Management of HIV/HCV Coinfection

Kristen M. Marks, MD
Assistant Professor
Weill Cornell Medical College
New York, NY
Dr. Marks has received grants and research support from Gilead Sciences and Merck.
Learning Objectives

- Consider HCV management issues unique to HIV coinfection
- Describe study data of direct-acting antivirals (DAAs) used in the treatment of HIV/HCV coinfection
- Describe post-treatment monitoring in HIV/HCV coinfected persons
CASE

62 y.o. African American M with HIV & HCV Geno 1b and cirrhosis, HCV RNA 1.8 million IU/mL

• HCV Hx:
  • Treatment naïve – IFN unwilling in past
  • Cirrhotic based on Bx 6 yrs ago
    • No decompensation events
    • EGD no varices
    • MRI no HCC
    • Fibroscan 20 kPa

• Other med hx includes:
  • HTN, CAD (s/p stents)
  • CRCL 55

HOW DO YOU CHOOSE A REGIMEN?
Minimum to Know Pre-Treatment

- HCV genotype/subtype
- Stage of fibrosis
  - Cirrhosis - yes/no
    - If yes, compensated? (e.g., ascites, encephalopathy, etc)
  - Method?
    - Liver biopsy
    - Transient elastography
    - Laboratory biomarkers
    - Imaging
- Prior HCV treatment?
  - Response?
  - DAA used? Medications
- HIV status
- Medications
  - To check for drug interactions
- Interferon “eligibility” and/or willingness
  - Comorbidities
  - Patient preference
- Child-bearing potential of patient/partner
  - Ribavirin is a teratogen

HIV/Hepatitis C helpline
1-866-637-2342
Factors that may influence results:

- Failures
  - Obesity
  - Ascites
  - Operator experience
- Misinterpretation (stiff but not fibrosed liver)
  - Post-hepatic congestion (e.g. Rt heart failure)
  - Meal
  - Inflammation
  - Amyloid
  - Cholestasis
  - Lymphoma

Fig. 1. Probability of remaining free of developing a hepatic decompensation and/or hepatocellular carcinoma according to (A) baseline liver stiffness, (B) baseline CTP stage, (C) different categories of baseline liver stiffness and CTP stage, and (D) different categories of baseline liver stiffness and MELD score. LS: liver stiffness; CTP: Child-Turcotte-Pugh; MELD: model for end-stage liver disease.

RECOMMENDATIONS ON TREATMENT OF HEPATITIS C 2015

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide. The long-term impact of HCV infection is highly variable, ranging from minimal histological changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma (HCC). The number of chronically infected persons worldwide is estimated to be about 160 million, but most are unaware of their infection.

The implementation of extended criteria for screening for HCV is a subject of major debate among different stakeholders. Clinical care for patients with HCV-related liver disease has advanced considerably during the last two decades, thanks to an enhanced understanding of the pathophysiology of the disease, and because of developments in diagnostic procedures and improvements in therapy and prevention.
Recommended Regimens for HIV/HCV-coinfected Individuals
Listed in order of level of evidence, then within group alphabetically.

- HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications (see Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed).
  Rating: Class I, Level B

- Daily daclatasvir (refer above for dose) plus sofosbuvir (400 mg), with or without RBV (refer to Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed sections for duration) is a Recommended regimen when antiretroviral regimen changes cannot be made to accommodate alternative HCV direct-acting antivirals.
  Rating: Class I, Level B
Newer strategy for HCV therapy: Direct acting antivirals target life cycle

---PREVIR
Protease inhibitors
e.g. telaprevir, boceprevir, faldaprevir, simeprevir, danoprevir, asunaprevir, paritaprevir, grazoprevir

---BUVIR
Polymerase inhibitors
– Nucleos(t)ide analogs: e.g. tegobuvir, sofosbuvir,
– Non-nucs: e.g. deleobuvir, dasabuvir

---ASVIR
NS5A inhibitors e.g. daclatasvir, ledipasvir, ombitasvir, elbasvir
Currently used combinations of DAA classes

NUC + PI + nonNuc
NUC + NS5A + nonNuc
PI + NS5A + nonNuc
PI + NS5A + nonNuc

NUC-SPARING HIV
Toxicity
Resistance
Renal insufficiency
Drug-drug interactions
Affordability

NUC-SPARING HCV
Affordability
Provider preference
Renal insufficiency
Drug-drug interactions
Toxicity
Resistance
## Approved Drug Regimens

<table>
<thead>
<tr>
<th>Interferon</th>
<th>PegIFN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribavirin</td>
<td>ribavirin</td>
</tr>
<tr>
<td>Nucs</td>
<td>sofosbuvir</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>simeprevir</td>
</tr>
<tr>
<td>NS5A</td>
<td>ledipasvir</td>
</tr>
<tr>
<td>Non-Nucs</td>
<td>dasabuvir</td>
</tr>
</tbody>
</table>

| G1 | X | X | X | X | X | X | X |
| G2 | X | X | X | X |   |   |   |
| G3 | X | X |   | X |   |   |   |
| G4 | X | X | X | X | X | X | X |
G1B Initial Treatment Recommended Regimens (including for coinfected)

NO CIRRHOSIS:
- Elbasvir/grazoprevir x 12 w
- Ledipasvir/sofosbuvir x 12w
- Paritaprevir /ritonavir/ombitasvir + dasabuvir x 12w
- Simperevir x sofosbuvir 12w
- Daclatasvir + sofosbuvir x 12w

CIRRHOSIS:
- Elbasvir/grazoprevir x 12 w
- Ledipasvir/sofosbuvir x 12w
- Paritaprevir /ritonavir/ombitasvir + dasabuvir x 12w*

*Based on TURQUOISE-3 study results of PrOD w/o RBV - 100% SVR12 in G1b + cirrhosis
G1A Initial Treatment Recommended Regimens (including for coinfected)

NO CIRRHOSIS:
- Elbasvir/grazoprevir x 12 w if no high level NS5A resistance
- Ledipasvir/sofosbuvir x 12w
- Paritaprevir/ritonavir/ombitasvir + dasabuvir x 12w
- Simperevir x sofosbuvir 12w
- Daclatasvir + sofosbuvir x 12w

CIRRHOSIS:
- Elbasvir/grazoprevir x 12 w if no high level NS5A resistance
- Ledipasvir/sofosbuvir x 12w

*Based on TURQUOISE-3 study results of PrOD w/o RBV - 100% SVR12 in G1b + cirrhosis
Grazoprevir/elbasvir x 12w in HIV/HCV Rx Naive

![Graph showing SVR12 results for different genotypes.](image)

**Figure 2. SVR12 (full analysis set).**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Patients, %</th>
<th>N (Expected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>95.0</td>
<td>207/218</td>
</tr>
<tr>
<td>GT1a</td>
<td>94.4</td>
<td>136/144</td>
</tr>
<tr>
<td>GT1b</td>
<td>95.5</td>
<td>42/44</td>
</tr>
<tr>
<td>GT4</td>
<td>96.4</td>
<td>27/28</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>All Patients</th>
<th>GT1a</th>
<th>GT1b</th>
<th>GT4</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTFU or discontinued unrelated to VF</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Breakthrough</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Relapse</td>
<td>6</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Reinfection</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

GT = genotype; LTFU = long-term follow-up; VF = virologic failure.

One patient with GT6 infection and 1 patient with GT1 not-otherwise subtyped were also included; both patients achieved SVR12.

ARVs: NUCS + RAL, DOL OR RIL

*EASL, 2015*
Ledipasvir/sofosbuvir x 12w in HIV/HCV Rx Naive

ARVs: TDF/FTC + EFV, RAL, OR RIL

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, NEJM 2015
Retreatment of HCV/HIV-Coinfected Patients Who Failed LDV/SOF x 12 w with LDV/SOF + RBV x 24 w

Naggie et al, CROI 2016

<table>
<thead>
<tr>
<th>GT</th>
<th>NS5A RAVs Before Primary Study (%)</th>
<th>NS5A RAVs at Virologic Relapse After Primary Study (%)</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>None</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>1a</td>
<td>None</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>1a</td>
<td>L31M (&gt;99), H58D (92)</td>
<td>L31M (&gt;99), H58D (&gt;99)</td>
<td>Yes</td>
</tr>
<tr>
<td>1a</td>
<td>Y93F (1), Y93N (10)</td>
<td>Y93N (&gt;99)</td>
<td>Yes</td>
</tr>
<tr>
<td>1a</td>
<td>L31M (&gt;99), Y93N (&gt;25)</td>
<td>L31M (&gt;99), Y93N (&gt;99)</td>
<td>Yes</td>
</tr>
<tr>
<td>1a*</td>
<td>None</td>
<td>Y93N (&gt;99)</td>
<td>Yes</td>
</tr>
<tr>
<td>1b</td>
<td>Y93H (&gt;99)</td>
<td>L31I (11), Y93H (&gt;99)</td>
<td>Yes</td>
</tr>
<tr>
<td>1b</td>
<td>None</td>
<td>L31V (&gt;99)</td>
<td>Yes</td>
</tr>
<tr>
<td>1a</td>
<td>None</td>
<td>L31M (&gt;99)</td>
<td>No</td>
</tr>
</tbody>
</table>

*Patient also had NS5B L159F (10%) at virologic relapse after primary study.

8/9 (89%) SVR
Including 6/7 with NS5A RAVs

Naggie et al, CROI 2016
PROD + RBV x 12w or 24w in HIV/HCV Rx Naive

ARVs Part 1: Nucs + ATZ/r or Dol
ARVs Part 2: Nucs + DRV QD or BID

Wyles AASLD 2015
Daclatasvir + Sofosbuvir x 8 or 12 wks

Figure 3. SVR12 Results

Percentage achieving SVR12

- EOT, end-of-treatment; FU, follow-up
- * Primary endpoint
- Non-adherent patient; received ≤1 week of treatment

Table 3. Baseline HIV Disease Characteristics and ARV Regimens

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment-naive 12 weeks treatment N=101</th>
<th>Treatment-naive 8 weeks treatment N=80</th>
<th>Treatment-experienced 12 weeks treatment N=72</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA &lt;50 copies/mL, n/total (%)*</td>
<td>94/100 (94.0)</td>
<td>45/48 (93.8)</td>
<td>4/40 (10.0)</td>
</tr>
<tr>
<td>CD4 cells/mm³, median (range)</td>
<td>520 (122–147)</td>
<td>575 (157–1430)</td>
<td>636 (262–1470)</td>
</tr>
<tr>
<td>HIV treatment, n (%)†</td>
<td>100 (99.0)</td>
<td>40 (50.0)</td>
<td>51 (69.4)</td>
</tr>
<tr>
<td>Darunavir/</td>
<td>19/100 (19.0)</td>
<td>21/40 (52.5)</td>
<td>13/51 (25.5)</td>
</tr>
<tr>
<td>Atazanavir/</td>
<td>19/100 (19.0)</td>
<td>5/40 (12.5)</td>
<td>12/51 (23.5)</td>
</tr>
<tr>
<td>Lopinavir/</td>
<td>9/100 (9.0)</td>
<td>3/40 (7.5)</td>
<td>0</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>18/100 (18.0)</td>
<td>8/40 (20.0)</td>
<td>8/51 (15.7)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>5/100 (5.0)</td>
<td>1/40 (2.5)</td>
<td>3/51 (5.9)</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>5/100 (5.0)</td>
<td>1/40 (2.5)</td>
<td>3/51 (5.9)</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>22/100 (22.0)</td>
<td>8/40 (20.0)</td>
<td>10/51 (19.6)</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>3/100 (3.0)</td>
<td>1/40 (2.5)</td>
<td>4/51 (7.8)</td>
</tr>
<tr>
<td>Nucleosides only</td>
<td>0</td>
<td>0</td>
<td>2/51 (3.9)</td>
</tr>
</tbody>
</table>

*Percent on antiretroviral therapy with available baseline HIV RNA data.
†Non-adherent in regimens not listed.

Four patients (2.0%) were not receiving cART

Study Medications
- Standard DCV dose of 60 mg OD, dose adjusted for concomitant cART regimen
  - 30 mg with ritonavir-boosted PIs, 90 mg with NNRTIs except rilpivirine (RPV)
- Standard SOF dose of 400 mg OD

Wyles, EASL, 2015
Drug-Drug Interactions with DAAS

- Acid-reducing drugs
- Anti-epileptics
- Antiretrovirals
- Amiodarone
- Lipid-lowering drugs

http://www.hep-druginteractions.org/
<table>
<thead>
<tr>
<th>Drug Regimen</th>
<th>Simeprevir</th>
<th>Sofosbuvir</th>
<th>Ledipasvir</th>
<th>Daclatasvir</th>
<th>Paritaprevir, ritonavir, ombitasvir plus dasabuvir (PrOD)</th>
<th>Paritaprevir, ritonavir, ombitasvir, elvitegravir, cobicistat, and preC/preB inhibitors plus dasabuvir (PrOD)</th>
<th>Grazoprevir/Elbasvir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir-boosted atazanavir</td>
<td>No data</td>
<td>No data</td>
<td>Ledipasvir</td>
<td>Daclatasvir</td>
<td>Paritaprevir, ritonavir, ombitasvir plus dasabuvir (PrOD)</td>
<td>Grazoprevir/Elbasvir</td>
<td>Grazoprevir/Elbasvir</td>
</tr>
<tr>
<td>Ritonavir-boosted darunavir</td>
<td>Simeprevir</td>
<td>Sofosbuvir</td>
<td>Ledipasvir</td>
<td>Daclatasvir</td>
<td>Paritaprevir, ritonavir, ombitasvir plus dasabuvir (PrOD)</td>
<td>Grazoprevir/Elbasvir</td>
<td>Grazoprevir/Elbasvir</td>
</tr>
<tr>
<td>Ritonavir-boosted lopinavir</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>Daclatasvir</td>
<td>Paritaprevir, lopinavir</td>
<td>Grazoprevir/Elbasvir</td>
<td>Grazoprevir/Elbasvir</td>
</tr>
<tr>
<td>Ritonavir-boosted tipranavir</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>Grazoprevir/Elbasvir</td>
<td>Grazoprevir/Elbasvir</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Simeprevir</td>
<td>Sofosbuvir</td>
<td>Ledipasvir</td>
<td>Daclatasvir</td>
<td>No pharmacokinetic data</td>
<td>No data</td>
<td>Grazoprevir/Elbasvir</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Simeprevir</td>
<td>Sofosbuvir</td>
<td>Ledipasvir</td>
<td>No data</td>
<td>Patitaprevir, rilpivirin</td>
<td>No data</td>
<td>Grazoprevir/Elbasvir</td>
</tr>
<tr>
<td>Etrovirine</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>Daclatasvir</td>
<td>No data</td>
<td>No data</td>
<td>Grazoprevir/Elbasvir</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Simeprevir</td>
<td>Sofosbuvir</td>
<td>Ledipasvir</td>
<td>No data</td>
<td>ProD, raltegravir</td>
<td>Grazoprevir/Elbasvir</td>
<td>Grazoprevir/Elbasvir</td>
</tr>
<tr>
<td>Cobicistat-boosted elvitegravir</td>
<td>No data</td>
<td>Cobicistat</td>
<td>Cobicistat</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>Grazoprevir/Elbasvir</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>No data</td>
<td>No data</td>
<td>Ledipasvir</td>
<td>Daclatasvir</td>
<td>Patitaprevir, dolutegravir</td>
<td>No data</td>
<td>Grazoprevir/Elbasvir</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>Grazoprevir/Elbasvir</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>Simeprevir</td>
<td>Sofosbuvir</td>
<td>Ledipasvir</td>
<td>Daclatasvir</td>
<td>ProD, tenofovir</td>
<td>No data</td>
<td>Grazoprevir/Elbasvir</td>
</tr>
</tbody>
</table>
Take-Home Points: Similarities between HIV and HCV Drug Interactions

- Drug interactions are common and can be clinically significant.
- Nucleoside analogs have a lower potential for drug interactions.
- Protease inhibitors have a higher potential for drug interactions.
- HIV drug interactions are for life; HCV drug interactions are for 8-12 weeks!
# Pan-genotypic Sofosbuvir/velpatasvir

## Study Population N Treatment Duration SVR12 Rates

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Treatment</th>
<th>Duration</th>
<th>SVR12 Rates</th>
</tr>
</thead>
</table>
| ASTRAL-1 | Genotypes 1,2,4,5,6                 | 624| SOF/VEL      | 12 weeks | Overall: 99% (618/624)  
|         | 116 patients received placebo (SVR12=0%) |    |              |          | GT1: 98% (323/328)  
|         | 19%(121/624) with cirrhosis       |    |              |          | GT2: 100% (104/104)  
|         |                                     |    |              |          | GT4: 100% (116/116)  
|         |                                     |    |              |          | GT5: 97% (34/35)     
|         |                                     |    |              |          | GT6: 100% (41/41)     |
| ASTRAL-2 | Genotype 2                          | 134| SOF/VEL      | 12 weeks | 99% (133/134)              |
|         | 14% (38/266) with cirrhosis        |    |              |          | 94% (124/132)               |
| ASTRAL-3 | Genotype 3                          | 277| SOF/VEL      | 12 weeks | 95% (264/277)               |
|         | 30% (163/552) with cirrhosis       |    |              |          | 80% (221/275)               |
| ASTRAL-4 | Genotypes 1-6                      | 90 | SOF/VEL      | 12 weeks | 83% (75/90)                  |
|         | All with Child-Pugh class B (decompensated) cirrhosis |    |              |          | 94% (82/87)                  |
|         |                                     | 87 | SOF/VEL+RBV  | 12 weeks | 86% (77/90)                  |
|         |                                     | 90 | SOF/VEL      | 24 weeks |                             |

Press release Oct 2015
Sofosbuvir/velpatasvir x 12 wks in HIV/HCV G1-6, Naïve + Rx-exp

N=106
29% Rx-exp
18% cirrhosis
12% NS5a RAVs

Of 2 relapses:
1 rx-exp, 0 cirrhosis, 0 baseline RAVS

Renal fxn looked unchanged in pts on boosted TDF

Wyles, EASL, 2016
Post HCV Treatment Monitoring – HIV/HCV

- **Wk 12 labs – confirm SVR, liver tests normalized?**
  - Cont to manage if abnl liver tests

- **See after Wk 12 labs**
  - Inform them of their cure (& provide that info to PMD)
    - Educate will always be Ab+
  - Review that can be reinfected
  - Harm reduction
  - Rescreen with HCV RNA if risk
  - Say goodbye to F0-F2

- **Schedule f/u HCC/cirrhosis monitoring for F3-F4 (e.g. sono r/o HCC, EGD r/o varices if cirrhosis)**
  - HCCs are expected
The MOSAIC (MSM Observational Study of Acute Infection with hepatitis C) trial in Amsterdam showed a high incidence of HCV reinfection in HIV-infected MSM who were previously diagnosed with a sexually transmitted acute HCV infection and who were HCV RNA-seronegative following HCV treatment of the acute primary infection.

- Reinfection was defined as a new detectable HCV RNA after successful treatment, accompanied by a switch in HCV genotype or clade.
- The incidence of HCV reinfection in this group was 15.2 per 100 person-years. The cumulative incidence was 33% within 2 years.
Acute HCV treatment in HIV+ MSM

- LDV x SOF x 6wks (n-26)
  - 69% 1a, 31% G4
  - Any ARVs

- SVR4 85%, SVR12 77%
  - 4 failures, 2 LTFU by wk 12

- Relapses with High baseline RNA

- 1 reinfection by Wk 12

Results: Baseline HCV RNA and Treatment Outcome (SVR)

Rockstroh, CROI 2016
Summary

- Remarkable advances in terms of HCV treatment tolerability & efficacy in coinfected
  - Response rates mirror monoinfection
  - Continued need for therapies without significant drug interactions & those that can be used in varied populations (ESRD, G3, etc)

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

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

Thank you