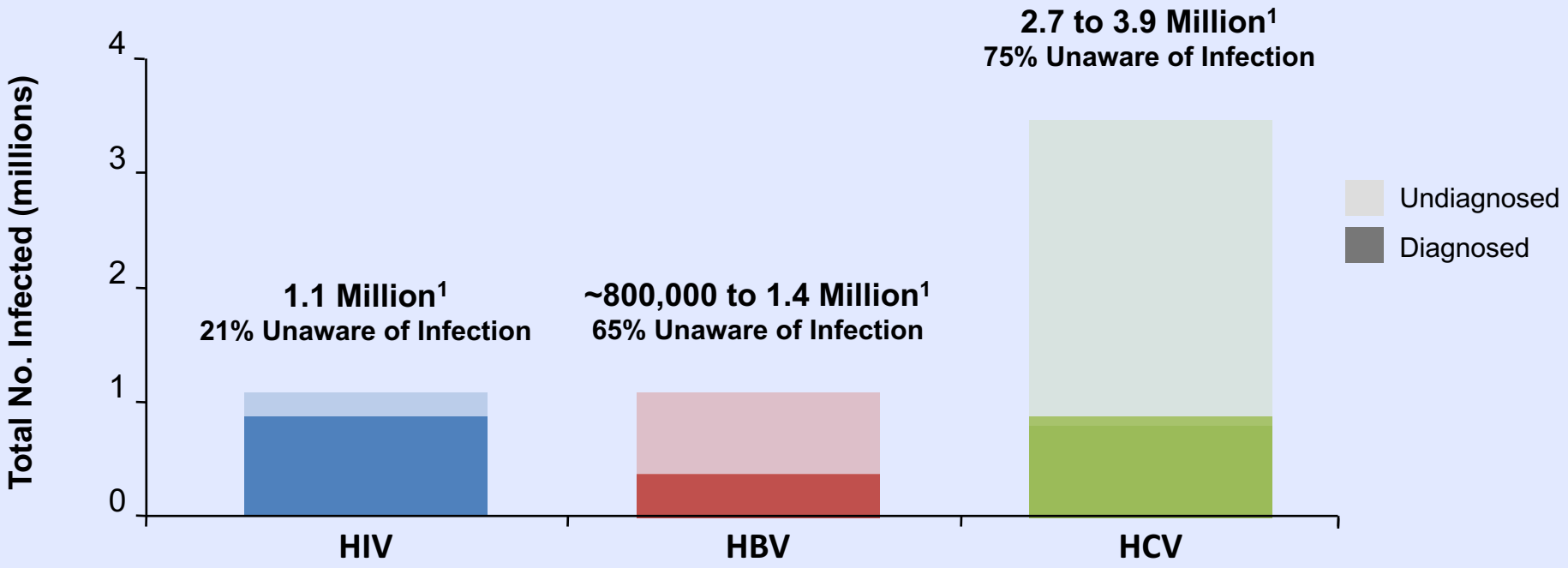
Case 1: Chronic Hepatitis C

Moderator
Dawn Pease, MSN, RN, ANP-BC
Seton Healthcare Family
University Medical Center Brackenridge
Brackenridge Specialty Clinics - Gastroenterology and Endocrinology
Austin, Texas

More Common Than You Think: HCV is Nearly 4x as Prevalent as HIV and HBV



- Based on a 2015 literature search that takes into account populations excluded from NHANEs, the number of US residents who have been infected with HCV is ~4.6 million (range 3.4 million-6.0 million)

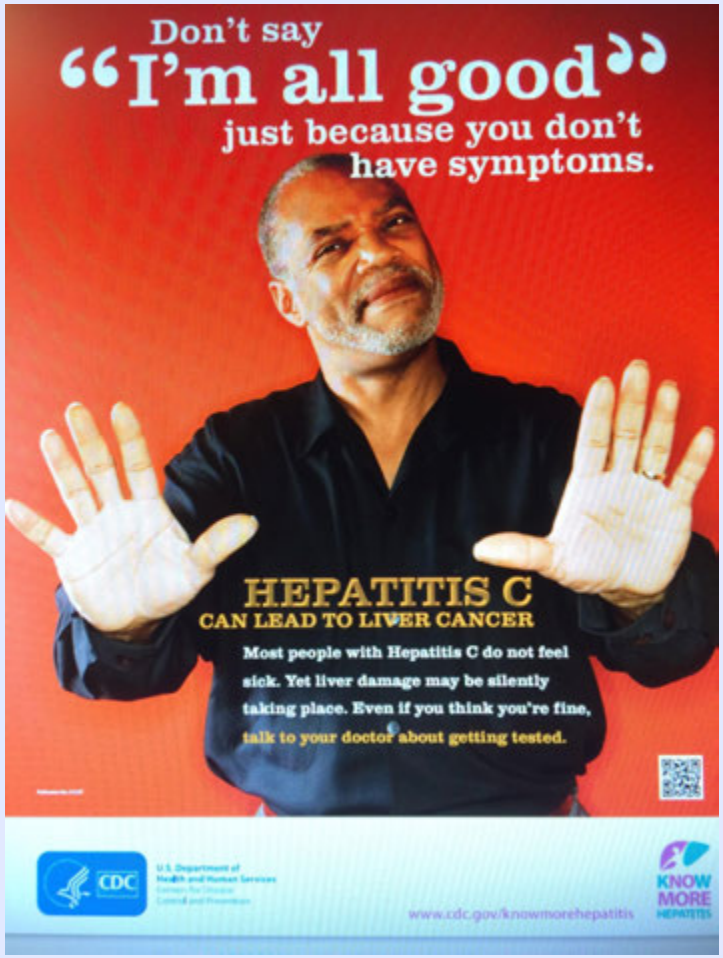
Institute of Medicine. Washington, DC: The National Academies Press; 2010; Edlin BR et al. *Hepatology*. 2015;62(5):1353-63.

Texas Liver Institute

UT Health Science Center San Antonio

Chronic Hepatitis C: A Silent Killer

- Many have no signs or symptoms
- Some have
  - Fatigue
  - Polyarthralgia and polymyalgia
  - Fever
  - Nausea or anorexia
  - RUQ tenderness

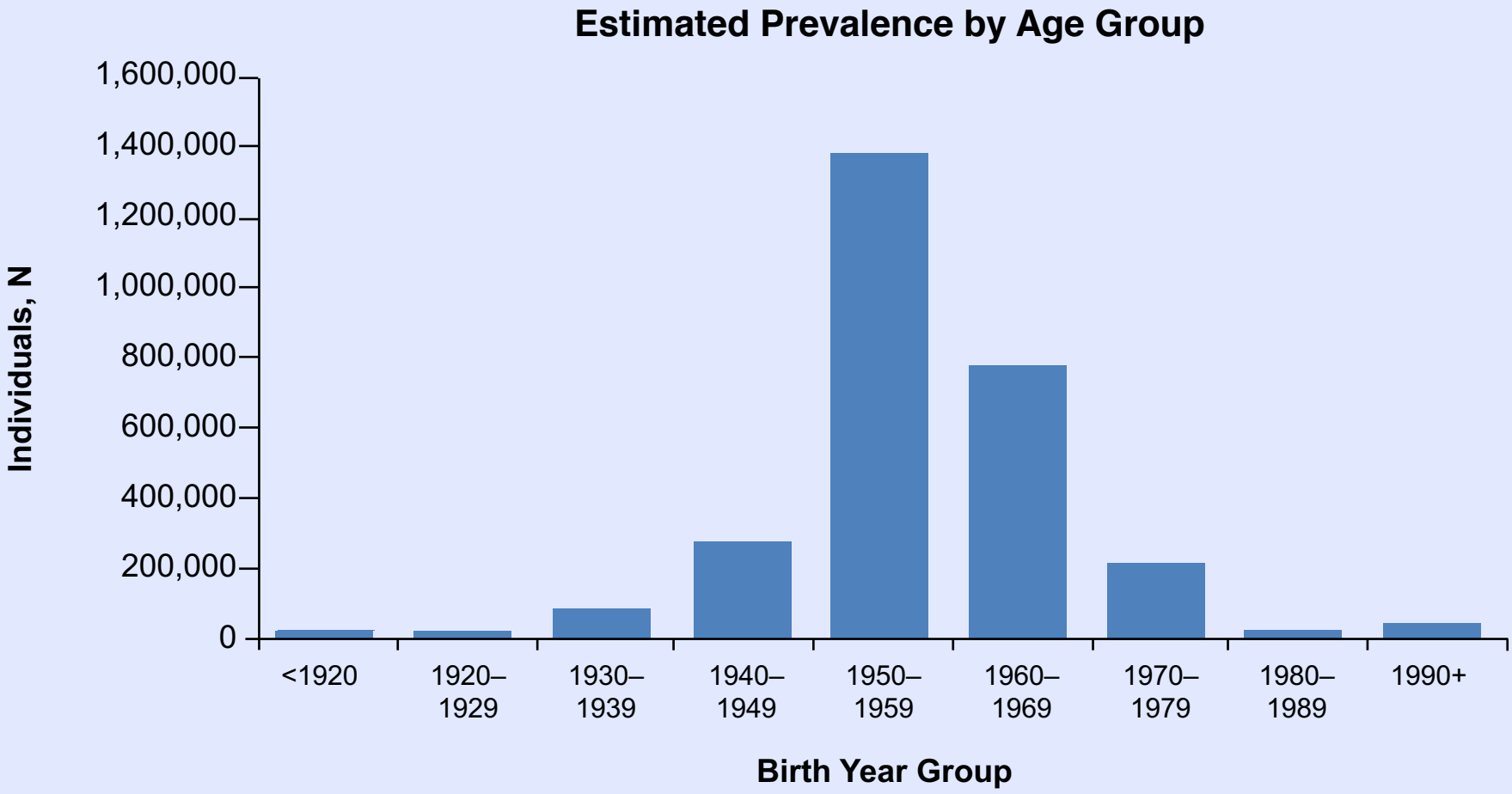


http://www.cdc.gov/knowmorehepatitis/media/Posters.htm

Texas Liver Institute

UT Health Science Center San Antonio

Majority of Persons Chronically Infected With HCV Are Baby Boomers (Those Born Between 1945-1965)

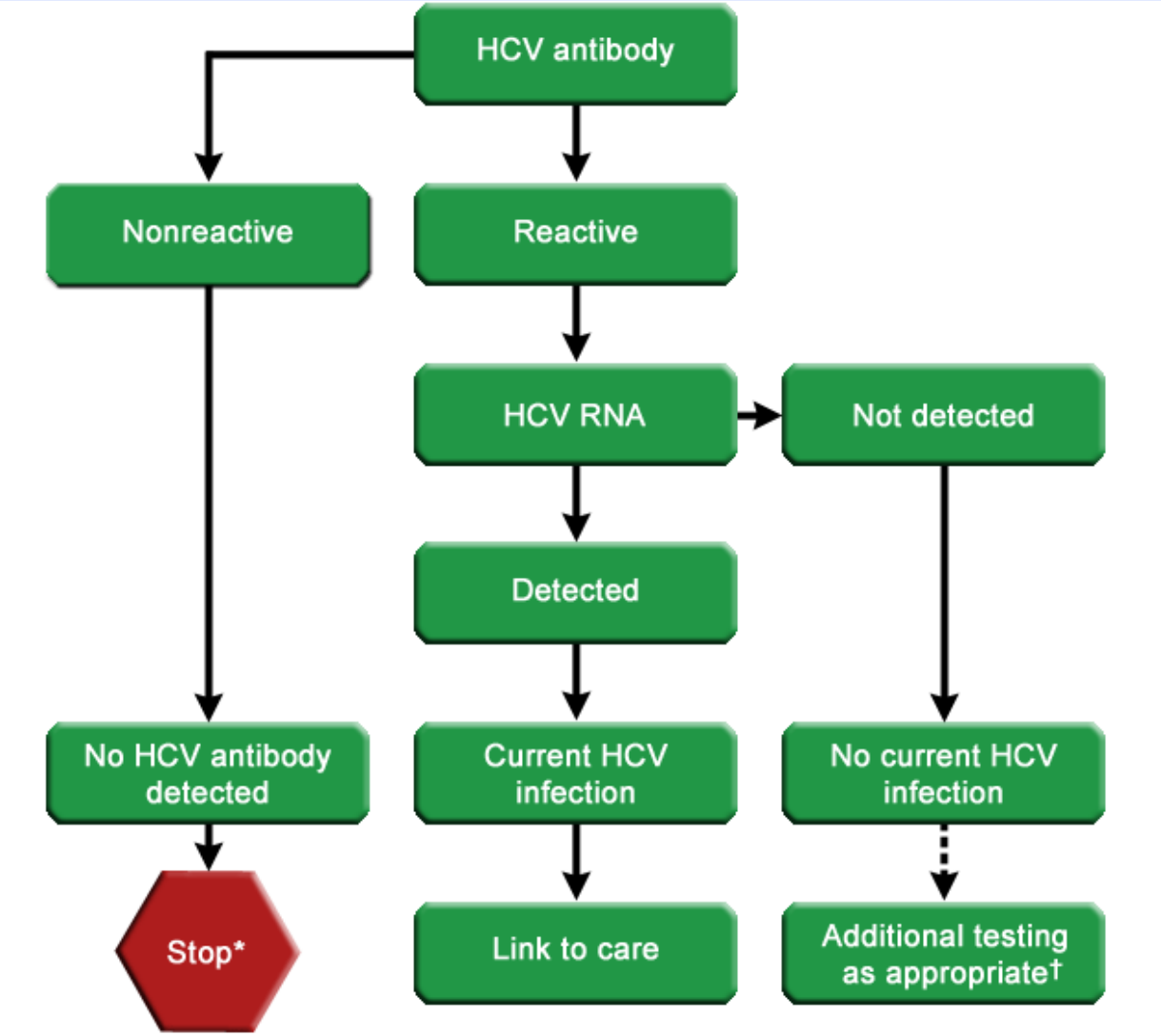


Centers for Disease Control and Prevention. *MMWR*. 2012;61(RR-4):1-32.

Texas Liver Institute

UT Health Science Center San Antonio

HCV Screening is Straightforward: Algorithm for Screening Asymptomatic Persons

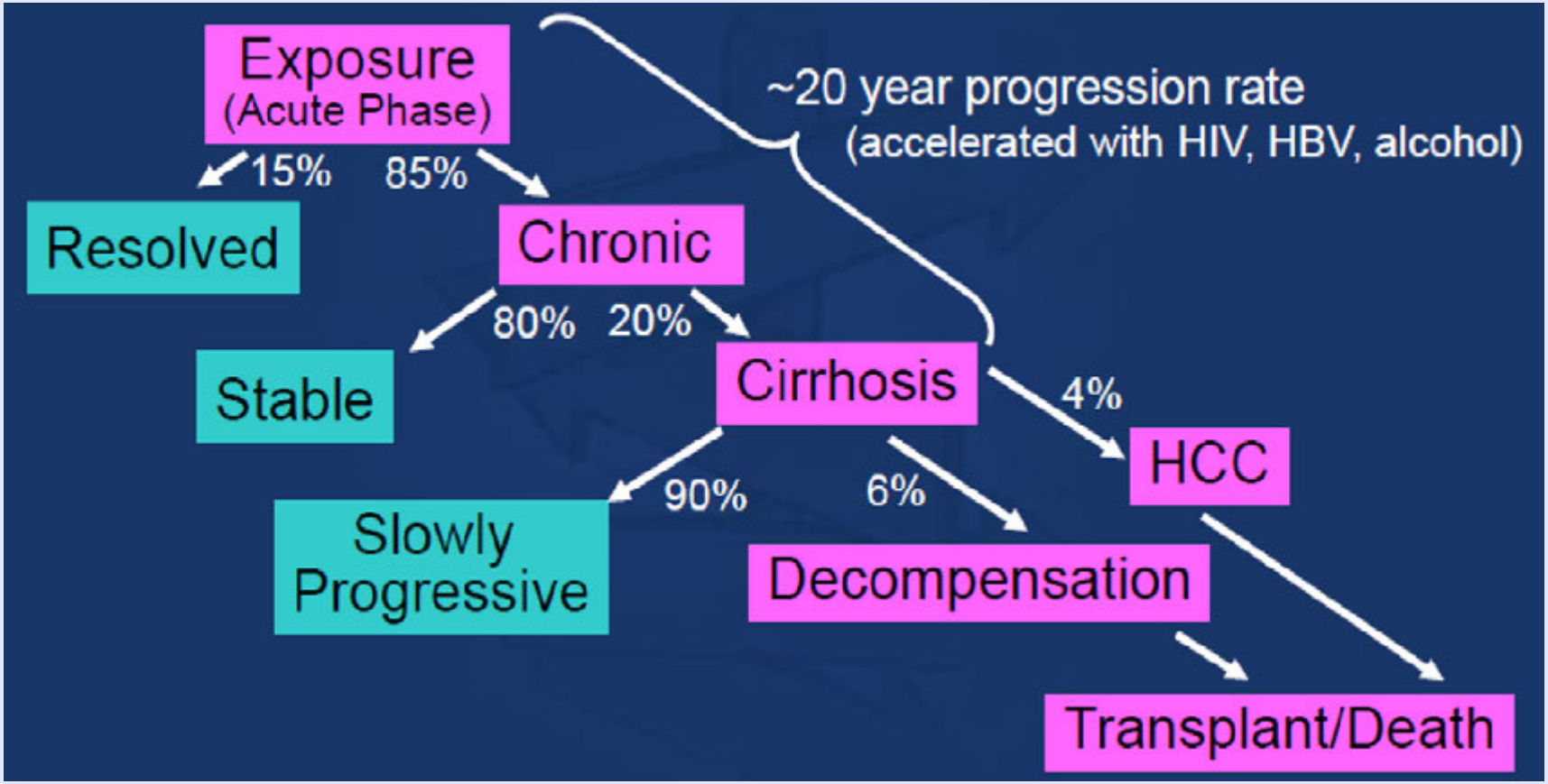


Available at: www.hcvguidelines.org. Accessed April 28, 2016. Adapted from Centers for Disease Control and Prevention (CDC), 2013.

Texas Liver Institute

UT Health Science Center San Antonio

Hepatitis C: Natural History



What Leads to Faster Progression?

Host

- **Modifiable**
  - **Alcohol consumption**
  - **Nonalcoholic fatty liver disease**
  - **Obesity**
  - **Insulin resistance**
- Non-modifiable
  - Fibrosis stage
  - Inflammation grade
  - Older age at time of infection
  - Male sex
  - Organ transplant

Viral

- Genotype 3
- Coinfection with HBV or HIV

AASLD, IDSA, IAS–USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed June 7, 2016

Basic Guidance for Patients with Active HCV

- Abstinence from alcohol
- Evaluation for other conditions that may lead to fibrosis (e.g. HIV, HBV, NASH)
- Evaluation for advanced fibrosis
  - APRI, Fib4, imaging
- Vaccination against HAV, HBV and pneumococcal infection (in patients with cirrhosis)
- Education on avoidance of transmission

Available at: www.hcvguidelines.org. Accessed April 28, 2016.

Case 1: Patient C.B.

- 64 yo African American female with obesity, poorly controlled DM, HTN, hyperlipidemia presents with hepatitis C for evaluation
- Social History
  - No alcohol or drug or tobacco use
  - Unemployed
- Current medications
  - metformin and atorvastatin
- Examination
  - central obesity with BMI 33

Case 1: Patient C.B.

- Hx blood transfusion 1977 (postpartum hemorrhage)
- Diagnosed with chronic hepatitis C in 2012 after mildly elevated LFTs on routine screening
  - Liver biopsy: Grade 2 inflammation, Stage 2 fibrosis, moderate fatty infiltration with some features of NASH
  - Genotype 1a
- Rebekah will update us on treatment options for HCV

Chronic Hepatitis C: Current Treatment Options

Rebekah Hamner, MSN, RN, AGCNS-BC
Texas Liver Institute
Austin, Texas

Texas Liver Institute

WE MAKE LIVES BETTER
UT Health Science Center
SAN ANTONIO

HCV is Curable in Most Patients

- SVR=Cure
  - SVR is when there is no detectable Hepatitis C RNA in the person's bloodstream 3 months after completing antiviral treatment.
- Unlike HIV and hepatitis B infection, HCV does not archive its genome
- There is no vaccine for HCV
- Cured patients will ALWAYS remain HCV antibody positive (Ab+) but that does not mean the infection is back.
- However, SVR ≠ immunity. Reinfection is possible if high risk factors are reintroduced.

Ghany MG, et al. *Hepatology.* 2009;49(4):1335-1374.

General Concepts About Selecting HCV Regimens

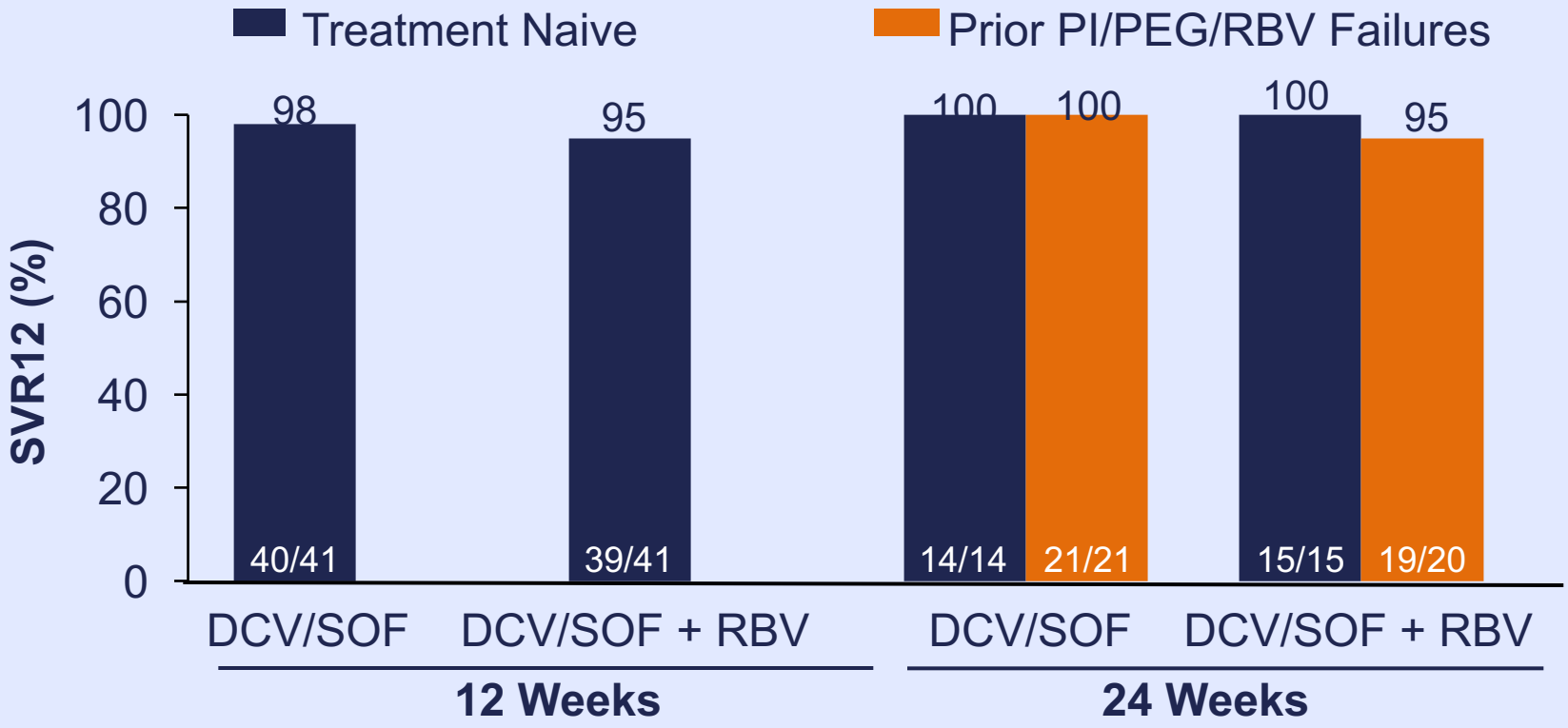
- Choice of regimen, treatment duration, and use of ribavirin depends on:
  - Presence of cirrhosis
  - Prior treatment experience
    - PEG-RBV failure
    - Prior protease inhibitor failure
    - Prior sofosbuvir failure
  - Genotype
    - Genotype 1a vs 1b
    - Genotypes 2-6

Approved Treatment Options Most Often Used for Genotype 1 Infection (Most Common Genotype in US) (alphabetical)

- Daclatasvir (DCV) + Sofosbuvir (SOF) (Daklinza + Sovaldi)
- Grazoprevir (GRZ)/Elbasvir (EBR) (Zepatier)
- Ledipasvir (LDV)/Sofosbuvir (SOF) (Harvoni)
- Paritaprevir/Ritonavir/Ombitasvir (PTV/RTV/OMV) + Dasabuvir (DSV) (Viekira Pak)

- Ribavirin (RBV) required for some regimens in certain populations.

Cure (SVR12) in GT 1 Patients Treated with Daklinza + Sovaldi for 12 or 24 Weeks (FDA Approved for 12 Weeks)

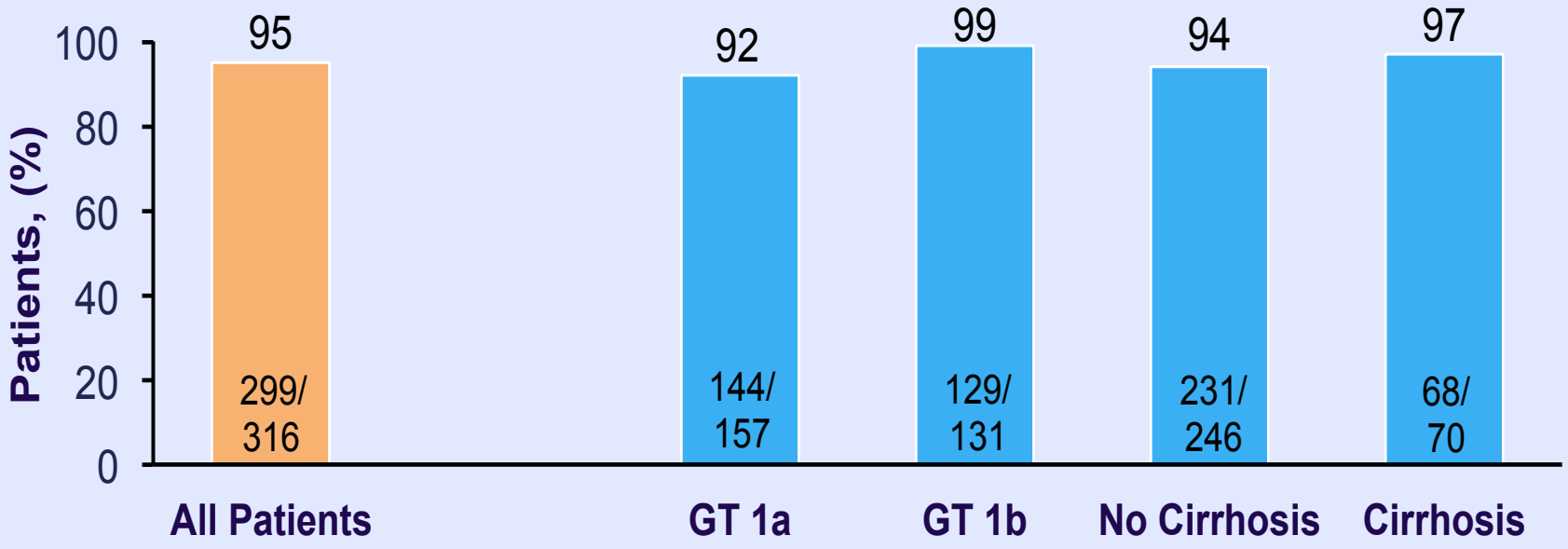


Sulkowski MS et al., *N Engl J Med* 2014;370: 211-21

Texas Liver Institute

UT Health Science Center San Antonio

Cure (SVR12) in GT 1 Patients Treated with Zepatier for 12 Weeks

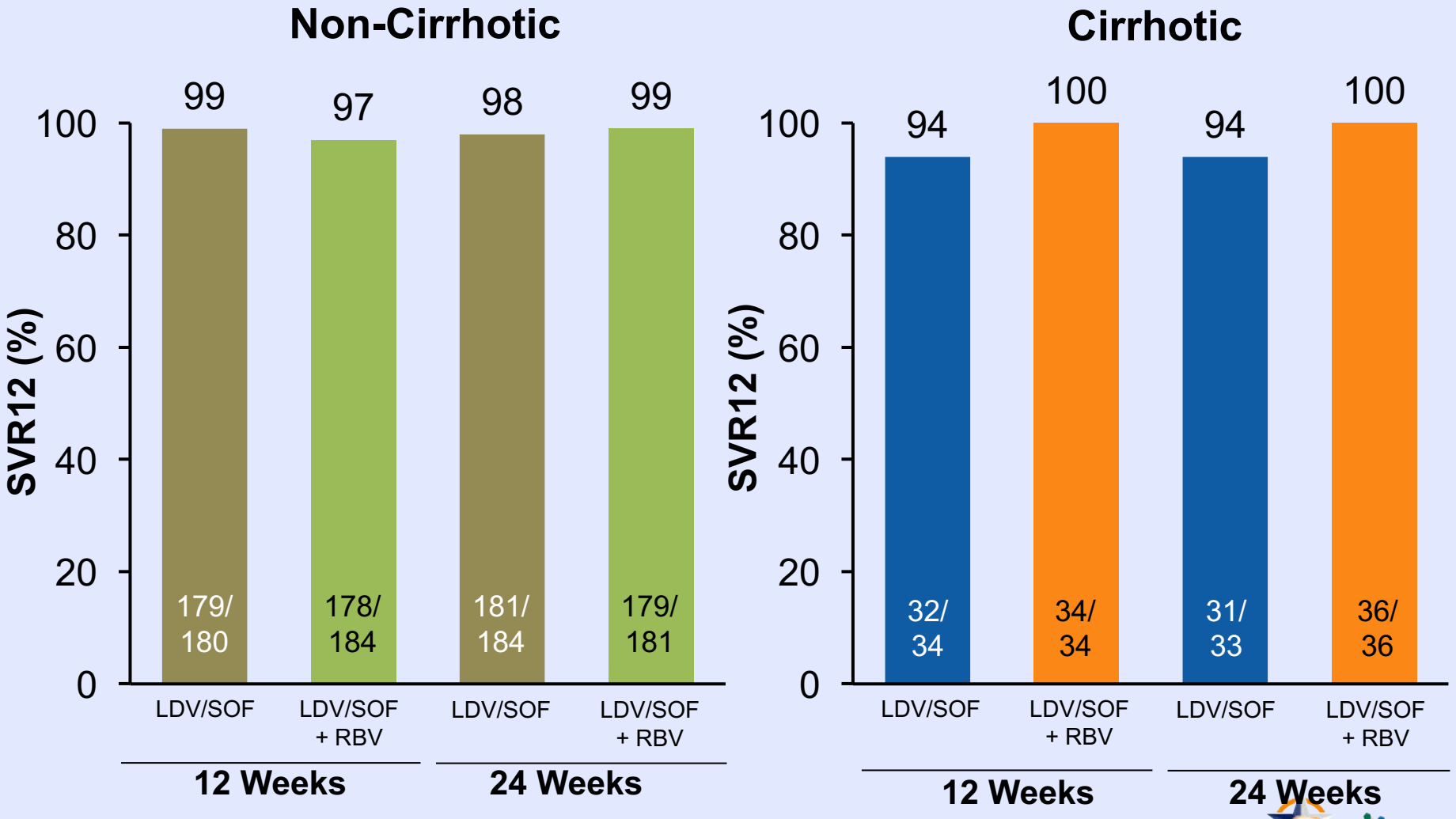


Zeuzem, et al. Abstract #G07, EASL 2015; published online at *Ann Intern Med* (www.annals.org) on 24APR15.

Texas Liver Institute

UT Health Science Center San Antonio

Cure (SVR12) in GT 1 Patients Treated with Harvoni for 12 or 24 Weeks (FDA Approved for 12 Weeks Without RBV; 8 Weeks for Some Patients)

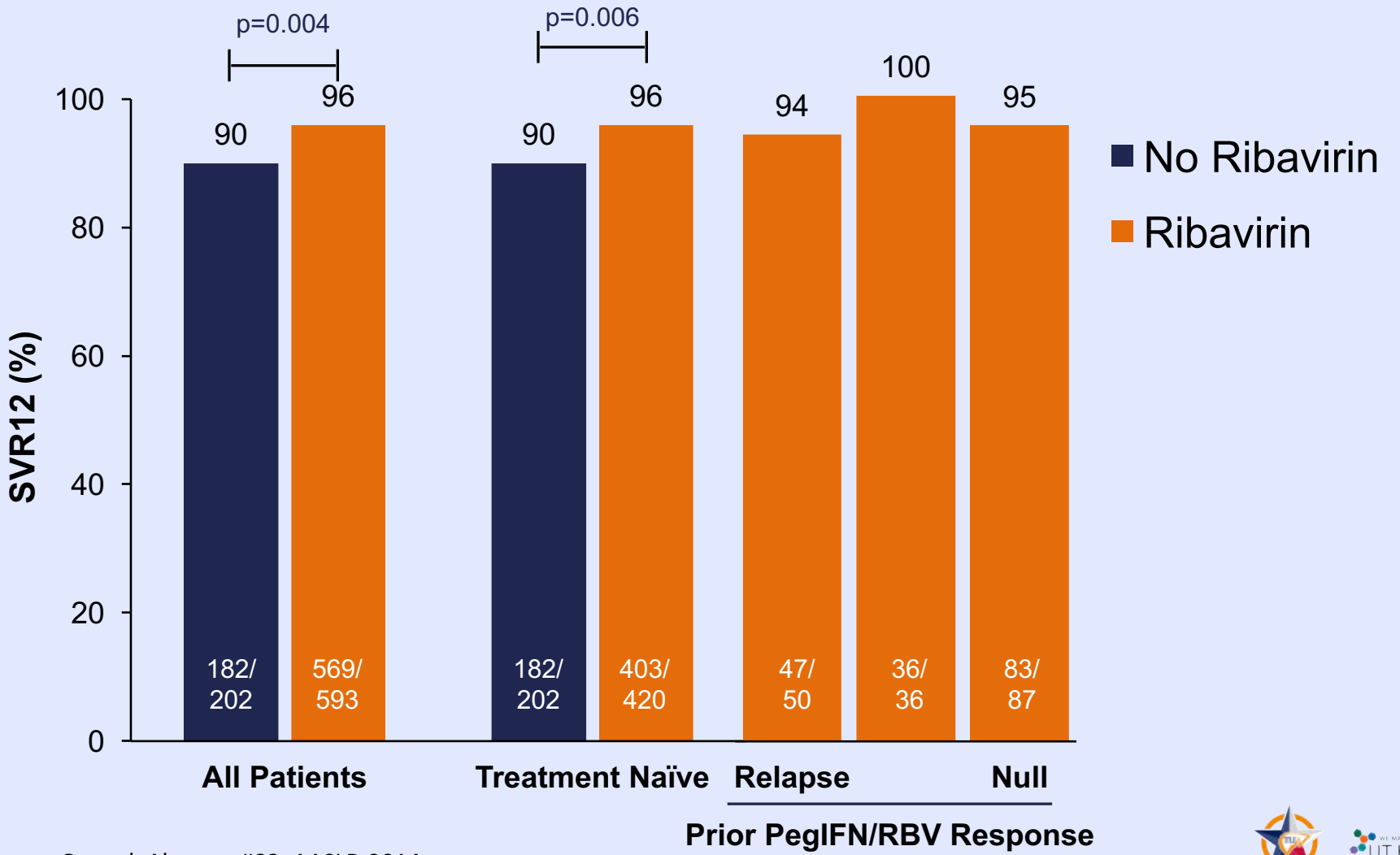


Afdhal, et al. *N Eng J Med*. 2014;370:1889-98.

Texas Liver Institute

UT Health Science Center San Antonio

Cure (SVR12) in GT 1a Patients Treated with Viekira Pak for 12 Weeks

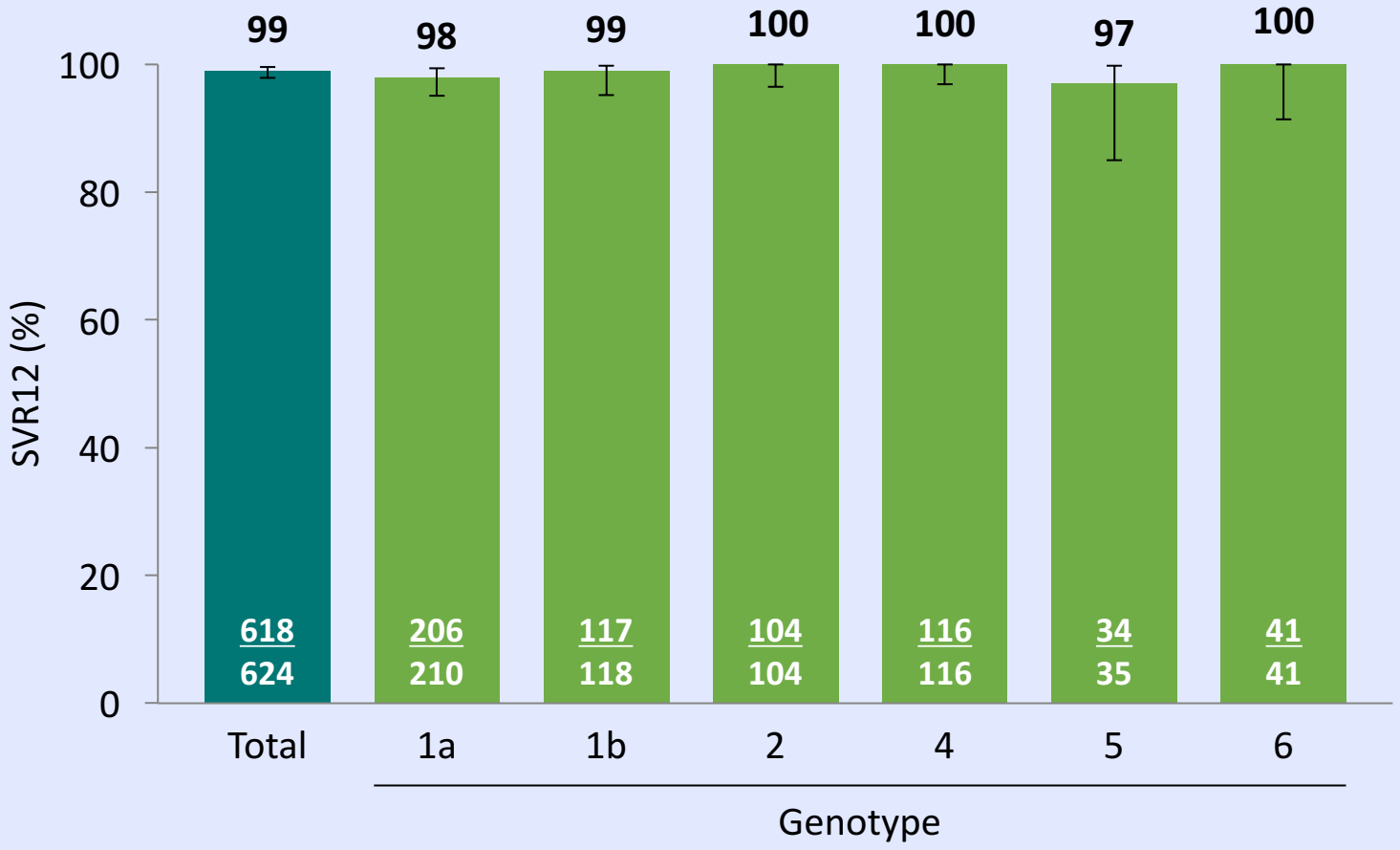


Everson G, et al. Abstract #83, AASLD 2014

Texas Liver Institute

UT Health Science Center San Antonio

Soon To Be Approved: Sofosbuvir/Velpatasvir (SOF/VEL) x 12 Weeks (Pangenotypic)



Feld JJ et al. Presented at: American Association for the Study of Liver Diseases 2015 Annual Conference; San Francisco, CA Nov 13-17, 2015.

Side Effects

- All regimens very well-tolerated, side effects minimal
- Nothing like past treatments that included interferon

Drug Interactions

- Can still be a concern
- Valuable resource: www.hep-druginteractions.org

Special Populations

- HIV/HCV Coinfection
- ESRD
- Decompensated cirrhosis
- Post liver transplant

- These patients do have options and need to be referred to a provider that can treat them.
- www.hcvguidelines.org is living document and regularly updated

More Pangenotypic Regimens in Development

Combination Treatment	Phase	Manufacturer
ABT-493 (NS3/4A protease inhibitor) + ABT-530 (NS5A inhibitor)	3	AbbVie
Sofosbuvir (nucleotide polymerase inhibitor) + GS-5816 (NS5A inhibitor) + GS-9857 (NS3/4A protease inhibitor)	3	Gilead
Grazoprevir (NS3/4A protease inhibitor), MK-3682 (NS5B polymerase inhibitor) and elbasvir (NS5A replication complex inhibitor)	2	Merck
Grazoprevir (NS3/4A protease inhibitor), MK-3682 (NS5B polymerase inhibitor) and MK-8408 (NS5A replication complex inhibitor)	2	Merck

Guidance

- Many options with high cure rates available for C.B.
- Consider concomitant medications and whether modifications must be made
- Review both www.guidelines.org and product labels when making choices

Case 1: Patient C.B.

- She was treated with SOF/LDV x 12 weeks
- Negative at EOT but relapsed at Week 4
- Admitted she missed several doses through course of therapy.
- She is now referred to another clinic to consider retreatment.
- A set of labs is done which shows she is resistant to ledipasvir and daclatasvir.
- Rossalynn will tell us a little bit about resistance and C.B.'s options…

Resistance: When and In Whom to Test

Rossalynn M. Salcido, PA-C

Texas Liver Institute

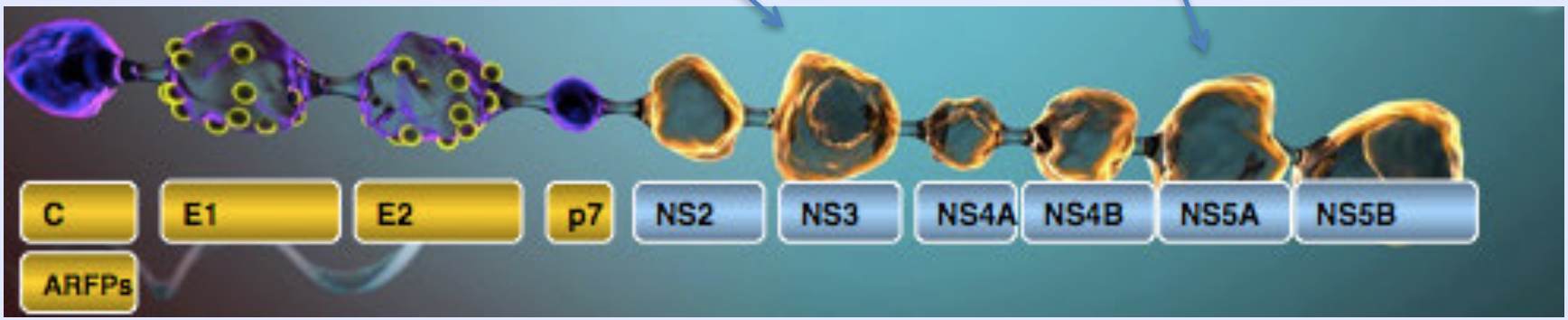
San Antonio, Texas

Texas Liver Institute

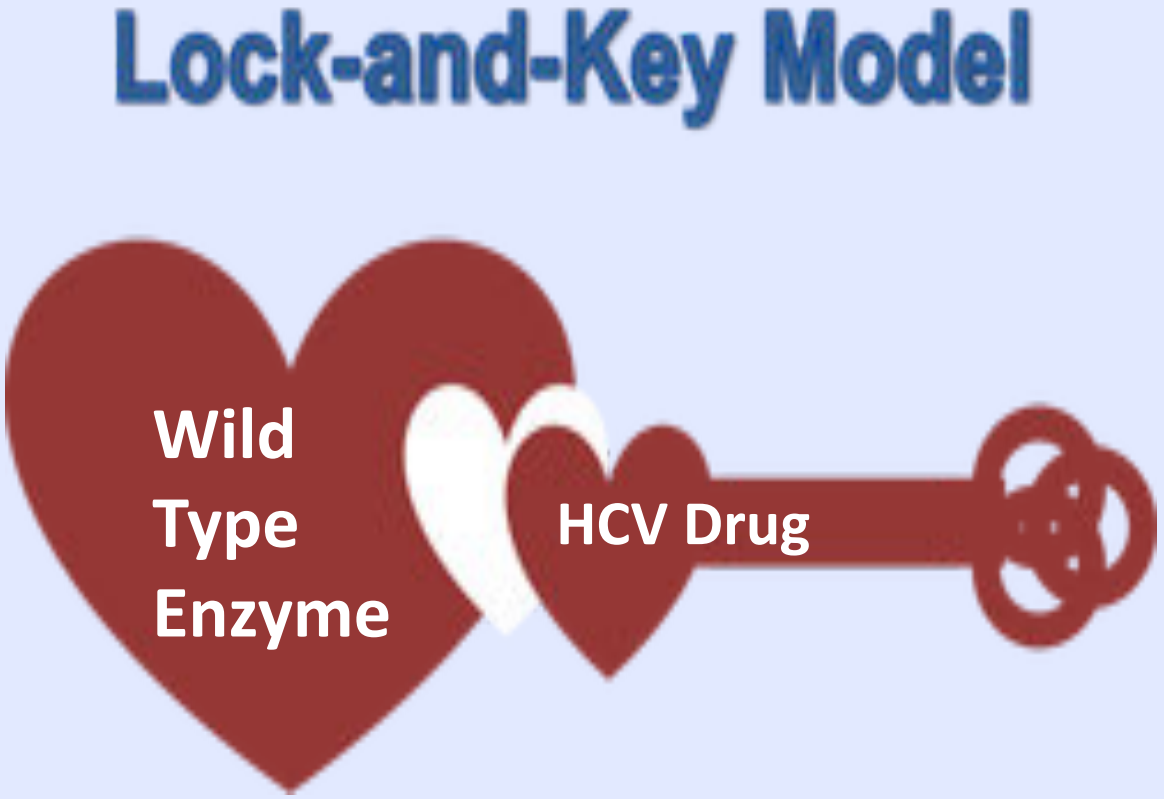
WE MAKE LIVES BETTER
UT Health Science Center
SAN ANTONIO

What is Resistance?

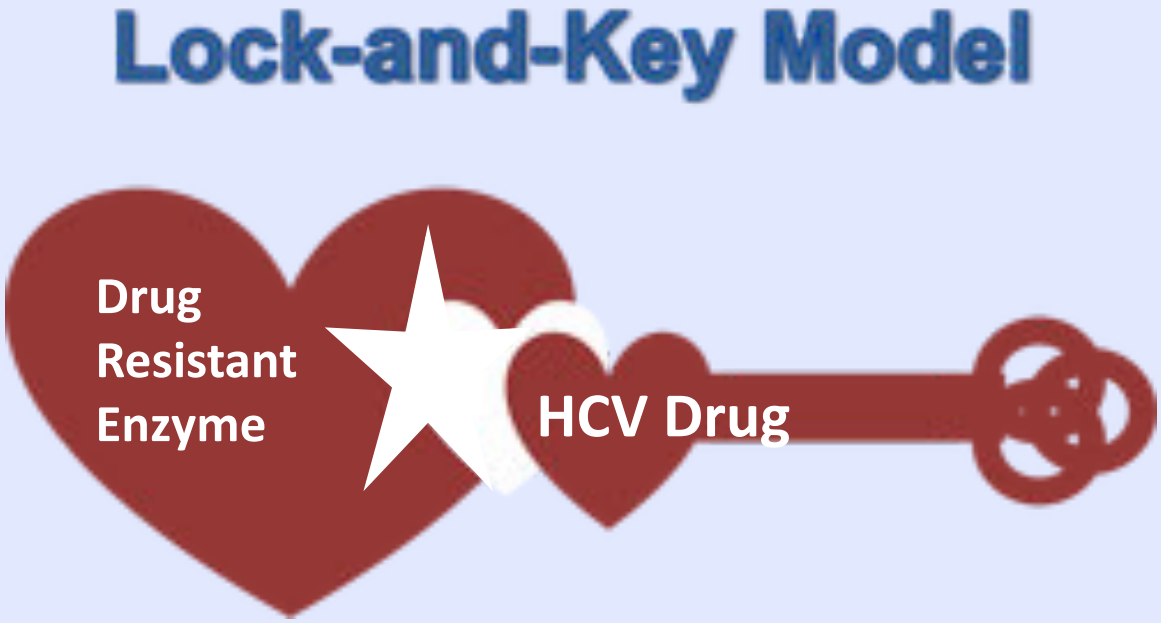
- These proteins are targeted by HCV medications
- Genetic variation can lead to structural changes in these proteins
- Hence, the drug may no longer bind to the protein efficiently



Ideal Situation: Enzyme Inhibition



How Drug Resistance Arises: Amino Acid Change (Mutation) at a Position That Decreases the Binding of a DAA



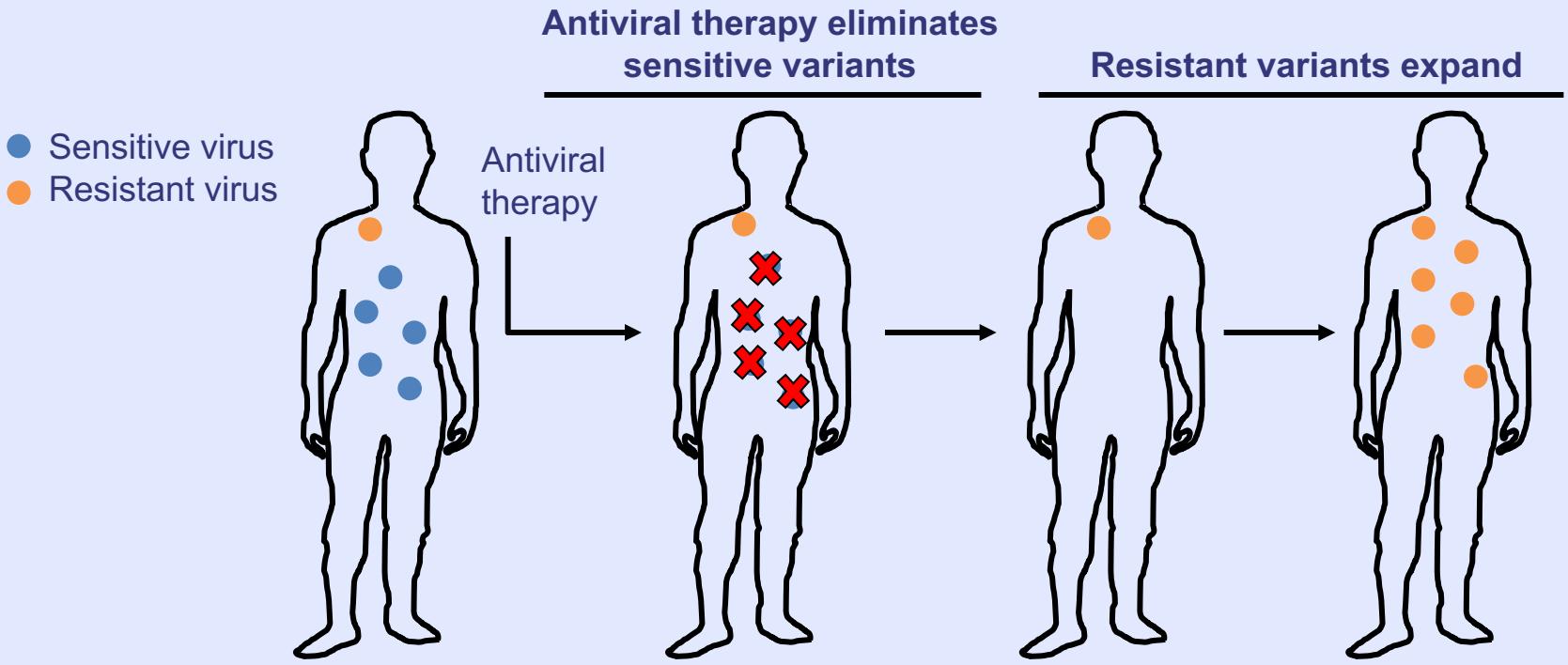
Barriers to Resistance and Are Mutated Viruses Tough or Wimpy?

- Genetic barrier
  - Describes the potency of the drug being used and how unlikely it is to fail due to resistant strains. High genetic barrier means “tough” drug
- Viral fitness
  - Not all resistant strains are “healthy”
  - Some resistance mutations can compromise viral enzyme function, and that virus is easy to eradicate
  - Other mutations make the virus quite tough and hard to eradicate

Rong L, et al. *Sci Transl Med*. 2010;2:30ra32.

Resistant Variants May Be Present Before and Can Be Selected During Treatment

- HCV is a mixture of related but distinct populations of virions in each patient[1]
- Most resistant variants are unfit and may be undetectable prior to therapy[2,3]

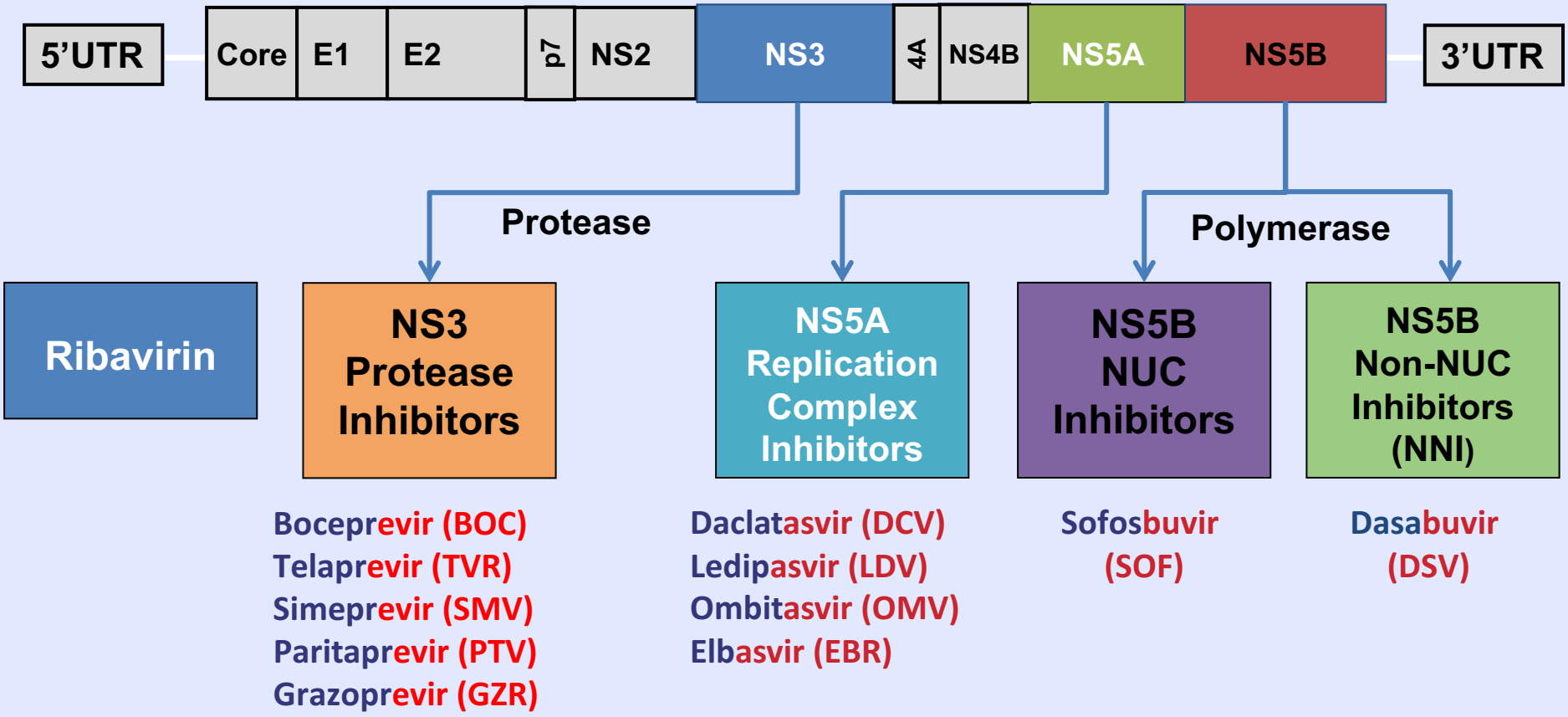


1. Pawlotsky JM, *Clin Liver Dis*. 2003;7:45-66; 2. Kuntzen T, et al. *Hepatology*. 2008;48:1769-1778;
3. Bartels DJ, et al. *J Infect Dis*. 2008;198:800-807. Image reproduced from Forum for Collaborative HIV Research (www.hivforum.org).

Two Ways to Deal with Resistance

- Use medications that have no weakness against the resistance present
- Use multiple medications, to increase chance of “covering” all the resistance strains

FDA Approved Direct-Acting Antiviral Agents (DAAs) from Multiple Classes



No Cross Resistance Between Drug Classes

Texas Liver Institute

UT Health Science Center San Antonio

Principles of all Oral Regimens for HCV

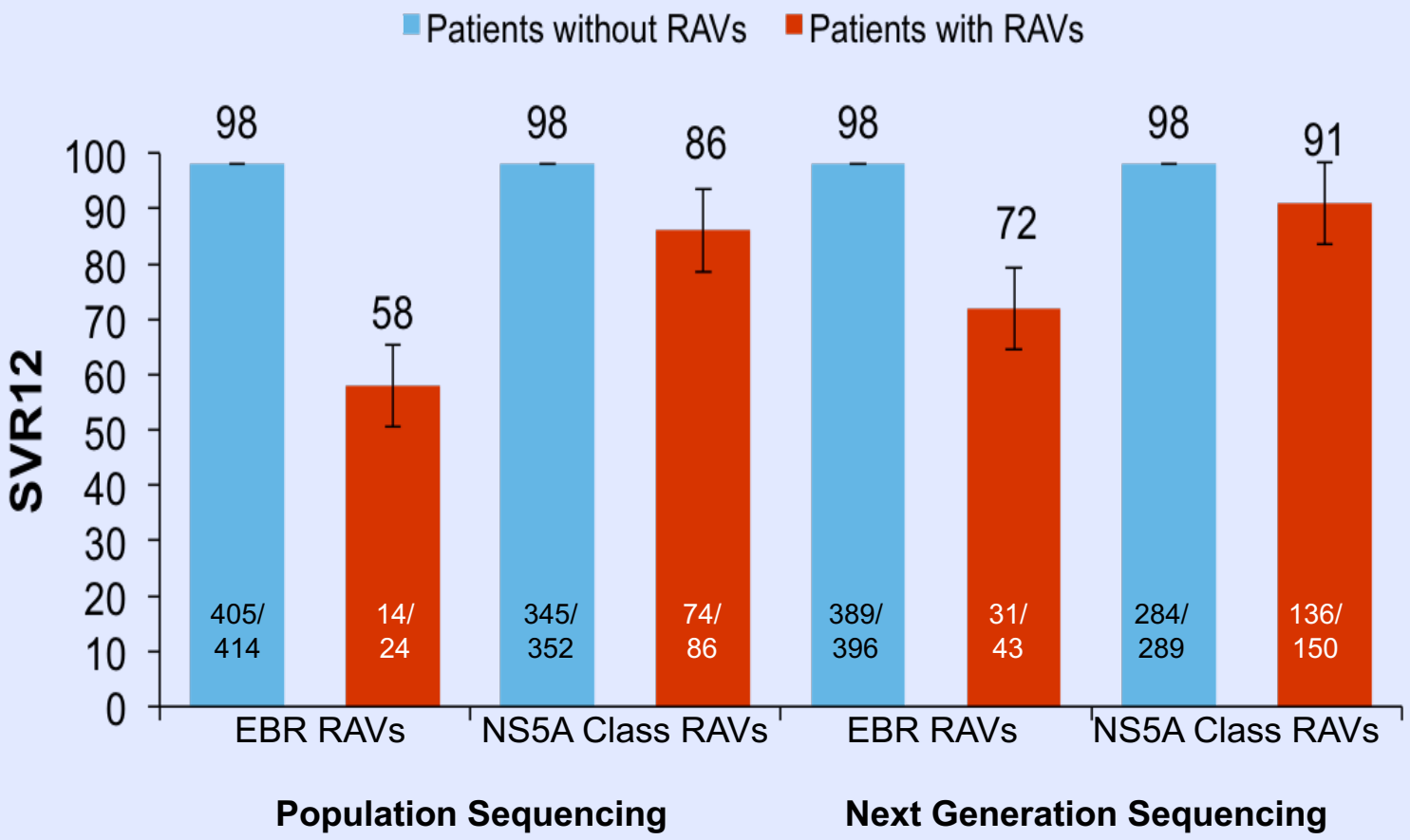
- Combine drugs from different classes
  - Hit multiple viral targets to increase efficacy
  - Diminishes risk of viral resistance
- Benefits of multi-drug strategies
  - Backbone/anchor drug plus additional agent(s)
  - Superior efficacy than expected from individual drugs
- If done properly
  - Near universal efficacy
  - Short duration of therapy
  - Side effects have minimal impact on QOL

Commercial Resistance Testing

- Widely available (Quest and LabCorp).
- Detects or reports RAVs as low as 10-20% prevalence.
- At least 2000 copies/mL must be present.
- Detects mutations associated within NS3/4a, NS5A, and NS5B in GT 1 and GT 3.

How Can Resistance Impact Efficacy?

NS5A Resistant Variants are Problematic: 12 Weeks of Potent Combo (Grazoprevir/Elbasvir) Not Enough

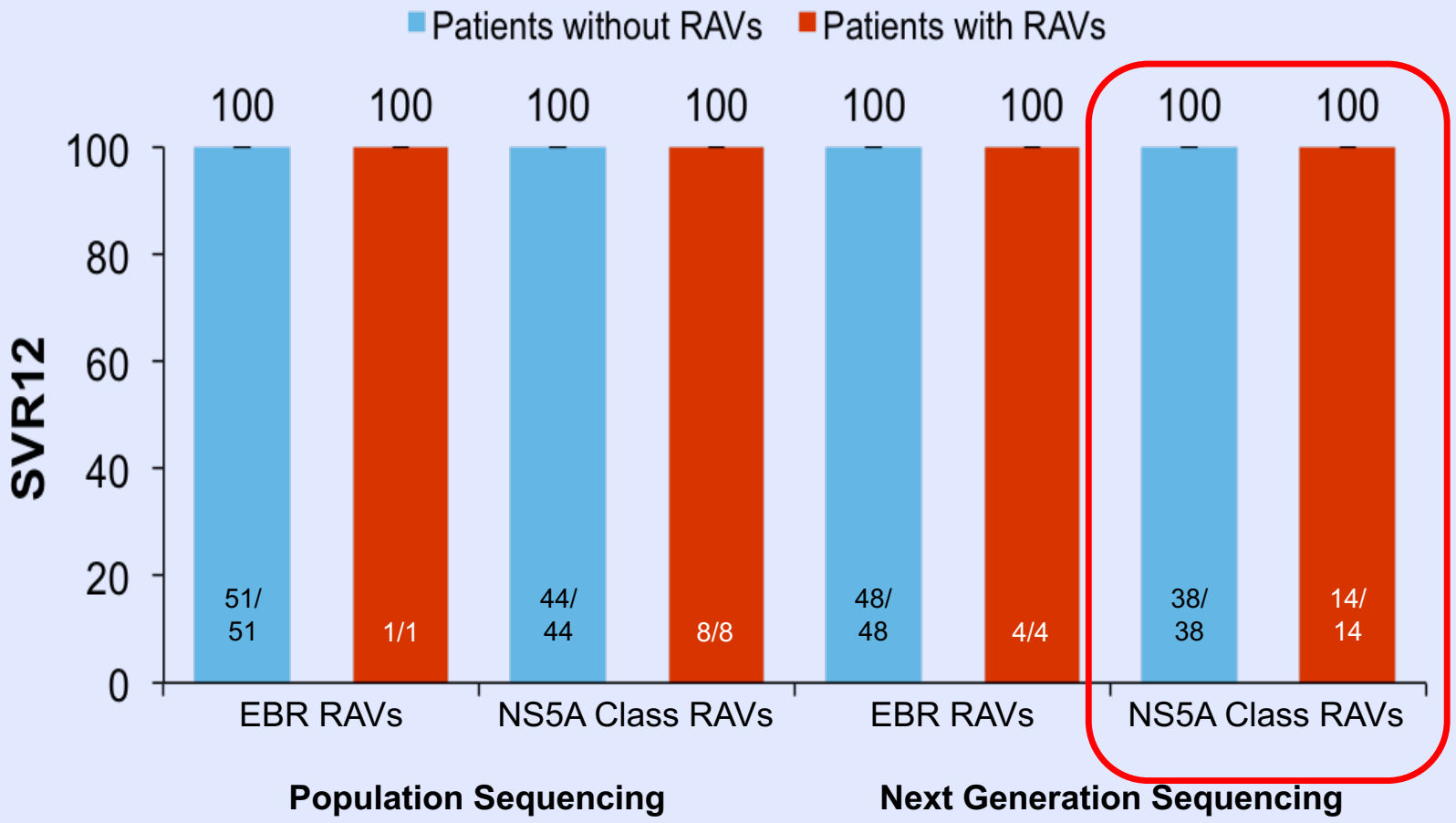


Jacobson, et al. Abstract #LB-22, AASLD 2015.

Texas Liver Institute

UT Health Science Center San Antonio

100% Cure Rate with Grazoprevir/Elbasvir + Ribavirin in Patients With Resistant Variants (16-18 Week Treatment; GT1a)

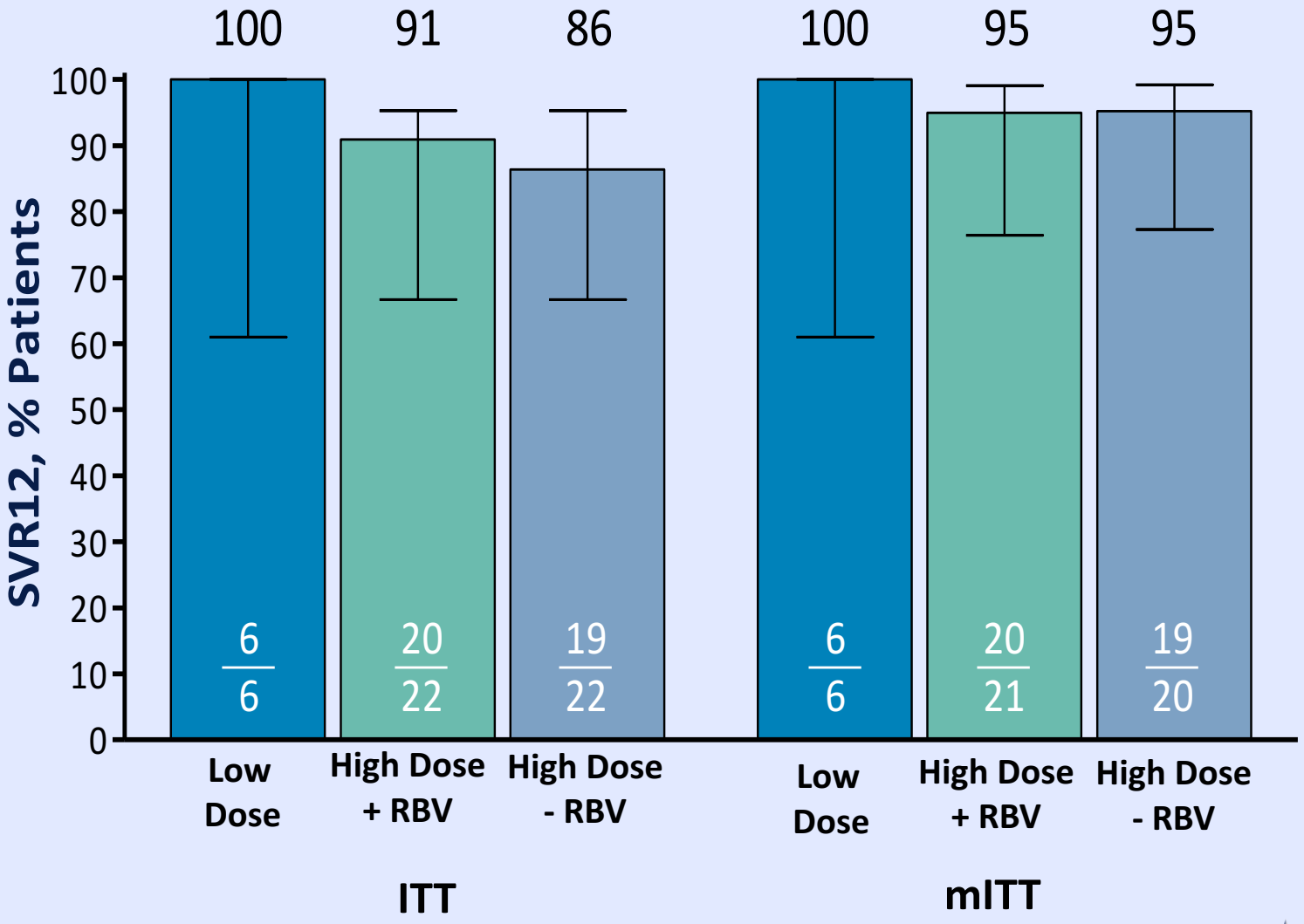


Jacobson, et al. Abstract #LB-22, AASLD 2015.

Texas Liver Institute

UT Health Science Center San Antonio

ABT-493/ABT-530 in Late-Stage Development: High Efficacy in Patients Who Failed DAA Regimens (12 Week Treatment)



Poordad F, et al. Abstract #GS11, EASL 2016.

Texas Liver Institute

UT Health Science Center San Antonio

Take Home Lesson on Resistance

- Know the genotype/subtype you are treating (eg, GT1a vs GT1b or G3)
- Know the assay the lab you order from is using (population sequencing most common in commercial labs)
- Know the specific RAVs that are most problematic and likely to affect treatment decision

Conclusion

- All viruses can become resistant
  - It's their defense mechanism against drugs
- Our job is to not create more mutations
- We can identify resistant strains and select medications that will be effective against them
- More potent drugs are being developed that have less potential for failure

Patient C.B.

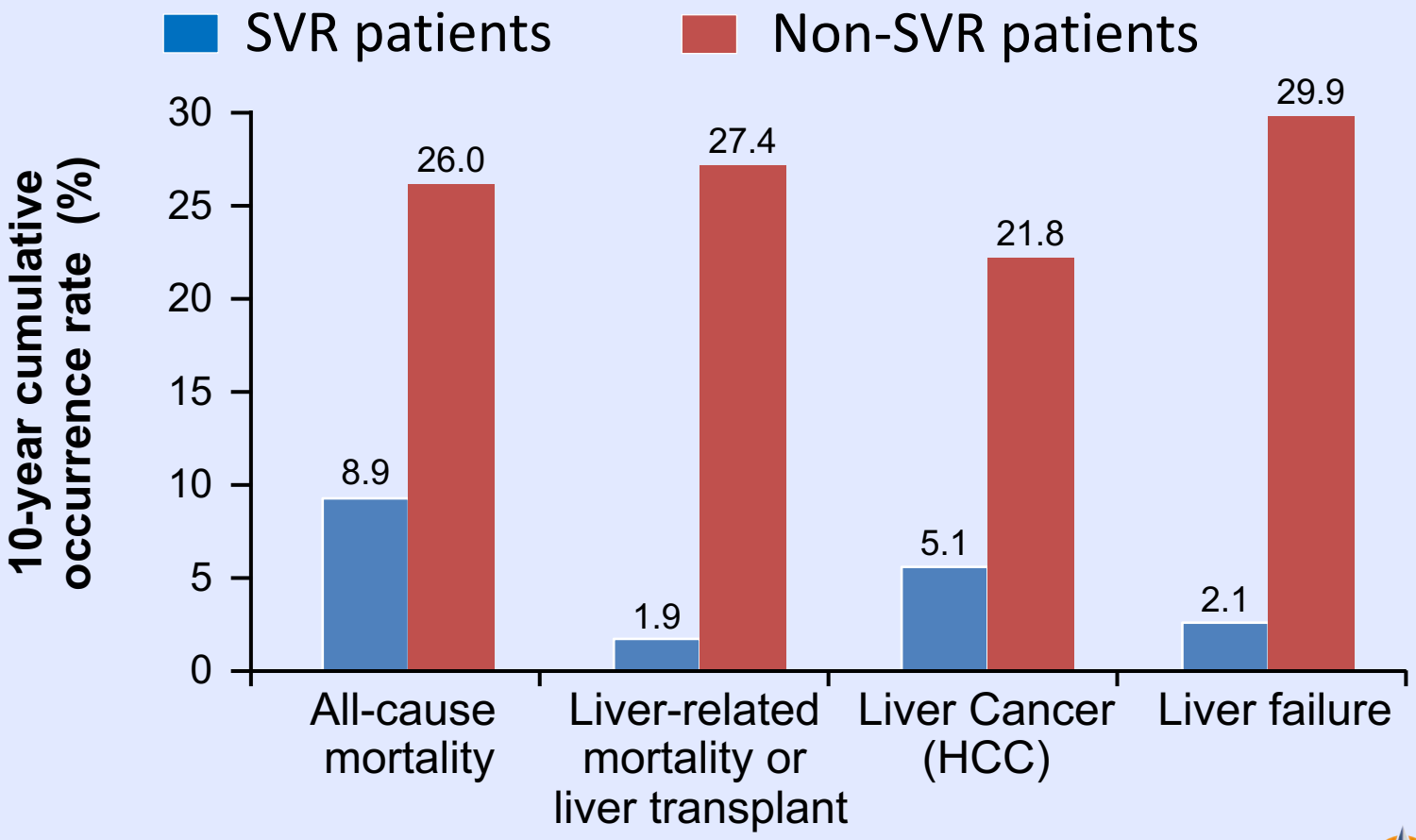
- C.B. is retreated in a clinical trial for DAA failures
- She is cured with next generation drugs
- Upon repeat biopsy to get into that study, it was noted that her biopsy stage was 3
- Now that she is cured, what should be done?

Long-term Management of Cured Patients

Yulia Lyuboslavsky, APN, ACNS-BC
Austin Gastroenterology
Austin, Texas

SVR Results in a Reduction in All-cause Mortality in Patients with Advanced Fibrosis

530 patients followed for a median of 8.4 years

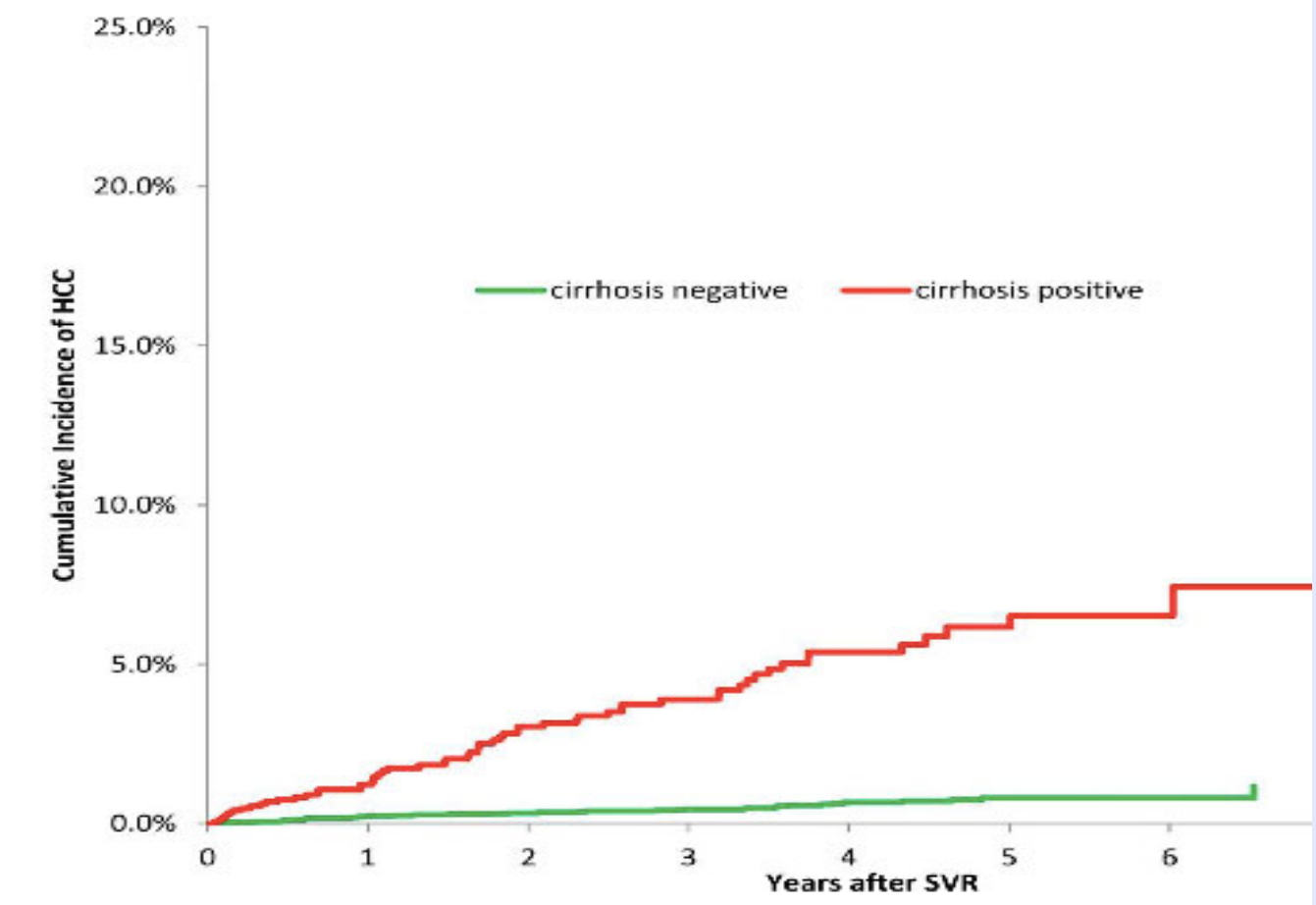


Van der Meer A, et al. *JAMA* 2012; 308:2584–2593.

Texas Liver Institute

UT Health Science Center San Antonio

Development of Liver Cancer After SVR Still Possible



- Once non-cirrhotic patients achieve SVR, the risk of liver cancer is very low and regular screening post SVR is not recommended.

El-Serag, Hepatology, 2016

Texas Liver Institute

UT Health Science Center San Antonio

Follow up: All Patients Achieving SVR

- Assessment of recurrence or reinfection ONLY if patient has ongoing risk of infection (eg, illicit drug use, high-risk sexual exposure) or unexplained hepatic dysfunction.
  - Must order HCV RNA test and not anti-HCV serology (remember: patient will always be antibody +)
- Assessment of other causes of liver disease for patients with persistently abnormal liver tests after SVR.

www.hcvguidelines.org; accessed June 7, 2016.

Follow up: Patients Achieving SVR

- No advanced fibrosis (earlier stage disease; F0-F2)
  - Manage the same as if patient was never infected with HCV
- Advanced fibrosis/cirrhosis (F3-F4)
  - Twice-yearly ultrasound for liver cancer surveillance
  - Baseline endoscopy to screen for esophageal varices if cirrhotic

www.hcvguidelines.org; accessed June 7, 2016.

Follow up: If Patient Did Not Achieve SVR

- Hepatic function panel, CBC, INR every 6-12 months
- Twice-yearly ultrasound for liver cancer surveillance in patients with advanced disease (F3-F4)
- Endoscopic screening for esophageal varices if cirrhosis present
- Evaluation for retreatment in a clinical trial
  - Be sure to test for HCV RAVs; may help eligibility for trial

www.hcvguidelines.org; accessed June 7, 2016.

General Advice: Keep Your Liver Healthy

- Vaccinate for HAV and HBV
- Maintain healthy BMI
- Control blood sugar and cholesterol (diabetes/HLD/metabolic syndrome)
- Limit ETOH use
- Milk Thistle?

Milk Thistle: The Jury is Still Out

- Phase III controlled clinical trial: Did not significantly reduce serum ALT levels more than placebo in participants with chronic HCV
- Clinical efficacy of milk thistle is not clearly established
  - Possible benefit has been shown most frequently, but not consistently, for improvement in aminotransferases
  - Available evidence is not sufficient to suggest whether milk thistle may be more effective for some liver diseases

Fried MW et al. JAMA. 2012 Jul 18;308(3):274-82
Mulrow, C et al. “Milk Thistle: Effects on Liver Disease and Cirrhosis and Clinical Adverse Effects: Summary”. AHRQ Evidence Report Summaries. 01 April, 2016

Patient C.B.

- Needs to be followed closely for progression of fibrosis
- She also has NASH and this could lead to advanced liver disease
- Abstain from alcohol
- Lose weight
- Control diabetes

Summary

- HCV is curable
- Screening
  - All baby boomers (born between 1945 and 1965) should have one time screening for hepatitis C.
  - Any person with high risk behavior as defined by the CDC should be screened.
- Linkage to liver experts that can assess disease progression and treatment options
- Highly efficacious, short duration regimens with favorable safety profiles are available