HCV in 2015: What's New?
(short answer: Lots!)

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- Nothing to Disclose: No conflict of interests
- Innovations outpace capacity of the FDA

Objectives

- Review epidemiology and Public Health considerations
- Determining priority for HCV treatment today
  - Evaluating for cirrhosis and hepatocellular carcinoma (HCC)
- Update on new HCV therapies
  - DAAs (direct-acting antivirals)
- Cost considerations

Question 1: Which of the following patient should be screened for HCV?

1. Anyone born before 1965
2. History of IV drug use once
3. History of intranasal cocaine use
4. Recipient of blood transfusion in 1990
5. **All of the above**

CDC: Effectiveness of HCV Testing for Persons Born During 1945-1965

- 3 large primary care health systems (2012-2014)
  - Systematic 1-time HCV test versus usual care (likely risk based or medical indication-based testing)
  - 3 independent HCV testing trials (results available for 2)
    - Trial 1: stratified multi-clinic, individually randomized (9 clinics)
    - Trial 2: cluster randomized (10 clusters)
  - No prior HCV test or infection
- Birth-cohort HCV testing
  - 4 times more effective in identifying persons with HCV infection compared with usual care

HCV Testing Results

	HCV Identified (per 1000 eligible)
Trial 1	
Birth cohort testing (n=2996)	2.7
Usual care (n=5996)	0.3
Trial 2	
Birth cohort testing (n=2996)	3.0
Usual care (n=5996)	1.1

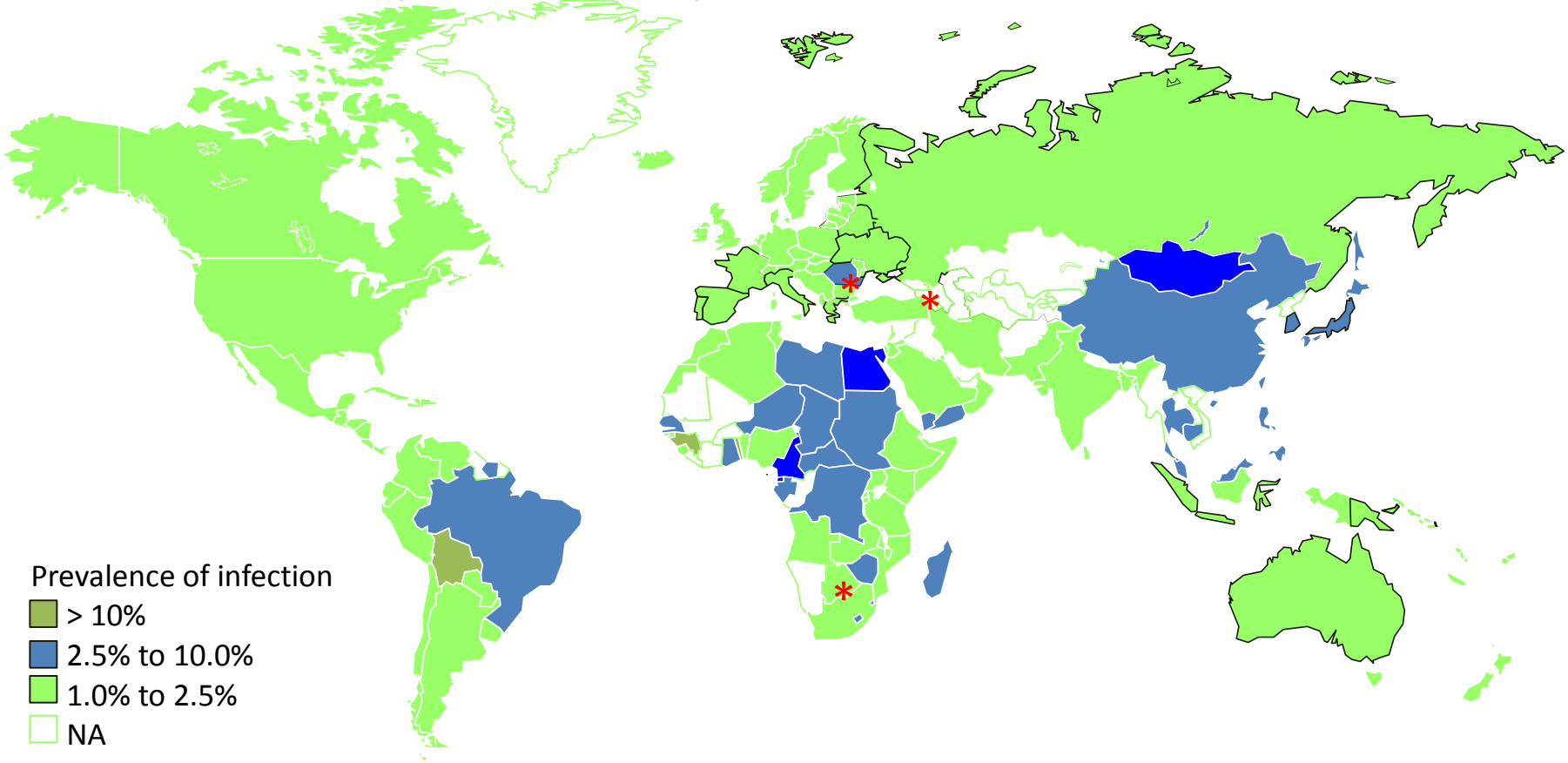
Relative Probability of Identifying HCV-Positive Patients Using Birth Cohort Versus Usual Care

Risk Ratio: 4.0 (1.9-8.7)

Smith BD, et al. *Hepatology.* 2014;60(suppl 1):295A. Abstract 194.

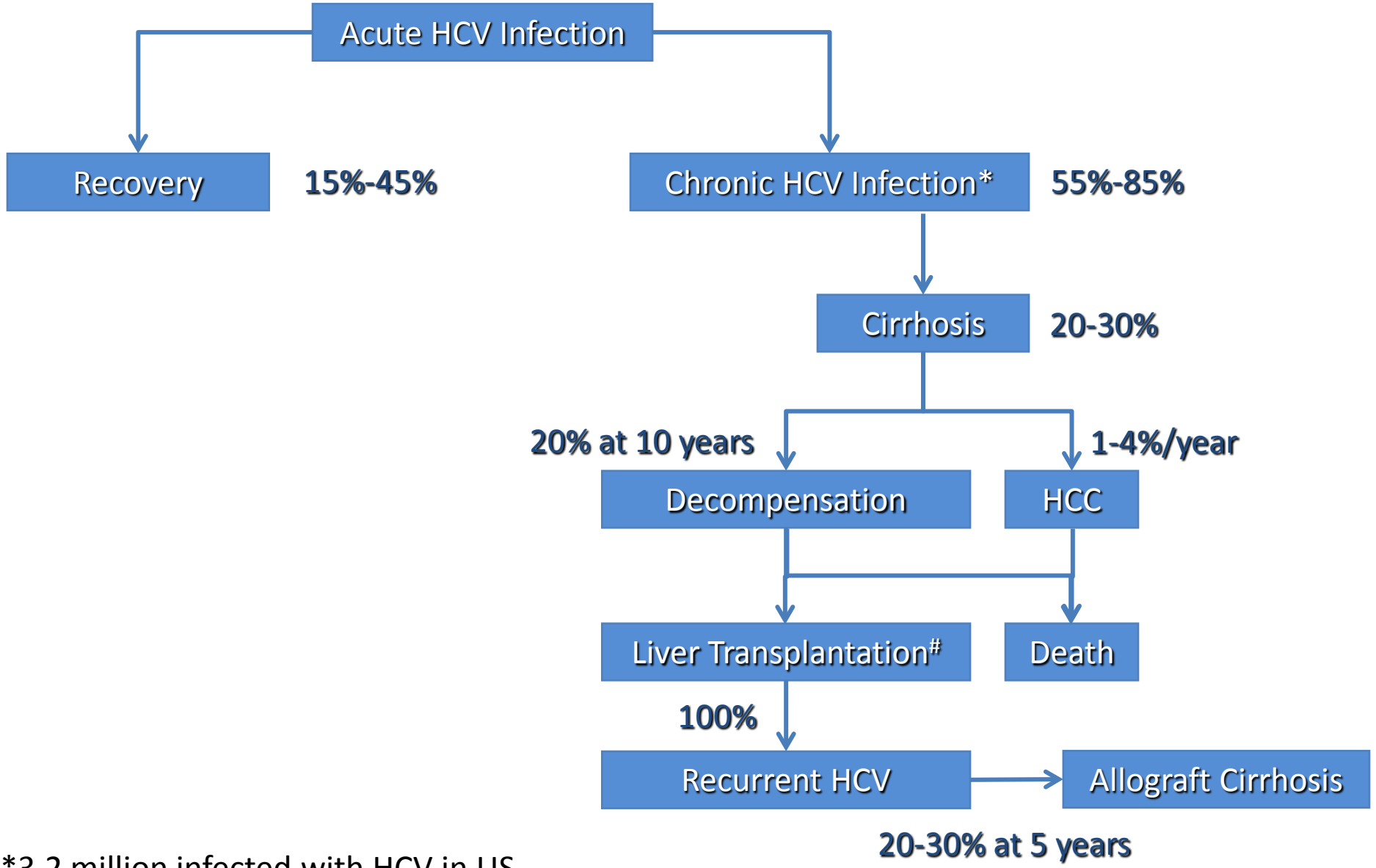
Estimated 170 Million Persons With HCV Infection Worldwide

- 3-4 million newly infected each yr worldwide

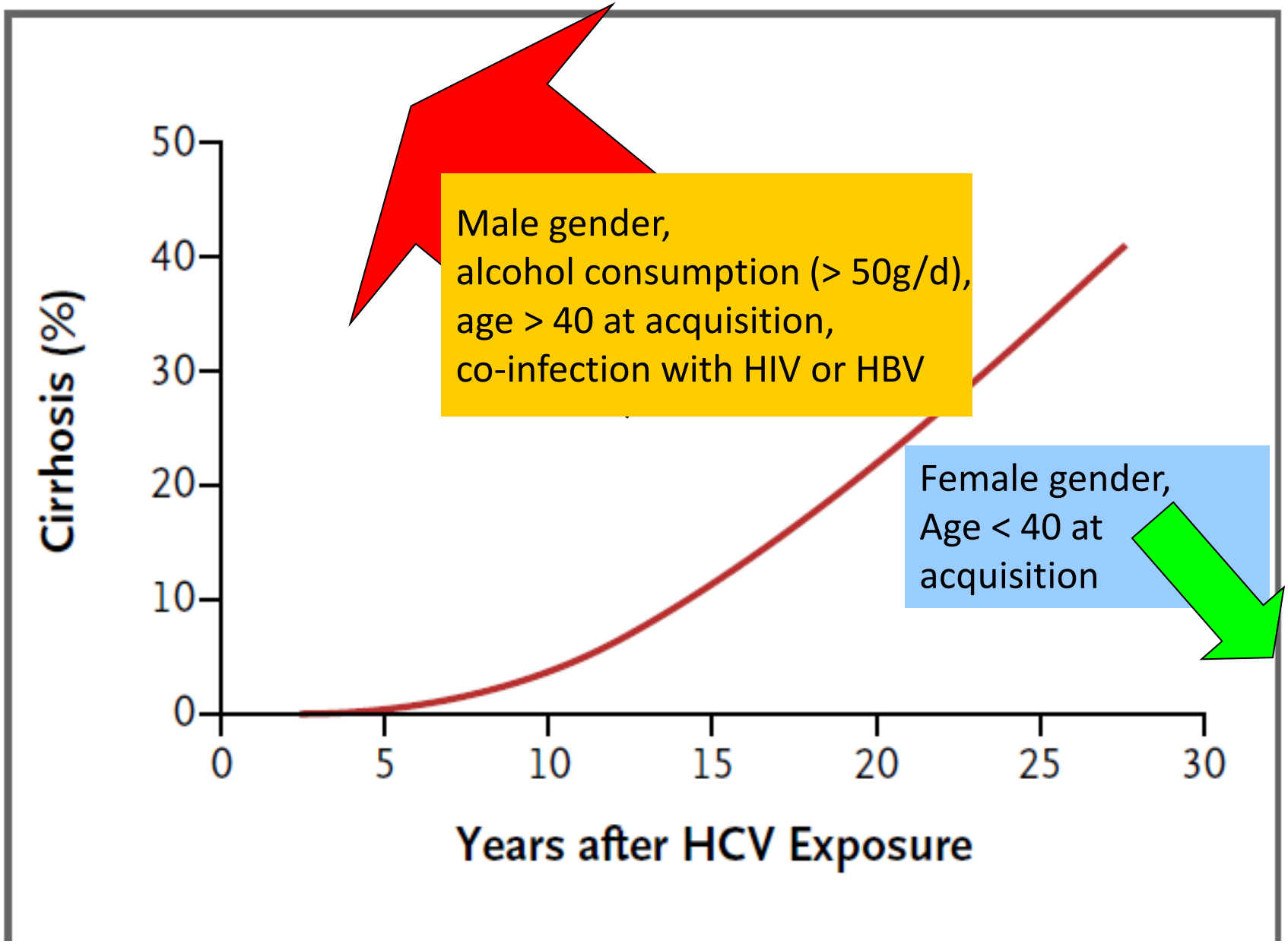


World Health Organization 2008. Available at: http://www.who.int/ith/es/index.html.

Natural History of HCV Infection



*3.2 million infected with HCV in US


Male gender,
alcohol consumption (> 50g/d),
age > 40 at acquisition,
co-infection with HIV or HBV
Female gender,
Age < 40 at acquisition
Cirrhosis (%)
50
40
30
20
10
0
0
5
10
15
20
25
30
Years after HCV Exposure

Measuring Fibrosis (F)

- Liver Biopsy Gold Standard
  Sampling Error
  Inconvenient and Risky

- Elastography US- or MR-based
  FDA-approved 2013
  Convenient and Safe
  Accuracy in high BMI?

- Serum Markers Good at high and low ends

Diagnosis of Cirrhosis

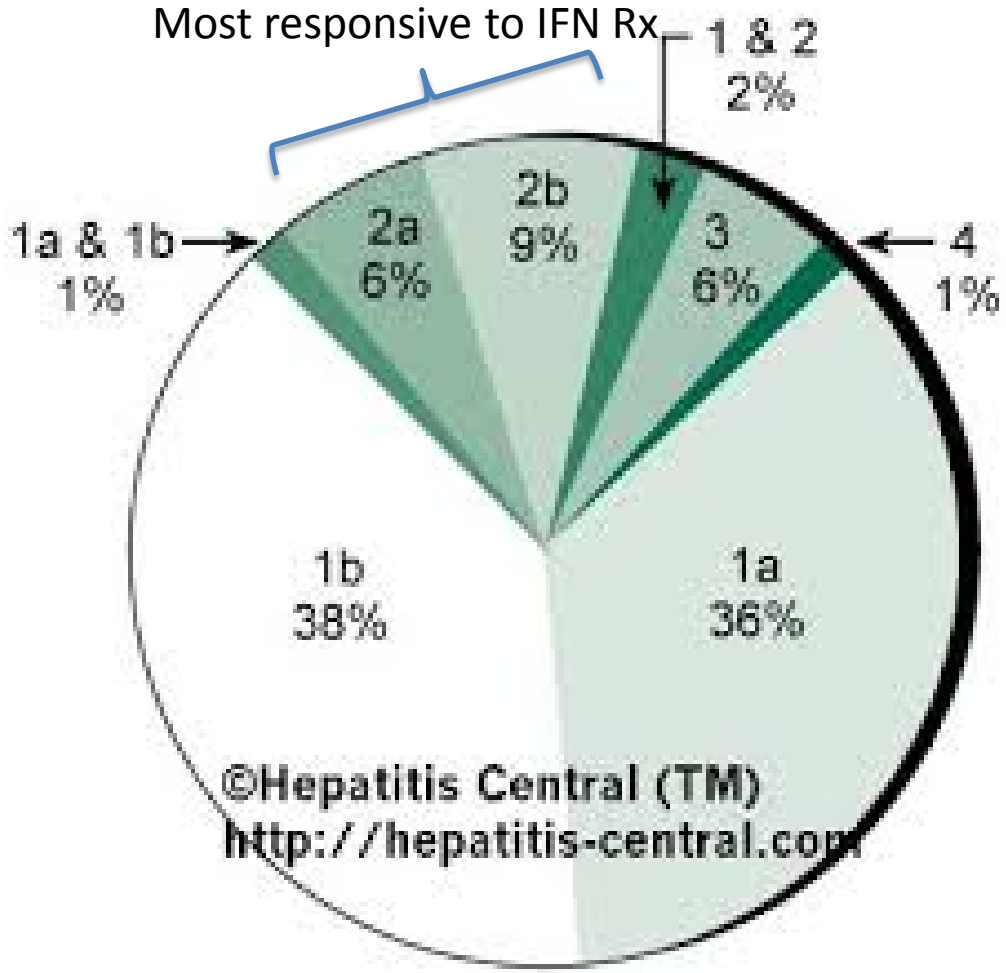
• Liver Biopsy	METAVIR Stage 4 (F4) ISHAK Stages 5 and 6
• Elastography	Varies somewhat with device >12.5 kPa
• APRI*	> 2
• FIBROSURE	> 0.73

*AST to Platelet Ratio Index = (AST/AST ULN) / (Platelets count (10^9/L)) x 100

Question 2: A 45 yo man with genotype 2a and stage I fibrosis is interested in HCV treatment. What do you recommend?

1. CT scan to r/o HCC
2. Pegylated IFN and Ribavirin
3. **Sofosbuvir and Ribavirin**
4. Simeprevir and Sofosbuvir
5. Wait for better drugs

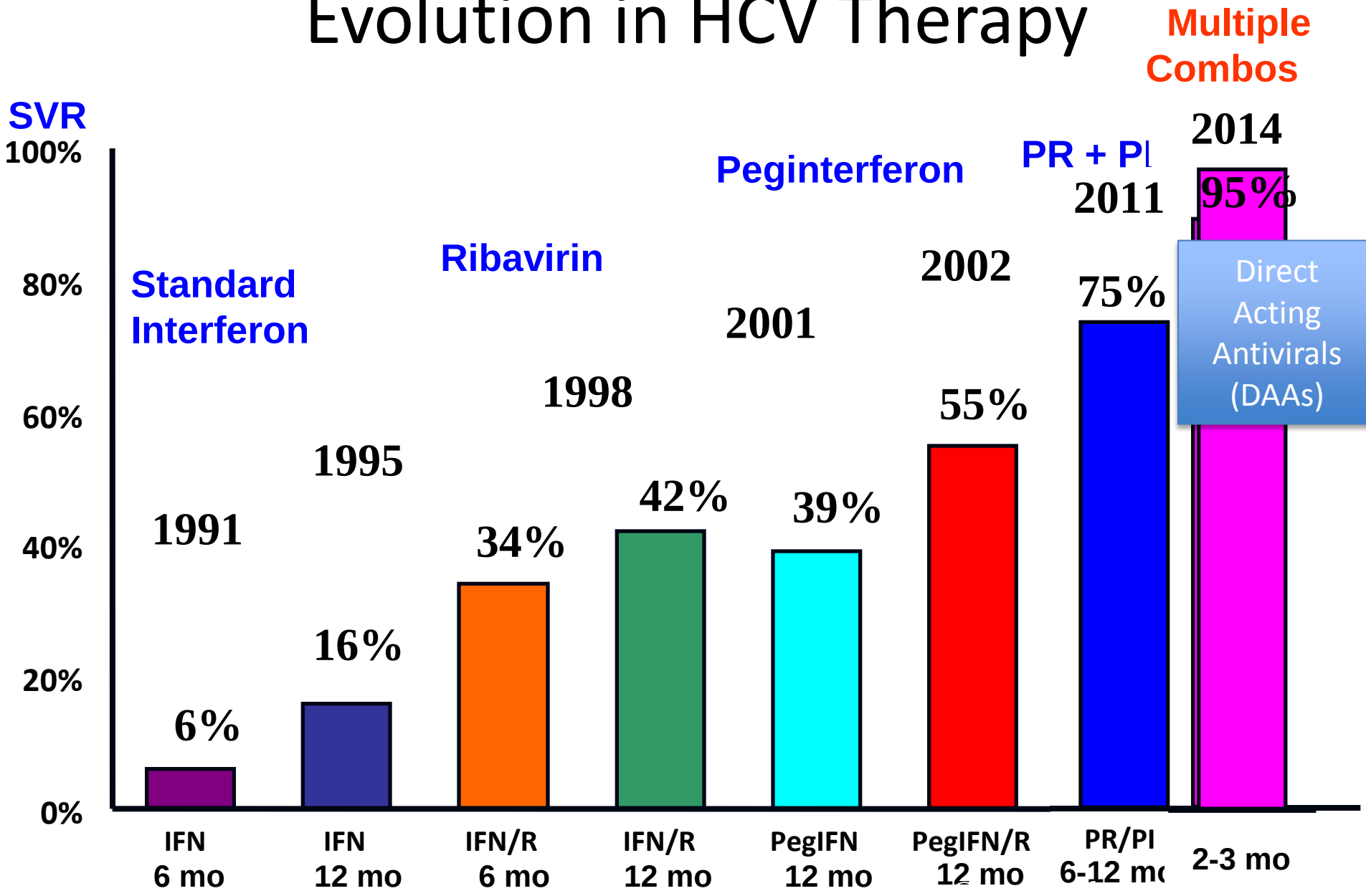
HCV Genotypes in U.S.



Goal is Sustained Virologic Response

- SVR: Sustained Virologic Response
- Definition: Undetectable HCV RNA weeks after end of treatment
  - SVR4
  - SVR12
  - SVR24

Evolution in HCV Therapy



Paradigm Shift

- From interferon-based treatment
  - Low efficacy
  - High toxicity (especially in cirrhosis)
  - Limited applicability

- To IFN-free treatments (DAAs)
  - Improved efficacy
  - Limited to no toxicity
  - Potential for drug-drug interactions
  - SOF should not be used if eGFR <30 mL/min

Multiple Classes of Direct Acting Antiviral Agents

Protease

-asvir

Polymerase

-buvir

Ribavirin

NS3 protease inhibitors

-previr

- Telaprevir
- Boceprevir
- → Simeprevir
- Asunaprevir
- → ABT-450
- MK-5172
- → Faldaprevir
- Sovaprevir
- ACH-2684

NS5A Replication Complex Inhibitors

- → Ledipasvir
- → Daclatasvir
- → Ombitasvir
- MK-8742
- GS-5885
- GS-5816
- ACH-3102
- PPI-668
- GSK2336805
- Samatasvir

NS5B NUC Inhibitors

Bind to polymerase

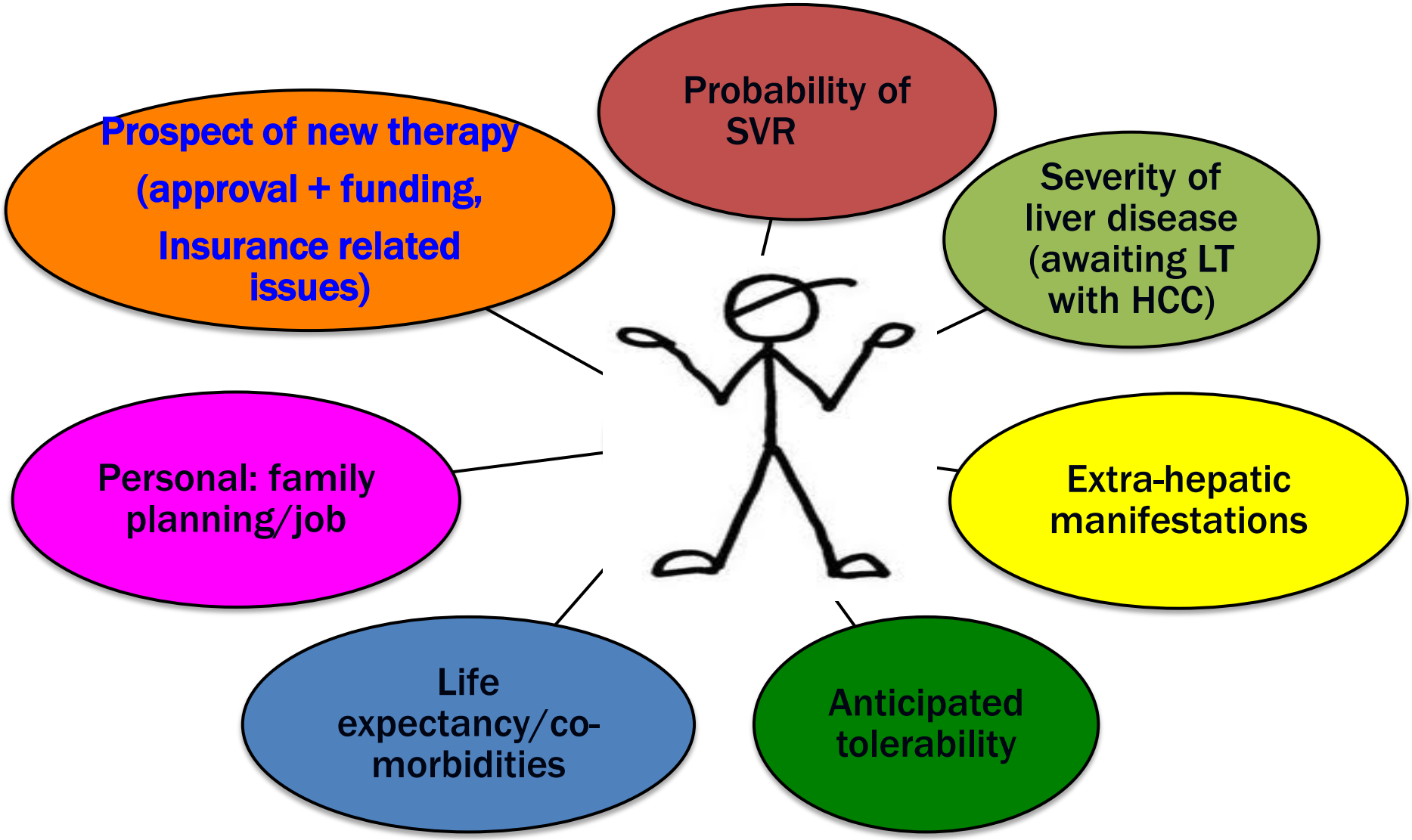
- → Sofosbuvir
- VX-135
- IDX20963
- ACH-3422

NS5B Non-NUC Inhibitors

Bind to allosteric sites

- → Dasabuvir
- Deleobuvir
- BMS-791325
- PPI-383
- GS-9669
- TMC647055

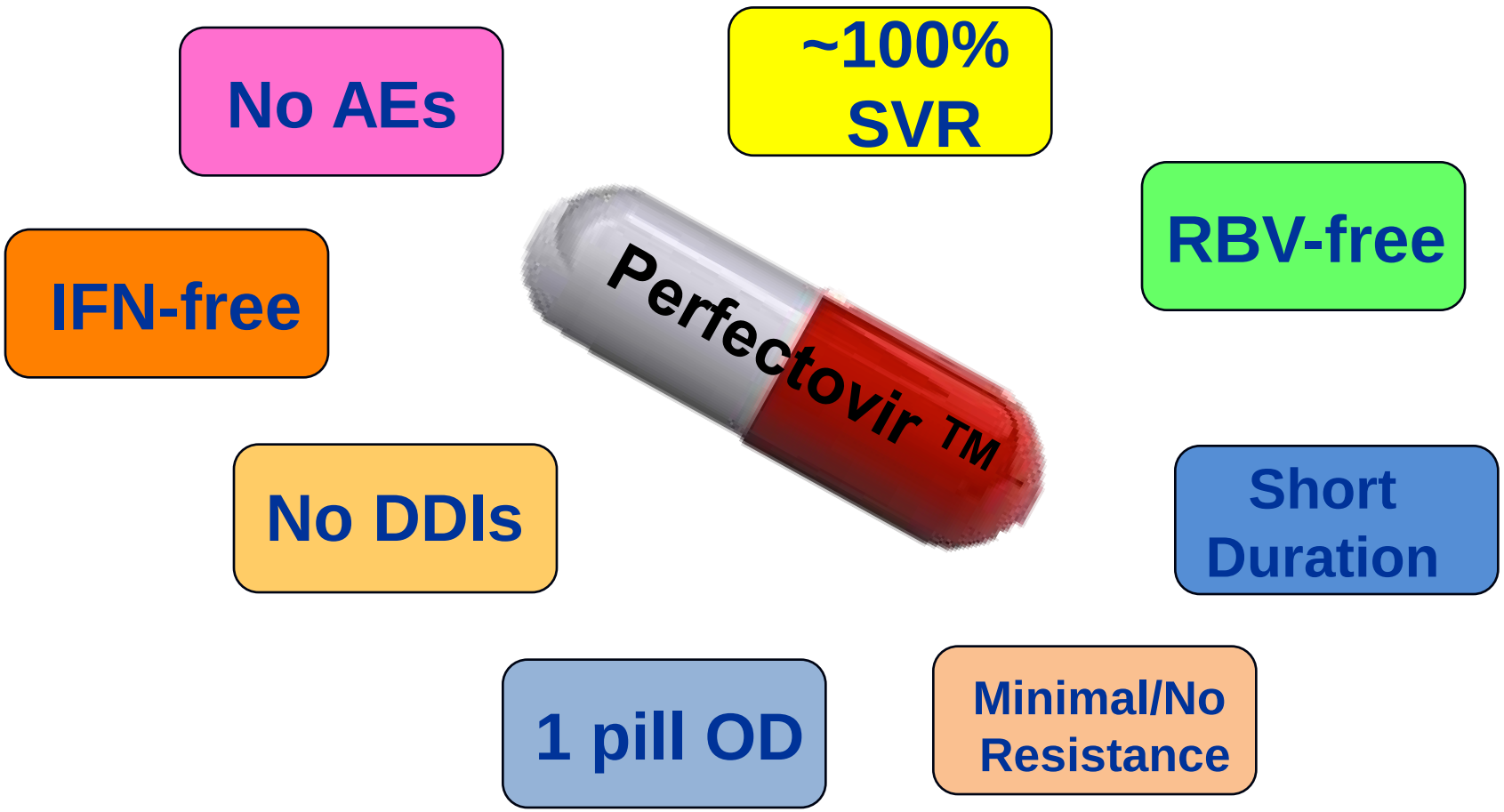
Treatment Decision



What is ideal anti-HCV therapy?

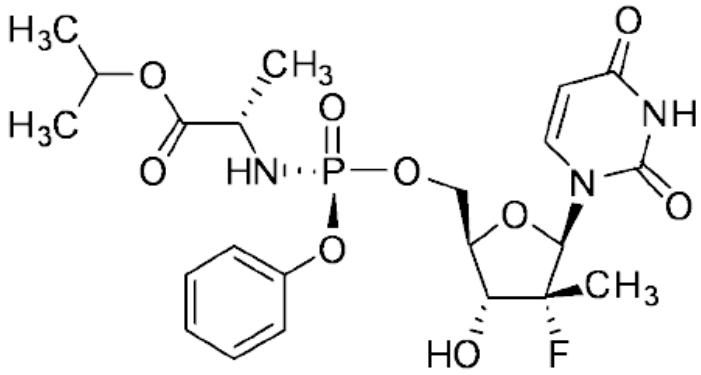
- High efficacy (>95%)
- Pan-genotypic
- Short course
- Few pills
- No side effects
- No drug-drug interactions
- Available to everyone

What are we waiting for?



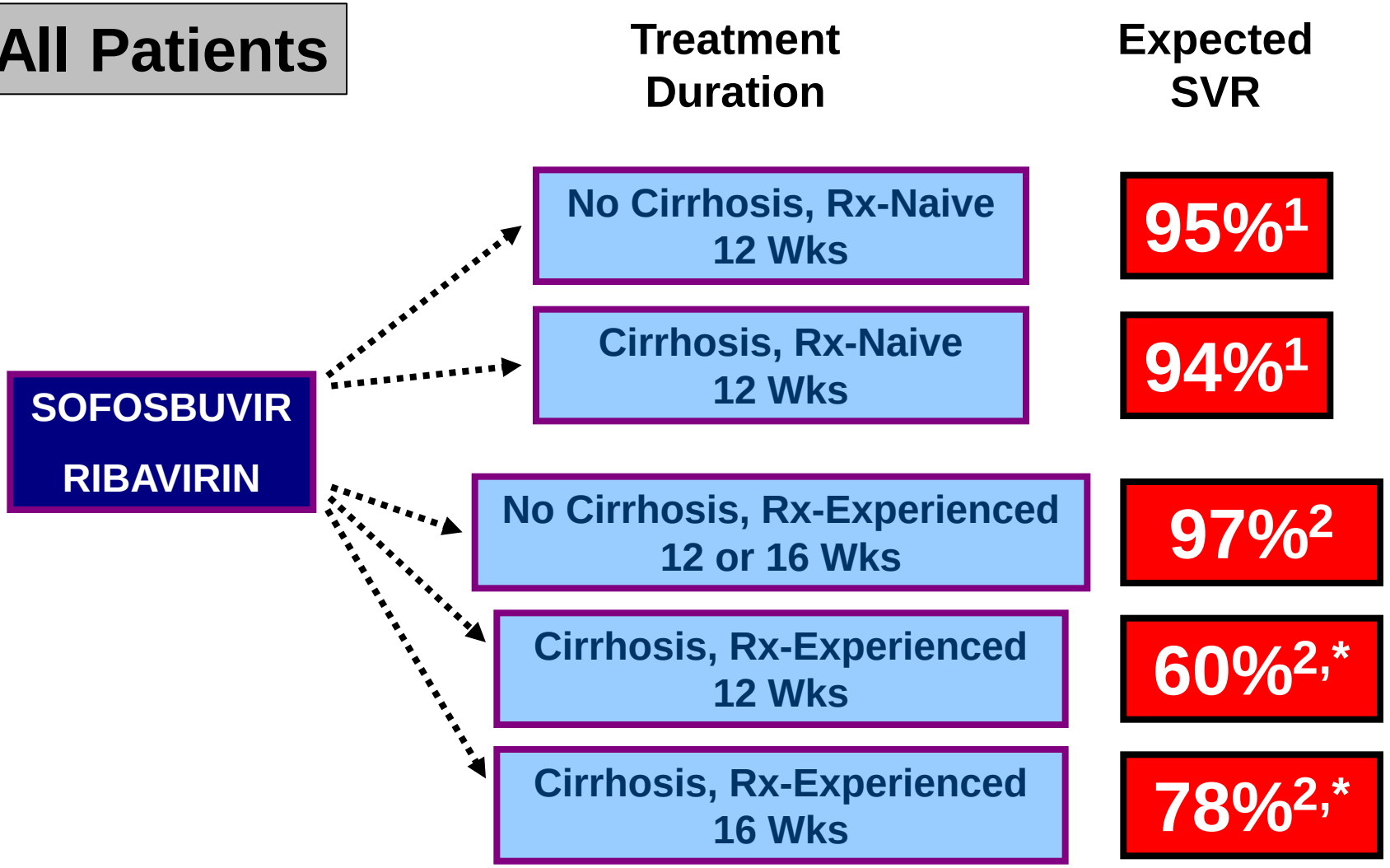
Sofosbuvir (SOF)

- HCV-specific nucleotide polymerase inhibitor (chain terminator)
- Antiviral activity and clinical efficacy in HCV GT 1–6
- High barrier to resistance
- Once-daily, oral, 400-mg tablet
- Favorable clinical pharmacology profile
  - No food effect
- Generally safe and well tolerated in clinical studies to date (>3000 patients)



Genotype 2
(almost no reason to withold therapy)

All Patients

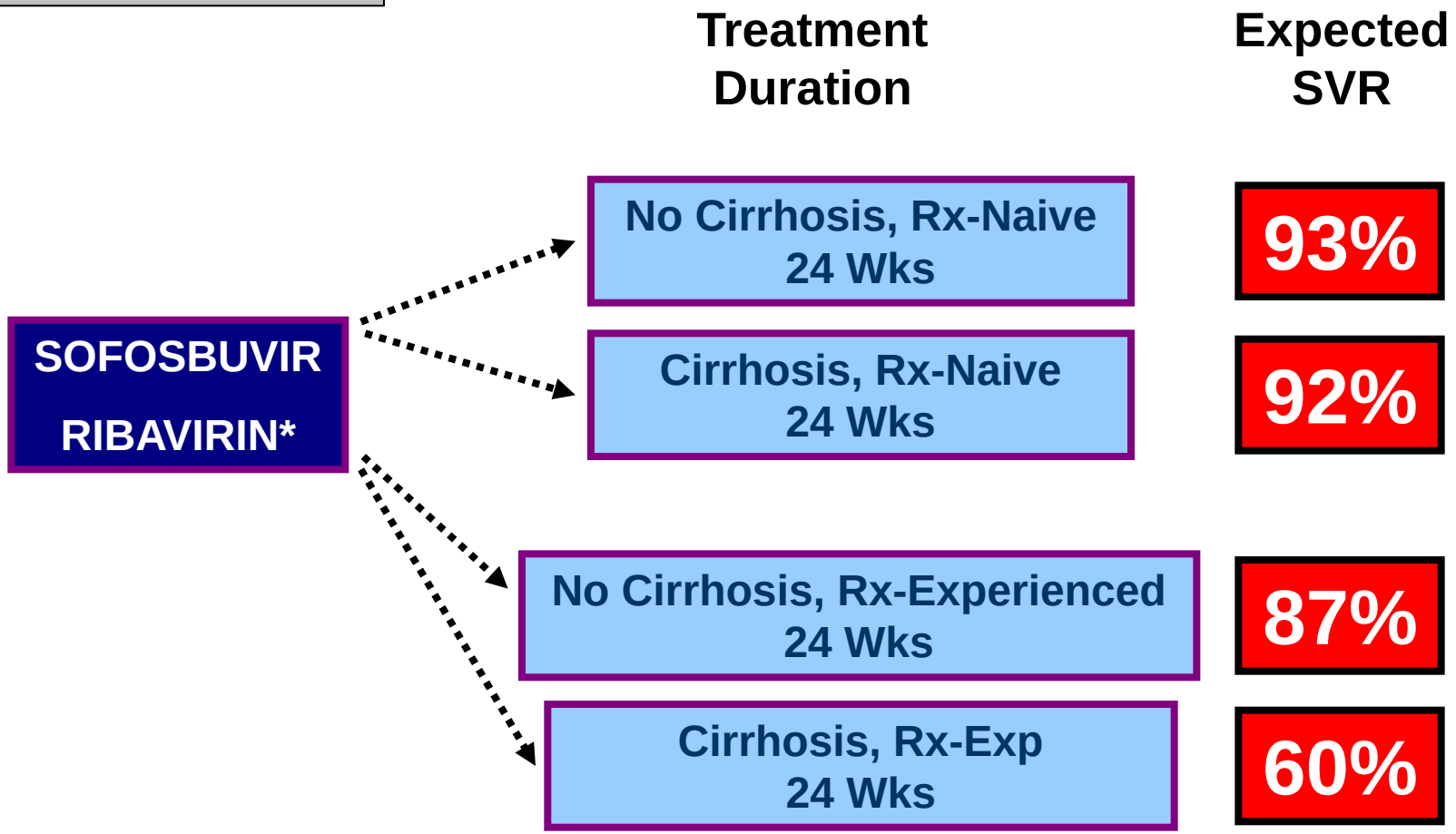


[1] Data from FISSION and POSITRON and [2] FUSION.

*In VALENCE, an SVR of 88% was achieved with 12 weeks SOF/RBV. Given the discordancy in results, optimal duration of SOF/RBV for Rx-experienced cirrhosis is unknown.

Genotype 3

All Patients



SOF + RBV for 12 weeks in non-cirrhotics (39%) and in cirrhotics 19%→
Extension to 16 wks 63% and 61%

Sofosbuvir-Based Regimens Are Associated With High SVR Rates Across Genotypes and Among Patients With Multiple Negative Predictive Factors

*HCV RNA level, cirrhosis, IL-28B, weight, prior treatment and gender

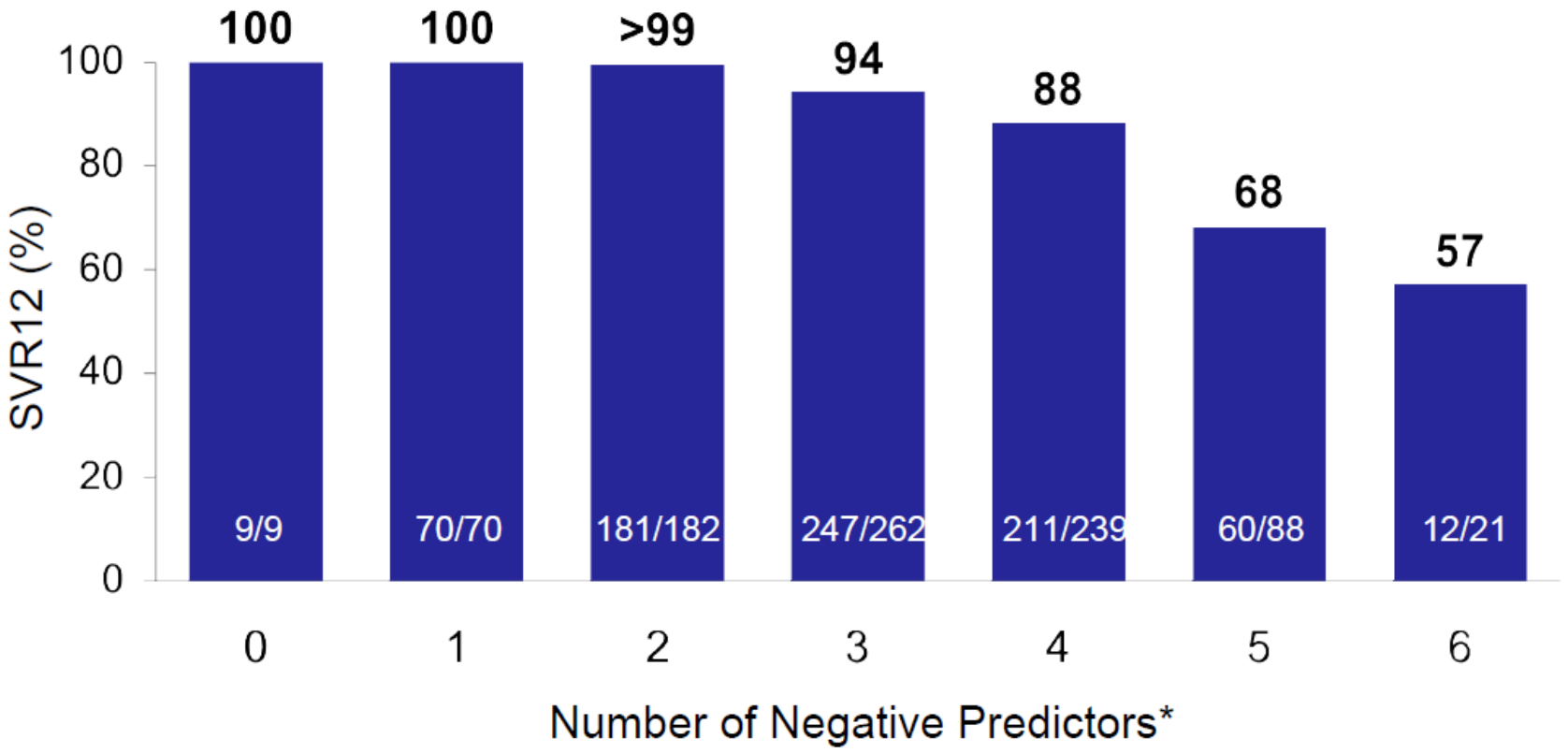
Ira M Jacobson,[1] Christopher Christensen,[2] Brian Conway,[3] Julie Ma,[4] B. Nebiyou Bekele,[4] Diana M. Brainard,[4] William T. Symonds,[4] John G. McHutchison,[4] Stefan Zeuzem[5]

[1]Weill Cornell Medical College, New York, New York; [2]Gastroenterology Associates, LLC, Baton Rouge, Louisiana, USA; [3]University of British Columbia, Vancouver, Canada; [4]Gilead Sciences, Inc, Foster City, California, USA; [5]Johann Wolfgang Goethe University, Frankfurt, Germany

Digestive Disease Week 2014, Chicago, IL

SVR12 Rates by Number of Negative Predictors

Derived From Multivariate Analysis (combined dataset)



*HCV RNA level, cirrhosis, IL-28B, weight, prior treatment and gender

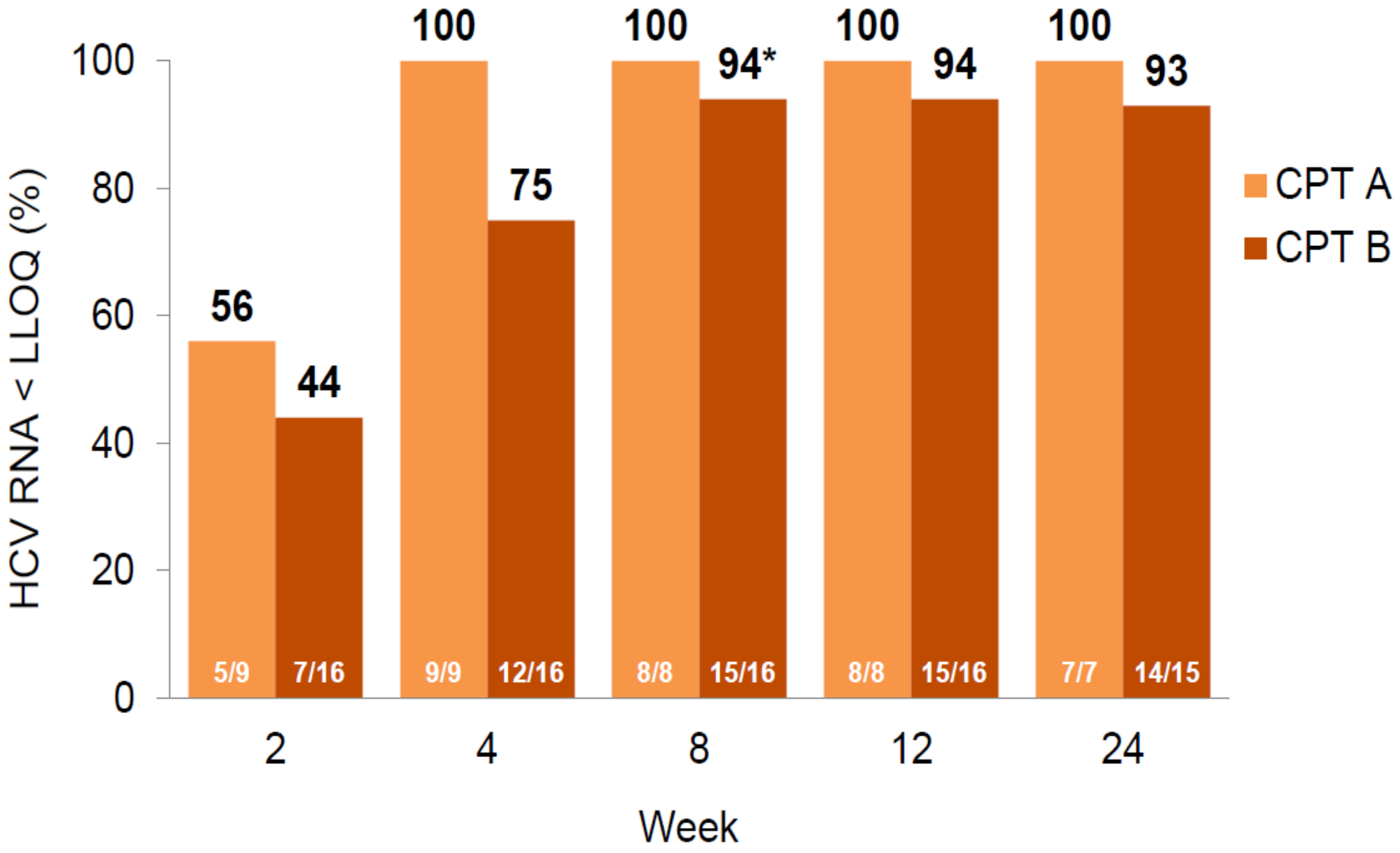
Sofosbuvir and Ribavirin for the Treatment of Chronic HCV With Cirrhosis and Portal Hypertension With and Without Decompensation: Early Virologic Response and Safety

Nezam Afdhal,[1] Gregory Everson,[2] Jose Luis Calleja,[3] Geoffrey McCaughan,[4] William T Symonds,[5] Diana Brainard,[5] Jill Denning,[5] Theo Brandt-Sarif,[5] Lindsay McNair,[5] John G. McHutchison,[5] Sarah Arterburn,[5] Jaime Bosch,[10] Michael Charlton,[6] Rajender Reddy,[7] Tarik Asselah,[8] Edward Gane,[9] Xavier Forns[10]

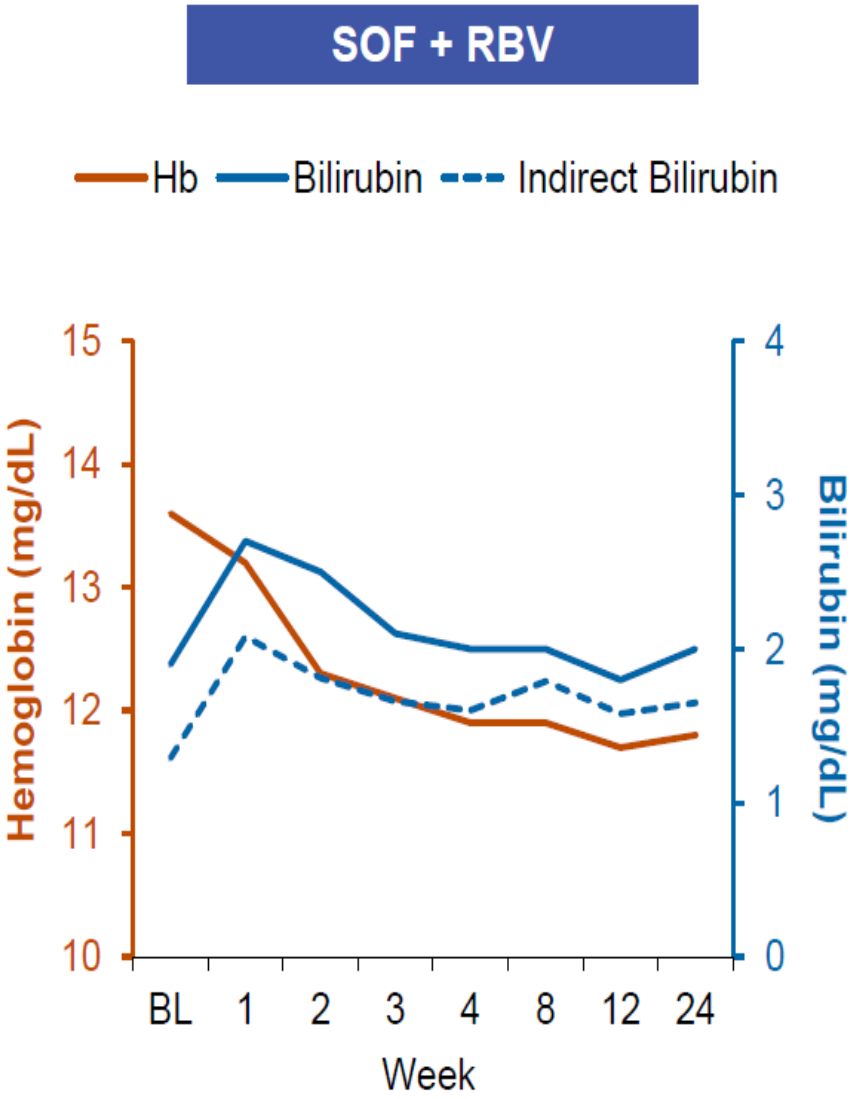
[1]Beth Israel Deaconess Medical Center, Boston, MA, USA; [2]University of Colorado Denver, Aurora, USA; [3]Hospital Puerta de Hierro, Madrid, Spain; [4]Royal Prince Alfred Hospital, University of Sydney, New South Wales, Australia; [5]Gilead Sciences, Inc., Foster City, CA, USA; [6]Mayo Clinic, Rochester, MN, USA; [7]University of Pennsylvania, Philadelphia, USA; [8]Hopital Beaujon, INSERM U773 and University Paris-Diderot, Clichy, France; [9]Auckland City Hospital, Grafton, Auckland, New Zealand; [10]Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Barcelona, Spain

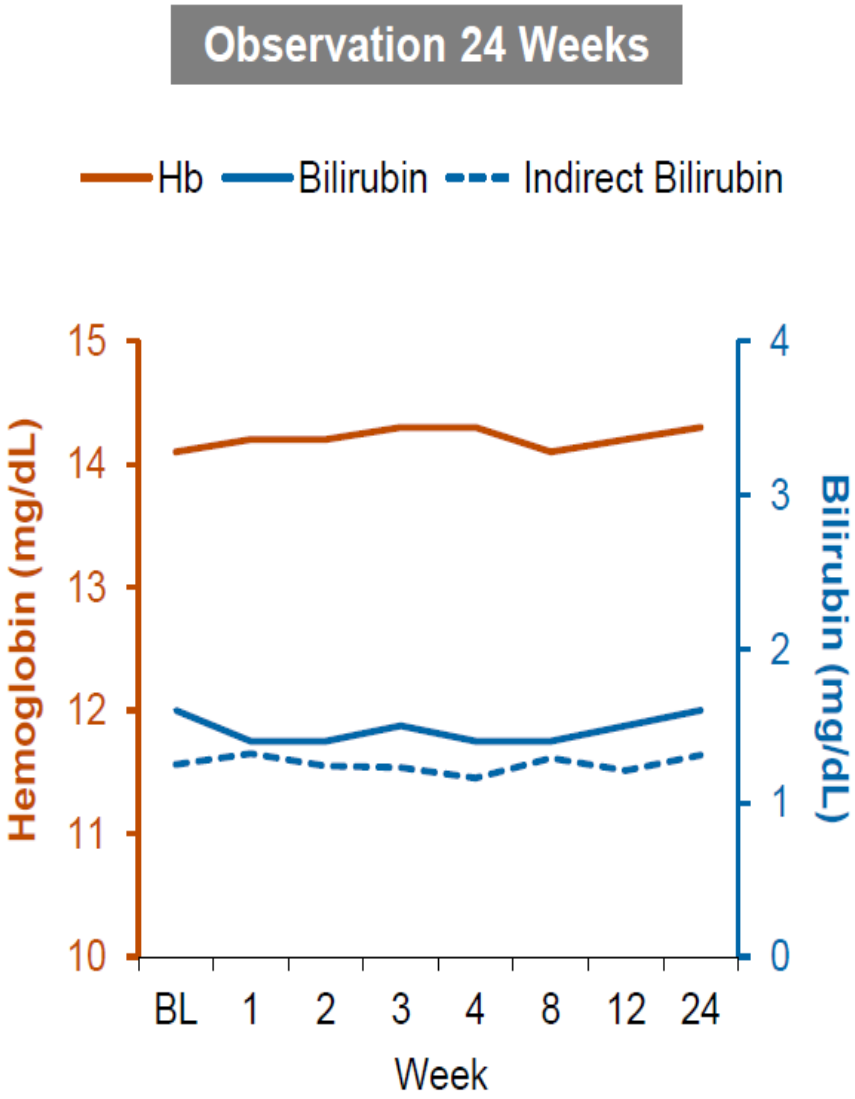
International Liver Congress 2014, London, UK

Results: Virologic Response on Treatment



Total and Direct Bilirubin vs. Hemoglobin



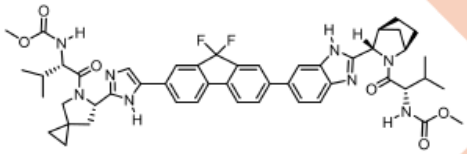


Conclusions

- In HCV-infected patients with portal hypertension with and without hepatic decompensation, treatment with SOF+RBV for up to 24 weeks resulted in:
  - High rates of virologic suppression irrespective of severity of liver disease
  - Decreased necroinflammation with ALT normalization
  - Improvements in platelet count and albumin
  - Improvement in ascites and hepatic encephalopathy
- SOF+RBV for up to 24 weeks was generally safe and well tolerated with low rates of treatment discontinuation due to AEs
  - No patients developed worsening or new onset hepatic decompensation

How about a single pill?

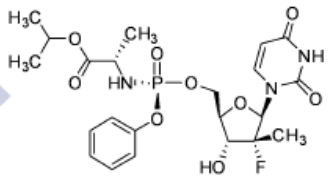
- **Ledipasvir**
  - Picomolar potency against HCV GT 1a and 1b[1]
  - Once-daily, oral, 90-mg



LDV
NS5A
inhibitor

- **Sofosbuvir**
  - Potent antiviral activity against HCV GT 1–6
  - High barrier to resistance
  - Once-daily, oral, 400-mg tablet approved for use with other agents to treat HCV

SOF
Nucleotide
polymerase
inhibitor



- **Ledipasvir/Sofosbuvir FDC[2]**
  - Once daily, fixed-dose (90/400 mg) combination tablet
  - No food effect
  - >2000 patients treated

SOF NS5B
Nucleotide
polymerase
inhibitor

LDV
NS5A
inhibitor

HARVONI

1. Lawitz E, et al. EASL 2011, poster 1219. 2. Lawitz E, et al. Lancet 383: 515-523

Sofosbuvir + Lepidasvir for genotype 1: The ION 1 and ION 2 Studies

ORIGINAL ARTICLE

Ledipasvir and Sofosbuvir for Untreated HCV Genotype 1 Infection

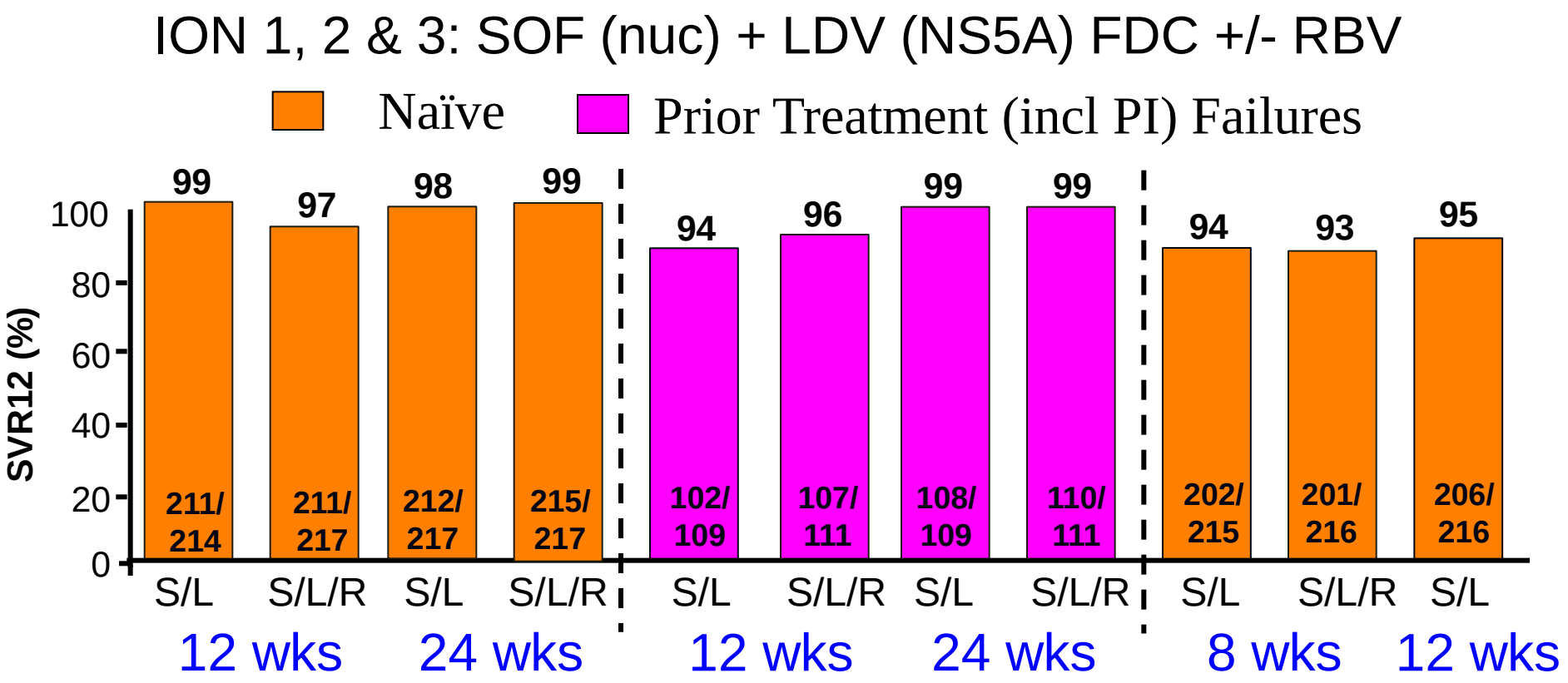
Nezam Afdhal, M.D., Stefan Zeuzem, M.D., Paul Kwo, M.D., Mario Chojkier, M.D., Norman Gitlin, M.D., Massimo Puoti, M.D., Manuel Romero-Gomez, M.D., Ph.D., Jean-Pierre Zarski, M.D., Ph.D., Kosh Agarwal, M.D., Peter Buggisch, M.D., Graham R. Foster, Ph.D., Norbert Bräu, M.D., M.B.A., Maria Buti, M.D., Ph.D., Ira M. Jacobson, M.D., G. Mani Subramanian, M.D., Ph.D., Xiao Ding, Ph.D., Hongmei Mo, M.D., Jenny C. Yang, Pharm.D., Phillip S. Pang, M.D., Ph.D., William T. Symonds, Pharm.D., John G. McHutchison, M.D., Andrew J. Muir, M.D., M.H.S., Alessandra Mangia, M.D., and Patrick Marcellin, M.D., Ph.D., for the ION-1 Investigators*

ORIGINAL ARTICLE

Ledipasvir and Sofosbuvir for Previously Treated HCV Genotype 1 Infection

Nezam Afdhal, M.D., K. Rajender Reddy, M.D., David R. Nelson, M.D., Eric Lawitz, M.D., Stuart C. Gordon, M.D., Eugene Schiff, M.D., Ronald Nahass, M.D., Reem Ghalib, M.D., Norman Gitlin, M.D., Robert Herring, M.D., Jacob Lalezari, M.D., Ziad H. Younes, M.D., Paul J. Pockros, M.D., Adrian M. Di Bisceglie, M.D., Sanjeev Arora, M.D., G. Mani Subramanian, M.D., Ph.D., Yanni Zhu, Ph.D., Hadas Dvory-Sobol, Ph.D., Jenny C. Yang, Pharm.D., Phillip S. Pang, M.D., Ph.D., William T. Symonds, Pharm.D., John G. McHutchison, M.D., Andrew J. Muir, M.D., Mark Sulkowski, M.D., and Paul Kwo, M.D., for the ION-2 Investigators*

SOF + Ledipasvir (NS5A) +/- RBV in G1: overall 97% SVR rate

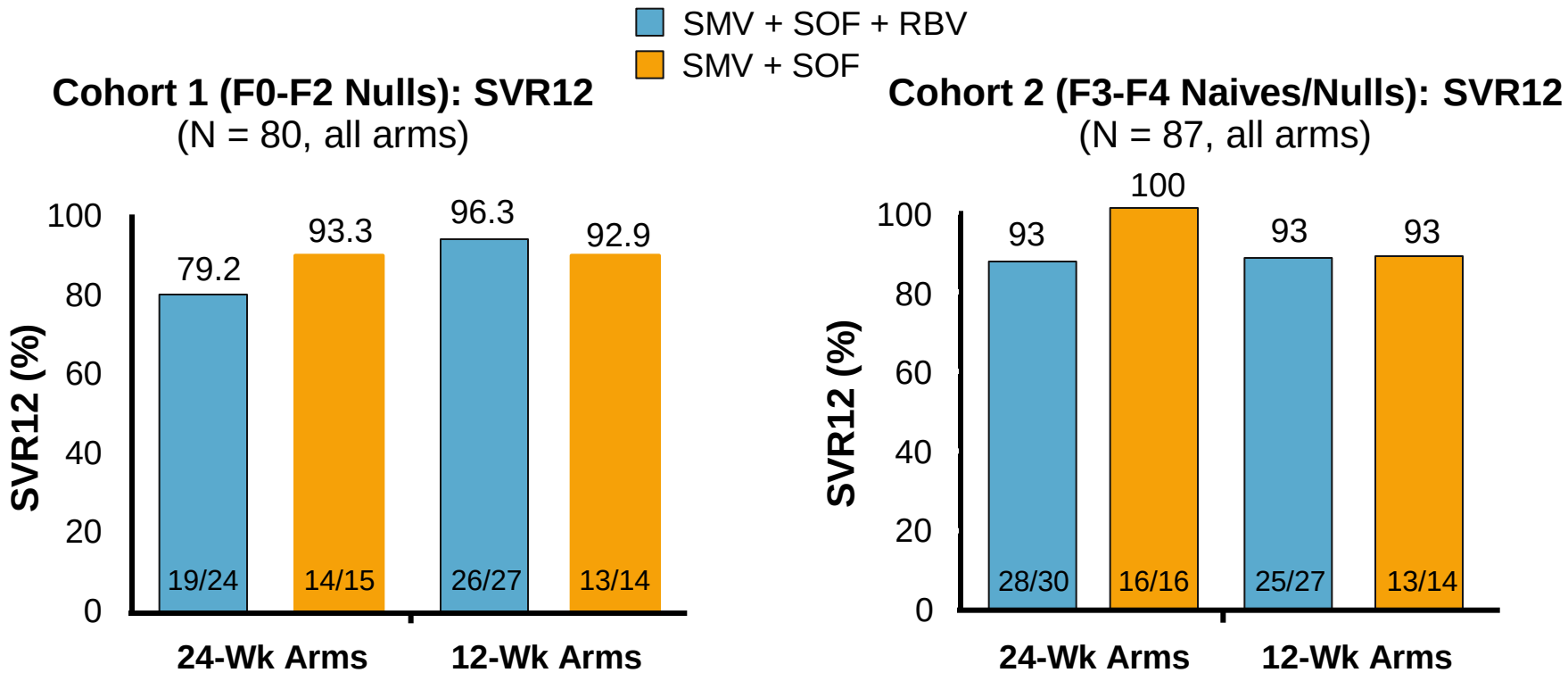


- 8 wks adequate for non-cirrhotic naïve
- RBV no benefit
- No resistance

Mangia EASL 2014, Afdahl EASL NEJM, Kowdley EASL 2014

If only we could all just get along…

Combination of Sofosbuvir (NUC) and Simeprevir (Protease Inhibitor): COSMOS



- Relapse in 3 pts in Cohort 1 and 3 pts in Cohort 2; all with GT 1a and 2 with Q80K polymorphism at BL
- AEs (anemia and indirect bilirubin increases) largely confined to RBV arms
- SVR in patients with GT 1a and Q80K+ = 88%-100%

Jacobson I, et al. AASLD 2013. Abstract LB-3. Lawitz, et al. EASL 2014. Abstract 165.

Question 3: A 60 yo man with HCV genotype 1a-related cirrhosis was a non-responder to treatment in 2010. What would you recommend?

1. **Referral to GI/Hepatology specialist**
2. Treatment with SOF/RIB for 24 weeks
3. Treatment with SOF/Ledipasvir for 12 weeks
4. Pegylated IFN with SOF and RIB for 24 weeks

What should Internist do before sending a patient for treatment?

- HCV genotype
- HCV viral level
- CBC, CMP, INR
- U/S
- r/o active alcohol or drug use (6 months)
- Understand insurance coverage issues (more to come)
  - Changing
  - Most Medicare Part D plans cover but patient has $10-20K copays
  - Colorado Medicaid not covering Harvoni, Viekira or Sim/Sof (approve Sof/Rib for advanced fibrosis)
  - Try *My Support Path* through Gilead

Management of Cirrhosis

- EGD to diagnose and treat varices
- Ongoing clinical evaluation for complications
  - Variceal hemorrhage
  - Ascites/SBP
  - Encephalopathy
- Radiologic imaging for HCC
  - Compensated stage – 6 to 12 months
  - Decompensated stage – more frequently?
- Alter the DAA prescription – multi-DAAs and/or longer duration

Recommended Treatment Duration for SOF/LDV

Patient Population	Recommended treatment duration
Treatment naïve w/ or w/o cirrhosis	12 weeks**
Treatment-experienced* w/o cirrhosis	12 weeks
Treatment-experienced* w/ cirrhosis	**24 weeks**

*Failed treatment with either peg + riba or an HCV protease inhibitor + peg + riba.

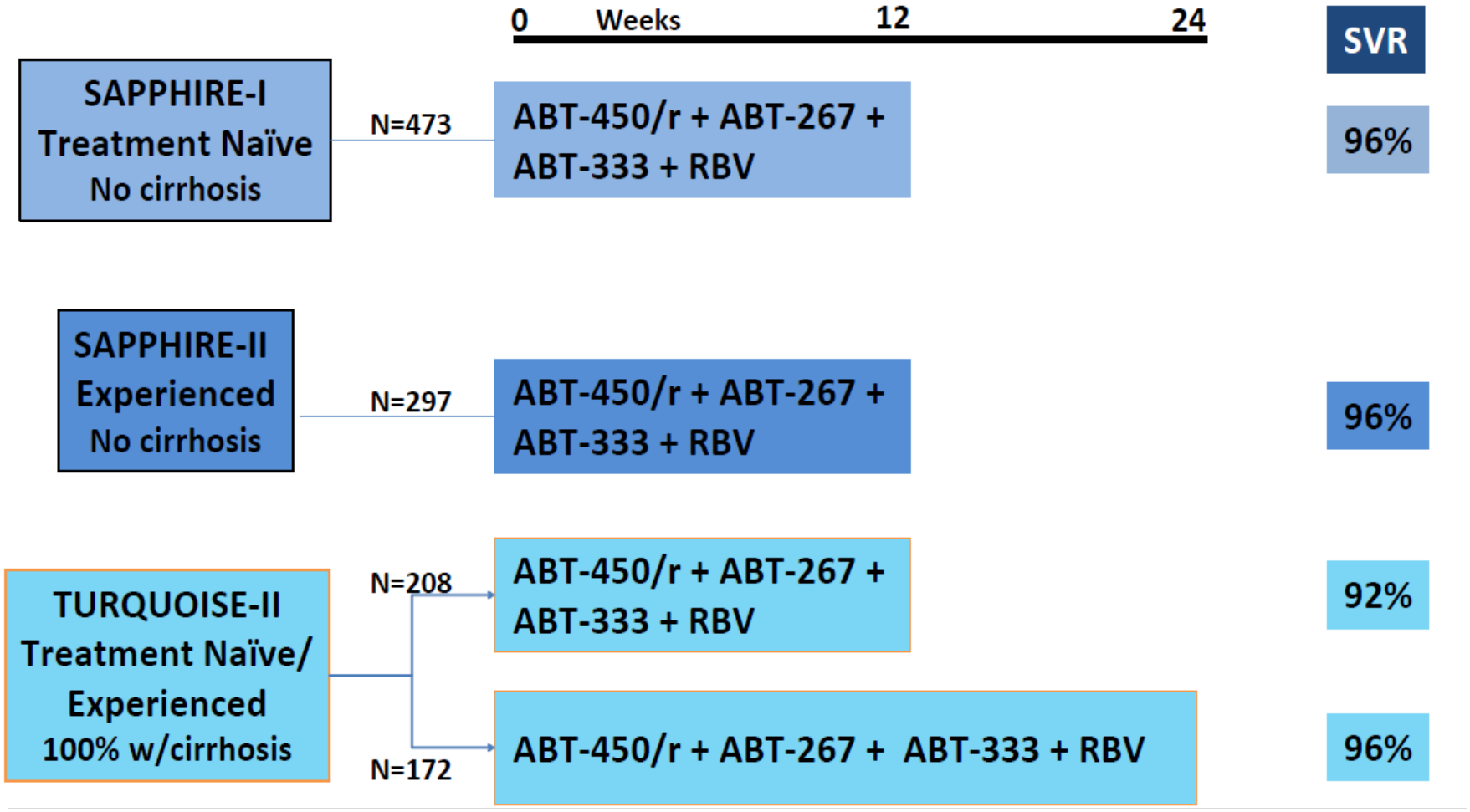
**8 weeks can be considered in treatment-naïve without cirrhosis who have pre-Rx HCV RNA <6 million IU/mL.

IFN-free Regimen
ABT 450/r (PI) + ABT 333 (NNI) + ABT 267 (NS5A) + RBV
(Viekira PAK)-Dec 2014 FDA

Abbvie

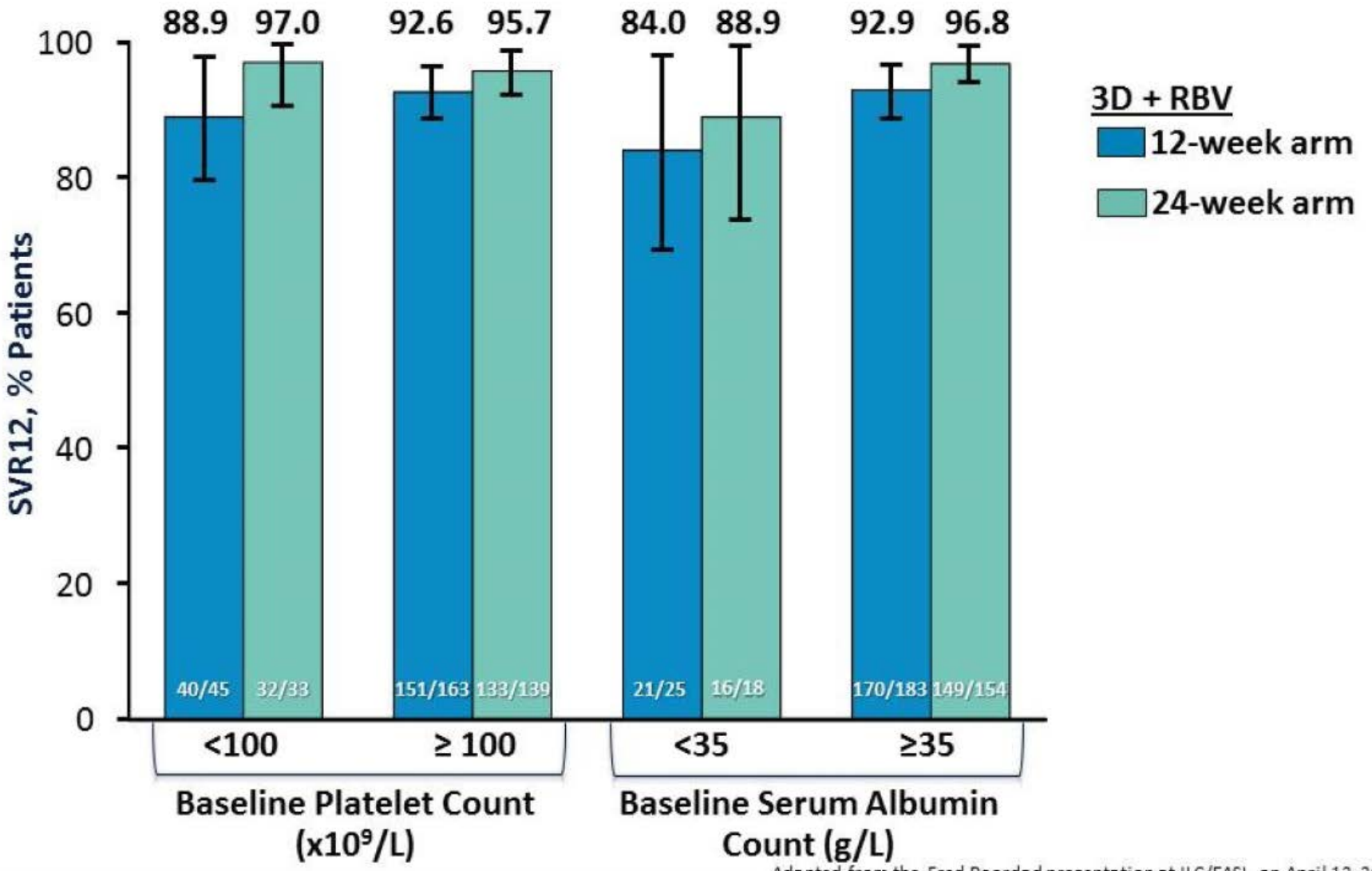
Coformulated “3D + Ribavirin”

ABT-450/r (PI) + ABT-267 (NS5A) + ABT-333 (NNI) + RBV SAPPHIRE and TURQUOISE:



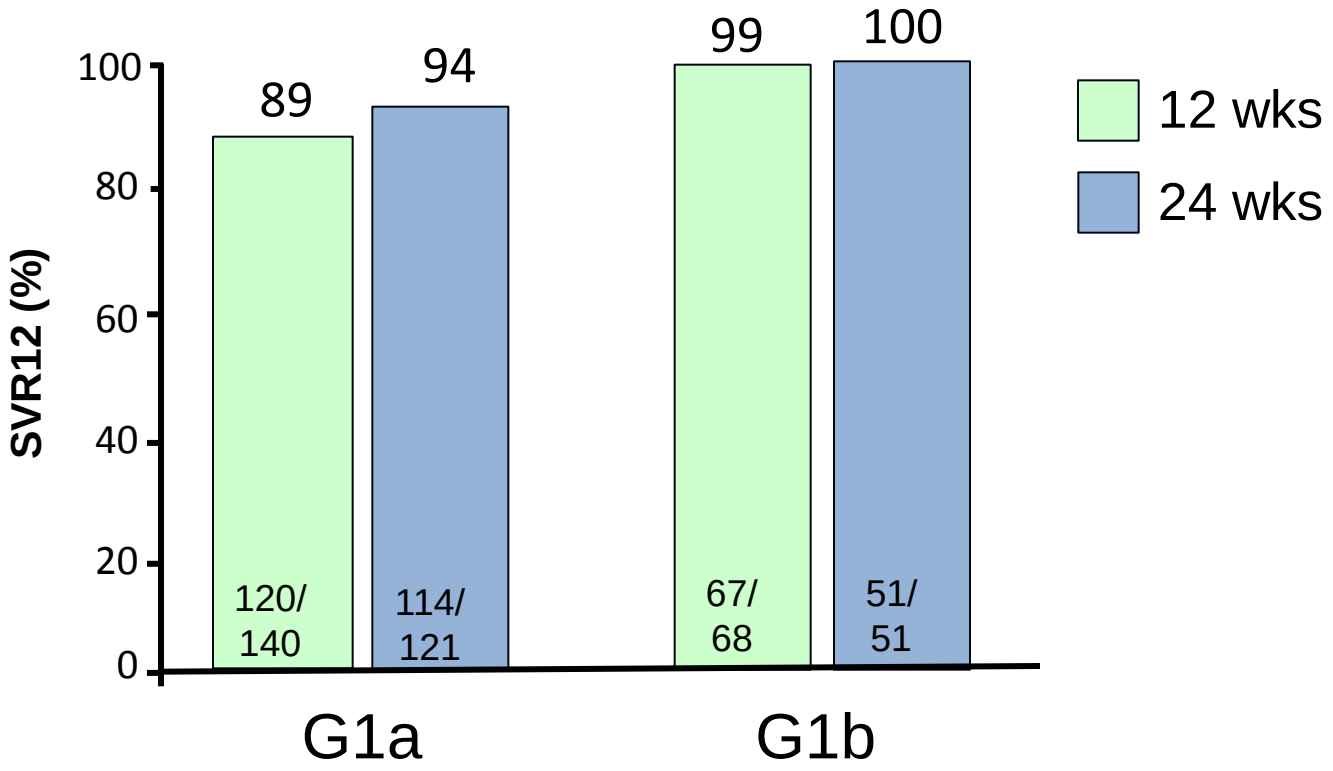
N Engl J Med. 2014;370:1594-603. N Engl J Med. 2014;370:1604-14.
N Engl J Med May 22, 2014

TURQUOISE-II Results: ITT SVR12 Rates by Surrogates of Portal Hypertension and Hepatic Function



Adapted from the Fred Poordad presentation at ILC/EASL on April 12, 2014

3D + RBV in Cirrhosis by G1 Subtype



- 12 weeks clearly adequate for G1b but not for genotype 1a

Viekira Pak interacts with multiple drugs and supplements

- anti-seizure medications
- buprenorphine/naloxone
- cardiac drugs
- ethinyl estradiol-containing contraceptives
- HIV antivirals
- immunosuppressants
- Lovastatin
- omeprazole
- oral midazolam (Versad)
- Rifampin,
- St. John's wort

Comparison HARVONI vs. Viekira

HARVONI

- 1 pill daily
- GT1 (a or b), Rx Naïve, Noncirrhotic, RNA<6MU – has potential for 8 week option with HARVONI
- Only indication for RBV with HARVONI is the pt with cirrhosis who you can reduce from 24 to 12 weeks HARVONI by adding RBV
- No or few DDIs – simpler management of transplant patients, HIV pts, and others with med issues
- Even though it is only FDA approved for GT1, HARVONI has activity against other genotypes

Viekira

- Multiple pills, bid
- No 8 week option
- GT1a – RBV needed
- GT1 cirrhosis – RBV needed – 24 weeks plus RBV needed (according to FDA – my own view of the data is that 24 weeks is mainly needed for GT1a prior Null Responders)
- Many DDIs – keeps the ClinPharm busy – more complex management in transplant pts, HIV pts, etc
- Can be used in renal failure (dialysis?)
- Not active against other genotypes (at least no data supporting its use there yet)

Daclatasvir plus Sofosbuvir for previously treated or untreated chronic HCV infection

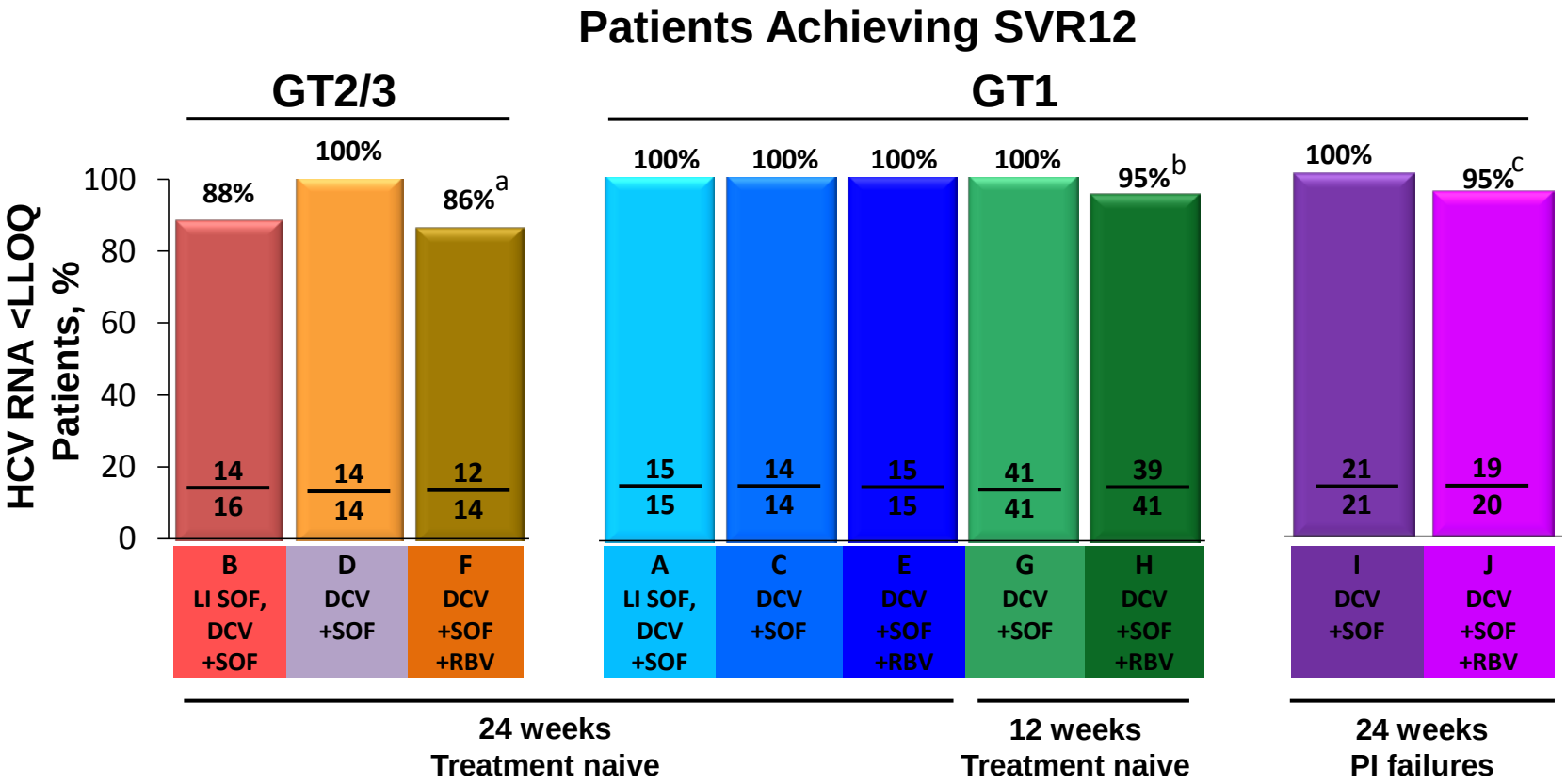
ORIGINAL ARTICLE

Daclatasvir plus Sofosbuvir for Previously Treated or Untreated Chronic HCV Infection

Mark S. Sulkowski, M.D., David F. Gardiner, M.D., Maribel Rodriguez-Torres, M.D., K. Rajender Reddy, M.D., Tarek Hassanein, M.D., Ira Jacobson, M.D., Eric Lawitz, M.D., Anna S. Lok, M.D., Federico Hinestrosa, M.D., Paul J. Thuluvath, M.D., Howard Schwartz, M.D., David R. Nelson, M.D., Gregory T. Everson, M.D., Timothy Eley, Ph.D., Megan Wind-Rotolo, Ph.D., Shu-Pang Huang, Ph.D., Min Gao, Ph.D., Dennis Hernandez, Ph.D., Fiona McPhee, Ph.D., Diane Sherman, M.S., Robert Hindes, M.D., William Symonds, Pharm.D., Claudio Pasquinelli, M.D., Ph.D., and Dennis M. Grasela, Pharm.D., Ph.D., for the AI444040 Study Group

- Open-label, randomized clinical trial of HCV genotypes 1, 2 and 3
- Previously treatment-naïve and geno-1 with prior telaprevir or boceprevir failure
- Daclatasvir 60 mg daily + sofosbuvir 400 mg daily ± ribavirin for 12 or 24 weeks
- Endpoint: SVR12

Daclatasvir and Sofosbuvir: SVR12 Primary Endpoint (mITT)



- SVR 12 rates were 100% in treatment-naive GT 1 and GT2/3 groups treated for 24 weeks with DCV + SOF without RBV
- SVR 12 rates were 100% in treatment-naïve GT1 group treated for 12 weeks with DCV + SOF without RBV
- SVR 12 rates were 100% in the GT1 PI-failure group treated for 24 weeks with DCV + SOF without RBV

[a]One patient with missing data at posttreatment week 12, who achieved SVR24.
[b]One patient with missing data at posttreatment week 12, who achieved SVR24 and one patient was lost to follow-up.
[c]One patient with missing data at posttreatment week 12, who achieved SVR24.
SOF = sofosbuvir; DCV = daclatasvir; RBV = ribavirin; EOT = end of treatment; SVR = sustained virologic response.
Sulkowski et al. *N Engl J Med.* 2014;370:211.

The emerging specter of hepatocellular carcinoma

- Each year, more than half a million people worldwide receive a diagnosis of HCC
- HCC related to HCV is the fastest rising cause of U.S. cancer-related deaths

HCC Surveillance recommendations

- no data proving increased survival
- abdominal imaging (q 6 to 12 m)
  - ultrasound
    - cheaper
    - effective, less effective for obese patients
    - non-definitive
  - CT/MR
    - more expensive
    - definitive (diagnostic)
    - radiation (with CT)

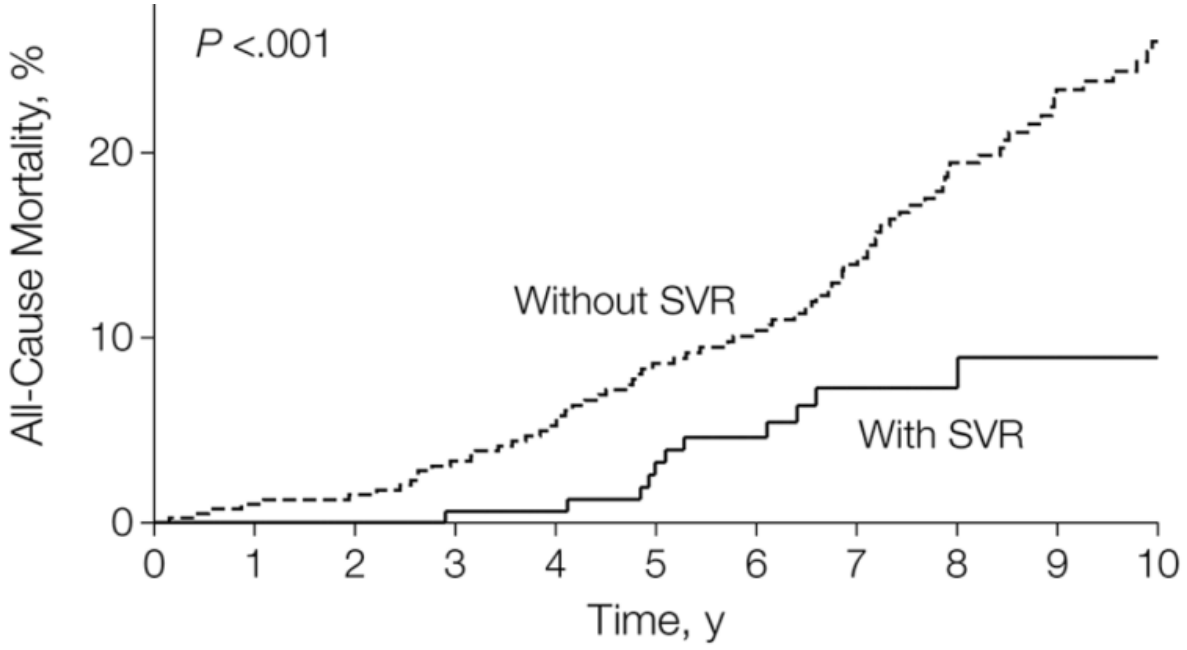
Surveillance recommendations

- **alpha-fetoprotein (q 6 to 12 m)**
  - **fair screening test**
  - **negative in 30 % HCC**
  - **key elements (for concern)**
    - **marked elevation > 200**
    - **progressive rise (20 – 40 – 80 – 160 . . .)**

Question 4: What is the % of patients with HCV-related cirrhosis who develop HCC despite SVR (based on IFN Rx data)?

1. Extremely rare, < 1% in next decade
2. **~5-10 % in next decade**

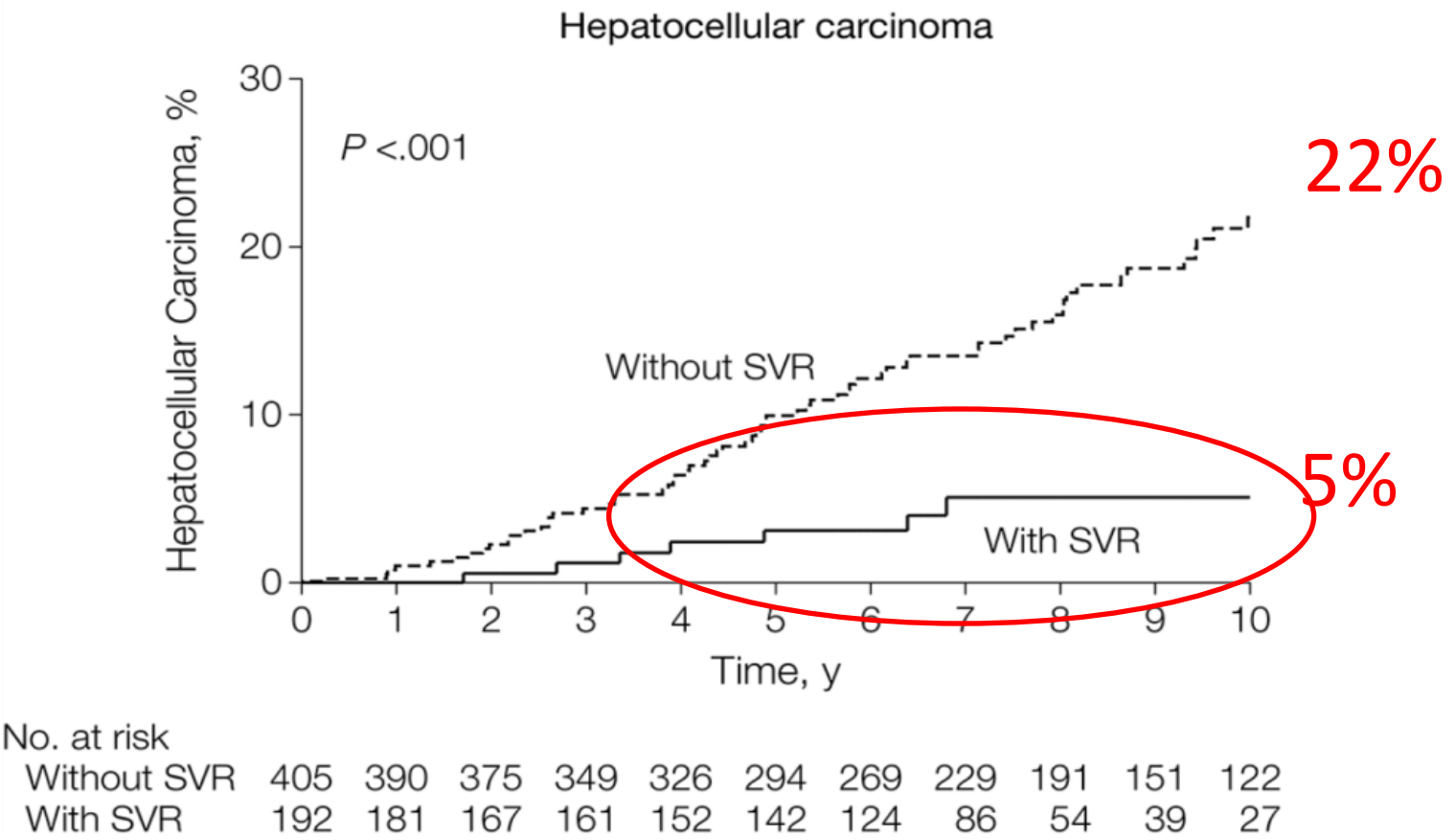
Association Between Sustained Virological Response and All-Cause Mortality Among Patients With Chronic Hepatitis C and Advanced Hepatic Fibrosis



No. at risk

Without SVR	405	393	382	363	344	317	295	250	207	164	135
With SVR	192	181	168	162	155	144	125	88	56	40	28

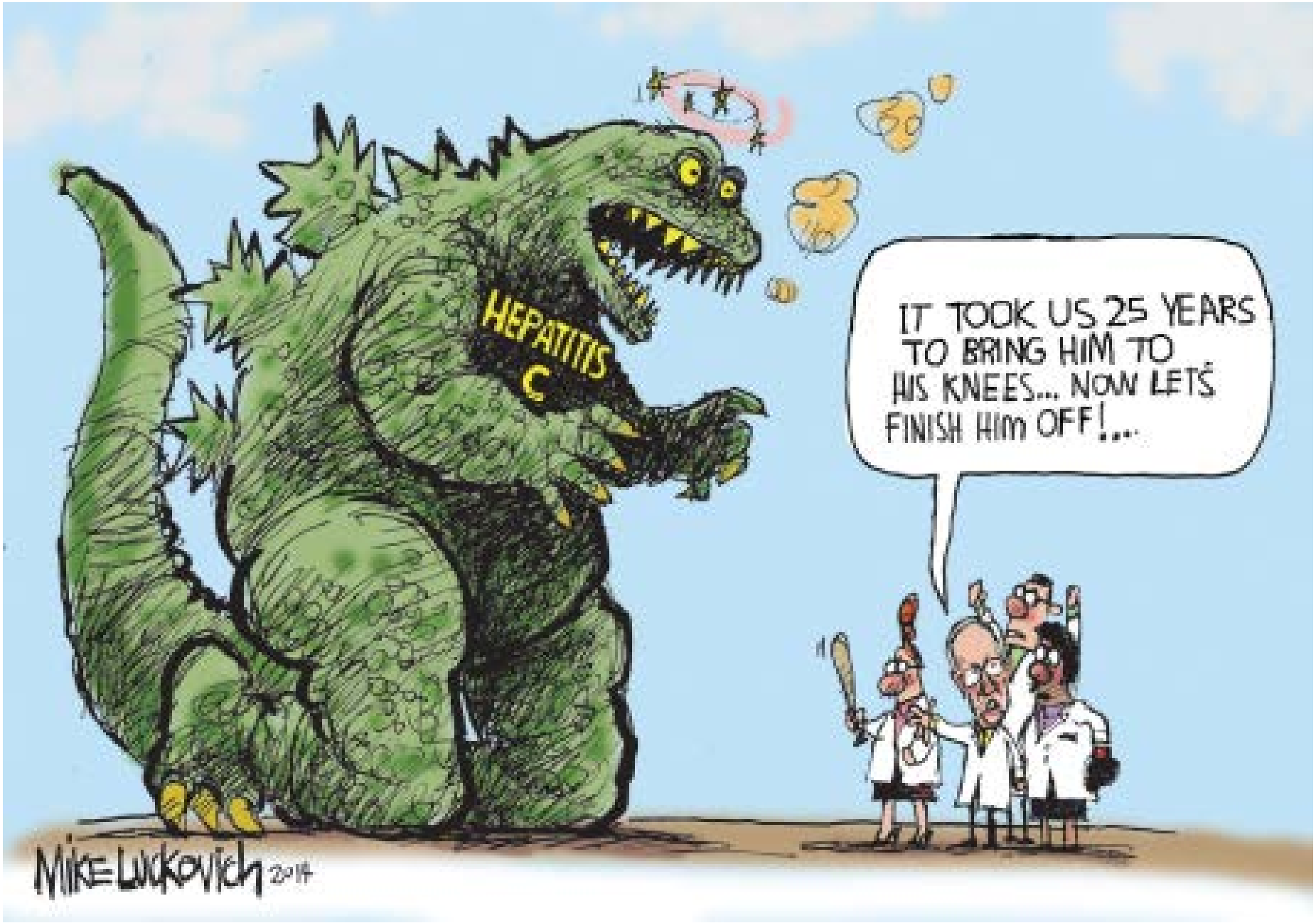
JAMA, December 26, 2012



- Decrease in HCC with SVR
- But SVR does not eliminate risk of HCC
- This group with SVR is likely to increase

Multivariate Cox Regression for HCC risk

HCC		HR	P-value
Age	<45 years	Reference	-
	45-60 years	8.54 (1.13-64.65)	0.038
	>60 years	8.91 (1.12-70.77)	0.039
Platelets		0.94 (0.87-1.0)	0.048
AST/ALT ratio		1.04 (0.99-1.09)	0.084
Diabetes		2.36 (1.02-5.42)	0.044


HEPATITIS C
IT TOOK US 25 YEARS TO BRING HIM TO HIS KNEES... NOW LETS FINISH HIM OFF!...
MIKE LUCKOVICH 2014

Whom to Treat?

Priority Lists for Resource Allocation

- AASLD/IDSA: No priority list
- EASL: Based on Fibrosis Stage
- Colorado Medicaid: (sof/rib)
  - Transplant recipients
  - Listed LT candidates
  - Cirrhosis
  - Extrahepatic manifestations (vasculitis)
  - F3

Not covered

  - F2
  - F0 – F1
  - Exclusions:
    - active EtOH
    - active IVDA
    - severe decompensation

Sovaldi (sofosbuvir) in the News

“New hepatitis C drugs’ price prompts an ethical debate: Who deserves to get them?”

Washington Post

“How Much Should Hepatitis C Treatment Cost?”

New York Times

“Prices of new hepatitis C drugs are tough to swallow for insurers.”

Los Angeles Times

“Hepatitis C breakthrough drug Sovaldi promises high cure rates, costs.”

Denver Post

“$1,000 hepatitis C pill a tough miracle to swallow.”

San Francisco Chronicle

Cost Considerations

- ***The 800 lb gorilla in the room……***
- The wholesale acquisition cost (WAC):
  - Sofosbuvir: $84,000/12 week course
  - Simeprevir: $66,360/12 week course
  - Telaprevir: $49,200/12 week course
  - Boceprevir: $26,400/24* week course
  - PEG/RBV: $~9,000/12 week course

What if we wanted to eradicate HCV this year?

3 million X $150,000

= $4.5 X 10^{11}

Total expenditures for public elementary and secondary schools in the United States amounted to $700 billion ($10^{9}$)

Cost Considerations

- However, efficacy (SVR) is higher and monitoring costs may be lower with newer therapies, so may consider "cost/SVR".....

- TVR+PEG+RBV cost/SVR: **$172,889 - $188,859***
- SOF + SMV cost/SVR: **~$164,885**
  - (assumes 12 wk course with 93% SVR and HCV RNA, CBC, HFP at time 0, 4, 12 and 24 weeks and 2 nursing visits)

*Sethi N, et al. *HEPATOLOGY* 2013;58(S1):1094A.
*Bichoupan K, et al. *HEPATOLOGY* 2013;58(S1):329A.

What have you learned?

- It is important to define severity of liver disease and identify patients with cirrhosis
- CHRONIC HEPATITIS C IS CURABLE with all oral IFN-free regimens!
- Emerging treatments are highly effective and very well-tolerated
  - Special populations are no longer “special”
- Paying for the CURE may be painful

Final Thoughts

- Hopefully, new guidelines will allow for improved access for patients in need
- Residual risk for HCC in cirrhotics
  - all patients with HCV-induced cirrhosis and SVR should be included in HCC surveillance programs

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Questions?

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