Hepatitis C Virus (HCV): An Overview

Jorge Mera, MD, FACP

Outline

Epidemiology

Diagnosis

Evaluation

Clinical presentation

Treatment

NEARLY **2.4 MILLION** AMERICANS ARE LIVING WITH HEPATITIS C*

1/2 MAY NOT KNOW THEY'RE INFECTED†

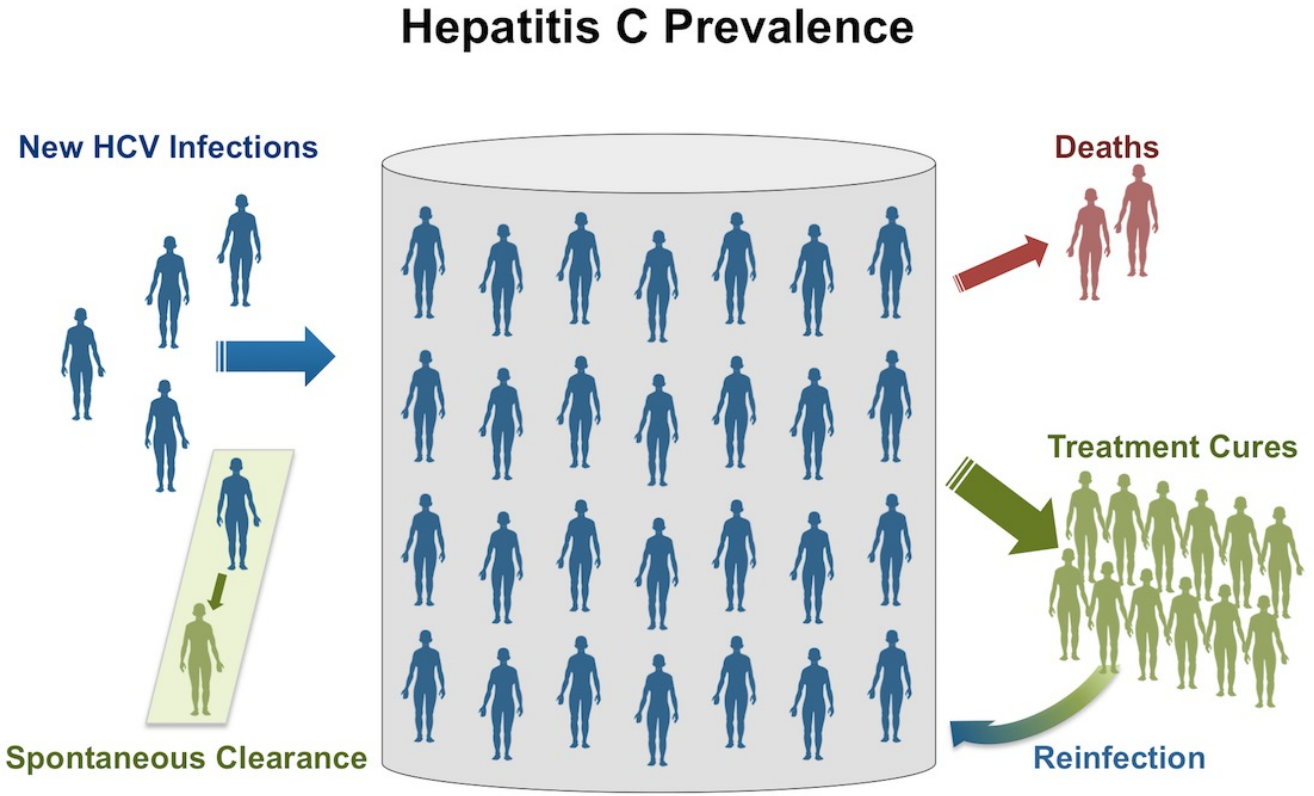
*Among adults aged ≥18 years
†According to 2014 study: *The Treatment Cascade for Chronic Hepatitis C Virus Infection in the United States: A Systematic Review and Meta-Analysis*

Visit www.cdc.gov/hepatitis for more information

DEPARTMENT OF HEALTH & HUMAN SERVICES USA
CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Dynamics of HCV Prevalence in the United States

This illustration shows the dynamics of HCV prevalence in the United States (persons living with chronic HCV infection) is impacted by multiple factors, including number of new infections, spontaneous resolution of new infections, deaths, and treatment-related HCV cure. Persons cured of HCV can become reinfected. In addition, a small number of persons have spontaneous resolution of chronic HCV infection.

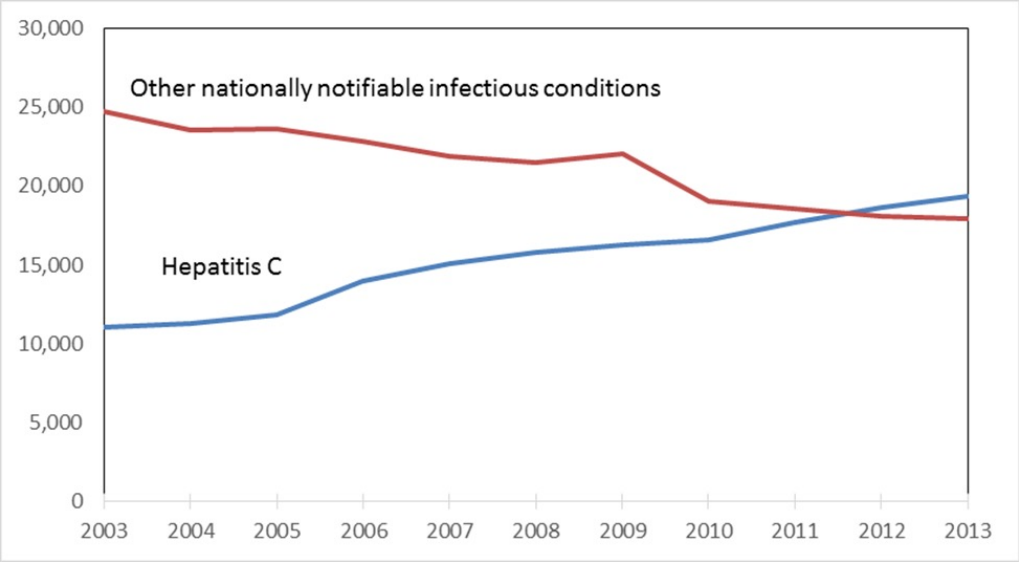


Source: Illustration by David H. Spach, MD

An estimated 2.4 million people in the United States were living with hepatitis C during 2013–2016[3]

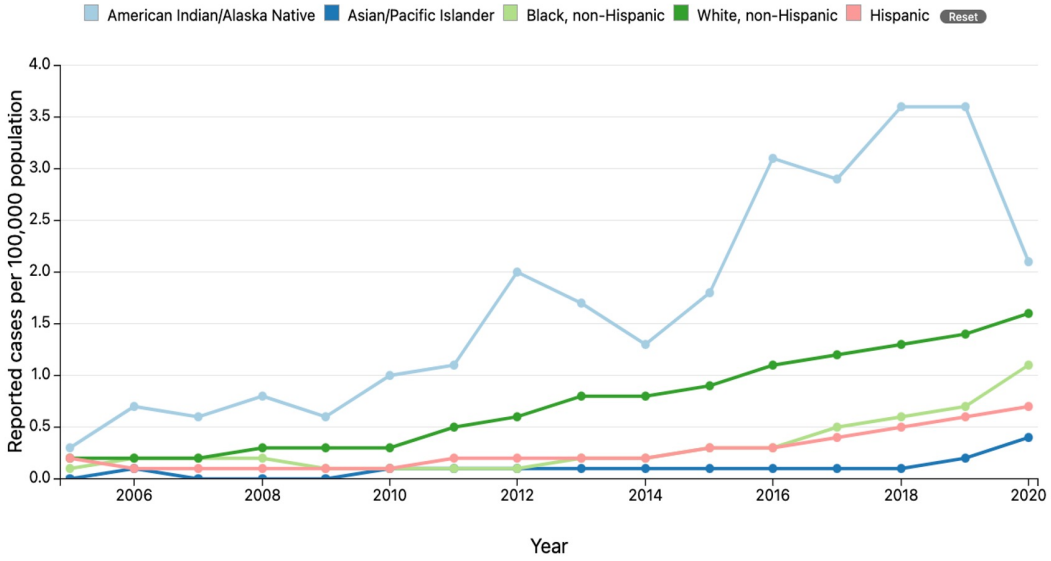
1.Hofmeister MG, Rosenthal EM, Barker LK, Rosenberg ES, Barranco MA, Hall EW, Edlin BR, Mermin J, Ward JW, Ryerson AB. Estimating prevalence of hepatitis C Virus Infection in the United States, 2013-2016. Hepatology. 2019;69:1020–31

HCV Deaths and Deaths from Other Nationally Notifiable Infectious Diseases,* 2003- 2013



* TB, HIV, Hepatitis B and 57 other infectious conditions reported to CDC

Rates* of reported cases† of acute hepatitis C virus infection, by race/ethnicity — United States, 2005-2020



https://www.cdc.gov/hepatitis/hcv/statisticshcv.htm. Accessed September 2, 2022

Division of Viral Hepatitis

Fast Facts about Chronic Hepatitis C in 2020

- During 2020, 41 states reported a total of 107,300 newly identified chronic hepatitis C cases in 2020, corresponding to 40.7 chronic hepatitis C cases per 100,000.
- **Hepatitis C-associated deaths during 2020 increased 4%** (3.45 deaths per 100,000 people), compared to 2019 (3.33 deaths per 100,000 people).
- The age-adjusted death rate for hepatitis C during 2020 decreased 22% from 2016 (4.42 deaths per 100,000 people).
- **The death rates were higher among AI/AN and non-Hispanic Black persons** (3.2 times and 1.8 times, respectively) than among non-Hispanic White persons.

Fast Facts about Acute Hepatitis C in 2020

2x

The incidence rate of acute hepatitis C has more than doubled since 2013, a 124% increase

American Indian/Alaska Native

Rates of acute hepatitis C are highest among American Indian / Alaska Native persons

20-39 years

Persons aged 20-39 years had the highest incidence of acute hepatitis C

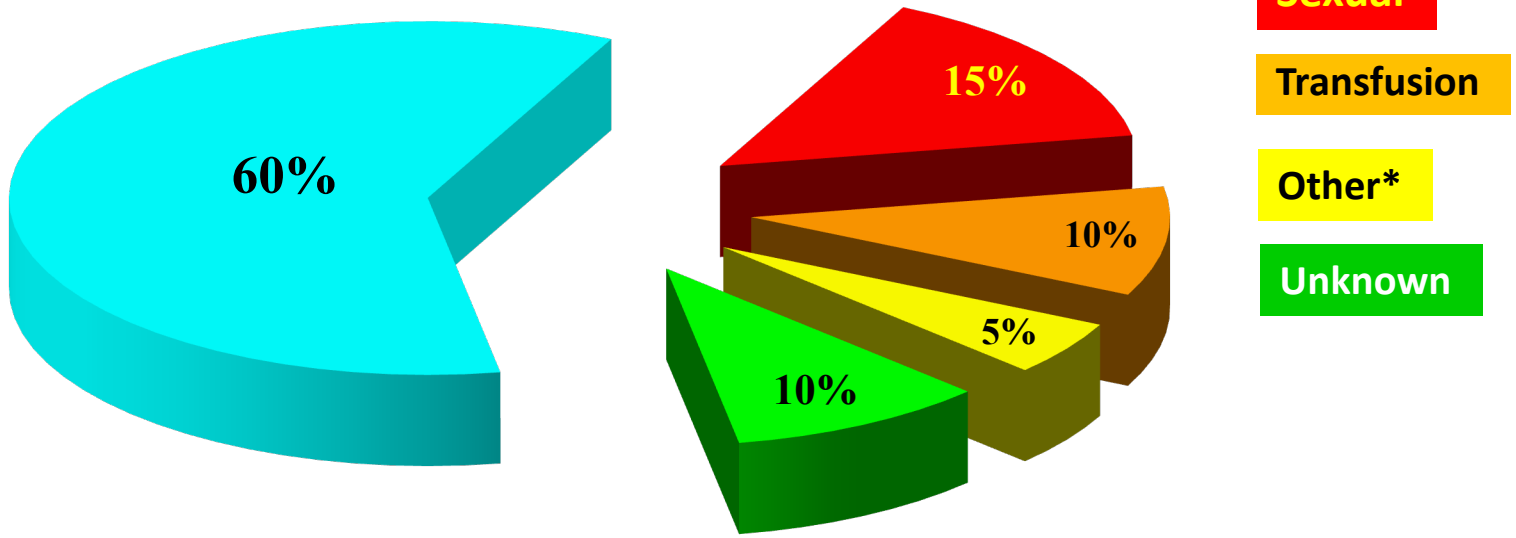
66%

66% of cases with risk information reported injection drug use

During 2020, rates of acute hepatitis C were highest among males, persons 20-39 years of age, American Indian/Alaska Native persons, those who reported using injection drugs, and those living in the eastern and southeastern states.

HCV: Transmission

- **Blood**
  - IVDU is the leading cause in the United States
    - Snorting
  - Percutaneous injuries
  - Dental
  - Tattooing
  - Blood transfusion (Before 1992)
- **Sexual contact**
  - Rare in heterosexual
  - More frequent in HIV + MSM
- **Mother-to-child**
  - The rate is 1.7% - 4.3 %
  - *Increased in IVDU, HIV co-infection, VL (?)*



*Nosocomial; Health-care work; Perinatal

Centers for Disease Control and Prevention. Viral Hepatitis Surveillance—United States, 2016. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2018. Available at: https://www.cdc.gov/hepatitis/statistics/2016surveillance/index.htm.

HCV and Injection Drug Use

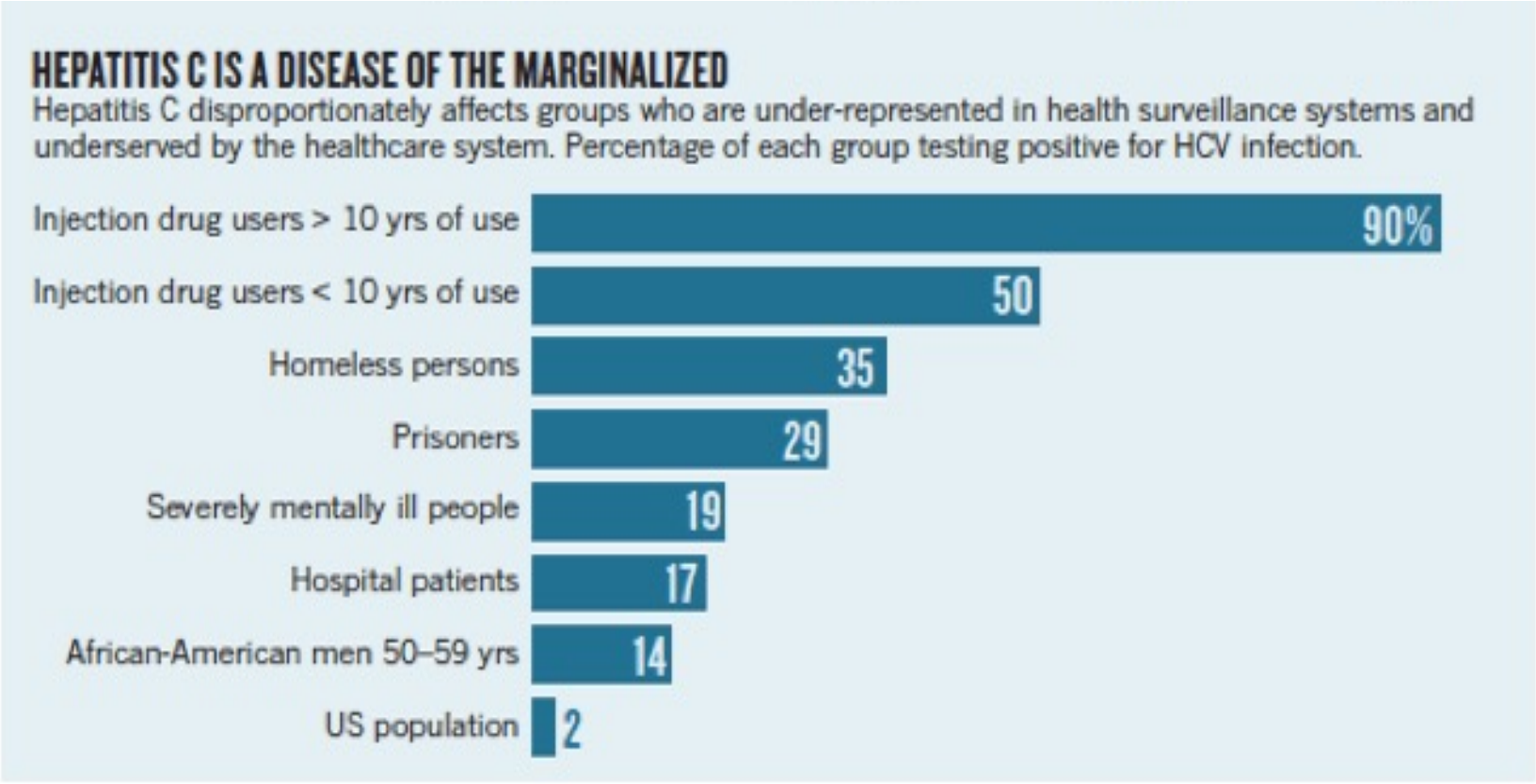
Today > 80% of HCV Transmission Occurs in PWID

Paraphernalia

Needle
Syringe
Cooker
Table
Tourniquet

Palmateer N, Hutchinson S, McAllister G et al. Risk of transmission associated with sharing drug injecting paraphernalia: analysis of recent hepatitis C virus (HCV) infection using cross-sectional survey data. J Viral Hepatol 2014 Jan;21(1):25-32

Social Determinants of Health Define the HCV Epidemic in the U.S.



Edlin, B.R., 2011. Perspective: test and treat this silent killer. Nature 474 (7350),S18–S19.

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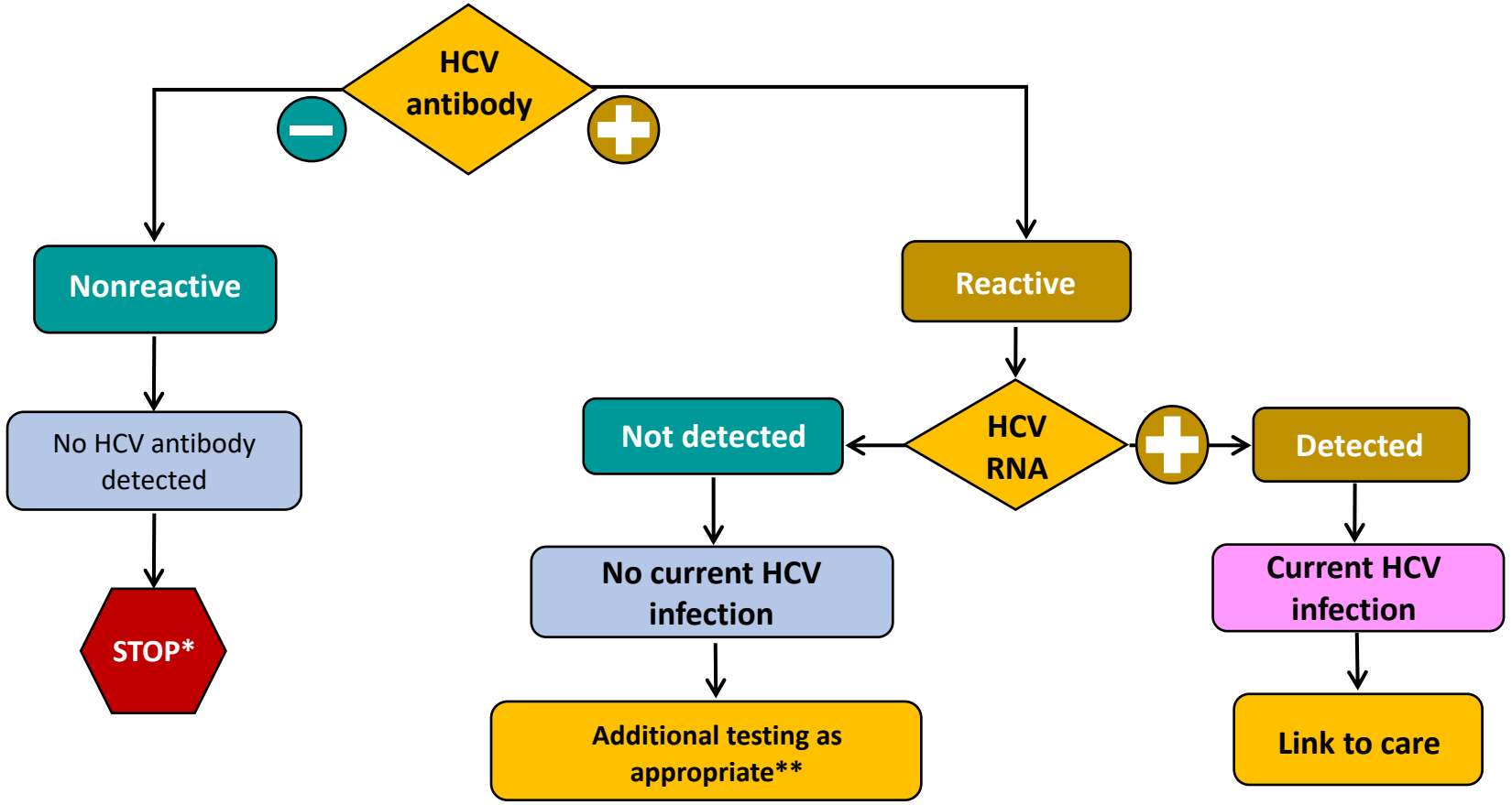
The Screening Cascade



* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

** To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

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

Confirm the Diagnosis

Legend:

Ab
Anti-HCV Antibody test
Indicates if patient has been exposed to HCV

RNA
RNA/PCR test
Indicates if patient is infected with HCV

Hepatitis C Test Results Interpretation

Ab +	+	RNA +	=	Prior exposure to HCV and current HCV infection
Ab +	+	RNA -	=	Prior exposure to HCV and not infected with HCV (due to spontaneous clearance of HCV or prior treatment)
Ab -	+	RNA -	=	Never exposed to HCV and not infected with HCV

Adapted from ASHM HCV Training Slides

Typical serologic course of hepatitis C virus infection

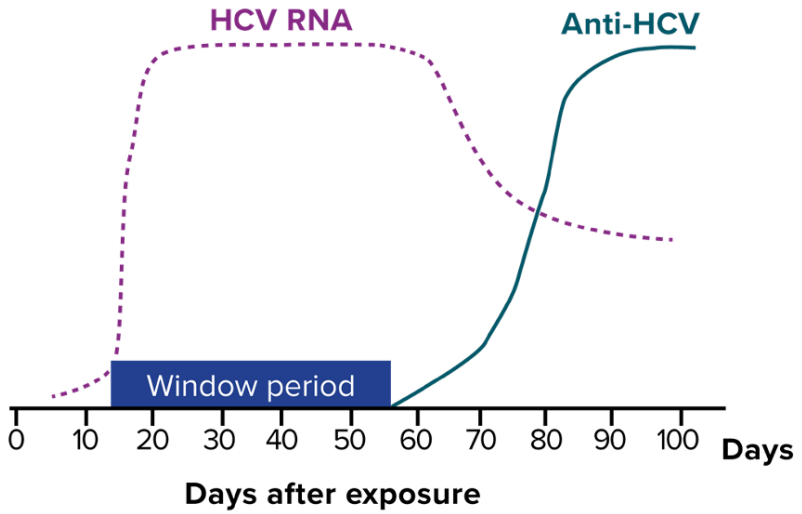
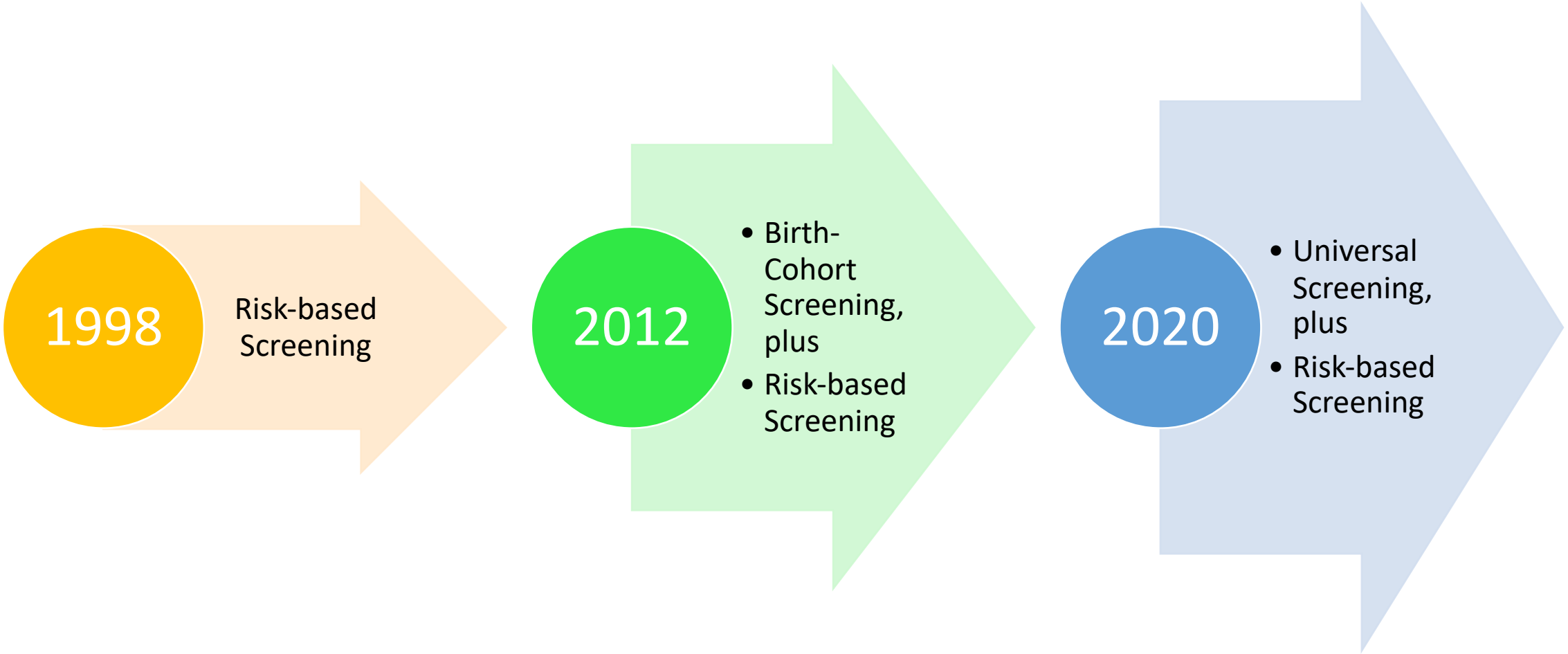


Figure obtained from https://www.aphl.org/aboutAPHL/publications/Documents/ID-2019Jan-HCV-Test-Result-Interpretation-Guide.pdf.

Evolution of HCV Screening Recommendations



(www.hepatitisc.uw.edu) Historical CDC HCV Testing Recommendations

CDC is Augmenting Previous Guidance With Two New Recommendations:

1) Hepatitis C screening at least once in a lifetime for all adults aged ≥18 years, except in settings where the prevalence of HCV infection is <0.1% and
2) Hepatitis C screening for all pregnant women during each pregnancy, except in settings where the prevalence of HCV infection is <0.1%.
3) The recommendation for HCV testing that remains unchanged is regardless of age or setting prevalence, all persons with risk factors should be tested for hepatitis C, with periodic testing while risk factors persist.
4) Any person who requests hepatitis C testing should receive it, regardless of disclosure of risk, because many persons might be reluctant to disclose stigmatizing risks.

Schillie S, Wester C, Osborne M, Wesolowski L, et al. MMWR Recomm Rep 2020;69(No. RR-2):1–17.

HCV Screening: Beyond Baby Boomers and Primary Care

Universal Screening

- Age-based
- Without regard for risk factors

Expanded Sites

- Opioid treatment programs
- Behavioral health clinics
- Emergency department/Urgent cares
- Prisons/Jails
- Homeless Shelters
- Clinics on the move – mobile units
- Community events
- Surgery centers

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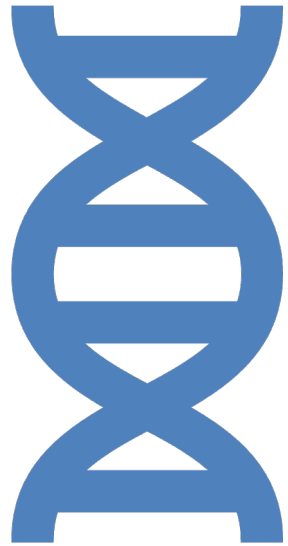
HCV Workflow

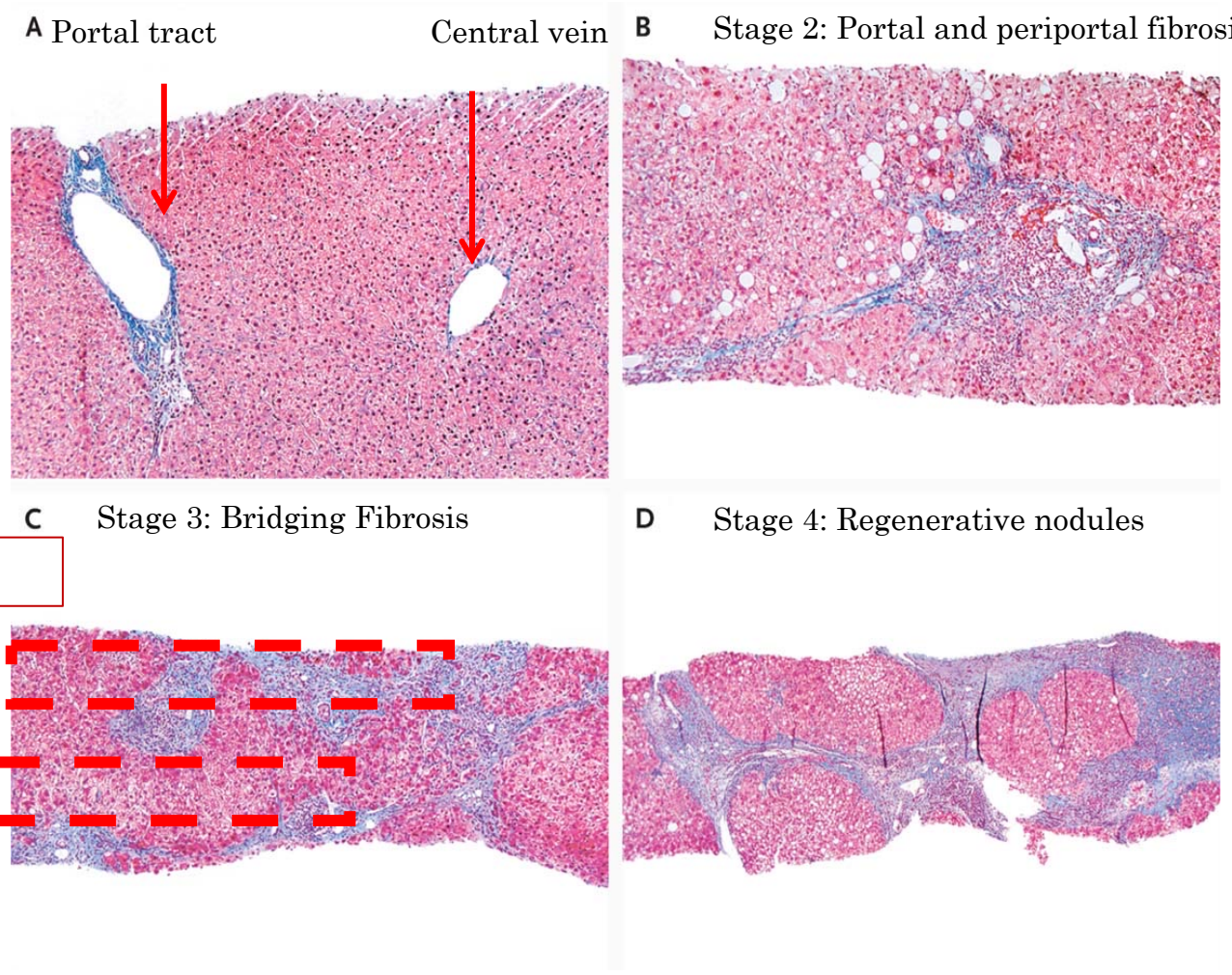
- Confirm Diagnosis
- Lab/Imaging workup
- Fibrosis Staging
- Critical Information
- Treatment
  - Cure
  - Surveillance

Viral Load

- **Number of virus particles** (RNA) per mL of blood
- **Confirms active infection**
  - 15-30% of acutely infected patients spontaneously resolve
- **Defines the duration of treatment**
  - For genotype 1 (when treating it with Sofosbuvir/Ledipasvir)
- **It 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**



Liver Biopsy



Liver Biopsy

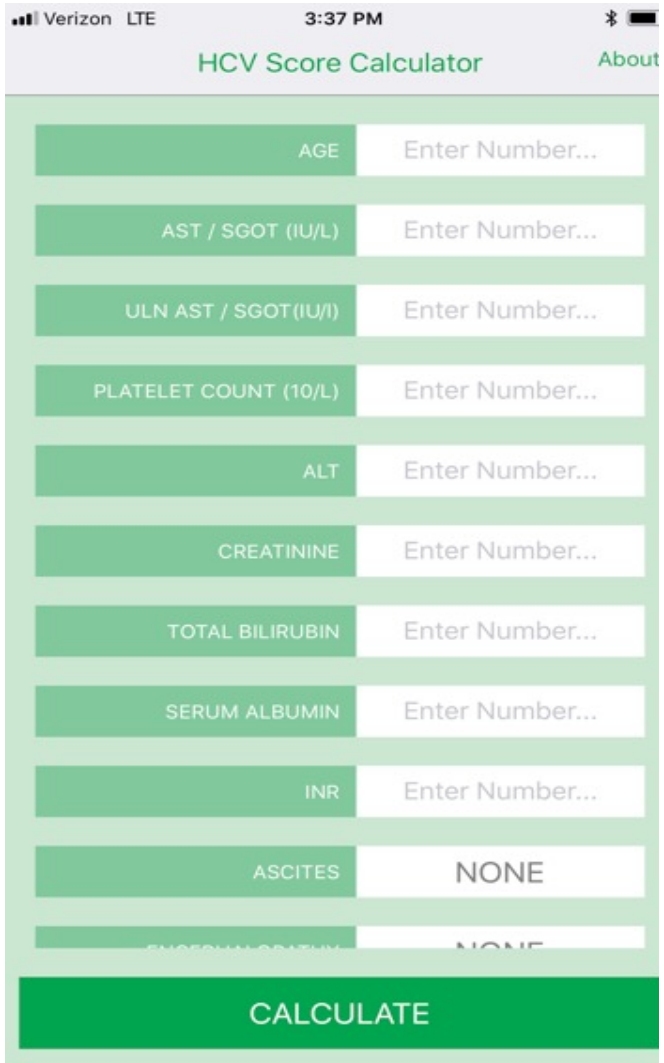
- **F0: No fibrosis**
- **F1 Scattered portal fibrosis**
- **F2. Diffuse periportal fibrosis**
- **F3. Bridging fibrosis**

- **F4 Cirrhosis**
  - ***Compensated***
  - ***Decompensated***
    - History or presence of ascites
    - Hx of esophageal bleeding due to esophageal varices
    - Hx or presence of hepatic encephalopathy

The NEW ENGLAND JOURNAL of MEDICINE

Rosen HR. N Engl J Med 2011;364:2429-2438

Non-Invasive Liver Fibrosis Staging in the Office



APRI: AST to Platelet Ratio Index

$$APRI = \frac{\text{AST Level (IU/L)}\ 126}{\text{AST (Upper Limit of Normal) (IU/L)}\ 39} \times 100 = \frac{\text{Platelet Count } (10^9/L)\ 155}{} = 2.084$$

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.

FIB–4 Index

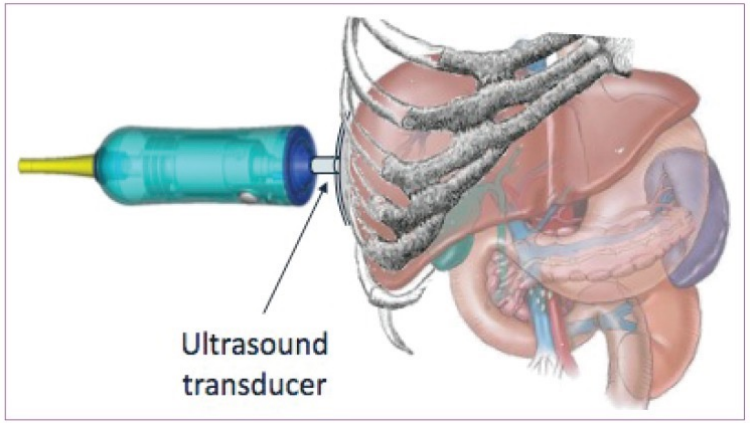
$$FIB\text{-}4 = \frac{\text{Age (years)}\ 56 \times \text{AST Level (U/L)}\ 129}{\text{Platelet Count } (10^9/L)\ 196 \times \sqrt{\text{ALT (U/L)}\ 96}} = 3.76$$

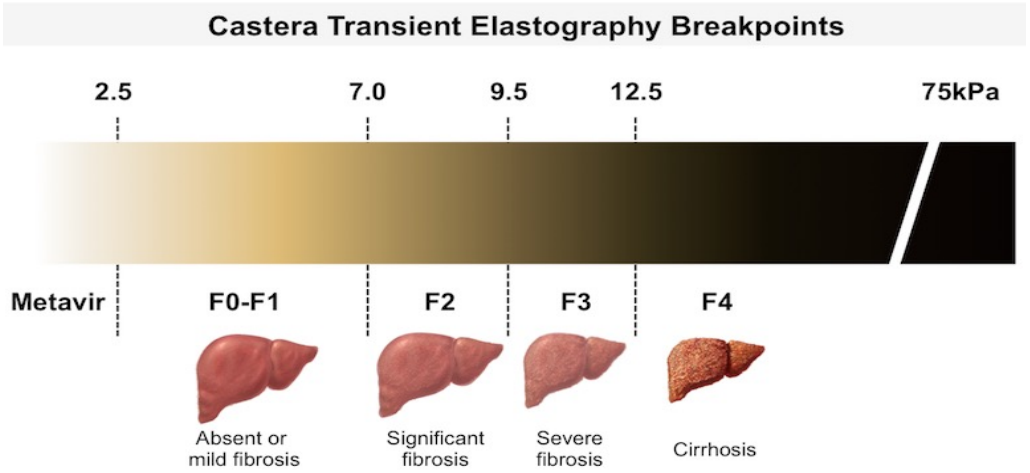
A FIB-4 score <1.45 has a negative predictive value of 90% for advanced fibrosis A FIB-4 >3.25 has a 97% specificity and a positive predictive value of 65% for advanced fibrosis.

Fibrotest/Fibrosure

Lin ZH, Xin YN, Dong QJ, et al. Hepatology. 2011;53:726-36 Sterling RK, Lissen E, Clumeck N, et. al. Hepatology 2006;43:1317-1325 University of Washington: Hepatitis C Online www.hepatitisc.uw.edu/

Liver Fibrosis Staging by Imaging: Transient Elastography





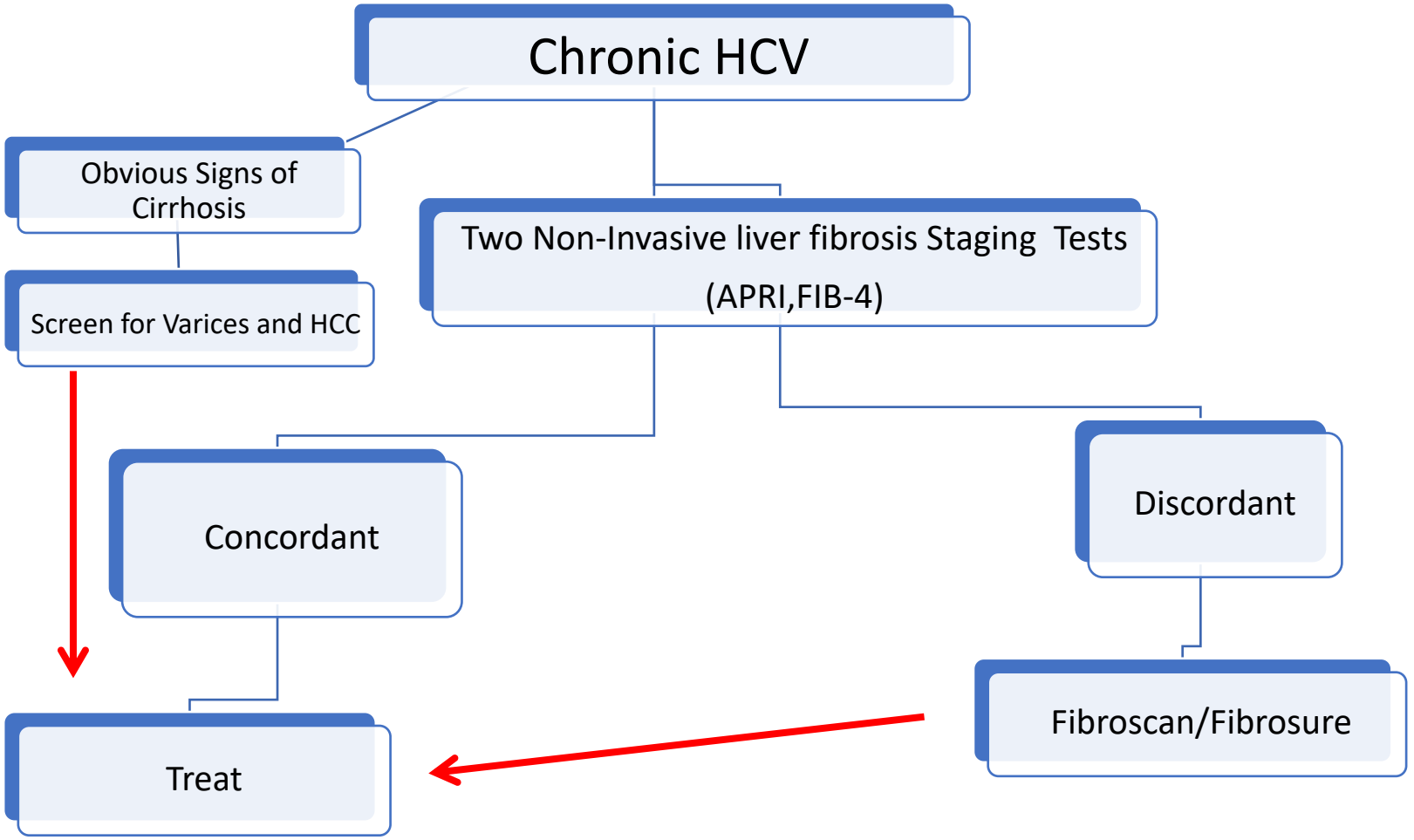
The probe of the Fibroscan device is positioned in an intercostal space near the right lobe of the liver, and a 50-MHz wave is passed into the liver from a small transducer on the end of the probe. The device then measures the velocity of the shear wave (in meters per second) as this wave passes through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

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

Fibrosis Staging Interpretation

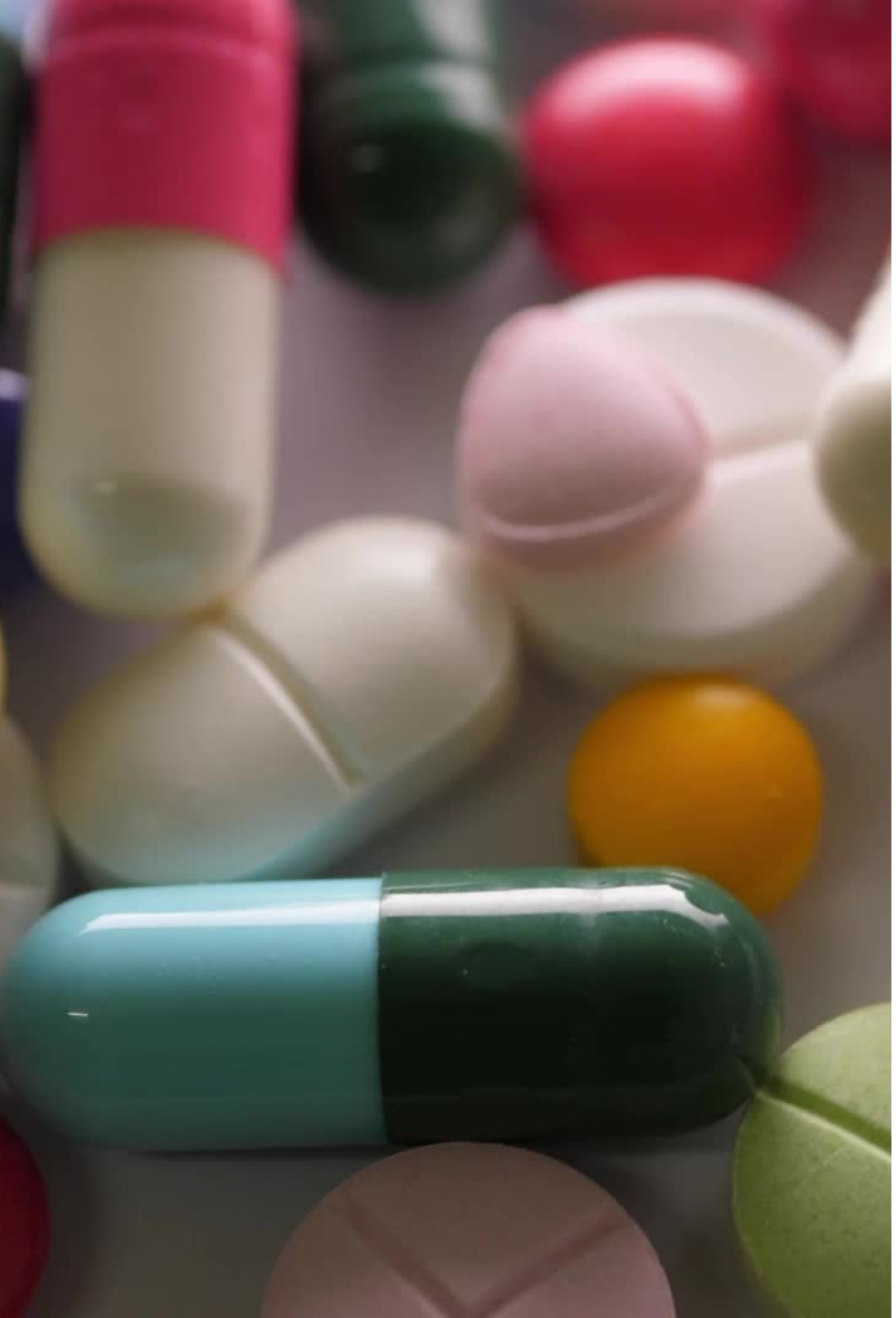
Metavir	Biopsy	Fibroscan	Fibrosure	APRI	FIB-4
F4	F4	≥ 12.5 kPa	≥ 0.75	≥ 1.0	> 3.25
F3	F3	9.6 12.4 kPa	0.58 – 0.74		
F2	F2	7.1-9.5 kPa	0.49 – 0.57	< 1.0	?
F1	F1	≤ 7.0 kPa	0.23 – 0.48		< 1.45
F0	F0		≤ 0.22		

Fibrosis Staging Algorithm



HCC: Hepatocellular Carcinoma

Adapted from Boghal H, Sterling RK, Infect Dis Clin N Am 26 (2012) 839-847



Why is it important to stage Liver Fibrosis?

- Treatment ***may be different between*** cirrhotic and non cirrhotic patients and ***will be different*** bin patients with decompensated cirrhosis vs non decompensated cirrhosis

- All patients with liver fibrosis (F3 or F4) will need:
  - Liver cancer surveillance

- All patients with liver fibrosis F4 (Cirrhosis) will need:
  - EGD: For esophageal varices screening
  - Screening for hepatic encephalopathy

- Patients with decompensated cirrhosis need to be referred to a liver transplant center

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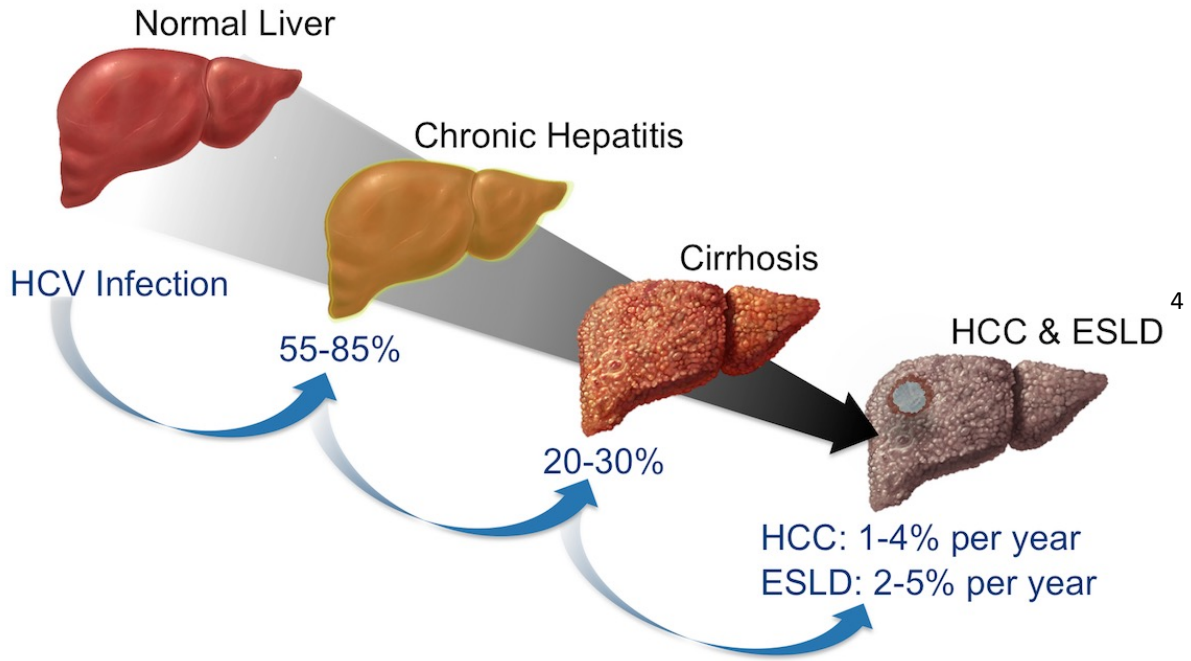
Natural History Following Initial Infection with HCV



Abbreviations: ESLD = end-stage liver disease HCC = hepatocellular carcinoma

Rates of progression to cirrhosis are increased in the presence of a variety of factors, including:

- Being male
- Being age >50 years
- Consuming alcohol
- Having nonalcoholic fatty liver disease, hepatitis B, or HIV coinfection
- Receiving immunosuppressive therapy[1,2,3]

1.Liang TJ, Rehermann B, Seeff LB, Hoofnagle JH. Pathogenesis, natural history, treatment, and prevention of hepatitis C. Ann Intern Med. 2000;132(4):296-305. 2. Thomas DL, Seeff LB. Natural history of hepatitis C. Clin Liver Dis. 2005;9(3):383-98. 3. Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol. 2014;61(1 Suppl):S58-68. 4. Lingala S, Ghany MG. Natural History of Hepatitis C. Gastroenterol Clin North Am. 2015;44:717-34.

Symptoms of HCV

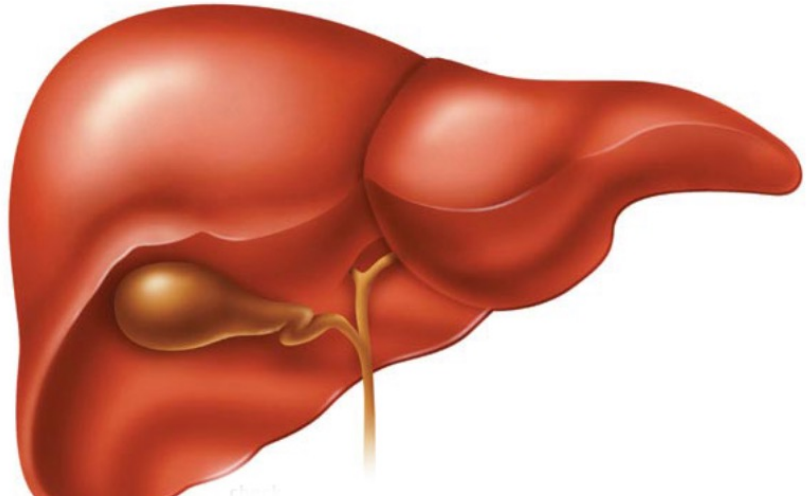
Most patients are asymptomatic

Common symptoms

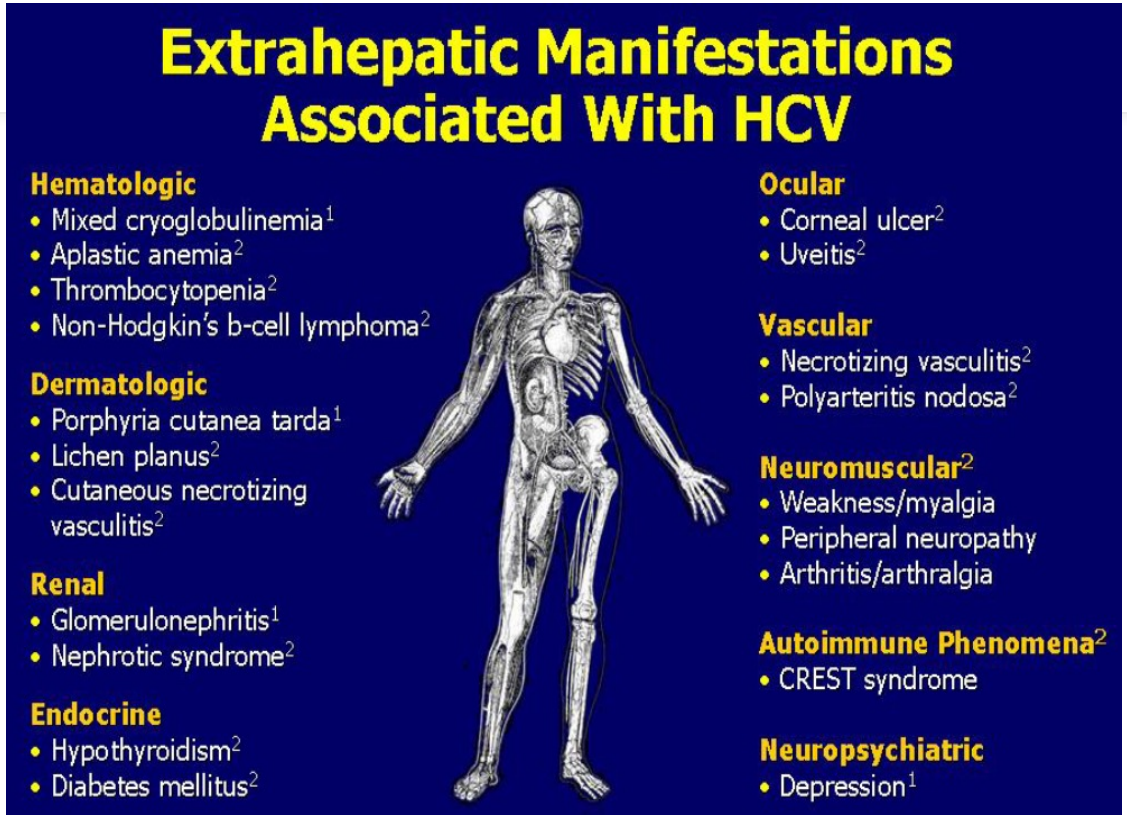
- Fatigue
- Impaired Cognitive Function - "Brain Fog"
- Migratory arthralgia/myalgia
  - Often misdiagnosed as rheumatoid arthritis
- Depression

Hepatitis C - Not Just a Liver Disease

- **Fibrosis of the liver leading to cirrhosis**
- HCV is not just a liver disease!
- **Many extrahepatic manifestations** (diabetes, kidney disease, cardiovascular disease, arthralgias, and many more)
  - 40% of people with HCV will develop at least 1 extrahepatic manifestation
  - Often not clinically recognized
  - Extrahepatic manifestations can occur at any stage of disease
  - Not just in advanced liver disease



HCV Extrahepatic Manifestations



Hepatitis C virus is associated with a broad range of clinical conditions other than liver disease

Clinicians should have an awareness of the potential for these conditions in their patients with HCV with or without the diagnosis of cirrhosis

Consider HCV as a potential etiology of these conditions in patients who do not carry an HCV diagnosis

[1]NIH. *NIH Consens State Sci Statements*. 2002;19(3):1-46.
[2]Sene et al. *Metab Brain Dis*. 2004;19(3-4):357-381.

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What Are We Trying To Prevent?

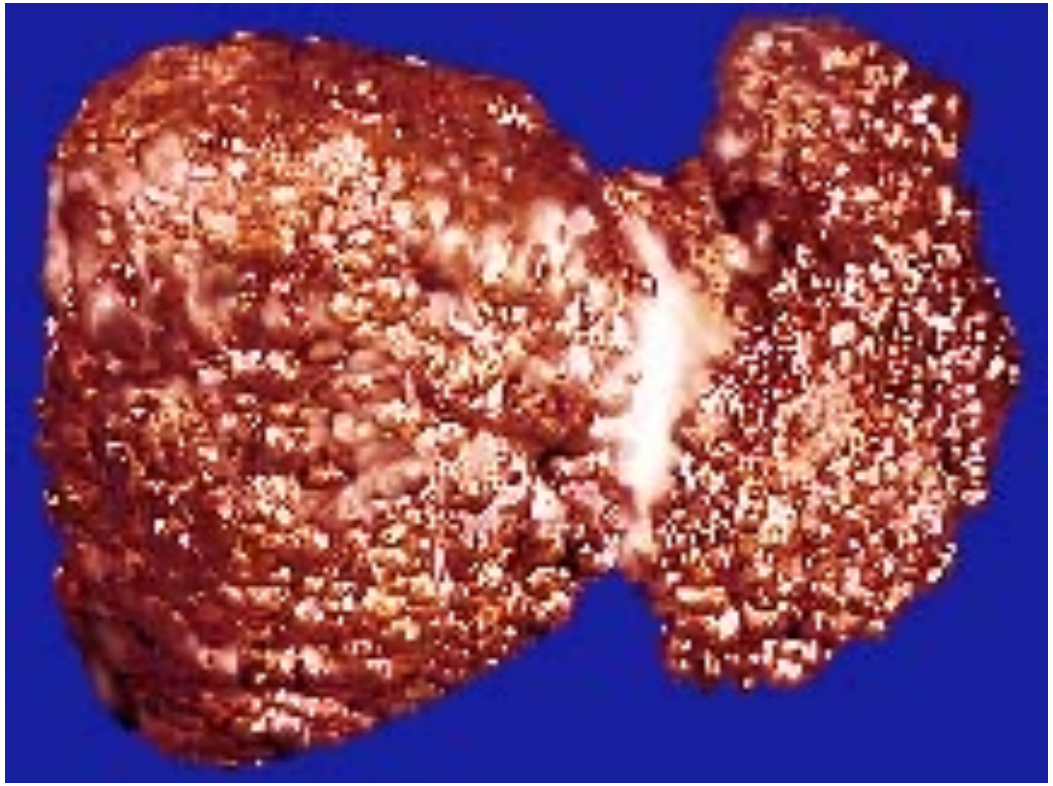
Ascites

Esophageal Varices

End Stage Liver Disease/Liver Cancer

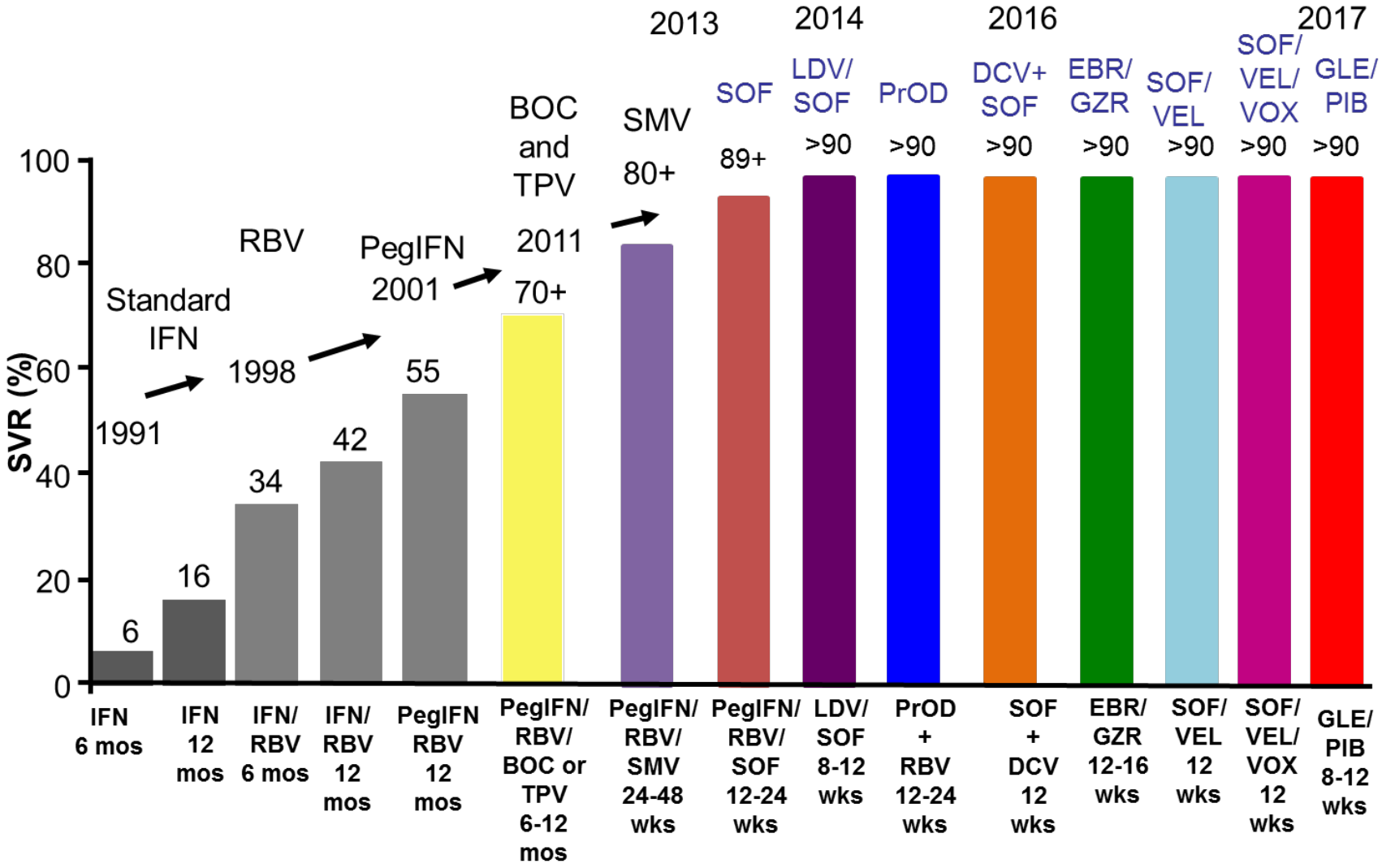
What Does HCV Treatment and Cure Accomplish?

- 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

The Evolution of Highly Effective Treatment



HCV Therapies – Direct Acting Antivirals (DAAs)

Medication	NS5B Inh	NS5A Inh	NS3/4A PI	Other
Epclusa®	sofos**buvir**	velpat**asvir**		
Mavyret®		pibrent**asvir**	glecapr**evir**	

NS5B Inh – Nonstructural protein 5B Polymerase Nucleotide Analog Inhibitor
NS5A Inh – Nonstructural protein 5A Inhibitor
NS3 PI – Nonstructural protein 3/4A Protease Inhibitor

Simplified HCV Treatment Algorithm for Treatment-Naive Adults Without Cirrhosis

WHO IS ELIGIBLE FOR SIMPLIFIED TREATMENT

Adults with chronic hepatitis C (any genotype)
who do not have cirrhosis
and have not previously received hepatitis C treatment

WHO IS *NOT* ELIGIBLE FOR SIMPLIFIED TREATMENT

Patients who have any of the following characteristics:

- Prior hepatitis C treatment
- Cirrhosis (see simplified treatment for treatment-naive adults with compensated cirrhosis)
- HIV or HBsAg positive
- Current pregnancy
- Known or suspected hepatocellular carcinoma
- Prior liver transplantation

PRETREATMENT ASSESSMENT*

- **Calculate FIB-4 score.**
- **Cirrhosis assessment**: Liver biopsy is not required. For the purpose of this guidance, a patient is presumed to have cirrhosis if they have a FIB-4 score >3.25 **or** any of the following findings from a previously performed test.
  - Transient elastography indicating cirrhosis (eg, FibroScan stiffness >12.5 kPa)
  - Noninvasive serologic tests above proprietary cutoffs indicating cirrhosis (eg, FibroSure, Enhanced Liver Fibrosis Test, etc)
  - Clinical evidence of cirrhosis (eg, liver nodularity and/or splenomegaly on imaging, platelet count <150,000/mm^3, etc)
  - Prior liver biopsy showing cirrhosis
- **Medication reconciliation:** Record current medications, including over-the-counter drugs, and herbal/dietary supplements.
- **Potential drug-drug interaction assessment:** Drug-drug interactions can be assessed using the AASLD/IDSA guidance or the University of Liverpool drug interaction checker.
- **Education:** Educate the patient about proper administration of medications, adherence, and prevention of reinfection.
- **Pretreatment laboratory testing**

Within 6 months of initiating treatment:

  - Complete blood count (CBC)
  - Hepatic function panel (ie, albumin, total and direct bilirubin, alanine aminotransferase [ALT], and aspartate aminotransferase [AST])
  - Calculated glomerular filtration rate (eGFR)

Any time prior to starting antiviral therapy:

  - Quantitative HCV RNA (HCV viral load)
  - HIV antigen/antibody test
  - Hepatitis B surface antigen

Before initiating antiviral therapy:

  - Serum pregnancy testing and counseling about pregnancy risks of HCV medication should be offered to women of childbearing age.

RECOMMENDED REGIMENS*

Glecaprevir (300 mg) / pibrentasvir (120 mg)
taken with food for a duration of 8 weeks

Sofosbuvir (400 mg) / velpatasvir (100 mg)
for a duration of 12 weeks

ON-TREATMENT MONITORING

- Inform patients taking diabetes medication of the potential for symptomatic hypoglycemia. Monitoring for hypoglycemia is recommended
- Inform patients taking warfarin of the potential for changes in their anticoagulation status. Monitoring INR for subtherapeutic anticoagulation is recommended.
- No laboratory monitoring is required for other patients.
- An in-person or telehealth/phone visit may be scheduled, if needed, for patient support, assessment of symptoms, and/or new medications.

POST-TREATMENT ASSESSMENT OF CURE (SVR)

- Assessment of quantitative HCV RNA and a hepatic function panel are recommended 12 weeks or later following completion of therapy to confirm HCV RNA is undetectable (virologic cure) and transaminase normalization.
- Assessment for other causes of liver disease is recommended for patients with elevated transaminase levels after achieving SVR.

FOLLOW-UP AFTER ACHIEVING VIROLOGIC CURE (SVR)

- No liver-related follow-up is recommended for noncirrhotic patients who achieve SVR.
- Patients with ongoing risk for HCV infection (eg, intravenous drug use or MSM engaging in unprotected sex) should be counseled about risk reduction, and tested for HCV RNA annually and whenever they develop elevated ALT, AST, or bilirubin.
- Advise patients to avoid excess alcohol use.

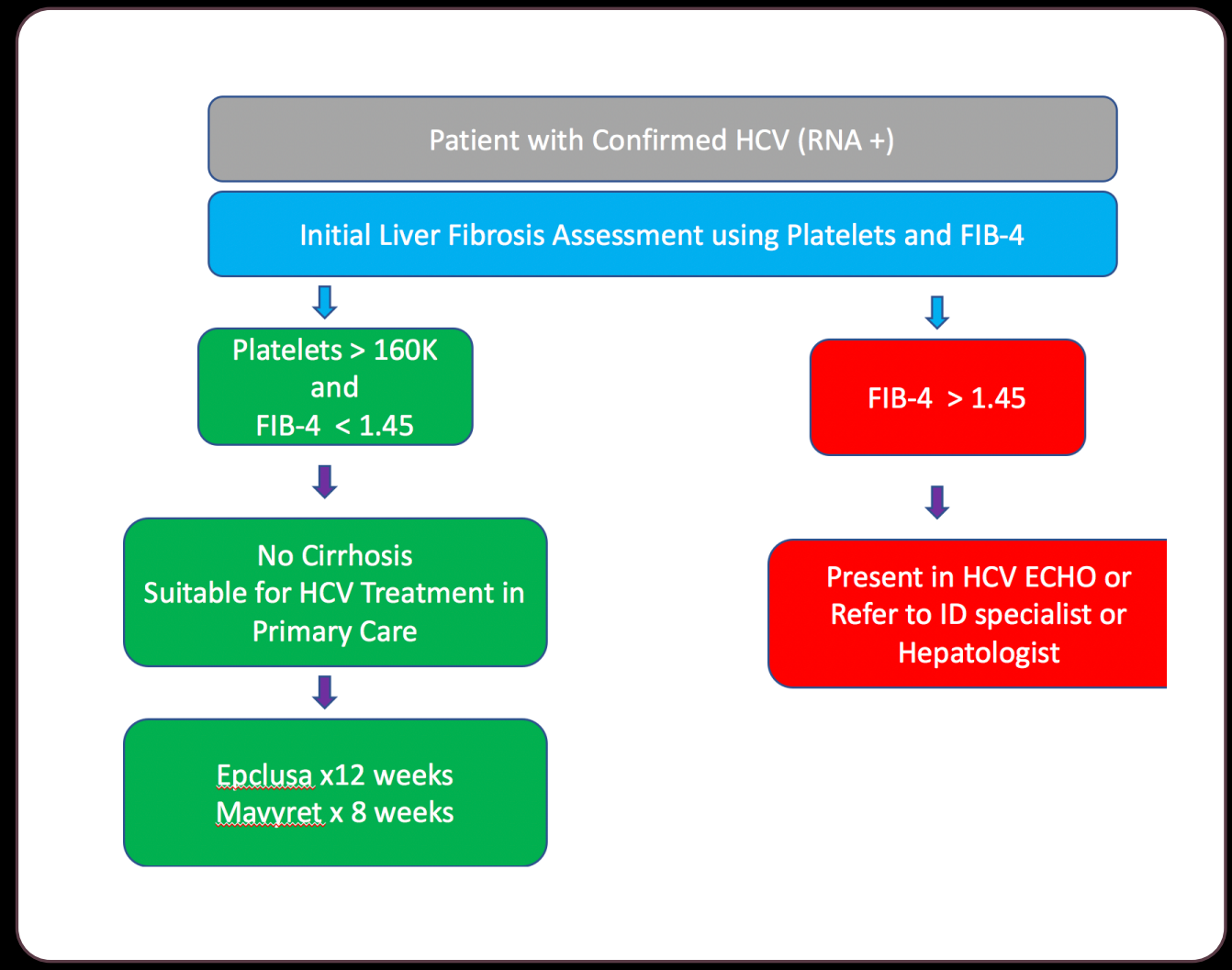
FOLLOW-UP FOR PATIENTS WHO DO *NOT* ACHIEVE A VIROLOGIC CURE

- Patients in whom initial HCV treatment fails to achieve cure (SVR) should be evaluated for retreatment by a specialist, in accordance with AASLD/IDSA guidance.
- Until retreatment occurs, assessment for disease progression every 6 to 12 months with a hepatic function panel, CBC, and INR is recommended.
- Advise patients to avoid excess alcohol use.

AASLD

*More detailed descriptions of the patient evaluation process and antivirals used for HCV treatment, including the treatment of patients with cirrhosis, can be found at www.hcvguidelines.org. Updated: August 27, 2020

IDSA



Helpful Resources

http://www.npaihb.org

Text HCV 97779

http://www.hcvguidelines.org/

http://www.hepatitisc.uw.edu/

On-line curriculum on liver disease and HCV, includes clinical studies, clinical calculators, slide lectures

ProjectECHO HCV guidelines

Thank You

GV (Wado)