Northwest Portland Area
Indian Health Board
Indian Leadership for Indian Health

HCV Treatment Overview

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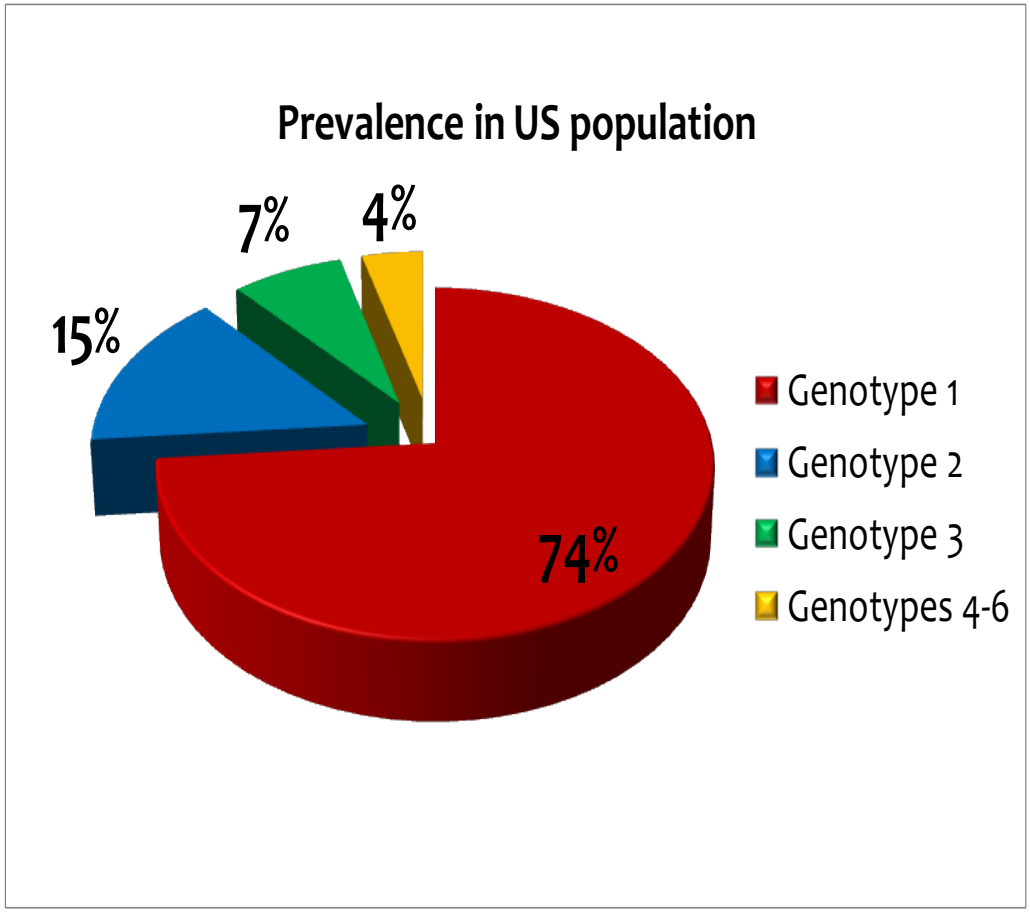
Presentation prepared by:
Date prepared:

Conflict of Interest Disclosure Statement

Paulina Deming has attended an HCV advisory meeting for Gilead

Brad Moran has no relevant conflicts of interest

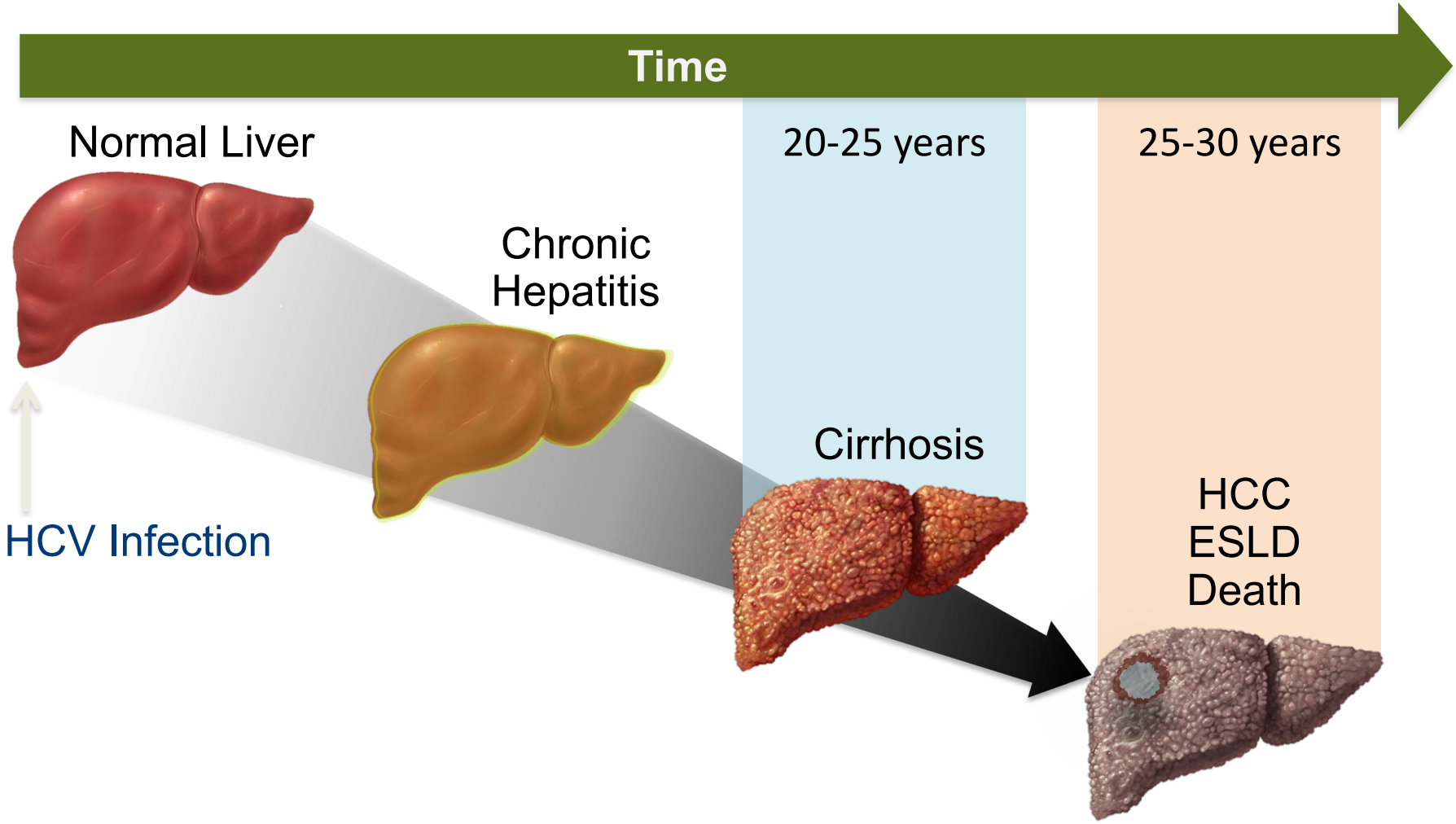
Hepatitis C Virus



- RNA virus
- 6 major genotypes (1-6), most with subtypes
- Genotype 1 is most common

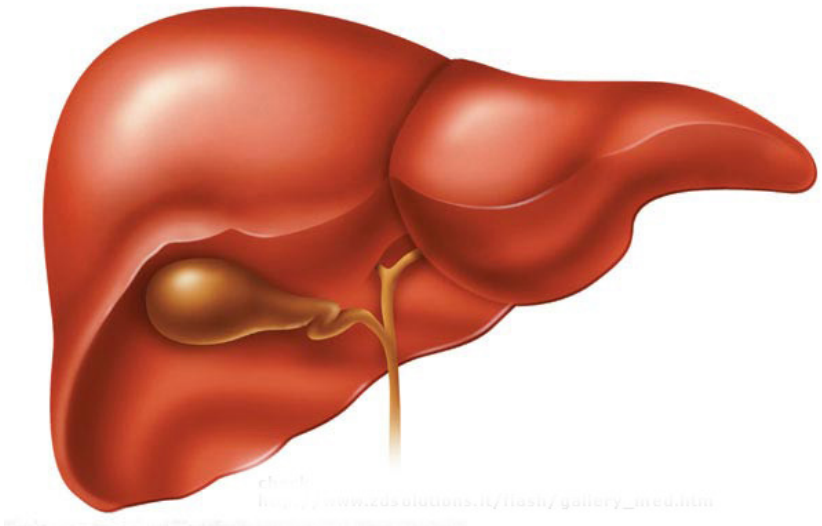
Alter MJ *et al. N Engl J Med* 1999; 341:556-62

Hepatitis C: Progression of Disease



Hepatitis web study

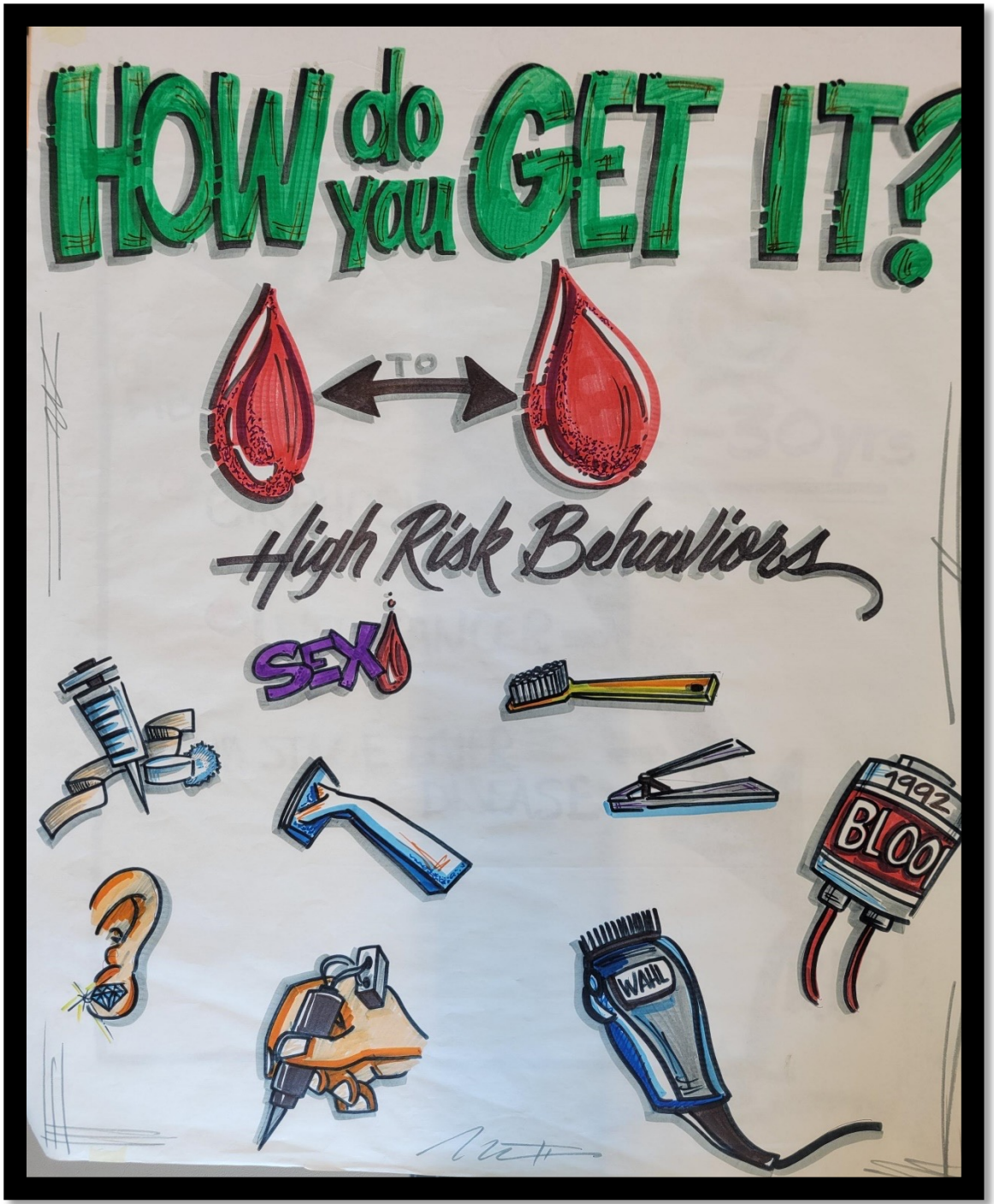
HCV IS NOT JUST A LIVER DISEASE



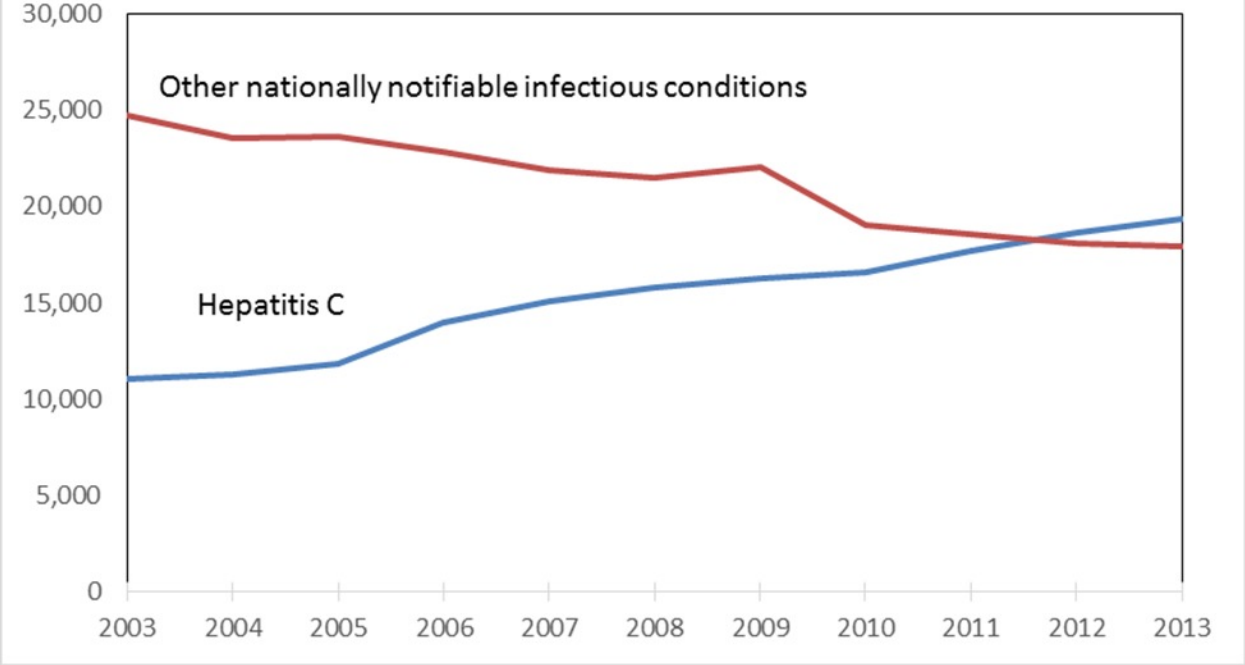
Common symptoms:
Fatigue
Impaired cognitive function (brain fog)
Migratory arthralgia or myalgia
Depression

Extrahepatic manifestations:
Renal Disease
Peripheral Neuropathy
Dermatologic Manifestations
Diabetes
Lymphomas

HCV is transmitted through blood



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

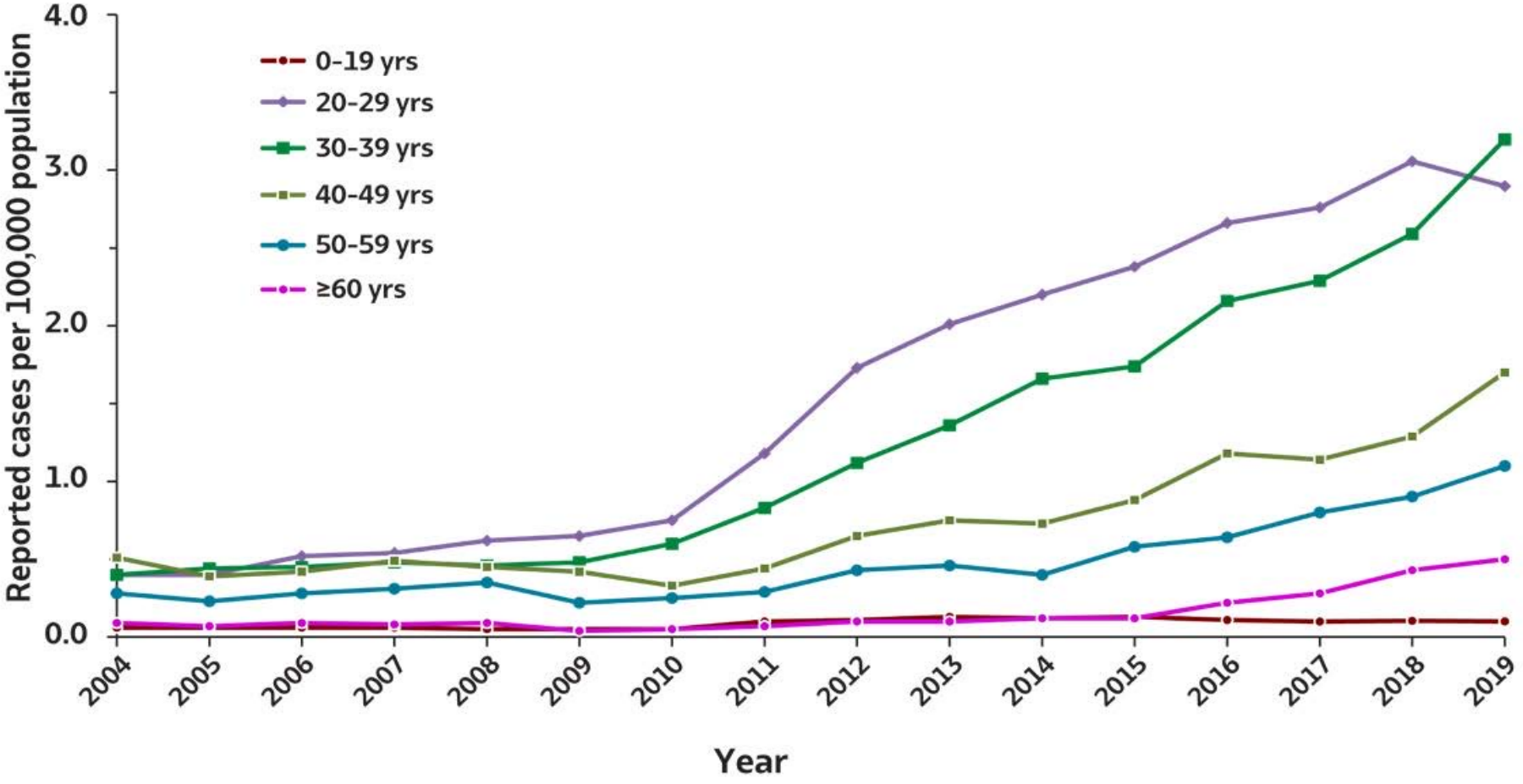


Division of Viral Hepatitis

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

Holmberg S, et al. "Continued Rising Mortality from Hepatitis C Virus in the United States, 2003-2013"
Presented at ID Week 2015, October 10, 2015, San Diego, CA

Figure 3.4. Rates of reported acute hepatitis C virus infection, by age group — United States, 2004–2019



Source: CDC, National Notifiable Diseases Surveillance System.

WHO SHOULD BE SCREENED FOR HCV?

Final Recommendation Statement

Hepatitis C Virus Infection in Adolescents and Adults: Screening

Recommendations made by the USPSTF are independent of the U.S. government. They should not be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Recommendation Summary

Population	Recommendation	Grade (What's This?)
Adults aged 18 to 79 years	The USPSTF recommends screening for hepatitis C virus (HCV) infection in adults aged 18 to 79 years.	B

To read the recommendation statement in *JAMA*, select here.

To read the evidence summary in JAMA, select here.

See the Clinician Summary for a more detailed summary of the recommendation for clinicians.

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https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/hepatitis-c-screening1

Alcohol and On-going Substance Use

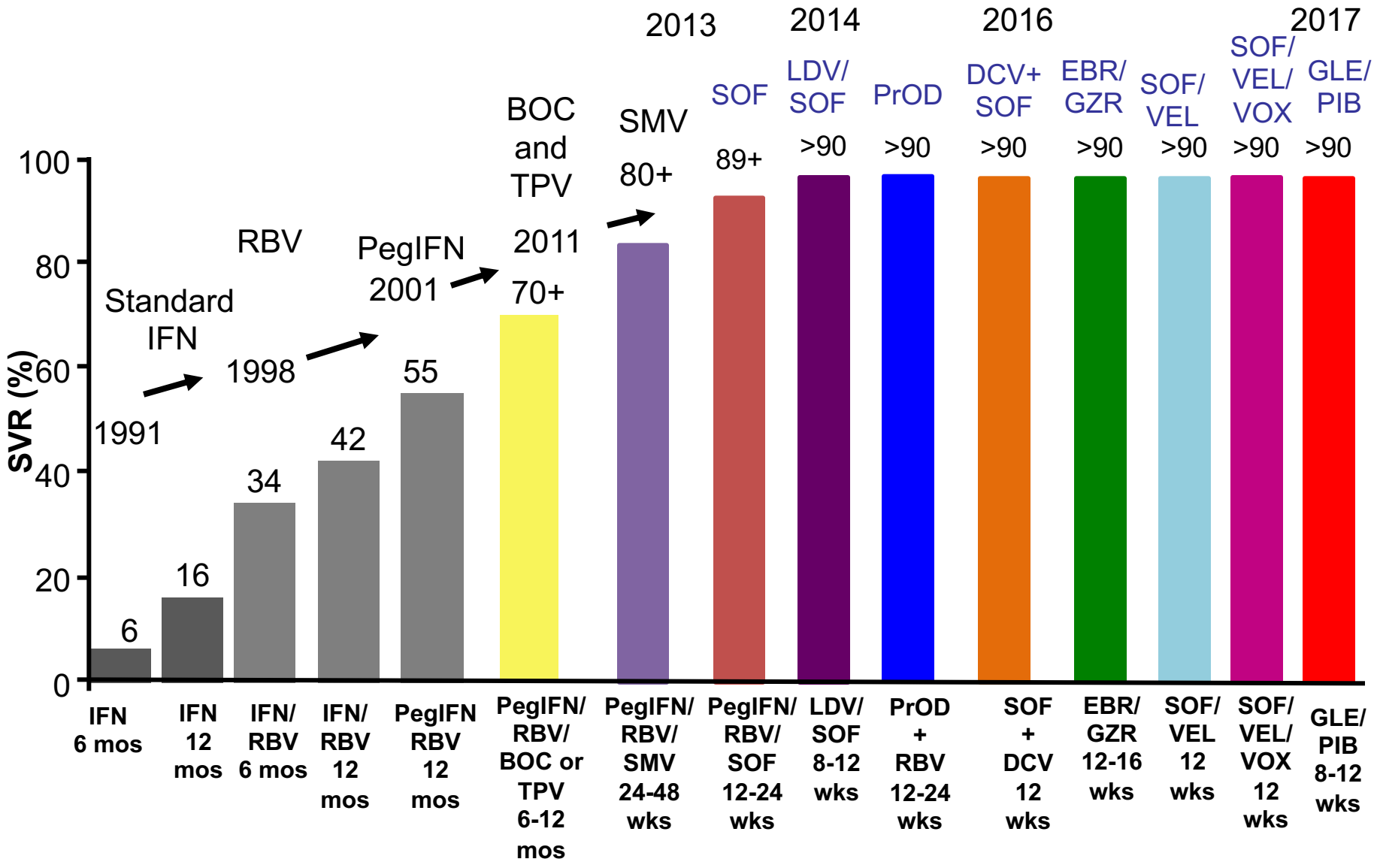
- **No indications to withhold HCV therapy based on active alcohol or substance use**

HCVguidelines.org
Accessed January 25, 2022

Goals of HCV Therapy

- Cure
  - Defined as sustained virologic response (SVR)
- Improvements in liver function
  - Improvements in fibrosis, reversal of cirrhosis?
  - Prevent decompensation
- Improvements in extrahepatic manifestations of HCV
- Prevent deaths due to liver disease complications
- Prevent liver cancer
- Reduce rates of liver cancer recurrence

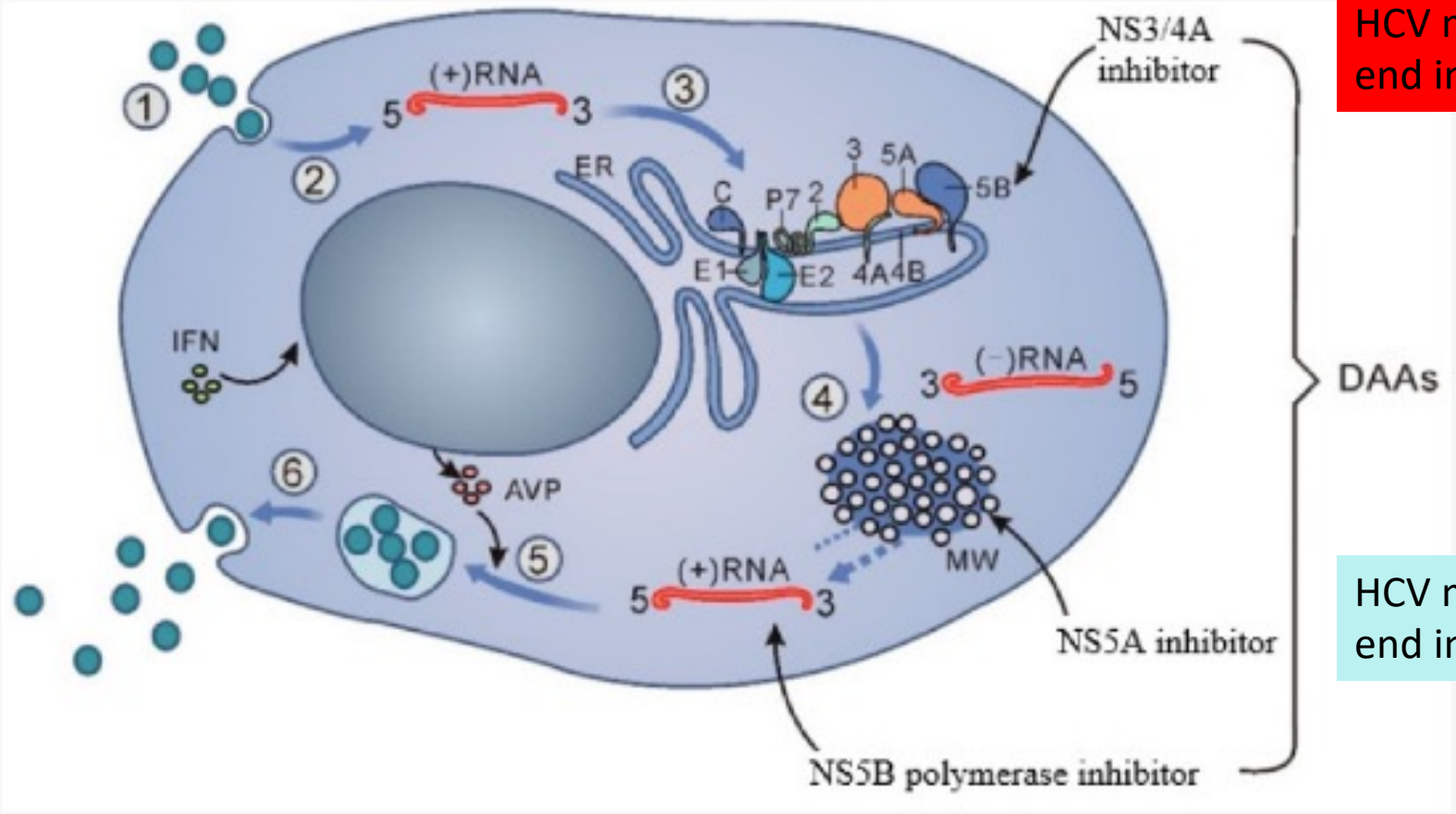
The Evolution of Highly Effective Treatment



Differences in HCV Therapy

- Interferon Based
  - Injectable
  - Long duration of treatment
  - High side effect profile
  - Multiple laboratory abnormalities
  - Low cure rates
- Direct Acting Antivirals
  - Oral
  - Short durations
  - Minimal side effects
  - Minimal laboratory abnormalities
  - High cure rates

Direct Acting Antivirals (DAAs) Work on the Hepatitis C Virus



HCV meds that end in "previr"

HCV meds that end in "asvir"

HCV meds that end in "buvir"

HCV Direct Acting Antivirals (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	Ledipasvir	Nucleotide: Sofosbuvir
	Glecaprevir	Elbasvir	
	Voxilaprevir	Velpatasvir	Non-nucleoside:
		Pibrentasvir	Dasabuvir*
Pulled from market	Boceprevir		
	Telaprevir	Ombitasvir*	
	Simeprevir	Daclatasvir*	
	Paritaprevir*		

*no longer available in US

HCV Direct Acting Antivirals (DAAs) Generic Name	Brand Name	
Glecaprevir/Pibrentasvir	Mavyret®	Pangenotypic- most commonly used
Sofosbuvir/ Velpatasvir	Epclusa® agEpclusa®	
Ledipasvir/Sofosbuvir	Harvoni® agHarvoni®	Limited use; effective against HCV genotypes 1 and 4 only
Elbasvir/ Grazoprevir	Zepatier®	
Sofosbuvir/ Velpatasvir/Voxilaprevir	Vosevi®	
Other Therapies		
Ribavirin	Ribasphere®, RibaPak®, Copegus®, Rebetol®	

HCV therapies which act on all HCV genotypes are considered "pan-genotypic"

Box Warning on All HCV DAAs: HBV Reactivation Risk

- 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***
  - ***Patients with reactive HBsAg require further evaluation prior to HCV treatment***

Glecaprevir/Pibrentasvir

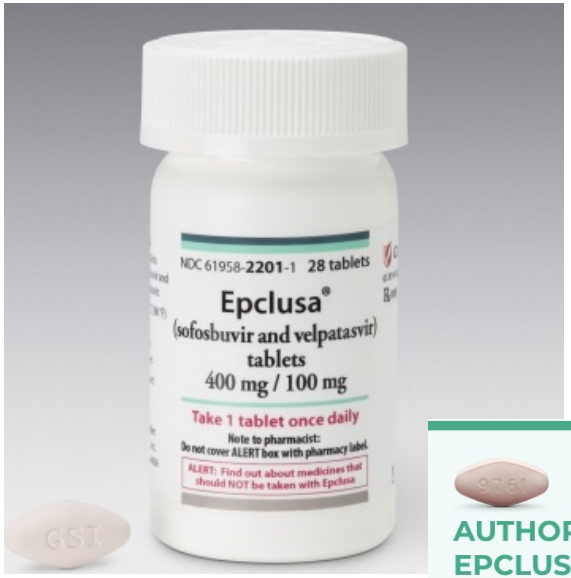
- Combination of
  - Glecaprevir an NS3/4A protease inhibitor
  - Pibrentasvir an NS5A inhibitor
- Dosage and administration: 3 tablets once daily with food
- Indicated for 8 weeks for HCV genotypes 1, 2, 3, 4, 5, or 6

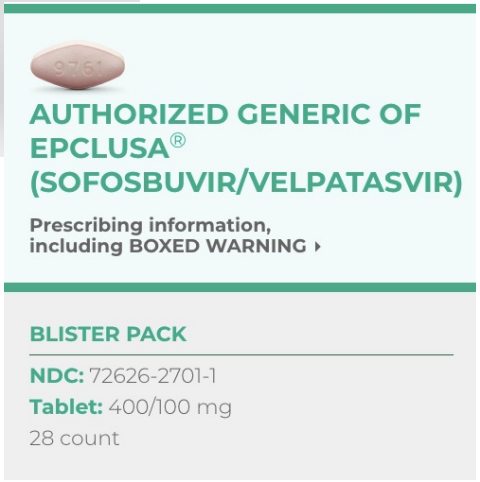
Who Can Be Treated with Glecaprevir/Pibrentasvir?

- Patients without cirrhosis
- Patients with Child's class A cirrhosis (compensated cirrhosis)
- Do not use in patients with Child's Class B or Child's Class C cirrhosis (decompensated cirrhosis)
- Patients with renal insufficiency including patients on dialysis

- Approved for use in children 3 yo and older

Sofosbuvir/Velpatasvir





- Fixed-dose combination of sofosbuvir (NS5B inhibitor) and velpatasvir (NS5A inhibitor)
- Approved for chronic HCV genotypes 1, 2, 3, 4, 5, or 6 for 12 weeks
- Administration
  - 1 tablet once daily with or without food
  - Requires acidic environment for absorption

Epclusa [package insert]. Foster City, CA: Gilead Sciences, Inc.; 2016.

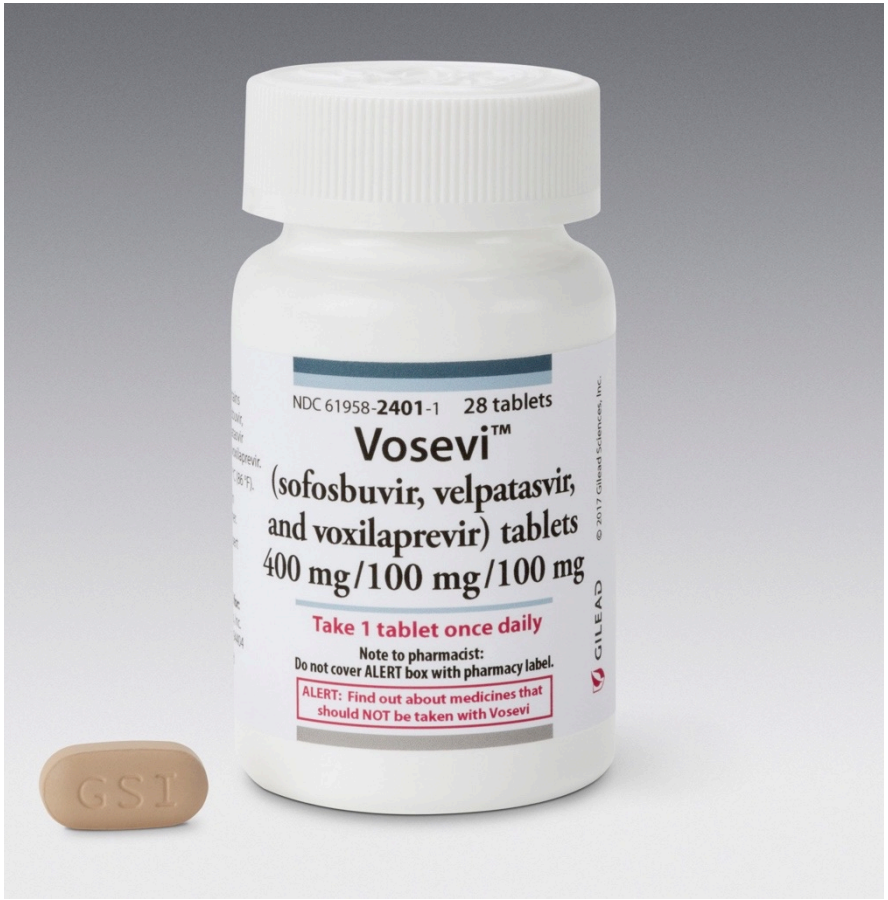
Who Can Be Treated with SOF/VEL?

- Patients without cirrhosis
- Patients with cirrhosis, including Child's class A, B or C cirrhosis

- Patients with renal insufficiency including patients on dialysis

- Approved for use in pediatric patients 3 years old and older

Sofosbuvir/Velpatasvir/Voxilaprevir



Vosevi [package insert]. Foster City, CA: Gilead Sciences, Inc.; 2017.

- Combination of
  - NS5B polymerase inhibitor (Sofosbuvir);
  - NS5A inhibitor (Velpatasvir);
  - NS3/4A protease inhibitor (Voxilaprevir)
- Administration
  - One tablet once daily with food
- Indicated for patients who previously failed DAA therapy, genotypes 1-6

Who Can Be Treated with SOF/VEL/VOX?

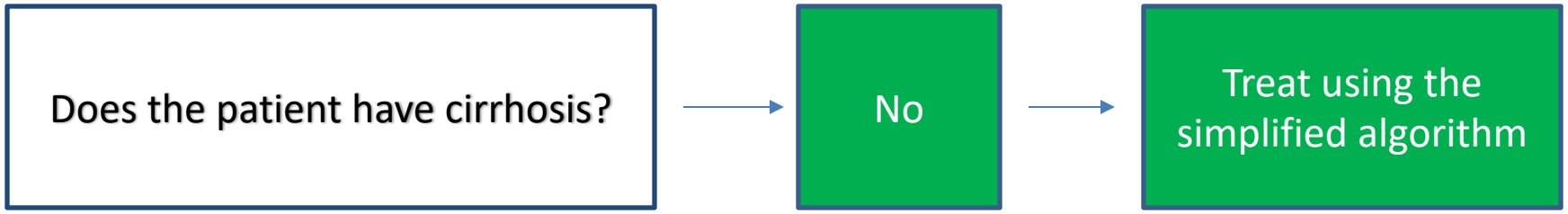
- Patients without cirrhosis
- Patients with Child's class A cirrhosis (compensated cirrhosis)
- Patients with renal insufficiency including hemodialysis

- Not recommended in patients with Child's Class B or C cirrhosis

Ribavirin

- Still utilized in combination with other HCV therapies in more difficult to treat patient populations and/or when specific resistance concerns exist
- Well-known to cause toxicity profile
  - Hemolytic anemia
    - Occurs within 1-2 weeks and peaks after 4-6 weeks
    - Can see increase in indirect bilirubin
  - Teratogenic
    - Pregnancy category X

General Approach to HCV Treatment



Version: 3/17/2020

Simplified HCV Treatment Algorithm, any Genotype

Perform Baseline Assessment

Within 6 months:

1. CBC
2. Hepatic panel (albumin, AST, ALT, total & direct bilirubin)
3. Chem7
4. PT/INR

Documentation of:

1. HCV RNA and genotype
2. HIV Ab
3. HBsAg, anti-HBc (IgG or total), anti-HBs

Does this patient have:

- Prior HCV treatment
- Cirrhosis (on imaging or labs)
- ESRD (GFR ≤ 30 ml/min/m^2)
- HIV
- HBsAg positivity
- Prior liver transplant
- Pregnancy
- Hepatocellular carcinoma (known or suspected)

NO

Check for drug-drug interactions:
hep-druginteractions.org
Check current medications and any over-the counter products
Avoid herbals/supplements during HCV treatment

Counsel on avoiding pregnancy

Counsel on medication adherence and follow up with patient as clinically indicated

Counsel on avoiding acid suppressive therapy (especially important for Epclusa)

Start HCV Treatment

(Mavyret) G/P x 8 wks

OR

(Epclusa) SOF/VEL x 12 wks

Repeat HCV RNA and LFTs ≥ 12 wks after end of treatment

If LFTs remain elevated after SVR, investigate for other causes of liver disease

YES

STOP
Do not use this algorithm

If there are any concerns regarding using this algorithm in a particular patient, please refer to individual genotype specific decision trees

Hepatitis Case Report Form

Body Mass Index	Height:	Weight:	BMI:

Hepatitis Vaccinations and Labs	Hepatitis A total or IgG antibody: ☐ Positive ☐ Negative	If needed has vaccination been started? ☐ Yes ☐ No
	Hepatitis B surface antibody (anti-HBs): ☐ Positive ☐ Negative Hepatitis B core antibody (anti-HBc): ☐ Positive ☐ Negative Hepatitis B surface antigen (HBsAg): ☐ Positive ☐ Negative	If needed has vaccination been started? ☐ Yes ☐ No

Laboratory

Basic Labs	**Date**	**Results**	**Basic Labs**	**Date**	**Results**	**Other Labs**	**Date**	**Results**
WBC			Alk Phos			AFP[3]		
HGB			AST					
HCT			ALT					
Platelets			T. Bili					
Creatinine			Direct Bili[1]					
Protime/INR			HIV Ab					
Total Prot			HCV RNA					
Albumin			HCV GT[2]					

[1]If available; [2] Genotype; [3] AFP for patients with known or suspected cirrhosis

Fibrosis Score	**Results**
APRI	
FIB-4	
For cirrhotic patients only	
MELD	
Child-Pugh	

Please list any imaging or transient elastography results, if applicable (e.g. ultrasound, fibroscan, etc.):

Hepatitis Case Report Form: HAV and HBV Serologies

Hepatitis A and B serologies to assess need for vaccination and risk of hepatitis B reactivation

Hepatitis Vaccinations and Labs	Hepatitis A total or IgG antibody: ☐ Positive ☐ Negative	If needed has vaccination been started? ☐ Yes ☐ No
	Hepatitis B surface antibody (anti-HBs): ☐ Positive ☐ Negative Hepatitis B core antibody (anti-HBc): ☐ Positive ☐ Negative Hepatitis B surface antigen (HBsAg): ☐ Positive ☐ Negative	If needed has vaccination been started? ☐ Yes ☐ No

Hepatitis Case Report Form: Assessing Liver Disease Severity

Laboratory

		Results	Basic Labs	Date	Results	Other Labs	Date	Results
WBC			Alk Phos			AFP[3]		
HGB			AST					
HCT			ALT					
Platelets			T. Bili					
[illegible]			Direct Bili[1]					
Protime/INR			HIV Ab					
Total Prot			HCV RNA					
Albumin			HCV GT[2]					

[1]If available; [2] Genotype; [3] AFP for patients with known or suspected cirrhosis

Complete Blood Count: Thrombocytopenia (<150K) associated with cirrhosis; other changes consistent with cirrhosis include neutropenia

Hepatitis Case Report Form: Assessing Liver Disease Severity

Laboratory

Basic Labs	Date	Results	Basic Labs	Date	Results	Other Labs	Date	Results
WBC			Alk Phos			AFP[3]		
HGB			AST					
HCT			[illegible]					
Platelets			T. Bili					
[illegible]			Direct Bili[1]					
Protime/INR			[illegible]					
[illegible]			HCV RNA					
Albumin			HCV GT[2]					

[1] If available; [2] Genotype; [3] AFP for patients with known or suspected cirrhosis

Identify changes consistent with cirrhosis- changes in hepatic synthetic function: elevated INR, low albumin, elevated direct bilirubin

Elevated AST and ALT are markers of inflammation, not of cirrhosis

A 2:1 ration of AST to ALT can be seen in cirrhosis

Findings of Cirrhosis

- Presence or history of ascites or esophageal varices
- Low platelet count (<150,000 mm^3)
- APRI $\geq$ 1.0
- FIB-4 $\geq$ 3.25
- Fibrosure $\geq$ 0.72
- Imaging with evidence of cirrhosis (nodular contour of liver or evidence of portal hypertension)
- Transient elastography consistent with cirrhosis
- Liver biopsy with F3 or F4 fibrosis

Hepatitis Case Report Form: Assessing Liver Disease Severity

Laboratory

Basic Labs	Date	Results	Basic Labs	Date	Results	Other Labs	Date	Results
WBC			Alk Phos			AFP[3]		
HGB			AST					
HCT			ALT					
Platelets			T. Bili					
Creatinine			Direct Bili[1]					
Protime/INR			HIV Ab					
Total Prot			HCV RNA					
Albumin			HCV GT[2]					

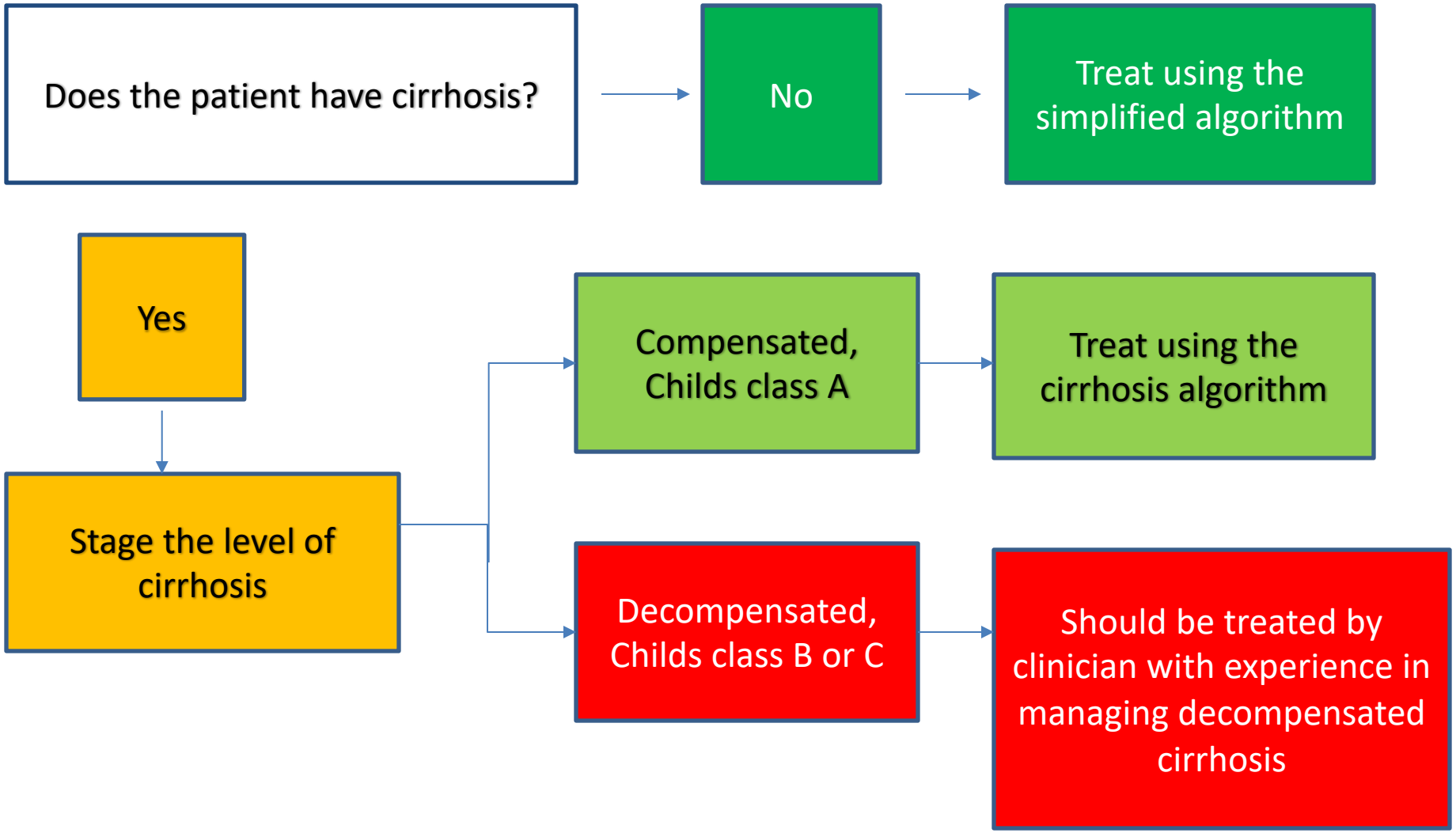
[1]If available; [2] Genotype; [3] AFP for patients with known or suspected cirrhosis

AFP obtained for patients with known or suspected cirrhosis

In patients with cirrhosis, AFP and imaging (ultrasound) used for screening and q 6 month surveillance of hepatocellular carcinoma (HCC). Surveillance is continued indefinitely due to estimated incidence of HCC at 2-8% per year in patients with advanced fibrosis/cirrhosis.

Marreno JA, Kulik LM, Sirlin CB et al. Diagnosis, staging, and management of hepatocellular carcinoma. 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2018;68:723-50.

General Approach to HCV Treatment



Child-Pugh Classification of Cirrhosis for Drug Dosing

	1 Point	2 Points	3 Points
Encephalopathy	None	Moderate	Severe
Ascites	Absent	Mild-Moderate	Severe/ Refractory
Bilirubin (mg/dL)	< 2	2 - 3	> 3
Albumin (g/dL)	> 3.5	2.8 - 3.5	< 2.8
INR (PT Prolongation *sec over control)*	<1.7 (0-4)	1.7-2.3 4-6	>2.3 (>6)

Note: Child Pugh Score is calculated only for patients with cirrhosis

Child-Pugh Interpretation of Hepatic Function in a Patient with Cirrhosis

C-P Score (Class)	***Liver Function***
5-6 (A)	Compensated
7-9 (B)	Decompensated
> 9 (C)	

Version: 1/26/22

Simplified HCV Treatment Algorithm for Patients with Compensated Cirrhosis

Perform Baseline Assessment

Within 3 months:
1. CBC
2. Hepatic panel (albumin, AST, ALT, total & direct bilirubin)
3. Chem7
4. PT/INR

Documentation of:
1. HCV RNA and genotype
2. HIV Ab
3. HBsAg, anti-HBc (IgG or total), anti-HBs
4. HAV Ab (IgG or total)

Does this patient have:
- Current or prior history of decompensated cirrhosis defined as CTP ≥7 (ascites, hepatic encephalopathy, total bilirubin >2 mg/dL, albumin ≤ 3.5 g/dL, or INR ≥ 1.7
- History of variceal bleed
- ESRD (GFR ≤ 30 ml/min/m^2)
- HIV or HBsAg positivity
- Prior HCV treatment
- Prior liver transplant
- Pregnancy
- Hepatocellular carcinoma (known or suspected)

NO → Check for drug-drug interactions:
hep-druginteractions.org
Check current medications and any over-the counter products
Avoid herbals/supplements during HCV treatment
Patients on diabetic medications may develop symptomatic hypoglycemia

Counsel on avoiding pregnancy

Counsel on medication adherence and follow up with patient as clinically indicated

Counsel on avoiding acid suppressive therapy *(especially important for Epclusa)*

For Patients with HCV Genotypes 1, 2, 4, 5, or 6*:

Start HCV Treatment

(Mavyret) G/P iii tabs PO daily x 8 wks with food
300 mg/120 mg^

OR

(Epclusa) SOF/VEL i tab PO daily x 12 wks
400 mg/100 mg

^Available as 100 mg/40 mg tab

Check LFTs q 4 wks during treatment

Repeat HCV RNA and LFTs ≥ 12 wks after end of treatment

If LFTs remain elevated after SVR, investigate for other causes of liver disease

YES → **STOP Do not use this algorithm**

* For patients with HCV GT3 and compensated cirrhois, consider presenting to HCV ECHO for discussion. Consider Mavyret (G/P) x 12 weeks because the level of evidence to use use G/P for 8 weeks in patients with cirrhosis is lower than for a 12 week course.
If using Epclusa (SOF/VEL), obtain NS5A RAS testing for GT3. If RAS test is negative for Y93, ok to use SOF/VEL.

Treatment Options for Patients with Decompensated Cirrhosis

- Sofosbuvir/velpatasvir plus ribavirin x 12 weeks
  - Use of ribavirin requires frequent monitoring for hemolytic anemia
- Sofosbuvir/velpatasvir x 24 weeks
- All protease inhibitor therapy is contraindicated in decompensated cirrhosis due to reports of serious liver injury

Side Effect Profile 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
- DAAs:
  - Overall very well tolerated
  - Most commonly reported side effects:
    - Headache
    - Fatigue
    - Nausea
    - Diarrhea (reported with voxilaprevir)

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
    - Changes in INR with warfarin

Rapid Viral Decline

Week	Baseline	Week 2	Week 3	Week 4
Actual Date	10/26/2016	11/14/2016	11/21/2016	11/28/2016
WBC	4.78	5.16		5.13
ANC	2.6	3		3
HGB	12.4	13.2		14.7
HCT	38.3	42.7		44.0
Platelets	93	73		84
Creatinine	0.83	0.80		0.83
AST SGOT	168	66		
ALT SGPT	91	39		
Total Prot	6.8	7.2		
Albumin	3.5	3.7		
T. Bili	1.0	1.2		
Dir Bili	0.7			
Alk Phos	241	202		
HCV RNA	614718			<15 ND
HCV Log				<1.18

- On-treatment HCV RNA testing no longer recommended

HCVguidelines.org
Accessed Oct. 18, 2022

Rapid Improvements in Inflammation

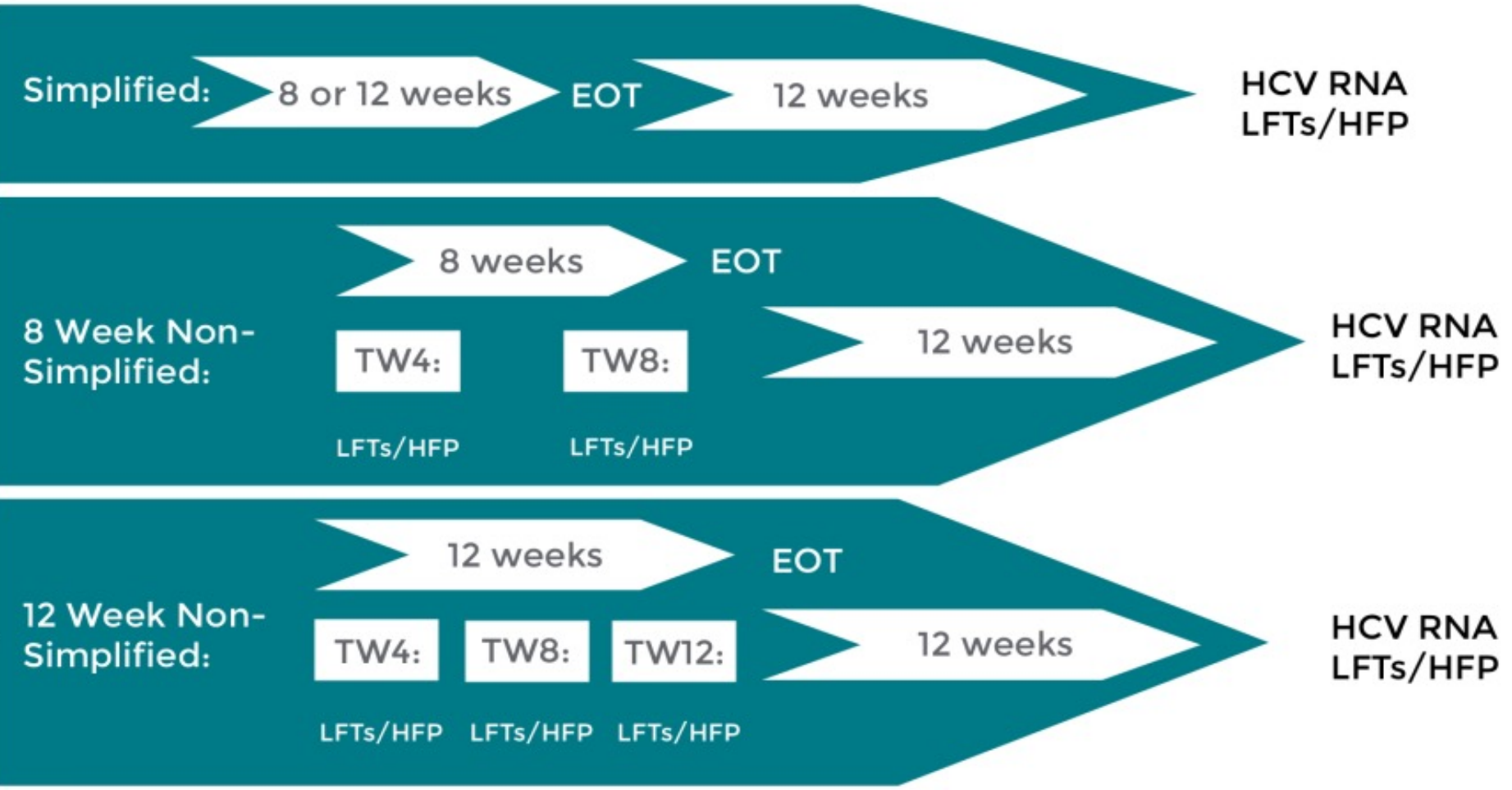
Week	Baseline	Week 1	Week 2	Week 4	Week 8	Week 12	Week 24
Actual Date	06/01/2017	06/08/2017	06/15/2017	06/29/2017	07/27/2017	08/24/2017	11/16/2017
WBC	5.9	6.8	6.1	4.8	5.3	5.6	7.0
ANC	3.5	2.8	3.4	2.2	2.6	3	3.4
HGB	14.1	13.9	13.3	14.2	13.8	14.3	14.2
HCT	43.6	41.0	40.8	42.8	41.3	42.5	43.3
Platelets	322	363	308	253	273	276	315
Creatinine	.088	0.89	0.87	0.82	0.89	0.82	0.78
AST SGOT	74	14	16	13	13	15	18
ALT SGPT	102	42	15	11	13	12	16
Total Prot	6.7	6.6	7.1	6.7	6.4	7.1	7.2
Albumin	3.9	3.8	4.2	4.2	4.0	4.3	4.2
T. Bili	0.3	0.2	0.3	0.4	0.4	0.3	0.5
Dir Bili							
Alk Phos	53	42	43	40	47	44	56
HCV RNA	5910			ND			
HCV Log	3.772						

Baseline Labs

CBC
Chem7
LFTs/HFP
HCV RNA and GT
Anti-HAV
Anti-HBc (igG or total)
Anti-HBs
HBsAg
Anti-HIV
PT/INR (only if presumed cirrhosis)

HCV On-Treatment Monitoring*

EOT: End of Treatment, **TW**: Treatment Week, *Does not apply to patients on DAA therapy plus ribravirin



What About Medications in Patients with HCV?

Current Medications:

Medication name:	Dosage:	Frequency	Medication name:	Dosage:	Frequency

Current Method of Birth Control: _____

If oral contraceptive, does it contain ethinyl estradiol? ☐ Yes ☐ No

- Avoid herbals
- Verify potential drug interactions using Liverpool website

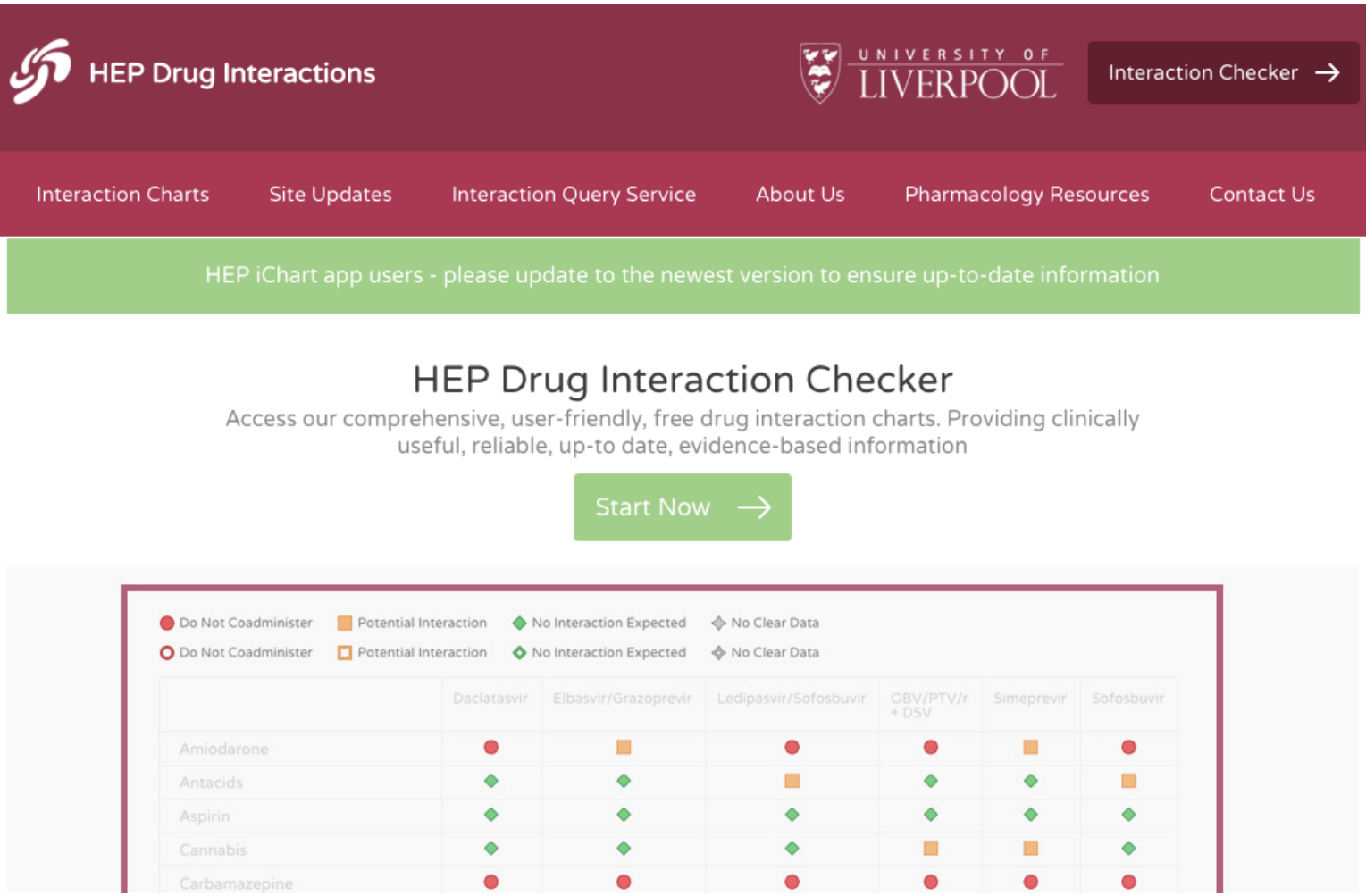
- In patients with cirrhosis
  - Avoid NSAIDs
  - Acetaminophen preferred for short-term pain management at <2 grams per day

Main Drug Interaction Concerns for DAAs

- Statins: interactions vary by statin and DAA
  - Safest option is to hold statin during HCV therapy
- Acid suppressive therapy:
  - **Velpatasvir requires acidity for absorption**
  - Recommend minimizing acid suppressive therapy in all patients undergoing HCV therapy
- Avoid amiodarone with sofosbuvir
  - Serious symptomatic bradycardia

Major Drug-Drug Interactions for all Direct Acting Antivirals

- **Carbamazepine**
- **Oxcarbazepine**
- **Phenytoin**
- **Phenobarbital**
- **Rifampin**
- Expected to ↓ concentrations
- DO NOT USE WITH HCV THERAPY!



www.hep-druginteractions.org

Also available as an app: hepichart

What About Medications in Patients with HCV?

Current Medications:

Medication name:	Dosage:	Frequency	Medication name:	Dosage:	Frequency

Current Method of Birth Control: _____

If oral contraceptive, does it contain ethinyl estradiol? ☐ Yes ☐ No

→ 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 benefits"

- **Bottom line: Recommend birth control in all female patients of childbearing age/capacity**

HCVguidelines.org

Accessed January 25, 2022

Resources

- ECHO HCV guidelines- link provided in weekly email
  - Includes links to decision trees, flowsheets, resources, patient education material
- AASLD/IDSA HCV Treatment Guidelines:
  - Available at: http://www.hcvguidelines.org
- HCV Drug Interactions (University of Liverpool):
  - Available at: http://www.hep-druginteractions.org
- Educational material, clinical calculators, HCV therapy summaries (University of Washington)
  - Available at: http://www.hepatitisc.uw.edu

Indian Country ECHO HCV

End of Presentation

Questions?

Northwest Portland Area
Indian Health Board
Indian Leadership for Indian Health