New Hepatitis C Treatment Guidelines: Treatment-naïve, HIV-uninfected & HIV-infected patients

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Faculty: Dr. Kristen Marks receives research support from Janssen, BMS, BI, and Gilead.

Special thanks to Arthur Kim & John Faragon for sharing their Guidelines slides.

Do you currently treat HCV infection in your practice?

A. Frequently
B. Sometimes
C. Rarely
D. Never
E. Not a health care provider

Objectives
1. To update the healthcare provider on new Hepatitis C treatment options available for treatment-naïve patients
2. To review recent recommendations for the management of Hepatitis C treatment
3. To apply these guidelines to real world cases
Lack of Awareness and Associated Deaths

<table>
<thead>
<tr>
<th>Virus</th>
<th>Prevalence</th>
<th>% of Population Unaware of Infection Status</th>
<th>Deaths in 2006 Related to Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>800,000−1.4 million</td>
<td>About 65%</td>
<td>3,000</td>
</tr>
<tr>
<td>HCV</td>
<td>2.7−3.9 million</td>
<td>About 75%</td>
<td>12,000</td>
</tr>
<tr>
<td>HIV</td>
<td>1.1 million</td>
<td>About 21%</td>
<td>14,016</td>
</tr>
</tbody>
</table>

Sources: CDC; Lin et al, 2007; Hagan et al 2006

Current CDC recommendations for HCV screening

Screen once (no risk assessment)
- Adults born 1945-1965
- Signs of liver disease (persistently elevated ALT)

Screen based on risk for exposure
- HIV-infected
- Past or present injection drug use
- Received clotting factor concentrates prior to 1987 or other blood products made prior to July 1992 or from known HCV+ patients
- Ever on chronic hemodialysis
- Received tissues/ organs prior to July 1992
- Infants of HCV-infected mothers
- Occupational exposures (needle stick or mucosal blood exposure)

DAA Development Timeline

HCV Therapies 101

- Protease inhibitors: e.g. telaprevir, boccaprevir, faldaprevir, simeprevir, danoprevir, asunaprevir
- Polymerase inhibitors (think “base pairs”): Nucleos(t)ide analogs: e.g. tegobuvir, sofosbuvir
- Non-nucs: e.g. deleobuvir
- ASVIR: NS5A inhibitors (none yet approved)
  e.g. daclatasvir, ledipasvir

---PREVIR
---BVIR
---ASVIR

Dose G, 19th IAC; Washington, DC, July 23-27, 2012; Abst. THSB202
Minimum need to know before starting treatment

- HCV genotype and subtype
- Stage of fibrosis
  - Cirrhosis: yes/no
    - F1, compensated: yes/no
  - May be achieved by one or more of the following:
    - Liver biopsy
    - Fibroscan
    - Non-invasive measures
    - Imaging
- Prior HCV treatment
  - Naïve
  - Intolerant
  - Nonresponder
    - Relapser, partial responder or null responder
- Medications
  - To check for drug interactions
- Interferon "eligibility" and/or willingness
- Comorbidities
- Patient preference
- Child-bearing potential of patient/partner
  - Ribavirin is a teratogen

What drugs are available for treating HCV today?

- Peginterferon (PEG IFN)
- Ribavirin (RBV)
- Boceprevir (BOC)
- Telaprevir (TEL)
- Simeprevir (SMV)
- Sofosbuvir (SOF)

Currently approved drugs

<table>
<thead>
<tr>
<th>PEG IFN</th>
<th>RBV</th>
<th>BOC or TEL</th>
<th>SMV</th>
<th>SOF</th>
</tr>
</thead>
</table>

Interferon-containing combinations studied

<table>
<thead>
<tr>
<th>PEG IFN</th>
<th>PEG IFN</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBV</td>
<td>RBV</td>
</tr>
<tr>
<td>BOC or TEL</td>
<td>SMV</td>
</tr>
</tbody>
</table>

Interferon-sparing combinations studied

<table>
<thead>
<tr>
<th>RBV</th>
<th>RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMV</td>
<td>SMV</td>
</tr>
</tbody>
</table>

Summary of major differences of approved DAAs

<table>
<thead>
<tr>
<th>drug interactions</th>
<th>boceprevir or telaprevir</th>
<th>simeprevir</th>
<th>sofosbuvir</th>
</tr>
</thead>
<tbody>
<tr>
<td>wk 4 viral load monitoring resistance (cost of failure) R155K and others Q80K negligible</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>course length</td>
<td>24-48 weeks</td>
<td>24 weeks</td>
<td>12-24 weeks</td>
</tr>
<tr>
<td>adherence only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>futility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>shortens course, futility adherence only</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Interferon-containing combinations studied

PEG IFN
RBV
BOC or TEL
SOF

Interferon-sparing combinations studied

RBV
RBV
SMV
SOF

Currently approved drugs

Recommendations for Testing, Managing, and Treating Hepatitis C

- HCV TESTING AND LINKAGE TO CARE
- COMING SOON: In Whom and When to Initiate Treatment
- INITIAL TREATMENT OF HCV INFECTION IN PATIENTS STARTING TREATMENT
- RETREATMENT OF PERSONS IN WHOM PRIOR THERAPY HAS FAILED
- COMING SOON: Monitoring Patients Who Are On or Have Completed Therapy
- UNIQUE PATIENT POPULATIONS
- COMING SOON: Management of Acute HCV Infection

Genotype 2

Recommended regimen for treatment-naive patients with HCV genotype 2, regardless of eligibility for IFN therapy:
Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for treatment-naive patients with HCV genotype 2 infection.
Rating: Class I, Level A

http://www.hcvguidelines.org, accessed 2/12/14
SVR rates for Sofosbuvir + RBV x 12 wks for Geno 2 infection

Lawitz et al. NEJM 2013, Jacobson et al. NEJM 2013

SVR 97% overall G2
Zeuzem et al. AASLD 2013

Side Effects and Important Points: sofosbuvir (SOVALDI™)

- Nucleotide analog with pan-genotypic activity
- One 400 mg tablet taken once daily with or without food.
- Safe and well-tolerated
  - Side effects of drugs that it is used with
    - With RBV >20% fatigue and headache
    - With PegIFN + RBV >20% fatigue, headache, nausea, insomnia, anemia
- Liver: No dose adjustment required for mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C).
  - Safety and efficacy have NOT been established in patients with decompensated cirrhosis
- Renal: Cannot use if CrCl <30 or ESRD
  - High exposures of metabolite (26x) GS-331007
- Geriatric:
  - 90 subjects aged 65 and over received and response rates were similar to that of younger subjects

Drug interactions: sofosbuvir

- P-gp inducers: Rifampin, St. John’s wort and certain anticonvulsants should not be used with sofosbuvir
  - Drugs that are potent P-gp inducers in the intestine (e.g., rifampin, St. John’s wort, phenytoin, phenobarbital) may significantly decrease sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect of sofosbuvir
  - OK to use with P-gp inhibitors b/c does not affect level of active metabolite
  - The intracellular metabolic activation pathway of sofosbuvir is mediated by generally low affinity and high capacity hydrolyse and nucleotide phosphorylation pathways that are unlikely to be affected by concomitant drugs
Sofosbuvir resistance

- S282T
  - Does not cause cross resistance to other classes
  - Other potentially significant mutations
    - M289L, L159F, V321A, S282R, L320F,
- However extremely rare to see breakthrough as failure, usually relapse with no resistance

Case 1

41 year old Female, HCV Genotype 2, HCV RNA 250K, Stage 3 fibrosis, 12 weeks pregnant. Wants treatment.

What is the recommended regimen?
A. PegIFN + sofosbuvir + RBV x 12 wks
B. Sofosbuvir + RBV x 12 wks
C. No treatment

Answer:
C. No treatment (RBV is a teratogen)

After delivery and done breastfeeding consider sofosbuvir + RBV x 12 wks (needs adequate contraception and pregnancy tests on treatment)

Genotype 3

Recommended regimen for treatment-naive patients with HCV genotype 3, regardless of eligibility for IFN therapy:
- Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for treatment-naive patients with HCV genotype 3 infection.

Rating: Class I, Level B

http://www.hcvguidelines.org, accessed 2/12/14
Sofosbuvir + RBV x 12 or 24 wks for Geno 3 infection:
- **naïve patients**
  - Lawitz et al. NEJM 2013, Jacobson et al. NEJM 2013, Antiviral Drugs Advisory Committee Meeting, Gilead Review 10/25/13; Zeuzem et al. AASLD 2013
  - 12 weeks: 61-68% SVR
  - 24 weeks: 94% SVR

- **treatment-experienced patients**
  - Lawitz et al. NEJM 2013, Jacobson et al. NEJM 2013, Antiviral Drugs Advisory Committee Meeting, Gilead Review 10/25/13; Zeuzem et al. AASLD 2013
  - 12 weeks: 37% SVR
  - 24 weeks: 87% SVR

Peg-IFN + sofosbuvir + RBV x 12 wks for GT3 infection
- LONESTAR2 included high rate of cirrhosis (55%) & nonresponders (85%)
- 2/4 nonresponders in GT3 LONESTAR2 group were lost to f/u
- This regimen achieved 96% SVR for GT2

Recommendations for Testing, Managing, and Treating Hepatitis C

**Alt Genotype 3**

- Alternative regimens for treatment-naïve patients with genotype 3 who are eligible to receive IFN.
- Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is an acceptable regimen for IFN-eligible persons with HCV genotype 3.
- Rating: Class Ia, Level A

[http://www.hcvguidelines.org](http://www.hcvguidelines.org), accessed 2/12/14
Case 2

70 year-old Female with HCV Genotype 3, HCV RNA 310K, compensated cirrhosis.

What is the recommended regimen?

A. Sofosbuvir + RBV x 12 wks
B. Sofosbuvir + RBV x 24 wks
C. Sofosbuvir + PegIFN + RBV x 12 wks

Answer: B. Sofosbuvir + RBV x 24 wks

ALT: Sofosbuvir + PegIFN + RBV x 12 wks

(uncertain which is better, however caution with PegIFN in cirrhotics)

http://www.hcvguidelines.org, accessed 2/12/14

SOF
PEG
RBV

Genotype 1

Recommended regimen for treatment-naive patients with HCV genotype 1 who are eligible to receive IFN.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons with HCV genotype 1 infection, regardless of subtype.

Rating: Class I, Level A

http://www.hcvguidelines.org, accessed 2/12/14

Sofosbuvir + PEG-IFN/RBV x 12 wks (NEUTRINO)

Phase III, Treatment-naive, GT1,4,5,6

SVR 80% in cirrhatics
SVR 71% if multiple bad prognostic factors (G1, F3/F4, IL28 non CC, HCV RNA>800k)
### Adverse Events ≥15% with Sofosbuvir and Ribavirin +/- Peg-IFN

<table>
<thead>
<tr>
<th>Event</th>
<th>SOF+PEG+RBV x 12 weeks (n=327)</th>
<th>PEG+RBV x 24 weeks (n=243)</th>
<th>SOF+RBV x 12 weeks (n=256)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>192 (59%)</td>
<td>134 (55%)</td>
<td>92 (36%)</td>
</tr>
<tr>
<td>Headache</td>
<td>118 (36%)</td>
<td>108 (44%)</td>
<td>64 (25%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>112 (34%)</td>
<td>70 (29%)</td>
<td>46 (18%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>81 (25%)</td>
<td>70 (29%)</td>
<td>31 (12%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>58 (18%)</td>
<td>44 (18%)</td>
<td>17 (7%)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>51 (16%)</td>
<td>44 (18%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Chills</td>
<td>54 (17%)</td>
<td>43 (18%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Pyrosis</td>
<td>58 (18%)</td>
<td>33 (14%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Rash</td>
<td>59 (18%)</td>
<td>43 (18%)</td>
<td>23 (9%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38 (12%)</td>
<td>42 (17%)</td>
<td>23 (9%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>54 (17%)</td>
<td>42 (17%)</td>
<td>19 (7%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>45 (14%)</td>
<td>40 (16%)</td>
<td>21 (10%)</td>
</tr>
<tr>
<td>Irritability</td>
<td>42 (13%)</td>
<td>40 (16%)</td>
<td>25 (10%)</td>
</tr>
</tbody>
</table>

### Side Effects and Important Points: simeprevir (OLYSIO™)

- HCV NS3/4A protease inhibitor
- Approved genotype 1
- Potent against genotypes 1,4,6; activity against 2,5
- One 150 mg capsule taken once daily with food. FIRST 12 WKS ONLY
- Safe and well-tolerated (n>3,800)
- Side effects of drugs that it is used with plus
  - rash (including photosensitivity), pruritus and nausea (occurred with >3% higher frequency compared to subjects receiving SIM placebo)
  - Asymptomatic increases in bilirubin detected
- Renal: No dose recommendation can be given for patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) due to higher simeprevir exposures
- Mean 44% less when higher levels
- Race:
  - Patients of East Asian ancestry exhibit higher simeprevir exposures, consider risks and benefits
- Renal: No dose adjustment required in patients with mild or moderate renal impairment
  - has not been studied in severe renal impairment (creatinine clearance below 30 mL/min) or end-stage renal disease, including patients requiring dialysis
  - Simeprevir is highly protein-bound; therefore, dialysis is unlikely to result in significant removal of the drug
- Geriatric:
  - Insufficient data
Drug interactions: simeprevir

- Co-administration with drugs that are moderate or strong inducers or inhibitors of CYP3A may significantly affect the plasma concentrations of simeprevir
  - E.g. PIs increase SMV and efavirenz decreases
- Simeprevir inhibits OATP1B1/3 and P-glycoprotein (P-gp) transporters
  - E.g. increases digoxin
- Simeprevir mildly inhibits CYP1A2 activity and intestinal CYP3A4 activity, but does not affect hepatic CYP3A4 activity
  - E.g. increases antiarythmics like amiodarone

Simeprevir resistance

- Efficacy in combination with pegIFN + RBV is substantially reduced in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism at baseline compared to patients infected with hepatitis C virus (HCV) genotype 1a without the Q80K
  - Q80K can be as high as 40% of gene 1a patients
  - Baseline testing is recommended before using PegIFN/RBV/SMV (e.g. HCV genosure)
- Don't know how it works in people who failed PIs in past = Recommendation = DON'T USE
- Mutations
  - NS3 positions Q80, S122, R155 and/or D168 were observed in 180 out of 197 (91%) subjects.
  - genotype 1a predominately had emerging R155K alone or in combination with amino acid substitutions at NS3 positions Q80, S122 and/or D168
  - In subjects with HCV genotype 1a with baseline Q80R amino acid substitution an emerging R155K substitution was observed most frequently at 88%,
  - genotypically R155K was the most frequent resistant substitution Substitutions D168V and R155S alone or in combination with other substitutions at these positions emerged most frequently
- Do confer cross-resistance with other PIs but may revert over time
  - 88% of baseline mutant variants contained an detectable level in 32 out of 66 subjects (48%) with single emerging R155K and in 16 out of 48 subjects (33%) with single emerging D168V.

Genotype 1

Recommended regimen for treatment-naive patients with HCV genotype 1 who are not eligible to receive IFN.

Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without weight-based RBV (1000 mg ±75 kg) to 1200 mg [≥75 kg] for 12 weeks is recommended for IFN-ineligible patients with HCV genotype 1 infection, regardless of subtype.

Rating: Class I, Level B

IFN-ineligible is defined as one or more of the below:

- Intolerance to IFN
- Autoimmune hepatitis and other autoimmune disorders
- Hypersensitivity to PEG or any of its components
- Decompensated hepatic disease
- History of depression, or clinical features consistent with depression
- Baseline Cytopenias
  - neutrophil count below 1500/μL
  - platelet count below 90,000/μL
  - hemoglobin below 10 g/dL
- A history of preexisting cardiac disease
Simeprevir + Sofosbuvir ± RBV for 12 and 24 wks in G1 Rx-Naive & Null Responders (COSMOS cohort 2 (F3-F4))

- Cohort 2 (n=84): Treatment naive and null responders with METAVIR F3-4
  - Genotype 1a, 76%; Q80K, 40%
  - Cirrhosis, 47%
  - Null response, 54%
- SVR for 12 wk groups only
  - SVR in cirrhotics: 17 of 18 (94%)
- Non-SVR patients (n=1)
  - No breakthrough
  - Relapse: n=1; null responder with cirrhosis and 1a/Q80K

<table>
<thead>
<tr>
<th>SMV</th>
<th>SOF</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Notes: Jacobson et al. AASLD Liver Meeting. LB-1

SOF/SMV +/-RBV: Response by HCV subtype and Q80K (COSMOS)

- Cohort 1: 12 & 24 Weeks arms
- Cohort 2: 12 Weeks arm

<table>
<thead>
<tr>
<th>Subtype</th>
<th>SVR4</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT1a Q80K</td>
<td>89</td>
</tr>
<tr>
<td>GT1a WT</td>
<td>100</td>
</tr>
<tr>
<td>GT1b</td>
<td>91</td>
</tr>
</tbody>
</table>

*Excludes non-virologic failures

Notes: Jacobsen et al. AASLD 2013

FDA labeling of indications and usage of SOF and SMV:
Components of "Combination antiviral treatment"

- **SMV** is indicated “for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen”
  - Efficacy has been established in combination with peginterferon alfa and ribavirin in HCV genotype 1 infected subjects with compensated liver disease (including cirrhosis).

- **SOF** is indicated “for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen”
  - Efficacy has been established in subjects with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection.

Recommendations for Testing, Managing, and Treating Hepatitis C

**Alt Genotype 1**

*Alternative regimens for treatment-naive patients with HCV genotype 1 who are not eligible to receive IFN.*

- Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 24 weeks is an acceptable regimen for IFN ineligible persons with HCV genotype 1 infection, regardless of subtype; however, preliminary data suggest that this regimen may be less effective than daily sofosbuvir (400 mg) plus simeprevir (150 mg), particularly among patients with cirrhosis.

Rating: Class Ib, Level B

http://www.hcvguidelines.org accessed 2/12/14
Case 3

34 year-old Male, HCV Genotype 1a, HCV RNA 725K, severe depression with suicide attempt 1 year prior, Stage 2 on liver biopsy, desires HCV treatment...

What is the recommended regimen?

POLL!

A. PegIFN + sofosbuvir + RBV x 12 wks
B. Simeprevir + sofosbuvir +/- RBV x 12 wks

Answer:

B. Simeprevir + sofosbuvir +/- RBV x 12 wks (IFN-ineligible because of severe depression)
**Summary of relative efficacy for various studies by regimens and genotypes: Rx naive**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Regimen</th>
<th>SVR4</th>
<th>SVR4 w/ Q80K</th>
<th>SVR4 w/ cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT1</td>
<td>x24-48w</td>
<td>89%</td>
<td>89%</td>
<td>99%</td>
</tr>
<tr>
<td></td>
<td>x12w</td>
<td>91%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>GT2</td>
<td>x12w</td>
<td>93%</td>
<td>93%</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td>x24w</td>
<td>97%</td>
<td>97%</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td>x12w</td>
<td>91%</td>
<td>91%</td>
<td>91%</td>
</tr>
<tr>
<td>GT3</td>
<td>x24w</td>
<td>93%</td>
<td>93%</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td>x12w</td>
<td>97%</td>
<td>97%</td>
<td>97%</td>
</tr>
</tbody>
</table>

**Recommendations for Testing, Managing, and Treating Hepatitis C**

**Genotype 4**

**Recommended regimen for treatment-naive patients with HCV genotype 4 who are eligible to receive IFN.**

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons with HCV genotype 4 infection.

Rating: Class IIa, Level B

**Alt Genotype 4**

**Alternative regimen for treatment-naive patients with HCV genotype 4 who are eligible to receive IFN.**

Daily simeprevir (150 mg) for 12 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 24 to 48 weeks is an alternative regimen for IFN-eligible persons with HCV genotype 4 infection.

Rating: Class IIb, Level B
What about HIV/HCV coinfection?

- Guidelines very similar
- Drug interactions affect choice of regimen

HIV/HCV Co-Infection, GT1

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naïve, prior PEG/RBV relapsers, IFN eligible: SOF + PEG/RBV(WB) x 12 weeks</td>
<td>Treatment naïve, prior PEG/RBV relapsers, IFN eligible: SMV x 12 weeks + PEG/RBV(WB) x 24 weeks</td>
</tr>
<tr>
<td>IFN ineligible: SOF + RBV(WB) x 24 weeks</td>
<td>IFN ineligible: None</td>
</tr>
<tr>
<td>SOF + SMV ± RBV(WB) x 12 weeks</td>
<td>Treatment experienced, prior PEG/RBV nonresponders, regardless of IFN eligibility: SOF + SMV ± RBV(WB) x 12 weeks</td>
</tr>
</tbody>
</table>

Not Recommended: TVR + PEG/RBV x 24 or 48 weeks (RGT), BOC + PEG/RBV x 28 or 48 weeks (RGT)

56 W HIV/HCV g1a, HCV RNA 13.3 million. Prior null responder to PegIFN/RBV with course c/b severe pancytopenia,
- She has cirrhosis by biopsy taken 10 years ago, platelets 37, albumin 3.5, AST 143, ALT 122, INR 1.0.

HIV hx: CD4 261, HIV RNA ND
- Current ARVs: atazanavir, ritonavir, etravirine, raltegravir, lamivudine (hx of TDF renal insuff)

Other medical conditions: DM, CAD, PVD
Social: single mother & sole breadwinner for 2 children
You order MRI for HCC screening, an EGD, & recommend treatment now. Which of the following would be the best therapeutic option at this time?

1. Sofosbuvir + RBV x 24 wks
2. PegIFN + RBV + simeprevir x 24 wks
3. PegIFN + RBV + sofosbuvir x 12 wks
4. Sofosbuvir + simeprevir x 12 wks
5. Other (Careful...you will be asked to specify)

Sofosbuvir and HIV Medications

**Concurrent Medication** | **Recommendation**
--- | ---
**HIV Integrase Strand Transfer Inhibitors**
Dolutegravir (Tivicay®) | Concurrent use at standard doses acceptable. Interactions not expected based upon metabolism of sofosbuvir.
Elvitegravir (contained in Stribild®) | Concurrent use at standard doses acceptable. Interactions not expected based upon metabolism of sofosbuvir.
Raltegravir (Isentress®) | Concurrent use at standard doses acceptable.
**HIV Entry Inhibitors**
Maraviroc (Selzentry®) | Concurrent use at standard doses acceptable.
**HIV Nucleoside/Nucleotide Reverse Transcriptase Inhibitors**
All NRTIs | Concurrent use at standard doses acceptable. Interactions not expected based upon metabolism of sofosbuvir.

Simeprevir and HIV Medications

**Concurrent Medication** | **Recommendation**
--- | ---
**HIV Protease Inhibitors**
All HIV PIs, with or without ritonavir | Significant increases or decreases in simeprevir levels expected when used with any HIV protease inhibitor, when used with or without ritonavir. Co-administration not recommended
**HIV Non Nucleoside Reverse Transcriptase Inhibitors**
Elvitegravir (contained in Stribild®) | Significant reductions in simeprevir levels and reduced simeprevir efficacy due to CYP3A4 induction. Co-administration not recommended.
Ritonavir (Norvir®) | Concurrent use at standard doses acceptable.
### Concurrent Medication Recommendation

#### HIV Integrase Strand Transfer Inhibitors

- **Dolutegravir (Tivicay®)**
  - Concurrent use at standard doses acceptable. Interactions not expected based upon metabolism of simeprevir.

- **Elvitegravir (contained in Stribild®)**
  - Significant increase in simeprevir levels expected when used with a cobicistat containing regimen. Co-administration not recommended.

- **Raltegravir (Isentress®)**
  - Concurrent use at standard doses acceptable.

#### HIV Entry Inhibitors

- **Maraviroc (Selzentry®)**
  - Concurrent use at standard doses acceptable. Interactions not expected based upon metabolism of simeprevir.

#### HIV Nucleoside/Nucleotide Reverse Transcriptase Inhibitors

- **All NRTIs**
  - Concurrent use at standard doses acceptable. Interactions not expected based upon metabolism of simeprevir.

---

### PHOTON Baseline Demographics

<table>
<thead>
<tr>
<th>Treatment Naive</th>
<th>Treatment Experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 1 n=114</td>
<td>GT 2/3 n=68</td>
</tr>
<tr>
<td>GT 2/3 n=41</td>
<td>GT 2/3 n=41</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean age, y (range)</th>
<th>48 (25-70)</th>
<th>49 (24-71)</th>
<th>54 (34-60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>93 (82%)</td>
<td>56 (81%)</td>
<td>57 (60%)</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>37 (32%)</td>
<td>8 (12%)</td>
<td>7 (17%)</td>
</tr>
<tr>
<td>Hispanic, n (%)</td>
<td>25 (22%)</td>
<td>19 (28%)</td>
<td>10 (24%)</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (range)</td>
<td>27 (18-46)</td>
<td>27 (20-43)</td>
<td>27 (19-40)</td>
</tr>
<tr>
<td>Genotype 1a, n (%)</td>
<td>90 (79)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Genotype 2, n (%)</td>
<td>NA</td>
<td>26 (38)</td>
<td>24 (58)</td>
</tr>
<tr>
<td>Genotype 3, n (%)</td>
<td>NA</td>
<td>42 (62)</td>
<td>17 (41)</td>
</tr>
<tr>
<td>IL28B CC, n (%)</td>
<td>30 (27)</td>
<td>25 (37)</td>
<td>20 (49)</td>
</tr>
<tr>
<td>Mean HCV RNA, log₁₀ IU/mL (range)</td>
<td>6.6 (4.7-7.5)</td>
<td>6.3 (5.0-7.4)</td>
<td>6.5 (4.5-7.5)</td>
</tr>
<tr>
<td>CD4 count (cells/μL), mean (SD)</td>
<td>636 (251)</td>
<td>585 (246)</td>
<td>658 (333)</td>
</tr>
</tbody>
</table>

### SOF+RBV in HIV/HCV (PHOTON) Study Design

- **Wk 0**
- **Wk 12**
- **Wk 24**
- **Wk 36**
- **Wk 48**

- **GT 1 TN**
  - SOF + RBV, n=114
  - SVR 12

- **GT 2/3 TN**
  - SOF + RBV, n=68
  - SVR 24

- **GT 2/3 TE**
  - SOF + RBV, n=41
  - SVR 24

- **Outcome, n (%)**
  - SVR12
    - GT 1
      - n=114
      - 87 (76) 23 (88) 28 (67) 22 (92) 16 (94)
    - GT 2
      - n=68
      - 26 (23) 1 (4) 12 (29) 1 (4) 1 (6)
    - GT 3
      - n=41
      - 25 (22) 0 12 (29) 1 (4) 1 (6)
  - Completed study drug
    - 19 0 11 0 1
  - Did not complete study drug
    - 6 0 1 1 0
  - HCV viral breakthrough
    - 1 (1) 1 (4) 0 0 0
    - Other
      - 1 (1) 2 (8) 2 (5) 1 (4) 0

*Both patients with HCV breakthrough were nonadherent to SOF, confirmed by PK analysis.*

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<https://www.nynjetc.org>
Case 2 - cont

- Decided to avoid interferon for fear of decompensation, serious complication and/or disabling side effects that she cannot afford.
- Attempted to get compassionate use of daclatasvir with plan to use in combination with sofosbuvir.
  - Denied because not high likelihood of death in next year.
- Started sofosbuvir plus ribavirin, plan to use x 24 weeks.
  - Hoping even if not successful might bridge her to more successful therapies.
- She tolerates first 2 weeks and is <43 but detected at Week 4.
  - You plan to continue to monitor her every other week until her HCV RNA is not detected and Hb is stable

Summary

- Guidelines cover most scenarios for G1-6
  - Based on available, but still limited study data
  - Provide guidance at this point on regimen when you have already decided to treat
  - Updated in real time
- HIV/HCV recommended regimens and outcomes similar to HCV monoinfection
  - Drug interactions affect choice of regimen
- Treatment efficacy and tolerability should continue to improve
  - Multiple IFN-sparing regimens in development

Questions from the audience?

Thank you!

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