Epidemiology and Natural History of HCV Infection
Approximately 3.2 Million People in the US Have Chronic HCV Infection

- ~3.2 million people are chronically infected with HCV based on NHANES (1999-2002) population\textsuperscript{1,2}
  - ~70\% born 1945-1964\textsuperscript{1}

- The number chronically infected with HCV in the US may be even higher\textsuperscript{3}
  - Accounting for populations not sampled in NHANES
    - Incarcerated
    - Homeless
    - Nursing home residents
    - Hospitalized
    - Those on active military duty

# Transmission of Hepatitis A, B, and C Virus

<table>
<thead>
<tr>
<th>Route</th>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV drug use</td>
<td><img src="#" alt="Common" /></td>
<td><img src="#" alt="Never" /></td>
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<tr>
<td>Transfusion</td>
<td><img src="#" alt="Common" /></td>
<td><img src="#" alt="Never" /></td>
<td><img src="#" alt="Never" /></td>
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<tr>
<td>Hemodialysis</td>
<td><img src="#" alt="Never" /></td>
<td><img src="#" alt="Never" /></td>
<td><img src="#" alt="Never" /></td>
</tr>
<tr>
<td>Intra-institutional</td>
<td><img src="#" alt="Never" /></td>
<td><img src="#" alt="Never" /></td>
<td><img src="#" alt="Never" /></td>
</tr>
<tr>
<td>Sexual</td>
<td><img src="#" alt="Common" /></td>
<td><img src="#" alt="Never" /></td>
<td><img src="#" alt="Infrequent" /></td>
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<tr>
<td>Household</td>
<td><img src="#" alt="Never" /></td>
<td><img src="#" alt="Infrequent" /></td>
<td><img src="#" alt="Infrequent" /></td>
</tr>
<tr>
<td>Mother-to-newborn</td>
<td><img src="#" alt="Common" /></td>
<td><img src="#" alt="Never" /></td>
<td><img src="#" alt="Infrequent" /></td>
</tr>
<tr>
<td>Oral-oral contact</td>
<td><img src="#" alt="Never" /></td>
<td><img src="#" alt="Infrequent" /></td>
<td><img src="#" alt="Infrequent" /></td>
</tr>
<tr>
<td>Food-borne</td>
<td><img src="#" alt="Never" /></td>
<td><img src="#" alt="Never" /></td>
<td><img src="#" alt="Never" /></td>
</tr>
<tr>
<td>Fecal (oral)</td>
<td><img src="#" alt="Never" /></td>
<td><img src="#" alt="Never" /></td>
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</tr>
<tr>
<td>Water-borne</td>
<td><img src="#" alt="Never" /></td>
<td><img src="#" alt="Never" /></td>
<td><img src="#" alt="Never" /></td>
</tr>
<tr>
<td>Raw shellfish</td>
<td><img src="#" alt="Never" /></td>
<td><img src="#" alt="Never" /></td>
<td><img src="#" alt="Never" /></td>
</tr>
</tbody>
</table>

- **Common**
- **Infrequent**
- **Never**

IV=intravenous.

Distribution of HCV Genotypes in the US

- Genotypes 1a and 1b account for 79%
- Genotype 2 accounts for 15%

Natural History of HCV Infection

Acute Infection*
- Clearance of HCV RNA: 15%-25%
- Extrahepatic Manifestations

Chronic Infection: 75%-85%

Cirrhosis: 10%-20% over 20 years
- Decompensated Cirrhosis: 5-yr survival rate 50%

HCC: 1%-4% per year

*20%-30% of individuals are symptomatic.
HCC=hepatocellular carcinoma.

HCV-Related Decompensated Cirrhosis and HCC Projected to Rise in the US

- HCV-related decompensated cirrhosis and HCC are rising as manifestations of liver disease in aging population
  
- 73.4% of HCV-related deaths occurred among persons 45-64 years of age
  - Median age was 57 years; ~20 years less than the average lifespan of persons living in the US

Projection based on a dynamic, multicohort, natural history model of data from the CDC, NHANES, and a review of the medical literature, with conservative estimates of disease progression and complications. Model assumes first-year mortality of 80%-85% for HCC.

*During the period from 1999 to 2007.

HCV Increased Risk of HCC in a VA Cohort Study

Kaplan Meier estimates. Follow-up: 1.37 million person-years. Outcomes matching criteria: age, sex, baseline visit date, type of visit, race, type of military service, number of inpatient and outpatient visits before baseline, specific potential confounders for each malignancy. HR=hazard ratio.

HCV Is Leading Cause of Liver Transplants in the US

Treatment May Reduce HCC Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized Controlled Trials (RCTs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valla (1999)</td>
<td>99</td>
<td>37.2</td>
</tr>
<tr>
<td>Azzaroli (2004)</td>
<td>60</td>
<td>60.0</td>
</tr>
<tr>
<td>Nishiguchi (1995/2001)</td>
<td>90</td>
<td>104.4</td>
</tr>
<tr>
<td>Soga (2005)</td>
<td>136</td>
<td>93.6</td>
</tr>
<tr>
<td>Cohort Studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mazzella (1996)</td>
<td>284</td>
<td>32.0</td>
</tr>
<tr>
<td>Fattovich (1997)</td>
<td>329</td>
<td>60.0</td>
</tr>
<tr>
<td>IIHCSG (1998)</td>
<td>913</td>
<td>NA</td>
</tr>
<tr>
<td>Benvegenu (1998)</td>
<td>189</td>
<td>71.5</td>
</tr>
<tr>
<td>Gramenzi (2001)</td>
<td>144</td>
<td>56.5</td>
</tr>
<tr>
<td>Imai (1998)</td>
<td>563</td>
<td>47.4</td>
</tr>
<tr>
<td>Okanoue (1999)</td>
<td>1,203</td>
<td>41.6</td>
</tr>
<tr>
<td>Yoshida (1999)</td>
<td>2,890</td>
<td>51.6</td>
</tr>
<tr>
<td>Tanaka (2000)</td>
<td>738</td>
<td>59.1</td>
</tr>
<tr>
<td>Ikeda (2001)</td>
<td>694</td>
<td>91.2</td>
</tr>
<tr>
<td>Shiratori (2005)</td>
<td>345</td>
<td>81.6</td>
</tr>
<tr>
<td>Ikeda (2006)</td>
<td>2,820</td>
<td>128.4</td>
</tr>
<tr>
<td>Yu (2006)</td>
<td>1,619</td>
<td>61.9</td>
</tr>
</tbody>
</table>

Random effect
Overall treatment effect: -7.8% (95% CI, -4.6 to -11.1) (P<.0001)

Region where study was conducted
- Ex-Asia
- Asia

Meta-analysis of published RCTs and cohort studies up to December 2010.
## Definitions of Virologic Response to Treatment

<table>
<thead>
<tr>
<th>Response Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid virologic response (RVR)</td>
<td>HCV RNA negative at treatment week 4 by a sensitive PCR-based quantitative assay</td>
</tr>
<tr>
<td>Early virologic response (EVR)</td>
<td>≥2 log reduction in HCV RNA level compared with baseline (partial EVR) or HCV RNA negative at treatment week 12 (complete EVR). Predictive of SVR</td>
</tr>
<tr>
<td>End-of-treatment response (ETR)</td>
<td>HCV RNA negative by a sensitive test at the end of treatment</td>
</tr>
<tr>
<td>Sustained virologic response (SVR)</td>
<td>HCV RNA negative at 24 weeks (SVR24) after cessation of treatment. Best predictor of long-term outcomes</td>
</tr>
<tr>
<td>Breakthrough</td>
<td>Reappearance of HCV RNA in serum while on therapy</td>
</tr>
<tr>
<td>Relapse</td>
<td>Reappearance of HCV RNA in serum after therapy is discontinued</td>
</tr>
<tr>
<td>Nonresponder</td>
<td>Failure to clear HCV RNA from serum after 24 weeks of therapy</td>
</tr>
<tr>
<td>Null responder</td>
<td>Failure to achieve a 2 log reduction in HCV RNA after 24 weeks of therapy</td>
</tr>
<tr>
<td>Partial responder</td>
<td>2-log reduction in HCV RNA but still HCV RNA positive at week 24</td>
</tr>
</tbody>
</table>

Virologic Response to Therapy

HCV RNA (log_{10} IU/mL)

Weeks After Start of Therapy

†Shown for 48-week fixed-treatment course; follow stopping rules for treatment.

Sustained Virologic Response (SVR) Achieved After Treatment Is Durable

- SVR = HCV RNA negative (by a sensitive assay, <50 IU/mL) at 24 weeks after cessation of treatment\(^1\)

- 99% of patients who achieved an SVR had undetectable levels of HCV RNA in serum samples throughout the follow-up period\(^2\,*\)
  - “These data suggest that the recurrence of HCV RNA is extremely rare in patients who achieve an SVR, and it now appears likely that such patients may be considered “cured” from a virologic standpoint”\(^2\)

- For patients with cirrhosis, current guidelines recommend monitoring those who have achieved an SVR at 6- or 12-month intervals for the development of HCC\(^1\)

*After treatment with peginterferon alfa-2a ± ribavirin; mean follow-up, 3.9 years (range, 0.8–7.1 years).

SVR Was Associated With Reduced Long-Term Risk of All-Cause Mortality in an International, Multicenter Study

International, multicenter, long-term follow-up study from 5 large tertiary care hospitals in Europe and Canada. Patients with chronic HCV infection started an interferon-based treatment regimen between 1990 and 2003 (n=530).

SVR Was Associated With Improved HRQOL in a Survey of Patients With Advanced Fibrosis or Cirrhosis

Study assessed change from baseline to week 72 in HRQOL and sexual health in patients with advanced fibrosis or cirrhosis in the HALT-C Trial. HRQOL=Health-related quality of life. HRQOL was assessed with the 36-item Short Form Health Survey (SF-36), plus 3 additional questions that addressed self-reported sexual functioning, desire, and satisfaction and were hypothesized to measure sexual effects of chronic HCV and its treatment.

HCV/HIV Coinfection

- Approximately 30% of HIV-infected persons in the United States and other parts of the world are coinfected with HCV
  - HCV coinfection is common among HIV+ injection-drug users
  - Risk of vertical and sexual transmission of HCV increases with HIV coinfection
  - Alcohol use disorders are common among HIV/HCV coinfected adults

- Since the introduction of HAART, HCV-related liver disease has become an increasingly important cause of morbidity and mortality in HIV+ persons
  - Important to screen HIV+ population
  - Liver disease is the second leading cause of death in HIV+ patients

- Likelihood of SVR is lower with HIV/HCV coinfection than with HCV monoinfection

HAART=highly active antiretroviral therapy.
Extrahepatic Manifestations of HCV Infection
Extrahepatic Manifestations of HCV

**Strongly associated**
- Mixed cryoglobulinemia
- Sjögren (sicca) syndrome
- Lymphoproliferative disorders
- Porphyria cutanea tarda
- Neuropathy
- Membranoproliferative glomerulonephritis
- Cryoglobulinemic vasculitis

**Possibly associated**
- Corneal ulcers (Mooren ulcers)
- Thyroid disease
- Lichen planus
- Pulmonary fibrosis
- Type 2 diabetes
- Systemic vasculitis (polyarteritis nodosa, microscopic polyangiitis)
- Arthralgias, myalgias, inflammatory polyarthritis
- Autoimmune thrombocytopenia

Cryoglobulinemia: Classification

- Expansion of rheumatoid factor–synthesizing B cells represents the biological hallmark of mixed cryoglobulinemia\(^1\)
- Cryoglobulins are immunoglobulins that reversibly precipitate at <37° C\(^2\)
- Mild elevation of cryoglobulins is common in HCV\(^2\)
  - ≤50% with chronic HCV infection have detectable serum cryoglobulins
  - 90% have no clinical symptoms and need no specific therapy
- Categories of cryoglobulinemias (all 3 types can occur in HCV)\(^2\)

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated monoclonal immunoglobulin (IgG or IgM); usually lymphoproliferative disease</td>
<td>Mixed polyclonal immunoglobulins (mainly IgG) plus monoclonal immunoglobulins (IgM, IgG, or IgA)</td>
<td>Both polyclonal IgG and polyclonal IgM</td>
</tr>
</tbody>
</table>

Sjögren (Sicca) Syndrome

- There is an epidemiologic link between HCV infection and lymphocytic sialoadenitis or Sjögren (sicca) syndrome
- 10% of HCV-infected patients have sicca symptoms, but up to 75% have histologic evidence or a test abnormality
- HCV-related sialoadenitis differs from classic Sjögren syndrome by the absence of anti-SSA/Ro, anti-SSB/La antibodies, milder lymphocytic pericapillaritis, and absence of xerostomia and xerophthalmia in about 90% of cases
- The pathogenesis of HCV-related sialoadenitis is not fully understood. The effects are likely indirect, as HCV virus has not been demonstrated in glandular tissue

Dermatological Manifestations

- Cryoglobulinemic vasculitis in >10% of HCV-infected patients with detectable cryoglobulins\(^1\)

- Porphyria cutanea tarda (<5% of cases)\(^1\)

- Lichen planus\(^1,2\)
  - Associated with liver disease, especially advanced hepatic disorders
  - The relationship between HCV infection and lichen planus is controversial

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B-Cell Lymphoproliferative Disorders

- Mixed cryoglobulinemia can evolve into a B-cell malignancy in ≤11% of cases

- The most common types of NHL associated with HCV infection
  - Follicular lymphoma
  - Lymphoplasmacytoid/immunocytoma (Lp/Ic) subtype

- Mechanism of malignant transformation is unclear

NHL=non-Hodgkin’s lymphoma.
Membranoproliferative Glomerulonephritis

- Most prevalent renal manifestation of HCV infection
  - ~60% of cases in Japan and 10%-20% in the US are associated with HCV infection
  - Higher prevalence in patients with cryoglobulinemia

- Pathogenesis is likely immune complex–mediated

**Insulin Resistance**

- **Specific feature of chronic HCV infection (but not HBV)**\(^1\)
  - Associated with genotypes 1 and 4, high serum HCV RNA level, and fibrosis\(^1\)
  - More common in carriers of the “T” IL28B allele\(^2\)

- **In a retrospective cohort study of patients treated with interferon therapy (± RBV), SVR was associated with a two-thirds reduction in development of type 2 diabetes mellitus**\(^3\)

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Histologic and Noninvasive Staging
## Scoring Systems for Histologic Stage

<table>
<thead>
<tr>
<th>Appearance</th>
<th>Ishak Description</th>
<th>Ishak Score(^1)</th>
<th>METAVIR Score(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No fibrosis</td>
<td></td>
<td>0</td>
<td>F0</td>
</tr>
<tr>
<td>Fibrous expansion of some portal areas ± short fibrous septa</td>
<td></td>
<td>1</td>
<td>F1</td>
</tr>
<tr>
<td>Fibrous expansion of most portal areas ± short fibrous septa</td>
<td></td>
<td>2</td>
<td>F2</td>
</tr>
<tr>
<td>Fibrous expansion of most portal areas with occasional portal to portal (P–P) bridging</td>
<td></td>
<td>3</td>
<td>F3</td>
</tr>
<tr>
<td>Fibrous expansion of most portal areas with marked bridging (P–P and portal to central [P–C])</td>
<td></td>
<td>4</td>
<td>F4</td>
</tr>
<tr>
<td>Marked bridging (P–P and/or P–C) with occasional nodules (incomplete cirrhosis)</td>
<td></td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td></td>
<td>6</td>
<td>F4</td>
</tr>
</tbody>
</table>


Figure adapted from Standish RA, et al. *Gut*. 2006;55:569-578.
## Invasive and Noninvasive Fibrosis Tests

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Liver Biopsy</th>
<th>Serum Markers</th>
<th>Transient Elastography</th>
<th>MRE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Direct observation</td>
<td>Measures direct and indirect serum markers* of fibrosis</td>
<td>Liver stiffness by detection of ultrasound-propagated shear waves</td>
<td>Liver stiffness by MRI of vibration-propagated shear waves</td>
</tr>
<tr>
<td>Accuracy for detecting cirrhosis</td>
<td>High</td>
<td>Moderate (APRI) to high (FibroSURE™, ELF)</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Accuracy for detecting intermediate fibrosis</td>
<td>High</td>
<td>Low (APRI) to moderate (FibroSURE™, ELF)</td>
<td>Moderate to high</td>
<td>High</td>
</tr>
<tr>
<td>Risk of complications</td>
<td>Risk of pain/bleeding</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Minimal</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Coagulopathy</td>
<td>Minimal</td>
<td>Obesity; narrow rib spaces</td>
<td>Claustrophobia; other MRI contraindications</td>
</tr>
<tr>
<td>Limitations</td>
<td>Sampling error</td>
<td>False-positives with hemolysis, inflammation, Gilbert’s syndrome</td>
<td>False-positives with inflammation, congestion</td>
<td>False-positives with inflammation, congestion</td>
</tr>
<tr>
<td>Longitudinal monitoring</td>
<td>Unsuitable</td>
<td>Indices may change with disease progression / therapy</td>
<td>Liver stiffness changes with disease progression / therapy</td>
<td>Liver stiffness changes with disease progression / therapy</td>
</tr>
<tr>
<td>Cost</td>
<td>Highest per-test cost</td>
<td>Low per-test cost</td>
<td>High initial equipment cost</td>
<td>Very high initial equipment cost</td>
</tr>
</tbody>
</table>

*Serum tests that incorporate markers of fibrogenesis are generally more accurate.

APRI=AST-to-platelet ratio index; AST=aspartate aminotransferase; ELF=enhanced liver fibrosis; MRE=magnetic resonance elastography, MRI=magnetic resonance imaging.

Screening
HCV Diagnostic Algorithm Based on Serologic Testing

**If patient lacks pre-existing antibodies to HAV or HBV.**
HAV=hepatitis A virus, HBV=hepatitis B virus.
Laboratory Diagnosis of Chronic HCV Infection

- RNA testing identifies active disease in HCV-seropositive patients
- HCV antibodies appear by 6–8 weeks following infection\(^1\)
  - Can be detected by EIA\(^2\)
- Serum ALT is not a reliable indicator of liver damage\(^1\)
- FDA-approved rapid point-of-care testing is available\(^3\)
  - OraQuick® HCV Test

ALT=alanine aminotransferase; EIA=enzyme immunoassay; RNA=ribonucleic acid; ULN=upper limit of normal.

Image adapted from MicrobiologyBytes:Virology:HCV\(^1\)
Presentation of Patients Infected With HCV

- Patients often asymptomatic in early stages of infection

Symptoms may include:
- Fever
- Fatigue
- Loss of appetite
- Nausea
- Vomiting
- Abdominal pain
- Dark urine
- Grey-colored stools
- Jaundice
- Joint pain

First symptoms may be those of extrahepatic manifestations:
- Arthralgias
- Paresthesias
- Myalgias
- Pruritus
- Sicca syndrome

Platelet Counts May Serve as a Marker of Progressive Liver Disease Based on the HALT-C Trial Database

Analysis of baseline values from HALT-C trial database.
A model that included baseline platelet count and albumin as well as severe worsening of AST/ALT ratio and albumin was the best predictor of liver-related outcomes.
AST=aspartate aminotransferase.

Counseling Recommendations for HCV-Infected Individuals

To Prevent HCV Transmission

- Avoid sharing toothbrushes and dental or shaving equipment
- Prevent blood contact with others
- Stop using illicit drugs; those who continue to inject drugs should take precautions to avoid viral transmission
- Risk of sexual transmission is low, but practice “safe sex”

Additional Recommendations

- Avoid alcohol consumption
  - Excess alcohol may lead to progressive liver disease, increased HCV RNA replication, and reduced response to treatment
- Consider treatment for hepatitis C*
- Vaccinate for hepatitis A and B
- Get tested for HIV
- Encourage family members to get screened

*If patient meets generally accepted indications for HCV treatment.
Current Estimates Show a Significant Gap in HCV Care

Approximately 3.2 million in the US have chronic HCV infection\textsuperscript{1,2,*}

\textbf{1.6 million (50\%) diagnosed}\textsuperscript{3,4}

\textbf{170,000 – 200,000 (5 – 6\%) were successfully treated}\textsuperscript{4,5}

\footnotesize*Prevalence estimate based on NHANES data from 1999 through 2002.\textsuperscript{1,2} NHANES data underestimate the actual prevalence of HCV in the US by not accounting for incarcerated, homeless, hospitalized, nursing home and active military duty populations.\textsuperscript{6,7}

1998 CDC Risk-Based HCV Screening Recommendations

Screening is recommended in persons who:

- Ever injected illegal drugs
- Received clotting factors made before 1987
- Received blood/organs before July 1992
- Have ever been on hemodialysis
- Have evidence of liver disease (elevated ALT)
- Were born to HCV infected mothers
- Have HIV infection
- Received a needle stick injury or mucosal exposure to HCV-positive blood (health care, emergency medical and public safety workers)

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*

Those at high risk for HCV infection:
  - 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”)
Cost-Effectiveness of HCV Testing vs Other Routine Preventive Services

*Birth cohort testing, 1945-1965.
2-drug treatment=PegIFN+RBV; 3-drug treatment=PegIFN+RBV+PI.
QALY=quality-adjusted life-year.
The Good News

Adapted from the US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring, MD.
HCV Life Cycle and DAA Targets

Receptor binding and endocytosis
Fusion and uncoating
Transport and release
Translation and polyprotein processing
NS3/4 protease inhibitors
NS5A inhibitors
NS5B polymerase inhibitors
RNA replication
Membranous web
ER lumen
Virion assembly
LD

Simeprevir + P/R for GT1 HCV: Approved Indications

- Simeprevir 150 mg/day with food, administered with P/R
  - Fixed duration (no RGT)

- Treatment-naive patients and relapsers (including cirrhotic patients)
  - 12 weeks
  - 12 weeks
  - Simeprevir + P/R
  - P/R

- Previous partial or null responders (including cirrhotic patients)
  - 12 weeks
  - 36 weeks
  - Simeprevir + P/R
  - P/R

- Stopping rules

<table>
<thead>
<tr>
<th>Treatment Wk</th>
<th>HCV RNA (IU/mL)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>≥ 25</td>
<td>Discontinue simeprevir, pegIFN, and RBV</td>
</tr>
<tr>
<td>12</td>
<td>≥ 25</td>
<td>Discontinue pegIFN and RBV (SMV stops at 12 wks)</td>
</tr>
<tr>
<td>24</td>
<td>≥ 25</td>
<td>Discontinue pegIFN and RBV</td>
</tr>
</tbody>
</table>

**QUEST-1: Simeprevir + P/R RGT in Treatment-Naive GT1 HCV**

**Stratified by GT1 subtype, IL28B genotype**

**Wk 12: RGT**

**Wk 24**

**Wk 48**

**Simeprevir 150 mg QD + P/R* (n = 264)**

**Placebo + P/R (n = 130)**

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

QUEST-1, QUEST-2, PROMISE: SMV + P/R in GT1 Treatment-Naive Patients/Relapsers

QUEST Studies: Subtype 1a ≠ 1b

Likely relates to presence of Q80K polymorphism in GT1a

QUEST: No Benefit of Simeprevir if Q80K Positive

Q80K present in 34% of GT1a patients
No benefit of simeprevir if Q80K positive

Please see full Prescribing Information available at this presentation.
DOSAGE AND ADMINISTRATION
Recommended Dose in Adults

- The recommended dose of SOVALDI is one 400 mg tablet, taken orally, once daily with or without food
- SOVALDI should be used in combination with ribavirin (RBV) or in combination with pegylated interferon (Peg-IFN) and RBV for the treatment of CHC in adults as listed below

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with genotype 1 or 4 CHC</td>
<td>SOVALDI + peginterferon alfa(^a) + ribavirin(^b)</td>
</tr>
<tr>
<td>Patients with genotype 2 CHC</td>
<td>SOVALDI + ribavirin(^b)</td>
</tr>
<tr>
<td>Patients with genotype 3 CHC</td>
<td>SOVALDI + ribavirin(^b)</td>
</tr>
</tbody>
</table>

\(^a\) See peginterferon alfa prescribing information for dosing recommendation for patients with genotype 1 or 4 CHC.

\(^b\) Dose of ribavirin is weight-based (<75 kg = 1000 mg and ≥75 kg = 1200 mg). The daily dose of ribavirin is administered orally in two divided doses with food. Patients with renal impairment (CrCl ≤ 50 mL/min) require ribavirin dose reduction; refer to ribavirin prescribing information.

DOSE FORMS AND STRENGTHS

• SOVALDI is available as a yellow colored, capsule-shaped, film-coated tablet debossed with “GSI” on one side and “7977” on the other side

• Each tablet contains 400 mg sofosbuvir
Clinical Trials in Subjects with Genotype 1 or 4 CHC
**Treatment-Naïve Adults — NEUTRINO (Study 110)**

- NEUTRINO was an open-label, single-arm trial that evaluated 12 weeks of treatment with SOVALDI in combination with Peg-IFN alfa 2a and RBV in treatment-naïve subjects with genotype 1, 4, 5 or 6 HCV infection compared to pre-specified historical control.

- **HCV GT 1, 4, 5, 6**
  - **Treatment-naïve**
  - **N=327**

- **SOVALDI**
  - 400 mg once daily
  - + Peg-IFN alfa 2a 180 mcg/week
  - + RBV 1000–1200 mg/day*

- **Primary endpoint:** SVR12

- **12 weeks of treatment**

*Weight-based.

# Response Rates in Study NEUTRINO

<table>
<thead>
<tr>
<th></th>
<th>SOVALDI + Peg-IFN alfa + RBV 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=327&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Overall SVR</td>
<td>90% (295/327)</td>
</tr>
<tr>
<td>Genotype 1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>89% (261/292)</td>
</tr>
<tr>
<td>Genotype 1a</td>
<td>92% (206/225)</td>
</tr>
<tr>
<td>Genotype 1b</td>
<td>82% (54/66)</td>
</tr>
<tr>
<td>Genotype 4</td>
<td>96% (27/28)</td>
</tr>
<tr>
<td>Outcome for subjects without SVR</td>
<td></td>
</tr>
<tr>
<td>On-treatment virologic failure</td>
<td>0/327</td>
</tr>
<tr>
<td>Relapse&lt;sup&gt;c&lt;/sup&gt;</td>
<td>9% (28/326)</td>
</tr>
<tr>
<td>Other&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1% (4/327)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Including seven subjects with genotype 5 or 6 infection.

<sup>b</sup> One subject had genotype 1a/1b mixed infection.

<sup>c</sup> The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.

<sup>d</sup> Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).
SVR Rates for Selected Subgroups in NEUTRINO

<table>
<thead>
<tr>
<th></th>
<th>SOVALDI + Peg-IFN alfa + RBV 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cirrhosis</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>92% (252/273)</td>
</tr>
<tr>
<td>Yes</td>
<td>80% (43/54)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>87% (47/54)</td>
</tr>
<tr>
<td>Non-black</td>
<td>91% (248/273)</td>
</tr>
<tr>
<td><strong>Multiple Baseline Factors</strong></td>
<td></td>
</tr>
<tr>
<td>Genotype 1, Metavir F3/F4 fibrosis, IL28B non-C/C, HCV RNA &gt;800,000 IU/mL</td>
<td>71% (37/52)</td>
</tr>
</tbody>
</table>

• SVR rates were 98% (93/95) in subjects with baseline IL28B C/C allele and 87% (202/232) in subjects with baseline IL28B non-C/C alleles.

• It is estimated that the response rate in patients who previously failed Peg-IFN and RBV therapy will approximate the observed response rate in NEUTRINO subjects with multiple baseline factors traditionally associated with a lower response to interferon-based treatment.
Sofosbuvir + RBV for GT2 and GT3 HCV: Approved Indications

- All GT2 patients receive same regimen, regardless of previous treatment history or fibrosis level
  
  12 weeks
  
  Sofosbuvir + RBV

- All GT3 patients receive same regimen, regardless of previous treatment history or fibrosis level
  
  24 weeks
  
  Sofosbuvir + RBV

- If drugs combined with sofosbuvir must be permanently discontinued, sofosbuvir should also be discontinued

FUSION: SVR by GT and Cirrhosis in Treatment-Experienced Patients

Sofosbuvir + RBV 12 wks
Sofosbuvir + RBV 16 wks

- 12 weeks sufficient for GT2
- 16 weeks better than 12 weeks for GT3... so what about 24 weeks?

VALENCE: Efficacy With 24-Week Sofosbuvir Plus Ribavirin in GT3 Patients

- Treatment Naive[^1]
  - SVR12 (%): 94/92 (24 Wks), 92/13 (24 Wks)
  - SVR12 (%): 87/100 (24 Wks), 27/45 (24 Wks)

- Treatment Experienced[^1]
  - SVR12 (%): 100/100 (24 Wks)
  - SVR12 (%): 60/45 (24 Wks), 61/23 (16 Wks)

- FUSION[^2]
  - SVR12 (%): 61/23 (16 Wks)

- 24 weeks better for treatment-naive patients
- Not ideal for cirrhotic treatment failures

Do We Still Need IFN for GT3?

LONESTAR-2: SOF + PegIFN + RBV x 12 wks

- SVR12 (%)
  - GT 2:
    - No cirrhosis: 9/9, 93%
    - Cirrhosis: 10/12, 83%
  - GT 3:
    - No cirrhosis: 10/12, 83%
    - Cirrhosis: 10/12, 83%

85% previous treatment failures

- Small single-center study but looks promising...
- IFN is not dead yet!

Will There Still Be a Role for IFN?

- Hard to cure
  - GT3
  - DAA failures – multi-DAA resistant
  - Prior nonresponders → Quad?

- Easy to cure
  - IL28B CC – high efficacy, short duration → Asia?
  - Mild disease – option of IFN vs waiting for progression

- Cost containment
  - Fewer or less effective DAAs
  - GT2?
Sofosbuvir + RBV for Special Populations: Approved Indications

- Sofosbuvir + RBV for treatment of patients with HCC awaiting liver transplantation for up to 48 weeks or until liver transplantation, whichever occurs first

- For HIV/HCV-coinfected patients, sofosbuvir should be administered according to HCV genotype
  - No differences between monoinfected and coinfected patients

Duration of Undetectable HCV RNA Before Transplantation Predicts Lack of Recurrence


Only 1 of 24 patients with undetectable HCV RNA > 30 days experienced recurrence

Median days undetectable ($P < .001$)
- No recurrence: 95
- Recurrence: 5.5
Sofosbuvir + RBV ± PegIFN in Post-LT HCV: Virologic and Safety Outcomes

- 69% of patients had SVR4; 56% had SVR12
  - 2/36 patients relapsed
  - 1/36 patients had on-treatment nonresponse
  - 8/36 patients died
- 64% of patients showed improvement of decompensation events
- 11% of patients showed stabilization of events

### Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

<table>
<thead>
<tr>
<th>Concomitant Drug Class: Drug Name</th>
<th>Effect on Concentrationb</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticonvulsants:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>carbamazepine</td>
<td>↓ sofosbuvir</td>
<td></td>
</tr>
<tr>
<td>phenytoin</td>
<td>↓ GS-331007</td>
<td>Coadministration of SOVALDI with carbamazepine, phenytoin, phenobarbital or oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of SOVALDI. Coadministration is not recommended.</td>
</tr>
<tr>
<td>phenobarbital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>oxcarbazepine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antimycobacterials:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rifabutin</td>
<td>↓ sofosbuvir</td>
<td></td>
</tr>
<tr>
<td>rifampin</td>
<td>↓ GS-331007</td>
<td></td>
</tr>
<tr>
<td>rifapentine</td>
<td></td>
<td>Coadministration of SOVALDI with rifabutin or rifapentine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of SOVALDI. Coadministration is not recommended. SOVALDI should not be used with rifampin, a potent intestinal P-gp inducer.</td>
</tr>
<tr>
<td><strong>Herbal Supplements:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>↓ sofosbuvir</td>
<td></td>
</tr>
<tr>
<td><em>(Hypericum perforatum)</em></td>
<td>↓ GS-331007</td>
<td>SOVALDI should not be used with St. John’s wort, a potent intestinal P-gp inducer.</td>
</tr>
<tr>
<td><strong>HIV Protease Inhibitors:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tipranavir/ritonavir</td>
<td>↓ sofosbuvir</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ GS-331007</td>
<td>Coadministration of SOVALDI with tipranavir/ritonavir is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of SOVALDI. Coadministration is not recommended.</td>
</tr>
</tbody>
</table>

a. This table is not all inclusive.
b. ↓ = decrease.

In addition to the drugs included on the previous slide, the interaction between SOVALDI and the following drug was evaluated in clinical trials and no dose adjustment is needed for either drug:

- Cyclosporine
- Darunavir/ritonavir
- Efavirenz
- Emtricitabine
- Methadone
- Raltegravir
- Rilpivirine
- Tacrolimus
- Tenofovir disoproxil fumarate
Example of Nuc Backbone + PI in Trt-Naive Pts and Nulls (COSMOS)

- SMV (PI) + SOF (Nuc) + RBV 12 wks
- SMV (PI) + SOF (Nuc) 12 wks

- 78% GT1a
- 50% Q80K
- 94% non-CC
- All nulls

- SVR12 (%)
- F0-F2 Fibrosis: 96/27, 93/14
- F3/F4 Fibrosis: 96/27, 100/14

- Major caveats: small n, no plan for phase III trial

IFN-Free Therapies: Considerations

- How many DAAs?
- Which combinations?
- One size fits all vs tailored therapy?
How Many DAAs Do We Need?

Assumptions:
1) Production of new virions = \(10^{12}/\text{day}\)
2) HCV genome length = \(9600\) nucleotides
3) Error rate = \(10^{-5}/\text{per nucleotide copied}\)

Therefore, average number of changes/genome = \(0.096/\text{replication cycle}\)

<table>
<thead>
<tr>
<th># of Nucleotide Changes</th>
<th>Probability</th>
<th># of Virions/Day</th>
<th># of All Possible Mutants</th>
<th>% of All Possible Mutants/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.91</td>
<td>(9.1 \times 10^{11})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.087</td>
<td>(8.7 \times 10^{10})</td>
<td>(2.9 \times 10^{4})</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>0.0042</td>
<td>(4.2 \times 10^{9})</td>
<td>(4.1 \times 10^{8})</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>0.00013</td>
<td>(1.3 \times 10^{8})</td>
<td>(1.0 \times 10^{12})</td>
<td>(3.4 \times 10^{-5})</td>
</tr>
</tbody>
</table>

If the theory is right: should need 3 DAAs

DAA Options

- **PI backbone – potent/modest barrier**
  - PI + another low-barrier DAA (NNI/NS5A) for GT1b
  - PI + 2 low-barrier DAAs for GT1a

- **Nuc backbone – potent/high barrier**
  - Nuc + low-barrier DAA for GT1a/b
  - Nuc + PI

- **Include ribavirin?**
  - May allow fewer DAAs (2 vs 3)
  - May allow shorter therapy
Example of PI Backbone + NNI + RBV for GT1b Only

Faldaprevir (PI) 120 mg QD + deleobuvir (NNI) 600 mg BID + RBV for 28 wks\textsuperscript{[1,2]} (N = 78)

Faldaprevir (PI) 120 mg QD + deleobuvir (NNI) 600 mg BID + RBV for 16 wks\textsuperscript{[3]} (N = 32)

<table>
<thead>
<tr>
<th>HCV Subtype and IL28B GT</th>
<th>1a Non-CC</th>
<th>1a CC</th>
<th>1b Non-CC</th>
<th>1b CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12 (%)</td>
<td>32/22</td>
<td>75/8</td>
<td>84/37</td>
<td>82/11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCV Subtype and IL28B GT</th>
<th>1a CC</th>
<th>1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12 (%)</td>
<td>17/12</td>
<td>95/20</td>
</tr>
</tbody>
</table>

Simple regimen for GT1b only?

Example of PI Backbone + NS5A in Prior Null Responders

- Likely adequate for GT1b but not for GT1a
- Overcome by addition of third drug: only 12 wks

US study 9/11 GT1a
Japanese study 10/10 GT1b

SVR4, 12, or 24 (%)

Example of PI Backbone + 2 Other DAAs

ABT-450/RTV (PI) ± ABT-333 (NNI) + ABT-267 (NS5A) ± RBV x 12 wks

<table>
<thead>
<tr>
<th>Treatment-Naive Patients</th>
<th>Null Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a ABT-450</td>
<td>1a ABT-450</td>
</tr>
<tr>
<td>1b ABT-333</td>
<td>1b ABT-333</td>
</tr>
<tr>
<td>ABT-267</td>
<td>ABT-267</td>
</tr>
<tr>
<td>RBV</td>
<td>RBV</td>
</tr>
</tbody>
</table>

Observed data (above bar)  
ITT (within bar)

5 drugs (3 pills) but 12 weeks, one size fits all

Example of PI Backbone + NS5A in GT1b Trt-Naive Pts and Nulls (PEARL-1)

ABT-450/RTV (PI) + ABT-267 (NS5A) for 16 wks (N = 32)

<table>
<thead>
<tr>
<th>SVR12 (%)</th>
<th>Naives</th>
<th>Nulls</th>
</tr>
</thead>
<tbody>
<tr>
<td>95</td>
<td>40/42</td>
<td>36/40</td>
</tr>
<tr>
<td>90</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SAPPHIRE Phase III Studies: PI Backbone + 2 Other DAAs

SAPPHIRE-1: GT1 treatment-naive noncirrhotic patients:
ABT-450/RTV/ABT-267 FDC + ABT-333 + RBV for 12 wks

SAPPHIRE-2: GT1 treatment-experienced noncirrhotic patients (49% null responders):
ABT-450/RTV/ABT-267 FDC + ABT-333 + RBV for 12 wks

Press release. These data are available in press release format only, have not been peer reviewed, may be incomplete, and we await presentation or publication in a peer-reviewed format before conclusions should be made from these data.
Another Option: Nuc Backbone + NS5A

SOF (Nuc) + daclatasvir (NS5A) ± RBV x 24 wks

Major caveats: small n, no plan for phase III trial

1-Pill Version of Nuc + NS5A

LONESTAR: SOF (Nuc) + ledipasvir (NS5A) FDC ± RBV

- Treatment-naive patients (noncirrhotic)
- PI failures (50% cirrhotic)

- No breakthrough; 2 relapses, both without RBV
- 1 case of resistance – retreated with SOF/LDV + RBV x 24 weeks → SVR

Phase III Studies of Sofosbuvir (Nuc) + Ledipasvir (NS5A) ± RBV in GT1 HCV

ION-1*: GT1 treatment-naive pts (16% cirrhotic): SOF/LDV FDC ± RBV for 12 wks

ION-3: GT1 treatment-naive pts: SOF/LDV FDC ± RBV for 8 or 12 wks

ION-2: GT1 treatment-experienced pts (20% cirrhotic): SOF/LDV FDC ± RBV for 12 or 24 wks

*24-wk arms not yet reported.

Press release. These data are available in press release format only, have not been peer reviewed, may be incomplete, and we await presentation or publication in a peer-reviewed format before conclusions should be made from these data.
Summary

- First-generation PIs have now been replaced
  - SMV + P/R x 24 weeks – issue with Q80K in GT1a
  - SOF + P/R x 12 weeks in GT1

- IFN will hang around for a short while . . .
  - IFN-free therapy coming soon for GT1

- Challenges
  - GT1a vs GT1b
  - One size fits all vs GT1b regimens
  - GT3 may still need IFN, at least for now

- Will simplify with time and we will have something for everyone
- The final challenge will be paying for perfectovir!