HCV ECHO®
WESTERN STATES

HCV Screening, Management, and Treatment Guidelines

Paulina Deming, PharmD, PhC
Associate Professor of Pharmacy-College of Pharmacy
Project ECHO
University of New Mexico Health Sciences Center

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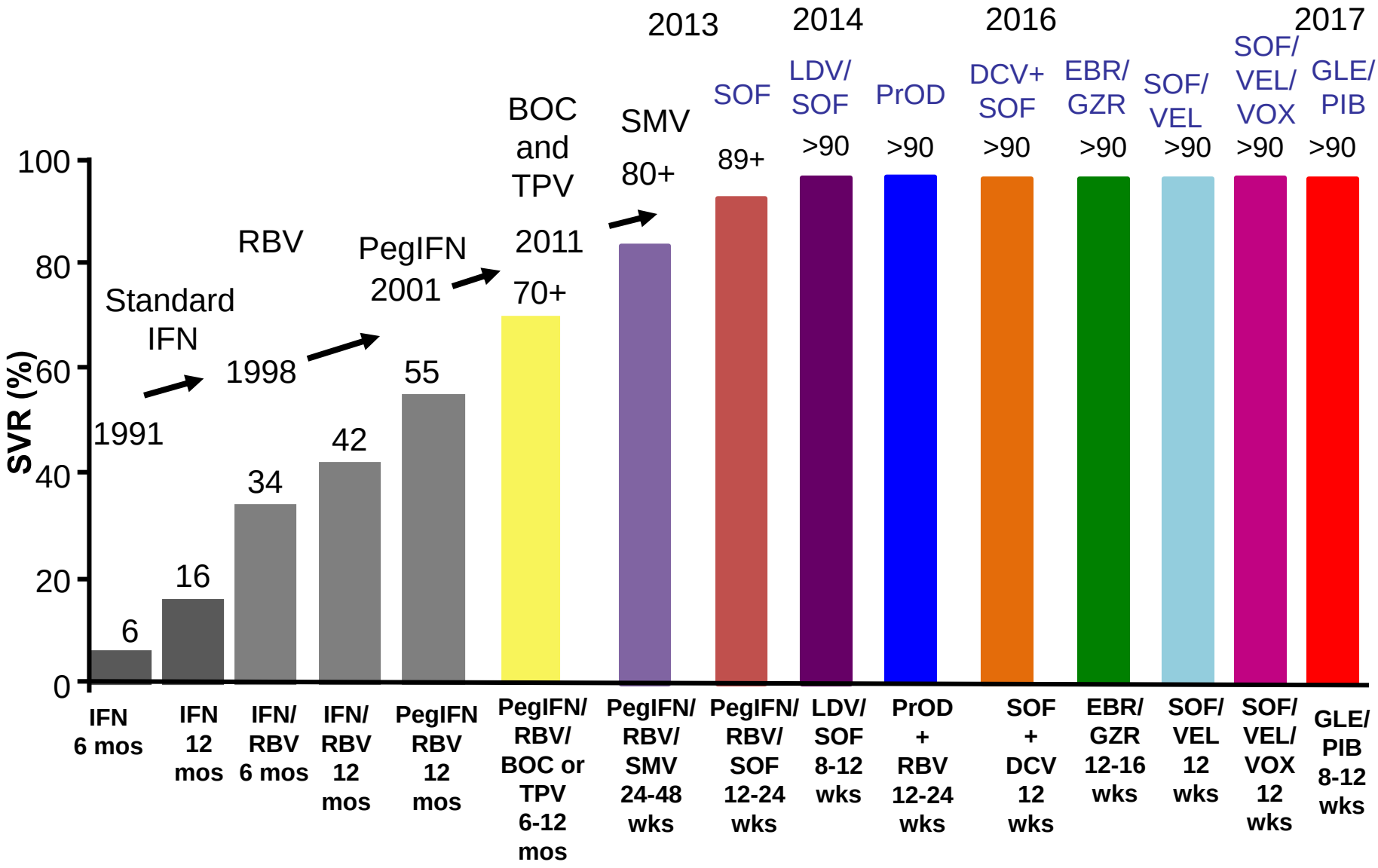
The Evolution of Highly Effective Treatment



HCV Direct Acting Antivirals (DAAs)

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

*no longer available in US

HCV Direct Acting Antivirals (DAAs) Generic Name	Brand Name
Glecaprevir/Pibrentasvir	Mavyret®
Sofosbuvir/ Velpatasvir	Epclusa® agEpclusa®
Ledipasvir/Sofosbuvir	Harvoni® agHarvoni®
Elbasvir/ Grazoprevir	Zepatier®
Sofosbuvir/ Velpatasvir/Voxilaprevir	Vosevi®
Other Therapies	
Ribavirin	Ribasphere®, RibaPak®, Copegus®, Rebetol®

Most commonly used and on formularies

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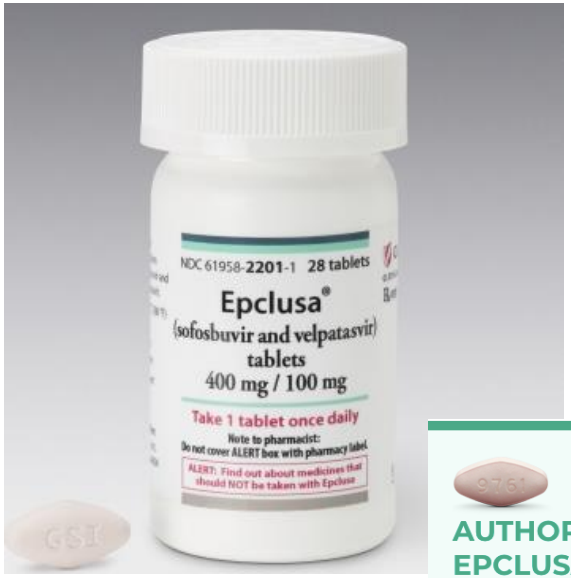
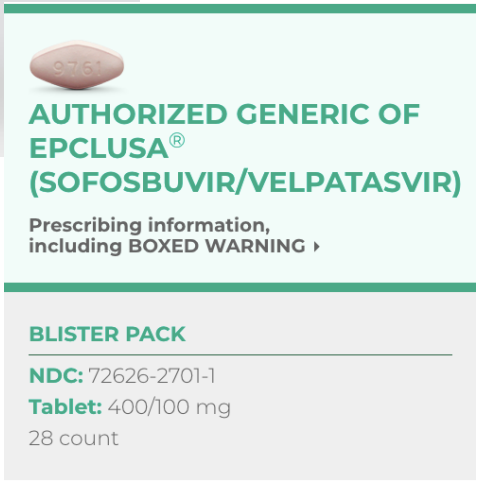
Sofosbuvir/Velpatasvir





- 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.

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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 6 years old and older or at least 17 kg

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 8-12 weeks

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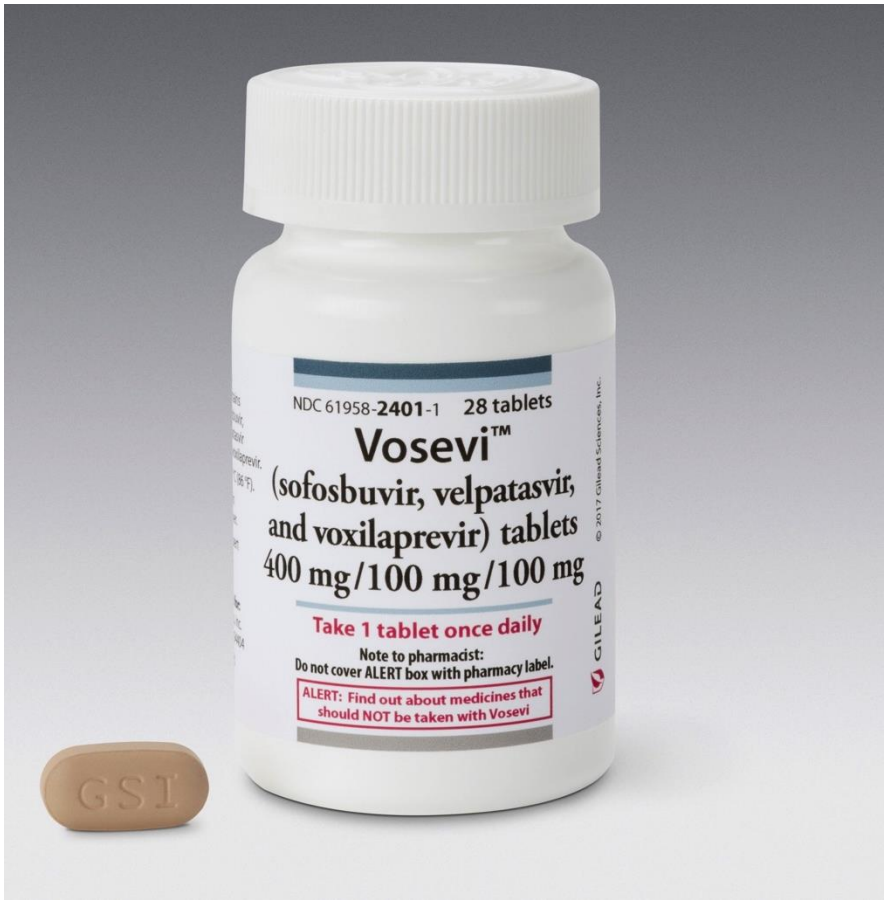
Who Can Be Treated with Glecaprevir/Pibrentasvir?

- 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 12 yo and older or 45 kg and above

Sofosbuvir/Velpatasvir/Voxilaprevir



- 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

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

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

Baseline Studies in Persons with Chronic HCV

- Complete blood count with differential
- Serum creatinine
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, serum albumin
- Protime/ International normalized ratio (INR)
- HCV genotype and subtype
- Quantitative HCV RNA
- HIV antibody
- Hepatitis A serology (IgG or total)
- Hepatitis B serology (HBsAg, anti-HBs, anti-HBc)
- Alpha-fetal protein (AFP)*
- Abdominal ultrasound with measurement of spleen size*

*if known or suspected cirrhosis

Baseline Studies in Persons for Evaluation of Liver: Step 1: Recognizing Cirrhosis

- Complete blood count with differential

Identify changes consistent with cirrhosis: neutropenia, thrombocytopenia (<150K); identify anemia especially if requiring ribavirin therapy

- Serum creatinine

Elevated creatinine may be associated with HCV related renal disease

- Alanine aminotransferase (ALT), aspartate aminotransferase (AST)

Recognize level of inflammation and liver injury: reversal of AST to ALT ratio associated with cirrhosis

- Protime/ International normalized ratio (INR), total bilirubin, serum albumin

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

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Baseline Studies in Persons with Chronic HCV

- HCV genotype/ subtype
- Quantitative HCV RNA

Demonstrate chronic HCV infection HCV RNA does **not** need to be repeated multiple times; one time genotype sufficient in most cases

- HIV antibody
- Hepatitis A serology (IgG or total)
- Hepatitis B serology (HBsAg, anti-HBs, anti-HBc)

Share similar routes of transmission; determine need for HAV and/or HBV vaccination; determine risk for HBV reactivation
HBV serologies needed irrespective of vaccination studies

- Alpha-fetal protein (AFP)
- Abdominal ultrasound with measurement of spleen size

For patients with cirrhosis: screen/ surveillance for hepatocellular carcinoma

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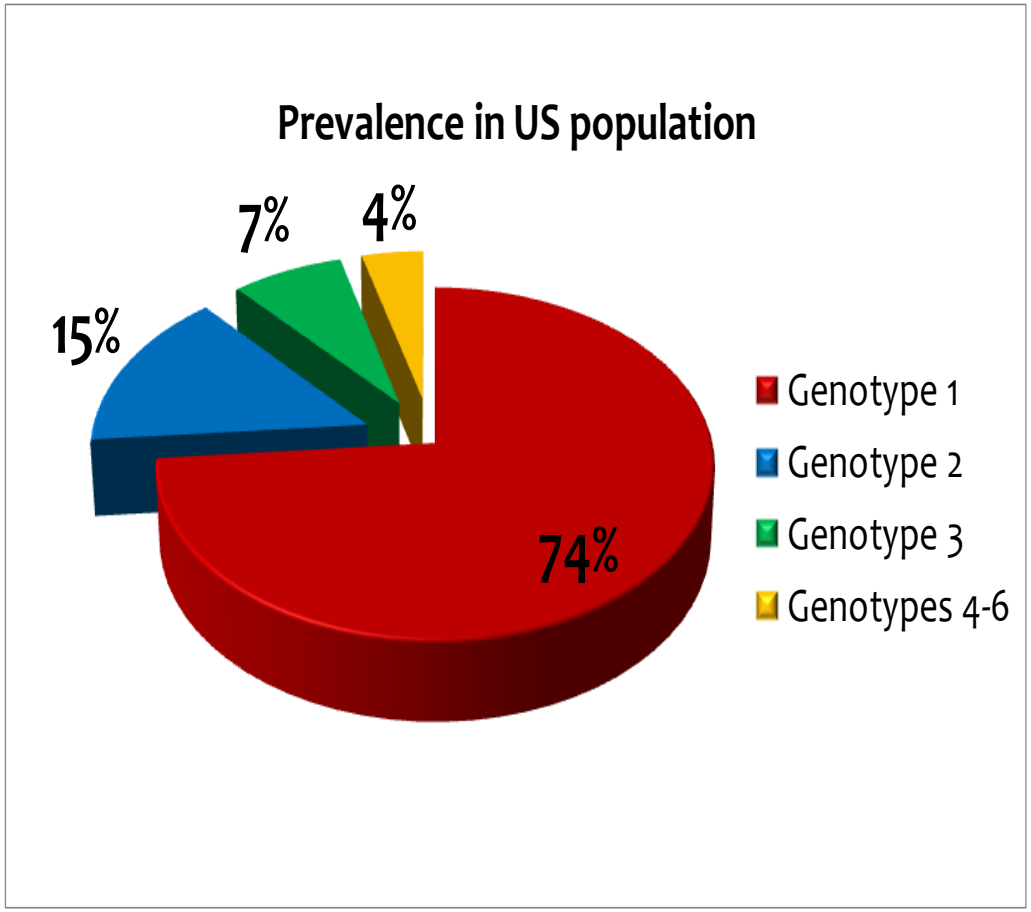
Hepatitis C Genotypes



- 6 major genotypes (1-6), most with subtypes
- Genotype 1
  - GT 1b *different* than GT 1a
- GT 2 easier to treat than GT 3
- GT 3 associated with higher mortality, steatohepatitis

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

Interpretation of Hepatitis B Serologies

HBsAg	Anti-HBs	Anti-HBc	Interpretation
+	-	+IgM	Acute infection
+	-/+	+IgG	Chronic Infection
-	+	-	Immunized
-	+	+	Exposure with immune control; low risk of reactivation *No need for vaccination*
-	-	+	Exposure with minimal or no immune control; higher risk of reactivation* *No need for vaccination*

*If ALT elevated, consider evaluation for occult HBV with quantitative HBV DNA

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”

Vaccinations

- HAV
- HBV
- Pneumococcal vaccine for all patients with chronic liver disease, including on-going alcoholism
- Annual flu

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)
- Liver biopsy with F3 or F4 fibrosis
- Transient elastography consistent with cirrhosis

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)

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)	

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

Hepatocellular Carcinoma

- Incidence of HCC is estimated at 2-8% per year in patients with chronic HCV and advanced fibrosis/cirrhosis
- All patients with cirrhosis should be screened for HCC and continue with HCC surveillance every 6 months (indefinitely)
  - Abdominal ultrasound plus AFP
  - MRI or CT for suspicious lesions or concerns for HCC
    - If AFP >20 ng/mL

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.

Evaluating Patients with Cirrhosis: Related Complications

- Physical exam for edema, muscle wasting, encephalopathy, and/or ascites
- Endoscopy for presence of esophageal varices and need for esophageal banding/prophylaxis

- Additional info at AASLD guidelines: https://www.aasld.org/publications/practice-guidelines-0

Alcohol and On-going Substance Abuse

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

- Tobacco- can increase risk of HCC
- Marijuana- daily use may be associated with increased fibrosis?
- Alcohol- hepatotoxic

Patient Health Questionnaire (PHQ-9)

Patient name: _____ Date: _____

1. Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not at all (0)	Several days (1)	More than half the days (2)	Nearly every day (3)
a. Little interest or pleasure in doing things.	☐	☐	☐	☐
b. Feeling down, depressed, or hopeless.	☐	☐	☐	☐
c. Trouble falling/staying asleep, sleeping too much.	☐	☐	☐	☐
d. Feeling tired or having little energy.	☐	☐	☐	☐
e. Poor appetite or overeating.	☐	☐	☐	☐
f. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down.	☐	☐	☐	☐
g. Trouble concentrating on things, such as reading the newspaper or watching TV.	☐	☐	☐	☐
h. Moving or speaking so slowly that other people could have noticed. Or the opposite; being so fidgety or restless that you have been moving around more than usual.	☐	☐	☐	☐
i. Thoughts that you would be better off dead or of hurting yourself in some way.	☐	☐	☐	☐

2. If you checked off any problem on this questionnaire so far, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

☐ Not difficult at all ☐ Somewhat difficult ☐ Very difficult ☐ Extremely difficult

- Mental health assessment
  - Patients with HCV have higher rates of depression
  - Underlying depression can affect medication adherence

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Other Counseling Points

- Encourage healthy weight
  - Patient should be counseled on maintaining a healthy diet and normal BMI (<25 kg/m^2)

- For patients with cirrhosis:
  - Avoid non-steroidal anti-inflammatory agents
  - Limit acetaminophen to < 2 grams and limit frequency of use

When Will There Be Good News?

- Coffee and tea may be liver protective
- Statins may be hepatoprotective and may decrease the risk of HCC

Jaruvongvanich V., et al. 2017. Clin Res Hepatol Gastroenterol.

Summary: Baseline Evaluation and Monitoring of Persons with Chronic HCV

Within 60 days of treatment start:

- Complete blood cell count
- PT/INR
- Serum creatinine
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and serum albumin

Documentation of:

- HCV Genotype and subtype
- Quantitative HCV RNA
- Hepatitis A serology (total or IgG)
- Hepatitis B serology (HBsAg, anti-HBs, anti-HBc)
- HIV Antibody

- *In patients with cirrhosis:*
  - *Alpha-fetal protein (AFP)*
  - *Abdominal ultrasound with spleen size*
  - *Endoscopy*

Patient Education Resources

- Available through resources
  - Link in guidelines
  - Clinic email link

- HCV Basics
- Treatment Information for Patients
- Educational Resources for Hepatitis C

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

Differences in 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

Treatment Terminology

- Treatment naïve (TN): no prior HCV therapy
- Treatment experienced (TE): prior HCV therapy- important to clarify which prior treatment
  - Interferon
  - Direct acting antivirals only
- Sustained virologic response (SVR): cure, defined as undetectable HCV RNA at least 12 weeks after end of treatment (EOT)
  - Durable
- Relapse: a detectable HCV RNA after treatment is completed

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

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

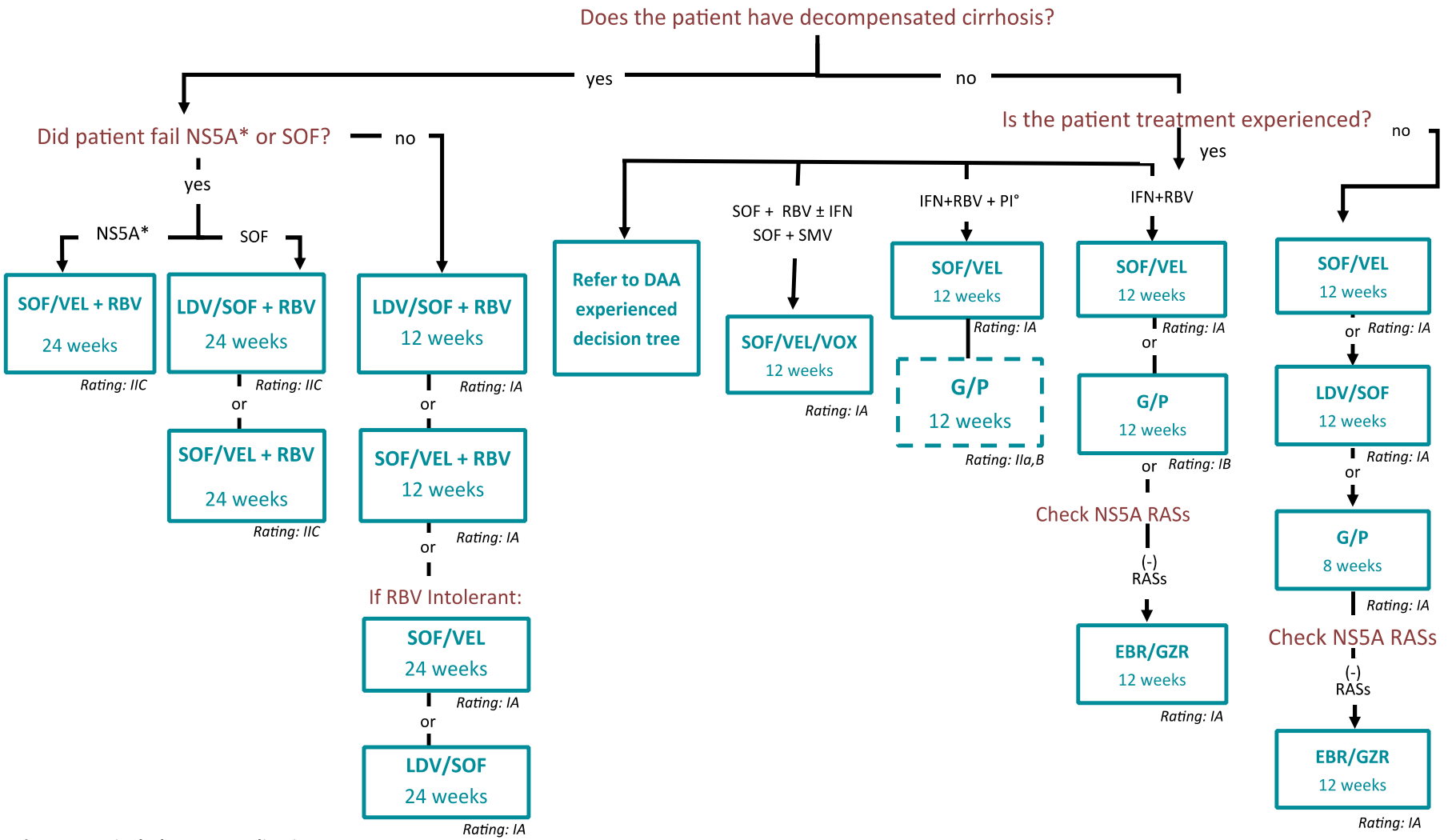
YES

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

Version: 2/28/2020

Hepatitis C : Genotype 1a Cirrhotic Treatment Regimen



° PI agents include DAA medications with the previr ending

*** NS5A agents include DAA therapies with the asvir ending**

Rating for Level of Recommendation

These are recommended in the AASLD/IDSA guidelines but have less evidence to support their use and are not ECHO preferred regimens

Direct Acting Antivirals (DAAs):

EBR/GZR: elbasvir/grazoprevir (Zepatier)
G/P: glecaprevir/pibrentasvir (Mavyret)
LDV/SOF: ledipasvir/sofosbuvir (Harvoni)
SOF/VEL: sofosbuvir/velpatasvir (Epclusa)
SOF/VEL/VOX: sofosbuvir/velpatasvir/voxilaprevir (Vosevi)

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:
  - Bilirubin elevations
    - Many DAAs inhibit bilirubin transporters
  - Anemia with concomitant use of ribavirin
    - Ribavirin causes hemolytic anemia

- Serious liver injury was reported in patients taking protease inhibitor therapy- **do not use protease inhibitor based therapies in patients with Childs B or C cirrhosis**

Potential Lab Abnormalities During DAA Therapy

- 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

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						

Ribavirin Induced Hemolytic Anemia

Week	Baseline	Week 1	Week 2	Week 4	Week 8	Week 13
Actual Date	03/15/2018	03/22/2018	03/29/2018	04/12/2018	05/10/2018	06/14/2018
WBC	4.1	3.8	4.7	2.8	3.2	3.0
ANC	3	2.5	3.3	1.7	2.1	2.1
HGB	15.2	14.0	14.1	12.5	12.1	11.5
HCT	42	40	41	38	38	37
Platelets	38	38	43	45		69
Creatinine	1.07	0.95	.99	1.00	0.99	1.02
AST SGOT	36	15	18	19	21	24
ALT SGPT	40	28	23	27	26	28
Total Prot	7.6	6.7	6.9	6.5	6.5	6.5
Albumin	4.1	4.1	3.8	3.8	3.7	3.8
T. Bili	1.5	1.0	1.3	1.3	0.9	1.2
Dir Bili						
Alk Phos	130	95	100	100	74	76
HCV RNA	7720000			ND		ND
HCV Log	6.9					
Ribavirin	1000 mg					
Sofosbuvir/Velpatasvir						

Treatment Flowsheet Example

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Hepatitis C Minimum Visit/ for 12 weeks Labs Flow Sheet

Week of Treatment	Screening	Wk 0 Start of Tx	Wk 2	Wk 4	Wk 8	Wk 12 End of Tx	Wk 24
Dates	N/A	01/01/19	01/15/19	01/29/19	02/26/19	03/26/19	06/18/19
Visit		x	x	x	x	x	x
HCV RNA	x					x	x
CBC w/ Diff	x			x	x	x	x
Chem 7	x			x	x	x	x
LFTs/HFP	x			x	x	x	x
HBsAg anti-HBs anti-HBc	x						

Key Points to Remember:

1) Week 0 Visit is the day of the first dose of medication.

2) Lab draws are done the end of the treatment week.

3) anti-HBc should be total or IgG.

Patient Name:	Date of Birth:	Patient ID:	Genotype:

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Treatment Flowsheet Example: With Ribavirin

+ Ribavirin x 12 weeks

Hepatitis C Minimum Visit/ Labs Flow Sheet

Week of Treatment	Screening	Wk 0 Start of Tx	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 12 End of Tx	Wk 24
Dates	N/A	01/01/19	01/08/19	01/15/19	01/22/19	01/29/19	02/12/19	02/26/19	03/26/19	06/18/19
Visit		X		X		X		X	X	X
HCV RNA	X								X	X
CBC w/ Diff	X		X	X	X	X	X	X	X	X
Chem 7	X					X		X	X	X
LFTs/HFP	X					X		X	X	X
Pregnancy	X	X				X		X	X	
HBsAg anti-HBs anti-HBc	X									

Key Points to Remember:

1) Week 0 Visit is the day of the first dose of medication.

2) Lab draws are done at the end of the treatment week.

3) anti-HBc should be total or IgG.

Patient name:	Date of Birth:	Patient ID:	Genotype:

REV: 01/14/19 RL

What About Medications in Patients with HCV?

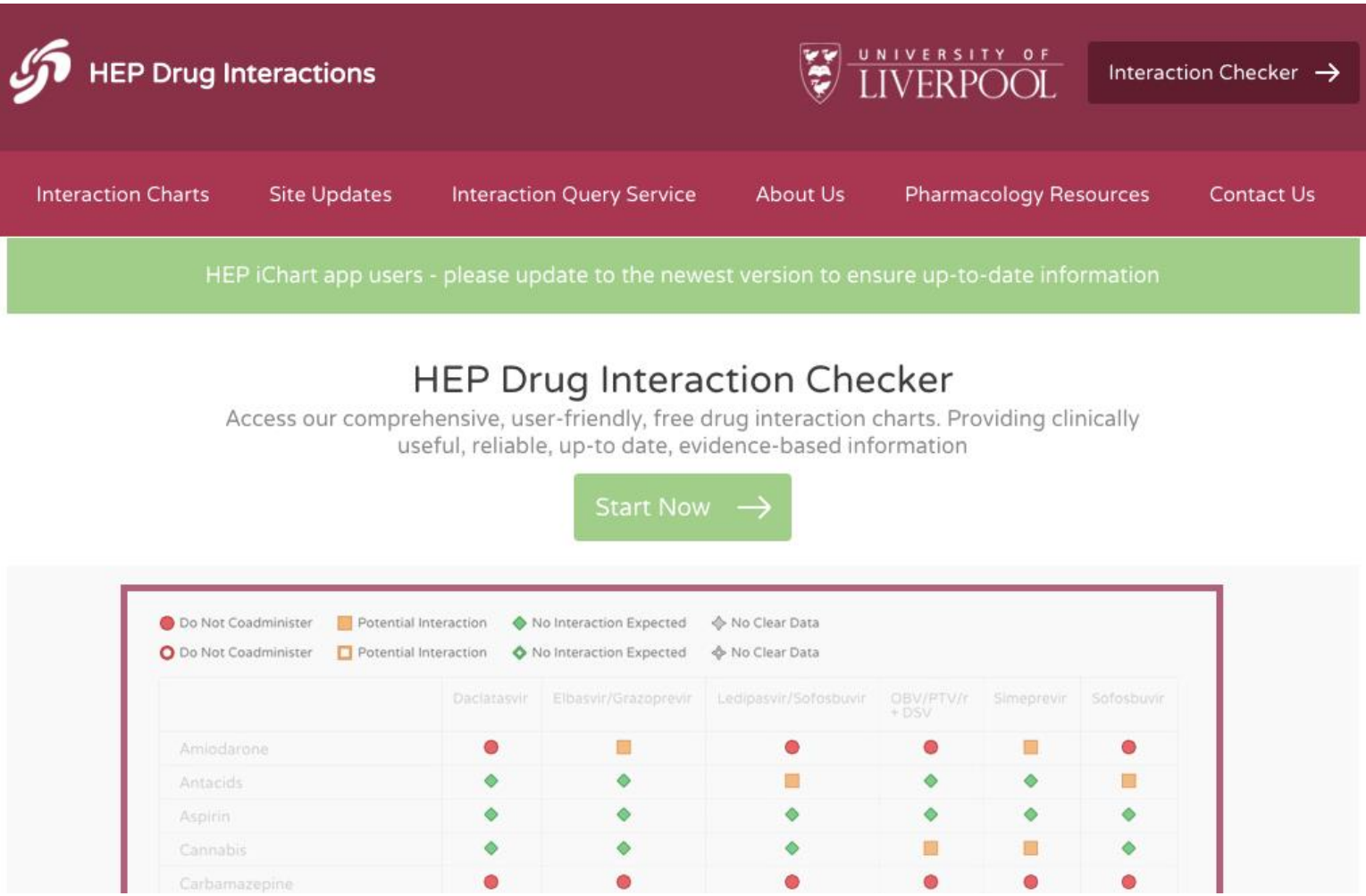
- In patients undergoing HCV therapy
  - Avoid herbals
  - Verify potential drug interactions using Liverpool website
- In patients with cirrhosis
  - Avoid NSAIDs
  - Acetaminophen preferred for short-term pain management at <2 grams per day

Other Main Drug Interaction Concerns for DAAs

- Statins:
  - Interactions vary by DAA and statin
  - Safest option may be 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
  - Amiodarone with sofosbuvir and other DAA: 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

DAAs and Pregnancy

- DAAs not approved/studied in patients who are pregnant

- Recommend birth control in all female patients of childbearing age/capacity
  - Avoid glecaprevir/pibrentasvir with ethinyl estradiol products

  - Ribavirin is teratogenic, pregnancy category X

Resources

- ECHO HCV guidelines- link provided in weekly email
  - Includes links to decision trees, flowsheets, resources
- 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