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
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
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)

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 **\(\frac{3}{4}\)** of a stroke
DIRECT-ACTING ANTIVIRAL AGENTS (DAA): KEEPING THEM STRAIGHT

DIRECT-ACTING ANTIVIRAL AGENTS (DAA):
KEEPING THEM STRAIGHT

**Protease**
- Ribavirin
- NS3 Protease Inhibitors: Boceprevir (BOC), Telaprevir (TVR), Simeprevir (SMV), Paritaprevir (PTV), Grazoprevir (GRZ), Glecaprevir (GLE), Voxilaprevir (VOX)
- NS5A Replication Complex Inhibitors: Daclatasvir (DCV), Ledipasvir (LDV), Ombitasvir (OMV), Elbasvir (ELB), Velpatasvir (VEL), Pibrentasvir (PIB)
- NS5B Non-NUC Inhibitors: Sofosbuvir (SOF)
- NS5B Non-NUC Inhibitors: Dasabuvir (DSV)

**Non-Enzyme Target**
- Polymerase:
  - NS2
  - NS4A
  - NS4B

**Core**
- E1
- E2
- p7
- NS2

**NS3**
- NS5A
- NS5B
<table>
<thead>
<tr>
<th>Medication</th>
<th>NS5B</th>
<th>NS5A Inh</th>
<th>NS3 PI</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sovaldi®</td>
<td>sofosbuvir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harvoni®</td>
<td>sofosbuvir</td>
<td>ledipasvir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epclusa®</td>
<td>sofosbuvir</td>
<td>velpatasvir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zepatier®</td>
<td></td>
<td>elbasvir</td>
<td>grazoprevir</td>
<td></td>
</tr>
<tr>
<td>Viekira Pak®</td>
<td>dasabuvir</td>
<td>ombitasvir</td>
<td>paritaprevir</td>
<td>ritonavir</td>
</tr>
<tr>
<td>Daklinza®</td>
<td></td>
<td></td>
<td>daclatasvir</td>
<td></td>
</tr>
<tr>
<td>Olysio®</td>
<td></td>
<td></td>
<td></td>
<td>simeprevir</td>
</tr>
<tr>
<td>Ribavirin</td>
<td></td>
<td></td>
<td></td>
<td>ribavirin</td>
</tr>
<tr>
<td>Vosevi®</td>
<td>sofosbuvir</td>
<td>velpatasvir</td>
<td>voxilaprevir</td>
<td></td>
</tr>
<tr>
<td>Mavyret®</td>
<td></td>
<td></td>
<td>pibrentasvir</td>
<td>glecaprevir</td>
</tr>
</tbody>
</table>
SOFOSBUVIR (SOVALDI®)

- 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
LEDIPASVIR/SOFOSBUVIR (HARVONI®)

- 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

Approved: Oct 10, 2014
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

Approved: June 28, 2016

VEL NS5A inhibitor

SOF - NS5B nucleotide polymerase inhibitor

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

VIEKIRA PAK [package insert]. North Chicago, IL: AbbVie Inc.

FDA approval Dec 19, 2014
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 antiacids

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

If patient is treatment experienced:

1. VEL/SOF 12 weeks
   - or
   - LDV/SOF 12 weeks
     - or
     - PBCD + RBV 12 weeks

Check for NS5A RAVs

If NS5A RAVs is negative:

- (-) RAVs: EBR/GZR 12 weeks

If NS5A RAVs is positive:

- (+) RAVs: EBR/GZR + RBV 16 weeks

If patient is not treatment experienced:

LDV/SOF 8 weeks

May consider if HCV RNA ≤ 6 million

(Alternative) LDV/SOF 8 weeks
SOFOSBUVIR/LEDIPASVIR (HARVONI) AND ACID SUPPRESSING AGENTS

**Antacids**
- aluminum hydroxide
- magnesium hydroxide
- Separate administration by four hours

**H$_2$RAs**
- famotidine
- ranitidine
- 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 ≤ omeprazole 20 mg
  - Pantoprazole mg ≠ 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 8.8million/ML
- Treatment naïve
  - Fibrosis Stage F3-F4
  - No history of
    - Esophageal varices/ encephalopathy or ascitis
  - 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
  - Treatment experienced?
  -- No
    - (Alternative) RAVs
    - (+) RAVs
  -- Yes
    - EBR/GZR
      - 12 weeks
      - (Alternative) DCV

Check NSSA RAVs

*EBR/GZR and PrOD are contraindicated with CTCP Class B or C cirrhosis
Genotypes 1 and 4

Elbasvir/Grazoprevir

- NS5A inhibitor - NS3/4A protease inhibitor

Oral and once daily w or wo food

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
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?
- 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
SOFOSBUVIR/VELPATASVIR/VOXILAPREVIR (VOSEVI®)

- 400mg/100mg/100mg tablet
  - One tablet daily with food
- **sofosbuvir**
  - NS5B polymerase inhibitor
- **velpatasvir**
  - NS5A Inhibitor
- **voxilaprevir**
  - NS3/4A protease inhibitor
- Pan-genotypic
  - genotypes 1,2,3,4,5,6
- Approved for treatment failures
- FDA approved on July 20, 2017
### SOFOSBUVIR/VELPATASVIR/VOXILAPREVIR - TREATMENT FAILURES

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Previous Regimen Included</th>
<th>Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 2, 3, 4, 5, 6</td>
<td>NS5SA inhibitor&lt;sup&gt;1&lt;/sup&gt;</td>
<td>12 weeks</td>
</tr>
<tr>
<td>1a, 3</td>
<td>Sofosbuvir without NS5A inhibitor&lt;sup&gt;2&lt;/sup&gt;</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

<sup>1</sup>—NS5A medications included in clinical trials: daclatasvir, elbasvir, ledipasvir, ombitasvir, or velpatasvir

<sup>2</sup>—Regimen tested in clinical trials included sofosbuvir with or without any of the following: peginterferon alfa/ribavirin, ribavirin, NS3/4A protease inhibitor (boceprevir, simeprevir or telaprevir). Additional benefit of VOSEVI over sofosbuvir/velpatasvir was not shown in adults with genotype 1b, 2, 4, 5, or 6 infection previously treated with sofosbuvir without an NS5A inhibitor.
Not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C)

- Due to higher exposure to protease inhibitor voxilaprevir

- Bilirubin increased $\leq 1.5 \times \text{ULN}$ in $\sim 10\%$ of patients in clinical studies
  
  - No jaundice
  
  - Levels decreased after completing treatment
GLECAPREVIR/PIBRENTASVIR
(MAVYRET®)

- 100mg/40mg tablet
  - Take 3 tablets once daily with food
- glecaprevir
  - NS3/4A protease inhibitor
- pibrentasvir
  - NS5A inhibitor
- Pan-genotypic
  - Genotypes 1,2,3,4,5,6
- Approved for some treatment failures
- No dosage adjustment in patients with mild, moderate, or severe renal impairment, including dialysis
  - FDA Approval August 3, 2017

Mavyret® [package insert]. North Chicago, IL: AbbVie Inc.
GLECAPREVIR/PIBRENTASVIR - TREATMENT NAÏVE

- All genotypes (no cirrhosis)
  - 8 weeks

- All genotypes (with cirrhosis - Child-Pugh A)
  - 12 weeks
# GLECAPREVIR/PIBRENTASVIR - TREATMENT EXPERIENCED

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Previous Treatment</th>
<th>Treatment Duration (No Cirrhosis)</th>
<th>Treatment Duration Compensated Cirrhosis (Child-Pugh A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NS5A inhibitor(^1) without prior treatment with NS3/4A protease inhibitor</td>
<td>16 weeks</td>
<td>16 weeks</td>
</tr>
<tr>
<td></td>
<td>NS3/4A protease inhibitor(^2) without prior treatment with NS5A inhibitor</td>
<td>12 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>1,2,4,5,6</td>
<td>PRS(^3)</td>
<td>8 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>3</td>
<td>PRS(^3)</td>
<td>16 weeks</td>
<td>16 weeks</td>
</tr>
</tbody>
</table>

---

\(^1\) – In clinical trials, subjects were treated with ledipasvir/sofosbuvir or daclatasvir + interferon + ribavirin

\(^2\) – In clinical trials, subjects were treated with simeprevir + sofosbuvir, or simeprevir, boceprevir, or telaprevir with interferon + ribavirin

\(^3\) – Prior treatment experience with interferon, ribavirin, and/or sofosbuvir, but no prior experience with NS3/4A protease inhibitor or NS5A inhibitor

Mavyret® [package insert]. North Chicago, IL: AbbVie Inc.
GLECAPREVIR/PIBRENTASVIR ADVERSE EFFECTS AND CAUTIONS

- Most common adverse effects (~10%)
  - Headache
  - Fatigue
  - Child-Pugh B

- Not Recommended
- Contraindicated in Child-Pugh C

- No additional monitoring parameters provided in package insert
GLECAPREVIR/PIBRENTASVIR - DRUG INTERACTIONS

- Glecaprevir is inhibitor of P-gp
  - May increase concentration of drugs that are substrates
    - Digoxin, dabigatran
- Ethinyl estradiol-containing products
  - Coadministration of Mavyret may increase the risk of ALT elevations and is not recommended
- Inducers of P-gp/CYP3A decrease plasma concentrations
  - rifampin, carbamazepine, efavirenz, St. John’s Wort
- HIV medications – see package insert
HMG-CoA Reductase Inhibitors
- Levels of statin drugs are increased; doses should be adjusted per package insert

Omeprazole
- Package insert states no dose adjustments required
  - 40mg daily is highest dose studied
  - 20mg: Coadminister with GLE/PIB
  - 40mg: Give one hour before GLE/PIB

No interaction with antacids or H2 blockers
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)
RIBAVIRIN

- **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

<table>
<thead>
<tr>
<th>Highest Priority for Treatment Owing to Highest Risk for Severe Complications</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), glecaprevir/pibrentasvir (Mavyret) Sofosbuvir/velpatasvir/voxilaprevir (Vosevi)

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) and glecaprevir/pibrentasvir (Mavyret) 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) glecaprevir/pibrentasvir (Mavyret) and Sofosbuvir/velpatasvir/voxilaprevir (Vosevi) are contraindicated
- May require addition of ribavirin or treatment extension
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 naive and non cirrhotic
- If elbasvir/grazoprevir (*Zepatier*) is used resistance testing needed
- Glecaprevir/pibrentasvir (*Mavyret*) recently approved.
  - 8 week treatment for patients without cirrhosis.

Genotype 2 and 3
- Sofosbuvir/velpatasvir (*Epclusa*) is first line therapy but PPI use and low GFR are a problem,
- Glecaprevir/pibrentasvir (*Mavyret*) recently approved.
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
CNHS HCV PROGRAM: CLINICAL CAPACITY EXPANSION* 1/2014 – 6/2017

Number of Patients Treated

- HCV ProjectECHO Introduced
- HCV Elimination Started

1 Specialist
2 Physicians
2 APRN
2 Pharmacists
7

1 Specialist
6 Physicians
5 APRN
8 Pharmacists
20

Quarterly
Cumulative

*preliminary data
HELPFUL RESOURCES

- http://www.hcvguidelines.org/

- http://www.hepatitisc.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 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**
      - VEL/SOF + RBV 12 weeks
      - Check NS3 and NS5A RAVs
      - If RBV Intolerant
        - VEL/SOF 24 weeks
      - LDV/SOF 24 weeks
      - DCV + SOF 24 weeks
  - Check NS3 and NS5A RAVs
    - (+) RAVs
      - EBR/GZR + RBV 12 weeks
    - (-) RAVs
      - EBR/GZR 12 weeks

- **No**
  - Is the patient treatment experienced?
    - **Yes**
      - VEL/SOF 12 weeks
      - (alternative) PrOD + RBV 24 weeks
    - **No**
      - LDV/SOF 12 weeks
      - (alternative) PrOD + RBV 24 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
        - check NS3 & NS5A RAVs and present to ECHO Panel
          - VEL/SOF + RBV 24 weeks
            - If RBV Intolerant:
              - VEL/SOF 24 weeks
              - or
              - LDV/SOF 24 weeks
              - or
              - DCV + SOF 24 weeks
    - SMV + SOF, DCV + SOF, LDV/SOF, ProD
      - SOF + RBV or PEG+SOF+RBV
        - Check NS3 & NS5A RAVs and present to ECHO Panel
          - VEL/SOF + RBV 24 weeks
          - or
          - LDV/SOF + RBV 12 weeks
          - or
          - VEL/SOF 12 weeks
          - or
          - LDV/SOF 24 weeks
      - IFN + RBV + PI (BOC, TPV, ... SMV)
        - VEL/SOF 12 weeks
        - or
        - LDV/SOF + RBV 12 weeks
        - or
        - ProD 12 weeks
        - or
        - EBR/GZR 12 weeks
      - IFN + RBV
        - VEL/SOF 12 weeks
        - or
        - LDV/SOF + RBV 12 weeks
        - or
        - ProD 12 weeks
        - or
        - EBR/GZR 12 weeks

Is patient treatment experienced?

- no
  - VEL/SOF 12 weeks
  - or
  - LDV/SOF 12 weeks
  - or
  - ProD 12 weeks
  - or
  - EBR/GZR 12 weeks

*ELB/GZR and ProD are contraindicated in patients with CTP Class B and C cirrhosis
**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**
          - VEL/SOF
            - 12 weeks
        - **no**
          - DCV + 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

or

*DCV + SOF + RBV
24 weeks

no

Is the patient treatment experienced with a SOF-based regimen?

yes

VEL/SOF + RBV
12 weeks

or

VEL/SOF 12 weeks

no

NS5A RAV Testing$ (+) Y93 (-) Y93

VEL/SOF + RBV
12 weeks

or

VEL/SOF 12 weeks

Is the patient treatment experienced?

yes

VEL/SOF 12 weeks

no

NS5A RAV Testing$ (+) Y93 (-) Y93

VEL/SOF + RBV
12 weeks

or

VEL/SOF 12 weeks

Is the patient treatment experienced?

yes

VEL/SOF 12 weeks

no

VEL/SOF 12 weeks

DCV + SOF + RBV
24 weeks

or

*DCV + 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?
    - No
    - Is the patient treatment experienced?
      - Yes—PEG/RBV
      - No
      - Is the patient treatment experienced?
        - Yes—PEG/RBV
        - No
          - LDV/SOF 12 weeks
          - Or
          - DCV + SOF 12 weeks
          - If RBV Intolerant:
            - DCV + SOF 24 weeks
            - Or
            - LDV/SOF 24 weeks
  - No
    - Is the patient treatment experienced?
      - Yes—PEG/RBV
      - No
        - LDV/SOF 12 weeks
        - Or
        - LDV/SOF 24 weeks
        - Or
        - EBR/GZR 16 weeks
        - PrO* + RBV 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.