Can we afford to Cure all HIV-HCV Co-infected Patients of HCV?

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Disclosure

- Dr Saag has received grants and research support from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Inc, Janssen Therapeutics, Merck & Co, Inc, and ViiV Healthcare. (Updated 3/3/15)

- As a volunteer co-chair of the AASLD/IDSA/IAS–USA Hepatitis Guidance effort, Dr Saag has divested himself of any personal financial relationships with commercial entities as of October 2013. (See www.HCVguidelines.org/node/63#methodspanel)
Learning Objectives

After attending this presentation, learners will be able to:

- Know the cure rates of HCV in co-infected patients
- Recognize drug-drug interactions
- Describe the costs of treatments
- Know the cost-effectiveness of HCV therapies
Which best describes the relative cure (SVR$_{12}$) rate of HCV in HIV patients using DAA therapies?

1. HCV is easier to cure in mono-infected patients than HIV-HCV co-infected patients
2. HCV is harder to cure in mono-infected patients than HIV-HCV co-infected patients
3. Response rates among HCV mono- and co-infected patients are about the same
The WAC of Ledipasvir / Sofosbuvir in the US for a 12-week course of Rx is:

1. $ 900
2. $ 9,000
3. $ 90,000
4. $ 900,000
5. $1 Billion
Natural History of HCV Infection

- **Exposure (Acute Phase)**
  - ~15% Resolved
  - ~85% Chronic
  - ~80% Stable
  - ~20% Cirrhosis

- **Progression Rate**
  - ~20-year progression rate may be accelerated with HIV, HBV, alcohol, and steatosis\textsuperscript{1,2}
  - ~4%/yr
  - ~6%/yr

- **5-year survival in patients with HCC is <5%*」

- **Time (yrs)**
  - 10
  - 20
  - 30

- **ESLD**
- **HCC**

- **Transplant/Death**

TIMELINE

YEARS

2012  2013  2014  2015  2016  2017

PI + PEG-IFN / RBV

DAA(1) + DAA(2) +/- RBV

DAA(1) + DAA(2) +/- DAA(3)

Liver Biopsy Result:
Figure 1: HCV Lifecycle

(a) Membranous web
(b) 5' (+) RNA
(c) 3'
(d) 3' (-) RNA
(e) 5' (+) RNA
(f) Membranous web

Naggie et al. J Antimicrob Chemother 2010
Chronic HCV prior SOC

- Pegylated IFN + RBV
- 48-72 weeks
- Significant AEs
- Response > GT 2/3

Fried MW, *NEJM* 2002
DAAs Approved in 2014

- **Sofosbuvir**: Nucleotide, All genotypes
- **Ledipasvir**: NS5A, Gen 1, 4, 6
- **Simeprevir**: Protease, Gen 1, 4
- **Daclatasvir**: NS5A, Gen 1, 3, 4, 5, 6
DAAs Approved in 2014

- **Dasabuvir**: Non-Nucleotide
  - Genotype 1,4

- **Ombitasvir**: NS5A
  - Gen 1,2,4

- **Paritaprevir**: Protease
  - Gen 1, 4

USA flags for each entity.
COSMOS: Nucleotide + Protease inhibitor

**Cohort 1**
- GT1 null
- F0-F2
- 78% 1a
- 50% Q80K
- 6% CC

- N=24
- N=15
- N=27
- N=14

**Cohort 2**
- GT1 naïve/null
- F3-F4
- 78% 1a
- 40% Q80K
- 21% CC

- N=30
- N=16
- N=27
- N=14

- SOF 400mg QD + SMV 150mg QD
- +/- RBV (weight-based)

COSMOS: Results

Cohort 1

- 24 R: 4
- 24 No R: 0
- 12 R: 4
- 12 No R: 5

Cohort 2

- SVR4: 96

Relapse in Null treated with RBV

Sofosbuvir plus Daclatasvir: GT1

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Naïve (n=126)</th>
<th>PI Failures (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1a: 79%</td>
<td>1a: 81%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL28CC: 32%</td>
<td>IL28CC: 2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F4*: 14%</td>
<td>F4*: 22%</td>
</tr>
</tbody>
</table>

- n=15 | SOF | SOF/DCV
- n=14 | SOF/DCV
- n=15 | SOF/DCV/R
- n=41 | SOF/DCV/R
- n=41 | SOF/DCV
- n=21 | SOF/DCV
- n=20 | SOF/DCV/R

Sofosbuvir plus Daclatasvir for GT1

No documented virologic failures. All failures due to missing sample/lost to follow-up or re-infection.

Phase 3: Sofosbuvir-Ledipasvir for treatment-experienced GT1 HCV

- **Treatment experienced**
  - Including HCV PI failures
- **20% cirrhosis**
- **LONESTAR**: SOF/LDV ± RBV 12 wks
  - 40 PI failures; 50% cirrhosis
  - 95-100% SVR$_{12}$

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AVIATOR Study: Ritonavir-boosted HCV PI-based IFN-free regimen

• 14-arm study: various combinations of ABT-450/rit, ABT-267, ABT-333, RBV

<table>
<thead>
<tr>
<th>Arm</th>
<th>Weeks</th>
<th>Naïve</th>
<th>Non-R</th>
</tr>
</thead>
<tbody>
<tr>
<td>450/267/333/R</td>
<td>8</td>
<td>68%</td>
<td>61%</td>
</tr>
<tr>
<td>450/267/333</td>
<td>12</td>
<td>28%</td>
<td>3%</td>
</tr>
<tr>
<td>450/267/333/R</td>
<td>24</td>
<td>29%</td>
<td>50%</td>
</tr>
</tbody>
</table>

AVIATOR Study SVR24 Results

- 1% discontinued therapy due to adverse events
- 1% with a serious adverse event
- 2% grade 3 total bilirubin elevation (indirect); 1% grade 3 ALT elevations

Dilemma #1: Do GT-1 HIV patients achieve same SVR with 12W of LDV/SOF?

Naggie et al, CROI 2015 LB152; Afdhal et al. NEJM 2014
ION-4 LDV/SOF X 12W in HIV/HCV

Predictors of relapse

- No difference in SVR in HCV mono-infected ION program (12 weeks) for black (89/90, 99%) versus non-black (431/448, 96%)
- LDV and SOF population PK levels
  - Similar across the different ARV regimens, black and non-black patients, relapse and SVR
- GWAS and whole genome sequencing analysis underway
Dilemma #1: Do GT-1 HIV patients achieve same SVR with P/r/O+D+RBV?

**Treatment Naïve – 12 Weeks**

- HIV/HCV: 93/39/42
- HCV: 96/454/473

**Treatment Experienced – 12-24 weeks**

- HIV/HCV: 90/19/21
- HCV: 96/286/297

<table>
<thead>
<tr>
<th></th>
<th>Simeprevir</th>
<th>Sofosbuvir</th>
<th>Ledipasvir</th>
<th>Daclatasvir</th>
<th>P/r/O + D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DDI</strong></td>
<td>Substrate of CYP3A4, OATP1B1/3</td>
<td>Substrate of P-gp and BCRP</td>
<td>Inhibitor/Substrate of P-gp and BCRP</td>
<td>Inhibitor of OATP1B1/3, BCRP, Substrate of P-gp and CYP3A4</td>
<td>Inhibit/Sub of UGT1A1, OATP1B1/3, BCRP, CYP3A4, CYP2C8, P-gp</td>
</tr>
<tr>
<td><strong>ATV/r</strong></td>
<td>No data</td>
<td>No data</td>
<td>LDV ↑; ATV ↑</td>
<td>DCV ↑*</td>
<td>ATV ↔; ABT450 ↑</td>
</tr>
<tr>
<td><strong>DRV/r</strong></td>
<td>SIM ↑; DRV ↔</td>
<td>SOF ↑; DRV ↔</td>
<td>LDV ↑; DRV ↔</td>
<td>No data</td>
<td>DRV ↓; 3D ↓</td>
</tr>
<tr>
<td><strong>LPV/r</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>LPV ↔; ABT450 ↑</td>
</tr>
<tr>
<td><strong>TPV/r</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td><strong>EFV</strong></td>
<td>SIM ↓; EFV ↔</td>
<td>SOF ↔; EFV ↔</td>
<td>LDV ↓; EFV ↓</td>
<td>DCV ↓*</td>
<td>No PK data**</td>
</tr>
<tr>
<td><strong>RPV</strong></td>
<td>SIM ↔; RPV ↔</td>
<td>SOF ↔; RPV ↔</td>
<td>LDV ↔; RPV ↔</td>
<td>No data</td>
<td>ABT450 ↑; RPV ↑</td>
</tr>
<tr>
<td><strong>ETV</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td><strong>RAL</strong></td>
<td>SIM ↔; RAL ↔</td>
<td>SOF ↔; RAL ↔</td>
<td>LDV ↔; RAL ↔</td>
<td>No data</td>
<td>3D ↔; ↑ RAL</td>
</tr>
<tr>
<td><strong>ELV/cobi</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td><strong>DLG</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td><strong>MVC</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td><strong>TDF</strong></td>
<td>SIM ↔; TFV ↔</td>
<td>SOF ↔; TFV ↔</td>
<td>LDV ↔; ↑TFV</td>
<td>DCV ↔; TFV ↔</td>
<td>3D ↔; TFV ↔</td>
</tr>
</tbody>
</table>

*Courtesy of Jennifer Kiser, PhD*
What is a truly pan-genotypic regimen?

- High efficacy across all genotypes *with*
  - The same treatment duration
  - No need for RBV for some genotypes

- Contenders: most are nucleotide + NS5A
  - SOF/GS-5816
  - SOF/DCV
  - Grazoprevir/Elbasvir
  - The next wave
    - ACH-3102/3422 or ABT-493/ABT-530
The DAAs Have Killed Interferon: Ribavirin Is Next
SVR Decreases All Cause Mortality

General: 18 studies  
n=29,269  
Avg. FU=4.6 years

Cirrhotic: 9 studies  
n=2,734  
Avg. FU=6.6 years

HIV/HCV: 5 studies  
n=2,560  
Avg. FU=5.1 years

% patients after 5 years

General  
SVR: 4.5%  
No SVR: 10.5%

Cirrhotic  
SVR: 3.6%  
No SVR: 11.3%

Co-infected  
SVR: 1.3%  
No SVR: 10.0%

5-Year All Cause Mortality

Saleem, Abst# 44
Clinical Benefits of SVR: Liver Failure, HCC

- 530 Europeans followed for a median 8.4 years after HCV treatment
- 192 (36%) achieved SVR

Price and Cost

- Price of a drug/regimen is set by the pharmaceutical company
  - Reported as Wholesale Acquisition Cost (WAC)
- Wholesale distributors add a mark-up
  - Average Wholesale Price (AWP)
  - This is typically the benchmark on which reimbursement is based
- PBMs (and some insurance plans) negotiate rebates, which determine actual cost
  - These have competitive implications and are confidential
- Mandated discounts with Federal plans
Costs of HCV Therapies?

Wholesale Acquisition Cost (WAC)
12 weeks of Therapy

- SOF: $84,000
- SOF / LED: $94,500
- SIM / SOF: $156,360
- “3D”: $85,820
## Cost-Effectiveness of HCV Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leidner, Hepatology 2015</td>
<td>For 55 y/o treated with $100,000 regimen and SVR = 90%, treating at F2 compared to waiting until F3 had CE = $37,300/QALY. Threshold cost for treating at F0 versus waiting until F1 to yield $50,000/QALY = $22,200.</td>
</tr>
<tr>
<td>Rein, CID 2015</td>
<td>Ledipasvir/sofosbuvir and ombitasvir/paritaprevir/r + dasabuvir tablets compared to no treatment yields $32,000 to $35,000/QALY. Compared to no treatment, threshold cost for treating F0 with all-oral regimen = $47,000.</td>
</tr>
<tr>
<td>Najafzadeh, Annals Int Med 2015</td>
<td>Compared to no treatment in genotype 1, costs per additional QALY gained for ledipasvir/sofosbuvir = $25,291 and Peg-IRN + RBV = $24,833. If ledipasvir/sofosbuvir &lt;$66,000/treatment course, would be cost saving.</td>
</tr>
<tr>
<td>Chhatwal, Annals Int Med 2015</td>
<td>Average ICER for sofosbuvir-based treatment compared to prior SOC = $55,378/QALY. Range = $9,703/QALY for naïve, cirrhotic geno 1 to $410,548 for treatment experienced, geno 3 without cirrhosis.</td>
</tr>
</tbody>
</table>
Are the new HCV regimens cost-effective?

Getting Smart in how we pay for HCV Drugs: KAOS vs CONTROL

Michael S. Saag

CID April 2015