Treatment of HCV in Patients with HIV Coinfection

Eliot Godofsky, MD, Director
University Hepatitis Center
Sarasota, Florida

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Lecture Outline

- Evolution of HCV Treatment in Patients with HIV Coinfection
- Timing of Treatment
  - Patient Evaluation and Selection
- Important Drug-Drug Interactions
  - Therapy Considerations for Patients on HIV ART
- Summary of Current AASLD/IDSA/IAS-USA Treatment Recommendations
Evolution of HCV Treatment in HIV Coinfection
HCV/HIV Treatment Outcomes: PegIFN plus RBV

Genotype 1
SVR 14–38%

Genotype 2/3
SVR 44–73%

Fried et al, NEJM 2002, 347: 975-982,
Torriani et al, NEJM 2004; 351: 438-50,
Chung R, et al, NEJM 2004: 351; 451-9,
Laguno et al, AIDS 2004; 18: F27-F36,
Nunez et al, JAIDS 2007: 45: 439-44
First Generation HCV Protease Inhibitors plus PegIFN/RBV in GT 1 Coinfection

SVRs comparable to GT1 HCV-monoinfected patients: Boceprevir 68% Telaprevir 75%

# Recently Released DAAs

<table>
<thead>
<tr>
<th><strong>Simeprevir</strong></th>
<th><strong>Sofosbuvir</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Multi-genotypic NS3/4A PI</td>
<td>- Pan-genotypic NS5B</td>
</tr>
<tr>
<td>- QD dosing</td>
<td>- QD dosing</td>
</tr>
<tr>
<td>- Second Wave PI</td>
<td>- Nucleotide analogue</td>
</tr>
<tr>
<td>- Low barrier to resistance</td>
<td>- Exceptional barrier to resistance</td>
</tr>
<tr>
<td>+ DDI with ARVs</td>
<td>- No significant DDI</td>
</tr>
<tr>
<td>- Rash, photosensitivity</td>
<td>- No AE</td>
</tr>
<tr>
<td>- HIV not a special pop</td>
<td>- Approved for HIV/HCV as special population</td>
</tr>
</tbody>
</table>
Sofosbuvir + PR for 12 weeks in HCV/HIV Coinfection: Treatment Outcomes

- No change in ART regimens
- SVR12 rates by ART regimen
  - PI: 93%
  - NNRTI: 91%
  - Raltegravir: 100%
- No on-treatment breakthroughs
- Relapse (n=1)
- HIV breakthroughs (n=2)
- Discontinuations due to adverse events: 9%
- Most common adverse events
  - Anemia (52%), fatigue (35%), neutropenia (17%), thrombocytopenia (17%), myalgia (13%)
  - Hyperbilirubinemia (17%)

PHOTON-1 Study: Treatment Outcomes

- SVR12 rates in genotype 1
  - Similar regardless of baseline HCV RNA, IL28b genotype, presence of cirrhosis, age, gender, race
  - Lower in genotype 1b versus 1a
- No resistance (deep sequencing) detected in virologic failures
- HIV breakthroughs (n=2)
- Discontinuations due to AEs: 3%
- Most common adverse events
  - Fatigue, insomnia, headache, nausea
  - Grade ≥3 hyperbilirubinemia in patients receiving atazanavir versus no atazanavir (13% versus 1%)
- SVR in treatment experienced pts receiving 24 weeks of therapy: 92% GT2 and 88% GT3

Study C212: Simeprevir + PR in HCV/HIV Infection: GT 1

- Phase III open label. Naïve/Relapse (RGT arm) and PR null/partials (48 week tx)
- SVR12 rates in HCV/HIV coinfected were similar to HCV monoinfected trials
  - SVR12 rates were high, regardless of baseline METAVIR fibrosis score
  - SVR12 67% GT1a + Q80k vs. 89% GT1b
- Safety profile similar to monoinfected patients
  - Pruritus and photosensitivity in 20% and 2%, respectively
- Grade 3/4 hemoglobin: 1.9%

COSMOS Study: Interim Results With Simeprevir + Sofosbuvir ± RBV in HCV Monoinfection

SVR12: No Cirrhosis (F0-F2)
(Prior PR Null Responders)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No RBV</th>
<th>With RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir + sofosbuvir</td>
<td>92.9% (n=24/15)</td>
<td>96.3% (n=15)</td>
</tr>
<tr>
<td>12 Weeks</td>
<td>93.3% (n=27/14)</td>
<td>79.2% (n=14)</td>
</tr>
<tr>
<td>24 Weeks</td>
<td>96.3% (n=15)</td>
<td>93.3% (n=14)</td>
</tr>
</tbody>
</table>

Cirrhosis (F3-F4)*
(Naives and Prior PR Null Responders)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No RBV</th>
<th>With RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir + sofosbuvir</td>
<td>100% (n=7/12)</td>
<td>100% (n=15)</td>
</tr>
<tr>
<td>Naives</td>
<td>100% (n=7/12)</td>
<td>100% (n=15)</td>
</tr>
<tr>
<td>Overall</td>
<td>96.3% (n=14)</td>
<td>100% (n=15)</td>
</tr>
</tbody>
</table>

*Interim analysis: SVR4 rates in patients receiving the 12-week regimens.

Timing of Treatment
HIV/HCV Coinfection: Who to Treat

- All HCV/HIV coinfected patients are candidates for HCV therapy
- Consider comorbid conditions that limit life expectancy or increase the risks associated with HCV therapy
- HCV cure may decrease risk of ART-associated liver injury
- HIV disease should be stable with or without ART
- IFN-based regimens
  - Defer HCV treatment if CD4 <200 cells/mm^3
  - Interferon can exacerbate pre-existing mental illness
    - Evaluate patients with underlying psychiatric disease before initiating HCV treatment
- Decompensated cirrhosis
  - Refer to medical practitioner with expertise
- Substance abuse
  - Active substance abuse is not a contraindication
  - Associated with high rates of treatment nonadherence and may compromise treatment outcomes

Specific Risks of Deferring Therapy in HIV/HCV-Coinfected Patients

- Accelerated rate of HCV-related hepatic fibrosis progression in coinfected patients with increasing immune deficiency
  - Progression to cirrhosis risk 3-fold higher in coinfecte...
Bonn Cohort: Benefits of ART on Mortality in HCV/HIV-Coinfection

- HCV/HIV-coinfected patients (n=285)
- Liver-related mortality rates (per 100 person-years)
- With ART: 0.45
  - No ART: 1.70
  - Predictors for increased liver-related mortality
- No ART
  - Low CD4 cell count
  - Increasing age
- ART therapy can slow fibrosis progression and decrease mortality in coinfection

ALIVE Study: HIV, Age, and Severity of HCV-Related Liver Diseases

- Prospective cohort of HCV-infected IDUs (2006-2011) (n=1176)
  - HIV co-infected (n=394)
  - Baseline and semi-annual elastography
- Fibrosis was significantly greater in HCV/HIV co-infected versus HCV monoinfection ($P<0.001$)
  - No cirrhosis (12.9% versus 9.5%)
  - With cirrhosis (19.5% versus 11.0%)
  - Independently associated with increasing age and HIV infection
- HCV/HIV patients have liver fibrosis similar to HCV mono-infected patients who are nearly 10 years older

HCV Coinfection vs Monoinfection: Cumulative Incidence of Decompensation

- 10-year hepatic decompensation risk 83% higher in coinfected patients
  - Adjusted HR 1.83 (95% CI: 1.54-2.18)

HCV Treatment and Incidence of ESLD, HCC, and Death

- Prospective US cohort (1993-2011) (n=638)
  - Liver biopsy at baseline
  - 35% underwent HCV treatment with PR
- Baseline ≥F2 versus <F2 fibrosis
  - Higher treatment rates: 54% versus 28% (P<0.001)
  - Similar SVR rates: 17% versus 16%
- No clinical events (ESLD, HCC, and death) among patients achieving SVR

### Assessing HIV+ Patients for Immediate or Deferred HCV Therapy

#### Antiretroviral therapy for HIV treatment-naive HIV/HCV-coinfected patients
- CD4+ cell count < 500 cells/mm³: initiate antiretroviral therapy for HCV treatment optimization
- CD4+ cell count > 500 cells/mm³: may defer antiretroviral therapy until HCV therapy completed

#### HCV Therapy in HIV/HCV-Coinfected, HCV Treatment-Naive Patients

<table>
<thead>
<tr>
<th>Liver Fibrosis</th>
<th>Consider HCV Therapy</th>
<th>Eligible to Defer HCV Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No/minimal fibrosis (F0-F2)</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Advanced fibrosis (F3-F4); cirrhosis</td>
<td></td>
<td>●</td>
</tr>
</tbody>
</table>

Staging of Liver Disease

- Staging is disease assessment with meaningful information for patients and providers
- Liver stage is the CD4 count of HCV
- Who and When to treat (i.e. now or later?)
- Screening for HCC and varices
- Modalities:
  - Liver biopsy
  - Blood markers,
  - Elastography,
  - Combination
Noninvasive Serum-Based Tests for Detection of Fibrosis

- **FibroTest**
  - Combines 5 markers: $\alpha_2$-macroglobulin, haptoglobin, GGT, total bilirubin, and apolipoprotein A1

- **FibroSpect II**
  - Combines 3 markers: $\alpha_2$-macroglobulin, hyaluronic acid, and tissue inhibitor of metalloproteinase-1

- **APRI**
  - AST-to-platelets ratio index

- **Forns fibrosis index**
  - Age, platelet count, GGT, cholesterol

- **FIB-4**
  - Combines 4 markers: platelets, ALT, AST, and age
## Validity of Noninvasive Methods of Detecting Cirrhosis

<table>
<thead>
<tr>
<th>Test</th>
<th>% Sens</th>
<th>% Spec</th>
<th>AUROC</th>
<th>Pos LR</th>
<th>Neg LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrotest(^1) &gt; .56</td>
<td>85</td>
<td>74</td>
<td>.86</td>
<td>3.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Fibrotest &gt; .73</td>
<td>56</td>
<td>81</td>
<td>-</td>
<td>2.9</td>
<td>0.54</td>
</tr>
<tr>
<td>FIB4(^2), &gt;1.45</td>
<td>90</td>
<td>58</td>
<td>.87</td>
<td>2.1</td>
<td>0.17</td>
</tr>
<tr>
<td>APRI(^3), &gt;1.0</td>
<td>77</td>
<td>75</td>
<td>0.73</td>
<td>3.1</td>
<td>0.31</td>
</tr>
<tr>
<td>Forns(^4), &gt;4.2</td>
<td>98</td>
<td>27</td>
<td>87</td>
<td>1.3</td>
<td>0.07</td>
</tr>
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</table>

Chou Ann Intern Med 2013
FibroScan (Elastography)

- The probe induces an elastic wave through the liver.
- The velocity of the wave is evaluated in a region located from 2.5 to 6.5 cm below the skin surface.

Diagnostic accuracy:
- Significant fibrosis: 0.79
- Advanced fibrosis: 0.91
- Cirrhosis: 0.97

FibroScan (kPa)

8.8  9.6  14.6

F0-F1  F2  F3  F4

(METAVIR)

Which staging test should be done?

- LSM-based models performed 8.4% better than liver biopsy prediction survival and liver-decompensation.
Which staging test should be done?

- Elastography provides the most, currently useful information when valid
- Elastography and noninvasive can confidently rule out cirrhosis when concordant
- Serum alone may confidently rule out cirrhosis
- Biopsy done by specialists and when discordance or other questions
- Do something
Drug-Drug Interactions
# DAA Drug Interactions

<table>
<thead>
<tr>
<th>ARV</th>
<th>BOC</th>
<th>TPV</th>
<th>SMV</th>
<th>SOF*</th>
<th>DCV</th>
<th>FDV</th>
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<tr>
<td>ATV/r</td>
<td>CAUTION</td>
<td>STAND</td>
<td>CONTRA</td>
<td>STAND</td>
<td>↓</td>
<td>DCV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓</td>
<td>FDV</td>
</tr>
<tr>
<td>DRV/r</td>
<td>CONTRA</td>
<td>CONTRA</td>
<td>CONTRA</td>
<td>STAND</td>
<td>N/A</td>
<td>↓</td>
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<tr>
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<td></td>
<td></td>
<td>FDV</td>
</tr>
<tr>
<td>EFV</td>
<td>CONTRA</td>
<td>↑ TPV</td>
<td>CONTRA</td>
<td>STAND</td>
<td>↑</td>
<td>DCV</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>↑</td>
<td>FDV</td>
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<tr>
<td>RPV</td>
<td>STAND</td>
<td>CAUTION</td>
<td>STAND</td>
<td>STAND</td>
<td>STAND</td>
<td>N/A</td>
</tr>
<tr>
<td>ETV</td>
<td>CAUTION</td>
<td>CAUTION</td>
<td>CONTRA</td>
<td>STAND</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>RGV</td>
<td>STAND</td>
<td>STAND</td>
<td>STAND</td>
<td>STAND</td>
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</tr>
<tr>
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<td>N/A</td>
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<td>CAUTION</td>
<td>STAND</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>MVC</td>
<td>↓ MVC</td>
<td>↓ MVC</td>
<td>STAND</td>
<td>STAND</td>
<td>STAND</td>
<td>STAND</td>
</tr>
</tbody>
</table>

*Tipranavir CONTRA with SOF

# AASLD and IDSA Guidelines: Preferred HCV Regimens in HCV/HIV Coinfection

## Genotype 1

<table>
<thead>
<tr>
<th>Status</th>
<th>Treatment Regimen</th>
</tr>
</thead>
</table>
| HCV treatment-naïve and prior PR relapsers | Sofosbuvir + PR 12 weeks  
| IFN eligible                  | Sofosbuvir + RBV 24 weeks  
| IFN ineligible                | Sofosbuvir + simeprevir† + RBV 12 weeks               |

*HCV treatment experienced*

| IFN eligible                  | Sofosbuvir + simeprevir† + RBV 12 weeks               |

**Allowable ART:** Sofosbuvir: all except the NRTIs didanosine and zidovudine.  
Simeprevir: INSTI (raltegravir); NNRTI (rilpivirine); Entry/Fusion Inhibitor (maraviroc, enfuvirtide);  
NRTIs (tenofovir, emtricitabine, lamivudine, abacavir).

## Genotype 2

- Regardless of HCV treatment history  
  - Sofosbuvir + RBV 12 weeks

## Genotype 3

- Regardless of HCV treatment history  
  - Sofosbuvir + RBV 24 weeks

## Genotype 4

- Regardless of HCV treatment history  
  - IFN eligible  
    - Sofosbuvir + PR 12 weeks  
    - Sofosbuvir + RBV 24 weeks
  - IFN ineligible  
    - Sofosbuvir + PR 12 weeks  
    - Sofosbuvir + RBV 24 weeks

## Genotypes 5 or 6

- Regardless of HCV treatment history  
  - Sofosbuvir + PR 12 weeks

**Allowable ART:** Sofosbuvir: all except the NRTIs didanosine and zidovudine.  
Simeprevir: INSTI (raltegravir); NNRTI (rilpivirine); Entry/Fusion Inhibitor (maraviroc, enfuvirtide);  
NRTIs (tenofovir, emtricitabine, lamivudine, abacavir).
**AASLD and IDSA Guidelines: Alternative HCV Regimens in HCV/HIV Coinfection**

<table>
<thead>
<tr>
<th>Genotype 1</th>
<th>IFN eligible</th>
<th>IFN ineligible</th>
<th>IFN ineligible</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV treatment-naïve and prior PR relapsers</td>
<td>Simeprevir† 12 weeks + PR 24 weeks</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>HCV treatment experienced*</td>
<td>Sofosbuvir + PR 12 weeks</td>
<td>Sofosbuvir + RBV 24 weeks</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotypes 2 or 3</th>
<th>IFN eligible</th>
<th>IFN ineligible</th>
<th>IFN ineligible</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV treatment-naïve and prior PR relapsers</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV treatment experienced*</td>
<td>Sofosbuvir + PR 12 weeks</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

| Genotypes 4, 5, or 6 | None |

*Prior PR non-responders.
†For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if present.

**Allowable ART:** Sofosbuvir: all except the NRTIs didanosine and zidovudine.
Simeprevir: INSTI (raltegravir); NNRTI (rilpivirine); Entry/Fusion Inhibitor (maraviroc, enfuvirtide);
NRTIs (tenofovir, emtricitabine, lamivudine, abacavir).
AASLD and IDSA Guidelines: HCV Regimens Not Recommended in HCV/HIV Coinfection

**Genotype 1**
- Telaprevir + PR 24 or 48 weeks (RGT)
- Boceprevir + PR 28 or 48 weeks (RGT)
- PR 48 weeks
- Simeprevir 12 weeks + PR 48 weeks

**Genotypes 2 or 3**
- Any regimen with telaprevir, boceprevir, or simeprevir
- PR 24 to 48 weeks

**Genotypes 4, 5, or 6**
- Any regimen with telaprevir, boceprevir, or simeprevir
- PR 48 weeks

NIAID ERADICATE Study: Sofosbuvir/Ledipasvir in HCV Genotype 1 With HIV Coinfection (Interim Analysis)

- No change within groups
  - CD4 counts or CD4 T-cell percentages
  - Serum creatinine or estimated GFR
- HIV RNA status during HCV treatment
  - ART-naïve: no clinically significant change
  - On ART: transient HIV RNA breakthrough (missed ART for 4 days), re-suppressed
  - No change within groups
- Sofosbuvir/ledipasvir was well tolerated
  - No deaths, grade 4 adverse events or discontinuations due to adverse events
  - Laboratory abnormalities
    - Grade 3: neutropenia (n=1), AST (n=1)
    - Grade 4: creatinine phosphatase (n=1)

HCV/HIV Coinfection: Summary

- Liver disease is a leading cause of morbidity and mortality
- Controlling HIV with ART may slow progression of HCV-related liver disease
- All HIV patients should be screened for HCV
- First-generation PIs + PR regimens present significant challenges and limitations
- Newer, once-daily DAAs
  - Simplify and shorten duration of regimens
  - Improve SVR rates with fewer adverse events
  - Minimize drug-drug interactions