Hepatitis C Update
Access to Care

Hepatitis C 101
Hepatitis C: Past Present Future
Hepatitis C Treatment Evolution
Hepatitis C Treatment Revolution
Hepatitis C elimination by 2030
Project ECHO/American Liver Foundation
Questions & Answers (hopefully)

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Digestive Health Service
Good Sam Hospital
Affiliate, Northwestern
Department of Hepatology
Conflicts and Confessions

- **Advisory Boards**: Abbvie, Gilead, Janssen, BMS, Prometheus

- **Speaker Boards**: Gilead, Forest Pharmaceutical, Allergan, BMS

- **Clinical Studies/Principle Investigator**: Gilead, Vertex, Merck, Tibotec,
What is Hepatitis C

• A virus that is acquired by exposure to blood or other body fluids
  • Flavidviridae family of virus (pestiviruses (cattle pig), flaviviruses (dengue, yellow fever), hepaciviruses (HCV)
• The virus can damage the liver over time (sometimes decades)
• Extensive scarring of the liver=cirrhosis
• Most people have no symptoms and do not know they have the virus
What is Hepatitis C

• 180 million infected worldwide
• 3.2 - 5 million in US
  – Almost 2% of the US population
• Associated with:
  – Cirrhosis
  – Hepatocellular carcinoma (liver cancer)
• Leading cause of liver related death and liver transplantation
• Can take decades to cause severe liver damage
• Genotypes 1, 2, 3, 4, 5, and 6
  – >100 different subtypes, and quasispecies
HCV: how it works

The image illustrates the replication process of Hepatitis C Virus (HCV). The virus enters the hepatocyte and infects the endoplasmic reticulum. The viral RNA (+RNA) is translated into viral proteins, and these proteins, along with the RNA, form a replication complex. The NS3/4A viral protease is involved in the processing of the viral RNA. The replication complex also contains the NSSA replication/assembly factor, which is essential for virus assembly. The assembled virions (HCV) are released from the cell, completing the viral life cycle.
Hepatitis C virus RNA

9600 nt bases

Gene encoding precursor polyprotein

5' NTR                   3' NTR

Structural proteins: p22, gp35, gp70, p7, p23, p70

Non-structural proteins: p8, p27, p56/58, p68

Envelop glycoproteins: C, E1, E2

Proteases, RNA helicase, co-factors

Transmembrane protein: NS1

RNA polymerase: NS2, NS3, NS4A, NS4B, NS5A, NS5B

Nucleocapsid: p22

Transmembrane protein: p7

Interferon resisting protein: p27, p56/58, p68
Hepatitis C Virus Genotypes in the USA

Type 1: 72%
Type 2: 17%
Type 3: 10%
All others: 1%

Factors Associated With Disease Progression

- Alcohol consumption
  - 30 g/day in men
  - 20 g/day in women

- Disease acquisition at >40 years
- Male gender
- HIV coinfection
- Hepatitis B virus coinfection
- Immunosuppression
- Obesity

Transmission:

• Direct blood or fluid exposure

• Sexual Activity

• Perinatal Transmission
Transmission:

- Other things thought to be associated with HCV:
  - Tattoos
  - Acupuncture
  - Ear piercing

These ARE NOT usual causes of HCV!
Hepatitis C Virus Infection

Natural History

Acute HCV

Resolved
15% (15%)

Chronic HCV
85% (85%)

Stable
80% (68%)

Cirrhosis
20% (17%)

Slowly progressive
75% (13%)

HCC
Liver failure
25% (4%)

HCC, hepatocellular carcinoma
Future Burden of HCV-Related Morbidity and Mortality in the US

1 out of every 3 persons living with HCV infection today will die prematurely of HCV-related causes\(^a\)

Treatment-induced HCV clearance reduces annual patient care costs by half ($1436 to $717)\(^b\)

Direct Medical Costs Associated with Extrahepatic Manifestations of HCV Infection in the USA

Costing analysis to estimate direct medical cost of extrahepatic manifestations (EHM);
EHM prevalence multiplied by resource utilization and drug costs
Prevalence rates were sourced from the literature; inpatient use and costs were calculated using Medicare billing data

<table>
<thead>
<tr>
<th>EHM</th>
<th>HCV</th>
<th>NON-HCV</th>
<th>ADJ</th>
<th>IP</th>
<th>OP</th>
<th>IP</th>
<th>PHARMACY</th>
<th>COST PPPY</th>
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<tbody>
<tr>
<td>ARTH</td>
<td>23.0%</td>
<td>0%</td>
<td>23.0%</td>
<td>3.2%</td>
<td>$166.99</td>
<td>$8,007.71</td>
<td>$0</td>
<td>$409</td>
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<td>DEP</td>
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<td>14.4%</td>
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<td>27.4%</td>
<td>$234.23</td>
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<td>0%</td>
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<td>$162.69</td>
<td>$17,795.74</td>
<td>$5.94</td>
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<td>14.8%</td>
<td>9.3%</td>
<td>5.5%</td>
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<td>$165.15</td>
<td>$5,693.39</td>
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<td>0%</td>
<td>4.3%</td>
<td>0.2%</td>
<td>$92.73</td>
<td>$17,998.64</td>
<td>$7.20</td>
<td>$127</td>
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<tr>
<td>GMN</td>
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<td>1.3%</td>
<td>3.5%</td>
<td>0.5%</td>
<td>$161.43</td>
<td>$8,436.31</td>
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<td>0%</td>
<td>3.0%</td>
<td>12.6%</td>
<td>$114.26</td>
<td>$16,409.41</td>
<td>$0</td>
<td>$2,156</td>
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<td>ESRD</td>
<td>0.4%</td>
<td>0.3%</td>
<td>0.1%</td>
<td>1.8%</td>
<td>$23,601.69</td>
<td>$8,407.92</td>
<td>$5,242.57</td>
<td>$28,993</td>
</tr>
</tbody>
</table>

Extrahepatic symptoms can result in substantial yearly per patient healthcare costs

ESRD = end-stage renal disease; T2DM = Type 2 diabetes mellitus; DEP = depression; PCT = porphyria cutanea tarda;
MCG = mixed cryoglobulinemia; ARTH = RA-like arthritis; GMN = glomerulonephritis; LP = lichen planus; OP = outpatient;
IP = inpatient; PPPY = per patient per year; EHM = extrahepatic manifestation; ADJ = adjusted prevalence

Younossi ZM, EASL, 2015, #P0724
Chronic HCV leading to Cirrhosis and HCC

Fibrosis
Chronic HCV infection can lead to the development of fibrous scar tissue within the liver

Cirrhosis
Over time, fibrosis can progress, causing severe scarring of the liver, restricted blood flow, impaired liver function, and eventually liver failure

Hepatocellular Carcinoma (HCC)
Cancer of the liver can develop after years of chronic HCV infection
Lots of Work to Do

Over 5 million in US with HCV

25% have HCV diagnosis

Of these, only 11% have been treated

Courtesy of Donald Jensen, MD
• Age Adjusted Mortality Rates of HCV

* Mortality Rates = HBV, HCV, HIV listed as cause of death. Because of decedent can have multiple causes of death, a record listing more than 1 type of infection was counted for each type of infection.

Why Is HCV Under-Recognized?

- Asymptomatic
  - 40% with normal liver enzymes
- High prevalence in groups with limited access to medical care
- Difficulty in implementing risk-based screening
  - Limited time during primary care appointments
  - Invasive questions may not be asked
  - Patients may not be forthright
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/organisms 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)

Incidence of HCV: Age

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

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Expanded Estimate of HCV Prevalence

Estimated Number of anti-HCV Positive Persons in U.S

HCV Prevalence Estimate: Expansion of NHANES Survey

- Addition of Groups
  - Incarcerated
  - Homeless
  - Nursing Home Residents
  - Hospitalized Persons
  - Active Military Duty
- Recalculation of Groups
  - Healthcare Workers
  - Chronic Hemodialysis
  - Veterans

5.2 million Antibody Positive for HCV

Why is Diagnosis so Important?

WE CAN CURE HEPATITIS C!!!!
Treatment Outcomes after Sustained Virologic Response (Cure)
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).

THE GOOD, BAD AND UGLY

A REMINDER OF OUR JOURNEY

• HISTORY
• FIRST TREATMENTS
• FIRST TREATMENT ..... THE BAD
• FIRST GENERATION DAA ..... THE UGLY
• SECOND GENERATION DAA
• THE WILD WILD WORLD COMING TO HCV TREATMENT...... THE GOOD
Hepatitis C Treatment
The bad old days, 4 years ago

• **INTERFERON** - Hematologic complications (i.e., neutropenia, thrombocytopenia), neuropsychiatric complications (i.e., memory and concentration disturbances, visual disturbances, headaches, depression, irritability), flulike symptoms, metabolic complications (i.e., hypothyroidism, hyperthyroidism, low-grade fever), gastrointestinal complications (i.e., nausea, vomiting, weight loss), dermatologic complications (i.e., alopecia), and pulmonary complications (i.e., interstitial fibrosis)

• **RIBAVIRIN** - Hematologic complications (i.e., hemolytic anemia), reproductive complications (i.e., birth defects), and metabolic complications (i.e., gout)
Hepatitis C Treatment
The bad old days, 2 years ago
Boceprevir and Telprevir

Major site effects
- Anemia
- Rash, Rectal Pain (Fire in the hole)
- Depression
- Major Drug/Drug interactions

- Time consuming for physicians, nursing staff, offices
- Genotype 1 only
- 24-48 weeks of therapy
- 30-40% failure of therapy
- It is BRUTAL on patients
NEW GENERATION OF DAA, BEGINNING OF THE END OF HCV

SOFOSBUVIR
SIMPREVIR
SOFOSBUVIR/LEDIPSAVIR (Harvoni)
VIEKIRA PAC
DACLATASVIR
SOFOSBUVIR-VEPATASVIR (Epclusa)
GRAZOPREVIR/ELBASVIR (Zepatier)
GS-9669 and GS-9451
Timeline of HCV Therapeutics

1986
1998
2014
HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C
Next Generation of HCV Medications

**Sofosbuvir (SOF)**
- HCV nucleotide NS5B polymerase inhibitor
- Indicated for therapy in treatment naïve

![Chemical structure of Sofosbuvir](image1)

**Simeprevir (SMV)**
- HCV NS3/4A protease inhibitor
- Indicated for therapy in treatment naïve and previous

![Chemical structure of Simeprevir](image2)
Simeprevir + sofosbuvir with or without RBV in genotype 1 treatment-naive and prior null responder patients: COSMOS

• Cohort 1 (n=80): Null responders with METAVIR F0-2
  – Black, 28.8%
  – Genotype 1a, 77%; Q80K 50%
  – IL28B CC, 6%
  – F2, 59%

• SVR$_{12}$ for 1a/Q80K: 24 of 27 (89%) excluding non-virologic failures

• Non-SVR patients (n=8)
  – No breakthrough
  – Viral relapse, n=3; all 1a/Q80K
  – Stop early, n=4
  – 1 patient achieved SVR$_4$ followed by fatal CVA

Jacobson IM et al. The Liver Meeting 2013; LB-3
Simeprevir plus Sofosbuvir with or without RBV in genotype 1 treatment-naïve and prior null responder patients: COSMOS

- Cohort 2 (n=84): Treatment naïve and null responders with METAVIR F3-4
  - Genotype 1a, 78%; Q80K, 40%
  - Cirrhosis, 47%
  - Null response, 54%
- SVR\(_4\) for 12 wk groups only
  - SVR\(_4\) in cirrhotics: 17 of 18 (94%)
- Non-SVR patients (n=1)
  - No breakthrough
  - Relapse: n=1; null responder with cirrhosis and 1a/Q80K

Jacobson IM et al. The Liver Meeting 2013; LB-3
Timeline of HCV Therapeutics

1986 1998 2014
HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C
Harvoni
Sofosbuvir/Ledipasvir FDC with or without RBV for patients with genotype 1 including patients with cirrhosis and prior protease inhibitor failure: LONESTAR

- Treatment naïve, n=60
  - SOF/LDV +/- RBV for 8 or 12 weeks
- PI virologic failure, n=40
  - Cirrhosis, n=22
  - SOF/LDV +/- RBV for 12 weeks
- Non-SVR, n=3
  - Lost to follow-up, n=1
  - Viral relapse, n=2
    - Naïve, 8 wks, no RBV
    - TE cirrhosis, 12 wks, no RBV
    - TN relapse patient was retreated
- No treatment discontinuation due to AE

Lawitz E et al. The Liver Meeting 2013; Abstract 215/1844
VIEKERA
paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed
dasabuvir (250 mg) and weight-based RBV for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis)

SVR12 Rates (SAPPHIRE-I and SAPPHIRE-II)

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>TN</th>
<th>TE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>GT1a</td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>GT1b</td>
<td>98</td>
<td>97</td>
</tr>
</tbody>
</table>

TN=treatment-naive; TE=treatment-experienced
AbbVie press releases, November 18, 2013 and December 10, 2013.
Risk for Late-Stage Liver-Related Events and Death by Genotype

- Observational cohort study of 128,769 HCV patients from the VA HCV Clinical Registry, which compiled electronic medical records data from 1999 to 2010.

NEW THERAPIES, RECENTLY APPROVED

C-EDGE TN: Efficacy Results

SVR12 With 12 Wks of Grazoprevir/Elbasvir According to Genotype

- Subgroup analysis: significantly lower SVR12 rates in pts with baseline HCV RNA > 800,000 IU/mL
  - No differences according to race, IL28B status, presence of cirrhosis
- Lower SVR12 rates in pts having baseline NS5A RAVs associated with > 5-fold loss of susceptibility to elbasvir

NEW THERAPIES, RECENTLY APPROVED

Epclusa (sofosbuvir/velpatasvir)

- Indicated for the treatment of chronic hepatitis C (all genotypes) in adults, with or without cirrhosis
- Warnings include bradycardia with amiodarone co-administration
- If given with ribavirin, contraindications and warnings for that drug also apply
- Drug interactions occur with P-gp inducers and moderate-to-potent CYP inducers; use of Epclusa with these products is not recommended
AASLD/IDSA Guideline
Recommendations*

Genotype 1a and 1b

- Zepatier for 12 weeks (compensated cirrhosis)
- Harvoni for 12 weeks (compensated cirrhosis)
  - Harvoni + ribavirin for 12 weeks (decompensated cirrhosis)
- Epclusa for 12 weeks (compensated cirrhosis)
  - Epclusa + ribavirin for 12 weeks (decompensated cirrhosis)
- Daklinza + Sovaldi for 12 weeks
  - Daklinza + Sovaldi + ribavirin for 12 weeks (decompensated cirrhosis)
- Viekira + ribavirin for 12 weeks (1a)
  - Viekira for 12 weeks (compensated cirrhosis) (1b)
- Sovaldi + Olysio for 12 weeks

*Treatment Naïve (not including alternative therapies), July 2016
AASLD/IDSA Guideline Recommendations*

Genotype 2

• Epclusa for 12 weeks (compensated cirrhosis)
  • Epclusa + ribavirin for 12 weeks (decompensated cirrhosis)
  • Daklinza + Sovaldi + ribavirin for 12 weeks for decompensated cirrhosis

Genotype 3

• Epclusa for 12 weeks (compensated cirrhosis)
  – Epclusa + ribavirin for 12 weeks (decompensated cirrhosis)
• Daklinza + Sovaldi for 12 weeks (for 24 weeks with or without ribavirin for compensated cirrhosis)
  – Daklinza + Sovaldi + ribavirin for 12 weeks (decompensated cirrhosis)

*Treatment Naïve (not including alternative therapies), July 2016
AASLD/IDSA Guideline Recommendations*

Genotype 4

- Zepatier for 12 weeks (compensated cirrhosis)
- Harvoni for 12 weeks (compensated cirrhosis)
  - Harvoni + ribavirin for 12 weeks (decompensated cirrhosis)
- Epclusa for 12 weeks (compensated cirrhosis)
  - Epclusa + ribavirin for 12 weeks (decompensated cirrhosis)
  - Daklinza + Sovaldi + ribavirin for 12 weeks (decompensated cirrhosis)
- Technivie + ribavirin for 12 weeks (compensated cirrhosis)

*Treatment Naïve (not including alternative therapies), July 2016
AASLD/IDSA Guideline Recommendations*

Genotype 5/6 (with or without cirrhosis)
• Harvoni for 12 weeks
• Epclusa for 12 weeks
1.46 million deaths in 2013, most of which from sequelae of chronic hepatitis B and C.

In the absence of additional efforts, 19 million hepatitis-related deaths are anticipated from 2015 to 2030 (2). Treatment now can prevent deaths in the short- and medium term.

With 1.46 million deaths in 2013, viral hepatitis was a leading cause of death, a toll comparable to that of HIV (1.3 million deaths), tuberculosis (1.2 million deaths) and malaria (0.5 million deaths)
## WHO 5 point plan for HBV/HCV Reduction

### TARGET AREAS

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Baseline 2015</th>
<th>2020 target</th>
<th>2030 target</th>
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</thead>
<tbody>
<tr>
<td>1 Three-dose hepatitis B vaccine for infants (coverage %)</td>
<td>82%</td>
<td>90%</td>
<td>90%</td>
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<tr>
<td>2 Prevention of mother-to-child transmission of HBV: hepatitis B birth-dose vaccination or other approaches (coverage %)</td>
<td>38%</td>
<td>50%</td>
<td>90%</td>
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<tr>
<td>3 Blood and injection safety (coverage %)</td>
<td>89%</td>
<td>95%</td>
<td>100%</td>
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<tr>
<td>4 Harm reduction (sterile syringe/needle set distributed per person per year for people who inject drugs [PWID])</td>
<td>20</td>
<td>200</td>
<td>300</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline 2015</th>
<th>2020 target</th>
<th>2030 target</th>
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</thead>
<tbody>
<tr>
<td>5a. Diagnosis of HBV and HCV (coverage %)</td>
<td>&lt;5%</td>
<td>30%</td>
<td>90%</td>
</tr>
<tr>
<td>5b. Treatment of HBV and HCV (coverage %)</td>
<td>&lt;1%</td>
<td>5 million (HBV) 3 million (HCV)</td>
<td>80% eligible treated</td>
</tr>
</tbody>
</table>

### Impact leading to elimination

| Incidence of chronic HBV and HCV infections | 6–10 million | 30% reduction | 90% reduction |
| Mortality from chronic HBV and HCV infections | 1.46 million | 10% reduction | 65% reduction |
ECHO-Chicago: Mission

The mission of ECHO-Chicago is to expand community-based primary care capacity to treat complex disease in underserved communities

Courtesy of Daniel Johnson, MD
Purpose

ECHO-Chicago uses *case-based, iterative, telehealth curricula* delivered via high-grade videoconference technology to bring advanced training and support to primary care providers in underserved communities throughout the Chicago metro area.

- Disseminate best practice management of complex, common, chronic disease in the primary care medical home
- Use case-based learning; the most widespread teaching method in medicine
- NOT Telemedicine
- Leverage advanced technology to reduce cost and time constraints, and eliminate travel
- Engage primary care providers in a local network to share knowledge and experience

*Courtesy of Daniel Johnson, MD*
You Can Become Certified to Treat Your HCV Patients

An estimated 3 million Americans including 70,000 Chicagoans are living with HCV. ECHO-Chicago invites you to become certified to treat your HCV infected patient population. Register for our free videoconference training series to understand and implement new guidelines and treatment strategies for HCV. CMEs are available.

For more information or to register, contact Isa Rodriguez, HepCCATT project coordinator, 773-322-6941 irodriguez@peds.bsd.uchicago.edu

HepCCATT (Hepatitis C Alliance to Test and Treat)

• Provide public education on hepatitis C risk factors and importance of testing
• Expand primary care provider (PCP) capacity to treat, and cure HCV at community health centers using ECHO-Chicago training
• Robust surveillance to monitor population-level changes in HCV testing, treatment, and cure
• Coordination among all stakeholders to improve access and reduce the cost of HCV care
• Convenient time (8:00-9:00 AM)
• Webinar Based Learning for healthcare professionals who want to treat HCV patients
• CME (AMA or AAFP)
The mission of the American Liver Foundation is to facilitate, advocate and promote education, support and research for the prevention, treatment and cure of liver disease. We offer educational resources for you and your patients in many ways - online, print or through webinars and live educational lectures. For more information call 312-377-9030, visit our website at liverfoundation.org, or email Sarah at skoltun@liverfoundation.org

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Follow us on Instagram: @ALFGREATLAKES

Follow us on Pintrest: https://www.pinterest.com/ALFGreatLakes/
ETHICS AND TREATMENT OF HEPATITIS C

• You can cure HCV
• Expensive Treatment
• Patients benefit from treatment at every stage of their disease
• We are always our patients advocate FIRST
• Treatment is being restricted, for financial, NOT Medical reasons
• How would you want to be treated? (or you wife, husband, mother father, son or daughter?)
Goal of treatment

• The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by an SVR.

• **Rating:** Class I, Level A

Recommendations for when and in whom to initiate treatment

• Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies owing to comorbid conditions.

• **Rating:** Class I, Level A

• Immediate treatment is assigned the highest priority for those patients with advanced fibrosis (Metavir stage F3), those with compensated cirrhosis (Metavir stage F4), liver transplant recipients, and patients with severe extrahepatic hepatitis C.

• Based on available resources, immediate treatment should be prioritized as necessary so that patients at high risk for liver-related complications are given high priority.
YOU CAN CURE HCV
YOU CAN CURE HCV
YOU CAN CURE HCV

AND MAKE A PROFOUND DIFFERENCE IN PEOPLES LIVES

THANK YOU!