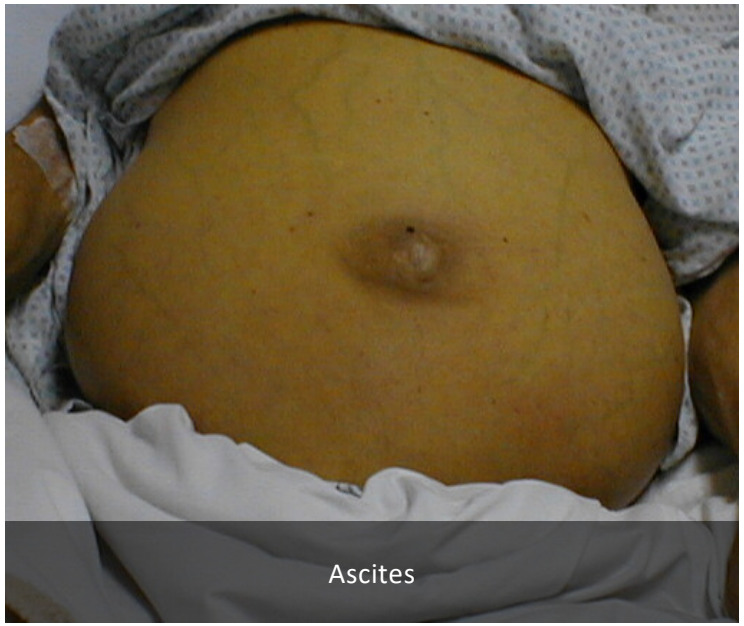
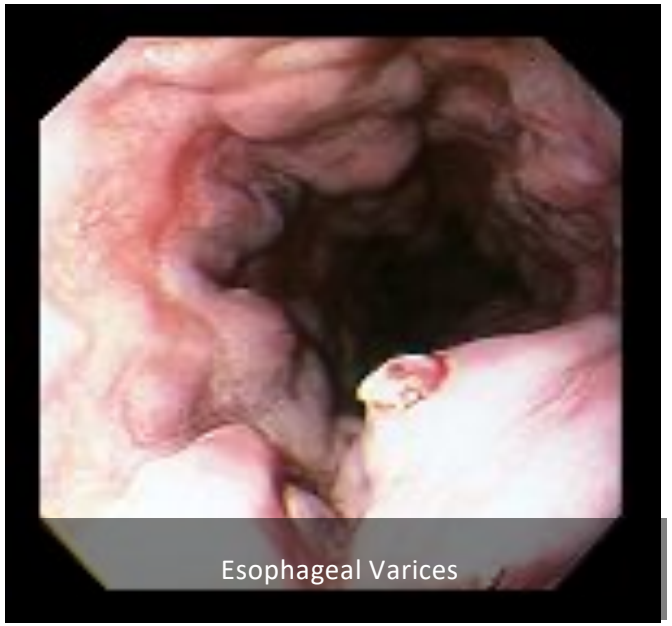
Hepatitis C Virus (HCV): An Overview

Jorge Mera, MD, FACP

HCV: What Are We Trying To Prevent at the Individual Level?



Ascites



Esophageal Varices

End Stage Liver Disease/Liver Cancer

HCV: What Are We Trying To Achieve at Public Health Level?
Eliminate HCV as a Public Health Problem

Decrease Mortality by 65%

Decrease Incidence by 90%

Outline

Virology

Epidemiology

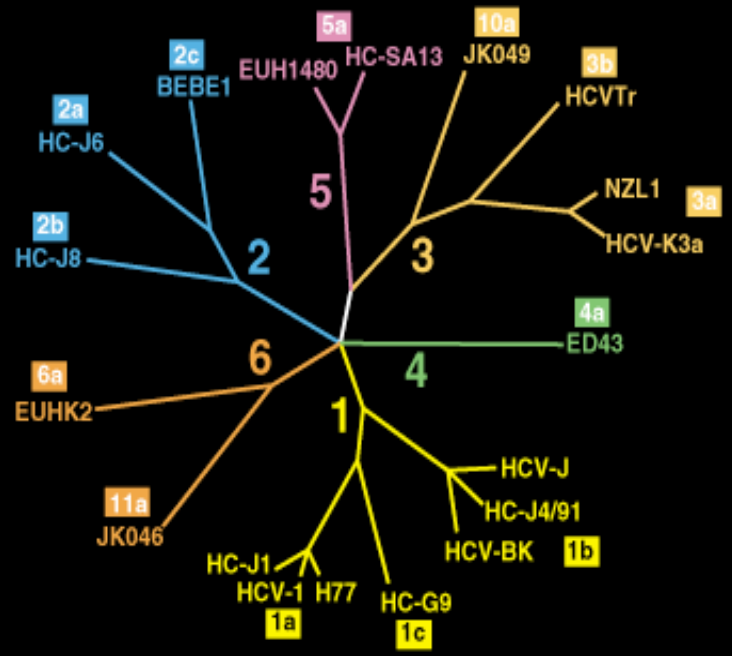
Clinical presentation

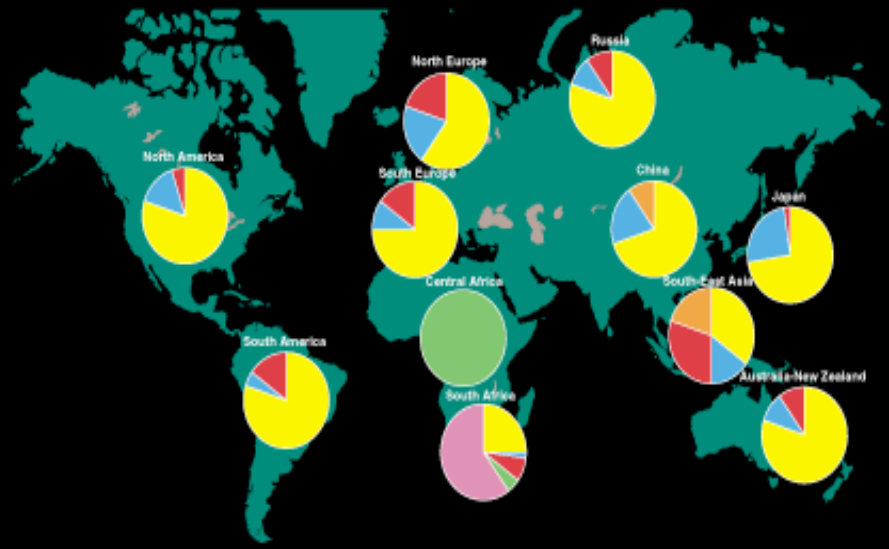
Diagnosis, evaluation treatment

HCV Virology and Life Cycle

Family Flaviviridae	• RNA virus
Genus: Hepacivirus	• HCV only infects humans • No animal model • Other related hepacivirus infect animals
Rapidly mutates and generates quacispecies	• > 30 % mutation creates a different Genotype • 15-30% mutations creates subtypes within a genotype

Hepatitis C Virus: Six Major Genotypes

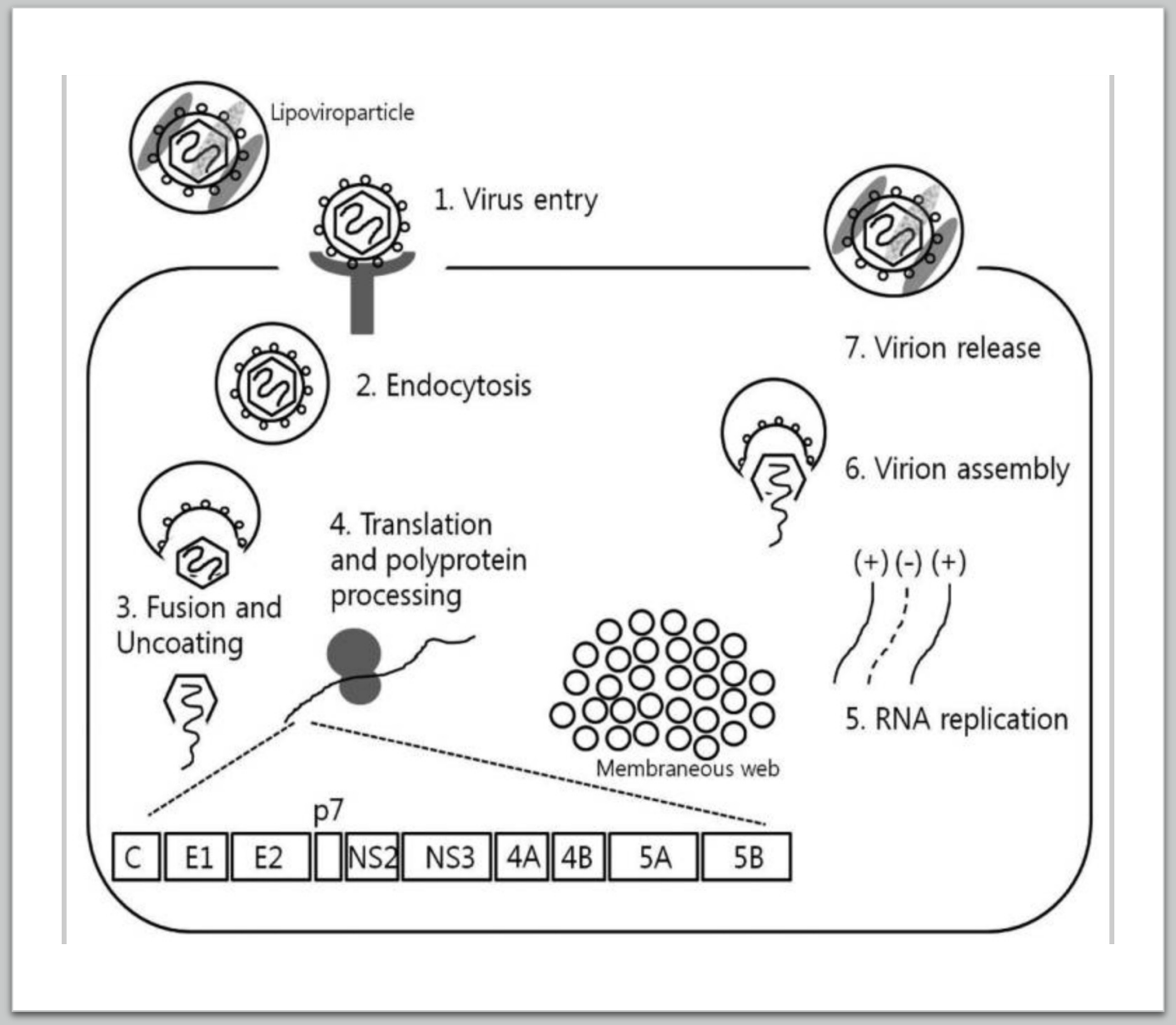




Based on a sequence divergence of > 30%

HCV Virology and Life Cycle

- Genus Hepacivirus (7 Genotypes)
  - ***Do not differ in:***
    - Transmissibility
    - Level of replication
    - Rate of progression of the resulting liver disease
  - ***Do differ***
    - Response to treatments
  - ***Does not integrate*** in Chromosomal DNA
  - ***Replicates*** in
    - Hepatocytes,
    - T cells, B cells and Monocytes



Where did HCV Originate?

a) Dogs
b) Horses
c) Non-Human Primates
d) a and b are correct
e) All are correct

From Where did HCV Originate?

a) Dogs

b) Horses

c) Non-Human Primates

d) a and b are correct

e) All are correct

ORIGINS OF HCV

ELSEVIER

Infection, Genetics and Evolution

Volume 93, September 2021, 104975

Research paper

Non-primate hepacivirus transmission and prevalence: Novel findings of virus circulation in horses and dogs in Morocco

Abbadi I, Lkhider M, Kitab B, eta al. Infect Genet Evol. 2021 Sep;93: 104975.

This epidemic was fueled by new parenteral transmission routes:

- Associated with medical treatments, immunization, blood transfusion and more recently injecting drug use.

The immediate sources of HCV associated with its pandemic spread:

- Now identified as areas in Central and West sub-Saharan Africa and South and Southeast Asia
- Where genetically diverse variants of HCV appear to have circulated for hundreds of years.

The actual source of HCV infection in these endemic areas?

- Recent findings of a non-primate hepacivirus (NPHV) in horses and potentially in dogs

Simmonds P. The origin of hepatitis C virus. Curr Top Microbiol Immunol. 2013;369:1-15. doi: 10.1007/978-3-642-27340-7_1. PMID: 23463195.

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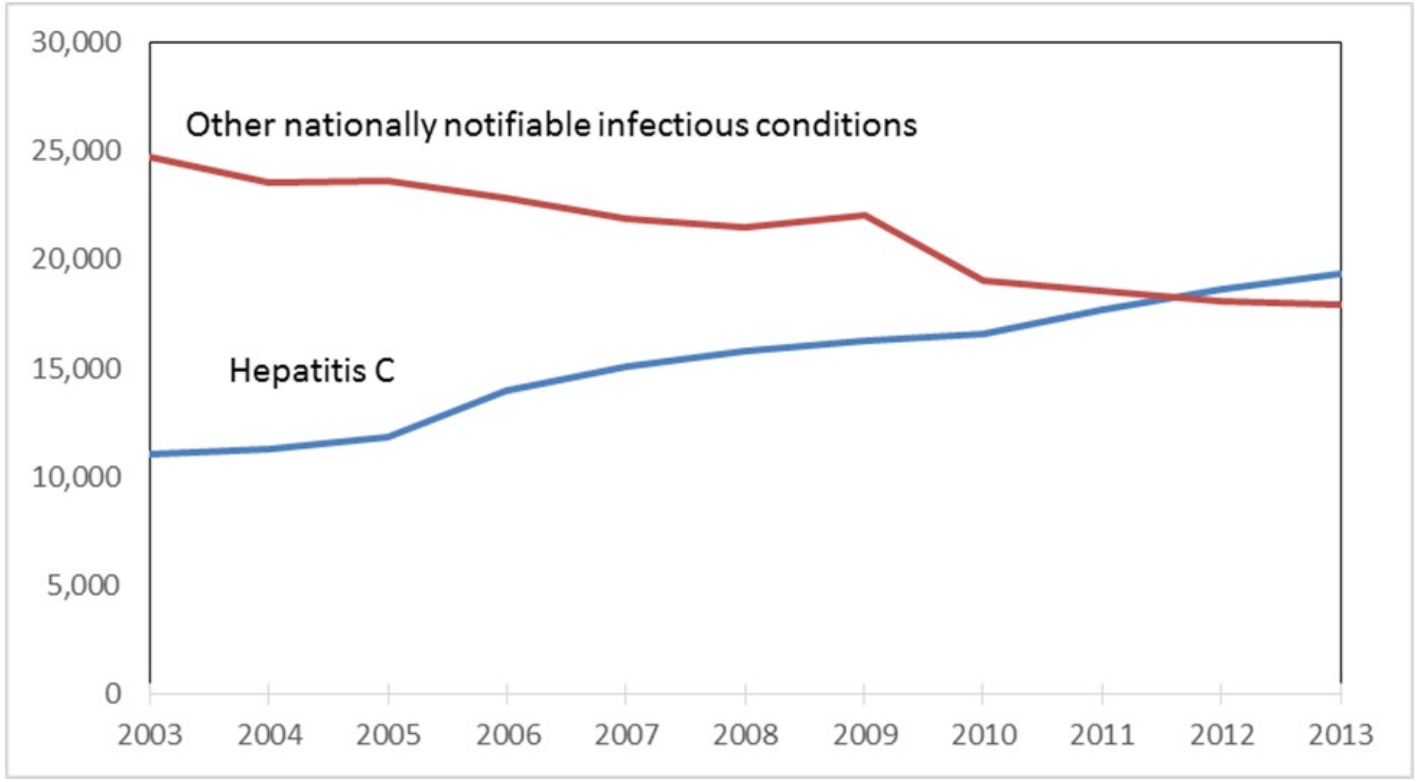
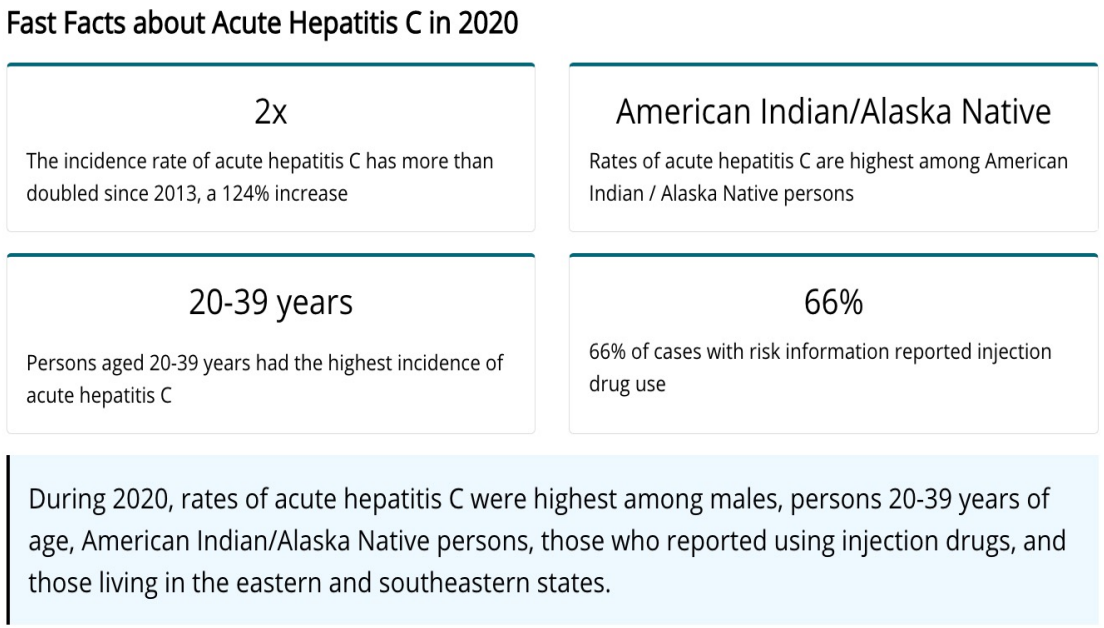
HCV Deaths and Deaths from Other Nationally Notifiable Infectious Diseases,* 2003- 2013



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

Division of Viral Hepatitis

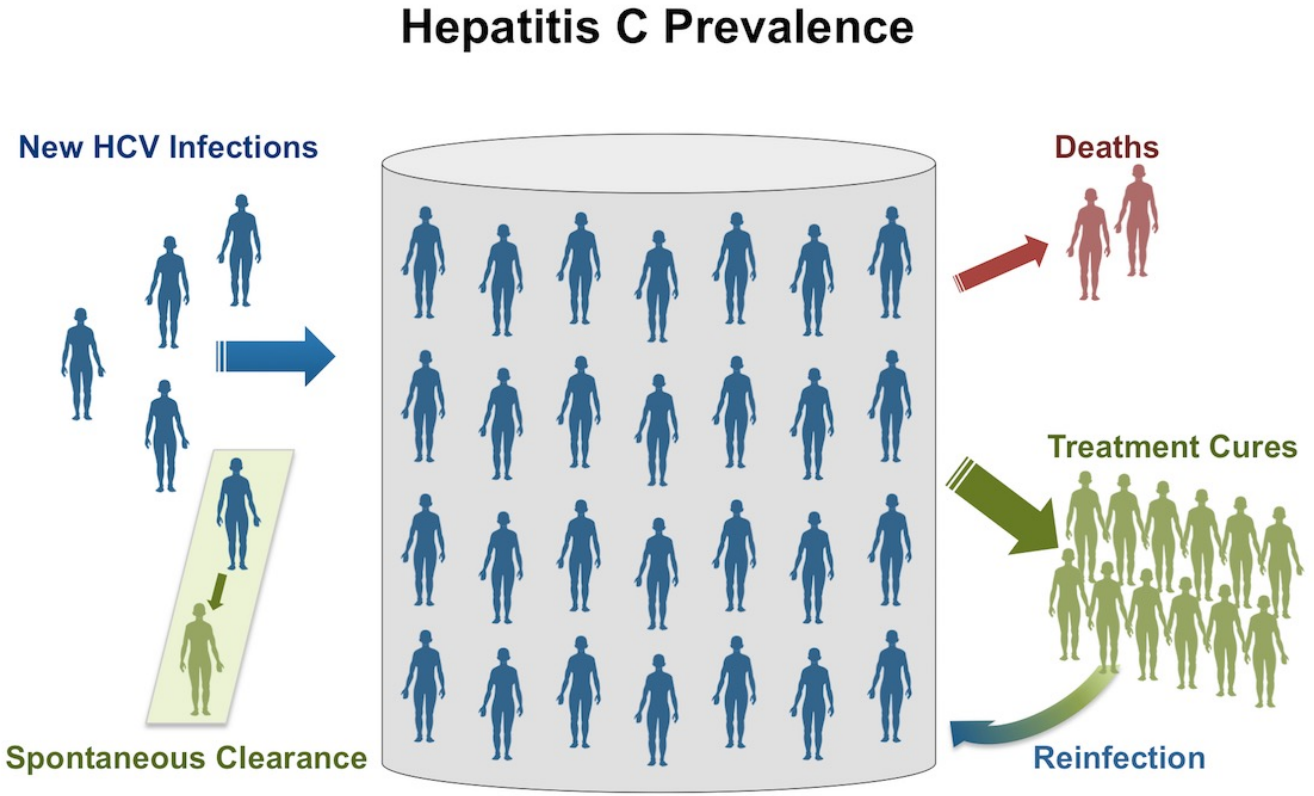
HCV FACTS in the United States, 2020



- **41 states reported a total of 107,300**
- **newly identified chronic HCV cases**
  - 40.7 chronic hepatitis C cases per 100,000.
- **HCV-associated deaths increased 4%**
  - (3.45 deaths per 100,000 people), compared to 2019 (3.33 deaths per 100,000 people).
- **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.

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.



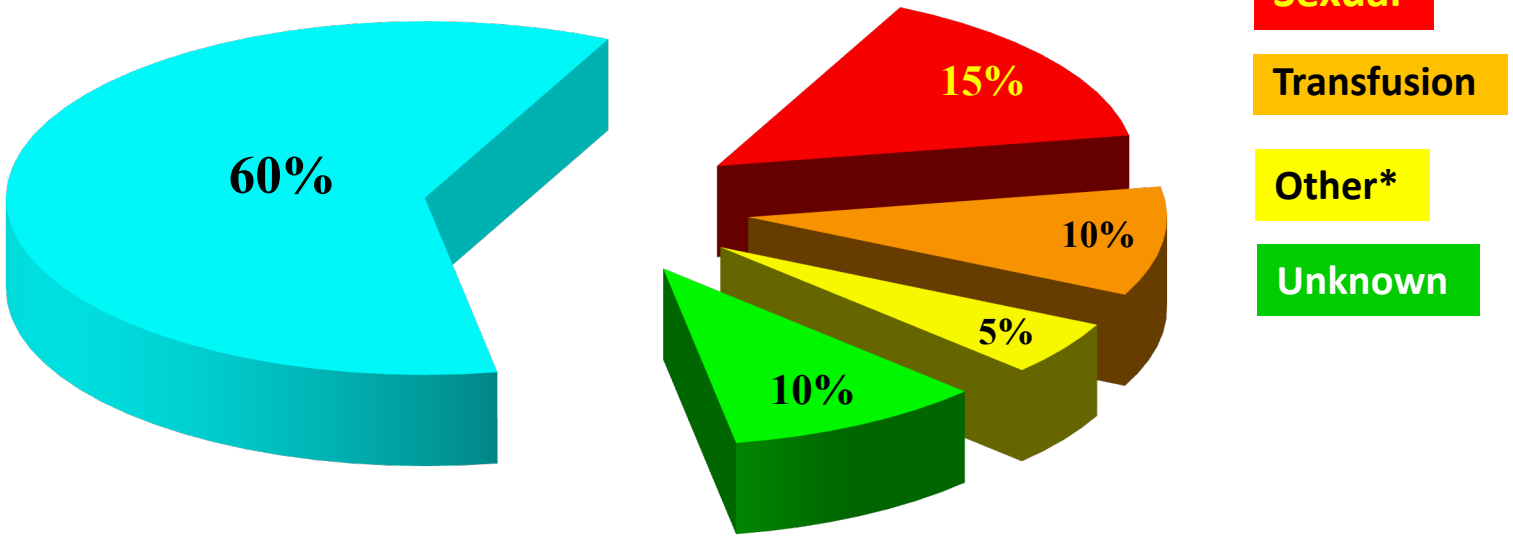
Source: Illustration by David H. Spach, MD

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: 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 (?)*

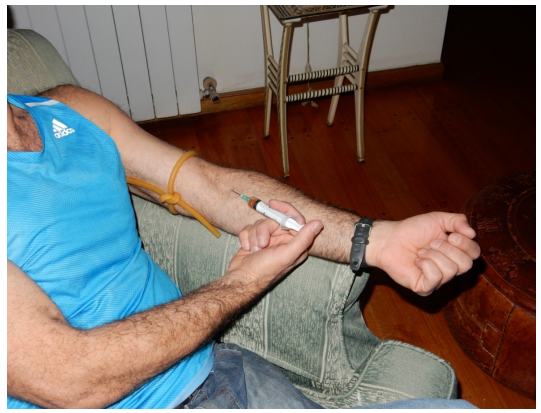


*Nosocomial; Health-care work; Perinatal

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 Transmission and Injection Drug Use

Today > 80% Occurs in PWID



Needle
Syringe
Cooker
Table
Tourniquet

Paraphernalia

~20 to 30% of PWID become infected with within the first 2 years of starting to inject drugs

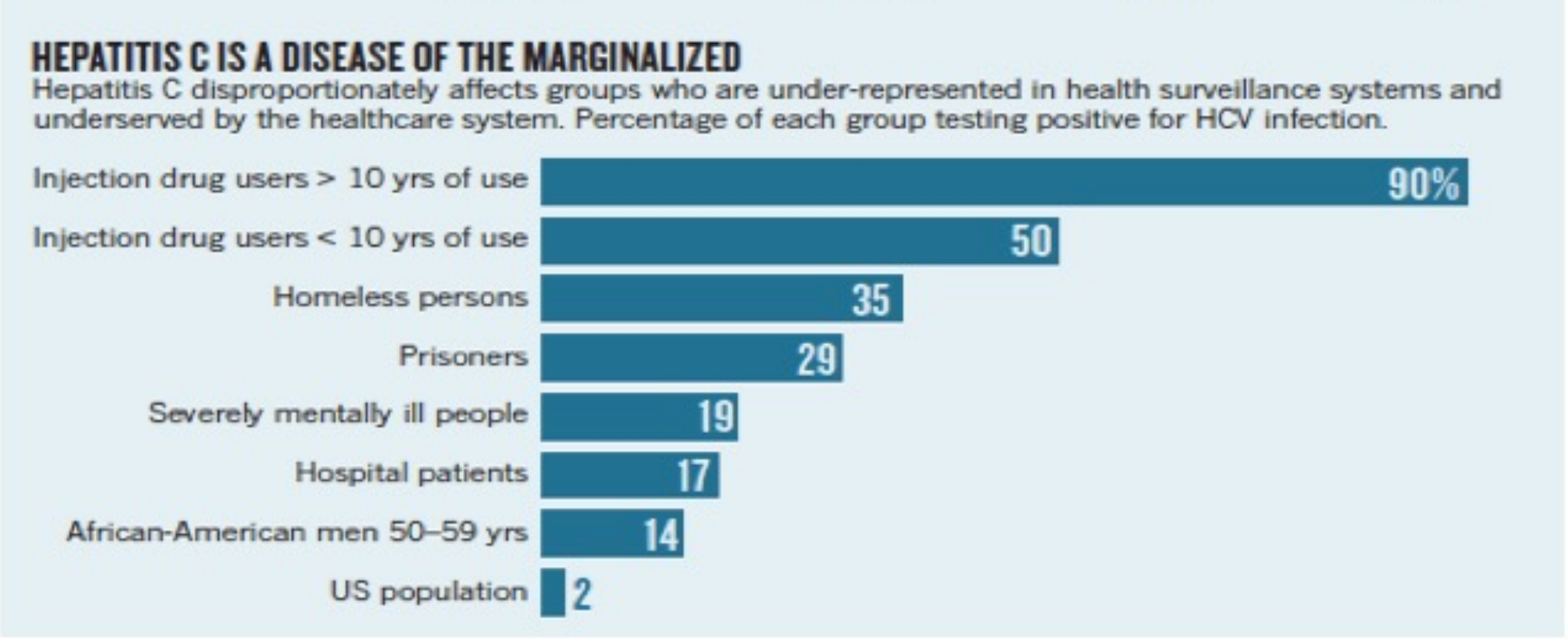
- 50% within 5 years

Transmission risk is greatest with "direct sharing" of needles and syringes

- But may also occur indirectly via sharing of injection paraphernalia

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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Symptoms of HCV

Most patients are asymptomatic

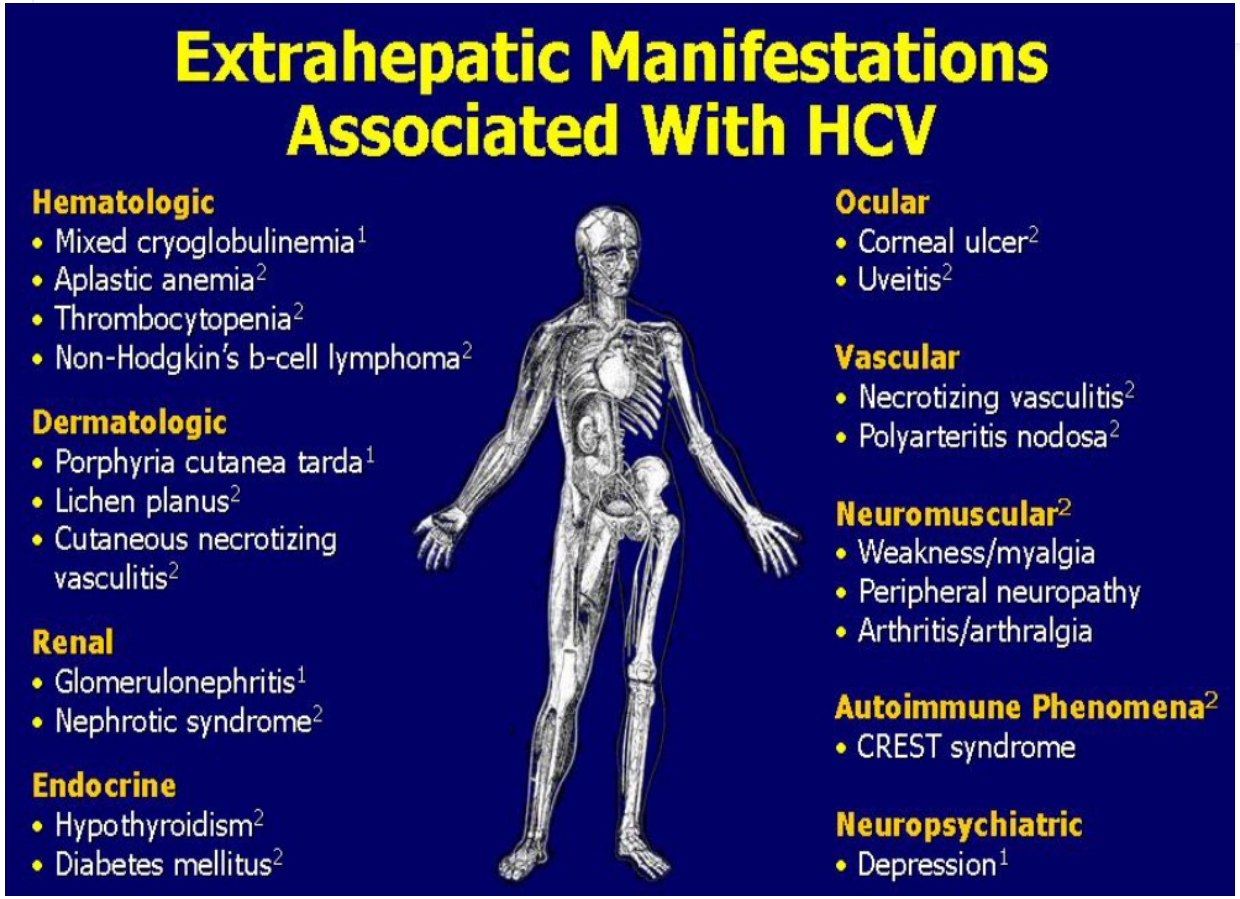
Common symptoms

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

Physical Findings

- **Most Patients do not have any abnormal physical findings**
- In patients with cirrhosis, you may find
  - Spider angiomas
  - Palmar erythema
  - Gynecomastia
  - Testicular atrophy
  - Jaundice
  - Firm liver
  - Parotid hypertrophy

HCV Extrahepatic Manifestations



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

High index of suspicion is needed for these conditions regardless of the presence 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.

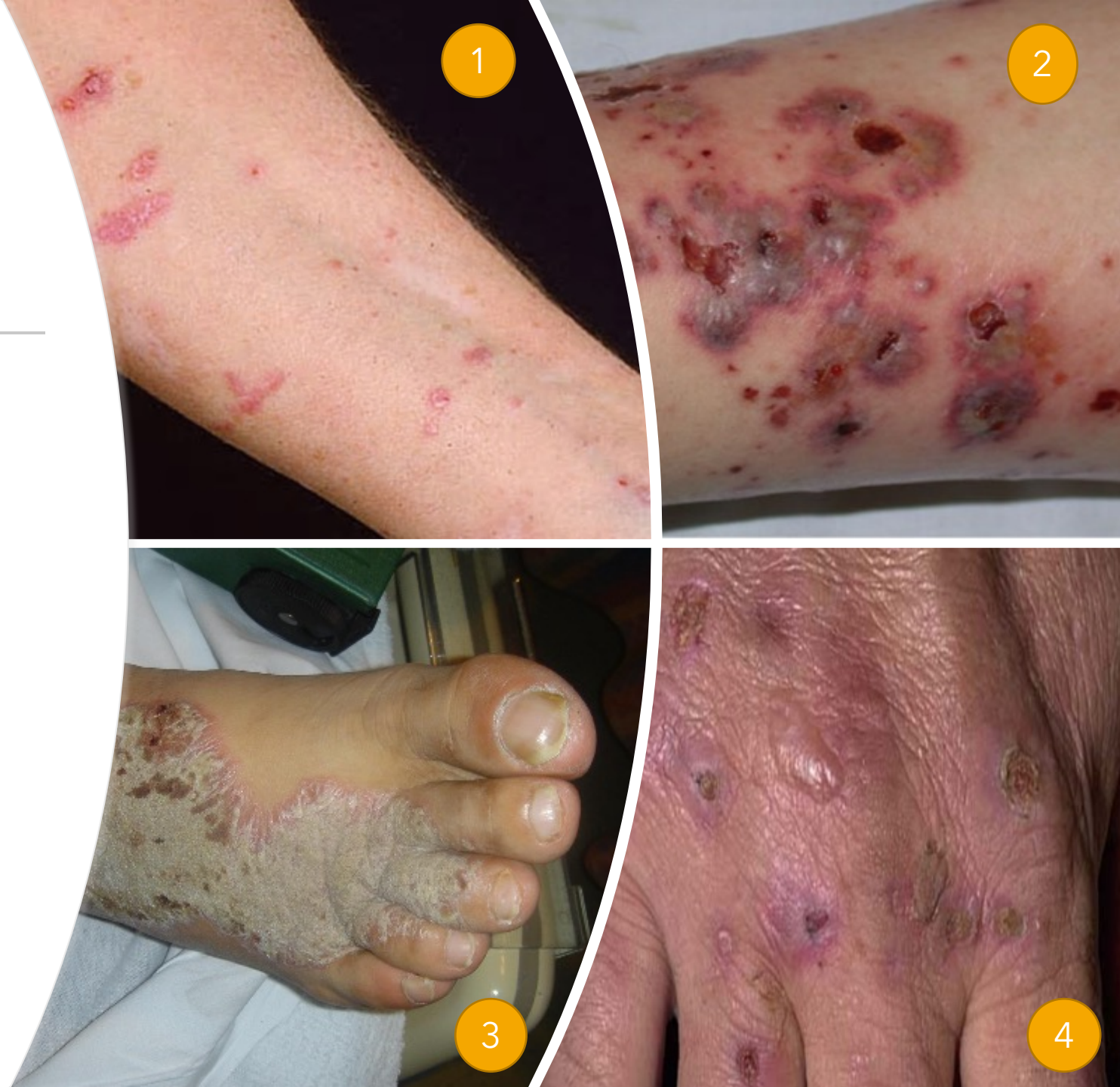
Dermatologic Manifestations

1: Lichen planus

2: Leukocytoclastic vasculitis

3: Necrolytic acral erythema

4: Porphyria cutaneous tarda



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HCV Workflow

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

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

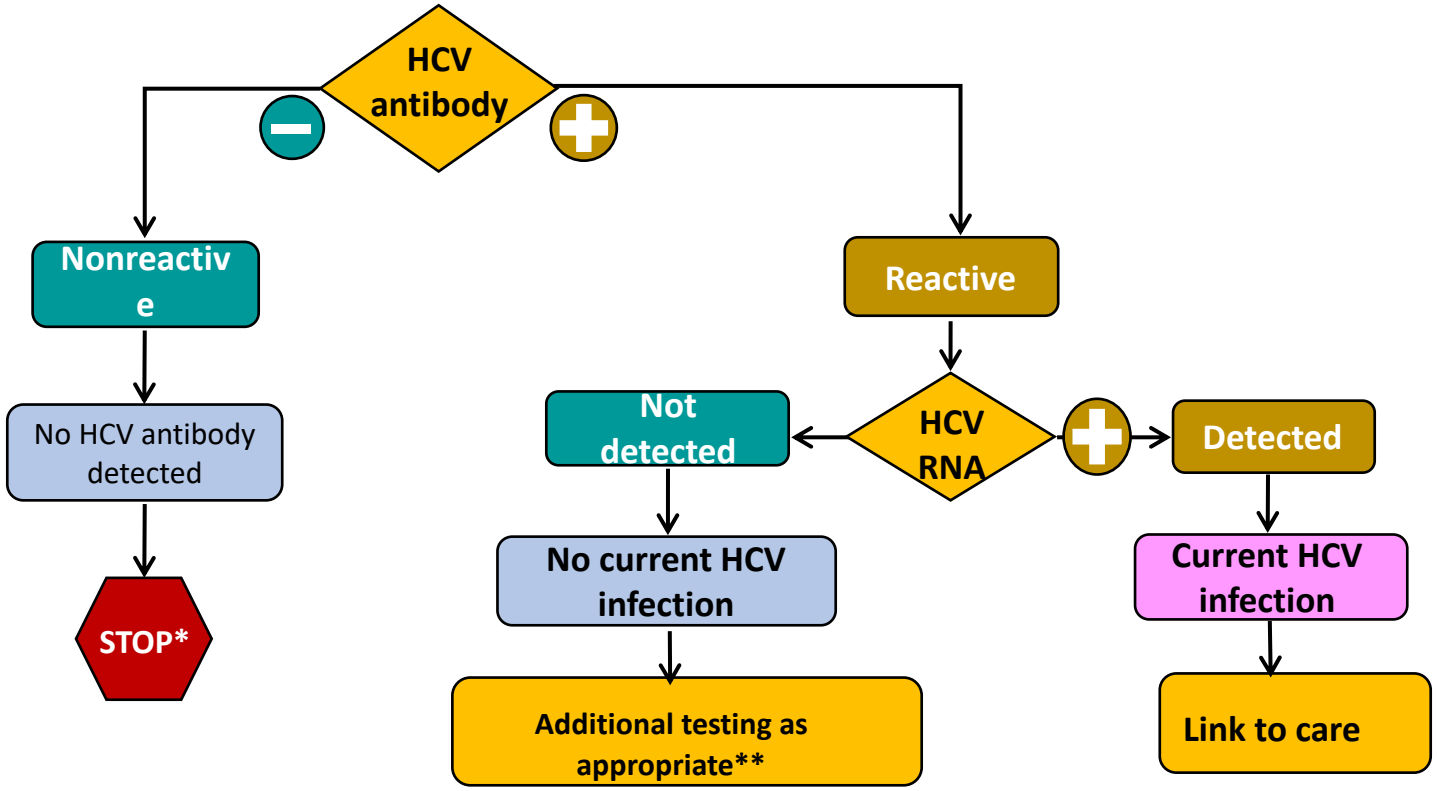
Universal Screening

- 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

Confirm the Diagnosis



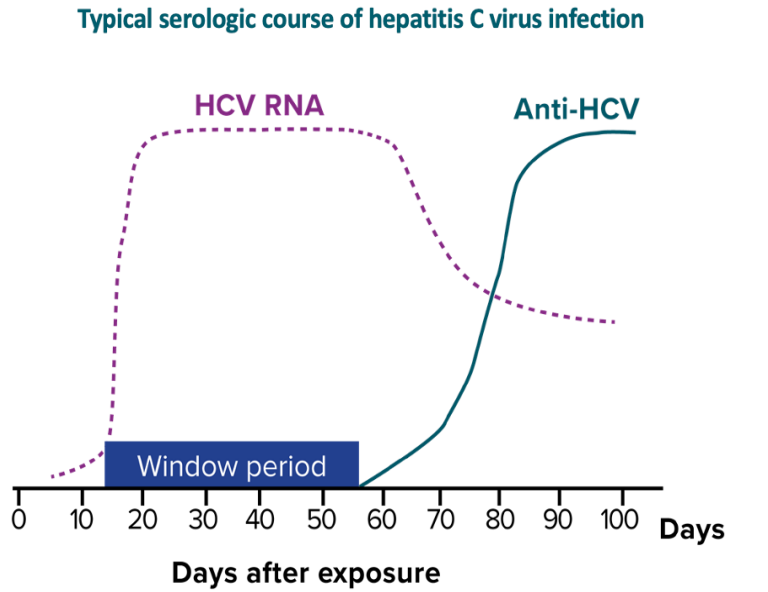


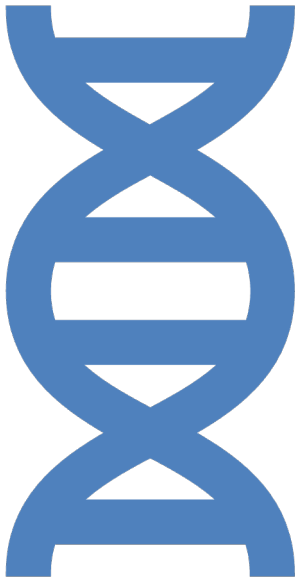
Figure obtained from https://www.aphl.org/aboutAPHL/publications/Documents/ID-2019Jan-HCV-Test-Result-Interpretation-Guide.pdf

* 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.

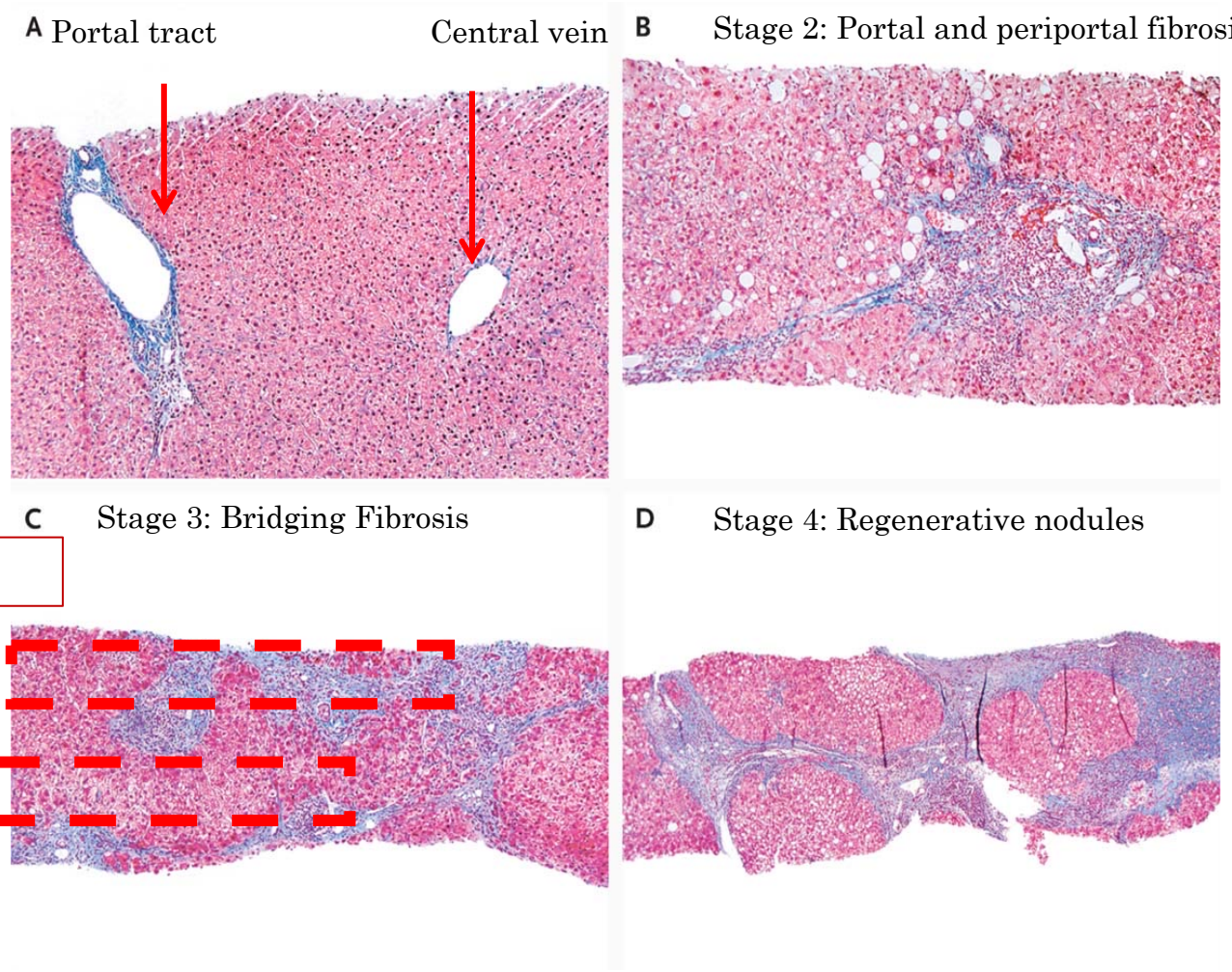
CDC. Testing for HCV infection. *MMWR*. 2013;62(18).

HCV RNA: Viral Load



- **Number of virus particles** (RNA) per mL of blood
- **Confirms active infection**
  - 15-30% of acutely infected patients spontaneously resolve
- **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

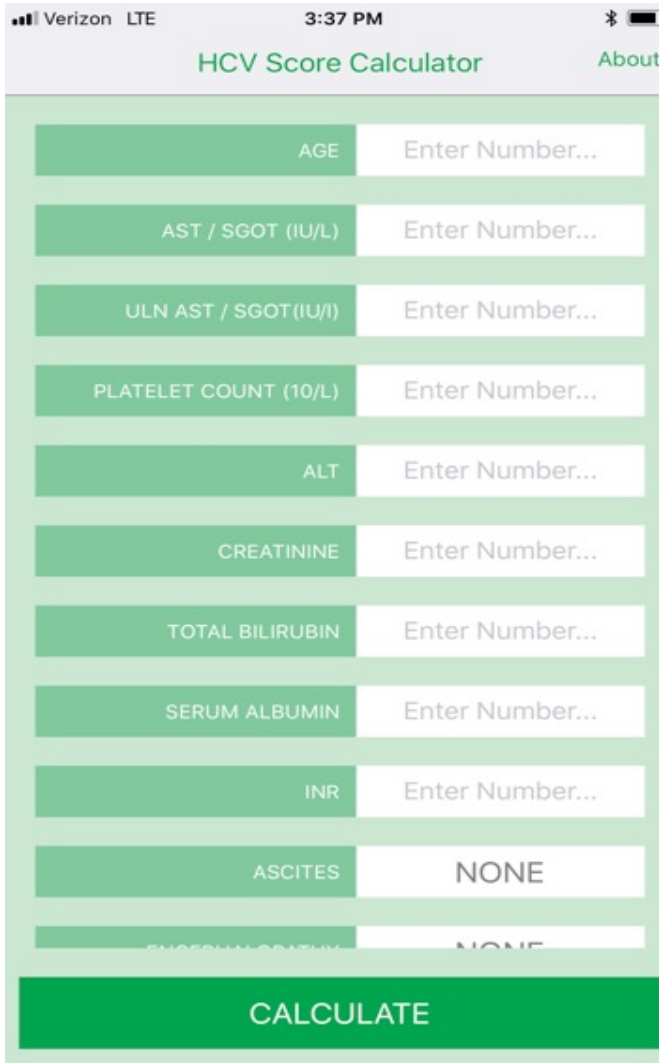
- **F0: No fibrosis**
- **F1 Scattered portal fibrosis**
- **F2. Diffuse periportal fibrosis**
- **F3. Bridging fibrosis**

- **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

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

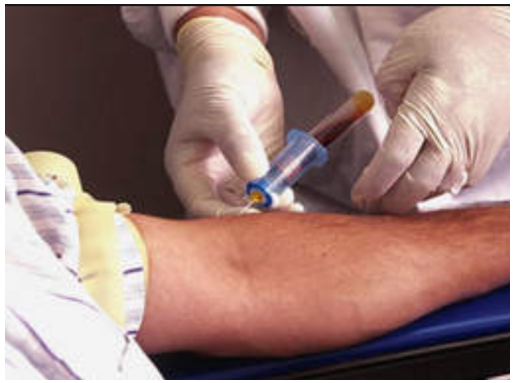
An APRI score greater than 1.0 had a sensitivity of 76% and specificity of 72% for predicting cirrhosis. APRI score greater than 0.7 had a sensitivity of 77% and specificity of 72% for predicting significant hepatic fibrosis.

FIB–4 Index

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

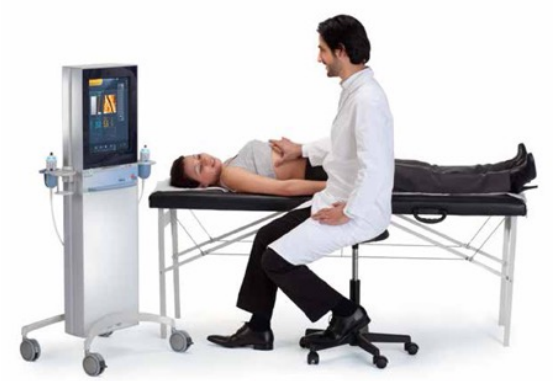
A FIB-4 score <1.45 has a negative predictive value of 90% for advanced fibrosis A FIB-4 >3.25 has a 97% specificity and a positive predictive value of 65% for advanced fibrosis.

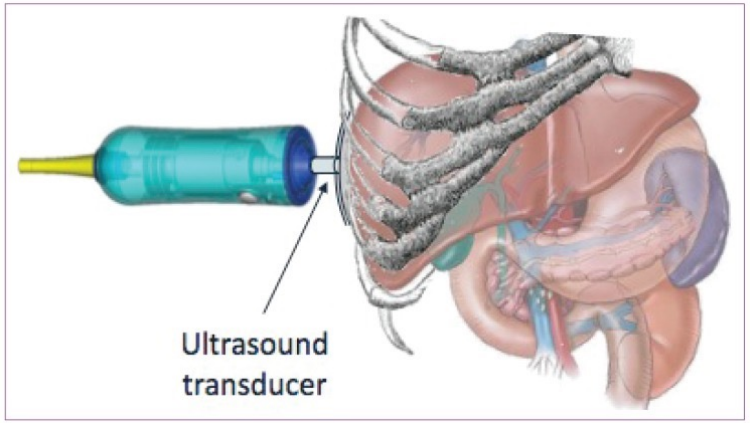
Fibrotest/Fibrosure

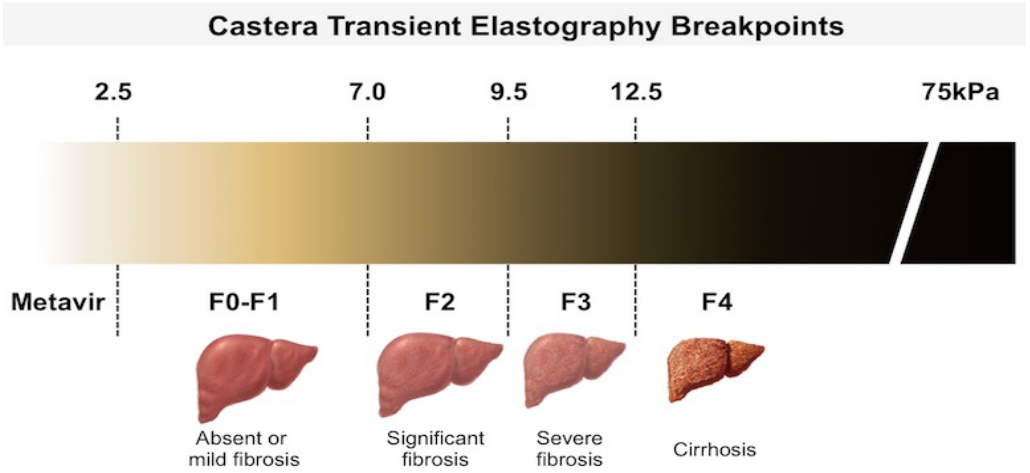


Lin ZH, Xin YN, Dong QJ, et al. Hepatology. 2011;53:726-36 Sterling RK, Lissen E, Clumeck N, et. al. Hepatology 2006;43:1317-1325 University of Washington: Hepatitis C Online www.hepatitisc.uw.edu/

Liver Fibrosis Staging by Imaging: Transient Elastography







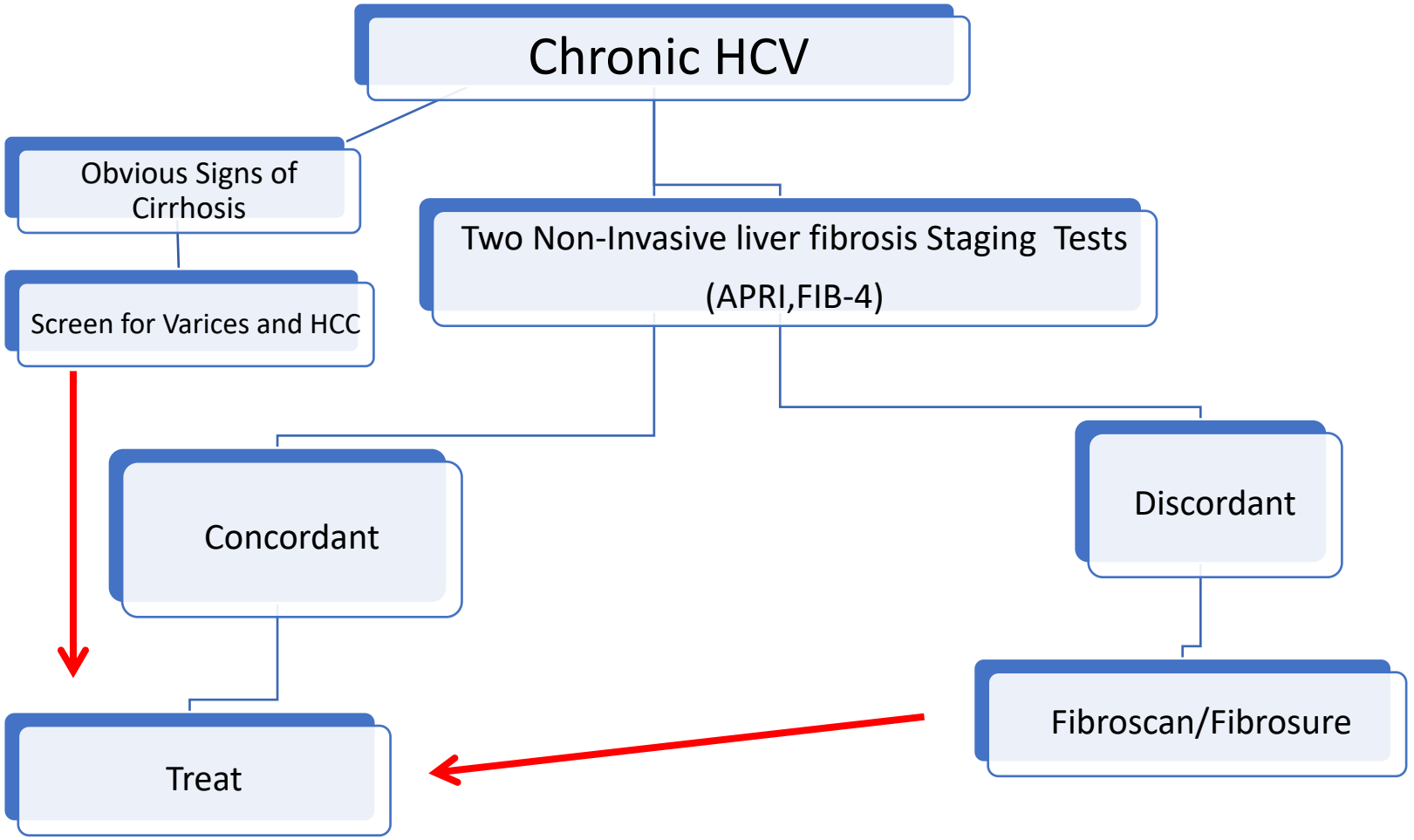
The probe of the Fibroscan device is positioned in an intercostal space near the right lobe of the liver, and a 50-MHz wave is passed into the liver from a small transducer on the end of the probe. The device then measures the velocity of the shear wave (in meters per second) as this wave passes through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

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

Fibrosis Staging Interpretation

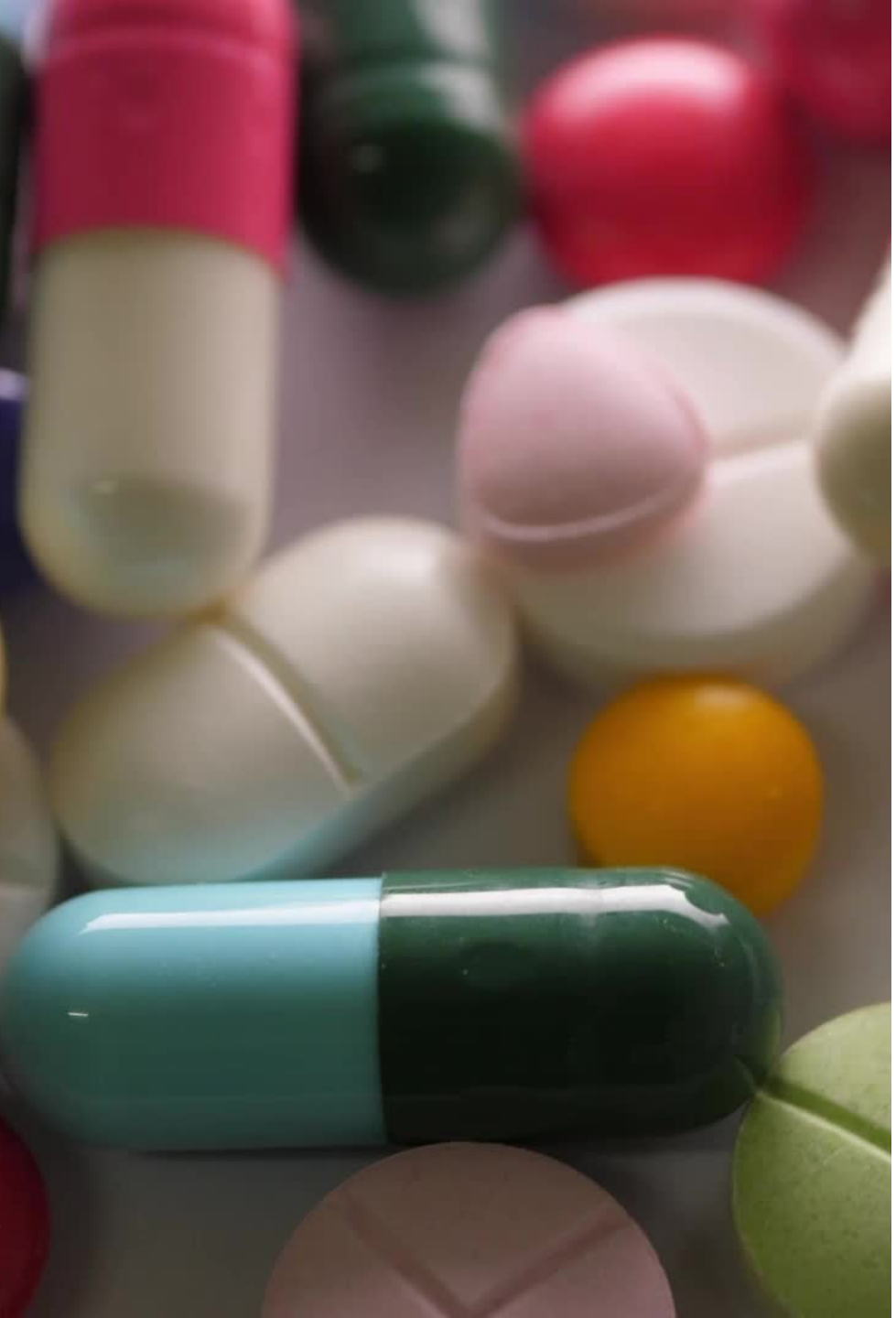
Metavir	Biopsy	Fibroscan	Fibrosure	APRI	FIB-4
F4	F4	≥ 12.5 kPa	≥ 0.75	≥ 1.0	> 3.25
F3	F3	9.6 12.4 kPa	0.58 – 0.74		
F2	F2	7.1-9.5 kPa	0.49 – 0.57	< 1.0	?
F1	F1	≤ 7.0 kPa	0.23 – 0.48		< 1.45
F0	F0		≤ 0.22		

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?

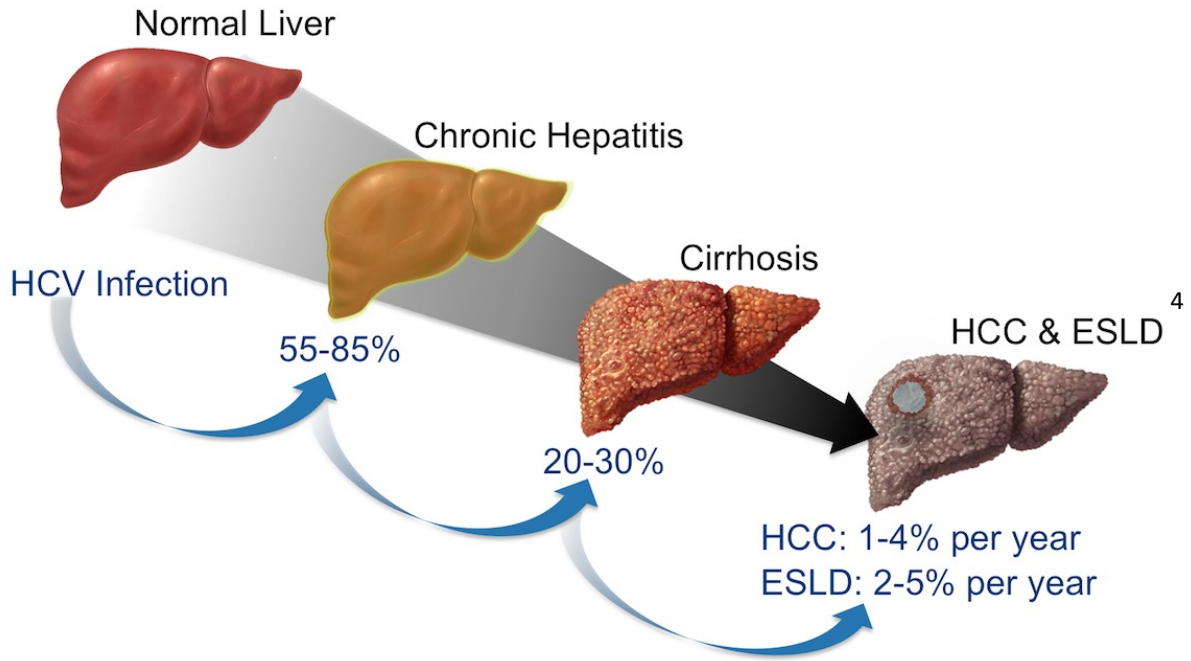
- Treatment ***may be different between*** cirrhotic and non cirrhotic patients and ***will be different*** in patients with decompensated cirrhosis vs non decompensated cirrhosis

- 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

Natural History Following Initial Infection with HCV



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

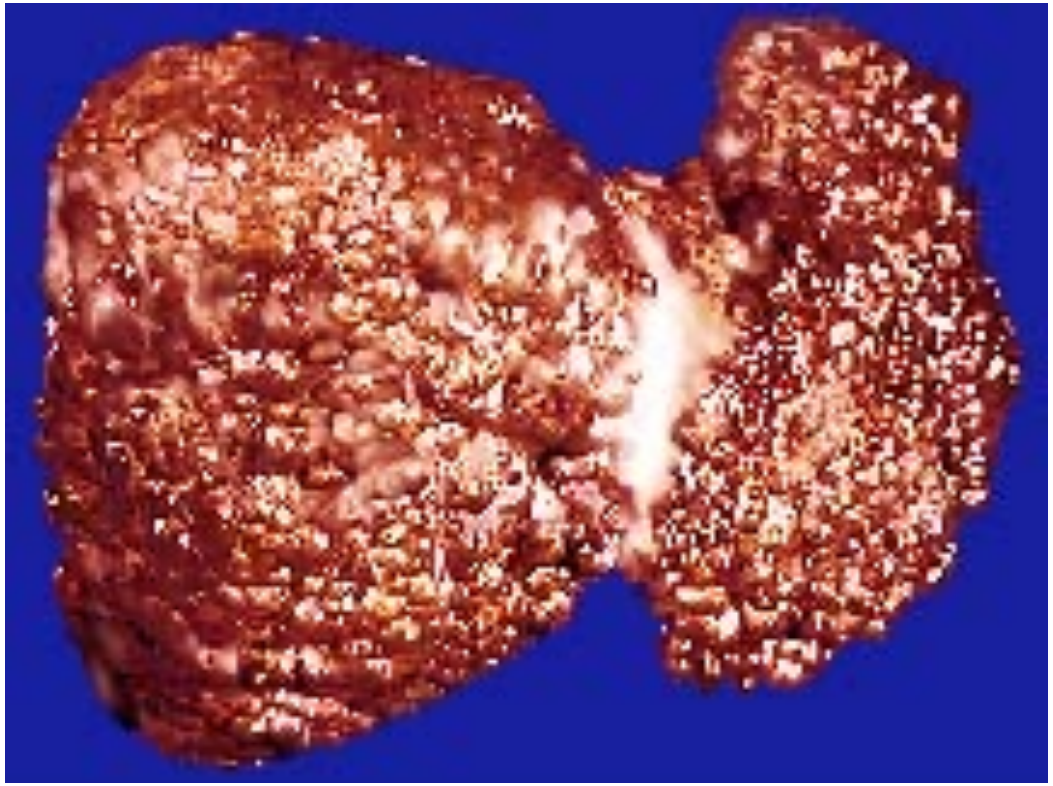
Rates of progression to cirrhosis are increased in the presence of a variety of factors, including:

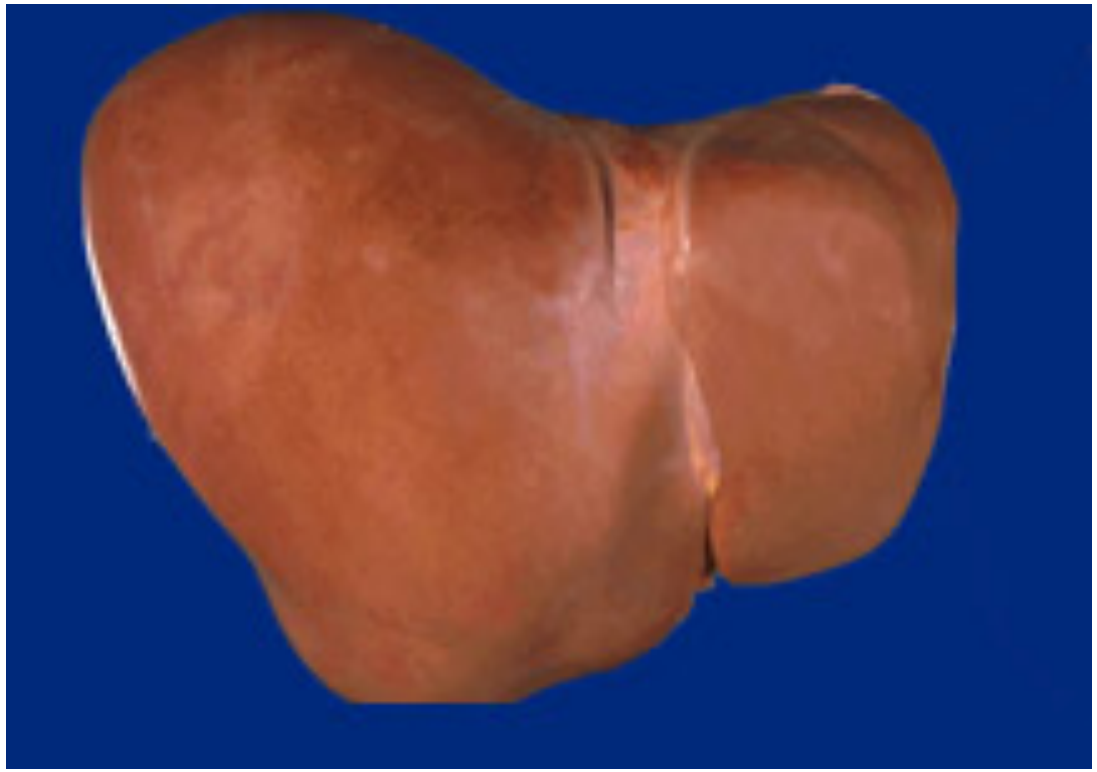
- Being male
- Being age >50 years
- Consuming alcohol
- Having nonalcoholic fatty liver disease, hepatitis B, or HIV coinfection
- Receiving immunosuppressive therapy[1,2,3]

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.

What Does HCV Treatment and Cure Accomplish?

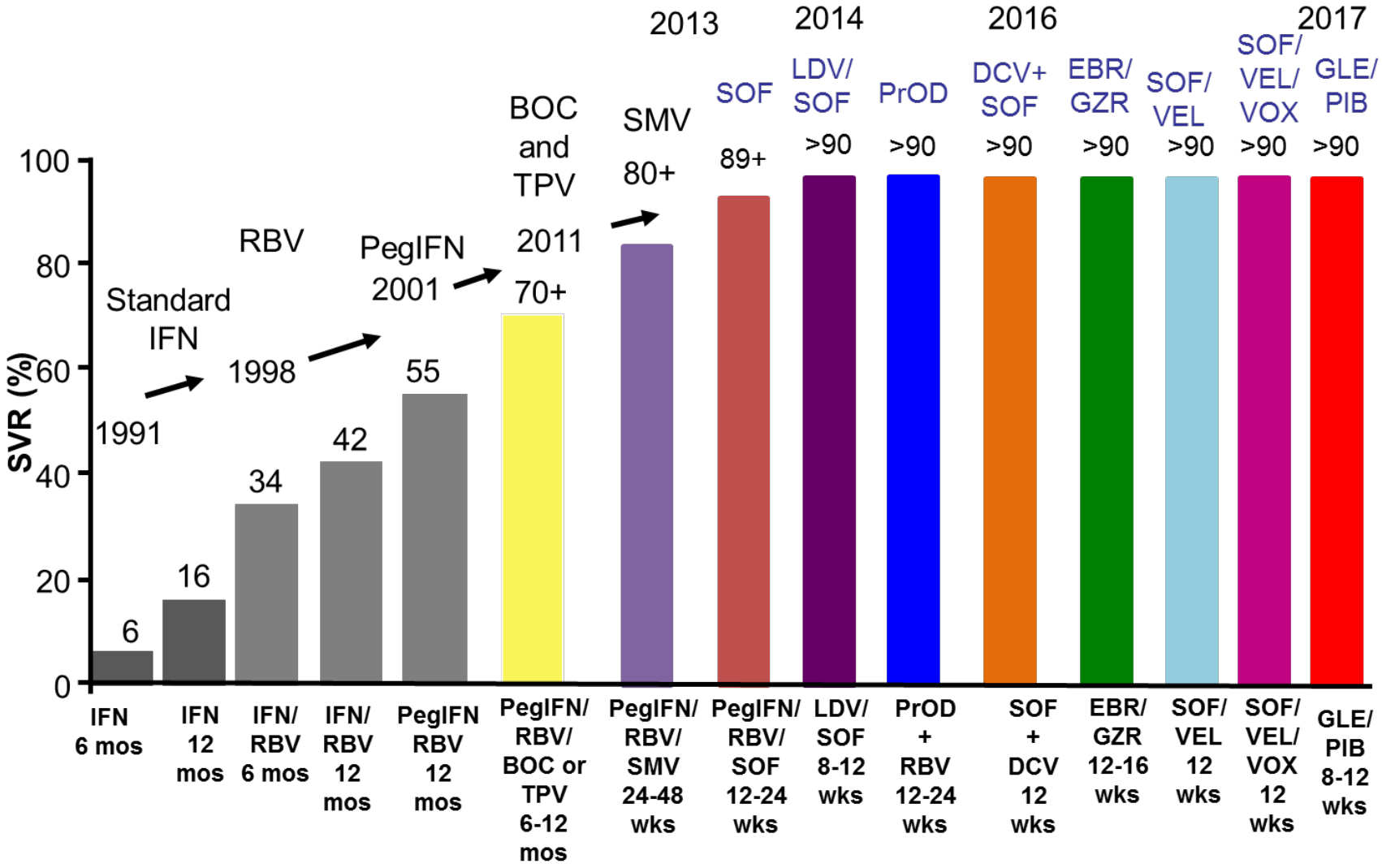
- 70% Reduction of Liver Cancer
- 50% Reduction in All-cause Mortality
- 90% Reduction in Liver Failure





- 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 (Without Cirrhosis)

Patients who have any of the following characteristics:

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

(see HCV guidance for treatment recommendations for these patients)

Simplified HCV Treatment Algorithm for Treatment-Naive Adults With Cirrhosis

Who Is Eligible for Simplified Treatment

Adults with chronic hepatitis C (any genotype) who have compensated cirrhosis (Child-Pugh A) and have not previously received hepatitis C treatment
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

Who Is *NOT* Eligible for Simplified Treatment (With Cirrhosis)

Patients who have any of the following characteristics:

- Current or prior episode of decompensated cirrhosis, defined as Child-Turcotte-Pugh (CTP) score ≥7 (ascites, hepatic encephalopathy, total bilirubin >2.0 mg/dL, albumin ≤3.5 g/dL, or INR ≥1.7)
- Prior hepatitis C treatment
- End-stage renal disease (ie, eGFR <30 mL/min/m^2) (see Patients with Renal Impairment section)
- HBsAg positive
- Current pregnancy
- Known or suspected hepatocellular carcinoma
- Prior liver transplantation

(see HCV guidance for treatment recommendations for these patients)

https://www.hcvguidelines.org/

What is the Earliest Laboratory Marker for Cirrhosis?

a) Low albumin level
b) Elevated AST
c) Elevated ALT
d) Thrombocytopenia
e) Anemia
f) Leucopenia

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Patient has Cirrhosis if any of the following are present

FIB-4 > 3.25

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

https://www.hcvguidelines.org/

Simplified Pretreatment Laboratory Testing in Patients with HCV

Patients without cirrhosis:

- ***Within 6 months of initiating treatment:***
  - Complete blood count (CBC)
  - Hepatic function panel (ie, albumin, total and direct bilirubin, alanine aminotransferase [ALT], 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.

Patients with cirrhosis, obtain the above labs Plus:

- ***Labs within 3 months of initiating treatment:***
- INR
- HCV genotype (if treating with sofosbuvir/velpatasvir)

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Simplified Pre-Treatment Assessment in Patients With or Without 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.
  - Drug-drug interactions are particularly important in HIV co-infection
  - In those with HIV, the simplified treatment approach should not be used in those on TDF containing regimens with eGFR <60 ml/min because of the need of additional monitoring.

Education:

- Educate the patient about proper administration of medications, adherence, and prevention of reinfection.

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Recommended Regimens

Patients without Cirrhosis

- Glecaprevir (300 mg) / pibrentasvir (120 mg) to be taken with food for a duration of 8 weeks
- Sofosbuvir (400 mg) / velpatasvir (100 mg) for a duration of 12 weeks

Patients with cirrhosis

- **Genotype 1-6**:
  Glecaprevir (300 mg) / pibrentasvir (120 mg) to be taken with food for a duration of 8 weeks

- **Genotype 1, 2, 4, 5, or 6**
  Sofosbuvir (400 mg) / velpatasvir (100 mg) for a duration of 12 weeks

NOTE: Patients with genotype 3 require baseline NS5A resistance-associated substitution (RAS) testing. Those without Y93H can be treated with 12 weeks of sofosbuvir/velpatasvir. If Y93H is present, see HCV guidance for treatment recommendations.

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On-Treatment Monitoring

Patients without cirrhosis

- 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.

Patients without decompensated cirrhosis

Same as without cirrhosis PLUS

- Providers may order blood tests to monitor for liver injury during treatment
- Because hepatic decompensation (eg, jaundice, etc) occurs rarely among patients with cirrhosis receiving HCV antiviral treatment.
- Patients should see a specialist
- If they develop worsening liver blood tests (eg, bilirubin, AST, ALT, etc); jaundice, ascites, or encephalopathy; or new liver-related symptoms.

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Post-Treatment Assessment of Cure (SVR) in Patients With or Without Cirrhosis

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.

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Follow-Up After Achieving Virologic Cure (SVR)

Patients without cirrhosis

- 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.

Patients with cirrhosis

- Ultrasound surveillance for HCC (with or without alpha-fetoprotein testing) every 6 months is recommended for patients with cirrhosis in accordance with AASLD guidance.
- Upper endoscopic surveillance for esophageal varices is recommended in accordance with AASLD guidance on portal hypertensive bleeding in cirrhosis.
- 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.
- Patients should abstain from alcohol to avoid progression of liver disease.

https://www.hcvguidelines.org/

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