The Pipeline of New HCV Therapies: What to Expect in the Next 5 Years

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University of Chicago
Learning Objectives

Upon completion of this presentation, learners should be better able to:

• Understand the evolving landscape of hepatitis C therapy and the preliminary efficacy

This presentation includes discussion of investigational agents.
Do you think that HCV therapy will be all oral in the next 5 years?

1. Yes for all patients
2. Yes for most patients
3. Yes for a few patients
4. No - not for any patients
Do you think that HCV will be treated by primary care physicians in the next 5 years?

1. Yes for nearly all patients
2. Yes for most patients
3. Yes for rare patients
4. No PCPs will not treat HCV
Affordable

Pan-Genotypic

Convenient

Potent • Safe • Oral

- Daily or twice a day dosing
- Easy: short duration, simple rules
- No Drug Interactions

- >80% SVR
Why SOC *needs* to be all oral

- Interferon toxicity
  - Interferon incapable
  - Interferon intolerant
- Interferon null responders
- Limited treatment access due to expertise required
  - In the U.S., there are ~4000-6000 ‘treaters’, but 80% of patients are treated by 20% of physicians
Can all oral therapy change the treatment paradigm?

Perhaps the most important question
Promising Therapeutic Targets for Direct Acting Antiviral Drug Development

Hepatitis C Virus Polyprotein

Structural Proteins
- Core
- E1
- E2
- P7

Non-Structural Proteins
- NS2
- NS3
- 4A
- NS4B
- NS5A
- NS5B

Protease Inhibitors
- High Potency
- Multi-genotypic coverage
- Intermediate to high barrier to resistance

NS5A Inhibitors
- High Potency
- Multi-genotypic coverage
- Low to intermediate barrier to resistance

NS5B Nucleoside Inhibitors
- Intermediate Potency
- Pan-genotypic coverage
- High barrier to resistance

NS5B Non-Nucleoside Inhibitors
- Intermediate Potency
- Limited genotypic coverage
- Low barrier to resistance

## New Drug Development

<table>
<thead>
<tr>
<th>Approval</th>
<th>Protease inhibitors</th>
<th>Polymerase inhibitors</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir</td>
<td>Telaprevir</td>
<td>GS-7977</td>
<td>BMS790052</td>
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<tr>
<td>BI-1335</td>
<td>TMC-435</td>
<td>RG-7128</td>
<td>ABT-333</td>
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<tr>
<td>RG7227r</td>
<td>ABT-450r</td>
<td>IDX184</td>
<td>ABT-072</td>
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<tr>
<td>GS-9451</td>
<td>MK-5172</td>
<td>PSI-938</td>
<td>GS-9190</td>
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<tr>
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<td>BMS650032</td>
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<td>Filibuvir</td>
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<td>PHX-1766</td>
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<td>CTS-1027</td>
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Preclinical

Slide compliments of Donald Jensen
INTERFERON CONTAINING NOVEL REGIMENS
Six Weeks of a **NS5A Inhibitor (GS-5885), Protease Inhibitor (GS-9451) plus Peginterferon/Ribavirin (PR)** Achieves High SVR4 Rates in genotype 1 IL28B CC Treatment Naïve HCV Patients: Interim Results of a Prospective, Randomized Trial

- PR+GS-5885+GS-9451 (Arm 1) vs PR (Arm 2)
- Arm 1: If HCV RNA <LLQ (vRVR) at **Week 2** with Week 4 RVR, re-randomized to receive 6 or 12 weeks
- Arm 2: If HCV RNA<LLQ at Week 4, received 24 weeks of PR
- Quad therapy for 24 weeks for vRVR failures in Arm 1, RVR failures in Arm 2

<table>
<thead>
<tr>
<th>Virologic Response</th>
<th>GS-5885 + GS-9451 + PEG/RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1 (n=94)</td>
<td>51/90 (54%)</td>
</tr>
<tr>
<td>Week 2 (n =91)</td>
<td>81/86 (95%)</td>
</tr>
<tr>
<td>Week 4 (n=74)</td>
<td>71/71(100%)</td>
</tr>
<tr>
<td>Week 6 (n=64)</td>
<td>64/64 (100%)</td>
</tr>
</tbody>
</table>

MATTERHORN Study: Phase II Study of Partials and Nulls

- Randomized (1:1:1), open-label, multicentre, parallel study of 2 cohorts
- Stratification: G1a/G1b

**Cohort A: G1 Prior Partial Responders**

- n=52: IFN-free: MCB + DNVr + RBV (Follow-up)
- n=49: Triple: DNVr + PR (Follow-up)
- n=50: QUAD: MCB + DNVr + PR (Follow-up)

**Cohort B: G1 Prior Null Responders**

- n=77: IFN-free: MCB + DNVr + RBV (Follow-up)
- n=77: QUAD: MCB + DNVr + PR (Follow-up)
- n=74: QUAD: MCB + DNVr + PR (Follow-up, PR)

Weeks:

- 0
- 12
- 24
- 36
- 48
- 72

DNVr = danoprevir/ritonavir 100 mg/100 mg BID; MCB = mericitabine 1000 mg BID; PR = peginterferon alfa-2a (40KD) 180 μg/week plus ribavirin 1000 mg or 1200 mg/day

**MATTERHORN Study:**
**High SVR in Genotype 1 Null responders**

**Efficacy of IFN-free Treatment for G1b**

<table>
<thead>
<tr>
<th>Virological Response (%) Patients</th>
<th>Prior Partial Response</th>
<th>Prior Null Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>EOT</td>
<td>20/23</td>
<td>28/32</td>
</tr>
<tr>
<td>SVR4</td>
<td>10/23</td>
<td>21/31</td>
</tr>
<tr>
<td>SVR12</td>
<td>9/23</td>
<td>17/31</td>
</tr>
<tr>
<td><strong>Virological Response (%) Patients</strong></td>
<td><strong>Prior Partial Response</strong></td>
<td><strong>Prior Null Response</strong></td>
</tr>
<tr>
<td>EOT</td>
<td>87</td>
<td>88</td>
</tr>
<tr>
<td>SVR4</td>
<td>44</td>
<td>68</td>
</tr>
<tr>
<td>SVR12</td>
<td>39</td>
<td>55</td>
</tr>
</tbody>
</table>

**Efficacy of DNVr +PR and QUAD for 24 Weeks**

<table>
<thead>
<tr>
<th>Virological Response (%) Patients</th>
<th>Prior Partial Response</th>
<th>Prior Null Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>EOT</td>
<td>46*/49</td>
<td>73/76*</td>
</tr>
<tr>
<td>SVR4</td>
<td>47/50</td>
<td>63/74</td>
</tr>
<tr>
<td>SVR12</td>
<td>45/50</td>
<td>62/74</td>
</tr>
<tr>
<td><strong>Virological Response (%) Patients</strong></td>
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</tr>
<tr>
<td>EOT</td>
<td>94</td>
<td>96</td>
</tr>
<tr>
<td>SVR4</td>
<td>94</td>
<td>85</td>
</tr>
<tr>
<td>SVR12</td>
<td>90</td>
<td>84</td>
</tr>
</tbody>
</table>

*Awaiting f/u on 1 pt in A2 and 2 patients in B2, all EOT responders

SVR12 by Subtype: Addition of MCB Improves SVR12 in G1a by 45%

- **Genotype 1a**
  - Triple DNVr + P/R: 75%
  - QUAD: DNVr + MCB + P/R: 73%

- **Genotype 1b**
  - Partial Responders: 91%
  - Partial Responders + MCB: 96%
  - Null Responders: 100%

SVR in G1 Null Responders with DCV (NS5A) and ASV (NS3) ± PR

- N=101 null responders
- Mean viral load 6.5 log
- G1b:
  - A1–2: 100%
  - B1–3: 14%
- F3 or higher 15-41%
- One IL28B CC (A1)

Prior null responders to PR

A1 (DUAL): DCV 60 mg QD + ASV 200 mg BID (G1b only)
A2 (DUAL): DCV 60 mg QD + ASV 200 mg QD (G1b only)
B1 (QUAD): DCV 60 mg QD + ASV 200 mg BID + PR (G1a/1b)
B2 (QUAD): DCV 60 mg QD + ASV 200 mg QD + PR (G1a/1b)
B3 (TRIPLE): DCV 60 mg QD + ASV 200 mg BID + RBV (G1a/1b)

Follow-Up

Week 24
SVR12 Primary endpoint
SVR48

Week 12
SVR4
SVR24

• 2 patients relapsed — 1 at PT Week 4 (B1); 1 at PT Week 12 (B2)
• Safety
  – DUAL: Headache and diarrhea most common AEs
  – QUAD: Addition of IFN AEs
• Resistance: Failure results in dual class (NS5A and NS3) resistance

*1 pt missed 24 wk follow up – failure on ITT analysis

Interferon-free, oral direct acting antiviral regimens
Protease or Nucleoside as Backbone?

• Protease inhibitor backbone ± NS5A inhibitor ± non-nucleoside polymerase inhibitor ± ribavirin
  – Danoprevir/r + mericitabine + ribavirin Genentech
  – Telaprevir + VX-222 + ribavirin Vertex
  – Faldaprevir + BI7227 + ribavirin Boehringer Ingelheim
  – ABT450/r + ABT267 + ABT333 ± ribavirin Abbott
  – Asunaprevir + daclatasvir ± BMS-325 BMS

• Nucleotide analogue polymerase inhibitor backbone with ribavirin or NS5A inhibitor/ribavirin
  – Sofosbuvir + daclatasvir ± ribavirin
  – Sofosbuvir + ribavirin
  – Sofosbuvir + GS5885 + ribavirin
  – Sofosbuvir + simeprevir
MATTERHORN Study: High SVR in Genotype 1 Null responders

Efficacy of IFN-free Treatment for *G1b*

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Efficacy of DNVr +PR and QUAD for 24 Weeks

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*Awaiting f/u on 1 pt in A2 and 2 patients in B2, all EOT responders

ZENITH Study: VX-222 + Telaprevir + Ribavirin

Phase 2b

Treatment-naïve
Genotype 1

Genotype 1b (n=23)

VX-222 (400 mg bid) +
Telaprevir (1125 mg bid)
+ RBV

Follow-Up*

PR*

Genotype 1a (n=23)

VX-222 (400 mg bid) +
Telaprevir (1125 mg bid)
+ RBV

Follow-Up*

PR*

Week 0  12*  24  36

PR: pegIFN + RBV (weight-based dosing: 1000-1200 mg).
HCV RNA $\geq 5 \log_{10}$ IU/mL; no cirrhosis (nonblack: 83%)

*Patients undetectable HCV RNA at weeks 2 and 8 discontinue treatment at week 12. Patients with
detectable HCV RNA at week 2 or 8 started PR at week 12 (until 24 weeks of PR are received).

ZENITH: Interim SVR12 Results

**Faldaprevir (PI) + Non-nucleoside polymerase inhibitor with or without ribavirin (16, 28 or 40 weeks)**

- **Phase IIb,** multicenter, open-label, randomized (1:1:1:1:1)\(^a\)
  - Treatment-naïve patients with chronic HCV GT-1
- Stratified by GT-1 subtype (1a vs 1b) and IL28B (CC vs non-CC)
- **Compensated cirrhosis included,** 18–75 years of age, HCV RNA >100,000 IU/mL
- **Stopping rule:** HCV RNA detectable between Weeks 6 and 8
- **Primary endpoint:** SVR 12 weeks after treatment completion

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**A Randomization to the non-RBV arm stopped early (FDA request based on perceived increased risk of breakthrough with other interferon-free and RBV-free combinations)**

- First dose of faldaprevir = 240 mg and BI 207127 = 1200 mg
- RBV dose, 1000 mg/day (<75 kg body weight) or 1200 mg/day (≥75 kg body weight)
- BID, twice daily; GT, genotype; QD, once daily; RBV, ribavirin; SVR, sustained virologic response; TID, three-times daily

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Soriano V, et al. 63rd AASLD; Boston, MA; November 9-13, 2012. Abst. 84.
SVR12 According to HCV Subtype (ITT)

IT, intention-to-treat
All groups received faldaprevir 120 mg QD for the same duration as BI 207127 (16, 28, or 40 weeks)

Soriano V, et al. 63rd AASLD; Boston, MA; November 9-13, 2012. Abst. 84.
SOUND-C2 Study sub-analysis: Efficacy and Safety of the IFN-free Combination of BI 201335 + BI 207127 ± RBV in Treatment-naive G1 Patients with Compensated Liver Cirrhosis

- SOUND-C2 (N=362); 33 patients (9%) had liver cirrhosis (liver biopsy or Fibroscan)
- Pooled data from pts who received BI 207127 TID + RBV (TID16W, TID28W and TID40W)

Soriano V, et al. 63rd AASLD; Boston, MA; November 9-13, 2012. Abst. 84.
ABT450/r (PI) + ABT267 (NS5A)+/- ABT333 (NNI) + RBV in Treatment Naive and Null Responders

<table>
<thead>
<tr>
<th>Regimen/Duration</th>
<th>ABT-450/r Dose (QD)</th>
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<tbody>
<tr>
<td>ABT-450 ABT-267 ABT-333 RBV</td>
<td>150/100</td>
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<tr>
<td>ABT-450 ABT-267 ABT-333 RBV</td>
<td>150/100</td>
</tr>
<tr>
<td>ABT-450 ABT-267 ABT-333 RBV</td>
<td>100/100,200/100</td>
</tr>
<tr>
<td>ABT-450 ABT-267 ABT-333 RBV</td>
<td>100/100,150/100</td>
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<td>ABT-450 ABT-267 ABT-333 RBV</td>
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</tr>
<tr>
<td>ABT-450 ABT-267 ABT-333 RBV</td>
<td>100/100,150/100</td>
</tr>
</tbody>
</table>

ABT-267 25mg QD; ABT-333 400mg BID; RBV weight-based 1000-1200 mg daily dose divided BID
All patients to be followed through 48 weeks post-treatment

SVR12 Rates (ITT) for 8- and 12-Week Arms

Percentage of patients (ITT) achieving SVR12

8 weeks

<table>
<thead>
<tr>
<th>Treatment-naïve Patients</th>
<th>12 weeks</th>
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</thead>
<tbody>
<tr>
<td>Naïve 450+267+333+RBV 8 Week</td>
<td>Naïve 450+333+RBV</td>
</tr>
<tr>
<td>Naïve RBV-free</td>
<td>Naïve 450+267+333+RBV 12 Week</td>
</tr>
<tr>
<td>Null 450+267+333+RBV 8 Week</td>
<td>Null 450+267+RBV</td>
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</tbody>
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<thead>
<tr>
<th>Treatment-naïve Patients</th>
<th>12 weeks</th>
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<tbody>
<tr>
<td>ABT-450</td>
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<tr>
<td>ABT-267</td>
<td>ABT-267</td>
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<tr>
<td>ABT-333</td>
<td>ABT-333</td>
</tr>
<tr>
<td>RBV</td>
<td>RBV</td>
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</table>

null responders

<table>
<thead>
<tr>
<th>Null Responders</th>
<th>12 weeks</th>
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<tbody>
<tr>
<td>ABT-450</td>
<td>ABT-450</td>
</tr>
<tr>
<td>ABT-267</td>
<td>ABT-267</td>
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<tr>
<td>ABT-333</td>
<td>ABT-333</td>
</tr>
<tr>
<td>RBV</td>
<td>RBV</td>
</tr>
</tbody>
</table>

Daclatasvir (NS5A) + Asunaprevir (PI) + Non-nucleoside polymerase inhibitor (no ribavirin)

- **Patients:** treatment-naïve, non-cirrhotic, HCV GT 1 stratified by subtype 1a/1b
- **Treatment:** DCV 60 mg QD + ASV 200 mg BID + BMS-791325 either 75 mg BID (Part 1) or 150 mg BID (Part 2)
- **HCV RNA endpoints:** per FDA guidance, HCV RNA < LLOQTD = target detected but below the assay lower limit of quantitation (LLOQ; 25 IU/mL); LLOQTND = below LLOQ and target not detected (previously referenced as HCV RNA undetectable or < LOD; ≈ 10 IU/mL for this study)
- **Primary endpoint:** HCV RNA < LLOQ 12 weeks post treatment (SVR12)
  - Modified intent-to-treat analysis: missing, breakthrough, or relapse = failure
- **Interim analysis:** Part 1 results reported through post treatment week 4 (Group 1; SVR4) or post treatment week 12 (Group 2; SVR12); Part 2 enrolled and ongoing, results not yet available

HCV RNA Endpoints: Modified Intention-to-Treat Analysis

HCV RNA Endpoints:
Modified Intention-to-Treat Analysis

24-Week Treatment
Group 1, N = 16

100 94 94

HCV RNA < LLOQ_TD or TND

Missing data

Patients achieving endpoint (%)

Study Week

4 12 EOT PT 4 (SVR_4)

100 94 94

HCV RNA < LLOQ_TD or TND

Missing data

12-Week Treatment
Group 2, N = 16

100 88 100

HCV RNA < LLOQ_TD or TND

Missing data

Patients achieving endpoint (%)

Study Week

4 12 EOT PT 4 (SVR_4) PT 12 (SVR_12)

100 94 94 % < LLOQ

Study Week

4 12 EOT PT 4 (SVR_4) PT 12 (SVR_12)

100 94 94 % < LLOQ


a Includes 1 patient with HCV RNA 118 IU/mL at last on-treatment visit but < LLOQTD 2 and 4 weeks post treatment (SVR4).
b EOT, end of treatment; includes patients who discontinued prior to the protocol-defined last treatment visit.
< LLOQTD or TND, HCV RNA below assay lower limit of quantitation (25 IU/mL) and target detected (LLOQTD) or target not detected (LLOQTND; HCV RNA < LOD ≈ 10 IU/mL, previously reported as HCV RNA undetectable); PT, posttreatment.
Nucleoside or Protease as Backbone?

- Protease inhibitor backbone ± NS5A inhibitor ± non-nucleoside polymerase inhibitor ± ribavirin
  - Telaprevir + VX-222 + ribavirin
  - Faldaprevir + BI7227 + ribavirin
  - ABT450/r + ABT267 + ABT333 ± ribavirin
  - Asunaprevir + daclatasvir ± BMS-325

- Nucleotide analogue polymerase inhibitor backbone with ribavirin or NS5A inhibitor/ribavirin
  - Sofosbuvir + ribavirin
  - Sofosbuvir + daclatasvir ± ribavirin
  - Sofosbuvir + GS5885 + ribavirin
  - Sofosbuvir + simeprevir
ELECTRON Study: Sofosbuvir + Ribavirin

- **Phase 2b**

  **Treatment-Naïve**
  - Genotype 2, 3 (n=10)
  - Sofosbuvir 400 mg qd + PR

  **Null Responders**
  - Genotype 1 (n=10)
  - Sofosbuvir 400 mg qd + RBV

  **Treatment-Naïve**
  - Genotype 1 (n=25)
  - Sofosbuvir 400 mg qd + RBV

  **Treatment-Experienced**
  - Genotype 2, 3 (n=25)
  - Sofosbuvir 400 mg qd + RBV

Sofosbuvir (NS3/4A inhibitor). PR: pegIFN + RBV.
HCV RNA ≥50,000 IU/mL. No cirrhosis.
Weight-based ribavirin dosing (800-1200 mg).

ELECTRON: SVR in HCV Genotype 2/3

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR12</th>
<th>SVR24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-Naïve</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Sofosbuvir + RBV 8 weeks (n=10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-Experienced</td>
<td></td>
<td>68%</td>
</tr>
<tr>
<td>Sofosbuvir + RBV 12 weeks (n=25)</td>
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<td></td>
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</tbody>
</table>

# 7977 G2/3 Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Genotype</th>
<th>Criteria</th>
<th>Cirrhosis</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positron</td>
<td>7977+RBV</td>
<td>G2/3</td>
<td>207 IFN intolerants</td>
<td>yes</td>
<td>G2: 93% G3 61%</td>
</tr>
<tr>
<td>Fission</td>
<td>7977+RBV 12 vs P/R24</td>
<td>G2/3</td>
<td>500 patients Naive</td>
<td>20%</td>
<td>67% overall vs 67% G2 97% v 78% G3 56% v 63%</td>
</tr>
<tr>
<td>Fusion</td>
<td>7977+RBV 12 vs 16 wks</td>
<td>G2/3</td>
<td>200 Treatment experienced</td>
<td>yes</td>
<td>73% in 16 wk (63 in G3, 94 in G2) 50% in 12 wk (30 in G3, 86 in G2)</td>
</tr>
</tbody>
</table>
ELECTRON: SVR in HCV 1

### NIAID Study: Sofosbuvir + RBV in Washington DC

#### Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>GS-7977+1200mg RBV N=10</th>
<th>GS-7977+1200mg RBV N=25</th>
<th>GS-7977+ 600mg RBV N=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>54 (30-65)</td>
<td>54 (30-65)</td>
<td>55 (26-78)</td>
</tr>
<tr>
<td>Male sex(%)</td>
<td>4 (40%)</td>
<td>20 (80%)</td>
<td>14 (56%)</td>
</tr>
<tr>
<td>Genotype 1a(%)</td>
<td>6 (60%)</td>
<td>20 (80%)</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>African American (%)</td>
<td>9 (90%)</td>
<td>18 (72%)</td>
<td>23 (92%)</td>
</tr>
<tr>
<td>Median BMI (range)</td>
<td>26 (22-43)</td>
<td>18 (72%)</td>
<td>23 (92%)</td>
</tr>
<tr>
<td>IL28B CT/TT (%)</td>
<td>6 (67%)</td>
<td>21 (84%)</td>
<td>21 (84%)</td>
</tr>
<tr>
<td>Median HCV RNA log (IQR)</td>
<td>6.85 (5.80-7.21)</td>
<td>6.16 (5.37-6.41)</td>
<td>6.05 (5.49-6.36)</td>
</tr>
<tr>
<td>Advanced fibrosis (%)</td>
<td>0</td>
<td>6 (24%)</td>
<td>7 (28%)</td>
</tr>
</tbody>
</table>

Osinusi A, et al. AASLD 2012, Boston, #LB-4
Treatment Response: NUC plus RBV for 24 weeks

96 % with HCV RNA <LOQ (ITT)

Wk 4: 1 drop out at week 3
Wk 12: 3 drop outs by week 8

1200 mg RBV: 75% SVR4 (mITT)
600 mg RBV: 64% SVR4 (mITT)

Osinusi A, et al. AASLD 2012, Boston, #LB-4
Sofosbuvir + Daclatasvir + Ribavirin

Phase 2a

**Treatment-naïve**

**Genotype 2/3**

LI*  
Sofosbuvir 400 mg qd + Daclatasvir 60 mg qd (n=16)

Sofosbuvir 400 mg qd + Daclatasvir 60 mg qd (n=14)

Sofosbuvir 400 mg qd + Daclatasvir 60 mg qd + RBV (n=14)

Follow-Up

**Genotype 1**

LI*  
Sofosbuvir 400 mg qd + Daclatasvir 60 mg qd (n=15)

Sofosbuvir 400 mg qd + Daclatasvir 60 mg qd (n=14)

Sofosbuvir 400 mg qd + Daclatasvir 60 mg qd + RBV (n=15)

Follow-Up

Sofosbuvir 400 mg qd + Daclatasvir 60 mg qd (n=14)

Sofosbuvir 400 mg qd + Daclatasvir 60 mg qd + RBV (n=15)

Follow-Up

*LI: 7-day lead-in with sofosbuvir 400 mg qd. HCV RNA >50K IU/mL, no cirrhosis. Primary outcome: SVR12.

Sofosbuvir + Daclatasvir ± Ribavirin: SVR24 in G2/3

LI/SOF/DCV (n=16)
- 88%

SOF/DCV (n=14)
- 100%

SOF/DCV + RBV (n=14)
- 93%

LI: 7-day lead-in with sofosbuvir 400 mg qd.

Sofosbuvir + Daclatasvir ± Ribavirin: SVR24 in G1

LI: 7-day lead-in with sofosbuvir 400 mg qd.

12-Week Treatment
SVR4 (G1)

Sofosbuvir + GS5885 and/or RBV: New Zealand

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Population</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + GS5885 + RBV for 12 weeks</td>
<td>GT 1 treatment-naive</td>
<td>100% (25/25) SVR4</td>
</tr>
<tr>
<td>Sofosbuvir + GS5885 + RBV for 12 weeks</td>
<td>GT 1 Nulls</td>
<td>100% (3/3) SVR4</td>
</tr>
</tbody>
</table>

COSMOS: SVR4 results of a once daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in HCV genotype 1 null responders

F0-F2 fibrosis

SMV 150 mg QD + AOF 400 mg QD w/wo RBV 1000-1200 mg

Lawitz CROI 2013 March
COSMOS: Efficacy

SVR8

95% GT1a, 100 GT1b

Lawitz CROI 2013 March
The early leaders: What we know and what we don’t

Protease/r
NS5A
Non-nuc
Ribavirin

- 3 pill regimen (5 drugs)
- 12 weeks
- Genotype 1

G1 naïve 98% SVR
G1 nulls 93% SVR

G1 cirrhatics G2/3

Nuc
NS5A/PI
Ribavirin

- 2 pill regimen (3 drugs)
- 12 weeks
- Genotype 1, ?2/3/4

G1 naïve 100% SVR
G1 nulls 100% SVR
G2/3 naïve 100% SVR

G1 cirrhatics G2/3 null
Do you think that HCV therapy will be all oral in the next 5 years?

1. Yes for all patients
2. Yes for most patients
3. Yes for a few patients
4. No - not for any patients
Do you think that HCV will be treated by primary care physicians in the next 5 years?

1. Yes for nearly all patients
2. Yes for most patients
3. Yes for rare patients
4. No PCPs will not treat HCV
Interferon-free Oral Therapy

• Several oral regimens have emerged from phase 2 clinical trials with high SVR rates in naïve and null
• Data in cirrhotic patients limited
• No pan genotypic option yet
• Expect 2014-2015 will be the time frame for initial approvals for G1 all oral regimens
• Several regimens by 2016
• Expect next generation drugs beyond this first wave
• Genotype 3 may now be “the hardest strain to cure”
The Future (as I see it)

- **PEG/RBV**
- **PI+PEG+RBV**
- **PI₂+PEG+RBV**
- **NUC+PEG+RBV**
- **DAA₁ + DAA₂ ± RBV (or)**
- **DAA₁ + DAA₂ + DAA₃ ± RBV**
- **QUAD: PEG/RBV/DAA₁/DAA₂ (???)**
All Oral May Allow Increased Access to Care

**Difficulties currently**
- Low screening rate
- Low specialist referral rate
- Limited specialist availability and numbers
- High cost of meds plus care delivery

**Ideal care system**
- Expanded screening
- PCP care delivery
- Less toxic drugs = less monitoring
- Greater volume + less monitoring may lower overall costs
Proposed “Provocative” Paradigm

- **All HCV cases**
- **Complicated cases**
  - Identified naïve HCV cases
- **Referred cases**
- **Specialist treated cases**
  - Known cirrhosis
  - Prior treatment failures
  - Complicated co-morbidities
- **PCP treatable cases**
- **SVR**
- **Treatment failures**

**Simple tool:** HCV RNA + Plts >150K

**Retest HCV RNA at EOT and/or 12 wks post-EOT**

**EMR linked HCV screening and high reported success rate**
Thank you