Hepatitis C – An Update

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Estimated 70 Million Persons With HCV Infection Worldwide
Hepatitis C Virus

- Nucleic Acid: 9.6 kb ssRNA
- Classification: *Flaviviridae, Hepacivirus*
- Genotypes: 1 to 6
- Enveloped
- In vitro model: primary hepatocyte and T cell cultures; replicon system
- In vivo replication: in cytoplasm, hepatocyte and lymphocyte; human and other primates
Future Burden of Hepatitis C Related Morbidity and Mortality in the US

- Markov model of health outcomes
  - Of 2.7 M HCV infected persons in primary care
    - 1.47 M will develop cirrhosis
    - 350,000 will develop liver cancer
    - 897,000 will die from HCV-related complications

Screening for HCV infection in Adults: USPSTF Recommendations

- Released June 24, 2013
- USPSTF Grade B recommendation
  - Adults at high risk
  - Adults born 1945-1965
- Grade B –
  - Co-pay support (ACA)
  - Priority for performance measures, and changes in EMR
- Consistent with CDC recommendations
Recommended Testing Sequence for Identifying Current Hepatitis C Virus (HCV) Infection

- **HCV antibody**
  - **Nonreactive**
    - No HCV antibody detected
      - STOP*
  - **Reactive**
    - **Not Detected**
      - No current HCV infection
        - Additional testing as appropriate†
    - **Detected**
      - Current HCV infection
      - Link to care

* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

† To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Educate Communities

BORN FROM 1945-1965?
CDC RECOMMENDS YOU
GET TESTED FOR HEPATITIS C.
Potential Impact on Future Burden of Hepatitis C Related Mortality in the US

HCV deaths prevented:
- 143,000 for treat 15%
- 238,000 for treat 25%
- 476,000 for treat 50%
- 714,000 for treat 75%

No Testing
Treatment Reduces All-Cause Mortality in Patients With Advanced Fibrosis

Impact of Treatment on HCC

Impact of Treatment on Liver Failure

Management of the Patient with Hepatitis C
Approach to the Patient with Newly Diagnosed HCV

- Patients need to be educated on
  - the natural history of disease
  - modes of transmission of
  - how to avoid transmission to family members
  - the availability of effective treatment
  - the promise of new highly effective and safe interferon free treatments in the near future

- Screen for depression
- Reassurance
- Patients may benefit from referral to a support group
Additional Measures for Newly Diagnosed Patients with HCV

• Vaccinate for hepatitis A and hepatitis B
• Counsel for weight loss if appropriate. Obesity increases likelihood of liver fibrosis
• Recommend avoiding doses of acetaminophen exceeding 1-2 grams per day
• Determine presence or absence of cirrhosis
• NSAIDs should be avoided in patients with advanced fibrosis or cirrhosis
Measures to Avoid Transmission of Hepatitis C

- Avoid Sharing Razors or Toothbrushes
- Cover Bleeding Wounds
- Stop Injection Drug Use
- Advise Not to Share Needles and Paraphernalia
- Advise Not to Donate Blood, Organs, Tissue or Semen
Sexual Transmission of HCV

- Risk of Sexual Transmission is Low in Monogamous Heterosexual Relationships
- Many Experts do not Recommend Barrier Protection for Couples that are in a Monogamous Long Term Relationship
- Patients with Multiple Sexual Partners, and Patients with HIV Should Use Barrier Protection
Steps to Slow Progress of Liver Disease

- Obesity and Smoking Increase Liver Fibrosis
- Daily Marijuana Use Increases Fibrosis Progression Rate. Odds Ratio = 3.4 (1.5 -7.4)
- Patients Should be Counseled to:
  - Lose Weight if Necessary
  - Stop Smoking
  - Discontinue Marijuana Use

- Hu SX: J Clin Gastroenterol. 2009 Sep;43(8):758-64
Hepatitis C and Alcohol

- Hepatitis C Infection Rates in Alcoholics are Significantly Higher Than Controls
- Alcohol Use in Patients with HCV Infection Increases Fibrosis Progression Rate, Risk for Liver Cancer and Overall Mortality
- Abstinence from Alcohol is Recommended
- Educate on Synergistic Damage to liver by Alcohol and HCV
- Refer to Alcohol Rehab Programs if appropriate

Baseline Studies in Persons with Chronic HCV Infection

- CBC, PT, INR
- Comprehensive metabolic panel including LFTs
- Serum ferritin level, serum iron and total iron binding capacity
- Urine analysis
- HCV genotype and subtype
- Quantitative HCV RNA
- Hepatitis A serology (total or IgG)
- Hepatitis B serology (HepBsAg, HepBsAb, HepBcAb)
- HIV Antibody

For Patients not interested or being considered for treatment repeat liver function tests every 3-6 months. It is not necessary to repeat HCV RNA or genotype.
Hepatitis B Vaccination

- Two hepatitis B vaccines have been licensed in the United States
  - Engerix-B contains 20 mcg HBsAg/ml. Adults receive series of 3 doses (1 mL each) given IM on a 0-, 1-, 6-month schedule;
  - Recombivax HB contains 10 mcg HBsAg/ml. Adults receive series (1 mL each) given IM on a 0-, 1-, 6-month schedule;

- Protection rates in clinical trials
  - 96% of patients aged 20-65 are seroprotected (HBsAb titers > 10 mIU/ml at month 7 of testing.
  - and 88-89% of patients over 40 are seroprotected
  - Intramuscular injection in deltoid is preferred
Hepatitis B Vaccination

• Post-vaccination testing to document anti-HBs sero-conversion is unnecessary except in health-care workers, patients on chronic dialysis, and sexual partners of patients with hepatitis B

• Patients on dialysis need higher doses and have lower response rates
  – Engerix B: Adults on dialysis receive 4 doses of 40 mcg (2 ml each) on a 0-, 1-, 2-, 6-month schedule
  – Recombivax: Adults on dialysis receive 3 doses of 40 mcg (1 ml each) on a 0-, 1-, 6-month schedule
Hepatitis A and Combination Vaccine

- Patients with HCV are at increased risk for morbidity and mortality from hepatitis A. All patients should be vaccinated unless immune

- Havrix: For adults a single 1-mL dose (1440 Elisa Units) and a 1-mL booster dose administered IM between 6 to 12 months later. Seroprotection 1 month after booster dose ranges from 95-98% in patients with liver disease

- VAQTA: For adults a single 1 mL dose (50 units) administered IM with a booster dose of 1 mL to be given 6-18 months after primary immunization

- Twinrix: A 1-mL dose of vaccine contains 720 ELISA Units of inactivated hepatitis A virus and 20 mcg of recombinant HBsAg protein. For adults a series of 3 doses (1 mL each) are given IM on a 0-, 1-, and 6-month schedule.
HCV and Diabetes Mellitus

- Meta analysis of 34 studies
  - Pooled estimators indicated significant DM risk in HCV-infected cases in comparison to non-infected controls.
    - Retrospective studies (OR(adjusted)=1.68, 95% CI 1.15-2.20)
    - Prospective studies (HR(adjusted)=1.67, 95% CI 1.28-2.06)
    - Excess DM risk was also observed in comparison to HBV-infected controls (OR(adjusted)=1.80, 95% CI 1.20-1.40)
    - Suggestive excess risk of DM observed in HCV+/HIV+ cases in comparison to HIV+ controls (OR(unadjusted)=1.82, 95% CI 1.27-2.38).
- Data suggests a potential direct viral role in promoting DM risk

• White DL: J Hepatol. 2008;49(5):831
Patients with Extrahepatic Manifestations should be prioritized for treatment

- Essential Mixed Cryoglobulinemia
- Leukocytoclastic vasculitis
- B Cell Non Hodgkin’s Lymphoma
- Porphyria Cutanea Tarda
- Necrolytic acral erythema
- Renal Disease
  - Membranoproliferative glomerulonephritis
  - Membranous nephropathy
  - Nephrotic syndrome
Classical Cryoglobulinemia-related small vessel vasculitis with erythematous palpable maculopapular rash in a HCV positive patient composed of monoclonal and polyclonal gamma globulins.

Room Temperature 4 degrees

http://openi.nlm.nih.gov/
Membranoproliferative Glomerulonephritis

There is increased lobulation, intracapillary hypercellularity (including neutrophil infiltration), and thickening of the capillary walls.

http://www.kidneypathology.com.ar/07.htm
Diagnosis of Cirrhosis Changes
Approach to Patients with HCV

- Screen for HCC every 6 months
- Evaluate for esophageal varices with endoscopy
- Avoid all hepatotoxic drugs
- Refrain from use of NSAIDs including aspirin, ibuprofen, naproxen, and others due to an increased risk of gastrointestinal bleed, potential for renal toxicity, and impaired response to diuretic therapy.
- **Prioritize for treatment**
- Recommend weight loss for obese patients
- Avoid use of aminoglycosides for treatment of infections
Findings Suggestive of Cirrhosis

• Clinical exam
  – Spider nevi, palmar erythema, gynecomastia, firm liver on palpation, splenomegaly

• Noninvasive diagnostic tests suggesting cirrhosis
  – Low platelet count (150 thousand)
  – Low serum albumin, AST/ALT ratio >1
  – Prolonged prothrombin time
  – High APRI score or Fibrosure test score
  – Ultrasound transient elastography
  – Platelets < 150 thousand
  – Neutropenia

• Liver biopsy
Commonly Used Biochemical Tests to Assess Severity of Liver Disease

- AST to Platelet Ratio Index (APRI score)
- FibroTest (Europe) and FibroSure (United States)
- MELD (Serum Bilirubin, Serum Creatinine and international normalized ratio for prothrombin time -INR)
AST to Platelet Ratio Index (APRI score)

- APRI = (AST elevation/platelet count) x 100
- A patient has an AST level of 80 IU/L in a lab with an ULN = 40 IU/L. AST Elevation is 80/40=2. Platelet count is 130,000/mm³. APRI score is: (2/130) x 100 = 1.54
- APRI score > 1.0 has a sensitivity of 76% and specificity of 72% for cirrhosis
- Area Under ROC curve is 0.80

Ultrasound based Transient Elastography (FibroScan)

- The more stiff/fibrotic the liver the faster the wave propagates.
- Liver Biopsy 1/50,000 of liver, Fibroscan 1/500 of liver
- Is reproducible and painless

Potential Benefits of Noninvasive Tests

• Ease of administration
• Lower cost
• Assessment of degree of fibrosis
• Assist with decision to treat or wait
• Can be repeated over time to monitor progress of liver disease
• May predict clinical outcomes better than liver biopsy
All HCV Patients Should be Considered for Treatment

Decision for an Individual Based On Risk/Benefit

– Fibrosis stage – type of assessment/accuracy

– Likelihood to tolerate – IFN + additional AEs

– Stage of life
  • Age, family planning, job, finances

– Other factors
  • Transmission risk, extra hepatic manifestations

– Patient Preference
SVR Rates with PegIFN/RBV According to Genotype

DAAs Uniquely Target Hepatitis C Virus

Potential targets for antiviral intervention in the HCV lifecycle and their location in the HCV genome

- Receptor binding and endocytosis
- Fusion and uncoating
- Transport and release
- RNA replication
- Viral assembly
- Translation and polyprotein processing
- N3/4 protease inhibitors (telaprevir, boceprevir)
- \( \alpha \)-glucosidase Inhibitors
- NS5B polymerase inhibitors
- Cyclophilin inhibitors

Sofosbuvir (SOF, GS-7977)

- HCV-specific uridine nucleotide NS5B polymerase inhibitor (chain terminator)
- Potent antiviral activity against HCV genotypes 1–6
- High barrier to resistance
- Once-daily, oral, 400-mg tablet
- Limited potential for drug interactions
- Generally safe and well tolerated in clinical studies to date (>3000 patients)
Nucleoside/tide Analog Polymerase Inhibitors Are Chain-Terminators

**RNA chain cannot be elongated**

**NI Chain-terminator**
STR: Single Tablet Regimen

SOF 400mg +
LDV 90mg
ION Phase 3 Program (ION-1, ION-2, ION-3)

Efficacy Summary

- 97% (1886/1952) overall SVR rate
- 3% (66/1952) did not achieve SVR
  - 1.4% (28) LTFU
  - 0.1% (2) virologic breakthrough (both due to non-adherence)
  - 1.8% (36) relapsed. Patients may be rolled over to a retreatment study

Error bars represent 95% confidence intervals.

Elbasvir/Grazoprevir

- Brand name: **Zepatier**
- Oral fixed-dose combination tablet
  - 50 mg elbasvir
    - NS5A replication complex inhibitor
  - 100 mg grazoprevir
    - NS3/4A protease inhibitor
  - Dosing: 1 tablet per day with or without food
## Indications

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a: Treatment naïve or pegIFN/RBV experienced without baseline NS5A polymorphisms</td>
<td>Elbasvir/grazoprevir</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1a: Treatment naïve or pegIFN/RBV experienced with baseline NS5A polymorphisms</td>
<td>Elbasvir/grazoprevir + ribavirin</td>
<td>16 weeks</td>
</tr>
<tr>
<td>Genotype 1b: treatment naïve or pegIFN/RBV experienced</td>
<td>Elbasvir/grazoprevir</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1a or 1b: pegIFN/RBV/PI experienced</td>
<td>Elbasvir/grazoprevir + ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 4 treatment naïve</td>
<td>Elbasvir/grazoprevir</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 4 treatment experienced</td>
<td>Elbasvir/grazoprevir + ribavirin</td>
<td>16 weeks</td>
</tr>
</tbody>
</table>
Use in Special Populations

- **Renal impairment**
  - No dose adjustment needed in any degree of renal impairment
  - No dose adjustment needed in hemodialysis

- **Hepatic Impairment**
  - No dose adjustment needed for CTP class A cirrhosis
  - Contraindicated in patients with CTP class B or C cirrhosis
Key Points

- Elbasvir/grazoprevir for treatment naïve or treatment experienced patients with HCV genotype 1a, 1b, or 4
  - Duration of therapy 12-16 weeks
  - May require ribavirin
  - 1 tablet daily with or without food
- Pre-treatment resistance testing required for patients with HCV genotype 1a
- Monitor LFTs on treatment
- Drug-drug interactions manageable
Epclusa®

- Fixed-dose combination of sofosbuvir (NS5B inhibitor) and velpatasvir (NS5A inhibitor)
- Approved June 28, 2016 for chronic HCV genotypes 1, 2, 3, 4, 5, or 6
  - Treatment naïve
  - Treatment experienced (Peg-IFN/RBV with or without PI)

# Dosage and Administration

<table>
<thead>
<tr>
<th>Patients</th>
<th>Recommended Treatment Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients without cirrhosis and patients with compensated cirrhosis (Child-Pugh class A)</td>
<td>Epclusa x 12 weeks</td>
</tr>
<tr>
<td>Patients with decompensated cirrhosis (Child-Pugh class B or C)</td>
<td>Epclusa + ribavirin x 12 weeks</td>
</tr>
</tbody>
</table>

- 1 table once per day with or without food
- No dosage recommendations in severe renal impairment and end stage renal disease

ASTRAL-1: SOF/VEL STR for 12 Weeks in GT 1, 2, 4, 5, 6 HCV-Infected Patients

SVR12 by Cirrhosis Status or Treatment History

<table>
<thead>
<tr>
<th></th>
<th>SVR12 (%)</th>
<th>Total</th>
<th>Non-Cirrhotic</th>
<th>Cirrhotic</th>
<th>Treatment-Naïve</th>
<th>Treatment-Experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>618/624</td>
<td>496/501</td>
<td>120/121</td>
<td>418/423</td>
<td>200/201</td>
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<tr>
<td></td>
<td></td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>99</td>
</tr>
</tbody>
</table>

Error bars represent 95% confidence intervals.
Adverse Effects and Laboratory Abnormalities

- Most common in clinical trials:
  - Headache (22%)
  - Fatigue (15%)
  - Nausea (9%)
  - Asthenia (5%)
  - Insomnia (5%)

- Adverse effects occurred at similar frequency or more frequently with placebo
  - Exception asthenia (3% in placebo vs. 5% with Epclusa)

- Irritability also observed in >5% of patients in ASTRAL-3 study (genotype 3 clinical trial)

- Laboratory abnormalities infrequent
  - Asymptomatic lipase elevations
  - Asymptomatic creatine kinase elevations
  - Elevated indirect bilirubin among HIV/HCV coinfected patients on atazanvir/ritonavir

### Drug Interactions: Acid Suppressive Therapy

<table>
<thead>
<tr>
<th>Concomitant Drug Class: Drug Name</th>
<th>Effect on Concentration</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacids</td>
<td>🕒 Velpatasvir</td>
<td>Avoid co-administration Separate antacid and Epclusa by 4 hours</td>
</tr>
<tr>
<td>H2-Antagonists: (e.g. famotidine, ranitidine)</td>
<td>🕒 Velpatasvir</td>
<td>Give at same time or 12 hours apart</td>
</tr>
<tr>
<td>Proton Pump Inhibitors: (e.g. omeprazole)</td>
<td>🕒 Velpatasvir</td>
<td>Do not co-administer If medically necessary: take Epclusa with food 4 hours before omeprazole 20 mg (max dose; no data with other PPIs)</td>
</tr>
</tbody>
</table>

*Velpatasvir requires acidic environment for absorption*

Hepatitis B Reactivation

Black Box Warning

Test for HBsAg and HBcAb

Monitor for Reactivation in people who have HBsAg or HBcAb alone
Key Points

- **Epclusa** (velpatasvir/sofosbuvir) approved for genotypes 1, 2, 3, 4, 5, and 6
  - For non-cirrhotic and patients with CTP class A cirrhosis: Epclusa x 12 weeks
  - For patients with decompensated cirrhosis including CTP class B and C: Epclusa and ribavirin x 12 weeks

- Headache and fatigue most commonly reported AEs

- Laboratory monitoring minimal- flowsheets to follow shortly

- Drug interactions include acid suppressive therapy and major drug interaction concerns previously identified for sofosbuvir
Sofosbuvir/Velpatasvir/Voxilaprevir

- Combination of
  - NS5B polymerase inhibitor (Sofosbuvir);
  - NS5A inhibitor (Velpatasvir);
  - NS3/4A protease inhibitor (Voxilaprevir)

- Administration
  - One tablet once daily with food

Patients with genotype 1, 2, 3, 4, 5, or 6 who were previously treated with an NS5A inhibitor

Patients with genotype 1a or 3 infection previously treated without an NS5A inhibitor

- Includes patients treated with sofosbuvir with or without boceprevir, telaprevir, simeprevir; peginterferon/ribavirin
- No advantage of using sofosbuvir/velpatasvir/voxilaprevir over sofosbuvir/velpatasvir for retreatment of patients with GT 1b, 2, 4, 5, or 6
Who Can Be Treated with SOF/VEL/VOX?

- Patients without cirrhosis
- Patients with Child’s class A cirrhosis (compensated cirrhosis)
- Restricted to patients with glomerular filtration rates greater than 30 mL/min/1.73 m²
SVR12 Results Overall and by Cirrhosis Status

POLARIS-1: SOF/VEL/VOX for 12 Weeks in NS5A Inhibitor-Experienced HCV GT 1–6

Bourliere M, AASLD 2016, Oral 194

* p <0.001 for superiority compared with prespecified 85% performance goal for SOF/VEL/VOX

** Exposure was consistent with non-adherence
Adverse Reactions and Laboratory Abnormalities

• Adverse reactions:
  – Headache
  – Fatigue
  – Diarrhea
  – Nausea

• Laboratory abnormalities: increases in total bilirubin
  – Voxilaprevir can inhibit bilirubin transporters
Mavyret Product Characteristics

- Mavyret approval was based on clinical trial data in over 2,300 patients including placebo- and active-controlled studies
- Mavyret is a fixed-dose combination of glecaprevir, an HCV NS3/4A protease inhibitor, and pibrentasvir, an HCV NS5A inhibitor, and is indicated for the treatment of patients with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection without cirrhosis and with compensated cirrhosis (Child-Pugh A)
- Mavyret is also indicated for the treatment of adult patients with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both

Mavyret is Indicated for the Treatment of Adult Patients with Chronic HCV Genotype 1–6

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>Prior Treatment Experience</th>
<th>Without Cirrhosis</th>
<th>With Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 2, 3, 4, 5, 6</td>
<td>Naïve</td>
<td>8 Weeks</td>
<td>12 Weeks</td>
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<tr>
<td>1, 2, 4, 5, 6</td>
<td>PRS</td>
<td>8 Weeks</td>
<td>12 Weeks</td>
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<tr>
<td>3</td>
<td>PRS</td>
<td>16 Weeks</td>
<td>16 Weeks</td>
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<tr>
<td>1</td>
<td>NS3/4A PI (NS5A inhibitor naive)*</td>
<td>12 Weeks</td>
<td>12 Weeks</td>
</tr>
<tr>
<td></td>
<td>NS5A inhibitor (NS3/4A PI naive)†</td>
<td>16 Weeks</td>
<td>16 Weeks</td>
</tr>
</tbody>
</table>

Dosage and durations are applicable to patients with:
- HCV mono-infection or HCV/HIV-1 co-infection
- Any stage of renal impairment including patients receiving dialysis

Mavyret is not recommended in patients with moderate hepatic impairment (CP-B) and is contraindicated in patients with severe hepatic impairment (CP-C)

Mavyret is not indicated for patients experienced to both NS5Ai and NS3/4A PIs

PI, protease inhibitor; PRS, regimens containing interferon, pegylated interferon, ribavirin and/or sofosbuvir (no experience with NS3/4A PI or NS5A inhibitors); CP, Child-Pugh.

*Regimens containing simeprevir and sofosbuvir or simeprevir, boceprevir, or telaprevir with interferon or pegylated interferon and ribavirin.
†In clinical trials, subjects were treated with prior regimens containing ledipasvir and sofosbuvir or daclatasvir with pegylated interferon and ribavirin.

Recommended Dosage in Adults

- Mavyret is a fixed-dose combination product containing glecaprevir 100 mg and pibrentasvir 40 mg in each tablet.
- The recommended oral dosage is 3 tablets (total daily dose: glecaprevir 300 mg and pibrentasvir 120 mg) taken once daily with food.
- G/P is packaged in monthly cartons containing 4 weekly cartons.
- Each weekly carton contains 7 daily dose wallets.
- Each daily dose wallet contains 3 tablets with instructions on how to remove the tablets.
### Registrational Trials Conducted with Mavyret in Adults with HCV GT1-6 Infection

<table>
<thead>
<tr>
<th>Phase 2</th>
<th>Population</th>
<th>N</th>
<th>Treatment</th>
<th>Prior Treatment*</th>
<th>Cirrhosis Status</th>
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</thead>
<tbody>
<tr>
<td>MAGELLAN-I</td>
<td>GT1</td>
<td>42</td>
<td>Mavyret for 12 or 16 wks</td>
<td>DAA-exp</td>
<td>NC, CC</td>
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<tr>
<td>SURVEYOR-I</td>
<td>GT5, 6</td>
<td>12</td>
<td>Mavyret for 12 wks</td>
<td>TN, TE</td>
<td>NC</td>
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<tr>
<td>SURVEYOR-II</td>
<td>GT2–6</td>
<td>364</td>
<td>Mavyret for 8, 12, or 16 wks</td>
<td>TN, TE</td>
<td>NC, CC</td>
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</table>

<table>
<thead>
<tr>
<th>Phase 3</th>
<th>Population</th>
<th>N</th>
<th>Treatment</th>
<th>Prior Treatment*</th>
<th>Cirrhosis Status</th>
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<tbody>
<tr>
<td>ENDURANCE-1</td>
<td>GT1</td>
<td>703</td>
<td>Mavyret for 8 or 12 wks</td>
<td>TN, TE</td>
<td>NC</td>
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<tr>
<td>ENDURANCE-2</td>
<td>GT2</td>
<td>302</td>
<td>Mavyret for 12 wks vs PBO</td>
<td>TN, TE</td>
<td>NC</td>
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<td>ENDURANCE-3</td>
<td>GT3</td>
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<td>NC</td>
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<td>ENDURANCE-4</td>
<td>GT5, 6</td>
<td>45</td>
<td>Mavyret for 12 wks</td>
<td>TN, TE</td>
<td>NC</td>
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<table>
<thead>
<tr>
<th>Special Populations</th>
<th>Population</th>
<th>N</th>
<th>Treatment</th>
<th>Prior Treatment*</th>
<th>Cirrhosis Status</th>
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</thead>
<tbody>
<tr>
<td>EXPEDITION-1</td>
<td>GT1, 2, 4–6; CC</td>
<td>146</td>
<td>Mavyret for 12 wks</td>
<td>TN, TE</td>
<td>CC</td>
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<tr>
<td>EXPEDITION-4</td>
<td>GT1–6; CKD</td>
<td>104</td>
<td>Mavyret for 12 wks</td>
<td>TN, TE</td>
<td>NC, CC</td>
</tr>
</tbody>
</table>

CC, compensated cirrhosis; DAA, direct-acting antiviral; DCV, daclatasvir; GT, genotype; NC, non-cirrhotic; SOF, sofosbuvir; TN, treatment-naive; TE, treatment-experienced; wks, weeks.

* TE patients received prior IFN or pegIFN ± RBV; or SOF + RBV ± pegIFN.
†Mavyret 12-week arm compared with DCV+SOF for 12 weeks.

Studies Evaluating the Efficacy of Mavyret in Patients with HCV GT1, 2, 4-6 Infection with or without Compensated Cirrhosis

Mavyret for 8 Weeks in TN/TE NC Patients: ENDURANCE-1 and SURVEYOR-2

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>GT1</th>
<th>GT2</th>
<th>GT4</th>
<th>GT5</th>
<th>GT6</th>
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<tbody>
<tr>
<td>SVR12 (%)</td>
<td>98</td>
<td>99</td>
<td>98</td>
<td>93</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>n</td>
<td>596</td>
<td>348</td>
<td>193</td>
<td>43</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>N</td>
<td>606</td>
<td>351</td>
<td>197</td>
<td>46</td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>

Mavyret for 12 Weeks in TN/TE CC Patients: EXPEDITION-1

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>GT1</th>
<th>GT2</th>
<th>GT4</th>
<th>GT5</th>
<th>GT6</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12 (%)</td>
<td>99</td>
<td>99</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>n</td>
<td>145</td>
<td>89</td>
<td>31</td>
<td>16</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>N</td>
<td>146</td>
<td>90</td>
<td>31</td>
<td>16</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>GT1</th>
<th>GT2</th>
<th>GT4</th>
<th>GT5</th>
<th>GT6</th>
</tr>
</thead>
<tbody>
<tr>
<td>BT</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Relapse</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Non-VF*</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

All analyses are using the ITT population.

TN, treatment-naïve; TE, treatment-experienced with IFN or pegIFN ± RBV, or SOF + RBV ± pegIFN; NC, non-cirrhotic; CC, compensated cirrhotic; ITT, intent-to-treat; BT, breakthrough; VF, virologic failure.

*Includes patients who discontinued due to adverse events, lost to follow-up, or withdrew.

Studies Evaluating the Efficacy of Mavyret in Patients with HCV GT3 Infection with or without Compensated Cirrhosis

**Mavyret for 8 or 12 Weeks in TN NC Patients: ENDURANCE-3**

- Mavyret 8 weeks: 95% (149/157)
- Mavyret 12 weeks: 95% (222/233)
- DCV + SOF 12 weeks: 97% (111/115)

**Mavyret for 12 Weeks in TN CC Patients, or 16 Weeks in TE NC/CC Patients: SURVEYOR-2 Part 3**

- TN CC 12 weeks: 98% (39/40)
- TE NC/CC 16 weeks: 96% (66/69)

<table>
<thead>
<tr>
<th>BT</th>
<th>Relapse</th>
<th>Non-VF*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TN CC 12 weeks</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>TE NC/CC 16 weeks</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

*Includes patients who discontinued due to adverse events, lost to follow-up, or withdrew.

All analyses are using the ITT population.

TN, treatment-naïve; TE, treatment-experienced with IFN or pegIFN ± RBV, or SOF + RBV ± pegIFN; BT, breakthrough; CC, compensated cirrhosis; NC, noncirrhotic; DCV, daclatasvir; ESRD, end-stage renal disease; SOF, sofosbuvir; TE, treatment experienced; TN, treatment naive; VF, virologic failure.

Efficacy and Safety of Mavyret in GT1-6 Patients with or without Compensated Cirrhosis with CKD Stage 4 or 5, Including Dialysis

Mavyret for 12 Weeks in GT1-6 Patients with CKD Stages 4 or 5 Including Those on Dialysis: EXPEDITION-4

Safety Summary

<table>
<thead>
<tr>
<th>Event</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious ADRs</td>
<td>0</td>
</tr>
<tr>
<td>d/c due to ADR</td>
<td>2</td>
</tr>
<tr>
<td>ADRs occurring in ≥5% of Patients</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>17</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12</td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
</tr>
<tr>
<td>Asthenia</td>
<td>7</td>
</tr>
<tr>
<td>Headache</td>
<td>6</td>
</tr>
</tbody>
</table>

90% of ADRs were mild or moderate

Although studied for 12 weeks, G/P is indicated for 8 weeks in GT1-6 TN NC patients regardless of renal impairment, including patients on dialysis.

All analyses are using the ITT population.
ADRs, adverse drug reactions considered related to study drug; BT, breakthrough; CKD, chronic kidney disease; VF, virologic failure; d/c, discontinuation.
*Includes patients who discontinued due to adverse events, lost to follow-up, or withdrew.

Less than 6% of the world’s population has been cured of HCV
Highly effective treatments exist
Primary care diagnosis, assessment and treatment of all patients with hepatitis C has the potential to save millions of lives around the world

Sarora@salud.unm.edu