HEPATITIS C CLINICAL TRAINING

Hepatitis C Treatment

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Empire Liver FOUNDATION

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Training Development and Funding

This training is funded by the NYC City Council

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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

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- 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/

Overarching Learning Objectives

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

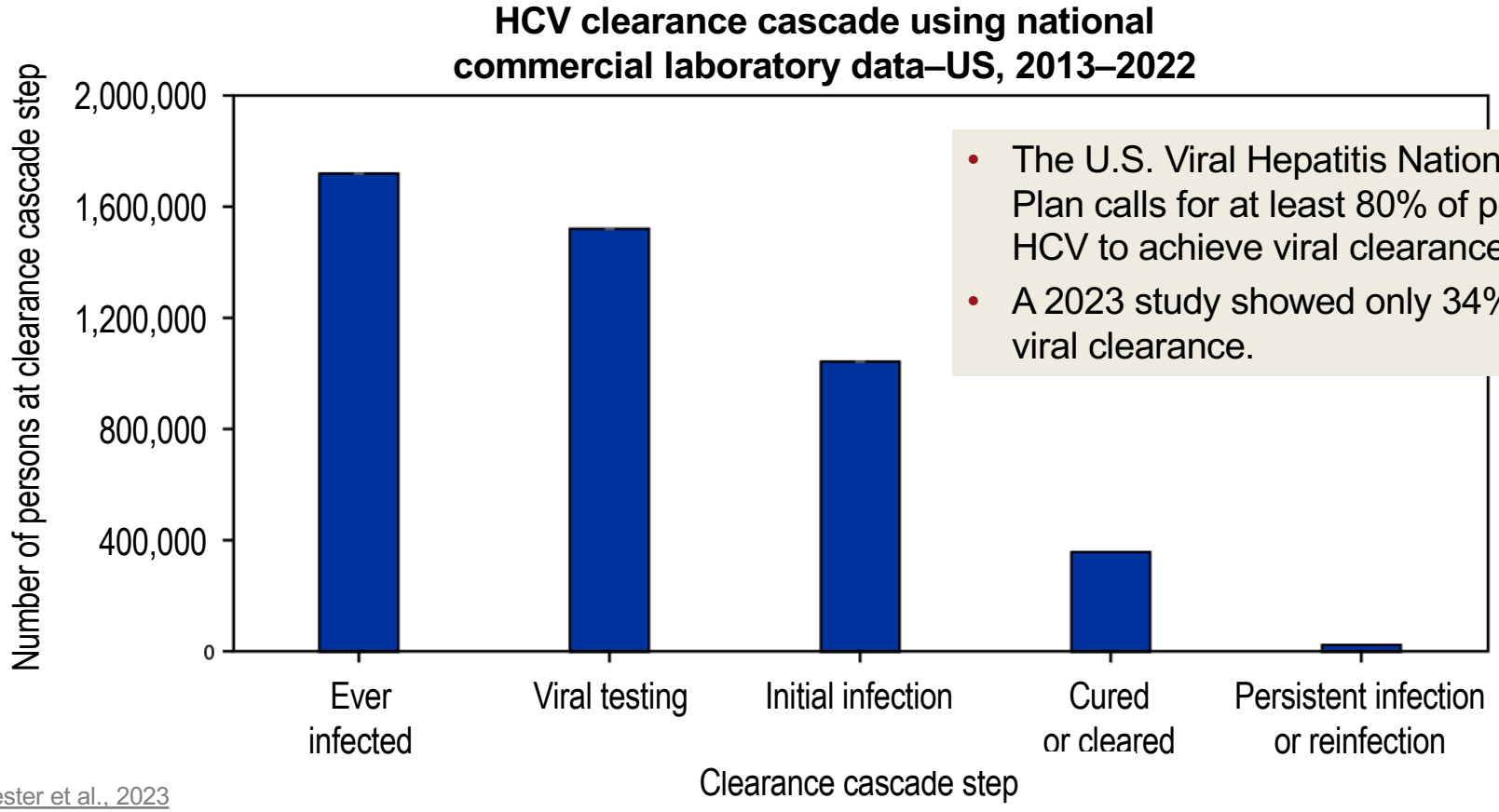
1. Describe the importance of interprofessional collaboration in effectively meeting the healthcare, educational, and psychosocial needs of patients living with hepatitis B or C infection.
2. Describe the epidemiology and natural history of hepatitis B and hepatitis C infection.
3. Use updated guidelines to identify patients at risk for hepatitis B and/or hepatitis C infection and provide screening according to these guidelines.
4. Select appropriate antiviral treatments for people living with hepatitis B or hepatitis C, including special populations such as people with advanced liver disease or HIV co-infection.
5. Explain the efficacy and safety of current and emerging therapies for hepatitis B and C, including use in special populations such as people who use drugs or alcohol or have substance use disorders.
6. Illustrate how to counsel patients diagnosed with hepatitis B or C regarding risks and benefits of therapies and involve them in shared treatment decisions.

Learning Objectives

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

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

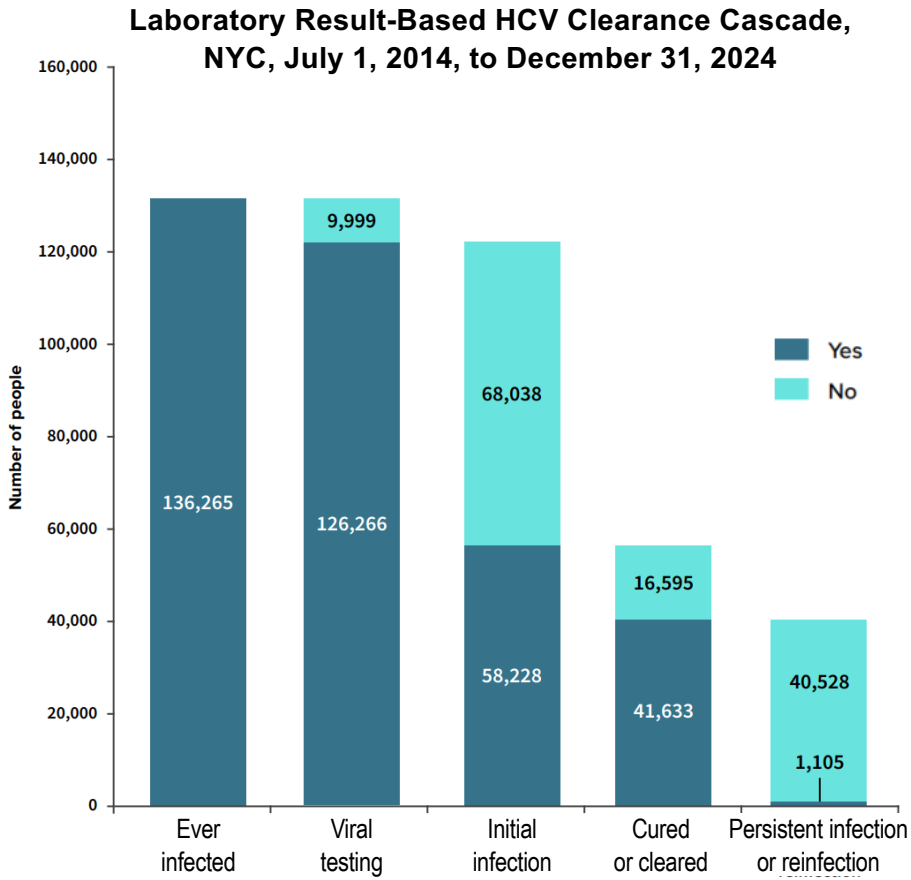
US HCV Clearance Cascade, 2013-2022



- The U.S. Viral Hepatitis National Strategic Plan calls for at least 80% of persons with HCV to achieve viral clearance by 2030.
- A 2023 study showed only 34% achieved viral clearance.

Wester et al., 2023

US NYC Clearance Cascade 2014-2024



NYC Health Department, 2026.

Case Study 1

- 55 year old male referred for hepatitis C treatment
- Newly diagnosed, never been treated
- PMH: HTN, DM
- PE: unremarkable
- ALT 65, HCV-RNA 987,000, platelet count 165K
- Ultrasound: normal liver, mild splenomegaly

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

Case Study 2

- 46-year-old black 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.

Pre-Therapy Assessment

Pre-DAA Therapy Assessment

Basic labs w/in 6 months of initiation:

- ***Viral load***
- ***HBsAg, HBsAb, HBcAb***
- ***Assessment of liver function (serum albumin, total and direct bilirubin, ALT, AST, ALP, INR)***
- ***Assessment of renal function (creatinine, GFR)***
- ***CBC with platelet count***
- ***Genotype***

Assessment of liver fibrosis

Assessment for decompensated cirrhosis

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 during and after completion of HCV DAA treatment who are 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
   - HIV PrEP (which has anti-HBV activity) can be safely continued during HCV therapy and should not be stopped unless pre-PrEP HBV status is confirmed to be immune or not exposed
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

Importance of Assessing Fibrosis

- Patients with advanced/bridging fibrosis (stage 3/F3) or cirrhosis (stage 4/F4) need additional screening
  - Varices
  - Hepatocellular carcinoma
- Allows for selection of proper treatment plan and duration of therapy
- Determines post-treatment follow-up and monitoring

Pre-Therapy Assessment:
Drug-Drug Interactions (DDIs)

- **Very important** element in pre-therapy assessment
- List of prohibited drugs is relatively short
- Be alert for interactions with common drugs
  - Statins, acid reducing agents, birth control preparations, amiodarone, rifampin
- No herbal therapies!
  - In particular, no St. John's Wort
- Use online tools to help assess DDI's
  - ***https://www.hep-druginteractions.org/checker***

Remember: Ask patients to tell you all the pills, medications or treatments (even "all natural" ones) that they are taking!

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	Enhanced Liver Fibrosis (ELF) score, FibroSure, FibroTest, FibroMeter, FIBROSpect II, 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
MRI elastography (MRE)	MRI with elastography	Non-invasive; evaluates entire liver	Not available at every imaging location. May not get insurance approval.

FIB-4: Identification of Advanced Fibrosis

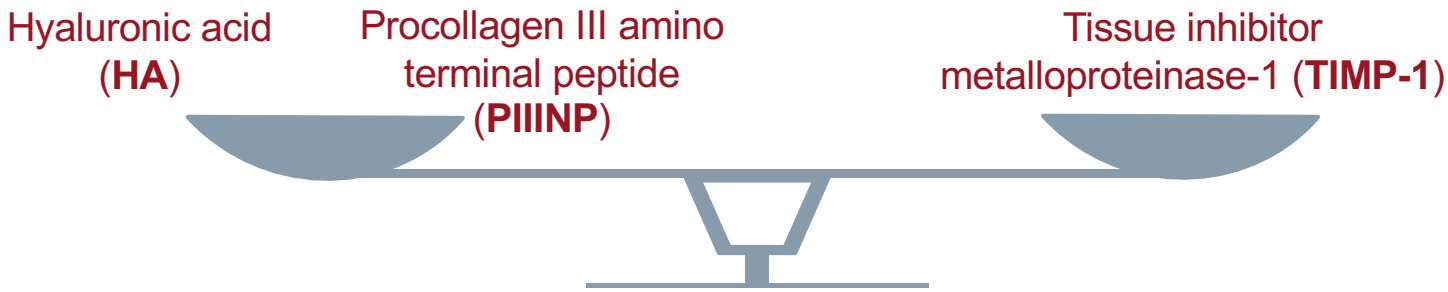
FIB-4 Index

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

Rule-Out		Rule-In
Low Probability < 1.30	Indeterminant 1.30 – 2.67	High Probability > 2.67

Kanwal et al. *Gastroenterology* 2020
Rinella et al. *Hepatology 2023*

Enhanced Liver Fibrosis (ELF™) Test for prognosis in Hepatitis C



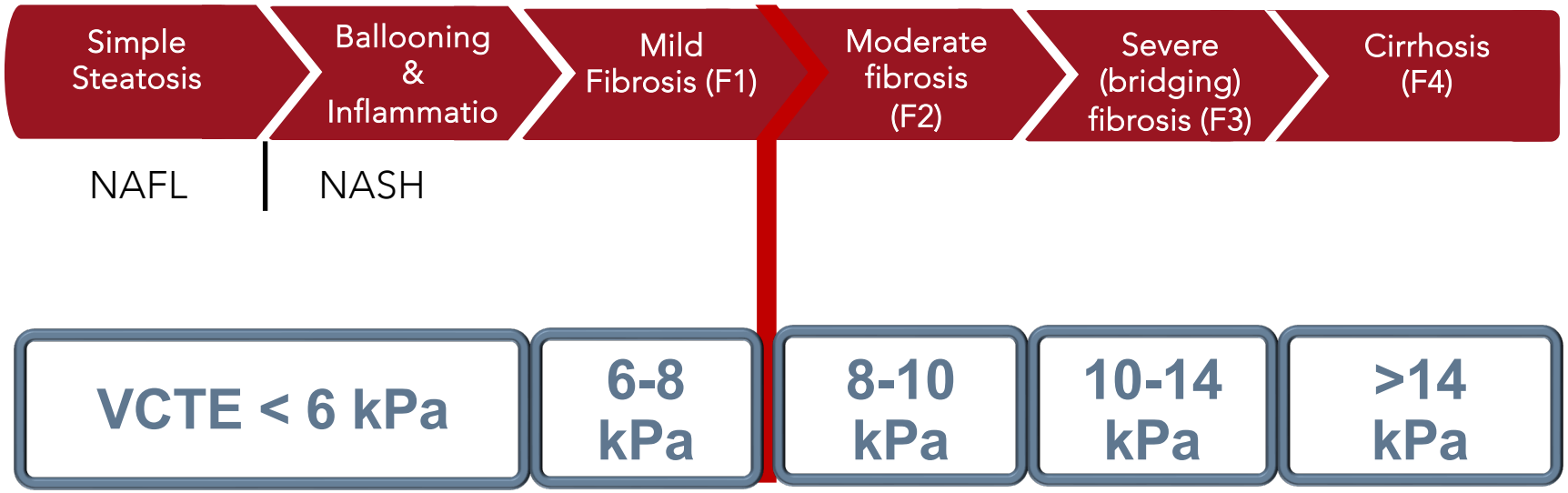
Fully Automated: ELF Score Calculated and Reported

None to Mild	Moderate	Severe	Cirrhosis
<7.7	≥7.7 - <9.8	≥9.8	≥11.3

ELF score*† = 2.278 + 0.851 ln (C_{HA}) + 0.751 ln (C_{PIIINP}) + 0.394 ln (C_{TIMP-1})

Arpino V, Brock M, Gill SE. Matrix Biol 2015;44-46:247-54.; Rosenberg WM, Voelker MT, Thiel R, et al. Gastroenterology 2004;127:1704-13.

Transient Elastography: Identification of Significant Fibrosis



Eddowes PJ et al. Gastroenterology 2019

Why Is Fibrosis Staging Still Important?

- Uncover undiagnosed cirrhosis
- Stage 3 or 4 fibrosis requires lifelong screening for HCC
- Protease inhibitors should not be used in advanced cirrhosis (Child's B or C patients)

Child-Turcotte-Pugh Classification

	1	2	3
Albumin (g/dl)	>3.5	2.8-3.5	<2.8
Total bilirubin (mg/dl)	<2	2-3	>3
Prothrombin time (INR)	<1.7	1.7-2.3	>2.3
Ascites	None	Medically controlled	Uncontrolled
Encephalopathy (grade)	0	I-II	III-IV

Class: A = 5-6 points, B = 7-9 points, C = 10-15 points

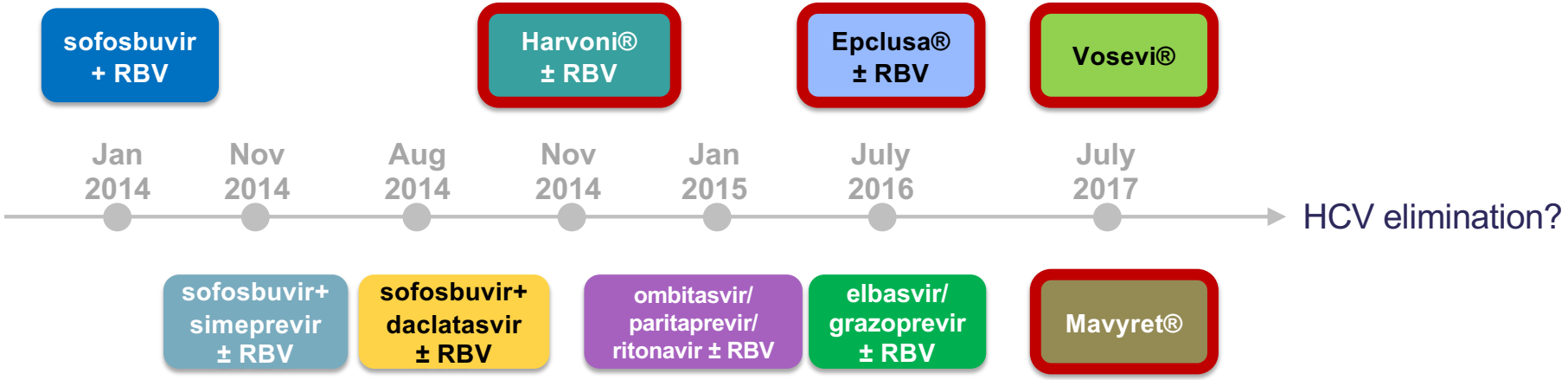
Assess Cirrhosis and HCC Risk with Platelet Count

- 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

Treatment

Rapid Therapeutic Advances In HCV



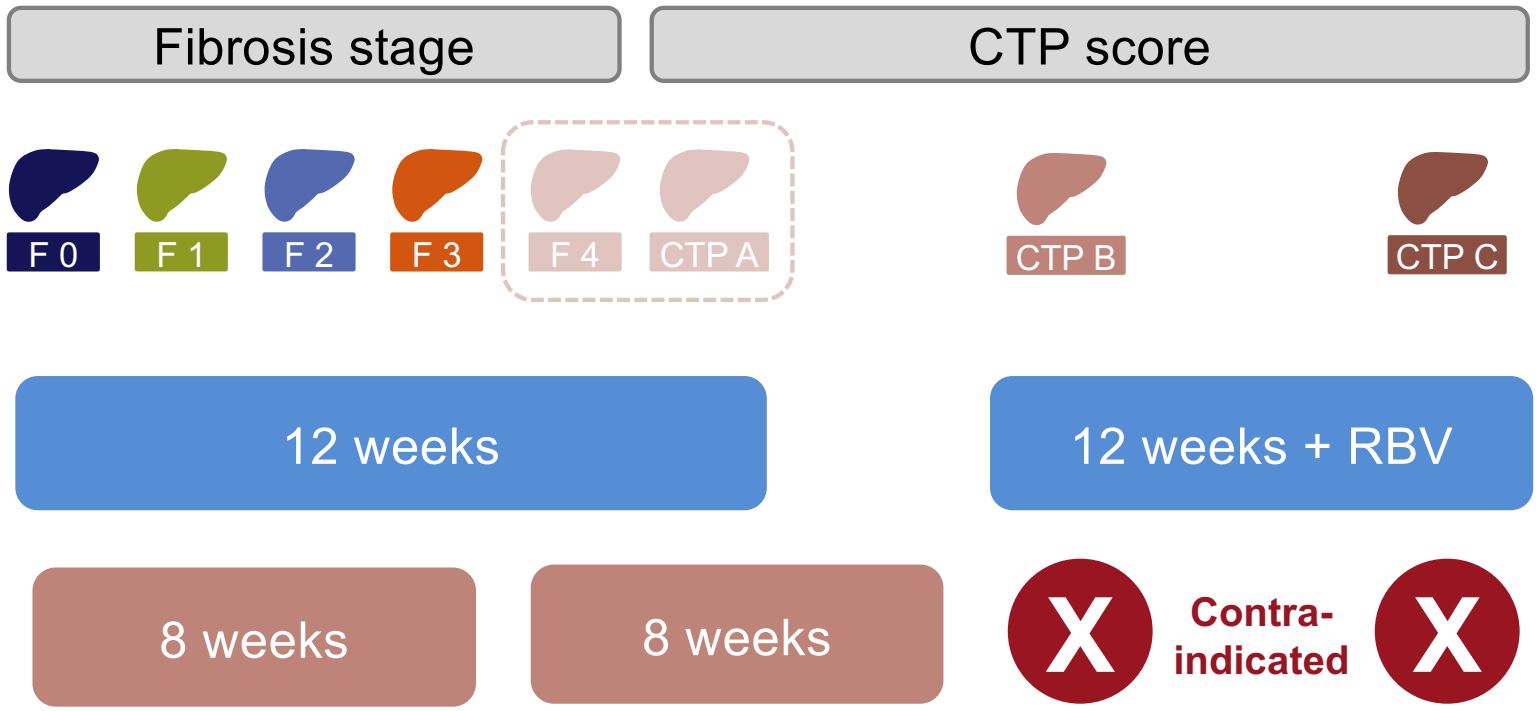
Current Therapies		Trade Name	GFR < 30	Decompensated Cirrhosis
Glecaprevir/Pibrentasvir	GLE/PIB	Mavyret®	Yes	No
Ledipasvir/Sofosbuvir	LDV/SOF	Harvoni®	Yes	Yes
Sofosbuvir/Velpatasvir	SOF/VEL	Epclusa®	Yes	Yes
Sofosbuvir/Velpatasvir/ Voxilaprevir	SOF/VEL/VOX	Vosevi®	Yes	No

First-line Treatment Options for Previously Untreated (Naïve) Patients

	Epclusa® (SOF/VEL)	Mavyret® (GLE/PIB)
Treatment duration, weeks (No cirrhosis or compensated cirrhosis)	12	8
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

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

Treatment of Special Populations: Patients with Cirrhosis



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

Special Population: Salvage Regimen Sofosbuvir/Velpatasvir/Voxilaprevir for Treatment Failures

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

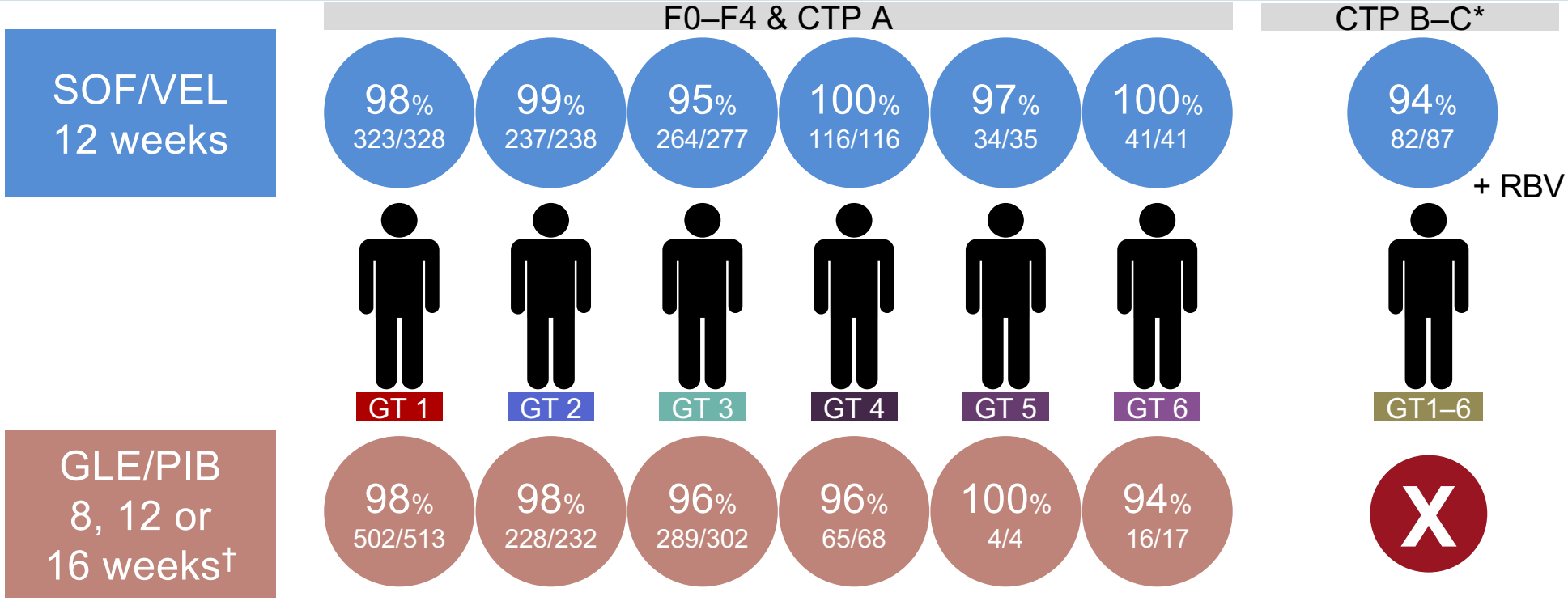
- **Genotype 1, 2, 3, 4, 5, or 6** infection that was previously treated* with an HCV regimen containing an **NS5A inhibitor**
- **Genotype 1a or 3** infection that was previously been treated with HCV regimen containing **sofosbuvir without an NS5A inhibitor**

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.

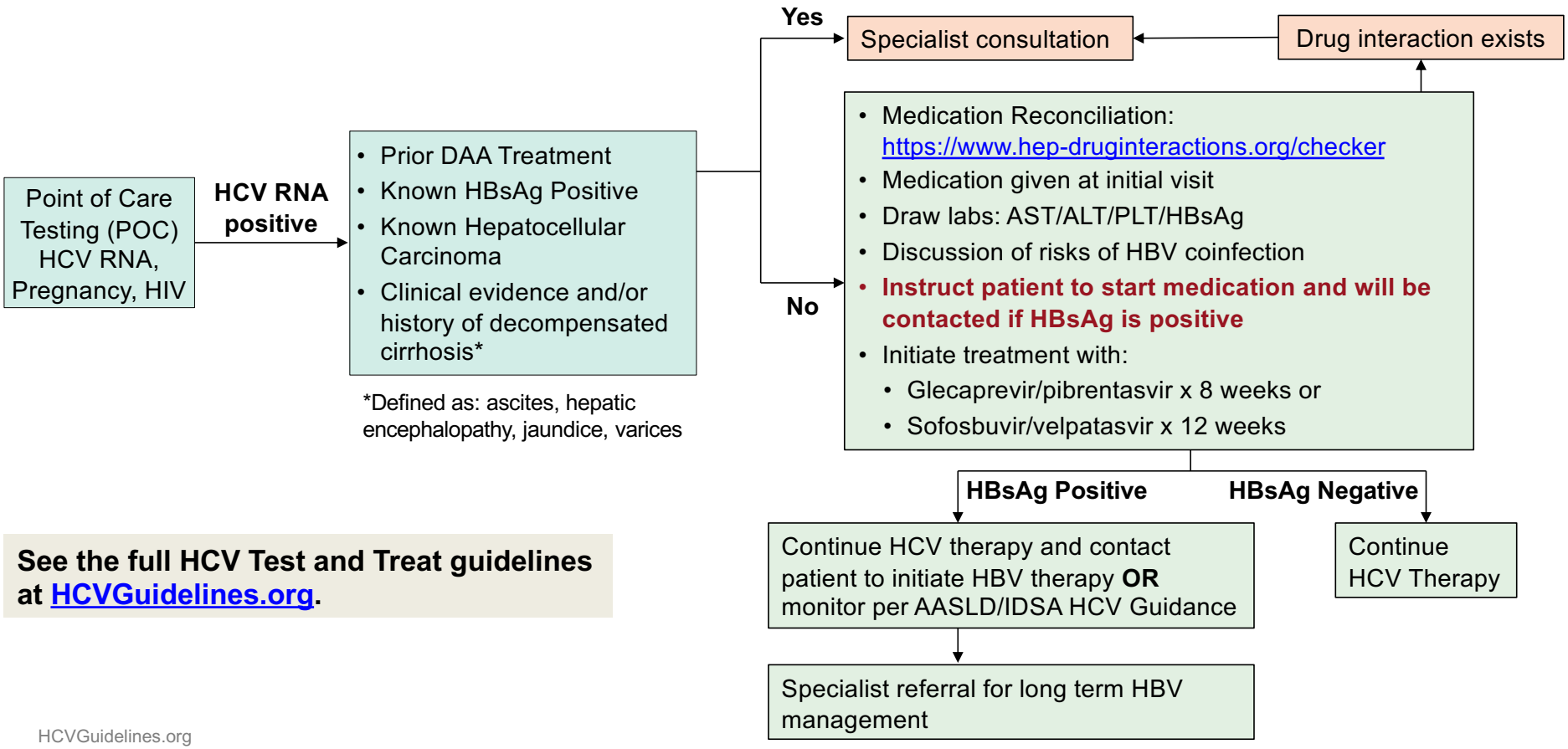
High SVR (Cure) Rates Achieved Across Patient Types



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

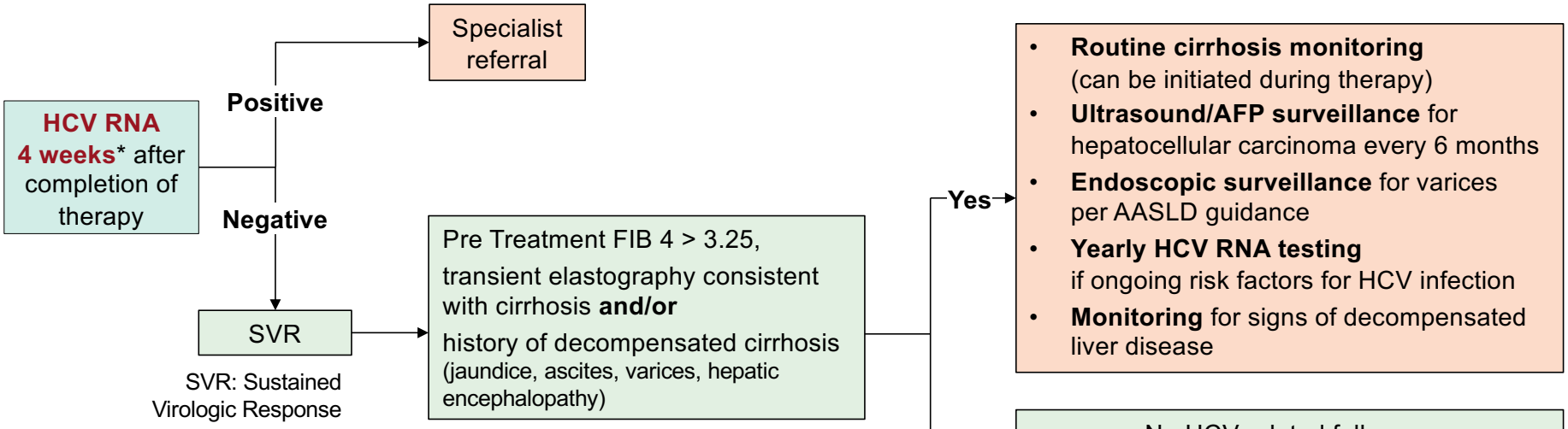
*Safety and efficacy of SOF/VEL has not been assessed in patients with CTP class C cirrhosis; †As approved in the Canadian Product Monograph. These are not head-to-head studies and direct comparisons cannot be made;
CTP: Child–Turcotte–Pugh; GLE/PIB: glecaprevir/pibrentasvir; GT: genotype;
RBV: ribavirin;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

AASLD/IDSA HCV Guidance Update for Simplified Treatment:
HCV Test and Treat Initial Visit



See the full HCV Test and Treat guidelines at HCVGuidelines.org.

AASLD/IDSA HCV Guidance Update for Simplified Treatment:
HCV Test and Treat Follow-Up Visit



*Quantitative PCR testing using venipuncture is recommended, but point-of-care qualitative tests can be used to determine sustained virologic response (SVR) in certain settings where venipuncture may be unavailable. Evaluation of SVR at 12 weeks (SVR 12) by HCV RNA testing should be performed as measure of HCV cure among people with cirrhosis.

See the full HCV Test and Treat guidelines at HCVGuidelines.org.

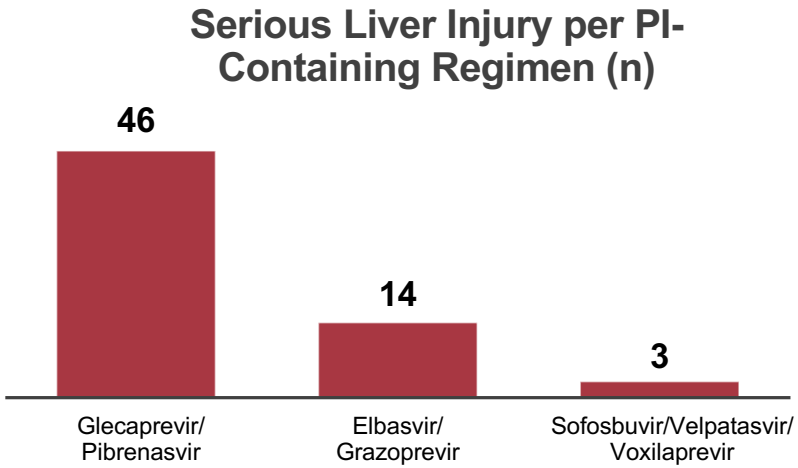
AASLD/IDSA HCV Guidance Update for Simplified Treatment: Takeaways

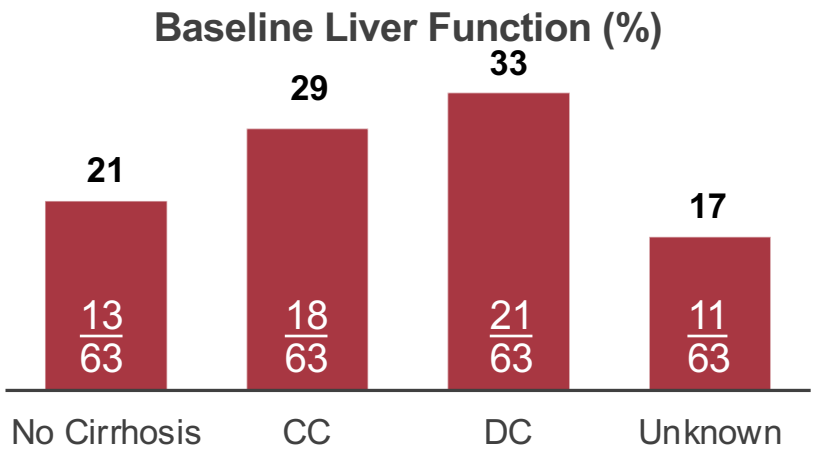
- Initiate HCV treatment same day, don't wait for HBV result, contact pt if positive to manage HBV
- Sustained virologic response testing at 4 weeks
- SVR can be confirmed via venipuncture for quant or POCT for qualitative

Treatment Safety

FDA Drug Safety Communication: Serious Liver Injury with Protease Inhibitor-Containing 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

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

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

Impact of Treatment on Natural History of Hepatitis C

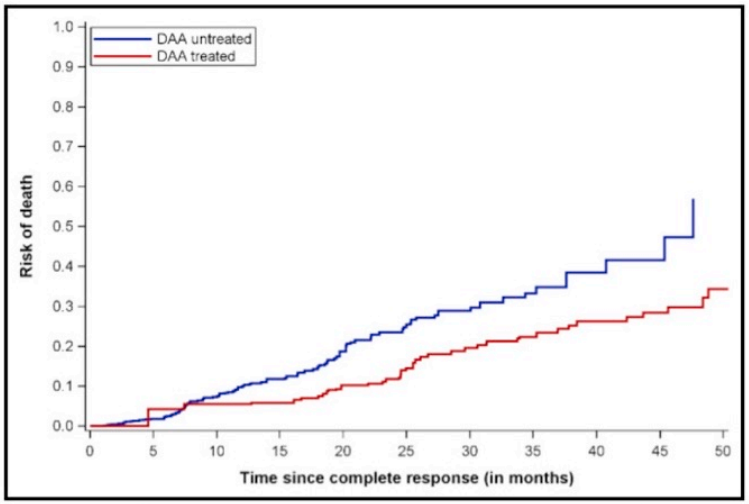
Direct Acting Antiviral (DAA) HCV Therapy Associated with Improved Survival in HCC Patients

Methods: Retrospective cohort study of 797 patients with HCV-related HCC from 31 health systems in U.S./Canada

Results:

DAA Treated:
4.6 deaths per 100 person-years follow-up

DAA Untreated:
19.6 deaths per 100 person-years follow-up



Multivariable analysis
- Adjusted for site, age, sex Child Pugh score, AFP, tumor burden and HCC treatment modality

→ **DAA therapy associated with lower mortality: HR: 0.54; 95%CI: 0.33 – 0.90**

Singal AG, al., Gastroenterology. 2019

Case Study 1

- 55 year old referred for hepatitis C treatment
- Newly diagnosed, never been treated
- PMH: HTN, DM
- PE: unremarkable
- ALT 65, HCV-RNA 987,000, platelet count 165K
- Ultrasound: normal liver, mild splenomegaly

What would you do next?

Case Study 1

- Screen for HBV, HAV (immunity), HIV
- 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

Case Study 2

- 46-year-old black 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 next?

Case Study 2

- Screen for HBV, HAV (immunity), HIV
- Pregnancy check
- Review for drug-drug interactions
- Inquire about alcohol, other substance use
- Inquire about OTC's and herbal products
- Start HCV 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:
  - ✓ Prescription for Buprenorphine (or referral)
  - ✓ 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

Summary of Key Messages

- HCV is curable with readily available combination therapies
- Curing HCV promotes 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 prevent, diagnose, link to care, treat and cure HCV, prevent re-infection
  - To eliminate HCV, we need to broaden our treating provider base
- Patients with advanced disease should be referred to a liver specialist
  - However, many patients can be safely and successfully treated by their PCPs, SUD providers and other non-specialists in community settings

Hepatitis C Treatment Guidelines and Resources

- Treatment Guidelines - HCVguidelines.org
  - Includes a simplified treatment algorithm for use by primary care providers
  - https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/HCV%20Test%20and%20Treat%20Final%20011725.pdf
- Drug-Drug Interactions - https://www.hep-druginteractions.org/

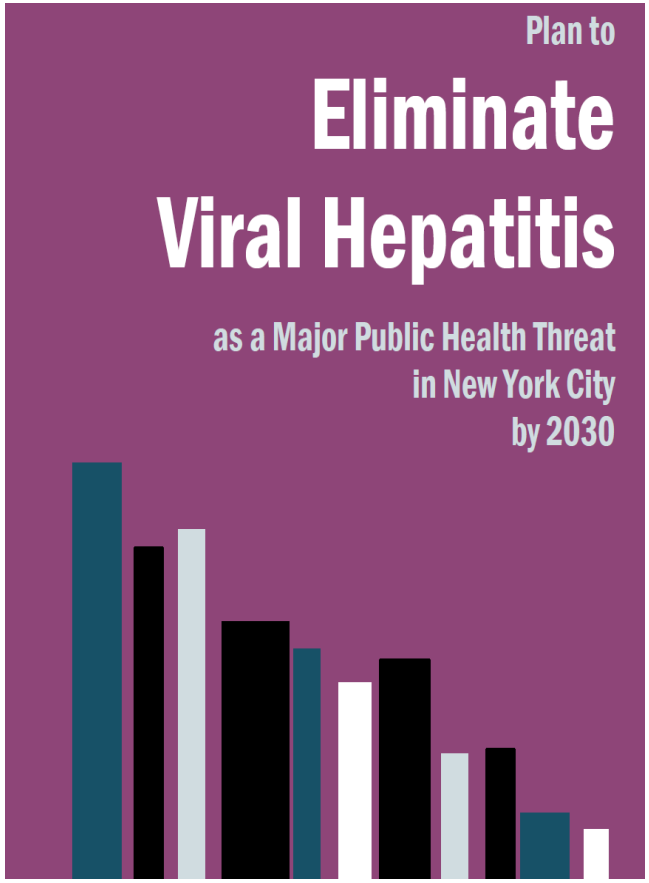
Hepatitis C Resources in NYC

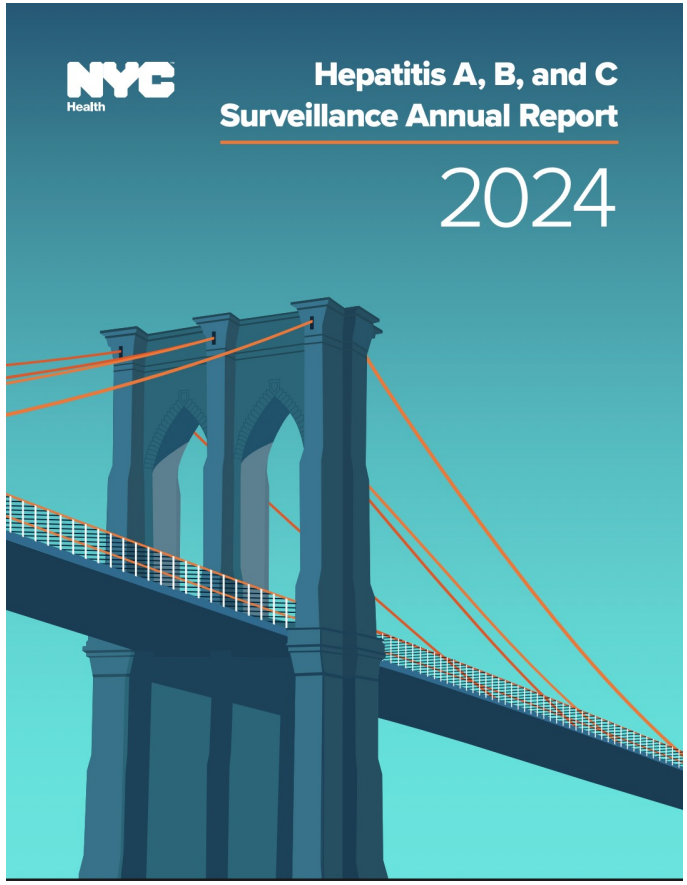
- NYS HCV CEI Clinical Consultation Hotline:
  (866) 637-2342 (leading hepatologist will answer questions)

- 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





Contact Us

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