Cirrhosis reversibility
Who and Why ?

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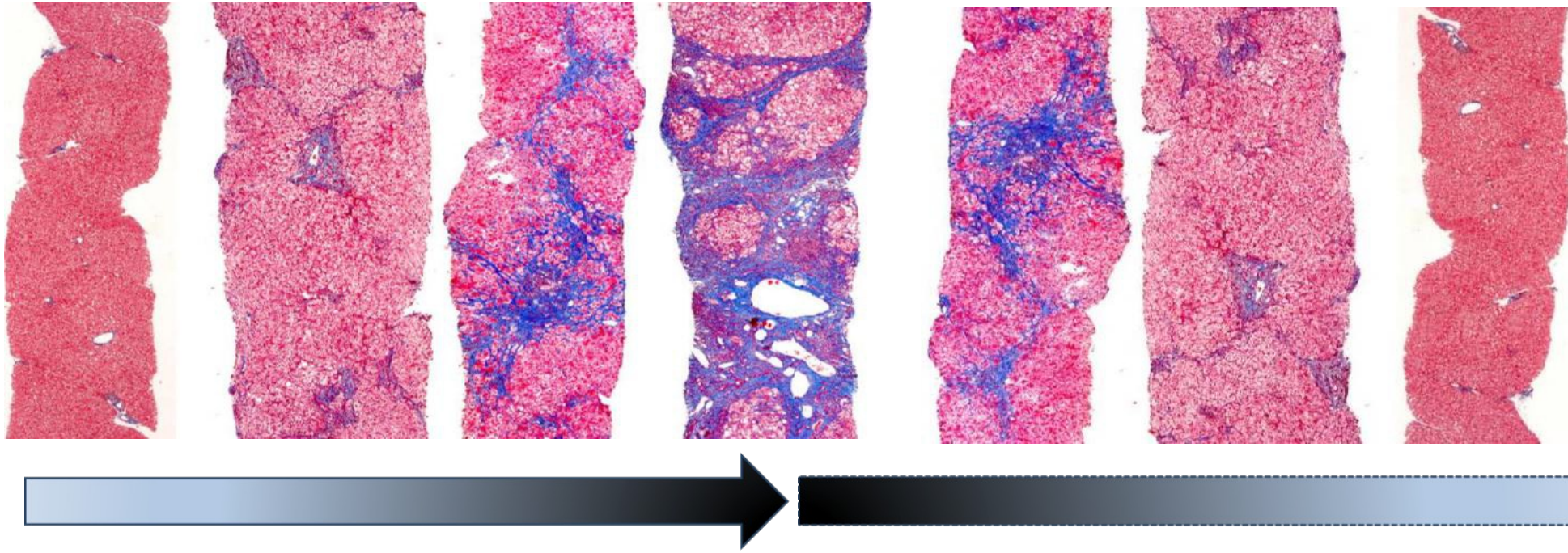
Fibrosis in Chronic Viral Hepatitis B



- F0: lobular organisation, no fibrous tissue
- F1-F3: fibrosis (periportal, then bridging)
- F4: Cirrhosis = annular fibrosis + architectural remodeling (lobule → nodule)

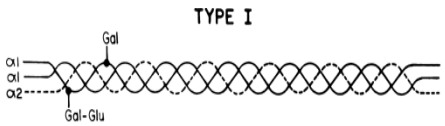
CIRRHOSIS REVERSION // REGRESSION

F4 ⟶ F3, F2 or F1

(nodule → lobule)

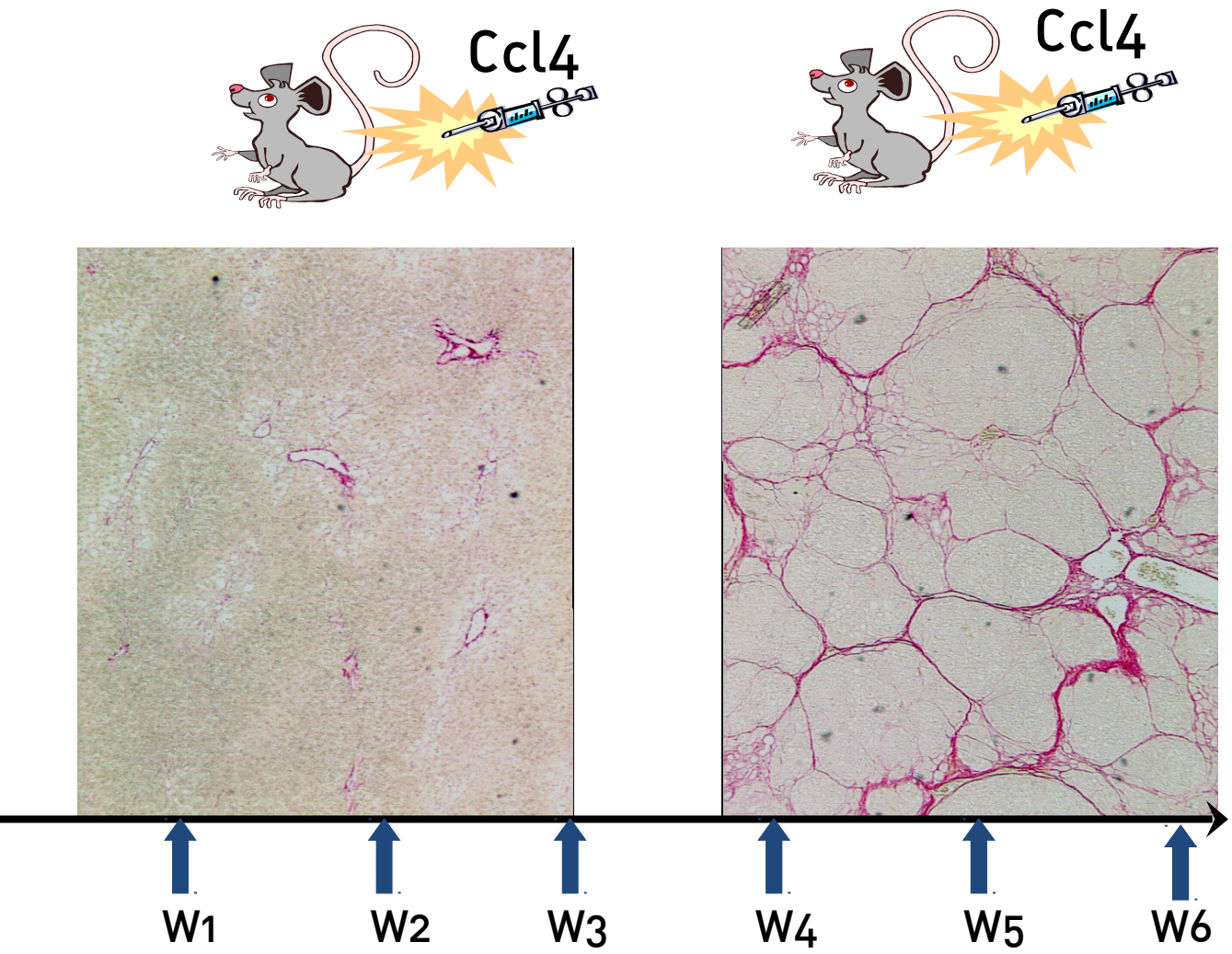
1. Degradation of fibrous tissue
2. Replacement by hepatocyte (regeneration)
3. Restoration of a lobular vascularisation

3-Dimensional organisation of fibrous tissue



Reversion of cirrhosis in animal models

- Cirrhosis of the liver: a reversible disease ? Perez-Tamayo R: Pathol Annu 1979;14:183-213
- Reversibility of hepatic fibrosis in experimentally induced cholestasis in rat. Abdel-Aziz G, et al. Am J Pathol 1990;137:1333–42



Reversibility of liver cirrhosis

Evidences from clinical trials in viral hepatitis

→ Histologically-proven with repeated biopsies

→ Adequate time interval between repeated biopsies

→ Large sample size (sampling error)

Cirrhosis regression after antiviral treatment

Impact of Pegylated Interferon Alfa-2b and Ribavirin on Liver Fibrosis in Patients With Chronic Hepatitis C

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GASTROENTEROLOGY 2002;122:1303–1313

See editorial on page 1525.

Background & Aims: **Liver fibrosis is an important prognostic factor in patients with hepatitis C. The effect of pegylated (PEG) interferon alone or its combination with ribavirin on fibrosis has not been established.** ***Methods:*** **We pooled individual data from 3010 naive patients with pretreatment and posttreatment biopsies from 4 randomized trials. Ten different regimens combining standard interferon, PEG interferon, and ribavirin were compared. The impact of each regimen was estimated by the percentage of patients with at least 1 grade improvement in the necrosis and inflammation (METAVIR score), the percentage of patients with at least 1 stage worsening in fibrosis METAVIR score, and by the fibrosis progression rate per year.** ***Results:*** **Necrosis and inflammation improvement ranged from 39% (interferon 24 weeks) to 73% (optimized PEG 1.5 and ribavirin; $P < 0.001$). Fibrosis worsening ranges from 23% (interferon 24 weeks) to 8% (optimized PEG 1.5 and ribavirin; $P < 0.001$). All regimens significantly reduced the fibrosis progression rates in comparison to rates before treatment. The reversal of cirrhosis was observed in 75 patients (49%) of 153 patients with baseline cirrhosis. Six factors were independently associated with the absence of significant fibrosis after treatment: baseline fibrosis stage (odds [OR] = 0.12; $P <$ 0.0001), sustained viral res OR = 0.36; $P <$

atitis C involves the gradual progression of hepatic fibrosis that can eventually lead to cirrhosis. Most of the complications related to chronic infection occurs in patients who have established cirrhosis.[3–5] Treatments that could halt or diminish the progression of fibrosis would theoretically be beneficial.[6]

We have previously reported that the combination regimen of interferon and ribavirin slows progression of liver fibrosis and even leads to regression in a proportion of patients. The impact on fibrosis was related both to the response to therapy and the duration of interferon treatment.[7]

Recently, it has been shown that the pegylated form of interferon (PEG-interferon) has a significantly higher efficacy in achieving sustained response in comparison to standard interferon. This greater efficacy has been observed both for monotherapy[8–10] or in combination with ribavirin.[11] The effect of these new regimens on histological changes has not been well characterized.[8–11]

The aim of this study was to compare the efficacy of these different regimens (PEG-interferon alone or in combination with ribavirin) on fibrosis progression and on the necrosis and inflammatory features and to identify risk factors for these changes. This analysis was undertaken to determine the impact of therapy in patients who eradicate the virus, and also in patients who do not

The reversal of cirrhosis was observed in 75 patients (49%) of 153 patients with baseline cirrhosis

Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study

Patrick Marcellin, Edward Gane, Maria Buti, Nezam Afdhal, William Sievert, Ira M Jacobson, Mary Kay Washington, George Germanidis, John F Flaherty, Raul Aguilar Schall, Jeffrey D Bornstein, Kathryn M Kitrinos, G Mani Subramanian, John G McHutchison, E Jenny Heathcote

Lancet 2013; 381: 468–75
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See Comment page 433

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Summary

Background Whether long-term suppression of replication of hepatitis B virus (HBV) has any beneficial effect on regression of advanced liver fibrosis associated with chronic HBV infection remains unclear. We aimed to assess the effects on fibrosis and cirrhosis of at least 5 years' treatment with tenofovir disoproxil fumarate (DF) in chronic HBV infection.

Methods After 48 weeks of randomised double-blind comparison (trials NCT00117676 and NCT00116805) of tenofovir DF with adefovir dipivoxil, participants (positive or negative for HBeAg) were eligible to enter a 7-year study of open-label tenofovir DF treatment, with a pre-specified repeat liver biopsy at week 240. We assessed histological improvement (≥2 point reduction in Knodell necroinflammatory score with no worsening of fibrosis) and regression of fibrosis (≥1 unit decrease by Ishak scoring system).

Findings Of 641 patients who received randomised treatment, 585 (91%) entered the open-label phase, and 489 (76%) completed 240 weeks. 348 patients (54%) had biopsy results at both baseline and week 240. 304 (87%) of the 348 had histological improvement, and 176 (51%) had regression of fibrosis at week 240 ($p<0·0001$). Of the 96 (28%) patients with cirrhosis (Ishak score 5 or 6) at baseline, 71 (74%) no longer had cirrhosis (≥1-unit decrease in score), whereas three of 252 patients without cirrhosis at baseline progressed to cirrhosis at year 5 ($p<0·0001$). Vi logical breakthrough occurred infrequently and was not due to resistance to tenofovir DF. The safety profile w favourable: 91 (16%) patients had adverse events but only nine patients had serious events related to the study dr

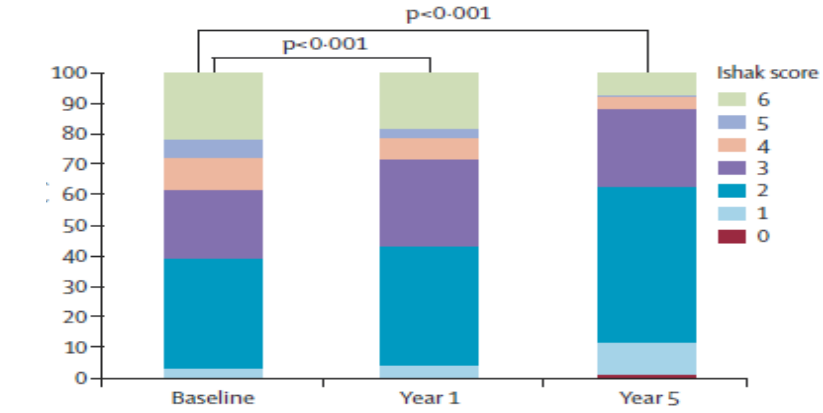
Interpretation In patients with chronic HBV infection, up to 5 years of treatment with t DF was safe and effective. Long-term suppression of HBV can lead to regression of fibrosis and cirrhosis.

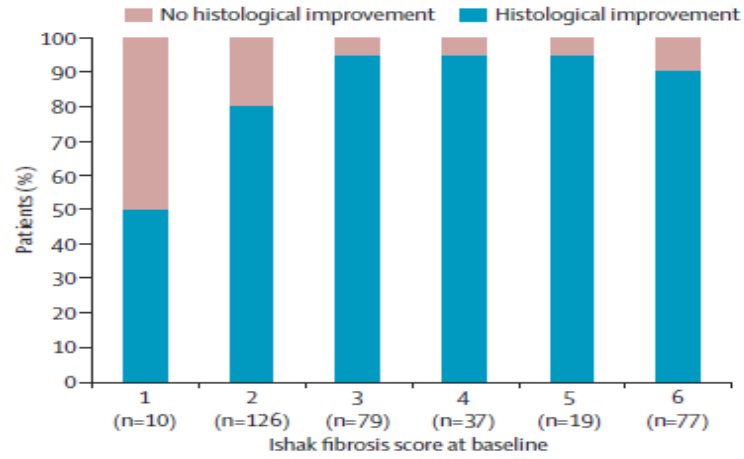
Of the 96 (28%) patients with cirrhosis (Ishak score 5 or 6) at baseline, 71 **(74%)** no longer had cirrhosis

Histological outcome in Hep B after long-term tenofovir treatment

- 348 patients with paired biopsies before and after 5 years treatment with tenofovir DF
- 51% (176/348) of patients had fibrosis regression (↘1 unit ↘ in Ishak score) and 96% had prevention of fibrosis progression
- Cirrhosis (Ishak ↘5) regression occurred in 71/96 of patients (74%) with cirrhosis at baseline

Long-term suppression of HBV can lead to regression of fibrosis and cirrhosis





Marcellin P, *et al*. Lancet 2013

Main clinical trials in HBV with histological follow-up

Reference	Virus	Number of patients enrolled	Therapy	Time to biopsy	Fibrosis regression (%)	Cirrhosis regression % (Regression / cirrhosis at baseline)
Dienstag (2003)	HBV	63	LMV	3 yrs	67 %	**73 % (8/11)**
Hadziyannis (2006)	HBV	185	ADF	5 yrs	71 %	**75 % (7/12)**
Marcellin (2008)	HBV	171	ADF	5yrs	60%	**NA**
Schiff (2011)	HBV	10	ETV	5yrs	NA	**100% (4/4)**
Chang (2010)	HBV	69	ETV	3 yrs	88 %	**100 % (10/10)**
Marcellin (2013)	HBV	348	TFV	5 yrs	51 %	**74 % (71/96)**

75-100% of cirrhosis may regress but :

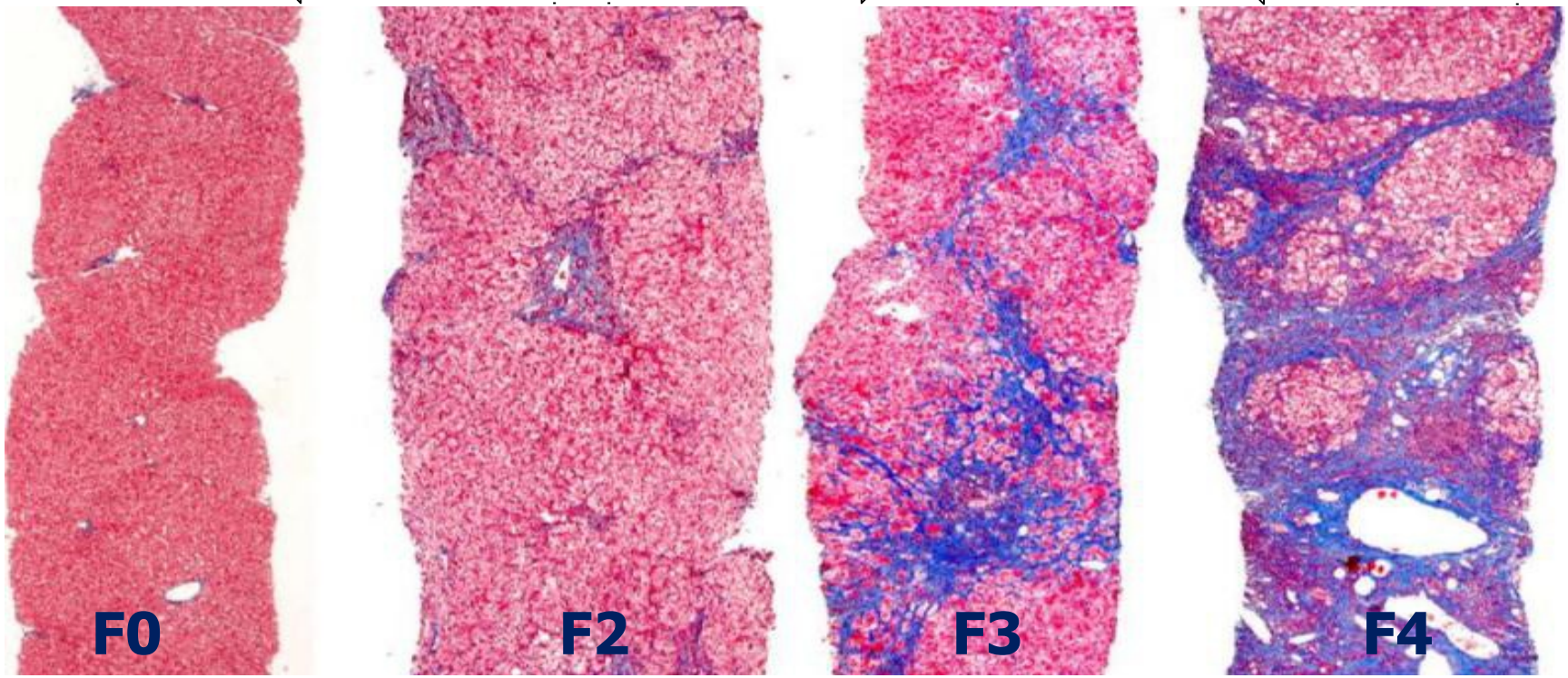
- Small sample size (except TFV study)
- Biais of selection : compensated cirrhosis
- % of cirrhosis regression ↑ % of fibrosis regression ??

The influence of sampling error in evaluation of cirrhosis regression

Sampling error Improvement

Worsening

Sampling error Improvement



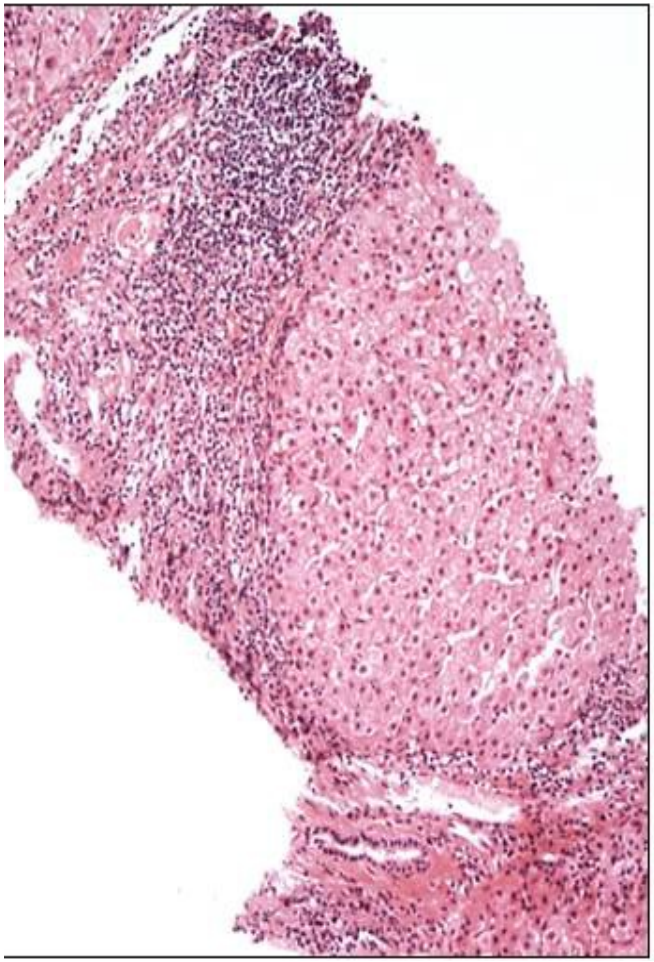
Overestimation of cirrhosis regression because of sampling error

Reversibility of cirrhosis : pending questions

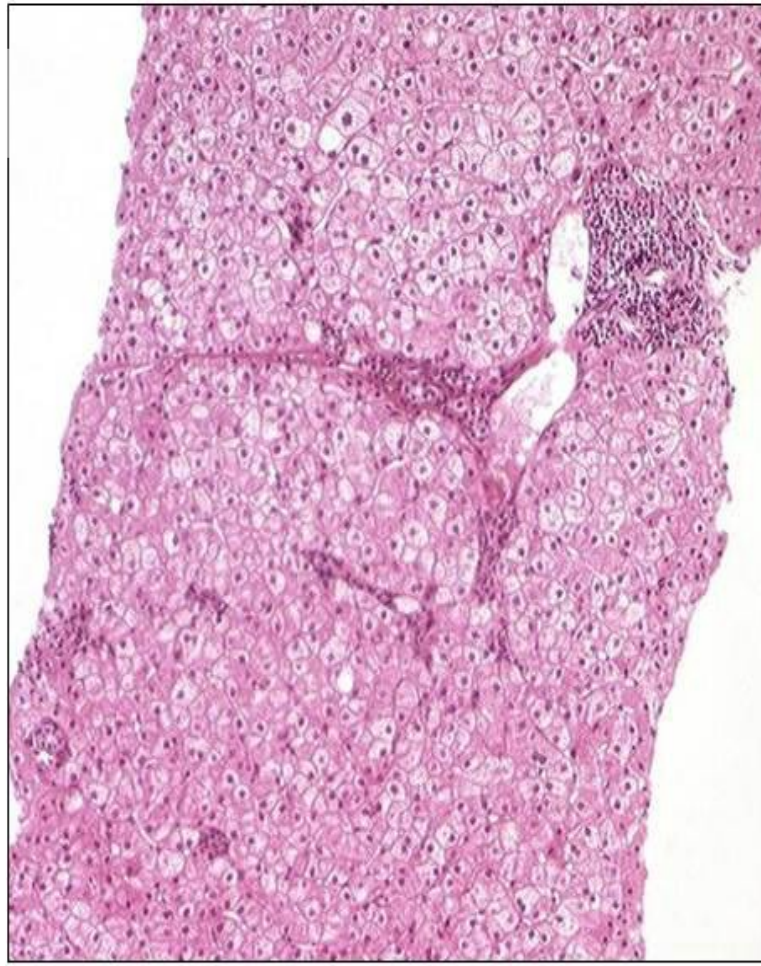
1. Which cirrhosis may reverse ?
2. How to assess fibrosis/cirrhosis reversion ?
3. What is the risk of HCC after HBV cirrhosis reversion ?

CIRRHOSIS : REGRESSION AFTER ANTIVIRAL TREATMENT

Before treatment
cirrhosis



6 years after SVR
«normal» organisation



D'Ambrosio R, Aghemo A, Rumi MG, Ronchi G, Donato MF, Paradis V, Colombo M, Bedossa P. A morphometric and immunohistochemical study to assess the benefit of a sustained virological response in hepatitis C virus patients with cirrhosis. Hepatology. 2012 Aug;56(2):532-43.

1 - Which cirrhosis are reversible ?

1. **Thinning of fibrous septa :**
   - Enzymatic degradation of fibrous tissue (metalloproteases, MMP)
   - Collagen cross-links and elastin fibers (old cirrhosis) more resistant to MMP degradation

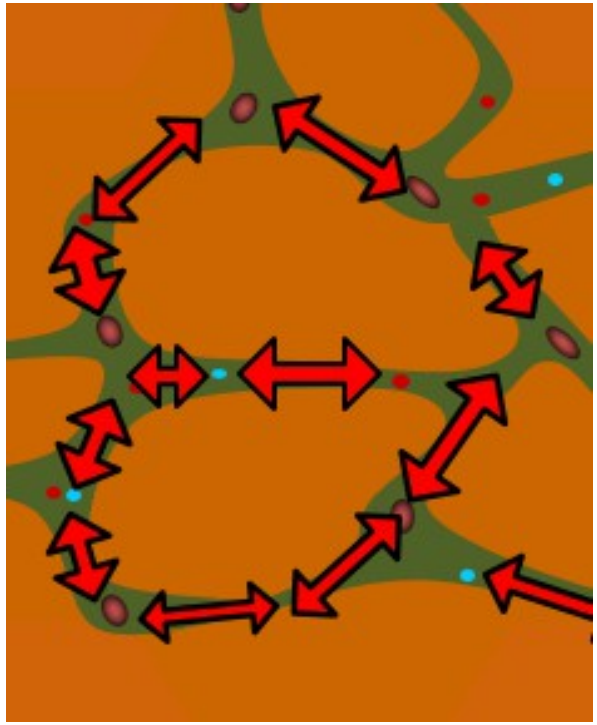
     → « early » cirrhosis more suitable for degradation

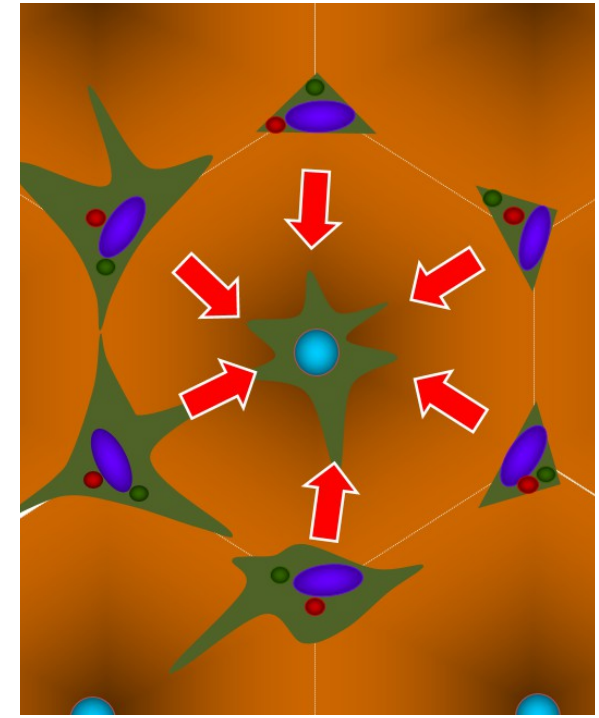
1. **Hepatic regeneration:**
   1. Halting inflammatory reaction

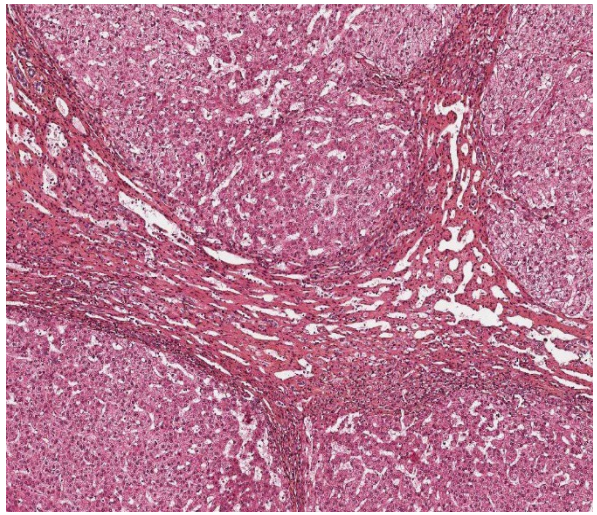
      → Sustained Viral elimination
   2. Internal regenerative potential is variable

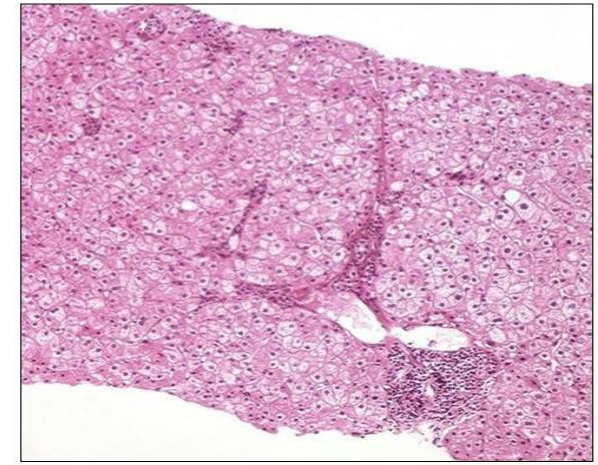
      → role of aging ? (major telomere shortening)

1. **From nodular to lobular architecture:**
   - Restoration of a trans-lobular blood stream from portal tract to central veins

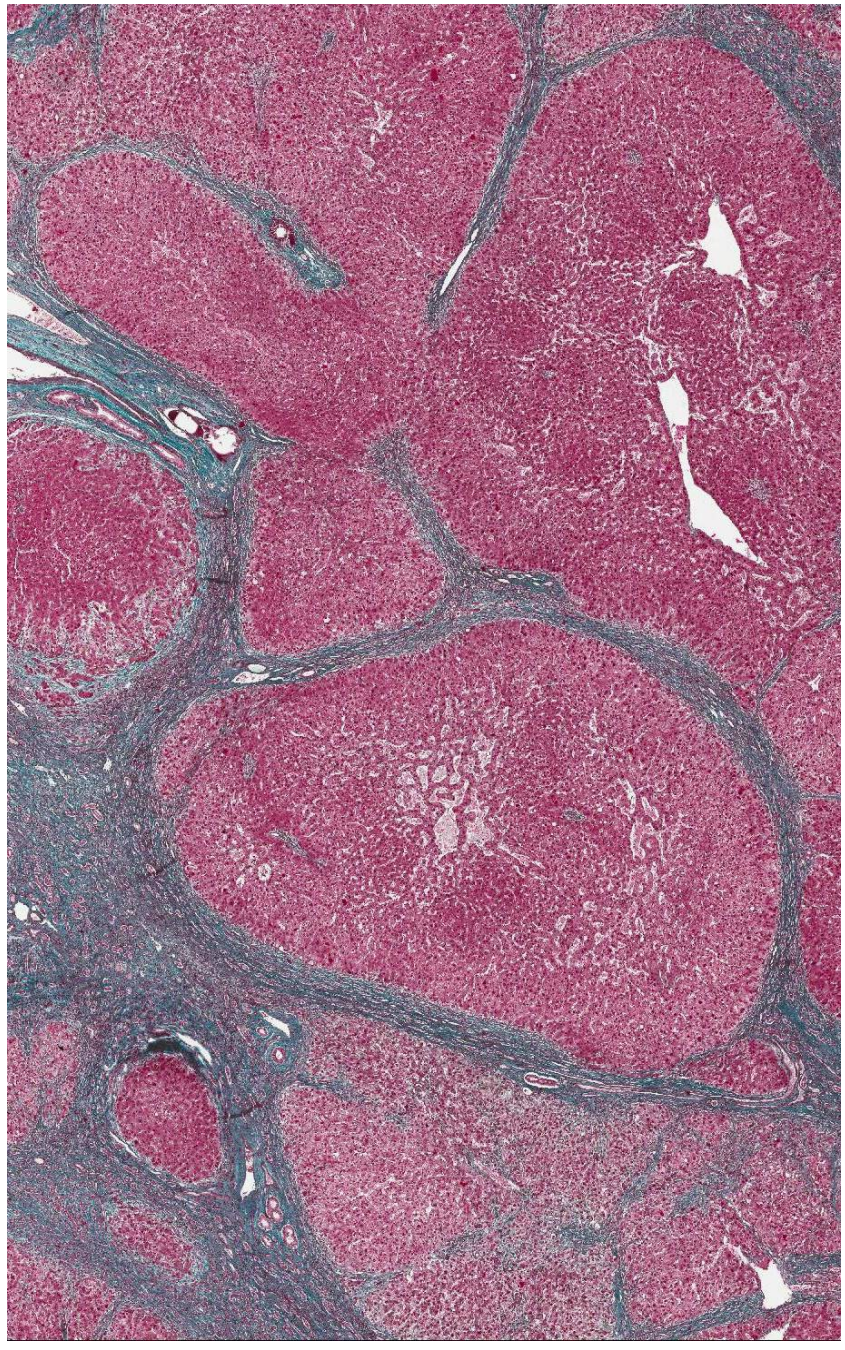




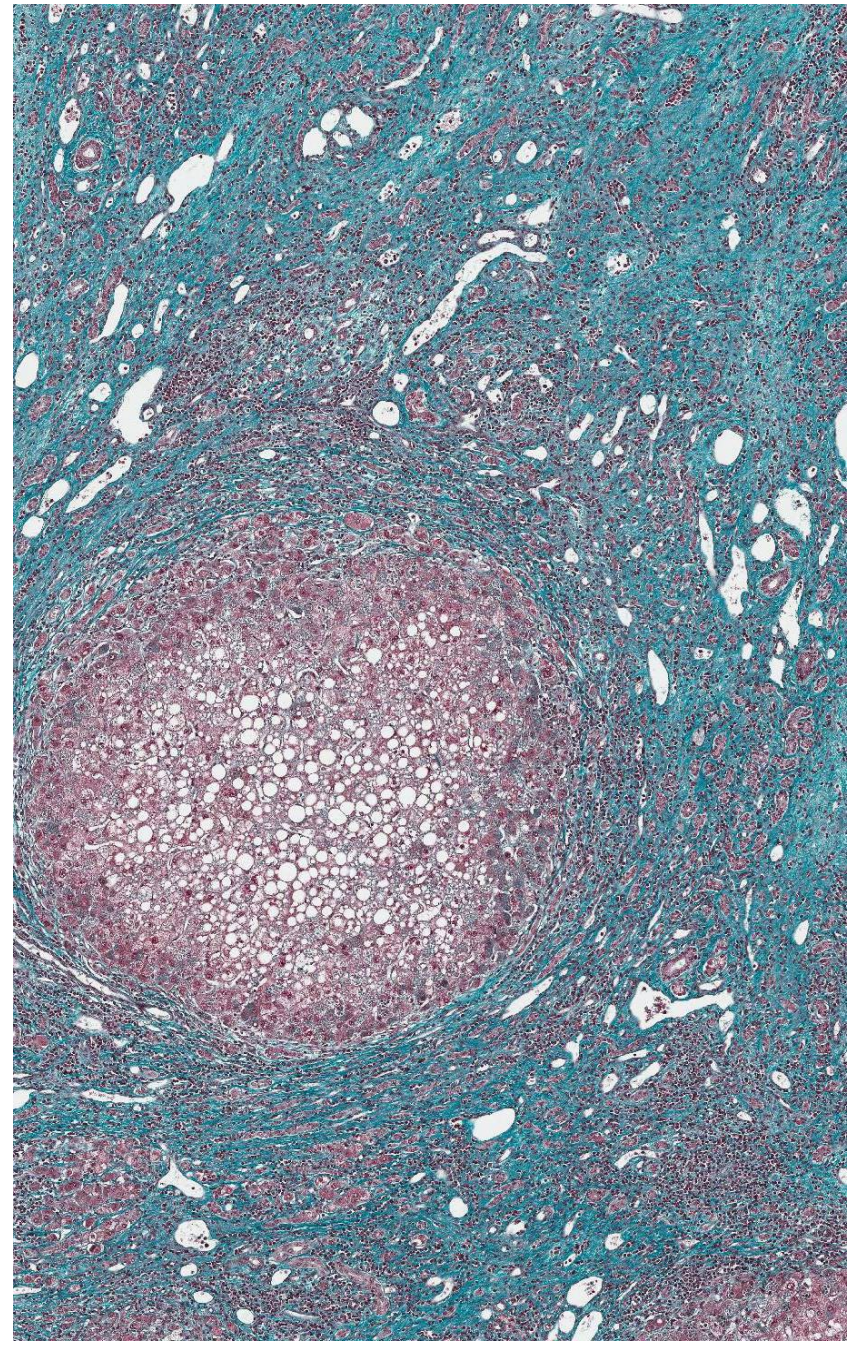




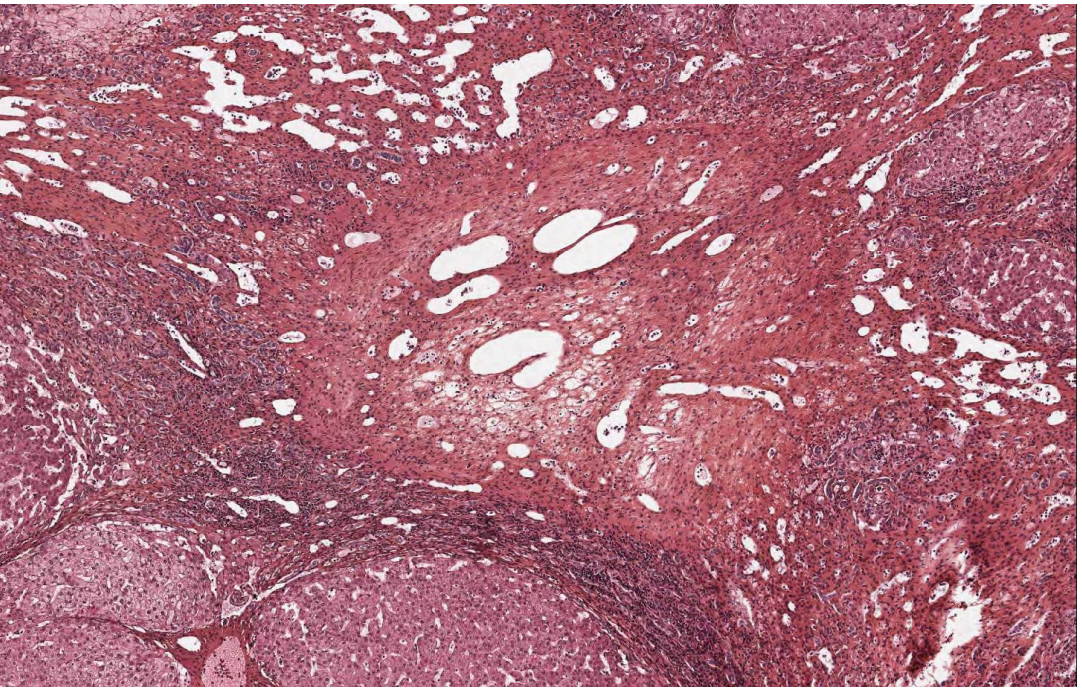
REVERSIBLE CIRRHOSIS



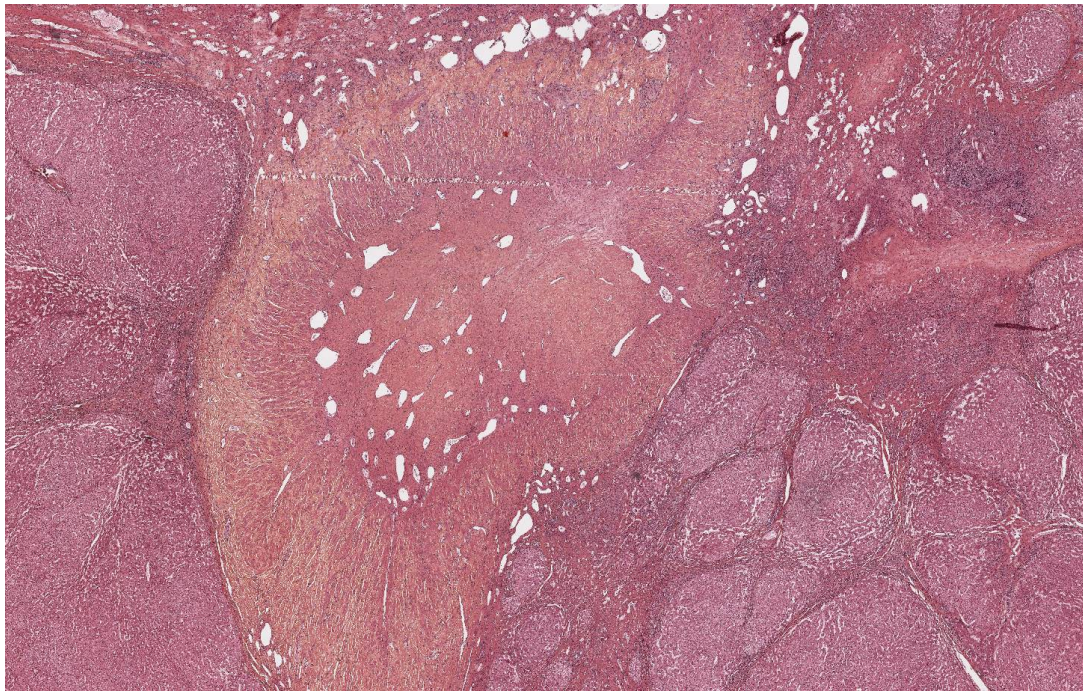
IRREVERSIBLE CIRRHOSIS



VASCULAR THROMBOSIS IN CIRRHOSIS



Portal Thrombosis



Central Vein Thrombosis

WHICH CIRRHOSIS MAY REGRESS ?

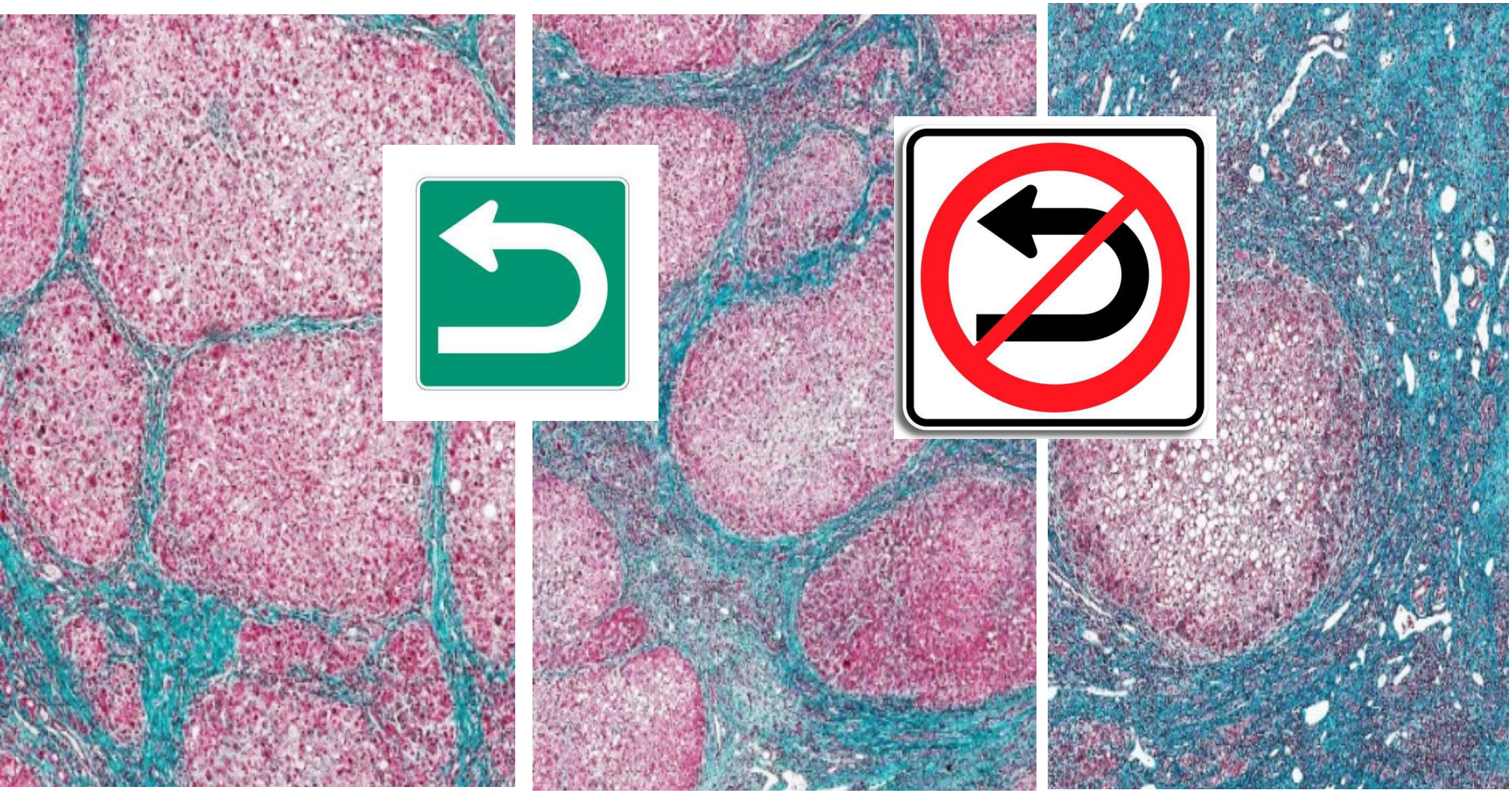
Necessary Mechanisms for regression	Physiopathology Molecular mechanisms	POTENTIAL REVERSION IF:
1. **Thinning of fibrous septa**	Enzymatic degradation	**EARLY CIRRHOSIS**
2. **Hepatocyte regeneration**	Halting inflammation	**CONTROL OF ETIOLOGY ANTIVIRAL DRUGS**
	Internal capacity to regenerate	**YOUNG PATIENT**
3. **Restoration of lobular architecture**	Persistent permeable portal and central veins	**NO VASCULAR THROMBOSIS**
4. **Others**		

Altogether, only a limited (?) percentage of cirrhosis may reverse

All Cirrhosis are not alike : a disease with a wide spectrum

The Laennec staging system of cirrrhosis

F4a **F4b** **F4c**



SU Kim, et al. The Laennec staging system for histological sub-classification of cirrhosis is useful for stratification of prognosis in patients with liver cirrhosis. J Hepatol 2012

Reversibility of cirrhosis : Chalenges for the future

1. Which cirrhosis may regress ?

2. How to assess cirrhosis reversion ?

3. The risk of HCC after cirrhosis regression ?

Regression of fibrosis/cirrhosis assessement with non-invasive markers

Longitudinal assessment of liver stiffness by transient elastography for chronic hepatitis B patients treated with NUCs

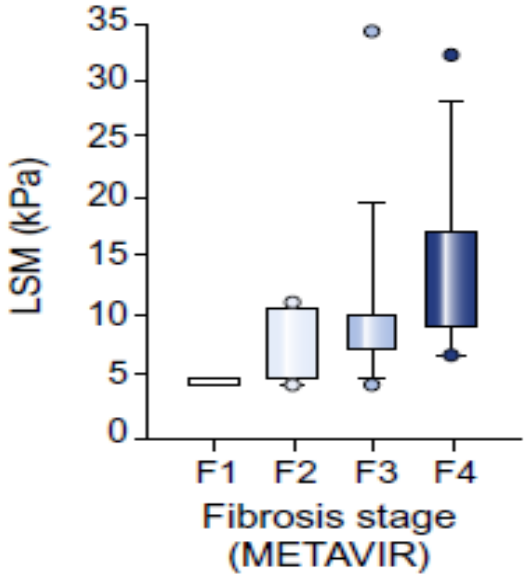
- Long term NUC treatment for patients with chronic hepatitis B
  - Group A: FibroScan at entry and annually for 3 years (n=22)
  - Group B: FibroScan from 3 to 5 years after the start of NUC treatment
- Results over 3 years after the start of NUC treatment
  - Group A: FibroScan values decreased annually
  - Group B: FibroScan values did not significantly improve
- Rapid decline of liver stiffness in patients with CHB treated with NUC in the first 3 years, followed by a more steady transition from 3 to 5 years

Group A (n=22)	FibroScan (kPa)
Baseline	8.2 (4.2–28.5)
FibroScan-1	6.4 (4.0–24.0)
FibroScan-2	5.8 (3.8–21.2)
FibroScan-3	5.3 (2.5–18.0)

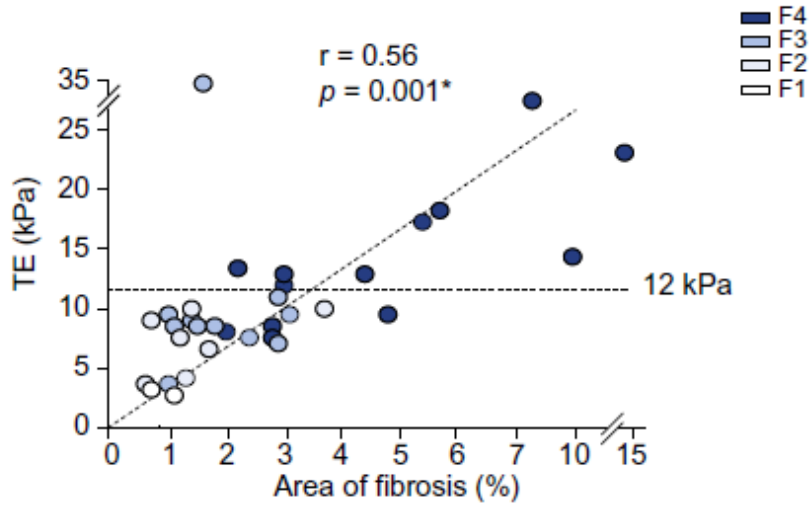
Group B (n=23)	FibroScan (kPa)
Baseline	Not tested
FibroScan-3	6.1 (3.2–20.5)
FibroScan-4	6.7 (3.5–23.3)
FibroScan-5	5.9 (3.0–21.8)

1. Ogawa E, et al. *Hepatology Research* 2011; 41:1178-1188

Correlation between fibrosis stage and TE values after treatment (HCV)



Distribution of LMS according to stage of fibrosis in post-treatment biopsies



*Spearman's rank correlation coefficient

- The diagnostic accuracy of TE for diagnosing F4 after treatment was **61% sensitivity**, 95% specificity, and AUROC 0.77

The diagnostic accuracy of Fibroscan for cirrhosis is influenced by liver morphometry in HCV patients with a sustained virological response. R. D'Ambrosio et al. Journal of Hepatology 2013;59:251–256

2 - How to assess cirrhosis reversion after antiviral treatment ?

- Non invasive markers validated for progressing fibrosis, not for regressing fibrosis/cirrhosis
    - Role of potential confunding factors other than regressing fibrosis
      (↓ necroinflammation)
- No study with // evaluation of NI markers and histology during regression of cirrhosis

Reversibility of cirrhosis : Challenges for the future

1. Which cirrhosis may reverse ?

2. How to assess fibrosis/cirrhosis reversion ?

3. What is the residual risk of HCC after HBV cirrhosis regression ?

Is it still a risk of liver-related complications after histologically-proven cirrhosis reversion ?

Viral suppression/eradication in cirrhotics has beneficial impact on clinical outcome :

- Better survival (van der Meer AJ et al. JAMA. 2012)
- Prevention of hepatic decompensation (Bruno S et al. Hepatology 2010)
- Less need for liver transplantation (van der Meer AJ et al. JAMA. 2012)
- Reduce risk of HCC (Cardoso et al. Journal of Hepatology 2010)

Viral suppression/erradication in cirrhotics has beneficial impact on histology:

- Reduce/reverse fibrosis and cirrhosis

Is cirrhosis reversion a surrogate marker of viral eradication or an independant factor of favourable clinical outcome (↓ HCC risk)

Take-home messages

- Only a subset of compensated cirrhosis may regress histologically even after

Thank You !