Treatment of HCV

Jorge Mera, MD, FACP
Director, Infectious Diseases
Cherokee Nation
OBJECTIVES

- Rationale and goals for the universal need of HCV treatment
- Describe FDA approved antivirals used in HCV treatment, their strengths and weaknesses
- Interpret decision trees to determine treatment options
GOAL OF TREATMENT

“The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by an SVR.”

SVR: sustained virological response
SVR WAS ASSOCIATED WITH REDUCED LONG-TERM RISK OF ALL-CAUSE MORTALITY IN AN INTERNATIONAL, MULTICENTER STUDY

International, multicenter, long-term follow-up study from 5 large tertiary care hospitals in Europe and Canada. Patients with chronic HCV infection started an interferon-based treatment regimen between 1990 and 2003 (n=530).

WHY DO WE NEED TO TREAT HCV

- **SVR (cure) of HCV** is associated with:
  - 70% Reduction of Liver Cancer
  - 50% Reduction in All-cause Mortality
  - 90% Reduction in Liver Failure

Lok A. NEJM 2012; Ghany M. Hepatol 2009; Van der Meer AJ. JAMA 2012
HCV-ASSOCIATED DISEASE BURDEN (2015–2050)

- Liver-related Death: 767,000
- HCC: 407,000
- Decomp. Cirrhosis: 651,000
- Liver Transplants: 63,000

50–70% reduction in HCV-associated disease burden

Chhatwal et al. AASLD 2015 Abstract 104
**IMPACT OF TREATMENT COMPARED TO OTHER COMMON DISEASES**

- HCV cirrhosis risk = 40% over 30 years
- Hepatocellular carcinoma (HCC) risk in HCV Cirrhosis = 17% over 5 years
- When we **cure 30 patients** with HCV we will prevent:
  - 12 cases of HCV related cirrhosis
  - 2 case of HCV related HCC

If we treat **104 patients** with hypercholesterolemia with statins (For 5 years), we will prevent **1** first time heart attack and **¾** of a stroke

[www.thennt.com](http://www.thennt.com)
DIRECT ACTING ANTIVIRAL AGENTS (DAAS): KEEPING THEM STRAIGHT

PROTEASE

Ribavirin

NS3 Protease Inhibitors

Boceprevir (BOC)
Telaprevir (TVR)
Simeprevir (SMV)
Paritaprevir (PTV)
Grazoprevir (GRZ)

NS3 Replication Complex Inhibitors

Daclatasvir (DCV)
Ledipasvir (LDV)
Ombitasvir (OMV)
Elbasvir (ELB)
Velpatasvir (VEL)

NS5A Non-NUC Inhibitors

Sofosbuvir (SOF)

NS5B NUC Inhibitors

Dasabuvir (DSV)

NS5B Non-NUC Inhibitors
<table>
<thead>
<tr>
<th>Medication</th>
<th>NS5B</th>
<th>NS5A Inh</th>
<th>NS3 PI</th>
<th>Other</th>
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<tr>
<td>Sovaldi®</td>
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<td></td>
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<td>sofosbuvir</td>
<td>ledipasvir</td>
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<td>Epclusa®</td>
<td>sofosbuvir</td>
<td>velpatasvir</td>
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<td>elbasvir</td>
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<tr>
<td>Olysio®</td>
<td>simeprevir</td>
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<tr>
<td>Ribavirin</td>
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<td>ribavirin</td>
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# HCV Treatment by Genotype

<table>
<thead>
<tr>
<th>Medication</th>
<th>GT1</th>
<th>GT2</th>
<th>GT3</th>
<th>GT4</th>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Harvoni®</td>
<td>X</td>
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</tr>
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<td>Epclusa®</td>
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</tr>
<tr>
<td>Zepatier®</td>
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<td>Viekira Pak®</td>
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<tr>
<td>Olysio®</td>
<td>X</td>
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<td></td>
</tr>
<tr>
<td>Ribavirin</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
- NS5B nucleotide inhibitor
- Few drug interactions
- Genotypes 1, 2, 3, 4
- **Contraindicated in patients with GFR < 30**
- Most common reported SE
  - Headache
  - Fatigue (with ribavirin)
- Pangenic in combination
  - Not used as monotherapy

SE: Side Effects

Sovaldi® [package insert]. Gilead Sciences, Foster City, CA
Once daily single oral tablet
Genotype 1 and 4
Minimal DDIs, no food effect
8 week treatment available
- Naïve/Non cirrhotic/VL < 6 million
Do not use in patients with GFR < 30
Avoid use with anti acids
- May use with 20 mg of omeprazole if necessary

DDI: Drug-Drug Interactions

Harvoni® [package insert]. Gilead Sciences, Foster City, CA
VELPATASVIR/SOFOSBUVIR (EPCLUSA®)

- Once daily single oral tablet
- Minimal DDIs, no food effect
- Genotype 1,2,3,4
- Do not co-administer with PPI
  - If medically necessary, take Epclusa with food 4 hours before omeprazole 20 mg
- Do not use in patients with GF<30

VEL - NS5A inhibitor
SOF - NS5B nucleotide polymerase inhibitor

Approved: June 28, 2016

Epclusa® [package insert]. Gilead Sciences, Foster City, CA
OBV/PTV/R AND DSV (VIEKIRA PAK)

- Includes 3 direct acting antivirals and ritonavir, triple therapy or PrOD
  - Ombitasvir, paritaprevir, dasabuvir
- Ritonavir (No HCV activity)
  - Used to boost the paritaprevir
- Genotype 1 and 4
- Administer orally twice a day with food
- Many pharmacological interactions
- GT1a requires addition of RBV
- May use with GFR < 30

2 tablets of ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg) combination tablet every am
1 dasabuvir 250 mg tablet every am and pm
Extended Release

- All 3 tablets at the same time
- Take with food

Same precautions as Viekira Pak

- Do not split, crush or chew
- Alcohol should not be consumed within 4 hours of taking VIEKIRA XR
DACLATASVIR (DAKLINZA)

- NS5A inhibitor
- High barrier to resistance
- Once daily oral tablet
  - In combination with sofosbuvir
- With or without food
- Genotype 1,2,3,4
- May use with antacid

No DDIs: 60 mg once daily
DDIs with strong CYP3A inhibitors: 30 mg once daily
DDIs with moderate CYP3A inducers: 90 mg once daily


DDI: Drug-Drug Interaction
Genotypes 1 and 4

Elbasvir/Grazoprevir

- NS5A inhibitor - NS3/4A protease inhibitor

Oral and once daily

Must perform resistance testing in genotype 1A

- If resistance present must add Ribavirin and extend therapy from 12 to 16 weeks

DO NOT use in advanced liver disease (Child Pugh B or C)

May use with GFR < 30 ml/min

May use in Dialysis

May use with PPI

FDA-approved Jan 28, 2016
CLINICAL CASE #1

- 55 year old HCV positive male with a hx of IVDU 10 years ago
- Genotype 1a
- VL 2.4 million/ML
- Treatment naïve
- Fibrosis Stage F0-F1
- Labs: GFR of 65 ml/min, Hg 13, Platelets 245
- Other medical conditions
  - HTN on amlodipine

What are your options?
Hepatitis C: Genotype 1a Non-Cirrhotic Treatment Regimen

Is patient treatment experienced?

Yes

No

VEL/SOF
12 weeks

LDV/SOF
12 weeks or 8 weeks

May consider if HCV RNA ≤ 6 million

(Alternative)
LDV/SOF 8 weeks

Check for NS5A RAVs

(-) RAVs

(+/-) RAVs makes this an alternative treatment choice

(-) RAVs

(+) RAVs

(Alternative)
EBR/GZR + RBV 36 weeks

(Alternative)
EBR/GZR + RBV 24 weeks

(Alternative)
EBR/GZR + RBV 12 weeks

(Alternative)
LDV/SOF 8 weeks

(Alternative)
LDV/SOF 12 weeks
SOFOSBUVIR/LEDIPASVIR (HARVONI) AND ACID SUPPRESSING AGENTS

**Antacids**
- aluminum hydroxide
- magnesium hydroxide

**H₂RAs**
- famotidine
- ranitidine

- Separate administration by four hours
- Administer concurrently or 12 hours apart
- Not to exceed doses >40 mg famotidine twice daily

Harvoni® [package insert]. Gilead Sciences, Foster City, CA
Consider discontinuation of acid suppression therapy if patient is able to tolerate
- Reduce PPI by 50% per week to lowest dose, then discontinue to minimize rebound acid hypersecretion

If you have to use a PPI and Harvoni is the best option
- Administer simultaneously on an empty stomach
  - Only doses \( \leq \) omeprazole 20 mg
- Pantoprazole mg \( \neq \) omeprazole mg
I DON'T ALWAYS TAKE A PPI

BUT WHEN I DO IT DECREASES THE EFFECTIVENESS OF MY HARVONI
CLINICAL CASE # 2

- 65 year old HCV positive female with a hx of a post partum blood transfusion 40 years ago
- Genotype 1a
- VL 8.8 million/ML
- Treatment naïve
  - Fibrosis Stage F3-F4
  - No history of
    - Esophageal varices/ encephalopathy or ascites
- Labs: GFR of 28 ml/min, Hg 13 Platelets 109
- Other medical conditions
  - Barrett's esophagus (on omeprazole 40 mg once a day)

What are your options?
Hepatitis C: Genotype 1a Cirrhotic Treatment Regimen

Does the patient have decompensated cirrhosis?

- yes
- no

Treatment experienced?

- no
- ...

Check NSSA RAVs

- (+) RAVs
- (-) RAVs

EBR/GZR 12 weeks

*(alternative) RAVs

*(alternative) DCV

*EBR/GZR and PrOD are contraindicated with CTP Class B or C cirrhosis
- Genotypes 1 and 4
- Elbasvir/Grazoprevir
  - NS5A inhibitor - NS3/4A protease inhibitor
- Oral and once daily
- **Must perform resistance testing in genotype 1A**
  - If resistance present must add Ribavirin and extend therapy from 12 to 16 weeks
- **DO NOT use in advanced liver disease (Child Pugh B or C)**
- May use with GFR < 30 ml/min
- May use in Dialysis
- May use with PPI

ELBASVIR/GRAZOPREVIR
ZEPATIER

FDA-approved Jan 28, 2016
CLINICAL CASE # 3

- 73 year old HCV positive male with no risk factors
  - Genotype 2
  - VL 3.4 million/ML
  - Treatment naïve
  - Fibrosis Stage F3-F4
  - History of ascites
  - Labs: GFR of 69 ml/min, Hg 13.4, Platelets 88
  - Other medical conditions
    - Prediabetes/40 pack/year smoking/HTN on amlodipine
    - Hypercholesteremia on atorvastatin

- What are your options?
Do I need any workup before I start Ribavirin?
What are his Drug - Drug Interactions with Epclusa?
VELPATASVIR/SOFOSBUVIR (EPCLUSA®)

- **Once Daily Single Oral Tablet**
- **Minimal DDIs, no food effect**
- **Genotype 1,2,3,4**
- **Do not co-administer with PPI**
  - *If medically necessary, take Epclusa with food 4 hours before omeprazole 20 mg and only doses < omeprazole 20 mg*
- **Do not use in patients with GFR < 30**

Epclusa® [package insert]. Gilead Sciences, Foster City, CA

Approved: June 28, 2016
RIBAVIRIN (RBV)

Administration
- Weight-based dosing (Twice daily)
  - 1000 mg if > 75 kg
  - 1200 mg if ≥ 75 kg
- Take evening dose (8 hours apart) in the afternoon to keep from disturbing sleep

Pregnancy category X
- Contraindicated in pregnant women or male partners of pregnant women
- Use 2 effective forms of contraception during treatment and for at least 6 months after completion of therapy (both male and female patients)
Adverse Events
- Headache
- Fatigue
- Nausea
- Insomnia
- Depression

Lab abnormalities:
- Hemolytic anemia
  - Decrease ribavirin dose by 200 mg daily for a 2g or more drop in Hgb

Monitoring RBV
- CBC & CMP
- At baseline, weeks 2 and 4, as clinically indicated
- TSH at week 12
- Preexisting cardiac issue

Ophthalmic exam
- Preexisting ophthalmic disorders

HCG
- At baseline
- Monthly during treatment and for 6 months after treatment
WHO TO TREAT, AND WHEN? WHO TO PRIORITIZE?

Who to treat?
- All patients with chronic HCV should be treated, unless:
  - Life expectancy is < 1 year that cannot be remediated by treating HCV or liver transplantation (AASLD)
  - Uncontrolled comorbidities that can cause HCV treatment discontinuation (Dr. Mera’s Opinion)

When to Prioritize
- Limited resources for medication procurement
- Limited clinical capacity to treat
WHO TO PRIORITIZE

- Prioritize treatment only if limited by clinical capacity
  - Decompensated cirrhotic
  - Non decompensated cirrhotic first, then F3, F2, F0-F1
  - HCV related nephropathy/vasculitis
  - PWID

### Highest Priority for Treatment Owing to Highest Risk for Severe Complications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced fibrosis (Metavir F3 or F4)</td>
<td>Class I, Level A</td>
</tr>
<tr>
<td>Organ transplant</td>
<td>Class I, Level B</td>
</tr>
<tr>
<td>Type 2 or 3 essential mixed cryoglobulinemia with endo organ manifestations (vasculitis)</td>
<td>Class I, Level B</td>
</tr>
<tr>
<td>Proteinuria, nephrotic syndrome, or MPGN</td>
<td>Class IIa, Level B</td>
</tr>
</tbody>
</table>

**Dr. Mera’s Opinion**
Most anti convulsants are contraindicated
- Due to decreased antiviral levels

Regimens with protease inhibitors tend to have more drug interactions
- PrOD (Viekira Pak) (has 2 PI), Simeprevir (Olysio), elbasvir/grazoprevir (zepatier)

Daclatasvir (Daklinza) has numerous DDI and may need dose adjustment

Sofosbuvir/velpatasvir (Epclusa) and sofosbuvir/ledipasvir (Harvoni)
- Decreased absorption with anti acids specially Proton Pump Inhibitors
Renal Impairment:

- elbasvir/grazoprevir (Zepatier) is approved in ESRD and dialysis
- PrOD (Viekira Pak) is approved with CrCl <30

Hepatic Impairment (Child Pugh B/C):

- PrOD (Viekira Pak) (has 2 PI), Simeprevir (Olysio) elbasvir/grazoprevir (Zepatier) are contraindicated
- May require addition of ribavirin or treatment extension
SPECIAL TREATMENT CONSIDERATIONS

GENOTYPES

- **Genotype 1a**
  - Will require Ribavirin if **PrOD (Viekira Pak)** is used
  - May treat for 8 weeks with sofosbuvir/ledipasvir (Harvoni) if viral load is < 6 million, treatment naïve and non cirrhotic
  - If elbasvir/grazoprevir (zepatier) is used resistance testing needed

- **Genotype 2 and 3**
  - Sofosbuvir/velpatasvir (Epclusa) is first line therapy but PPI use and low GFR are a problem
SPECIAL TREATMENT CONSIDERATIONS
HEPATITIS B STATUS

Project ECHO HBV Monitoring for Patients on HCV Treatment

Check HBSAg, anti-HBc and anti-HBS

+ Is anti-HBC (+)?

- HBSAg
  - No
  - Yes
    - ALT ≥2x baseline OR 2xULN
      - No
        - Draw ALT every 4 weeks
      - Yes
        - Draw HBSAg*

+ ALT ≥2x baseline OR 2xULN
  - No
    - Draw HBVDNA quant
  - Yes
    - Draw HBSAg*
      - No
        - Draw HBVDNA quant
        - AND
          - Start TDF/or ETV
      - Yes
        - Consult viral hepatitis specialist regarding the management of HBV treatment after completing HCV DAA treatment.

HBV Vaccination if anti-HBS negative.

No additional HBV monitoring required.

*HBSAg can be drawn at the same as HBVDNA for convenience or can ask for HBSAg with reflex HBVDNA.
SUMMARY: WHAT DO YOU NEED TO KNOW TO SELECT THE BEST TREATMENT OPTION

- Genotype
- Viral load for GT1a (< 6 million ?)
- Liver Fibrosis Staging
  - Cirrhosis vs no Cirrhosis
  - If Cirrhotic
    - Compensated vs Decompensated
- Previous treatment status
- Kidney function
  - CrCl < or > 30
  - Dialysis
- Drug interaction check
  - Anti seizure meds, PPI, etc.
- Check Hepatitis B status to monitor reactivation
WHAT NOW?

Join the ECHO Community and start Paving the Road to HCV Elimination in Native America
TELEMEDICINE IMPROVES ACCESS BY USING TECHNOLOGY TO BRIDGE DISTANCE
THE ECHO MODEL IMPROVES CAPACITY AND ACCESS SIMULTANEOUSLY
MOVING KNOWLEDGE INSTEAD OF PATIENTS
SHARING EVIDENCE BASED BEST MEDICAL PRACTICES
Benefits to Rural Clinicians

• Professional interaction with colleagues with similar interest
  – Less isolation with improved recruitment and retention
• A mix of work and learning
• Obtain HCV certification
• Access to specialty consultation with GI, hepatology, psychiatry, infectious diseases, addiction specialist, pharmacist, patient educator
Benefits of ECHO® model to Health System

- Quality and Safety
- Rapid Learning and best-practice dissemination
- Reduce variations in care
- Access for Rural and Underserved Patients, reduced disparities
- Workforce Training and Force Multiplier
- De-monopolize Knowledge
- Improving Professional Satisfaction/Retention
- Supporting the Medical Home Model
- Cost Effective Care- Avoid Excessive Testing and Travel
- Prevent Cost of Untreated Disease (e.g.: liver transplant or dialysis)
- Integration of Public Health into treatment paradigm
IMPACT OF ECHO IN CNHS HCV PROGRAM

CNHS: Cherokee Nation Health Services
HELPFUL RESOURCES

- http://www.hcvguidelines.org/
- http://www.hepatitiscisc.uw.edu/
  - On-line curriculum on liver disease and HCV, includes clinical studies, clinical calculators, slide lectures
- ECHO guidelines
REFERENCES

1. Sovaldi® [package insert]. Gilead Sciences, Foster City, CA
2. Harvoni® [package insert]. Gilead Sciences, Foster City, CA
7. Project ECHO. University of New Mexico. http://echo.unm.edu/
IT TOOK US 25 YEARS TO BRING HIM TO HIS KNEES... NOW LET'S FINISH HIM OFF!...
ECHO DECISION TREES
Hepatitis C: Genotype 1a Non-Cirrhotic Treatment Regimen

Is patient treatment experienced?

- yes
  - DCV + SOF
  - LDV/SOF
  - SMV + SOF
  - PEG + SOF + RBV
  - PrOD
  - Check NS3 and NS5A RAVs and present to ECHO panel

- no
  - SOF + RBV
  - IFN + RBV + PI (BOC, TPV, SMV)
  - IFN + RBV
  - VEL/SOF 12 weeks
  - LDV/SOF 12 weeks
  - VEL/SOF 12 weeks
  - DCV + SOF 12 weeks
  - PrOD + RBV 12 weeks
  - Check for NS5A RAVs

  - Check for NS5A RAVs
    - EBR/GZR + RBV 12 weeks
      - (-) RAVs
        - EBR/GZR 12 weeks
      - (+) RAVs
        - Presence of RAVs makes this an alternative treatment choice

  - Check for NS5A RAVs
    - EBR/GZR 12 weeks
      - (+) RAVs
        - (alternative) EBR/GZR + RBV 16 weeks

May consider if HCV RNA ≤ 6 million

(alternative) LDV/SOF 8 weeks
Hepatitis C: Genotype 1b Cirrhotic Treatment Regimen

Does the patient have decompensated cirrhosis?

yes →
Did patient fail

PEG+SOF+RBV or SOF+RBV

yes →
LDV/SOF + RBV 24 weeks

no →
SMV + SOF

LDV/SOF or PEG+SOF+RBV

no →
SOF + RBV

Check NS3 & NS5A RAVs and present to ECHO Panel

VEL/SOF + RBV 24 weeks

no →

If RBV Intolerant:

VEL/SOF 24 weeks

or

LDV/SOF 24 weeks

or

DCV + SOF 24 weeks

no →

VEL/SOF 12 weeks

or

LDV/SOF + RBV 12 weeks

or

VEL/SOF 12 weeks

no →

LDV/SOF + RBV 12 weeks

or

VEK/SOF 12 weeks

or

VEL/SOF 12 weeks

or

PrODe 12 weeks

or

EBR/GZR 12 weeks

or

LDV/SOF + RBV 24 weeks

or

ELB/GZR + RBV 12 weeks

or

(alternative) DCC + SOF ±RBV 24 weeks

or

(alternative) DCC + SOF ±RBV 24 weeks

no →

VEL/SOF 12 weeks

or

PrODe 12 weeks

or

EBR/GZR 12 weeks

or

(alternative) DCC + SOF ±RBV 24 weeks

*ELB/GZR and PrODe are contraindicated in patients with CTP Class B and C cirrhosis

Version: 7/25/2016
Hepatitis C Genotype 2 Treatment Regimen Decision Tree

Genotype 2 Patients

Is the patient treatment experienced with SOF + RBV?

- yes
  - DCV + SOF + RBV
    - 24 weeks
  - or
  - VEL/SOF + RBV
    - 12 weeks

- no
  - Does the patient have cirrhosis?
    - yes
      - Is the patient decompensated?
        - yes
          - DCV + SOF
            - 12 weeks
        - no
          - VEL/SOF
            - 12 weeks
    - no
      - VEL/SOF
        - 12 weeks
      - or
      - DCV + SOF
        - 12 weeks
      - or
        - (alternative)
          - DCV + SOF
            - 16-24 weeks
Hepatitis C Genotypes 3 Treatment Regimen Decision Tree

Genotype 3 Patients

Does the patient have cirrhosis?

- Yes
  - Is the patient decompensated and/or treatment experienced?
    - Yes
      - VEL/SOF + RBV
        - 12 weeks
    - No
      - NS5A RAV Testing
        - (+) Y93
          - VEL/SOF + RBV
            - 12 weeks
        - (-) Y93
          - DCV + SOF + RBV
            - 24 weeks

- No
  - Is the patient treatment experienced?
    - Yes
      - NS5A RAV Testing
        - (+) Y93
          - VEL/SOF + RBV
            - 12 weeks
        - (-) Y93
          - DCV + SOF + RBV
            - 24 weeks
    - No
      - VEL/SOF + RBV
        - 12 weeks
      - VEL/SOF
        - 12 weeks

*The optimal duration of therapy for patients with cirrhosis is unknown. The AASLD/ISDA guidelines recommend 24 weeks in patients with compensated cirrhosis and 12 weeks with decompensated cirrhosis. The DCV package insert recommends 12 weeks of therapy in patients with cirrhosis regardless of severity. All patients should receive RBV if they are RBV eligible.

§ If RAV testing is not available, add RBV
Hepatitis C Genotypes 4 Treatment Regimen Decision Tree

**Genotype 4 Patients**

- **Is the patient decompensated?**
  - Yes
  - **Does the patient have cirrhosis?**
    - Yes—PEG/RBV
    - No—LDV/SOF 12 weeks or DCV + SOF + RBV 12 weeks

- No—Is the patient treatment experienced?
  - Yes—PEG/RBV
  - No—Is the patient treatment experienced?
    - Yes—LDV/SOF 12 weeks or EBR/GZR + RBV 16 weeks
    - No—LDV/SOF 12 weeks or EBR/GZR 12 weeks

*PrO is paritaprevir/ritonavir and ombitasvir (does not include dasabuvir) - Technivie.
ELB/GZR and PrO are contraindicated in patients with CTP Class B and C cirrhosis.*