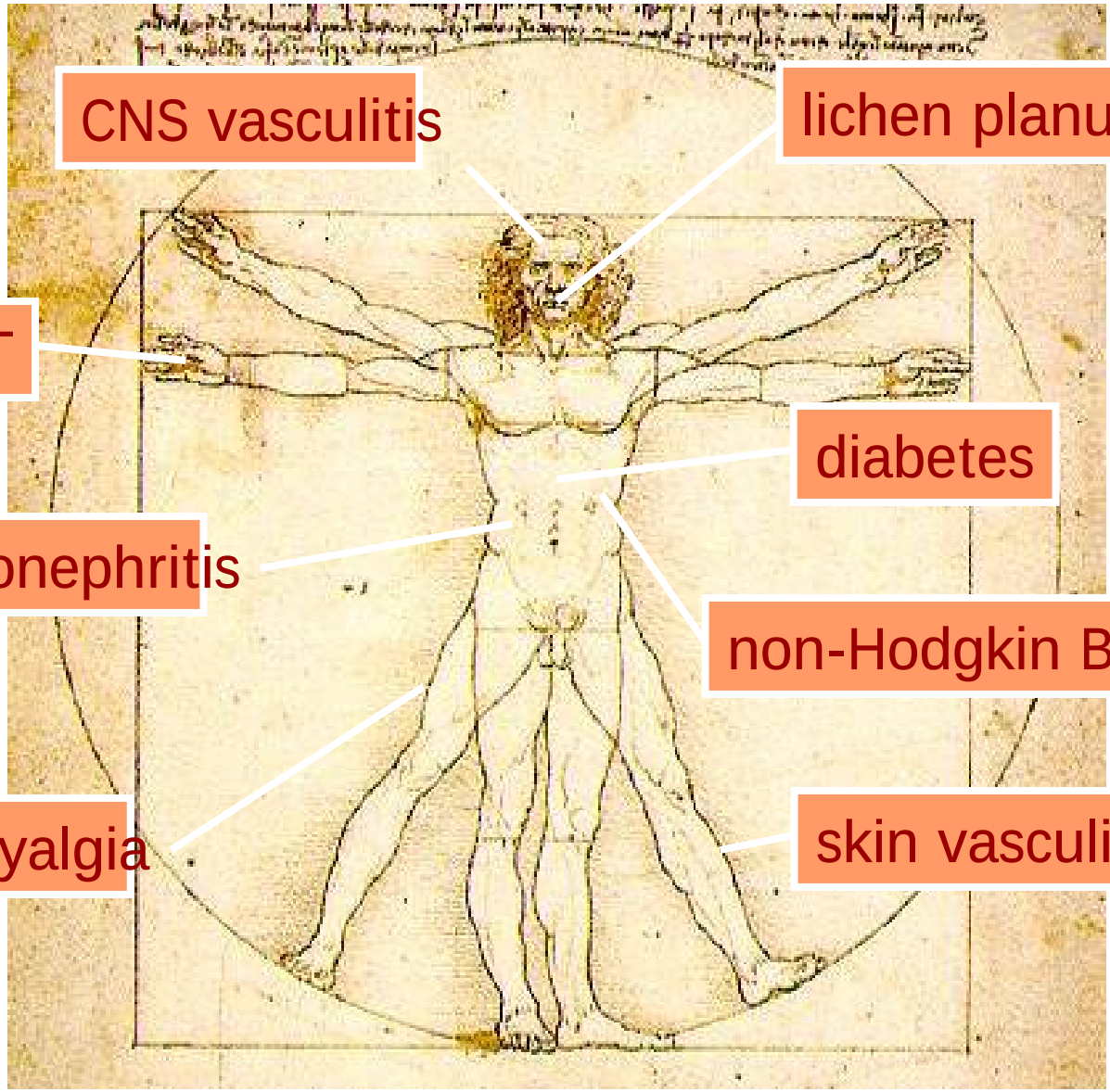
- HBV resistance can be delayed
  - By using highly potent antivirals
  - By improving adherence
  - By using combination therapies
- When resistance occurs
  - Consider add-on therapy rather than switching to second monotherapy
  - Consider using the most potent available antiviral combination

HBV treatment

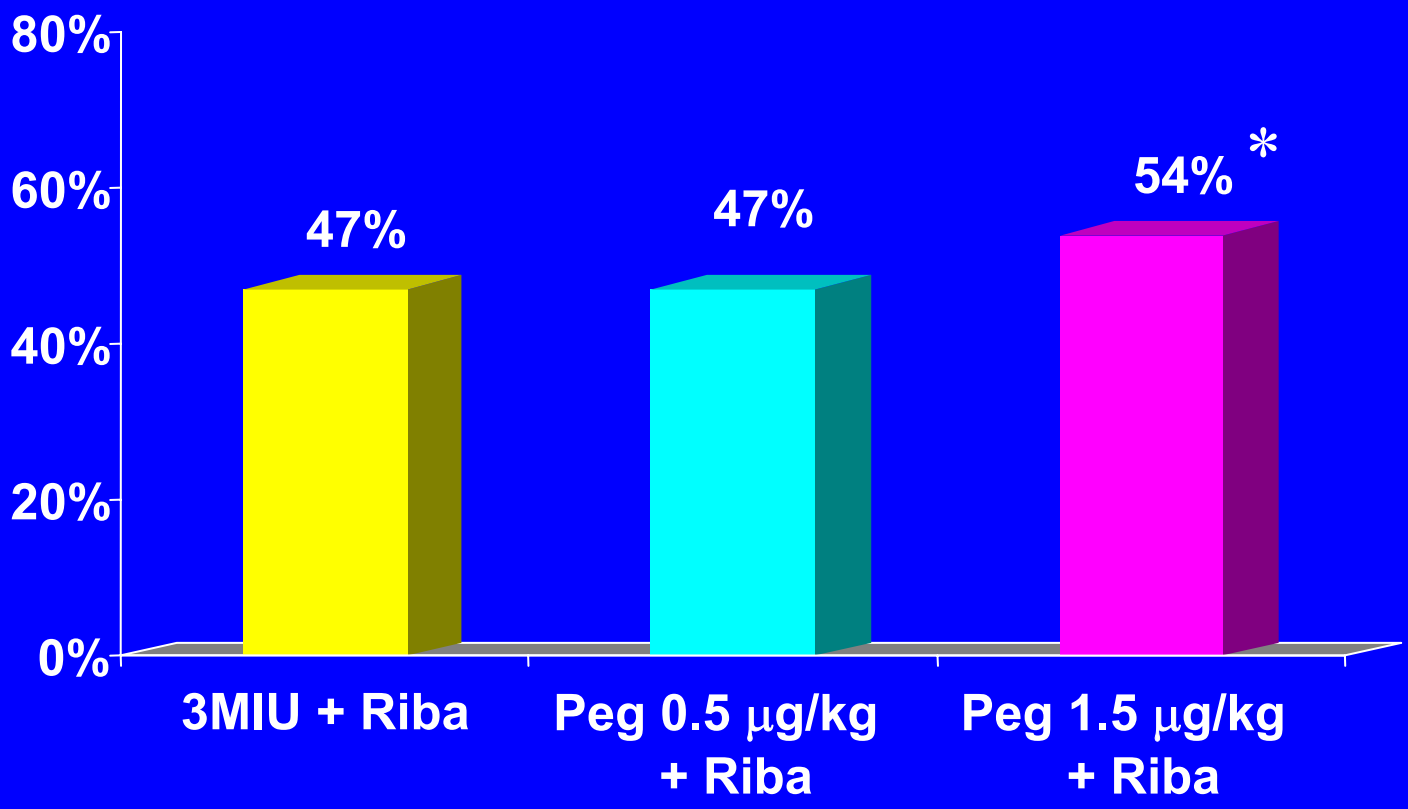
- many slides have been provided by Clinical Care Options Hepatitis:
  - Professor Ching-Lung Lai
  - Professor Robert G. Gish
  - Professor Jean-Michel Pawlotsky


Acute HCV infection
FLF
<0.1%
~20%
~80%
Symptomatic
Asymptomatic
~50%
Prob. 100%
Persistent HCV infection
80%
Chronic hepatitis C
2-20% over 20 years
(disease modifiers)
Liver cirrhosis
2-5% per year
2-4% per year
Liver failure
Primary liver cancer

HCV and extrahepatic manifestations

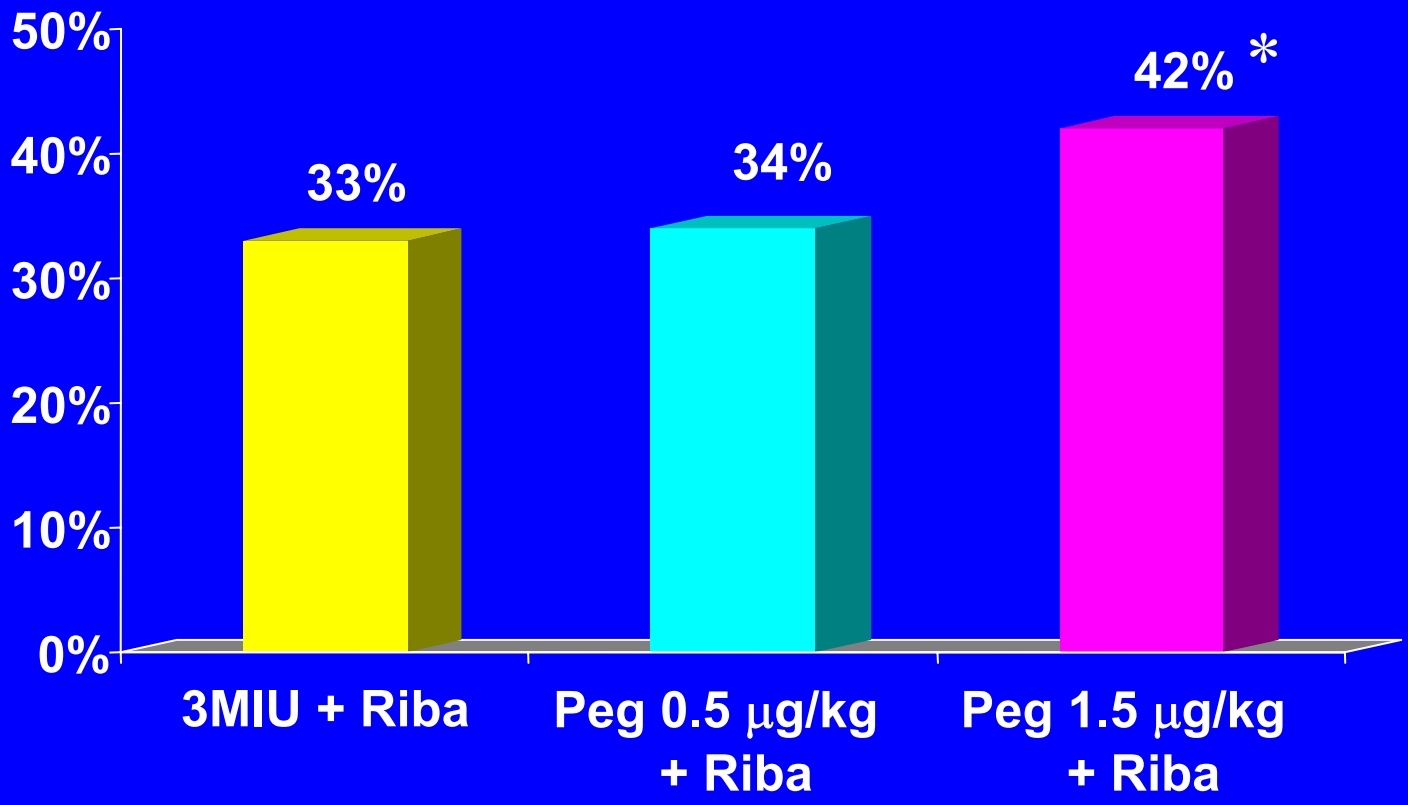


PegIntron + Rebetol
Sustained Virologic Response - All Genotypes



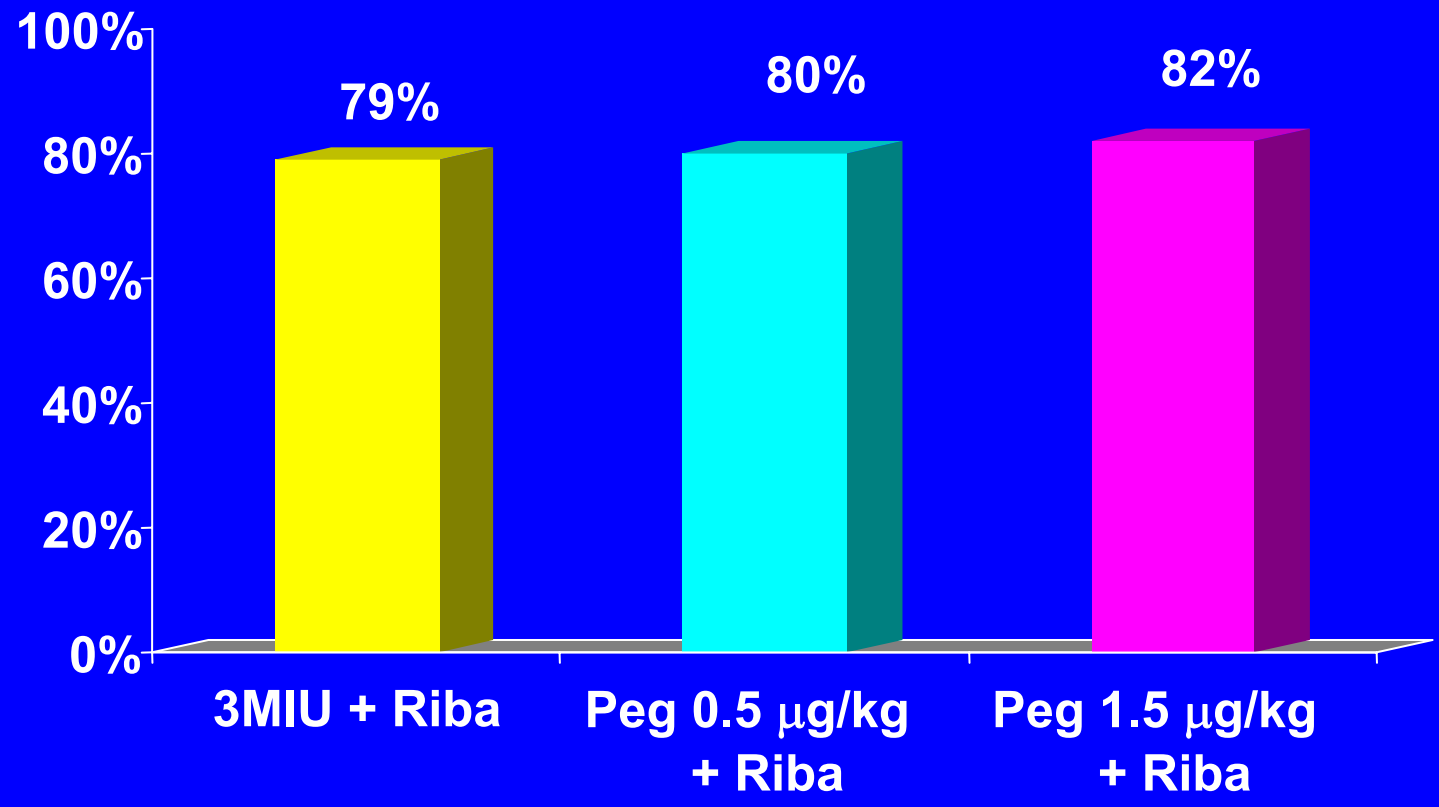
* Peg 1.5/800 vs. I/R p=0.01

PegIntron + Rebetol
Sustained Virologic Response - Genotype 1

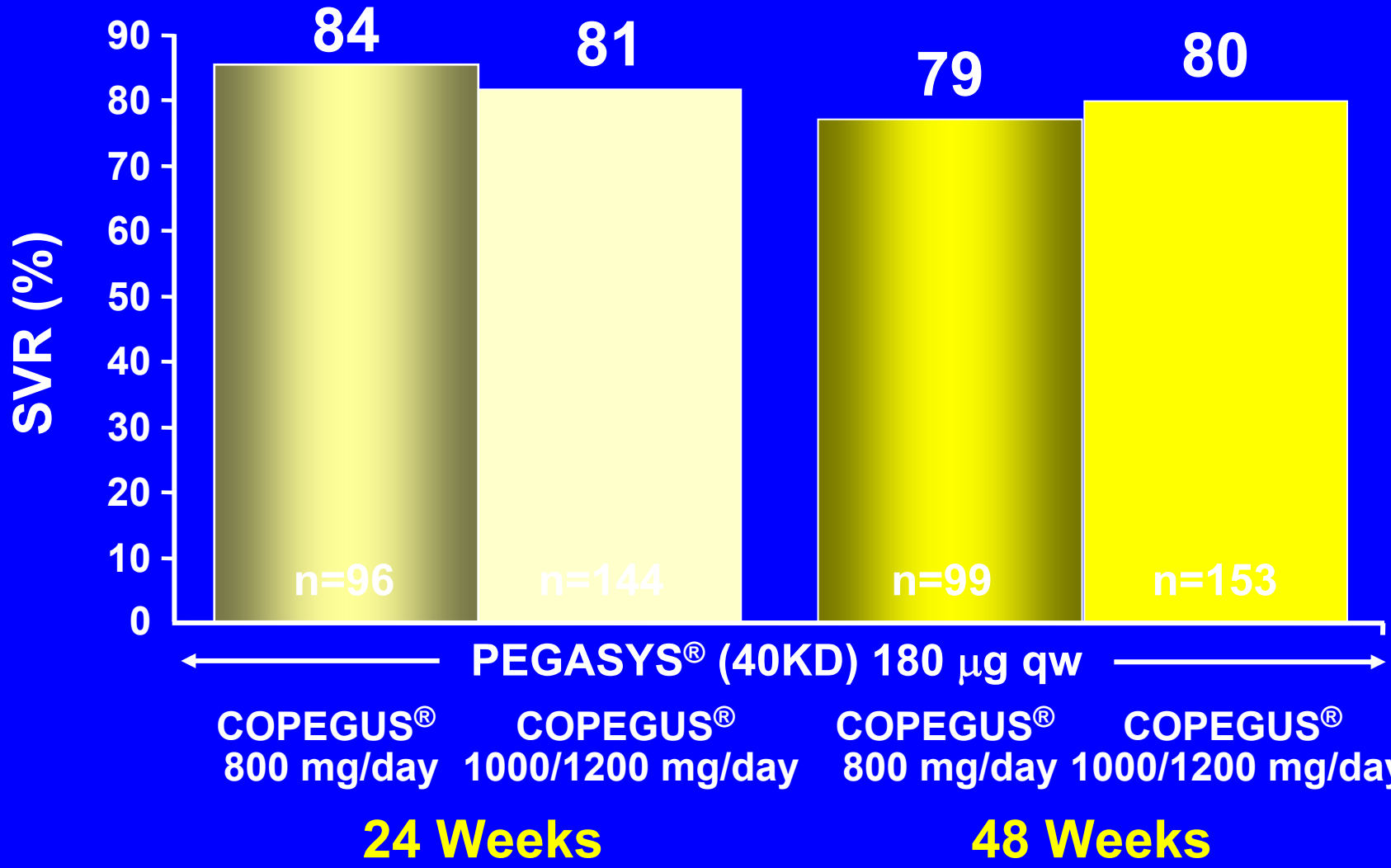


* Peg 1.5/800 vs. I/R p=0.02

PegIntron + Rebetol
Sustained Virologic Response - Genotype 2/3



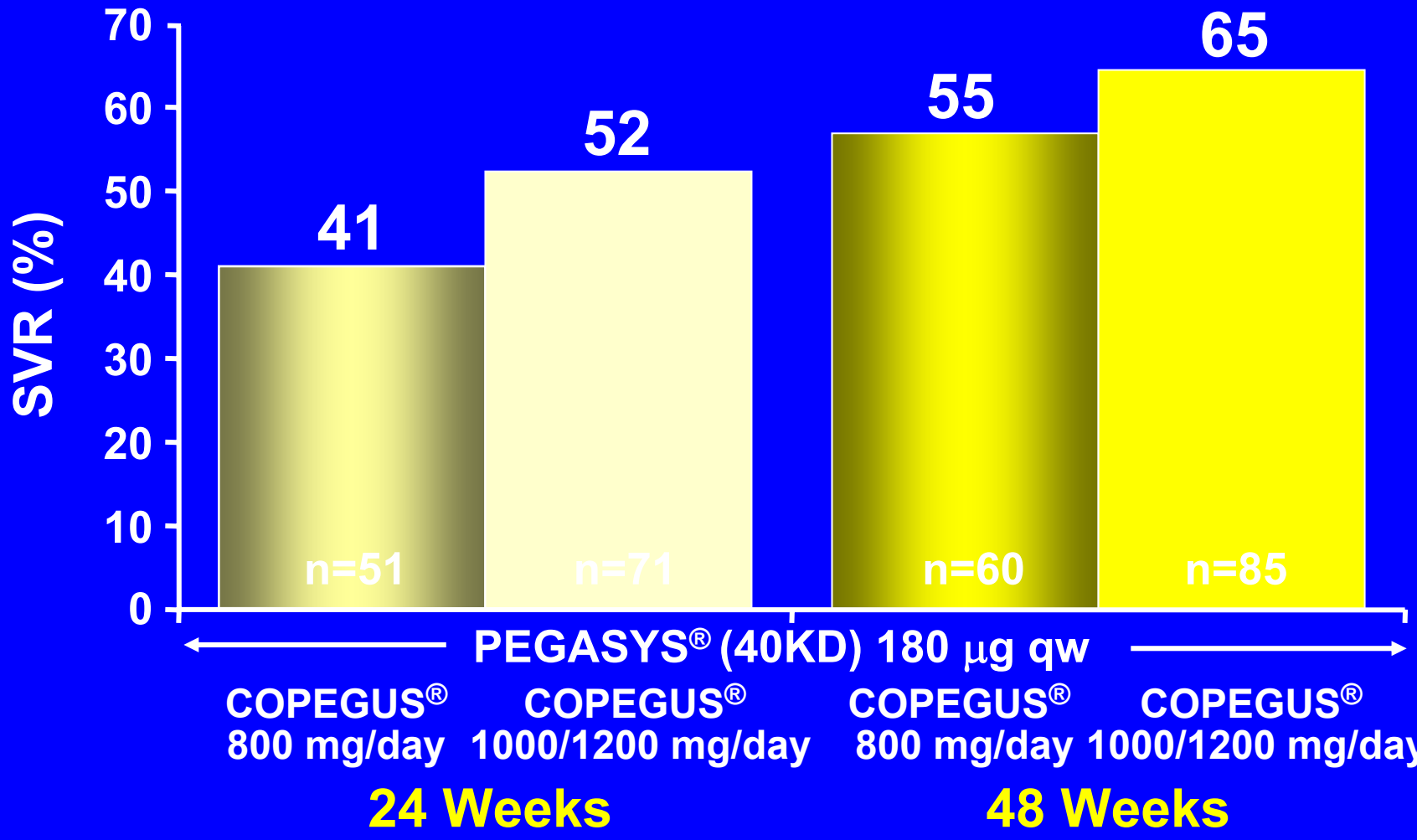
PEGASYS® (40KD) Plus COPEGUS®:
SVR in Patients With HCV Genotype 2 or 3 (ITT Analysis)*



*Intent-to-treat analysis.

Hadziyannis et al. *Ann Intern Med*. 2004.

PEGASYS® (40KD) Plus COPEGUS®:
SVR in Patients With HCV Genotype 1 and Low Viral Load*

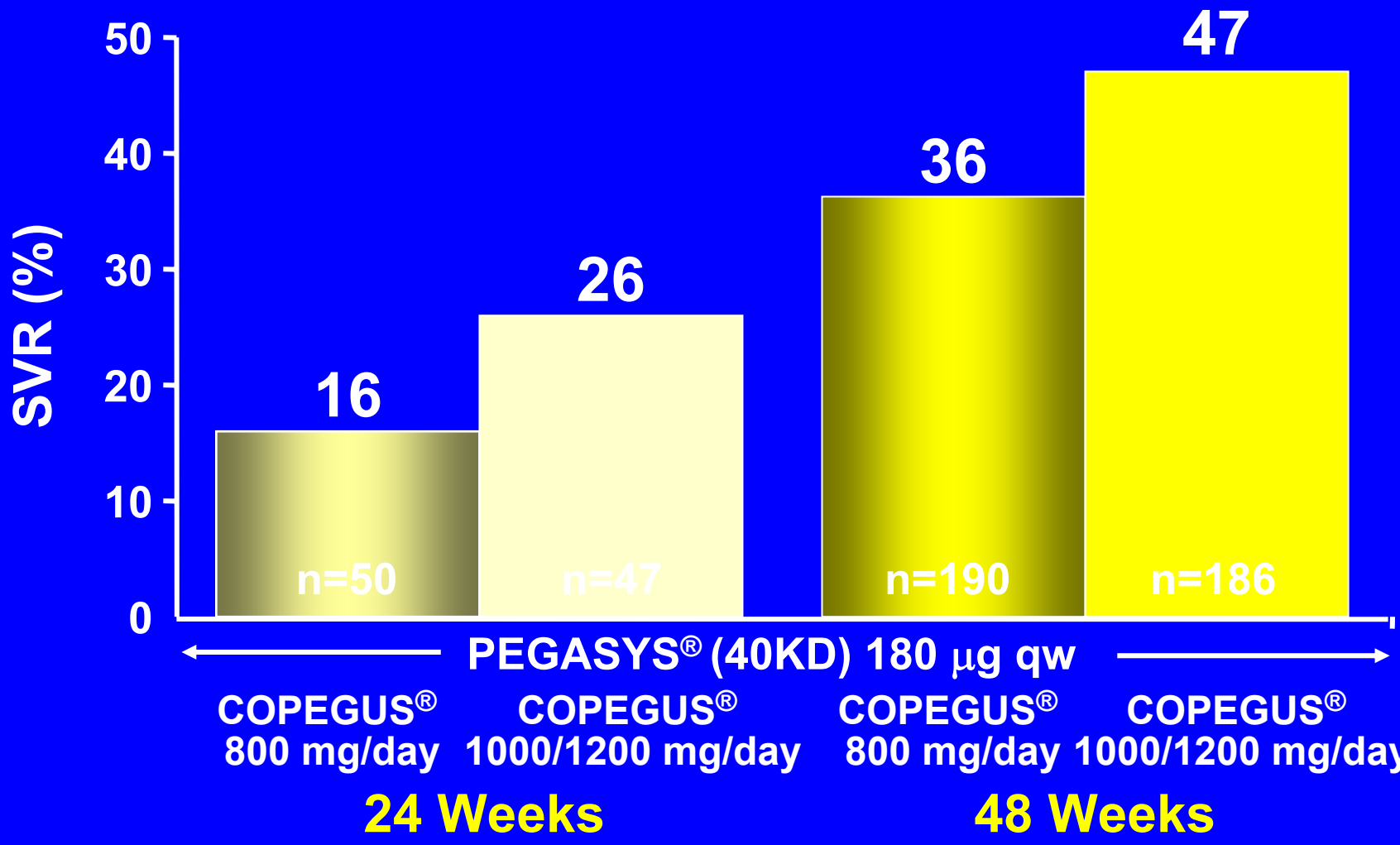


*Intent-to-treat analysis.

Hadziyannis et al. *Ann Intern Med*. 2004.

PEGASYS® (40KD) Plus COPEGUS®:

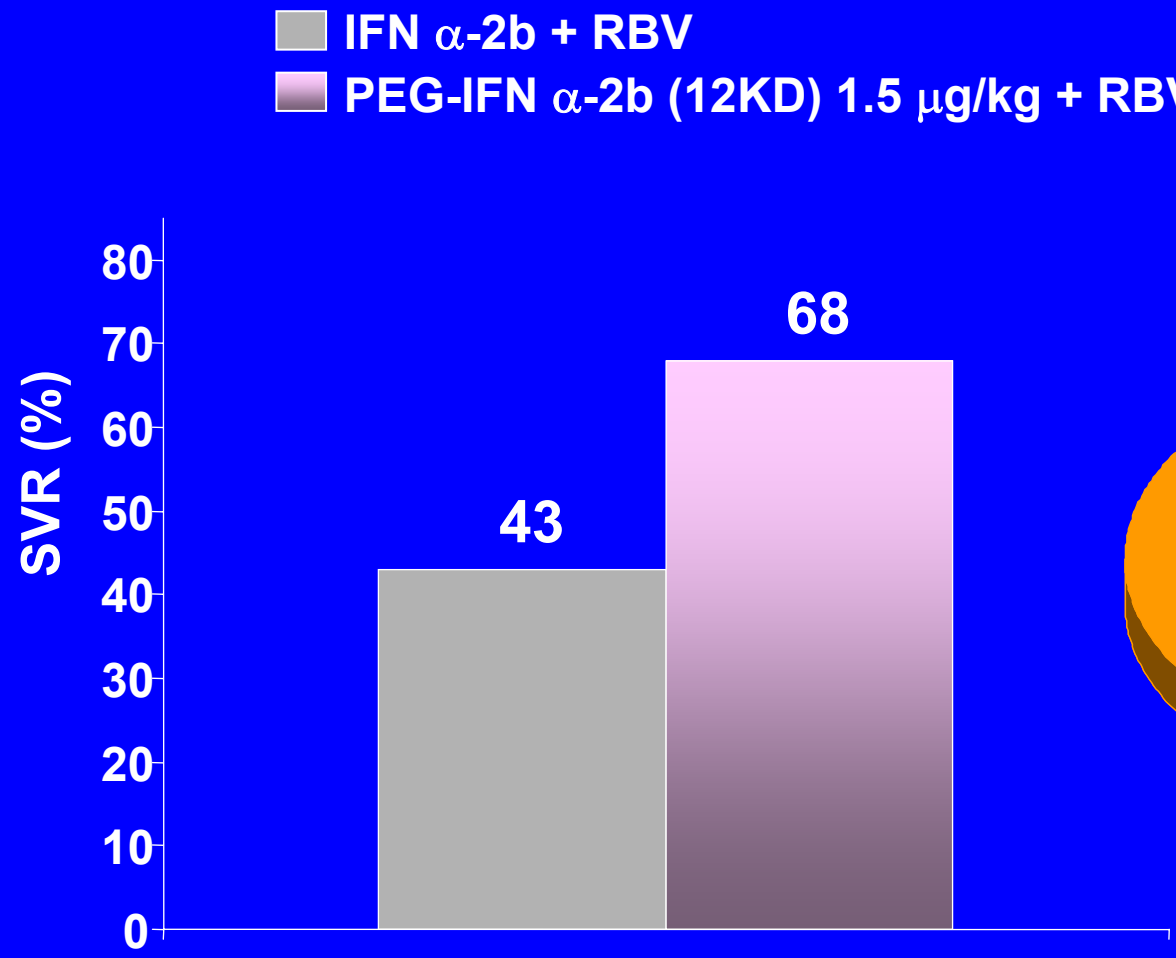
SVR in Patients With HCV Genotype 1 and High Viral Load*

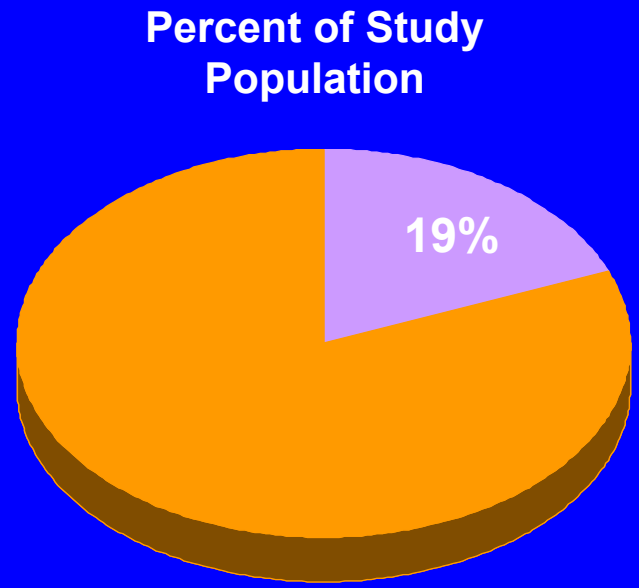


*Intent-to-treat analysis.

Hadziyannis et al. *Ann Intern Med*. 2004.

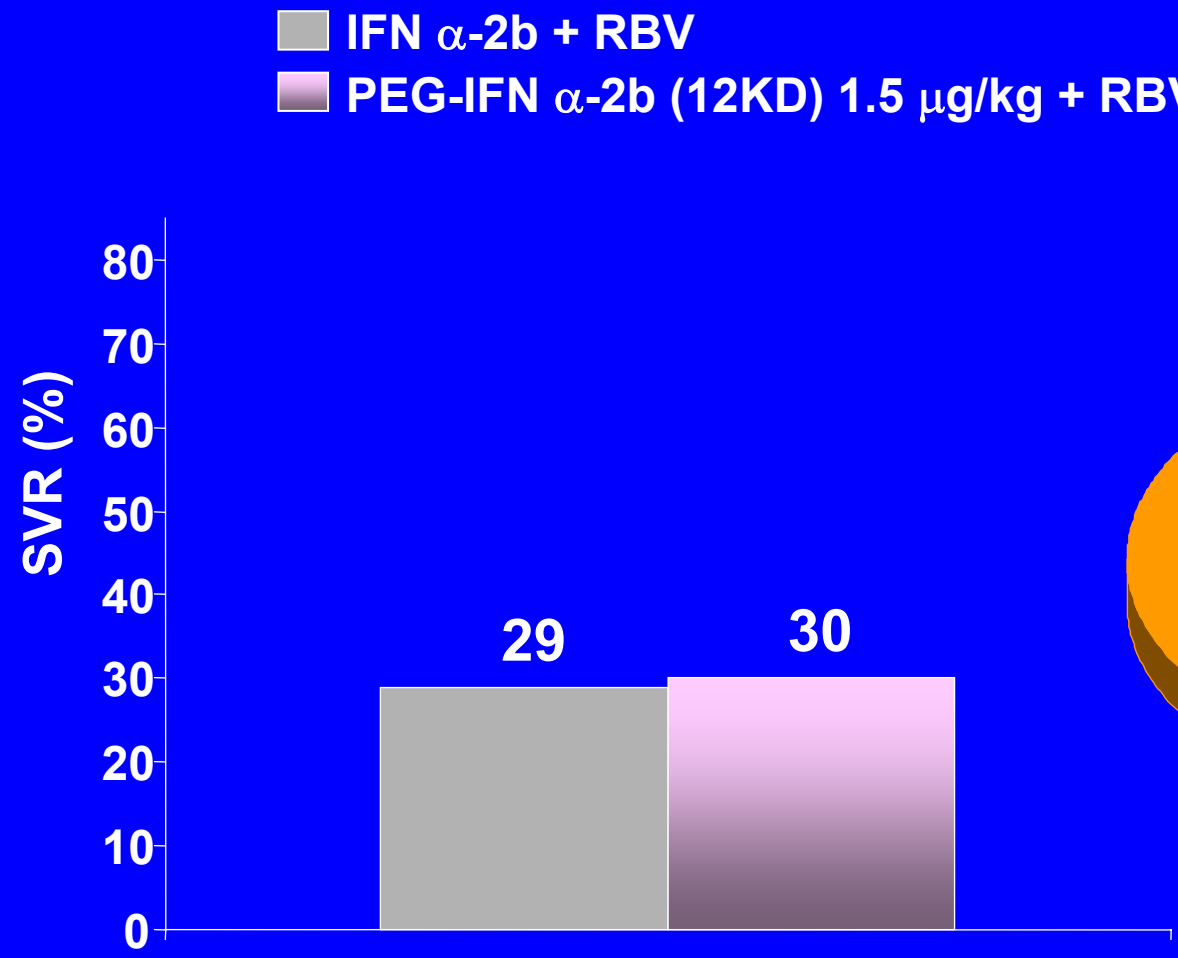
Peginterferon Alfa-2b (12KD) Plus RBV: SVR in HCV Genotype 1 Low Viral Load

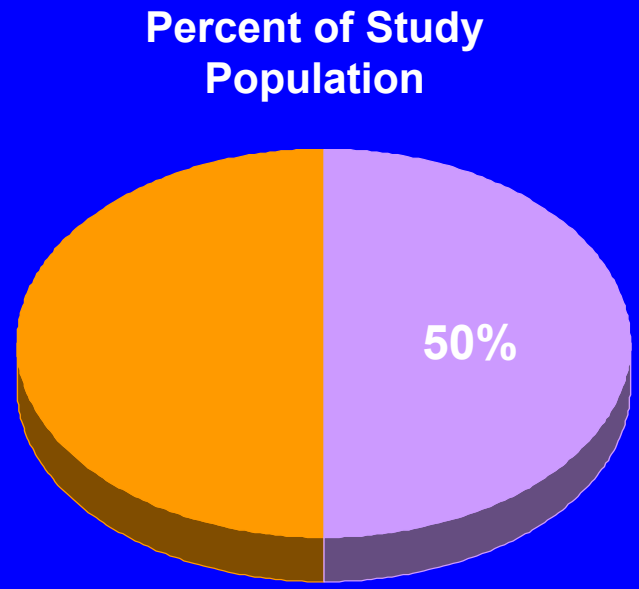




PEG-Intron™. *PDR*®. 56th ed. 2002.

Peginterferon Alfa-2b (12KD) Plus RBV: SVR in HCV Genotype 1 High Viral Load





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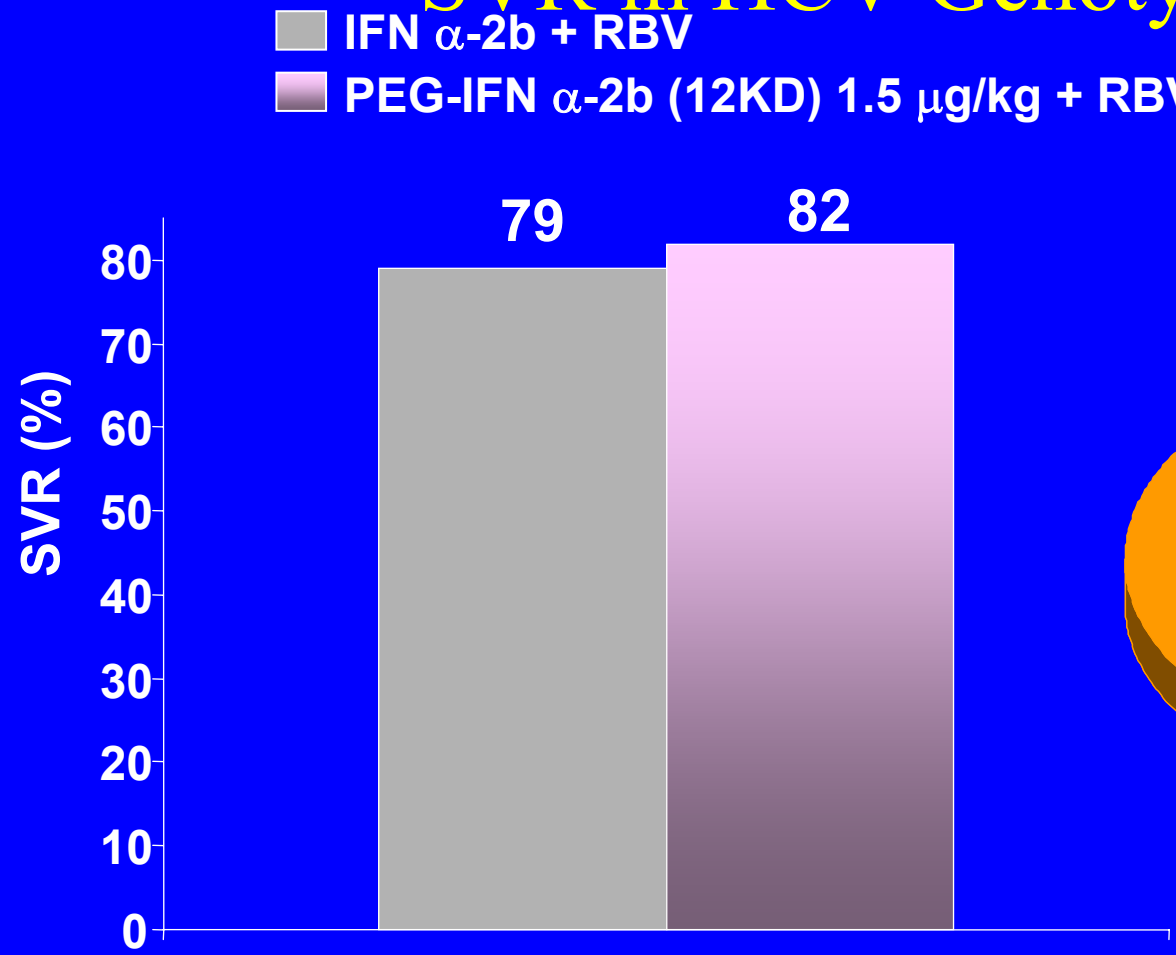
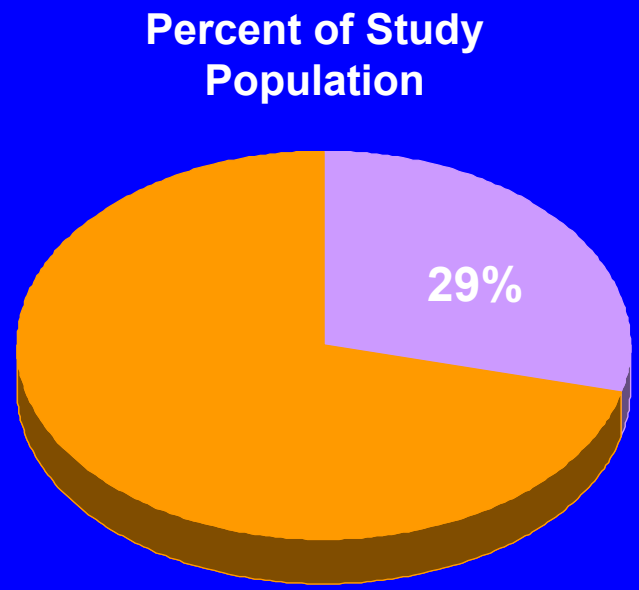
Peginterferon Alfa-2b (12KD) Plus RBV: SVR in HCV Genotype 2/3





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Treating Patients with Chronic Hepatitis C: Whom?

- Consider patient's wish, contraindications
- Monitor patients with F0 - F1 (irrespectively of the A score), due to the low risk of progression of liver disease in the absence of cofactors
- Consider treatment of F0 – F1 only if:
  - patient presents with extra-hepatic manifestation (e.g. vasculitis due to cryoglobulinemia)
  - patient is highly motivated and wishes to become virus free
- Treat if the fibrosis score is $\geq$ F2 (irrespectively of the A score)

Factors affecting fibrogenesis and response to therapy in HCV infection

Factor	Affects fibrogenesis	Affects treatment response
Age	Yes	Yes
Sex	Yes	Yes
Genotype	Unclear	Yes
Viral load	No	Yes
Alcohol abuse	Yes	Yes
HIV coinfection	Yes	Yes
HBV coinfection	Yes	Unclear
Overweight	Yes	Yes
Steatosis	Yes	Yes
Insulin resistance	Yes	Yes

Treatment of hepatitis C: conclusions

- Only a minority of chronic hepatitis C patients will progress to cirrhosis, depending on the presence of several disease modifiers

- Current treatment options are limited, poorly accepted by patients, and should be offered only to potential « progressors »

- HCV eradication is possible in more than half of patients who complete therapy