The (ongoing) Evolution of Hepatitis C Treatment

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Topics To Be Covered

• HCV screening update
• Approved HCV treatments
• Progress in HCV drug development
  – IFN-based regimens
  – IFN-sparing strategies
## Lack of Awareness and Associated Deaths

<table>
<thead>
<tr>
<th>Virus</th>
<th>Prevalence</th>
<th>% of Population Unaware of Infection Status</th>
<th>Deaths in 2006 Related to Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>800,000 – 1.4 million</td>
<td>About 65%</td>
<td>3,000</td>
</tr>
<tr>
<td>HCV</td>
<td>2.7 – 3.9 million</td>
<td>About 75%</td>
<td>12,000</td>
</tr>
<tr>
<td>HIV</td>
<td>1.1 million</td>
<td>About 21%</td>
<td>14,016</td>
</tr>
</tbody>
</table>

Sources: CDC; Lin et al, 2007; Hagan et al 2006

## Of people living with HIV in the US:

1 in 3 are co-infected with HCV
1 in 20 are co-infected with HBV
Current CDC recommendations for HCV screening

Screen once (no risk assessment)
- **Adults born 1945-1965**
- Signs of liver disease (persistently elevated ALT)

Uncertain
- Long term sexual partner of HCV+
- STIs or multiple sex partners
- Intranasal drug use
- Tattooing/bodypiercing

Screen based on risk for exposure
- HIV-infected
- Past or present injection drug use
- Received clotting factor concentrates prior to 1987 or other blood products made prior to July 1992 or from known HCV+
- Ever on chronic hemodialysis
- Received tissues/organs prior to July 1992
- Infants of HCV-infected mothers
- Occupational exposures (needle stick or mucosal blood exposure)

Overview of Rapid HCV Test

- **OraQuick Only** FDA approved HCV Rapid Test
  - **Finger stick**, or venipuncture whole blood
  - CLIA waived
  - 20 minute **screening** test
  - Clinical performance with >98% accuracy

Remember:
**Anti-HCV antibody positive = Ever infected**
**HCV RNA to confirm active HCV infection**
Post-test counseling message

• Contact a health-care provider for:
  – medical evaluation of the presence or development of chronic liver disease
  – advice on possible treatment options and strategies
  – advice on how to monitor liver health, even if treatment is not recommended

• Protect the liver from further harm by:
  – considering hepatitis A and B vaccination if susceptible
  – reducing or discontinuing alcohol consumption
  – avoiding new medicines, including over-the-counter and herbal agents without first checking with their health-care provider
  – obtaining HIV risk assessment and testing
  – reduce fatty liver risk by losing weight if overweight or obese, following a healthy diet and staying physically active

• To minimize the risk for transmission to others:
  – do not donate blood, tissue, or semen
  – do not share appliances that might come into contact with blood, such as toothbrushes, dental appliances, razors, and nail clippers

HCV Treatment: IFN-based Regimens
HCV treatment entered a new era with approval of HCV protease inhibitors

The New York Times
Merck’s Hepatitis C Drug Wins F.D.A. Approval
By ANDREW POLLACK
Published May 13, 2011

The Food and Drug Administration approved Vertex Pharmaceuticals Inc.’s hepatitis C drug Incivek on Monday, making it the second new treatment to be approved in the last two weeks.

Case

• 43 African American man with well-controlled HIV presents in consultation to determine if he should be treated for his chronic HCV infection.
  – HIV Hx: RF IVD, dx ’98, on tdf/ftc+ darunavir/r
    • CD4 450 (nadir 170)
    • HIV RNA UD
    • h/o known EFV resistance
  – HCV Hx: RF IVD, dx ’98, no prior treatment

What next? Offer treatment?
More information:

- HCV gt 1a
- HCV RNA 3,500,000 IU/ml
- Stage of liver fibrosis
  - Biopsy in 2011 with bridging fibrosis St 3/4
- IL28B: CT
- No evidence of hepatic decompensation or liver cancer

Does he need treatment now or can he wait until later?

Increased Potential for Significant Drug-Drug Interactions

- Telaprevir
  - CYP3A4 and P-gp substrate
  - CYP3A4 inhibitor
- Boceprevir
  - Aldoketoreductase (AKR) and CYP3A4/5 substrate
  - CYP3A4 and P-gp inhibitor
- Interactions with statins, antiarrhythmics, oral contraceptives, HIV PIs or NNRTIs
- Always check package insert and other drug interaction resources
ARV Drug Interaction Summary: Boceprevir

Table 2. Interaction Between Boceprevir and Antiretroviral Therapies (Source: Merck)

<table>
<thead>
<tr>
<th>Boceprevir dose</th>
<th>ARV</th>
<th>BOC AUCtau</th>
<th>BOC Cmin</th>
<th>ARV AUCtau</th>
<th>ARV Cmin</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOC 800 mg every 8 h</td>
<td>ATV-300 mg</td>
<td>15% (NS)</td>
<td>18%</td>
<td>32%</td>
<td>42%</td>
<td>Avoid co-administration</td>
</tr>
<tr>
<td>BOC 800 mg every 8 h</td>
<td>LPV-400 mg</td>
<td>45%</td>
<td>57%</td>
<td>32%</td>
<td>43%</td>
<td>Avoid co-administration</td>
</tr>
<tr>
<td>BOC 800 mg every 8 h</td>
<td>ATV-100 mg bid</td>
<td>19%</td>
<td>14% (NS)</td>
<td>—</td>
<td>—</td>
<td>Avoid co-administration</td>
</tr>
<tr>
<td>BOC 800 mg every 8 h</td>
<td>EFV 600 mg qds</td>
<td>19%</td>
<td>44%</td>
<td>20%</td>
<td>—</td>
<td>Avoid co-administration</td>
</tr>
<tr>
<td>BOC 800 mg every 8 h</td>
<td>TDF 300 mg qd</td>
<td>18%</td>
<td>18% (NS)</td>
<td>15%</td>
<td>—</td>
<td>Dose: BOC 800 mg every 8 h + TDF 300 mg qd</td>
</tr>
</tbody>
</table>

Abbreviations: ARV, antiretroviral; ATV, atazanavir; AUCtau, area under plasma concentration curve; BOC, boceprevir; Cmin, minimum concentration; bid, twice a day; DRV, darunavir; EFV, efavirenz; LPV, lopinavir; NS, not statistically significant; qhs, at bedtime; r, ritonavir; TDF, tenofovir

SVR-12 with BOC/PR by ARV Regimen

<table>
<thead>
<tr>
<th></th>
<th>PR (N=34)</th>
<th>B/PR (N=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir/r</td>
<td>8/13 (62%)</td>
<td>12/18† (67%)</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>0/10 (0%)</td>
<td>10/15†† (67%)</td>
</tr>
<tr>
<td>Darunavir/r</td>
<td>0/5 (0%)</td>
<td>8/12 (67%)</td>
</tr>
<tr>
<td>Other PI/r*</td>
<td>0/3 (0%)</td>
<td>4/7 (57%)</td>
</tr>
<tr>
<td>Raltegravir**</td>
<td>1/3 (33%)</td>
<td>3/7 (43%)</td>
</tr>
<tr>
<td>Other††</td>
<td>0</td>
<td>0/2 (0%)</td>
</tr>
</tbody>
</table>

†Excludes 2 patients not yet at FW12 but undetectable at FW4 and †† 1 not yet at FW12 but undetectable at FW4.
*Includes saquinavir, fosamprenavir and tipranavir; **Raltegravir without concurrent HIV PI/r; †Other ARVs were maraviroc and efavirenz
HIV Breakthroughs in B/PR Group

Overall, 7 patients had HIV breakthrough (>50 copies HIV RNA at 2 consecutive visits): 3/64 (5%) randomized to B/PR, and 4/34 (9%) to PR

<table>
<thead>
<tr>
<th>Regimen</th>
<th>BL</th>
<th>TW4</th>
<th>TW12</th>
<th>TW24</th>
<th>TW36</th>
<th>EOT</th>
<th>FW4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>---</td>
<td>659</td>
<td>---</td>
<td>53</td>
<td>2990</td>
</tr>
<tr>
<td>†LPV/r</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>55</td>
<td>59</td>
<td>67</td>
<td>68</td>
</tr>
<tr>
<td>ATV/r</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>243</td>
<td>---</td>
<td>7870</td>
<td></td>
</tr>
</tbody>
</table>

ATV/r, atazanavir/ritonavir; LPV/r, lopinavir/ritonavir
†The only subject to change ART. LPV/r changed to ATV/r at TW42; ATV/r to DRV/r at FW24.

ARV Drug Interaction Summary: Telaprevir

| Table 1. Interactions Between Telaprevir and Antiretroviral Therapies (7, 8) |
|-----------------------------|-------------------------------|----------------|----------------|----------------|----------------|
| TVR Dose | ARV | TVR AUC<sub>0-8</sub> | TVR C<sub>m</sub> | ARV AUC<sub>0-8</sub> | ARV C<sub>m</sub> | Comments |
| TVR 750 mg every 8 h | ATV 300/100 qd | 120% | 15% | 117% (INS) | 185% | Dose TVR 750 mg every 8 h + ATV 300/100 mg qd |
| DRV 600/100 mg bid | 136% | 132% | 140% | 142% | Avoid coadministration |
| FPV 700/100 mg bid | 132% | 130% | 137% | 156% | Avoid coadministration |
| LPV 600/100 mg bid | 154% | 102% | 10% (INS) | 114% (INS) | Avoid coadministration |
| TVR 1125 mg every 8 h | EFV 800 mg qhs (with TDF) | 128% | 125% | 118% | 110% | Dose; TVR 1125 mg every 8 h + EFV 800 mg qhs |
| TDF 300 mg qd (with EFV) | 110% | 117% | Dose; TDF 300 mg qd |
| TVR 750 mg every 8 h | TDF 300 mg qd | No change | 13% (INS) | 130% | 141% | Dose; TVR 750 mg every 8 h + TDF 300 mg qd |
| TVR 750 mg every 8 h | RAL 400 mg bid | 17% (INS) | 114% | 131% | 178% | Dose; TVR 750 mg every 8 h + RAL 400 mg bid |

Abbreviations: ARV, antiretroviral; ATV, atazanavir; AUC<sub>0-8</sub>, area under plasma concentration curve; C<sub>m</sub>, minimum concentration; bid, twice a day; DRV, darunavir; EFV, efavirenz; FPV, fosamprenavir; LPV, lopinavir; NS, not significant; qd, once a day; qhs, at bedtime; r, low-dose ritonavir; RAL, ritonavir; TDF, tenofovir; TVR, telaprevir.

Thomas et al. CID, 2011
### HIV/HCVg1 Recommendations:

**Peg/R + BOC or TEL:**

<table>
<thead>
<tr>
<th></th>
<th>BOC</th>
<th>TEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ART</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>RAL + 2 NRTI</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>EFV + 2 NRTI</td>
<td></td>
<td>X*</td>
</tr>
<tr>
<td>ATV/r + 2 NRTI</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Other ART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Increased dose TEL

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**Back to Case:**

ARVS were switched to tdf/ftc + atazanavir /r 3 months prior to treatment and patient remained undetectable on it

Baseline factors:
- HCV 1a: 3.5 million IU/ml
- CBC: WBC 3.4, Hgb 14.4, Plt 175
- Peg-2a 180mg SC qwk
- RBV 600mg PO BID
- Telaprevir 750 mg PO TID with food containing 20 g of fat begun
3 Drug Combo for HCV: 2013

**8AM**
- TVR +
- RBV +
- Peg

Within 30 min of food including 20 g of fat

**4PM**

**12 MID**

**PegIFN+RBV+PI Ph 3 Results: G1 Rx Naive**

<table>
<thead>
<tr>
<th>Study</th>
<th>SVR (%)</th>
<th>RVR (%)</th>
<th>D/C AEs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILLUMINATE (Telaprevir 12, PegIFN/RBV 24-48)</td>
<td>Overall Study (T12PR24-48)</td>
<td>72</td>
<td>72 (eRVR 65%)</td>
</tr>
<tr>
<td></td>
<td>eRVR randomized to 24 wks (T12PR24)</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td></td>
<td>eRVR randomized to 48 wks (T12PR48)</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ADVANCE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SVR (%)</td>
<td>RVR (%)</td>
<td>D/C AEs (%)</td>
</tr>
<tr>
<td></td>
<td>Cauc AA</td>
<td>75</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>RVR 8 wk</td>
<td>69</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>9</td>
<td>3.6</td>
</tr>
<tr>
<td>HCV SPRINT-2 (PegA2B/RBV 4wk lead in followed by Boceprevir 800 tid, PegIFN2b, RBV 48 wk OR Resp-guided)</td>
<td>Boceprevir (PR4/BPR44)</td>
<td>66</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>Resp-guide boceprevir (PR4/BPR24/+-PR)</td>
<td>63</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Control (PR 48)</td>
<td>38</td>
<td>23</td>
</tr>
</tbody>
</table>

~30% Improvement over Peg/r alone
TVR & Anorectal complaints

- 29% with Peg/r/TVR experienced anorectal compared to 7% peg/r alone
- E.g. Hemorrhoids, anorectal discomfort, anal pruritus, and rectal burning
  - Onset typically within the first 4 weeks
  - Usu mild to moderate in severity
  - Less than 1% led to treatment discontinuation
- Events resolved during or after completion of TVR

Tolerability of Pis in HIV/HCV

TVR Generally well tolerated
- 7 (18%) SAEs in TVR arms (9% control)
  - No cases of severe rash (grade 3/4)
  - 3 discontinuations due to AEs (0 in P/R control arm)

<table>
<thead>
<tr>
<th>%</th>
<th>TVR/ P+R</th>
<th>P+R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>34</td>
<td>23</td>
</tr>
<tr>
<td>Pruritus</td>
<td>40</td>
<td>9</td>
</tr>
<tr>
<td>Rash</td>
<td>34</td>
<td>23</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>21</td>
<td>9</td>
</tr>
<tr>
<td>Depression</td>
<td>21</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>9</td>
</tr>
</tbody>
</table>

BOC Generally well tolerated
- 11 (17%) SAEs in BOC treated (21% control arm)
- 20% discontinuation due to AE (9% control)

<table>
<thead>
<tr>
<th>%</th>
<th>BOC / P+R</th>
<th>P+R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgeusia</td>
<td>28</td>
<td>15</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28</td>
<td>18</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>36</td>
<td>21</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28</td>
<td>15</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>Anemia</td>
<td>41</td>
<td>26</td>
</tr>
</tbody>
</table>
Case: Week 4

Rectal discomfort improved with topical hydrocortisone and increased fat consumption.

Wk 4 HCV RNA: 4000 IU/ml
CBC: WBC 1.7, Hgb 11.2, Plt 107

Case: Week 5

• Patient was continued on TVR/Peg/RBV (did not follow recommendations)
• HCV RNA was repeated in 1 week

• HCV RNA: 6500 IU/ml
• Instructed to stop treatment
Patients Who Met the >1000 IU/mL HCV RNA Week 4 Futility Rule: TVR

Lessons Learned with BOC and TEL

- RBV still needed
- Response-guided therapy for naïve and relapsers
- Appropriate futility stopping rules differ from Peg/R
- “Traditional” predictors response less important
  - Advanced fibrosis harder to treat
- Genotype subtype (e.g. 1a v. 1b) matters
- Prior response to PegIFN/RBV predicts response
- Lead-in response with PegIFN/RBV predicts response
- Drug interactions, esp. with ARVs
- Anemia management by dose reduction
- Resistance emergences with virologic failure (esp. breakthrough)
Next Generation HCV PIs + PegIFN/RBV

- Once/day
- Less side effects
- Higher SVRs
  - But not directly compared to BOC or TEL
- More subjects qualified for shorter duration (RGT)
  - Higher RVR rates
- Higher barrier to resistance
- Additional drug interactions worked out
  - E.g. faldaprevir with darunavir/r

A Potential Evolution Scenario for HCV G1

Next generation:
- Once/day
- Less SEs
- Better SVRs
- Shorter duration

1st Stage
1989-1998
35%
10%
PEG-IFN +
ribavirin

2nd Stage
1998-2001
42-50%

3rd Stage
2001-2011
65-70% to est. 90%

4th Stage
2011-current

5th Stage
2011-2014

6th Stage
2014+

All Oral Therapy

?
### Anti-HCV DAA Names 101

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

--- **ASVIR**
- NS5A inhibitors
  - e.g. daclatasvir, ledipasvir

--- **BUVIR**
- Nucleos(t)ide analogs
  - e.g. tegobuvir, sofosbuvir
Anti-HCV DAA Names 101

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---ASVIR
- NS5A inhibitors
  - e.g. daclatasvir, ledipasvir

---BUVIR
- Nucleos(t)ide analogs = “base pairs”
  - e.g. tegobuvir, sofosbuvir

ATOMIC: Sofosbuvir (GS-7977) + PegIFN/RBV in Rx-Naive G1 Patients

- SVR12 in ~ 90% patients with 12 or 24 wks of treatment
- High rates of SVR12 in genotype 4/6 with 24 wks of treatment
- Sofosbuvir well tolerated up to 24 wks

- 11 patients (1 in 12-wk group) who attained SVR12 subsequently lost to follow-up
- No relapse after SVR12 in any group

- 11/11 patients with genotype 4 HCV achieved RVR and EOT response
  - 2 LTFU without posttreatment data
- No relapse after SVR12 in either group

NEUTRINO: Sofosbuvir + PegIFN/RBV in Rx-Naïve G1,4,6 Patients (n=327)

Results: SVR12 by HCV Genotype

HCV Treatment: IFN-sparing Regimens
**Proof of Principle**

*Daclatasvir + Asunaprevir ± PegIFN/RBV for 24 Wks in GT1 Null Responders*

**Slides #44 & #45**

- **Slide #44**
  - **Stratified by HCV subgenotype**
  - **Week 24**
  - **Follow-up 48 wks**
  - **BMS-790052 60 mg QD + BMS-650032 600 mg BID (n = 11)**
  - **BMS-790052 60 mg QD + BMS-650032 600 mg BID + PegIFN/RBV (n = 10)**

*< 2 log10 IU/mL decline in HCV RNA with ≥ 12 wks of pegIFN/RBV.*

- **In dual therapy arm, 2/2 GT1b vs 2/9 GT1a patients reached SVR12 and SVR24**
- **No viral breakthrough with quadruple therapy**
- **BMS-790052 and BMS-650032 alone or with pegIFN/RBV generally well tolerated**

**Lok A, et al. NEJM, 2012**

<table>
<thead>
<tr>
<th>Undetectable HCV RNA, % (n)</th>
<th>BMS-790052 + BMS-650032 (n = 11)</th>
<th>BMS-790052 + BMS-650032 + PR (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVR</td>
<td>64% (7)</td>
<td>60% (6)</td>
</tr>
<tr>
<td>SVR12</td>
<td>36% (4)</td>
<td>100% (10)</td>
</tr>
<tr>
<td>SVR24</td>
<td>36% (4)</td>
<td>90% †(9)</td>
</tr>
</tbody>
</table>

*1 patient not achieving SVR24 had HCV RNA < 25 IU/mL at EOT and undetectable on retesting at Day 35 of follow-up.

**Slide #45**

- **Sofosbuvir (GS-7977) + RBV**
- **for 12 wks in Naïve & Null Responders**

<table>
<thead>
<tr>
<th>Genotype 2/3 Treatment-naïve (GS-7977 + RBV)</th>
<th>SVR24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1 Null Responders (GS-7977 + RBV)</td>
<td>SVR12</td>
</tr>
<tr>
<td>Genotype 1 Treatment-naïve (GS-7977 + RBV)</td>
<td>SVR12</td>
</tr>
</tbody>
</table>

**Gene E, et al. #540 CROI 2012; Gane et al, EASL, Apr2012**
**FISSION** = Ph 3: Sofosbuvir + RBV for 12 Weeks vs. PEG/RBV for 24 Weeks in Rx-Naïve GT 2/3

Results: SVR12 Rates by HCV Genotype

- **Overall**: 67% (SOF + RBV) vs. 97% (Peg-IFN + RBV)
- **Sofosbuvir + RBV**: 170/239 vs. 180/243 vs. 68/72
- **Peg-IFN + RBV**: 96/137 vs. 46/56 vs. 62/69

Results: SVR12 by Genotype and Cirrhosis

- **GT 2**
  - No cirrhosis: 98% (SOF + RBV) vs. 82% (Peg-IFN + RBV)
  - Cirrhosis: 91% (SOF + RBV) vs. 62% (Peg-IFN + RBV)

- **GT 3**
  - No cirrhosis: 61% (SOF + RBV) vs. 71% (Peg-IFN + RBV)
  - Cirrhosis: 34% (SOF + RBV) vs. 30% (Peg-IFN + RBV)

*Mark bars represent 95% confidence intervals.*

**FUSION** studied 12 v. 16 wks w/ improved SVR for g3 & cirrhosis.

Failure = Relapse
No resistance described

Lawitz, NEJM 2013.

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**ELECTRON**: Sofosbuvir + Ledipasvir + RBV for 12 wks in G1 Naïve and Null Responders

**Patients with HCV RNA < LOD* over Time, n/N (%)**

<table>
<thead>
<tr>
<th></th>
<th>SOF + RBV</th>
<th>SOF + LDV + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naïve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Null responder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>8/25 (32)</td>
<td>11/25 (44)</td>
</tr>
<tr>
<td>Week 2</td>
<td>17/25 (68)</td>
<td>22/25 (88)</td>
</tr>
<tr>
<td>Week 4</td>
<td>25/25 (100)</td>
<td>25/25 (100)</td>
</tr>
<tr>
<td>EOT</td>
<td>25/25 (100)</td>
<td>25/25 (100)</td>
</tr>
<tr>
<td>SVR4</td>
<td>22/25 (88)</td>
<td>25/25 (100)</td>
</tr>
<tr>
<td>SVR12</td>
<td>21/25 (84)</td>
<td>25/25 (100)</td>
</tr>
</tbody>
</table>

*Analyzed by TaqMan® HCV Test 2.0 with limit of detection (LOD) of 15 IU/mL.
*Includes 1 patient who stopped all treatment due to an SAE at week 8; this patient subsequently achieved SVR24.

Gane et al. CROI 2013. Abstract 41LB.
**Slide #48**

**Daclatasvir + Sofosbuvir ± RBV for 12 or 24 wks in Rx-naive**

- Very high SVR24 rates with all 24-wk regimens across genotypes
- Similar high SVR4 rates with 12-wk regimens
  - SVR12 in all 68 pts who have reached time point


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**Slide #49**

**Daclatasvir + Sofosbuvir ± RBV for 24 wks in BOC/TEL failures**

- No virologic breakthrough or treatment discontinuations through EOT

* 1 patient missing at post-treatment (PT) Week 12: HCV RNA was undetectable at PT Week 4 and at PT Week 24 (preliminary)
  - 21/41 patients have reached PT Week 24; all have achieved SVR12
AVIATOR: ABT 450/r + 267 + 333 ± RBV for 12 or 24 wks in G1 Naïve and Null Responders

Response Rates, All Groups, N=571

<table>
<thead>
<tr>
<th>Regimen/Duration</th>
<th>SVR12 %</th>
<th>SVR12* %</th>
<th>Breakthrough/Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-450 ABT-267 ABT-333 RBV</td>
<td>89</td>
<td>88</td>
<td>0/10</td>
</tr>
<tr>
<td>ABT-450 ABT-333 RBV</td>
<td>85</td>
<td>83</td>
<td>1/4</td>
</tr>
<tr>
<td>ABT-450 ABT-267 RBV</td>
<td>91</td>
<td>89</td>
<td>1/8</td>
</tr>
<tr>
<td>ABT-450 ABT-267 ABT-333</td>
<td>90</td>
<td>87</td>
<td>1/5</td>
</tr>
<tr>
<td>ABT-450 ABT-267 ABT-333 RBV</td>
<td>99</td>
<td>96</td>
<td>0/1</td>
</tr>
<tr>
<td>ABT-450 ABT-267 ABT-333</td>
<td>93</td>
<td>90</td>
<td>0/2</td>
</tr>
</tbody>
</table>

Kowdley et al. AASLD 2012 LB-1

COSMOS: Simeprevir + Sofosbuvir ± RBV for 12 and 24 wks in G1 Null Responders

<table>
<thead>
<tr>
<th>Patients</th>
<th>24 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>SMV + SOF + RBV</td>
<td>SMV + SOF</td>
</tr>
<tr>
<td>RVR1, n/N (%)</td>
<td>18/22 (81.8)</td>
<td>10/15 (66.7)</td>
</tr>
<tr>
<td>Undetectable end of treatment, n/N (%)</td>
<td>10/12 (83.3)</td>
<td>8/9 (88.9)</td>
</tr>
<tr>
<td>Relapse, n</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SVR4, n/N (%)</td>
<td>4/6 (66.7)</td>
<td>5/5 (100.0)</td>
</tr>
<tr>
<td>SVR8, n/N (%)</td>
<td>4/6 (66.7)</td>
<td>5/5 (100.0)</td>
</tr>
</tbody>
</table>

Of the patients in the 12 week arms who achieved SVR8:
- 24/24 who reached post-treatment Week 12 had undetectable HCV RNA (SVR12)
- 28/28 who reached post-treatment Week 24 had undetectable HCV RNA (SVR24)

Lawitz et al. CROI 2013. Abstract 155LB
HIV/HCV: Treat Now or Later? Individualized Decision

Treat now:
- Advanced liver disease (but not decompensated)
  - Lower response
  - More complications
- Cryoglobulinemia or HCV-related symptoms
- High likelihood of response
  - Favorable IL28B or HCV geno
- Desires treatment
- Acute HCV
  - High response rates with Peg/r

Treat later:
- IFN unwilling
- IFN intolerant
- IFN contraindicated
- Drug interaction (e.g. no compatible ARV options or salvage ARV regimen)
- Prior null responders?
  - Lower response rates, esp. if not IFN responsive
  - Lack of data about Cirrhotics with newer agents

CONSIDER A WELL-DESIGNED CLINICAL TRIAL

Summary
- HCV common in US and many remain unaware of diagnosis
  - Screen baby boomers and risk-based screening
  - Good time to link patients to care
- Currently approved treatments offer improved response for HCV G1
  - But side effects, drug interactions and low response rates for cirrhosis, prior null responders
- New drugs promise less side effects, high SVR rates, and potential for IFN-sparing regimens
  - More data still needed for conventionally hard to treat e.g. cirrhosis, prior null response, ESRD, HIV
Thank you