HEPATITIS C: Balancing Cost and Cure Rates in a Managed Care Environment
Faculty Disclosure

• The **faculty** reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

Vanita K. Pindolia, PharmD, BCPS

  – *No financial interest/relationship relating to the topic of this activity*
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
</table>
| 6:20 AM – 6:55 AM | The Evolving Treatment Guidelines: Therapeutic Recommendations for Various Hepatitis C Virus Patient Types  
*Paul Kwo, MD* |
| 6:55 AM – 7:30 AM | The Unprecedented Evolution of the Hepatitis C Treatment Armamentarium: Challenges for Payers  
*Vanita K. Pindolia, PharmD, BCPS* |
| 7:30 AM – 7:45 AM | Faculty Discussion/Question & Answer Session                           |
Educational Objectives

After completing this activity, the participant should be better able to:

• Apply evidence-based treatment strategies to optimize outcomes for patients with HCV within a managed care setting

• Explain recently updated AASLD, IDSA, and ACG treatment guidelines on current and emerging treatment options for HCV, including efficacy, safety, and tolerability

• Develop benefit design to address the economic challenges presented to payers with the introduction of new HCV treatment options

• Evaluate pharmacy management strategies, including specialty pharmacy services and disease management, that MCOs can implement to improve overall patient outcomes for HCV patients

• Provide accurate and appropriate counsel as part of the managed care treatment team
HEPATITIS C:
Balancing Cost and Cure Rates in a Managed Care Environment
The Evolving Treatment Guidelines: Therapeutic Recommendations for Various Hepatitis C Virus Patient Types

Paul Kwo, MD
Professor of Medicine
Division of Gastroenterology and Hepatology
Indiana University
The **faculty** reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

**Paul Kwo, MD**

- **Consulting Fees:** AbbVie, Inc., Bristol-Myers Squibb, Gilead Sciences, Inc., Janssen Pharmaceuticals, and Merck & Co., Inc.

- **Research Grant Funding:** AbbVie, Inc., Bristol-Myers Squibb, Gilead Sciences, Inc., Janssen Pharmaceuticals, and Merck & Co., Inc.
Agenda

- Hepatitis C virus (HCV) infection and associated complications
- HCV treatment guidelines
- Emerging therapies
- Summary
HCV Infection and Associated Complications
Risk Factors Associated with Faster Fibrosis Progression in Chronic HCV

- **Disease state factors**
  - Fibrosis stage
  - HCV onset after 40 years of age
  - Persistently elevated ALT

- **Host factors**
  - Male gender
  - Age >45 years
  - Obesity/steatosis
  - Diabetes
  - HIV, HBV co-infection
  - Immune system compromise
  - Iron overload
  - Life style (ETOH, smoking)

- **Viral factors**
  - Genotype 3


ALT=alanine transaminase
Disease Progression in HCV is Not Linear: Importance of Early Treatment

SVR and All-Cause Mortality in Chronic HCV Patients with Advanced Fibrosis

Baseline factors significantly associated with all-cause mortality:
- Older age
- Diabetes
- Genotype 3 (2-fold increase in mortality and HCC)
- Higher fibrosis score
- Severe alcohol use

Patients (n=530) Followed for a Median of 8.4 Years

SVR=sustained virologic response; HCC=heptocellular carcinoma.

HCV Genotype 3 Associated with Significantly Higher Risk of Cirrhosis and HCC vs. GT 1

- Analysis of the VA Clinical Case Registry of patients with active HCV viremia (n=110,484)
  - GT 1: n=88,348 (80%)
  - GT2: n=13,077 (12%)
  - GT3: n=8,337 (7.5%)
- Mean follow-up: 5.4 years
- 31% higher risk of cirrhosis and HCC in patients with GT 3 vs. GT1 independent of age, diabetes, BMI, and antiviral treatment

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>1.31</td>
<td>1.22-1.39</td>
</tr>
<tr>
<td>HCC</td>
<td>1.80</td>
<td>1.61-2.03</td>
</tr>
</tbody>
</table>

HCC=heptocellular carcinoma; GT=genotype.
HCV/HIV Coinfected Patients Have Higher Rates of Hepatic Decompensation Despite ART

ART-treated HCV/HIV coinfected patients
HCV monoinfected patients

Cumulative incidence of decompensation

Time to hepatic decompensation, y


*P< 0.001

ART=antiretroviral therapy.
HCV Infection Associated with Significantly Higher Prevalence of Comorbidities

<table>
<thead>
<tr>
<th>Incidence of Comorbidities (%)</th>
<th>Employees w/ HCV (n=1329)</th>
<th>Employees w/out HCV (n=26,580)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasm</td>
<td>19*</td>
<td>13</td>
</tr>
<tr>
<td>Metabolic abnormality (eg, diabetes)</td>
<td>34*</td>
<td>27</td>
</tr>
<tr>
<td>Mental disorder</td>
<td>20*</td>
<td>10</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>31*</td>
<td>24</td>
</tr>
<tr>
<td>Metabolic abnormality (eg, diabetes)</td>
<td>36*</td>
<td>28</td>
</tr>
<tr>
<td>Mental disorder</td>
<td>42*</td>
<td>18</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>35*</td>
<td>28</td>
</tr>
</tbody>
</table>

*P<0.0001 vs. employees without HCV infection

- Significantly higher prevalence of comorbidities in the HCV-infected vs. non-infected cohort


Achievement of SVR Decreases Complications Associated with HCV Management

Cumulative incidence of ESRD in three study cohorts, analyzed by the modified log rank test with death adjusted as a competing risk event

- **Treated cohort**
- **Untreated cohort**
- **Uninfected cohort**

Cumulative incidence of acute coronary event in three study cohorts, analyzed by the modified log rank test with death adjusted as a competing risk event

- **Treated cohort**
- **Untreated cohort**
- **Uninfected cohort**

ESRD=end stage renal disease.
HCV Screening and Engagement in Care
Who Should Be Tested For HCV?

One-time HCV testing is recommended for persons born between 1945 and 1965*, without prior ascertainment of risk.

Rating: Class I, Level B

Birth cohort screening

Other persons should be screened for risk factors for HCV infection, and 1-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection.

<table>
<thead>
<tr>
<th>Risk Behaviors</th>
<th>Risk Exposures</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection-drug use (current or ever, including those who injected once)</td>
<td>Long-term hemodialysis (ever)</td>
<td>HIV infection</td>
</tr>
<tr>
<td>Intranasal illicit drug use</td>
<td>Getting a tattoo in an unregulated setting</td>
<td>Unexplained chronic liver disease and chronic hepatitis including elevated alanine aminotransferase levels</td>
</tr>
<tr>
<td></td>
<td>Health care, emergency medical, and public safety workers after needlesticks, sharps, or mucosal exposures to HCV-infected blood</td>
<td>Solid organ donors (deceased and living)</td>
</tr>
<tr>
<td></td>
<td>Children born to HCV-infected women</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prior recipients of transfusions or organ transplants, including persons who:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o were notified that they received blood from a donor who later tested positive for HCV infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o received a transfusion of blood or blood components, or underwent an organ transplant before July 1992</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o received clotting factor concentrates produced before 1987</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Persons who were ever incarcerated</td>
<td></td>
</tr>
</tbody>
</table>

Rating: Class I, Level B

*Regardless of country of birth

Baby Boomers Account for 76.5% of HCV in the US

Up to 75% of people with HCV in the US are undiagnosed
An estimated 35% of undiagnosed baby boomers with HCV currently have advanced fibrosis (F3-F4, bridging fibrosis to cirrhosis)

Screening by Birth Cohort May Prevent >120,000 Deaths Due to HCV Infection

1,070,840 new HCV cases identified with birth-cohort screening

552,000 patients treated

364,000 patients cured*

121,000 deaths averted

*With pegylated interferon and ribavirin plus DAA treatment.
†Deaths due to decompensated cirrhosis or hepatocellular carcinoma within 1945-1965 birth cohort. 470,000 deaths under birth cohort screening vs 592,000 deaths under risk-based screening.


DAA=direct-acting antiviral agents against the NS3/4A serine protease.
Patient Engagement in HCV Care

3.2

1.6

1.0-1.2

0.63-0.75

0.38-0.56

0.22-0.36

0.17-0.2

Number of People in Millions

Chronic HCV Infection
Tested for HCV
Referred to Care
Received HCV RNA Test
Received Liver Biopsy
Treated for HCV Infection
Achieved Sustained Virologic Response

HCV Treatment Guidelines
Rapidly Evolving HCV Treatment Landscape

HCV=hepatitis C virus; PEGIFN=peg interferon; RBV=ribavirin; GT=genotype.

Recommendations for when and in whom to initiate treatment

Treatment is recommended for patients with chronic HCV infection

Rating: Class I, Level A

**Immediate** treatment is assigned the highest priority for those patients with advanced fibrosis (Metavir F3), those with compensated cirrhosis (Metavir 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 and severe extrahepatic hepatitis C complications are given high priority.

Ratings: See tables
HCV Treatment Benefits All Patients

• Evidence clearly supports treatment in all HCV-infected persons*
  – Successful hepatitis C treatment results in SVR and is expected to benefit nearly all chronically infected persons

• Urgent treatment initiation recommended for
  – Advanced fibrosis (Metavir F3)
  – Compensated cirrhosis (Metavir F4)
  – Liver transplantation
  – Severe extrahepatic HCV

• Reduced HCV transmission expected with treatment of:
  – Women wishing to become pregnant
  – Long-term hemodialysis pts
  – MSM with high-risk sexual practices
  – Injection drug users
  – Incarcerated persons

*except those with limited life expectancy due to non-liver related comorbidities

Achievement of SVR Associated with Reduced Mortality

- 530 adults with advanced fibrosis prospectively followed for median 8.4 years after HCV treatment
- 192 (36%) achieved SVR

# Recommended Regimens for Treatment-Naïve HCV Genotype 1 Patients

**Subtype** | **Non-Cirrhotic** | **Compensated Cirrhosis**
--- | --- | ---
**Regimen** | **Duration (wks)** | **Regimen** | **Duration (wks)**
GT 1a or 1b | LDV/SOF | 12 | LDV/SOF | 12
GT 1a | OMV/PTV/RTV + DSV + RBV | 12 | OMV/PTV/RTV + DSV + RBV | 24
GT 1b | OMV/PTV/RTV + DSV | 12 | OMV/PTV/RTV + DSV + RBV | 12
GT 1a | SMV + SOF ± RBV | 12 | SMV + SOF ± RBV | 24
GT 1b | SMV + SOF | 12 | SMV + SOF | 24

*Shorter course can be considered in patients with pretreatment HCV RNA < 6 million IU/mL at provider’s discretion but should be done with caution.

LDV=ledipasvir; SOF=sofosbuvir; OMV=ombitasvir; PTV=paritaprevir; RTV=ritonovir; DSV=dasabuvir; RBV=ribavirin; SMV=simeprevir.

### Recommended Regimens for Treatment-Experienced HCV Genotype 1 Patients

<table>
<thead>
<tr>
<th>Subtype/ Prior Therapy</th>
<th>Non-Cirrhotic</th>
<th>Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regimen</td>
<td>Duration (wks)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Pegylated Interferon/Ribavirin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• GT 1a or 1b</td>
<td>LDV/SOF</td>
<td>12</td>
</tr>
<tr>
<td>• GT 1a or 1b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• GT 1a</td>
<td>OMV/PTV/RTV + DSV + RBV</td>
<td>12</td>
</tr>
<tr>
<td>• GT 1b</td>
<td>OMV/PTV/RTV + DSV</td>
<td>12</td>
</tr>
<tr>
<td>• GT 1a or 1b</td>
<td>SMV + SOF ± RBV</td>
<td>12</td>
</tr>
<tr>
<td>Prior SOF</td>
<td>Defer therapy*</td>
<td></td>
</tr>
<tr>
<td>Prior PI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• GT 1b or 1b</td>
<td>LDV/SOF</td>
<td>12</td>
</tr>
<tr>
<td>• GT 1a or 1b</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Based on limited available data, pts without advanced fibrosis and without an urgent need for HCV treatment should defer antiviral therapy pending additional data or consider clinical trial. 12 weeks of retreatment with LDV/SOF/RBV achieved 100% SVR.

LDV=ledipasvir; SOF=sofosbuvir; OMV=ombitasvir; PTV=paritaprevir; RTV=ritonovir; DSV=dasabuvir; RBV=ribavirin; SMV=simeprevir

## All Oral Regimens for Other Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Regimen</th>
<th>Duration (wks)</th>
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<tbody>
<tr>
<td>GT 2</td>
<td>SOF + RBV</td>
<td>12</td>
</tr>
<tr>
<td>GT 3</td>
<td>SOF + RBV</td>
<td>24</td>
</tr>
<tr>
<td>GT 4</td>
<td>OMV/PTV/RTV + DSV + RBV LDV/SOF</td>
<td>12</td>
</tr>
<tr>
<td>GT 6</td>
<td>LDV/SOF</td>
<td>12</td>
</tr>
<tr>
<td>GT 1/2/3/4 HCC pre-OLT</td>
<td>SOF + RBV</td>
<td>48*</td>
</tr>
<tr>
<td>GT 1, post-OLT (Metavir ≤F2; including compensated cirrhosis)</td>
<td>OMV/PTV/RTV + DSV + RBV LDV/SOF + RBV</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>GT 1/4 decompensated cirrhosis (CTP B or C)</td>
<td>LDV/SOF + RBV‡</td>
<td>12†</td>
</tr>
<tr>
<td>GT 2/3 decompensated cirrhosis (CTP B or C)</td>
<td>SOF + RBV‡</td>
<td>Up to 48 weeks</td>
</tr>
</tbody>
</table>

*Up to 48 weeks or until transplantation, whichever occurs first.
‡Not FDA approved but recommended in AASLD/IDSA guidance.
†24 weeks of SOF/LDV if anemia or RBV intolerance; 24 weeks of SOF/LDV + RBV (600 mg/day with increasing dose if tolerated) if prior SOF failure.

LDV=ledipasvir; SOF=sofosbuvir; OMV=ombitasvir; PTV=paritaprevir; RTV=ritonovir; DSV=dasabuvir; RBV=ribavirin; HCC=hepatocellular carcinoma; OLP=orthotopic liver transplantation; CTP=Child-Turcotte-Pugh

AASLD/IDSA Guidance for Patients with HCV/HIV Coinfection

• Same recommendations as in HCV-monoinfected patients

• Drug–drug interactions must be assessed
  – Need to adjust or withhold RTV if receiving a boosted PI with OMV/PTV/RTV + DSV
  – Potential for LDV-mediated increase in tenofovir levels, especially if tenofovir used with RTV
    • Avoid LDV if CrCl <60 mL/min or if receiving tenofovir with RTV-boosted PI
  – Do not interrupt antiretroviral therapy

• Do not use OMV/PTV/RTV ± DSV in coinfected patients not taking antiretroviral therapy

RTV=ritonavir; PI=protease inhibitor; OMV=ombitasvir; PTV=paritaprevir; DSV=dasabuvir; LDV=ledipasvir; CrCl=creatinine clearance

Summary of Current Treatment Recommendations

• PegIFN no longer recommended for first-line therapy of any patient
• 3 FDA-approved pegIFN-free regimens for genotype 1
• No differences in treatment recommendations for HCV mono-infected vs HCV/HIV-co-infected patients
  – Drug–drug interactions must be assessed

PegIFN=pegylated interferon

Emerging Therapies
HCV Therapies in Development

**On Market**
- IFN & PEG IFN
- Ribavirin
- Boceprevir
- Simeprevir
- Sofosbuvir
- Ombitasvir
- Ledipasvir
- Paritaprevir
- Dasabuvir

**Phase III**
- Asunaprevir
- Daclatasvir†
- Beclabuvir
- Elbasvir
- Grazoprevir
- GS-5816

**Phase II**
- Sovaprevir
- Samatasvir
- VX-135
- ABT-493
- ABT-530
- ACH-3102

**Phase I**
- TT-034
- VGX-6150

**Research/Preclinical**
- Many others, including immune stimulants and gene therapy

*Sample, not an exhaustive list.*
†NDA submitted March 2015.

C-WORTHY: Grazoprevir + Elbasvir ± RBV x 12 or 18 Weeks in GT1 HCV Patients

Randomized phase IIb trial

- **Treatment-naive cirrhotic patients with GT1 HCV (n=123)**
  - Grazoprevir + Elbasvir (n = 29)
  - Grazoprevir + Elbasvir + RBV (n = 31)
  - Grazoprevir + Elbasvir (n = 31)
  - Grazoprevir + Elbasvir + RBV (n = 32)

- **Cirrhotic and noncirrhotic patients with GT1 HCV and previous null response to pegIFN/RBV (n=130)**
  - Grazoprevir + Elbasvir (n = 33)
  - Grazoprevir + Elbasvir + RBV (n = 32)
  - Grazoprevir + Elbasvir (n = 32)
  - Grazoprevir + Elbasvir + RBV (n = 33)

Grazoprevir 100 mg once daily; elbasvir 50 mg once daily; weight-based RBV 800, 1200, or 1400 mg daily.

C-WORTHY: SVR12 Rates of Grazoprevir + Elbasvir ± RBV x 12 or 18 Weeks

SVR12 was 92% in null responders with cirrhosis treated for 12 weeks with grazoprevir + elbasvir ± RBV

- High efficacy without RBV and with only 12 weeks of treatment
- Grazoprevir + elbasvir were generally safe and well-tolerated

C-SWIFT: Grazoprevir/Elbasvir + SOF x 4, 6, or 8 Weeks in Treatment-Naive GT1 HCV

- Randomized, open-label phase II trial
- Primary endpoint: SVR12

Grazoprevir/elbasvir 100/50 mg QD FDC; sofosbuvir (SOF) 400 mg QD

C-SWIFT Interim Results: Modified ITT SVR4/8 With Grazoprevir/Elbasvir + SOF

Percent achieving SVR 4/8 (<15 IU/mL)

<table>
<thead>
<tr>
<th></th>
<th>Non-Cirrhotic</th>
<th>Cirrhotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Weeks</td>
<td>38.7</td>
<td></td>
</tr>
<tr>
<td>6 Weeks</td>
<td>86.7</td>
<td></td>
</tr>
<tr>
<td>6 Weeks</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>8 Weeks</td>
<td>94.7</td>
<td></td>
</tr>
</tbody>
</table>

SVR4/8 by HCV Subtype, % (n/N)

<table>
<thead>
<tr>
<th></th>
<th>No Cirrhosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Weeks (n = 31)</td>
<td>35 (9/26)</td>
<td>81 (13/16)</td>
</tr>
<tr>
<td>6 Weeks (n = 30)</td>
<td>85 (22/26)</td>
<td>93 (14/15)</td>
</tr>
<tr>
<td>6 Weeks (n = 20)</td>
<td>80</td>
<td>75 (3/4)</td>
</tr>
<tr>
<td>8 Weeks (n = 21)</td>
<td>94.7</td>
<td>100 (4/4)</td>
</tr>
</tbody>
</table>

C-SWIFT: Summary

• Combined regimen of grazoprevir/elbasvir + SOF may be able to shorten treatment duration to 6-8 weeks among cirrhotic and noncirrhotic treatment-naïve GT1 patients

• Factors that may have impacted likelihood of SVR in the 4 and 6 week arms include
  – Genotype (GT 1a vs. 1b)
  – Baseline viral load
  – IL28B status
  – PK of component medicines in the regimens

UNITY-2: Daclatasvir/Asunaprevir/Beclabuvir ± RBV in Patients with GT 1 Infection and Compensated Cirrhosis

- All-oral daclatasvir-based regimen (DCV TRIO)
  - Daclatasvir (NS5A inhibitor)
  - Asunaprevir (NS3 protease inhibitor)
  - Beclabuvir (non-nucleoside NS5B polymerase inhibitor)

- UNITY-2 study
  - Fixed dose combination of DCV TRIO twice daily ± RBV in GT 1 treatment-naïve and treatment experienced compensated cirrhotics

UNITY-2: SVR12 in GT1 Treatment-Naïve and Treatment-Experienced Cirrhotic Patients

DCV = Daclatasvir + Asunaprevir + Beclanabuvir

UNITY-2: SVR12 in GT 1 vs. GT 1b

DCV=Daclatasvir+Asunaprevir+Beclanabuvir


DCV=Daclatasvir+Asunaprevir+Beclanabuvir

UNITY-2: Summary

- DCV TRIO ± RBV was safe and well-tolerated with low rates of serious adverse events and discontinuation due to adverse events
- Most common adverse events (AEs) with DCV TRIO were headache, nausea, diarrhea, and fatigue

DCV=Daclatasvir+Asunaprevir+Beclanabuvir

ALLY-3: SVR12 in GT 3 Patients Treated with Daclatasvir + Sofosbuvir

- ALLY-3: Phase 3 open-label trial
- Once daily 60 mg daclatasvir + 400 mg sofosbuvir for 12 weeks without ribavirin
- Baseline characteristics:
  - Median age: 55 years
  - Baseline VL: >800,000 IU/ml
  - Unfavorable IL28B gene variants: 60%
  - Cirrhosis was present in 19% of TN and 25% of TE
- Patients with cirrhosis were less likely to achieve SVR12
- Combination was generally safe and well tolerated

Summary
Summary

• >4.5 million Americans are infected with HCV
• One time HCV testing is recommended for persons born between 1945-1965; other persons should be screened for risk factors for HCV infection
• Birth cohort screening increases the potential number of patient eligible for treatment, but treatment engagement and achievement of SVR is low
• Treatment is recommended for patients with chronic HCV infection; the evidence clearly supports treatment in all HCV-infected persons
  – PegIFN no longer recommended for first-line therapy of any patient
• Several additional therapies are in late phase development
HEPATITIS C:
Balancing Cost and Cure Rates in a Managed Care Environment
The Unprecedented Evolution of the Hepatitis C Treatment Armamentarium: Challenges for Payers

Vanita K. Pindolia, PharmD, BCPS
VP, Ambulatory Clinical Pharmacy Programs
Henry Ford Health System/Health Alliance Plan
Overview

- Economic Overview: Challenges for Payers and Healthcare Purchasers
- HCV Treatment: Ethical Dilemmas
- HCV Drug Management Strategies
- HCV Drug Contracting Strategies
- Role of Specialty Pharmacies
Sens. Ron Wyden (D-Ore.), Chairman of the Senate Finance Committee, and Chuck Grassley (R-Iowa), the Judiciary Committee's ranking member asked drug makers how they justify the high price of HCV therapy:

“The large patient population HCV patients combined with the high price of each individual treatment creates a question as to whether payors of health care, including Medicare and Medicaid, can carry such a load.”

“HCV drug cost also could dramatically increase the government’s spending on other programs, including …prisoners with HCV. Over 1.8 million people with HCV are incarcerated (32.8% of total cases of HCV in US). Even with 44% discount for treating prison populations, American taxpayers could end up paying billons of dollars …”
Analysis of HCV drug therapy impact on 2015 Medicare Part D spending:

“We estimate that the cost of HCV drug therapies … will increase 2015 federal spending on the individual Medicare Part D program by approximately $2.9 billion to $5.8 billion.”

“We estimate that the cost of HCV drug therapies will increase total annual individual Medicare Part D beneficiary premiums by $481 million to $965 million in 2015.”

CMS data on Hep C drug spend in 2014 to ProPublica:

“Medicare spent more than $4.7 billion on Hep C drugs in 2014 – more than 15 times what it spent on Hep C drugs in 2013.”

“The federal government spent $65 billion on all Part D drugs in 2013.”

Although the newer drugs have a higher SVR12 rate and “curing Hep C will likely prevent liver cancer, prevent liver transplantation and save other health care dollars down the road … still, the drugs may not save money for Medicare, even in the long run.”

A recent cost-effectiveness study published in Annals of Internal Medicine found that only 25% of the Hep C drug cost would be offset by avoiding hospitalizations and other treatment costs.


Southeastern Pennsylvania Transportation Authority filed class action suit in US District Court on December 9, 2014 due to high cost associated with HCV drug therapy ($2.4 million for HCV drugs for its employees in 2014)

California Technology Assessment Forum (CTAF) Report:

“Because chronic infection with HCV is relatively common, the cost of hepatitis c drugs translates into an enormous potential budget impact for federal, state, and private health insurers.”

Treatment of HCV: Uncertainties and Ethical Quandaries

- Determining the population that will need treatment HCV…not a simple answer
  - Acute HCV: 15% of HCV infections
    - 849 confirmed cases of acute HCV in US (2007)
    - CDC estimates ~17,000 cases of new HCV infections in US after adjusting for asymptomatic infections and underreporting (2007)
    - No treatment needed
  - Chronic HCV: 85% of HCV infections
    - ~3.2 million Americans
    - Most prevalent among those born from 1945 to 1965
    - An estimated 50% of population is unaware they have chronic HCV
  - CDC estimates that one time testing for HCV for those born between 1945-1965 could identify an estimated 800,000 undiagnosed cases

Treatment of HCV: Uncertainties and Ethical Quandaries (cont’d)

• Could widespread screening for HCV lead to unnecessary treatment or overtreatment?

• Course of HCV progression
  – Retrospective studies of natural course of HCV suggests that end stage liver disease is common; cirrhosis develops within 20 years and liver cancer with 30 years
    • These studies were usually composed of sicker people with multiple medical problems (ie, referral bias)
    • Of this sicker HCV population (symptomatic population found to have HCV), 80-85% will die from non-hepatic causes
  – Based upon CDC 2011 data, 2.7 million people are infected with HCV in US
  – ~16,000 people die or have liver transplantation each year due to HCV
    • Equates to ~<0.6% of infected HCV patients

Treatment of HCV: Uncertainties and Ethical Quandaries (cont’d)

- HCV treatment efficacy
  - Impact on clinical outcomes (morbidity and mortality) is most compelling data to assure treatment effectiveness
    - Such trials for HCV limited to interferon-based therapy
    - HCV clinical trials: surrogate markers are used as outcome measures (e.g., SVR12 or SVR24)
      - Few patients develop end stage liver disease
      - Often takes years to manifest end stage liver disease
      - SVR does not equate to cure
        - Simeprevir PILLAR study: undetectable HCV RNA declined from 336 pts at end of treatment to 303 (SVR12), 300 (SVR24) and 293 (SVR72)
        - Long-term data for newer HCV drug regimens are not yet available

Correlation of SVR into long-term clinical benefit

- Patients who develop a SVR...
  - Usually do not show evidence of viral RNA in other body tissues
  - Exhibit less liver-related morbidity and mortality vs. patients with no SVR

- Studies suggest that patients who achieved SVR were less likely to have risk factors associated with disease progression
  - Selection bias: Those less likely to progress to liver failure respond to treatment; few patients progress to liver failure
Treatment of HCV: Uncertainties and Ethical Quandaries (cont’d)

- Harm in treating all patients found to be HCV-positive?
  - Actual AEs and their severity are found during post-marketing when larger populations are exposed to the drug
  - Harvoni® and Sovaldi® - Recent new serious and life-threatening drug warning added to drug labels (March 20, 2015)
    - Serious and Life-threatening cases of symptomatic bradycardia as well as one case of fatal cardiac arrest with coadministration of Amiodarone
  - Negative experience with telaprevir
    - Based upon clinical trials evaluated for telaprevir approval in 2011, serious AEs occurred in 3% of patients
    - December 2012 black box warning added to the label due to severe and fatal skin reactions
- Could we be exposing a large population to drug therapy that may not need it?
  - Large, randomized, long-term studies can provide insight on disease progression with/without HCV treatment, correlation of SVR12 with cure rates, and true clinical outcomes
  - Observational study of 3.5 years of follow up for 2800 participants who received HCV treatment is expected to be completed in 2016

Treatment of HCV: Uncertainties and Ethical Quandaries (cont’d)

- Economic analyses conducted to inform California Medicaid of the financial gain/loss of treating its HCV population with newer HCV drug therapies
- **Health system value analysis** based on clinical trial data for Harvoni® and available statistics on HCV-related complications
  - Per 1,000 patients treated with any stage of liver involvement, Harvoni® prevents
    - 6 cases of cirrhosis and 2 HCV-related deaths in the first year alone
    - 44 cases of cirrhosis, 5 of HCC and 17 HCV-related deaths at five years
      - 7% of incremental treatment costs would be offset by these reductions
    - 6-fold reduction in cirrhosis, 50% reduction in HCC and 140 HCV-related deaths at 20 years
      - 25% of treatment costs would be offset by these reductions

HCC=hepatocellular carcinoma
• **Health System Value Analysis** for 33,000 Medi-Cal and Department of Corrections’ patients with chronic HCV
  
  – Treatment of HCV at any stage of liver involvement increases costs by $3 billion or $33 PMPM
    
    • Costs offsets after 5 years: Total $254 million (net expenditure of $2.8 billion)
    • Cost offsets after 20 years: Total $1.2 billion (net expenditures of $1.8 billion
    • This represents a 5% increase in $PMPM for Medi-Cal
      
      – 0.5% to 1% increase in $PMPM is considered manageable increase in expenditure

  – If treatment with chronic HCV was restricted to those with patients with fibrosis levels of F3 or F4
    
    • Initial expenditures for new therapies would be $800 million (1.4% increase in $PMPM)
    • Total net expenditures after 20 years would be $475 million (<1% increase in $PMPM)

Treatment of HCV: Uncertainties and Ethical Quandaries (cont’d)

- **Care Value Analysis**
  - “While treating patients at all fibrosis stages was more expensive in comparison to waiting to treat until patients reached F3 or F4, it was also more effective.”

- **Dilemma of using Care Value Analysis demonstrating cost-effectiveness with Health System Value Analysis demonstrating unmanageable costs**
  - If the one-year PMPM increase were to be < 1%, only 16,500 of the Medi-Cal/Department of Corrections could be treated
  - Not enough funds to treat entire population of patients at all stages of fibrosis

Institute for Clinical and Economic Review.  
Effect of High Prescription Drug Costs on Patient’s Out-of-Pocket Costs

- Healthcare Purchasers have had to increase patient out-of-pocket expenses for medications (eg premiums/deductibles/copayment) to help offset the high cost of drugs.

- Increased out-of-pocket costs are not limited to new medications such as those for HCV.
  - Many patients must now pay substantially higher co-pays for generic drugs that their insurers have recently designated “non-preferred” or “higher cost generics”.
  - Drugs placed into this category includes many recommended as first-line treatment in evidence-based guidelines for highly prevalent chronic conditions such as hypertension, diabetes, epilepsy, schizophrenia, migraine headache, osteoporosis, Parkinson’s disease, and HIV.
  - 5-tier drug plans or high deductible plans.

HCV Drug Management Strategies

- Utilize prior authorization
  - Ensures appropriate genotype, drug selection, and duration
  - Utilize fibrosis staging to prioritize the need for therapy
    - Accurate assessment of fibrosis is vital in assessing the urgency for treatment
    - Degree of hepatic fibrosis is a robust predictor of disease progression and clinical outcomes
    - Metavir scores versus liver biopsy
      - Metavir score is a standardized measure of fibrosis and inflammation seen on a liver biopsy
- Identify and encourage use of preferred agents
  - May be different per line of business
- Encourage collaborative and coordinated care

HCV Drug Management Strategies

• Contracts with pharmaceutical manufacturer
  – Value-based contracts
    • Coordination with specialty pharmacy providers
    • Including disease education and adherence programs
    • Monitoring HCV RNA response to therapy (SVR 12 or SVR 24)
  – Single vs. multiple formulary HCV drugs
    • Gilead: Harvoni® and Sovaldi® as ‘single’ HCV drug
    • Abbvie: Viekira Pak® as single HCV drug
    • Combination of pharmaceutical industries’ drug products

HCV Drug Contracting Strategies

METAVIR FIBROSIS SCORE
(n=1000 Chronic Genotype 1 HCV patients)

- **F0 (17%)**
  - 50% tx naïve + baseline HCV RNA < 6 million IU/ml
  - 8 wk H = 85 12 wk H = 85
  - 12 wk V+R = 170
  - 8 wk H = 175 12 wk H = 175
  - 12 wk V+R = 350

- **F1 (35%)**
  - 50% tx naïve + baseline HCV RNA < 6 million IU/ml
  - 8 wk H = 55 12 wk H = 165
  - 8 wk H = 3 12 wk H = 137
  - 12 wk V+R = 220
  - 12 wk V+R = 140

- **F2 (22%)**
  - 25% tx naïve + baseline HCV RNA < 6 million IU/ml
  - 8 wk H = 55 12 wk H = 165
  - 8 wk H = 3 12 wk H = 137
  - 12 wk V+R = 220
  - 12 wk V+R = 140

- **F3 (14%)**
  - 2% tx naïve + baseline HCV RNA < 6 million IU/ml
  - 8 wk H = 3 12 wk H = 137
  - 8 wk H = 3 12 wk H = 137
  - 12 wk V+R = 140
  - 12 wk V+R = 140

- **F4 (Compensated Cirrhosis; 12%)**
  - 100% tx experienced with cirrhosis
  - 8 wk H = 55 12 wk H = 165
  - 8 wk H = 3 12 wk H = 137
  - 12 wk V+R = 220
  - 12 wk V+R = 140

H=Harvoni®; V=Viekira Pak®; R=Ribavirin

HCV Drug Contracting Demo
# HCV Drug Contracting Strategies

## HARVONI ($31,500/4-wk at WAC) for n=1000

<table>
<thead>
<tr>
<th></th>
<th>Option A</th>
<th>Option B</th>
<th>Total Cost (Option A /Option B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-wk H</td>
<td>12 wk H</td>
<td>12 wk HR/24 wk H</td>
<td></td>
</tr>
<tr>
<td>$63,000/pt (n=318)</td>
<td>$94,500/pt (n=562)</td>
<td>$99,000/pt/$189,000 pt (n=114/n=6)</td>
<td></td>
</tr>
<tr>
<td>0% Rebate</td>
<td>$20. M</td>
<td>$53.1 M</td>
<td>$12.4 M</td>
</tr>
<tr>
<td>20% Rebate</td>
<td>$16. M</td>
<td>$42.5 M</td>
<td>$9.9 M</td>
</tr>
<tr>
<td>25% Rebate</td>
<td>$15. M</td>
<td>$39.8 M</td>
<td>$9.3 M</td>
</tr>
<tr>
<td>30% Rebate</td>
<td>$14. M</td>
<td>$37.2 M</td>
<td>$8.7 M</td>
</tr>
<tr>
<td>40% Rebate</td>
<td>$12. M</td>
<td>$31.9 M</td>
<td>$7.5 M</td>
</tr>
</tbody>
</table>

## VIEKIRA ($27,773/4-wk at WAC) for n=1000

<table>
<thead>
<tr>
<th></th>
<th>12 wk V + R (n = 880)</th>
<th>24 wk V + R (n = 120)</th>
<th>Total Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$87,819/pt</td>
<td>$175,638</td>
<td></td>
</tr>
<tr>
<td>0% Rebate</td>
<td>$77.3 M</td>
<td>$21.1 M</td>
<td>$98.4 M</td>
</tr>
<tr>
<td>20% Rebate</td>
<td>$61.8 M</td>
<td>$16.9 M</td>
<td>$78.7 M</td>
</tr>
<tr>
<td>25% Rebate</td>
<td>$58. M</td>
<td>$15.8 M</td>
<td>$73.8 M</td>
</tr>
<tr>
<td>30% Rebate</td>
<td>$54.1 M</td>
<td>$14.8 M</td>
<td>$68.9 M</td>
</tr>
<tr>
<td>40% Rebate</td>
<td>$46.4 M</td>
<td>$12.6 M</td>
<td>$59. M</td>
</tr>
</tbody>
</table>

H=Harvoni®; V=Viekira Pak®; R=Ribavirin
HCV Pharmacy Management Strategies

• Coordinate with specialty pharmacy providers
  – Including disease education and adherence programs
  – Monitoring response to therapy

• Partial prescription fills to decrease waste
  – Limit fills to 2-week supply
    • Real world drug discontinuation rates are typically higher than within clinical trials
    • CVS/Caremark data
      – In real world, 10.2% of 738 patients (sofosbuvir + PEG-RBV) discontinued therapy vs 2% in clinical trial
      – In real world, 9% of 680 patients (sofosbuvir + RBV) discontinued therapy vs 0-2% in the pivotal clinical trials

  – Coordinate next fill with timely HCV RNA test results

Opportunities for Specialty Pharmacies

- Specialty pharmacy services can achieve evidence-based and patient-centered approaches to evaluating and managing HCV therapies to both improve patient outcomes and facilitate cost savings
  - Specialty pharmacy services that view HCV patients holistically are important because of the potential for comorbid conditions

- A multifaceted approach is needed to support the patient, including direct education, clinical outreach, ongoing adherence messaging and reminders, and technology-based tools to create a sense of patient connection
  - Trained HCV care teams of clinical pharmacists, pharmacy technicians, nurses, and call center personnel are needed to deliver focused services for patients with HCV
Partnership Between Specialty Pharmacy and Health Plans Can Improve Outcomes

• As many as three-quarters of plans now mandate specialty pharmacy use to access HCV products
  – Specialty pharmacists are uniquely positioned close to HCV patients providing plans an ally in their attempts to manage HCV product use and ensure patient adherence to their treatment

• One-on-one counseling by pharmacists with expertise specifically in managing HCV patients will enhance collaboration that is needed to continually monitor adherence, side effects and drug interactions, and communicate with the treating physician when adjustments are needed

# Adherence Counseling for Patients with HCV

<table>
<thead>
<tr>
<th>Initial</th>
<th>Ongoing</th>
<th>Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy and disease state overview including</td>
<td>• Discuss diagnosis and treatment</td>
<td>• Adherence assessment including medication possession and refills</td>
</tr>
<tr>
<td>• Disease state education</td>
<td>• Review dose, administration, duration of therapy</td>
<td>• Address barriers to adherence</td>
</tr>
<tr>
<td>• Drug administration</td>
<td>• Depression screening</td>
<td>• Enact dispensing and/or prescriber engagement to support adherence</td>
</tr>
<tr>
<td>• Treatment-related adverse events (AEs)</td>
<td>• Address barriers to adherence</td>
<td></td>
</tr>
<tr>
<td>• Importance of adherence</td>
<td>• Provide guidance for missed doses and AE management</td>
<td></td>
</tr>
<tr>
<td>• Depression screening</td>
<td>• Laboratory reminders and importance of follow up testing</td>
<td></td>
</tr>
</tbody>
</table>

# Utilizing Technology to Improve Adherence

<table>
<thead>
<tr>
<th><strong>Medication Reminders</strong></th>
<th>Reminders pop up when it’s time to take a medication; user can mark as taken, snooze, or mark as skipped</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adherence graph</strong></td>
<td>Users can view a graph that charts their adherence through the course of therapy</td>
</tr>
<tr>
<td><strong>Viral load graph</strong></td>
<td>Users can enter viral load following lab work and app graphs their data over time</td>
</tr>
<tr>
<td><strong>E-mail</strong></td>
<td>Medication regimen, adherence graph, and viral load graph can all be emailed to the doctor/nurse/caregiver</td>
</tr>
<tr>
<td><strong>Online tracking</strong></td>
<td>Users document their viral load, doctor visits, symptoms using an app or web-based system</td>
</tr>
</tbody>
</table>

## HCV Management Plan

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Timing</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV Baseline Assessment</td>
<td>Week 0</td>
<td>Collect/verify labs (eg, weight, viral load, biopsy, Hb) and previous HCV therapy, duration, and outcome</td>
</tr>
<tr>
<td>Pharmacist Verification</td>
<td>New RXs</td>
<td>Evaluate therapy by genotype, treatment history, effectiveness, and safety; resolve actual or potential drug-related problems</td>
</tr>
<tr>
<td>Care Plan</td>
<td>Week 0, PRN</td>
<td>Identify treatment goals and document care plan</td>
</tr>
<tr>
<td>Medical Assessment</td>
<td>Week 0, Monthly</td>
<td>Collect/verify allergies, comorbidities, concomitant medications; clinician triage</td>
</tr>
<tr>
<td>Patient Education and Training</td>
<td>Week 0, PRN</td>
<td>Clinician initial consult (drug, disease, expectations, AE management; adherence); HCV educational packet; injection training</td>
</tr>
<tr>
<td>Support Program Referral</td>
<td>Week 0, PRN</td>
<td>Facilitate enrollment in manufacturer programs and other supportive organizations</td>
</tr>
<tr>
<td>Side Effect Management</td>
<td>Week 0, PRN</td>
<td>HCV Care Kits, side effect management guides, and clinician counseling</td>
</tr>
<tr>
<td>Adherence and Distribution Calls</td>
<td>At Least Monthly</td>
<td>Outbound call by patient care coordinator to arrange refills, evaluate side effects, education needs, and administration</td>
</tr>
<tr>
<td>Futility Rules and Treatment Outcomes</td>
<td>Varies by Regimen</td>
<td>Collect VL and provide recommendations for treatment plan; outreach to obtain SVR results</td>
</tr>
</tbody>
</table>

Audience Question and Answer Session
HEPATITIS C:
Balancing Cost and Cure Rates in a Managed Care Environment

Jointly provided by

in collaboration with

This activity is supported by independent educational grants from AbbVie, Inc. and Merck & Co., Inc.
Key Takeaways and Closing Comments
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Balancing Cost and Cure Rates in a Managed Care Environment
To Download the Slides and Excel Model From Today’s Program Please Go To

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