HCV Treatment Now? When and How to Manage HCV in Treatment-Naive and Treatment-Experienced Patients

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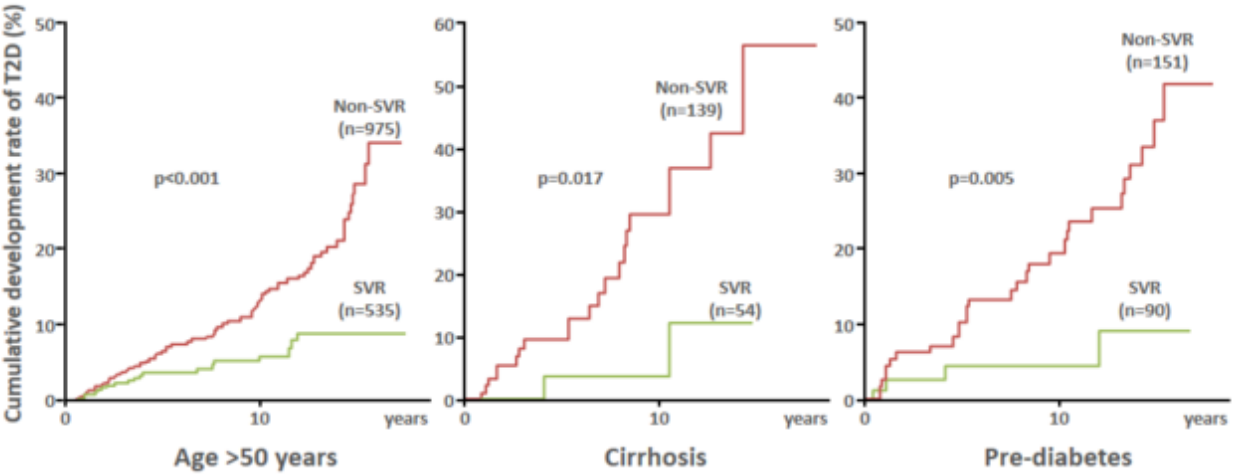
Cumulative incidence of type 2 diabetes in chronic hepatitis C: SVR vs non-SVR

2842 Japanese non-diabetic patients with chronic hepatitis C followed for an average of 6.4 years after antiviral therapy



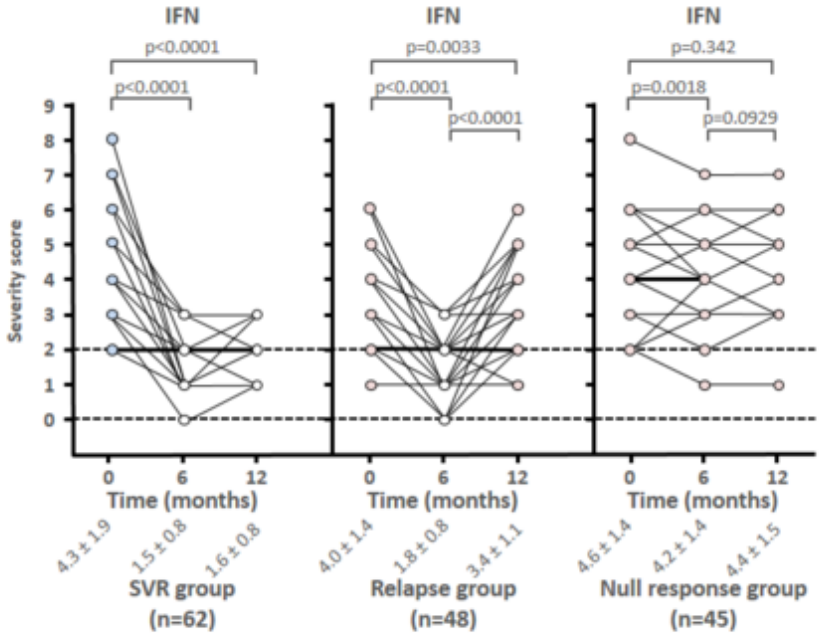
Cure of HCV reduces the risk of developing T2D by more than two-thirds

SVR, sustained virological reponse; T2D, type 2 diabetes

Arase Y et al. *Hepatology* 2009;49:739–744

HCV cure improves the severity score of myocardial perfusion defects

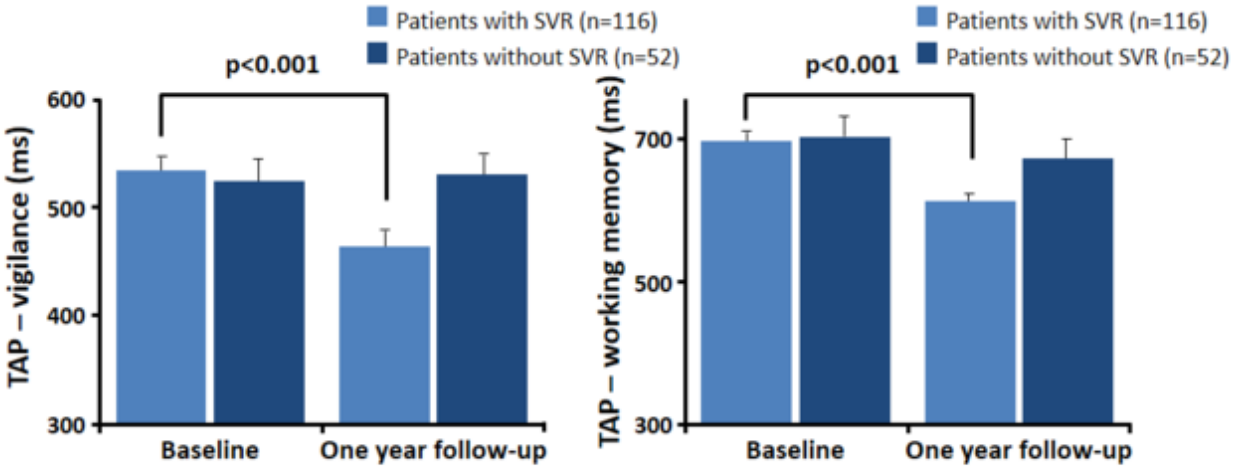
SVR, relapse and null response groups after 24-week IFN-based therapy



The dotted lines indicate the normal range. Significances of individual differences were evaluated with Bonferroni's multiple comparison test

Maruyama S et al. *J Hepatol* 2013;58:11–15

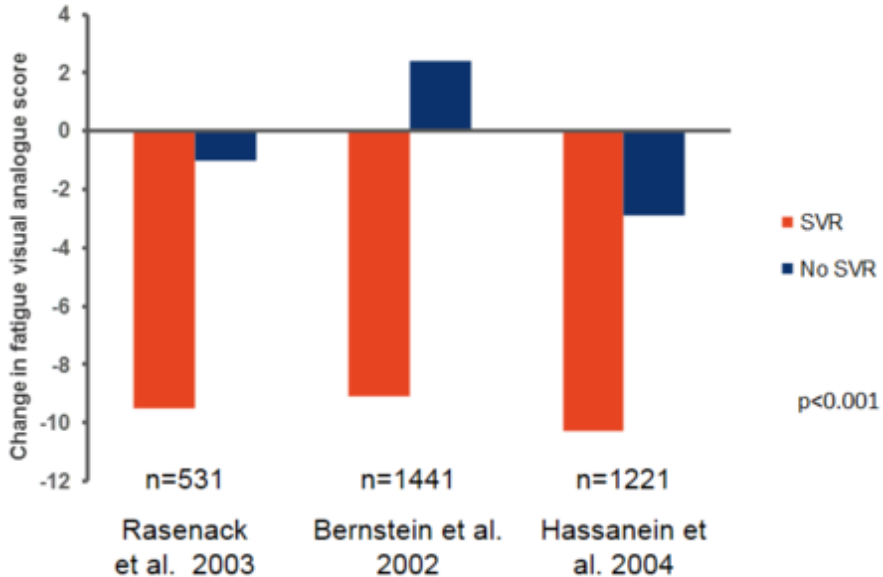
Effect of cure on cognitive function in HCV infection



- Patients with SVR had significant improvements in cognitive performance at least 1 year after the end of treatment
- Non-responders were unchanged

Kraus MR et al, *Hepatology* 2012; 'Accepted Article', doi: 10.1002/hep.26229

Effect of HCV cure on fatigue



SVR, sustained virological response

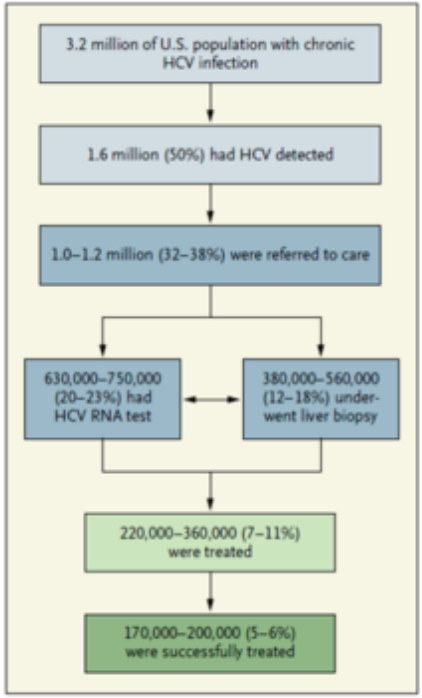
Rasenack J et al, *Pharmacoeconom 2003*;21:341–349
Bernstein D et al, *Hepatology* 2002;35:704–708
Hassanein T et al, *J Hepatol* 2004;40:675–681

If HCV cure is beneficial, why have so few patients been cured?

- SVR rates with current therapy are ~ 75% for HCV genotype 1
- PegIFN alfa + Ribavirin plus:

  Telaprevir 750 mg PO q8 hrs with 20 grams of fat

  Boceprevir 800 mg PO q8 hrs with a light snack



S.D. Holmberg, P.R. Spradling, A.C. Moorman, and M.M. Denniston. Hepatitis C in the United States. New Eng J Med 2013; 368: 1859-1861

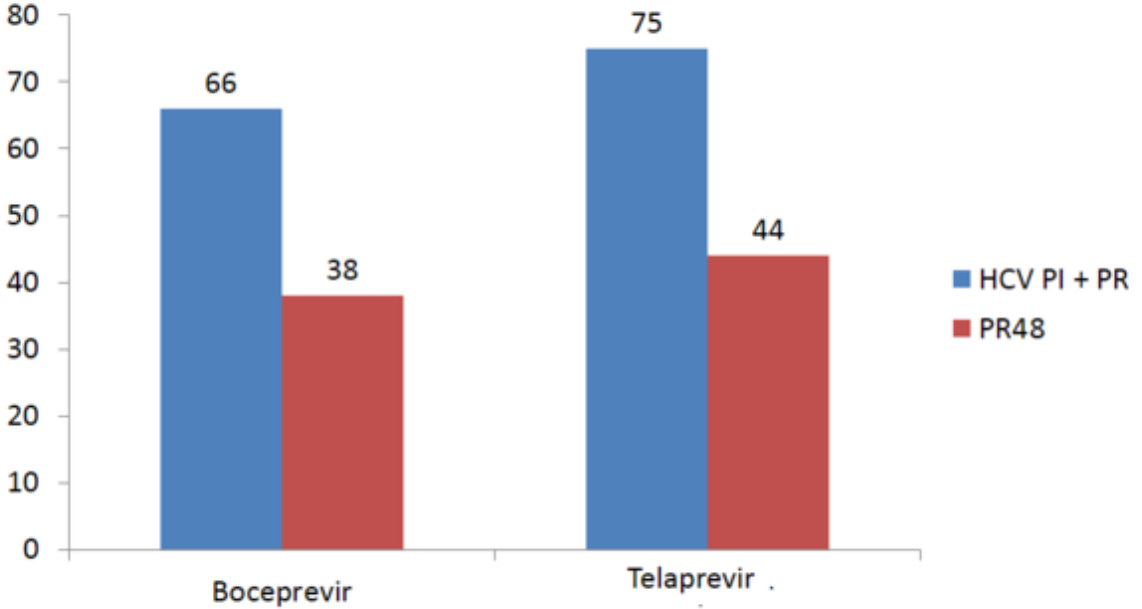
HCV NS3/4A Protease Inhibitors, Contraindications and Specific Populations

- All contraindications to PegIFN/RBV apply
- Co-administration with other drugs that are:
  - Highly dependent on CYP3A for clearance or
  - Strongly induce CYP3A
- Safety and efficacy not established
  - Organ transplantation
  - ESLD
  - Co-infection with HIV or HBV
  - Pediatrics

Telaprevir [package insert] 2012.
Boceprevir [package insert] 2012.

Boceprevir/PR and Telaprevir/PR for HCV genotype 1 treatment naïve patients

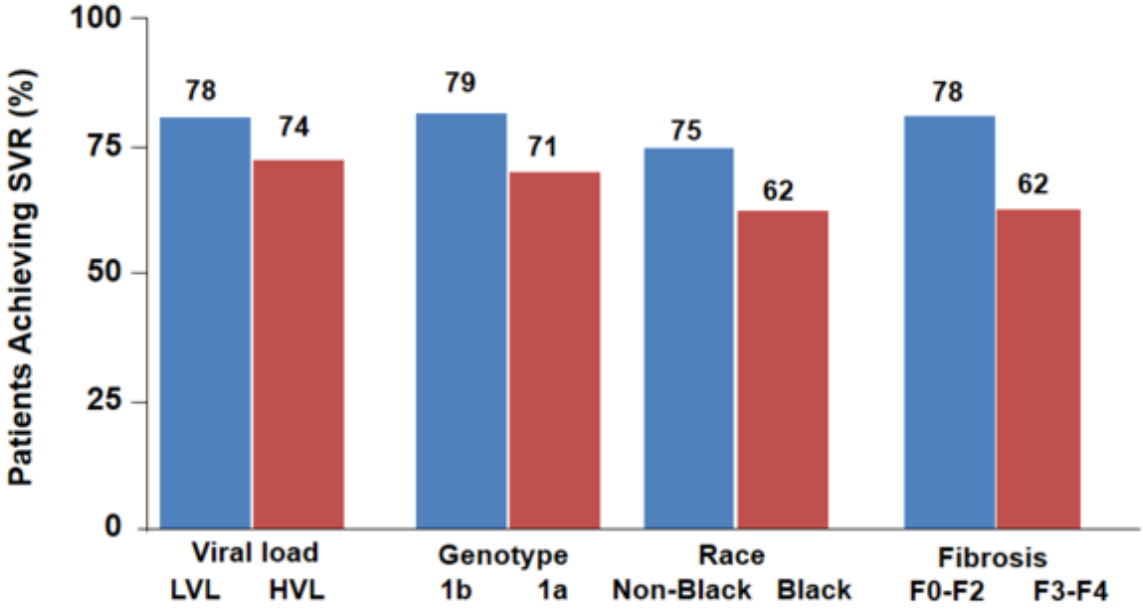
Sustained Virologic Response



Poordad F, et al. New Eng J Med. 2011;364:1195-1206. Jacobson et al. New Eng j Med 2011

Telaprevir/PR in Genotype 1, Treatment-Naïve Patients

Impact of Host and Viral Factors



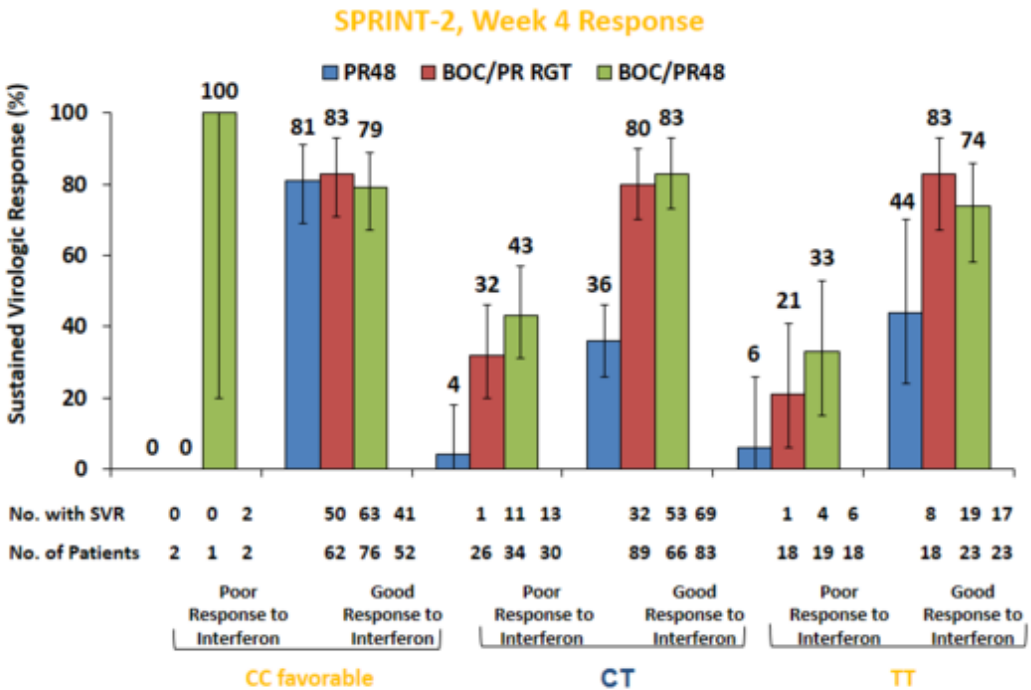
Marcellin P, et al. Poster 451; Dusheiko GM, et al. Poster 415. Posters presented at: EASL: The International Liver Congress 2011; March 30-April 3, 2011; Berlin, Germany. Jacobson IM, et al. *N Engl J Med*. 2011;364:2405-2416.

Boceprevir/PR: Baseline Predictors of SVR

Effect	Odds Ratio (95% CI)	*P* value
Baseline HCV-RNA: ≤400,000 vs >400,000	11.6 (1.5, 87.8)	0.02
IL28B rs12979860 genotype: CC vs TT	2.6 (1.3, 5.1)	0.006
IL28B rs12979860 genotype: CC vs CT	2.1 (1.2, 3.7)	0.01
IL28B rs12979860 genotype: CT vs TT	1.2 (0.7, 2.2)	0.48
Cirrhosis: no vs yes	4.3 (1.6, 11.9)	0.004
Genotype: 1b vs 1a	2.0 (1.2, 3.4)	0.005
Race: non-black vs black	2.0 (1.1, 3.7)	0.03
BMI ≤30 vs >30	1.6 (1.0, 2.5)	0.07

Data from Poordad F, et al. *Gastroenterology.* 2012; 143: 608-618.

HCV RNA Suppression After 4 Weeks of PegIFN + RBV According to IL28B Genotype

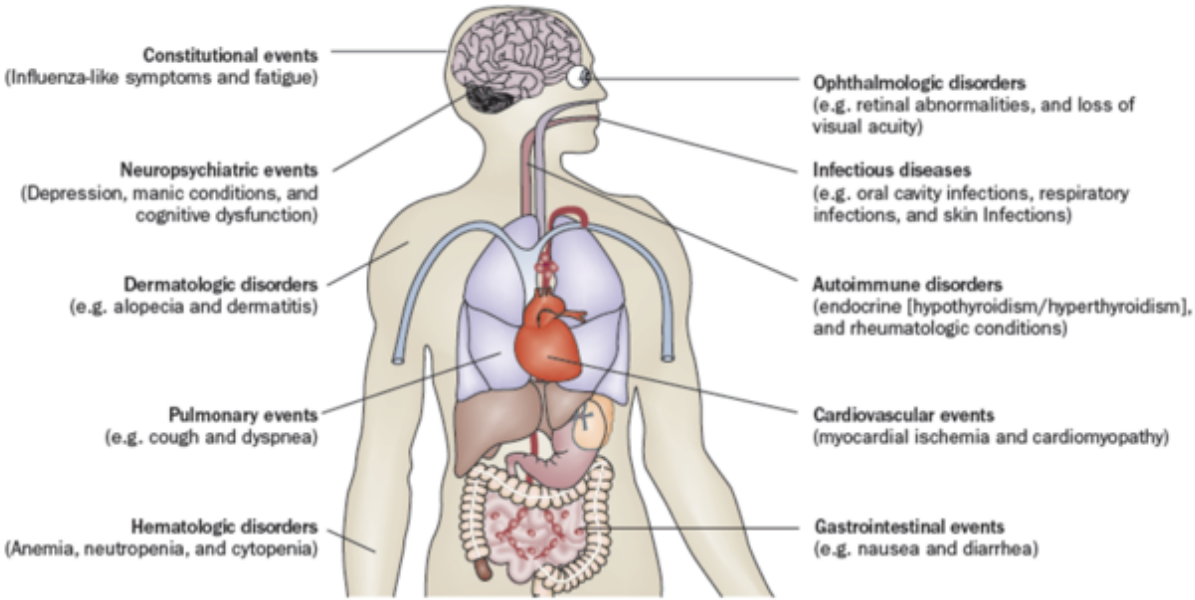


Data from Poordad F, et al. *Gastroenterology*. 2012; 143:608-618.

Disclosure

- Dr Sulkowski has served as a consultant or scientific advisor for AbbVie, Boehringer Ingelheim Pharmaceuticals, Inc, Bristol-Myers Squibb, Gilead Sciences, Inc, Janssen, Merck & Co, Inc, and Vertex Pharmaceuticals, Inc; and has received research grants awarded to his institution from AbbVie, Boehringer Ingelheim Pharmaceuticals, Inc, Bristol-Myers Squibb, Gilead Sciences, Inc, Janssen, Merck & Co, Inc, and Vertex Pharmaceuticals, Inc. (Updated 06/12/13)

Interferon adversely impacts nearly every body system



Sulkowski MS et al. *Nature Reviews Gastroenterol Hepatol* 2011;8:212–223

Telaprevir or Boceprevir + PR – more adverse events than PR alone

Telaprevir

Adverse Event, %	Telaprevir-Containing Arms (n= 1,797)	PegIFN + RBV Arm (n = 493)
Rash	56	34
Pruritus	47	28
Anemia*	36	17
Anorectal AEs**	29	7

Boceprevir

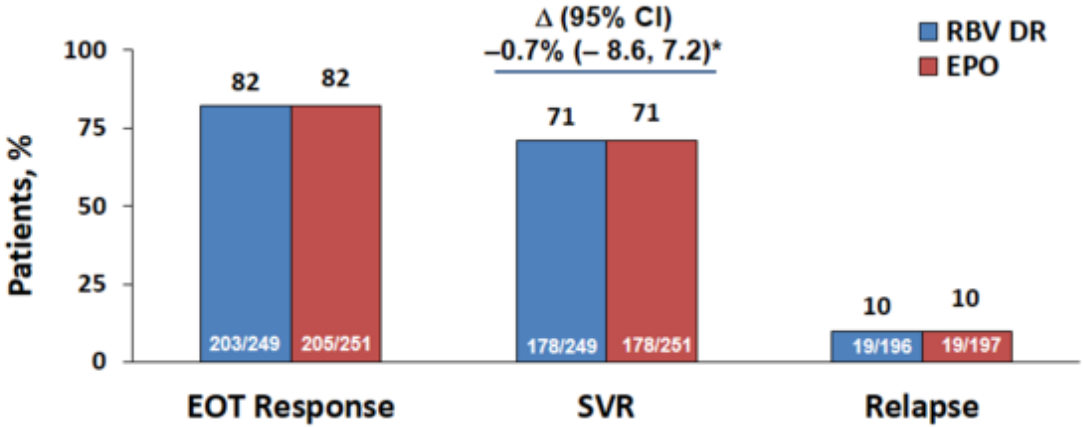
Adverse Event, %	Boceprevir-Containing Arms (n = 734)	PegIFN + RBV Arm (n = 363)
Anemia*	45-50	20-30
Dysgeusia	35-44	11-16
Neutropenia	26-31	13-18

*No EPO used in TVR trials; EPO commonly used in BOC trials
**hemorrhoids, anorectal discomfort, anal pruritus, and rectal burning

Boceprevir: FDA Approved Label Information, May 2011; Telaprevir: FDA Approved Label Information, March 2012.

SVR With RBV Dose Reduction Comparable to Epoetin Alfa

- End-of-treatment response, relapse, and SVR were comparable between RBV DR and EPO arms

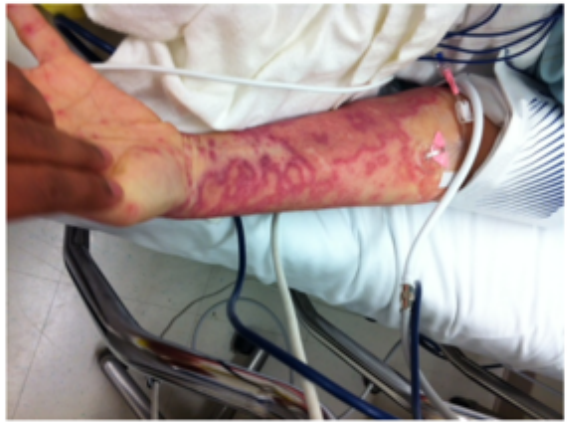


CI, confidence interval; DR, dose reduction; EOT, end of treatment; EPO, erythropoietin; RBV, ribavirin; SVR, sustained virologic response.
*The stratum-adjusted difference (EPO vs RBV DR) in SVR rates, adjusted for stratification factors and protocol cohort.

Data from Poordad F, et al. *J Hepatol*. 2012; 56:S559.

Stevens-Johnson Syndrome (SJS)/Drug Rash With Eosinophilia and Systemic Symptoms (DRESS)

- SJS: Fever, target lesions, mucosal erosions/ulcerations
- Drug rash with eosinophilia and systemic symptoms
  - Rash, fever, facial edema, internal organ involvement
  - ± Eosinophilia
- Urgent dermatology referral



Rash Management Plan: Telaprevir

Rash Description	Management
Mild to moderate rashes	— Continue all drugs; TVR dose should not be reduced or interrupted — Monitor for rash progression or development of systemic symptoms — Oral antihistamines and/or topical corticosteroids • Systemic corticosteroids are not recommended*
Severe rash	— Discontinue TVR, continue PegIFN + RBV — If no improvement within 7 days (or earlier if indicated), consider D/C of PegIFN and/or RBV — Oral antihistamines and/or topical corticosteroids • Systemic corticosteroids are not recommended* — Consider dermatology consult *Serious skin reactions (SJS or DRESS):* Discontinue all medications immediately; Refer for urgent medical care
All patients with rash	Consider **good skin care practices**: limit sun exposure, wear loose-fitting clothing, use oatmeal or baking soda baths, apply moisturizers at least twice daily after bathing, laundry with mild, unscented detergents

***Systemic corticosteroids & TVR DDI: Prednisone/methylprednisolone (CYP3A substrates) and TVR (potent CYP3A inhibitor) –plasma concentrations of corticosteroids can be increased significantly. Systemic dexamethasone (induces CYP3A) can decrease TVR plasma concentrations (may result in loss of therapeutic effect)**

FDA Drug Safety Communication. *Serious skin reactions after combination treatment with the Hepatitis C drugs telaprevir, peginterferon alfa, and ribavirin.* December 19, 2012. Telaprevir [package insert] 2012.

Patient Case

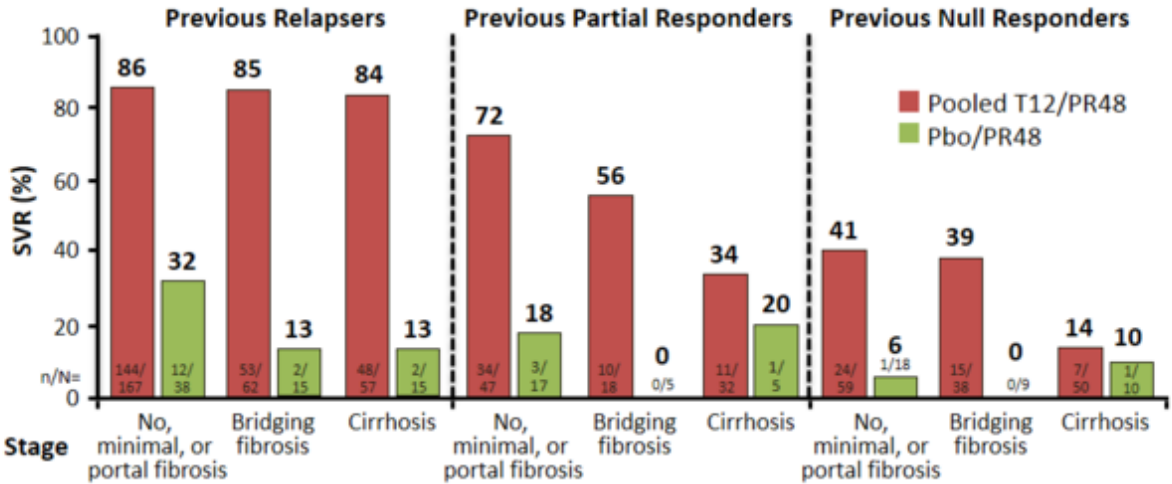
- 63 y/o male with hemophilia
- No stigmata of chronic liver disease on exam
- Platelets = 137,000
- Ultrasound: "liver with increased echogenicity"
- EGD 2011 for GERD was normal
- Treated in 2006 with Peg/RBV for 12 weeks
  - Pre-treatment HCV RNA = 2.4×10^6 IU
  - Treatment wk 12 HCV RNA = 5.9×10^4 IU
- **Should this prior null responder to PegIFN/RBV be treated with PegIFN/RBV plus first generation PI?**

Triple Therapy in Treatment-Experienced Patients: Definitions of Prior Response

Response	Definition
Relapse	HCV RNA undetectable at the end of therapy, but detectable HCV RNA during follow-up
Partial Response	HCV RNA decline ≥ 2 $\log_{10}$ IU/mL from baseline at week 12, but never achieved undetectable HCV RNA
Null Response	HCV RNA decline < 2 $\log_{10}$ IU/mL from baseline at week 12 of prior therapy

Boceprevir [package insert]. May 2011.
Advisory Committee Briefing Document for NDA 201-917 Telaprevir 375 mg tablets.
Vierling JM, et al. AASLD 2011. Poster 931.

REALIZE: SVR by Baseline Fibrosis Stage and Prior Response



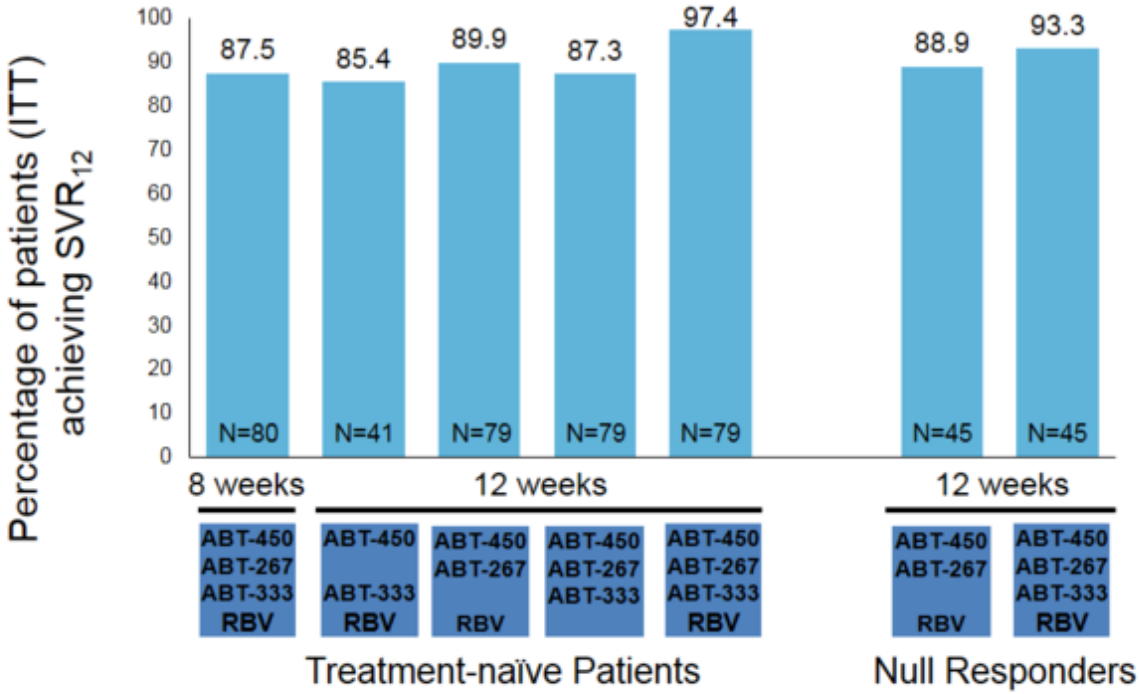
Zeuzem S, et al. EASL 2011. Abstract 5.

DAA Regimens in Phase 3 Trials

PI	NS5A	Non-nucleoside polymerase	Nucleo(t)ide polymerase	Ribavirin	PegIFN
			Sofosbuvir	RBV	+/- PegIFN alfa
	GS5885		Sofosbuvir	+/- RBV	
ABT450/r	ABT267	ABT333		+/- RBV	
Asunaprevir*	DCV				
Faldaprevir*		BI7127		RBV	
Simeprevir				RBV	PegIFN alfa
Faldaprevir				RBV	PegIFN alfa
			Sofosbuvir	RBV	PegIFN alfa
	DCV			RBV	PegIFN lambda

*Genotype 1b only

SVR_{12} Rates for 8- and 12-Week Arms



Kowdley K, et al. 63rd AASLD; Boston, MA; November 9-13, 2012. Abst. LB-1.

Learning Objectives

After attending this presentation, learners will be able to:

- **Discuss the potential clinical benefits of HCV treatment leading to sustained virologic response (SVR)**
- **Evaluate the likelihood of virologic response to triple therapy with peginterferon alfa/ribavirin plus telaprevir or boceprevir**
- **Describe modalities available to assess the risk of clinically significant HCV disease**

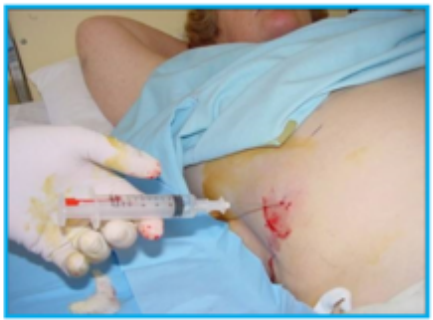
NS5B (sofosbuvir) and NS5A (ledipasvir, aka 5885) for 12 weeks for genotype 1 HCV

34 patients with sofosbuvir and ledipasvir (coformulation) for 12 weeks

Genotype/Rx experience	N	Undetectable HCV RNA (%)			
		Wk 1	Wk2	Wk12	SVR4
1 naive	25	11 (44)	22 (88)	25 (100)	25 (100)
1 null response	9	0	4 (44)	10	9 (100)

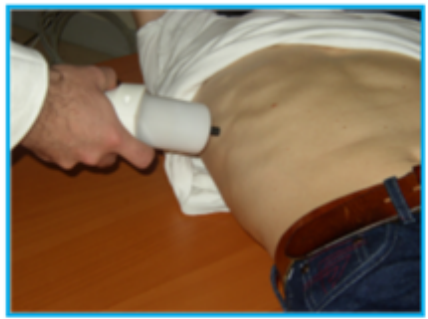
Gane E, CROI LB 1003

Liver Disease Staging Needed to Determine if "Watch and Wait" is Appropriate



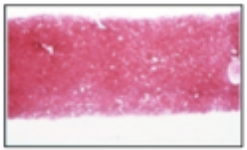
Liver Biopsy

Serum Biomarkers

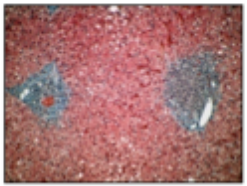


Elastography

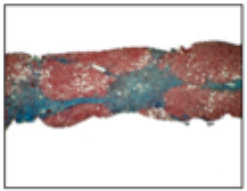
HCV Disease Progression: METAVIR stages



No Fibrosis

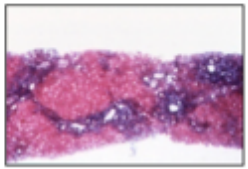


Stage 1: Fibrous expansion of some portal areas



Stage 2: Fibrous expansion of most portal areas with occasional portal to portal bridging

Stage 3: Fibrous expansion of portal areas with marked bridging (portal to portal and portal to central)



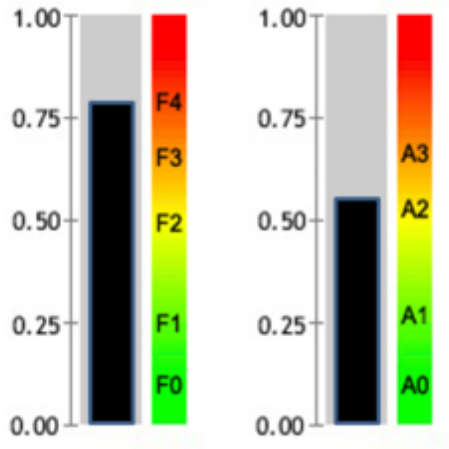
Stage 4: Cirrhosis, probable or defined

Cirrhotic liver: Gross anatomy of cadaver

Courtesy of Gregory Everson, MD

Non-invasive serum markers to stage fibrosis

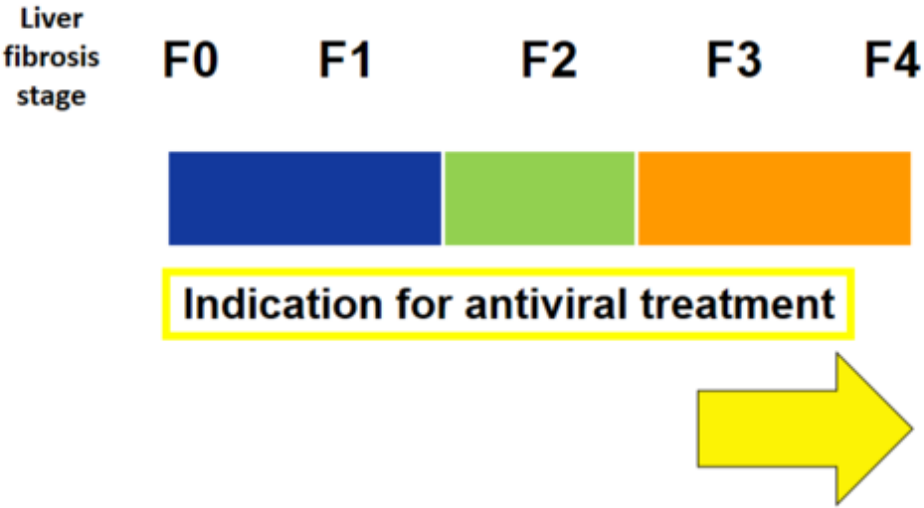
- Fibrosis index
  - GGT
  - Bilirubin
  - Haptoglobin
  - Apolipoprotein A1
  - α2 macroglobulin
- Necroinflammatory activity
  - Markers + ALT
- Should not be used for patients with Gilbert disease, acute hemolysis, acute viral hepatitis, drug-induced hepatitis, genetic liver disease, autoimmune hepatitis, or extrahepatic cholestasis



GGT = γ-glutamyl transpeptidase.

Technical Report, 2006

Fibrosis Staging informs risk:benefit of HCV treament



HCV Treatment Now?

HCV Genotype	**Liver Disease Stage**	IL28B genotype
Personal Factors	Age	Prior response and tolerability of PegIFN/RBV
Patient Mindset	Insurance coverage anticipated	Occupation
Extrahepatic disease	HIV Coinfection	Contraindications & Comorbidities

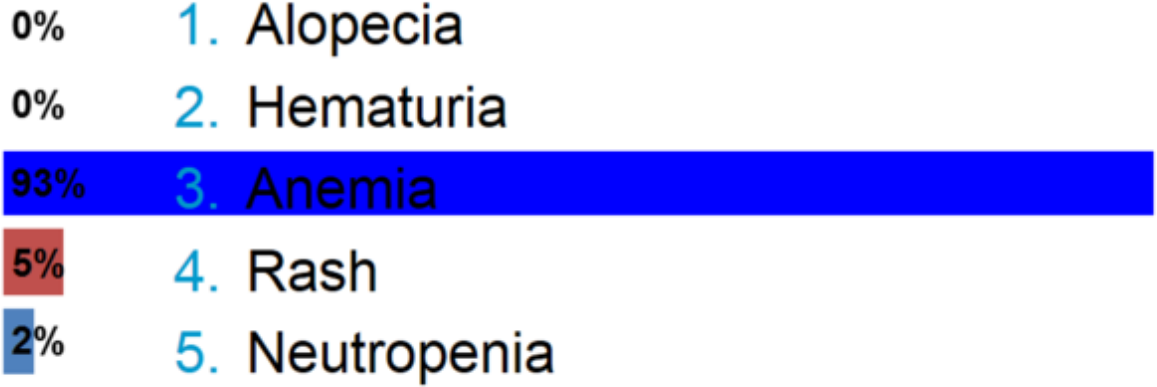
Proximity and promise of novel DAA Regimens

Analogy: Chronic HCV infection is like a single tree in a forest that must be removed

Current therapy

Future therapy

Which of the following is an adverse effect associated with both telaprevir and boceprevir?



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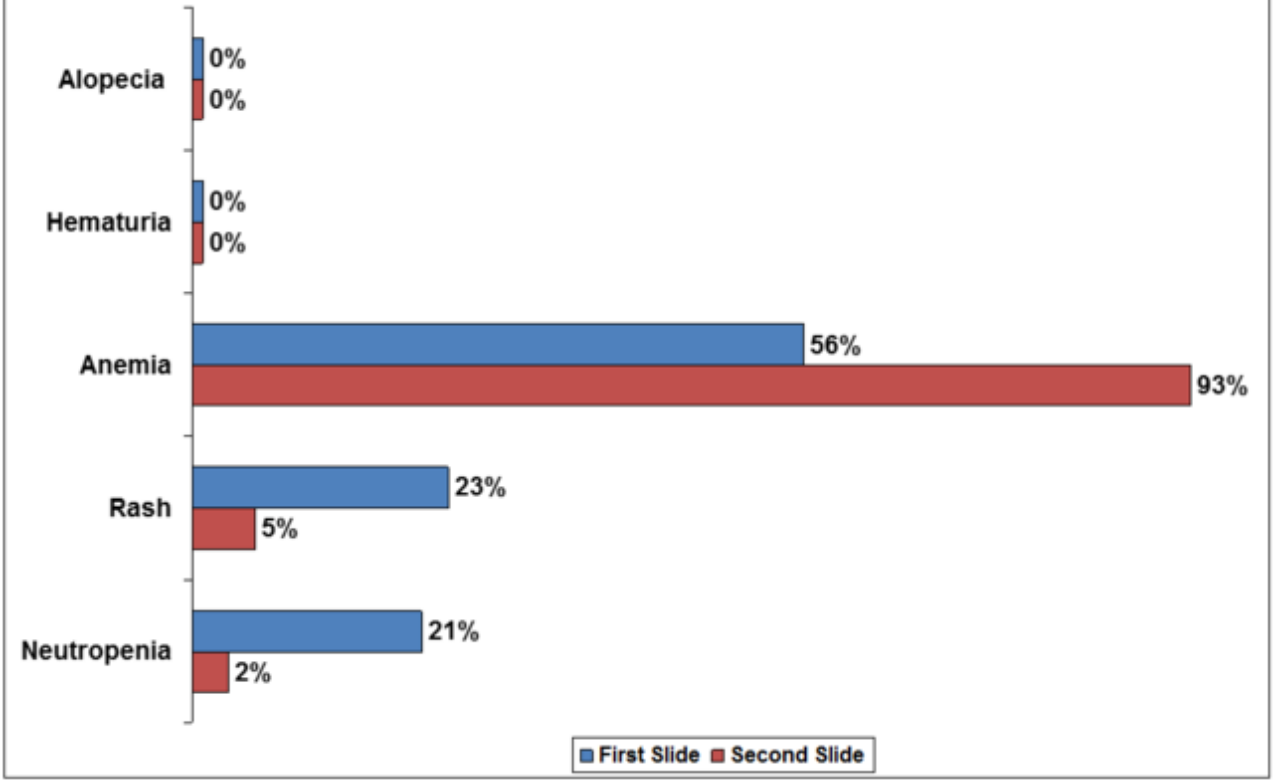

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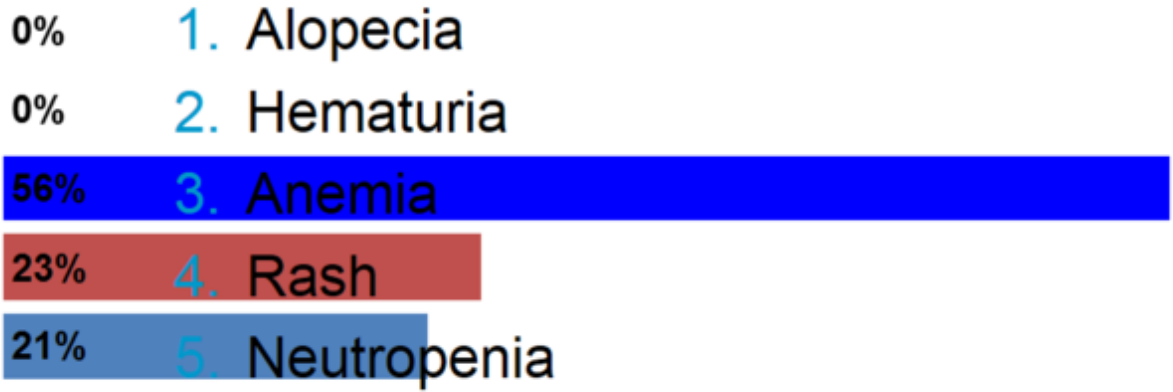
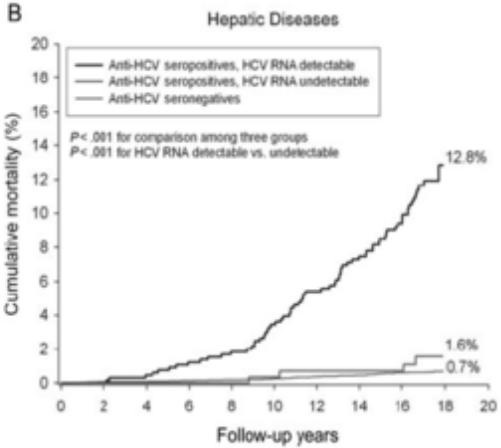


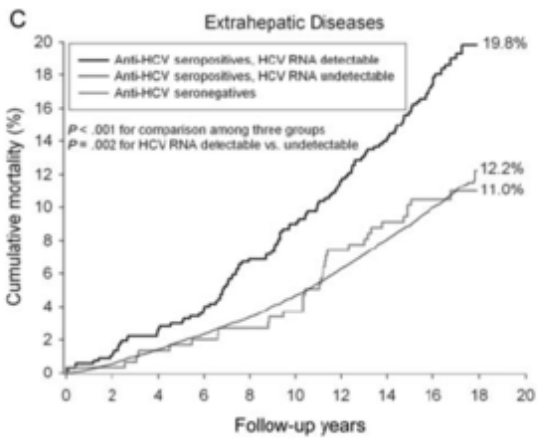
Patient Case

- 55-year-old business executive with hypertension and type 2 DM presents after evaluation for an increase to his life insurance coverage
  - ALT 43 (15-45)
  - AST 36 (14-45)
  - HCV antibody is reactive
- He had been unaware of his diagnosis and is surprised at this new diagnosis
  - After direct questioning, he reports that he injected drugs 3 or 4 times with friends in the 1980s but he does not consider himself a drug user
- He has started to take silymarin
- **Should the treatment naïve patient be treated with PegIFN/RBV and a first generation PI?**

Chronic HCV increases mortality for hepatitic and non-hepatic diseases

- 23, 820 adults in Taiwan prospectively followed since 1991-92
- 1095 were anti-HCV positive; 69.4% had detectable HCV RNA





Lee M-H et al. Journal of Infectious Diseases 2012;206:69

Excess mortality associated with HCV

The REVEAL HCV Cohort Study

- 19 636 HBsAg-seronegative adults, aged 30–65 years
- 1095 anti-HCV+ [5.6%]
- 2394 deaths after an average follow-up of 16.2 years

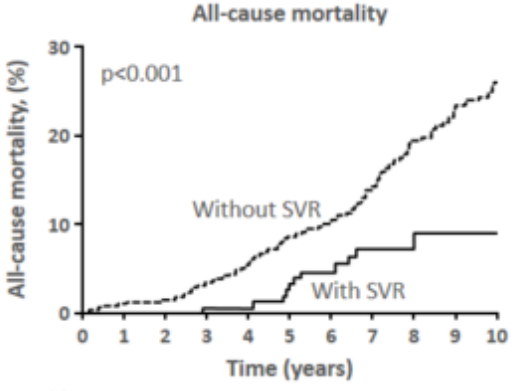
Causes of death	Multivariate-adjusted HR (95% CI)
All causes	1.89 (1.66–2.15)
All liver-related	12.48 (9.34–16.66)
HCC	21.63 (14.83–31.54)
All extrahepatic diseases	1.35 (1.15–1.57)
All cancers, except HCC	1.32 (1.00–1.74)
Diabetes	1.49 (0.91–2.42)
Cardiovascular diseases	1.50 (1.10–2.03)
Nephritis/nephrosis	2.77 (1.49–5.15)

CI, confidence interval; HBsAg, hepatitis B surface antigen;
HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio

Lee M et al, *J Infect Dis* 2012;206:469–477

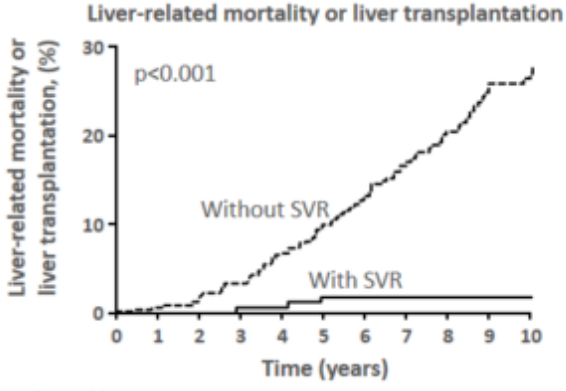
Cure is associated with reduced mortality among HCV-infected persons

- 530 adults in Europe prospectively followed for a median of 8.4 years after HCV treatment
- 192 (36%) achieved SVR



Number at risk

Without SVR	405	393	382	363	344	317	295	250	270	164	135
With SVR	192	181	168	162	155	144	125	88	56	40	28



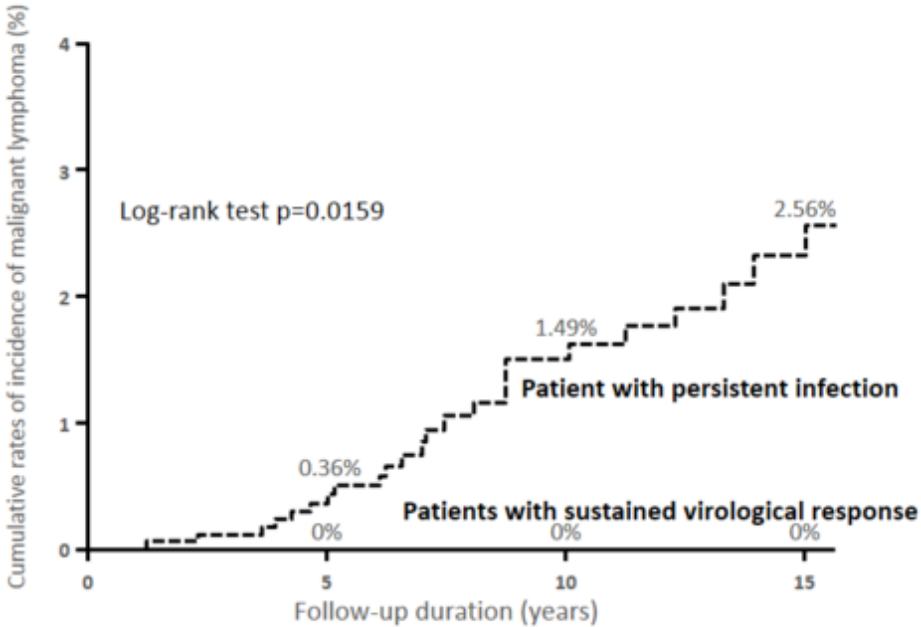
Number at risk

Without SVR	405	392	380	358	334	305	277	229	187	146	119
With SVR	192	181	168	162	155	144	125	88	56	40	28

Van der Meer AJ et al. *JAMA* 2012:308:2584–2593

Effect of cure on the incidence of lymphoma

HCV patients with SVR (n=1048) vs persistently infected (n=2161)



Kawamura et al, *Am J Med* 2007;120:1034–1041