Hepatitis C Introduction and Overview

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Financial Relationships with Commercial Entities

Dr Saag has received research grants and support awarded to his institution from and served as scientific advisor to Merck, Proteus, ViiV Healthcare, and Gilead Sciences, Inc. (Updated 09/18/18)

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Learning Objectives

After attending this presentation, learners will be able to:

- List the genotypes of HCV and how they relate to treatment effects
- Stage HCV infection and describe why it is important to accurately stage
- Recall the clinical presentation of advanced liver disease (cirrhosis)
- Describe emerging treatments of HCV and how the changing landscape will impact treatment decisions in the near future
- List the new changes to the HCV Guidelines (Sept 2018)

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ARS Question #1: Which test most accurately stage liver fibrosis?

1. Fibroscan
2. Fibrosure
3. APRI
4. Liver biopsy
5. Liver percussion

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ARS Question #2: What percent of persons with chronic HCV infection develop cirrhosis over 30 years?

1. 0 – 5%
2. 5% – 20%
3. 20% – 50%
4. 50% – 75%
5. >75%

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ARS Question #3: What is the most common genotype of HCV in the United States?

1. Genotype 1
2. Genotype 2
3. Genotype 3
4. Genotype 4
5. Genotype 5–6

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Objectives

- Epidemiology
- Natural History
- Staging
- Genome and Drug Targets
- Viral Kinetics With Therapy
- Current Treatments
- What Does SVR Really Mean?

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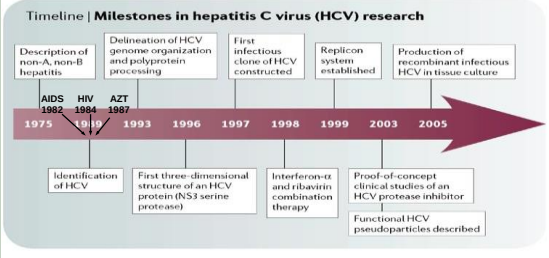
HCV Research Timeline



Moradpour Nature Reviews 2007; 5:453-463

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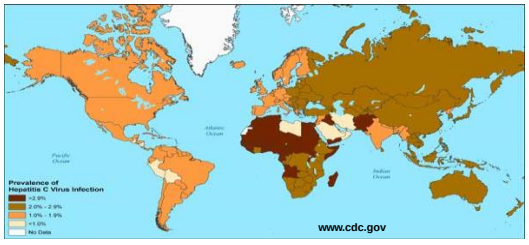
HCV Worldwide



- 170 million infected
- Highest Asia & Africa
- Egypt > 15%
- USA 1.6%
  - 3-4 million infected

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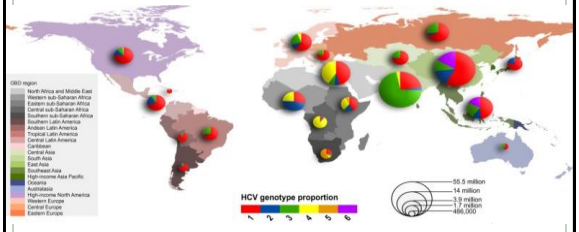
Worldwide prevalence of each HCV genotype by GBD



HCV genotype 1 (83.4 million cases: 46.2%)- one-third of which are in East Asia.
Genotype 3 (54.3 million: 30.1%); genotypes 2, 4, and 6 (22.8%); genotype 5 <1%.
While genotypes 1 and 3 dominate in most countries irrespective of economic
Status: largest proportions of genotypes 4 and 5 are in lower-income countries.

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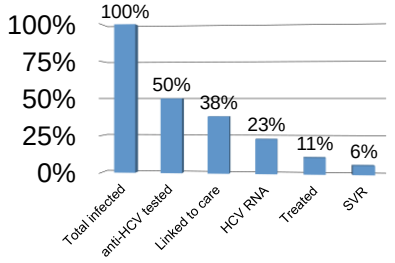
The Treatment Cascade of HCV infection in the US: ~3 – 4 million persons infected



Adapted from Holmberg et al. NEJM 2013

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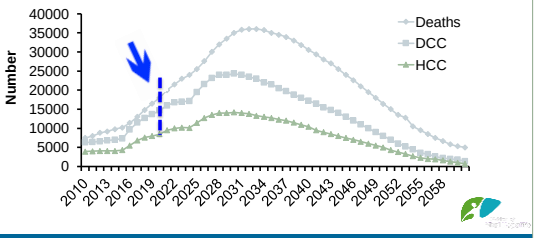
Future Burden of Hepatitis C Related Morbidity and Mortality in the US

- Markov model of health outcomes
  - Of 2.7 M HCV infected persons in primary care
    - 1.47 M will develop cirrhosis
    - 350,000 will develop liver cancer
    - **897,000 will die from HCV-related complications**



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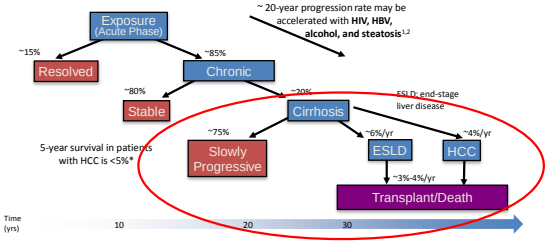
Natural History of HCV Infection



*NIH Consens Statement. June 10-12, 2002;19(3):1-46. NIH Consens Statement. March 24-26, 1997;15(3):1-41.
1. Di Bisceglie AM. Hepatology. 2000;31(4):1014-1018. 2. Bialek SR, Terrault NA. Clin Liver Dis. 2006;10(4):697-715.

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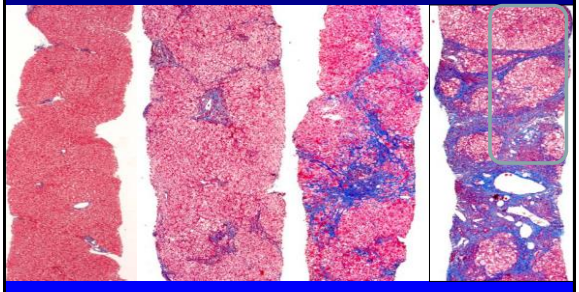
Fibrosis/Cirrhosis



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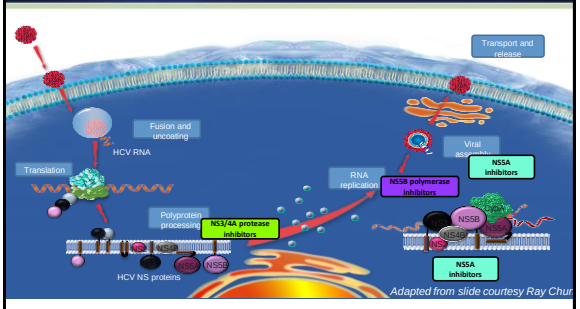
Potential Therapeutic Targets in the HCV Replication Cycle



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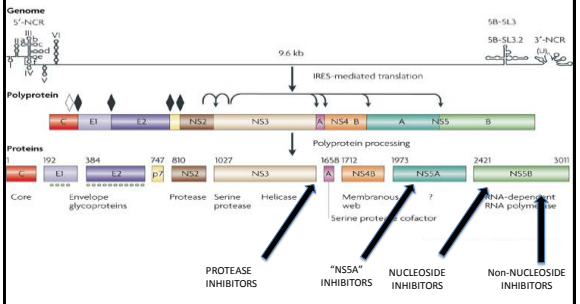

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Suffixes Matter!

- --- PREVIR (Protease / NS3-4a)
- --- ASVIR (NS5a)
- --- BUVIR (NS5b)

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Agents and Regimens: Fall 2017

	Antiviral			
	NS3	NS5A	Non-Nuc NS5B	Nuc NS5B
Ledipasvir/sofosbuvir FDC		⊙		⊙
Paritaprevir/r/ombitasvir FDC + dasabuvir	⊙	⊙	⊙	
Simeprevir + sofosbuvir	⊙			⊙
Glecaprevir / pibrentasvir FDC	⊙	⊙		
Sofosbuvir + daclatasvir		⊙		⊙
Elbasvir/grazoprevir FDC	⊙	⊙		
Velpatasvir/sofosbuvir FDC Velpat/ Sof / voxilaprevir FDC	⊙ ⊙	⊙ ⊙		⊙ ⊙

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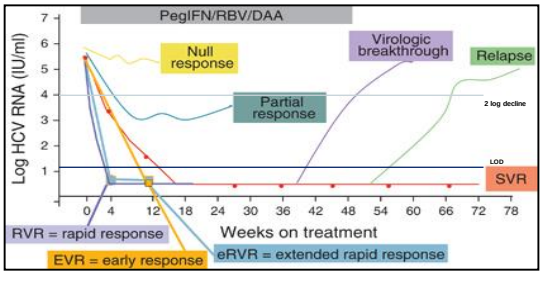
On Treatment Viral Kinetics



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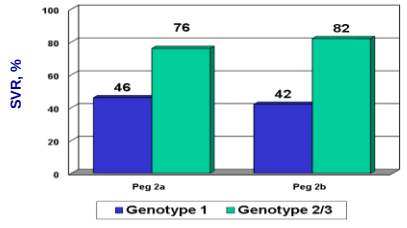
Chronic HCV prior SOC



- Pegylated IFN + RBV
- 48-72 weeks
- Significant AEs
- Response > GT 2/3

Fried MW, *NEJM* 2002
Manns MP, *Lancet* 2001

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Antiviral HCV treatments (FDA-approved as of September, 2017)

Monotherapies

IFN-2a
IFN-2b
PEG-IFN 2a
PEG-IFN 2b

IFN-2a + Ribavirin
IFN-2b + Ribavirin
PEG-IFN 2a + Ribavirin*
PEG-IFN 2b + Ribavirin

PEG-IFN + ribavirin plus either:
Boceprevir (GT1)
Telaprevir (GT1)
Simeprevir (GT1)

In combination with other agents:
Sofosbuvir

Combination Therapies

Elbasvir + Grazoprevir (GT 1, 4)

Ledipasvir + Sofosbuvir (FDC, GT1,4,5,6)

Daclatasvir + Sofosbuvir (GT1,3)*§

Simeprevir + Sofosbuvir (GT1)

Paritaprevir / ritonavir / ombitasvir (FDC) + dasabuvir (GT1)

Paritaprevir / ritonavir/ ombitasvir (FDC) (GT4)

Pangenotypic Regimens (GT 1 – 6)

Velpatasvir / Sofosbuvir FDC

Voxilaprevir / Velpatasvir / Sofosbuvir FDC

Glecaprevir / Pibrentasvir FDC

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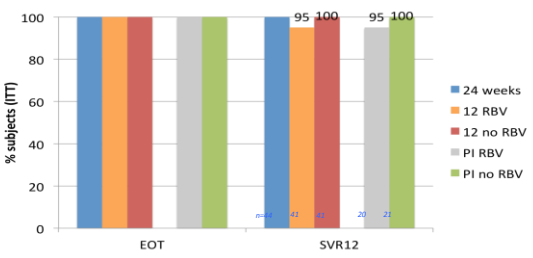
Sofosbuvir plus Daclatasvir for GT1



No documented virologic failures.
All failures due to missing sample/lost to follow-up or re-infection.

Predictors of relapse to sofosbuvir-based regimens

RB
SO

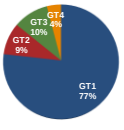
12 week
FISSION
POSITRON
FUSION
VALENCE
n=285

RBV
SOF

24 week
VALENCE
n=247

PE
RB
SO

12 week
ATOMIC
NEUTRINO
n=339



Who will do poorly with currently-available SOF-based regimens?

Results: Predictors of Relapse
Univariate Regression Analysis (combined dataset)

Factor	Odds Ratio	p-Value
Black race	1.7	0.15
Hispanic ethnicity	0.9	0.86
Male	3.5	<0.001
Age ≥50 y	1.9	0.02
Weight ≥75 kg	3.2	<0.001
IL28B non-CC	2.8	0.001
Cirrhosis	4.3	<0.001
HCV RNA ≥800,000 IU/mL	3.9	0.002
Baseline ALT >1.5 x ULN	1.3	0.23
GT 3 (vs 2)	2.5	0.003
GT 1 (vs 2)	1.5	0.18
GT 3 (vs 1)	1.6	0.06
Treatment experienced	2.8	<0.001

Foster et al. EASL 2014 Abstract 66

Predictors of relapse to sofosbuvir-based regimens

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RB
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12 week
ATOMIC
NEUTRINO
n=339

Who will do poorly with currently-available SOF-based regimens?

Results: Predictors of Relapse
Multivariate Regression Analysis (combined dataset)

Factor	Odds Ratio	p-Value
Treatment experienced	2.3	0.001
Male	2.3	0.01
Weight ≥75 kg	2.5	0.01
IL28B non-CC	3.4	<0.001
Cirrhosis	4.0	<0.001
HCV RNA ≥800,000 IU/mL	4.7	<0.001

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Foster et al. EASL 2014 Abstract 66

Predictors of relapse to sofosbuvir-based regimens

RB
SO

12 week
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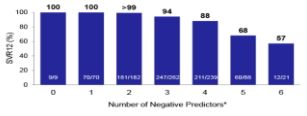
NEUTRINO
n=339

Who will do poorly with currently-available SOF-based regimens?

Six factors associated with relapse:
Treatment-experienced
IL28B non-CC
Male sex
Weight > 75 kg
Cirrhosis
High viral load >800,000 IU/mL

SVR12 Rates by Number of Negative Predictors
Derived From Multivariate Analysis (combined dataset)



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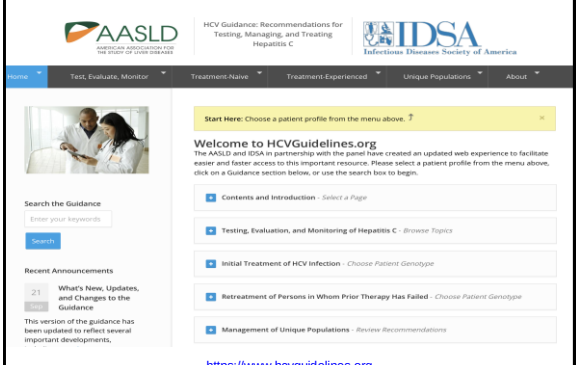
Foster et al. EASL 2014 Abstract 66

Updated Guidelines



https://www.hcvguidelines.org

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ARS Question #4:

Which of the following statements is true of FDA approval of glecaprevir/pibrentasvir?

1. It is an 8 week regimen only in patients without cirrhosis
2. It is a 12 week regimen regardless of presence of cirrhosis
3. It is an 8 week regimen only in treatment naïve patients
4. It is a 16 week regimen in patients with prior treatment experience to DAA
5. It is a single daily dosed pill

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Glecaprevir (NS3)/pibrentasvir (NS5A)

- Co-formulated – 3 pills once daily
- Pangenotypic
- Next generation
  - Active vs NS3 RAS at 80, 155, 168 and NS5A RAS at 28, Q30, 31, 93
  - A30K associated with failure in GT3 infection
- Negligible renal excretion
- Contains a protease inhibitor
- Has interaction with acid suppressing meds

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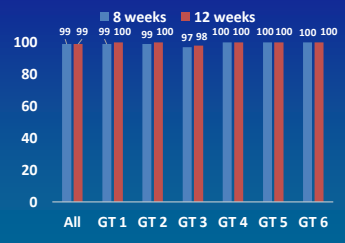
Glecaprevir/pibrentasvir: no cirrhosis

- 8 (N=828) vs 12 (N=1076) weeks
- TN and TE
  - PEG, RBV, SOF
  - No DAA otherwise
- Relapse <1%
- Tx emergent RAS
- TN GT3 may need 12W
- TE GT3 – may need 16 weeks



Puoti et al. EASL 2017

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ARS Question #5:

Which of the following statements is true of FDA approval of sofosbuvir/velpatasvir/voxilaprevir?

1. It is an 8 week regimen only in patients without cirrhosis
2. It is a 12 week regimen regardless of presence of cirrhosis
3. It is an 8 week regimen regardless of prior treatment experience to DAA
4. It is approved for all genotypes across all DAA failures

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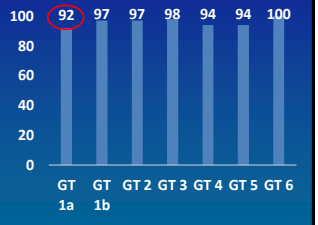
Sofosbuvir/velpatasvir/voxilaprevir: 8 vs 12 weeks of SOF/VEL

- POLARIS 2
  - GT 1-6 w/ and w/o cirrhosis
- POLARIS 3
  - GT 3 with cirrhosis
  - 2 relapses
- Pooled analysis
  - N=611
- 8 weeks of therapy failed non-inferiority in POLARIS-2
  - 3.8% relapse
  - 14 GT1a (regardless of cirrhosis)



Roberts et al. EASL 2017; Jacobson et al. Gastro 2017

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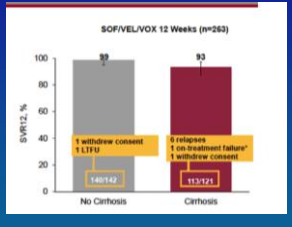
Sofosbuvir/velpatasvir/voxilaprevir NS5A Inhibitor DAA -Experienced

- POLARIS 1
  - GT 1-6 (30% GT3)
- 12 weeks of therapy
  - vs placebo
- Including compensated cirrhosis (46%)
- 2.2% relapse
- 4 GT 3 relapse – all 3a and ¾ had BL NS5A RAS
- No treatment emergent RAS
- all VF had cirrhosis (6 R, 1 VBT)



Bourliere et al. NEJM 2017

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Does Failure = Resistance?

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Key HCV Resistance Concepts

- HCV resistance associated substitutions (RASs) can be present without drug exposure
- HCV RASs impacts treatment responses in specific situation
- HCV is resistance is NOT absolute
- Patient characteristics are just (if not more) important than RASs
- Future regimens appear to obviate the need for most resistance testing

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Resistance Characteristics of HCV Antiviral Classes

Class	Antiviral Potency	Genotype Activity	Resistance Barrier	FDA Approvals
NS3 Protease Inhibitors	+++ to ++++	1, 4 (± 2, 3, 6)	Low to High ↓	**Simeprevir (2013)** **Paritaprevir (2014)** **Grazoprevir (2016)** **Voxilaprevir (2017)** **Glecaprevir (2017)**
NS5B Nucleotide	++++	1-6	Very High	**Sofosbuvir (2013)**
NS5B Nonnucleoside	++	1	Low	**Dasabuvir (2014)**
NS5A Inhibitors	++++	1, 4, 6 (± 2, 3)	Low To High ↓	**Ledipasvir (2014)** **Daclatasvir (2015)** **Ombitasvir (2014)** **Elbasvir (2016)** **Velpatasvir (2016)** **Pibrentasvir (2017)**

*anticipated US FDA approvals

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Broad Cross-Resistance With "Early Generation" NS5As

Fold Change	Genotype 1a				Genotype 1b	
	M28T	Q30R	L31M/V	Y93H/N	L31V	Y93H/N
Ledipasvir	20x	> 100x	> 100x/ > 100x	> 1000x/ > 10,000		> 100x/--
Ombitasvir	> 1000x	> 100x	< 3x / > 100x	> 10,000x/ > 10,000x	< 10x	20x/50x
Daclatasvir	> 100x	> 1000x	> 100x/ > 1000x	> 1000x/ > 10,000x	< 10x	20x/50x
Elbasvir	20x	> 100x	> 10x / > 100x	> 1000x/ > 1000x	< 10x	> 100x/--
Velpatasvir	< 10x	< 3x	20x/50x	> 100x/ > 1000x	< 3x	< 3x/--
Pibrentasvir	< 3x	< 3x	< 3x	< 10x/< 10x	< 3x	< 3x/< 3x
Ruzasvir	< 10x	< 10x	< 10x	< 10x	< 10x	< 10x

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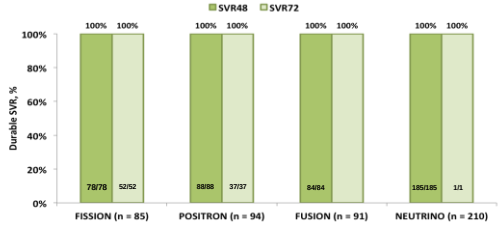
Long-Term Follow-Up of SOF Phase 3 Studies



- Median time to follow-up: 170 days (~ 24 weeks) after SVR24
- Of 480 patients with SVR24 from phase 3 trials, 435 (91%) and 90 (19%) had post-treatment week 48 and 72 data, respectively

Cheng W, et al. EASL 2014. P1112.

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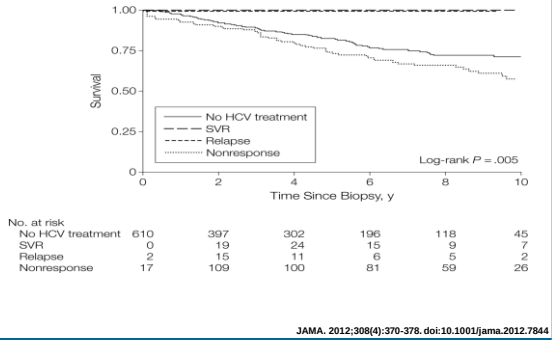
The JAMA Network

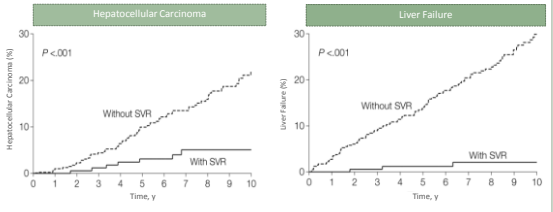


No. at risk

No HCV treatment	610	397	302	196	118	45
SVR	0	19	24	15	9	7
Relapse	2	15	11	6	5	2
Nonresponse	17	109	100	81	59	26

JAMA. 2012;308(4):370-378. doi:10.1001/jama.2012.7844

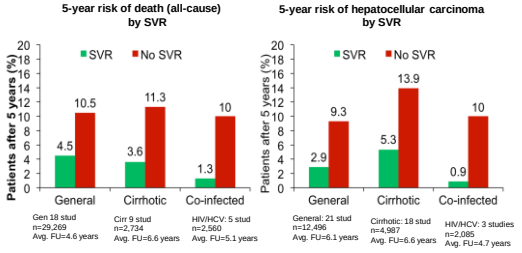
Clinical Benefits of SVR: Liver Failure, HCC



- 530 Europeans followed for a median 8.4 years after HCV treatment
- 192 (36%) achieved SVR

van der Meer AJ, et al. *JAMA*. 2012;308(24):2584–2593.

Effects of SVR on the risk of liver transplant, hepatocellular carcinoma, death and re-infection:
meta analysis, 129 studies, 34,563 patients



Question-and-Answer

Remember to raise your hand and wait until you have the microphone before you ask your question—we are recording!

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