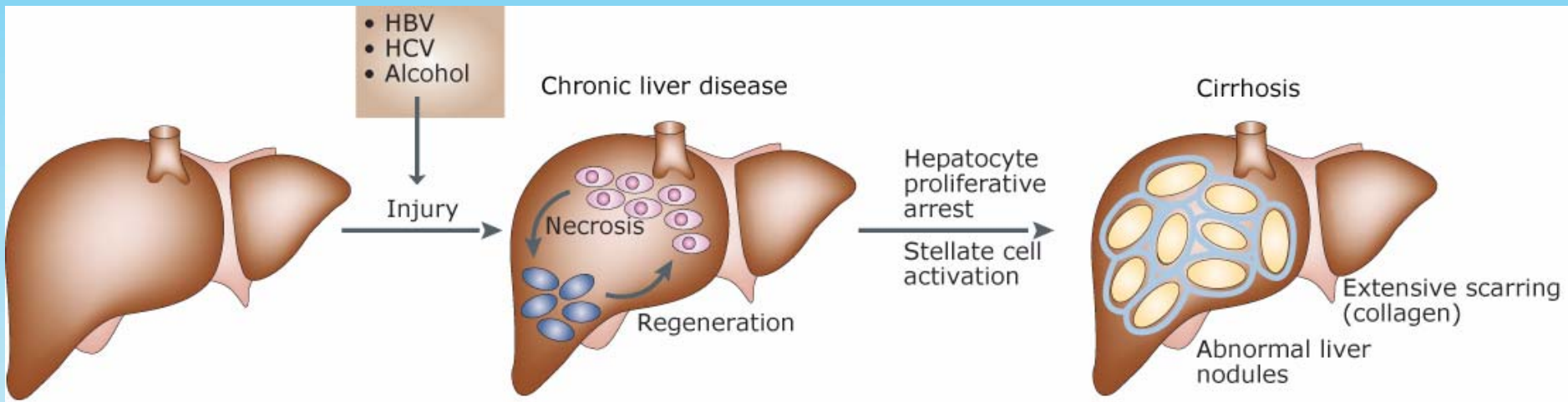


Impact of antiviral treatment on fibrosis and cirrhosis regression

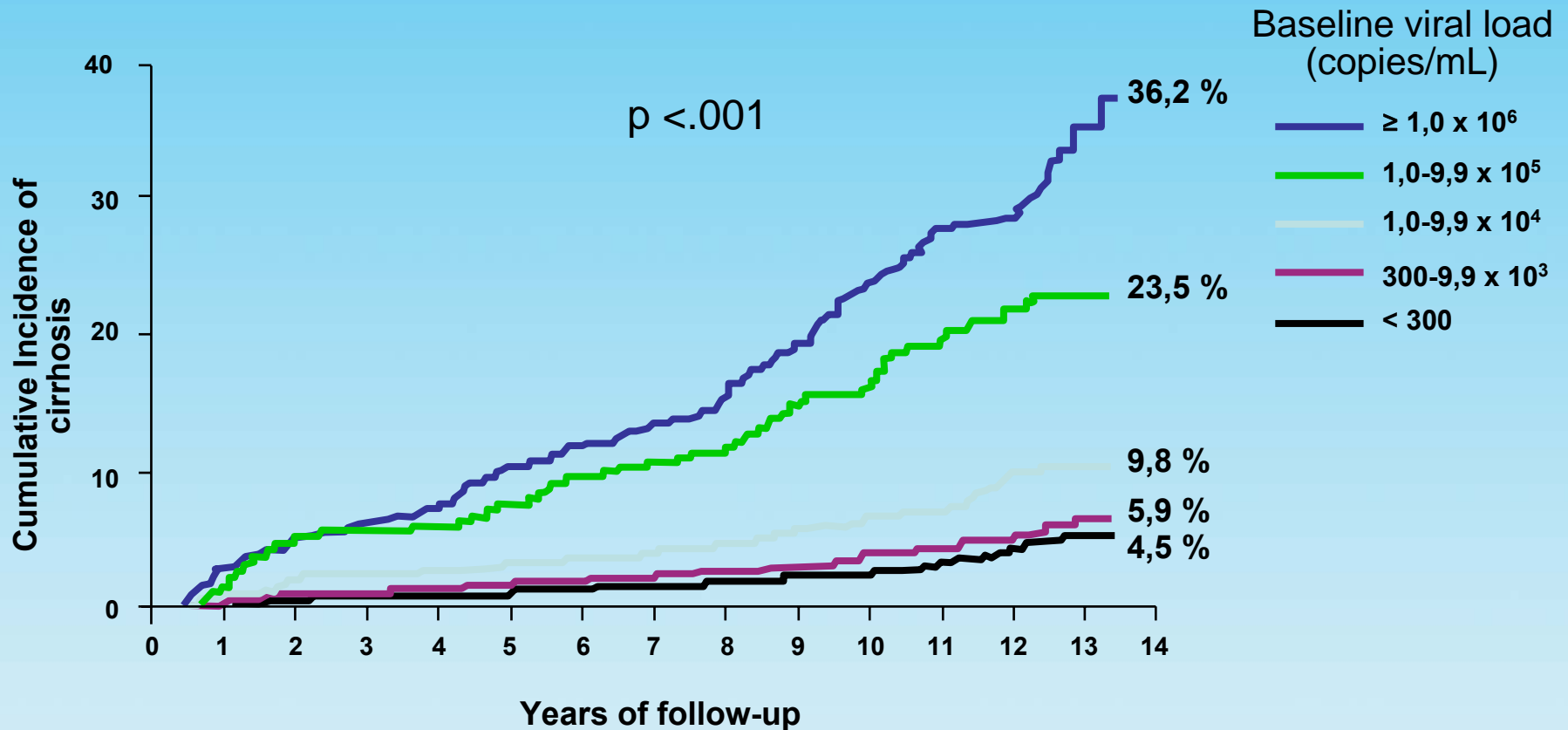
4th Annual Egyptian French Scientific Meeting
Cairo, Egypt
24.01.2010

Stanislas Pol, MD, PhD
Université Paris Descartes; Inserm U 567
Hôpital Cochin, Paris, France

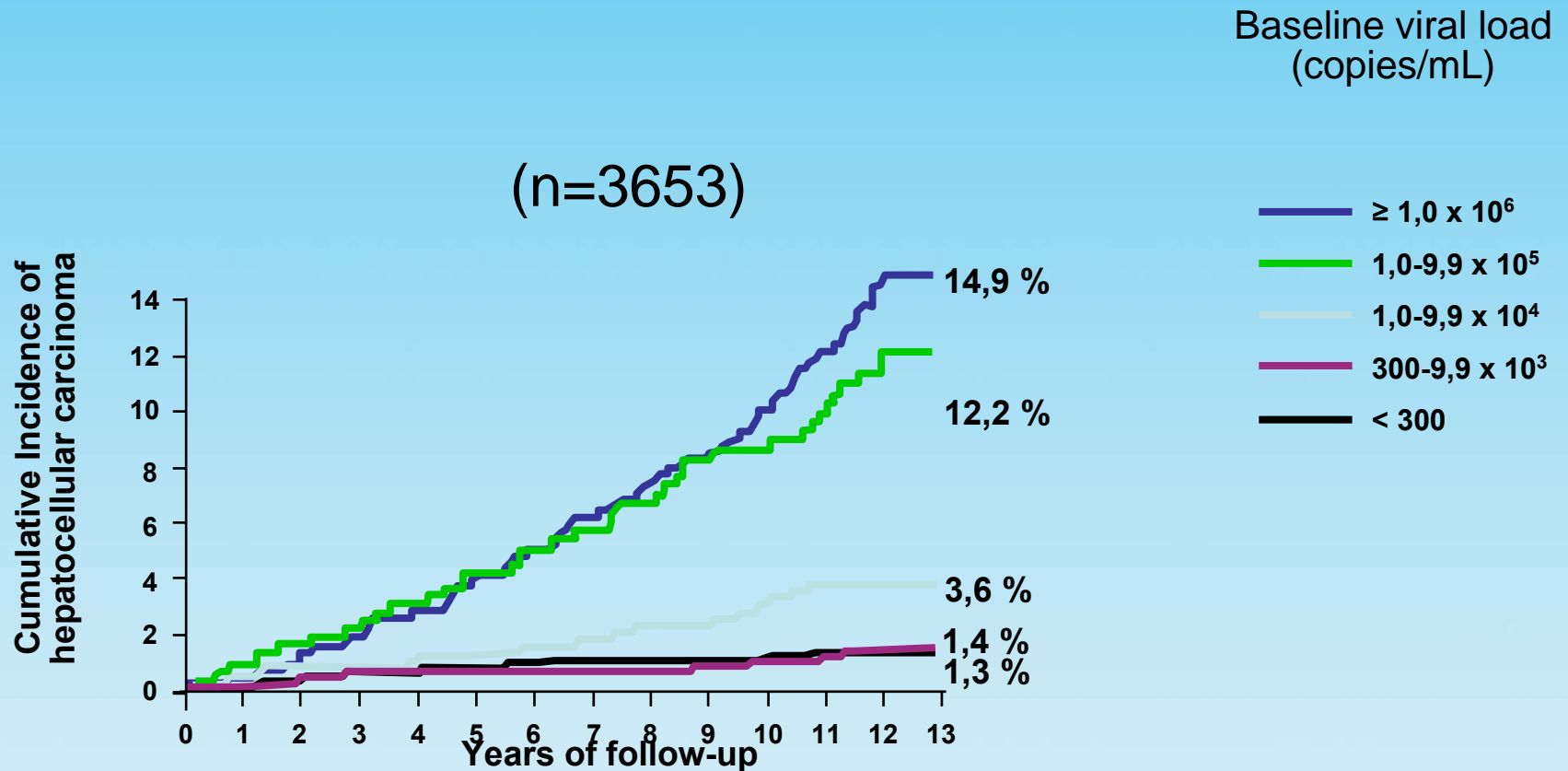
Pathobiology of fibrosis



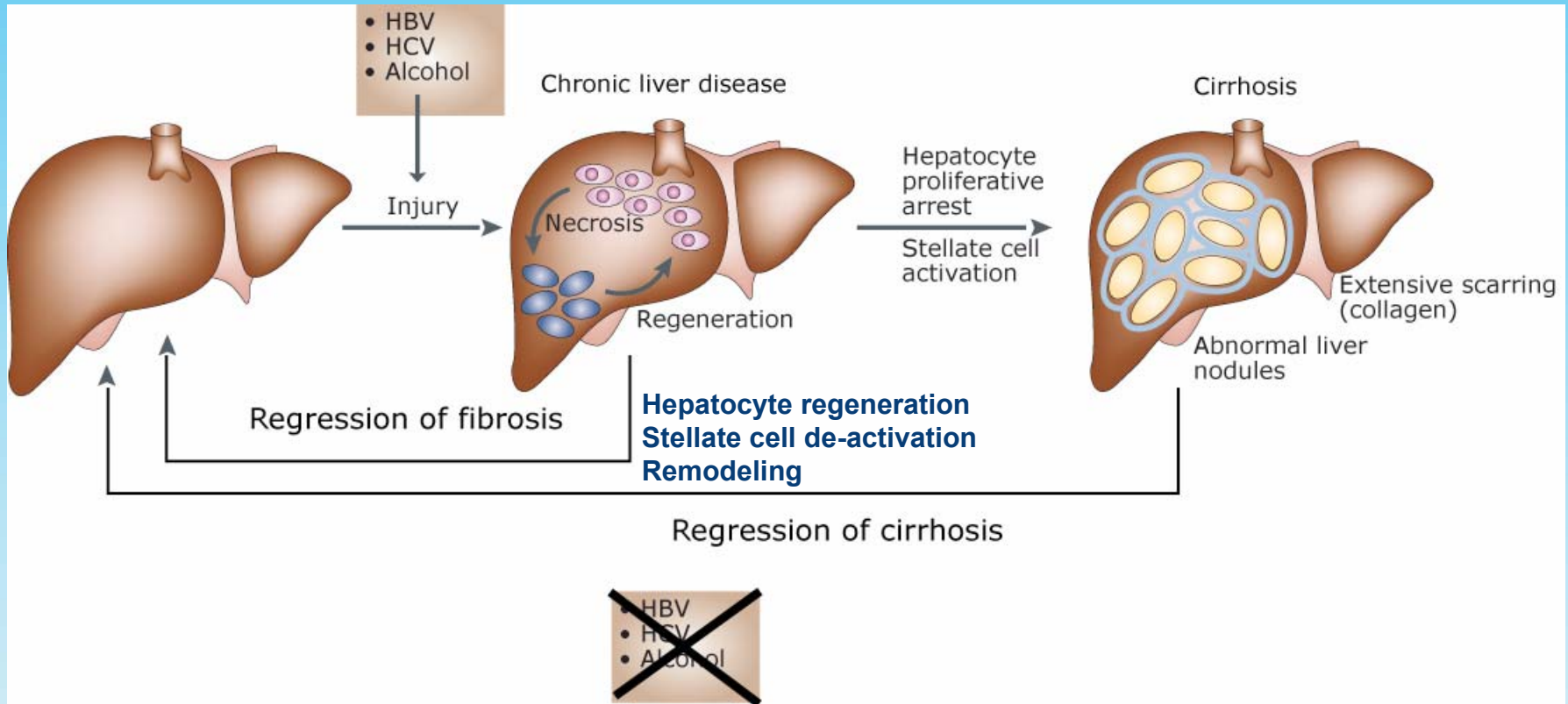
HBV viral load and cirrhosis (REVEAL)



HBV viral load and hepatocellular carcinoma (REVEAL)



Pathobiology of fibrosis-regression



Inactivation of viral-related chronic liver disease

Treatment of chronic hepatitis C

Recommendations

Genotype 2 or 3

Ribavirin 800 mg + PEG Interferon* 180 μ g α 2a or 1.5 μ g α 2b /w, 24 w.

Genotype 1 or 4

Ribavirin 1000-1200 mg + PEG Interferon 180 μ g α 2a or 1.5 μ g α 2b /w 48 w.

Treatment of chronic hepatitis C

Recommendations

Genotype 2 or 3

Ribavirin 800 mg + PEG
Interferon* 180 μ g α 2a or
1.5 μ g α 2b /w, 24 w.

SVR ~ 80%

Genotype 1 or 4

Ribavirin 1000-1200 mg +
PEG Interferon 180 μ g α 2a or
1.5 μ g α 2b /w 48 w.

SVR ~ 45%

SVR = sustained virological response, i-e undetectable HCV
RNA 6 months after treatment = virologic recovery

Treatment of chronic hepatitis C Recommendations

Genotype 2 or 3

Ribavirin 800 mg + PEG
Interferon* 180 μ g α 2a or
1.5 μ g α 2b /w, 24 w.

HIV co-infection
Baseline Viral load
Age
Liver steatosis
Fibrosis grade
Race
Genetics

SVR ~ 80%

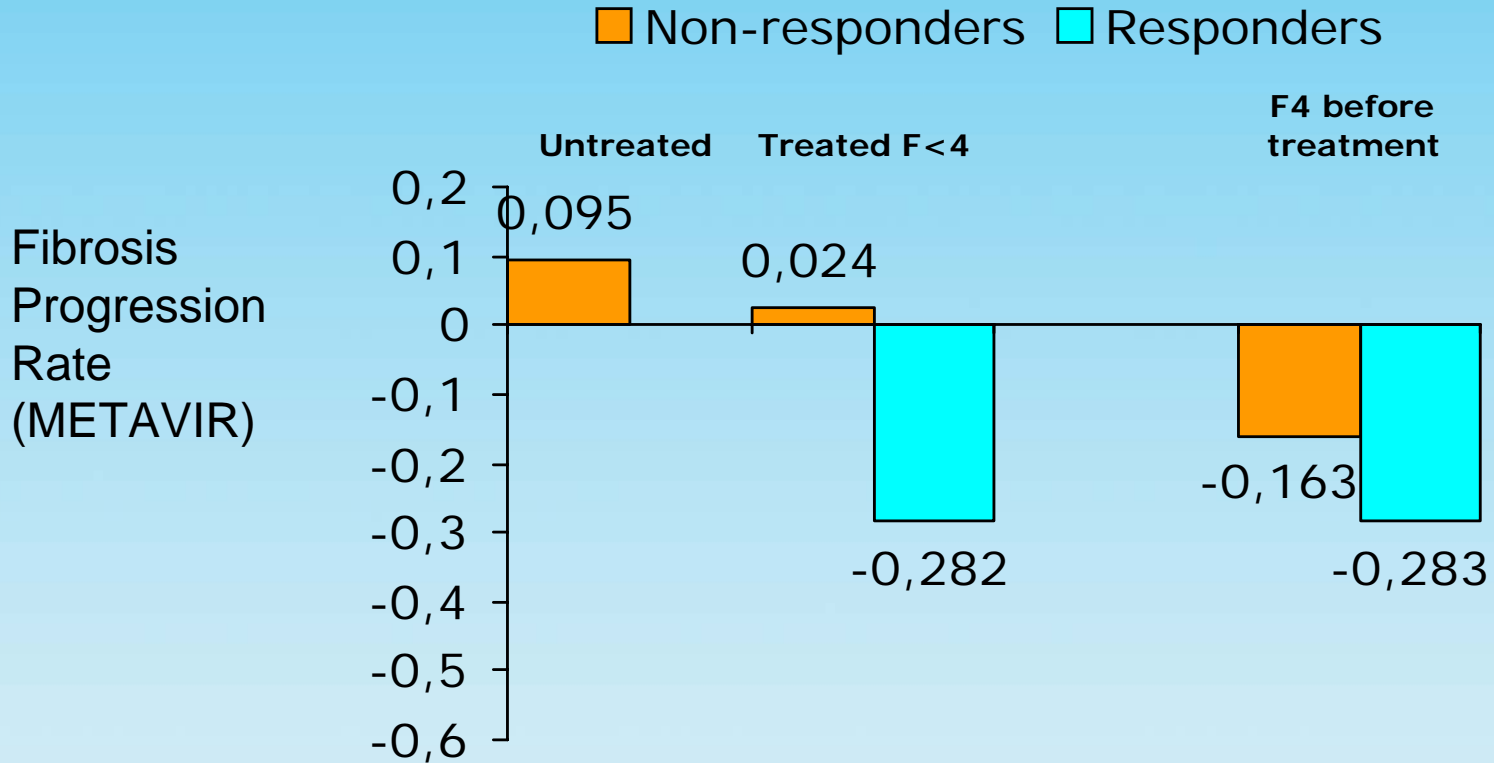
Genotype 1 or 4

Ribavirin 1000-1200 mg +
PEG Interferon 180 μ g α 2a or
1.5 μ g α 2b /w 48 w.

SVR ~ 45%

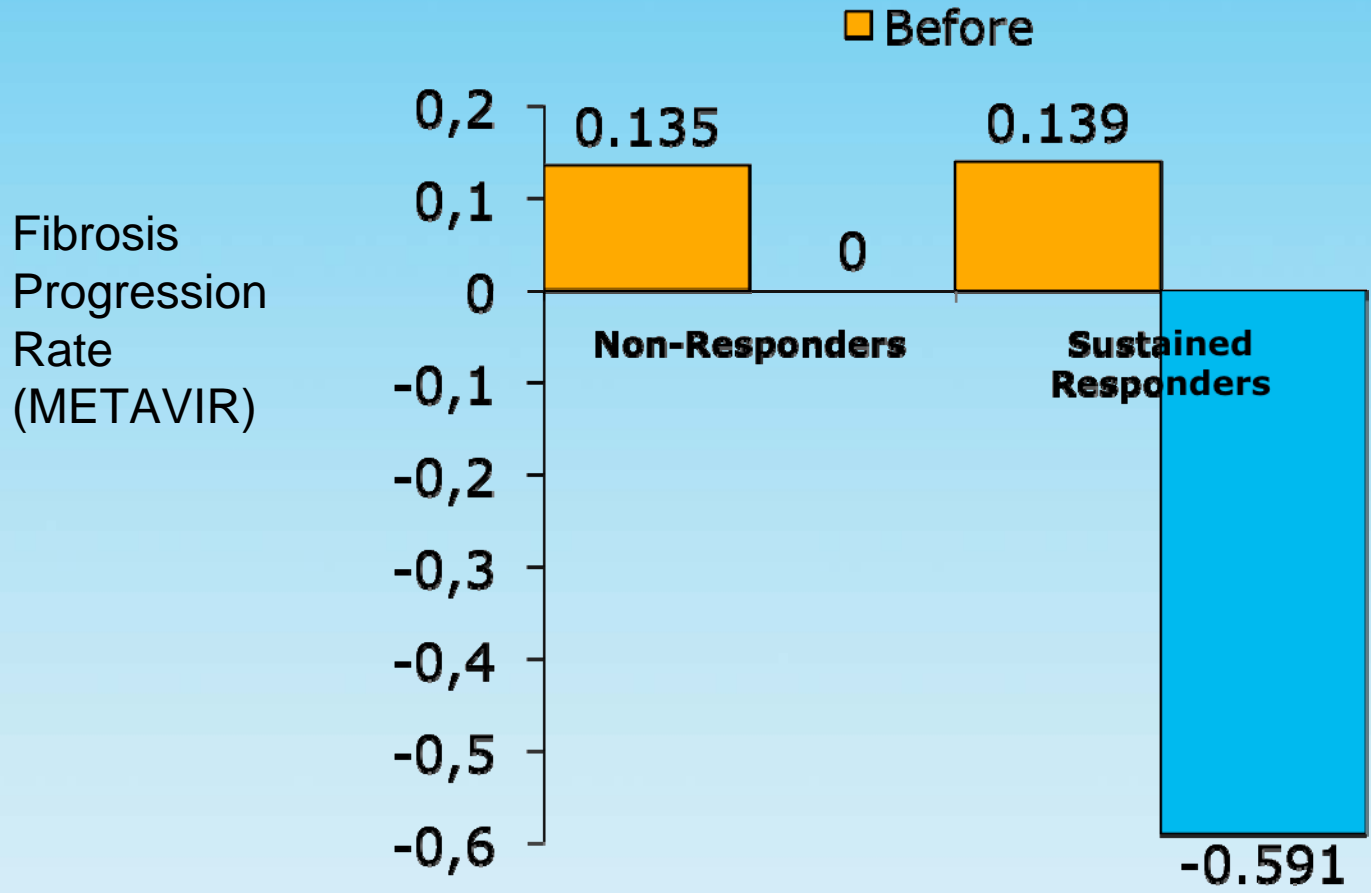
Cancelling necro-inflammation = regression of HCV-related fibrosis

593 treated or not treated HCV patients F0-F4 with paired liver biopsies

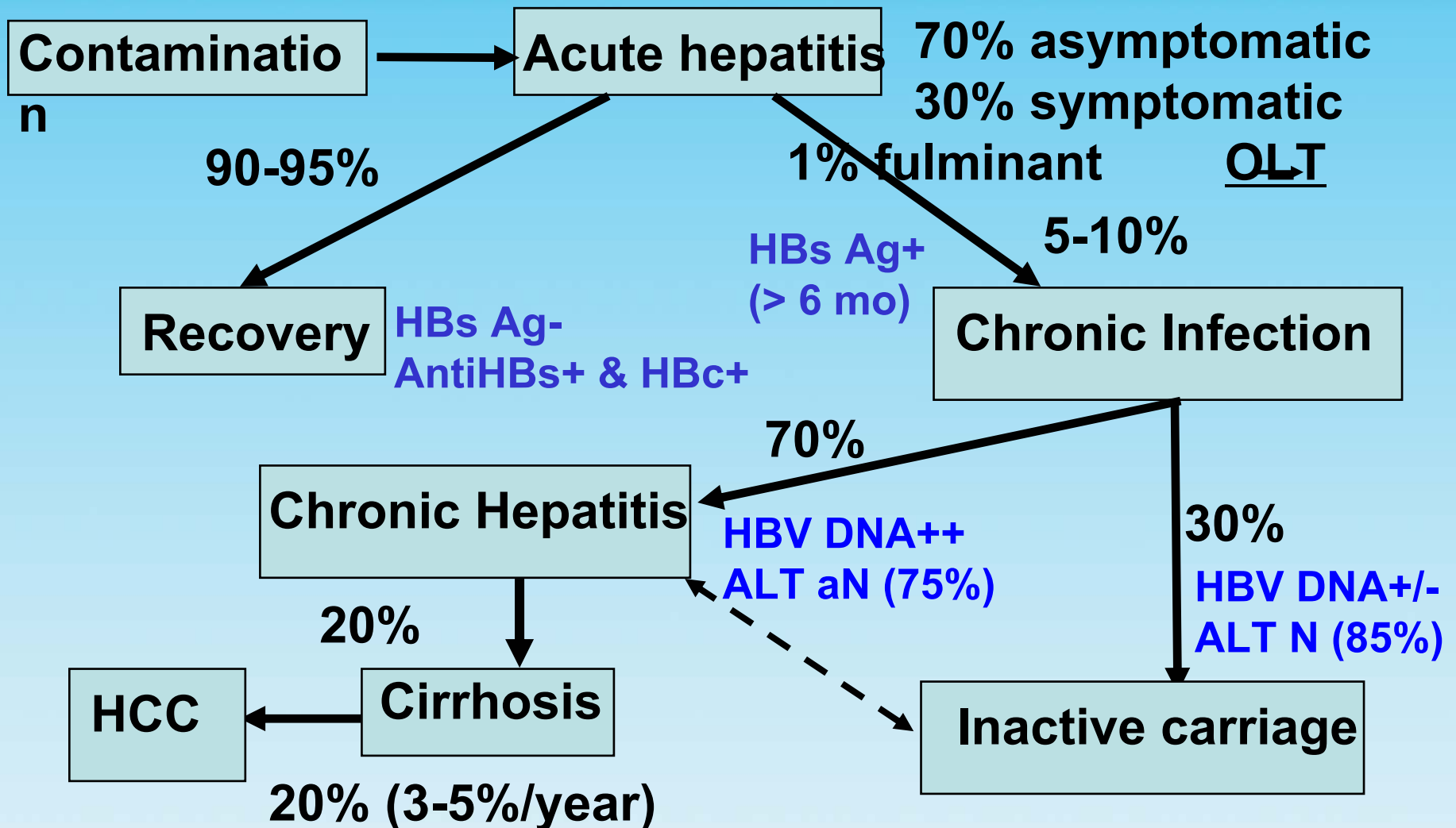


Cancelling necro-inflammation = regression of HCV-related fibrosis

679 HCV patients F2-F3-F4 with paired biopsies and known duration of infection



Natural history of HBV



EASL clinical practical guidelines

- Treatment when patients have HBV DNA > 2000 UI/ml (i.e. around 10 000 copies/ml)

and/or

- ALT levels > the upper normal value

and

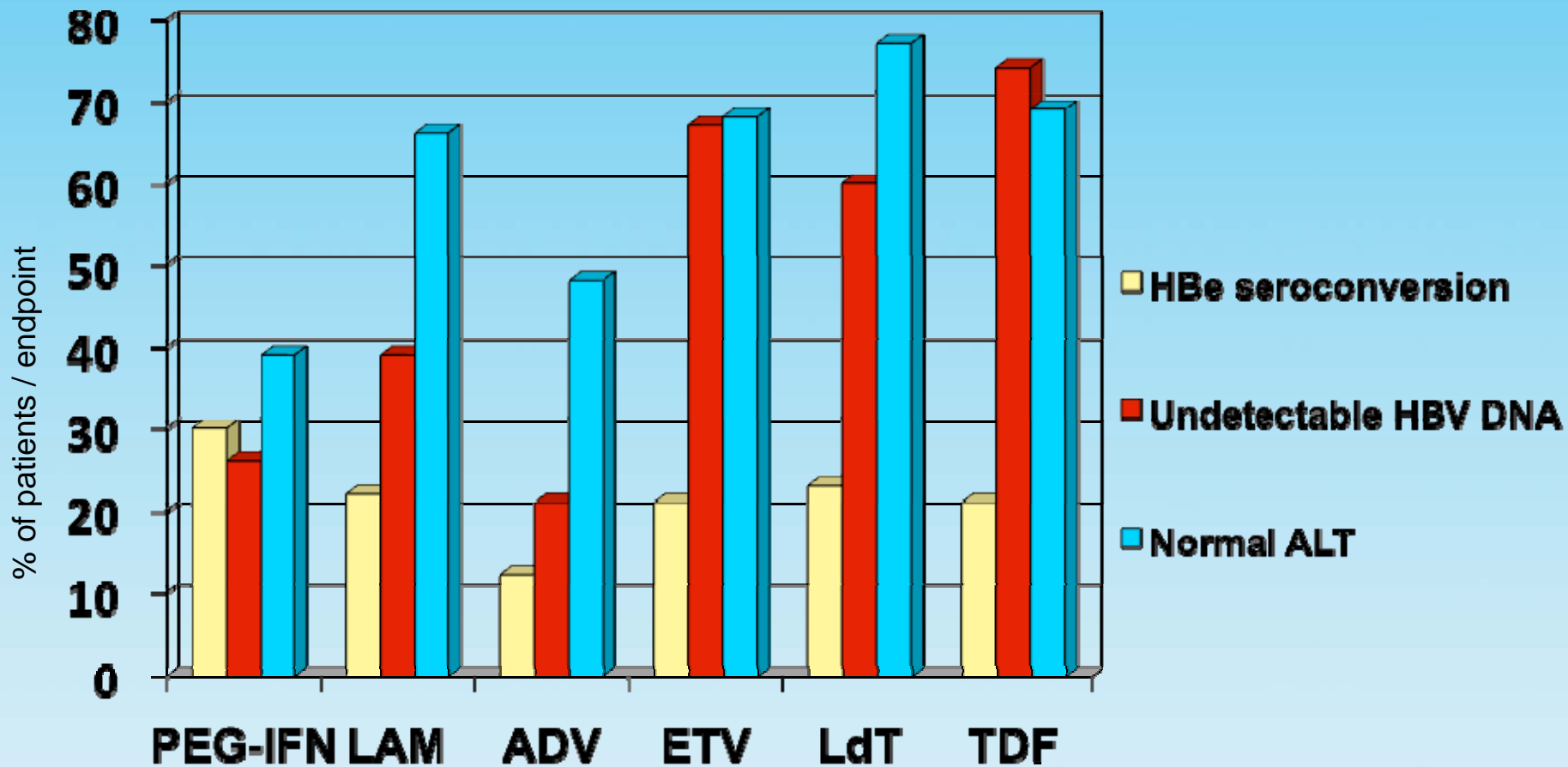
- A liver biopsy indicating necro-inflammation and/or moderate to severe fibrosis with a standardized score (e.g. a grade A2 or a stage F2 with the METAVIR score)

Management strategies for CHB

- HBV agents currently approved for CHB treatment:
 - PegIFN- α ¹
 - ADV²
 - ETV³
 - LdT⁴
 - LVD⁵
 - TDF⁶
 - Clevudine (approved in South Korea and Philippines): discontinued in 2009

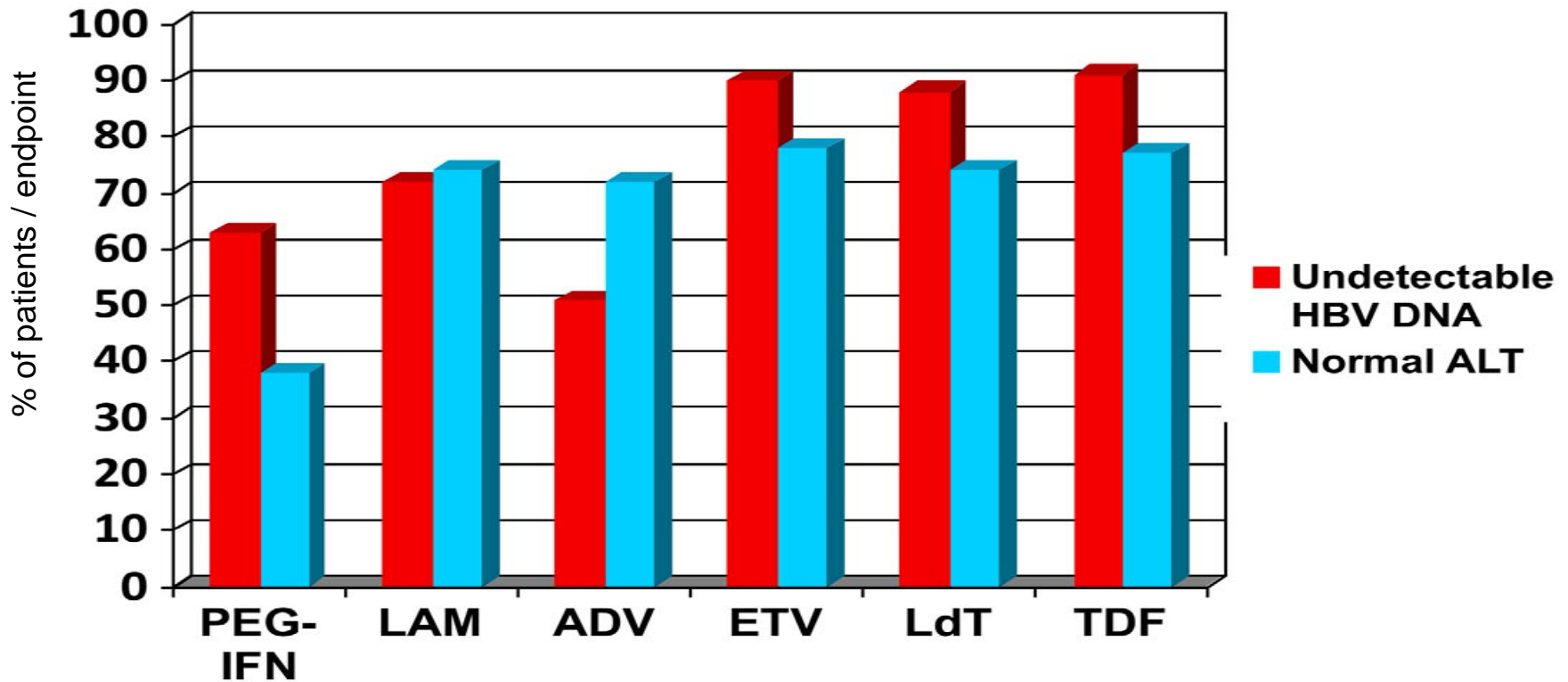
Treatment of chronic hepatitis B

HBe Ag+



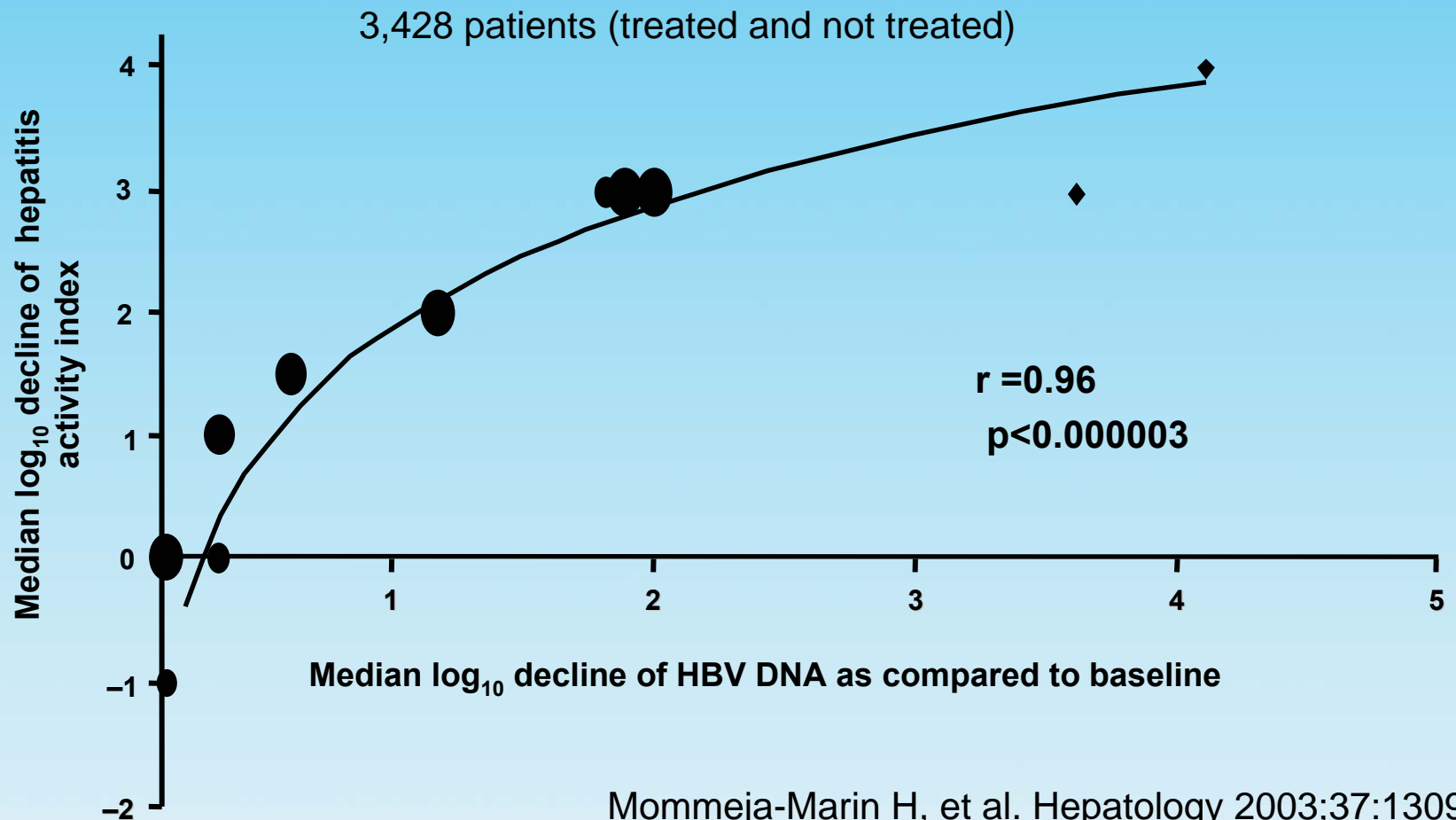
Treatment of chronic hepatitis B

HBe Ag-

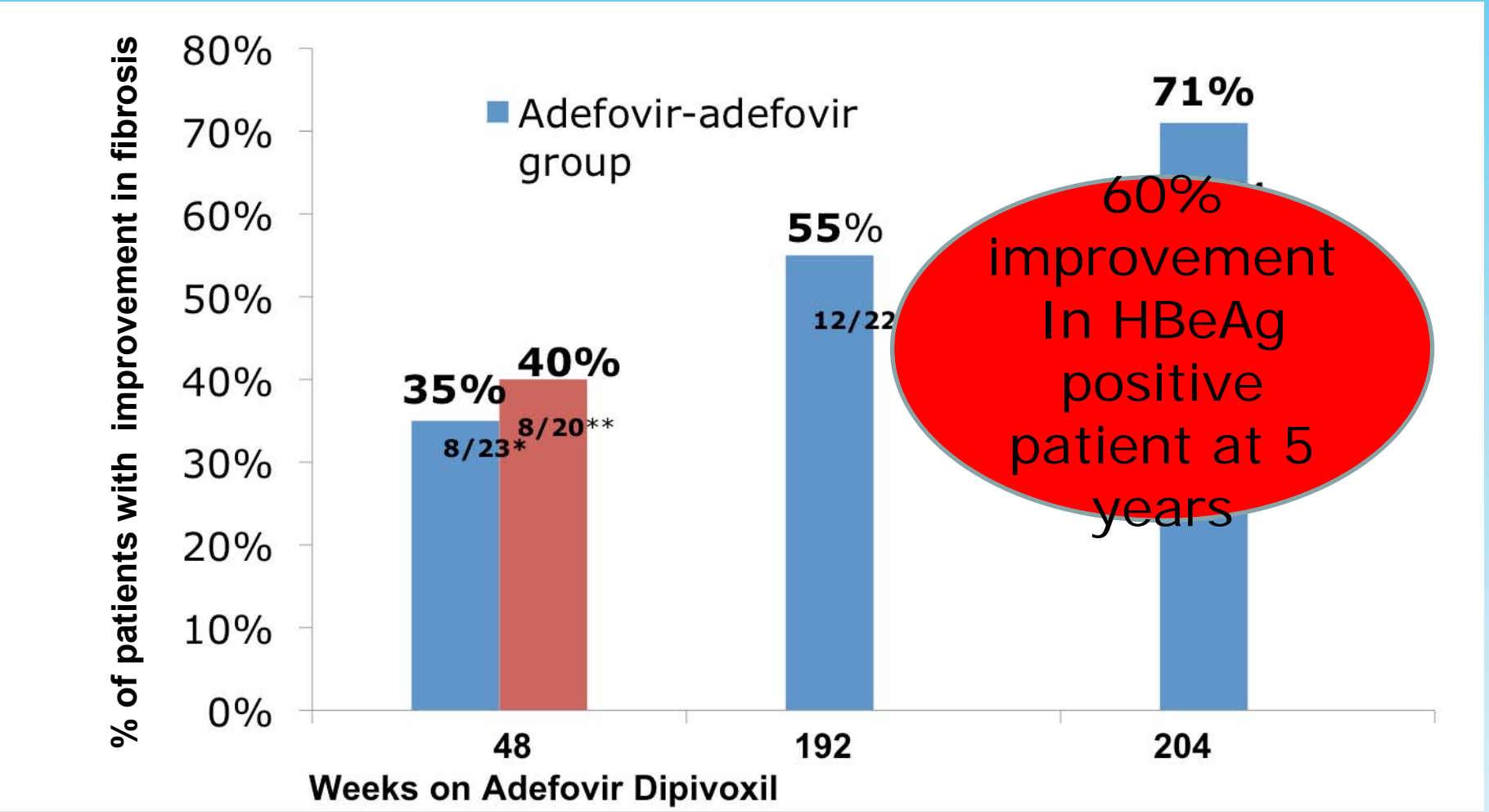


Cancelling necro-inflammation by Interferon in HBV-related fibrosis

Meta-analysis of 26 prospective studies with Interferon



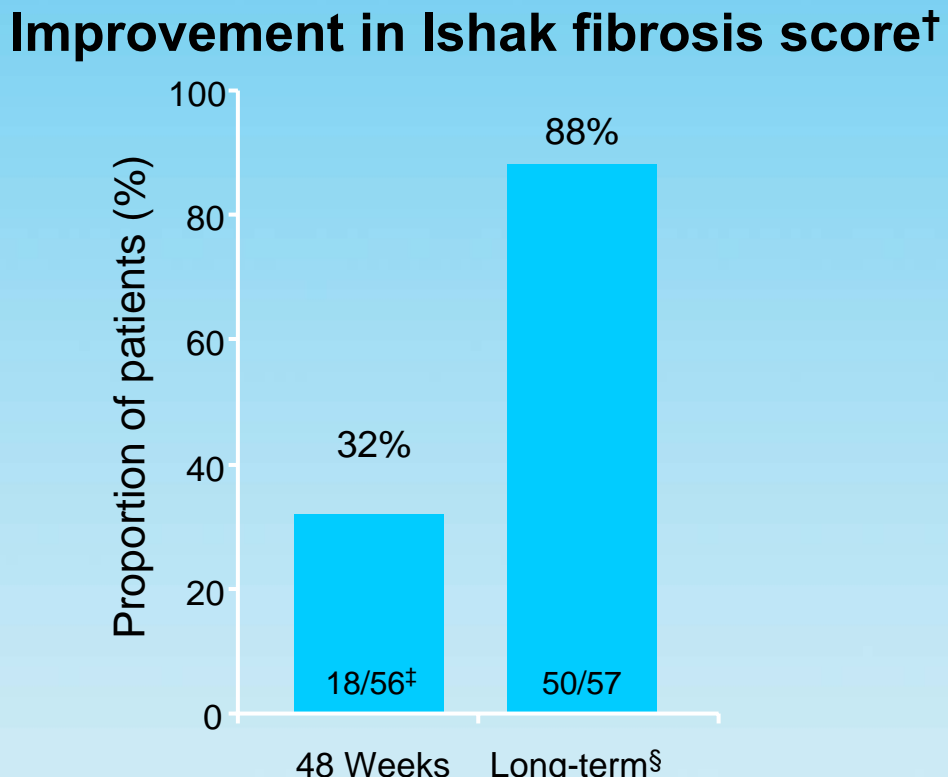
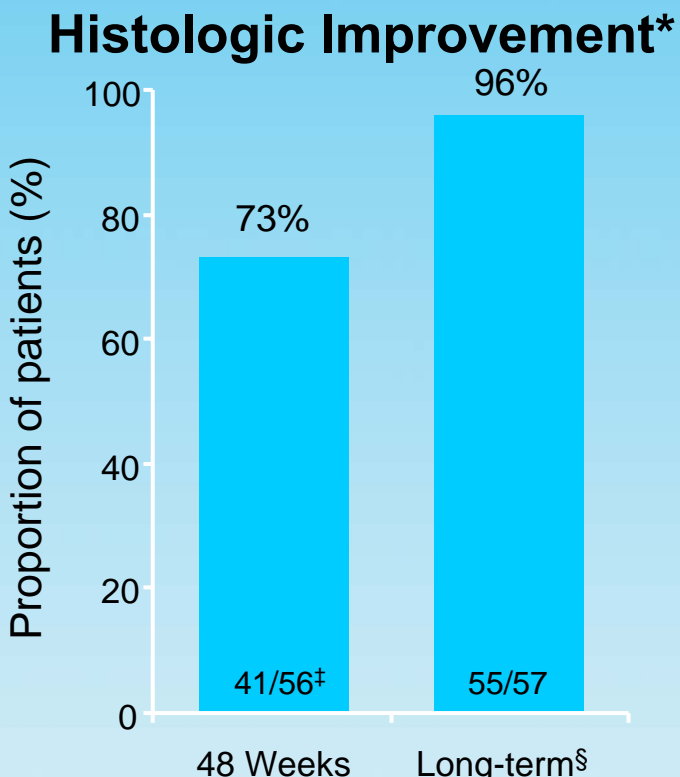
Cancelling necro-inflammation = regression of HBV-related fibrosis



Hadziyannis S et al. Gastroenterology 2006; Marcellin P et al. Hepatology 2008

Cancelling necro-inflammation = regression of HBV-related fibrosis

Long term benefit associated with Entecavir



*≥2-point decrease in Knodell necroinflammatory score and no worsening of Knodell fibrosis score compared with baseline

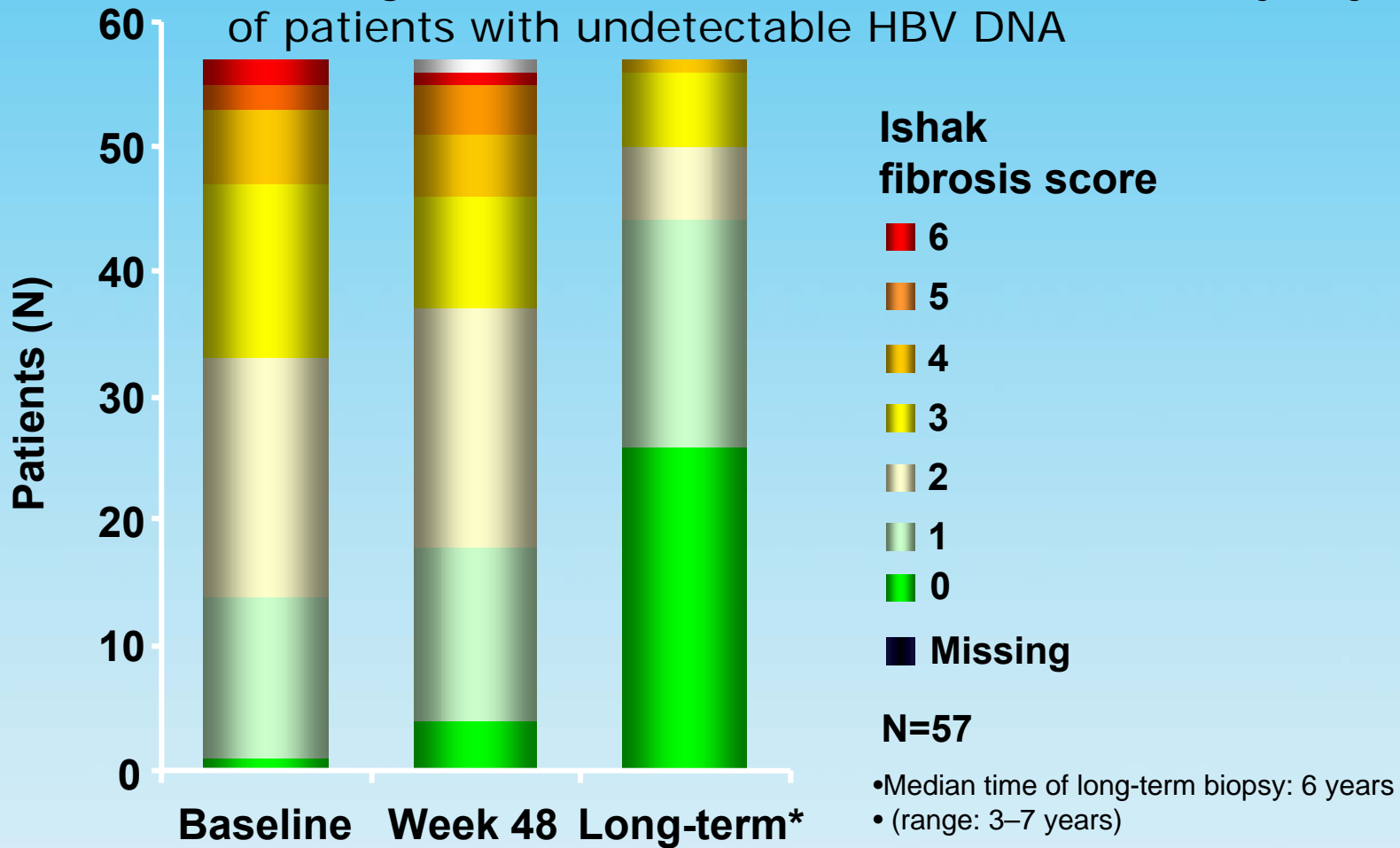
[†] ≥1-point decrease

[‡] One patient had an inadequate Week 48 biopsy

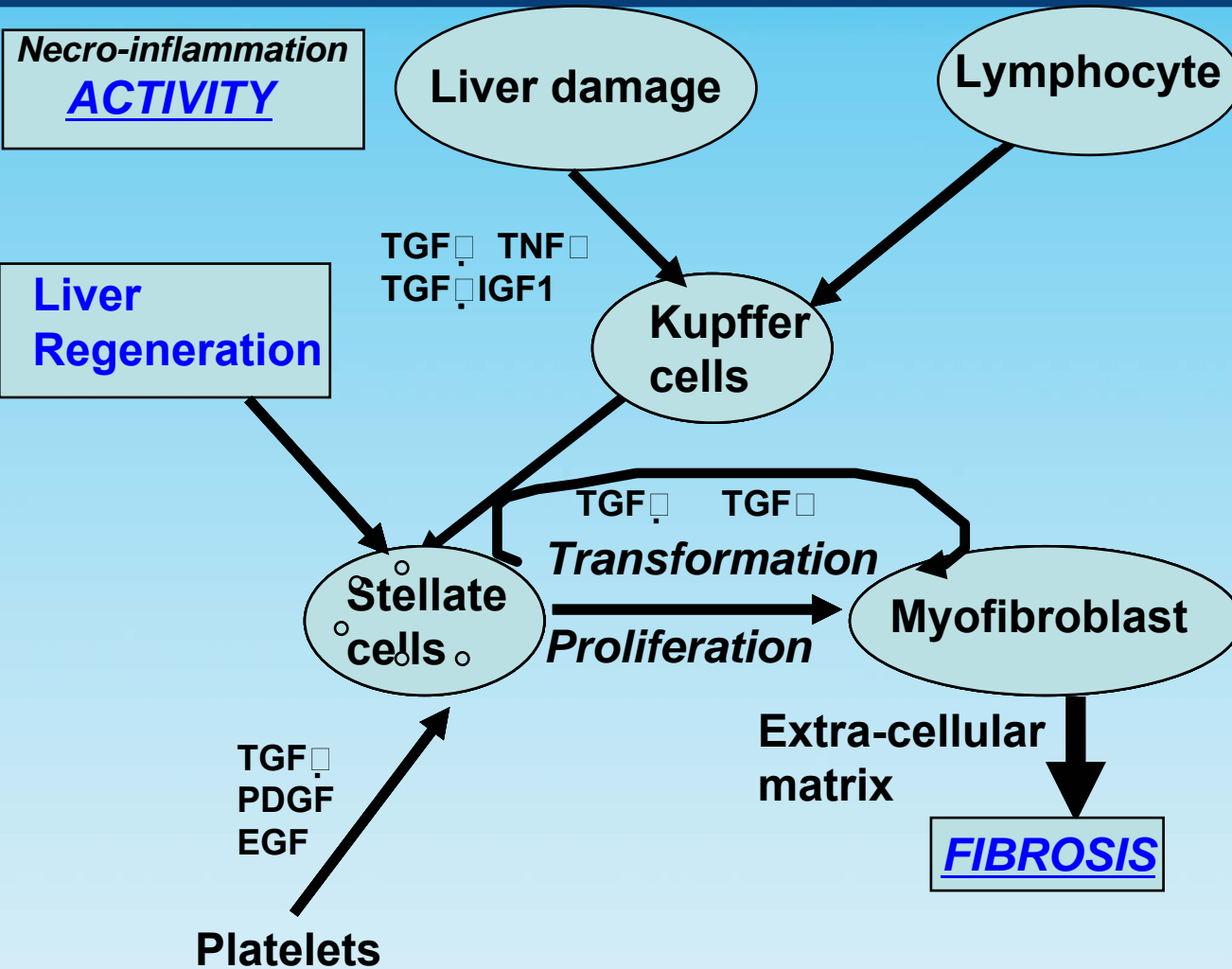
[§] Median time of long-term biopsy: 280 weeks

Cancelling necro-inflammation = regression of HBV-related fibrosis

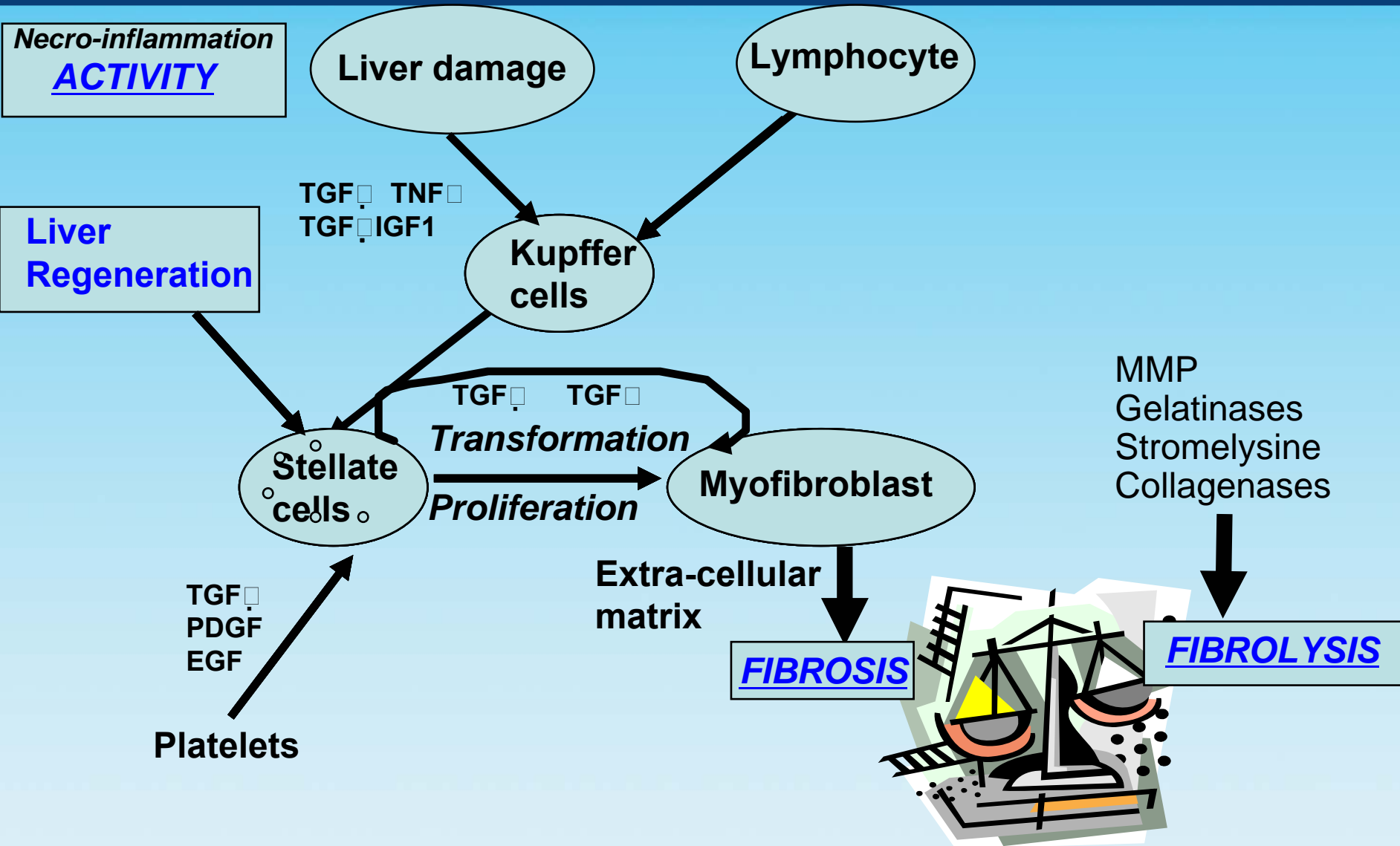
Entecavir achieves regression of Ishak fibrosis score in the majority of patients with undetectable HBV DNA



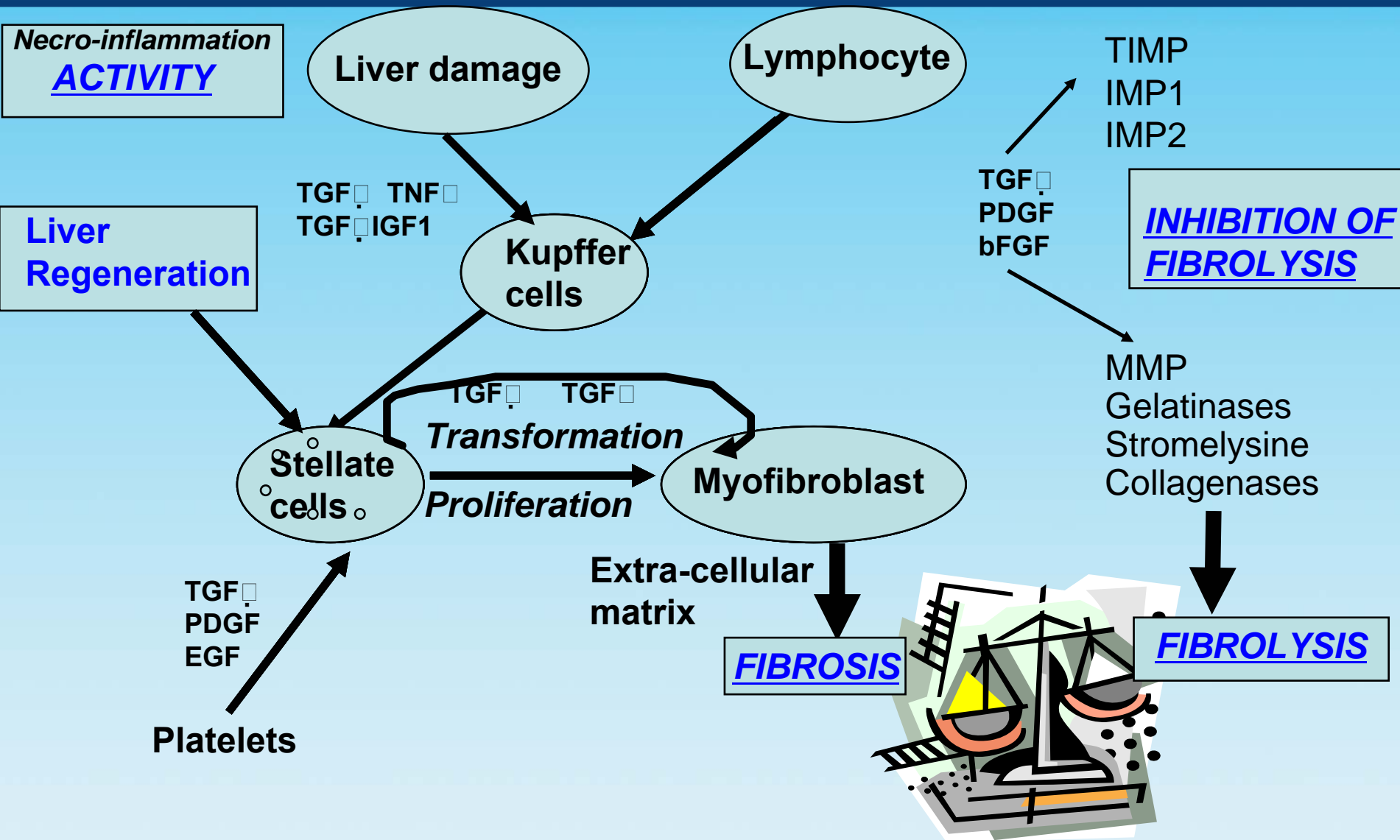
Fibrogenesis is a dynamic process



Fibrogenesis is a dynamic process



Fibrogenesis is a dynamic process



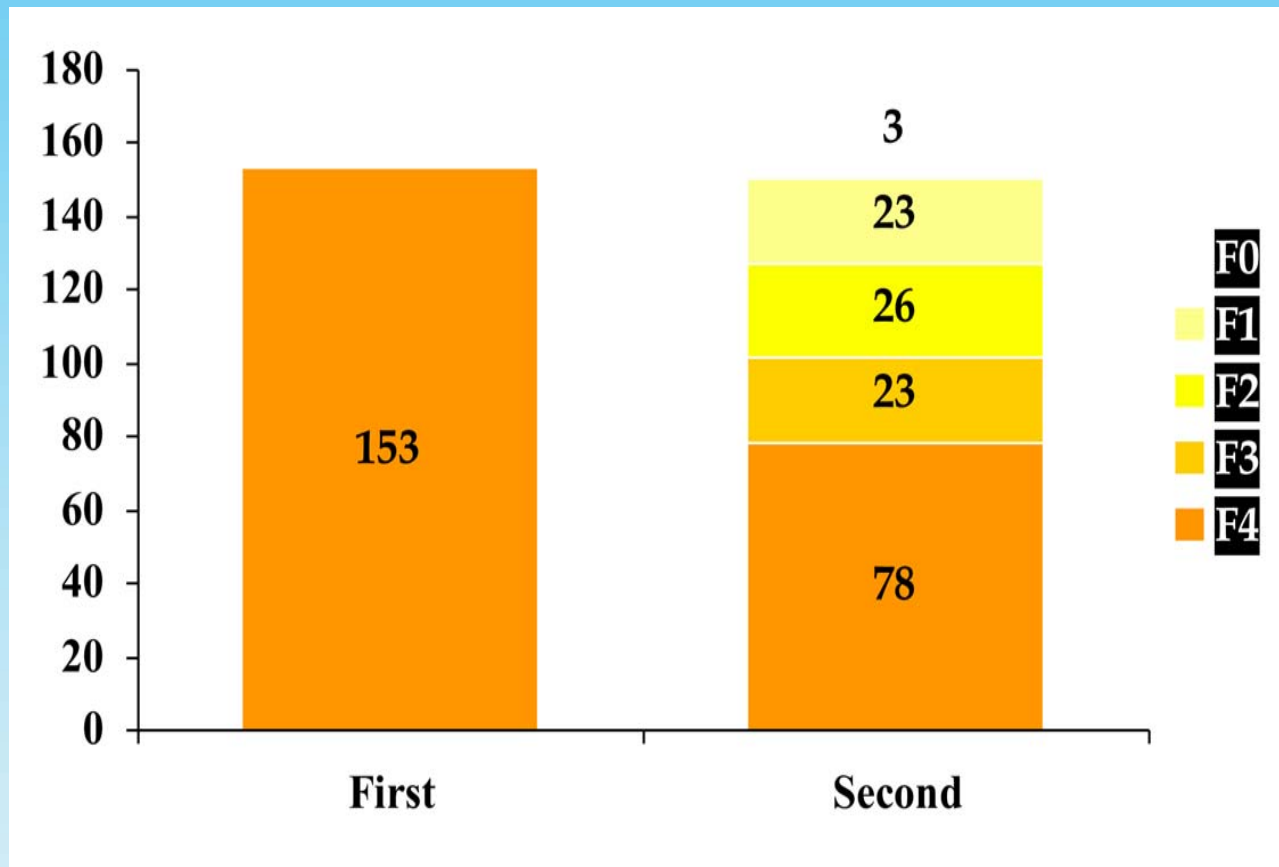
Inactivation of viral-related chronic liver disease and cirrhosis reversal

The dogma of irreversibility

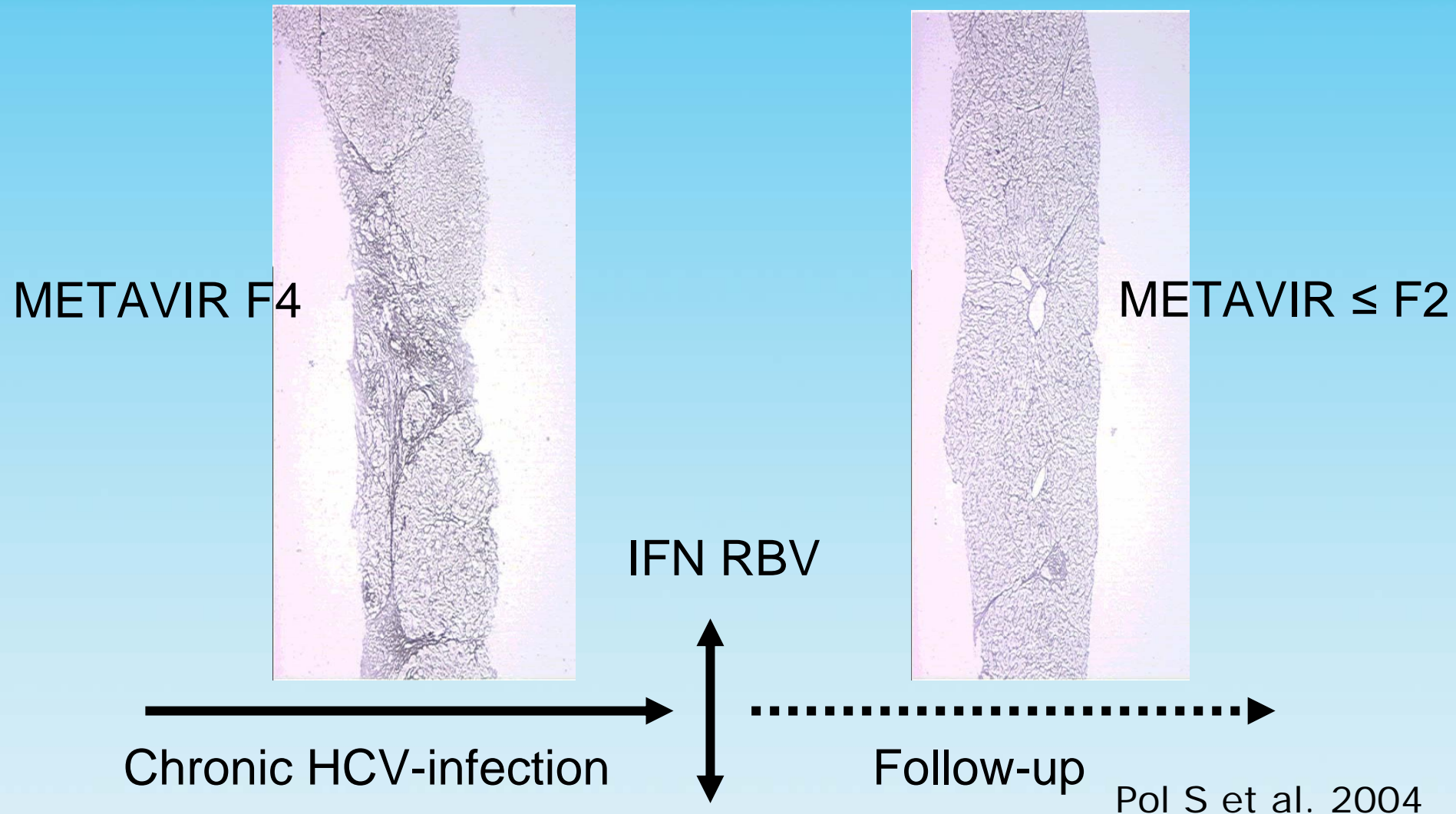
- “. . . cirrhosis is not a progressive chronic process, but an end-product.”
 - Mallory TS. 1914
- “ According to present available evidence, cirrhosis is not completely reversible. ”
 - Desmet VJ et al. 2004

Histological evidence of HCV-related cirrhosis reversal

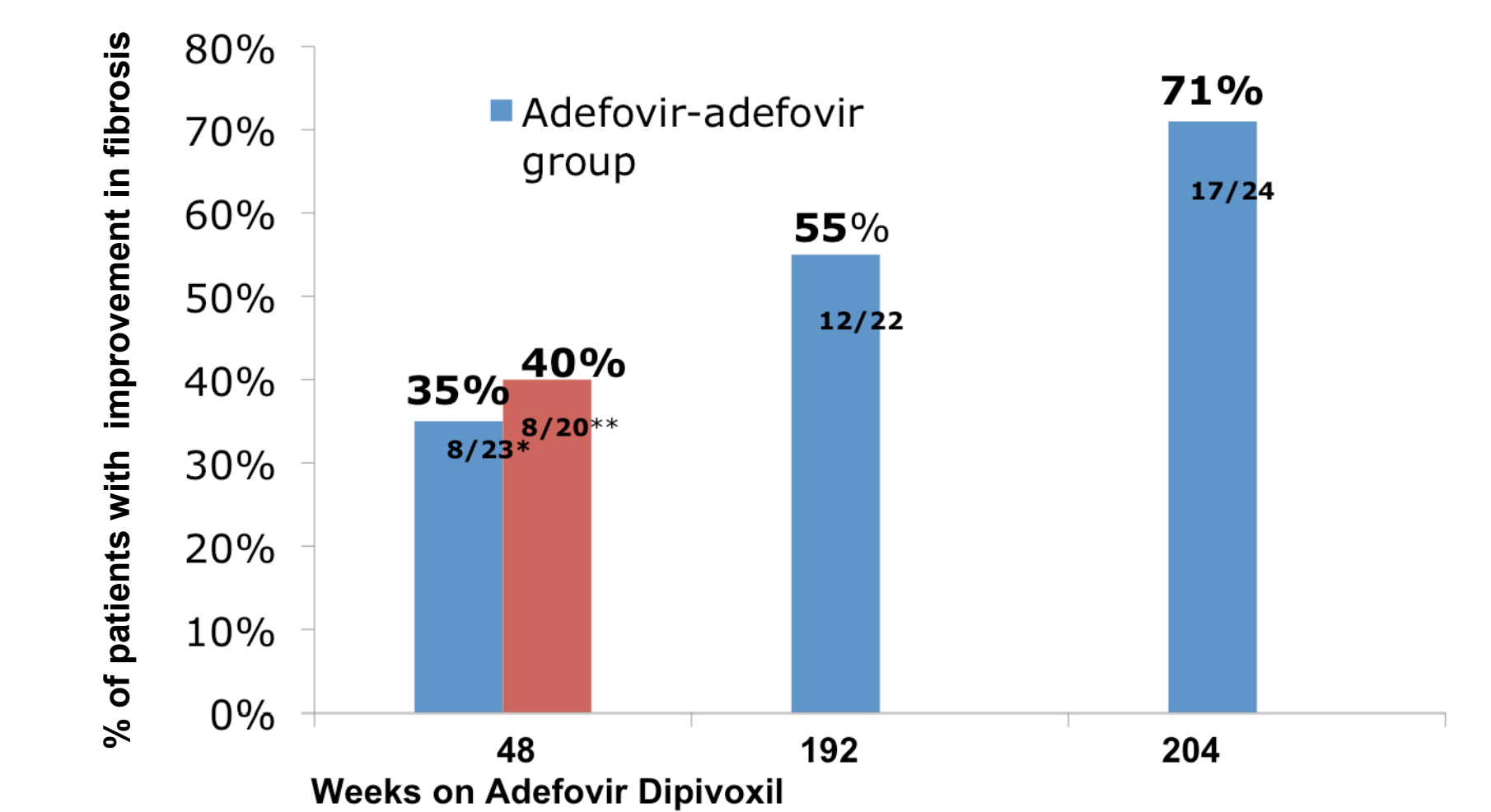
Reversal of cirrhosis in 75/153 (49%) of patients



Histological evidence of HCV-related cirrhosis reversal

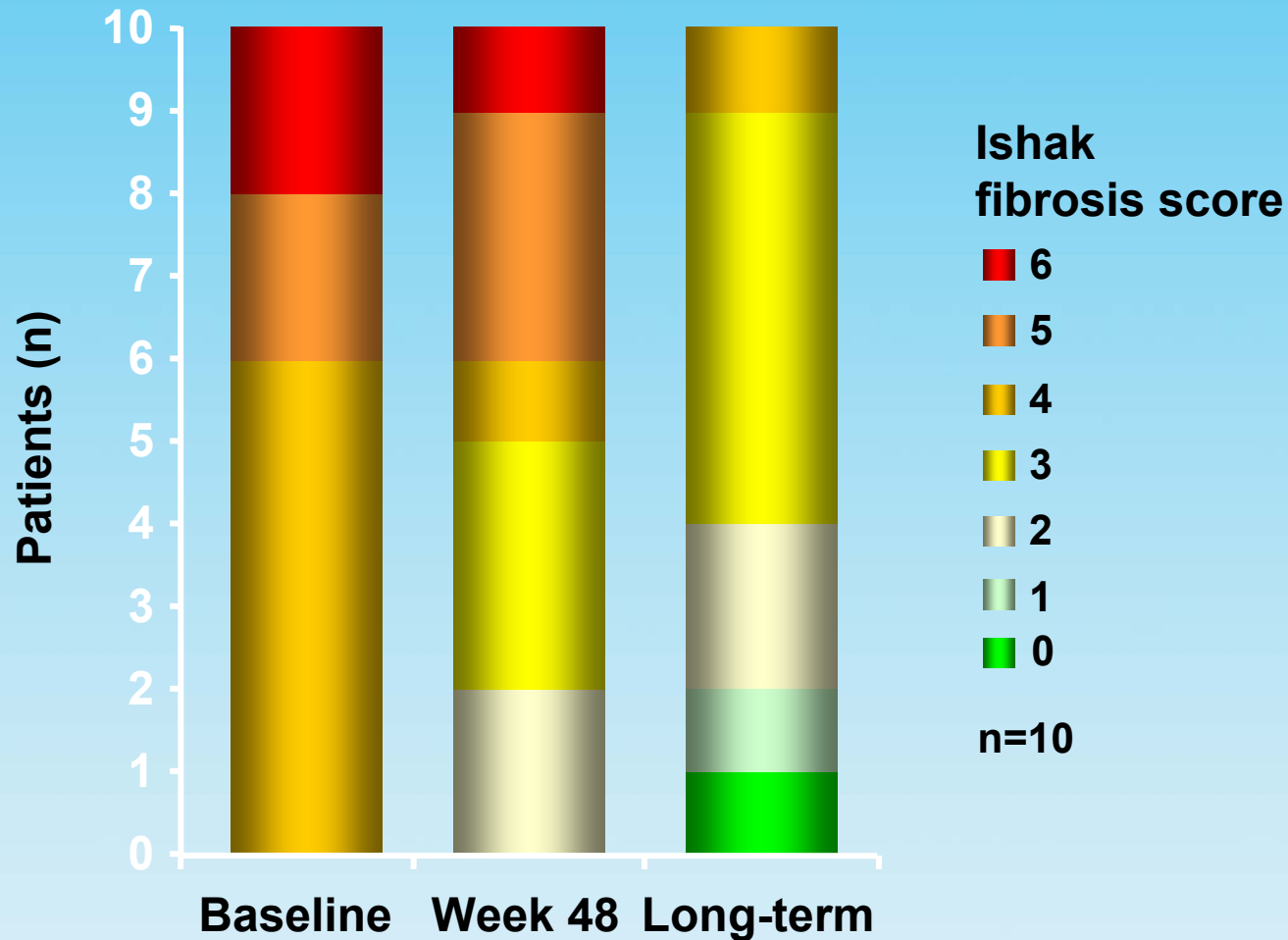


Cancelling necro-inflammation = regression of HBV-related fibrosis



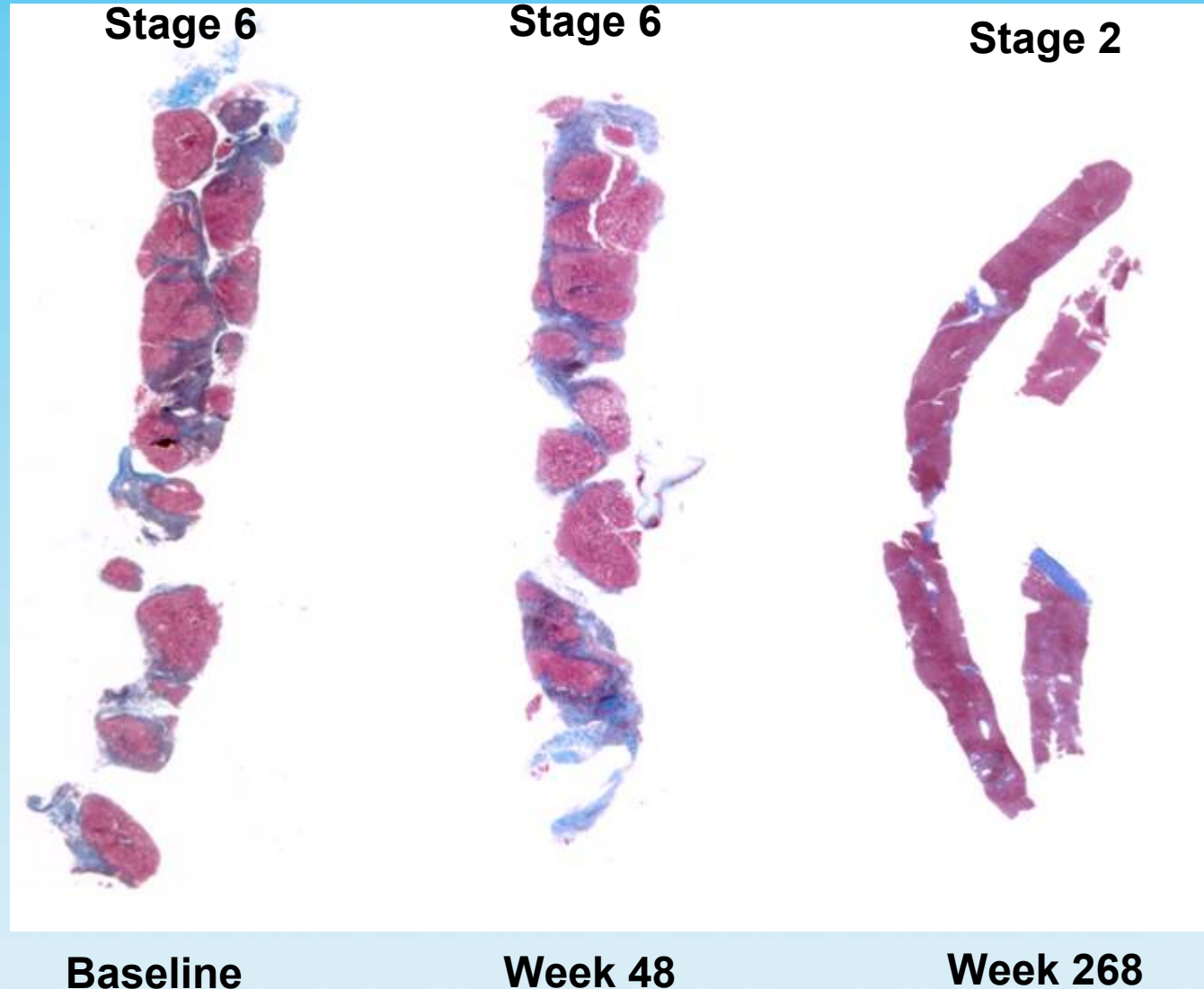
3 / 4 patients with cirrhosis improved by 4 points : regression of cirrhosis
Hadziyannis S et al. Gastroenterology 2006; Marcellin P et al. Hepatology 2008

Histological evidence of HBV-related cirrhosis reversal



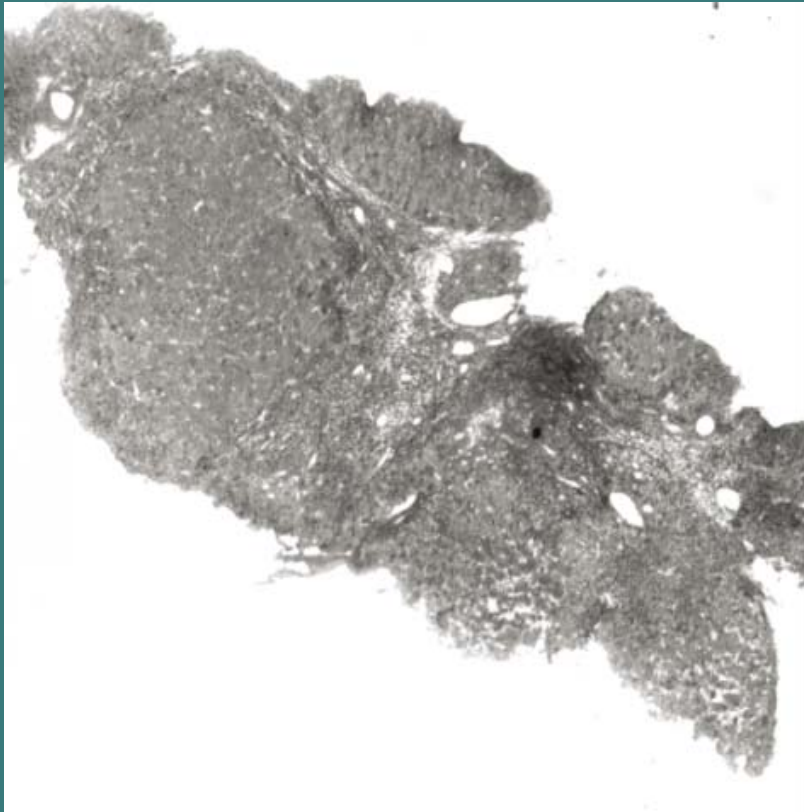
Histological evidence of HBV-related cirrhosis reversal

Masson trichrome stain:
blue is scar tissue

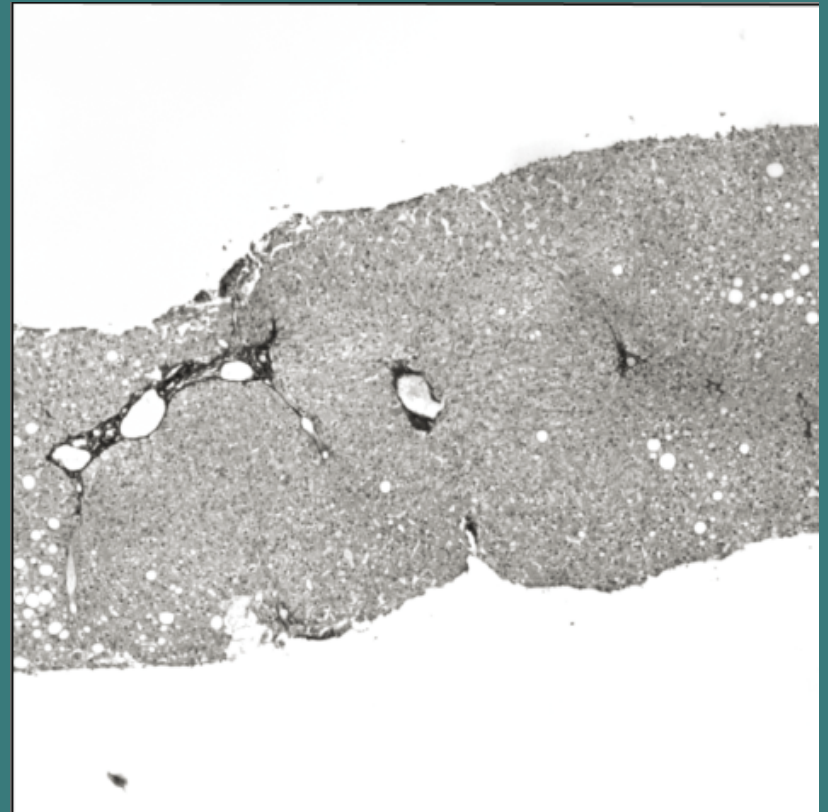


Histological evidence of regression of HIV/HBV-related cirrhosis

A

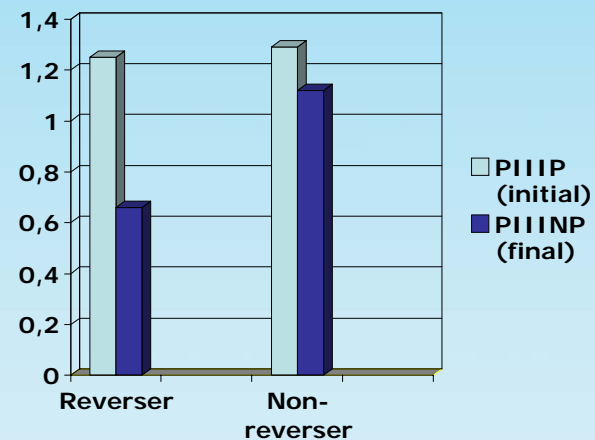
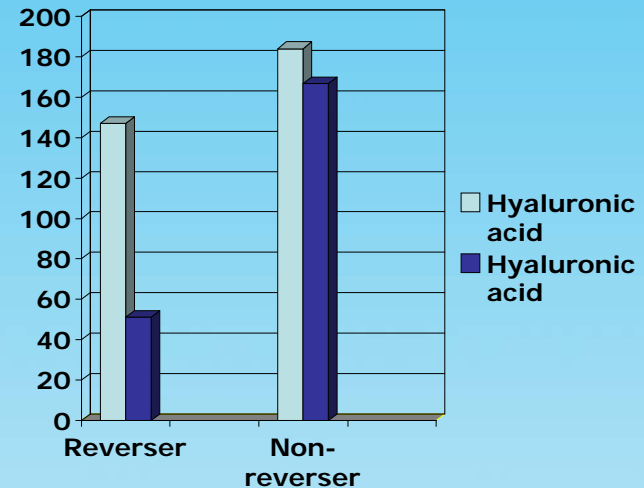


B



Non-histological evidence of cirrhosis reversal

- Significant decrease of portal hypertension
- Regression of biochemical abnormalities
- Cirrhosis regression in two liver-explants



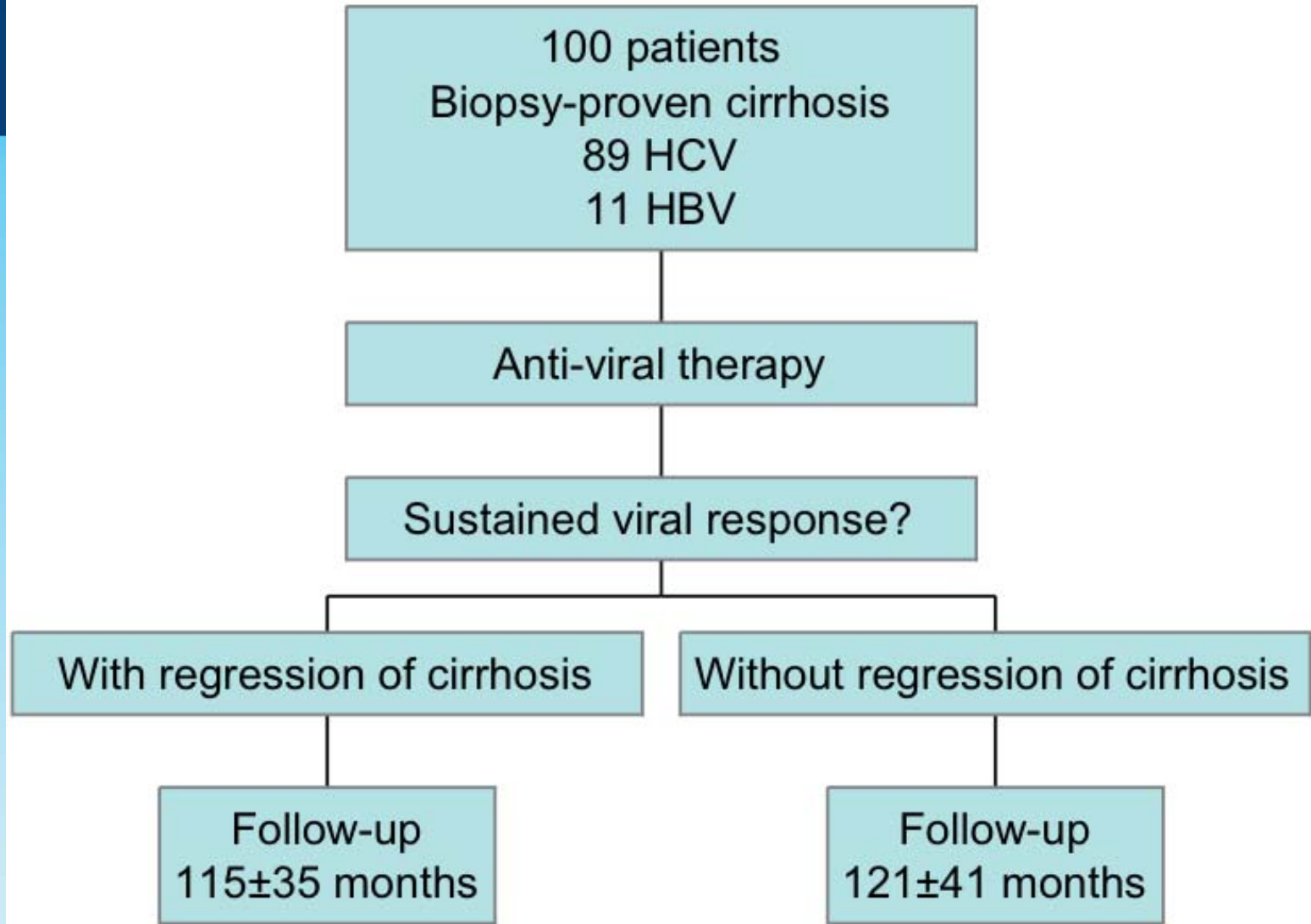
Regression of cirrhosis: the evidence mounts

METAVIR F4 Before treatment	METAVIR \leq F2 on a follow-up liver biopsy	
Shiratory Y et al. 2000	HCV	9/54 patients (17%)
Poynard T et al. 2002	HCV	52/153 patients (34%)
Serpaggi J et al. 2006	HCV, HBV, AIH	14/113 patients (12%)
Hadziyannis S et al. 2007	HBV	14/22 patients (64%)

Regression in the entire spectrum of liver diseases

- Biliary obstruction
 - Hammel P et al. 2001
- Iron overload
 - Murreto P et al. 2002 and Falize L et al. 2006
- Copper overload
 - Pradhan AM et al. 1995
- Non-alcoholic steatohepatitis
 - Kral JG et al. 2004 and Dixon JB et al. 2004
- Autoimmune hepatitis
 - Dufour JF et al. 1997

Clinical impact of cirrhosis reversal



Cirrhosis reversal = fibrosis score below 3

Univariate analysis

Cirrhosis reversal = fibrosis score below 3

	Total N=100	Without regression N=76	With regression N= 24	
BMI	24.6±4.2	25.1±4.3	23±3.3	P=0.05
AST — U/liter	88±56	97±57	62±45	P<0.01
Prothrombin time — percent of normal	86±13	85±13	92±9	P<0.01
Albumin — g/liter	42±4	41±4	44±3.5	P=0.01
Platelets per mm³	161±58	153±49	185±76	P=0.02
Sustained viral response — no. (%)	44	23 (30.2)	21 (87.5)	P<0.01

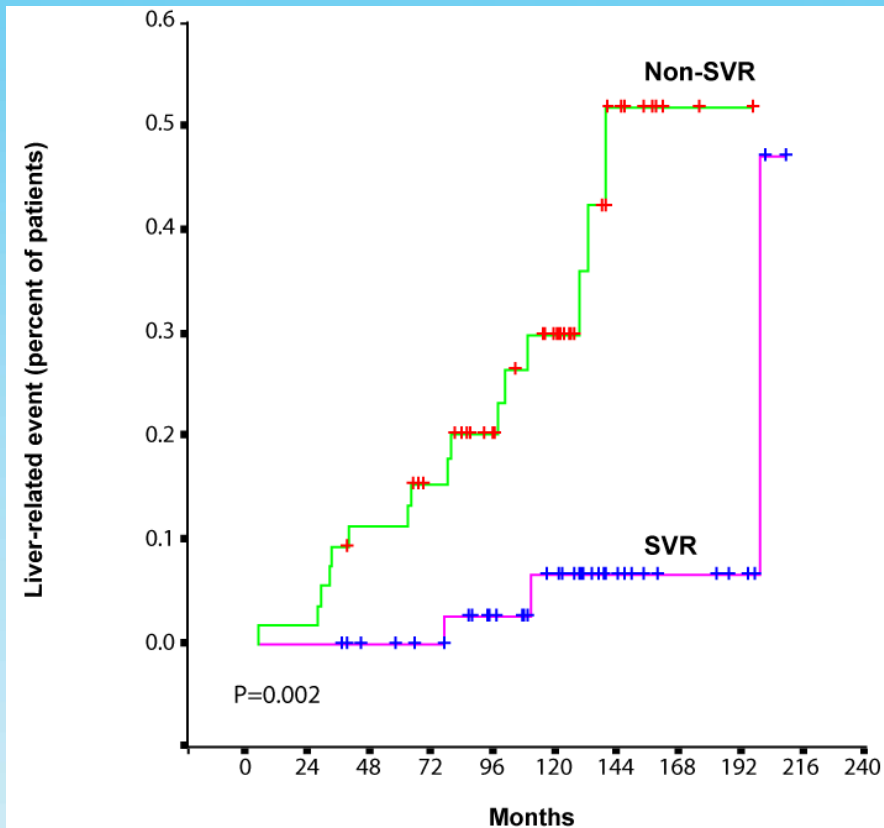
Multivariate analysis

	Total N=100	Without regression N=76	With regression N= 24	
BMI	24.6±4.2	25.1±4.3	23±3.3	
AST — U/liter	88±56	97±57	62±45	
Prothrombin time — percent of normal	86±13	85±13	92±9	OR 1.12 (95 % CI: 1.04-1.22)
Albumin — g/liter	42±4	41±4	44±3.5	
Platelets per mm³	161±58	153±49	185±76	OR 1.01 (95 % CI: 1.00-1.02)
Sustained viral response — no. (%)	44	23 (30.2)	21 (87.5)	OR 35.39 (95 % CI: 6.67-187.90)

Cirrhosis-related events

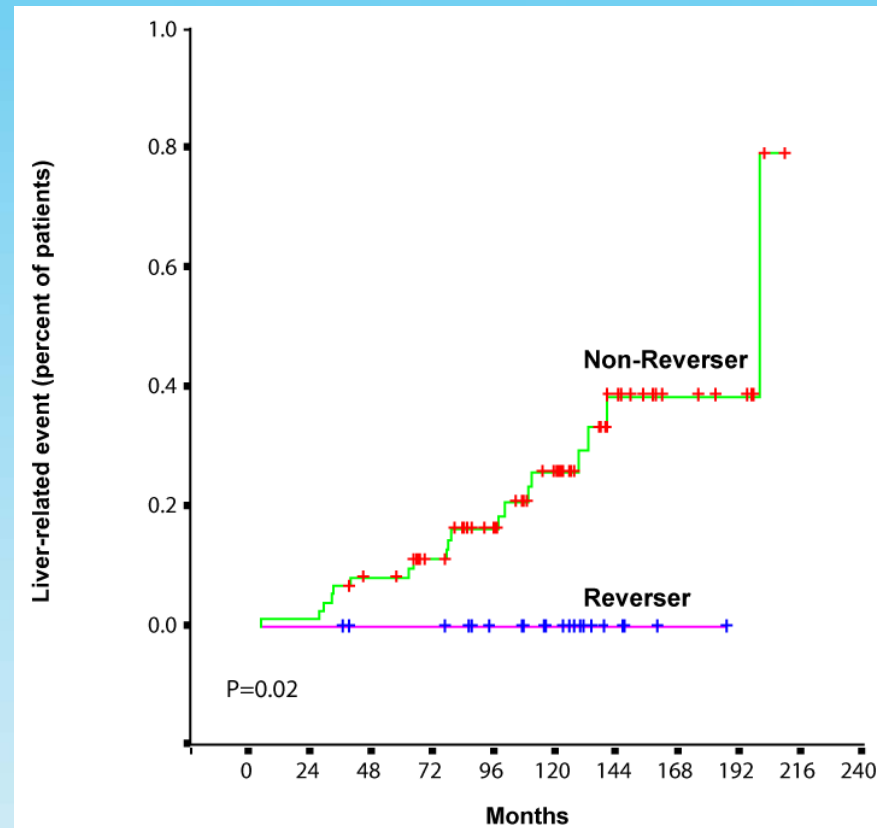
(Bleeding, ascitis, encephalopathy, cancer)

Stratified on viral-response



	0	24	48	72	96	120	144	168	192
Non-SVR	56	55	47	39	31	19	6	2	1
SVR	44	43	40	36	29	19	11	7	3

Stratified on histological response

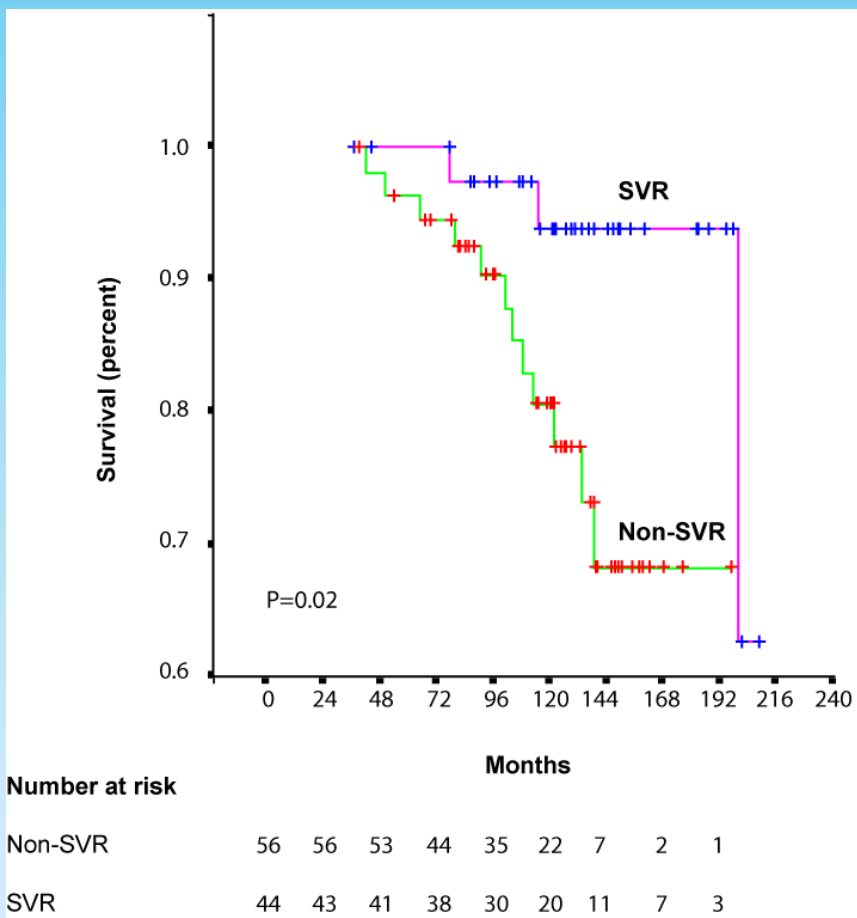


	0	24	48	72	96	120	144	168	192
Non-Reverser	76	74	65	56	44	29	14	8	
Reverser	24	23	22	20	15	9	3	1	

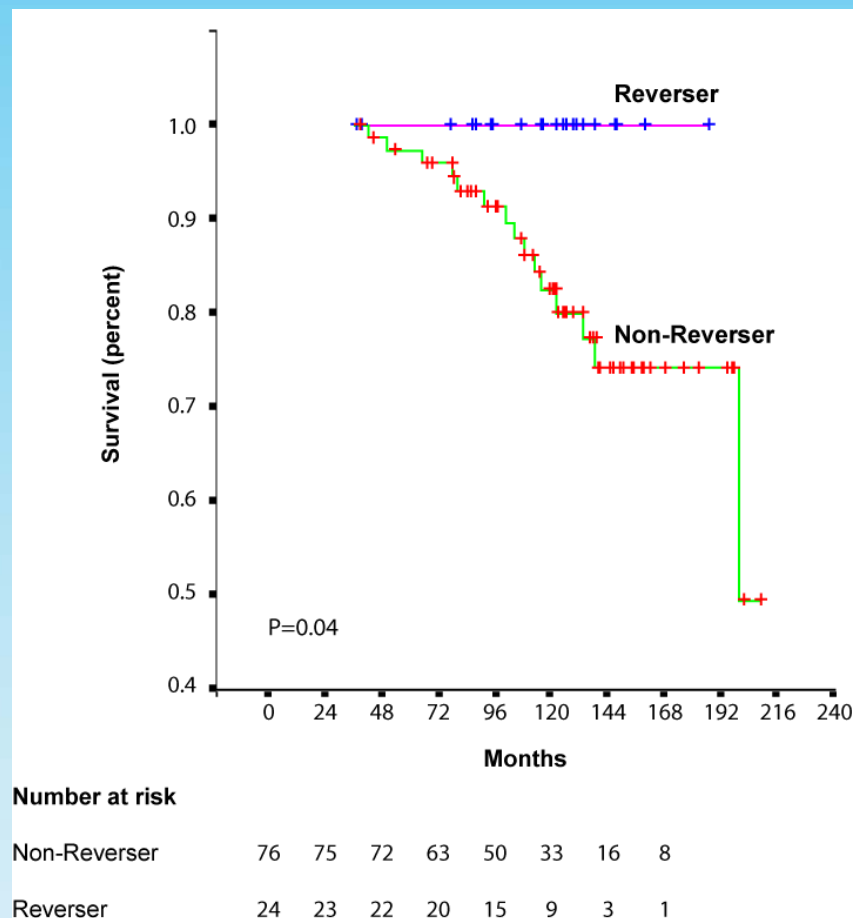
Overall survival

(Death or transplantation)

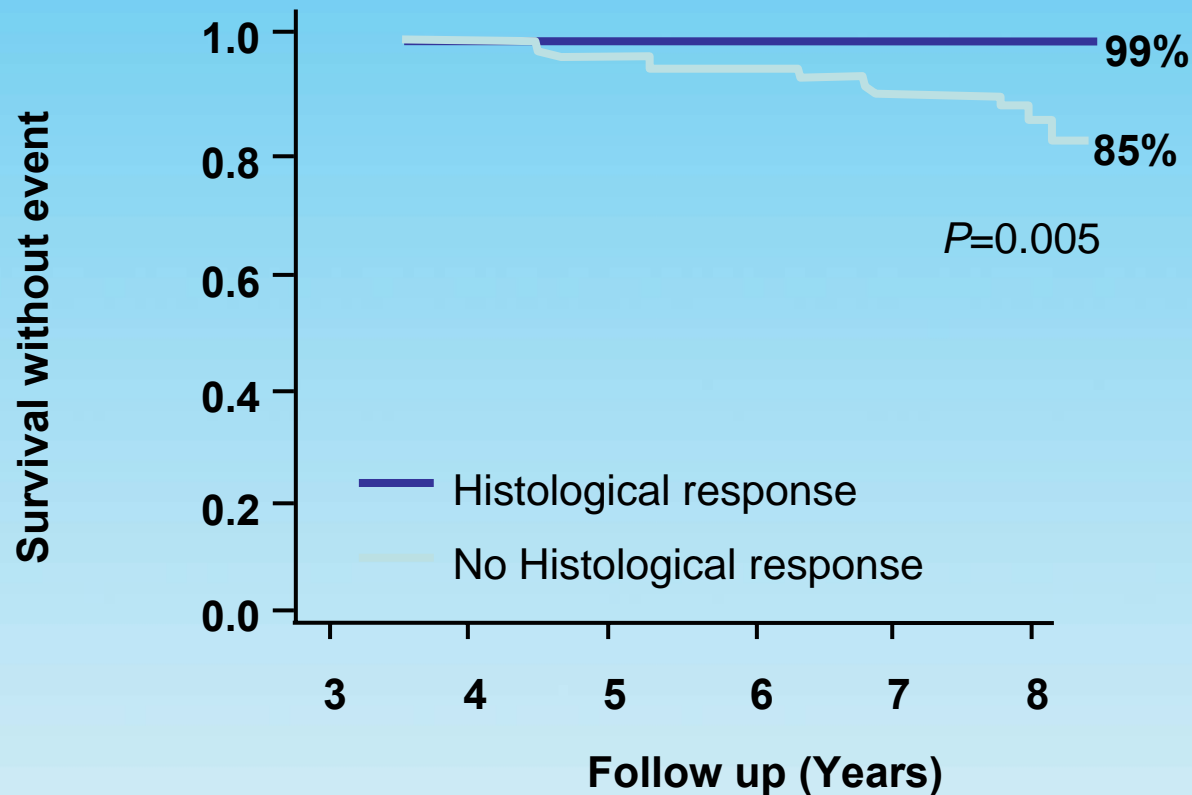
Stratified on viral-response



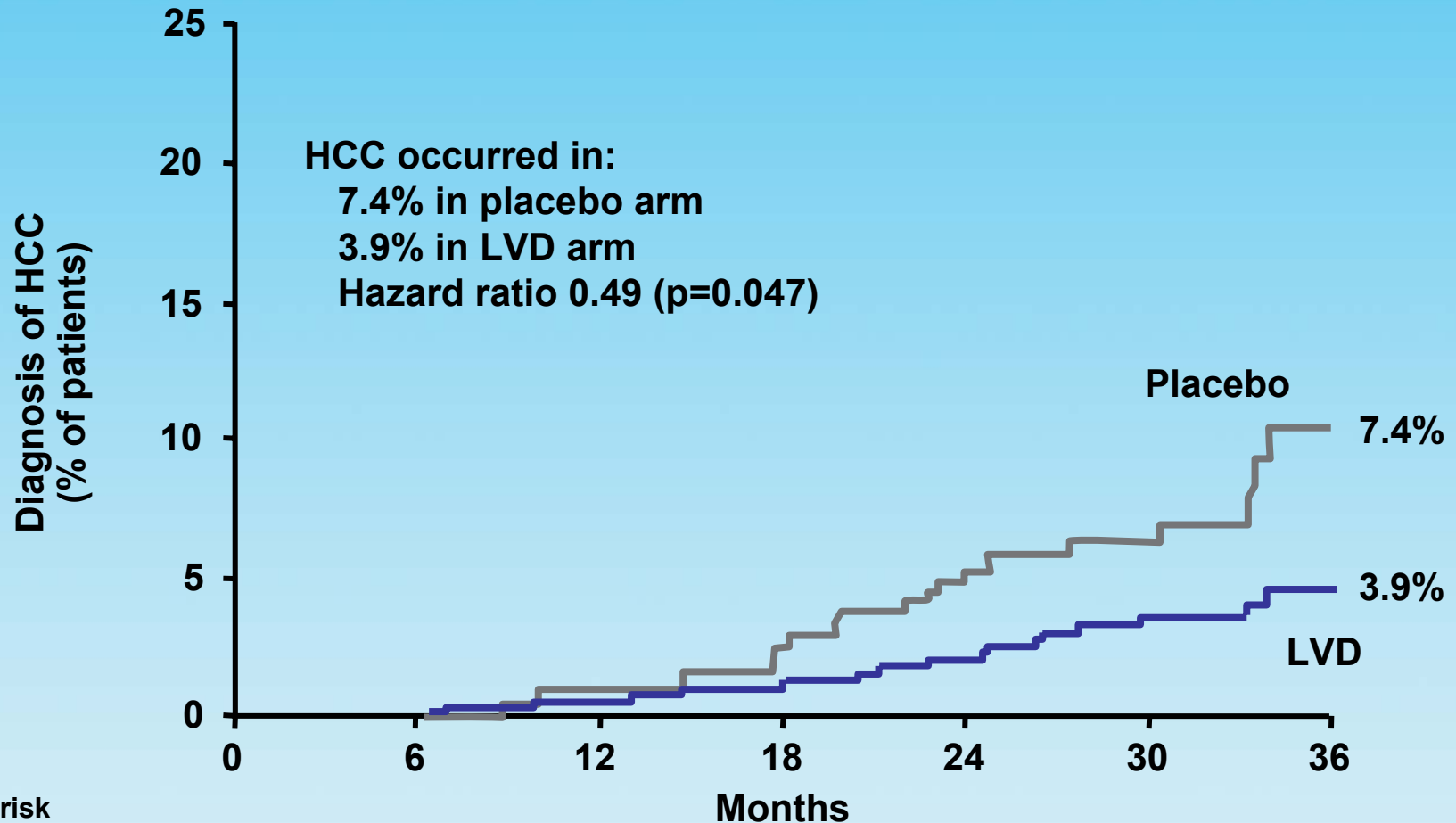
Stratified on histological response



Clinical benefit is associated with the histological response



Antiviral therapy reduced progression to HCC



No. at risk

Placebo

215

209

198

184

173

153

43

LVD

436

429

417

400

385

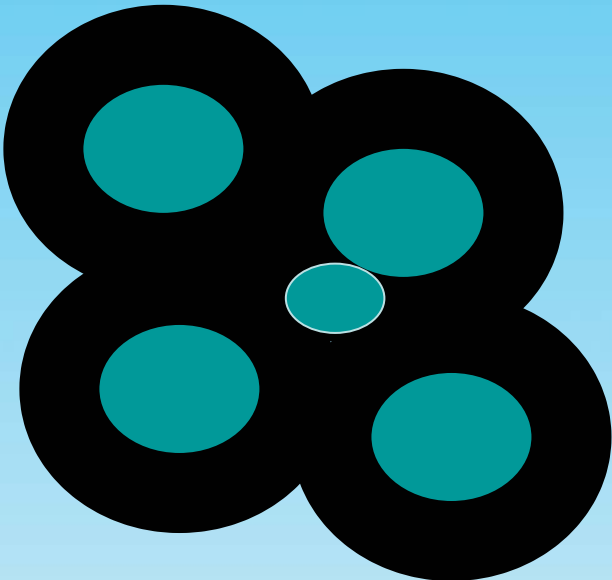
347

122

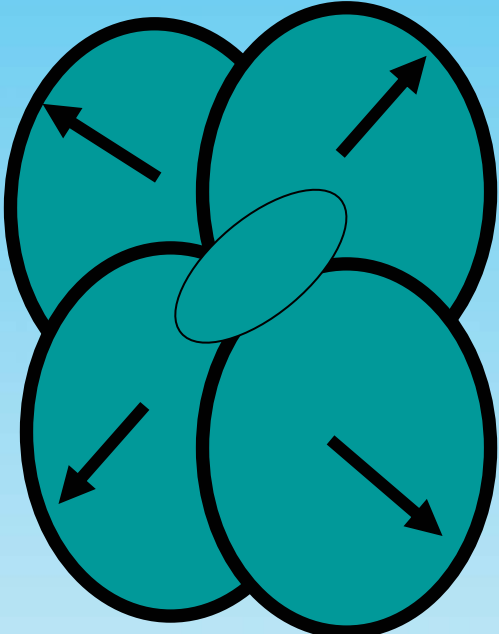
Benefits associated with HBV viral suppression

	Number of HCC		RR	IC 95 %	p
	IFN	PBO			
Total Population	59/1292	131/1450	0.66	0.48-0.89	0.006
Cirrhotics	28/241	102/475	0.51	0.35-0.74	0.001
	Analogues	PBO			
Total Population	31/1125	117/898	0.22	0.09-0.53	0.0008
Cirrhotics	17/436	71/317	0.17	0.04-0.79	0.02
Non cirrhotics	9/488	31/386	0.21	0.10-0.47	0.0001
Without resistance	9/313	31/410	0.36	0.17-0.77	0.009
HBe Ag+	9/445	34/344	0.20	0.09-0.45	< 0.0001

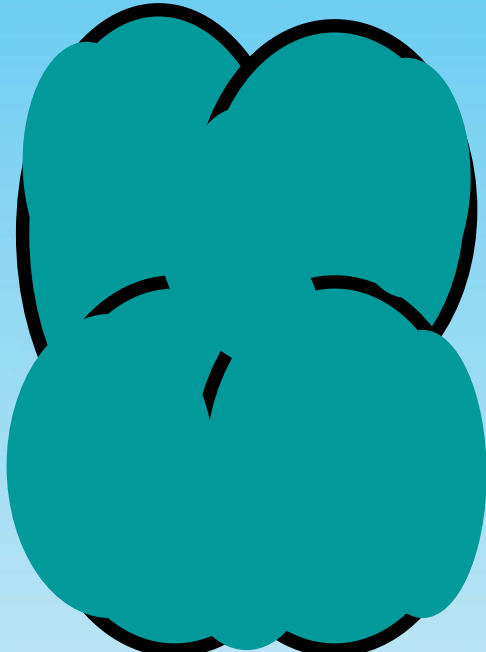
Pathobiology of cirrhosis reversal



Micronodular
cirrhosis



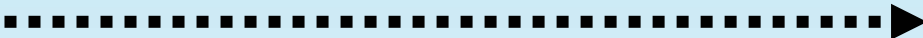
Macronodular
cirrhosis



Incomplete
septal
cirrhosis



Insulting agent

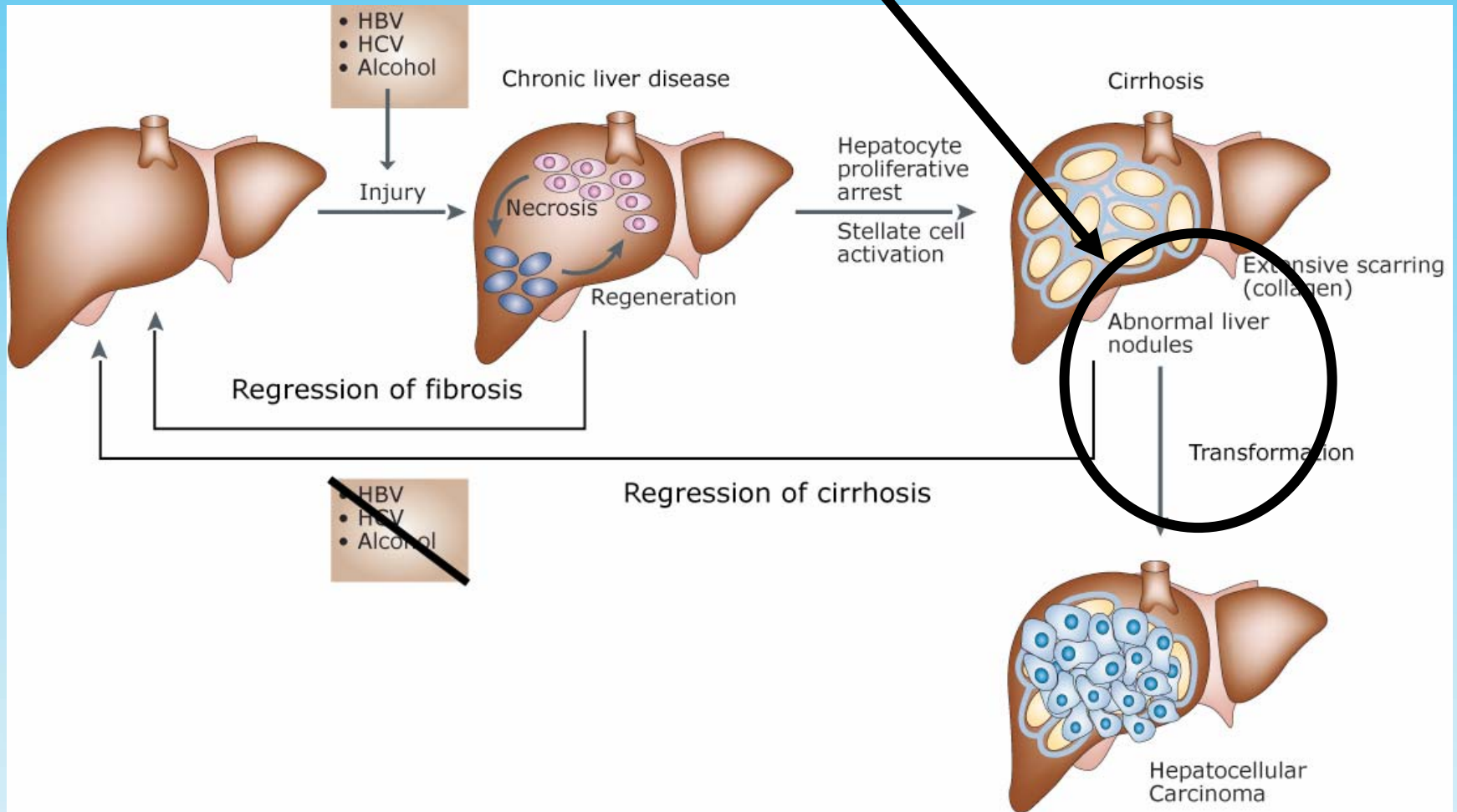


Regeneration

Is there a check-point to irreversibility?

- “all experimental models of cirrhosis are reversible providing that the inciting agent is discontinued and sufficient time is allowed. . .”
 - Perez-Tamayo R. 1979
- “increased reticulum fibers are more easily resorbed than thick collagenous bundles.”
 - Perez-Tamayo R. 1979

Is there a check-point to irreversibility?



Conclusions

- Regression happens, at least in early cirrhosis
 - Pathological, biochemical, morphological, clinical evidences
- Regression = No liver-related morbidity and mortality
- Viral response without regression = persistent risk of liver-related events (cancer)

Aknowledgements

- Hélène Gilgenkrantz,
INSERM U-567
- Vincent Mallet, Jeanne Serpaggi,
Anaïs Vallet-Pichard, Hélène Fontaine,
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