Activation of Hepatic Stellate Cells Drives the Rapid Onset of Liver Fibrosis During Acute HCV Infection in HIV-infected Men

No conflict of interests

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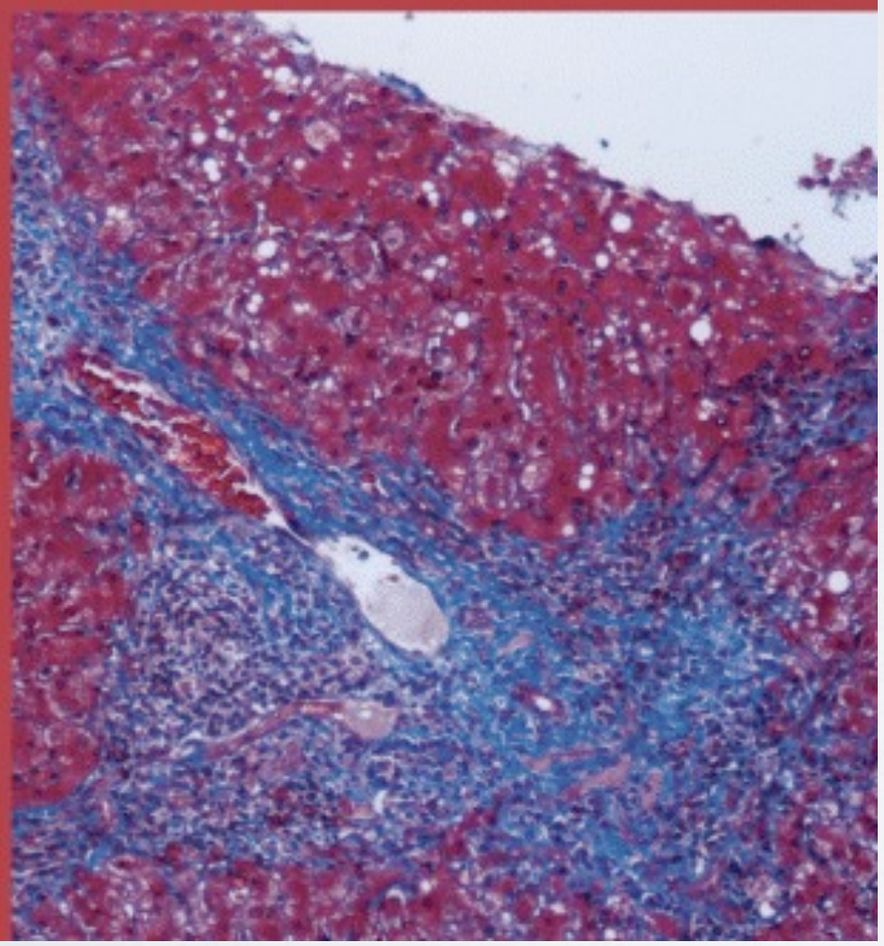
1 September 2008
Volume 198
Number 5

The Journal of Infectious Diseases



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Liver Fibrosis during an Outbreak of Acute Hepatitis C Virus Infection in HIV-Infected Men: A Prospective Cohort Study

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- 11 men underwent liver biopsy, median 3.3 months (range: 0.75–16 months) after diagnosis of acute HCV infection
- 9/11 (81%) had stage 2; 1 had stage 1 fibrosis

Fierer J Infect Dis 2008

Hepatitis C virus infection in HIV-infected men who have sex with men: sustained rising incidence in Antwerp, Belgium, 2001–2009

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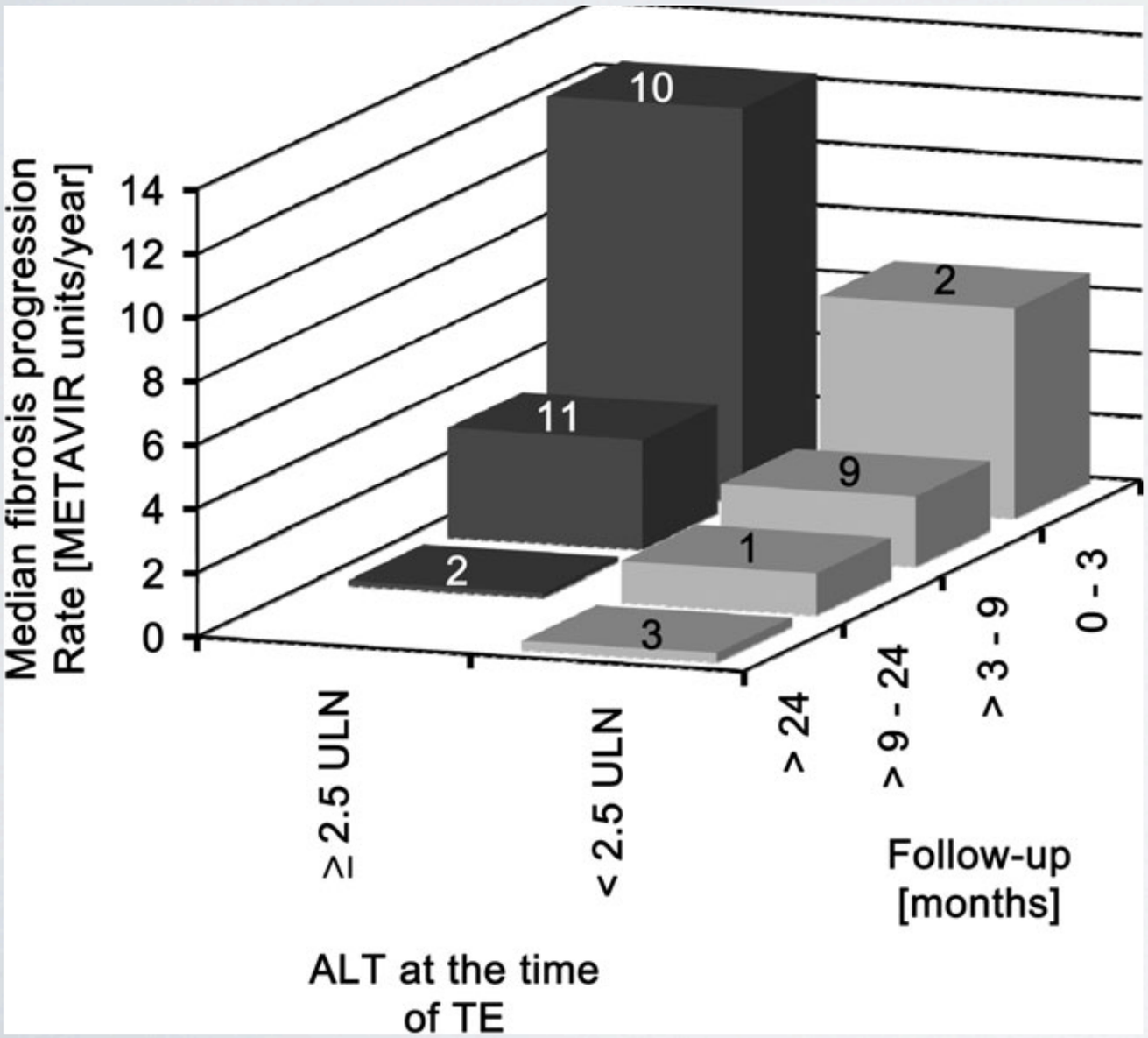
- Antwerp, Belgium 2001 through April 2010
- 37 patients had liver biopsy, median 7 months (range: 3–36 months) after diagnosis of HCV infection:
- 22/37 (59%) had stage 2 or 3 fibrosis

Liver Fibrosis Progression After Acute Hepatitis C Virus Infection in HIV-Positive Individuals

Martin Vogel,[1] Emma Page,[2] Christoph Boesecke,[1] Thomas Reiberger,[3] Carolynne Schwarze-Zander,[1] Stefan Mauss,[4] Axel Baumgarten,[5] J-C Wasmuth,[1] Mark Nelson,[2] Jürgen K. Rockstroh,[1] and the European AIDS Treatment Network (NEAT) Study Group



- 38 men underwent TE median 4.8 (IQR 2.4-7.2) months after diagnosis of acute HCV infection
- stiffness dramatically affected by ALT (inflammation=>stiffness)
  - stiffness lower with longer time to evaluation

Vogel Clin Infect Dis 2012

Early-Onset Liver Fibrosis Due to Primary Hepatitis C Virus Infection Is Higher Over Time in HIV-Infected Men

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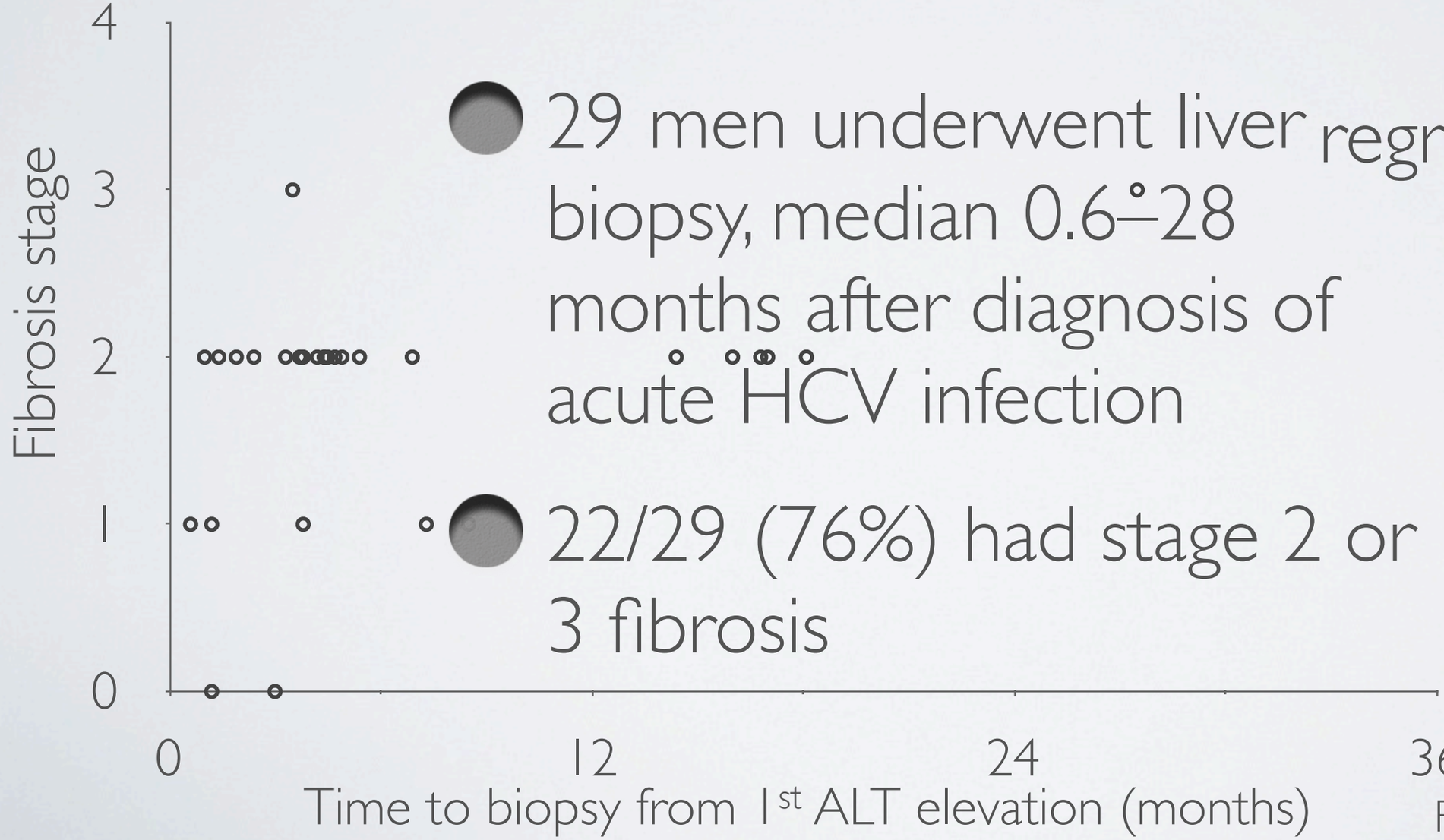


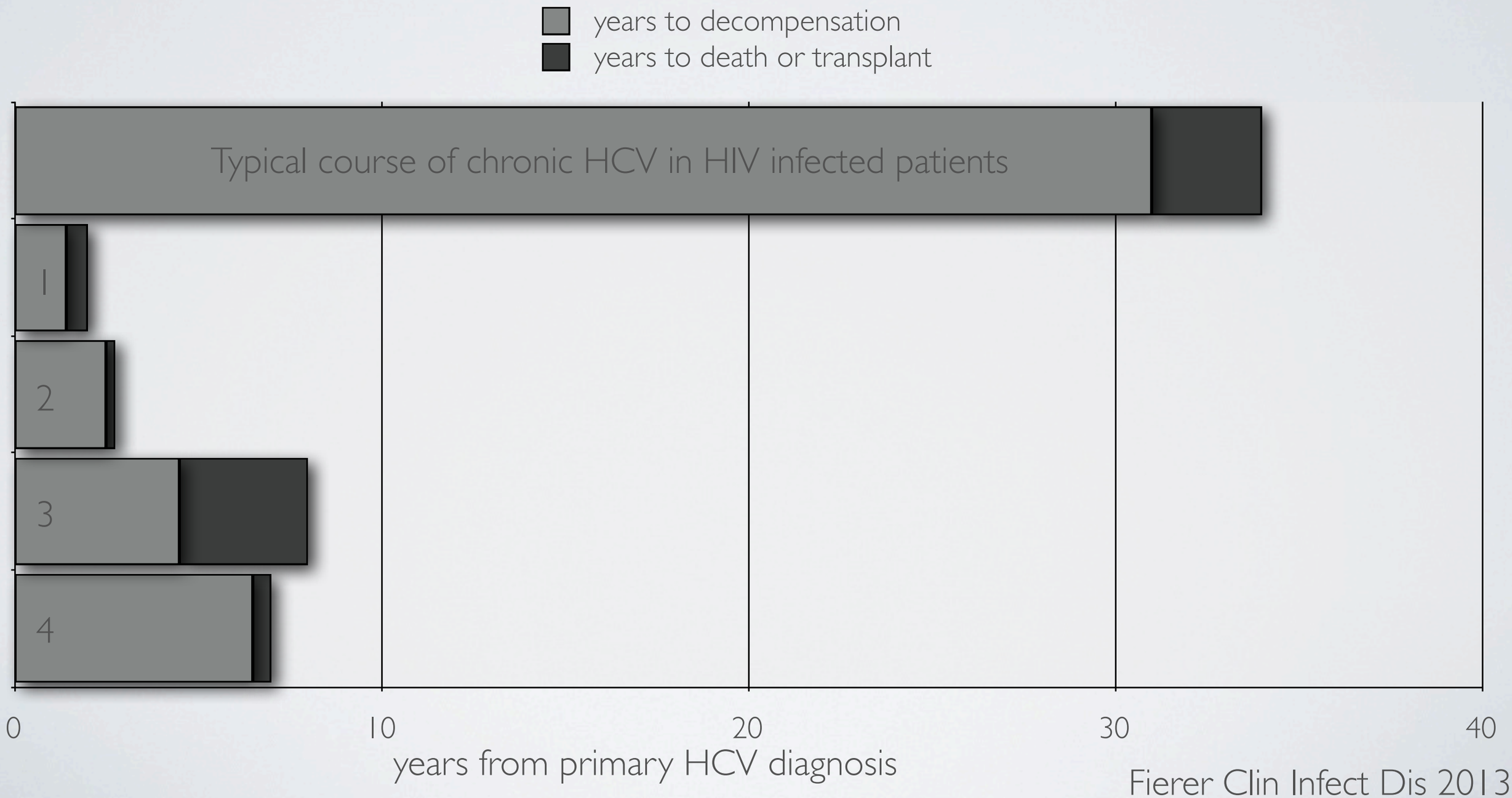
- 29 men underwent liver biopsy, median 0.6–28 months after diagnosis of acute HCV infection
- 22/29 (76%) had stage 2 or 3 fibrosis

regression analysis
$p = 0.04$

Fierer Clin Infect Dis 2012

Rapid Progression to Decompensated Cirrhosis, Liver Transplant, and Death in HIV-Infected Men After Primary Hepatitis C Virus Infection

Daniel S. Fierer,[1] Douglas T. Dieterich,[2] M. Isabel Fiel,[3] Andrea D. Branch,[2] Kristen M. Marks,[4] Dahlene N. Fusco,[4] Ricky Hsu,[5] Davey M. Smith,[6,7] and Joshua Fierer[6,7]



Fierer Clin Infect Dis 2013

Fibrosis During Acute HCV Infection in HIV+ Men

- HIV-infected men who acquire HCV infection undergo rapid-onset liver fibrosis of unknown mechanism(s)
- We hypothesized that this increased fibrogenesis during acute HCV infection results from activation of hepatic stellate cells (HSCs), the principal collagen-producing cell in liver injury

Fibrosis During Acute HCV Infection in HIV+ Men

- Aims:

- To determine whether the number of activated HSCs, as measured by α-smooth-muscle-actin (α-SMA) staining, is high early in HCV infection

- To determine whether the collagen proportionate area (CPA) of liver specimens, as measured by Sirius red staining, increases with increasing time to biopsy

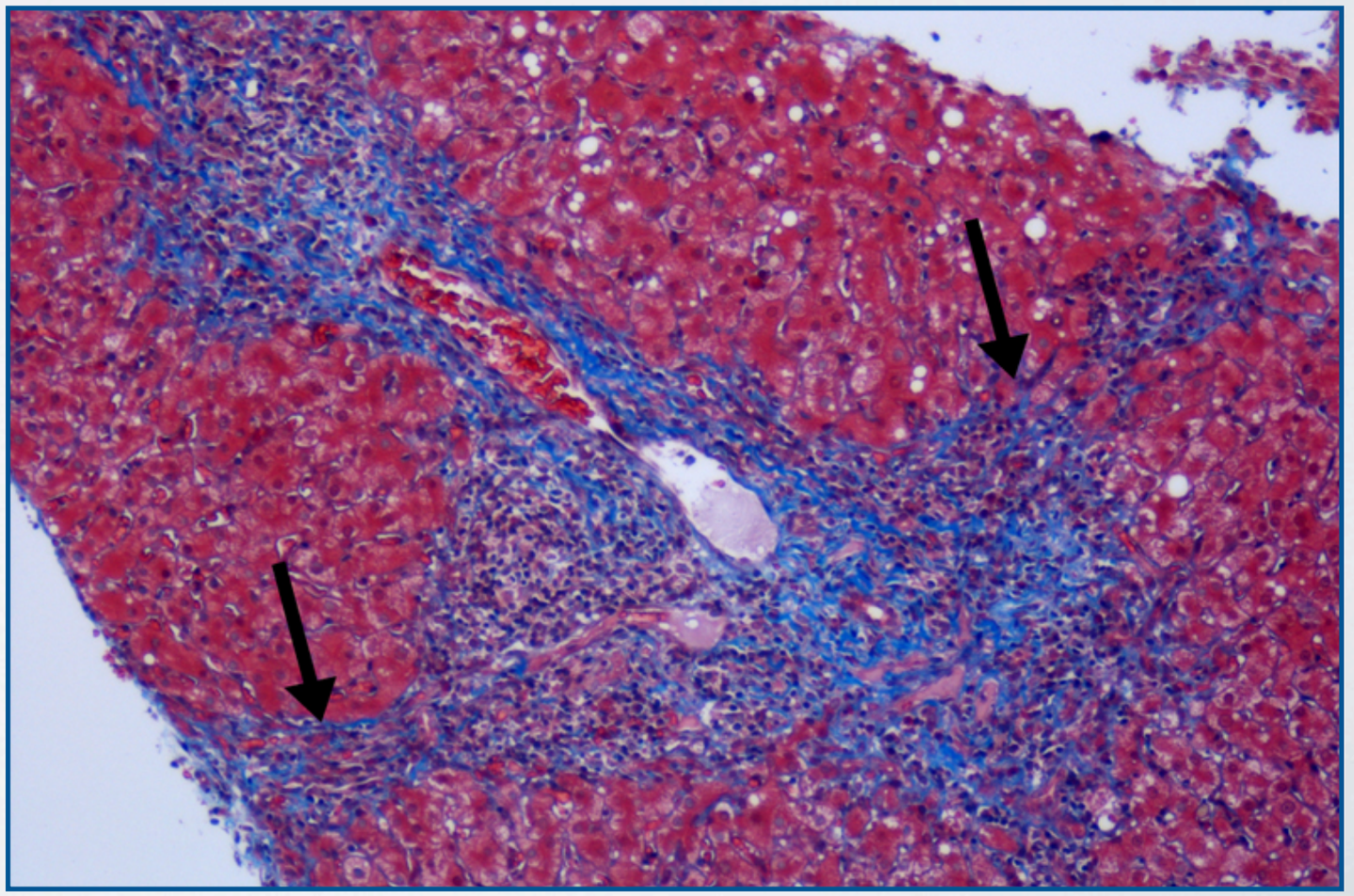
- To re-confirm whether the stage of fibrosis, as measured by trichrome staining, increases with increasing time to biopsy

Fibrosis During Acute HCV Infection in HIV+ Men

subject	age at biopsy	genotype	HCV VL (IU/mL)	ALT (U/L)	ALT elevation to biopsy (mo)	stage (Scheuer, 0-4)
1	40	1a	10,700	57	1.0	2
2	35	1b	10,300,000	88	1.2	1
3	40	1b	9,180,000	258	1.4	3
4	63	3a	1,968,876	61	1.7	2
5	46	1a	4,180,000	810	1.9	2
6	44	1a	1,360,000	195	3.3	2
7	37	1a	787,000	378	3.8	1
8	38	1a	4,143,987	278	3.9	2-3
9	38	1a	4,875,000	495	4.2	2
10	32	1a	4,950	54	4.4	2
11	47	1a	4,430,000	187	4.7	2
12	49	1a	200,000	400	4.9	2
13	42	1a	<5	46	6.9	2
14	30	1a	15,000,000	198	6.9	0-1
15	26	1a	<5	24	7.3	1
16	37	1a	1,016,200	216	16.0	2
17	61	1a	8,040,000	37	17.0	2
18	40	1a	10,400,000	324	27.5	3
19	46	1a	1,549,233	95	28.3	4
20	45	1a	855,026	122	30.4	4
median	40	–	1,759,055	191	4.6	2

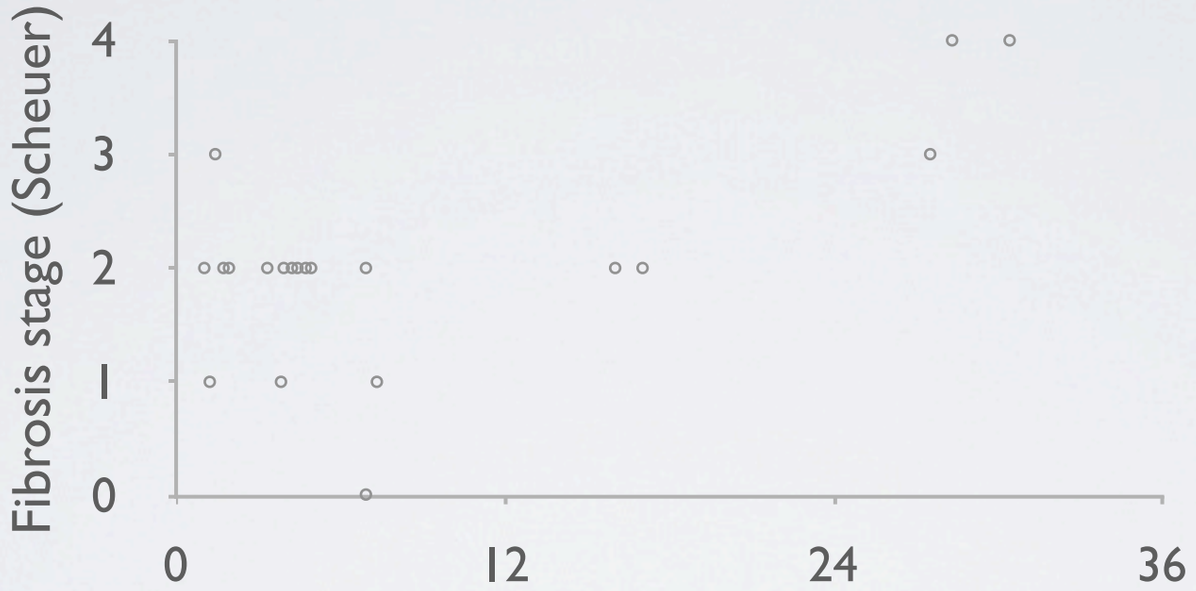
Fibrosis During Acute HCV Infection in HIV+ Men

- Masson's trichrome stain–traditional stain to assess liver fibrosis– stains mature collagen dark blue
  - Staging system (e.g. Scheuer) is qualitative
  - e.g. stage 2

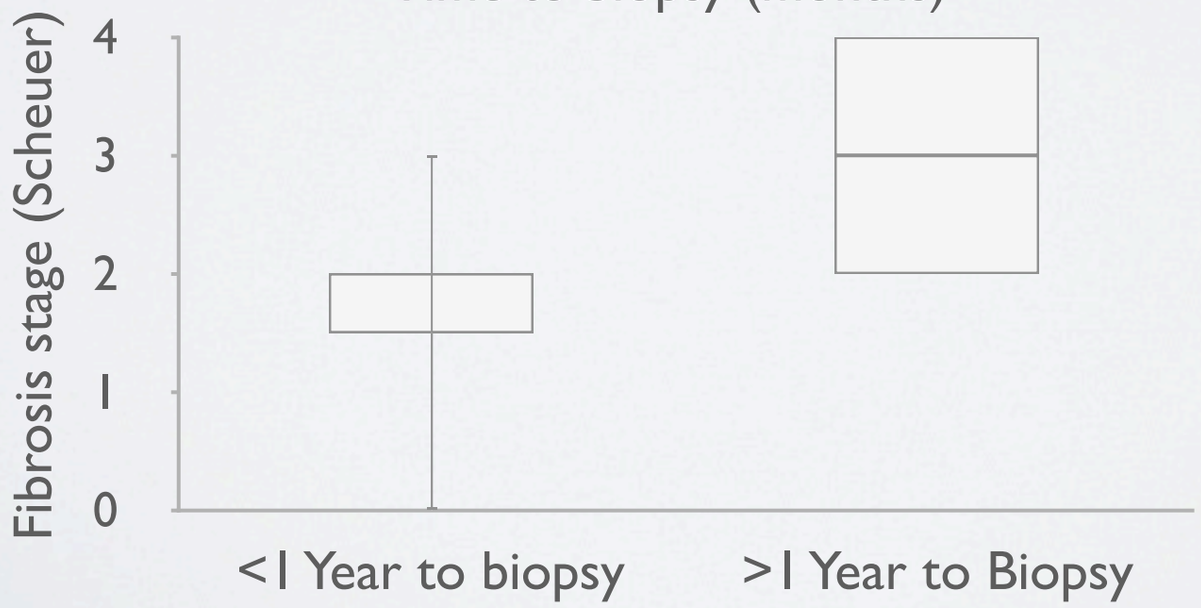


Fibrosis During Acute HCV Infection in HIV+ Men

- Masson's trichrome stain



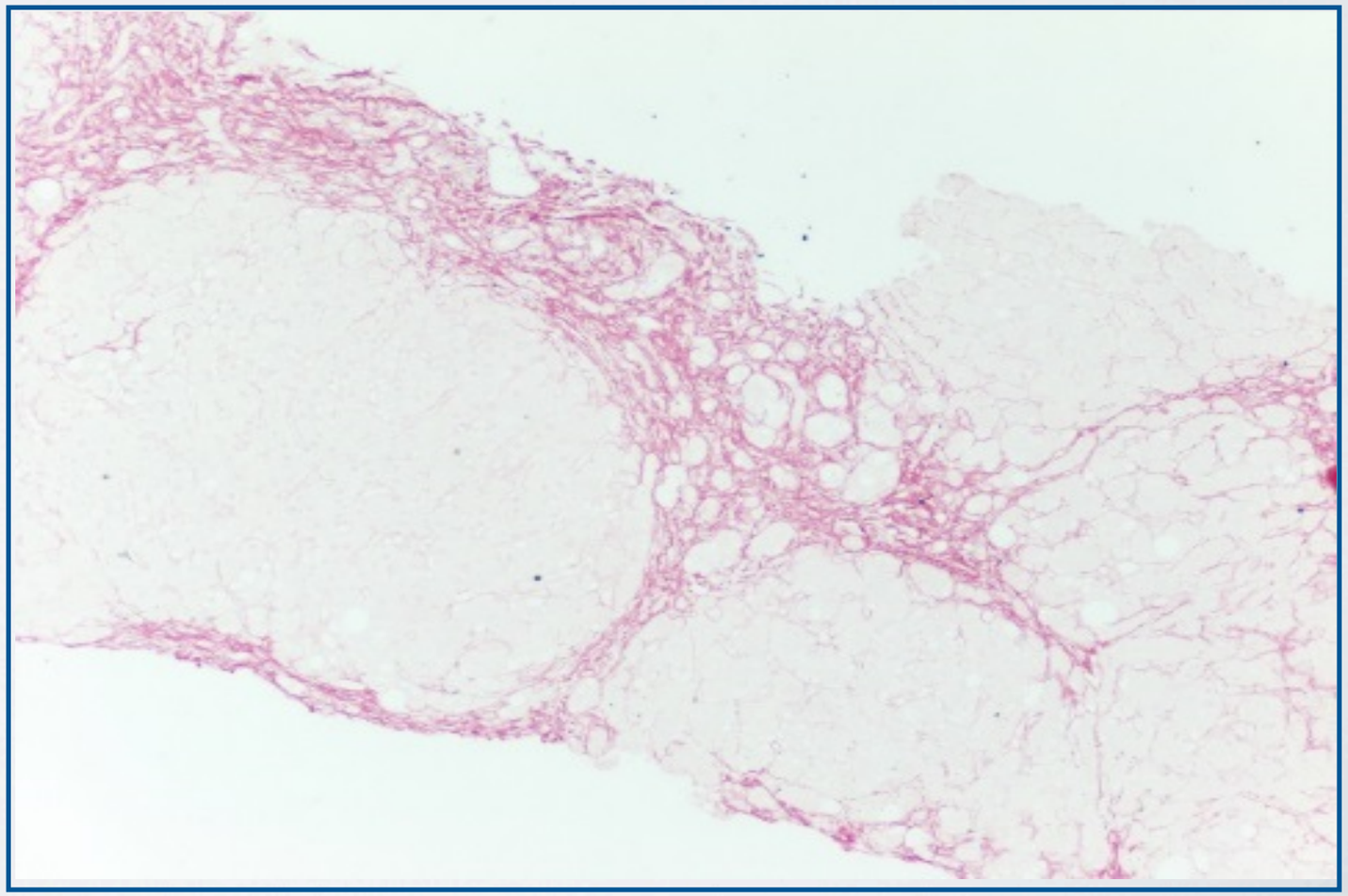
$r^2 = 0.42$



$p < 0.005$

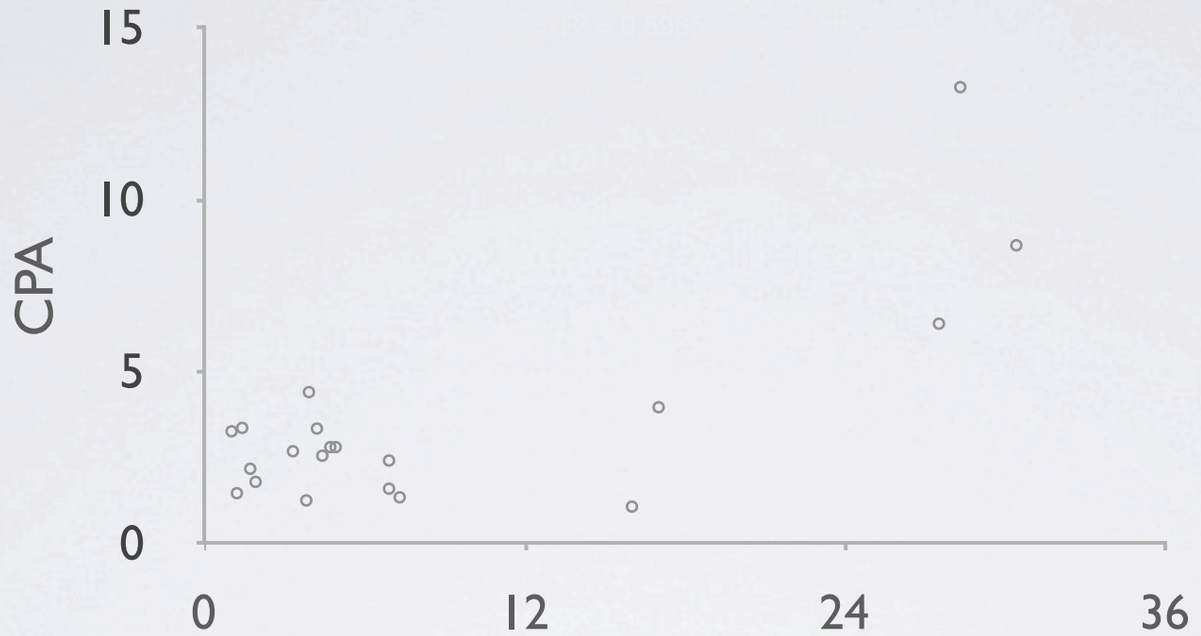
Fibrosis During Acute HCV Infection in HIV+ Men

- Sirius red stains mature collagen red
  - Amenable to quantification of area of fibrosis ("collagen-proportionate area")

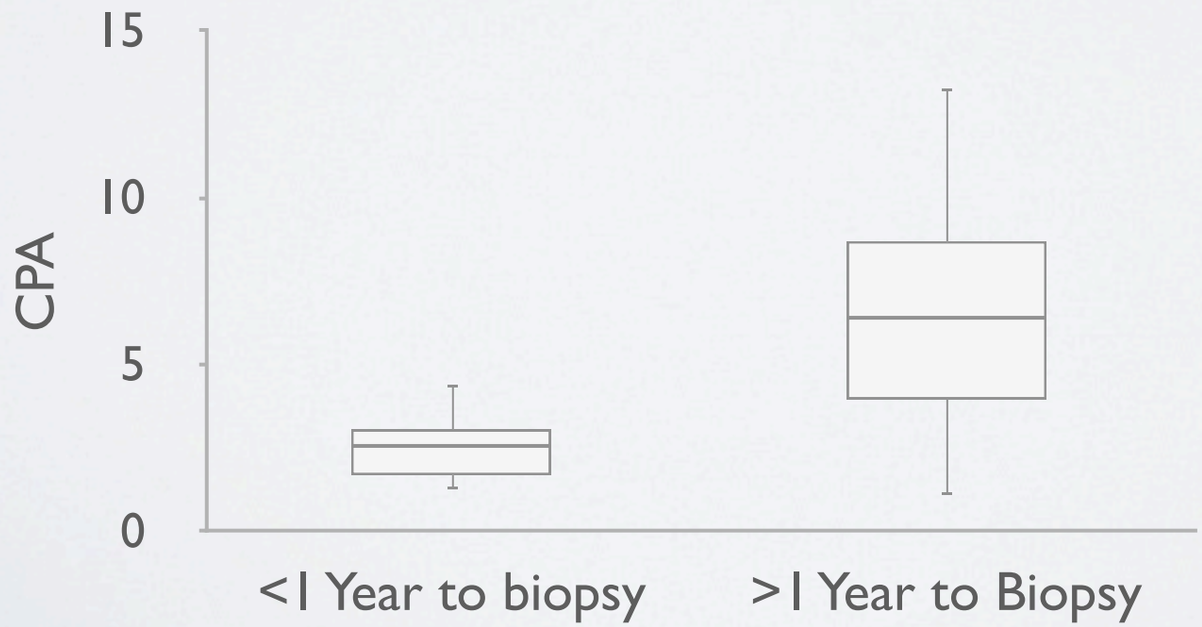


Fibrosis During Acute HCV Infection in HIV+ Men

- CPA



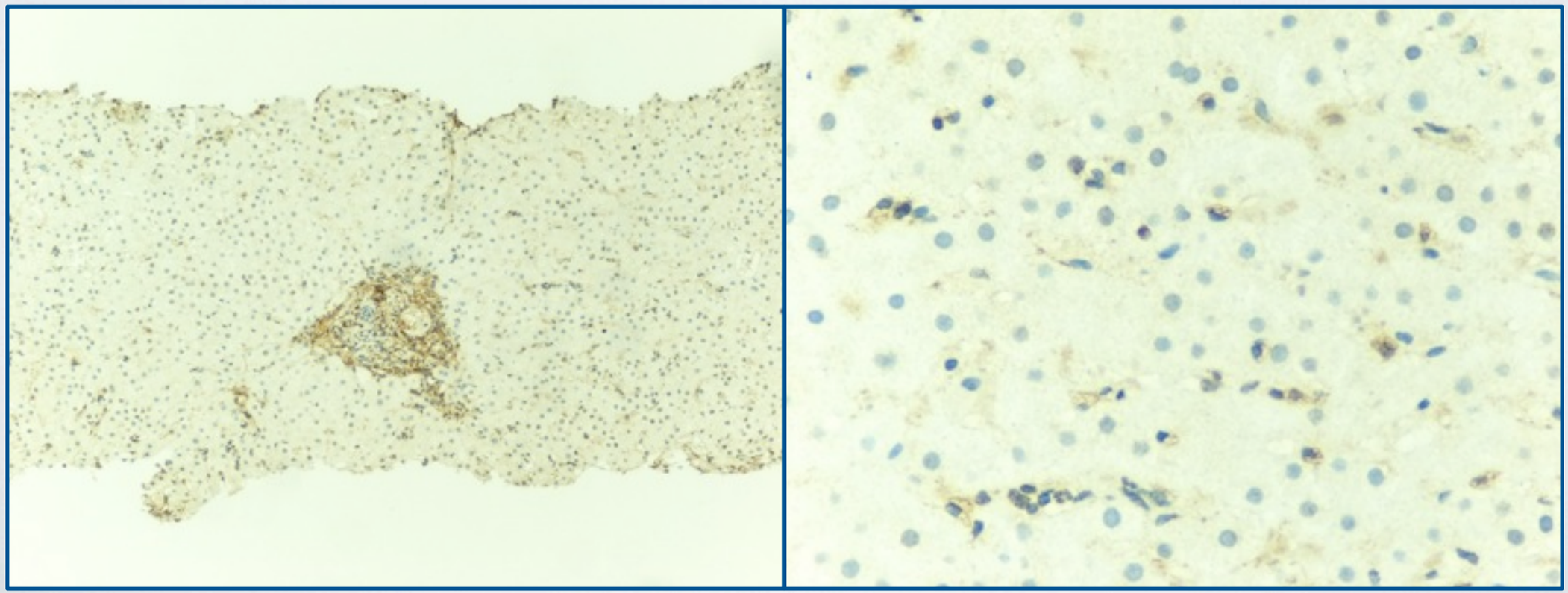
$r^2 = 0.60$



$p < 0.002$

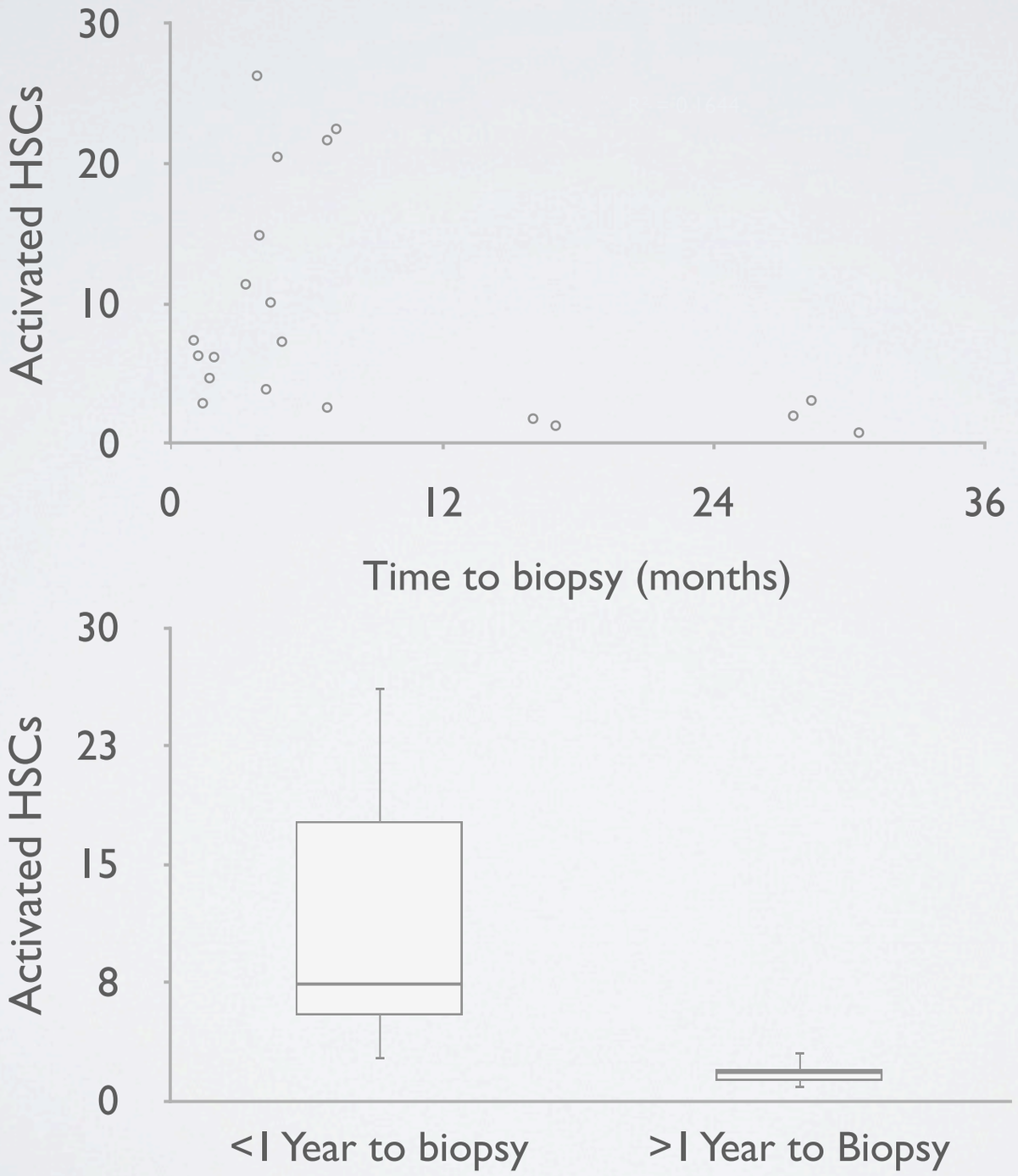
Fibrosis During Acute HCV Infection in HIV+ Men

- Hepatic stellate cells (HSC) produce collagen upon activation (e.g. HCV infection)
  - Mature collagen composes the scar tissue that is liver fibrosis
- α-smooth actin is a marker of activated HSC



Fibrosis During Acute HCV Infection in HIV+ Men

- HSCs



$r^2 = 0.16$

$p < 0.001$

Fibrosis During Acute HCV Infection in HIV+ Men

	biopsy < 1 year after HCV (N=15)	biopsy > 1 year after HCV (N=5)	statistical test
Scheuer stage, median	2	3	$p < 0.005$
CPA (%), median	2.6	6.4	$p < 0.002$
activated HSC/ hpf, median	7.4	1.8	$p < 0.001$

Fibrosis During Acute HCV Infection in HIV+ Men

- Limitations:
- Not all men with acute and recent HCV underwent biopsy
- Insufficient biopsy material for complete analysis of almost half who underwent biopsy
- Significantly fewer biopsies analyzed from >1 year after onset compared to <1 year after onset

Fibrosis During Acute HCV Infection in HIV+ Men

- Conclusions:
- The mechanism of rapid-onset fibrosis formation appears to be early activation of HSCs into fibrogenic myofibroblasts
- This activation results in stage 2 fibrosis in most HIV-infected men within 6 months of HCV infection
- Significantly fewer activated HSCs persist after the first year but fibrosis increases nonetheless

Acknowledgments

- Robbie Gillies
- Marcus Yip

> Monash University

- Scott Friedman
- Andrea Branch
- Douglas Dieterich
- Isabel Fiel