HCV Treatment Update: Outline

♦ HCV Epidemiology
  – Global and US Prevalence of Hepatitis C Infection
  – Morbidity and Mortality associated with HCV
  – Healthcare Costs associated with HCV

♦ HCV Screening Guidelines

♦ HCV Pathophysiology and Disease Progression
  – Pathogenesis and Pathophysiology of HCV
  – Clinical Complications of Cirrhosis, HCC and Liver Failure
  – Extrahepatic manifestations

♦ HCV Treatment Goal and Justification for Treatment
  – SVR
  – Regression of Disease

♦ Current HCV Therapies

♦ Barriers to Treatment

♦ Investigational HCV Therapies

♦ The Next Paradigm of HCV Treatment

♦ Summary
HCV Epidemiology
Global Prevalence of Chronic HCV Infection

- About 2% of world population estimated to have chronic HCV
- Egypt, Pakistan, and China have high rates of chronic HCV infection due to lack of standard precautions
- In the U.S. 3.2 million people, with estimates as high as 7 million, have chronic HCV, and ~12,000 die each year

![Map of global prevalence of chronic HCV infection]

* Miller et al. estimate about 18 million overall prevalence; In another study, Guerra et al estimated ~ 12.1 million 15-59 year olds are infected.

The US Prevalence of Hepatitis C Infection Is Likely Underestimated

- The CDC estimates US prevalence to be 2.7-3.9 million (1%-1.5%)\(^1,2\)
  - Based on NHANES data, which excludes homeless and incarcerated populations\(^2\)

- HCV infection prevalence may be as high as ~7 million with inclusion of populations omitted or underrepresented* by NHANES\(^3\)

Estimates of US HCV Infection Prevalence\(^1,3\)

*Homeless, incarcerated, Veterans, active military duty, healthcare workers, nursing home residents, and patients on chronic hemodialysis or with hemophilia who received transfusions before 1992.

CDC=Centers for Disease Control and Prevention; NHANES=National Health and Nutrition Examination Survey; HCV=hepatitis C virus.

Distribution of HCV Genotypes in the US

- Genotype 1 accounts for 78%
- Genotype 2 accounts for 13%

While HCV Incidence Has Peaked, Cirrhosis Is Projected to Peak in the Coming Decades

It has been estimated that the number of people who have been infected for > 20 years could quadruple between 1990 and 2015

Projected Incidence of HCV-Related Liver Cancer and Death Also Expected to Peak in Coming Decades

DCC=decompensated cirrhosis; HCC=hepatocellular carcinoma

Increasing Health Care Costs Associated With Progressive Liver Disease in the Aging HCV-Infected Population

- While the prevalence of HCV infection is declining from its peak, the incidence of advanced liver disease and associated health care costs continue to rise

- Modeling does not take into account any impact of birth cohort screening

A system dynamic modeling framework was used to quantify the HCV-infected population, the disease progression, and the associated cost from 1950-2030.
CI=confidence interval.

HCV is a Progressive Disease and HCV-Related Healthcare Costs are Directly Related to Disease Severity

Numbers in parentheses are ±SD.

*P<.001 vs non-cirrhotic liver disease.

Hepatitis C Screening
The US Prevalence of Hepatitis C Infection Is Highest in the 1945-1965 Birth Cohort

- Based on CDC estimates, 77% of individuals infected with HCV (~2.06 million) were born between 1945 and 1965

2012 CDC Recommendations for Birth Cohort (1945–1965) Screening

♦ Recommendation 1
  – Adults born from 1945 to 1965 should receive one-time testing for HCV without prior ascertainment of HCV risk
    
    Grade: strong recommendation
    Evidence: moderate-quality

♦ Recommendation 2
  – All persons identified with HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions as indicated
    
    Grade: strong recommendation
    Evidence: moderate-quality

2013 Updated USPSTF HCV Screening Recommendations

♦ In June 2013, the USPSTF issued its final recommendations regarding HCV screening:
  – Those at high risk for HCV infection
  – Those born from 1945 to 1965 (one-time screening of “Baby Boomers”, regardless of risk)
♦ For this update, the USPSTF reviewed the indirect chain of evidence showing benefits of screening through
  – Improvements in SVR with current treatments
  – Reductions in all-cause and liver-related mortality, and HCC associated with SVR
♦ A Grade B recommendation by the USPSTF means:
  – There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial
♦ The Affordable Care Act:
  – Requires nongrandfathered private health plans to cover clinical preventive services given an A or B Grade by USPSTF without cost sharing
  – Provides incentives for Medicaid programs to cover these services

USPSTF=United States Preventive Services Task Force.
2013 Updated USPSTF HCV Screening Recommendations

♦ Those at high risk:
  – Most important risk factor is past or current injection drug use
  – Additional risk factors include:
    • Receiving a blood transfusion before 1992
    • Long-term hemodialysis
    • Being born to an HCV-infected mother
    • Incarceration
    • Intranasal drug use
    • Getting an unregulated tattoo, and other percutaneous exposures
♦ Adults born between 1945 and 1965 ("Baby Boomers")

*Grade B recommendation for persons at high risk for infection and adults born between 1945 and 1965.

HCV Pathophysiology and Disease Progression
Natural History of HCV Infection

- Infection with HCV can also cause extrahepatic diseases including mixed cryoglobulinemia, types II and III

HCV Disease Progression Diagram

STAGE 0: No Fibrosis
STAGE 1: Portal Fibrosis – No Septa
STAGE 2: Few Septa
STAGE 3: Numerous Septa
STAGE 4: Cirrhosis

Compensated Cirrhosis

- Diuretic Sensitive Ascites
- Variceal Hemorrhage
- Hepatic Encephalopathy
- Hepatocellular Carcinoma

Liver Transplantation

Death

Refractory Ascites
Treatment Goals & Justification for Treatment of Chronic Hepatitis C Infection
The Goal of HCV Treatment Is Sustained Virologic Response (SVR)

Definition: 
- Undetectable HCV RNA by PCR assay at a specific time point after antiviral therapy completion\(^1\)
  - Traditionally 24 weeks although studies have shown assessment of serum HCV RNA 12 weeks after the end of treatment using a highly sensitive assay may be as relevant as after 24 weeks to predict SVR
  - Patients with cirrhosis who achieved an SVR should continue to be monitored at 6- or 12-month intervals for the development of HCC

Current HCV treatment recommendations available from AASLD, NIH, EASL, and APASL\(^1,2,3,4,5\)
- Varies in regimen and duration based on genotype and other virus/disease factors

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AASLD=American Association for the Study of Liver Diseases; NIH=National Institutes of Health; EASL= European Association for the Study of Liver; APASL= Asia Pacific Association for the Study of Liver; PCR=polymerase chain reaction; RNA=ribonucleic acid.

Unlike HIV and HBV, HCV Can Be Cured

Achieving of a sustained virologic response (SVR) following completion of treatment is indicative of a cure\textsuperscript{2}

Sustained Virologic Response Is Associated With a Reduction in Liver-Related Mortality and HCC

Why Treat Chronic Hepatitis C?

♦ The disease
  – Common, chronic, and potentially progressive
  – Complications are becoming more common\(^1,2\)
    • Liver failure, HCC

♦ The treatment
  – Viral cure, or SVR, is achievable
  – SVR associated with histologic improvement and gradual regression of fibrosis\(^3\)
  – SVR reduces risk for liver failure and HCC, improves survival\(^4,5\)

Current Treatment Options for Chronic Hepatitis C Infection
Milestones in Therapy of Genotype 1 HCV

Adapted from US FDA Antiviral Drugs Advisory Committee Meeting; April 27-28, 2011; Silver Spring, MD.
## Two Protease Inhibitors Approved for GT1 HCV Infection Combined With PR

<table>
<thead>
<tr>
<th>Protease Inhibitor</th>
<th>Recommendations</th>
<th>Administration</th>
</tr>
</thead>
</table>
| **Boceprevir 800 mg TID (every 7-9 hrs)**<sup>[1,2]</sup> | - Naive to previous therapy  
- Previous treatment failure  
- Compensated cirrhosis  
- Response-guided therapy  
- Take with food | - All patients initiate therapy with 4-wk pegIFN/RBV lead-in phase  
- After completion of lead-in phase, boceprevir should be added to continued pegIFN/RBV for 24-44 wks |
| **Telaprevir 750 mg TID (every 7-9 hrs)**<sup>[2,3]</sup> | - Naive to previous therapy  
- Previous treatment failure  
- Compensated cirrhosis  
- Response-guided therapy  
- Take with food (not low fat) | - All patients initiate therapy with 12-wk period of triple therapy with telaprevir plus pegIFN/RBV  
- Followed by 12-36 wks of pegIFN/RBV |

Addition of BOC or TVR to PegIFN/RBV Improves SVR in Genotype 1 Patients

- BOC and TVR each indicated in combination with pegIFN/RBV for genotype 1 HCV patients who are previously untreated or who have failed previous therapy.


*BOC was administered with pegIFN-α2b; TVR was administered with pegIFN-α2a in these trials.

- SVR (%) for Treatment Naive, Relapsers, Partial Responders, and Null Responders:
  - Treatment Naive: PegIFN + RBV 38-44, BOC/TVR + pegIFN* + RBV 63-75
  - Relapsers: PegIFN + RBV 24-29, BOC/TVR + pegIFN* + RBV 69-83
  - Partial Responders: PegIFN + RBV 7-15, BOC/TVR + pegIFN* + RBV 40-59
  - Null Responders: PegIFN + RBV 5, BOC/TVR + pegIFN* + RBV 29-40
RGT With TVR + PegIFN/RBV in *Tx-Naive Patients and Previous Relapsers*

- Indicated for all noncirrhotic treatment-naive pts and previous relapsers*[^1,^3]

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**HCV RNA**

- **Undetectable**
- **Undetectable**
- **Undetectable**

**TVR + PegIFN/RBV**

- **PegIFN/RBV**

**eRVR stop at Wk 24, f/u 24 wks**

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**HCV RNA**

- **Detectable**
- **Undetectable or detectable**
- **Undetectable**

**TVR + PegIFN/RBV**

- **PegIFN/RBV**

**No eRVR extend pegIFN/ RBV to Wk 48; f/u 24 wks**

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*AASLD guidelines say RGT "may be considered" for previous partial responders[^2] but package inserts recommend 48 wks of therapy.[^1,^3]*

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**References:**

Limited Efficacy With Telaprevir and Boceprevir in Some Patient Groups


*Pooled TVR arms of REALIZE trial.
### Adverse Events Are Common With Current PI Therapy

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>ADVANCE(^{[1]})</th>
<th>SPRINT-2(^{[2]})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T12 + PR</td>
<td>PR</td>
</tr>
<tr>
<td>Discontinued due to adverse events</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Discontinued due to rash</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Anemia, g/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ &lt; 10.0</td>
<td>36</td>
<td>14</td>
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<tr>
<td>▪ &lt; 8.5</td>
<td>9</td>
<td>2</td>
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<tr>
<td>Use of EPO</td>
<td>Not permitted</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24</td>
</tr>
</tbody>
</table>
Challenges With Adherence to Complex Regimens

♦ Triple therapy regimens are complex, presenting challenges to medication adherence\(^1,2\)
  – TID dosing
  – Food requirements

♦ Data show pegIFN/RBV adherence decreases over time\(^3\)
  – Addition of PIs may exacerbate this trend

# Medicines That Are Contraindicated With BOC and TVR

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Alpha 1-adrenoreceptor antagonists</td>
<td>Alfuzosin</td>
<td>Alfuzosin</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine, phenobarbital, phenytoin</td>
<td>N/A</td>
</tr>
<tr>
<td>Antimycobacterials</td>
<td>Rifampin</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Antiretrovirals</td>
<td>EFV, all RTV-boosted PIs</td>
<td>DRV/RTV, FPV/RTV, LPV/RTV</td>
</tr>
<tr>
<td>Ergot derivatives</td>
<td>Dihydroergotamine, ergonovine, ergotamine, methylergonovine</td>
<td>Dihydroergotamine, ergonovine, ergotamine, methylergonovine</td>
</tr>
<tr>
<td>GI motility agents</td>
<td>Cisapride</td>
<td>Cisapride</td>
</tr>
<tr>
<td>Herbal products</td>
<td>Hypericum perforatum (St John’s wort)</td>
<td>Hypericum perforatum</td>
</tr>
<tr>
<td>HMG CoA reductase inhibitors</td>
<td>Lovastatin, simvastatin</td>
<td>Lovastatin, simvastatin</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Drospirenone</td>
<td>N/A</td>
</tr>
<tr>
<td>Neuroleptic</td>
<td>Pimozide</td>
<td>Pimozide</td>
</tr>
<tr>
<td>PDE5 inhibitor</td>
<td>Sildenafil or tadalafil when used for treatment of pulmonary arterial HTN</td>
<td>Sildenafil or tadalafil when used for treatment of pulmonary arterial HTN</td>
</tr>
<tr>
<td>Sedatives/hypnotics</td>
<td>Triazolam; orally administered midazolam</td>
<td>Orally administered midazolam, triazolam</td>
</tr>
</tbody>
</table>

*Studies of drug–drug interactions incomplete.

Several Patient Populations With Continued Need in Current Era

- Contraindication or poor tolerance to pegIFN or RBV
- Safety and efficacy of boceprevir and telaprevir not fully established
  - Organ transplant recipients
  - Patients with end-stage liver disease
  - Patients with HIV and/or HBV coinfection
  - Pediatric patients
- Patients with decompensated cirrhosis or moderate to severe hepatic impairment
- Although pegIFN/RBV effective for non–genotype 1, comes with all of the issues related to the use of IFN
- Patients with poor IFN responsiveness
- Patients unable to adhere to complex, lengthy regimens

Barriers to Treatment
Treatment-Related Barriers Exclude Most HCV Patients From a Treatment Option

Psychiatric/Medical Ineligibility

- Major uncontrolled depressive illness\(^1\)
- Significant CV disease\(^1\)
- Untreated thyroid disease\(^1\)
- Autoimmune disorder\(^1\)

Intolerant to Therapy

Treatment discontinuation rates due to side effects range from 14% to 21%\(^2-4\)

CV = cardiovascular

Increased Awareness, Education and Support Are Needed to Overcome Barriers to HCV Treatment

A Small Proportion of HCV Patients Are Currently Being Treated

Treated – Synovate chart audits 2011
Effectiveness of HCV Therapy Has Been Reduced by Eligibility Restrictions and Low Rates of Initiation

Results of a Literature Review on the Course of HCV Treatment in Clinical Care Settings

All Patients (N=13,583)
- Treatment Eligible: 39%
- Started Treatment: 19%
- Completed Treatment: 13%
- SVR: 3%

Will Investigational HCV Therapies Improve Upon Current HCV Therapies?
HCV Life Cycle and DAA Targets

Receptor binding and endocytosis

Fusion and uncoating

Translation and polyprotein processing

(+)-RNA

Translation and polyprotein processing

NS3/4 protease inhibitors

NS5A* inhibitors

NS5B polymerase inhibitors

Nucleoside/nucleotide inhibitors

Nonnucleoside inhibitors

Membranous web

ER lumen

LD

Transport and release

Virion assembly

*Block replication complex formation, assembly

What Are the Key Elements of an Ideal HCV Regimen?

- **All Oral**
  - PegIFN/RBV replaced with alternate backbone with low chance of resistance

- **Pan-Genotypic**
  - Regimen can be used across all genotypes

- **Easy Dosing**
  - Once daily, low pill burden

- **Safe and Tolerable**
  - Few or easily manageable adverse effects

- **Highly Effective**
  - Efficacy in challenging populations (i.e., poor IFN sensitivity, cirrhosis)

- **Simple Regimen**
  - Short duration, simple, straightforward stopping rules
## Characteristics of HCV DAA Classes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Protease Inhibitors</th>
<th>Nucleos(t)ide Polymerase Inhibitors</th>
<th>Nonnucleoside Polymerase Inhibitors</th>
<th>NS5A Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potency</td>
<td>High; variable among HCV genotypes</td>
<td>Moderate-high; consistent across genotype, subtype</td>
<td>Variable; variable among HCV genotypes</td>
<td>High; multiple HCV genotypes</td>
</tr>
</tbody>
</table>
| Barrier to resistance   | Low  
1a < 1b                          | High  
1a = 1b                          | Very low  
1a < 1b                          | Low  
1a < 1b                          |
| Drug interaction potential | High                     | Low                                | Variable                      | Low to moderate |
| Toxicity                | Rash; anemia; ↑ bilirubin          | Mitochondrial; nuc interactions (ART) | Variable                      | Variable |
| Pharmacokinetics        | Variable; QD to TID               | QD                                  | Variable; QD to TID           | QD             |
| Comments                | 2nd-generation PIs: better barrier, pangenotypic | Single target; good tolerability in agents progressing in PhIII | Many targets | Multiple antiviral MOA |
# Investigational HCV Regimens in Phase III Clinical Trials

## Regimens With 1 DAA + PegIFN alfa/RBV
- Faldaprevir (BI 201335, PI)
- Sofosbuvir (GS-7977, NI)
- Simeprevir (TMC-435, PI)
- Daclatasvir (BMS-790052, NS5A)
  - Alisporivir (CYP)
  - Vaniprevir (MK-7009, PI)

## Regimens With 2 DAAs + PegIFN alfa/RBV
- Daclatasvir + asunaprevir

## IFN-Free Regimens
- Sofosbuvir + RBV
- FDC of Sofosbuvir + Ledipasvir (formerly GS-5885, NS5A) ± RBV
- Asunaprevir (PI) + daclatasvir
- FDC of ABT-267 (NS5A)/ABT-450/r (PI) + ABT-333 (NNI) + RBV
- Faldaprevir (PI) + BI 207127 (NNI) + RBV

## Alternative Dosing
- TVR BID (approved PI)

Some of the Most Promising Phase III Investigational Agents for HCV Treatment

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Dosing</th>
<th>Genotypic Activity</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS5B nucleotide analogue polymerase inhibitor</td>
<td>Sofosbuvir (GS-7977)</td>
<td>QD</td>
<td>Pangenotypic[^1,2]</td>
<td>Phase III*</td>
</tr>
<tr>
<td>NS3A protease inhibitor</td>
<td>Faldaprevir (BI 201335)</td>
<td>QD</td>
<td>GT 1, 4, 5, 6[^3]</td>
<td>Phase III</td>
</tr>
<tr>
<td>NS3A protease inhibitor</td>
<td>Simeprevir (TMC435)</td>
<td>QD</td>
<td>GT 1, 2, 4, 5, 6[^4]</td>
<td>Phase III*</td>
</tr>
</tbody>
</table>


*New Drug Application submitted to the FDA.*
QUEST-1: Simeprevir + P/R RGT in Treatment-Naive GT 1 HCV

- Randomized, double-blind, placebo-controlled phase III trial
  - 12% to 13% had cirrhosis, 56% to 57% had GT 1a HCV

*Response-guided therapy: Patients with HCV RNA < 25 IU/mL at Wk 4 and HCV RNA undetectable at Wk 12 received a total of 24 wks of therapy. Those not achieving this on-treatment response received 48 wks of therapy.

P/R, peginterferon alfa-2a 180 µg/wk + ribavirin 1000-1200 mg/day.

QUEST-1: Virologic Response to Simeprevir + P/R Treatment

Virologic Outcomes

- **Week 4**: 80/202 (39.7%) in SMV arm, 12/254 (4.7%) in P/R arm
- **SVR12**: 80/210 (38.1%) in SMV arm, 50/65 (76.9%) in P/R arm

SVR12 by RGT Group

- **85% of pts in SMV arm met RGT criteria**

QUEST-1: SVR12 by Fibrosis Level, Subtype, and Baseline Resistance

Differences in SVR12 by Subgroup (95% CIs)

GT 1a/other HCV
- With baseline Q80K vs Pbo
- Without baseline Q80K vs Pbo

GT 1b HCV

SMV (n)  Pbo (n)
28.2 (13.4-42.9)   147   74
4.7 (-14.6 to 24.1)   60   74
40.3 (25.8-54.8)   86   74
42.1 (26.5-57.6)   117   56

**QUEST-2: Simeprevir + P/R RGT in Treatment-Naive GT 1 HCV**

- Phase III, randomized, double-blind, placebo-controlled trial
  - 7% to 11% had cirrhosis, 58% had GT 1b HCV

*63% of patients in each arm were randomly assigned to receive pegIFN alfa-2a or pegIFN alfa-2b; the remainder were assigned pegIFN alfa-2a.*

†RGT: Patients with HCV RNA < 25 IU/mL at Wk 4 and HCV RNA undetectable at Wk 12 received a total of 24 wks of therapy. Those not achieving this on-treatment response received 48 wks of therapy.

QUEST-2: Virologic Response to Simeprevir + P/R Treatment


91% of pts in SMV arm met RGT criteria

SVR12 (%)

n/N = 209/257 67/134 202/235 7/22
Higher rates of SVR12 with SMV, irrespective of HCV genotype or cirrhosis
Baseline Q80K mutation not a predictor of response (unlike in QUEST-1)

Safety profiles similar between groups through first 12 wks of treatment
- No increase in anemia with SMV; slightly higher rash or photosensitivity
- Mild, transient bilirubin increases with SMV; other liver parameters did not change

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td></td>
<td>SMV + PR (n = 264)</td>
<td>PR (n = 130)</td>
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<tr>
<td>Grade 1/2 AEs</td>
<td>72</td>
<td>65</td>
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<tr>
<td>Grade 3/4 AEs</td>
<td>23</td>
<td>29</td>
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<tr>
<td>Serious AEs</td>
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<td>4</td>
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<tr>
<td>AEs leading to SMV/placebo discontinuation</td>
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<td>3</td>
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<tr>
<td>AEs of interest</td>
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<tr>
<td>Pruritus</td>
<td>21</td>
<td>11</td>
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<td>Rash (any type)</td>
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<td>25</td>
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<tr>
<td>Anemia</td>
<td>16</td>
<td>11</td>
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<tr>
<td>Bilirubin increase</td>
<td>9</td>
<td>4</td>
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<tr>
<td>Photosensitivity conditions</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

STARTVerso1: Faldaprevir + P/R RGT in Treatment-Naive in GT 1 HCV

- 78% were white, 81% Europe, 19% Japan; 66% had GT 1b HCV; 39% had *IL28B* CC; 6% were cirrhotic

<table>
<thead>
<tr>
<th>Treatment-naive patients with GT 1 HCV (N = 656)</th>
<th>Wk 12</th>
<th>Wk 24</th>
<th>Wk 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faldaprevir 120 mg QD + P/R* (n = 261)</td>
<td>Placebo + P/R</td>
<td>Faldaprevir + P/R</td>
<td>P/R</td>
</tr>
<tr>
<td>Faldaprevir 240 mg QD + P/R (n = 262)</td>
<td>Placebo + P/R†</td>
<td>P/R</td>
<td>P/R</td>
</tr>
<tr>
<td>Placebo + P/R (n = 133)</td>
<td></td>
<td></td>
<td>P/R</td>
</tr>
</tbody>
</table>

*RGT: At Wk 12, patients with ETS continued P/R to Wk 24; patients without ETS continued triple therapy to Wk 24 followed by P/R to Wk 48.
†RGT: At Wk 24, patients with ETS stopped treatment; patients without ETS continued P/R to Wk 48. ETS defined as HCV RNA < 25 IU/mL at Wk 4 and HCV RNA < 25 IU/mL, target not detected at Wk 8.

STARTVerso1: SVR12 According to ETS, Genotype, and Fibrosis Level

ETS defined as HCV RNA < 25 IU/mL at Wk 4 and HCV RNA < 25 IU/mL, target not detected at Wk 8.

- 23% of pts with GT 1a HCV had Q80K at baseline; not predictive of SVR12

Summary of Safety Data With Faldaprevir

- FDV + PR relatively safe and well tolerated
  - Most frequent AEs: gastrointestinal events, rash, and jaundice
- Transient, dose-dependent bilirubin increases, primarily in FDV 240-mg arm
  - Not associated with concomitant increases in other liver parameters

<table>
<thead>
<tr>
<th>Safety Outcome, %</th>
<th>FDV 120 mg + PR (n = 259)</th>
<th>FDV 240 mg + PR (n = 261)</th>
<th>PR (n = 132)</th>
</tr>
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<tbody>
<tr>
<td>Serious AE</td>
<td>7</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>AEs leading to discontinuation of all drugs</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>AEs leading to discontinuation of FDV or placebo</td>
<td>1</td>
<td>3</td>
<td>0</td>
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<tr>
<td>Grade 2-4 AEs*</td>
<td>52</td>
<td>55</td>
<td>48</td>
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<tr>
<td>- Anemia</td>
<td>13</td>
<td>12</td>
<td>11</td>
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<tr>
<td>- Gastrointestinal events</td>
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<td>12</td>
<td>3</td>
</tr>
<tr>
<td>- Rash</td>
<td>8</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>- Jaundice</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>- Photosensitivity</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3/4 laboratory abnormalities*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Total bilirubin</td>
<td>12</td>
<td>53</td>
<td>1</td>
</tr>
<tr>
<td>Rash</td>
<td>32</td>
<td>33</td>
<td>22</td>
</tr>
<tr>
<td>- Grade 2-4 rash*</td>
<td>8</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

*AEs graded according to Division of AIDS grading system.

NEUTRINO: Sofosbuvir + P/R for 12 Wks in Treatment-Naive GT 1/4/5/6 HCV Patients

Open-label, single-arm study of sofosbuvir 400 mg QD + P/R for 12 wks in treatment-naive patients with GT 1/4/5/6 HCV
- 17% had cirrhosis; 89% had GT 1, 9% had GT 4, < 1% had GT 5, 2% had GT 6 HCV

P/R: pegIFN alfa-2a 180 µg/wk + RBV 1000-1200 mg/day

HCV RNA < LLOQ (%)

<table>
<thead>
<tr>
<th></th>
<th>Wk 4</th>
<th>EOT</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>321/325</td>
<td>326/327</td>
<td>295/327</td>
</tr>
<tr>
<td>99</td>
<td>99</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

NEUTRINO: SVR12 With Sofosbuvir + P/R
According to Genotype and Fibrosis Level

FISSION: Sofosbuvir/RBV vs PegIFN/RBV in Treatment-Naive GT 2/3 HCV Patients

Randomized, controlled, open-label phase III noninferiority trial
- 20% to 21% had cirrhosis; 72% had GT 3 HCV

Stratified by HCV GT (2 vs 3), HCV RNA (< vs ≥ 10^6 IU/mL), cirrhosis (yes vs no)

Wk 24

Wk 12

Treatment-naive patients with GT 2/3 HCV (N = 499)

Sofosbuvir 400 mg QD + RBV 1000-1200 mg/day (n = 256)

PegIFN alfa-2a 180 µg/wk + RBV 800 mg/day (n = 243)

FISSION: Sofosbuvir/RBV Noninferior to P/R in Tx-Naive GT 2/3 HCV Patients


<table>
<thead>
<tr>
<th></th>
<th>Sofosbuvir + RBV</th>
<th>PegIFN + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>On Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wk 4</td>
<td>249/250</td>
<td>158/236</td>
</tr>
<tr>
<td>Wk 12</td>
<td>242/244</td>
<td>207/224</td>
</tr>
<tr>
<td>Wk 24</td>
<td>188/190</td>
<td>170/253</td>
</tr>
<tr>
<td>SVR12</td>
<td>162/243</td>
<td>162/243</td>
</tr>
</tbody>
</table>

HCV RNA < LLQ (%)

- Wk 4: 99/67
- Wk 12: 99/92
- Wk 24: 99/67
- SVR12: 67/67

P < .001

FISSION: SVR12 According to Genotype and Fibrosis Level


<table>
<thead>
<tr>
<th>Genotype 2</th>
<th>No Cirrhosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + RBV</td>
<td>98/59</td>
<td>82/11</td>
</tr>
<tr>
<td>PegIFN + RBV</td>
<td>10/54</td>
<td>62/13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype 3</th>
<th>No Cirrhosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + RBV</td>
<td>89/145</td>
<td>34/38</td>
</tr>
<tr>
<td>PegIFN + RBV</td>
<td>99/139</td>
<td>30/37</td>
</tr>
</tbody>
</table>

n/N = 100
**FISSION: Better Tolerability Profile With Sofosbuvir/RBV vs PegIFN/RBV**

- Grade $\geq 3$ AEs: 7% with SOF/RBV vs 19% for pegIFN/RBV
- Discontinuations due to AEs: 1% for SOF/RBV vs 11% for pegIFN/RBV

<table>
<thead>
<tr>
<th>AEs Occurring in $\geq 15%$ in Either Arm,</th>
<th>SOF/RBV (n = 256)</th>
<th>PegIFN/RBV (n = 243)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>36</td>
<td>55</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Headache</td>
<td>25</td>
<td>44</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
<td>29</td>
<td>.0057</td>
</tr>
<tr>
<td>Insomnia</td>
<td>12</td>
<td>29</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Rash</td>
<td>9</td>
<td>17</td>
<td>.0052</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>17</td>
<td>.0075</td>
</tr>
<tr>
<td>Irritability</td>
<td>10</td>
<td>17</td>
<td>.0328</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7</td>
<td>18</td>
<td>.0001</td>
</tr>
<tr>
<td>Myalgia</td>
<td>8</td>
<td>17</td>
<td>.0060</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7</td>
<td>17</td>
<td>.0009</td>
</tr>
<tr>
<td>Influenzalike symptoms</td>
<td>3</td>
<td>18</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Chills</td>
<td>3</td>
<td>18</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

Gane E, et al. EASL 2013. Abstract 5..
FUSION: Sofosbuvir + RBV for 12 or 16 Wks in Tx-Experienced GT 2/3 HCV Pts

♦ Randomized, double-blind, placebo-controlled phase III trial
  – 62% to 64% had GT 3 HCV, 33% to 35% had cirrhosis, 75% to 76% were previous relapsers

FUSION: Overall Efficacy Outcomes of Sofosbuvir + RBV in GT 2/3


- **Wk 4 End of Treatment**
  - HCV RNA < LLOQ (%)
  - Sofosbuvir + RBV 12 wks: 100/100
  - Sofosbuvir + RBV 16 wks: 100/100

- **SVR12**
  - n/N = 50/100
  - Sofosbuvir + RBV 16 wks: 73/95
FUSION: SVR12 With Sofosbuvir + RBV by Genotype and Fibrosis Level

POSITRON: Sofosbuvir + RBV for 12 Wks in GT 2/3 IFN-Unwilling/Intolerant/Ineligible

♦ Randomized, double-blind, placebo-controlled phase III trial

![Diagram showing treatment groups and outcomes]

**Baseline Factor, n (%)**

<table>
<thead>
<tr>
<th>Baseline Factor</th>
<th>Sofosbuvir + RBV (n = 207)</th>
<th>Placebo (n = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 2</td>
<td>109 (53)</td>
<td>34 (48)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>31 (15)</td>
<td>13 (18)</td>
</tr>
<tr>
<td>Interferon unwilling</td>
<td>102 (49)</td>
<td>30 (42)</td>
</tr>
<tr>
<td>Interferon ineligible</td>
<td>88 (43)</td>
<td>33 (47)</td>
</tr>
<tr>
<td>Interferon intolerant</td>
<td>17 (8)</td>
<td>8 (11)</td>
</tr>
</tbody>
</table>

POSITRON: Virologic Response in GT 2/3 IFN-Unwilling/Intolerant/Ineligible

- SVR12 0% for placebo

## Topline Summary of Sofosbuvir Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient Population</th>
<th>n</th>
<th>Regimen</th>
<th>Duration, Wks</th>
<th>SVR12, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEUTRINO</td>
<td>Tx-naive GT 1</td>
<td>292</td>
<td>SOF + P/R</td>
<td>12</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>Tx-naive GT 4</td>
<td>28</td>
<td>SOF + P/R</td>
<td>12</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>Tx-naive GT 5/6</td>
<td>7</td>
<td>SOF + P/R</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>FISSION</td>
<td>Tx-naive GT 2</td>
<td>70</td>
<td>SOF + RBV</td>
<td>12</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>Tx-naive GT 3</td>
<td>183</td>
<td>SOF + RBV</td>
<td>12</td>
<td>56</td>
</tr>
<tr>
<td>FUSION</td>
<td>Tx-experienced GT 2</td>
<td>36</td>
<td>SOF + RBV</td>
<td>12</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>Tx-experienced GT 3</td>
<td>64</td>
<td>SOF + RBV</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Tx-experienced GT 2</td>
<td>32</td>
<td>SOF + RBV</td>
<td>16</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>Tx-experienced GT 3</td>
<td>63</td>
<td>SOF + RBV</td>
<td>16</td>
<td>62</td>
</tr>
<tr>
<td>POSITRON</td>
<td>IFN-UII GT 2</td>
<td>109</td>
<td>SOF + RBV</td>
<td>12</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>IFN-UII GT 3</td>
<td>98</td>
<td>SOF + RBV</td>
<td>12</td>
<td>61</td>
</tr>
</tbody>
</table>

Summary of Safety Findings From Phase III Trials

♦ Sofosbuvir\[^{1-4}\]
  - Generally well tolerated; low rates of grade 3/4 AEs, serious AEs, and treatment discontinuation due to AEs; improved profile with SOF/RBV vs pegIFN/RBV

♦ Greatly improved Hb profile with simeprevir and faldaprevir vs boceprevir or telaprevir with no significant increase over pegIFN/RBV\[^{5-7}\]

♦ Simeprevir\[^{5,6}\]
  - Generally well tolerated; no added safety signals with triple therapy

♦ Faldaprevir\[^{7}\]
  - Generally well tolerated (clinically benign and transient bilirubin increases with 240 mg dose; higher incidence of gastrointestinal events and rash)

## Additional Investigational HCV Agents

**Presented at EASL 2013**

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Dosing</th>
<th>Genotypic Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NS3/4A protease inhibitor</strong></td>
<td>ABT-450/RTV</td>
<td>100/100 mg, 150/100 mg, or 200/100 mg QD</td>
<td>Genotype 1</td>
</tr>
<tr>
<td><strong>NS3 protease inhibitor</strong></td>
<td>Asunaprevir</td>
<td>200 mg BID</td>
<td>Genotype 1</td>
</tr>
<tr>
<td><strong>NS3 protease inhibitor</strong></td>
<td>GS-9451</td>
<td>200 mg QD</td>
<td>Genotype 1</td>
</tr>
<tr>
<td><strong>NS3/4A protease inhibitor</strong></td>
<td>MK-5172</td>
<td>100 mg, 200 mg, 400 mg, or 800 mg QD</td>
<td>Genotype 1</td>
</tr>
<tr>
<td><strong>NS3/4A protease inhibitor</strong></td>
<td>Vaniprevir (MK-7009)</td>
<td>300 mg or 600 mg BID</td>
<td>Genotype 1</td>
</tr>
<tr>
<td><strong>NS5A nonnucleoside inhibitor</strong></td>
<td>ABT-267</td>
<td>25 mg QD</td>
<td>Genotype 1</td>
</tr>
<tr>
<td><strong>NS5B nonnucleoside polymerase inhibitor</strong></td>
<td>ABT-333</td>
<td>400 mg BID</td>
<td>Genotype 1</td>
</tr>
<tr>
<td><strong>NS5B nonnucleoside polymerase inhibitor</strong></td>
<td>BMS-791325</td>
<td>75 mg or 150 mg BID</td>
<td>Genotype 1</td>
</tr>
<tr>
<td><strong>NS5B nonnucleoside polymerase inhibitor</strong></td>
<td>GS-9669</td>
<td>500 mg QD</td>
<td>Genotype 1</td>
</tr>
<tr>
<td><strong>NS5B nucleotide polymerase inhibitor</strong></td>
<td>GS-0938</td>
<td>300 mg QD</td>
<td>Genotypes 1-4</td>
</tr>
<tr>
<td><strong>NS5B nucleotide polymerase inhibitor</strong></td>
<td>Sofosbuvir (GS-7977)</td>
<td>400 mg QD</td>
<td>Pangenotypic</td>
</tr>
<tr>
<td><strong>NS3/4A protease inhibitor</strong></td>
<td>MK-5172</td>
<td>100 mg, 200 mg, 400 mg, or 800 mg QD</td>
<td>Genotype 1</td>
</tr>
<tr>
<td><strong>NS5A inhibitor</strong></td>
<td>Ledipasvir (GS-5885)</td>
<td>30 mg or 90 mg QD</td>
<td>Genotype 1</td>
</tr>
</tbody>
</table>
So Where Is This Heading?
FDA Breakthrough Therapy

♦ On July 9, 2012 the Food and Drug Administration Safety and Innovation Act (FDASIA) was signed. FDASIA Section 902 provides for a new designation - Breakthrough Therapy Designation.

♦ A breakthrough therapy is a drug:
  – intended alone or in combination with one or more other drugs to treat a serious or life threatening disease or condition and
  – preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

♦ If a drug is designated as breakthrough therapy, FDA will expedite the development and review of such drug. All requests for breakthrough therapy designation will be reviewed within 60 days of receipt, and FDA will either grant or deny the request.
The New Waves of HCV Therapy

♦ Wave 1 (2011-2013): First-generation PI added to pegIFN/RBV
  – Naives → consider Rx with pegIFN/RBV/PI only for advanced stage pts
  – Experienced → offer Rx
  – Nulls → stratify by stage

♦ Wave 2 (2013-2016): a paradigm shift
  – Oral cocktails of DAAs, host cofactor inhibitors, RBV
  – Substitution of better-tolerated IFNs
  – Substitution of second-generation PIs, nucs (better PK, tolerability)
  – 4-drug regimens for pegIFN/RBV/PI failures
Expected Improvements in Dosing Strategies and Tolerability

- **BID dosing with current PIs**
  - Less frequent dosing, improved tolerability, no food requirement, fewer DDIs

- **QD DAA + PR, RGT**
  - QD-BID dosing, IFN free, more tolerable, fewer DDIs

- **1-2 DAAs + RBV**
  - QD-BID dosing, shorter duration, IFN free, more tolerable

- **IFN-free DAA combo**
  - QD-BID dosing, shorter duration, IFN free, more tolerable

- **QD DAA (single drug or FDC), IFN/RBV free**
  - Short duration, pangenotypic, very tolerable, few DDIs
The Iceberg That Sank the Titanic
The Many Icebergs of the Hepatitis C Waters

Genotype

Fibrosis

Not yet treated

Not yet diagnosed
Chronic HCV Infection

Normal vs Elevated Serum ALT

Chronic HCV Infection
Not Yet (successfully) Treated

Current HCV Care¹

False horizon

Actual horizon

Iceberg obscured in mirage layer
In this real world cohort, there were 17% African-Americans, 47% prior PEG-IFN+RBV non-responders, 12% HIV/HCV co-infected, and 36% with advanced fibrosis/cirrhosis.

- Erythropoietin was used in almost 50% of patients and blood transfusions in 10%.
- 43% of patients achieved SVR12.
- Almost half of all costs (47%) were spent on patients who did not achieve an SVR12.

The median cost per SVR12 was $195,495*.

<table>
<thead>
<tr>
<th>Total Cost for Patients who Achieved an SVR</th>
<th>Total Cost for Study Group*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=58</td>
<td>n=134</td>
</tr>
<tr>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Did not include personnel costs; Hash marks denote patients who did not achieve SVR.

Bichoupan K, et al. EASL 2013. Amsterdam, The Netherlands. #795
Grants to States for Medicaid

- The FY 2014 Medicaid request totals $284.2 billion, an increase of $13.5 billion above the FY 2012 level. The majority of this increase is attributed to the ACA Medicaid expansion in FY 2014. This appropriation consists of $177.9 billion for FY 2014 and $106.3 billion in an anticipated advance appropriation from FY 2013. These funds, together with a $22.0 billion projected unobligated end-of-year balance from FY 2013 and a $0.3 billion anticipated offsetting collection for Medicare Part B premiums, will finance $306.5 billion in estimated obligations in FY 2014. These obligations consist of:
  - $283.3 billion in Medicaid medical assistance benefits;
  - $2.4 billion for benefit obligations incurred but not yet reported;
  - $16.5 billion for Medicaid administrative functions including Medicaid survey and certification and State fraud control units; and
  - $4.3 billion for the Centers for Disease Control and Prevention’s Vaccines for Children program.
## Potential Impact of Future HCV Treatment on State Medicaid

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients with chronic hepatitis C</td>
<td>5,000,000</td>
</tr>
<tr>
<td>% treated</td>
<td>50.00%</td>
</tr>
<tr>
<td>Number treated</td>
<td>2,500,000</td>
</tr>
<tr>
<td>Cost per course of treatment</td>
<td>$75,000</td>
</tr>
<tr>
<td>Total cost</td>
<td>$187,500,000,000</td>
</tr>
</tbody>
</table>
The Big One

Must Treat

Can Treat
Treat Now vs Wait: Many Issues to Consider

**Treat now**
- Triple therapy increases SVR
- Earlier treatment has higher success rates
- Successful treatment may arrest progression of liver disease
- Uncertainty about timelines for approval and reimbursement

**Defer**
- First-generation PIs complex, associated with adverse events
- Does current treatment failure affect future treatment?
- Potential for higher SVR, including in challenging populations
- Potential for simpler regimens, QD or BID, fewer adverse effects, eventually IFN-free
- Activity in non–genotype 1
Summary

♦ Approximately 3.2 million persons in the US have chronic HCV infection\(^1\)

♦ If left untreated, HCV infection can lead to advanced liver disease
  – There is an increasing burden of liver disease in aging baby boomers due to manifestations of HCV infection acquired 20-30 years ago\(^2\)

♦ Screening is easy and reliable\(^3,4\)
  – CDC and USPSTF recommend screening all baby boomers in addition to those with other specific risk factors

♦ HCV infection is curable (SVR=virologic cure)\(^5,*\)
  – SVR reduces the risk of mortality and of developing advanced liver disease\(^6,7\)
  – Patients with cirrhosis who achieved an SVR should continue to be monitored at 6- or 12-month intervals for the development of HCC\(^8\)
  – New medications will be available soon that will be safer, more tolerable, and more effective
  – These new treatments are likely to be very expensive and will likely result in some very difficult management decisions

*Outcomes based on 2-drug therapy with PegIFN and RBV.
Questions?
Natural History of HCV Infection

- Characteristics associated with more rapid progression to cirrhosis
  - Male gender
  - Older at age of infection (>40 years)
  - History of/current alcohol abuse
    - Fibrosis
    - Obesity
    - Steatosis
  - Metabolic syndrome/Insulin resistance
  - Diabetes mellitus
  - HIV co-infection

- Characteristics associated with less rapid progression to cirrhosis
  - Female gender
  - Younger at age of infection (<40 years)
  - No fibrosis
  - Healthy
  - No confounding comorbidities

HCC=hepatocellular carcinoma.
Active HCV Infection is Associated With Higher All-Cause Mortality

♦ REVEAL study: a prospective community-based cohort study in Taiwan designed to study the natural history and long-term disease burden of chronic hepatitis C

♦ Risk of all causes mortality, hepatic diseases and extrahepatic diseases, significantly higher in anti-HCV seropositives with detectable HCV RNA vs. anti-HCV seropositives with undetectable HCV RNA and anti-HCV seronegatives (P<0.001)

REVEAL., Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer)

Survival Probability in HCV Patients With Cirrhosis


Survival Probability

- **Compensated**
- **After first major complication**

Patients (%)

- 100
- 80
- 60
- 40
- 20
- 0

Patients at Risk

- 384
- 376
- 342
- 288
- 236
- 165
- 126
- 79
- 52
- 39
- 25

Months

0 12 24 36 48 60 72 84 96 108 120
HCV Is Leading Cause of Liver Transplants in the US

Between 1995 and 2010, 41% of the 126,862 new primary registrants for liver transplants carried a diagnosis of HCV infection.

1. Available at: www.ustransplant.org/annual_reports/current/chapter_iv_forprint.pdf
Routes of Transmission

Other possible routes:
- Tattoo/body piercing or needle-stick injuries
- Hemodialysis
- Sexual contact
- Maternal-fetal transmission

No risk factor identified in 10% of HCV cases
40% of HCV-infected persons unaware of their risk

HCV infection is also more prevalent in men, HIV-positive persons, and individuals of Hispanic or African American heritage²,³

HIV=human immunodeficiency virus.

HCV Diagnostic Algorithm Based on Serologic Testing

- Anti-HCV Antibody
  - Positive: HCV RNA
    - Positive: HCV Genotype
      - Consider Liver Biopsy
      - Vaccinate for HAV / HBV*
    - Negative: No Active Disease
    - Negative: No Further Testing†
  - Negative: No Further Testing†

*If patient lacks pre-existing antibodies to HAV or HBV.
HAV=hepatitis A virus, HBV=hepatitis B virus.
† HCV RNA testing should be performed in Patients with unexplained liver disease whose anti-HCV test is negative and who are immunocompromised or suspected of having acute HCV infection.
Modeling predicts higher treatment rates with improved efficacy will result in significant reductions in liver-related mortality.


### Mortality Prevented by 2030 (%)

- Trend with PegIFN/RBV: 14.5%
- 75% SVR: 21.7%
- 50% More Patients Treated: 30.2%
- 75% More Patients Treated With 75% SVR: 57.2%
Sustained Virologic Response Is Associated With a Reduction in All-Cause Mortality


Proportion of patients who achieved SVR = 36% (n=192)
Thirteen patients with SVR and 100 patients without SVR died, with a 10-year cumulative all-cause mortality rate of 8.9% [95% CI, 3.3%-14.5%] with SVR and 26.0% [95% CI, 20.2%-28.4%] without SVR.


![Graph showing all-cause mortality over time with and without SVR.](image)
RGT Paradigm With BOC + PegIFN/RBV in Tx-Naive Patients

- Indicated for all noncirrhotic treatment-naive patients

**HCV RNA**

- Early response: stop at Wk 28; f/u 24 wks
  - Undetectable
  - < 100 IU/mL
  - Undetectable

- Slow response: extend triple therapy to Wk 36; PR to Wk 48; f/u 24 wks
  - Detectable
  - < 100 IU/mL
  - Undetectable

Response-Guided Therapy Paradigm With BOC + PegIFN/RBV in Tx-Exp Patients

- Indicated for noncirrhotic previous relapsers or partial responders*[^1,2]

<table>
<thead>
<tr>
<th>HCV RNA</th>
<th>PegIFN/RBV</th>
<th>BOC + PegIFN/RBV</th>
<th>PegIFN/RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetectable</td>
<td>&lt; 100 IU/mL</td>
<td>Undetectable</td>
<td>Early response stop at Wk 36; f/u 24 wks</td>
</tr>
<tr>
<td>Detectable</td>
<td>&lt; 100 IU/mL</td>
<td>Undetectable</td>
<td>Slow response PR to Wk 48; f/u 24 wks</td>
</tr>
</tbody>
</table>

*RGT for this group indicated in US only; European prescribing information indicates that noncirrhotic previous relapsers or partial responders should receive 4 wks of pegIFN/RBV followed by 32 wks of BOC + pegIFN/RBV and then 12 wks of pegIFN/RBV, regardless of early response.[^3]

---

Safety Concerns Increased in Patients With More Advanced Disease

- CUPIC trial: early access program with telaprevir and boceprevir from France enrolling treatment-experienced patients with cirrhosis
  - Wk 16 interim analysis of 497 patients
- High rate of serious adverse events: 33% to 45%
- High rate of anemia
  - Grade 2: 19% to 23%
  - Grade 3/4: 4% to 12%
- High rate of premature discontinuation: 23% to 26%

Higher Discontinuation Rates in Real-World Settings Than in Clinical Trials

- Retrospective studies from the US: data from medical records review and included patients with genotype 1 HCV infection\(^1,2\)

<table>
<thead>
<tr>
<th>2 centers in Dallas and Miami with 12-wk follow-up(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusions: transplantation, dialysis, or HIV coinfected</td>
</tr>
<tr>
<td>Of 498 patients identified</td>
</tr>
<tr>
<td>- 18% began triple therapy</td>
</tr>
<tr>
<td>- 21% discontinued triple therapy before Wk 12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mount Sinai Medical Center and Montefiore with 12-wk follow-up(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Of 174 patients who initiated TVR-based triple therapy</td>
</tr>
<tr>
<td>- 33% discontinued TVR prematurely</td>
</tr>
<tr>
<td>- 21% discontinued treatment due to adverse events</td>
</tr>
</tbody>
</table>

Summary of Resistance Findings From Phase III Trials

♦ Sofosbuvir\(^{1-4}\)
  - No S282T mutations identified; other NS5B genetic variants not associated with change in phenotypic susceptibility

♦ Simeprevir\(^{5,6}\)
  - Baseline Q80K polymorphism present in 41% of patients with GT 1a HCV and associated with lower SVR12 rate in QUEST-1\(^{5}\)
  - Emergent NS3 protease mutations in > 90% of patients without SVR (GT 1a: R155K alone, with mutations at positions 80 and/or 168; GT 1b: most common mutation D168V, Q80R + D168E)\(^{5,6}\)

♦ Faldaprevir\(^{7}\)
  - Baseline Q80K present in 23% of patients with GT 1a HCV but not associated with SVR12 rate

New Data on Approved HCV Therapies
CUPIC: Telaprevir or Boceprevir + P/R in GT 1 Treatment-Experienced Cirrhotics

- French compassionate use program for early access to TVR and BOC before approval

HCV-TARGET: Triple Therapy (TVR or BOC + P/R) in a Broad Patient Population

- Interim analysis of longitudinal observational study of sequentially enrolled patients in academic and community medical centers in North America

<table>
<thead>
<tr>
<th>Patient Disposition, n (%)</th>
<th>DAA + P/R (N = 1919)</th>
<th>Patient Disposition</th>
<th>DAA + P/R (N = 1457)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients in current analysis</td>
<td>1457</td>
<td>Early discontinuation, % (n)</td>
<td>335 (23)</td>
</tr>
<tr>
<td>- Patients with cirrhosis</td>
<td>550</td>
<td>- Lack of efficacy</td>
<td>8</td>
</tr>
<tr>
<td>- Still on treatment, &lt; 16 wks</td>
<td>139 (6)</td>
<td>- Adverse event</td>
<td>9</td>
</tr>
<tr>
<td>- Still on treatment, &gt; 16 wks</td>
<td>664 (46)</td>
<td>- Other reasons</td>
<td>5</td>
</tr>
<tr>
<td>- Completed full course</td>
<td>319 (22)</td>
<td>- Multiple reasons</td>
<td>2</td>
</tr>
</tbody>
</table>

## HCV-TARGET: Baseline Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Cirrhotic (n = 550)</th>
<th>Noncirrhotic (n = 787)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-64 yrs of age, %</td>
<td>84</td>
<td>80</td>
</tr>
<tr>
<td>Male, %</td>
<td>69</td>
<td>55</td>
</tr>
<tr>
<td>White, %</td>
<td>78</td>
<td>70</td>
</tr>
<tr>
<td>Genotype, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>1b</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Not otherwise specified</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Treatment naive, %</td>
<td>41</td>
<td>52</td>
</tr>
<tr>
<td>Mean hemoglobin &gt; 12 g/dL</td>
<td>94</td>
<td>84</td>
</tr>
<tr>
<td>Mean platelets, cells/mm³</td>
<td>126,000</td>
<td>203,000</td>
</tr>
<tr>
<td>Mean total bilirubin, mg/dL (range)</td>
<td>1.0 (0.2-5.0)</td>
<td>0.63 (0.2-2.5)</td>
</tr>
<tr>
<td>Mean albumin, g/dL (range)</td>
<td>3.9 (1.4-5.0)</td>
<td>4.2 (1.9-5.4)</td>
</tr>
<tr>
<td>Mean Meld score (range)</td>
<td>8 (6-22)</td>
<td>N/A</td>
</tr>
<tr>
<td>Presence of varices, %</td>
<td>33</td>
<td>1</td>
</tr>
</tbody>
</table>

HCV-TARGET: Virologic Response by Previous Treatment Category

In interim analysis, on-treatment efficacy of telaprevir and boceprevir in real-world setting comparable to registrational trials

<table>
<thead>
<tr>
<th>Treatment Category</th>
<th>TVR Wk 4</th>
<th>TVR Wk 12</th>
<th>BOC Wk 8</th>
<th>BOC Wk 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Naive</td>
<td>54</td>
<td>61</td>
<td>86</td>
<td>78</td>
</tr>
<tr>
<td>Previous Relapser</td>
<td>54</td>
<td>28</td>
<td>25</td>
<td>48</td>
</tr>
<tr>
<td>Previous Partial or Null Response</td>
<td>43</td>
<td>73</td>
<td>15</td>
<td>44</td>
</tr>
<tr>
<td>Unknown Response</td>
<td>45</td>
<td>16</td>
<td>37</td>
<td>32</td>
</tr>
</tbody>
</table>

## HCV-TARGET: Safety Assessment of Triple Therapy in Patients With Cirrhosis

<table>
<thead>
<tr>
<th>Event, %</th>
<th>Cirrhotic (n = 550)</th>
<th>Noncirrhotic (n = 787)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAE</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Death, n</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Early discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Due to adverse event</td>
<td>44</td>
<td>33</td>
</tr>
<tr>
<td>- Due to lack of efficacy</td>
<td>31</td>
<td>38</td>
</tr>
<tr>
<td>Decompensation</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Infection</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>Severe rash (grade 3/SCAR)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin &lt; 8.5 g/dL</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>RBV dose reduction</td>
<td>42</td>
<td>31</td>
</tr>
<tr>
<td>EPO</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Transfusion</td>
<td>11</td>
<td>5</td>
</tr>
</tbody>
</table>

CONCISE: Telaprevir + P/R for Patients With GT 1 HCV and IL28B CC

♦ Interim analysis of ongoing, multicenter, randomized, active-controlled, exploratory phase IIIb study

Treatment-naive patients or previous relapsers with GT 1 HCV, IL28B CC genotype, and no cirrhosis (N = 239)

Telaprevir + P/R

Wk 12

2:1 randomization*

T12/PR24
Continue P/R alone (n = 52)

T12/PR12
Stop all treatment (n = 107)

Wk 24

*Patients with RVR randomly assigned 2:1 to T12/PR12 or T12/PR24.

CONCISE: Virologic Response With T12/PR12 vs T12/PR24 in Pts With RVR

By SVR12 time point, relapse had occurred in 8% of patients in T12/PR12 arm vs 0% in T12/PR24 arm.

Safety profile consistent with that observed in previous telaprevir studies.

eRVR: undetectable HCV RNA at Wks 4 and 12.
Meta-analysis of BOC + P/R in Pts With GT 1 HCV and Compensated Cirrhosis

Pooled analysis of SPRINT-2, RESPOND-2, PEG2a, PROVIDE, and Anemia Management Study, including treatment-naive and treatment-experienced patients

Cirrhotics more frequently experienced SAEs, dose modification due to AEs and/or anemia, infections, Hb < 10 g/dL, grade 2/3 thrombocytopenia, grade 3/4 neutropenia

<table>
<thead>
<tr>
<th>Event, %</th>
<th>BOC/P/R</th>
<th>P/R</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F0-2</td>
<td>F3</td>
</tr>
<tr>
<td>SAE</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Dose mod due to AEs</td>
<td>39</td>
<td>40</td>
</tr>
<tr>
<td>- Due to anemia</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>Discontinue due to AEs</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>- Due to anemia</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Transfusions</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Life-threatening treatment-emergent AEs</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Death</td>
<td>&lt; 1</td>
<td>0</td>
</tr>
</tbody>
</table>

TARGET-C: TVR With Reduced RBV + PegIFN in HCV Hemodialysis Patients

- Increased incidence of select AEs in TVR arms vs pegIFN/RBV:
  - Anemia (54% vs 33%)
  - Neutropenia (50% vs 33%)
  - Thrombocytopenia (37% vs 25%)
  - Rash (42% vs 17%)
  - Anorectal dysfunction (33% vs 0%)
  - Dysgeusia (42% vs 17%)

Safety and Efficacy of PegIFN lambda-1a vs PegIFN alfa-2a in GT 2/3 Tx-Naive Pts

♦ EMERGE study: each group received pegIFN + RBV for 24 wks

![Graph showing SVR24 (%) for different dosages of PegIFN lambda-1a and PegIFN alfa-2a]

♦ PegIFN lambda-1a 180 μg/wk dosage chosen for phase III trials

<table>
<thead>
<tr>
<th>Hematologic Adverse Event</th>
<th>Lambda 180 μg (n = 29)</th>
<th>Alfa 180 μg (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin low (&lt; 10 \text{ g/dL or } \Delta &gt; 3.4 \text{ g/dL})</td>
<td>6.9</td>
<td>44.8</td>
</tr>
<tr>
<td>RBV dose reduction (\text{hemoglobin associated})</td>
<td>0</td>
<td>23.3</td>
</tr>
<tr>
<td>Neutrophils low (&lt; 750 \text{ cells/mm}^3)</td>
<td>0</td>
<td>27.6</td>
</tr>
<tr>
<td>Platelets low (&lt; 100,000 \text{ cells/mm}^3)</td>
<td>0</td>
<td>24.1</td>
</tr>
<tr>
<td>PegIFN dose reduction (\text{hematologic abnormality})</td>
<td>0</td>
<td>23.3</td>
</tr>
</tbody>
</table>