HEPATITIS C
Treatment update 2012

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Disclosures

• None
HEPATITIS C

- Epidemiology
- Spectrum of disease
- Treatment perspective
- Review of recent clinical trials
- Current standard of care
- New problems: increased side effects, resistance, drug-drug interactions
- The future
- Who to treat, why, when, how?
HEPATITIS C

• 170 million people infected worldwide (estimated)
  • 4 million in the US
    • 0.5 million diagnosed
• Annual death toll of 8,000 to 10,000

• 25%- 40% of all chronic liver disease and 40% of OLT
  • Remains leading cause of liver transplant

• The burden of chronic infections continues to grow, expected
to triple / quadruple over the next generation

• Very large reservoir of chronic infections

• Estimated annual direct medical costs: >$5.5 billion

Figure 4.1. Reported and adjusted* number of acute hepatitis C cases — United States, 1992–2009

* Adjusted for underreporting.
Note: Until 1995, acute hepatitis C was reported as “acute hepatitis, non-A /non-B.”
Source: National Notifiable Diseases Surveillance System (NNDSS)

Source: CDC
ACUTE VIRAL HEPATITIS C

• Acute infection rates declining.
  – 230,000 cases per year in the 1980s
  – 36,000 new cases in 1996

• The majority of cases now related to IVDU in the US

• In >40% of cases (CDC data) there was no identifiable risk factor

• Clinical symptomatology as in other forms of viral hepatitis, and the disease can be distinguished only by serologic testing
Figure 4.5. Distribution of risk exposures/behaviors associated with acute hepatitis C — United States, 2009

*Includes case reports indicating the presence of at least one of the following risks 6 weeks to 6 months prior to onset of acute, symptomatic hepatitis C: 1) using injection drugs; 2) having sexual contact with suspected/confirmed hepatitis C patient; 3) being a man who has sex with men; 4) having multiple sex partners concurrently; 5) having household contact with suspected/confirmed hepatitis C patient; 6) having had occupational exposure to blood; 7) being a hemodialysis patient; 8) having received a blood transfusion; 9) having sustained a percutaneous injury; and 10) having undergone surgery.

Source: National Notifiable Diseases Surveillance System (NNDSS)
<table>
<thead>
<tr>
<th>Year</th>
<th>Estimated Acute Cases</th>
<th>Estimated Total New Infections</th>
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<tr>
<td>2010</td>
<td>2,800</td>
<td>17,000</td>
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Source: CDC
Prevalence of Blood-Borne Chronic Viral Infections in the US

- HCV: 2,475,000
  - Unaware: 75%
  - Aware: 25%

- HBV: 825,000
  - Unaware: 65%
  - Aware: 35%

- HIV: 715,000
  - Unaware: 21%
  - Aware: 79%

Institute of Medicine. Available at: http://www.nap.edu/catalog/12793.html.
Why should baby boomers get tested for Hepatitis C?

More than 75% of adults with Hepatitis C are baby boomers. Baby boomers are people born from 1945 through 1965. Most of them don’t know they are infected.

- Baby boomers are five times more likely to be infected with Hepatitis C.
- Liver disease, liver cancer, and deaths from Hepatitis C are on the rise.
- As baby boomers age, there is a greater chance that they will develop serious, life-threatening liver disease from Hepatitis C.
- Testing people in this generation will help them learn if they are infected and get them into lifesaving care and treatment.
- Early diagnosis and treatment can help prevent liver damage, cirrhosis, and even liver cancer.

Why do baby boomers have such high rates of Hepatitis C?

The reason that baby boomers have the highest rates of Hepatitis C is not completely understood. Most boomers are believed to have become infected in the 1970s and 1980s when rates of Hepatitis C were the highest. Since chronic Hepatitis C can go unnoticed for up to several decades, baby boomers could be living with an infection that occurred many years ago.

Hepatitis C is primarily spread through contact with blood from an infected person. Many baby boomers could have gotten infected from contaminated blood and blood products before widespread screening of the blood supply began in 1992 and universal precautions were adopted. Others may have become infected from injecting drugs, even if only once in the past. Still, many baby boomers do not know how or when they were infected.

What should baby boomers know about Hepatitis C?

Hepatitis C is a liver disease that results from infection with the Hepatitis C virus. The disease can cause serious health problems including liver damage, cirrhosis, liver cancer and even death. In fact, Hepatitis C is a leading cause of liver cancer and the leading cause of liver transplants.

People with Hepatitis C:

- Often have no symptoms
- Can live with an infection for decades without feeling sick
- Can be successfully treated with medications

CDC now recommends that anyone born from 1945 through 1965 get tested for Hepatitis C.

Is there a test for Hepatitis C?

Yes. There is a simple blood test to determine if a person has ever been infected with the Hepatitis C virus.

For more information

Talk to your health professional, call your health department, or visit www.cdc.gov/knowmorehepatitis.
HEPATITIS C

Clinical manifestations
Spectrum of Disease
ACUTE VIRAL HEPATITIS

• Acute icteric hepatitis in the US:
  • 47%-49% acute HAV infection
  • 33%-35% acute HBV infection
  • 15%-16% acute HCV infection
ACUTE VIRAL HEPATITIS

• **Asymptomatic**
  - acute viral hepatitis: ↑LFTs + serologic markers
  - 10-30 times more common

• **Symptomatic with or without jaundice**
  - Incubation period (14 to 160 days), preicteric, icteric, and convalescent phases
  - Symptoms: malaise/fatigue, joint aches/myalgia, anorexia, nausea/vomiting, and RUQ abdominal discomfort
  - Patients may present with only "flu-like" illness
  - Low risk of acute liver failure with acute HCV

Ray S, Thomas D. Mandell’s Principles and Practice of Infectious Diseases 7th Edition 2009
The Natural History of HCV Infection and Its Variability from Person to Person

CHRONIC VIRAL HEPATITIS C

- 6 major HCV genotypes, geographic variation
- Most common clinical presentation: asymptomatic
- Symptomatology according to stage of disease
- Predictors of disease progression:
  - Histologic features, advanced age, ALT.
  - Moderate and severe hepatitis/fibrosis progress to cirrhosis almost invariably over 20 to 10 years, respectively
- Rate of progression is variable, not linear
- ALT > AST
- Hypersplenism: thrombocytopenia, leukopenia

Ray S, Thomas D. Mandell's Principles and Practice of Infectious Diseases 7th Edition 2009
CHRONIC HCV: EXTRAHEPATIC MANIFEST.

- Sjögren's (sicca) syndrome
- Essential mixed cryoglobulinemia
- Lymphoproliferative disorders (MGUS, B-cell non-Hodgkin's lymph)
- Idiopathic Thrombocytopenic purpura
- Lichen planus and porphyria cutanea tarda
- Leukocytoclastic vasculitis
- Type 2 diabetes mellitus is more common in chronic Hep. C
- Membrano-proliferative GN, membranous nephropathy
CHRONIC VIRAL HEPATITIS C

Hepatocellular Carcinoma (HCC):

- Mechanism of hepatocarcinogenesis is unknown
- ↑ risk of HCC among patients with chronic hepatitis C:
  - Cirrhosis
  - male gender
  - ETOH and tobacco abuse
  - hepatic iron overload
  - concomitant HBV infection
  - Infection with HCV genotype 1b

CHRONIC VIRAL HEPATITIS C

• Over the next decade:
  • frequency of cirrhosis expected to increase by $> 500\%$
  • frequency of HCC expected to increase by $> 250\%$
  • frequency of liver-related deaths by $> 200\%$
  • frequency of both decompensated cirrhosis and OLT by $> 60\%$
Figure 3. Stacked prevalence curves showing number of cases by year with cirrhosis according to gender and age at time of initial hepatitis C virus infection.

HVC-HIV co-infection

- 1/3 of HIV-infected patients have chronic Hep. C

- 75% of HIV-infected IVDU have chronic Hep.

- Chronic Hepatitis C is a growing cause of morbidity and mortality given improvement in life expectancy for HIV-infected patients:
  - increased level of HIV viremia
  - higher rate of hepatic fibrosis. More rapid progression
  - clinical course of chronic hepatitis C is accelerated
  - increased frequency of liver failure
  - 5-fold increase in mortality secondary to Hep. C-related ESLD since the introduction of HAART for HIV infection

Sherman K et al. Hepatology 2011;54:2245-5
HIV-related
- Immunosuppression
- Antiretrovirals (NNRTIs, NRTIs, or PIs)
- Opportunistic infection
- Immune reconstitution
- Pro-inflammatory state
- Insulin resistance
- Dyslipidemia
- Microbial translocation

HCV-related
- Insulin resistance
- Pro-inflammatory state

Steatosis
Necro-inflammation
Stellate cell activation

Host
- Alcohol use
- Older age
- BMI/central obesity
- Insulin resistance
- Non-alcoholic fatty liver disease
- Medications
- HBV co-infection

Fibrosis

Cirrhosis
HVC-HIV co-infection

- PegInterferon + Ribavirin treatment is less effective
- Liver transplantation is not widely available
- Safety and efficacy of HCV PIs unproven in HIV/HCV-coinfected persons
- Drug to drug interactions are more complex, data still limited
- Cost concerns

## Supplementary Table 1. Randomized Controlled Trials of PEG-IFN and RBV in Coinfected Patients

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<td>PEG-IFN formulation</td>
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<td>2a&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2b&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2a&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Dose of RBV</td>
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<td>1000–1200&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>White (%)</td>
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HVC-HIV co-infection

- PegIF + ribavirin remain the standard of care for treatment of genotype 2, 3, or 4
- Some co-infected patients should receive HCV PI + PR
- Use of HCV PIs alone (or with only peginterferon) is contraindicated given rapid selection of resistant-associated variants (RAVs)
- HCV-PI and/or PR should not be used with decompensated cirrhosis
- Treatment is more efficacious in early disease, but in general benefits outweighs risks in advanced fibrosis
- HIV infection should be controlled before HCV treatment is initiated
- Drug-drug interactions should be closely monitored, dose changes considered

Sherman K et al. Hepatology 2011;54:2245-53
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<td>750 mg every 8 hours</td>
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<td>↓ 20%</td>
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HVC-HIV co-infection: Use of Telaprevir

- Telaprevir + PR x 12 weeks followed by PR x 48 weeks
  - Ritonavir-boosted atazanavir + Truvada – safe to use
  - Raltegravir is considered safe despite expected increase in raltegravir level (about 30%)
  - Efavirenz + Truvada (Atripla) – safe to use
  - PR + TVR should be stopped if HCV RNA is not <1,000 IU/ml at treatment weeks 4 and 12.
  - Stop also if HCV RNA is detectable at week 24

Sherman K et al. Hepatology 2011;54:2245-53
HVC-HIV co-infection: Use of Boceprevir

- PR for 4 weeks, followed by BOC + PR x 44 wks (total 48 wks)
- Raltegravir plus tenofovir/emtricitabine is safe
- Avoid using boceprevir with ritonavir-boosted lopinavir (Kaletra), atazanavir, or darunavir
- BOC should NOT be used with efavirenz, etravirine, or nevirapine
- Treatment with PR + BOC should be stopped if HCV RNA is >100 IU at treatment week 12. Also if detectable at week 24
- Clinical trials should be considered an option

Sherman K et al. Hepatology 2011;54:2245-53
HEPATITIS C

GOAL OF TREATMENT

- Erradication of the Hepatitis C virus defined as sustained virologic response (SVR)

- **SVR:** Undetectable serum HCV RNA level 6 months after treatment cessation
RAPID VIROLOGIC RESPONSE (RVR):
- HCV RNA undetectable at week 4

EXTENDED RAPID VIROLOGIC RESPONSE (eRVR):
- undetectable HCV RNA level at week 4 and week 12 (for Telaprevir), weeks 8 and 24 for Boceprevir
- term used in response-guided therapy (RGT)

EARLY VIROLOGIC RESPONSE:
- ≥ 2-log decrease in HCV RNA VL at week 12 of therapy
- Lack of such a response has a very high NPV for SVR

END OF TREATMENT RESPONSE (EOTR):
- HCV RNA undetectable at the end of treatment
RELAPSE:
HCV RNA levels undetectable at the end of treatment, but detectable during follow-up

PARTIAL RESPONSE:
≥2-log$_{10}$ decline in HCV RNA from baseline at week 12, but never achieved undetectable HCV RNA

NULL RESPONSE:
<2-log$_{10}$ decline in HCV RNA from baseline at week 12 of prior therapy
CHRONIC HEPATITIS C: TREATMENT

• Historical background

• recombinant interferon-alfa introduced in the early 1980s.
• Initially SVR’s < 25% for 6-moth therapy (end-point: ALT)
  • HCV RNA-PCR showed those SVR’s to be <10%
  • Double duration of therapy (12 months) improved SVR’s to 20%
• Combination with PO Ribavirin (weight-based) ↑ SVRs to 40%
• Introduction of Pegylated interferons improved SVRs to 55%
• Introduction of NS3/4A serine protease inhibitors. ↑ SVRs to 70%
• SVR after completion of therapy: maintenance of virologic, biochemical, clinical, and histologic benefit = CURE
The HCV Genome and Expressed Polyprotein

Hepatitis C virus life cycle

1. Receptor-virus binding
2. Endocytosis
3. Fusion and uncoating
4. Polyprotein processing
5. Cleavage
6. Formation of viral replication complex
7. Viral RNA replication
8. Assembly of progeny virions
9. Release

Butt A et al. CID 2012;54(1):96–104
HEP. C TREATMENT: INTERFERON

• Pegylated interferons: long-acting interferons bound to polyethylene glycol (PEG) – long half life

• Once weekly injections;
  • Peg-Interon - pegylated interferon-alfa-2b
  • Pegasys - pegylated interferon-alfa-2a
  • Infergen. Consensus IF- non-naturally occurring IF
• Both Pegylated IF are comparable in efficacy

• Maintenance of the Ribavirin dose is essential to achieve SVR for up to 20 wks. Dose reductions after that, if needed, do not reduce SVR rates
HEP. C TREATMENT: RIBAVIRIN

- Nucleoside analog
- Unknown mechanism of action
- No antiviral activity when used alone
- Proposed mechanism of action: immunologic modulation (shift from Th2 response to Th1 response), inhibition of host inosine monophosphate dehydrogenase (IMPDH) activity, or induction of viral mutational catastrophe
- Addition of weight-based ribavirin to interferon substantially reduces virologic relapse, increasing SVR
HEP. C TREATMENT: Telaprevir and Boceprevir

• Early generation Serine Protease Inhibitors
• Both directly inhibit the HCV NS3/4A serine protease, preventing cleavage of the HCV polyprotein chain and halting viral replication

• Both are approved for HCV genotype 1 infection only

• Telaprevir:
  • Extensively metabolized in the liver, primarily by cytochrome P450 CYP3A4.
  • Telaprevir is a strong inhibitor of CYP3A4, and Inhibitor of P-glycoprotein
  • 80% eliminated in feces

• Boceprevir:
  • Extensively metabolized, by aldo-keto reductase and by CYP3A4/5 enzymes.
  • Inhibitor of CYP3A4 and P-glycoprotein
  • Eliminated primarily by hepatic clearance. 80% eliminated in feces
  • No dose adjustment needed for mild / moderate hepatic impairment / renal failure
Adverse effects:

- **Interferons:**
  - Flu-like symptoms, marrow suppression, irritability/depression, and thyroiditis / other autoimmune reactions

- **Ribavirin:**
  - Hemolytic anemia, nasal/chest congestion, pruritus, rashes, gout
  - Teratogenic: strict birth control
  - Careful in renal insufficiency
  - Management of anemia: dose reduction, erythropoietin, transfus.
    - Dose reduction: for hemoglobin < 10 – decrease by 200 mg/d for hemoglobin < 8.5 – discontinue
CHRONIC HEPATITIS C: TREATMENT

• Side effects:

**Telaprevir** — rash – up to 50%. Severe rash: 4%
pruritus, anemia, nausea, hemorrhoids, diarrhea, ano-rectal
discomfort, dysgeusia, fatigue, vomiting, and anal pruritus

**Boceprevir** — fatigue, anemia, nausea, headache, and dysgeusia
Other side effects include dry mouth, vomiting, and diarrhea.
Neutropenia and thrombocytopenia
55 yo AA male with chronic Hep C and cirrhosis undergoing treatment with PR and Boceprevir. He experienced >2 log reduction in his HCV RNA at week #4, and HCV was undetectable at week 12. He presents (week #12) for evaluation and reports worsening tiredness. He works as maintenance crew member in a large company, frequent performing outdoor jobs. His hemoglobin is 9.1

What should you do?

A. Start treatment with Erythropoietin
B. Ribavirin dose reduction
C. Start treatment with Erythropoietin and reduce ribavirin dose
D. Reduce dose of Boceprevir
E. Continue close clinical observation, no change in management indicated.
**Table 1. Predictors of a Favorable Response to Treatment with Peginterferon and Ribavirin.**

<table>
<thead>
<tr>
<th>General characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV genotype other than 1</td>
</tr>
<tr>
<td>Low baseline viral level</td>
</tr>
<tr>
<td>White race</td>
</tr>
<tr>
<td>Interleukin-28B genotype*</td>
</tr>
<tr>
<td>Absence of fibrosis</td>
</tr>
<tr>
<td>Body weight &lt;85 kg</td>
</tr>
<tr>
<td>Age &lt;40 yr</td>
</tr>
<tr>
<td>Female sex</td>
</tr>
<tr>
<td>ALT quotient ≥3†</td>
</tr>
<tr>
<td>HCV-specific immune response</td>
</tr>
<tr>
<td><strong>Before treatment</strong></td>
</tr>
<tr>
<td>Absence of both insulin resistance and steatosis</td>
</tr>
<tr>
<td>Statin use</td>
</tr>
<tr>
<td><strong>During treatment</strong></td>
</tr>
<tr>
<td>Response during treatment (RVR or EVR)‡</td>
</tr>
<tr>
<td>Adherence to treatment</td>
</tr>
<tr>
<td>Standard dose of ribavirin</td>
</tr>
</tbody>
</table>

CHRONIC HEPATITIS C: NEW THERAPIES

- GOAL of new therapies
  - Decrease toxicity
  - Increase efficacy
  - Broaden indications: early and late stage, young and old, patients with co-morbid conditions, post-transplant patients, co-infected patients (HIV, HBV)
What do we accomplish when treatment is successful?
# Table 2. Frequency and Rate of Events During Follow-Up in 711 Patients Positive for HIV/HCV Stratified According to Response to IFN-RBV

<table>
<thead>
<tr>
<th>Event</th>
<th>Non-SVR (N = 493)</th>
<th>SVR (N = 218)</th>
<th>P</th>
<th>Rate/100 Person-Years (95% CI)</th>
<th>Non-SVR</th>
<th>SVR</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up-months, median (IQR)</td>
<td>22.1 (12.7-39.1)</td>
<td>18.7 (11.3-36.9)</td>
<td>0.071</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up-n (%)</td>
<td>25 (5)</td>
<td>13 (6)</td>
<td>0.955</td>
<td></td>
<td>2.3 (1.49-3.39)</td>
<td>2.97 (1.75-5.36)</td>
<td>0.413</td>
</tr>
<tr>
<td>Deaths-n (%)</td>
<td>34 (6.9)</td>
<td>2 (0.9)*</td>
<td>0.001</td>
<td></td>
<td>3.12 (2.16-4.37)</td>
<td>0.46 (0.06-1.65)</td>
<td>0.003</td>
</tr>
<tr>
<td>Liver-related-n (%)</td>
<td>18 (3.7)</td>
<td>1 (0.5)*</td>
<td>0.029</td>
<td></td>
<td>1.65 (0.98-2.61)</td>
<td>0.23 (0.01-1.27)</td>
<td>0.028</td>
</tr>
<tr>
<td>AIDS-related-n (%)</td>
<td>2 (0.4)</td>
<td>0 (0)</td>
<td>0.826</td>
<td></td>
<td>0.18 (0.02-0.66)</td>
<td>0 (0-0.84)</td>
<td>0.855</td>
</tr>
<tr>
<td>Other causes-n (%)</td>
<td>14 (2.8)</td>
<td>1 (0.5)</td>
<td>0.079</td>
<td></td>
<td>1.29 (0.7-2.17)</td>
<td>0.23 (0.01-1.27)</td>
<td>0.075</td>
</tr>
<tr>
<td>Liver decompensation-n (%)†</td>
<td>45 (9.1)</td>
<td>1 (0.5)*</td>
<td>&lt;0.001</td>
<td></td>
<td>4.33 (3.16-5.8)</td>
<td>0.23 (0.01-1.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hepatocarcinoma-n (%)</td>
<td>9 (1.8)</td>
<td>0 (0)</td>
<td>0.100</td>
<td></td>
<td>0.83 (0.38-1.58)</td>
<td>0 (0-0.84)</td>
<td>0.099</td>
</tr>
<tr>
<td>Liver transplantation-n (%)</td>
<td>11 (2.2)</td>
<td>0 (0)</td>
<td>0.058</td>
<td></td>
<td>1.02 (0.50-1.82)</td>
<td>0 (0-0.84)</td>
<td>0.034</td>
</tr>
</tbody>
</table>

*By log-rank test.
†Ascites, upper gastrointestinal bleeding, hepatic encephalopathy.
CI, confidence interval; HCV, hepatitis C virus; IFN, interferon; IQR, interquartile range; RBV, ribavirin; SVR, sustained virological response.

NR: no response
BT/R: breakthrough / relapse
SVR: Sustained Virologic Response

Morgan TM, and the HALT-C Trial Group. Hepatology 2010;52:833-44
PROTEASE INHIBITORS: PHASE 3 TRIALS

• **TELAPREVIR**
  • Naïve patients
    • **ADVANCE**
    • **ILLUMINATE**
  • Experienced patients
    • **REALIZE**

• **BOCEPREVIR**
  • Naïve patients
    • **SPRINT-2**
  • Experienced patients
    • **RESPOND-2**
Telaprevir for Previously Untreated Chronic Hepatitis C Virus Infection

Ira M. Jacobson, M.D., John G. McHutchison, M.D., Geoffrey Dusheiko, M.D.,
Adrian M. Di Bisceglie, M.D., K. Rajender Reddy, M.D., Natalie H. Bzowej, M.D.,
Patrick Marcellin, M.D., Andrew J. Muir, M.D., Peter Ferenci, M.D.,
Robert Flisiak, M.D., Jacob George, M.D., Mario Rizzato, M.D., Daniel Shouval, M.D.,
Ricard Sola, M.D., Ruben A. Terg, M.D., Eric M. Yoshida, M.D., Nathalie Adda, M.D.,
Leif Bengtsson, B.Sc., Abdul J. Sankoh, Ph.D., Tara L. Kieffer, Ph.D.,
Shelley George, M.D., Robert S. Kauffman, M.D., Ph.D., and Stefan Zeuzem M.D.,
for the ADVANCE Study Team*

ABSTRACT
ADVANCE TRIAL

  - 1,088 patients randomized to 1 of 3 treatment arms:

  1. **T12PR**: 12 weeks of TPR followed by PR alone x 12 weeks (if eRVR) or 36 weeks (no eRVR)
  2. **T8PR** followed by PR x 16 weeks (if eRVR) or 40 weeks (no eRVR)
  3. PR x 48 weeks

- **T8PR** arm was introduced to explore if an AE (rash) could be minimized while keeping same efficacy

**eRVR**: extended Rapid Virologic Response: Undetectable plasma HCV RNA at week 4 and at week 12
1095 Patients underwent randomization

365 Were assigned to the T12PR group
  363 Received at least one dose of study drugs
  2 Did not receive study drugs

  210 Were assigned to 24 wk of treatment
    195 Completed treatment
    15 Discontinued treatment
      9 Had adverse event
      1 Had virologic failure
      5 Had other reason

  153 Were assigned to 48 wk of treatment
    73 Completed treatment
    80 Discontinued treatment
      27 Had adverse event
      4 Were lost to follow-up
      37 Had virologic failure
      12 Had other reason

  207 Were assigned to 24 wk of treatment
    191 Completed treatment
    16 Discontinued treatment
      10 Had adverse event
      1 Was lost to follow-up
      5 Had other reason

  157 Were assigned to 48 wk of treatment
    69 Completed treatment
    88 Discontinued treatment
      27 Had adverse event
      2 Were lost to follow-up
      1 Withdrew consent
      40 Had virologic failure
      18 Had other reason

271/363 (75%) Had SVR

365 Were assigned to the T8PR group
  364 Received at least one dose of study drugs
  1 Did not receive study drugs

  202 Completed treatment
    159 Discontinued treatment
      26 Had adverse event
      1 Died
      4 Were lost to follow-up
      2 Withdrew consent
      118 Had virologic failure
      8 Had other reasons

250/364 (69%) Had SVR

365 Were assigned to the PR (control) group
  361 Received at least one dose of study drugs
  4 Did not receive study drugs

158/361 (44%) Had SVR
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>T12PR (N=363)</th>
<th>T8PR (N=364)</th>
<th>PR (N=361)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age — yr</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>49</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>Range</td>
<td>19–69</td>
<td>19–68</td>
<td>18–69</td>
</tr>
<tr>
<td><strong>Body-mass index†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>25.7</td>
<td>26.2</td>
<td>26.4</td>
</tr>
<tr>
<td>Range</td>
<td>18–47</td>
<td>17–46</td>
<td>17–48</td>
</tr>
<tr>
<td><strong>Distribution — no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>155 (43)</td>
<td>145 (40)</td>
<td>130 (36)</td>
</tr>
<tr>
<td>25 to &lt;30</td>
<td>129 (36)</td>
<td>131 (36)</td>
<td>144 (40)</td>
</tr>
<tr>
<td>≥30</td>
<td>77 (21)</td>
<td>86 (24)</td>
<td>87 (24)</td>
</tr>
<tr>
<td><strong>Male sex — no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>214 (59)</td>
<td>211 (58)</td>
<td>211 (58)</td>
</tr>
<tr>
<td><strong>Race — no. (%)‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>325 (90)</td>
<td>315 (87)</td>
<td>318 (88)</td>
</tr>
<tr>
<td>Black</td>
<td>26 (7)</td>
<td>40 (11)</td>
<td>28 (8)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (1)</td>
<td>5 (1)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (2)</td>
<td>4 (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td><strong>Ethnic group — no. (%)‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>35 (10)</td>
<td>44 (12)</td>
<td>38 (11)</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>328 (90)</td>
<td>320 (88)</td>
<td>323 (89)</td>
</tr>
<tr>
<td><strong>Alanine aminotransferase — IU/liter</strong></td>
<td>84±69</td>
<td>80±62</td>
<td>88±67</td>
</tr>
<tr>
<td><strong>Total bilirubin — µmol/liter§</strong></td>
<td>10±5</td>
<td>9±4</td>
<td>9±4</td>
</tr>
<tr>
<td><strong>Serum albumin — g/liter</strong></td>
<td>45±3</td>
<td>44±3</td>
<td>44±3</td>
</tr>
<tr>
<td><strong>Platelet count — x10^9/liter</strong></td>
<td>250±73</td>
<td>236±65</td>
<td>243±70</td>
</tr>
<tr>
<td><strong>HCV subtype — no. (%)¶</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>213 (59)</td>
<td>210 (58)</td>
<td>208 (58)</td>
</tr>
<tr>
<td>1b</td>
<td>149 (41)</td>
<td>151 (41)</td>
<td>151 (42)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (&lt;1)</td>
<td>3 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Characteristic</td>
<td>T12PR (N=363)</td>
<td>T8PR (N=364)</td>
<td>PR (N=361)</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
<td>---------------</td>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>HCV RNA — log₁₀ IU/ml</td>
<td>6.3±0.7</td>
<td>6.3±0.7</td>
<td>6.3±0.7</td>
</tr>
<tr>
<td>HCV RNA ≥800,000 IU/ml — no. (%)</td>
<td>281 (77)</td>
<td>279 (77)</td>
<td>279 (77)</td>
</tr>
<tr>
<td>Stage of fibrosis and cirrhosis — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None or minimal fibrosis</td>
<td>134 (37)</td>
<td>128 (35)</td>
<td>147 (41)</td>
</tr>
<tr>
<td>Portal fibrosis</td>
<td>156 (43)</td>
<td>151 (41)</td>
<td>141 (39)</td>
</tr>
<tr>
<td>Bridging fibrosis</td>
<td>52 (14)</td>
<td>59 (16)</td>
<td>52 (14)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>21 (6)</td>
<td>26 (7)</td>
<td>21 (6)</td>
</tr>
</tbody>
</table>
### Table 2. Response during and after the Treatment Period, According to Treatment Group.

<table>
<thead>
<tr>
<th>Response</th>
<th>T12PR (N=363)</th>
<th>T8PR (N=364)</th>
<th>PR (N=361)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetectable HCV RNA during treatment period — no. (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At week 4</td>
<td>246 (68)</td>
<td>242 (66)</td>
<td>34 (9)</td>
</tr>
<tr>
<td>At weeks 4 and 12</td>
<td>212 (58)</td>
<td>207 (57)</td>
<td>29 (8)</td>
</tr>
<tr>
<td>Undetectable HCV RNA at end of treatment period — no. (%)</td>
<td>314 (87)</td>
<td>295 (81)</td>
<td>229 (63)</td>
</tr>
<tr>
<td>Undetectable HCV RNA 24 wk after end of treatment: sustained virologic response — no./total no. (%) †</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients‡</td>
<td>271/363 (75)</td>
<td>250/364 (69)</td>
<td>158/361 (44)</td>
</tr>
<tr>
<td>Patients with undetectable HCV RNA at weeks 4 and 12</td>
<td>189/212 (89)</td>
<td>171/207 (83)</td>
<td>28/29 (97)</td>
</tr>
<tr>
<td>Patients with detectable HCV RNA at weeks 4 or week 12</td>
<td>82/151 (54)</td>
<td>79/157 (50)</td>
<td>130/332 (39)</td>
</tr>
<tr>
<td>Patients with undetectable HCV RNA at week 4</td>
<td>206/246 (84)</td>
<td>188/242 (78)</td>
<td>32/34 (94)</td>
</tr>
<tr>
<td>Patients with detectable HCV RNA at week 4</td>
<td>65/117 (56)</td>
<td>62/122 (51)</td>
<td>126/327 (39)</td>
</tr>
<tr>
<td>Undetectable HCV RNA at 72 wk — no. (%)‡</td>
<td>265 (73)</td>
<td>243 (67)</td>
<td>158 (44)</td>
</tr>
<tr>
<td>Relapse among patients with undetectable HCV RNA at end of treatment period — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>27/314 (9)</td>
<td>28/295 (9)</td>
<td>64/229 (28)</td>
</tr>
<tr>
<td>Patients who completed treatment</td>
<td>17/264 (6)</td>
<td>18/247 (7)</td>
<td>51/189 (27)</td>
</tr>
</tbody>
</table>

* Patients with undetectable HCV RNA at week 4 met the criterion for a rapid virologic response, and patients with undetectable HCV RNA at weeks 4 and 12 met the criterion for an extended rapid virologic response.
† Sustained virologic response (undetectable HCV RNA 24 weeks after the end of treatment) was the primary end point.
‡ All patients who received at least one dose of study drug were included in the analysis. The difference in response rates was 31 percentage points (95% confidence interval [CI], 24 to 38) between the T12PR and PR groups and 25 percentage points (95% CI, 18 to 32) between the T8PR and PR groups.
§ The 72-week assessment was performed 24 weeks after the end of treatment in patients who received 48 weeks of treatment and 48 weeks after end of treatment in patients who received 24 weeks of treatment.
ADVANCE TRIAL: results

• SVR occurred in:
  1. T12PR- 75%
  2. T8PR - 69%
  3. PR - 44%

• Relapse rate:
  1. T12PR- 9%
  2. T8PR - 9%
  3. PR - 28%

• RVR occurred in:
  1. T12PR- 68%
  2. T8PR - 67%
  3. PR - 9%

• eRVR occurred in:
  1. T12PR- 58%
  2. T8PR - 57%
  3. PR - 8%
ADVANCE TRIAL: results

- Patients in the **T12 PR** arm who had eRVR achieved 89% SVR
  - Patients in the T12 PR arm with **no** eRVR: 54% SVR

- Significant increase in SVR in African-American patients: from 25% (PR) to 62% (T12PR)

- Advanced fibrosis: SVR in 62% (T12PR), and 33% (PR alone)

- Rate of virologic failure:
  - first 12 weeks: 3% (T12PR), and 3% (PR alone)
  - after week #12: 5%(T12PR), and 10% (PR alone)

- Virologic failure in first 12 wks associated with high-level T-resist. variants
- Virologic failure after12 wks associated with wild type or low-level T-resist. variants
ADVANCE TRIAL: results

• AE’s:
  • patients receiving Telaprevir were more likely to develop rash, pruritus, anemia, nausea, diarrhea, ano-rectal symptoms
  • overall D/C% due to AE’s: T12PR:10%, T8PR:10%, PR:7%

• T12PR became the approved regimen, better benefit / risk ratio

SUMMARY:

• Significantly improved response rates (RVR)
• Introduction of response-guided therapy - RGT
• Decrease treatment time in a subset of patients: 24 weeks of therapy was sufficient for patients who achieved eRVR (Undetectable plasma HCV RNA at week 4 and at week 12)
• Small increase in reversible AE’s
PROTEASE INHIBITORS: PHASE 3 TRIALS

**TELAPREVIR**
- Naïve patients
  - ADVANCE
  - ILLUMINATE
- Experienced patients
  - REALIZE

**BOCEPREVIR**
- Naïve patients
  - SPRINT-2
- Experienced patients
  - RESPOND-2
Response-Guided Telaprevir Combination Treatment for Hepatitis C Virus Infection

Kenneth E. Sherman, M.D., Ph.D., Steven L. Flamm, M.D., Nezam H. Afdhal, M.D.,
David R. Nelson, M.D., Mark S. Sulkowski, M.D., Gregory T. Everson, M.D.,
Michael W. Fried, M.D., Michael Adler, M.D., Ph.D., Hendrik W. Reesink, M.D., Ph.D.,
Marie Martin, Ph.D., Abdul J. Sankoh, Ph.D., Nathalie Adda, M.D.,
Robert S. Kauffman, M.D., Ph.D., Shelley George, M.D.,
Christopher L. Wright, M.D., Ph.D., and Fred Poordad, M.D.,
for the ILLUMINATE Study Team*

ABSTRACT
ILUMINATE TRIAL

• Patients who achieved eRVR on a T12PR regimen were randomized to receive 24 vs. 48 weeks of therapy (arms T12PR24, and T12PR48 respectively)
• Patients who did not have eRVR received T12PR48

• RESULTS: SVR in T12PR24: 92%
  SVR in T12PR48: 88%
  SVR in T12PR48 and no eRVR: 64%
  T12PR24 was non-inferior

Patients with cirrhosis who had eRVR:
  SVR in T12PR24: 67%
  SVR in T12PR48: 92%

Figure 1. Enrollment, Randomization or Assignment, and Follow-up of the Study Patients.
Virologic failure was defined as an HCV RNA level greater than 1000 IU per milliliter at week 4, a decline from baseline by less than 2 log_{10} units in the level of detectable HCV RNA at week 12, or a detectable HCV RNA level at any time between weeks 24 and 36.
<table>
<thead>
<tr>
<th>Time Point</th>
<th>Total (N=540)</th>
<th>Randomly Assigned to T12PR24 (N=162)</th>
<th>Randomly Assigned to T12PR48 (N=160)</th>
<th>Nonrandomly Assigned to T12PR48 (N=118)</th>
<th>Discontinued Treatment before Wk 20 (N=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number/total number (percent)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wk 4 (rapid virologic response)</td>
<td>389 (72)</td>
<td>162 (100)</td>
<td>159 (99)</td>
<td>15 (13)</td>
<td>53 (53)</td>
</tr>
<tr>
<td>Wk 4 and wk 12 (extended rapid virologic response)</td>
<td>352 (65)</td>
<td>162 (100)</td>
<td>159 (99)</td>
<td>0</td>
<td>31 (31)</td>
</tr>
<tr>
<td>End of treatment</td>
<td>469 (87)</td>
<td>159 (98)</td>
<td>154 (96)</td>
<td>97 (82)</td>
<td>59 (59)</td>
</tr>
<tr>
<td>24 Wk after end of treatment (sustained virologic response): primary end point</td>
<td>388 (72)</td>
<td>149 (92)</td>
<td>140 (88)</td>
<td>76 (64)</td>
<td>23 (23)</td>
</tr>
<tr>
<td>Wk 4 (rapid virologic response)</td>
<td>317/389 (81)</td>
<td>149/162 (92)</td>
<td>139/159 (87)</td>
<td>11/15 (73)</td>
<td>18/53 (34)</td>
</tr>
<tr>
<td>Yes</td>
<td>71/151 (47)</td>
<td>0/0</td>
<td>1/1 (100)</td>
<td>65/103 (63)</td>
<td>5/47 (11)</td>
</tr>
</tbody>
</table>
ILLUMINATE TRIAL

**SUMMARY:**
- 24 wks of Telaprevir + PR in treatment-naïve Chronic Hep C patients who achieve eRVR is non-inferior to a 48-week course
- eRVR achieved in nearly two thirds of patients
- Study confirms RGT approach
- Low relapse rates
- Overall SVR: 72%
- High rates of response among blacks (60%) and Hispanics/Latinos (67%)
- Few patients with cirrhosis in the study
- Treatment failure frequently associated with Telaprevir-res. Variants (55% cleared at 43-wk follow-up)
- D/C rates, AE’s, similar to ADVANCE trial

PROTEASE INHIBITORS: PHASE 3 TRIALS

• **TELAPREVIR**
  - Naïve patients
    - ADVANCE
    - ILLUMINATE
  - Experienced patients
    - REALIZE

• **BOCEPREVIR**
  - Naïve patients
    - SPRINT-2
  - Experienced patients
    - RESPOND-2
Telaprevir for Retreatment of HCV Infection

Stefan Zeuzem, M.D., Pietro Andreone, M.D., Stanislas Pol, M.D., Eric Lawitz, M.D., Moises Diago, M.D., Stuart Roberts, M.D., Roberto Focaccia, M.D., Zobair Younossi, M.D., Graham R. Foster, F.C.R.P., Andrzej Horban, M.D., Peter Ferenci, M.D., Frederik Nevens, M.D., Beat Müllhaupt, M.D., Paul Pockros, M.D., Ruben Terg, M.D., Daniel Shouval, M.D., Bart van Hoek, M.D., Ola Weiland, M.D., Rolf Van Heeswijk, Pharm.D., Sandra De Meyer, Ph.D., Don Luo, Ph.D., Griet Boogaerts, M.Sc., Ramon Polo, Pharm.D., Gaston Picchio, Ph.D., and Maria Beumont, M.D., for the REALIZE Study Team*

ABSTRACT
REALIZE TRIAL

  - Enrolled relapsers, partial responders, and null responders in previous treatment
  - 3 arms:
    1. Triple therapy (T12PR48) from the beginning x48 wks
    2. 4-week lead-in phase of PR followed by 12 wks of TPR x48 wks (lead-in T12PR48)
    3. PR x48 wks

- Response-guided therapy (RGT) – not evaluated

**Partial responders:** $\geq 2$ log decline in HCV RNA at week 12 of prior therapy but never achieved undetectable HCV RNA

**Null responder:** $< 2$ log decline in HCV RNA at week 12 of prior therapy
Figure 1. Enrollment and Outcomes.
Patients who completed all three study drugs were classified as having completed treatment.

REALIZE TRIAL: results

• SVR occurred in:

  • Relapsers:
    1. T12PR48 - 83%
    2. lead-in T12PR48 - 88%
    3. PR48 - 24%

  • Partial responders:
    1. T12PR48 - 59%
    2. lead-in T12PR48 - 54%
    3. PR48 - 15%

  • Null responders:
    1. T12PR48 - 29%
    2. lead-in T12PR48 - 33%
    3. PR48 - 5%

No significant differences between lead-in and non-lead-in arms.
<table>
<thead>
<tr>
<th>Subgroup and End Point</th>
<th>T12PR48</th>
<th>Lead-in T12PR48</th>
<th>PR48 (Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previous relapse</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetectable viral load</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 4 wk</td>
<td>101/145 (70)</td>
<td>4/141 (3)</td>
<td>2/68 (3)</td>
</tr>
<tr>
<td>At 8 wk</td>
<td>135/145 (93)</td>
<td>126/141 (89)</td>
<td>7/68 (10)</td>
</tr>
<tr>
<td>Sustained virologic response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>121/145 (83)†</td>
<td>124/141 (88)†</td>
<td>16/68 (24)</td>
</tr>
<tr>
<td>Patients with undetectable viral load</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 4 wk</td>
<td>91/101 (90)</td>
<td>4/4 (100)</td>
<td>2/2 (100)</td>
</tr>
<tr>
<td>At 8 wk</td>
<td>121/135 (90)</td>
<td>116/126 (92)</td>
<td>7/7 (100)</td>
</tr>
<tr>
<td>Patients with bridging fibrosis or cirrhosis‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse at 72 wk§</td>
<td>10/135 (7)</td>
<td>9/138 (7)</td>
<td>30/46 (65)</td>
</tr>
<tr>
<td>Virologic failure¶</td>
<td>2/145 (1)</td>
<td>1/141 (1)</td>
<td>18/68 (26)</td>
</tr>
<tr>
<td><strong>No response or partial response to previous therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained virologic response</td>
<td>50/121 (41)†</td>
<td>51/123 (41)†</td>
<td>6/64 (9)</td>
</tr>
<tr>
<td><strong>Previous partial response</strong></td>
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</tr>
<tr>
<td>Undetectable viral load</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 4 wk</td>
<td>32/49 (65)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>At 8 wk</td>
<td>40/49 (82)</td>
<td>31/48 (65)</td>
<td>0</td>
</tr>
<tr>
<td>Sustained virologic response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>29/49 (59)†</td>
<td>26/48 (54)†</td>
<td>4/27 (15)</td>
</tr>
<tr>
<td>Patients with undetectable viral load</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 4 wk</td>
<td>23/32 (72)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>At 8 wk</td>
<td>27/40 (68)</td>
<td>18/31 (58)</td>
<td>NA</td>
</tr>
<tr>
<td>Patients with bridging fibrosis or cirrhosis‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse at 72 wk§</td>
<td>8/39 (21)</td>
<td>9/36 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Virologic failure¶</td>
<td>9/49 (18)</td>
<td>9/48 (19)</td>
<td>19/27 (70)</td>
</tr>
<tr>
<td>Subgroup and End Point</td>
<td>T12PR48</td>
<td>Lead-in T12PR48</td>
<td>PR48 (Control)</td>
</tr>
<tr>
<td>------------------------------------------------------------</td>
<td>---------</td>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>No previous response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetectable viral load</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 4 wk</td>
<td>19/72 (26)</td>
<td>0</td>
<td>1/37 (3)</td>
</tr>
<tr>
<td>At 8 wk</td>
<td>34/72 (47)</td>
<td>31/75 (41)</td>
<td>1/37 (3)</td>
</tr>
<tr>
<td>Sustained virologic response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>21/72 (29)†</td>
<td>25/75 (33)†</td>
<td>2/37 (5)</td>
</tr>
<tr>
<td>Patients with undetectable viral load</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 4 wk</td>
<td>10/19 (53)</td>
<td>NA</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>At 8 wk</td>
<td>20/34 (59)</td>
<td>21/31 (68)</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>Patients with bridging fibrosis or cirrhosis‡</td>
<td>12/43 (28)</td>
<td>10/45 (22)</td>
<td>1/19 (5)</td>
</tr>
<tr>
<td>Relapse at 72 wk§</td>
<td>8/30 (27)</td>
<td>9/36 (25)</td>
<td>3/5 (60)</td>
</tr>
<tr>
<td>Virologic failure¶</td>
<td>41/72 (57)</td>
<td>35/75 (47)</td>
<td>31/37 (84)</td>
</tr>
</tbody>
</table>
REALIZE TRIAL

**SUMMARY:**
- Telaprevir combined with peginterferon plus ribavirin significantly improved rates of SVR in previously treated patients.
- No difference lead-in phase vs no lead-in phase.
- In previous null responders, T + PR increased SVR from 5% to a range of 29 to 33%.
- High baseline HCV VL, advanced liver fibrosis: predictors of poor response among previous null responders and partial responders.
- Virologic failure rates were lower in previous relapsers and partial responders than in null responders.
- 58% of patients with Telaprevir-resistant variants: no longer detectable at the end of the study.
- AE’s in Telaprevir arm: fatigue, GI symptoms, pruritus, rash.
- 8-12% increase in discontinuation rates.

PROTEASE INHIBITORS: PHASE 3 TRIALS

- **TELAPREVIR**
  - Naïve patients
    - ADVANCE
    - ILLUMINATE
  - Experienced patients
    - REALIZE

- **BOCEPREVIR**
  - Naïve patients
    - SPRINT-2
  - Experienced patients
    - RESPOND-2
Boceprevir for Untreated Chronic HCV Genotype 1 Infection

Fred Poordad, M.D., Jonathan McCone, Jr., M.D., Bruce R. Bacon, M.D., Savino Bruno, M.D., Michael P. Manns, M.D., Mark S. Sulkowski, M.D., Ira M. Jacobson, M.D., K. Rajender Reddy, M.D., Zachary D. Goodman, M.D., Ph.D., Navdeep Boparai, M.S., Mark J. DiNubile, M.D., Vilma Sniukiene, M.D., Clifford A. Brass, M.D., Ph.D., Janice K. Albrecht, Ph.D., and Jean-Pierre Bronowicki, M.D., Ph.D., for the SPRINT-2 Investigators*

ABSTRACT
SPRINT-2 TRIAL

• 1,099 patients randomized to 1 of 3 treatment arms:

  1. PegInterferon α-2b + weight-based R x 48 wks - PR
  2. Lead-in PR x 4 followed by Boceprevir PR x 24 wks (RGT) followed by PR for 20 wks - RGT
  3. Lead-in PR x 4 followed by Boceprevir PR x 44 wks - 48W

• The trial was divided into on-black and black cohorts
• Study treatment was discontinued for all patients with HCV-VL detectable at wk 24, according to a standard futility rule

The diagram illustrates a study design for evaluating the effectiveness of antiviral treatments for hepatitis C virus (HCV) infection. The study is divided into a lead-in period and a period where HCV RNA levels are assessed.

**Control Group 1:**
- Peginterferon-ribavirin
- Placebo and peginterferon-ribavirin
- Follow-up

**Experimental Groups:**
- **Group 2:**
  - Peginterferon-ribavirin
  - Boceprevir and peginterferon-ribavirin
  - Detectable HCV RNA levels at wk 8–24
  - Follow-up

- **Group 3:**
  - Peginterferon-ribavirin
  - Boceprevir and peginterferon-ribavirin
  - Follow-up

The timeline ranges from week 0 to week 72, with specific phases marked for the lead-in period and assessment of HCV RNA levels.
SPRINT-2 TRIAL: RESULTS

• Cohort 1 (non-black):
  • SVR achieved in :
    1. PR: 40%
    2. RGT: 67%
    3. 48W: 68%

Patients in cohort 1 who had undetectable HCV RNA in weeks 8 and 24 and stopped therapy at week 28 – SVR: 97%. In the 48W arm: 96%

Relapse rates: 23%, 9%, and 8% respectively

• Cohort 1 (black):
  • SVR achieved in :
    1. PR: 23%
    2. RGT: 42%
    3. 48W: 53%

Relative increase near double

Relapse rates: 14%, 12%, and 17%

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonblack Cohort</th>
<th>P Value for Group 2 vs. Group 1</th>
<th>Nonblack Cohort</th>
<th>P Value for Group 3 vs. Group 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (N=311)</td>
<td></td>
<td>Group 2 (N=316)</td>
<td></td>
</tr>
<tr>
<td>Response at end of therapy†</td>
<td>176/311 (57)</td>
<td>&lt;0.001</td>
<td>235/316 (74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rate of relapse‡</td>
<td>37/162 (23)</td>
<td>&lt;0.001</td>
<td>21/232 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sustained virologic response§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients who received treatment</td>
<td>125/311 (40)</td>
<td>&lt;0.001</td>
<td>211/316 (67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Modified ITT population</td>
<td>125/297 (42)</td>
<td>&lt;0.001</td>
<td>211/303 (70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HCV RNA level at wk 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetectable or decreased by ≥1 log_{10} IU/ml</td>
<td>121/234 (52)</td>
<td>&lt;0.001</td>
<td>187/228 (82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Decreased by &lt;1 log_{10} IU/ml</td>
<td>3/62 (5)</td>
<td>&lt;0.001</td>
<td>21/73 (29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HCV RNA detectability at wk 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetectable¶</td>
<td>27/28 (96)</td>
<td>0.55</td>
<td>16/18 (89)</td>
<td>0.56</td>
</tr>
<tr>
<td>Detectable∥</td>
<td>97/268 (36)</td>
<td>&lt;0.001</td>
<td>192/283 (68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HCV RNA detectability at wk 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetectable</td>
<td>48/56 (86)</td>
<td>0.47</td>
<td>170/190 (89)</td>
<td>0.31</td>
</tr>
<tr>
<td>Detectable∥</td>
<td>73/233 (31)</td>
<td>0.38</td>
<td>38/104 (37)</td>
<td>0.046</td>
</tr>
<tr>
<td>HCV RNA detectability wk 8 through wk 24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetectable</td>
<td>37/40 (93)</td>
<td>0.17</td>
<td>143/147 (97)</td>
<td>0.38</td>
</tr>
<tr>
<td>Detectable**</td>
<td>78/118 (66)</td>
<td>0.26</td>
<td>52/70 (74)</td>
<td>0.32</td>
</tr>
<tr>
<td>Baseline Metavir fibrosis score††</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, 1, or 2</td>
<td>111/277 (40)</td>
<td>&lt;0.001</td>
<td>194/279 (70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3 or 4</td>
<td>9/23 (39)</td>
<td>0.57</td>
<td>13/26 (50)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

*Data were analyzed using the chi-squared test or Fisher’s exact test as appropriate.†Response at end of therapy includes all patients who received at least one dose of any study medication.‡Relapse is defined as detectable HCV RNA after 12 weeks of treatment, regardless of when it occurred.§Sustained virologic response is defined as undetectable HCV RNA at 12 weeks of treatment.¶HCV RNA undetectability at week 4.∥HCV RNA detectability at week 8.**HCV RNA undetectability at weeks 8 through 24.
SPRINT-2 TRIAL: RESULTS

• Response rates were better with the addition of boceprevir to PR
• Rates were similar with 24 weeks and 44 weeks of boceprevir
• Patients with (+) HCV RNA at week #8, and (-) at week # 24 (late responders)
  - 66% SVR in RGT
  - 75% SVR in 48W

  late responders should receive:
  - 4-week lead-in + 32 weeks of BPR + 12 weeks of PR

• HCV RNA detectability at week 4 – strong predictor of SVR, and correlates with risk of having resistant variants of the virus
• Cirrhotics: under-represented

AE’s: Anemia, dysgeusia

### Table 3. Common Clinical Adverse Events, Resistance-Associated HCV Variants, and Hematologic Abnormalities, According to Treatment Group.*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Group 1 (N=363)</th>
<th>Group 2 (N=368)</th>
<th>P Value for Group 2 vs. Group 1</th>
<th>Group 3 (N=366)</th>
<th>P Value for Group 3 vs. Group 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator-reported clinical adverse events — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>217 (60)</td>
<td>196 (53)</td>
<td>0.09</td>
<td>209 (57)</td>
<td>0.50</td>
</tr>
<tr>
<td>Headache</td>
<td>153 (42)</td>
<td>168 (46)</td>
<td>0.37</td>
<td>167 (46)</td>
<td>0.37</td>
</tr>
<tr>
<td>Nausea</td>
<td>153 (42)</td>
<td>175 (48)</td>
<td>0.16</td>
<td>159 (43)</td>
<td>0.76</td>
</tr>
<tr>
<td>Anemia</td>
<td>107 (29)</td>
<td>182 (49)</td>
<td>&lt;0.001</td>
<td>179 (49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>121 (33)</td>
<td>123 (33)</td>
<td>0.99</td>
<td>118 (32)</td>
<td>0.81</td>
</tr>
<tr>
<td>Chills</td>
<td>102 (28)</td>
<td>134 (36)</td>
<td>0.02</td>
<td>121 (33)</td>
<td>0.15</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>64 (18)</td>
<td>137 (37)</td>
<td>&lt;0.001</td>
<td>156 (43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insomnia</td>
<td>118 (33)</td>
<td>117 (32)</td>
<td>0.87</td>
<td>122 (33)</td>
<td>0.81</td>
</tr>
<tr>
<td>Boceprevir-resistance-associated variants — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Overall</td>
<td>59/350 (17)</td>
<td>52/354 (15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA level at wk 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease of ≥1 log₁₀ IU/ml from baseline</td>
<td>10/232 (4)</td>
<td></td>
<td></td>
<td>13/231 (6)</td>
<td></td>
</tr>
<tr>
<td>Decrease of &lt;1 log₁₀ IU/ml from baseline</td>
<td>49/95 (52)</td>
<td></td>
<td></td>
<td>38/94 (40)</td>
<td></td>
</tr>
</tbody>
</table>
Baseline predictors of SVR: SPRINT-2

<table>
<thead>
<tr>
<th>Effect</th>
<th>Odds Ratio (95% CI)</th>
<th>p -value</th>
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</thead>
<tbody>
<tr>
<td>HCV RNA before therapy ≤400,000 vs &gt; 400,000</td>
<td>11.6 (1.5, 87.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>IL28B genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC vs TT</td>
<td>2.6</td>
<td>0.006</td>
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<tr>
<td>CC vs CT</td>
<td>2.1</td>
<td>0.01</td>
</tr>
<tr>
<td>CT vs TT</td>
<td>1.2</td>
<td>0.48</td>
</tr>
<tr>
<td>Cirrhosis: No / yes</td>
<td>4.3</td>
<td>0.004</td>
</tr>
<tr>
<td>HCV genotype: 1b vs 1a</td>
<td>2.0</td>
<td>0.005</td>
</tr>
<tr>
<td>Race: black vs non-black</td>
<td>2.0</td>
<td>0.03</td>
</tr>
<tr>
<td>BMI: ≤30 vs &gt; 30</td>
<td>1.6</td>
<td>0.07</td>
</tr>
</tbody>
</table>

PROTEASE INHIBITORS: PHASE 3 TRIALS

• TELAPREVIR
  • Naïve patients
    • ADVANCE
    • ILLUMINATE
  • Experienced patients
    • REALIZE

• BOCEPREVIR
  • Naïve patients
    • SPRINT-2
  • Experienced patients
    • RESPOND-2
Boceprevir for Previously Treated Chronic HCV Genotype 1 Infection

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