

Hepatitis C Update

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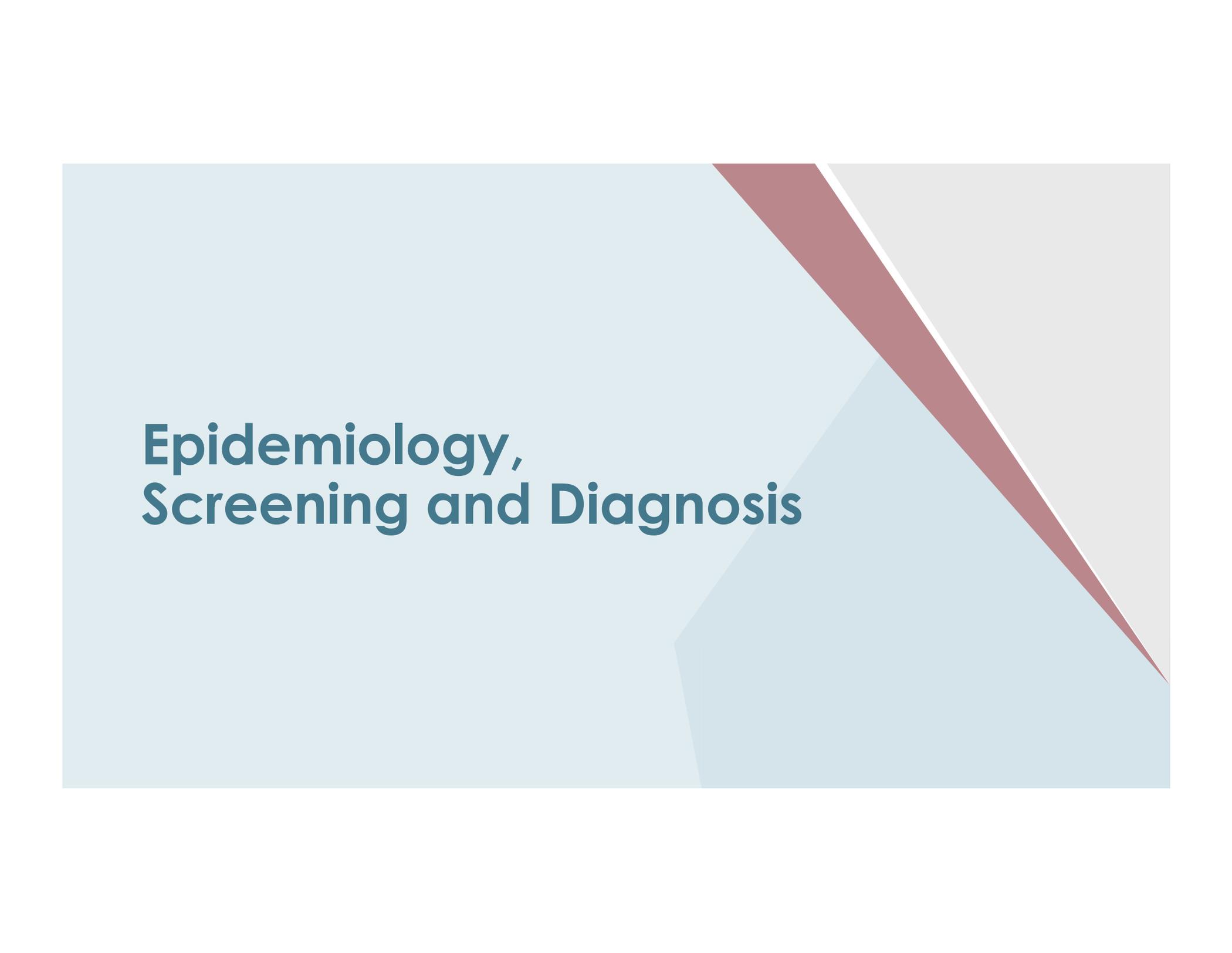
Learning Objectives

By the end of this presentation, participants should be able to describe:

1. The epidemiology of hepatitis C (HCV) in the United States and in New York City (NYC)
2. CDC screening recommendations for HCV and the New York State (NYS) testing law
3. Key steps in pre-therapy assessment
4. Candidates for HCV treatment with direct acting antiviral therapy
5. Patients that require monitoring after treatment

Outline

1. Epidemiology, Screening and Diagnosis
2. Pre-Therapy Assessment
3. Treatment of HCV with Direct Acting Antivirals
4. Drug-Drug Interactions
5. Special Populations
6. Access to Direct Acting Antivirals
7. Resources



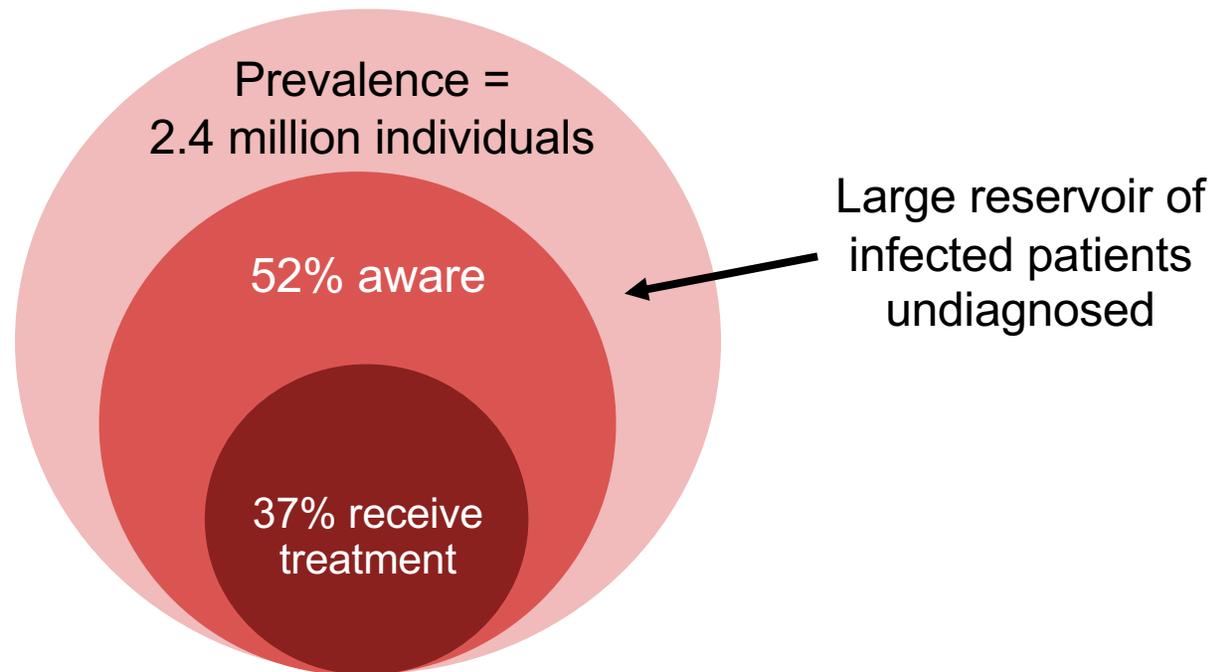
Epidemiology, Screening and Diagnosis

Introduction to HCV

- Estimated 2.4 million infected in the USA
- Estimated 91,000 infected in NYC¹
 - 40% undiagnosed
- Leading indication for liver transplantation
- Leading predisposing factor to development of hepatocellular carcinoma (HCC)

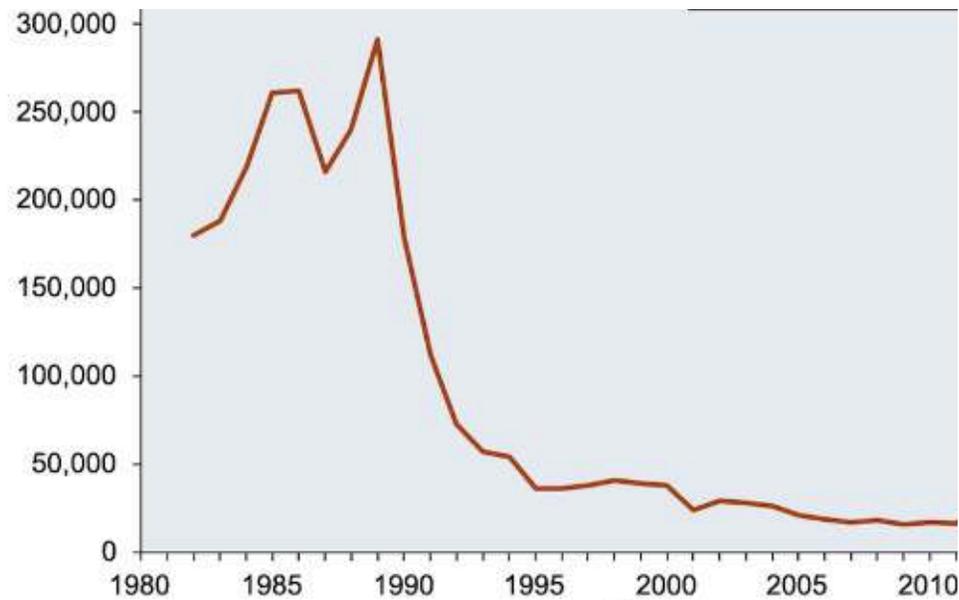
1. [NYC Health Department \(2020\)](#)

HCV is Underdiagnosed in the US



HCV Incidence in the United States

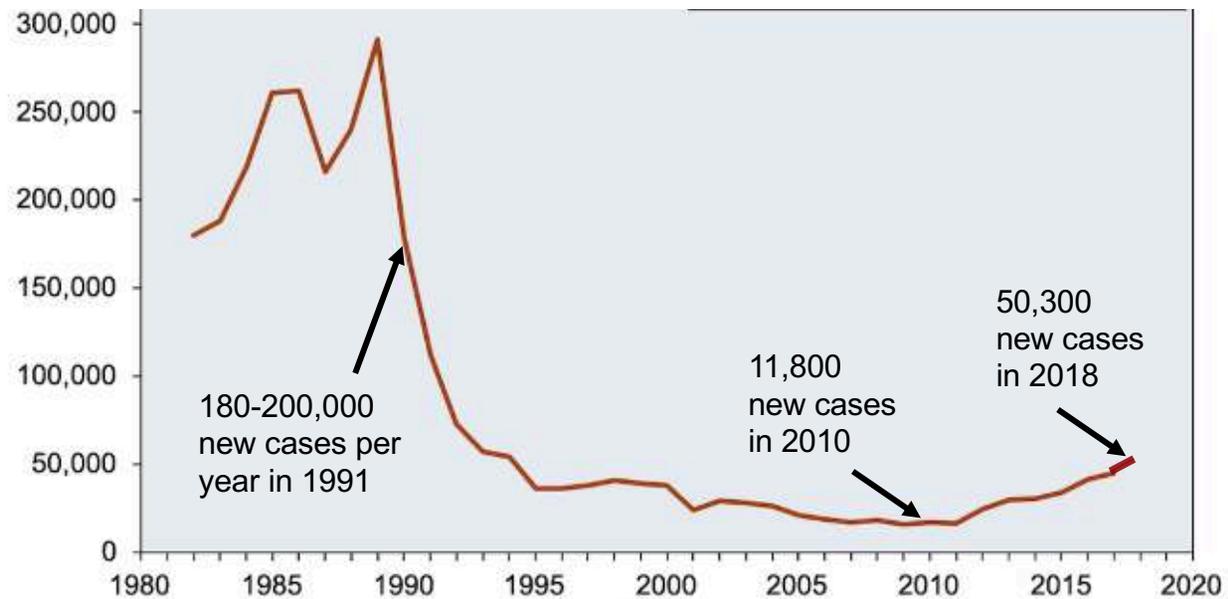
Estimated
total new HCV
infections



www.hepatitis.c.uw.edu/go/screening-diagnosis/epidemiology-us/core-concept/all.
As derived from CDC data, 2017. Ryerson AB et al. MMWR 2020;69:399.

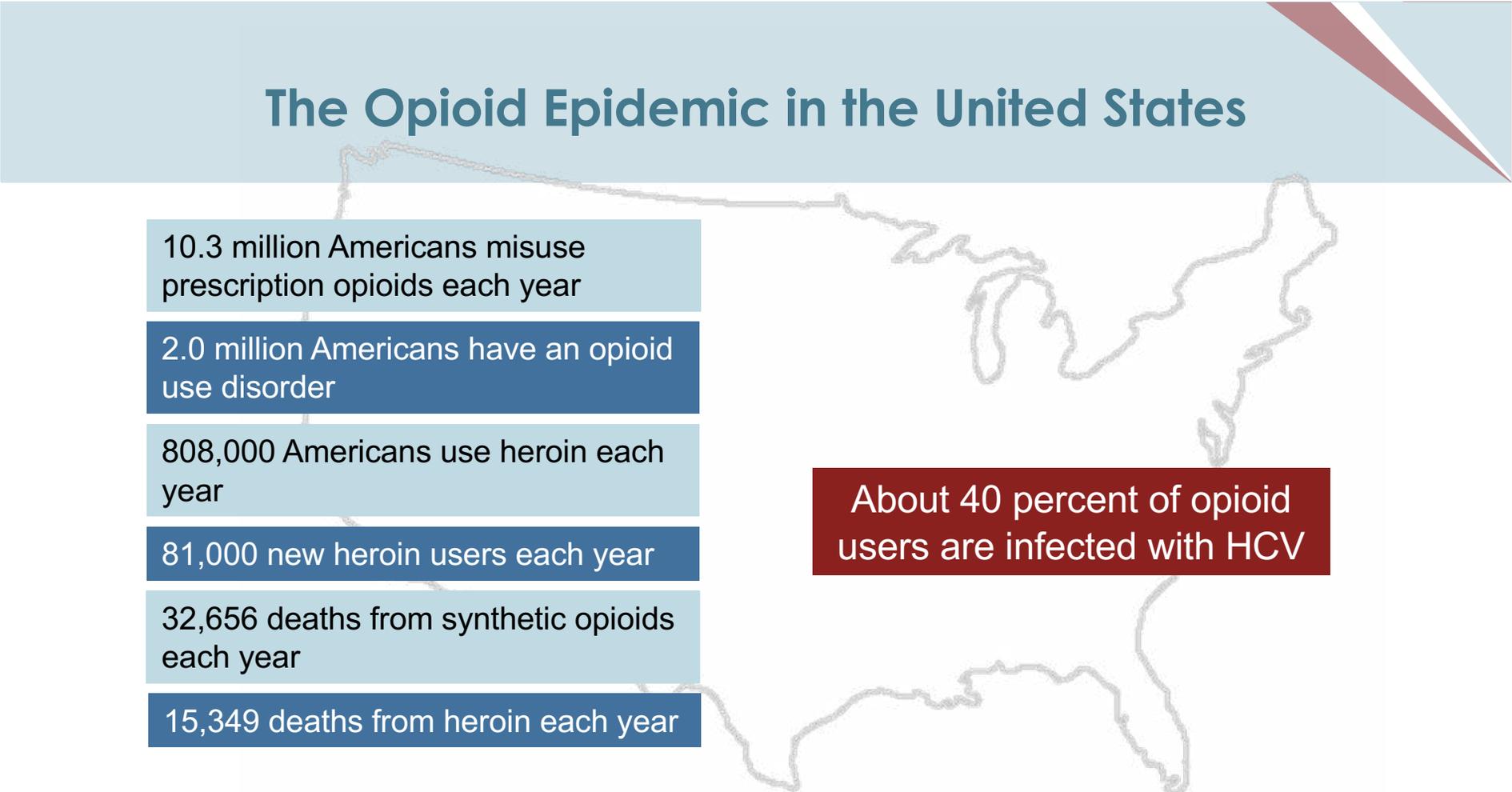
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The Opioid Epidemic in the United States



10.3 million Americans misuse prescription opioids each year

2.0 million Americans have an opioid use disorder

808,000 Americans use heroin each year

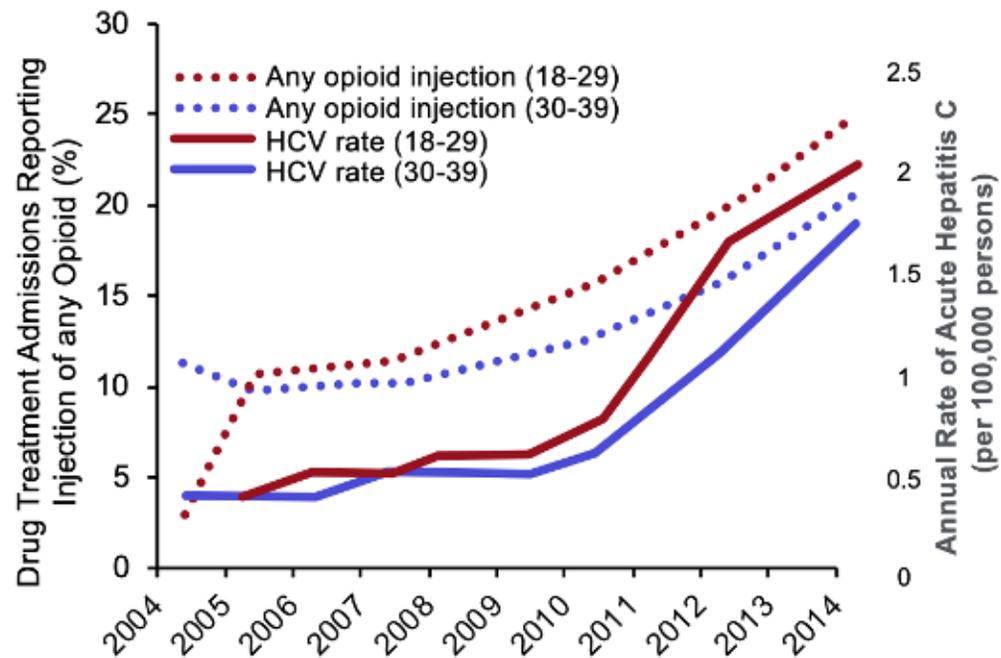
81,000 new heroin users each year

32,656 deaths from synthetic opioids each year

15,349 deaths from heroin each year

About 40 percent of opioid users are infected with HCV

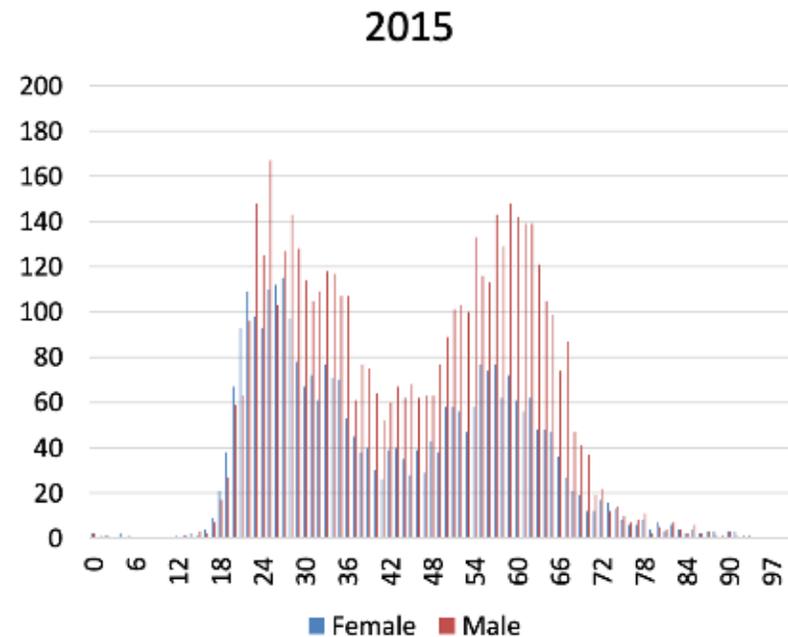
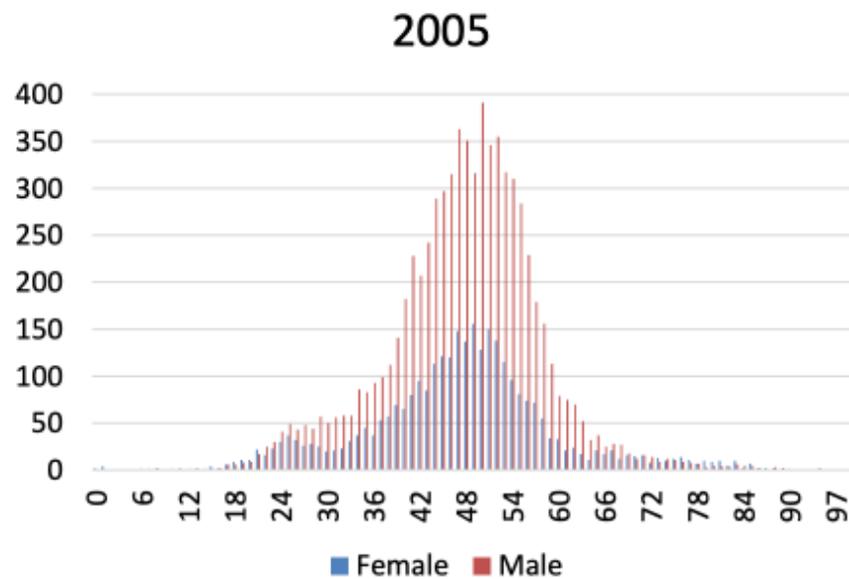
Rising Incidence of HCV in Youth in the U.S.



<https://www.cdc.gov/nchhstp/newsroom/2017/hepatitis-c-and-opioid-injection.html#Graphics>

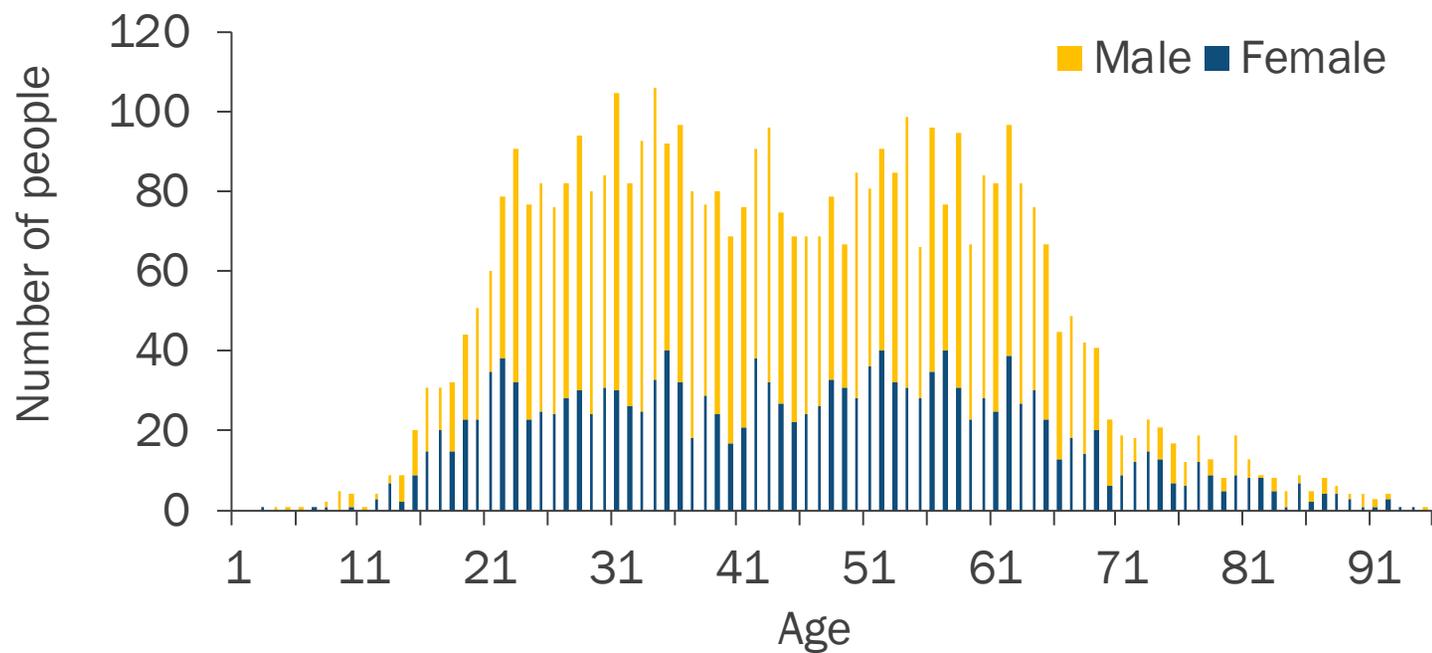
Rising Incidence of HCV in Youth: Newly Reported Cases by Age in NYS, 2005 and 2015

Reported cases of hepatitis C infection
in New York State (exclusive of NYC)



https://harmreduction.org/wp-content/uploads/2017/04/HepCure_Webinar_NYS_HCV_Elimination_final.pdf

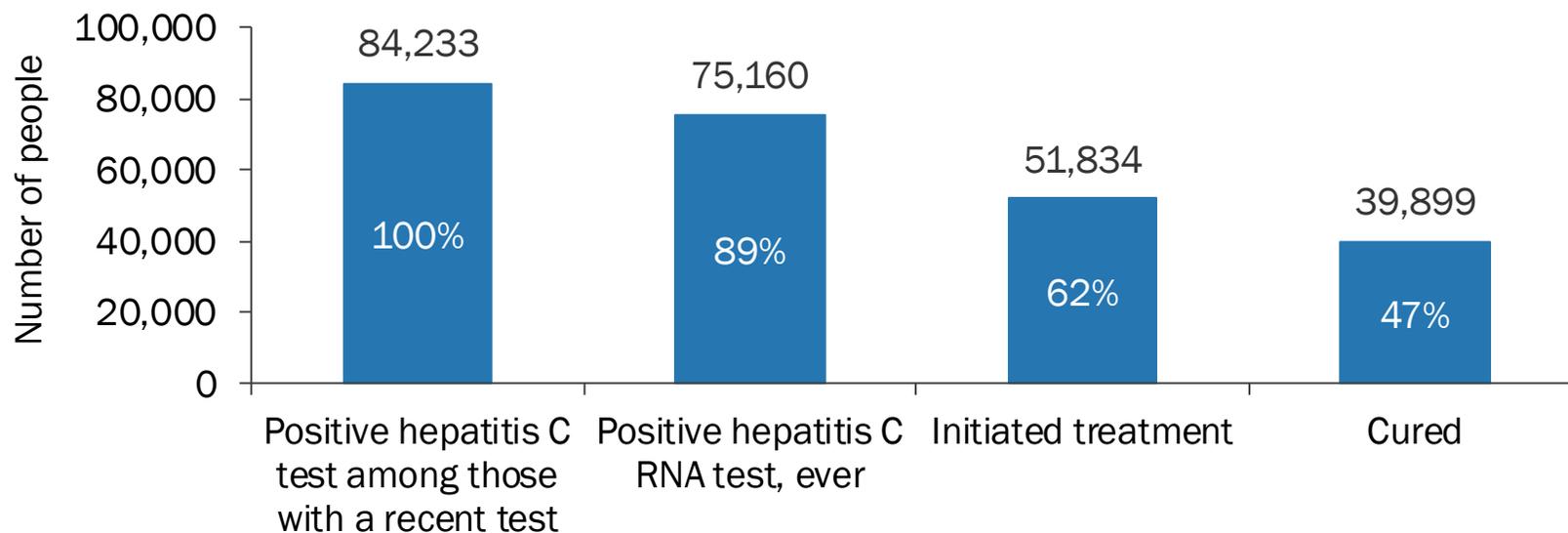
Number of Newly Reported HCV Cases in NYC By Age, 2019



Source: [NYC Health Department \(2020\)](#)

HCV Care Cascade in NYC, 2019

Care cascade for people in NYC with chronic hepatitis C recently reported (from July 1, 2014 to June 30, 2019) with a positive hepatitis C test, regardless of year of first report



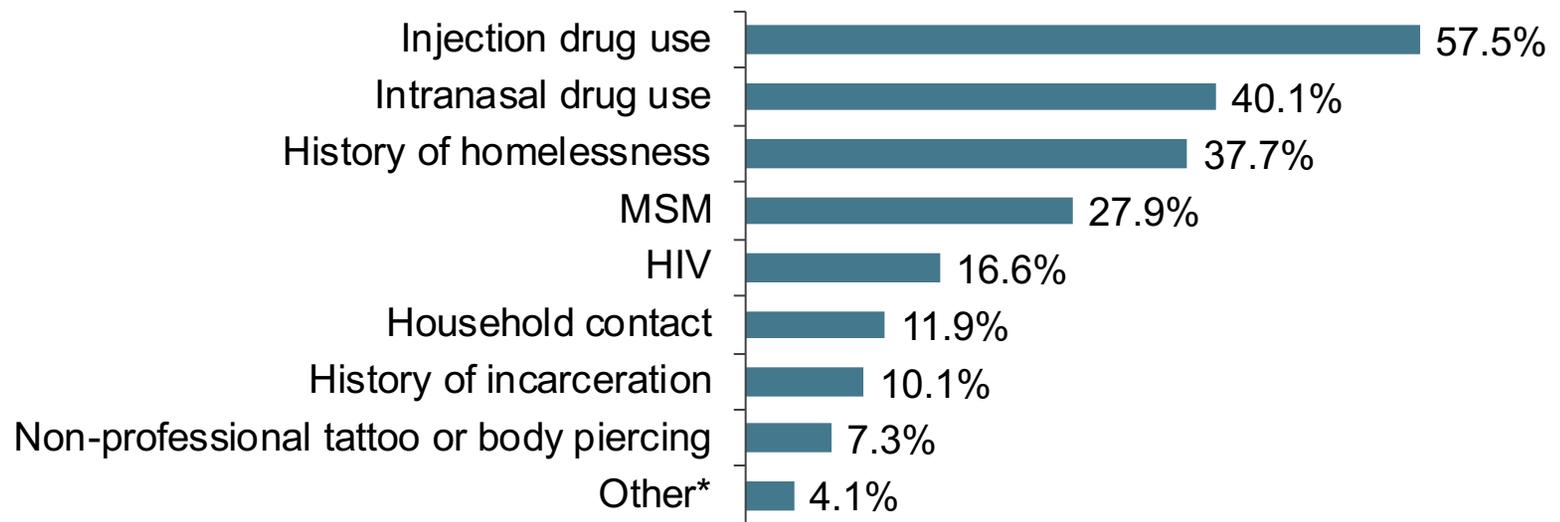
Source: [NYC Health Department \(2020\)](#)

Transmission of HCV

- Sharing supplies for injection or intranasal drug use
- Transfusion of blood/blood products prior to 1992
- Needle stick injury in health care
- Sharing personal care items (straight razors)
- Being born to a mother who has HCV
- Tattoos, body piercing in unlicensed setting
- Sex with an infected person (blood exposure)

HCV Risk Factors

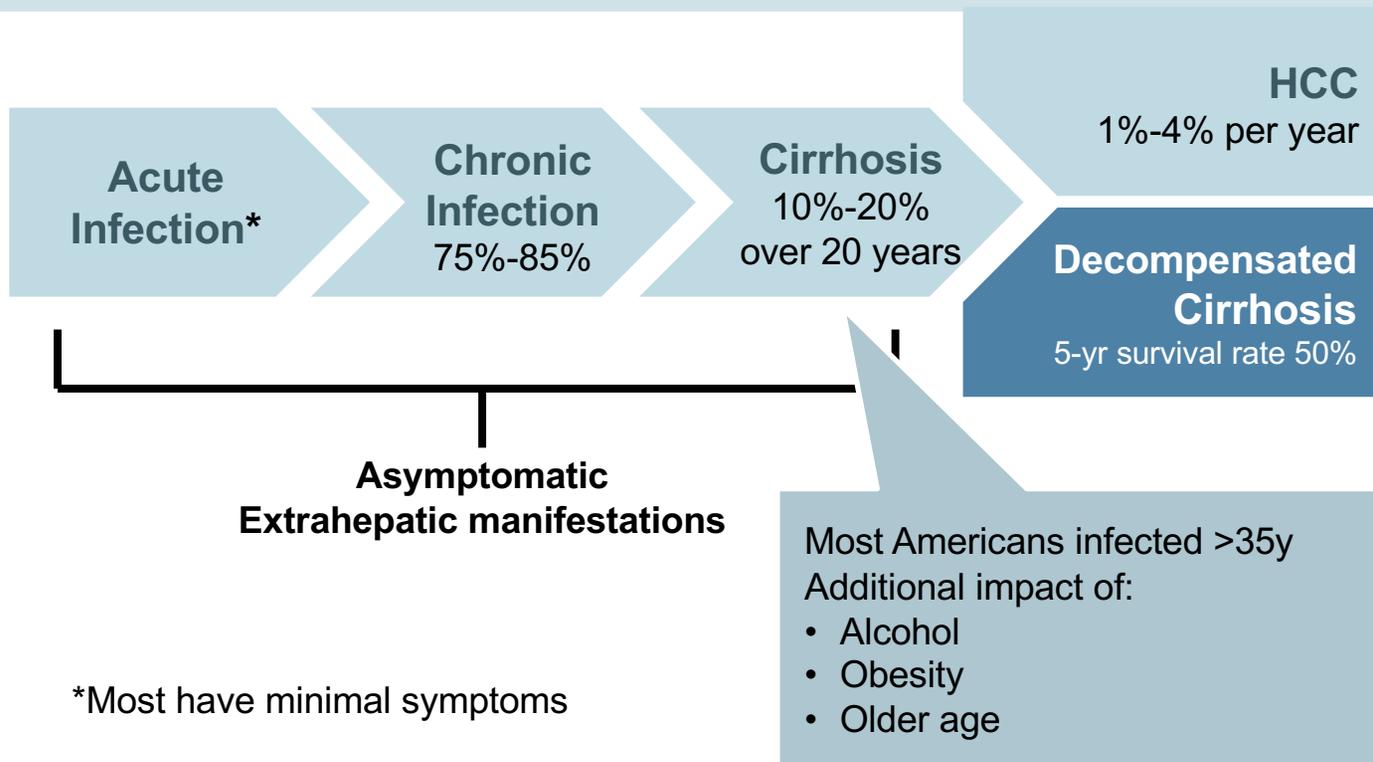
Risk factors (not mutually exclusive) for HCV infection of people ages 18–34 years newly reported with chronic HCV in NYC in 2019, interviewed through enhanced surveillance (n=496)



*Other includes: transfusion or transplant before 1992 or outside of the U.S.; employed in the medical or dental field; and received dialysis

Source: NYC Health Department (2020)

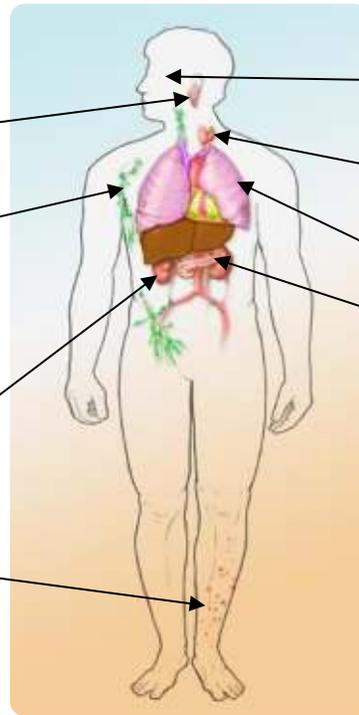
Natural History of HCV



Extrahepatic Manifestations of HCV

Strongly associated

- Mixed cryoglobulinemia
- Sjögren (sicca) syndrome
- Lymphoproliferative disorders
- Porphyria cutanea tarda
- Neuropathy
- Membranoproliferative glomerulonephritis
- Cryoglobulinemic vasculitis



Possibly associated

- Corneal ulcers (Mooren ulcers)
- Thyroid disease
- Lichen planus
- Pulmonary fibrosis
- Type 2 diabetes
- Systemic vasculitis (polyarteritis nodosa, microscopic polyangiitis)
- Arthralgias, myalgias, inflammatory polyarthritis
- Autoimmune thrombocytopenia

2020 CDC Recommendations HCV Screening Among Adults in the US



1. Universal Screening

Screen at least once in a lifetime for **all adults ≥ 18 years**
(except in settings where HCV RNA-positivity is $< 0.1\%$)



2. Pregnancy

Screening **all pregnant women during each pregnancy**
(except in settings where HCV RNA-positivity is $< 0.1\%$)



3. Exposure

One-time testing among people with recognized conditions or exposures
(more info on <https://www.cdc.gov/hepatitis/hcv/guidelinesc.htm>), regardless of age or setting prevalence



4. Periodic testing

Routine periodic testing for people with on-going risk factors

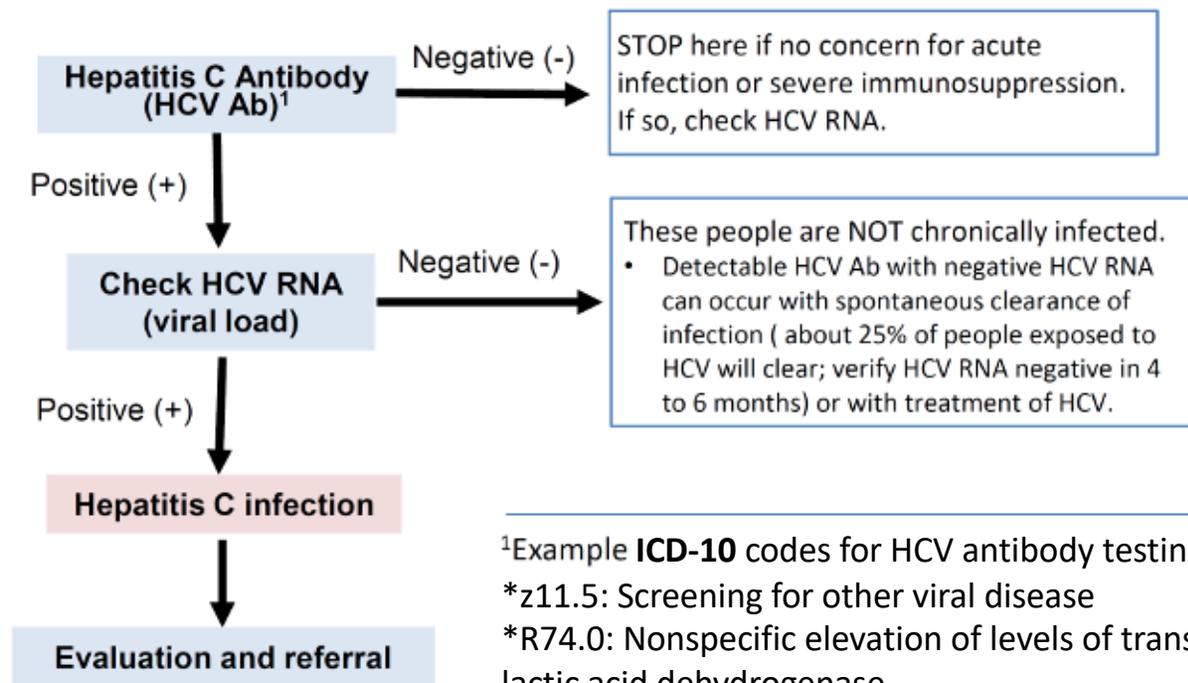
New York State HCV Testing Law (Effective January 1, 2014)

Hepatitis C Virus Testing (Chapter 425 of the Laws of 2013)

This law requires a **hepatitis C virus screening test** to be offered to all patients **born between 1945 and 1965** who are receiving health services as a hospital **inpatient or receiving primary care services** and applies to physician, physician assistant, or nurse practitioner.

The law further requires that the health care provider refer a patient who receives a **positive screening test** to another provider to **receive confirmatory testing and follow-up care**.

How Do You Diagnose HCV?



Medical Provider Responsibilities Diagnosing and Confirming HCV

Screen all adults 18-79 years, including pregnant women	<p>In March 2020, USPSTF expanded its recommendation for one-time HCV screening to include all asymptomatic adults ages 18-79 years, including pregnant women: https://jamanetwork.com/journals/jama/fullarticle/2762186</p>
Use HCV antibody with reflex to RNA testing	<p>Since 2017, NYC Health Code requires labs to automatically perform HCV RNA confirmatory test on all positive antibody test for HCV</p> <p>Since 2015, NYS Department of Health recommends reflex testing and provides resources for implementation: https://www.health.ny.gov/diseases/communicable/hepatitis/hepatitis_c/providers/reflex_testing.htm</p>

Recommendations For HCV Screening In Persons Less Than 18 Years Of Age

- One-time testing should be performed for all persons less than 18 years of age with behaviors, exposures or risk factors or circumstances associated with an increased risk of HCV exposure

Re-testing for Patients at Risk for HCV

- Periodic repeat HCV testing should be offered to all persons with behavioral, exposures or risk factors associated with HCV
- Annual HCV testing is recommended for all persons who inject drugs and for HIV-infected men who have unprotected sex with men

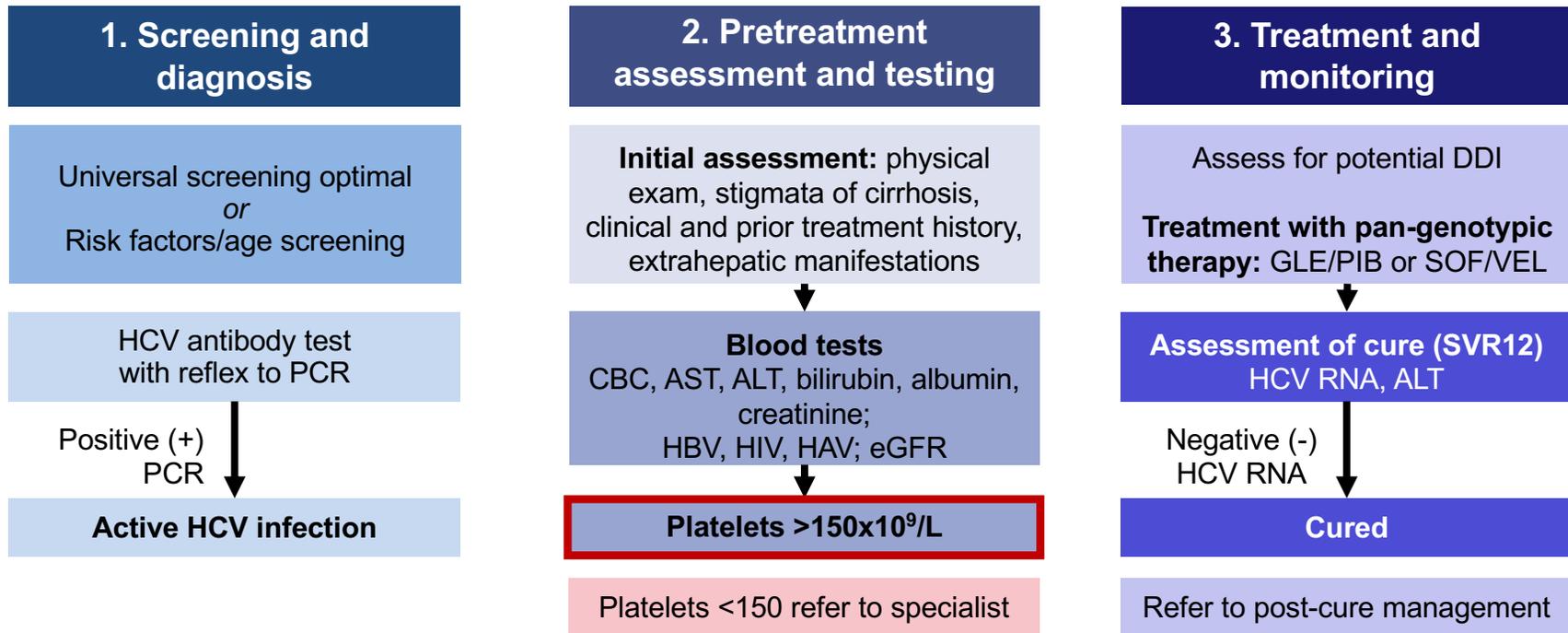
Case Study

- 48 year old man with history of IVDU
- Asymptomatic
- Takes milk thistle, St Johns wort
- ALT 45, AST 65, platelet count 100,000
- HCV RNA 655,000
- Genotype 1a
- Fibroscan 23 kPa (F4)



Pre-Therapy Assessment

Simplified Algorithm for Management of HCV Infection



Acute HCV: Interpretation of Tests

Test	Interpretation
HCV Ab	<ul style="list-style-type: none">• Test may be negative during first 6 weeks after exposure• Seroconversion may be delayed or absent in immunosuppressed individuals• Presence of HCV Ab alone does not distinguish between acute and chronic infection
HCV RNA	<ul style="list-style-type: none">• Viral fluctuations $> 1 \log_{10}$ IU/ml may indicate acute HCV infection• HCV RNA may be transiently negative during acute HCV infection• Presence of HCV RNA alone does not distinguish between acute and chronic infection
ALT	<ul style="list-style-type: none">• Fluctuating ALT peaks suggests acute infection• ALT may be normal during acute HCV infection• ALT may be elevated due to other liver insults, such as ETOH use

HCV Provider Responsibilities

Obtain Basic Blood Tests

- **CBC, platelets**
- **Comprehensive metabolic profile**
 - Renal function
 - Liver chemistries
 - Albumin
 - Total bilirubin
 - Alkaline phosphatase
 - Aspartate aminotransferase
 - Alanine aminotransferase
- **INR**
- **Viral studies**
 - HIV Ab
 - HAV Ab (total, not IgM!)
 - HBcAb (total, not IgM!)
 - HBsAg
 - HBsAb (quantitative)

HCV Provider Responsibilities

Evaluate for Coexisting Liver Disease

History

- Heart disease
- Diabetes, obesity → NAFLD
- Alcohol abuse → alcoholic liver disease
- Family history of autoimmunity
 - Autoimmune hepatitis
 - Primary biliary cholangitis
 - Primary sclerosing cholangitis
- Family history of liver disease
 - Hereditary hemochromatosis
 - Alpha-1 antitrypsin deficiency

Labs

- Antinuclear antibody (ANA)
- Antismooth muscle antibody (ASMA)
- Anti mitochondrial Ab (AMA)
- Fe / TIBC / Ferritin
- [Ceruloplasmin]
- [Alpha-1 antitrypsin level & phenotype]
- Alpha fetoprotein

Imaging

- Ultrasound

Pre-Therapy Assessment: Drug-Drug Interactions

- **Very important element in pre-therapy assessment**
- List of prohibited drugs is relatively short
 - Varies depending on regimen chosen
- List of “potential interaction” drugs is longer
- Be alert for interactions with common drugs
 - Statins, proton pump inhibitors, birth control, amiodarone, digoxin
- No herbs! In particular, no St. John’s Wort
- Use online tools to help assess DDI’s

Patients rarely tell you all the pills they are taking!

Assess for Potential Drug-Drug Interactions

	SOF/VEL	GLE/PIB
Key DDI	anticonvulsants, rifampicin, efavirenz, St. John's wort	
	<ul style="list-style-type: none"> ▪ amiodarone ▪ proton pump inhibitors ▪ statins 	<ul style="list-style-type: none"> ▪ dabigatran ▪ ethinyl estradiol-containing contraceptives ▪ atazanavir ▪ darunavir ▪ ritonavir ▪ statins ▪ cyclosporine
Common drugs without interactions	ARBs, methadone, buprenorphine, calcium channel blockers, lamotrigine, omeprazole, progestin-only contraceptives	

HCPs should consult prescribing information, their local pharmacist and/or online tools (eg, HEP Drug Interactions; <http://www.hep-druginteractions.org>) to confirm interaction or lack of interaction for specific drugs within a class, as exceptions may exist.

HIV/HCV Co-infection: Drug-Drug Interactions

- Need to assess carefully:
 - www.hcvguidelines.org
 - www.aidsinfo.nih.gov
 - www.hep-druginteractions.org
- If antiretroviral switch needed, should be done in collaboration with HIV practitioner

Importance of Assessing Fibrosis

- Patients with bridging fibrosis (stage 3 fibrosis) or cirrhosis (stage 4 Fibrosis) need additional screening:
 - Esophageal Varices
 - Hepatocellular carcinoma
- Allows for selection of proper treatment plan and duration of therapy
 - Protease inhibitors should NOT be used in patients with Child Class B or C cirrhosis.

Methods for Staging Fibrosis

Method	Procedure	Advantages	Disadvantages
Indirect serum markers	APRI, FIB-4*	Noninvasive; inexpensive	Limited ability to differentiate intermediate stages of fibrosis
Direct markers	FibroSure, FibroTest, FibroMeter, FIBROSpect II, and HepaScore	Noninvasive; easily accessible	Limited ability to differentiate intermediate stages of fibrosis
VCTE	Shear wave velocity	Noninvasive; assesses large volume of liver parenchyma	May be difficult to interpret in F2 and F3 liver disease; limited availability
Liver biopsy (rarely used)	Pathologic examination	Diagnostic standard; diagnoses concurrent liver disease	Invasive procedure; costly; sampling error

*See Hepatitis C online for the following: [APRI Calculator](#) and [FIB-4 Calculator](#)

Non-invasive Formulae to Assess Fibrosis

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

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count (10}^9\text{/L)} \times \sqrt{\text{ALT (U/L)}}} = \text{[]}$$

Non-invasive Formulae to Assess Fibrosis

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

Aspartate aminotransferase-to-platelet ratio index (APRI)

< 0.5%	Low risk of advanced fibrosis (F3-F4)
Between 0.5 and 1.5	Intermediate risk of advanced fibrosis
> 1.5%	High risk of advanced fibrosis

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

Fibrosis-4 Index (FIB-4)

< 1.45	Low risk of advanced fibrosis (F3-F4)
Between 1.45 and 3.25	Intermediate risk of advanced fibrosis
> 3.25	High risk of advanced fibrosis

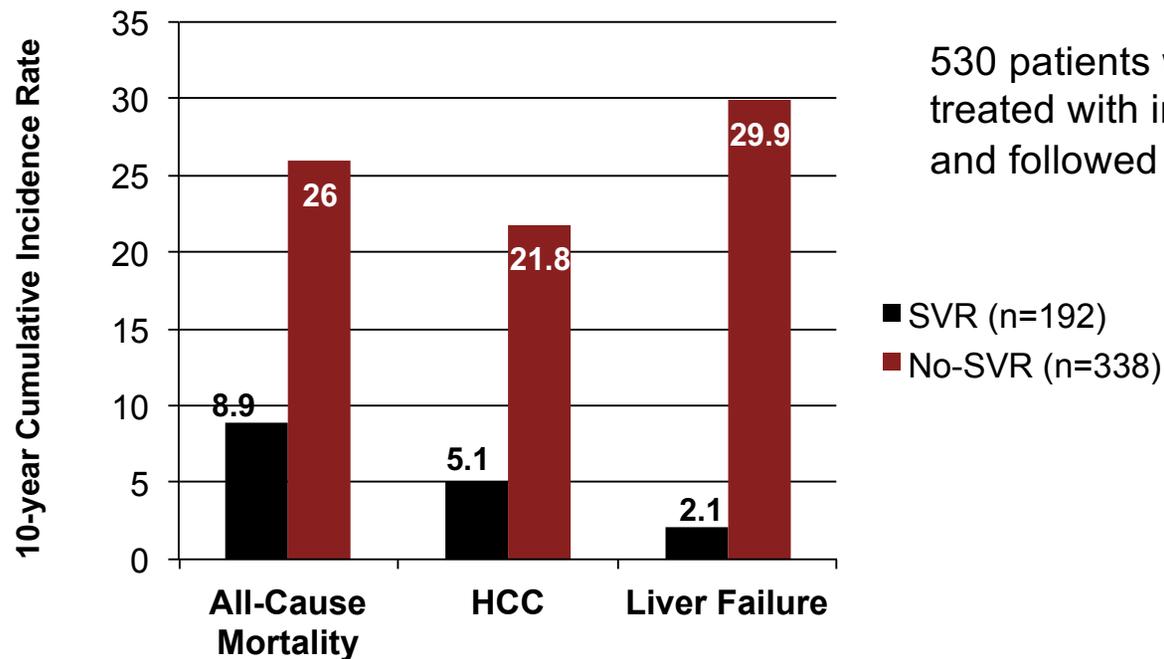


Treatment of HCV with Direct Acting Antivirals

Goals of Treatment for HCV

- Goal is sustained viral response (SVR) = cure
 - Undetectable virus at least 12 weeks after cessation of anti-viral therapy
- Treatment selection generally dictated by genotype but pangenotypic options are now available
- HCV SVR rates = HCV/HIV SVR rates

SVR (Cure) Associated with Decreased All-Cause Mortality



The New World of HCV Therapy

- Interferon-free therapy is here
 - Direct acting antivirals (DAAs) treatment are the standard of care
- Cure is an almost certain outcome

Patient assessment prior to therapy is important

Patients with HCV Viremia Should Be Considered Treatment Candidates

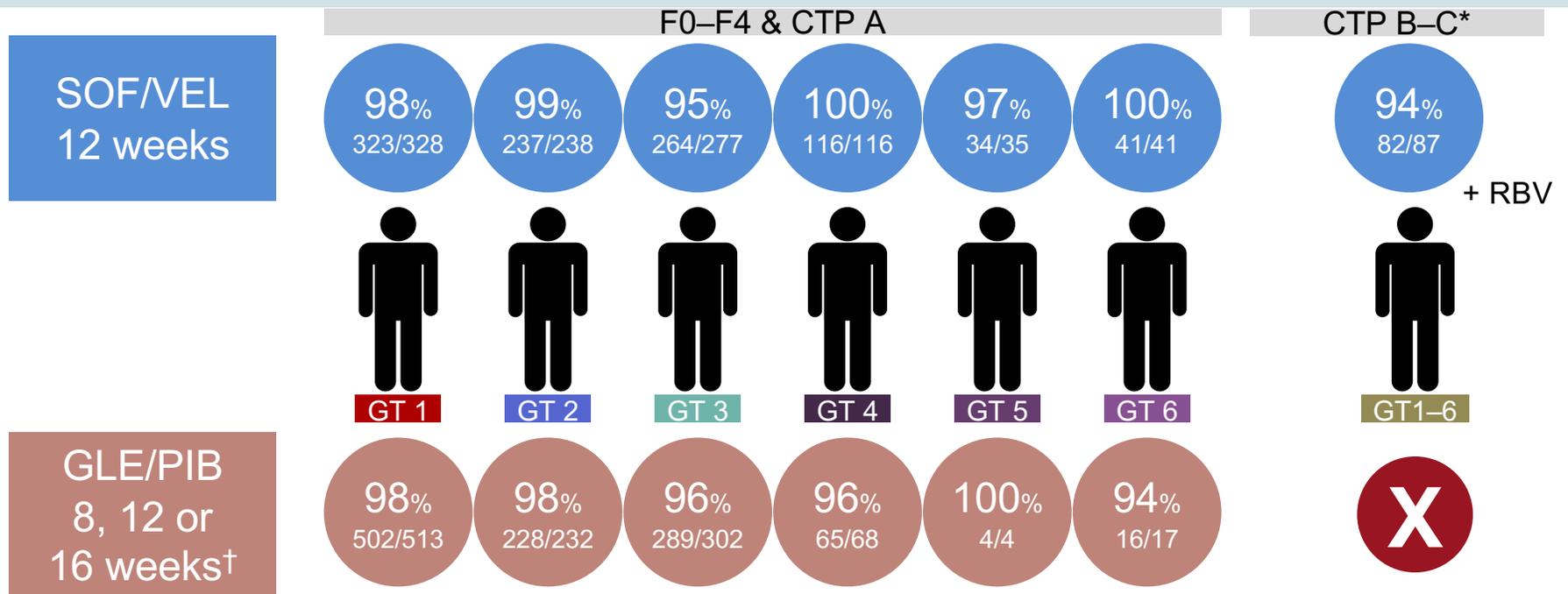
AASLD-IDSA AND NYS DOH TREATMENT GUIDELINES:

All patients with chronic HCV infection, regardless of fibrosis stage, are considered candidates for antiviral therapy

HCVGuidelines.org

http://www.hivguidelines.org/hcv-infection/treatment-with-daa/#tab_0,

High SVR Rates Achieved Across Patient Types



Agarwal K, et al. ILC 2016 Poster #SAT-195; Gane E, et al. AASLD 2017; Oral #74; Puoti M, et al. ILC 2017 Poster #SAT-233; AbbVie Corporation. MAVIRET (glecaprevir/pibrentasvir) Product Monograph, August 2017; Gilead Sciences Canada Inc. EPCLUSA (sofosbuvir/velpatasvir) Product Monograph, April 2018

*Safety and efficacy of SOF/VEL has not been assessed in patients with CTP class C cirrhosis; †As approved in the Canadian Product Monograph. These are not head-to-head studies and direct comparisons cannot be made; CTP: Child-Turcotte-Pugh; GLE/PIB: glecaprevir/pibrentasvir; GT: genotype; RBV: ribavirin; SOF/VEL: sofosbuvir/velpatasvir;

Classes of Medications Used for Treatment

NS3-4A Protease Inhibitors (“previr”)**	NS5A Inhibitors (“asvir”)	NS5B Inhibitors: (“buvir”)	Other
Glecaprevir	Ledipasvir	Sofosbuvir	Ribavirin
Grazoprevir	Pibrentasvir		
Voxilaprevir	Velpatasvir		

** cannot use in decompensated disease

Combination Therapies

Combination Therapies		Trade Name	GFR < 30	Decompensated Cirrhosis
Glecaprevir/Pibrentasvir	GLE/PIB	Mavyret®	Yes	No
Ledipasvir/Sofosbuvir	LDV/SOF	Harvoni®	Yes	Yes
Sofosbuvir/Velpatasvir	SOF/VEL	Epclusa®	Yes	Yes
Sofosbuvir/Velpatasvir/ Voxilaprevir	SOF/VEL/VOX	Vosevi®	Yes	No

Bold = protease inhibitor

Test for HBV Before Initiating HCV DAA Therapy



ESAL: Patients commencing DAA-based treatment for hepatitis C should be tested for HBs antigen, anti-HBc antibodies and anti-HBs antibodies (B1)



AASLD: All patients initiating HCV DAA therapy should be assessed for HBV coinfection with HBsAg, anti-HBs, and anti-HBc (B1)

		Anti-HBc test result	
		Negative	Positive
HBsAg test result	Negative	No risk of HBV reactivation	Very low risk of HBV reactivation
	Positive		Moderate risk of HBV reactivation (depending on HBV DNA)

Monitoring During DAA Therapy: Hepatitis B Reactivation Risk

- In patients who are hepatitis B virus (HBV) surface antigen (**HBsAg**) **positive and have no detectable HBV DNA**:
 - **Monitor for HBV reactivation** by performing aspartate aminotransferase (AST), ALT, and HBV DNA tests every 4 weeks during HCV treatment.
- In patients who are **HBsAg positive and detectable HBV DNA**:
 - Monitor or treat as clinically indicated
- Clinicians new to HCV treatment should consult an [experienced HCV care provider](#) for further evaluation of patients who develop detectable HBV DNA.

Monitoring During DAA Therapy: Pregnancy

If a woman becomes pregnant during therapy with any DAA regimen...



the clinician should discuss with her the benefits and risks of using DAAs during pregnancy.



Special Considerations

Consult With An Expert

- Treatment of decompensated cirrhosis
- Treatment of renal disease
- HIV/HCV coinfection
- Active alcohol / drug use
- Monitoring for hepatocellular carcinoma after SVR in patients with bridging fibrosis or cirrhosis

HIV/HCV Co-infection Treatment

- HIV/HCV co-infected persons should be treated the same as persons without HIV infection
- Treatment courses
 - 12 weeks of pangenotypic therapy
 - Gelcaprevir/Pibrentasvir (GLE/PIB)
 - Sofosbuvir/Velpatasvir (SOF/VEL)

Substance Use and HCV Treatment

- Do NOT withhold HCV treatment solely due to current drug/alcohol use
- Offer suboxone
- Refer to methadone clinics
- Write a prescription for syringes
 - Refer to syringe exchanges (for new cookers, cotton, etc)
- Provide naloxone kit or prescription for naloxone
- Assess for alcohol use and encourage cessation/reduction
- Discuss harm reduction and reinfection
- Treat sexual or drug-using partner together

HCV and Hepatocellular Carcinoma (HCC)

- SVR decreases risk of HCC development but does not eliminate risk
- All HCV patients with bridging fibrosis and cirrhosis need HCC screening, even after SVR
- Recommended HCC screening:
 - Hepatic imaging every 6 months
 - AFP

Removal of HCV Medication Prior Authorization

- As of July 23rd the NYS Medicaid Drug Utilization Review Board (DURB) unanimously voted to recommend removal of prior authorizations for patients awaiting their first HCV DAA treatment for NYS Medicaid Managed Care plans.

Contact Empire Liver Foundation if interested in learning more on how to advocate for removal of Prior Authorizations for Medicare & commercial insurance plans.

Summary

- HCV is curable with readily available combination therapies
- Elimination will require a multifactorial approach to diagnose, link to care, treat and cure HCV
 - To eliminate HCV, we need to broaden our treater base
- The **Simplified Algorithm** provides a roadmap for non-specialists to treat
- Costs of treatments have come down drastically
- Risk of HCC in cured patients with cirrhosis is decreased but patients still need to be screened for life
- The biggest issue now is getting people tested and treated
- Patients with advanced disease should be referred to a liver specialist