Hepatitis C: Screening and Management in a New Age of Treatment

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☑️ I will discuss therapies under investigation
Presentation Overview

1. Epidemiology
2. Emerging trends for screening
3. Evaluation and staging
4. Treatment
5. Follow up
6. Outlook
1. Epidemiology

2. Emerging trends for screening
3. Evaluation and staging
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5. Follow up
6. Outlook
Global Preventable Death Rates

Caused by viruses
- HIV
- HBV + HCV
- Measles
- RSV, Rota
- Flu
- Dengue
- HPV
- West Nile
- SARS
- Ebola
- Polio
- Hanta

Other causes
- Tobacco
- Malaria
- Road accidents
- Non-HIV TB
- Hospital infection
- Suicide
- vCJD

Source: WHO 2003
Annual Age-Adjusted Mortality Rates: Hepatitis C Virus and HIV infections

Natural History of Hepatitis C

- HCV Infection
- Acute Infection, 20-30% with symptoms
  - Clearance of HCV RNA, 15%-25%
  - Fulminant Hepatitis, Rare
- Chronic Infection, 75%-85%
- Chronic Active Hepatitis
- Cirrhosis, 10%-20% over 20 years
- Decompensated Cirrhosis, 5-year survival rate of 50%
- HCC, 1%-4% per year

Estimates by Year: HCV Prevalence and Cirrhosis

Prevalent HCV: All Cases
Chronic HCV
Cirrhosis
Acute HCV

Davis. Gastroenterology. 2010
HCV Antibody Prevalence by Year of Birth

NHANES 1988 - 2002
Hepatitis C is a disease of marginalized groups

Rates of infection:

US population 2 - 3%

- IDU > 10 years of use 90%
- IDU < 10 years of use 50%
- Homeless persons 35%
- Prisoners 29%
- Severely mentally ill 19%

Newly Reported Chronic HCV: New York City

Average annual rate per 100,000 people:
- 0.0
- 0.1 - 75.0
- 75.1 - 150.0
- 150.1 - 225.0
- 225.1 - 300.0
- > 300.0

NYCDOHMH
### Table 10. People Newly Reported with Chronic Hepatitis C in New York City, 2008 and 2009.

<table>
<thead>
<tr>
<th>Group</th>
<th>2008</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percentage (%) of each group</td>
</tr>
<tr>
<td>Overall</td>
<td>13,932</td>
<td>n/a</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8,952</td>
<td>64.3</td>
</tr>
<tr>
<td>Female</td>
<td>4,866</td>
<td>34.9</td>
</tr>
<tr>
<td>Unknown</td>
<td>114</td>
<td>0.8</td>
</tr>
<tr>
<td>Age (in years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–19</td>
<td>152</td>
<td>1.1</td>
</tr>
<tr>
<td>20–29</td>
<td>875</td>
<td>6.3</td>
</tr>
<tr>
<td>30–39</td>
<td>1,746</td>
<td>12.5</td>
</tr>
<tr>
<td>40–49</td>
<td>3,437</td>
<td>24.7</td>
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<tr>
<td>50–59</td>
<td>4,793</td>
<td>34.4</td>
</tr>
<tr>
<td>60–69</td>
<td>1,819</td>
<td>13.1</td>
</tr>
<tr>
<td>70–79</td>
<td>718</td>
<td>5.1</td>
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<tr>
<td>80+</td>
<td>364</td>
<td>2.6</td>
</tr>
<tr>
<td>Unknown</td>
<td>28</td>
<td>0.2</td>
</tr>
</tbody>
</table>
U.S. HCV Epidemiology

Liver Transplantation: Supply vs Demand

- Additions to List
- Waiting List
- Deceased Donors
- Liver Transplants

Year:
- 1992
- 1993
- 1994
- 1995
- 1996
- 1997
- 1998
- 1999
- 2000
- 2001

Number of Cases:
- 0
- 2000
- 4000
- 6000
- 8000
- 10000
- 12000
- 14000
- 16000
- 18000
- 20000
All Cause Mortality Among US Veterans: HCV Ab+ vs Ab-

195,585 HCV Ab+ 202,739 HCV Ab-

43.9* 24*

*Per 1,000 person years

Erqou S, et al. 48th EASL; Amsterdam, Netherlands; April 24-28, 2013. Abst. 453.
Predictions for 2010-2019

- 193,000 HCV deaths
  - 720,700 million years of advanced liver disease
  - 1.83 million years of life lost
- $11 billion in direct medical care costs
- $21.3 and $54 billion societal costs from premature disability and mortality

CDC; Wong et al. 2010
2. Emerging trends for screening

3. Evaluation and staging

4. Treatment

5. Follow up

6. Outlook
Hepatitis C is Under-Diagnosed

<table>
<thead>
<tr>
<th>Number infected</th>
<th>HIV</th>
<th>HBV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undiagnosed</td>
<td>~21%</td>
<td>~65%</td>
<td>~75%</td>
</tr>
<tr>
<td>Diagnosed</td>
<td>~80%</td>
<td>~35%</td>
<td>~25%</td>
</tr>
</tbody>
</table>

HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus.
Rising Cure Rates for Chronic HCV

*Cure rates based on data from clinical trials*
# Hepatitis C Risk Factors

Ever injected drugs, even once

Medical conditions associated with HCV, including:
- HIV
- Hemophilia if received clotting factor (prior to 1987)
- Hemodialysis
- Unexplained abnormal aminotransferase levels

Transfusion or organ transplant (prior to July 1992)

Children born to HCV-positive mothers

Health Care Workers: needle stick or mucosal exposure

Current sex partners of HCV-infected individuals
CDC\(^1\) and USPSTF\(^2\) Screening Recommendations for Hepatitis C

In addition to testing adults of all ages at risk for HCV infection, CDC now recommends:

- **Age-based testing:** All adults born during 1945–1965 should receive one-time antibody testing for HCV without prior ascertainment of HCV risk.

- **Referral to care:** All persons with identified HCV infection should be referred to appropriate care and treatment services for HCV infection and related conditions.

- **Alcohol screening:** All persons identified with HCV infection should receive a brief alcohol screening and intervention as clinically indicated.

\(^1\) Centers for Disease Control
\(^2\) US Preventive Services Task Force
Hepatitis C Virus Testing (Chapter 425 of the Laws of 2013)
This new law requires a hepatitis C virus screening test to be offered to all patients born between 1945 and 1965 who are receiving health services as a hospital inpatient or receiving primary care services and applies to physician, physician assistant, or nurse practitioner.

The law further requires that the health care provider refer a patient who receives a positive screening test to another provider to receive confirmatory testing and follow-up care.

In effect as of January 1, 2014
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HCV: Pre-treatment Evaluation

- Complete medical history with emphasis on:
  - Hepatitis C risk factors, dates of exposure, prior treatment and outcomes, extent of liver injury
  - Detailed alcohol and substance use history
  - Cardiovascular disease and risk factors
  - Thorough psychiatric history with focus on treatment readiness
  - Diabetes history and risk factors including dyslipidemia and obesity
  - Age and gender appropriate cancer risk and screening history
Labs / Imaging

- HCV-specific
  - RNA/quant
  - genotype

- Liver Labs
  - Complete blood count
  - Complete fasting chemistry
  - Alpha Feto Protein
  - PT/INR
  - Vitamin D

- Medication-related
  - TSH and thyroid antibodies
  - Renal panel
  - Serum uric Acid

- Shared risk factors
  - Hep A and B panels
  - HIV Ab
  - RPR

- Comorbidities
  - Hgb A1C
  - Fasting lipids

- Imaging
  - Abdominal ultrasound
  - CT or MRI
  - Biliary imaging

- Fibrosis
  - Biopsy
  - Fibroscan
  - Serum markers
Risk Stratification

- Determining degree of liver fibrosis is important:
  - Risk of end-stage disease
  - Response to treatment
  - Adverse events during treatment
  - Post-treatment “healing” and expected course
  - Morbidity and aging of the population
Liver Biospy

• Previously:
  • Most patients routinely biopsied
  • Rationale: delay treatment in early stage disease
    • Not everyone progresses to ESLD
    • Risk/benefit ration of previous treatments

• Current rationale:
  • No longer routine
    • Risk and cost associated with the biopsy itself
    • Demographics suggest more will progress
    • Safer and more efficacious treatments
  • No longer a barrier
  • More challenging to evaluate fibrosis
FIB-4, APRI, FibroSure™

- Derived indicators of cirrhosis
- All have limitations
- FIB-4 Score:
  - \( \frac{(AGE \times AST)}{(platelets \times \sqrt{ALT})} \)
  - \( >3.25 \) sensitive and specific for significant fibrosis
- APRI = AST: Platelets ratio
  - \( \frac{AST}{ASTULN/Platelets} \)
  - \( \geq 1 \) significant fibrosis likely
- Fibrosure
  - \( >72 \) significant fibrosis likely
Transient Elastography

- Measures liver stiffness
- Non-invasive
- Office procedure
- Score correlates with degree of fibrosis
- More sensitive at high and low ends

Source: www.echosens.com
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History of Treatment for Chronic HCV

* Cure rates based on data from clinical trials

- **1991**: IFN
- **1998**: IFN + RBV
- **2001**: PegIFN + RBV
- **2011**: TVR or BOC + pegIFN + RBV
- **2013**: SOF or SMV +/- pegIFN +/- RBV
- **2014+**: All-Oral DAA’s

Cure Rates:
- **1991**: 35%
- **1998**: 44%
- **2001**: 70%
- **2011**: >90%
- **2013**: >95%
Treatment Outcomes: Virological Response


RVR: rapid virological response
eRVR: extended rapid virological response
EVR: early virological response
ETR: end of treatment response
SVR: sustained virological response

HCV RNA Log10 IU/mL

Treatment Period

Null Response
Partial Response
Relapse

RVR: rapid virological response
eRVR: extended rapid virological response
EVR: early virological response
ETR: end of treatment response
SVR: sustained virological response

Medications to Treat HCV

Drug Summaries, Clinical Studies, and Slide Decks
All materials are available for download in their original formats as PDF or PowerPoint.

FDA-Approved

**Boceprevir**  
*(Victrelis)*  
Drug Summary »  
Clinical Trials »  
References »  
Download »

**Peginterferon alfa-2a**  
*(Pegasys)*  
Drug Summary »  
Clinical Trials »  
References »  
Download »

**Peginterferon alfa-2b**  
*(PegIntron)*  
Drug Summary »  
Clinical Trials »  
References »  
Download »

**Ribavirin**  
*(Copegus, Rebetol, Ribasphere)*  
Drug Summary »  
Clinical Trials »  
References »  
Download »

**Simeprevir**  
*(Olysio)*  
Drug Summary »  
Clinical Trials »  
References »  
Download »

**Sofosbuvir**  
*(Sovaldi)*  
Drug Summary »  
Clinical Trials »  
References »  
Slide Deck »  
Download »

**Telaprevir**  
*(Incivek)*  
Drug Summary »  
Clinical Trials »  
References »  
Download »
HCV Medications

Medication Summaries
Clinical Studies
Slide Decks

Learn about medications to treat HCV »

About Hepatitis C Online

Hepatitis C Online is a free educational website from the University of Washington. The site is a comprehensive resource that addresses the diagnosis, monitoring, and management of hepatitis C virus infection.

Contributors
Site Overview

Hepatitis C Guidelines

The American Association for the Study of Liver Disease (AASLD) and the Infectious Diseases Society of America (IDSA), in collaboration with the International Antiviral Society–USA (IAS–USA), have developed new recommendations for HCV management.

AASLD/IDSA HCV Guidelines

Take the Free Online Course

Browse or create an account and track your progress as you work through the course. After registering, you can obtain free CME or CNE credit.

Browse the Course Modules
Sign In to Track Progress
Create an Account
### Current (On Label) Standard of Care Treatment

#### Genotype 1 - Agents

<table>
<thead>
<tr>
<th>Duration</th>
<th>SVR 12/notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 weeks</td>
<td>90% overall (NEUTRINO) 80% cirrhotics</td>
</tr>
</tbody>
</table>

1. Sovaldi™ (sofosbuvir, SOF)
2. Ribavirin (RBV)
3. Peg-interferon alfa (PEG)

1. Olysio™ (simeprevir, SMV)
2. Ribavirin (RBV)
3. Peg-interferon alfa (PEG)

<table>
<thead>
<tr>
<th>Duration</th>
<th>SVR 12/notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 or 48 weeks</td>
<td>80% in rx naïve 24 weeks for prior relapse or treatment naïve 48 weeks for prior partial and null response 10% diminished response in genotype 1a Q80K polymorphism Simeprevir given for the first 12 weeks only</td>
</tr>
</tbody>
</table>

1. SOF
2. RBV

<table>
<thead>
<tr>
<th>Duration</th>
<th>SVR 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 weeks</td>
<td>70% Interferon ineligible only</td>
</tr>
</tbody>
</table>

#### Genotype 2/3 - Agents

<table>
<thead>
<tr>
<th>Duration</th>
<th>SVR 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 weeks (gt 2)</td>
<td>90%</td>
</tr>
<tr>
<td>24 weeks (gt 3)</td>
<td>90%</td>
</tr>
</tbody>
</table>

1. SOF
2. RBV

#### Genotype 4 - Agents

<table>
<thead>
<tr>
<th>Duration</th>
<th>SVR 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 weeks</td>
<td>97%</td>
</tr>
</tbody>
</table>

1. SOF
2. RBV
3. PEG
SOVALDI is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen. (1)

- SOVALDI efficacy has been established in subjects with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection. (1)

DOSAGE AND ADMINISTRATION

- One 400 mg tablet taken once daily with or without food. (2.1)
- Should be used in combination with ribavirin or in combination with pegylated interferon and ribavirin for the treatment of CHC. Recommended combination therapy: (2.1)

<table>
<thead>
<tr>
<th>HCV Mono-infected and HCV/HIV-1 Co-infected</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1 or 4</td>
<td>SOVALDI + peg-interferon alfa + ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>SOVALDI + ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>SOVALDI + ribavirin</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

- SOVALDI in combination with ribavirin for 24 weeks can be considered for CHC patients with genotype 1 infection who are interferon ineligible. (2.1)

- Should be used in combination with ribavirin for treatment of CHC in patients with hepatocellular carcinoma awaiting liver transplantation for up to 48 weeks or until liver transplantation, whichever occurs first. (2.1)

- A dose recommendation cannot be made for patients with severe renal impairment or end stage renal disease. (2.4, 8.6)

DRUG INTERACTIONS

Drugs that are potent intestinal P-gp inducers (e.g., rifampin, St. John’s wort) may alter the concentrations of sofosbuvir. Consult the full prescribing information prior to use for potential drug-drug interactions. (5.2, 7, 12.3)

USE IN SPECIFIC POPULATIONS

- Patients with HCV/HIV-1 co-infection: Safety and efficacy have been studied. (8.8, 14.4)
- Patients with hepatocellular carcinoma awaiting liver transplantation: Safety and efficacy have been studied. (8.9)
### Current Off-Label Uses

<table>
<thead>
<tr>
<th>Agents</th>
<th>Duration</th>
<th>SVR 12/ notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. SOF</td>
<td>12 weeks</td>
<td>98 – 100% (COSMOS)</td>
</tr>
<tr>
<td>2. SMV</td>
<td></td>
<td>89% in GT 1a Q80k (add RBV)</td>
</tr>
<tr>
<td>3. +/- RBV</td>
<td></td>
<td><em>Genotype 1 or 4</em></td>
</tr>
<tr>
<td>1. SOF</td>
<td>24 weeks</td>
<td>100% 93% (AASLD)</td>
</tr>
<tr>
<td>2. RBV</td>
<td></td>
<td><em>Genotype 4 (On label for gt 1)</em></td>
</tr>
</tbody>
</table>
**Treatment Notes**

- On-treatment monitoring as with previous treatment regimens
- RBV
  - dosing is weight-based
  - dose reduction for anemia (no affect on SVR\(^2\))
- SOF
  - Check HCV RNA at treatment week 4
  - Do not use in GFR <30
  - No stopping rules (only relapses were observed)\(^1\)
- SMV
  - Significant drug/drug interactions with SMV (follow package insert)
  - Check HCV RNA at treatment weeks 4, 12, and 24
  - Discontinue if ≥25 IU/ml

\(^1\)92 – 100% SVR (COSMOS)
\(^2\)Sulkowski (HepDart)
Upcoming Regimens (Fall 2014)

• Abbvie
  – Genotype 1 only (SVR12: 95 – 98%)\(^1\)
  – 5 drugs:
    • Protease inhibitor/ritonavir/NS5A fixed dose combination once daily
    • Non-nucleoside/tide polymerase inhibitor (BID)
    • RBV (BID)

• Gilead
  – Genotype 1 (SVR 95% – 100%)\(^2, 3\)
  – SOF(NS5B)/ledipasvir(NS5A) FDC daily

\(^1\)Sapphire 1 and 2; \(^2\)ION 1, 2 and 3; \(^3\)Lonestar
Triaging Treatment

- **Consider treating now**
  - >F3 fibrosis/Cirrhosis
  - Extra-hepatic manifestations
  - PMHx HCC
  - Genotype 2, 3

- **Consider Deferring**
  - GT 1 early stage fibrosis (F0-2) for new regimens
  - Interferon intolerant/ineligible/unwilling
  - Potential insurance issues

- **Caution in Renal impairment**
  - No data on SOF in GFR < 30 (don’t use)
  - SMV OK
Triaging Treatment

• Co-infection
  – Treat on label (same regimens as monoinfection)
  – Caution: SMV/HAART drug/drug interactions

• Transplant
  – Pre-transplant
    • Treat on label (SOF/RBV x up to 365 days)
  – Post-transplant
    • Off label
    • SOF/RBV supported by data\(^1\)
    • Compassionate use daclatasvir (+SOF) in early 2014

\(^1\) ~70% SVR Charlton AASLD
Cirrhosis

- No contraindication for SOF in cirrhosis
  - No data on SOF in GFR <30 (don’t use)

- Intrahepatic levels of SMV are increased in cirrhosis:
  - SMV contraindicated in Child’s B and C cirrhosis

- BMS compassionate use Daclatasvir protocol (IRB Pending)
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Sustained Virologic Response (SVR) Leads to Improved Outcome

- Viral Eradication
- Improved Clinical Outcomes
- Improved Liver Histology

Decreased

- Decompensation
- Hepatocellular Carcinoma
- Mortality

SVR Is Associated with Lower Incidence of ESLD, HCC or Death: Results from the HALT-C Trial

SVR Durability with TVR + PegIFN + RVB: EXTEND Study

- 223 patients in the SVR cohort, 222 (99.6%) patients had persistent undetectable HCV RNA levels
  - Median of 21 months of follow-up, ranging from 4.4 to 47.9 months with an interquartile range: 7.2, 34.2 months
- One late relapse in a patient treated for only 9 weeks with TVR + PegIFN + RBV in the PROVE-2 study

Post-Treatment Follow Up

Is the cure durable?
*SVR-12, SVR-24
Periodically thereafter*

Is there risk for reinfection?
*Address any ongoing risk behaviors
Antibodies are not protective*

Fibrosis/Cirrhosis?
*Pre-treatment fibrosis may not revert
Ongoing risk for HCC, ESLD*

Other liver risks?
*Fatty Liver
Alcohol
Others*

Other medical conditions?
*A comorbid population*

Does the patient know her/his status?
*Will retain antibodies*
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Investigational Agents for HCV

- Interferons
- Antiviral agents
- Therapeutic vaccines
- Host target
  - miRNA-122
  - Cyclophilin
  - CYP inhibitors

Entry

Replication, polyprotein processing and/or assembly

- NS5B polymerase inhibitors
- NS3 protease inhibitors
- NS5A replication complex inhibitors
### Investigational HCV Regimens in Phase 3

#### Regimens with one DAA + PegIFN alfa + RBV
- BI 201335 (PI)
- Daclatasvir (NS5A)
- Asunaprevir (PI)
- GS-7977 (NI)
- Simeprevir (TMC-435) (PI)
- Alisporivir (CYP)
- Vaniprevir (MK-7009, PI)

#### Regimens with two DAAs (± PegIFN alfa and/or RBV)
- Daclatasvir + asunaprevir

#### IFN-free Regimens
- Sofosbuvir (GS-7977) + RBV
- Daclatasvir + asunaprevir
- Alisporivir ± RBV

#### New Interferons
- Peginterferon-lambda-1a

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NNI = non-nucleoside NS5B inhibitor, NI = nucleoside NS5B inhibitor, PI = protease inhibitor, RBV = ribavirin, NS5A = replication complex inhibitor
Cyp= cyclophilin inhibitor
Different drugs can contribute variably to each goal. Not all components must be direct-acting antivirals (DAAs).
Future Treatment Paradigms

- Multiple DAAs have entered phase 2 and phase 3 clinical trials
  - If safe and effective, approval can be anticipated by 2014 – 2015
  - Improved dosing (daily), improved AEs, different resistance profile (NS5A, polymerase inhibitors)

- Interferon free regimens are promising
  - Larger studies are needed to confirm findings
  - Diverse patient populations must be evaluated
    - Black Americans, null responders, cirrhotics, telaprevir or boceprevir failures
Resources

- Treatment guidelines:
  - www.aasld.org
  - www.easl.eu

- Psychosocial readiness:
  - www.prepc.org

- Medication interactions:
  - www.hep-druginteractions.org

- Screening:
  - www.cdc.gov

- Special Populations:
  - www.hcvcme.com
‘Stigma is the process by which the reaction of others spoils normal identity'.  

E. Goffman