Hepatitis C

In the U.S., approximately 3.2 million people have chronic HCV, and many remain undiagnosed.
Maryland Hepatitis C Epidemiology

- An estimated 47,000-73,000 people in Maryland have been infected with HCV in their lifetime.
- Acute symptomatic rate: 0.7 per 100,000
  - National rate = 0.6 per 100,000
  - Four Maryland counties have rates between 5.4 to 9.8
- In 2012, there were 7,955 lab reports for chronic hepatitis C infection.

Maryland Hepatitis C Epidemiology

Rates of Acute/Symptomatic Hepatitis C Infection, Maryland 2012

- ≥9.0
- 5.0-8.9
- 1.0-4.9
- 0.1-0.9
- 0.0 (Not Reported)
## Reported cases of Hepatitis C in Maryland 2014 (past/present case counts)

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Count</th>
<th>Rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allegany</td>
<td>90</td>
<td>122.5</td>
</tr>
<tr>
<td>Frederick</td>
<td>129</td>
<td>53.0</td>
</tr>
<tr>
<td>Garrett</td>
<td>13</td>
<td>43.3</td>
</tr>
<tr>
<td>Montgomery</td>
<td>461</td>
<td>44.8</td>
</tr>
<tr>
<td>Washington</td>
<td>194</td>
<td>129.1</td>
</tr>
<tr>
<td>Baltimore City</td>
<td>2321</td>
<td>372.2</td>
</tr>
</tbody>
</table>
Medicaid Enrollees with Chronic Hepatitis C Diagnosis by Race/Ethnicity, Maryland (FY 2013)

**Sex/Gender**
- Male: 53%
- Female: 47%

**Race/Ethnicity**
- White: 42%
- Black: 52%
- Hispanic: 1%
- Other: 4%
- Asian: 1%

**Age Group**
- <1-18: 1%
- 19-39: 15%
- 40-64: 84%
CDC PS14-1413
Outcome Goals

- Increase the number of persons who receive HCV antibody testing
- Increase the number of persons diagnosed with current HCV infection
- Increase the number of persons who complete treatment and are cured of HCV infection
- Increase the capacity of primary care providers to utilize Electronic Medical Records (EMR)
- Increase health department capacity to gather and follow-up on reports of current HCV cases
CDC PS14-1413
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Hepatitis C

HCV Treatment Advances Through the Years

- Ribavirin Approved
- 1991: Interferon Approved
- 1998
- 2001: PEGylated Interferon Approved
- 2011-Present: Direct-Acting Antiviral Agents Approved
Hepatitis C

Liver complications due to HCV are continuing to increase°

- In the US, HCV is the leading cause of liver transplantation° and liver cancer°
- The diagnosis and treatment gap — combined with the progressive nature of HCV — have contributed to an increase in HCV-related liver complications that is projected to continue for the next decade or more°

PROJECTED INCREASE IN CIRRHOSIS

By 2030, 45% of untreated patients are projected to have developed cirrhosis°

By 2015, 30% of untreated patients are projected to have developed cirrhosis°
### Screening Guidelines Updated

**Risked based testing alone failed to identify more than 50 % of HCV infections**

<table>
<thead>
<tr>
<th>AASLD with IDSA &amp; IAS-USA</th>
<th>CDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>In addition to baby boomers (those born from 1945-1965, all persons at increased risk for HCV infection ( based on behaviors exposures and other medical concerns should be tested for HCV)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>USPSTF</th>
</tr>
</thead>
<tbody>
<tr>
<td>In June of 2013 the United States Preventative Service Task Force (USPSTF) made a grade B recommendation for both the testing of persons at high risk for HCV and the one time testing for adults born from 1945-1965</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Center for Medicaid and Medicare Services (CMS) agrees with the USPSTF recommendation and has been covering test for HCV when ordered by the primary care provider within the context of a primary care setting and performed by an eligible Medicaid provider in Baby Boomers and others at high risk using FDA approved lab test</td>
</tr>
</tbody>
</table>
Guidelines

HCV Guidelines Updated Feb 24 2016

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

www.natap.org

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

IDSA
Infectious Diseases Society of America
Hepatitis C

HCV AFFECTS BABY BOOMERS IN THE U.S. MORE THAN ANY OTHER GENERATION

75% Baby Boomers—people born from 1945 through 1965—account for up to 75% of all chronic HCV infections among adults

5x Baby Boomers in the U.S. are 5x more likely to have been infected with HCV than adults from other generations

The CDC recommends a one-time testing for HCV of all adults born from 1945 through 1965
HCV Screening Recommendations

• Testing recommended at least once for persons born between 1945 and 1965
• Others: Screen for risk factors and perform one-time testing if risk factors present
• Annual HCV testing recommended for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men
• Periodic testing should be offered to other persons with ongoing risk factors for exposure to HCV

Who is at risk for HCV

- Born between 1945-1965
- Current or past IDU
- Unsanitary piercing or tattoos
- Children of HCV infected mothers
- HCW-occupational exposure

- Hemophiliacs tx before 1987
- Received blood transfusion or organ transplant before 1992
- HIV infection
- Incarceration
- Chronic liver disease/chronic hepatitis
Primary Providers as Successful as Specialists in Treating HCV Infection
Conference on Retroviruses and Opportunistic Infections (CROI), February 22-25, 2016, Boston
BACKGROUND

- New direct-acting antivirals promise high cure rates for the majority of HCV positive patients
- It is unknown whether high cure rates will be obtained in clinical practice, particularly among persons who use drugs (PWUDs)

OBJECTIVES

- We investigated the effectiveness of onsite HCV treatment with care coordination on HCV cure rates for patients accessing primary care at a federally qualified health center (FQHC)
- We specifically explored differences in cure rates for PWUD versus non-PWUD
Implications

• On-site treatment with care coordination may help to mitigate barriers to specialty care and improve HCV cure rates for PWUD
• Similar treatment models should be replicated and tested throughout the 1200 FQHCs in the United States, settings that are known to serve high numbers of PWUD
Implications

- On-site treatment with care coordination may help to mitigate barriers to specialty care and improve HCV cure rates for PWUD
- Similar treatment models should be replicated and tested throughout the 1200 FQHCs in the United States, settings that are known to serve high numbers of PWUD
Hepatitis C

HCV CAN HAVE SERIOUS HEALTH CONSEQUENCES, EMPHASIZING THE NEED FOR PROPER DIAGNOSIS AND TREATMENT\(^1\)\(^-\)\(^3\)

The more than 16,500 deaths with HCV listed as a cause on death certificates may underrepresent the total number of deaths attributable in whole or in part to chronic Hepatitis C virus\(^4\).

HCV-related mortality

Listed as a cause of death in

More than 16,500 deaths in 2010 in the U.S. (per CDC\(^4\))

An estimated 7\% higher HCV mortality than AIDS in 2010\(^4\)\(^-\)\(^5\).
Hepatitis C is Curable

**HCV IS A CURABLE VIRUS**

HIV

- **T-Cell**
- Proviral DNA
- In many viral infections, such as HIV, genetic material is stored in the host cell nucleus and integrates into the host DNA.

HCV

- **Hepatocyte**
- HCV RNA
- In contrast, HCV RNA remains in the cytoplasm and is a target for host cell antiviral mechanisms; one reason why virologic cure of HCV is possible.
Co-infection Background and Epidemiology

- HIV accelerates the natural course of Hepatitis C
- Successful antiretroviral therapy can slow fibrosis progression but not back to the rate in HCV monoinfection
- Liver disease associated with HCV infection has become a leading cause of morbidity and mortality among HCV/HIV-coinfected patients
- HIV/HCV epidemiology
  - Approximately 25% of HIV+ patients are coinfected with HCV
  - Approximately 80% of HIV+ patients who inject drugs are coinfected with HCV
  - All patients with HIV infection should be tested for HCV
- HIV+ patients are at 4.1 times the risk of HCV as HIV- patients
Sexual Transmission of HCV Among HIV+ MSM: An Emerging Population

• Reports of epidemic of sexually transmitted HCV among HIV+ MSM
  – United States: 6-fold higher incidence rate in HIV+ vs HIV- MSM
  – Swiss HIV Cohort Study: HCV incidence increased 18-fold from 1998 to 2011
  – Sydney, Australia: 9% of HIV+ MSM coinfectected with HCV vs 1.9% HIV- MSM
  – Amsterdam, Netherlands: HIV/HCV coinfection prevalence increased from 14.6% to 20.9% from 2000-2007

• Phylogenic analysis indicates HCV transmission clusters in some areas[9,10]
Risk Factors for Sexual HCV Transmission Among HIV+ MSM

• Multiple factors associated with HCV transmission
  – Unprotected receptive anal intercourse
  – Online casual sexual partners
  – Sex at sex venues
  – Older age
  – Syphilis
  – Recreational drug use
  – Drinking > 13 alcoholic drinks per week

AASLD/IDSA: When and in Whom to Initiate HCV Therapy

• **ALL** pts are candidates for HCV therapy, regardless of disease stage
• In regions where limited resources preclude treatment of all pts, the following groups should be prioritized for therapy:
  – **Highest Priority** (based on highest risk for disease complications)
    – Advanced fibrosis (F3) or compensated cirrhosis (F4)
    – Organ transplant
    – Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations
    – Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis
  – **High Priority** (based on high risk for disease complications)
    – HIV-1 coinfection
    – Fibrosis (Metavir F2)
    – HBV coinfection
    – Debilitating fatigue
    – Other coexistent liver disease (eg, NASH)
    – Type 2 DM (insulin resistant)
    – Porphyria cutanea tarda
HCV Treatment Improves Health

- **Advanced fibrosis**
  - Multicenter study\(^1\)
    - 5 hospitals (Europe, Canada)
  - 530 pts with HCV
    - IFN regimens 1990-2003
    - Advanced fibrosis or cirrhosis
    - Median follow-up: 8.4 yrs

- **Early-stage disease**
  - Extra-hepatic manifestations\(^2\)
  - Health-related quality of life\(^3\)

---

**10-Yr Cumulative Incidence\(^1\)**

<table>
<thead>
<tr>
<th></th>
<th>SVR</th>
<th>No SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>26</td>
<td>8.9</td>
</tr>
<tr>
<td>Liver-related mortality or transplant</td>
<td>1.9</td>
<td>1.9</td>
</tr>
<tr>
<td>HCC</td>
<td>5.1</td>
<td>21.8</td>
</tr>
</tbody>
</table>

---

Key Data for HCV decisions

• HCV treatment history
  – Interferon and ribavirin regimen?
  – Protease inhibitor? Sofosbuvir?

• Fibrosis stage?
  – Options for fibrosis assessment

http://www.hcvguidelines.org
BACKGROUND

- HCV NS5A inhibitor, 50 mg
- HCV NS3/4A inhibitor, 100 mg

Elbasvir (MK-8742)  Grazoprevir (MK-5172)

- Broad genotypic activity\(^{1-3}\)
- Retains activity against many clinically relevant RAVs\(^{1-3}\)
- All-oral, once-daily regimen

OVERALL CONCLUSIONS

- EBR/GZR has a generally favorable safety profile
  - Very few SAEs or discontinuations
  - Common AEs occurred at a similar frequency on active and placebo
  - RBV-containing regimens were associated with an increase in AEs and drug-related AEs
  - Tolerability was not affected by treatment duration or compensated cirrhosis

- Elevations in ALT from normal levels to >5 x ULN occurred in 0.8% of patients who received EBR/GZR
  - These events generally resolved with continued therapy or scheduled end of therapy
OVERALL CONCLUSIONS

- The safety of EBR (50 mg) with GZR (100 mg) has been evaluated in a large, diverse patient population including patients with Childs Pugh A, compensated cirrhosis

- EBR/GZR, with or without RBV, has a generally favorable safety profile
  - Very few SAEs or discontinuations
  - Common AEs of fatigue, headache, and nausea occurred at a similar frequency on active and placebo treatments
  - RBV-containing regimens were associated with an expected increase in reported AEs and drug-related AEs
  - Tolerability was not affected by treatment duration or compensated cirrhosis

- Elevations of ALT from normal levels to greater than 5 times the upper level of normal occurred in 0.8% of subjects who received EBR/GZR
  - These events generally resolved with continued therapy or scheduled end of therapy
Advantages of Today’s HCV Therapies

• Once-daily dosing
• Shorter duration
• Simpler regimens—no response-guided therapy
• Fewer adverse events
• Interferon-free
• High efficacy
## AASLD Guidance on HIV/HCV DDIs

<table>
<thead>
<tr>
<th></th>
<th>SMV + SOF</th>
<th>SOF</th>
<th>LDV/SOF</th>
<th>DCV + SOF</th>
<th>OBV/PTV/RTV + DSV</th>
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</thead>
<tbody>
<tr>
<td>Atazanavir + RTV</td>
<td>![X]</td>
<td>![✓]</td>
<td>≈</td>
<td>≈</td>
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</tr>
<tr>
<td>Darunavir + RTV</td>
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<td>![✓]</td>
<td>≈</td>
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<td>![X]</td>
</tr>
<tr>
<td>Lopinavir/RTV</td>
<td>![X]</td>
<td>![✓]</td>
<td>≈</td>
<td>![✓]</td>
<td>![X]</td>
</tr>
<tr>
<td>Tipranavir + RTV</td>
<td>![X]</td>
<td>![X]</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>Rilpivirine</td>
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<tr>
<td>Elvitegravir + COBI</td>
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<tr>
<td>Dolutegravir</td>
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<td>Tenofovir DF</td>
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<td>![✓]</td>
<td>≈</td>
<td>![✓]</td>
<td>![✓]</td>
</tr>
</tbody>
</table>

- **No clinically significant interaction expected**
- **Potential interaction may require adjustment to dosage, timing of administration, or monitoring**
- **Do not coadminister**

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*Slide credit: clinicaloptions.com*

MidAtlantic AETC
No Relevant DDIs Between LDV/SOF and E/C/F/TAF or R/F/TAF*

- 2 multiple-dose phase I DDI studies in healthy volunteers

<table>
<thead>
<tr>
<th>GMR for AUC (90% CI)</th>
<th>E/C/F/TAF + LDV/SOF vs E/C/F/TAF</th>
<th>R/F/TAF + LDV/SOF vs R/F/TAF</th>
<th>E/C/F/TAF + LDV/SOF vs LDV/SOF</th>
<th>R/F/TAF + LDV/SOF vs LDV/SOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAF</td>
<td>0.86 (0.78-0.95)</td>
<td>1.32 (1.25-1.40)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>TDF</td>
<td>1.27 (1.23-1.31)</td>
<td>1.75 (1.69-1.81)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>EVG</td>
<td>1.1 (1.0-1.2)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>COBI</td>
<td>1.5 (1.5-1.6)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>RPV</td>
<td>NA</td>
<td>0.95 (0.91-0.98)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>FTC</td>
<td>0.97 (0.93-1.00)</td>
<td>1.00 (0.98-1.02)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>LDV</td>
<td>NA</td>
<td>NA</td>
<td>1.79 (1.63-1.96)</td>
<td>1.02 (0.97-1.06)</td>
</tr>
<tr>
<td>SOF</td>
<td>NA</td>
<td>NA</td>
<td>1.47 (1.35-1.59)</td>
<td>1.05 (1.01-1.09)</td>
</tr>
<tr>
<td>GS-331007</td>
<td>NA</td>
<td>NA</td>
<td>1.48 (1.44-1.53)</td>
<td>1.08 (1.06-1.10)</td>
</tr>
</tbody>
</table>

*Note that RPV/FTC/TAF is not currently approved by the US FDA.


Slide credit: clinicaloptions.com
Other Important Drug–Drug Interactions: Ledipasvir

- Acid-reducing agents: increased gastric pH decreases concentration of ledipasvir
  - Separate antacids (e.g., aluminum and magnesium hydroxide) by 4 hrs
  - H2 blockers can be given at same time or 12 hrs apart at doses equivalent to famotidine 40 mg BID or lower
  - PPIs at doses equivalent to omeprazole 20 mg/day or lower can be given simultaneously under fasted conditions
 Guidance on HCV/HIV DDIs: OBV/PTV/RTV + DSV

• Phase III study of OBV/PTV/RTV + DSV + RBV in HCV/HIV coinfection included pts with ATV or RAL only, pts with DRV being evaluated in ongoing part 1b[1]

• Do not coadminister OBV/PTV/RTV with:[2]
  – DRV (DRV C_{min} decreases 43% to 48%)
  – LPV (PTV AUC increases 117%)
  – ATV/COBI, DRV/COBI, FPV, SQV, TPV, EFV, EVG (no data)
  – RPV (RPV AUC increases 150% to 225%)
  – ETR, NPV (DAA decrease possible)

• Adjust/withhold RTV if receiving a boosted PI with OBV/PTV/RTV + DSV[3]
Take-Home Points

• There has been an increase in injecting drug use in the United States and with it transmission of HCV
• New direct-acting antiviral regimens for treating HCV infection are potent but differ in their potential for drug-drug interactions with antiretroviral agents and other medications
• Treatment of HIV/HCV coinfection may require consideration for the modification of HIV therapy during HCV treatment
Quality Referral Checklist

• Effective counseling and education about Hepatitis C can help motivate patients to see a Hepatitis C Specialist
• Select a specialist with experience in treating Hepatitis C
• Choose a specialist who is conveniently located for the patient
• Assist in scheduling the appointment
• Chart the referral and follow up
**DISCUSSION**

- Project INSPIRE successfully recruited participants from two neighborhoods with the highest rates of HCV in New York City.
- Care coordinators supported participants through medical evaluation and treatment by administering a goal-oriented risk assessment, creating a patient-specific plan, and providing alcohol and harm reduction counseling, health promotion, treatment readiness, treatment adherence, and medication coordination, including prior authorization application.
- The vast majority of participants on 12-week regimens completed treatment.
- There were no differences in treatment initiation rates for participants with or without a history of injection drug or alcohol use or mental illness.
- Participants deemed high-risk initiated treatment at the same rate as low-risk participants.
Summary Points

• The goal of antiviral therapy for Hepatitis C is a sustained virologic response, defined as a negative HCV RNA level 24 weeks after stopping antivirals.

• An SVR is durable, can reverse hepatic inflammation and fibrosis and can reduce the chance of dying from Hepatitis C by 60 to 70%.

• African-Americans may respond at lower rates a difference largely attributable to genetic differences at the IL28B gene locus. Older patients and patients with advanced fibrosis have lower cure rates*
Summary Points

• Patients with more advanced fibrosis have lower response rates to treatment than those with less advanced fibrosis, even when regimens consist of protease inhibitor-based therapy.

• Genotype 1 Hepatitis C infection is the most common type in the United States and requires the most intensive therapy.
Final Thought

IFN-free combination therapy in real-life cohorts has demonstrated high HCV cure rates and good safety. However, ribavirin and longer treatment durations still seem to play a role at least in the more challenging cirrhotic previous treatment non-responders.
Final Thought

Reducing HCV disease burden is possible with a two-pronged effort, where active screening programs find and identify HCV infected individuals and where active management with antiviral therapy is maintained.
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