IHS National Pharmacy Council Antimicrobial Stewardship 2023 Webinar Series

Hepatitis C Virus (HCV) Infection

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Biography

- **LCDR Monica Orsborn, PharmD, BCPS, CTTS** is a United States Public Health Service Officer currently serving as the Coordinator for Pharmacy Clinical Services at the Fort Belknap Tribal Health Program in Harlem, MT. Prior to her current role, she worked for ten years within the Indian Health Services (IHS), where she served in numerous capacities, including inpatient, outpatient, and clinical settings, and has also held positions such as Chief Pharmacist in the Yankton Services Unit at Wagner, SD. Prior to her service in the USPHS Commissioned Corps, LCDR Orsborn served in the United States Navy.

Presenter Disclosure Information

Financial Disclosure: I do not have a financial relationship with any commercial entity which may represent, in perception or reality, a conflict of interest in the context of this presentation.

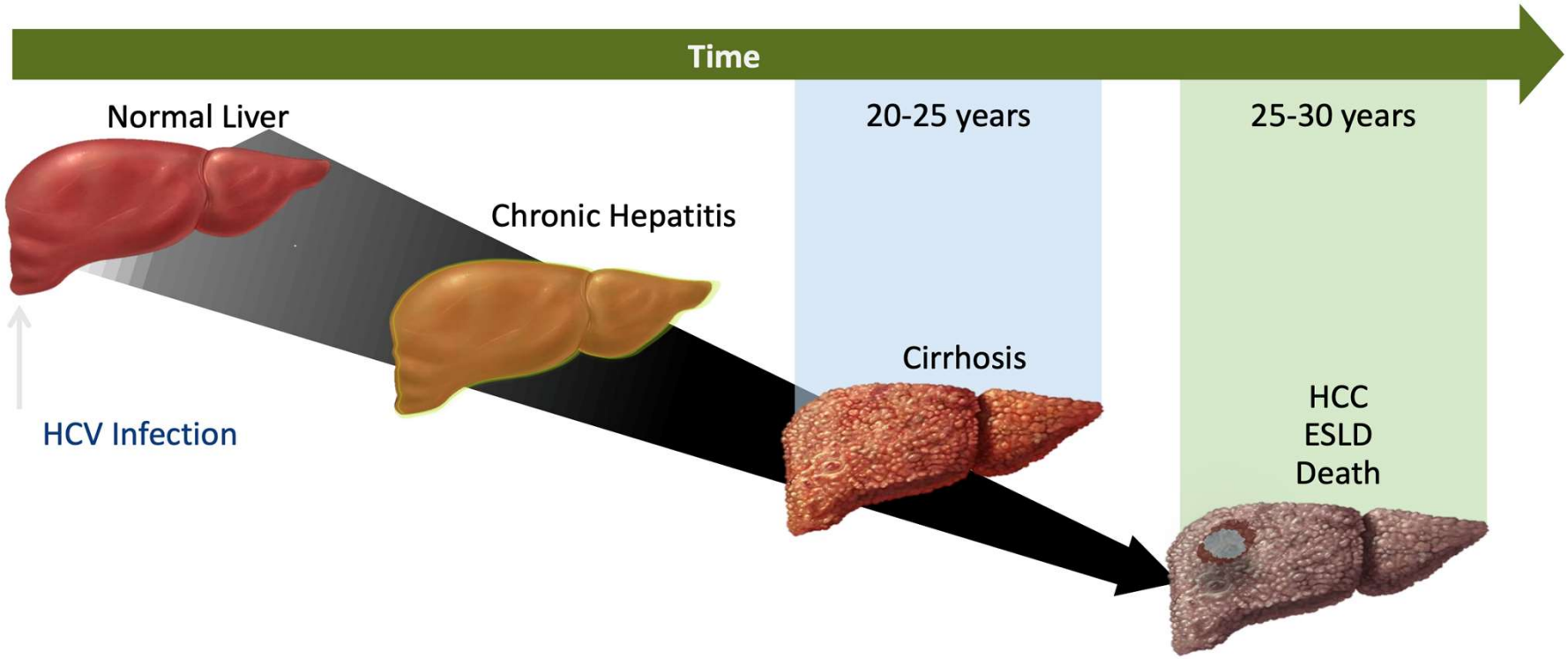
The views expressed in this presentation reflect those of the author, and not necessarily those of the Public Health Service. The contents do not represent the views of the Indian Health Service or the United States Government

Learning Objectives

- Interpret laboratory tests used to diagnose and monitor Hepatitis C Virus (HCV)
- Provide evidence-based treatment recommendations for the treatment of HCV
- Select appropriate patient-specific treatment plans based on patient, efficacy, drug interactions and adverse effects

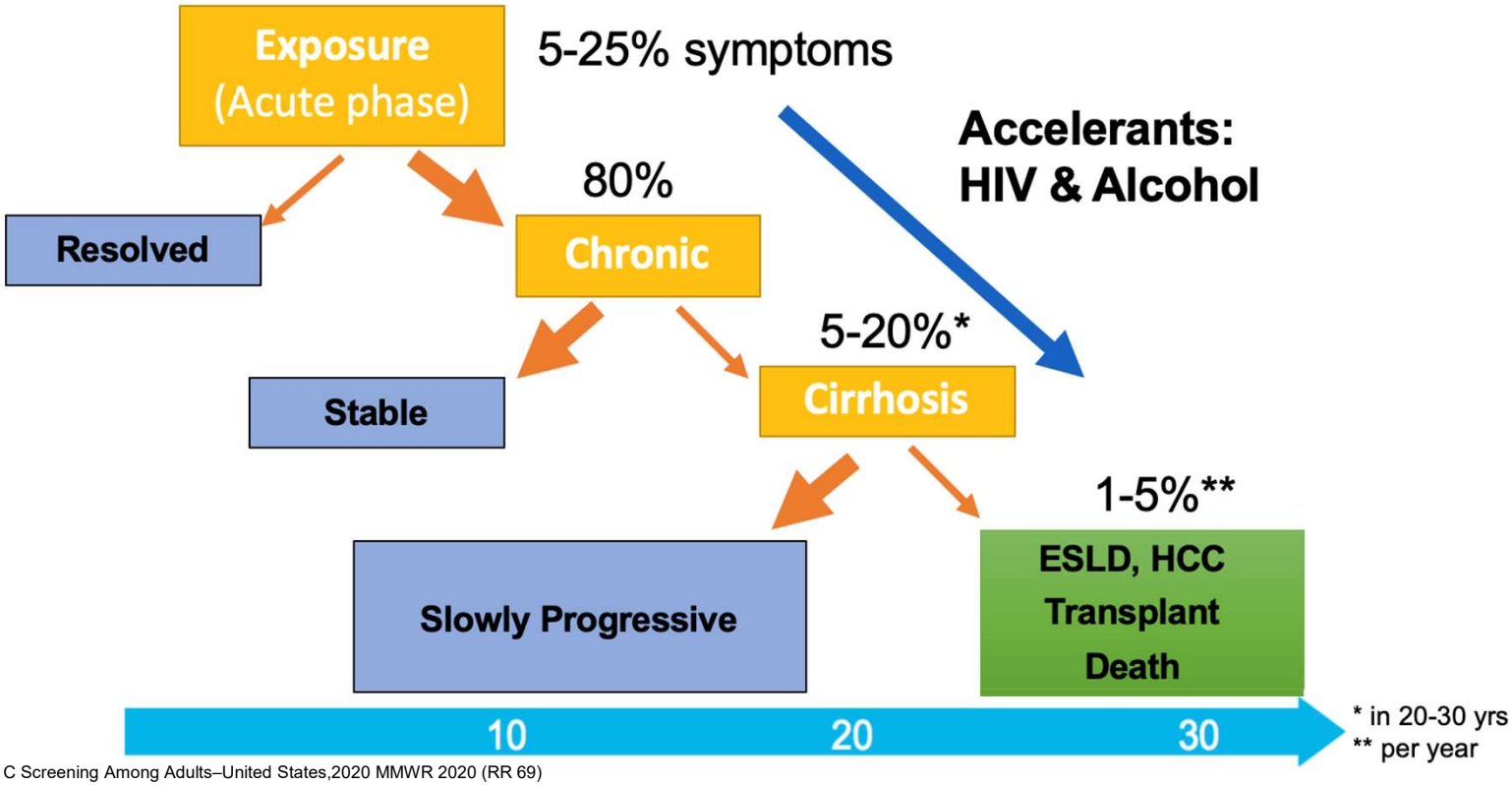
Hepatitis C Virus (HCV)

Hepatitis C: Progression of Disease



University of Washington, Hepatitis C

Natural History of Hepatitis



CDC Recommendations for Hepatitis C Screening Among Adults–United States,2020 MMWR 2020 (RR 69)

Who should be Tested?

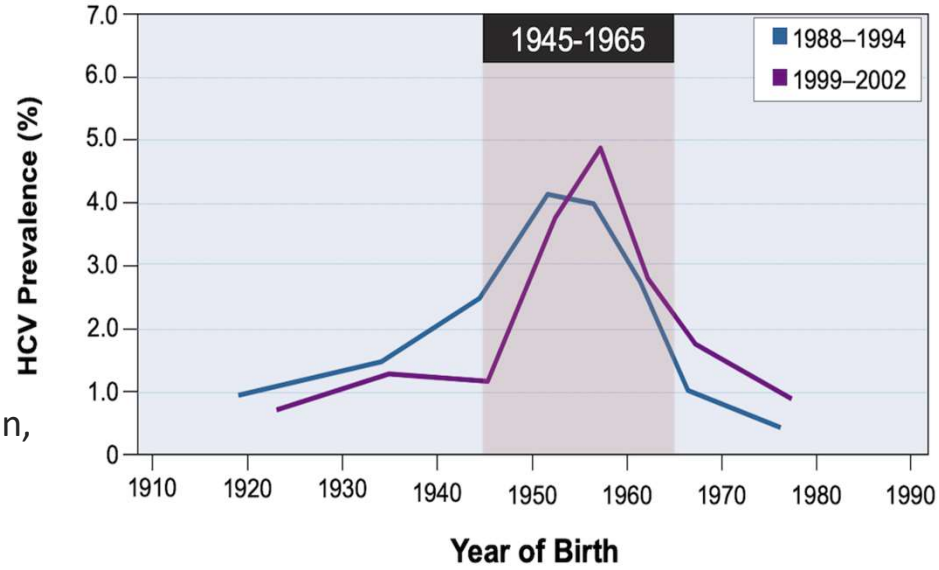
Table 1.
CDC Recommendations for Hepatitis C Screening Among Adults — United States

Persons Recommended for Screening
Universal hepatitis C screening:
• Hepatitis C screening at least once in a lifetime for all adults aged ≥18 years, except in settings where the prevalence of HCV infection (HCV RNA-positivity) is <0.1%
• Hepatitis C screening for all pregnant women during each pregnancy, except in settings where the prevalence of HCV infection (HCV RNA-positivity) is <0.1%
One-time hepatitis C testing regardless of age or setting prevalence among persons with recognized risk factors or exposures:
• Persons with HIV
• Persons who ever injected drugs and shared needles, syringes, or other drug preparation equipment, including those who injected once or a few times many years ago
• Persons with selected medical conditions, including persons who ever received maintenance hemodialysis and persons with persistently abnormal alanine aminotransferase (ALT) levels
• Prior recipients of transfusions or organ transplants, including persons who received clotting factor concentrates produced before 1987, persons who received a transfusion of blood or blood components before July 1992, persons who received an organ transplant before July 1992, and persons who were notified that they received blood from a donor who later tested positive for HCV infection
• Health care, emergency medical, and public safety personnel after needle sticks, sharps, or mucosal exposures to HCV-positive blood
• Children born to mothers with HCV infection
Routine periodic testing for persons with ongoing risk factors, while risk factors persist:
• Persons who currently inject drugs and share needles, syringes, or other drug preparation equipment
• Persons with selected medical conditions, including persons who ever received maintenance hemodialysis
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

Source: Schillie S, Wester C, Osborne M, Wesolowski L, Ryerson AB. CDC Recommendations for Hepatitis C Screening Among Adults - United States, 2020. MMWR Recomm Rep. 2020;69:1-17. [PubMed Abstract]

Who should be Tested? (Continued)

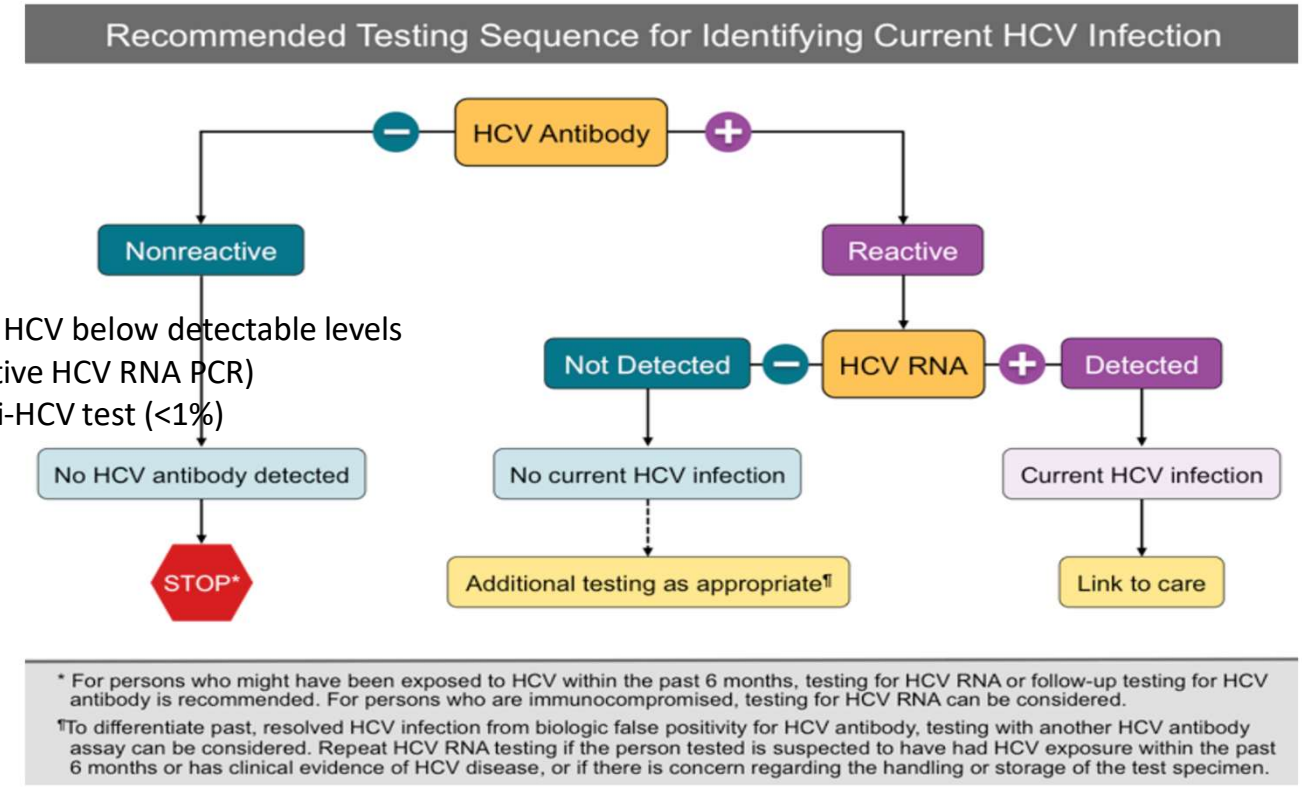
- **Universal Screening**
  - **One time, opt-out HCV testing for all adults**, except where prevalence of HCV is less than 0.1%
- One-time testing regardless of age or prevalence among people with high-risk conditions/exposures
  - HIV, PWID, hemodialysis, persistent ALT elevation, prior transfusion or organ transplant
- Annual screening recommended for current PWID, HIV-infected MSM, persons on PrEP



CDCRecommendationsforHepatitisCScreeningAmongAdults–UnitedStates,2020 MMWR 2020 (RR 69); Picture Adapted from Pyenson B, et al. *Consequences of Hepatitis C Virus (HCV): Costs of a baby boomer Epidemic of Liver Disease*. New York, NY: Milliman, Inc; May 18, 2009.

HCV Testing and Interpretation for Chronic Infection

- Resolved infection
- Treated infection, HCV below detectable levels (verify with qualitative HCV RNA PCR)
- False-positive anti-HCV test (<1%)



Source: Centers for Disease Control and Prevention (CDC). Testing for HCV infection: an update of guidance for clinicians and laboratorians. MMWR Morb Mortal Wkly Rep. 2013;62:362-5.

Goals and Benefits of Achieving (SVR)

- Eradicate virus
  - Hepatitis C can be ***cured***
  - **Sustained Virological Response (SVR):** undetectable HCV RNA 12 weeks after treatment completion
- Prevent Disease Progress
  - Histologic regression of fibrosis
    - Fibrosis and early cirrhosis can improve with successful treatment
  - **Reduced risk of hepatocellular cancer (HCC)**
  - **Reduce risk of death**
- Reduce transmission
  - Treatment is prevention

HEPATIC

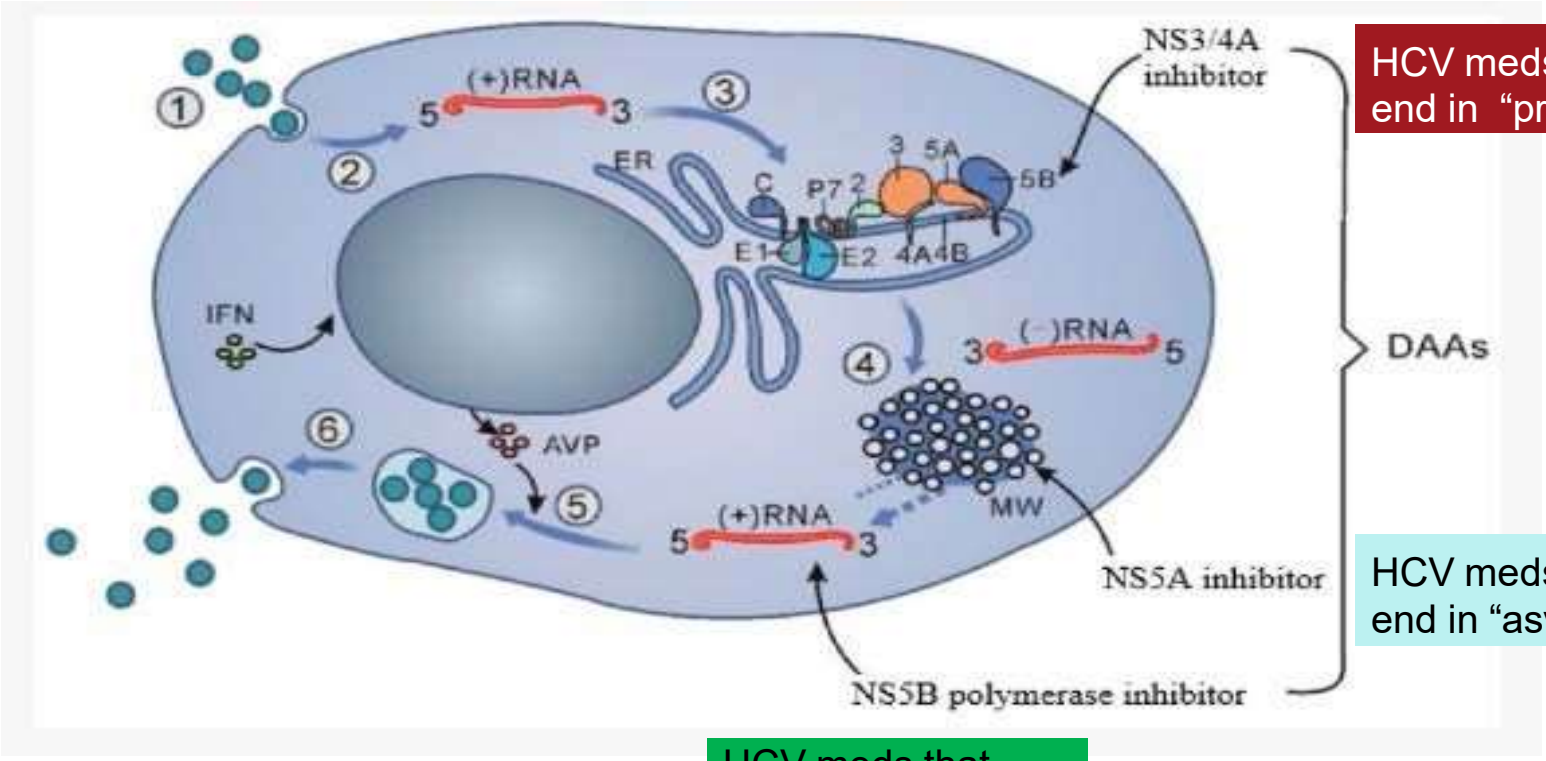
Improved liver histology
↓ Cirrhosis
↓ Decompensation
↓ HCC
↓ Transplantation

EXTRAHEPATIC

↓ All-cause mortality
Improved QoL
Malignancy
Diabetes
Cardiovascular Disease
Renal
Neurocognitive
Cryoglobulinemia vasculitis

Smith-Palmer J, et al. BMC Infect Dis. 2015;15:19. Hsu YC. Hepatology 2014;5:1293-1302. Negro F, et al. Gastroenterology. 2015;149:1345-1360. Arase Y Hepatology 2009;49:739-44. George SL, et al. Hepatology. 2009;49:729-738.

Direct Acting Antivirals (DAA's)



Direct Acting Antivirals (DAA's)

- There are 3 targets on the hepatitis C virus that currently recommended DAA medications attack to destroy the virus. Each DAA medication attacks one of the following targets, and combination DAA tablets attack more than one target:
  - NS3/4A protease inhibitors
  - NS5A polymerase inhibitors
  - NS5B polymerase inhibitors

DAAs Name shows where the drug is working on the virus

Target	NS3/4A: Protease Inhibitors (-previr)	NS5A: Replication Complex Inhibitors (-asvir)	NS5B: Polymerase Inhibitors (-buvir)
	Grazoprevir Glecaprevir Voxilaprevir Boceprevir* Telaprevir* Simeprevir* Paritaprevir*	Ledipasvir Elbasvir Vepatasvir Pibrentasvir Ombitasvir* Daclatasvir*	Nucleotide: Sofosbuvir Non-nucleoside: Dasabuvir*

*no longer available in US

Trade and Generic Names for HCV DAA Medications

DAA Trade Name	DAA Generic Name	Abbreviation
Harvoni®	ledipasvir/sofosbuvir	LDV/SOF
Zepatier®	elbasvir/grazoprevir	EBR/GZR
Epclusa®	sofosbuvir/velpatasvir	SOF/VEL
Vosevi®	sofosbuvir/velpatasvir/voxilaprevir	SOF/VEL/VOX
Mavyret®	glecaprevir/pibrentasvir	GLE/PIB

HCV Treatment Regiments by Class

DAA Treatment Regimen	NS3/4A Protease Inhibitor	NS5B Nucleotide Polymerase Inhibitor	NS5A Polymerase Inhibitor
LDV/SOF ± RBV		✔	✔
EBR/GZR ± RBV	✔		✔
SOF/VEL ± RBV		✔	✔
SOF/VEL/VOX	✔	✔	✔
GLE/PIB	✔		✔

RBV = ribavirin

HCV Regimens by Genotype

Regimen	Class	GT1	GT2	GT3	GT4	GT5/6
Ledipasvir/sofosbuvir (LDV/SOF) *1 tablet QD* *Harvoni®*	NS5A/NS5B	✓			✓	✓
Elbasvir/grazoprevir (EBR/GZR) *1 tablet QD* *Zepatier®*	NS5A/PI	✓			✓	
Glecaprevir/pibrentasvir (G/P) * *3 tablets QD with food* *Mavyret®*	NS5A/PI	✓	✓	✓	✓	✓
Sofosbuvir/velpatasvir (SOF/VEL) * 1 tablet QD *Epclusa®, agEpclusa®*	NS5B/NS5A	✓	✓	✓	✓	✓
Sofosbuvir/velpatasvir/voxilaprevir (S/V/V) * 1 tablet QD with food *Vosevi®*	NS5A/PI/ NS5B	✓	✓	✓	✓	✓

Treatment duration is usually between 8-12 weeks

**DAAs which work on all the genotypes are considered "pan-genotypic"*

PI Protease inhibitor

Defining Cirrhosis for Treatment

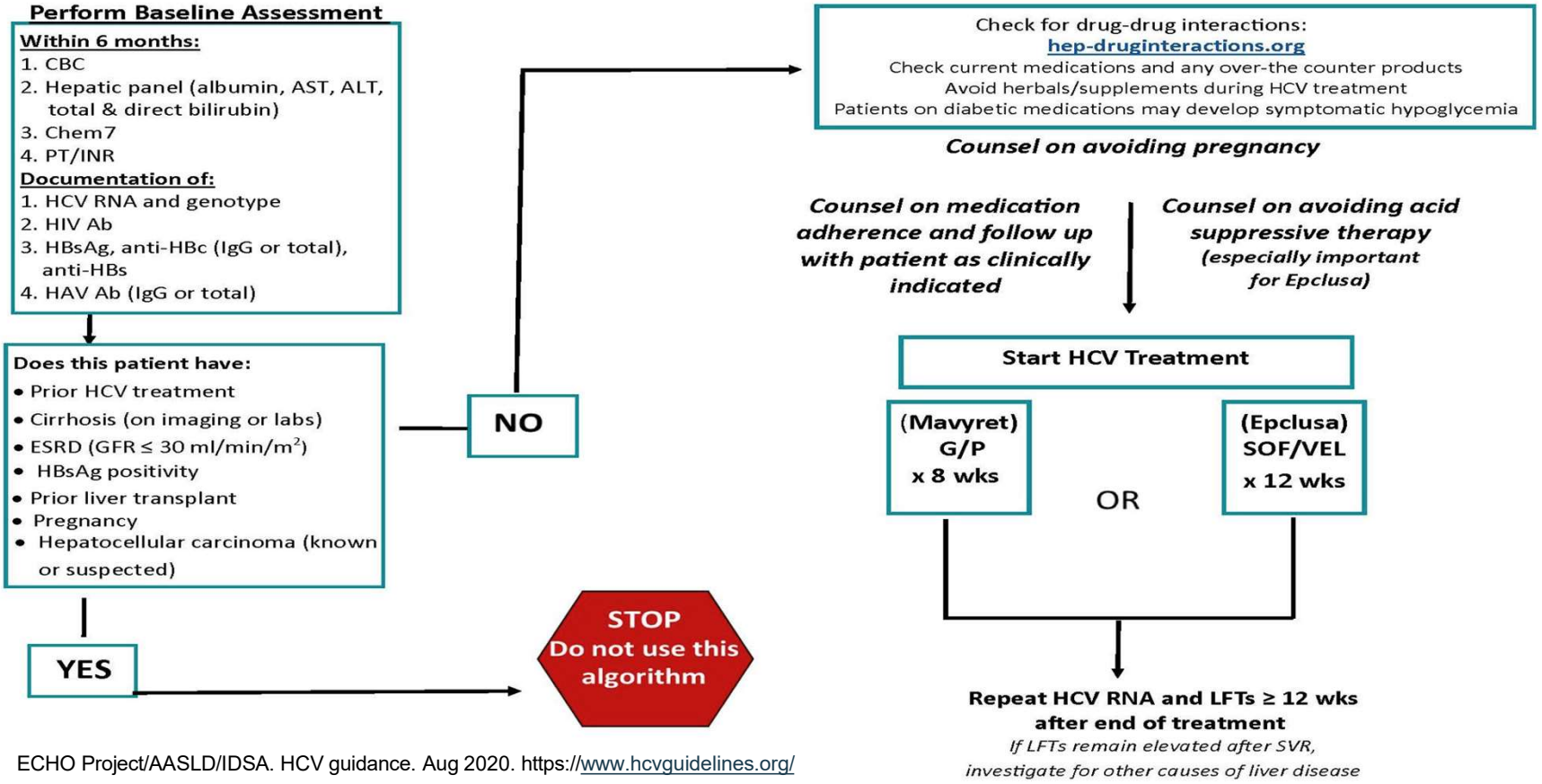
- Transient elastography (e.g., Fibroscan stiffness >12.5 kPa)
- Clinical evidence: abdominal ultrasound (nodularity, splenomegaly), platelets <150k
- Serum markers:
  - APRI score > 2 (uses AST and age)
  - FIB-4 score > 3.25 (uses AST, platelets, age)

Compensated	Decompensated
CTP A + Not experienced any of the following: ▪ Ascites ▪ Variceal bleed ▪ Hepatorenal syndrome ▪ Hepatic encephalopathy ▪ Jaundice	CTP B/C OR Experienced any of the following: ▪ Ascites ▪ Variceal bleed ▪ Hepatorenal syndrome ▪ Hepatic encephalopathy ▪ Jaundice

CTP = Childs Turcotte Pugh score

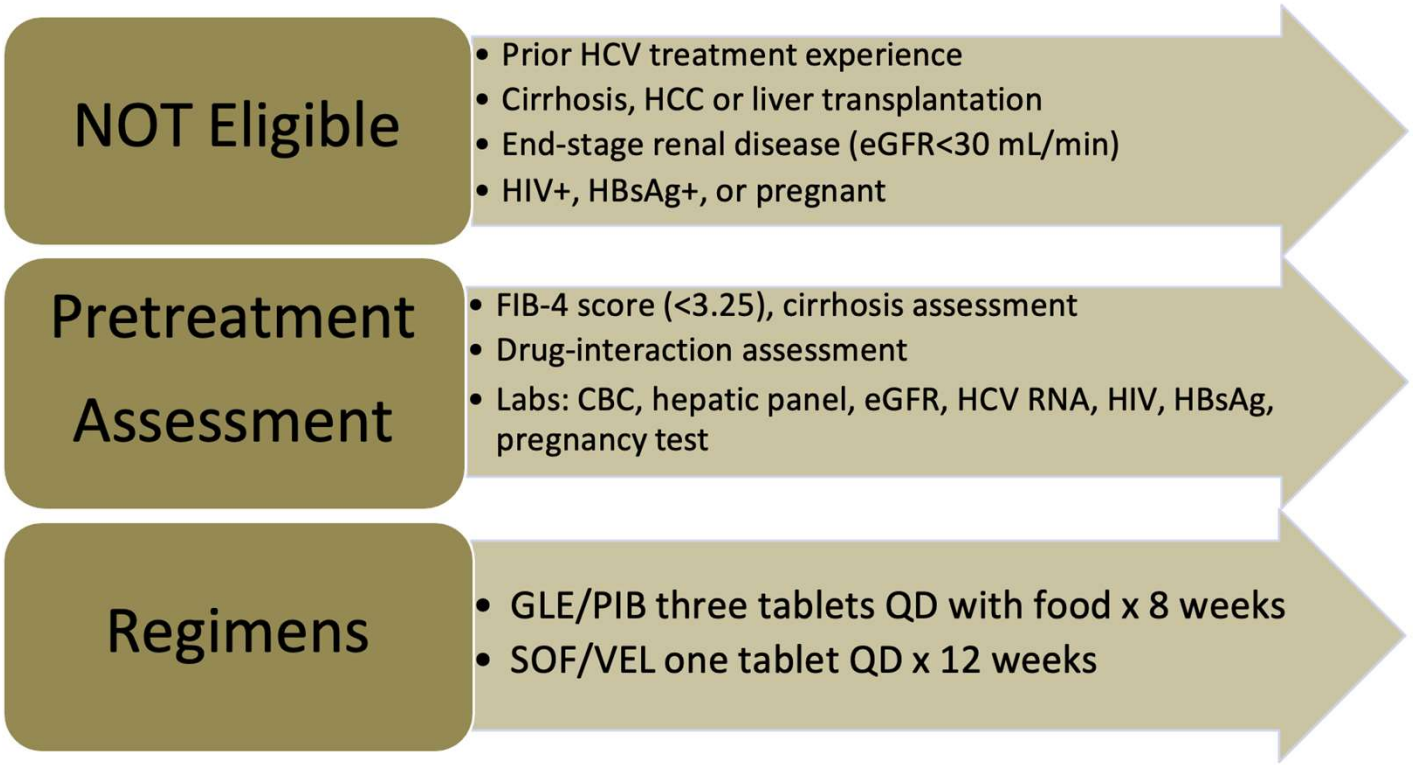
https://www.hepatitisc.uw.edu/page/clinical-calculators/ctp

Simplified HCV Treatment Algorithm Any Genotype



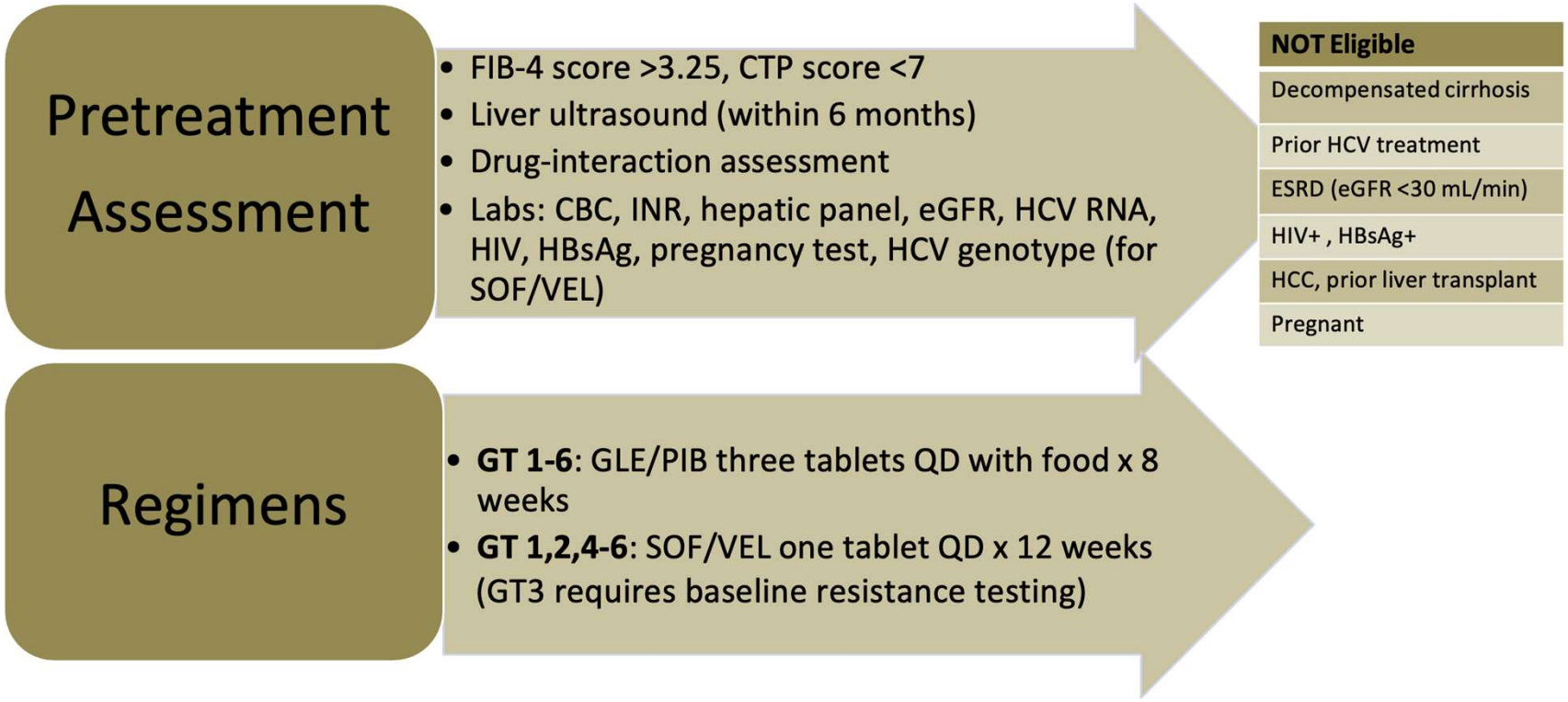
ECHO Project/AASLD/IDSA. HCV guidance. Aug 2020. https://www.hcvguidelines.org/

Simplified HCV Treatment: Naïve, Without Cirrhosis, Any Genotype



AASLD/IDSA. HCV guidance. Aug 2020. https://www.hcvguidelines.org/

Simplified HCV Treatment: Naïve, With Compensated Cirrhosis, Any Genotype



AASLD/IDSA. HCV guidance. Aug 2020. https://www.hcvguidelines.org/

Recommended Guidance: DAA - Experienced

Failed Regimen	Recommended Treatment	Duration
SOF-based failure *Epclusa®Harvon®* ELB/GZR failure *Zepatier®*	SOF/VEL/VOX	12 weeks
GLE/PIB failure *Mavyret®*	GLE/PIB + SOF + RBV SOF/VEL/VOX*	16 weeks 12 weeks
SOF/VEL/VOX failure *Vosevi®*	GLE/PIB + SOF + RBV SOF/VEL/VOX + RBV	16 weeks 24 weeks
Any regimen in a patient with decompensated cirrhosis	Refer to specialist	

* Add RBV if cirrhosis

AASLD/IDSA. HCV guidance. Aug 2020. https://www.hcvguidelines.org/

What About Medications in Patients with HCV?

- Avoid herbals
- Verify potential drug interactions using the ***Liverpool*** website
- In patients with cirrhosis
  - Avoid NSAIDs
  - Acetaminophen preferred for short-term treatment of pain management at <2 grams per day
- **Recommend birth control in all female patients of childbearing age/capacity**
  - Avoid ethinyl estradiol with glecaprevir/pibrentasvir
- Studies in pregnancy currently enrolling

  "Despite the lack of a recommendation, treatment can be considered during pregnancy on an individual basis after a patient-physician discussion about the potential risks and benefit

HCV guidelines.org. Accessed July 1, 2023

Main Drug Interaction Concerns for DAAs

- **Acid-reducing agents:** ↓ in LDV and VEL concentrations; dosing/administration adjustments with ledipasvir and velpatasvir containing products
- **Amiodarone:** *AVOID* sofosbuvir-containing regimens: risk of bradycardia/cardiac arrest
- **Antiepileptics:** *AVOID* carbamazepine, phenytoin, phenobarbital, oxcarbazepine: ↓ in DAA concentration and potential subtherapeutic antiviral effect
- **Antimycobacterials:** *AVOID* rifampin, rifabutin, **rifapentine:** ↓ in DAA concentration
- **HIV Antiretrovirals:** Integrase inhibitor-based regimens generally preferred
- **Statins:** some require dosing adjustments; others avoid use while on treatment
- **St. John's Wort:** *AVOID* due to ↓ in DAA concentration

Refer to FDA Package Labeling for complete drug interaction information /University of Liverpool HEP Drug Interactions: www.hep-druginteractions.org

DAAs With Acid Reducing Agents

HCV Drug	QD PPI*	H_2 Blocker†	Al or Mg Antacids
Ledipasvir/sofosbuvir *Harvoni®*	Administer together on empty stomach	Administer together or 12 hrs apart	Separate by 4 hours
Sofosbuvir/velpatasvir *Epclusa®, ag Epclusa®*	Not recommended, but *if medically necessary,* take with food 4 hrs before omeprazole ≤ 20 mg/day	Administer together or 12 hrs apart	Separate by 4 hours
Sofosbuvir/velpatasvir/ voxilaprevir *Vosevi®*	Omeprazole ≤ 20 mg/day	Administer together with food or 12 hrs apart	Separate by 4 hours
Glecaprevir/pibrentasvir *Mavyret®*	No significant interaction (studied with omeprazole doses up to 40mg QD; GLE Cmax and AUC reduced by 46% and 49%)	No clinically significant interaction	No interaction

Velpatasvir requires acidity for absorption

*Not to exceed omeprazole 20 mg/day (or comparable PPI dose); do not use BID PPI

†Not to exceed famotidine 40 mg BID

Drug interactions: https://www.hep-druginteractions.org/

Considerations: Statins in Cirrhosis

- Pharmacokinetics of Statins are Altered in Cirrhosis
  - Most statins metabolized via CYP P450 system prior to biliary excretion
  - Also reliant on transport mechanisms such as OATPs, P-gp, and BCRP
  - Synthetic dysfunction in cirrhosis causes altered pharmacokinetics
  - Rosuvastatin and Pravastatin require minimal metabolization prior to biliary excretion, and thus have pharmacokinetics closer to baseline despite decreased liver function
- Statins safe in compensated cirrhosis
  - Preponderance of evidence shows that statins are still safe despite the change in pharmacokinetics
  - Meta-analysis shows that rather than worsening of liver function, there was a statistically significant improvement in disease progression and mortality
- Statins in decompensated cirrhosis –approach with caution
  - Concern that as the pharmacokinetics of statins become more altered in advanced cirrhosis, there will be an increase in adverse events
  - Cautious approach with close monitoring

Francis P and Lisa Forman L. Use of Statins in Patients With and Without Liver Disease. Clinical Liver Disease. Volume 15, Issue 1 p. 40-45 https://doi.org/10.1002/cld.866

Statins – DAA's Medication Interactions

	EBR/GZR *Zepatier®*	GLE/PIB Mavyret®	LDV/SOF *Harvoni®*	SOF/VEL Epclusa®	SOF/VEL/VOX Vosevi®
Rosuvastatin	dose ≤10 mg once daily	dose ≤10 mg once daily	X potential for myopathy and rhabdomyolysis	dose ≤10 mg daily	X potential for myopathy and rhabdomyolysis
Atorvastatin	dose ≤20 mg once daily	X potential for myopathy and rhabdomyolysis	use lowest necessary dosage	use lowest necessary dosage	Use lowest approved statin dose
Simvastatin, Lovastatin	use lowest necessary dosage, titrate carefully; monitor closely	x potential for myopathy and rhabdomyolysis)	use lowest necessary dosage	use lowest necessary dosage	Use lowest approved statin dose
Pravastatin	√	Reduce statin dose by 50%	√	√	dose ≤40 mg daily
Fluvastatin	use lowest necessary dosage, titrate carefully; monitor closely	use lowest necessary dosage, titrate carefully; monitor closely	use lowest necessary dosage	use lowest necessary dosage	Use lowest approved statin dose

Refer to package Insert for the most up-to-date full information on drug interactions and adverse effects

Ribavirin

- Limited Use
  - Added to treatment in specific clinical scenarios
    - Patients with decompensated cirrhosis who can tolerate ribavirin
  - Well-known toxicity profile
    - Hemolytic anemia
    - Teratogenic
      - Pregnancy category X
      - Pregnancy testing and CBC (at least every 4 weeks)

https://www.cdc.gov/lyme/index.html

Treatment Options for Patients with Decompensated Cirrhosis

- Sofosbuvir/velpatasvir (*Epclusa*®) plus ribavirin x 12 weeks
  - Use of ribavirin requires frequent monitoring for hemolytic anemia
    - Patients with decompensated cirrhosis who can tolerate ribavirin
  - Sofosbuvir/velpatasvir (*Epclusa*®) x 24 weeks
  - All protease inhibitor therapy is contraindicated in decompensated cirrhosis due to reports of serious liver injury

https://www.cdc.gov/lyme/index.html

DAAs: Treatment Specific Considerations

	LDV/SOF *Harvoni®*	EBR/GZR *Zepatier®*	SOF/VEL *Epclusa®*	GLE/PIB *Mavyret®*	SOF/VEL/VOX *Vosevi®*
Pill burden	1 pill	1 pill	1 pill	3 pills	1 pill
Frequency	QD	QD	QD	QD	QD
Food requirement	none	none	none	With food	With food
Duration	8-12 wks	12-16 wks	12 wks	8-16 wks	12 -24 wks
Special Packaging	traditional	2 week bubble pack	traditional	daily packet	traditional
Common drug Interactions	PPIs/H2RA, antacids, statins	Ketoconazole; statins; PDE inhibitors	PPI's/H2RA antacids	statins, EE, dabigatran	Statins, EE, H2RA antacids, dabigatran, edoxaban
Decompensated Cirrhosis	OK	Do not Use in CTP B or C	OK	Do not Use in CTP B or C	Do not Use in CTP B or C
Resistance testing	+/- GT1a	GT1a	GT3		
Adverse Effects	fatigue, headache, nausea	fatigue, headache, nausea	headache, fatigue, nausea	headache, fatigue, nausea	headache, fatigue, diarrhea, nausea

Refer to package Insert for the most up-to-date full information on drug interactions and adverse effects

Side Effect Profiles of DAAs

- Prior treatments:
  - Interferon:
    - Flu-like symptoms: fever, headache, myalgia
    - Fatigue
    - Depression
    - Irritability
    - Insomnia
    - Nausea/ vomiting
    - Anorexia
    - Cognitive dysfunction
  - Ribavirin:
    - Rash
    - Nausea/vomiting
    - Headache

- Direct Acting Antivirals:
  - Overall very well tolerated
  - Most commonly reported side effects:
    - Headache
    - Fatigue
    - Nausea
    - Diarrhea (reported with voxilaprevir)

Refer to package Insert for the most up-to-date full information on drug interactions and adverse effects

What Predicts Treatment Success or Failure?

- Patients who are treatment naïve and non-cirrhotic have very high SVR rates
- Underlying cirrhosis can decrease SVR
- Medication adherence

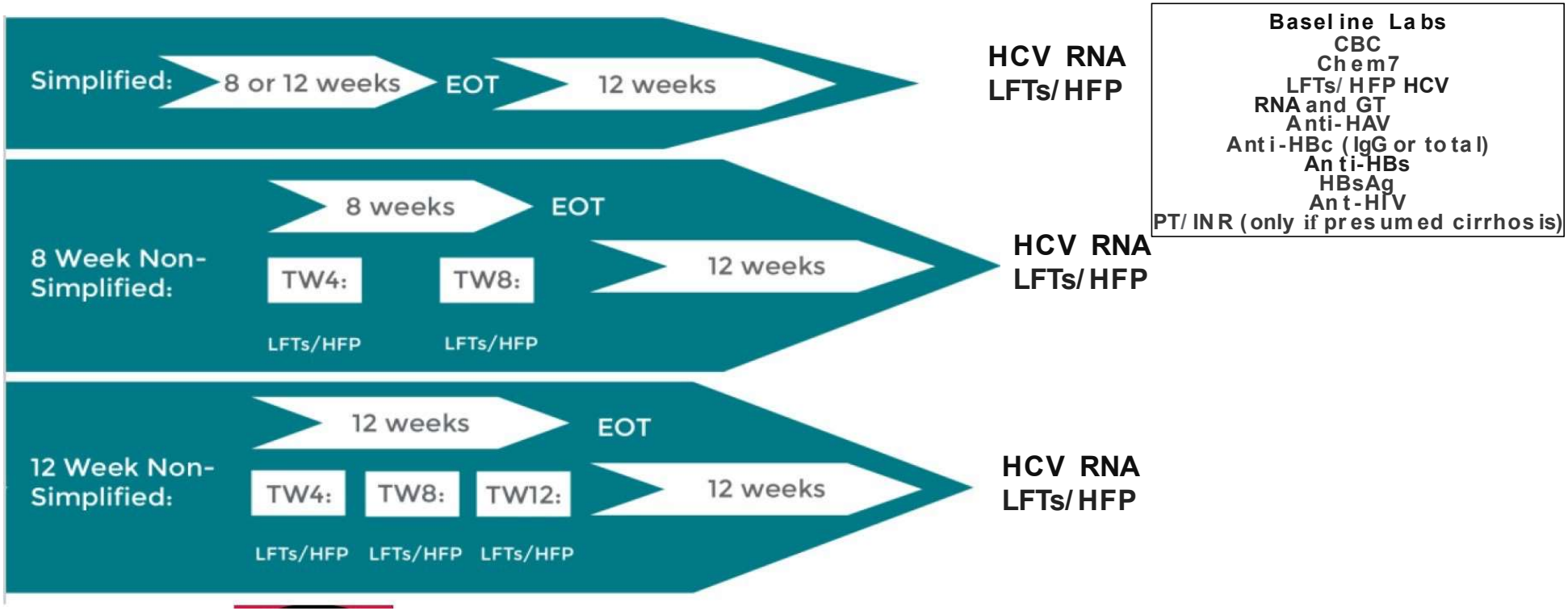
Laboratory Abnormalities with DAAs

- Overall not common
- Observed laboratory abnormalities:
  - Anemia with concomitant use of ribavirin
    - Ribavirin causes hemolytic anemia
- Potential laboratory abnormalities:
  - Improvement in liver disease can affect other medications:
    - Hypoglycemia: Patients on diabetic medications may require closer follow-up and reduction in diabetic medication, "*particularly true for diabetic medications known to cause hypoglycemia*"
  - Changes in INR with warfarin

HBV Reactivation Risk in HCV

- FDA warning issued 2016 following 24 reported cases of HBV reactivation in patients treated with HCV DAAs
  - 2 deaths
  - 1 liver transplant
- Mechanism of reactivation unclear
  - HCV DAAs do not have immunosuppressive effects
- Current recommendations are to “evaluate patients for potential coinfection of HCV and HBV”
  - ***All patients should be tested for anti-HBc, HBsAg, anti-HBs***

HCV On-Treatment Monitoring



EOT: End of Treatment, TW: Treatment Week

UNM ECHO Project HCV On-Treatment Monitoring Accessed July 1, 2023

Key Monitoring During and After HCV Treatment

- Cirrhotics
  - Clinical signs of decompensation
  - Liver panel as clinically indicated
- EBR/GZR (*Zepatier*®): ALT at baseline and Wk 8; If elevated at Wk 8, re-assess at Wk 12
- Ribavirin
  - Pregnancy testing and CBC (at least every 4 weeks)

Post-treatment

- SVR →HCV RNA 12 weeks after treatment completion
- No need to re-check HCV RNA after SVR unless suspect re-infection
- HCV antibody *will remain positive*!! No need to recheck
- Ongoing risk? Recheck HCV RNA annually
- Cirrhotics → continue to monitor for HCC q6months (ultrasound + AFP)

Review Questions

In addition to confirming acute HCV infection, a positive HCV Ab result is also used for?

a) To measure a patient's baseline viral load prior to starting HCV therapy
b) To monitor a patient's response to therapy
c) To determine whether a patient has achieved a sustained virologic (SVR) response
d) All of the above
e) Only b and c

Review Questions

A provider has decided to start a patient with reactive HCV RNA and compensated cirrhosis on glecaprevir/pibrentasvir for the treatment of Hepatitis C, but the patient was diagnosed with chronic GERD last week and the gastroenterologist recommended starting a PPI. The provider asks you for your recommendation on what to start. Which of the following is the best recommendation:

a) Omeprazole 40mg cap by mouth daily
b) Omeprazole 20mg cap by mouth twice daily
c) Omeprazole 20mg cap by mouth daily
d) Only b and c

Review Questions

What pair of Direct Acting Antivirals are considered Pangenotypic and first-line regiments on naïve treatment, non-cirrhotic patients?

a) GLE/PIB (100/40 mg, Mavyret®) x 8 weeks, SOF/VEL (400/100 mg, Epclusa®) x 12 weeks
b) GLE/PIB (100/40 mg, Mavyret®) x 8 weeks, EBR/GZR (50/100 mg, Zepatier®) x 12 weeks
c) SOF/VEL (400/100 mg, Epclusa®) x 12 weeks, SOF/VEL/VOX (400/100/100 mg, Vosevi®) x 12 weeks
d) Only a and c

References

- AASLD-IDSA Hepatitis C Guidance Update: Recommendations for testing, managing, and treating hepatitis C virus infection. https://www.hcvguidelines.org/
- EASL Recommendations on Treatment of Hepatitis C 2018. Journal of hepatology 2018: 69; 461- 511.
- Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945-1964. MWWR 2012;61(RR04);1-18: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6104a1.htm
- U.S. Preventive Services Task Force. Final Recommendation Statement: Hepatitis C: Screening.
  April 2020
  https://www.cdc.gov/mmwr/volumes/69/rr/rr6902a1.htm
- CDC Division of Viral Hepatitis: https://www.cdc.gov/hepatitis/index.htm
- University of Liverpool HEP Drug Interactions: www.hep-druginteractions.org

Questions?