HEPATITIS C CLINICAL TRAINING

Hepatitis C Treatment

Sonal Kumar, MD, MPH
Assistant Professor of Medicine
Director of Clinical Hepatology
Weill Cornell Medicine

Empire Liver
FOUNDATION

Training Development and Funding

- This training is designed in collaboration with the NYC Department of Health and Mental Hygiene (DOHMH)

- This training is funded by the NYC City Council

Housekeeping Notes

Have a question for the presenter

- Type the question into the chat box and Meg will read them aloud to the presenter at the end

Claiming CE

- After the training, you will receive an e-mail with instructions, the course number, and the access code
- CE certificate can be printed or stored in your account
- Questions about CEs, contact Joycambe@empireliverfoundation.org

For Additional Information

- Visit https://empireliverfoundation.org/about-us/cme-accreditation/

Disclosures

- Gilead

Learning Objectives

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

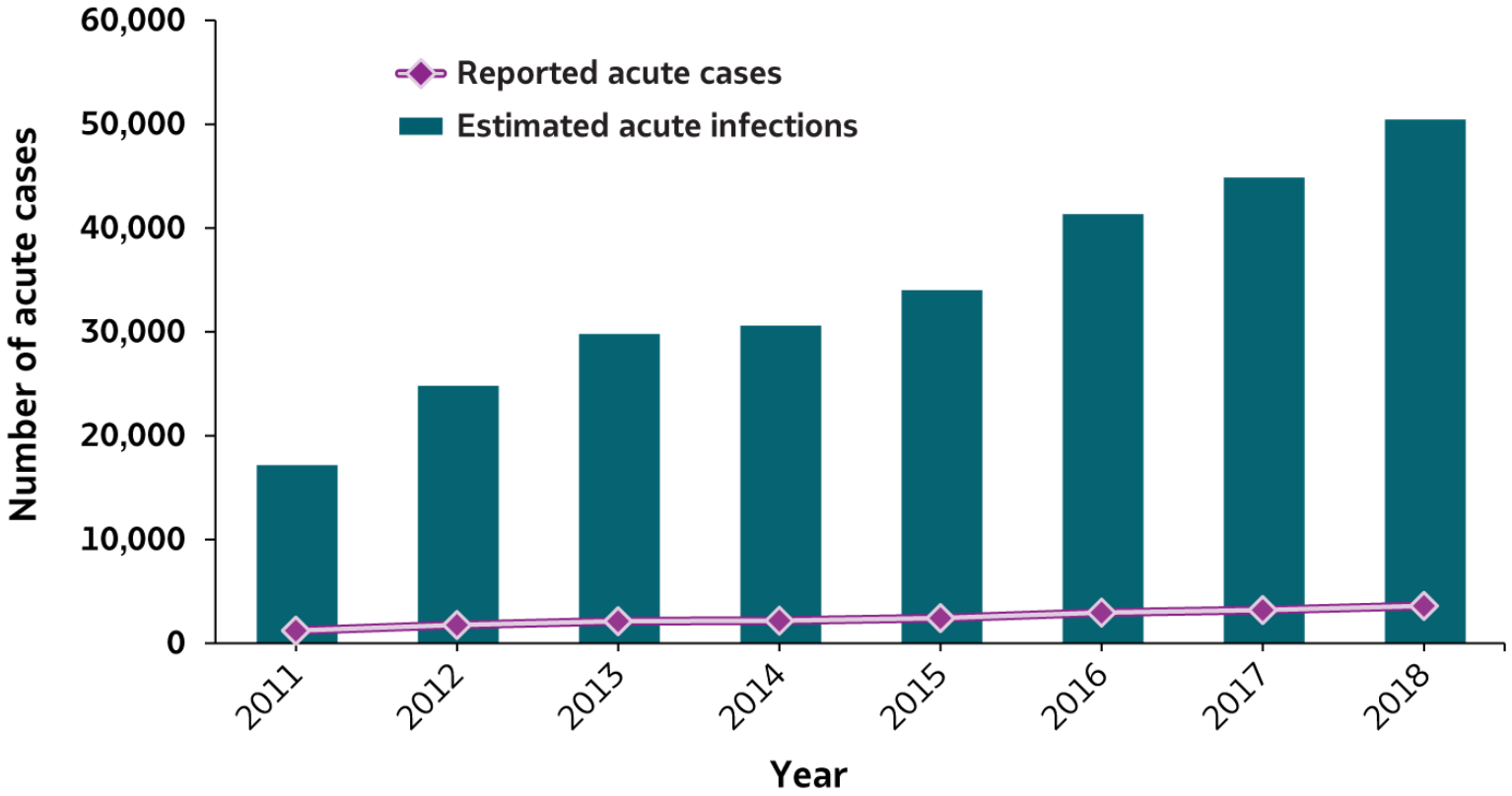
- Identify patients appropriate for hepatitis C (HCV) screening
- Recall the simplified algorithm for assessing patients for and initiating HCV therapy
- Assess patient's risk for HBV reactivation
- Explain the role of fibrosis testing in HCV treatment
- Recognize potential drug-drug interactions of HCV therapies

Case Study 1

- 46 year-old African-American female diagnosed with HCV two months ago
  - Complains of fatigue
  - PMH: Hypertension
  - Has a history of intravenous drug use; last used 10 years ago
  - ALT 45, AST 56, total bilirubin 1.1, platelet count 165,000
  - HCV RNA 6,680,056, genotype 1a
  - Transient elastography with F2, S2

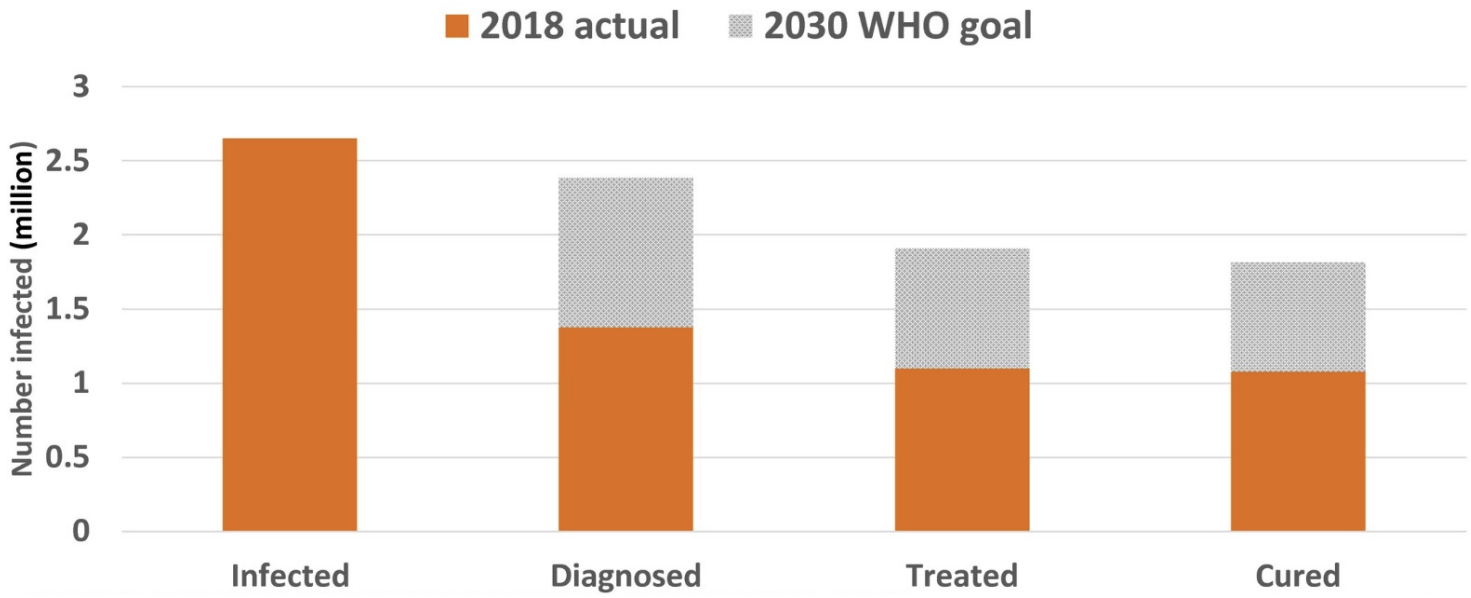
Think about what you would do next. We will review at end of presentation.

Number of Reported Acute Hepatitis C Cases and Estimated Infections* — United States, 2011–2018



Source: CDC, National Notifiable Diseases Surveillance System.

US HCV Treatment Cascade, 2018

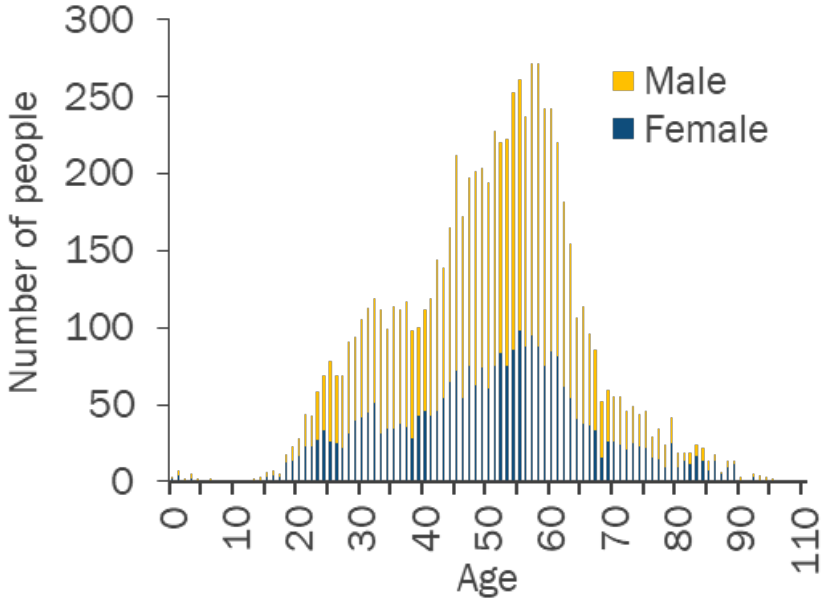


By the end of 2018, it has been estimated there were 2.71 million persons with ongoing HCV infection; 50% to 60% were aware of their infection, whereas 1.58 million had already been cured.

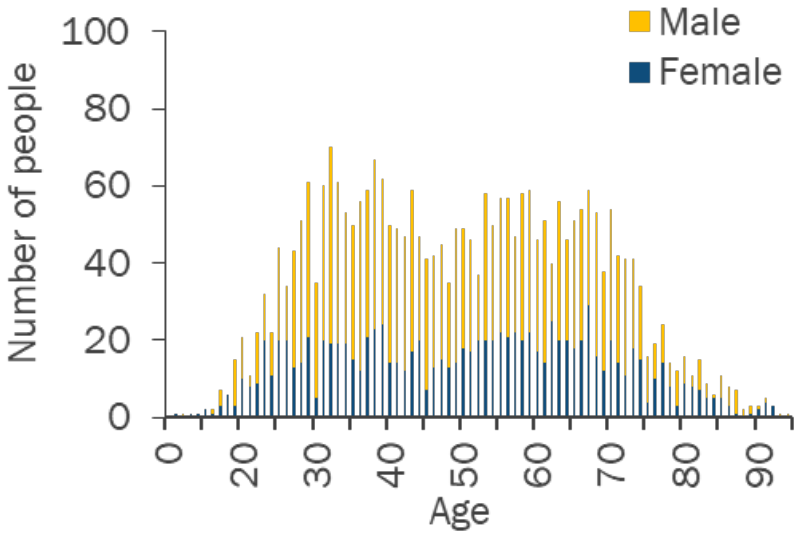
Source: Thomas, 2020. https://aasldpubs.onlinelibrary.wiley.com/doi/10.1002/cld.915

Newly Reported Chronic HCV Age Distribution in New York City, 2011 and 2021

2011

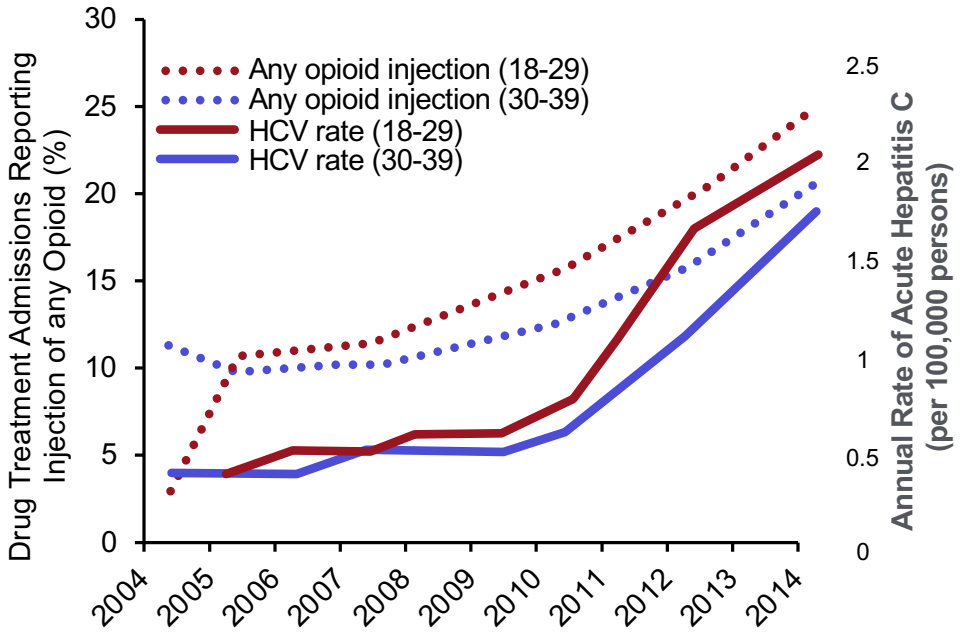


2021



NYC Health Department, 2022.

From 2004-2014, HCV and Opioid Injection Drug Use Increased Significantly Among People Aged 18-39 Years[1,2]



Among people aged 18-29 years[1]:

622% Admission for opioid injection

400% Rate of acute HCV

Among people aged 30-39 years[1]:

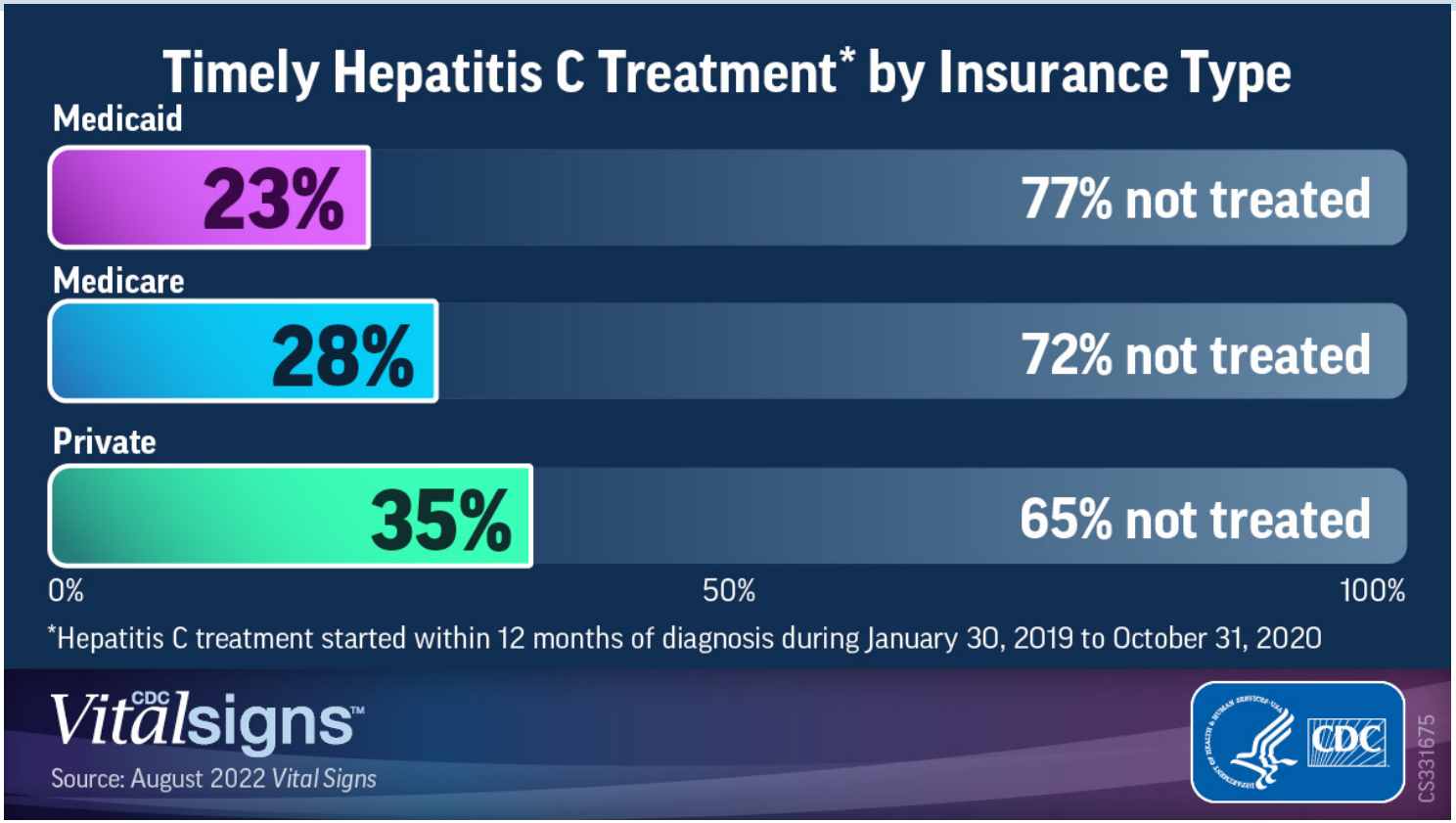
83% Admission for opioid injection

325% Rate of acute HCV

The national increase in acute HCV infection is associated with the nation's opioid epidemic.[1]

CDC, Centers for Disease Control and Prevention.
1. Zibbell JE, et al. *Am J Public Health*. 2018;108(2):175-181. 2. CDC. https://www.cdc.gov/nchhstp/newsroom/2017/hepatitis-c-and-opioid-injection-press-release.html. December 21, 2017. Accessed August 9, 2019.

Less Than 1/3 People With HCV Are Treated In First Year of Diagnosis



CDC, 2022. https://www.cdc.gov/nchhstp/newsroom/2022/2022-Hep-C-Vital-Signs.html

More People Need to Be Treated to Achieve HCV Elimination

- Minimum annual number of people in the U.S. who should be treated annually to achieve HCV elimination:

  260,000

- Average annual number of people in the U.S. treated for HCV (2014-2020):

  120,000

CDC, 2022. https://www.cdc.gov/nchhstp/newsroom/2021/2014-2020-hepatitis-c-treatment-estimates.html

HCV Screening Recommendations

Summary: 2020 HCV Screening Recommendations

	Adults	Under 18 years
One-time HCV screening	• All adults 18 to 79 years of age • All pregnant women during each pregnancy (CDC, USPSTF)	• All children born to women infected with HCV • People under 18 with HCV risk factors (AASLD, IDSA, IAS-USA)
Repeat HCV testing (e.g. annual)	Adults with HCV risk factors, including: • People with a history of or active injection drug use • HIV-positive men who have unprotected sex with men (CDC, USPSTF, AASLD, IDSA, IAS-USA)	

HCV Treatment Progress

1975 1980 1985 1990 1995 2000 2005 2010 2015 2020

1975: Description of non-A, non-B hepatitis

1989: HCV identified

1993: HCV genome delineation

1996: 3D structure of HCV enzymes: HCV protease

1997: Infectious clone of HCV constructed

1999: Replicon system established

2005: Recombinant infectious HCV

1998: Interferon (IFN) + ribavirin (RBV)

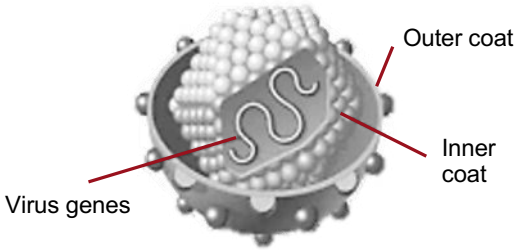
2001: Pegylated interferon (PEG-IFN) + RBV

2003: Protease inhibitors (PIs) developed

2011: First all-oral direct-acting antiviral (DAA) data presented

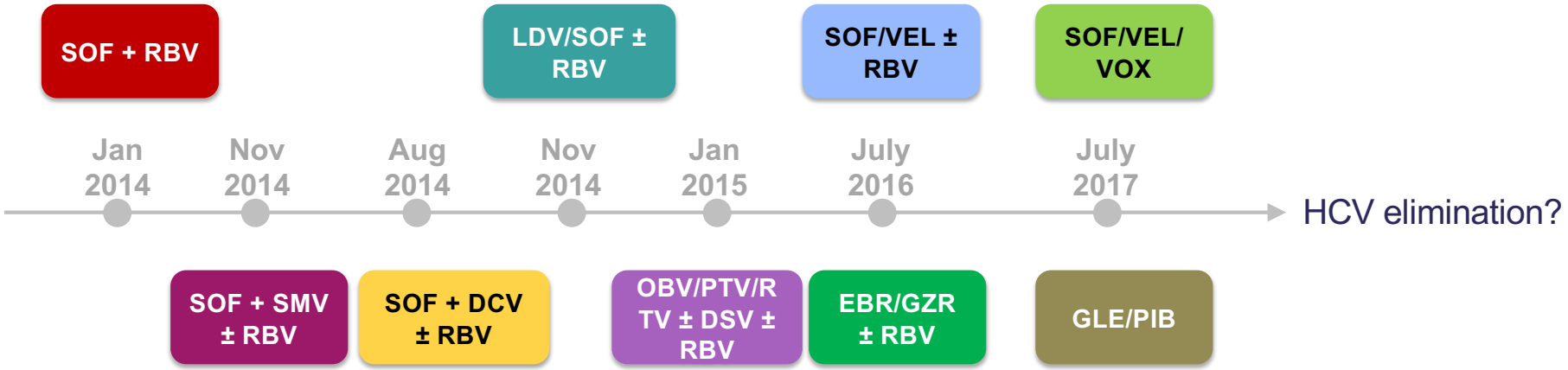
2014: Launch of first all-oral DAA regimen

Hepatitis C virus



Adapted from Sahoo SS. Epidemiology of hepatitis B and C. Available at: https://www.slideshare.net/drswaroopsoumya/epidemiology-of-hepatitis-b-and-c (accessed June 2018);
Yau AHL, Yoshida EM. Can J Gastroenterol Hepatol 2014;288:445–51;
Seifert LL, et al. World J Hepatol 2015;7:2829–33

Rapid Therapeutic Advances In HCV



Gilead Sciences Ltd. SOVALDI▼ (sofosbuvir), SmPC, September 2017; WHO. Patent situation of key products for treatment of hepatitis C: Simeprevir Working Paper; June 2016; Bristol-Myers Squibb Pharmaceuticals Ltd. DAKLINZA▼ (daclatasvir), SmPC, January 2018; Gilead Sciences Ltd. HARVONI▼ (ledipasvir/sofosbuvir), SmPC, December 2017; AbbVie Ltd. VIEKIRAX▼ (ombitasvir//paritaprevir/ritonavir), SmPC, January 2018; Gilead Sciences Ltd. EPCLUSA▼ (sofosbuvir/velpatasvir), SmPC, March 2018; Merck Sharp & Dohme Ltd. ZEPATIER▼ (elbasvir/grazoprevir), SmPC, July 2017; Gilead Sciences Ltd. VOSEVI▼ (sofosbuvir/velpatasvir/voxilaprevir), SmPC, August 2017; AbbVie Ltd. MAVIRET▼ (glecaprevir/pibrentasvir), SmPC, May 2018

Not all regimens are approved in all patient populations and/or in all countries. Please refer to your local country authorisation. The addition of RBV is recommended in some patient populations; HCPs should refer to the respective SmPCs.

DCV: daclatasvir; DSV: dasabuvir; EBR: elbasvir; GLE: glecaprevir; GZR: grazoprevir; HCP: healthcare professional; LDV: ledipasvir; OBV: ombitasvir; PIB: pibrentasvir; PTV: paritaprevir; RTV: ritonavir; SMV: simeprevir; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir

A Simplified Algorithm for Management of HCV Infection

Simplified Algorithm: Background

- WHO objective: HCV elimination by 2030
- Treatment access limited by availability of specialists
- Current guidelines are comprehensive and most appropriate for experienced treaters, but non-specialists may consider them too complex
- A simplified treatment algorithm targeting non-traditional HCV treaters to drive HCV elimination is needed

HCVGuidelines.org:
Treatment is recommended for **ALL** patients with chronic HCV infection

Dieterich *et al*, Gastroenterology & Hepatology; volume 15, issue 5, supplement 3, May 2019
HCV guidance: recommendations for testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org/ (accessed March 2020)

Test for HBV Before Initiating HCV Direct-Acting Antiviral (DAA) Therapy

EASL: 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)

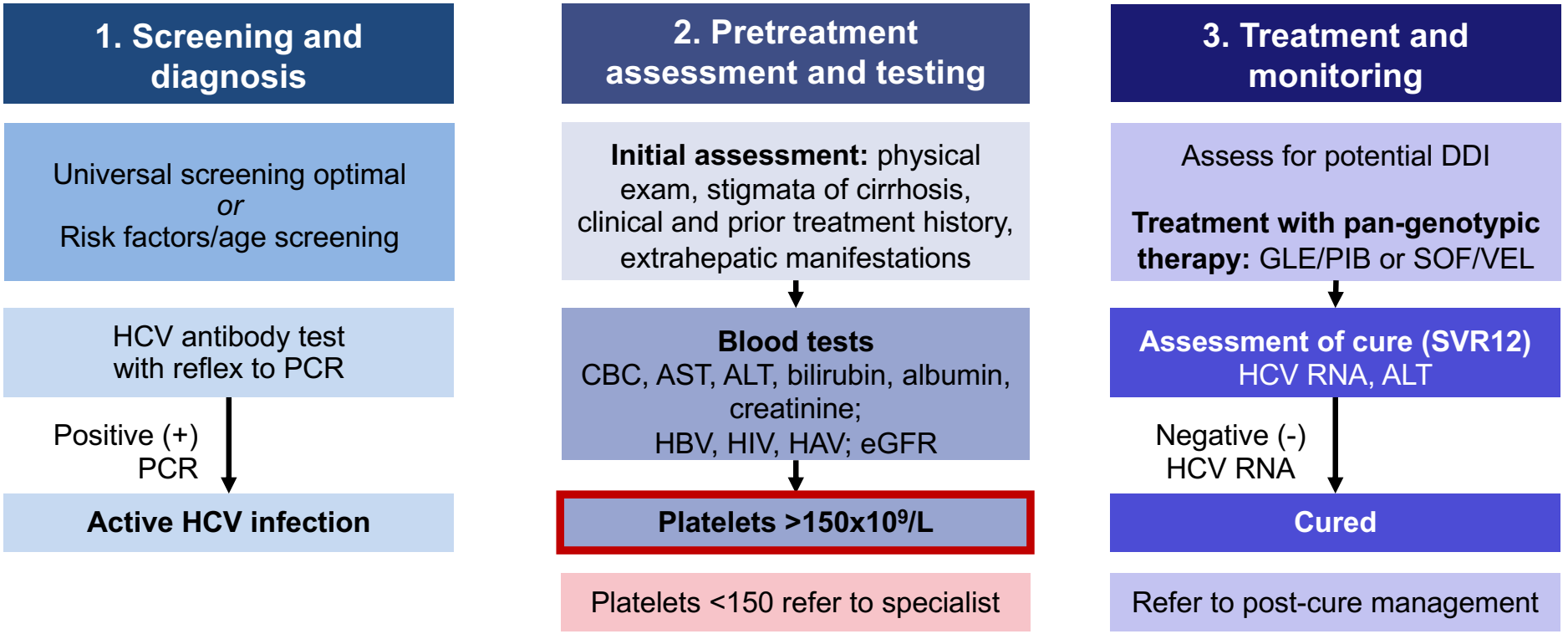
		Anti-HBc test result	
		Negative	**Positive**
HBsAg test result	**Negative**	No risk of HBV reactivation	Very low risk of HBV reactivation
	Positive		Moderate risk of HBV reactivation (depending on HBV DNA)

Boxed Warning: Risk Of HBV Reactivation with DAA Use in HCV/HBV Coinfected Patients[1]

1. **Test all patients for HBV** before initiating treatment with any HCV DAA therapy
   - HBV reactivation has been reported in HCV/HBV coinfected patients undergoing or completed HCV DAA treatment and not receiving HBV antiviral therapy
   - Some cases have resulted in fulminant hepatitis, hepatic failure, and death
   - Cases have been reported in patients who:
     - Are HBsAg positive
     - Have serologic evidence of resolved HBV
     - Receive certain immunosuppressant or chemotherapeutic agents
2. **Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation** during HCV treatment and post-treatment follow-up
3. **Initiate appropriate patient management for HBV infection** as clinically indicated

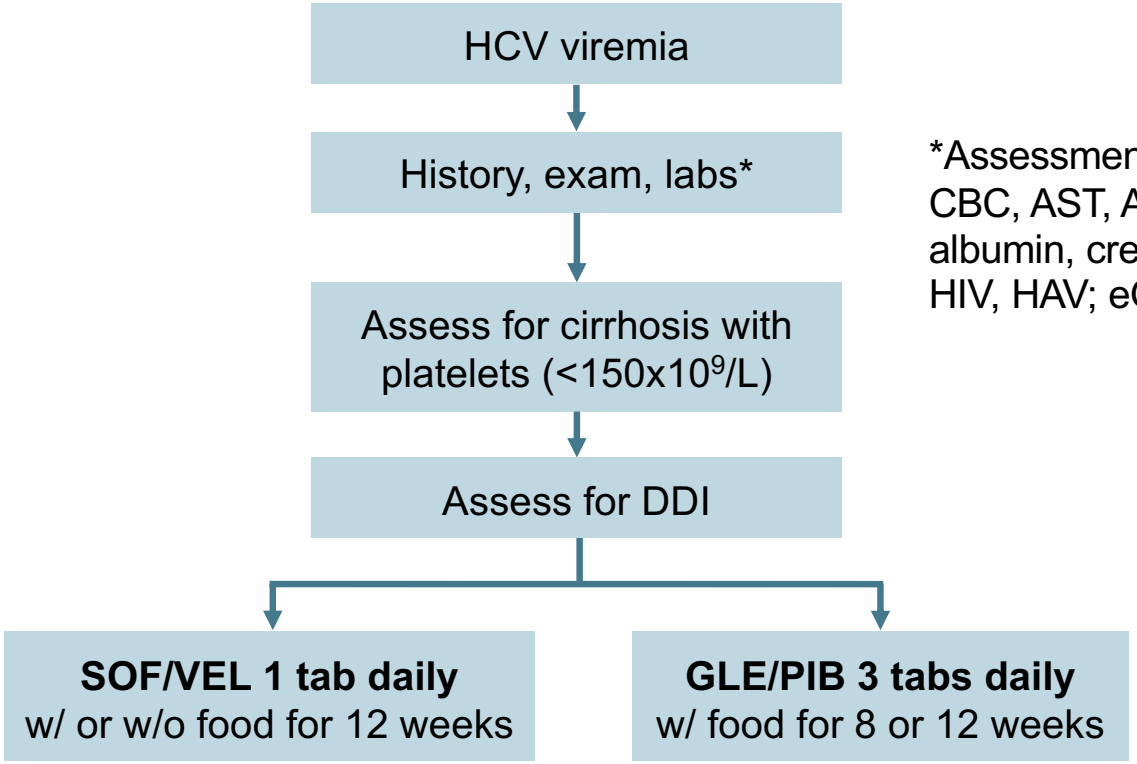
1. https://www.hcvguidelines.org. accessed April 20, 2020

Simplified Algorithm for Management of HCV Infection



Dieterich *et al*, Gastroenterology & Hepatology; volume 15, issue 5, supplement 3, May 2019

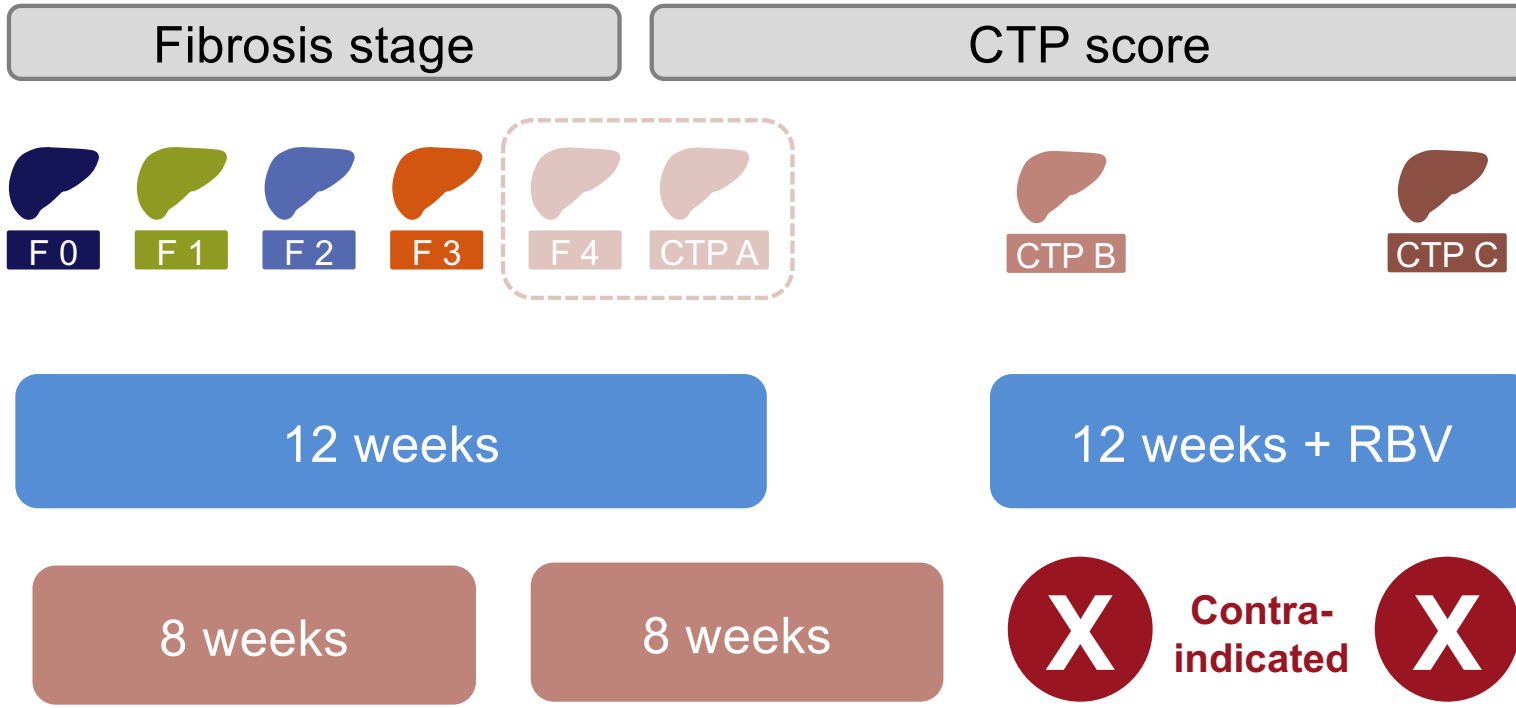
How Simple Can Treatment Be For Most Patients?



*Assessment Labs:
CBC, AST, ALT, bilirubin, albumin, creatinine, HBV, HIV, HAV; eGFR

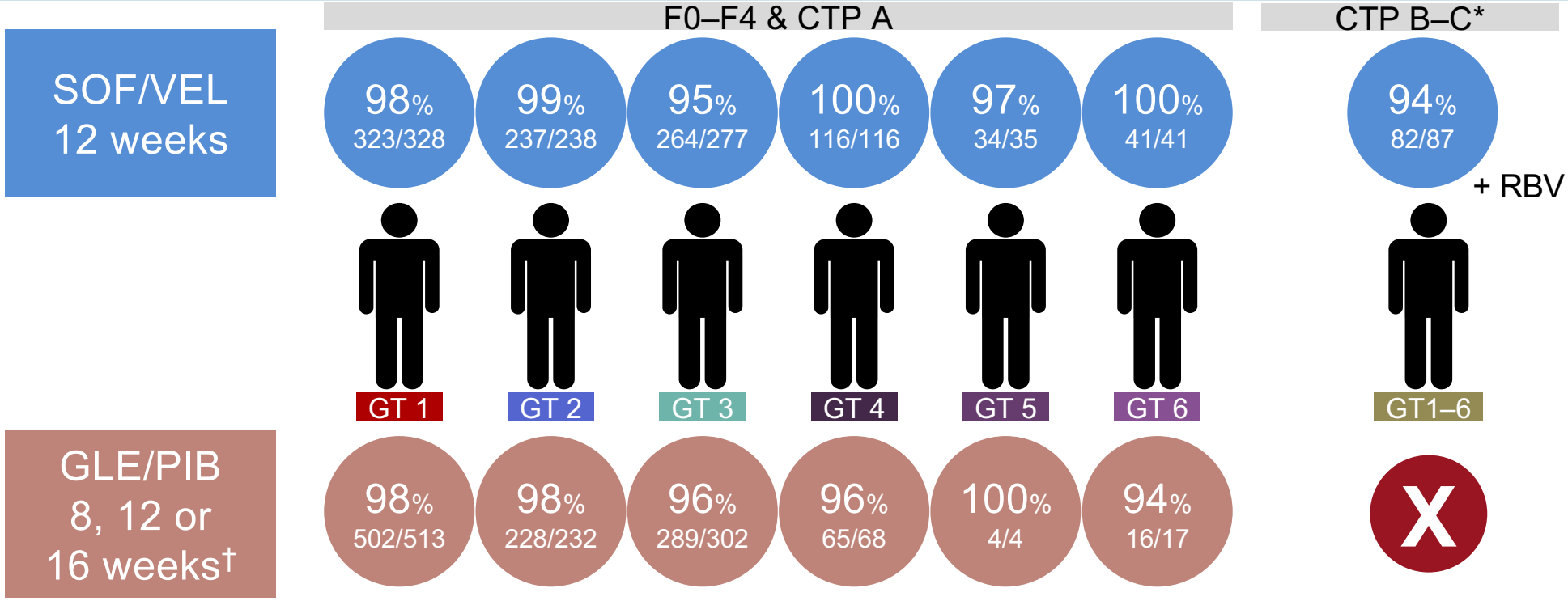
Dieterich *et al*, Gastroenterology & Hepatology; volume 15, issue 5, supplement 3, May 2019

Treatment of DAA-Naive Patients: Liver Disease Stage Considerations



AbbVie Corporation. MAVIRET (glecaprevir/pibrentasvir) Product Monograph, August 2017; Gilead Sciences Canada Inc. EPCLUSA (sofosbuvir/velpatasvir) Product Monograph, April 2018

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;

Why Is Fibrosis Staging Still Important?

- Uncover undiagnosed cirrhosis
- In some states, but not in New York, there are still fibrosis requirements to treat
- Most importantly any stage 3 or 4 fibrosis requires (for now) lifelong screening for HCC
- Protease inhibitors should not be used in Childs B or C patients

Assess Cirrhosis and HCC Risk with Platelet Count

- Thrombocytopenia is a surrogate for cirrhosis and a marker for the identification of patients at high-risk for hepatocellular carcinoma (HCC)
- The best cutoff platelet count is **150,000/mm** for a diagnosis of cirrhosis
- The proportion of thrombocytopenia was significantly greater in patients with HCV-related HCC(63%) than in patients with HBV-related HCC (42%)

Cancer Volume107, Issue91 November 2006

Thrombocytopenia Is a Hallmark of Cirrhosis and Portal Hypertension

- A meta-analysis of 86 studies evaluated the accuracy of clinical findings for identifying histologically proven cirrhosis
- **Platelet count <160** x 10^3/μL (LR, 6.3; 95% CI, 4.3-8.3) strongly correlates with the presence of cirrhosis
- All patients with liver disease and platelet counts below 160,000 should be considered to have cirrhosis until proven otherwise

JAMA. 2012 Feb 22;307(8):832-842. doi: 10.1001/jama.2012.186

FDA Drug Safety Communication on the Use of PI-Containing DAA Regimens for HCV

- On August 28, 2019, FDA issued a safety announcement:

  Protease-inhibitor (PI)-containing regimens for HCV, including:

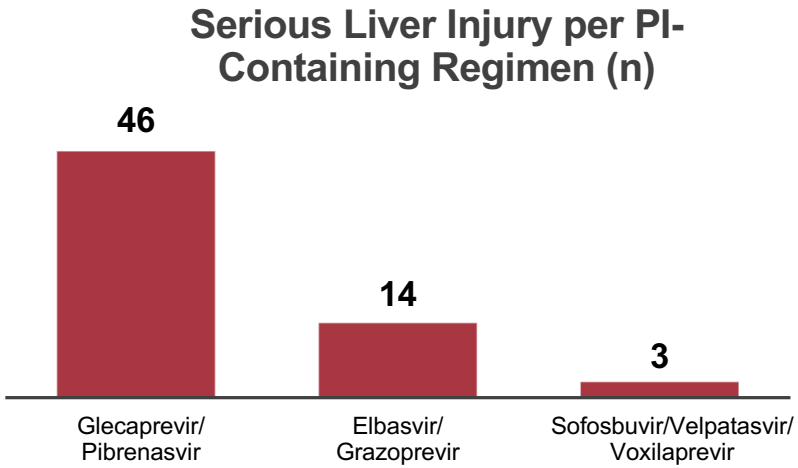
  - glecaprevir/pibrenasvir,
  - elbasvir/grazoprevir
  - sofosbuvir/velpatasvir/voxilaprevir

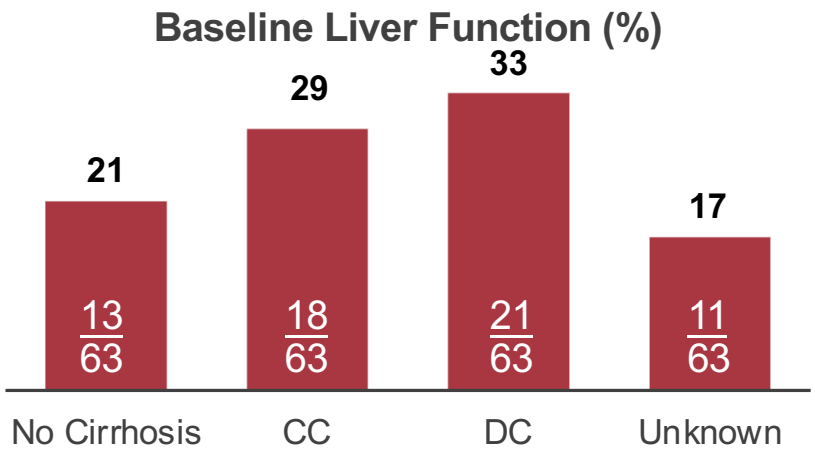
  – Has resulted in rare cases of worsening liver function or liver failure in patients with moderate to severe liver impairment
  – Not indicated for use in patients with moderate to severe liver impairment

https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-occurrence-serious-liver-injury-use-hepatitis-c-medicines-mavyret-zepatier-and
Accessed on August 28, 2019

FDA Drug Safety Communication: Serious Liver Injury with PI-Containing DAA Regimens

- FDA received reports of 63 cases of worsening liver function, including liver failure and 8 deaths, in HCV patients treated with PI-containing DAA regimens:





- More than half of the cases with no cirrhosis or compensated cirrhosis (CC) were misclassified and had evidence of advanced liver disease or risk factors for decompensation (low platelets, portal hypertension, alcohol abuse, other liver comorbidities)

https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-occurrence-serious-liver-injury-use-hepatitis-c-medicines-mavyret-zepatier-and
Accessed on August 28, 2019

Summary: *FDA Drug Safety Communication* Recommendations

- Perform liver chemistries at baseline and as clinically indicated
- Monitor for clinical signs and symptoms of hepatic decompensation (e.g. jaundice, ascites, hepatic encephalopathy, and variceal hemorrhage
- Discontinue glecaprevir/pibrenasvir, elbasvir/grazoprevir, sofosbuvir/velpatasvir/voxilaprevir in patients who develop hepatic decompensation or as clinically indicated
- Report adverse events involving glecaprevir/pibrenasvir, elbasvir/grazoprevir, sofosbuvir/velpatasvir/voxilaprevir or other medicines to the FDA MedWatch program: call 1-800-332-1088 or access https://www.accessdata.fda.gov/scripts/medwatch/

https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-occurrence-serious-liver-injury-use-hepatitis-c-medicines-mavyret-zepatier-and
Accessed on August 28, 2019

Assess for Potential Drug-Drug Interactions

	SOF/VEL	GLE/PIB
Key DDI	anticonvulsants, rifampicin, efavirenz, St. John's wort	
	▪ amiodarone ▪ proton pump inhibitors ▪ statins	▪ 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	

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.

Dieterich *et al*, Gastroenterology & Hepatology; volume 15, issue 5, supplement 3, May 2019

Treatment Options

	SOF/VEL†	GLE/PIB‡
Treatment duration, wk		
No cirrhosis	12	8
Compensated cirrhosis	12§	8
Decomp. cirrhosis	12¶	Contraindicated
Dosage	1 tablet (400 mg SOF + 100 mg VEL) Once daily With or without food	3 tablets (100 mg GLE + 40 mg PIB per tablet) Once daily Food required
Common side effects (≥ 5%)	Headache, fatigue, nausea, asthenia, insomnia	Headache, fatigue, nausea

†Treatment duration of SOF/VEL for treatment-experienced patients is 12 weeks.
‡GLE/PIB is also indicated for patients with HCV GT 1 infection with no cirrhosis or compensated cirrhosis (Child-Pugh A) who have been treated with a regimen containing an HCV NS5A inhibitor or NS3/4A protease inhibitor, but not both. Duration of treatment for patients with prior NS5A inhibitor experience or NS3/4A protease inhibitor experience is 16 weeks or 12 weeks, respectively.
§Prescribing information in the EU, but not the US, states that addition of RBV may be considered for patients with HCV GT 3 and compensated cirrhosis.
¶For patients with decompensated cirrhosis, SOF/VEL is indicated in combination with ribavirin.

Dieterich *et al*, Gastroenterology & Hepatology; volume 15, issue 5, supplement 3, May 2019

sofosbuvir/velpatasvir/voxilaprevir Prescribing Information

Indicated for treatment of adults with chronic HCV without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have:

- **Genotype 1, 2, 3, 4, 5, or 6** infection and previously treated with an HCV regimen containing an **NS5A inhibitor**
- **Genotype 1a or 3** infection and previously been treated with HCV regimen containing **sofosbuvir without an NS5A inhibitor**

Additional benefit of sofosbuvir/velpatasvir/voxilaprevir over sofosbuvir/velpatasvir was not shown in adults with genotype 1b, 2, 4, 5, or 6 infection previously treated with sofosbuvir without an NS5A inhibitor.

- Take once daily with food for 12 weeks
- **Not recommended in patients with moderate or severe hepatic impairment** (Child-Pugh B or C) due to higher exposures of voxilaprevir (up to 6-fold in non-HCV infected subjects)

VOSEVI US Full Prescribing Information, Gilead Sciences Inc, Foster City CA. November 2017.

Monitoring Recommendations

- Advise patients, particularly those with prior HBV infection, to contact their HCP if they experience unexpected or severe symptoms
- At least 12 weeks after treatment completion, confirm cure by assessing HCV RNA by PCR
  - Refer patients with detectable HCV RNA to a specialist
- At least 12 weeks after treatment completion, obtain ALT level
  - If ALT remains abnormal on repeated measure, refer the patient to a specialist

Dieterich *et al*, Gastroenterology & Hepatology; volume 15, issue 5, supplement 3, May 2019

Case Study 1

- 46-year-old African-American female diagnosed with HCV 2 months ago
  - Complains of fatigue
  - PMH: Hypertension
  - History of intravenous drug use; last used 10 years ago
  - ALT 45, AST 56, total bilirubin 1.1, platelet count 165,000
  - HCV RNA 6,680,056, genotype 1a
  - Transient elastography with F2, S2

- What would you do for this patient?

Case Study 1

- Screen for HBV, HIV
- Pregnancy check
- Review for drug-drug interactions
- Inquire about alcohol, other substance use
- Inquire about OTC's and herbal products
- Start DAA therapy
  - Either
    - GLE/PIB for 8 weeks
    - SOF/VEL for 12 weeks

Post-Cure Recommendations

- Inform patients who are cured that they are susceptible to reinfection
- Provide patients with appropriate HCV harm-reduction resources such as:
  - ✓ Buprenorphine
  - ✓ Prescription for naloxone
  - ✓ Referral to SSP (Syringe Services Program) and prescription for new syringes

Dieterich *et al*, Gastroenterology & Hepatology; volume 15, issue 5, supplement 3, May 2019

Renal Impairment Labeling Updates for Sofosbuvir-Based HCV Therapies 11/20/2019

- FDA has approved updated labeling in renal disease for:
  - sofosbuvir/velpatasvir
  - ledipasvir/sofosbuvir
  - sofosbuvir/velpatasvir/voxilaprevir
- Prescribing information now states that **no dosage adjustment is recommended in patients with any renal impairment** including patients on dialysis

Things to Remember when Treating HCV

- Screen for HBV: HBsAg, HBsAb, HBcAb
- Screen for HIV
- Vaccinate for HAV and HBV when indicated
- Platelet count < 150,000 concerning for advanced fibrosis
- All patients with bridging fibrosis or cirrhosis need to be screened for life
- DO NOT use Protease Inhibitors in Child's B or C patients

Summary of Key Messages

- HCV is curable with readily available combination therapies
- Curing HCV promote increased quality of life
- The **Simplified Algorithm** provides a roadmap for non-specialists to treat HCV
- 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
- 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
- Patients with advanced disease should be referred to a liver specialist

Hepatitis C Treatment Guidelines and Resources

- Treatment Guidelines - HCVguidelines.org
  - Includes a simplified treatment algorithm for use by primary care providers
- Drug-Drug Interactions - https://www.hep-druginteractions.org/

Hepatitis C Resources in NYC

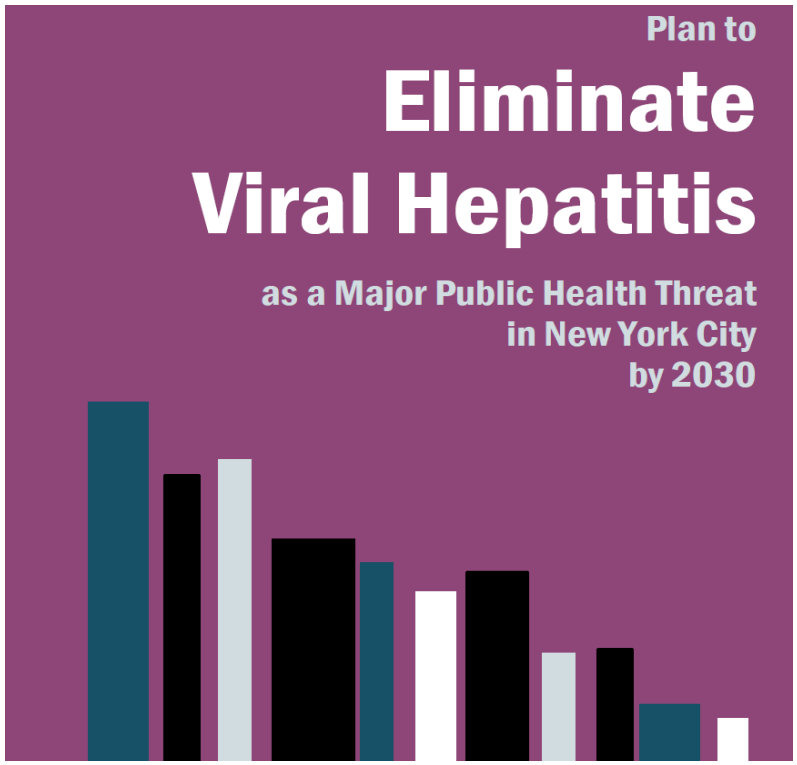
- NYS HCV CEI Clinical Consultation Hotline:
  (866) 637-2342 (leading hepatologist will answer questions)

- www.HepFree.NYC
  - Hep C Task Force
  - Clinical Resources
  - Capacity building tools
  - Advocacy Committee

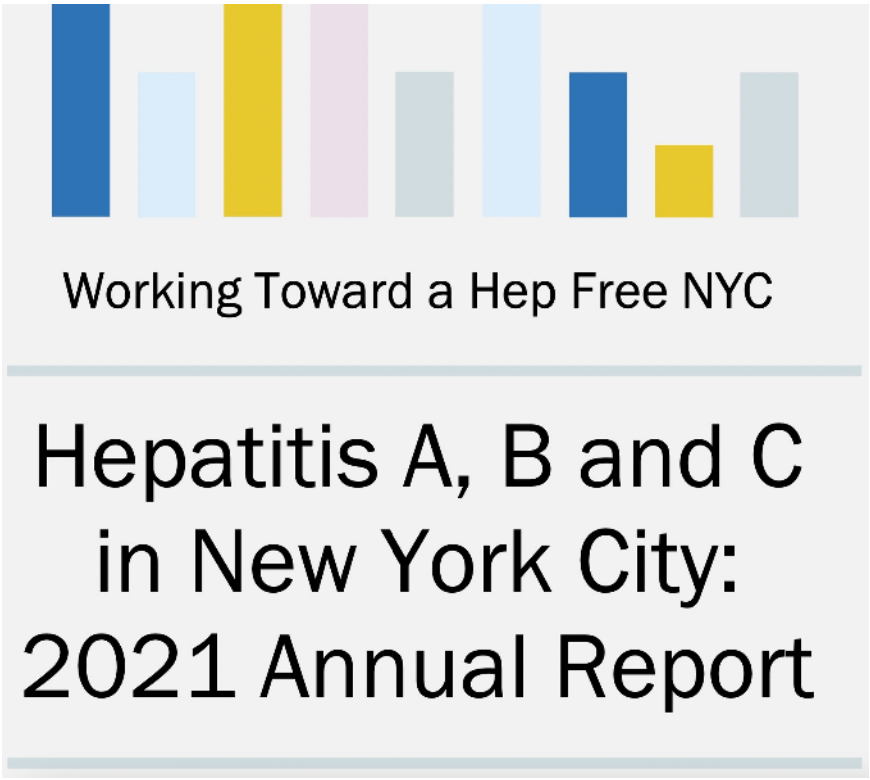
- Hepatitis C patient information page: www.nyc.gov/health/hepc
  - Free or low-cost testing and treatment

Elimination Plan and Annual Report

Find on NYC.gov website here



Find on Hep Free NYC website here



Contact Us

For CMEs or educational opportunities, contact:

Meg Chappell, MPH
Program Manager
Empire Liver Foundation
megchappell@empireliverfoundation.org
www.empireliverfoundation.org

For questions about resources, contact:

Marie P. Bresnahan, MPH
Director, Training
Viral Hepatitis Program
New York City Health Department
mbresnahan@health.nyc.gov
www.hepfree.nyc

HCV Provider Training Series

Date	Topic
September 28, 2023	Hepatitis C : Epidemiology, Natural History and Diagnosis with Dr. Arun Jesudian
October 5, 2023	Hepatitis C Treatment with Dr. Sonal Kumar
October 12, 2023	Hepatitis C Complications with Dr. Paul Gaglio
October 19, 2023	Hepatitis C Treatment in People Who Inject Drugs (PWID) with Dr. Sara Lorenz-Taki

Upcoming Webinars

Hepatitis C in People of Reproductive Age, Pregnancy and Children
November 2, 2023 @ 4:30PM

PRESENTER

Tatyana Kushner, MD, MSCE
Assistant Professor of Medicine
Division of Liver Diseases
Icahn School of Medicine at Mount Sinai

CONTINUING EDUCATION

1 CME/CNE/CEU offered per webinar. Join both webinars or a single session!