Implementing HCV Therapy in a Primary Care Practice

Anthony Martinez, MD
Associate Professor of Medicine
Medical Director, Hepatology
University at Buffalo

Disclosures
Speaker’s Bureaus: Genentech, Kadmon, Salix, Gilead, Bayer
Consultant: Genentech, Kadmon
Research Support: Gilead, BMS, Abbott, Vertex

HCV: A New Era
Objectives
• Update HCV related epidemiology
• Review of new HCV screening guidelines
• Review new agents for HCV
• Discuss HCV treatment among special populations

Hepatitis C: A Global Health Problem
170-200 Million Carriers Worldwide (2% of the World’s population)

* Chak, Liver International, 2011
Most Patients with Chronic Hepatitis C in the US Are Not Aware That They Are Infected

~5,300,000 individuals are infected with the hepatitis C virus in the United States

1,325,000 (~25%) AWARE

3,975,000 (~75%) UNAWARE

Annual age adjusted rates of mortality for HBV, HCV, HIV 1999-2008

~73% of HCV related deaths were in persons age 45-64 years

HCV Cases 2001-2009

Number of HCV Cases

- NYS (prevalence 0.6%)*
- Erie County (prevalence 1.4%)
- Erie County (prevalence 2.0%)**

* Excludes NYC
** Based on CDC estimates

Acute HCV Cases by age in the United States 1992 - 2009

~3-19 yrs
~20-29 yrs
~30-39 yrs
~40-49 yrs
~50-59 yrs
~60 yrs
Past Month and Past Year Heroin Use among Persons Aged 12 or Older: 2002-2012

HCV Infected Persons In The US and Estimated Rates of Detection, Referral to Care and Treatment

Worldwide Heroin Routes

Institute of Medicine – Hepatitis and Hepatocellular Carcinoma Survey

Barriers to prevention and control efforts

Lack of knowledge and awareness – providers, public

Inadequate screening for viral hepatitis

Inadequate immunization

Need for better integration of viral hepatitis treatment services
IOM: Comprehensive viral hepatitis services should have five core components-

1. Identification of infected people
2. Outreach and awareness
3. Medical Management of chronically infected people
4. Prevention of new infections
5. Social and peer support

Institute of Medicine – Recommendations to the CDC

- Comprehensive evaluation of the national HBV and HCV public health surveillance system; to support core surveillance at the state level.
- Work with stakeholders to develop HBV and HCV educational programs for health care and social service providers.
- All states mandate the HBV vaccine series be completed or in progress as a requirement for school attendance.
- That federally-funded health insurance programs incorporate guidelines for risk-factor screening for HBV and HCV as a required core component of preventive care.

Prevalence of HCV among Persons Born 1945–1965

- 74% of 2.7-3.9 M HCV infected
- Prevalence 5.3 times higher than other ages (3.29% vs 0.55%)²
- 73% of all HCV-associated mortality ⁴
New CDC Recommendation

- Adults born during 1945 through 1965 should receive one-time testing for HCV without prior ascertainment of HCV risk factor. (strong recommendation, moderate quality of evidence)
- Benefits
  - 70% reduction in HCC
  - 50% reduction in all cause mortality

CDC HCV Screening Guidelines 2012

Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965

- Adults born during 1945–1965 should receive one-time testing for HCV without prior ascertainment of HCV risk factor.
- Individuals with identified 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.

Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

- HIV-infected persons should be tested annually for evidence of chronic HCV infection. Initial testing for HCV should be performed using the most sensitive commercially available enzyme immunoassay or rapid test. Follow-up testing is recommended if the initial test results are negative.

Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-Related Chronic Disease

- A one-time HCV screening test is recommended for
  - Persons who ever injected drugs, including those who injected once or a few times many years ago and do not currently or have not used drugs.
  - Persons with selected medical conditions, including history of perinatal exposure to parenteral drugs, type 1 diabetes mellitus, end-stage renal disease treated with dialysis, liver disease, or heart, lung, or kidney transplantation.

U.S. Preventative Services Task Force Endorsement

Annals of Internal Medicine

Screening for Hepatitis C Virus Infection in Adults: Clinical Summary of U.S. Preventive Services Task Force Recommendation

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Summary of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening Test</td>
<td>CDC recommends offering screening to all adults born between 1945–1965 who receive care in the primary care or inpatient settings.</td>
</tr>
<tr>
<td>Cautions</td>
<td>None</td>
</tr>
</tbody>
</table>

New York State HCV Screening Law

January 1, 2014

Screening test be offered to all individuals born between 1945–65 receiving services in the inpatient or primary care outpatient settings by an MD, PA, or NP.

If the screening test is reactive the provider must offer follow-up care or referral to a specialist who can provide care such as diagnostic testing (ie. HCV RNA testing).
HCV Screening Algorithm

- HCV Antibody Screen
  - HCV Antibody Positive
    - Check HCV RNA Quant and Genotype
  - HCV Antibody Negative
    - Repeat HCV RNA screen until positive
    -或
    - If HCV RNA negative, and patient is a probable spontaneous resolver (antibody positive, negative viral load), refer to Liver Clinic.

HCV Treatment

Evolution of HCV Therapy

SVR=Sustained Virologic Response; PIs=Protease Inhibitors

HCV Lifecycle
The Evolution Continues:
2011

2011-2013
The Era of Specifically Targeted Antiviral Therapy for HCV

Boceprevir / Telaprevir
G1 = G2, 3
SVR = 75%

2014
The beginning of the end? Or, the end of the beginning?

Sofosbuvir
Simeprevir
SVR > 90%

HCV Treatment 2014

Higher SVR rates across all genotypes

All oral regimens

Ease of dosing, QD, reduced # pills

Limited Resistance Development

Sofosbuvir (Sovaldi)

• HCV-specific uridine analog chain terminating polymerase inhibitor
• Potent pan-genotypic antiviral activity against HCV GT1-6
• High barrier to resistance
• Once-daily, oral, 400-mg tablet
• Favorable clinical pharmacology profile
  • No food effect
  • Few drug interactions
• Generally safe and well-tolerated in clinical studies to date (> 2,000 patients)
• No safety signal in preclinical/clinical studies
Sovaldi (Sofosbuvir)

Recommended Regimens and Treatment Duration for SOVALDI Combination Therapy in HCV Mono-infected and HCV/HIV-1 Co-infected Patients

<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 + ribavirin</td>
</tr>
<tr>
<td>Patients with genotype 2 CHC</td>
<td>SOVALDI + ribavirin</td>
</tr>
<tr>
<td>Patients with genotype 3 CHC</td>
<td>SOVALDI + ribavirin</td>
</tr>
</tbody>
</table>

Indicated for:
- All HCV genotypes (NOT as monotherapy)
- HCV / HIV co-infection
- HCV related HCC awaiting transplant

NO response guided therapy

VALENCE: GT 2 and 3, naïve and experienced

<table>
<thead>
<tr>
<th>Genotype 2</th>
<th>SOVALDI + RBV 12 weeks N=73</th>
<th>Genotype 3</th>
<th>SOVALDI + RBV 24 weeks N=250</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall SVR</td>
<td>93% (68/73)</td>
<td>84% (210/250)</td>
<td></td>
</tr>
<tr>
<td>Non-cirrhotic</td>
<td>97% (23/24)</td>
<td>93% (86/92)</td>
<td></td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>100% (2/2)</td>
<td>92% (12/13)</td>
<td></td>
</tr>
<tr>
<td>Treatment-experienced</td>
<td>96% (27/28)</td>
<td>77% (132/145)</td>
<td></td>
</tr>
<tr>
<td>Non-cirrhotic</td>
<td>91% (30/33)</td>
<td>85% (85/100)</td>
<td></td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>88% (7/8)</td>
<td>60% (27/45)</td>
<td></td>
</tr>
</tbody>
</table>

Simeprevir: (Olysio)

- Oral HCV NS3/4A protease inhibitor
- One-pill, once-daily
- Genotype 1
Simeprevir

### Table 1: Duration of Treatment with OLYSIO, Peginterferon Alfa and Ribavirin

<table>
<thead>
<tr>
<th>Treatment with OLYSIO, Peginterferon Alfa and Ribavirin*</th>
<th>Treatment with Peginterferon Alfa and Ribavirin*</th>
<th>Total Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naïve and prior relapse patients (including those with cirrhosis)</td>
<td>First 12 weeks</td>
<td>Additional 12 weeks</td>
</tr>
<tr>
<td>Prior non-responder patients (including partial and null responders) including those without cirrhosis</td>
<td>First 12 weeks</td>
<td>Additional 36 weeks</td>
</tr>
</tbody>
</table>

- Indicated in combination with peginterferon alfa and ribavirin in HCV genotype 1 infected subjects with compensated liver disease (including cirrhosis).
- NO monotherapy.
- Screening patients with HCV genotype 1a infection for the presence of the NS3 Q80K polymorphism at baseline is strongly recommended. Alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism.

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**QUEST-1, QUEST-2 and PROMISE Study Designs**

**Response Guided Treatment**

- **SVR Stratified by Stages of Fibrosis/Cirrhosis (QUEST-2)**

- Similar results seen in QUEST-1 and PROMISE studies

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**Overall SVR rates: Tx naïve and prior relapers**

<table>
<thead>
<tr>
<th>Patients Achieving SVR12 (%)</th>
<th>SMV + PEG/RBV</th>
<th>PEG/RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>QUEST-1</td>
<td>80%</td>
<td>50%</td>
</tr>
<tr>
<td>QUEST-2</td>
<td>81%</td>
<td>50%</td>
</tr>
<tr>
<td>PROMISE</td>
<td>79%</td>
<td>37%</td>
</tr>
</tbody>
</table>

**Patient Achieving SVR12 (%)**

<table>
<thead>
<tr>
<th>SVR Stratifed by Stages of Fibrosis/Cirrhosis (QUEST-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0-F2</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>SMV + PEG/RBV</td>
</tr>
<tr>
<td>PEG/RBV</td>
</tr>
<tr>
<td>Flexible</td>
</tr>
</tbody>
</table>

*PEG/RBV= Peginterferon/Ribavirin*
Genotype 1A, Q80K Mutation

COSMOS: Phase IIa, randomized, open-label study investigating simeprevir + sofosbuvir +/- ribavirin

Cohort 1: SVR12 in Null Responders (F0-2)

Cohort 2: Naive and prior null responders (F3-4); Interim Analysis, SVR4
Special Populations

Special populations: HIV/HCV Co-Infection

HIV/HCV Co-infection

Co-infection rates among people who inject drugs ~100%

Epidemiology

- HIV 75%
- HCV V 25%

Low SVR with PegIFN/RBV in HCV/HIV Coinfected patients

SVR (%)

- Genotype 1
  - APRICOT (n=176)
  - ACTG A5071 (n=51)
  - PRESCO (n=191)
  - PARADIGM (n=135/275)

- Genotype 2/3
  - APRICOT (n=15)
  - ACTG A5071 (n=80)
  - RIBA VIC (n=46)
  - Laguno (n=65)

ARMS 2010, 24:1537-1548

ESLD Emerges as a Leading Cause of Non-AIDS Death in HCV/HIV Co-Infected Patients in the ART Era

- Renal 1%
- Lactic Acidosis/Pancreatitis 1%
- Bacterial Infection 7%
- CVD-related 11%
- Non-AIDS Cancers 12%
- Liver-related 14%
- AIDS-related 32%
- Other/Unknown 13%


PR: pegIFN + RBV

11
HIV accelerates natural history of HCV

- HIV accelerates rate of liver fibrosis progression
  - 2.9 times higher in HIV/HCV co-infection
- Time to progression to cirrhosis
  - 6 to 10 years in HIV/HCV co-infected individuals
  - 20 to 30 years in HCV mono-infected patients
- Limited access to liver transplantation
  - 48 centers out of 242 in 2011 up from 25 centers in 2005
  - 198 HIV-positive people received organ transplants in 2011, an increase from ~58 in 2005
- Effective HCV Tx is associated with 66% reduction in liver mortality/ESLD/HCC

Challenges

- Drug interactions are likely and difficult to predict
  - CYP3A4 inhibition (ritonavir); induction (Efavirenz)
- DAAs are promising
  - DDI studies are essential for HCV and ARV regimens
  - FDA mandates “on-label” status (300 patient study)

PHOTON-1: Sofosbuvir + RBV in Individuals Co-infected with HCV and HIV-1

**Primary endpoint:** SVR12

**Primary endpoint:** SVR12

SOF + RBV in HIV Co-infected Patients

7% Cirrhotic

- Genotype 1: 76%
- Genotype 2: 88%
- Genotype 3: 92%
Preliminary SVR rates in HIV/HCV coinfected patients treated with Simprevir+PR

Data presented for patients with SVR data available at the time of the interim analysis
RGT-eligible patients: non-cirrhotic treatment-naïve and non-cirrhotic relapse patients

<table>
<thead>
<tr>
<th>Overall</th>
<th>Naïve*</th>
<th>Relapse*</th>
</tr>
</thead>
<tbody>
<tr>
<td>30/35</td>
<td>10/13</td>
<td>21/25</td>
</tr>
<tr>
<td>86</td>
<td>77</td>
<td>80</td>
</tr>
</tbody>
</table>

*Including only non-cirrhotic patients

Barriers to Treatment Uptake

- Lack of HCV-related knowledge that treatment cures
- Fear of side effects, stigmatization
- Mistrust of health care system
- Low perceived need for treatment
- Concern regarding adherence, reinfection
- Coexisting mental health diagnoses or active drug use
- Many PWID uninsured
- Less than 1/3 of those referred to specialty clinics appear for appointment
- Lack of provision of services

Special Populations: People Who Inject Drugs (PWID)

Injection drug use accounts for 80% of new cases, 60% of chronic HCV in the developed world

- Heroin users age 12 and over
- Injectors age 15-29
- Non-Hispanic white population, particularly suburban
- Hispanic
- African American

PWID: Treatment Uptake

Willing to be treated 80%
Unwilling 20%
1-2% treated annually
HCV Treatment is Effective Among PWID (Dual Therapy Era – P/R)

55.5% SVR (95% CI, 50.6% - 60.3%)

Dimov a, CID, 2013

PWID Linkage to Care and Treatment Export

Education and Screening
- Patient and Provider
- POC tests

Guideline Development
- Collaboration between academia, industry, government and professional societies

Discipline Modality Setting

HCV Evaluation Maximization

Prevention, Evaluation and Treatment of HCV (PET-C)

Telemedicine offers opportunity to remotely link patients with physicians geographically separated.

HCV management via tele-care
- Prior limited attempts in prisons1,2 and at rural clinics2
- Never attempted in drug treatment facility.

Study objectives
- To assess staff and patient knowledge and perception changes towards HCV treatment after educational intervention
- To demonstrate feasibility of HCV management via tele-care in opiate treatment program

1 Sterling et al, Amer J Gastro, 2004;99:866; 2 Arora, Hepatology 2010; 52:1124
### Education and Treatment Acceptance

<table>
<thead>
<tr>
<th>Tested for HCV (antibody)</th>
<th>320</th>
<th>269 (83.44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you have hepatitis C?</td>
<td>320</td>
<td>Yes 148 (46.25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No 175 (53.44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Don’t know 17 (5.31)</td>
</tr>
<tr>
<td>If ever diagnosed, would you be willing to be treated?</td>
<td>318</td>
<td>Yes 249 (77.99)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No 59 (18.83)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not sure 10 (3.20)</td>
</tr>
<tr>
<td>Would you be willing to attend an HCV educational activity?</td>
<td>318</td>
<td>Yes 249 (78.30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No 69 (21.70)</td>
</tr>
<tr>
<td>If not willing, would you be willing if compensated?</td>
<td>48</td>
<td>Yes 26 (54.17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No 22 (45.83)</td>
</tr>
<tr>
<td>If willing, what type of compensation?</td>
<td>26</td>
<td>Metrocard 9 (34.62)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Money 17 (65.38)</td>
</tr>
</tbody>
</table>

### Most are Aware of Basic HCV Facts

Basic facts mostly correctly identified:
- 90% identified HCV spread via injection drug use
- 87% knew that medication exists to treat HCV
- 78% knew reinfection possible after clearance

Topics for educational intervention:
- 57% knew majority of HCV infected are asymptomatic
- 51% knew that “everyone with positive antibody test has chronic infection” is a false statement
- 67% incorrectly thought that vaccine is available.

### HCV Outcomes

- SVR quickly approaching 100%
- Even more new agents on the way
- IFN almost gone
- Can we engage the epidemic’s base?
- Infrastructure?
- Cost?