Be Confident: Primary Care Office-Based Treatment of Hepatitis C

Project ECHO is Here for YOU!

Crystal David, PharmD, BCPS
Clinical Assistant Professor
Oklahoma State University Center for Health Sciences
Crystal.David@okstate.edu
April 27, 2019

Disclosures

I have nothing to disclose.

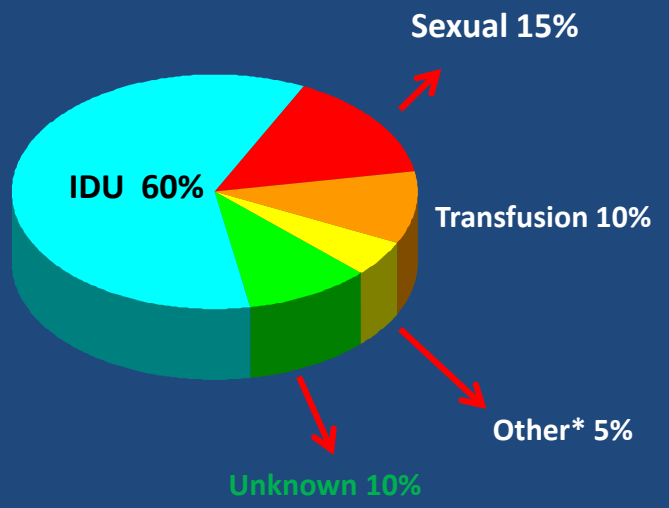
Objectives

- Describe risk factors for hepatitis C
- Define hepatitis C screening recommendations
- Review diagnostic workup for hepatitis C
- Discuss the specific direct acting antivirals (DAA) used for hepatitis C treatment today
- Interpret the ECHO treatment algorithms to select a hepatitis C treatment regimen

HCV Epidemiology

HCV: Transmission

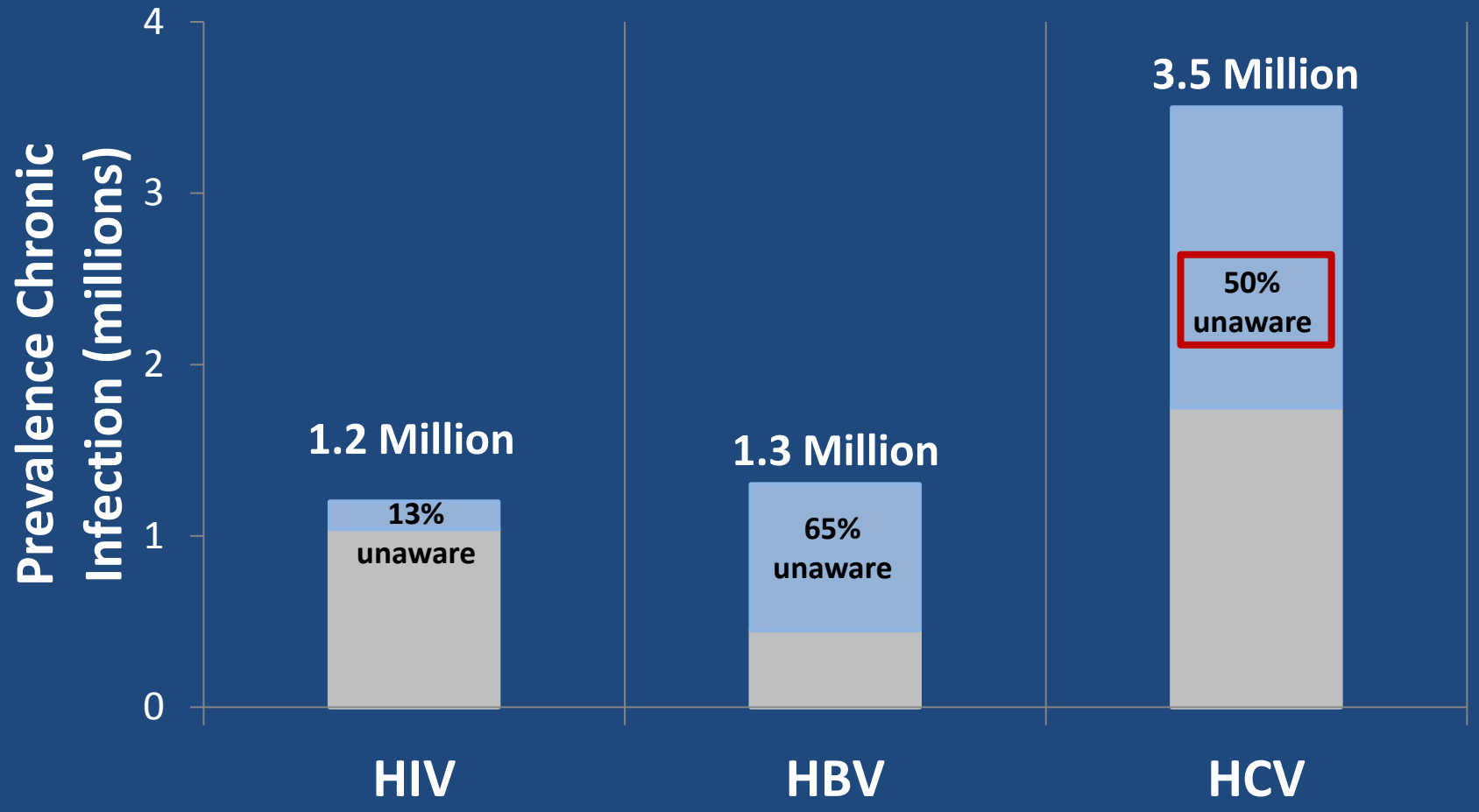
- **Blood**
  - IVDU is the leading cause in the US
  - Blood transfusion (Before 1992)
  - Percutaneous/mucosal
    - Needle stick
    - Tattoo
- **Sexual contact**
  - Rare in heterosexual
  - More frequent in MSM
- **Mother-to-child**
  - The rate is 1.7% - 4.3 %



*Nosocomial; Health-care work; Perinatal

CDC
Centers for Disease Control and Prevention

HCV is the Most Common Blood-Borne Chronic Viral Infection in the US

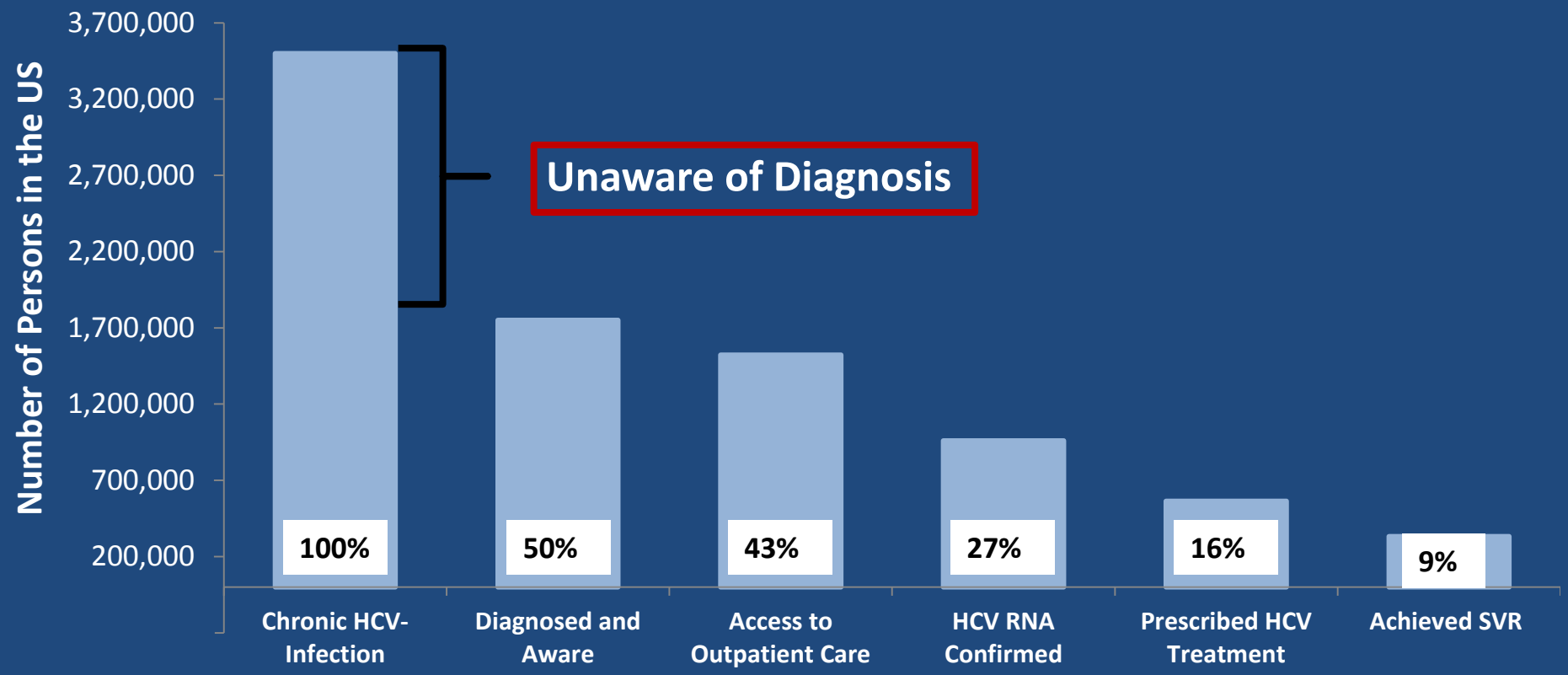


HBV = hepatitis B virus; HIV = human immunodeficiency virus; US = United States; CDC = Centers for Disease Control and Prevention.

CDC. HIV/AIDS Basic Statistics. www.cdc.gov. Accessed 9/25/17; CDC. Viral Hepatitis Statistics and Surveillance. www.cdc.gov. Accessed 9/25/17; National Academies of Sciences, Engineering, and Medicine. *A National Strategy for the Elimination of Hepatitis B and C: Phase Two Report.* Washington, DC: The National Academies Press; 2017.

Mortality Rates from HBV, HCV, and HIV in United States

Gaps Along the HCV Care Cascade

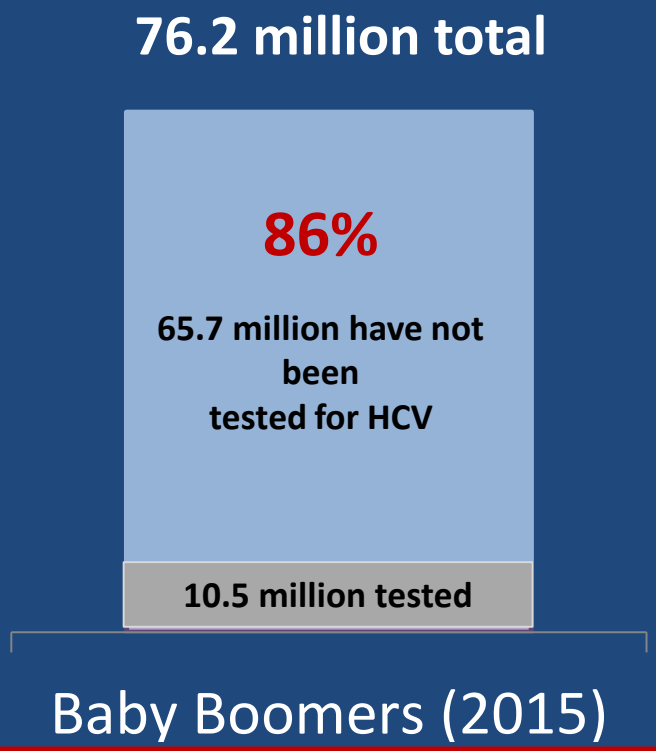


RNA = Ribonucleic acid.

Yehia BR, et al. *PLoS One*. 2014;9(7):e101554.

Persistent Gaps in HCV Testing Leave Millions at Risk

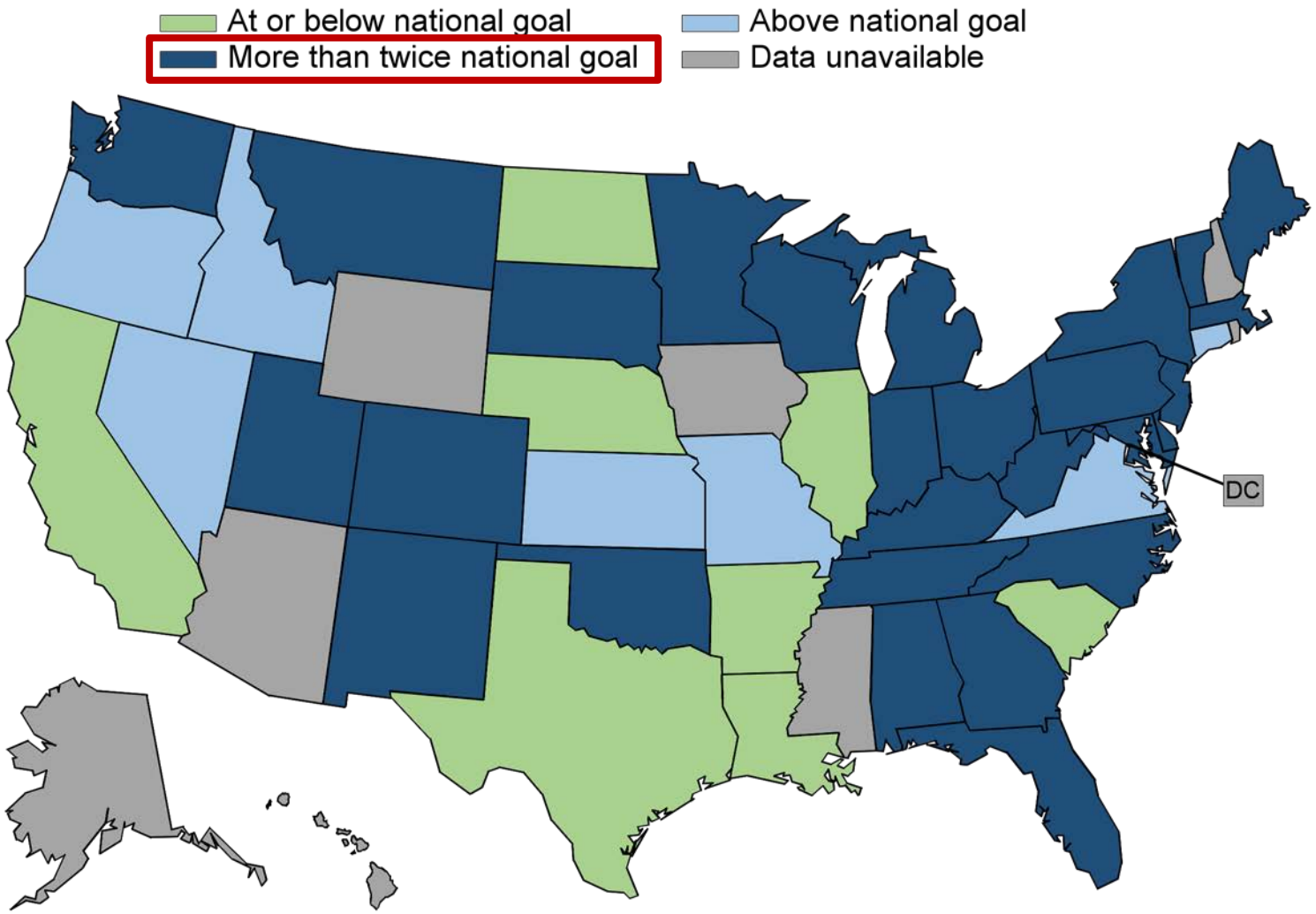
- 80% of patients with chronic HCV were born between 1945–1965
- In 2012, the CDC recommended 1-time HCV testing for baby boomers
- Testing among baby boomers remains low despite these recommendations:
  - 12.3% in 2013
  - 13.8% in 2015



Curative therapy alone is not enough to reduce HCV prevalence. Expanded screening and linkage-to-care efforts are needed as well.

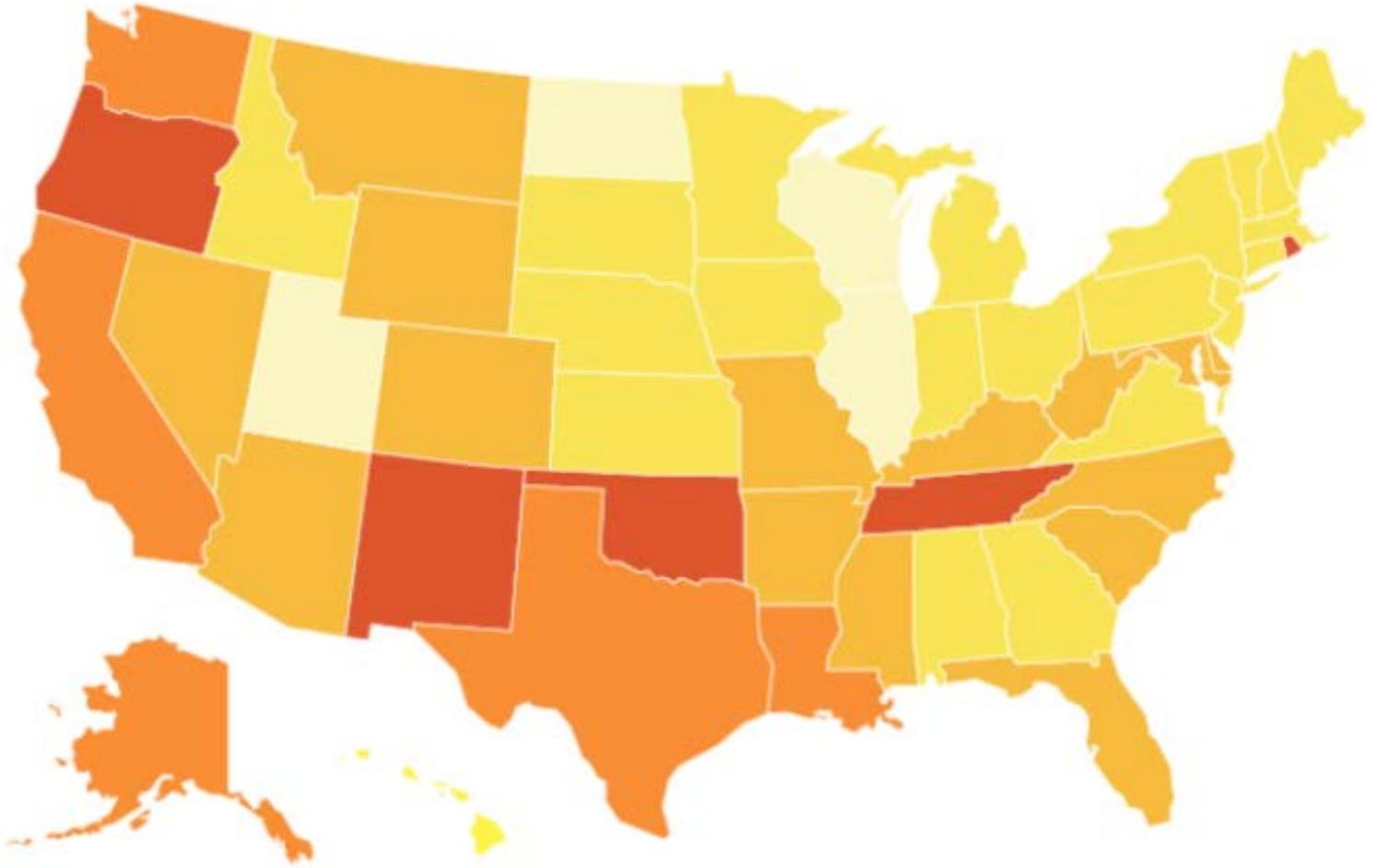
Smith BD, et al. *MMWR Recomm Rep*. 2012; 61(RR-4):1-32; Jemal A, et al. *Am J Prev Med*. 2017;53(1):e31-e33; Durham DP, et al. *Clin Infect Dis*. 2016;62(3):298-304.

Map 4.1 State Acute Hepatitis C Incidence Compared to Healthy People 2020 National Goal*
United States, 2016



Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)

*National goal: 0.25 cases/100,000 population



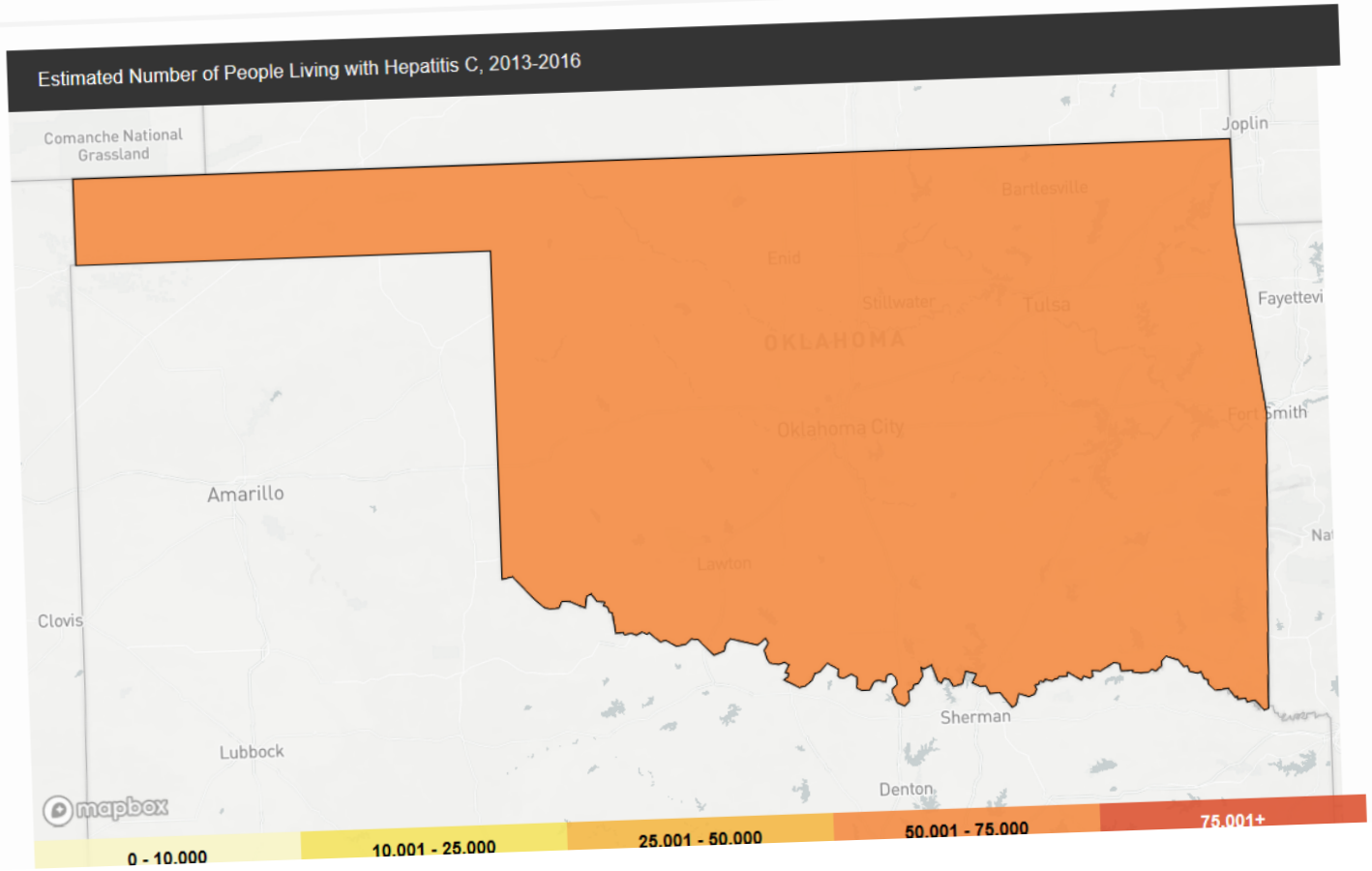
Estimated Hepatitis C Antibody Prevalence Rate per 100,000 Persons, 2010

710-1,000	1,001-1,500	1,501-2,000	2,001-2,500	2,501-3,340

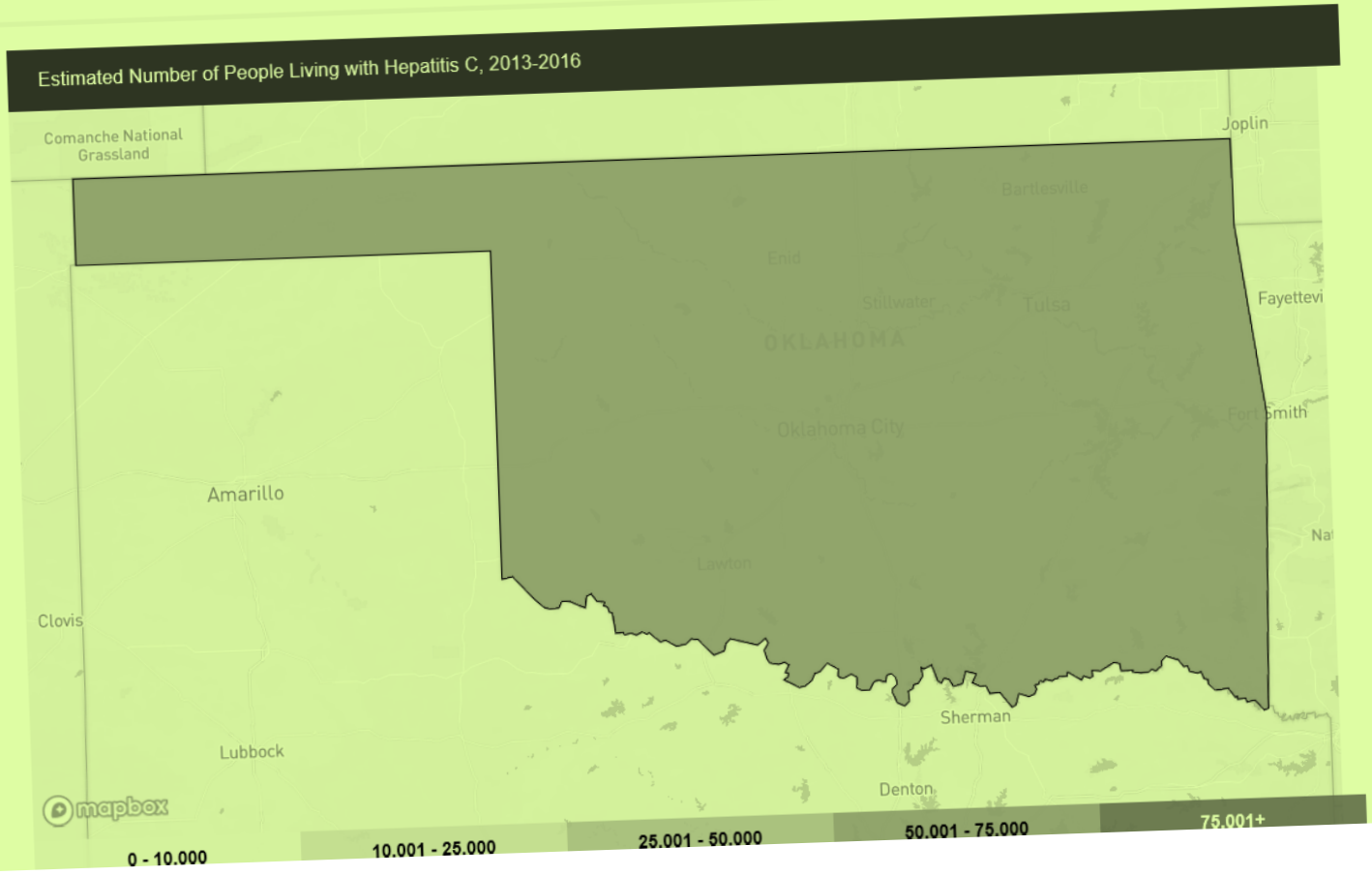
HepVu

* Data are not shown to protect privacy. See Data Methods. | ** DATA NOT RELEASED TO HEPVU | * DATA NOT SHOWN

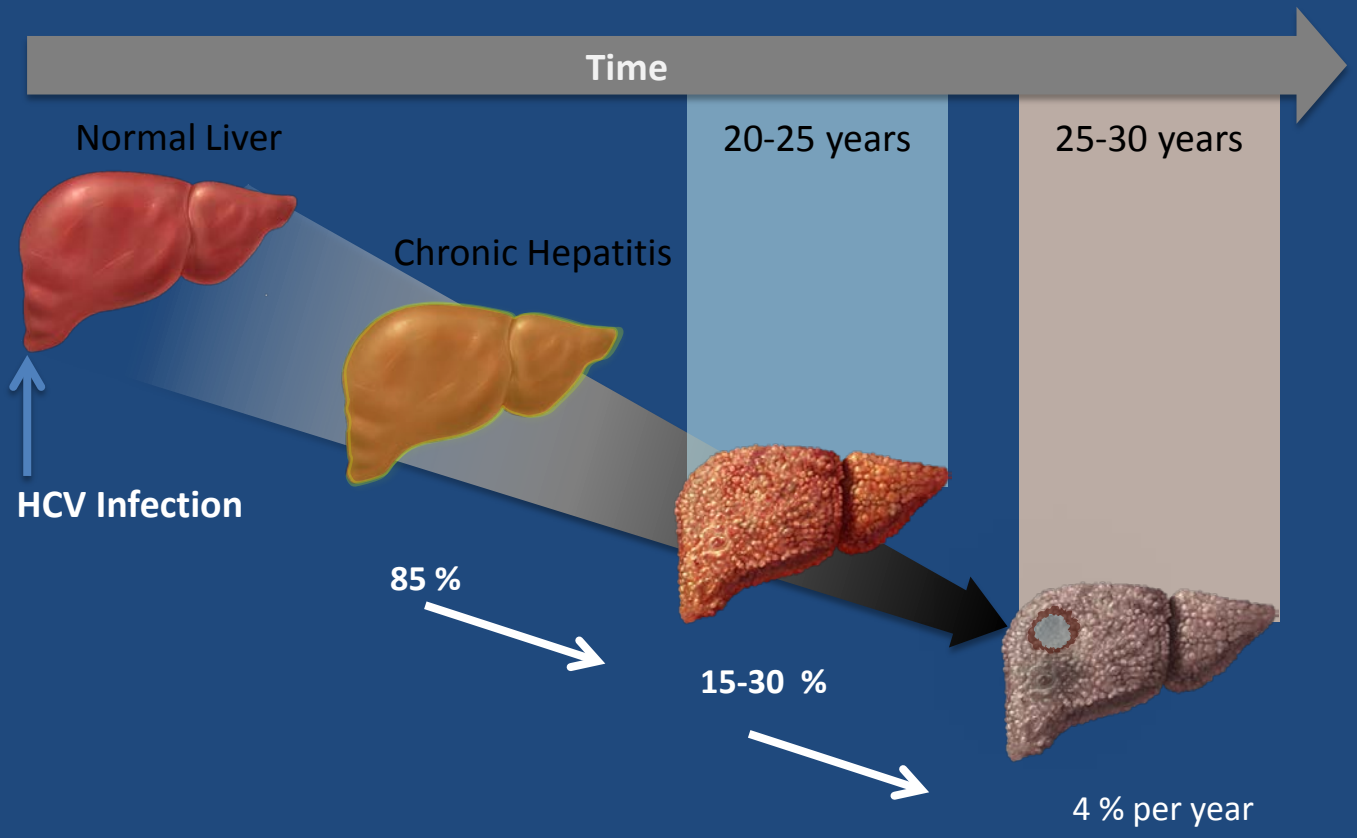
There are approximately 53,900 people living with Hepatitis C in Oklahoma.



There are approximately 53,900 people living with Hepatitis C in Oklahoma.



Hepatitis C: Progression of Disease



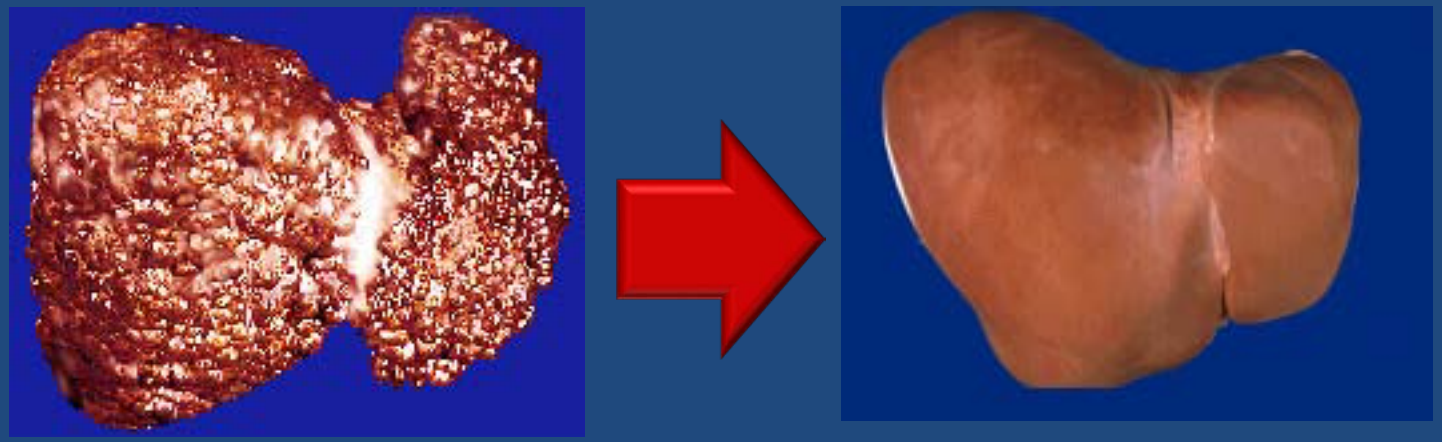
Goal of treatment

"The goal of treatment of HCV-infected persons is to ***reduce all-cause mortality*** *and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the* ***achievement of virologic cure*** *as evidenced by an SVR"*

SVR: sustained virological response
hcvguidelines.org

What is the impact of HCV treatment?

- SVR (cure) of HCV is associated with:
  - 70% Reduction of Liver Cancer
  - 50% Reduction in All-cause Mortality
  - 90% Reduction in Liver Failure



Lok A. NEJM 2012; Ghany M. Hepatol 2009; Van der Meer AJ. JAMA 2012

Why Treat?

- HCV cirrhosis risk = 20% over 20 years
- Hepatocellular carcinoma (HCC) risk in HCV Cirrhosis = 17% over 5 years
- When we cure 30 patients with HCV we will prevent:
    - 6 cases of cirrhosis
    - 1 case of HCC

HCV Screening

Who to Screen

- Baby Boomers (1945-1965)
- Any history of
  - IVDU
  - Intranasal drug use
  - Hemodialysis
  - Unregulated percutaneous exposure
  - Incarceration
  - Healthcare exposure (needlestick, sharps, etc)
- Children of HCV-infected women

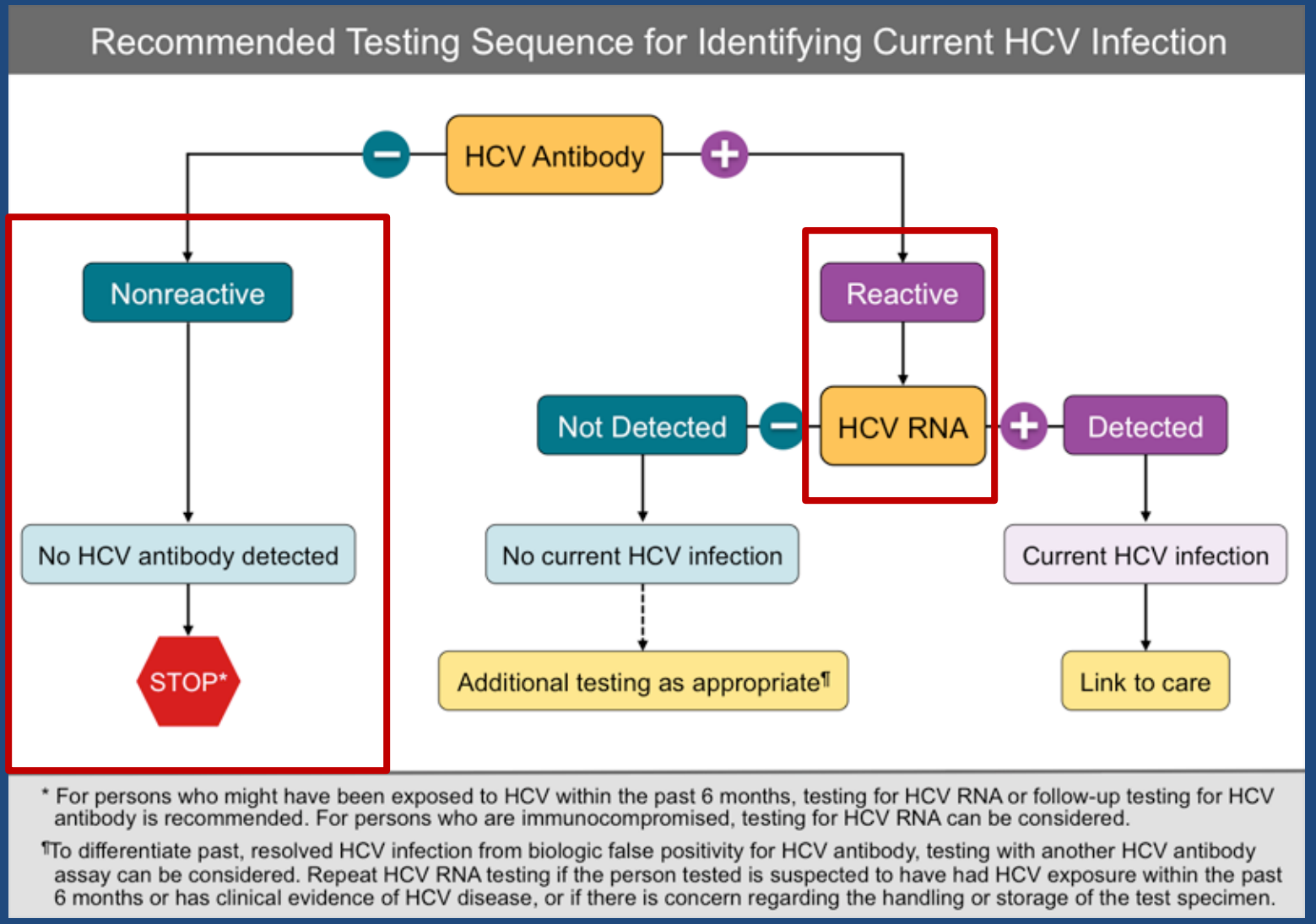
https://www.hcvguidelines.org/evaluate/testing-and-linkage

Who to Screen

- Transfusion or organ transplant before 1992
  - Clotting factors before 1987
- HIV infection
- Unexplained elevated AST/ALT, chronic liver disease or chronic hepatitis
- Solid organ donors
- Before starting PreP for HIV

https://www.hcvguidelines.org/evaluate/testing-and-linkage

Screening Cascade



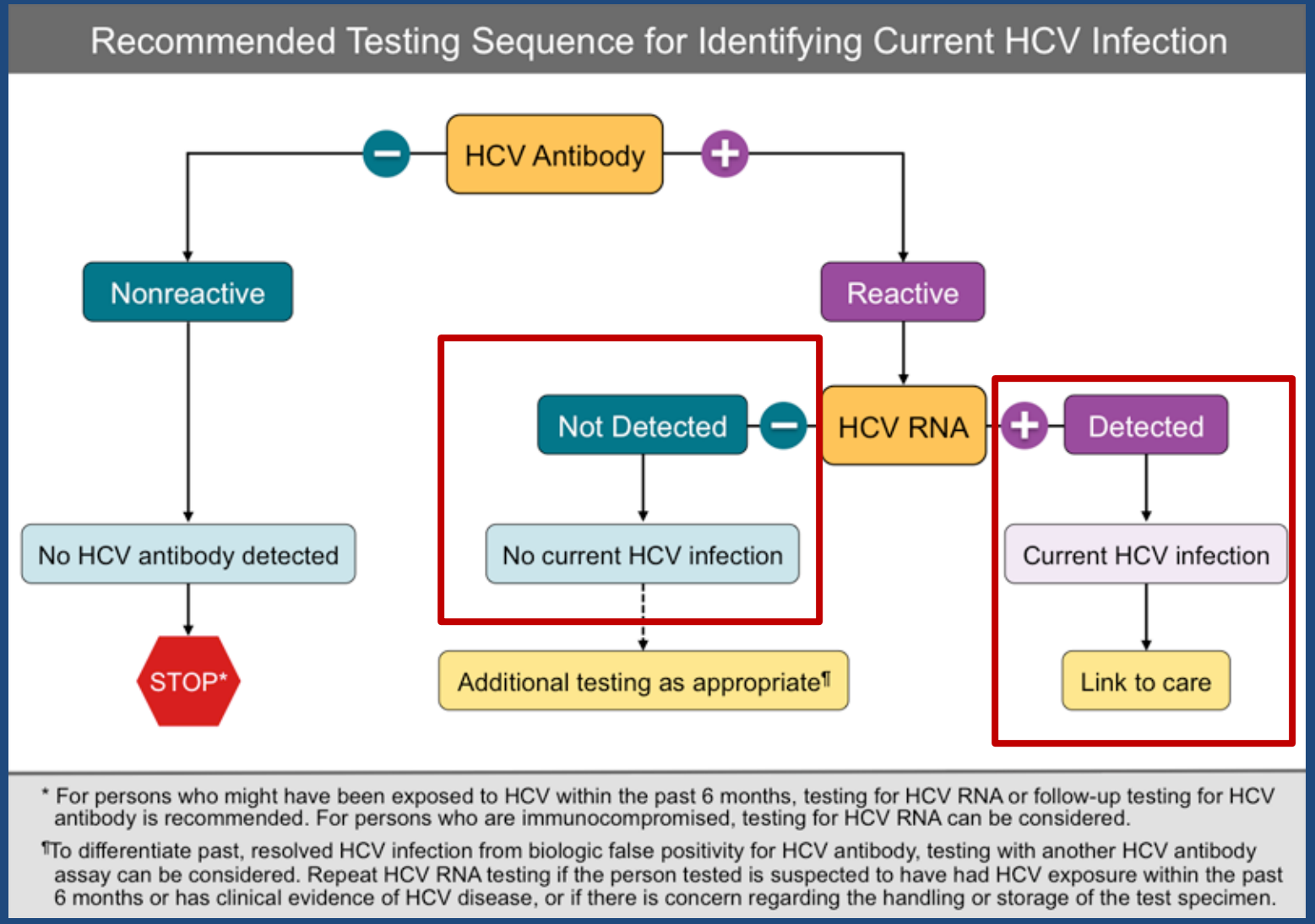
http://www.hepatitisc.uw.edu

CDC. Testing for HCV infection. *MMWR*. 2013;62(18).

Viral Load

- Number of virus particles (RNA) per mL of blood
- Confirms active infection
  - 15-30% of acutely infected patients spontaneously resolve
- May define the duration of treatment
  - For genotype 1 (when treating it with sofosbuvir/ledipasvir)
- Defines cure
  - when the viral load is not detected 12 weeks after treatment is complete - sustained virological response (SVR 12)
- Does not predict liver disease progression

Screening Cascade



http://www.hepatitisc.uw.edu

CDC. Testing for HCV infection. *MMWR*. 2013;62(18).

Who Should Receive Treatment

When and Whom to Treat

- Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by (Rating: Class I, Level A)
  - Treating HCV
  - Transplantation
  - Other directed therapy

AASLD/ IDSA HCV Guidelines

Selecting a Treatment Plan

HCV Workup

- Genotype
  - Three main genotypes in the US: GT1, GT2 and GT3
- Viral load
- Hep A serology
  - Order total Hep A total antibody or IgG antibody
  - If non-reactive, patient needs vaccination
- Hep B serology
  - Immunization and to monitor for reactivation
  - Order HBsAg, HBcAb (total or IgG) and HBsAb

HCV Workup

- CBC
  - Platelets are critical for liver fibrosis staging
- CMP
  - ALT/AST are important for liver fibrosis staging calculators
  - Bilirubin is Important for Child Pugh Score if necessary
  - GFR
    - Will determine treatment options (if GFR < 30)
- HIV status
  - Important to treat HIV
  - Important to know when treating HCV (interactions with some HIV medications)

Other Considerations

- Concomitant medications
  - **Antacids, PPIs,** anticonvulsants and others
    - Drug interaction should be conducted for all patients prior to determining treatment
- Previous treatment status
- Pregnancy risk
- Urine Drug Screen
  - Important to address issue and refer to
    - Behavioral health
    - Opioid substitution program if pertinent and available

Other Considerations

- Adherence
  - Untreated psychiatric illness/Active drug use/Active alcohol abuse
- Liver Fibrosis Staging

Liver Fibrosis Staging

F0 No fibrosis

F1 Scattered portal fibrosis

F2 Diffuse periportal fibrosis

F3 Bridging fibrosis

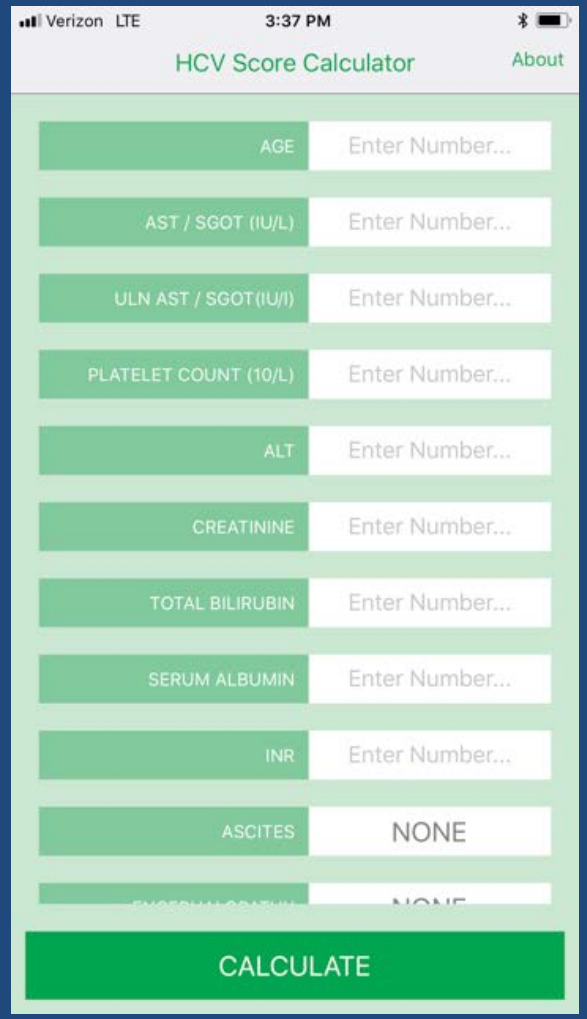
F4 Cirrhosis

- Compensated
- Decompensated
  - History or presence of ascites
  - Hx of esophageal bleeding due to esophageal varices
  - Hx or presence of hepatic encephalopathy

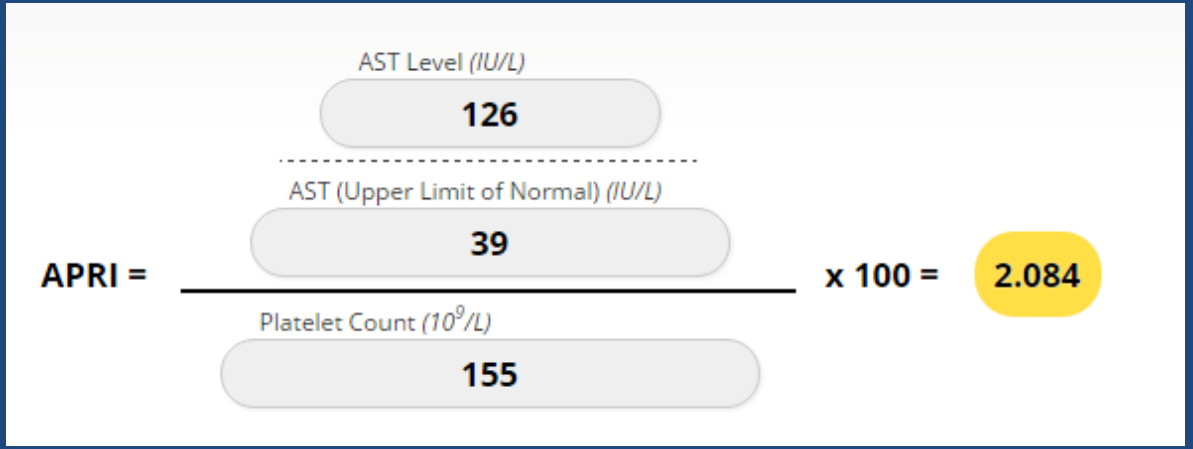
How do we stage liver fibrosis?

- Non Invasive
  - Laboratory
    - **A**ST **P**latelet **R**atio **I**ndex
    - FIB-4
    - Fibrosure
  - Imaging
    - Fibroscan/MRE

- Invasive
  - Liver biopsy



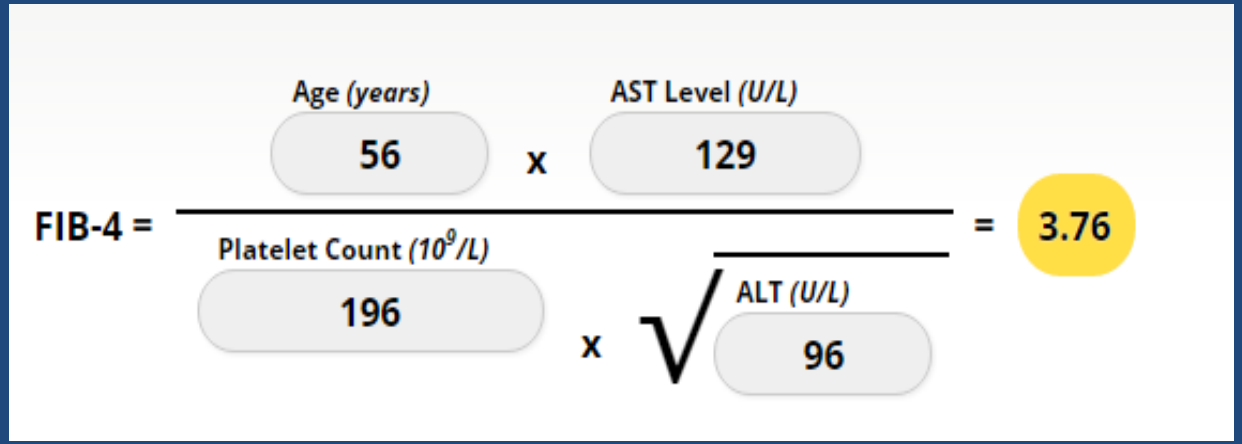
APRI: **A**ST to **P**latelet **R**atio **I**ndex



An APRI score greater than 1.0 had a sensitivity of 76% and specificity of 72% for predicting cirrhosis. APRI score greater than 0.7 had a sensitivity of 77% and specificity of 72% for predicting significant hepatic fibrosis.

Lin ZH, Xin YN, Dong QJ, et al. Hepatology. 2011;53:726-36 University of Washington: Hepatitis C Online www.hepatitisc.uw.edu/

Fib-4



A FIB-4 score <1.45 has a negative predictive value of 90% for advanced fibrosis A FIB-4 >3.25 has a 97% specificity and a positive predictive value of 65% for advanced fibrosis.

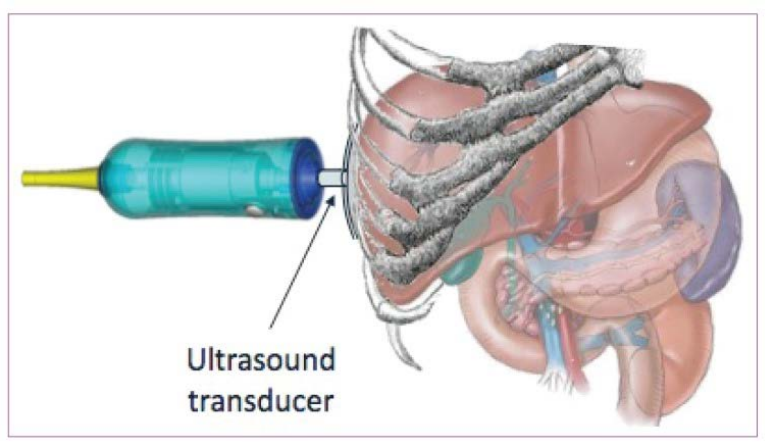
Sterling RK, Lissen E, Clumeck N, et. al. Hepatology 2006;43:1317-1325 University of Washington: Hepatitis C Online www.hepatitisc.uw.edu/

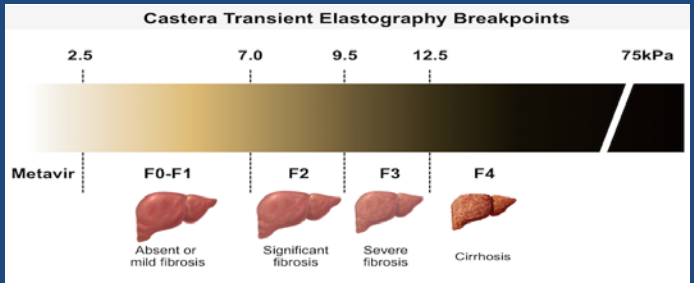
Imaging

- **Ultrasound**
  - Specific for advanced liver disease but ***not sensitive***
    - Nodular liver
    - Ascites
    - Splenomegaly
    - Portal vein flow
  - Screens for liver cancer
  - May find other comorbidities such as fatty liver

- **Fibroscan**
  - Used for liver fibrosis staging

Fibroscan





The probe of the Fibroscan device is positioned in an intercostal space near the right lobe of the liver, and a 50-MHz wave is passed into the liver from a small transducer on the end of the probe. The device then measures the velocity of the shear wave (in meters per second) as this wave passes through the liver, and this measurement is converted to a liver stiffness measurement.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3594956/

Why is it important to stage?

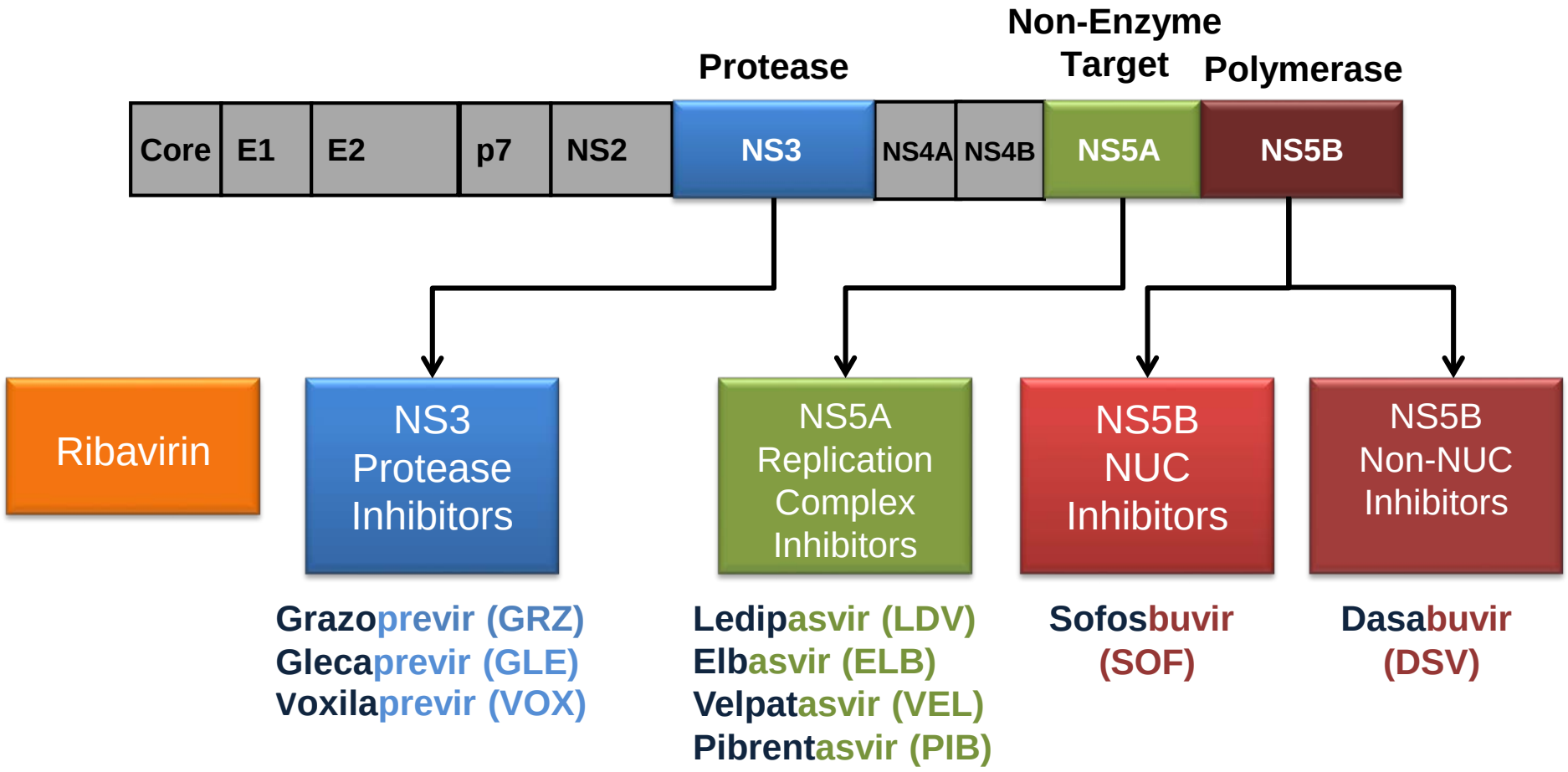
- Treatment **may be different** between cirrhotic and non cirrhotic patients
- Treatment **will be different** between those patients with decompensated vs compensated cirrhosis
- Patients with decompensated cirrhosis should to be referred to a liver transplant center
- STAGING IS NOT TO DECIDE IF THE PATIENT SHOULD BE TREATED
  - **EVERYONE SHOULD BE OFFERED TREATMENT**

Cirrhosis

- Recommended for all patients with cirrhosis
  - Liver US and AFP for HCC surveillance Q6M for the rest of their life regardless of HCV treatment (consider for F3 as well)
  - Pneumococcal vaccination
- EGD to check for varices
- Cirrhosis and elevated AFP
  - r/o HCC with 3 phase CT before starting treatment
- Decompensated cirrhosis
  - Child Pugh score / Meld score

Treatment Options

Direct-Acting Antiviral Agents (DAA): Keeping them Straight



HCV Therapies - DAAs

Medication	NS5B	NS5A Inh	NS3 PI
Harvoni®	sofos**buvir**	ledip**asvir**	
Epclusa®	sofos**buvir**	velpat**asvir**	
Vosevi®	sofos**buvir**	velpat**asvir**	voxila**previr**
Mavyret®		pibrent**asvir**	gleca**previr**
Zepatier®		elb**asvir**	grazo**previr**

HCV Treatment by Genotype

Medication	Genotype 1	Genotype 2	Genotype 3	Genotype 4	Genotype 5	Genotype 6
Harvoni®	X			X	X	X
Epclusa®	X	X	X	X	X	X
Vosevi®	X	X	X	X	X	X
Mavyret®	X	X	X	X	X	X
Zepatier®	X			X		

Zepatier®
elbasvir/grazoprevir

Mavyret®
glecaprevir/pibrentasvir

Harvoni®
ledipasvir/sofosbuvir

Epclusa®
sofosbuvir/velpatasvir

Vosevi®
sofosbuvir/velpatasvir/voxilaprevir

AASLD/IDSA Guidelines

Treatment-Naive Genotype 1a Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 1a Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[a] for elbasvir	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are non-black, HIV-uninfected, and whose HCV RNA level is <6 million IU/mL	8 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), with weight-based ribavirin	12 weeks	I, A
Daily simeprevir (150 mg) plus sofosbuvir (400 mg)	12 weeks	I, A
Daily daclatasvir (60 mg)[c] plus sofosbuvir (400 mg)	12 weeks	I, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for patients with baseline NS5A RASs[a] for elbasvir	16 weeks	IIa, B

[a] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

For genotype 1a-infected, treatment-naive patients without cirrhosis, there are 4 recommended regimens with comparable efficacy. Four regimens are classified as alternative because, compared to the recommended regimens, they require a longer duration of treatment, involve greater prescribing complexity, are potentially less efficacious, and/or there are limited supporting data.

hcvguidelines.org

Common 1st Line Therapies
Treatment Naïve

	Genotype Specific	Genotype 1-6
RENAL: Can be used in ESRD and HD **HEPATIC: Do not use in Child Pugh B or C (decompensated cirrhosis)**	**Zepatier®** elbasvir/grazoprevir 12-16 weeks 1 tablet daily GT 1 or 4 Requires RAS testing for 1A May require RBV	**Mavyret®** glecaprevir/pibrentasvir 8-12 weeks 3 tablets daily with food PPI Interactions
RENAL: Do not use if GFR<30 or HD **HEPATIC: Can be used in decompensated cirrhosis**	**Harvoni®** ledipasvir/sofosbuvir 8-12 weeks 1 tablet daily GT 1, 4, 5 or 6 PPI Interactions Pediatrics	**Epclusa®** sofosbuvir/velpatasvir 12 weeks 1 tablet daily PPI Interactions

Common Adverse Effects for All DAAs

- Most commonly reported side effects (~10%)
  - Headache
  - Fatigue
- Less common side affects (<10%)
  - Nausea
  - Diarrhea
  - Insomnia

Drug Interactions

Drug Interactions

- Always perform a drug interaction check before beginning treatment with any of the hepatitis C medications

- Lexicomp

- University of Liverpool HEP C Drug Interactions – This is generally the most up to date information available on HCV interactions
  - https://hep-druginteractions.org/checker

Acid Suppressing Agents and NS5A Inhibitors ledipasvir & velpatasvir

- Proton Pump Inhibitors
  - Only doses ≤ omeprazole 20 mg
  - **SOF/LED** – Administer simultaneously on an empty stomach
  - **SOF/VEL (/VOX)** - Take with food 4 hours before omeprazole
- Consider discontinuation of acid suppression therapy if patient is able to tolerate
  - Reduce PPI by 50% per week to lowest dose, then discontinue to minimize rebound acid hypersecretion

Acid Suppression Agents and NS5A Inhibitors ledipasvir and velpatasvir

Antacids

- aluminum hydroxide
- magnesium hydroxide

- Separate administration by four hours

H_2RAs

- famotidine
- ranitidine

- Administer concurrently or 12 hours apart
- Not to exceed doses >40 mg famotidine twice daily

glecaprevir/pibrentasvir - Drug Interactions

- **Ethinyl estradiol-containing products**
  - Coadministration of GLE/PIB may increase the risk of ALT elevations and is not recommended
  - Change patients to progesterone only birth control

- Omeprazole
  - 40mg daily is highest dose studied

- No interaction with antacids or H2 blockers

Mavyret® [package insert]. North Chicago, IL: AbbVie Inc.

Common Interactions

- Statins – All reviewed DAAs have interactions with many of the statins
  - Reference the package insert and Liverpool interaction checker for necessary adjustments

- Inducers of P-gp/CYP3A decrease plasma concentrations of all DAAs (Do not use with DAAs)
  - Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, and phenytoin (no interaction with levetiracetam)

This is not a complete list of interactions!

Project ECHO

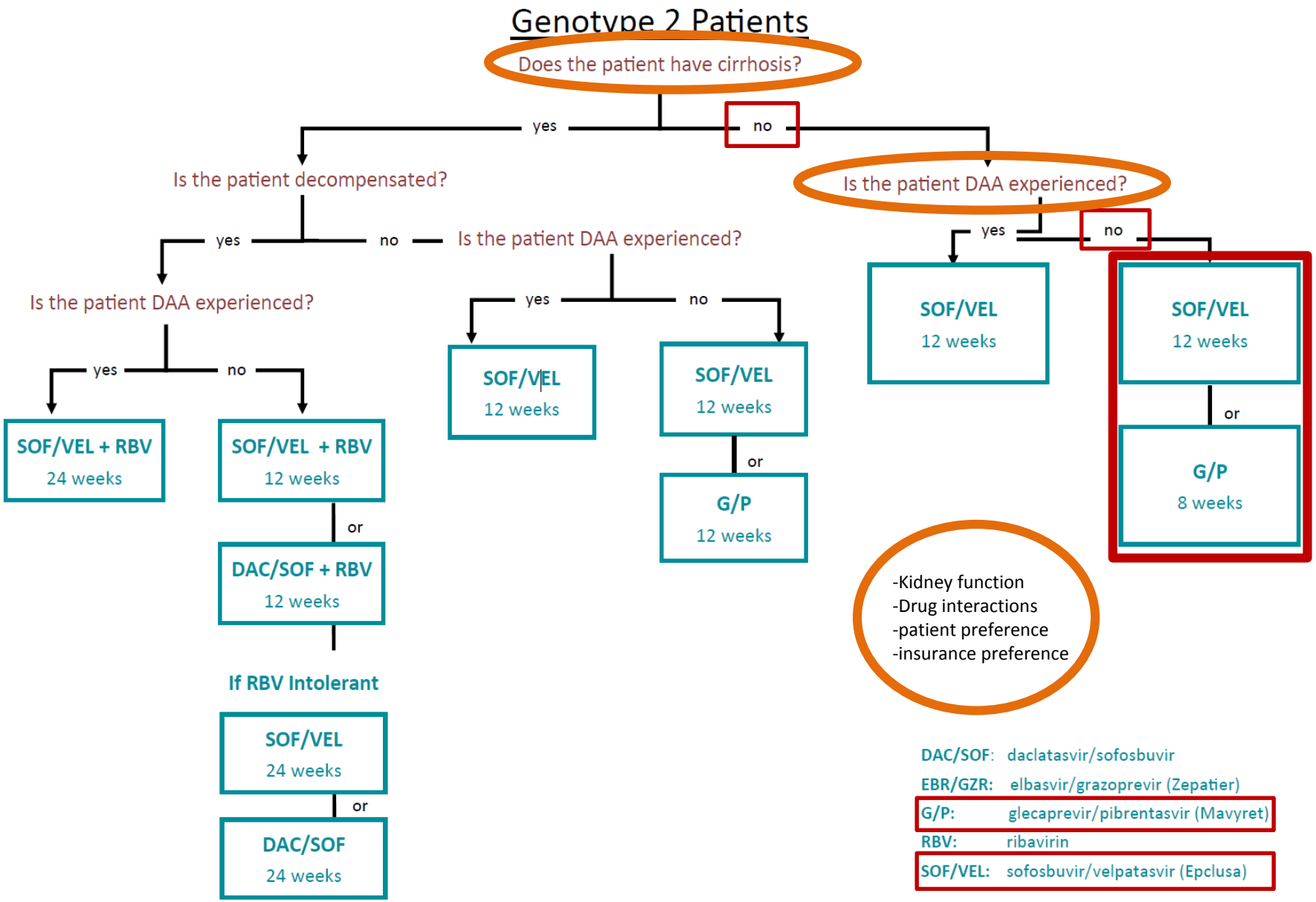
Project ECHO

- Extension for Community Healthcare Outcomes
- echo.okstate.edu
- Category 1-A CME credit for participation
- HCV ECHO- every Thursday from Noon-1:00

https://youtu.be/JYDigrvyRV8

Version: 10/18/2017

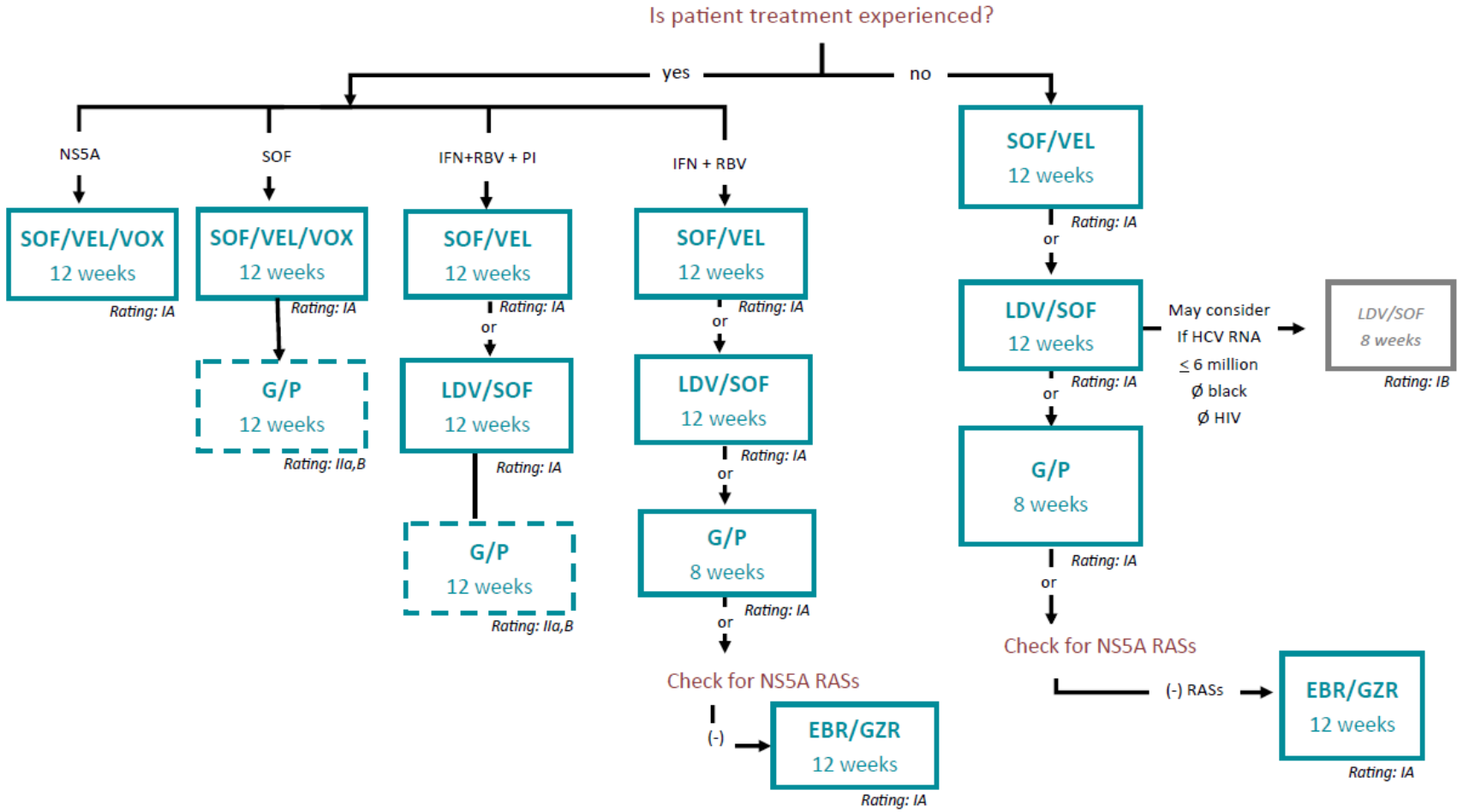
Hepatitis C Genotype 2 Treatment Regimen Decision Tree



DAC/SOF: daclatasvir/sofosbuvir
EBR/GZR: elbasvir/grazoprevir (Zepatier)
G/P: glecaprevir/pibrentasvir (Mavyret)
RBV: ribavirin
SOF/VEL: sofosbuvir/velpatasvir (Epclusa)

Version: 12/11/2017

Hepatitis C : Genotype 1a Non-Cirrhotic Treatment Regimen



Direct Acting Antivirals (DAAs):

EBR/GZR: elbasvir/grazoprevir (Zepatier)
G/P: glecaprevir/pibrentasvir (Mavyret)
LDV/SOF: ledipasvir/sofosbuvir (Harvoni)
SOF/VEL: sofosbuvir/velpatasvir (Epclusa)
SOF/VEL/VOX: sofosbuvir/velpatasvir/voxilaprevir (Vosevi)

**Rating for Level of Recommendation*

These are recommended in the AASLD/IDSA guidelines but have less evidence to support their use and are not ECHO preferred regimens

YOU Can Treat HCV

- Project ECHO can help you!
- Get all the labs
- Look at the algorithms
- Perform a drug interaction check
- Consider patient preference

Helpful Resources

- http://www.hcvguidelines.org/
- http://www.hepatitisc.uw.edu/
  - On-line curriculum on liver disease and HCV, includes clinical studies, clinical calculators, slide lectures
  - Free CME!
- echo.okstate.edu
  - Find all of the ECHO lines for OSU-CHS
  - Free CME!

Be Confident: Primary Care Office-Based Treatment of Hepatitis C

Project ECHO is Here for YOU!

Crystal David, PharmD, BCPS
Clinical Assistant Professor
Oklahoma State University Center for Health Sciences
Crystal.David@okstate.edu
April 27, 2019

References

1. "HCV Epidemiology in the United States." Hepatitis C online. University of Washington. http://www.hepatitisc.uw.edu/. Accessed 10 April 2016.
2. Centers for Disease Control and Prevention (CDC)."People Born 1945-1965 & Hepatitis C". 31 May, 2015 Web.
3. World Health Organization (WHO). "Hepatitis C" Media Centre, Fact Sheet # 164, July 2015, Web.
4. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. http://hcvguidelines.org
5. Maylin S, et al. Eradication of hepatitis C virus in patients successfully treated for chronic hepatitis C. Gastroenterology. 2008;135(3):821-829
6. Singal AG, et al. A Sustained Viral Response Is Associated With Reduced Liver-Related Morbidity and Mortality in Patients With Hepatitis C Virus. Clinical Gastroenterology and Hepatology. 2010;8(3):280-288
7. Morgan TR, et al. Outcome of Sustained Virological Responders with Histologically Advanced Chronic Hepatitis C. Hepatology. 2010;52(3):833-844
8. Kwong AD, et al. Current Opin Pharmacology. 2008; 8(5):S22-31
9. Ly KN, et al. Rising mortality associated with hepatitis C virus in the United States,2003–2013. Clinical Infectious Diseases Brief Report. Published 17 March 2016.
10. NATAP Conference Report. http://www.natap.org/2015/AASLD/AASLD_168.htm. Accessed 17 January 2016.
11. Project ECHO. University of New Mexico. http://echo.unm.edu/
12. **CDC. HIV/AIDS Basic Statistics. www.cdc.gov. Accessed 9/25/17; CDC. Viral Hepatitis Statistics and Surveillance. www.cdc.gov. Accessed 9/25/17; National Academies of Sciences, Engineering, and Medicine.**
13. ***A National Strategy for the Elimination of Hepatitis B and C: Phase Two Report.* Washington, DC: The National Academies Press; 2017.**
14. **Smith BD, et al. *MMWR Recomm Rep*. 2012; 61(RR-4):1-32; Jemal A, et al. *Am J Prev Med*. 2017;53(1):e31-e33; Durham DP, et al. *Clin Infect Dis*. 2016;62(3):298-304.**
15. **Yehia BR, et al. *PLoS One*. 2014;9(7):e101554**
16. CDC. https://www.cdc.gov/hepatitis/statistics/2016surveillance/index.htm#tabs-3-13
17. HepVU. https://www.hepvu.org