Chronic Hepatitis C: An Update on Screening, Evaluation, and Management

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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
Presentation Overview

1. Epidemiology

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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

Estimates by Year: HCV Prevalence and Cirrhosis

Prevalent HCV: All Cases

Chronic HCV

Cirrhosis

Acute HCV

Davis. Gastroenterology. 2010
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%

<table>
<thead>
<tr>
<th>Group</th>
<th>2008</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>Percentage (%)</td>
<td>Rate per 100,000 people</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>
</tr>
<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>
</tr>
<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

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

Year: 1992-2001

- 1992: 0
- 1993: 2000
- 1994: 4000
- 1995: 6000
- 1996: 8000
- 1997: 10000
- 1998: 12000
- 1999: 14000
- 2000: 16000
- 2001: 18000

- 1992: 0
- 1993: 2000
- 1994: 4000
- 1995: 6000
- 1996: 8000
- 1997: 10000
- 1998: 12000
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- 1992: 0
- 1993: 2000
- 1994: 4000
- 1995: 6000
- 1996: 8000
- 1997: 10000
- 1998: 12000
- 1999: 14000
- 2000: 16000
- 2001: 18000
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
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Hepatitis C is Under-Diagnosed

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number Infected</th>
<th>Undiagnosed %</th>
<th>Diagnosed %</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>1,000,000</td>
<td>~21%</td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>2,000,000</td>
<td>~65%</td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>3,000,000</td>
<td>~75%</td>
<td></td>
</tr>
</tbody>
</table>

HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus.
### 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.

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\(^1\) 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
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:
  - \((\text{AGE} \times \text{AST}) / (\text{platelets} \times \sqrt{\text{ALT}})\)
  - >3.25 sensitive and specific for significant fibrosis
- APRI = AST: Platelets ratio
  - \(\text{AST}/\text{ASTULN}/\text{Platelets}\)
  - \(\geq 1\) 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
Presentation Overview

1. Epidemiology
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4.1. Follow up
4.2. Outlook
Treatment Outcomes: Virallogical Response

Null Response
Partial Response
Relapse
SVR
ETR

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

History of Treatment for Chronic HCV

Cure Rate*  
- 0%  
- 20%  
- 40%  
- 60%  
- 80%  
- 100%

Year  
- 1991  
- 1998  
- 2001  
- 2011  
- 2013  
- 2014+

IFN  
- IFN + RBV  
- PegIFN + RBV  
- TVR or BOC + pegIFN + RBV  
- SOF or SMV +/- pegIFN +/- RBV  
- All-Oral DAA’s

*Cure rates based on data from clinical trials
Real World Efficacy and Costs per SVR of TVR-Based Triple Therapy

Review of TVR-based triple therapy in 147 patients at the Mount Sinai Medical Center

- 44% of patients achieved SVR
- Almost half of all costs (45%) were spent on patients who did not achieve an SVR
- Cost per SVR is substantially higher when you consider AEs, premature DC, and virologic failures

The median cost per SVR was $188,859

Bichoupan K, et al. AASLD 2013. Washington, DC. Oral #244
Cost Per Cure of Sofosbuvir vs PIs:
- Treatment-Naïve and Experienced
- Genotype 1

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Treatment</th>
<th>Cost Per Cure</th>
<th>Percentage Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Naïve</td>
<td>BOC + PR</td>
<td>$11,641</td>
<td>(-10%)</td>
</tr>
<tr>
<td>Treatment Naïve</td>
<td>TVR + PR</td>
<td>$19,847</td>
<td>(-17%)</td>
</tr>
<tr>
<td>Treatment Naïve</td>
<td>SOF + PR</td>
<td>$74,996</td>
<td>(-52%)</td>
</tr>
<tr>
<td>Treatment Experienced</td>
<td>BOC + PR</td>
<td>$58,091</td>
<td>(-40%)</td>
</tr>
<tr>
<td>Treatment Experienced</td>
<td>TVR + PR</td>
<td>$74,996</td>
<td>(-52%)</td>
</tr>
<tr>
<td>Treatment Experienced</td>
<td>SOF + PR</td>
<td>$58,091</td>
<td>(-40%)</td>
</tr>
</tbody>
</table>

AMCP Dossier Data on file, Gilead Sciences December 2013
Cost of Care
USA, per capita, per year

Per capita: $8,608\textsuperscript{1}
Diabetes: $10,845\textsuperscript{2}

\textsuperscript{1}WHO
\textsuperscript{2}Fu et al, Diabetes Care 2009
# Cost of Care

**USA, per capita, per year**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cost (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Hepatitis C:</td>
<td>$24,176</td>
</tr>
<tr>
<td>No cirrhosis</td>
<td>$17,277</td>
</tr>
<tr>
<td>Compensated Cirrhosis</td>
<td>$22,752</td>
</tr>
<tr>
<td>End Stage Liver Disease</td>
<td>$59,995</td>
</tr>
<tr>
<td>HCC</td>
<td>$112,537</td>
</tr>
<tr>
<td>Post-OLT</td>
<td>$145,045</td>
</tr>
<tr>
<td>Transplant + year 1</td>
<td>$575,000</td>
</tr>
</tbody>
</table>

Gordon et al, Hepatology 2012; National Foundation for Transplants
Cost Effectiveness

Cost of SVR

Interferon + ribavirin therapy: $27,876
(medication only)

Cost per SVR:

First generation DAA: $189,000\textsuperscript{1}
Second generation DAA: $136,000\textsuperscript{2}

\textsuperscript{1}Bichoupan et al Hepatology 2014
\textsuperscript{2}Silva et al EASL 2014
Current Medications
<table>
<thead>
<tr>
<th>Genotype</th>
<th>Previous treatment</th>
<th>Cirrhosis?</th>
<th>Treatment options</th>
<th>SOF</th>
<th>Viekira™</th>
<th>Harvoni®</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Naive</td>
<td>No</td>
<td>+ SMV +/- RBV 12 weeks</td>
<td>+ RBV 12 weeks</td>
<td>12 weeks¹</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>+ SMV +/- RBV 24 weeks</td>
<td>+ RBV 24 weeks</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Experienced⁹</td>
<td>No⁷</td>
<td>+ SMV +/- RBV 12 weeks</td>
<td>+ RBV 12 weeks</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes⁸</td>
<td>+ SMV +/- RBV 24 weeks</td>
<td>+ RBV 24 weeks</td>
<td>24 weeks² -or- + RBV 12 weeks</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>Naive</td>
<td>No</td>
<td>+ SMV 12 weeks</td>
<td>12 weeks</td>
<td>12 weeks¹</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>+ SMV 24 weeks</td>
<td>+ RBV 12 weeks</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Experienced⁹</td>
<td>No⁷</td>
<td>+ SMV +/- RBV 12 weeks</td>
<td>12 weeks</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes⁸</td>
<td>+ SMV +/- RBV 24 weeks</td>
<td>+ RBV 12 weeks</td>
<td>24 weeks² -or- + RBV 12 weeks</td>
<td></td>
</tr>
</tbody>
</table>

¹: Treatment duration for Naive patients.
²: Treatment duration for Experienced patients.

⁷: Cirrhosis status not specified for these cases.
⁸: Treatment option change for experienced patients.

- SOF: Sofosbuvir
- Viekira™: Velpatasvir + Sofosbuvir
- Harvoni®: Ledipasvir + Sofosbuvir

Note: The table provides a summary of treatment options based on genotype, previous treatment status, cirrhosis status, and treatment duration for both Naive and Experienced patients.
<table>
<thead>
<tr>
<th>Genotype</th>
<th>Previous treatment</th>
<th>Cirrhosis?</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>SOF</strong></td>
</tr>
<tr>
<td>2</td>
<td>Naive</td>
<td>No</td>
<td>+ RBV 12 weeks⁴</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>+ RBV 16 weeks⁴</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Experienced⁹</td>
<td>No⁷</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes⁸</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>No</td>
<td>+ RBV 24 weeks⁴</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>+ RBV 12 or 24 weeks⁶</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>+ RBV + PEG 12 weeks</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Treatment notes:
1. Consider 8 weeks for HCV RNA<6 million
2. Add RBV if previous failure was a SOF regimen
3. Consider extending to 16 weeks
4. Alternate: add PEG
5. No dasabuvir
6. Alternates: add PEG or SMV (12 weeks)
7. If previously treated with a SOF-containing regimen, consider deferring treatment
8. If previously treated with a SOF-containing regimen consider Harvoni® +/- RBV for 24 weeks
9. If previous failure was a SOF, TVR or BOC regimen, do not use a SOF or Viekira™ regimen

Medication Abbreviations:
BOC = boceprevir
PEG = pegylated interferon
RBV = ribaivirin (weight based dosing)
SMV = simeprevir
SOF = sofosbuvir
TVR = telaprevir

Harvoni® = ledipasvir 90mg + sofosbuvir 400mg
Viekira™/viekira pak™ = ombitasvir 12.5mg + paritaprevir 75 mg + ritonavir 50 mg and dasabuvir 250 mg
Prioritizing Treatment: Highest Priority

• Highest Risk of Severe Complications
• Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4)
  • Rating: Class I, Level A

• Organ transplant
  • Rating: Class I, Level B

• Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations
  • Rating: Class I, Level B

• Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis
  • Rating: Class IIa, Level B
Prioritizing Treatment: High Priority

- High Risk of Complications
- Fibrosis (Metavir F2)
  - Rating: Class I, level B
- HIV-1 coinfection
  - Rating: Class I, Level B
- Hepatitis B virus (HBV) coinfection
  - Rating: Class IIa, Level C
- Other coexistent liver disease (eg, [NASH])
  - Rating: Class IIa, Level C
- Debilitating fatigue
  - Rating: Class IIa, Level B
- Type 2 Diabetes mellitus (insulin resistant)
  - Rating: Class IIa, Level B
- Porphyria cutanea tarda
  - Rating: Class IIb, Level C

Source: www.hcvguidelines.org
Prioritizing Treatment: High Risk of Transmission

- Men who have sex with men (MSM) who engage in high-risk sexual practices
- Active injection drug users
- Incarcerated persons
- Persons on long-term hemodialysis
- HCV-infected women of child-bearing potential wishing to become pregnant
  - Rating: Class IIa, Level C
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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

References:
All Cause Mortality Among US Veterans: HCV Ab+ vs Ab-

195,585 HCV Ab+  43.9*  24*

202,739 HCV Ab-  

*Per 1,000 person years

Erogu S, et al. 48th EASL; Amsterdam, Netherlands; April 24-28, 2013. Abst. 453.
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
    - Range: 4.4 to 47.9 months
  - One late relapse
    - patient treated for only 9/12 weeks with TVR
    - All others had durable SVR

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

Does the patient know her/his status?  
Will retain antibodies

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
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Investigational Agents for HCV

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

Entry

Replication, polyprotein processing and/or assembly

- NS5B polymerase Inhibitors
- NS3 protease inhibitors
- NS5A replication complex inhibitors
- CYP inhibitors
## Coming Agents:

<table>
<thead>
<tr>
<th>Agent</th>
<th>Status</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Daclatasvir</td>
<td>NDA Submitted</td>
<td>NS5A Inhibitor</td>
</tr>
<tr>
<td>Asuneprevir</td>
<td>NDA Submitted</td>
<td>NS3 Protease Inhibitor</td>
</tr>
</tbody>
</table>
Resources

- Treatment guidelines:
  - www.aasld.org/www.hcvguidelines.org
  - www.easl.eu
- Psychosocial readiness:
  - www.prepc.org
- Medication interactions:
  - www.hep-druginteractions.org
- Screening:
  - www.cdc.gov
- Special Populations:
  - www.hcvcme.com
Thank You