INDIAN COUNTRY ECHO

LEADING THE WAY

*Growing the Ability to Deliver Quality Healthcare to American Indian and Alaska Native People.*

# HCV Medications and Approach to Treatment

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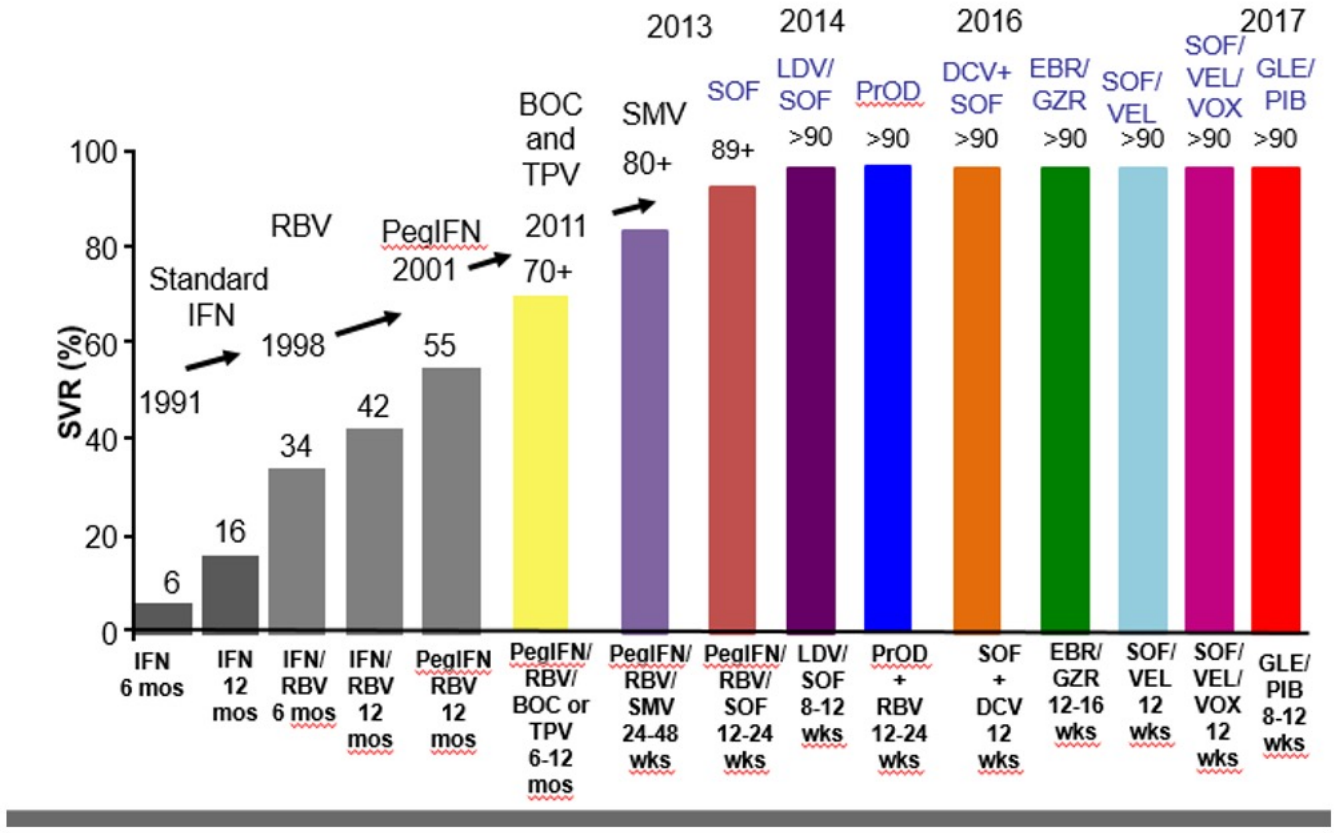
# The Evolution of Highly Effective Treatment

SVR: sustained virologic response= CURE

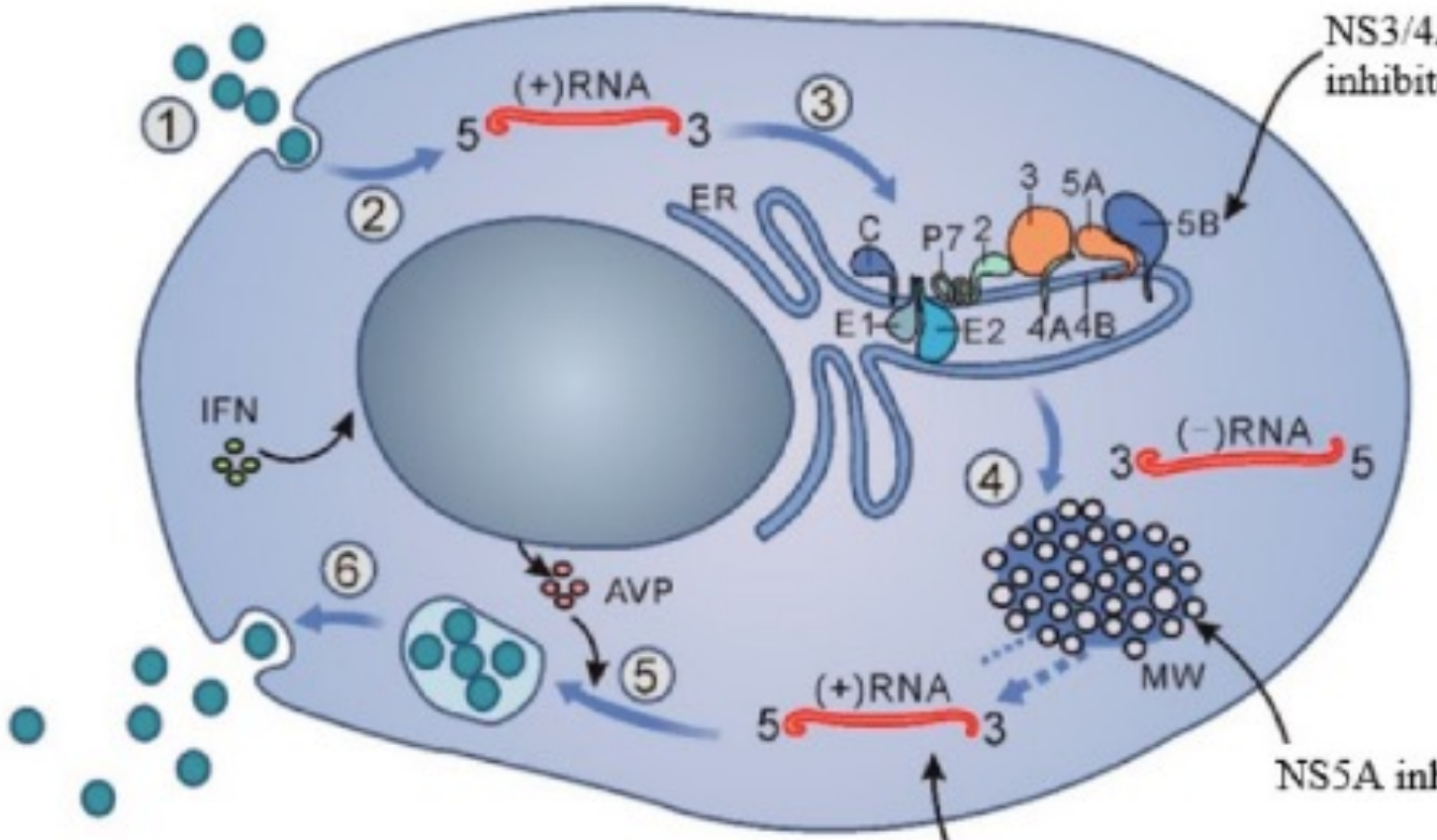
HCV RNA not detected 12 weeks or more after end of HCV therapy



# 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

# 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"

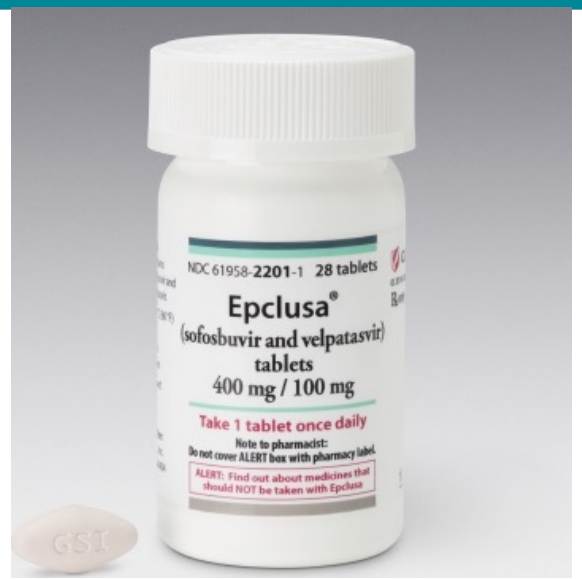
| HCV Direct Acting Antivirals (DAAs) Generic Name | Brand Name | Comments |
|---|---|---|
| Glecaprevir/Pibrentasvir | Mavyret® | Pan-genotypic |
| Sofosbuvir/ Velpatasvir | Epclusa®<br>agEpclusa® | Pan-genotypic |
| Ledipasvir/Sofosbuvir | Harvoni®<br>agHarvoni® | Limited use, for genotype 1 and 4 only |
| Elbasvir/ Grazoprevir | Zepatier® | Limited use, for genotype 1 and 4 only |
| Sofosbuvir/ Velpatasvir/ Voxilaprevir | Vosevi® | Pan-genotypic |
| *Other Therapies* | | |
| Ribavirin | Ribasphere®, RibaPak®, Copegus®, Rebetol® | |

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

# 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***

# Sofosbuvir/Velpatasvir (SOF/VEL)




- 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

# Who Can Be Treated with Sofosbuvir/Velpatasvir?

- 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

# Glecaprevir/Pibrentasvir (G/P)



- 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

# 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 years old and older

# 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 were previously failed by DAA therapy

# Who Can Be Treated with SOF/VEL/VOX?

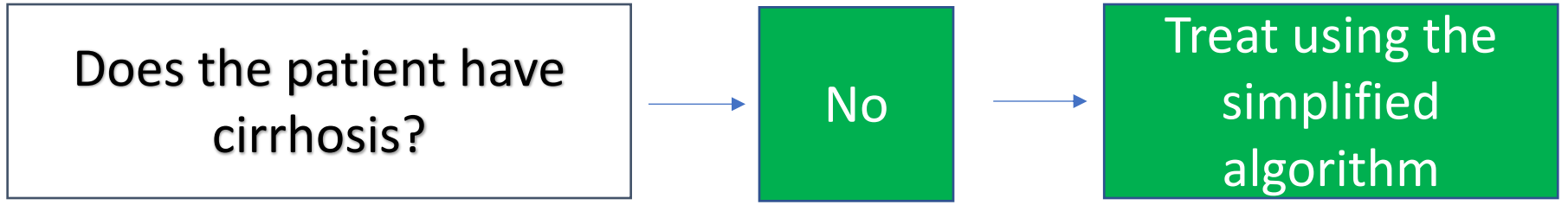
- Patients without cirrhosis
- Patients with Child's class A cirrhosis (compensated cirrhosis)
- Patients with renal insufficiency including hemodialysis

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

# Ribavirin

- **Limited use**
  - Added to treatment in specific clinical scenarios
    - Patients with decompensated cirrhosis who can tolerate ribavirin
    - For patients who have specific HCV resistance concerns
- Well-known toxicity profile
  - Hemolytic anemia
  - Teratogenic
    - Pregnancy category X

# General Approach to HCV Treatment



# Simplified HCV Treatment Algorithm, any Genotype

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## 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
4. HAV Ab (IgG or total)

**Does this patient have:**

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

**NO**

**YES**

**STOP**
**Do not use this algorithm**

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)*

**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*

# Hepatitis Case Report Form

| Body Mass Index | Height: | Weight: | BMI: |
|---|---|---|---|

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

# 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 | | | | | |
| [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 | | | 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

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

# Finding of Cirrhosis

- Presence or history of ascites or esophageal varices
- Low platelet count (<150,000 $mm^3$)
- Imaging with evidence of cirrhosis (nodular contour of liver or evidence of portal hypertension)
- Transient elastography consistent with cirrhosis
- Can be helpful but not sensitive or specific for cirrhosis:
  - APRI $\geq$ 1.0
  - FIB-4 $\geq$ 3.25
- Not routinely recommended: liver biopsy

# 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] | | | | | |

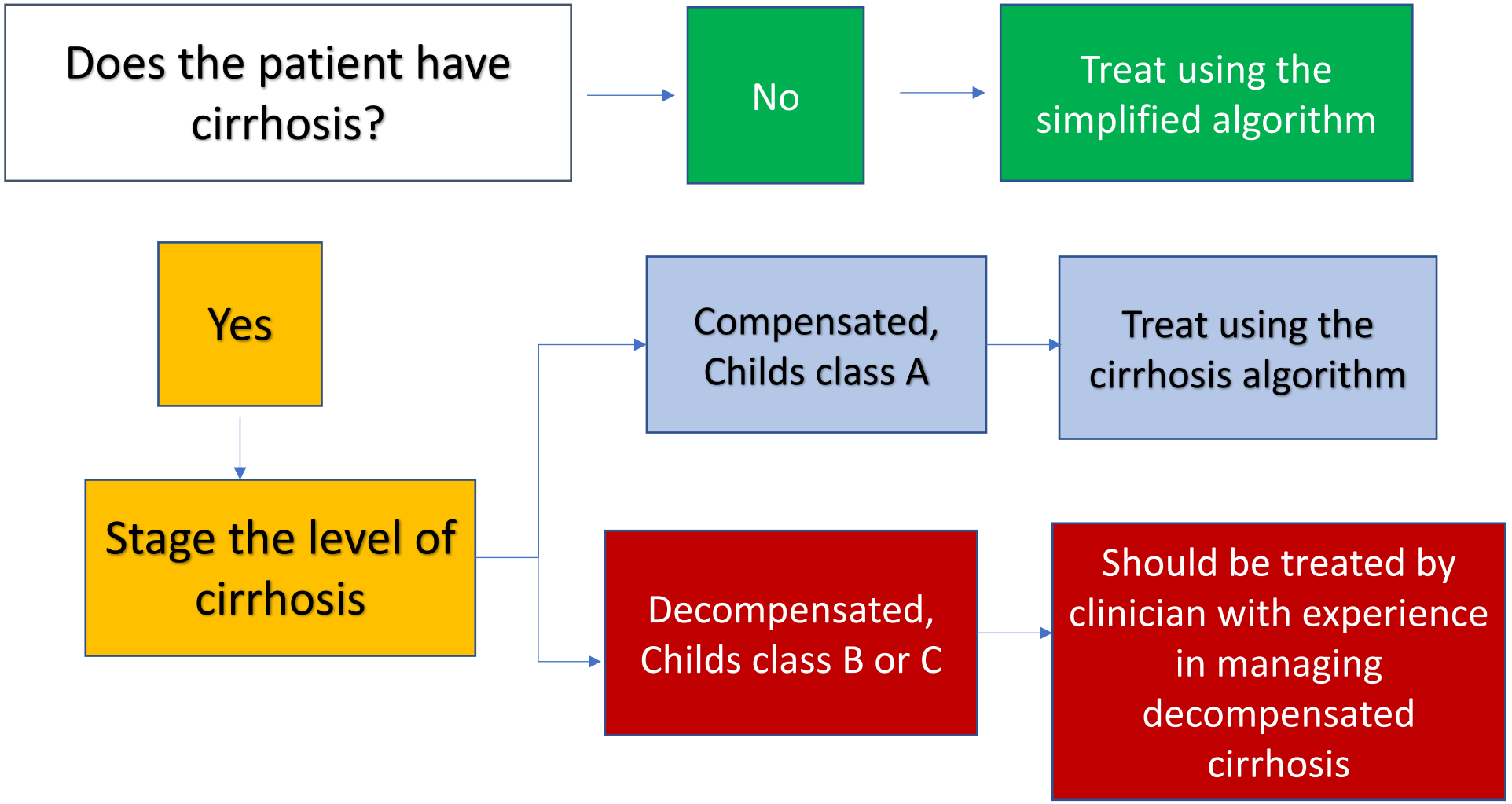
[1]If available; [2]Genotype; [3]AFP for patients with known or suspected cirrhosis

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

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

| | 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<br>(PT Prolongation *sec over control)* | <1.7<br>(0-4) | 1.7-2.3<br>4-6 | >2.3<br>(>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) | |

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**

# 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

# 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

# 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- *particularly true for diabetic medications known to cause hypoglycemia*
    - 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**

# Rapid Improvements in Inflammation

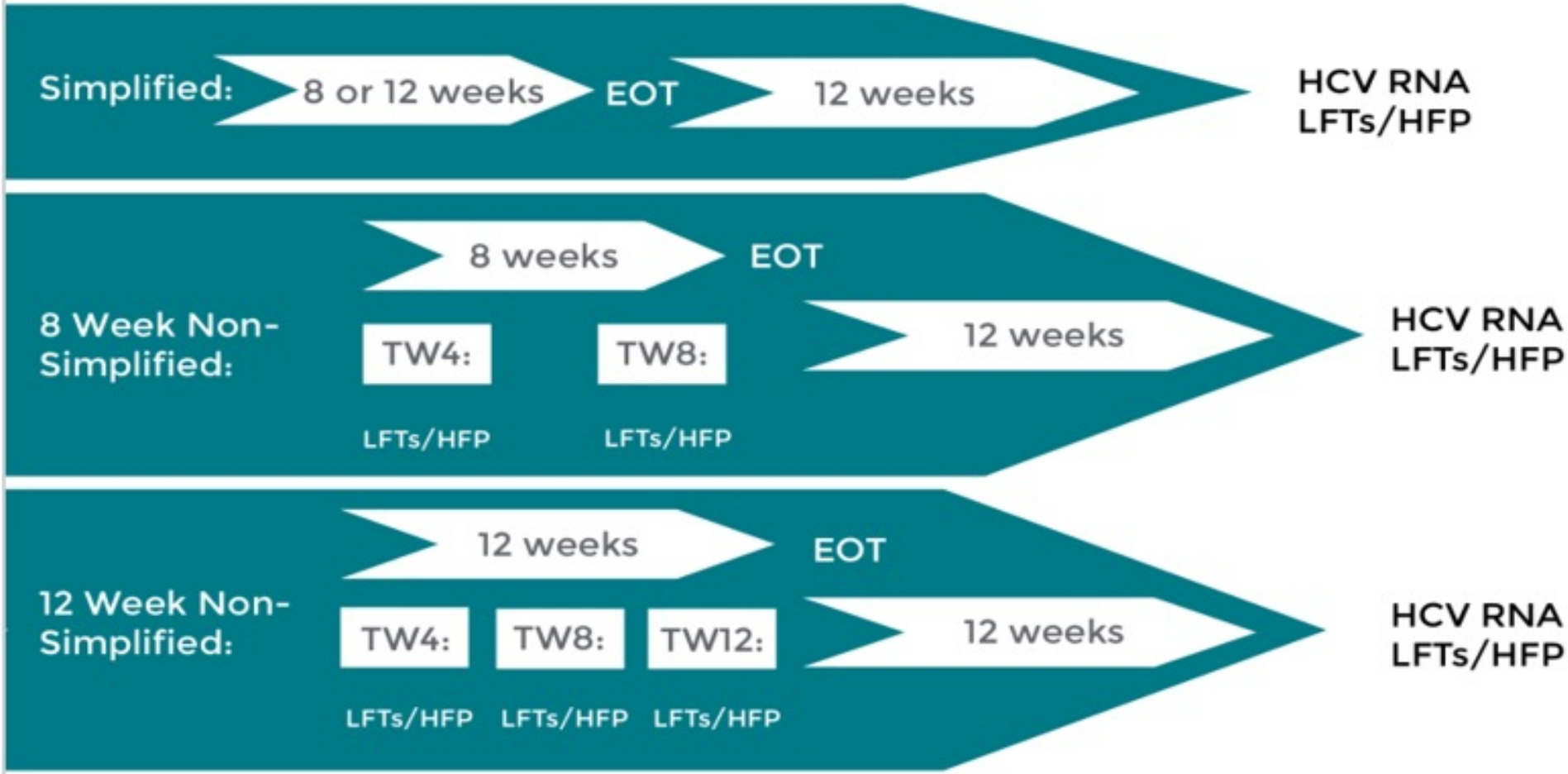
| Week | Baseline | Week 1 | Week 2 | Week 4 | Week 8 | Week 12 | Week 24 |
|---|---|---|---|---|---|---|---|
| Actual Date | 06/01/2017 | 06/08/2017 | 06/15/2017 | 06/29/2017 | 07/27/2017 | 08/24/2017 | 11/16/2017 |
| WBC | 5.9 | 6.8 | 6.1 | 4.8 | 5.3 | 5.6 | 7.0 |
| ANC | 3.5 | 2.8 | 3.4 | 2.2 | 2.6 | 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

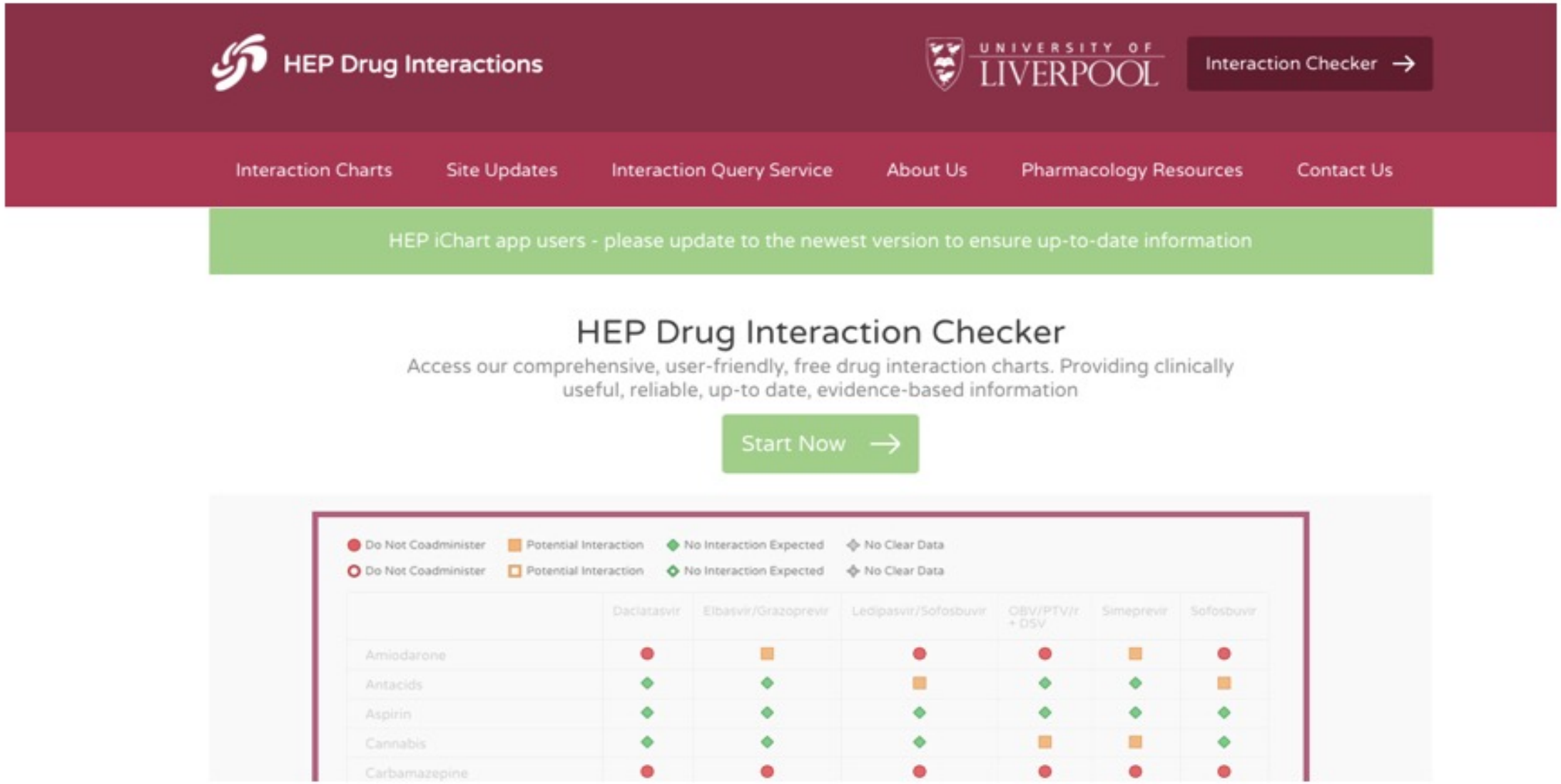
- In patients with cirrhosis
  - Avoid NSAIDs
  - Acetaminophen preferred for short-term pain management at <2 grams per day

# 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
    - If cannot stop PPI, glecaprevir/pibrentasvir **always** preferred
- 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

# 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 >20 mcg ethinyl estradiol with glecaprevir/pibrentasvir

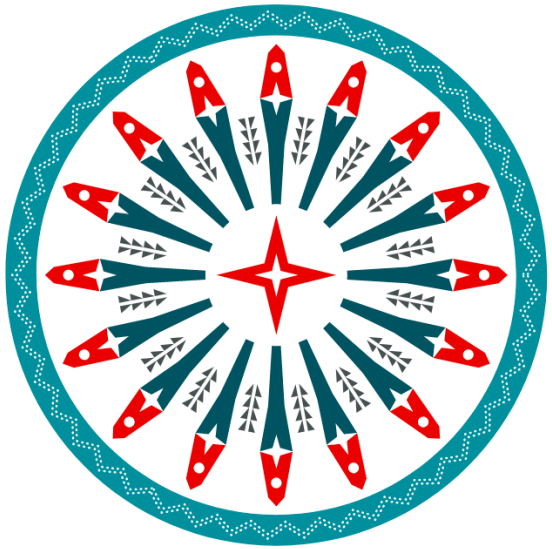
- Studies in pregnancy currently enrolling

*"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"*

- **Recommend birth control in all female patients of childbearing age/capacity**
- **Children born to mom with HCV should be screened for HCV at 2 months of age**

# Resources

- ECHO HCV
  - Includes links to algorithm, 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



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