HCV Genotype 1 and 4
Initial Treatment and Retreatment
Case-Based Scenarios

Ricardo A Franco, MD
Assistant Professor of Medicine
University of Alabama at Birmingham
Birmingham, AL

HCV Therapeutics Timeline

IFN-free Treatment Options in 2016 (FDA Approved)

Direct Antiviral Agents - DAAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Activity</th>
<th>Potency</th>
<th>Resistance Barrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir</td>
<td>NS5B</td>
<td>Nucleotide</td>
<td>Pangenotypic</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Dasabuvir</td>
<td>Non-Nuc</td>
<td>GT1</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
<tr>
<td>Velpatasvir</td>
<td>NS3</td>
<td>PI</td>
<td>GT1,2,4,5 &amp; 6</td>
<td>Low</td>
</tr>
<tr>
<td>Elbasvir</td>
<td>NS3</td>
<td>PI</td>
<td>GT1,2,4,5 &amp; 6</td>
<td>Low</td>
</tr>
<tr>
<td>Ombitasvir</td>
<td>NS3</td>
<td>PI</td>
<td>GT1,2,4,5 &amp; 6</td>
<td>Low</td>
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<tr>
<td>Ledipasvir</td>
<td>NS3</td>
<td>PI</td>
<td>GT1,2,4,5 &amp; 6</td>
<td>Low</td>
</tr>
<tr>
<td>Paritaprevir</td>
<td>PI</td>
<td>GT1</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>NS5A</td>
<td>GT 1,3</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Grazoprevir</td>
<td>PI</td>
<td>GT 1,4 &amp; 5</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>PI</td>
<td>GT1</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>NS5B</td>
<td>Nucleotide</td>
<td>Pangenotypic</td>
<td>Intermediate</td>
</tr>
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<td>Dasabuvir</td>
<td>Non-Nuc</td>
<td>GT1</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
</tbody>
</table>
Requirements for HCV Therapy

- SVR > 90%
- Toxicity
- Tolerability
- Short duration
- High barrier to resistance
- One size fits all: pangenotypic
- No drug-drug interactions
- Low pill burden

Helpful

Must have

DDIs (DAA vs Other Selected Drugs)

<table>
<thead>
<tr>
<th>Concomitant Medication</th>
<th>SOF</th>
<th>SIM</th>
<th>LDV</th>
<th>PISI/PROT/2DPI</th>
<th>DCV</th>
<th>GS/ABT</th>
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<tbody>
<tr>
<td>Acid reducing agents</td>
<td></td>
<td></td>
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<tr>
<td>Anticoagulants</td>
<td>X</td>
<td>x</td>
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<td>X</td>
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<tr>
<td>Anticonvulsants</td>
<td>X</td>
<td>x</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Digoxin</td>
<td></td>
<td>x</td>
<td></td>
<td>X</td>
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<tr>
<td>Ether-containing-containing products</td>
<td></td>
<td>x</td>
<td></td>
<td>X</td>
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<tr>
<td>Glucocorticoids</td>
<td></td>
<td>x</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>HMG-CoA reductase inhibitors</td>
<td></td>
<td>x</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Rifampicin and/or rifabutin</td>
<td></td>
<td>x</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Sedatives</td>
<td></td>
<td>x</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>St John’s wort</td>
<td></td>
<td>x</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Statins</td>
<td></td>
<td>x</td>
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</table>

Adapted from AASLD/IDSA Guidelines. February 2016.

HCV GT1
Case 1

- A 55yo CM returns to Viral Hepatitis Clinic for evaluation. He is doing well, with no complaints. The patient has chronic hepatitis C with VL of 6,000,000 IU/mL (GT1a), and he is treatment naïve. Further basic work up shows ALT 65, AST 80 albumin 3.9, platelet count 160,000/mL and APRI = 1.3. Liver US is normal.

- He has no other co-morbidities. He acquired HCV many years ago (remote IVDU), but denies current use of illicit drugs. He quit drinking. He works and is doing well in real estate business. He is interested in HCV treatment.

- You attend at a clinic where transient elastography or liver biopsy are not available. You refer to outside clinic and TE = 10.5 Kpa (F3 disease).

What would be your next step in management?

1. SOF/LDV x 8 weeks
2. SOF/LDV x 12 weeks
3. Liver biopsy
4. Check for NS5A and PI resistance
5. PrOD x 12 weeks
6. EBR/GZR x 12 weeks

Sofosbuvir/Ledipasvir:
FDA Approved Indication

Population (Genotype 1) | Recommended Treatment Duration | Pivotal Trials
---|---|---
Naive with or without cirrhosis | 12 wks* | ION-1: 12wk arm SVR in non-cirrhotic ≥ 99%
| 12wk arm SVR in cirrhotic ≥ 97%
Experienced without cirrhosis | 12 wks | ION-2: 12wk arm SVR ≥ 94%
Experienced with cirrhosis | 24 wks | ION-2: 12wk arm SVR ≥ 86%

*Treatment duration can be considered in treatment naive pts without cirrhosis who have pretreatment HCV RNA < 6 million IU/mL (ION 3 trial).
†Treatment experienced pts who have failed treatment with pegIFN/RBV or HCV PI.
### SOF/LDV x 8wks – Clinical Trial and Real World Experience

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SOF/LDV for 8wk (N=215)</th>
<th>SOF/LDV + RBV for 8wk (N = 216)</th>
<th>SOF/LDV for 12wk (N = 216)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ION-3 Trial 60% GT1a 40% GT1b</td>
<td>Fibrosis score by liver biopsy – N (%)</td>
<td>156 (73)</td>
<td>156 (72)</td>
</tr>
<tr>
<td>F0-F2</td>
<td>127 (59)</td>
<td>127 (59)</td>
<td>127 (59)</td>
</tr>
<tr>
<td>F3</td>
<td>29 (13)</td>
<td>29 (13)</td>
<td>29 (13)</td>
</tr>
<tr>
<td>SVR</td>
<td>94%</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td>HCV-Target 60% GT1a 35% GT1b Cirrhosis</td>
<td>SVR</td>
<td>2/154 (13)</td>
<td>2/154 (13)</td>
</tr>
<tr>
<td></td>
<td>97%</td>
<td>97%</td>
<td>97%</td>
</tr>
</tbody>
</table>

Odds of SVR12 if no baseline PPI: 3.02 (95% CI 1.51 – 6.05); p .001

Terrault et al. AASLD 2015. Abstract 94

### Sofosbuvir + simeprevir

**FDA-Approved Indications**

<table>
<thead>
<tr>
<th>Population (GT-1)</th>
<th>Treatment</th>
<th>Duration</th>
<th>Pivotal Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>TN and TE* without cirrhosis</td>
<td>SOF + SMV</td>
<td>12 wks</td>
<td>OPTIMIST-1 8wk arm SVR ≥ 82% 12wk arm SVR ≥ 97%</td>
</tr>
<tr>
<td>TN and TE* with cirrhosis</td>
<td>SOF + SMV</td>
<td>24 wks</td>
<td>OPTIMIST-2** 12wk arm SVR ≥ 93% (74% in 1a with Q80K)</td>
</tr>
</tbody>
</table>

* Treatment-experienced relapsers, partial responders and null responders to IFN-based therapy
** Consider screening for QBK polymorphism at baseline in GT-1a cirrhosis


### Case 2

- A 55yo CF returns to Viral Hepatitis Clinic for evaluation. She is doing well, with no complaints. The patient has chronic hepatitis C with VL of 4,000,000 (GT1b), and she is treatment naive. Further basic work up shows ALT 65 IU/L, AST 80 albumin 3.9, platelet count 100,000/mL and APRI = 2.1. Liver US is normal.
- She has a hx of HTN, DM and PUD and takes metformin, lisinopril and omeprazole. She acquired HCV many years ago (remote blood transfusion). No drinking. No use of illicit drugs.
- TE = 16 Kpa
According to the AASLD/IDSA hepatitis C guidance, which one of the following would you recommend as initial therapy for this patient?

1. Ombitasvir-paritaprevir-ritonavir and dasabuvir x 12 weeks
2. Ombitasvir-paritaprevir-ritonavir and dasabuvir plus ribavirin x 24 weeks
3. Simeprevir plus sofosbuvir x 12 weeks
4. Ledipasvir-sofosbuvir x 24 weeks

Paritaprevir/ombitasvir + dasabuvir
FDA-Approved Indication

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment</th>
<th>Duration</th>
<th>Pivotal Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT1a, without cirrhosis</td>
<td>3DAA + RBV</td>
<td>12 wks</td>
<td>SAPPHIRE I: SVR 95%, SAPPHIRE II: SVR 96%, PEARL-I: SVR 90% (w/o RBV)</td>
</tr>
<tr>
<td>GT1a, with cirrhosis</td>
<td>3DAA + RBV</td>
<td>24 wks</td>
<td>TURQUOISE-II: 12-wk arm: SVR 89%, 24-wk arm: SVR 95% (Difference driven by null responders)</td>
</tr>
<tr>
<td>GT1b w/wo cirrhosis</td>
<td>3DAA</td>
<td>12 wks</td>
<td>PEARL-II (TE): SVR 100%, PEARL-II (TN): SVR 99%</td>
</tr>
</tbody>
</table>

Case 3

- A 57 yo AAM with hx of HTN, CKD, compensated cirrhosis and HIV/HCV co-infection comes for follow up at Viral Hepatitis Clinic. He is doing well, very engaged in care currently and interested in HCV rx options.

- He has hx of HIV resistance (M184V and N155H - resistance to 3TC, FTC, RAL, EVG). Further labs show:

- HCV GT1a, creat 1.5 mg/dL, AST 40, ALT 70, PTL 140K, Alb 4.3, normal PT/INR.

- His med list includes TDF/FTC + DRV/r, HCTZ and lisinopril.
Assuming the patient (and you) are not interested in ART switches, what treatment would you recommend?

1. SOF/LDV x 12 weeks
2. SOF/LDV x 24 weeks
3. SOF/SIM x 24 weeks
4. SOF/DCV x 24 weeks
5. PrOD + RBV x 24 weeks

Case 3

- Potential for drug-drug interactions between SOF/LED and ARVs

Options for patients on TDF + boosted-PI
- Change TDF
- Change PI
- Await another HCV regimen
- If combo required, close monitoring recommended

ALLY-2: SOF+DCV in HIV/HCV

HCV GT1 & 4
Pts & TGs
Comp cirrhosis (<50%)
ARVs allowed: TDF, FTC, ABC, 3TC, AZT, DDI/r, ARVs, LPV/r, EFV, NVP, DTV, RAL, TMC, MVC
DCV dosing in ALLY-2:
30mg with RTV-boosted PI
50mg with MMR/Is except RPV
Package insert:
30mg with ATPc and EVG/c
Case 4

A 58 yo CM with hx of depression, HIV/HCV and cirrhosis comes for follow up at Viral Hepatitis Clinic. He is doing well on TDF/FTC/RAL. He has no history of hepatic encephalopathy, GIB or SBP. His HCC surveillance is up to date. A recent EGD showed 1+ varices and was placed on low dose nadolol and omeprazole 20mg.

Other labs show AST 44, ALT 54, albumin 3.2, total bill 1.8, PT 16.5, INR 1.33, creat 0.6, Hgb 14, PTL 66K.

He is interested in HCV treatment. He was a null responder to Peg-INF and ribavirin.

According to the AASLD/IDSA hepatitis C guidance, which one of the following would you recommended as re-treatment for this patient?

1. SOF/LDV x 12 weeks
2. SOF + DCV + RBV x 12 weeks
3. SOF + DCV x 24 weeks
4. SOF/LDV x 24 weeks
5. Refer and co-manage decompensated cirrhosis w Hepatology

AASLD/IDSA Guidance for Pts With Decompensated Cirrhosis

- Refer to experienced HCV practitioner (ideally liver transplant center)
- Avoid BOC, GZR/EBV, IFN, PTV/RTV/OBV + DSV, SIM, TVR, or monotherapy with RBV or DAA

<table>
<thead>
<tr>
<th>Population</th>
<th>RBV Eligible</th>
<th>RBV Ineligible</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 1/4</td>
<td>SOF + DCV</td>
<td>SOF/LEV</td>
</tr>
<tr>
<td></td>
<td>12 wks + low-dose RBV*</td>
<td>12 wks + low-dose RBV*</td>
</tr>
<tr>
<td></td>
<td>24 wks</td>
<td>24 wks</td>
</tr>
<tr>
<td>GT 1/4, SOF failure</td>
<td>Not recommended</td>
<td>24 wks + low-dose RBV*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

*Initial dose of RBV high, increased as tolerated.
Case 5

• A 62yo CF has chronic hepatitis C with VL of 4,000,000 (GT1a), and she is treatment naïve. Further basic work up showed F4 disease. Liver US is normal.

• She is doing well and tolerated SOF/LDV for 12 weeks with no complaints. HCV VL at week 4 was undetectable and she did not missed doses. Today she returns for SVR12 check and unfortunately HCV VL is detectable at 200,000 IU/mL.

What would you recommend next?

1. Wait until newer agents are approved
2. Treat with SOF/LDV + RBV
3. Treat with SOF + SIM + RBV
4. Treat with PrOD
5. Refer to clinical trials
6. Order NSSA resistance and Q80K polymorphism testing

Mechanisms of Resistance
Virolologic Barriers to Resistance

Genetic barrier
- Number and type of nucleotide changes required for a virus to acquire resistance to an antiviral regimen[1]

Viral fitness
- Relative capacity of a viral variant to replicate in a given environment


Fitness of Polymerase Inhibitor Mutants [2,3]

Selecting Treatment Based on Resistance Testing Results

- If genotype 1a or 1b HCV infection and previous failure with any NS5A inhibitors and cirrhotic or other need for urgent treatment:

<table>
<thead>
<tr>
<th>RA Testing Result</th>
<th>Retreatment Regimen</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>No NS5A RA vs</td>
<td>Ledipasvir/sofosbuvir + ribavirin</td>
<td>24 wks</td>
</tr>
<tr>
<td>NS5A but no NS3 RA vs</td>
<td>Simeprevir + sofosbuvir + ribavirin</td>
<td>24 wks</td>
</tr>
<tr>
<td>NS5A and NS3 RA vs</td>
<td>Retreatment in a clinical trial setting</td>
<td></td>
</tr>
</tbody>
</table>

Case 6

- 69 yo AAM with hx of ESRD on HD, CAD, Gout, GERD and cirrhosis comes for evaluation of chronic hepatitis C. Treatment naïve.

- Labs show:
  - AST 23, ALT 30, creat 7.7, Hgb 11.9, PTL 78K;
  - HCV GT1a and TE = 17.5 KPa
Which regimen would you use?

1. Sofosbuvir/ledipasvir x 12 wks
2. Paritaprevir/ritonavir/ombitasvir + dasabuvir + RBV x 12 weeks
3. Grazoprevir/elbasvir x 12 weeks
4. Grazoprevir/elbasvir + RBV x 16 weeks
5. Need further testing

Grazoprevir/elbasvir
FDA-Approved Indication - GT1

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment</th>
<th>Duration</th>
<th>Pivotal Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT1aTN or PR-TE Without NS5A RAVs</td>
<td>GZR/EBR</td>
<td>12 wks</td>
<td>C-EDGE TN (N = 421) GT1a = 92% SVR; GT1b = 99% SVR (HCV VL &gt; 800,000; BL NS5A RAVs) C-EUROPEAN (N = 122; stage 4/5 CKD (76% on HD) SVR 94%</td>
</tr>
<tr>
<td>GT1aTN or PR-TE With NS5A RAVs</td>
<td>GZR/EBR + RBV</td>
<td>16 wks</td>
<td></td>
</tr>
<tr>
<td>GT1bTN or PR-TE</td>
<td>GZR/EBR</td>
<td>12 wks</td>
<td></td>
</tr>
<tr>
<td>GT1bTN or PR-TE</td>
<td>GZR/EBR + RBV</td>
<td>12 wks</td>
<td>C-AALEUGIE (N = 79) 67% cirrhotic SVR 90% overall</td>
</tr>
</tbody>
</table>

HCV GT4
Case 7

- 40 y.o. Egyptian M with HCV G4 and no other significant medical problems.

- HCV hx: uncertain risk factors. No h/o IVD or IN cocaine. No MSM. Multiple childhood surgeries for leg fracture but uncertain if blood transfusions.
  - No evidence cirrhosis by Fibrosure, imaging, PE or labs.
  - HCV RNA 4.1 million IU/ml
  - Prior HCV Rx with PegIFN+RBV x 48 wks – relapse.

Which regimen has poor efficacy for G4 treatment and would NOT be recommended?

1. Ledipasvir/sofosbuvir x 12w
2. Sofosbuvir + ribavirin x 12w
3. Sofosbuvir + ribavirin x 24w
4. Peginterferon + ribavirin + sofosbuvir x 12w
5. Paritaprevir/ritonavir/ombitasvir + ribavirin x 12w

[Graph showing % success rates for different regimens]
### GT-4 AASLD/IDSA Endorsed Regimens

<table>
<thead>
<tr>
<th>Population</th>
<th>SOF/RBV</th>
<th>PR/SOF</th>
<th>SOF/LDV</th>
<th>P/OD</th>
<th>GZR/EBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>TN w cirrhosis</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks</td>
</tr>
<tr>
<td>TN w cirrhosis</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks</td>
</tr>
<tr>
<td>TE w cirrhosis</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks</td>
</tr>
<tr>
<td>TE w cirrhosis</td>
<td>24 wks</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks</td>
</tr>
</tbody>
</table>

AASLD/IDSA Guidance – Feb 2016

### Case 7

- 40 y.o. Egyptian M with HCV G4
  - The patient received LDV/SOF x 12 wks (FDA approved).
  - By Wk 4 his enzymes had normalized and no new lab abnormalities.
  - HCV RNA not detected Wk4 and 12 wks post treatment.
  - He developed insomnia while on treatment, managed with OTC sleep aids. It resolved post-Rx.

### Summary

- Remarkable HCV G1 treatment tolerability & efficacy
  - Continued efforts being made to make shorter, safer, more effective
  - Continued need for therapies without significant drug interactions & those that can be used in varied populations (HIV+, ESRD, opiate substitution, etc)
  - Retreatment of DAA failures requires further study

- Successful early treatment prevents cirrhosis, end stage liver disease, and hepatocellular cancer
Resources

- HCVguidelines.org
- Hepatitis.uw.edu
- IASUSA.org
- nynjaetc.org
- http://www.hep-druginteractions.org

Thank you