Management of Hepatitis C Infection in HIV-Coinfected Patients

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Learning Objectives
After attending this presentation, participants will be able to:

• Describe the recent advances in the current management strategies for hepatitis C infection in HIV-positive patients

• Identify the major drug-drug interactions when using HCV DAAs in HIV/HCV-coinfected patients
Unlabeled/Unapproved Use

The following will be discussed: oral direct-acting HCV drugs (that are not yet FDA approved)

Hepatitis C and HIV

Deaths Associated With Hepatitis C Are Comparable to Deaths Caused by HIV in the US

Ly KN et al., Ann of Int Med 2012:156
**Slide 11 of 42**

**HCV Coinfection is Very Common in HIV-Infected Subjects**

![Graph showing the prevalence of HCV coinfection in HIV-infected subjects.](image)


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**Slide 12 of 42**

**In HIV Co-infection, Hepatitis C is a Major Cause of Mortality and Liver Failure**

![Bar graph and pie chart showing causes of mortality and liver failure in HIV-infected patients.](image)


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**Slide 13 of 42**

**Cure Rates for HCV**

![Graph showing cure rates for HCV with and without protease inhibitors.](image)

DAAs for HIV/HCV Coinfection

Sofosbuvir Target

PHOTON-1: Virologic Response

Sulkowski et al. JAMA 2013

Washington, DC: May 13, 2015
### ProD Targets

- **Ombitasvir**
- **Dasabuvir**
- **Paritaprevir**

**Note:** NCI lifecycle not well defined

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### Study Design: TURQUOISE

- **Week 0:**
  - Ombitasvir-Paritaprevir-ritonavir (25mg/150mg/100mg single tablet) with Dasabuvir 250mg twice daily
  - Weight-based Ribavirin 1g/day for <75kg and 1.2g/day for >75kg

- **Week 12:** 3D + RBV
- **Week 24:** 3D + RBV

(N=31) + RBV (N=32)

Sulkowski et al. *JAMA* 2015

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### TURQUOISE: Virologic Response

- **SVR 4:**
  - 29/31 (95.5%)
  - 30/31 (99.8%)

- **SVR 12:**
  - 29/31 (95.5%)
  - 29/32 (90.6%)

Sulkowski et al. *JAMA* 2015
**Sofosbuvir/Ledipasvir Targets**

- NS5A inhibitors
- NS5B polymerase inhibitors
- Cyclophilin inhibitors
- HCV RNA degradation

**Study Design: ERADICATE**

- **Week 0 - Week 12 - Week 36**
  - **GT 1 (N=13)**
    - ARV Untreated
      - CD4 count stable + HIV RNA <500 copies
      - CD4 count > 500 cells/mm³
    - ARV Treated
      - CD4 count > 100 cells/mm³
      - HIV RNA < 40 copies
      - Current ARVs ≥ 8 weeks

- **GT 1 (N=37)**
  - ARV Untreated
  - ARV Treated

- **ERADICATE: Treatment Response**

- **ARV Untreated**
- **ARV Treated**

- **% of patients with HCV RNA < LLOQ**
  - Week 4
  - EOT
  - SVR4
  - SVR8
  - SVR12

- **Overall 98%**

**Osinusi et al. JAMA 2015**
**ION-4 Study Design**

- Wk 0
- LDV/SOF
- N=335
- Wk 12
- Wk 24
- SVR 12

Phase III Multicenter Open-label Study
Genotype 1 or 4 patients in USA, Canada or New Zealand
Inclusion Criteria
- Treatment naïve or experienced
- 20% Compensated cirrhosis
- Platelets >50K, hemoglobin >10g/dl, Cr Cl >60min/ml
- HIV positive, HIV RNA <50 copies/ml, CD4 counts > 100cells/cmm
- ART regimens included tenofovir, emtricitabine, plus efavirenz, raltegravir and riplivirine

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**ION-4 Virologic Response**

Overall 96%

- 10 Relapses
- 2 on treatment failures (non compliance)
- 1 Lost to follow up
- 1 death (IVDU endocarditis/sepsis)

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**Sofosbuvir/Daclatasvir Targets**

- Sofosbuvir
- Daclatasvir
- NS5A inhibitors
- NS5B polymerase inhibitors
- Cytosine kinase inhibitors
- Viral RNA abundance
- HCV replication cycle
- Target TEDA
- TEGD
- NPSA inhibitors
- *Role in HCV lifecycle not well defined*

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ALLY-2 Study Design

- Primary endpoint: SVR12 in treatment-naive patients with GT 1 treated for 12 weeks
- Standard HCV dose 4-60 mg
- Dose adjusted for concomitant HIV therapy: 30 mg with ritonavir-boosted PI, 60 mg with NS5B ns3 ns5a

* SVR12/12 wks: (prior to or after antiretroviral Week 12, assessed using the ROC method). [CROI 2015: Tuesday, May 13, 2015]

ALLY 2: Virologic Response

- 96% SVR at 12 weeks
- 98% SVR at 24 weeks

Grazoprevir/Elbasvir: Targets

- Grazoprevir
- Elbasvir
- NS3/4a protease inhibitors
- NS5A inhibitors
- *Role in HCV lifecycle not well defined

Washington, DC: May 13, 2015
**C-WORTHY Study Design**

Sulkowski et al. AASLD 2014

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**Virologic Response**

Sulkowski et al. AASLD 2014

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**DAAs for Treatment of HCV in HIV-infected patients**

Sulkowski et al. AASLD 2014

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- LDV/SOF 12 weeks
- 3D + RBV* 12 weeks
- SOF + SIM +/- RBV 12 weeks

* AASLD-IDSA-IAS-USA HCV Guidance

Washington, DC: May 13, 2015
**Drug-Drug Interactions**

**Enzyme Inducers—common**
- Decrease LDV and possibly SOF exposure (risk of HCV treatment failure)
- Antiepileptics
  - Phenytin (and fosphenytoin)
  - Phenobarbital (and primidone)
  - Carbamazepine
  - Oxcarbazepine
- St. John’s Wort
- Rifamycins: rifampin, rifabutin, rifapentine

**Ledipasvir/Sofosbuvir: Acid Suppressants**
- PPIs
  - Decrease LDV absorption
  - Max dose omeprazole 20 mg daily
- H2RAs
  - Decrease LDV absorption
  - Max dose famotidine 40 mg BID
- Antacid
  - Decrease LDV absorption
  - Separate from LDV/SOF by 4 hours

Esomeprazole not recommended
### Ledipasvir/Sofosbuvir: Cardiovascular Drugs

**Digoxin**
- LDV increases digoxin level
- Monitor digoxin level

**Rosuvastatin**
- LDV increases rosuvastatin
- Consider pravastatin
- Lowest dose of other statins

**Amiodarone**
- Bradycardia, one death

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### Viekira Pak Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction Potential</th>
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<tbody>
<tr>
<td>Ritonavir*</td>
<td>CYP3A4 inhibition to boost paritaprevir</td>
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<tr>
<td></td>
<td>Many more CYP and transporter interactions</td>
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<tr>
<td>Dasabuvir</td>
<td>Metabolized by CYP2C8</td>
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<tr>
<td></td>
<td>• Inhibitors of CYP2C8</td>
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<tr>
<td></td>
<td>• Gemfibrozil – increased single dose dasabuvir by &gt;1125%</td>
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<tr>
<td></td>
<td>• Trimethoprim</td>
</tr>
<tr>
<td></td>
<td>• Inducers of CYP2C8</td>
</tr>
<tr>
<td></td>
<td>• Rifampin</td>
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</tbody>
</table>

* Only use in co-infected HIV/HCV if patient is on effective antiretroviral regimen

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### Contraindicated Combos

<table>
<thead>
<tr>
<th>Drug</th>
<th>Contraindicated</th>
<th>Alternatively, consider...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfuzosin (alpha-blocker)</td>
<td>Terazosin</td>
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<tr>
<td>Ethinyl estradiol (OC, patch)</td>
<td>Progesterone only contraception</td>
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<tr>
<td>Triazolam, oral midazolam</td>
<td>Lorazepam</td>
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<tr>
<td>Temazepam</td>
<td>zaleplon</td>
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</table>

- Contraindicated
  - Pimozide (antipsychotic)
  - Ergot derivatives (e.g., dihydroergotamine)
  - Phosphodiesterase 5 inhibitors for pulmonary arterial hypertension

- More commonly used...
  - Phosphodiesterase 5 inhibitors for erectile dysfunction
  - Generally, use lowest dose q 48 hours (Levitra Q 72 h)
  - Eg, sildenafil 25 mg every 48 hours prn
  - Titrate to effect
**Other Cautions**

- SSRIs and bupropion
  - HIV PI/ritonavir tends to decrease these
- Trazodone and quetiapine may be ↑
- Immunosuppressants (tacrolimus, sirolimus, cyclosporine, etc)
  - Huge interactions with ritonavir
  - Sometimes dosed q week instead of BID
  - Drug levels
- Salmeterol and fluticasone (all formulations)
  - Preferred: beclomethasone
  - Avoid steroid injections

**Conclusions**

- New DAA agents offer high rates of SVR in HIV/HCV-coinfected subjects
- Drug-drug interactions remain the major road block in initiating HCV therapy for HIV/HCV-coinfected patients