Hepatitis C Treatment in the HIV/HCV Coinfected Patient: A New Era

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Disclosure Statement for Arthur Kim

• Grant/research support from Bristol-Myers Squibb, Gilead
• Consultant: Abbvie, Gilead
  (Updated 5/22/14)

• I will discuss the following off-label use in this presentation:
  • Telaprevir / Boceprevir / Simeprevir for HIV-1 / HCV co-infection
  • Unapproved direct-acting agents

• Funding: National Institutes of Health
  • (National Institute of Allergy and Infectious Diseases,
    National Institute of Drug Abuse)
1. Update on HIV/HCV Coinfection

2. HCV Treatment Guidelines (January 2014, updated March)

3. Future regimens

   – CROI 2014 / EASL 2014 / Every few weeks in the NEJM

**Scope of the problem**

- HIV-1 and HCV share routes of transmission
- Worldwide burden:
  - Co-infection is common, between 16-33% prevalence in HIV infected persons
  - Liver disease (largely due to HCV) is 2nd leading cause of death if HIV+
Natural history of HCV

Acute infection

~20%

Chronic infection

~80%

Viral clearance

Stable or slowly progressive

Cirrhosis

Liver failure

HCC

Death

Other liver diseases
(such as EtOH, NASH)
Coinfections (HIV, HBV)

HCV Exceeds HIV as Cause of Death in USA

Death Rates Among HCV Cases in Massachusetts, by age at death, 2000-2009

The highest average annual mortality rate for those with HCV was among the 50 to 54 year age group, with 38 deaths per 100,000

HCV data Source: MDPH Office of Integrated Surveillance and Informatics Services, data as of 2/10/12
HCV diagnosis date is the earliest known date of documented HCV infection

HIV / HCV co-infection is double trouble

- Compared to HIV-negative HCV-positive (monoinfected) individuals, those with HIV suffer from:

1. Higher rates of persistence (lower rates of clearance)

2. Accelerated rate of fibrosis, higher rates of cirrhosis

3. Higher rates of decompensation & liver-related mortality

4. Decreased survival (52 years vs 56 years in NYC)

HIV still associated with higher rates of HCV-related liver decompensation

Figure 3. Liver fibrosis and age among persons coinfected with HIV and HCV (dashed line) and those with only HCV (solid line).

HIV+HCV
HCV


HIV associated with higher rates of HCV-related liver decompensation, even when on ART

Lo Re V et al. Annals of Internal Medicine 2014
RVR = rapid virologic response = negative HCV RNA at week 4  
pEVR = partial early virologic response = 2 log drop at week 12 compared to baseline  
cEVR = complete early virologic response = negative HCV RNA at week 12  
ETR = end of treatment response  
SVR = sustained virologic response = negative HCV RNA 24 weeks after therapy  

Koziel and Peters NEJM 2009  
AASLD/IDSA 2009 Guidelines

Substantial benefit of SVR, all-cause mortality, liver-related mortality, hepatocellular carcinoma

All cause mortality  
Liver-related mortality or OLT  
Hepatocellular carcinoma  
Liver failure

Van der Meer et al. JAMA 2012

5 year mortality without SVR is ~10%
Potential Therapeutic Targets in the HCV Replication Cycle

Antiviral HCV treatments (FDA-approved)

- **Monotherapy**
  - IFN-2a
  - IFN-2b
  - PEG-IFN 2a
  - PEG-IFN 2b

- **Combination Therapy**
  - IFN-2a + Ribavirin
  - IFN-2b + Ribavirin
  - PEG-IFN 2a + Ribavirin
  - PEG-IFN 2b + Ribavirin

  **PEG-IFN + ribavirin:**
  - Boceprevir (GT1)
  - Telaprevir (GT1)
  - Simeprevir (GT1)

  In combination with other agents:
  - Sofosbuvir
Pipeline of direct acting agents-HCV
*Phase III

Protease inhibitors (-previr)
telaprevir (APPROVED)
boceprevir (APPROVED)
simeprevir (APPROVED)

faldaprevir*
asunaprevir*
ABT-450/R*
MK-5172*

GS-9451
inaravir
danoprevir/R
vaniprevir
sovaprevir
ACH-2684
ABT-493
VX-500
IDX 320

NS5A inhibitors (-asvir)
daclatasvir*
ledipasvir*
ombitasvir* (ABT-267)
MK-8742*

GSK2336805 samatasvir
ACH-2928
BMS-824383
PPI-461
PPI-667
AZD-7295
ACH-3102
ABT-530

Polymerase inhibitors
sofosbuvir (APPROVED)
mericitabine
VX-135 (ALS-2200)
dasabuvir* (ABT-333)

ABT-072
filibuvir
setrobuvir (ANA-598)
BMS-791325
tegobuvir
RG7129
lombivir (VX-222)
TMC-649128
MK-3281
INX-189
IDX-375

Possible Combinations of HCV treatments
Genotypes

PEG IFN
RBV
BOC

TLV
SMV
GS-9451
ABT-450
ASV
MK-5172

LDV
ABT-267
DCV
MK-5742

GS-9669
ABT-333
BMS-791325

GT1 77%
GT2 9%
GT3 10%
GT4 4%

## Comparison of two 1st generation approved protease inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Boceprevir</th>
<th>Telaprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype activity</td>
<td>GT 1 (-2)</td>
<td>GT 1 (-2)</td>
</tr>
<tr>
<td>PEG-IFN regimen</td>
<td>PEG-IFN-2b</td>
<td>PEG-IFN-2a</td>
</tr>
<tr>
<td>Dosing</td>
<td>q7-9h (with food)</td>
<td>q7-9h (with food)</td>
</tr>
<tr>
<td>Pharmacology</td>
<td>CYP3A4, p-glycoprotein</td>
<td>CYP3A4, p-glycoprotein</td>
</tr>
<tr>
<td>Pregnancy category</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Duration of PI</td>
<td>24-44 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Additive side effects</td>
<td>Dysgeusia, anemia</td>
<td>Rash, pruritus, anal sx, anemia</td>
</tr>
</tbody>
</table>
HCV versus HIV/HCV, genotype 1 in Clinical Trials
Not head to head comparison

SVR rates at CROI using BOC/TLV + PEG/RBV

~78% for naive GT1 in Swiss Cohort Study
~59% for nonresponders with boceprevir,
~80% for nonresponders with telaprevir (ANRS) - including 72 week arm
~64% all comers in Spain/Germany

1st generation protease inhibitor therapy for Nonresponders REALIZE

Viruses can evolve under external pressure

Selection Pressure
(medication or immune system)

Mutant strain (R155K etc)

CUPIC: High rates of serious adverse events in nonresponders with compensated cirrhosis

Patients treated with telaprevir or boceprevir plus PEG/RBV

<table>
<thead>
<tr>
<th>Patients, n (% patients with at least one event)</th>
<th>Telaprevir n = 296</th>
<th>Boceprevir n=159</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events (%)</td>
<td>48.6</td>
<td>38.4</td>
</tr>
<tr>
<td>Premature discontinuation</td>
<td>26.0</td>
<td>23.9</td>
</tr>
<tr>
<td>Due to SAEs (%)</td>
<td>14.5</td>
<td>7.4</td>
</tr>
<tr>
<td>Death (%)</td>
<td>2.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Infection (Grade 3/4) (%)</td>
<td>8.8</td>
<td>2.5</td>
</tr>
<tr>
<td>Asthenia (Grade 3/4) (%)</td>
<td>4.7</td>
<td>5.7</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 (%)</td>
<td>6.8</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4 (SCAR) (%)</td>
<td>0.7</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus (Grade 3/4) (%)</td>
<td>3.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Hepatic decompensation (%)</td>
<td>4.4</td>
<td>4.4</td>
</tr>
</tbody>
</table>

Hezode et al. J Hepatol 2013
simeprevir is a potent, specific HCV NS3/4A protease inhibitor

Safe and well-tolerated (n>3,800)

Asymptomatic increases in bilirubin detected

Rash, photosensitivity reactions

150 mg once daily, better absorption with food, higher levels in E. Asians

Potent against genotypes 1,4,6; activity against 2,5

Resistance possible with Q80K mutation within protease
sofosbuvir is a potent, specific HCV nucleotide

Safe and well-tolerated

400 mg once daily, with or without food

Broad HCV genotype coverage

High barrier to resistance, no known breakthrough if adherent to date

All adherent patients suppress on treatment, all failures are relapses

Kirby et al. Poster #1877 AASLD, Boston, MA, November 2012

sofosbuvir or GS-7977 + ribavirin
No breakthroughs while on therapy

Gane et al. NEJM 2012

SVR
SOF/RBV (n=50) 100%
SOF (n=10) 60%

SVR
SOF/RBV naive (n=10) 84%
SOF/RBV null (n=10) 10%
<table>
<thead>
<tr>
<th>Drug Interactions</th>
<th>++</th>
<th>++</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>wk 4 viral load</td>
<td>shortens</td>
<td>shortens</td>
<td>adherence</td>
</tr>
<tr>
<td>monitoring</td>
<td>course</td>
<td>course</td>
<td>only</td>
</tr>
<tr>
<td>resistance (cost of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>failure)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R155K and others</td>
<td></td>
<td>Q80K</td>
<td>negligible</td>
</tr>
<tr>
<td>course length</td>
<td>24-48 weeks</td>
<td>24-48 weeks</td>
<td>12-24 weeks</td>
</tr>
</tbody>
</table>

**Genotype 2**

*Recommended regimen for treatment-naive patients with HCV genotype 2, regardless of eligibility for IFN therapy:*

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for treatment-naive patients with HCV genotype 2 infection.

Rating: Class I, Level A

[http://www.hcvguidelines.org](http://www.hcvguidelines.org), accessed 2/12/14
Sofosbuvir + RBV for GT2 infection

Naive, no cirrhosis

- 92-98%

Naive with cirrhosis

- 91-93%
- 25/26

Tx Exp, cirrhosis

- 96%
- 6/10
- 78%
- 7/9

Sofosbuvir + RBV x 12w for GT2 infection

Naive, no cirrhosis

- 97%
- 29/30

Naive with cirrhosis

- 100%
- 2/2

Tx Exp, cirrhosis

- 91%
- 30/33
- 88%
- 7/8

Lawitz et al. NEJM 2013, Jacobson et al. NEJM 2013

Zeuzem et al. NEJM 2014 Epub May 4
Recommended regimen for treatment-naive patients with HCV genotype 3, regardless of eligibility for IFN therapy:

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for treatment-naive patients with HCV genotype 3 infection.

Rating: Class I, Level B

Sofosbuvir + RBV for GT3 infection, naïve patients

![Graph showing response rates for naive patients with GT3 infection treated with sofosbuvir and RBV for 12 and 24 weeks.](image)

- 61-68% for naïve, no cirrhosis at 12 weeks
- 37% for naïve with cirrhosis at 24 weeks
- 94% for naïve, no cirrhosis at 24 weeks
- 92% for naïve, cirrhosis at 24 weeks

Lawitz et al. NEJM 2013, Jacobson et al. NEJM 2013, Antiviral Drugs Advisory Committee Meeting, Gilead Review 10/25/13, Zeuzem et al. AASLD 2013
Sofosbuvir + RBV for GT3 infection
treatment experienced patients

Lawitz et al. NEJM 2013, Jacobson et al. NEJM 2013, Antiviral Drugs Advisory Committee Meeting, Gilead Review 10/25/13, Zeuzem et al. NEJM 2014 Epub May 4

12 weeks

- Tx Exp, no cirrhosis: 37%
- Tx Exp, cirrhosis: 19%

24 weeks

- Tx Exp, no cirrhosis: 87%
- Tx Exp, cirrhosis: 60%

Peg-IFN + sofosbuvir + RBV x 12 wks for GT3 infection

LONESTAR2 included high rate of cirrhotics (55%) & nonresponders (85%)

2/4 nonresponders in GT3 LONESTAR2 group were lost to f/u

Regimen achieved 96% SVR for GT2

PROTON, & ELECTRON, Lawitz et al. Lancet 2013, LONESTAR2 (Lawitz et al. AASLD 2013)
**Genotype 3**

Alternative regimens for treatment-naive patients with genotype 3 who are eligible to receive IFN.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is an acceptable regimen for IFN-eligible persons with HCV genotype 3.

Rating: Class IIa, Level A

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**Sofosbuvir + PEG-IFN/RBV - NEUTRINO**

Phase III, Treatment-naive, GT1,4,5,6

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![Graph](image-url)
### Adverse Events ≥15% with Sofosbuvir and Ribavirin +/- Peg-IFN

<table>
<thead>
<tr>
<th>Event</th>
<th>SOF+PE+RBV x 12 weeks (n=327)</th>
<th>PE+RBV x 24 weeks (n=243)</th>
<th>SOF+RBV x 12 weeks (n=256)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>192 (59%)</td>
<td>134 (55%)</td>
<td>92 (36%)</td>
</tr>
<tr>
<td>Headache</td>
<td>118 (36%)</td>
<td>108 (44%)</td>
<td>64 (25%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>112 (34%)</td>
<td>70 (29%)</td>
<td>46 (18%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>81 (25%)</td>
<td>70 (29%)</td>
<td>31 (12%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>58 (18%)</td>
<td>44 (18%)</td>
<td>17 (7%)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>51 (16%)</td>
<td>44 (18%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Chills</td>
<td>54 (17%)</td>
<td>43 (18%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>58 (18%)</td>
<td>33 (14%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Rash</td>
<td>59 (18%)</td>
<td>43 (18%)</td>
<td>23 (9%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38 (12%)</td>
<td>42 (17%)</td>
<td>23 (9%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>54 (17%)</td>
<td>42 (17%)</td>
<td>19 (7%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>45 (14%)</td>
<td>40 (16%)</td>
<td>21 (10%)</td>
</tr>
<tr>
<td>Irritability</td>
<td>42 (13%)</td>
<td>40 (16%)</td>
<td>25 (10%)</td>
</tr>
</tbody>
</table>

**NEJM 2013**

### Recommendations for Testing, Managing, and Treating Hepatitis C

**Genotype 1**

*Recommended regimen for treatment-naive patients with HCV genotype 1 who are eligible to receive IFN.*

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons with HCV genotype 1 infection, regardless of subtype.

**Rating:** Class I, Level A

[http://www.hcvguidelines.org](http://www.hcvguidelines.org), accessed 2/12/14
Simeprevir + PEG-IFN/RBV - QUEST 1/2, PROMISE
Phase III, GT1

1st 12 weeks simeprevir, 48 week-regimen PR; shortened to 24 if RVR

Jacobson et al. EASL 2013; Manns et al. EASL 2013; Lawitz et al. DDW 2013

Recommendations for Testing, Managing, and Treating Hepatitis C

Genotype 1

Alternative regimens for treatment-naive patients with HCV genotype 1 who are eligible to receive IFN.

Daily simeprevir (150 mg) for 12 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) plus weekly PEG for 24 weeks is an acceptable regimen for IFN-eligible persons with either

1. HCV genotype 1b or
2. HCV genotype 1a infection in whom the Q80K polymorphism is not detected prior to treatment.

Rating: Class IIa, Level A

http://www.hcvguidelines.org, accessed 2/12/14
### Summary of relative efficacy for various regimens and genotypes

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Genotype</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG IFN</td>
<td>GT1</td>
<td>~80% naives Lower for 1a with Q80K</td>
</tr>
<tr>
<td>PE</td>
<td>GT1</td>
<td>~89% naives only 10% T-exp</td>
</tr>
<tr>
<td>RBV</td>
<td>GT1</td>
<td>~70-75% (including nulls and cirrhosis)</td>
</tr>
<tr>
<td>SOF</td>
<td>GT1</td>
<td>~95%</td>
</tr>
<tr>
<td>RBV</td>
<td>GT2</td>
<td>~97% including T-E, cirrhosis</td>
</tr>
<tr>
<td>SOF</td>
<td>GT2</td>
<td>~88-95% 60-88% T-E+ cirrhosis</td>
</tr>
<tr>
<td>RBV</td>
<td>GT2</td>
<td>93% naives 86% TE 60% TE+ cirrhosis</td>
</tr>
<tr>
<td>SOF</td>
<td>GT3</td>
<td>97% Naives, 87% overall</td>
</tr>
<tr>
<td>RBV</td>
<td>GT3</td>
<td>~70-75%</td>
</tr>
<tr>
<td>SMV</td>
<td>GT3</td>
<td>~70-75%</td>
</tr>
<tr>
<td>RBV</td>
<td>GT4</td>
<td>~95%</td>
</tr>
<tr>
<td>SOF</td>
<td>GT4</td>
<td>10/11 SVR</td>
</tr>
<tr>
<td></td>
<td>GT4</td>
<td>96% Naive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>59% (TE)-79% (naive) 21/31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100% naives 14/14 87% TE 13/15</td>
</tr>
</tbody>
</table>

### Pipeline of direct acting agents-HCV

**Protease inhibitors (-previr)**
- telaprevir (APPROVED)
- boceprevir (APPROVED)
- simeprevir (APPROVED)
- faldaprevir*
- asunaprevir*
- ABT-450/R*
- MK-5172*

**NS5A inhibitors (-asvir)**
- daclatasvir*
- ledipasvir*
- ombitasvir* (ABT-267)
- MK-8742*
- daclatasvir
- ledipasvir
- ombitasvir
- MK-8742
- GSK2336805 samatasvir
- ACH-2928
- BMS-824383
- PPI-461
- PPI-667
- AZD-7295
- ACH-3102
- ABT-530

**Polymerase inhibitors**
- sofosbuvir (APPROVED)
- mericitabine
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- BMS-791325
tegobuvir
- RG7129
- lomibuvir (VX-222)
- TMC-649128
- MK-3281
- INX-189
- IDX-375
# Drug interactions of DAAs with ARVs

**Table 2 | Direct-acting antiviral and antiretroviral scorecard**

<table>
<thead>
<tr>
<th>HIV therapy</th>
<th>Bocceprevir</th>
<th>Telaprevir</th>
<th>Simeprevir</th>
<th>Faldaprevir</th>
<th>Daclatasvir</th>
<th>Sofosbuvir</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/ampinavir</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>darunavir/ritonavir</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>fosamprenavir/ritonavir</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>lopinavir/ritonavir</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>nevirapine</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
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<td>efavirenz</td>
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<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<td>✔</td>
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<tr>
<td>Etravirine</td>
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<td>✔</td>
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<tr>
<td>Raltegravir</td>
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<td>✔</td>
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<tr>
<td>maraviroc</td>
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<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

* indicates the presence of an interaction, / indicates the absence of a clinically important interaction, */ indicates that the combination is acceptable but requires dose adjustment (see main text), ? indicates the presence of an interaction with uncertain clinical importance. No data indicates no interaction data are currently available with the combination.

*Kiser et al., Nature Rev Gastro Hep 2013*
Sofosbuvir for HIV/HCV coinfection
PHOTON-1

- Treatment naïve, cirrhosis permitted
- ART included: rilpivirine, raltegravir, efavirenz, boosted PIs
- SAE 7%

Naggie et al. CROI 2014. Abstract 26
HCV versus HIV/HCV, genotype 1 in Clinical Trials
Not head to head comparison


Antiviral Drugs Advisory Committee Meeting, FDA review, 10/24/13
C208, C216, C206, C212, HPC3007, Dieterich, 14th European AIDS Conference, 2013
Lawitz et al. NEJM 2013 versus Torres-Rodriguez et al., IDSA 2013
Osinusi et al., JAMA 2013;310(8):804-11 versus Sulkowski et al. AASLD 2013 (PHOTON)

SVR Rate

BOC TLV SMV (Naive) SMV (Relapser) SMV (Partial)

POG RBV PEG RBV PEG RBV

86/114 86/114 86/114 86/114

GT1 TN GT2 TE GT3 TE GT2 TN GT3 TN

24 Weeks (n=155) 12 Weeks (n=68)

AEs

Fatigue 39 35
Insomnia 15 21
Headache 14 13
Nausea 15 18
Diarrhea 11 9
Irritability 10 10
URI 12 12

Grade 3-4 AEs 12 10

Serious AEs 6 7

*Weight loss, insomnia/agitation, pneumonia, suicide attempt, foreign body sensation in throat, increased anxiety, dyspnea.
†Suicide 9 days after completing study treatment; patient had history of depression and was being treated for ADHD and insomnia before entering study.

Naggie et al. CROI 2014. Abstract 26
The patient’s view of interferon
**Prix fixe menus?**

Due to regulations, no alcohol will be served.

**Protease inhibitors**
- boceprevir 44
- telaprevir 12
- asunaprevir 12
- MK-5172 12
- narlaprevir 12
- danoprevir 12
- faldaprevir 12
- ABT-450/IR 12

**NS5A inhibitors**
- daclatasvir 12
- ledipasvir 12
- ombitasvir 12

**Polymerase inhibitors**
- sofosbuvir 12
- BMS-791325 12
- dasabuvir 12

**Notice:** The consumption of raw or undercooked eggs, meat, poultry, seafood or shellfish, and most of these choices are not approved by the FDA for Hepatitis C.

Please ask your server whether Ribavirin is suggested.

Due to regulations, no alcohol will be served.

---

**Comparison of two 1st generation approved protease inhibitors**

<table>
<thead>
<tr>
<th></th>
<th>Simeprevir</th>
<th>Daclatasvir</th>
<th>Sofosbuvir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genotype activity</strong></td>
<td>GT 1,2,4,5,6</td>
<td>Pangenotypic</td>
<td>Pangenotypic</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>daily (with food)</td>
<td>daily</td>
<td>daily</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>CYP3A4</td>
<td>Low potential</td>
<td>Low potential</td>
</tr>
<tr>
<td><strong>Pregnancy category</strong></td>
<td>C</td>
<td>?</td>
<td>B</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Well tolerated (n~3,800)</td>
<td>Well tolerated (n&gt;5,500)</td>
<td>Well tolerated</td>
</tr>
</tbody>
</table>
Mix and Match Agents

**DCV**

**SOF**

**SMV**

---

**COSMOS Cohort 1 (null responders, F0-2)**

SVR 12 by HCV subtype and Q80K

Excluding non-virologic failures

---

<table>
<thead>
<tr>
<th>GT1a Q80K</th>
<th>GT1a WT</th>
<th>GT1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>89/9</td>
<td>100/100</td>
<td>100/100</td>
</tr>
<tr>
<td>4/4</td>
<td>7/7</td>
<td>7/7</td>
</tr>
<tr>
<td>3/3</td>
<td>7/7</td>
<td>3/3</td>
</tr>
</tbody>
</table>

SOF + SMV x 24 Weeks

SOF + SMV x 12 Weeks

RB presence no major effect on SVR

Sułkowski et al. EASL 2014
COSMOS Cohort 2 (F3 and F4)
SVR 12 by HCV subtype and Q80K
Excluding non-virologic failures

<table>
<thead>
<tr>
<th></th>
<th>GT1a Q80K</th>
<th>GT1a WT</th>
<th>GT1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMV/SOF/RBV</td>
<td>11/11</td>
<td>6/6</td>
<td>4/4</td>
</tr>
<tr>
<td>SMV/SOF</td>
<td>4/4</td>
<td>7/7</td>
<td>4/4</td>
</tr>
<tr>
<td>SMV/SOF/RBV</td>
<td>7/8</td>
<td>13/14</td>
<td>5/5</td>
</tr>
<tr>
<td>SMV/SOF</td>
<td>3/3</td>
<td>7/8</td>
<td>3/3</td>
</tr>
</tbody>
</table>

SOF + SMV x 24 Weeks

SOF + SMV x 12 Weeks

Presence no major effect on SVR

Lawitz et al. EASL 2014

Recommendations for Testing, Managing, and Treating Hepatitis C

GT 1

Recommended regimen for treatment-naive patients with HCV genotype 1 who are not eligible to receive IFN.

Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 12 weeks is recommended for IFN-ineligible patients with HCV genotype 1 infection, regardless of subtype.

Rating: Class I, Level B

GT1 currently excluded from 12 weeks SMV/SOF are treatment-experienced protease inhibitor failures
**Daclatasvir + Sofosbuvir +/- RBV**

Genotype 1 arms only, 12 or 24 weeks

Sulkowski et al. NEJM 2014

<table>
<thead>
<tr>
<th>12 weeks for naives*</th>
<th>24 weeks for naives</th>
<th>24 weeks for nonresponder</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCV/SOF</td>
<td>DCV/SOF/RBV</td>
<td></td>
</tr>
<tr>
<td>95/41</td>
<td>93/41</td>
<td></td>
</tr>
<tr>
<td>100/14</td>
<td>100/15</td>
<td></td>
</tr>
<tr>
<td>100/21</td>
<td>95/20</td>
<td></td>
</tr>
</tbody>
</table>

*3 patients missed SVR24 appointment
SVR12 rate 100%/95%

**LEAGUE-1 AI444-062**

Daclatasvir / Simeprevir +/- RBV, 12 to 24 wks

<table>
<thead>
<tr>
<th>Naive</th>
<th>Nulls</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 1b</td>
<td>GT 1b +RBV</td>
</tr>
<tr>
<td>DCV</td>
<td>DCV</td>
</tr>
<tr>
<td>SMV</td>
<td>SMV</td>
</tr>
<tr>
<td>RBV</td>
<td>RBV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SVR12 (ITT)</th>
<th>SVR12 (ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>85/53</td>
<td>75/51</td>
</tr>
<tr>
<td>45/38</td>
<td>65/23</td>
</tr>
<tr>
<td>19/20</td>
<td></td>
</tr>
</tbody>
</table>

- Completers did much better 79-95%
- 1a had high rate of breakthrough in both naives (33%) and nulls (77%)
Mix and Match Agents

High efficacy

SOF

High efficacy

DCV

SMV

not for 1a

high cost of failure

Ribavirin may or may not be necessary

MK5172 (protease)

Naive

All F0-F2

1 virologic breakthrough had low drug levels, Y93N baseline + relapse, D168A at relapse

Compatible:

TDF, RAL*

EFV decreases 8742

ATVr, DRVr, LPVr increases 8742

*coinfected patients on RAL with:

RBV: 97% SVR4

no RBV: 90% SVR4

C-WORTHY

Lawitz et al. AASLD 2013 Abstract 76, Yeh et al. AASLD 2013 Abstract 479

Szulkowski et al. EASL 2014, D63; Yeh et al. CROI 2014, Abstracts 498, 638
MK5172 (protease inhibitor) plus MK8742 (NS5A inhibitor) for genotype 1

Lawitz et al. EASL 2014 Abstract

SVR 4-8

5/5 patients with baseline NS3 R155K/D168A achieved SVR4/8

Everson et al. Gastroenterology 2014; 148:420-4

Everson et al. CROI 2014 Abstract 25
PEARL-III, 3D Abbvie Regimens for 1b infection

- Ribavirin appears unnecessary for 1b infection treated with 3D regimen

Regimens in Phase 3 for GT1

ION-1 and 2: RBV addition did not enhance SVR

Cirrhotics (TURQUOISE) 24 weeks 95.9% SVR

Tx-Exp (ION-2) 24 wks LDV/SOF 108/109 SVR

FDA filings LDV/SOF 2/10/14 3D 4/22/14

SAPPHIRE/ION-1 and 2: RBV addition did not enhance SVR

SAPPHIRE/TURQUOISE are 12 week arms only. ION studies are RBV-sparing arms only
### Adverse Events 3D regimen 12 weeks in SAPPHIRE-1

<table>
<thead>
<tr>
<th>Event</th>
<th>3D + RBV x 12 weeks (n=473)</th>
<th>Placebo (n=217)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation due to AE</td>
<td>3 (0.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Serious AE</td>
<td>10 (2.1%)*</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>164 (34.7%)</td>
<td>45 (28.5%)</td>
</tr>
<tr>
<td>Headache</td>
<td>156 (33.0%)</td>
<td>42 (26.6%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>112 (23.7%)</td>
<td>21 (13.3%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>66 (14.0%)</td>
<td>12 (7.6%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>57 (12.1%)</td>
<td>6 (3.8%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>65 (13.7%)</td>
<td>11 (7.0%)</td>
</tr>
<tr>
<td>Rash</td>
<td>51 (10.8%)</td>
<td>9 (5.7%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>80 (16.9%)</td>
<td>6 (3.8%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>27 (5.8%)**</td>
<td>0</td>
</tr>
</tbody>
</table>

* 2 were possibly related to 3D by investigator
**no cases of anemia < 8.0 g/DL

Feld et al. NEJM 2014; Epub ahead of print

### Adverse Events LDV/SOF 12 weeks in ION-1

<table>
<thead>
<tr>
<th>Event</th>
<th>LDV/SOF weeks (n=214)</th>
<th>LDV SOF RBV weeks (n=217)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation due to AE</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious AE</td>
<td>1 (&lt;1%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>44 (21%)</td>
<td>79 (36%)</td>
</tr>
<tr>
<td>Headache</td>
<td>53 (25%)</td>
<td>49 (23%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>24 (11%)</td>
<td>37 (17%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>17 (8%)</td>
<td>45 (21%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>14 (7%)</td>
<td>23 (11%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 (11%)</td>
<td>37 (17%)</td>
</tr>
<tr>
<td>Rash</td>
<td>16 (7%)</td>
<td>21 (10%)</td>
</tr>
<tr>
<td>Irritability</td>
<td>11 (5%)</td>
<td>17 (8%)</td>
</tr>
<tr>
<td>Cough</td>
<td>6 (3%)</td>
<td>21 (10%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11 (5%)</td>
<td>22 (10%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>25 (12%)</td>
</tr>
</tbody>
</table>

Afshal et al. NEJM 2014; Epub ahead of print
LDV/SOF FDC x 12 weeks in HIV/HCV coinfection
SVR 4: Treatment naive, F0-3

Mean age 58
>80% Black Race

n=37 on TDF/FTC plus various ART
No discontinuations
No renal toxicity
High CD4
(Range 113-1612)

49/50 remained HIV suppressed throughout study (1 patient non adherent to ART)
ION-4 phase III study open at MGH & BWH

Osinuri et al. EASL 2014, Abstract 14

SYNERGY TRIAL - Viral Kinetics

Kohli et al. SYNERGY Abstract 27LB, CROI 2014
SYNERGY TRIAL - high rates of SVR12 with just 6 weeks of 3 DAA therapy

Kohli et al. SYNERGY Abstract 27LB, CROI 2014

A potential future menu of options

Gilead Goose
6-8 weeks of GS-9451, pan-seared topped with ledipasvir flakes on a sofosbuvir backbone

Abbott am jus
12 weeks of ABT-450/r, slow-roasted, infused with ombitasvir, served with dasabuvir chutney

Bristol-Myers Squab
12 weeks of grilled asunaprevir marinated in daclatasvir with BMS-791325 Béchamel sauce

Merck (nuc-free option)
12 weeks of sous-vide MK5172 topped with fresh MK6742 salsa

Due to regulations, no alcohol will be served

Notice regarding protease inhibitors: boceprevir and telaprevir will no longer be offered due to high calories, dysgeusia and/or allergic reactions.

Notice: The consumption of raw or undercooked eggs, meat, poultry, seafood or shellfish, and all of these choices are not approved by the FDA for Hepatitis C.
Treatment of HCV

• Rapidly shifting paradigms - 2014 and beyond

Ideal regimen:
- High potency
- Little resistance
- Tolerable
- Once daily
- Shorter duration
- Few DDIs
- Lower cost

Will payers be deciding?

“It’s the only treatment option he has under his current health plan.”
The continuum of care in HCV infection in the U.S.
~3 million persons infected

Adapted from Holmberg et al. NEJM 2013

HCV Treatment Cascade in HIV-infected patients
UCSD Owen Clinic, 2008-2012

Figure 1: HCV cascade of care in HIV-infected patients following HCV infection diagnosis. UCSD Owen Clinic: 2008-2012

Cachay et al. CROI 2014; Abstract 672
**Barriers to addressing & treating HCV**

- **Biologic**
  - High viral loads
  - Fibrosis / cirrhosis
  - HIV

- **Psychosocial**
  - Stigma
  - Lack of awareness
  - Fear of evaluation and treatment
  - Substance abuse
  - Neuropsychiatric comorbidities
  - Poor adherence to treatment

- **Medications**
  - Side effects of treatment
  - Drug Interactions
  - Lack of insurance
  - High cost

- **Provider**
  - Dearth of providers
  - Lack of provider knowledge

---

**HIV/HCV Coinfection Treatment**

- **Novel interferon-free and ribavirin-free paradigms**
  - Potent combinations can remove RBV
  - Tantalizing proof-of-concept of 6 weeks of 3 DAAs

- **No evidence that DAA-based regimens will have lower efficacy for HIV/HCV co-infected patients**
  - for HIV, main issue will be drug-drug interactions

- **Data needed in subpopulations, esp. acute, renal insufficiency**

- **Improving cascade of care and ensuring adherence will be critical in upcoming era**
"Do... or do not. There is no try."