Learning Objectives

After attending this presentation, participants will be able to:

• Evaluate patients with HIV/HCV coinfection for drug interactions prior to starting HCV treatment
• Discuss the current studies using direct-acting antivirals (DAAs) for the treatment of HIV/HCV coinfection
• Understand issues related to switching ARV regimens prior to initiating HCV treatment

Case 1

• 53 y.o. AA man with HIV-1 infection and HCV infection. He complains of extreme fatigue which is debilitating.
• He has been on RAL/TDF/FTC for 2 years.
• Initial HIV genotype showed no RT or PR mutations and he has never had HIV virologic failure.
• He had never had a liver biopsy and is HCV treatment naïve.
• You obtain the following tests:

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA</td>
<td>copies/mL</td>
<td>&lt;48</td>
</tr>
<tr>
<td>CD4 absolute</td>
<td>cells/cmm</td>
<td>555</td>
</tr>
<tr>
<td>CD4 percent</td>
<td>%</td>
<td>34</td>
</tr>
<tr>
<td>HCV RNA</td>
<td>IU/mL</td>
<td>16,600,000</td>
</tr>
<tr>
<td>HCV genotype</td>
<td></td>
<td>1a</td>
</tr>
<tr>
<td>WBC</td>
<td>4.58 x 10^9/L</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>g/dL</td>
<td>14</td>
</tr>
<tr>
<td>Platelets</td>
<td>200,000</td>
<td></td>
</tr>
<tr>
<td>Fibroscan F2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lab Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.9 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>26 U/L</td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>26 U/L</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>111 U/L</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>FIB-4 score</td>
<td>1.35</td>
<td></td>
</tr>
<tr>
<td>APRI</td>
<td>0.33</td>
<td></td>
</tr>
</tbody>
</table>
When and in Whom to Initiate HCV Therapy

**Highest Priority for Treatment Owing to Highest Risk for Severe Complications**
- Advanced fibrosis (Metavir F3) or compensated cirrhosis (F4)
- Type 2 or 3 essential mixed cryoglobulinemia with and organ manifestations (e.g. vasculitis)
- Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis
- Organ Transplant
- Type II or III diabetes mellitus (insulin resistant)
- Porphyria cutanea tarda

**Rating:** Class I, Level A

**High Priority for Treatment Owing to High Risk for Complications**
- Fibrosis (Metavir F2)
- HIV-1 coinfection
- Hepatitis B Virus (HBV) coinfection
- Other coexistent liver disease (e.g. NASH)
- Debilitating fatigue
- Type II Diabetes mellitus (insulin resistant)

**Rating:** Class I, Level B

**Rating:** Class IIa, Level C

**Rating:** Class IIb, Level C

---

HCV Treatment Options

<table>
<thead>
<tr>
<th>NS3 Protease Inhibitors</th>
<th>NSSA Replication Complex Inhibitors</th>
<th>NS5B Nucleoside Inhibitors</th>
<th>NS5B Non-nucleoside Inhibitors</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Approved Agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telaprevir</td>
<td>Ledipasvir</td>
<td>Sofosbuvir</td>
<td>Peginterferon</td>
<td></td>
</tr>
<tr>
<td>Boceprevir</td>
<td></td>
<td></td>
<td>Ribavirin</td>
<td></td>
</tr>
<tr>
<td>Simeprevir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paritaprevir</td>
<td>Ombitasvir</td>
<td>Dasabuvir</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FDA, US Food and Drug Administration

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Genotype 1 Treatment: HCV Monoinfection and HCV/HIV Coinfection

<table>
<thead>
<tr>
<th>Recommended</th>
<th>NOT Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a: Treatment-naïve, noncirrhotic</td>
<td>Tx-naïve and prior Peg/ RBV relapers</td>
</tr>
<tr>
<td>LDV+SOF x 12 weeks</td>
<td>PegIFN/RBV, SOF, SMV, TEL, BOC x 12/24 to 48 weeks</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/ombitasvir + dasabuvir + RBV x 12 weeks</td>
<td>PegIFN, RBV, or DAA Monotherapy</td>
</tr>
<tr>
<td>Genotype 1b: Treatment-naïve, cirrhotic</td>
<td></td>
</tr>
<tr>
<td>LDV+SOF x 12 weeks</td>
<td></td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/ombitasvir + dasabuvir + RBV x 24 weeks</td>
<td></td>
</tr>
<tr>
<td>Genotype 1b: Treatment-naïve, noncirrhotic</td>
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</tr>
</tbody>
</table>

Efficacy in HIV/HCV co-infection

Effectiveness of Sofosbuvir/Simeprevir for HIV/HCV Patients in Clinical Practice

Specific Aim: To assess sustained virologic responses and tolerability of sofosbuvir + simeprevir (sof/sim) in HIV/HCV coinfected patients compared to those with HCV alone.

Baseline characteristics of HIV/HCV-coinfected and HCV-monoinfected patients prescribed Sof/Sim

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HIV/HCV (n=335)</th>
<th>HCV (n=5,134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years (mean)</td>
<td>51.1</td>
<td>51.3</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>60%</td>
<td>59%</td>
</tr>
<tr>
<td>Female</td>
<td>40%</td>
<td>41%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>33%</td>
<td>39%</td>
</tr>
<tr>
<td>White</td>
<td>67%</td>
<td>61%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Previous HIV Treatment</td>
<td>48%</td>
<td>31%</td>
</tr>
<tr>
<td>Previous Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Relapse</td>
<td>1%</td>
<td>5%</td>
</tr>
<tr>
<td>Response to Treatment</td>
<td>46%</td>
<td>46%</td>
</tr>
<tr>
<td>HCV Virus Load</td>
<td>&lt;6.1 millions</td>
<td>&lt;6.1 millions</td>
</tr>
<tr>
<td>Baseline HCV RNA</td>
<td>&gt;6.1 millions</td>
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</tr>
<tr>
<td>Percent Stu</td>
<td>170,000</td>
<td>170,000</td>
</tr>
<tr>
<td>Percent Ctv</td>
<td>30%</td>
<td>17%</td>
</tr>
<tr>
<td>Percent No Cirr</td>
<td>70%</td>
<td>83%</td>
</tr>
<tr>
<td>Percent Cirr</td>
<td>30%</td>
<td>17%</td>
</tr>
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Virologic Responses to SOF/SIM

Failures:  
- 10 relapses  
- 2 on-treatment  
- 1 lost to f/u  
- 1 death

Safety and tolerability:  
- 2% Serious AEs  
- No discontinuations due to AEs  
- 1 death

Naggie S. #152LB CROI 2015.
TURQUOISE I:

- Two patients in 24 week arm were re-infected causing decrease to 90.6% at SVR12
- Two virologic failures - both 1a cirrhotic null responders
- One patient withdrew consent

Wyles, EASL 2014.

Case 2

- 52 y.o. man with HIV-1/HCV coinfection and hemophilia. Recently hospitalized for severe anemia requiring transfusion from rectal hemorrhoids. PMH sig for nephrolithiasis with renal dysfunction.
- He has been on DRV/r/TDF/FTC for 2 years.
- Heavily ARV treatment experienced with h/o of HIV virologic failure.
- No hx of liver biopsy and is prior null responder to PEG/RBV.
- You obtain the following tests:

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<tr>
<td>Albumin</td>
<td>4.0</td>
</tr>
<tr>
<td>Ultrasound</td>
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</tbody>
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Genotype 1 Treatment: HCV Monoinfection and HCV/HIV Coinfection

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</tr>
<tr>
<td></td>
<td>SOF+SMV+RBV x12 weeks (noncirrhotic)</td>
</tr>
<tr>
<td></td>
<td>LDV+SOF x 24 weeks (cirrhotic)</td>
</tr>
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<thead>
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<th>Recommended</th>
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<td></td>
<td>LDV+SOF x 12 weeks (noncirrhotic)</td>
</tr>
<tr>
<td></td>
<td>LDV+SOF x 24 weeks (cirrhotic)</td>
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</table>

<table>
<thead>
<tr>
<th>Recommended</th>
<th>PI Failures, GT 1b</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
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<td></td>
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</tr>
<tr>
<td></td>
<td>LDV+SOF+RBV x 12 weeks (cirrhotic)</td>
</tr>
</tbody>
</table>
Drug-Drug Interactions

• Simeprevir
  – Mild inhibitor of CYP1A2 and intestinal CYP3A4, inhibits OATP1B1/3 and P-gp
  – Multiple drug interactions

• Sofosbuvir
  – Substrate of P-gp and BCRP; potent P-gp inducers may decrease sofosbuvir concentrations
  – Tipranavir, rifampin, St. John's wort induces P-gp at steady state
  – Do not use with amiodarone

• Ledipasvir
  – Inhibits P-gp and BCRP, substrate of P-gp and BCRP
  – Solubility decreases as gastric pH increases, alkaline environment will decrease LDV concentrations

Drug-Drug Interactions-ARVs

• Sofosbuvir+Ledipasvir
  – Decreased EFV concentrations (35%)
  – Increased TDF concentrations, should be avoided in CrCl < 60
  – Moderate (~30-60%) increase in TDF exposure with SOF/LDV when added to PI/r/TDF/FTC compared to PI/r/TDF/FTC alone
  – When coadministered with boosted PI, consider alternate HCV or ARV therapy to avoid increased TDF
    • If coadministered, monitor renal function

ARV Interaction Score Card

*Watch renal function, TFV levels increased*
*bDecrease DCV dose to 30mg QD, Increase DCV dose to 90mg QD,
*c3D + EFV led to premature study discontinuation due to toxicities*
*Slide generated by JEN KISER, University of Colorado*
Simeprevir AE

- Potential AE related to increased SMV exposure
  - Rash
  - Pruritis
  - Photosensitivity
  - Increased bilirubin
- Strategies for reducing SMV exposure
  - Avoid significant DDI
  - Take medication on an empty stomach

Adverse Reactions: PrOD Regimen

- Skin Reactions: 7-9% without RBV, 10-16% with ribavirin. Higher in HIV coinfected.
- Anemia/decreased hemoglobin
  - Mean change from BL in ~0.5 mg/dL without RBV vs ~2.4 mg/dL with RBV
- Effect of RBV Dose Reductions on SVR12
- Serum Bilirubin Elevations
  - Not associated with serum ALT elevations
- Serum ALT Elevations
  - Pooled analyses of clinical trials: Approximately 1% patients experienced serum ALT levels >5xULN after starting treatment
  - Not associated with bilirubin elevations and cirrhosis was not a risk factor for elevated ALT
  - ALT elevations in 25% among women on ethinyl estradiol or estradiol-containing medication.

Adverse Reactions: FDC SOF/LDV

<table>
<thead>
<tr>
<th>Adverse Reactions (All Grades) Reported in ≥ 5% of Subjects Receiving 8, 12, or 24 Weeks of Treatment with HARVONI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HARVONI 8 weeks</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>N=215</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
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</table>
Monitoring

• HCV VL is recommended after 4 wks on therapy and 12 weeks after EOT
  – If HCV VL detectable at week 4, repeat HCV VL at week 6. If week 6
    HCV VL > 1 log_{10} IU/ml then discontinue therapy
  – Antiviral therapy should not be stopped if week 4 HCV VL result unavailable

Monitoring

• CBC, Cr, CrCl, and hepatic function panel are recommended after 4
  weeks of treatment and as clinically indicated
• TDF-containing/ ritonavir boosted PI
  regimens: Cr, CrCl, electrolytes, phosphorus, urinary protein and glucose q2-4 weeks

Other Drug-Drug Interactions

• Acid-suppressing medications and SOF/LDV
  – Decreased absorption of ledipasvir
• Salmeterol and paritaprevir/ritonavir/ombitasvir + dasabuvir
  – Prolonged QT
• St. John’s Wort and Milk Thistle
  – St John’s wort will decrease ombitasvir/paritaprevir/ritonavir + dasabuvir levels and SOF/LDV levels
LDV and acid-reducing agents

- Decreased solubility with increasing pH
- Separate administration with antacids by 4 hours
- H2-receptor antagonists to be administered simultaneously with or 12 hours apart
  - Do not exceed comparable dose of famotidine 40mg twice daily
- Administer PPIs simultaneously
  - Do not exceed comparable dose of omeprazole 20mg daily

Ledipasvir and statins

<table>
<thead>
<tr>
<th>HMG-CoA Reductase Inhibitors:</th>
<th>Coadministration of LDV/SOF with rosuvastatin may significantly increase the concentration of rosuvastatin which is associated with increased risk of myopathy, including rhabdomyolysis. Coadministration of LDV/SOF with rosuvastatin is not recommended.</th>
</tr>
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<tbody>
<tr>
<td>Inhibitor</td>
<td>Rosuvastatin</td>
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Case 3

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</tr>
<tr>
<td>AST</td>
<td>65 IU/L</td>
</tr>
<tr>
<td>ALT</td>
<td>68 IU/L</td>
</tr>
</tbody>
</table>
| Alkaline
    phosphatase | 161 U/L         |
| Albumin         | 4.0             |
| Ultrasound      | Cirrhosis, no masses |
**ART switches in HIV/HCV coinfection**

**Objectives:**
- Determine need for ART switch prior to initiation of simeprevir-containing HCV regimen
- Determine feasibility of ART switch to allow for use of simeprevir

**Key Results:**
- Majority of our HIV-HCV patients (76%) will need a change to antiretroviral therapy in order to accommodate use of simeprevir for treatment of HCV
- Limitations were primarily driven by protease inhibitor (PI) regimens
  - 40% on a boosted PI could not be switched to a safe and effective ART regimen
  - Most often due to use of salvage regimen where PI has become indispensable

**Safe Regimens**
- SMV + RAL, RPV, T20, MVC, TDF, FTC, 3TC, ABC
- LDV + all regimens except EVG/cobi and TDF + EFV or PI/r
- PTV/r + RAL, TDF, FTC, 3TC, ATZ, T20

---

**Regimen Switching in the Setting of Viral Suppression Prior to Starting Hep C Treatment**

- Cardinal principle of regimen switching
  - Maintain viral suppression without jeopardizing future options
- Virologic failure with emergence of new resistance mutations
  - Increases need for more complex, difficult-to-follow, or expensive regimens

---

**Principles for Successful Regimen Switching**

- Review ART history
  - Virologic suppression, resistance test results, and past adverse events
  - If resistance data are unavailable, resistance may often be inferred by treatment history
  - Consult with an HIV specialist for patients with a history of resistance ≥1 drug classes
- During first 3 months after a regimen switch
  - More intensive monitoring of tolerability, viral suppression, adherence, and laboratory changes is recommended
Principles for Successful Regimen Switching

- Switching from a ritonavir-boosted PI regimen to a regimen with drugs having a lower barrier to resistance
  - Avoid if any doubt about the activity of any drugs in the new regimen
- Within-class switches
  - Success depend on no drug resistance to other drugs in the same drug class
- In the absence of likely drug resistance, switching from complex regimens, parenteral drug, or drugs known to be more toxic or a higher pill burden or dosing frequency to ritonavir-boosted darunavir or to agents in a new drug class (eg, an INSTI)
  - Generally results in similar or improved adherence, continued viral suppression and possibly improved quality of life

Monitoring After Switching Regimens

- Evaluate more closely for several months after a treatment switch
  - 1 to 2 weeks post switch: a clinic visit or phone call
  - 4 to 8 weeks post switch: viral load test (rebound viremia)
- Goal of the intensive monitoring
  - Conduct targeted laboratory testing within 3 months after the regimen switch (ie, pre-existing laboratory abnormalities or potential concerns with the new regimen)
  - Absent any specific complaints, laboratory abnormalities, or evidence of viral rebound at this 3-month visit, clinical and laboratory monitoring of the patient may resume on a regularly scheduled basis

Summary

- Efficacy in HIV/HCV co-infection patients treated with DAAs appears to mimic efficacy seen in mono-infected patients
- Drug interactions and management have become easier in HCV treatment but still exist
- Remains “unique” population due to frequent complex drug regimens and co-morbid conditions