Oh, the Places You'll Go: Hepatitis C in 2025

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Case of XY

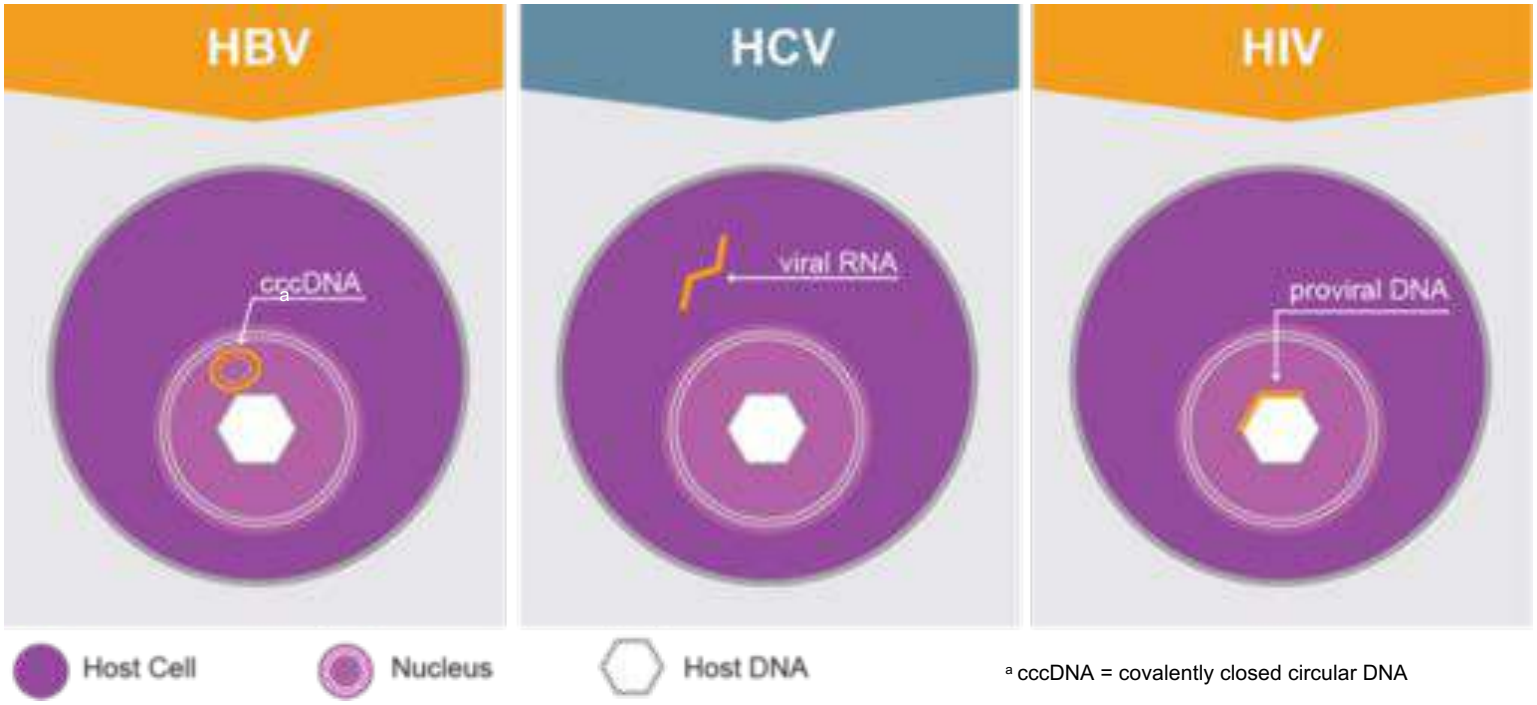
- 27 year old Caucasian man found to have "abnormal LFTs" during life insurance evaluation.
- No symptoms
- BMI 34 kg/m^2
- 2-3 beers on the weekends
- Remote history of intranasal cocaine
- No family history of liver disease
- PE: central obesity

Hepatitis C: The Basics

- Flaviviridae family:
  - Relatives: Yellow fever, Dengue.
- (+) single stranded linear RNA virus
- Mimics the cellular mRNA (messenger RNA) molecule
- Exploits host cellular apparatus to synthesize proteins during replication

Why is HCV Curable?

- Unlike some other viruses, HCV RNA is only present in the cytoplasm (not in the nucleus) of the host cell[1]
- Without the stable, genetic-material reservoir of the nucleus created by other viruses, the possibility exists for HCV cure by treatment[1]

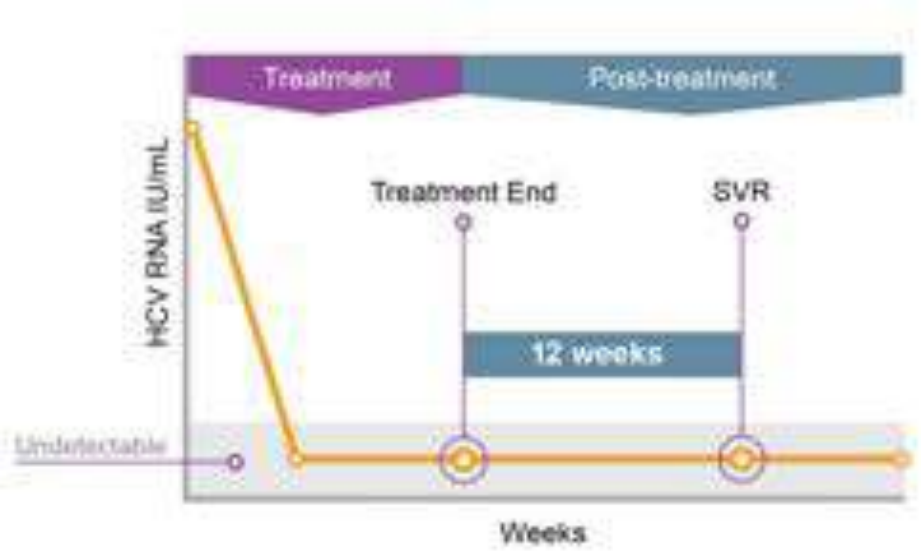


[a] cccDNA = covalently closed circular DNA

1. Soriano V, Perelson AS, Zoulim F. Why are there different dynamics in the selection of drug resistance in HIV and hepatitis B and C viruses? *J Antimicrob Chemother*. 2008;62(1):1-4.

Defining HCV Cure

- **Goal of treatment is cure**
- Cure = sustained virologic response (SVR12) = undetectable levels of HCV in the blood at 12 weeks after therapy is complete[1,2]
- In some instances, HCV treatment does not result in cure
  - Virus does not reach undetectable levels (non-responder)
  - Virus does not stay undetectable after therapy completion (relapser)



1. US Department of Health and Human Services, Center for Drug Evaluation and Research. Draft Guidance for Industry. Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment. October 2013.
2. AASLD, IDSA, IAS-USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed December 7, 2015.

Good News: CDC Update

- **Universal hepatitis C screening**: Hepatitis C screening at least once in a lifetime for **all adults** aged 18 years and older

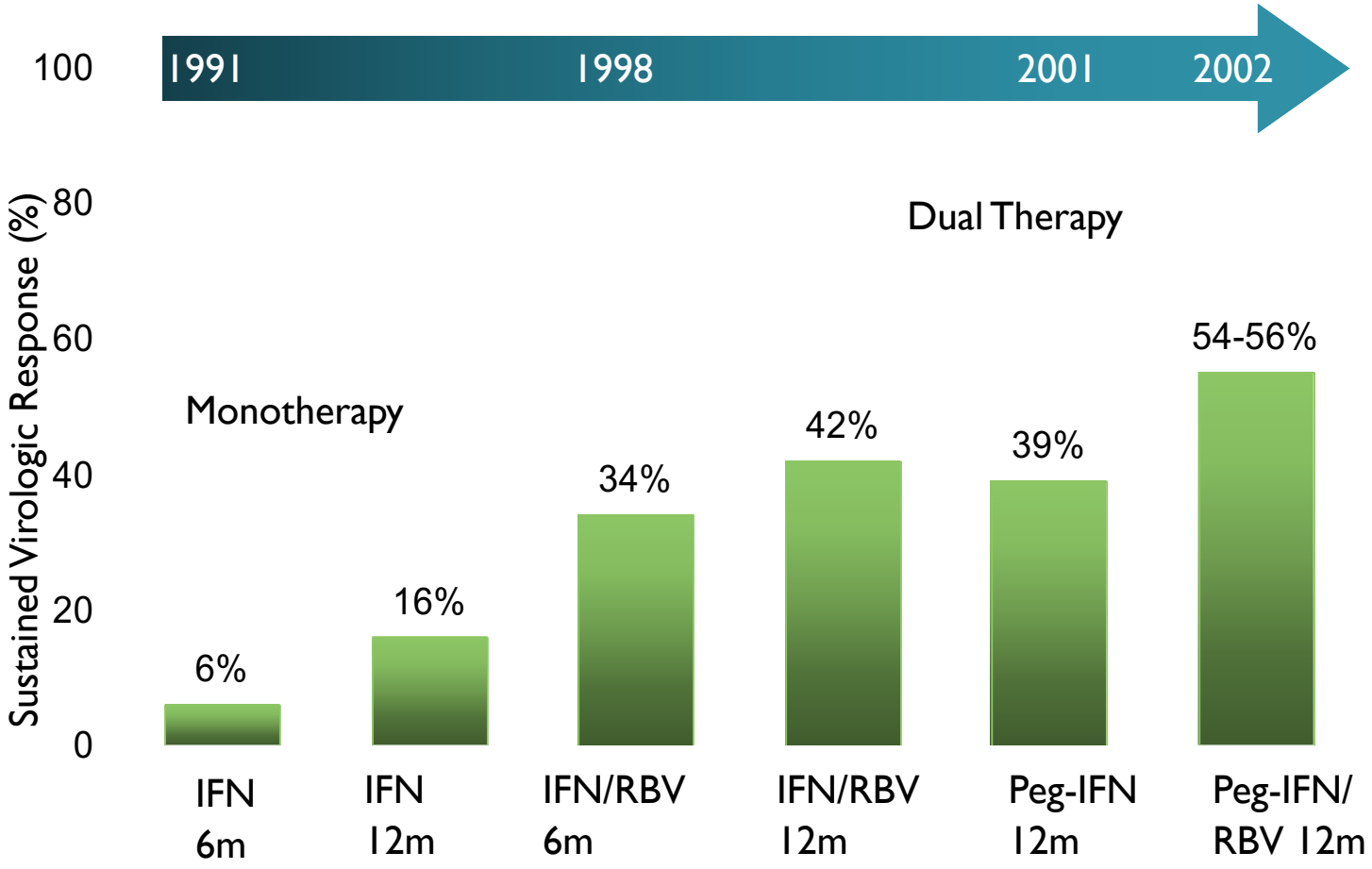
- Hepatitis C screening for **all pregnant women during each pregnancy**

Hepatitis C: How to Treat?

"You have brains in your head.
You have feet in your shoes.
You can steer yourself
any direction you choose.
You're on your own. And you know what you know.
And YOU are the one who'll decide where to go..."

Dr. Seuss

Improvements in Therapy of HCV: 20th century

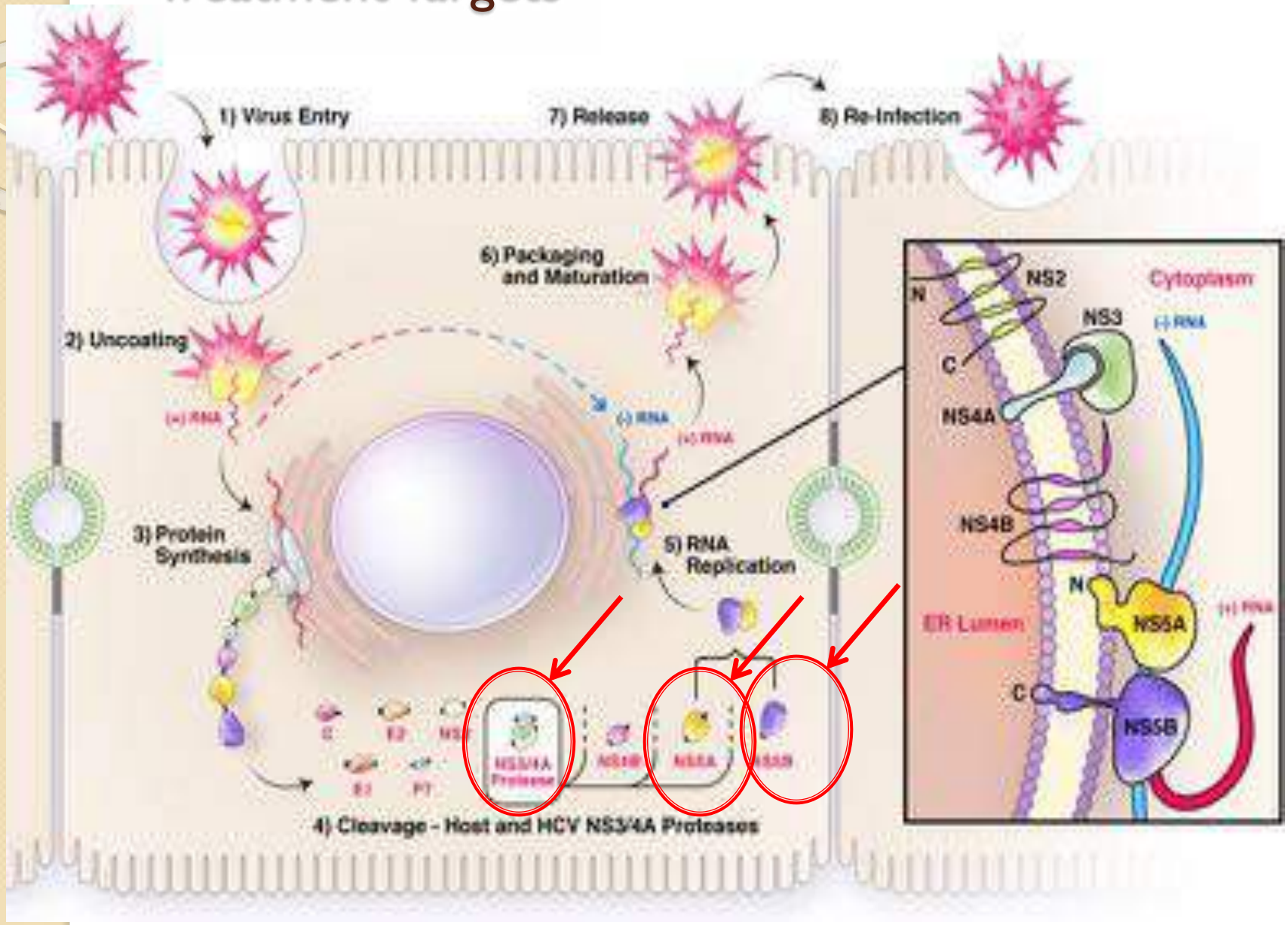


Strader DB et al. *Hepatology* 2004;39:1147-1171

Side effects of pre-DAA Hepatitis C therapy

- Interferon:
  - Flu-like symptoms
  - Bone marrow suppression
  - Neuropsychiatric disorders
- Ribavirin
  - Hemolytic anemia
- **Potential for worsening liver disease**

Treatment Targets



Sofosbuvir: The Game Changer

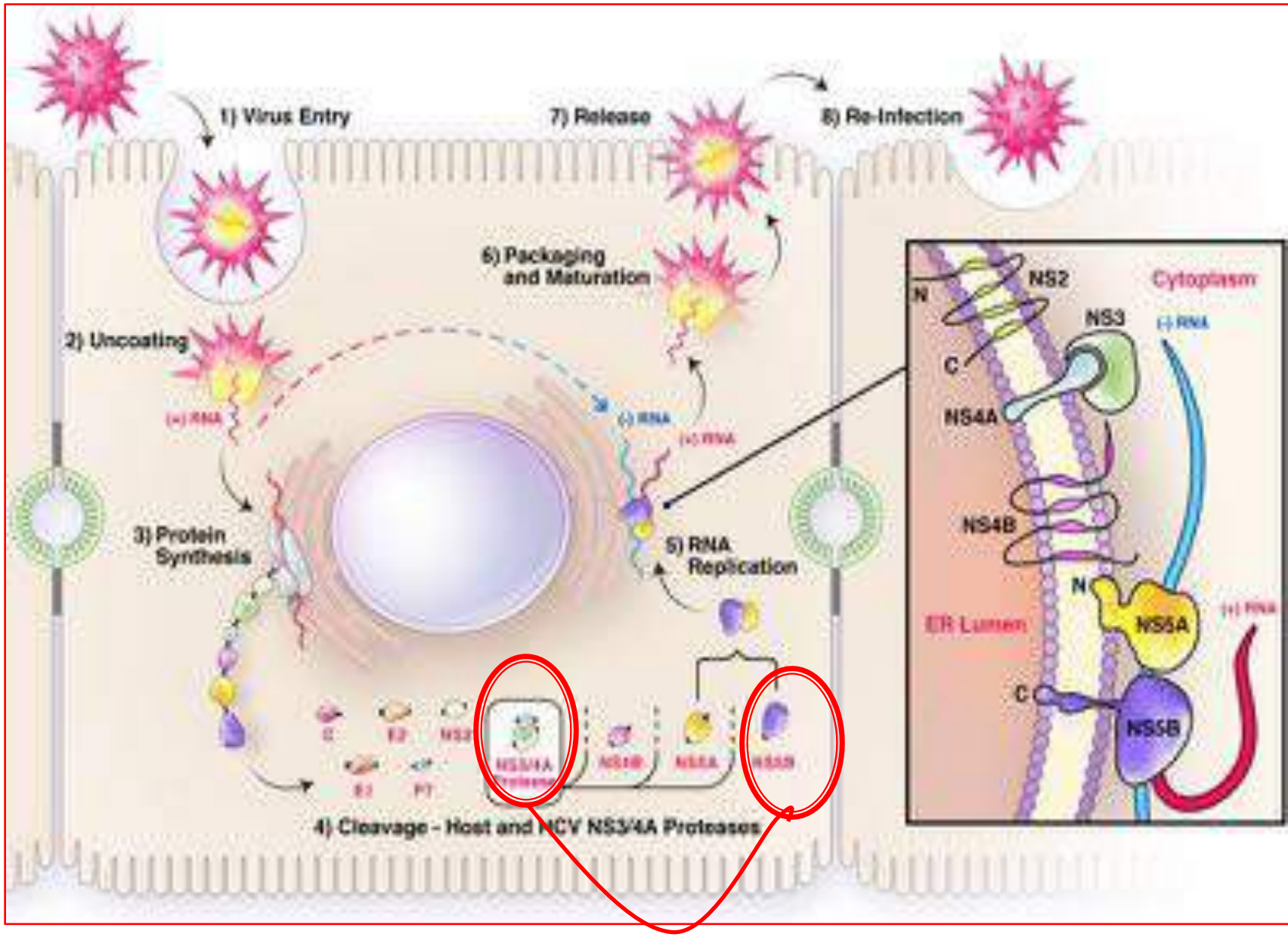
- NEUTRINO
  - Primarily Genotype 1 and 4
  - 12 weeks of triple therapy (still with INF)
  - 90% SVR
  - 2% discontinuation rate due to side effects
- FISSION/POSITRON/VALENCE
  - Genotype 2 and 3
  - 12-24 weeks of dual, all pill therapy
  - Genotype 2: 97 % SVR in non-cirrhotics, 12 wks
  - Genotype 3: 84% SVR, 24 wks
  - 2% discontinuation rate due to side effects
- FDA approval December, 2013

NEJM, April 23, 2013

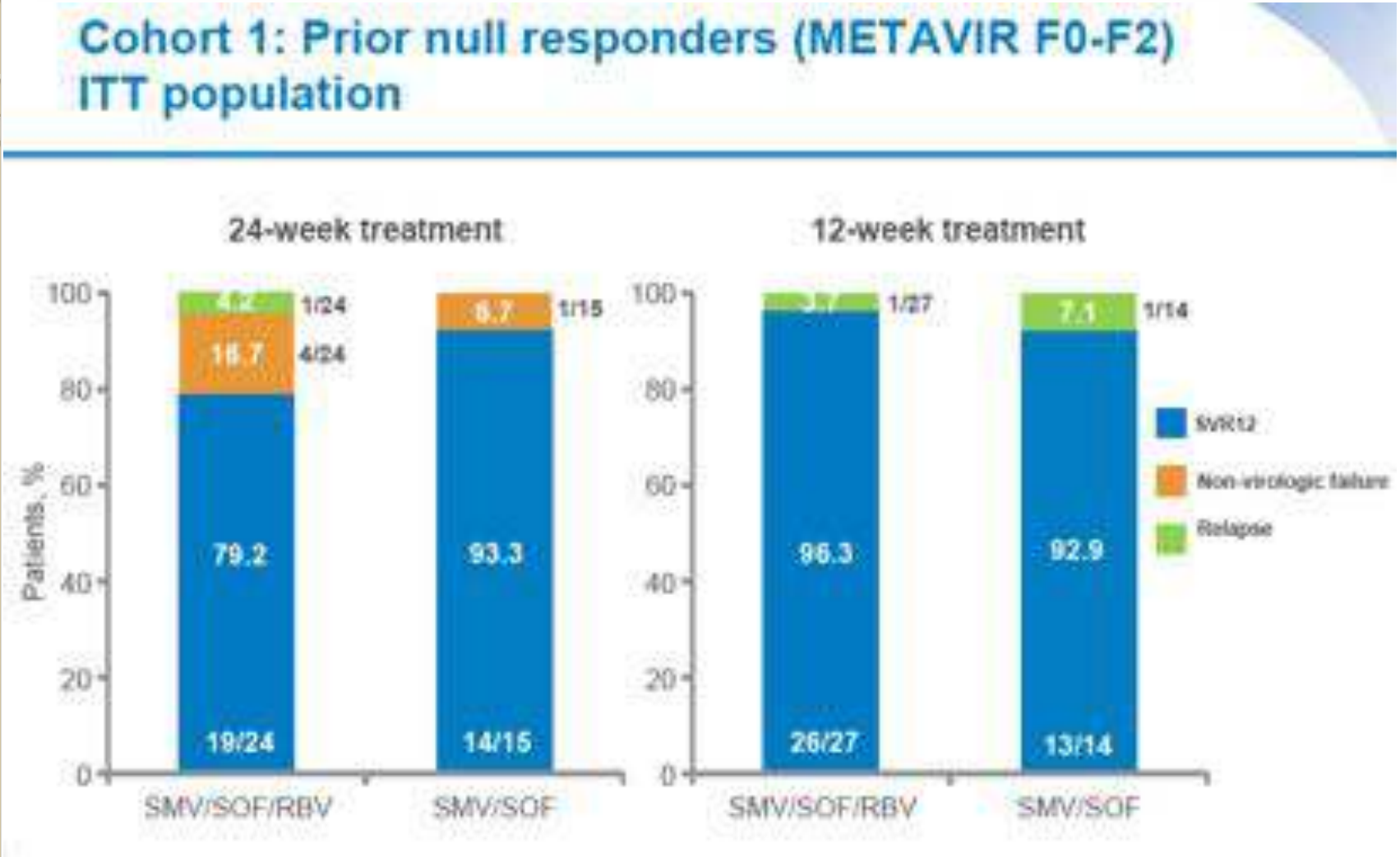
Unmet needs

- Decompensated cirrhosis
- End stage renal disease
- Interferon intolerant
- Pre- and post-transplant

Simeprevir: new NS3/4A protease inhibitor. A me too drug?



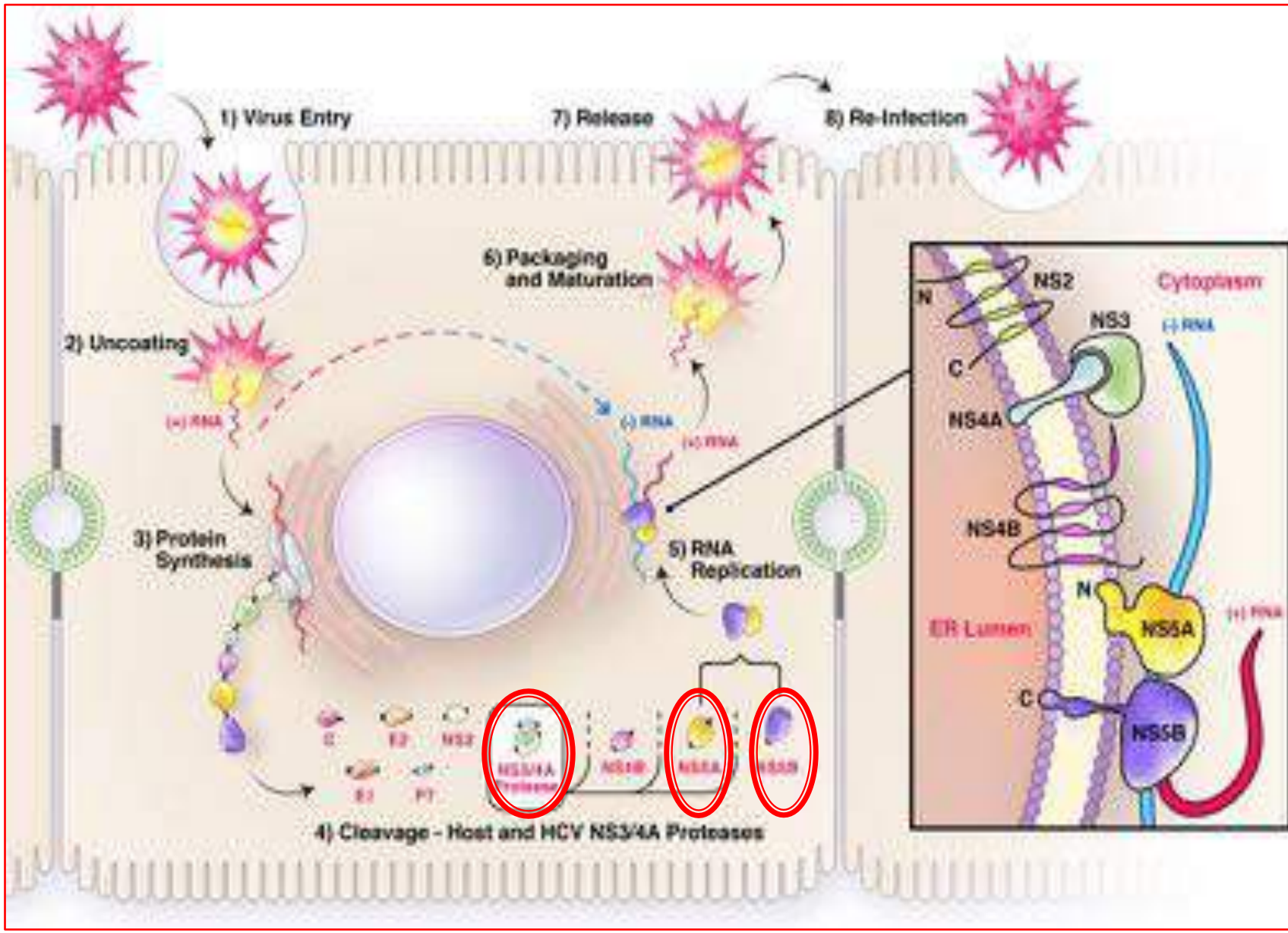
COSMOS: Sofosbuvir +Simeprevir



Thinking outside the FDA box

- Many patients are interferon ineligible and are dying
- Off label prescribing soars
- AASLD guidelines 2014 support the use of SIM+SOF in certain populations
- FDA approval of SIM-SOF Nov, 2014

More Combinations Please!



Treatment Targets in 2025

- NS3/4A protease: SimePRevir
  - Protease inhibitor
  - Resistance possible
- NS5A: ElbAsvir
  - inhibitor of the NS5A protein
  - Resistance possible
- NS5B: SofosBuvir
  - Polymerase inhibitor
  - High barrier to resistance

Shall we play?

	NS3/4A	NS5A	NS5B
NS3/4A	STOP	Glecaprevir/Pibrentasvir GT 1, 2, 3, 4, 5 ,6	STOP
NS5A	Glecaprevir/Pibrentasvir GT 1, 2, 3, 4, 5 ,6	STOP	Ledipasvir/Sofosbuvir GT 1,4, 5, 6 Velpatasvir/Sofosbuvir GT 1, 2, 3, 4, 5, 6
NS5B	STOP	Ledipasvir/Sofosbuvir GT 1, 4, 5, 6 Velpatasvir/Sofosbuvir GT 1, 2, 3, 4, 5, 6	STOP

Sofosbuvir + Velpatasvir, and Voxilaprevir = NS5B +NS5A + NS3/4A = used for prior DAA failures, all genotypes

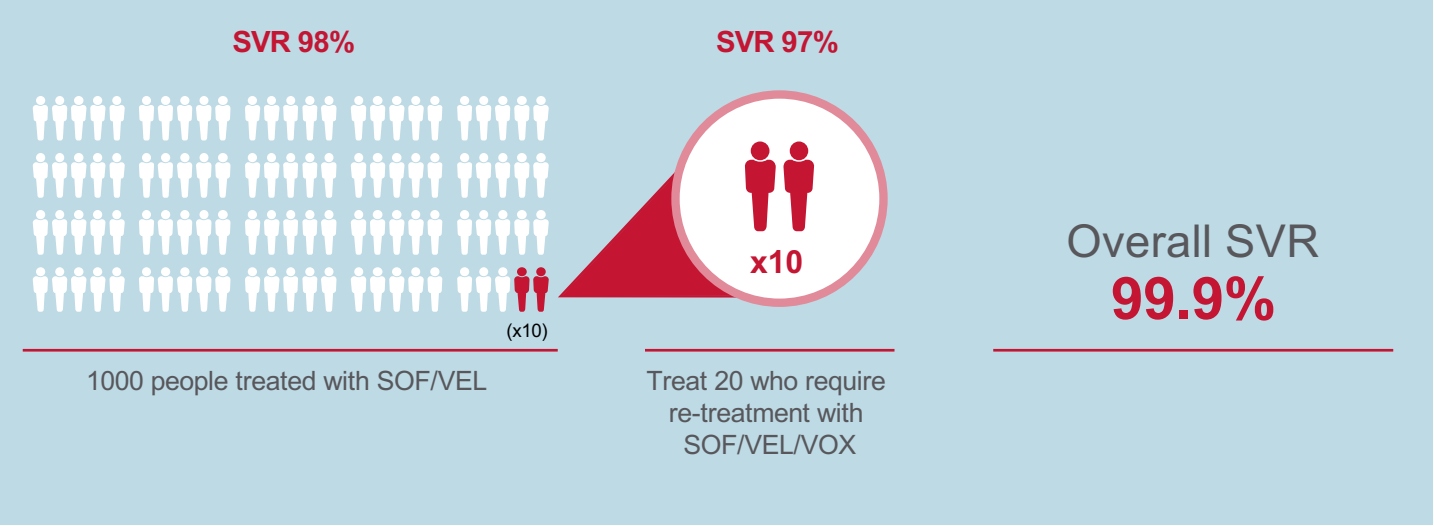
Drug-Drug Interactions and Other Precautions

	NS5A + NS3/4A	NS5A + NS5B
GFR < 30 ml/min	Yes	Yes
Decompensated cirrhosis	No	Yes
Acid Blockers	No	Yes
Amiodarone interaction	No	Yes
Potential for HBV reactivation	Yes	Yes
Causes liver cancer	No	No

Things to know before starting HCV treatment

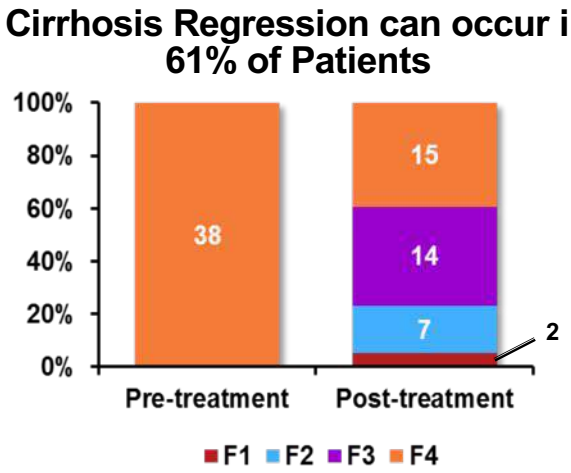
Labs	Imaging	Clinical
• Quantitative HCV RNA • HCV genotype • HBsAg, HBcAb total, HBsAb • Renal function	• R/o HCC • Fibrosis level	• Acid blockers • Amiodarone • Prior HCV Rx • Cirrhosis • Decompensated cirrhosis

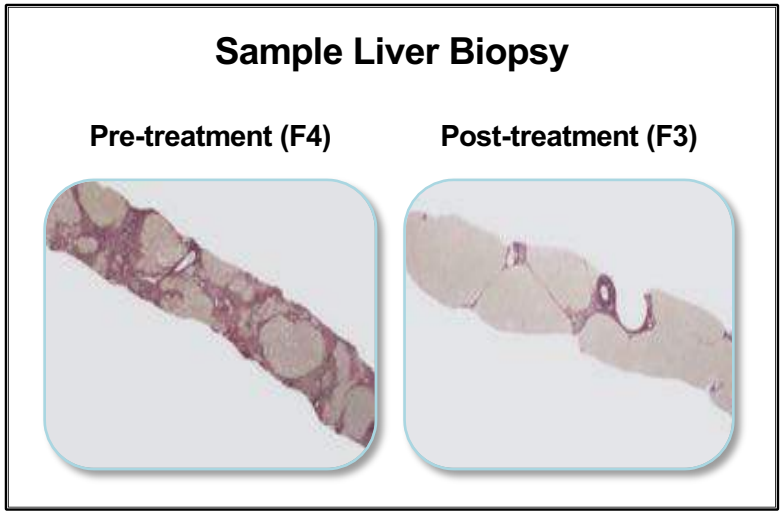
With 99.9% SVR, Elimination of HCV is Achievable



Roberts S, et al. ILC 2017; Poster #SAT-280;

Cirrhosis Regression and Fibrosis Reduction Following SVR

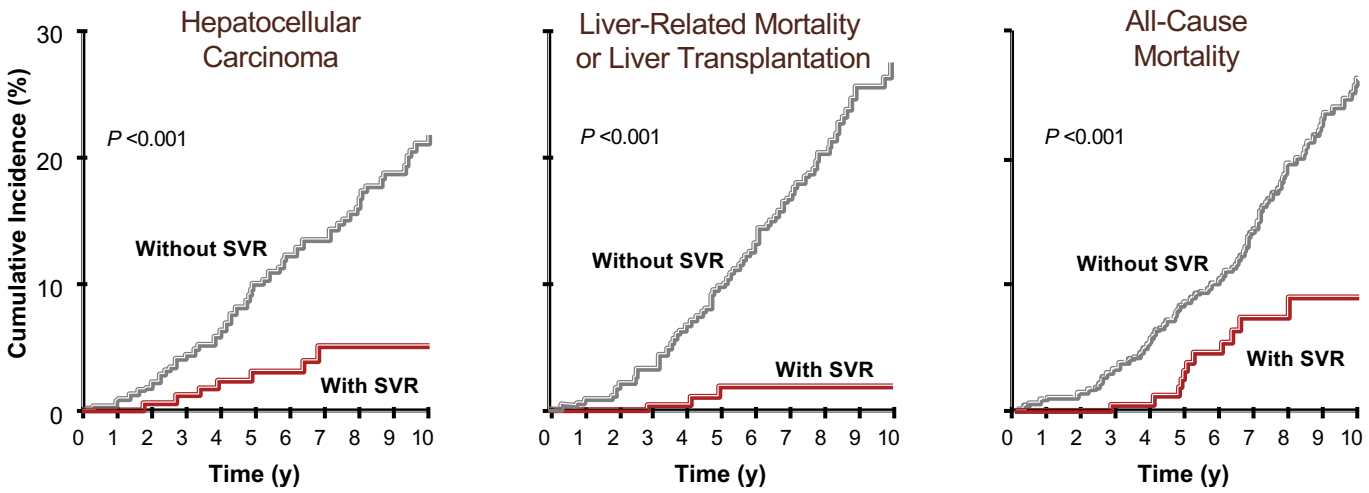




- **Fibrosis Reduction**
  - After treatment, the area of fibrosis decreased in 34/38 (89%) of patients
  - Post-treatment liver biopsies showed a significantly reduced area of fibrosis, with a median individual decrease of 71.8%

D'Ambrosio R, et al. *Hepatology*. 2012;56:532-543.

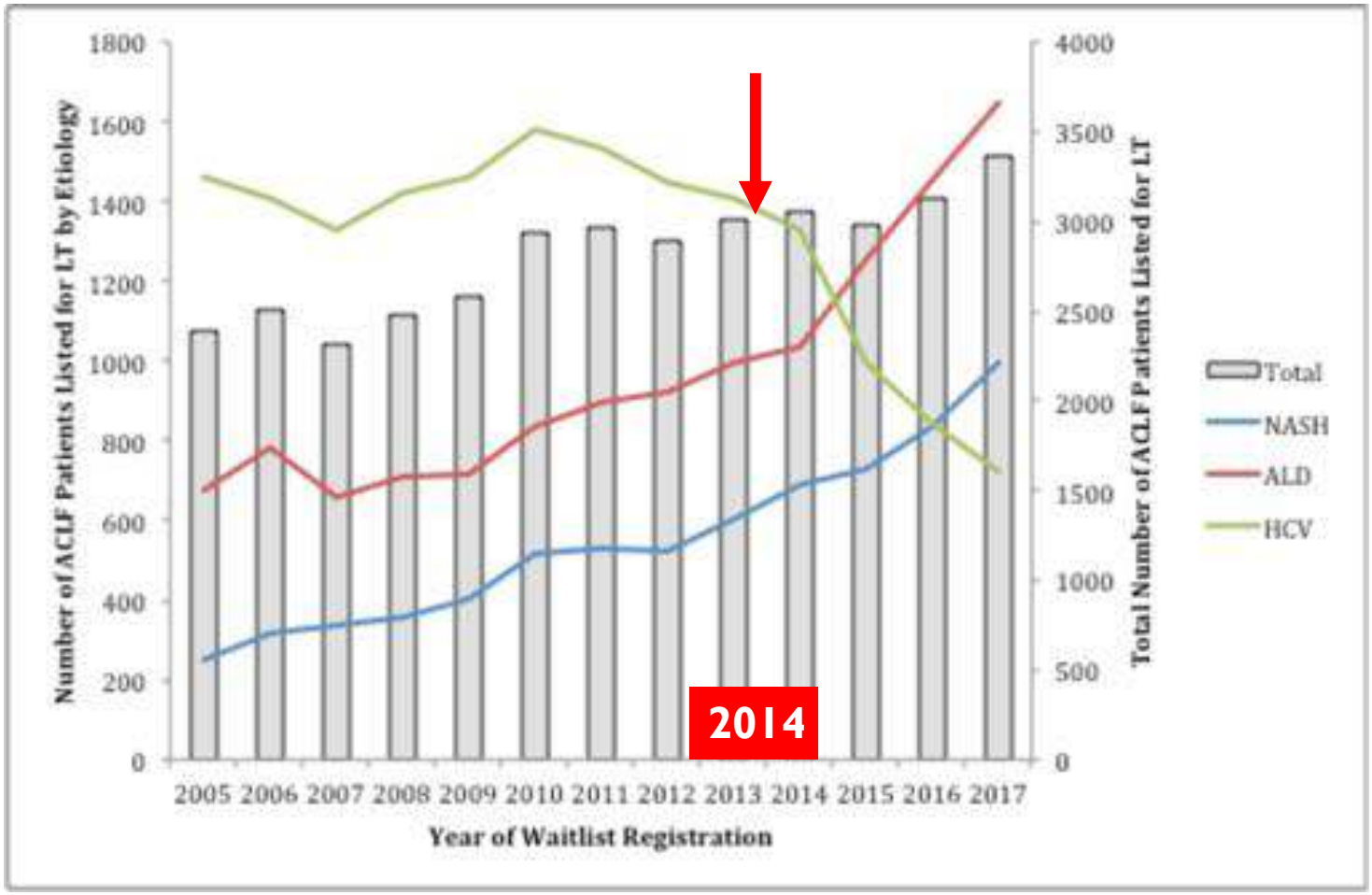
SVR Associated With a Reduction in HCC, Liver-Related Mortality, Transplantation, and All-Cause Mortality



- International, multicenter, long-term follow-up study of 530 consecutive CHC patients with advanced hepatic fibrosis or cirrhosis, who started an IFN-based treatment regimen between 1990 and 2003.
- Median follow-up duration 8.4 years
- Significant reduction of 10-year cumulative incidence of HCC, liver-related mortality or transplantation, and all-cause mortality in patients who achieved SVR

van der Meer AJ, et al. *JAMA*. 2012;308:2584-2593.

Trends in Liver Transplant Etiology of Acute on Chronic Liver Failure: UNOS Registry



In 2017 ALD was the leading etiology nationally, among listed patients with ACLF (n=1649), followed by NASH (n=998), then HCV (n=720)

V. Sundaram et al. Hepatology 2019 #1072

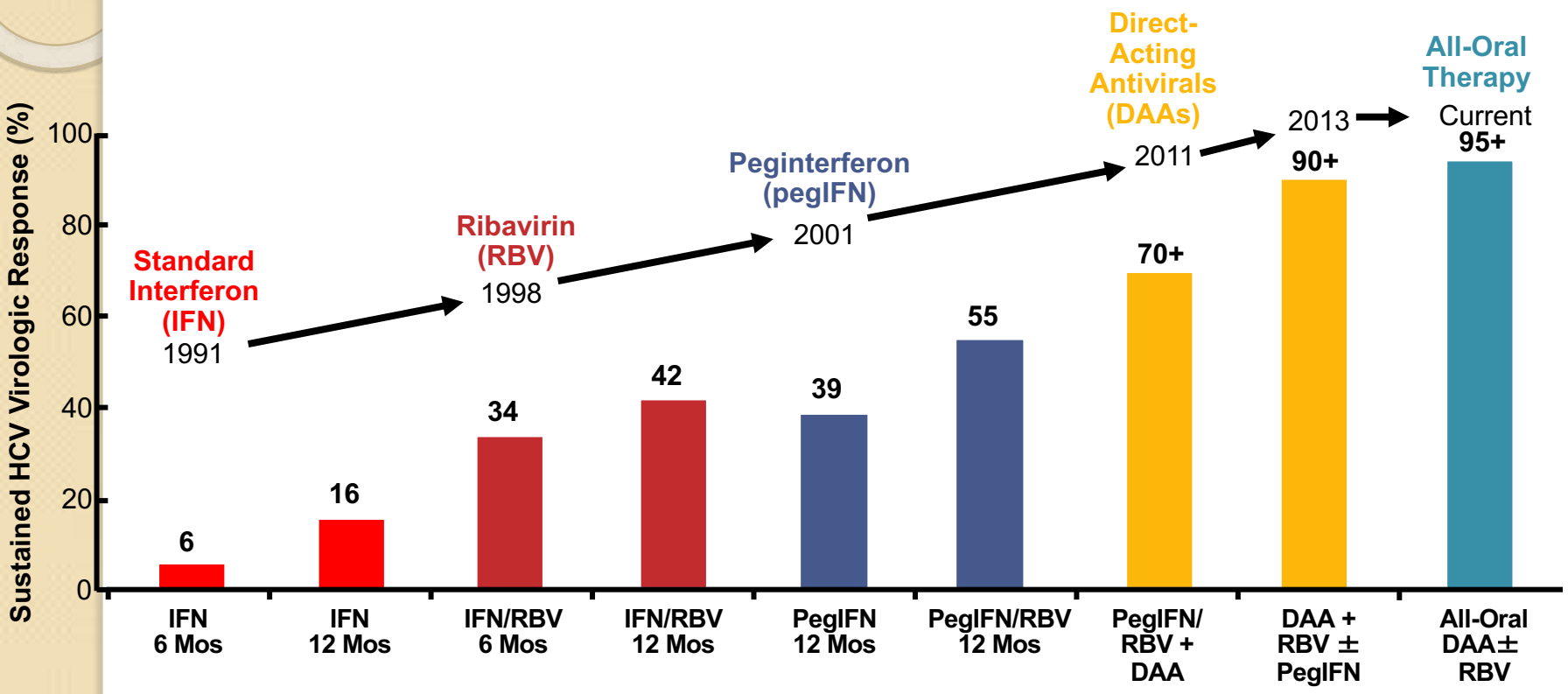
Case of XY

- AST 110, ALT 90
- Normal Alk phos, TB, albumin
- US: increased echogenicity
- FibroScan: F2 fibrosis, S2 steatosis
- HCV ab +, HCV RNA 2 mln, GT1a
- Treated and cured with an 8 week regimen.

What have we learnt?

- Hepatitis C is common
- Only a fraction of patients are diagnosed and even fewer are treated
- CDC advises universal screening!
- Non-invasive assessment of liver fibrosis is available
- Hepatitis C can be cured with a SIMPLE regiment in 8-12 weeks!
- Cirrhosis is reversible!

Current All-Oral Therapies Highly Effective, Simple, Well Tolerated



Everyone should know their ABCs of Hepatitis!

A

HAV ab total
=
immunity

B

HBsAb = immunity
HBsAg = infection
HBcAb total =
exposure

C

HCV Ab
=
infection

And will you succeed?
Yes! You will, indeed!
(98 and ¾ percent guaranteed.)…

You are off to Great Places!
Today is your day!
Your mountain is waiting.
So…get on you way!

Dr. Seuss

Acknowledgements

- Dr. Naoky Tsai
- Dr. Theodor Seuss Giesel