Hepatitis C in 2015
Primary Care Providers: Linkage to Care

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Disclosures

• I have NO disclosures
• I will talk of Off Label use of drugs (specifically those in pipeline with possible imminent approval).
Primary care providers should be at forefront of expanding access/linkage to care for the HCV epidemic.

Outline

• Epidemiology of HCV and health care impact
• Best practices Screening/surveillance/establish severity of liver disease: HCV infectious disease, AND LIVER disease.
• Review: screening, evaluation of liver disease, testing (diagnosis, genotyping).
• Primer in Drug therapy and monitoring for HCV.
The New Era in HCV Management. Primary Care Management of HCV with All Oral Therapy: As Effective as Specialist Care?

- Chronic HCV infection affects ~5 million in US is leading cause of cirrhosis, liver cancer, liver failure, need for liver transplantation and is leading cause of death in HIV co-infection.

- In the past HCV treatment involved prolonged treatment with toxic oral and injectable agents (Peg-Interferon), with unpleasant and dangerous side effects.

- Since October 2014: the FDA has approved several oral direct acting agents (DAA) that offer short duration curative treatments with minimal side effects.
HCV is Prevalent and Leading Cause of Death and Morbidity

• HCV infects ~ 5 million people in the US today (80% Genotype 1)

• The risk of cirrhosis is 20-40% over a follow-up of 20-40 years

• HCV increases all cause (non-liver) mortality (it is a systemic disease)

• HCV is a leading cause of Hepatocellular Cancer (the #2 cause of cancer death world-wide)
HCV Basics

- Incubation 6 - 26 weeks
- Mild to severe acute hepatitis in 70-80% or asymptomatic
- Chronic in 75-85%
- No Vaccine

- Genotypes (6 Major) differ geographically.
- Different Responses to treatment
- Genotype 1 is most common in US
Chronic HCV Infection Affects Many Sites Beyond the Liver

- Neurological (e.g. cognitive impairment)
- Pulmonary fibrosis
- Renal (e.g. glomerulonephritis)
- Lymphoproliferative (e.g. B cell lymphoma)
- Dermatological (e.g. porphyria cutanea tarda)
- Cardiovascular Diseases (CAD)
- Metabolic (e.g. diabetes)
- Autoimmune (e.g. cryoglobulinemic)
Healthcare Costs will Continue rise Due to ESLD Despite Declining HCV Incidence

Razavi et al HEPATOLOGY 2013;57:2164-2170
Increasing Use of High SVR Therapy (~ 90%) Will Eliminate HCV in the US by 2029

HCV is associated with increased ALL-CAUSE Mortality

And Liver related mortality
And Liver cancer mortality
Sustained Viral Response ((SVR) = Cure) is Associated with Reduced Liver AND ALL-CAUSE Mortality Among HCV Infected Persons

530 patients with advanced fibrosis, treated with interferon-based therapy, and followed for 8.4 (IQR 6.4-11.4) years

van der Meer et al. JAMA 2012; 308:2584
Access to care US: 50% Unaware of Infection and <15% treated


Scott D. Holmberg, M.D. Hepatitis C in the United States
N Engl J Med 368;20, 2013
HCV: Best Practices.

• **Whom to test** for HCV? (and surveillance) - CDC and USPTF
• **How to test**: HCV Ab, HCV RNA (special testing)
• **General measures** and education.
• **How to evaluate** the patient? (HCV and liver aspects)
• **Whom to treat** and when to initiate treatment.
HCV transmission (Whom to Test)

- HCV is primarily transmitted through percutaneous exposure to blood.
  - Blood products < 1992, Tattoos, clotting factors < 1987, Hemodialysis, needle sticks in HCW, shared needles with Injection drug use, shared straws with nasal drug use, Incarceration, health care with poor infection control

- Other modes of transmission include
  - mother-to-infant
  - contaminated devices shared for non-injection drug use;
  - sexual transmission (inefficient except among HIV-infected men who have unprotected sex with men. (Schmidt, 2014)
Whom to test

- **HCV testing is recommended at least once for persons born between 1945 and 1965.** (~10% prevalence and >70% of all cases)
- **One-time testing:** all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection.
  - 1. *Risk behaviors* Injection-drug use (current or ever, including those who injected once) Intranasal illicit drug use, MSM
  - 2. *Risk exposures*
    - Long-term hemodialysis (ever) Tattoo
    - Healthcare, emergency medical, and public safety (after needle sticks, sharps, or mucosal exposures to HCV-infected blood)
    - Children born to HCV-infected women
    - Prior recipients of transfusions or organ transplants, before July 1992
    - received clotting factor concentrates produced before 1987
    - were ever incarcerated
  - 3. *Other medical conditions*
    - HIV infection
    - Unexplained chronic liver disease and chronic hepatitis including elevated alanine aminotransferase levels
    - Organ donors
BPA for Hepatitis C Screening at UIHC: Alerts Fired vs Tests Ordered (Burstain et al)

**Alerts Vs Orders**

<table>
<thead>
<tr>
<th></th>
<th>Distinct Patients</th>
<th>Screening Done</th>
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<tbody>
<tr>
<td>Inpatient</td>
<td>3191</td>
<td>742</td>
</tr>
<tr>
<td>Outpatient</td>
<td>9658</td>
<td>2640</td>
</tr>
<tr>
<td>Total</td>
<td>12204</td>
<td>3213</td>
</tr>
</tbody>
</table>

**Response Rate**

- Inpatient: 0.23
- Outpatient: 0.27
- Total: 0.26
Testing algorithm

- **Antibody Test: 3rd Generation EIA (CIA)**

- **HCV-RNA for**
  - Early acute HCV (False neg Ab)
  - Immunocompromized (including dialysis) (False neg Ab)
  - Re-infection (+ Ab not-informative)

EIA: Enzyme Linked Immunoassay
CIA: Chemiluminescence Linked Immunoassay
HCV Rapid Antibody Test

- OraQuick HCV is a new diagnostic tool to screen at risk patients for Hepatitis C
  - Clinical performance
    - Similar to lab results
    - Detects antibodies 3.6 days earlier than EIA
  - Results in 20 minutes
    - Done onsite
    - NO special lab equipment required
  - Medicare Reimbursable
    - Current Status: Moderately Complex; CLIA-waiver pending
Steps for Fingerstick or Venipuncture Specimen Collection

Collect

or

Mix

Read
Take Home Point #1:

- Screen patients WITH RISK FACTORS and
- Screen by Birth Cohort: Baby Boomers (1945-1965)
HCV-linkage to care: Education and intervention

1. Intervention to reduce progression of liver disease and prevent transmission of HCV.
   1. Abstinence /cessation of alcohol consumption (Obesity?)
   2. Evaluate for comorbidities EG HBV and HIV infections, that could accelerate fibrosis

2. Evaluation for advanced fibrosis using liver biopsy, imaging, or non-invasive markers to facilitate decision making regarding HCV treatment and to determine the need for initiating additional screening measures (eg, hepatocellular carcinoma [HCC] screening).

3. Vaccination against hepatitis A and hepatitis B, pneumonia

4. Education on how to avoid HCV transmission to others.

5. Evaluation by a practitioner who is prepared to provide comprehensive management, including consideration of antiviral therapy, is recommended for all persons with current (active) HCV infection.
Linkage to Care: Assessing Severity/fibrosis

• The severity of fibrosis is THE key factor in determining management.
• Patients more advanced disease
  • lower response to HCV therapy,
  • BUT derive the greatest survival benefit. (Ghany, 2011) A
• Liver biopsy:
  • objective, semi-quantitative fibrosis score;
  • Liver inflammation,
  • steatosis, and
  • exclude competing causes of liver injury. (Kleiner, 2005).
Limitations of Liver Biopsy

- Invasive
  - Morbidity (3/1,000)
  - Mortality (3/10,000)
- Costly-$1500
- Patient reluctance
- Contraindications
- Observer variability
  - Concordance 80%
  - Sampling error
    - 1/50,000th of the liver
    - 33% discordance of 1 stage

Regev A. Am J Gastro. 2002
Alternatives to Liver biopsy

- **APRI score** = \((\frac{AST}{40})/Plts*100\)
- **Fib-4 score** = \((\frac{AST*Age}{Plts*\sqrt{ALT}})\)
- **Fibrosure** – blood test
- **Fibroscan**: blind elastic recoil US
- **US** (enhanced shear wave) – augmented U/S test
- **MRE** – Magnetic Resonance Elastography

(http://www.hepatitisc.uw.edu/page/clinical-calculators/apri)
Shear Wave Elastography

- Supersonic Elastance (stiffness)
- Combined elasticity + lab (platelet and GGT) score AUROC=0.93

Friedrich-Rust et al AJR 2007
Fibrosis/Cirrhosis: Rule of 12:

- Spleen >12 cm
- Portal Vein > 12 mm diameter
- Platelets < $12^2 \text{ K}$ (144)
Take Home Point # 2

• Every patient MUST have assessment of Severity of Liver Disease (Bx or non invasive)

• Provide the Link to CARE
  • Education and prevention
  • Comorbidities
  • Public Health
  • Immunization
Treatment

http://www.hcvguidelines.org/

Recommendations for Testing, Managing, and Treating Hepatitis C
Quantum Change: CURE; 8-12 wks.
Minimal Side Effects

Adapted from the US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring, MD.
SVR 12 is ND HCV RNA at 12 wks equivalent to SVR at 24 weeks
FDA NEWS RELEASE
For Immediate Release: Nov. 22, 2013
Media Inquiries: Stephanie Yao, 301-796-0394, stephanie.yao@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

Simeprevir (Olysio) 11/5/2013

FDA NEWS RELEASE
For Immediate Release: Dec. 6, 2013
Media Inquiries: Stephanie Yao, 301-796-0394, stephanie.yao@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

Sofosbuvir (Sovaldi) 12/6/2013

FDA NEWS RELEASE
For Immediate Release: October 10, 2014

Ledipasvir-Sofosbuvir Harvoni 10/10/2014

FDA NEWS RELEASE
For Immediate Release: December 19, 2014

FDA Approves Olysio (simeprevir) in Combination with Sofosbuvir for Genotype 1 Chronic Hepatitis C Infection

FDA approves first combination pill to treat hepatitis C

FDA approves Viekira Pak to treat hepatitis C
Treatment: Depends on Efficacy (genotype specific); Tolerability and Cost (and don’t fall into traps (Drug Drug Interactions).

• How to treat: Updated frequently. http://www.hcvguidelines.org/
  • Treatment differs according to genotype.


• Majority of patients will be treatment inexperienced with no cirrhosis or HIV.
Hard to Treat Groups and Special Populations Should Include Expertise To Manage All Aspects Of Care

- Prior Treatment failures
- Cirrhosis
- Decompensated cirrhosis
- Renal Failure
- HCV/HIV co-infection
- Post-Liver Transplantation
- Cirrhosis with Hepatocellular Cancer
Treatment Tips and Tricks

• Use “oral-only” treatment
  • Harvoni (Sofosbuvir-Ledipasvir)
  • Viekera (Paritaprevir/rotinavir- Ombitasvir-Dasabuvir)
  • Ribavirin
  • (Simeprevir-Olysio)

• All the Oral-Only regimens have similar efficacy (> 90%) in standard patients

• Serious Adverse events (< 1%) and when present AEs mostly due to ribavirin
  • Ribavirin: Rash and anemia
  • DDI- Headache/fatigue (20%) Nausea, diarrhea (8-10%)
Factors that make patients respond progressively less well to treatment

- **Viral:** GT 3 > 4 > 1a > 1b > 2
- **Host:** Cirrhosis > no cirrhosis
- **RxF:** Sofosbuvir > telaprevir/boceprevir > Peg-Riba

HARD to Rx | EASY to Rx
Drug Interactions for DAAs – (not including Rotinovir in Viekera)

- Amiodarone- bradycardia (deaths)
- St Johns wort
- Rifampin
- PPI and acid reducing agents- reduce LDV absorption
- Statins- Rosuvastatin not recommended. Reduced dose other PPIs (increased absorption via p-glycoprotein mechanism)
- Seizure Meds-contraindicated
- Digoxin: may increase levels
- ARVs: Most okay: always check
Initial Treatment Genotype 1a or 1b
Treatment Naive

• 12 weeks Harvoni OR
• 12 weeks Viekira OR
• 12 weeks SIM-SOF
Initial Treatment Genotype 1a/1b

- Daily Harvoni (ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks)
- Daily Vikiera (paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks).
- Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks (no cirrhosis).
$94,500

Sovaldi costs $1,000 a pill, or $84,000 for a typical 12-week course of treatment, but it must be used with other drugs. Harvoni is even more expensive at $1,125 a pill, or $94,500 for a 12-week course of treatment. Oct 10, 2014

Harvoni, a Hepatitis C Drug From Gilead, Wins FDA Approval
www.nytimes.com/.../harvoni-a-hepatitis-c-drug-from...

$83,320

The wholesale acquisition cost of twelve weeks of Viekira Pak is $83,320, plus the cost of ribavirin (around $2500 for 12 weeks). Patients needing 24 weeks of treatment, with a price tag of $157,640 plus the cost of ribavirin (around $5000 for 12 weeks). Dec 22, 2014

AbbVie’s Viekira Pak: What You Need to Know about the ...
blogs.hepmag.com/lucindakporter/2014/12/abbvies_viekira_pak.html
ION 1, 2, and 3: Sofosbuvir/Ledipasvir ± RBV in Tx-Naive Pts and Previous Failures

- 8 wks adequate for noncirrhotic treatment-naive pts
- RBV provides no benefit
- No SOF resistance observed; most virologic failures have LDV resistance

# Sofosbuvir-Ledipasvir Fixed-Dose Combination +/- RBV: ION-1, ION-2, and ION-3

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Treatment</th>
<th>Duration</th>
<th>SVR 12 Rates</th>
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</thead>
<tbody>
<tr>
<td>ION-1*</td>
<td>GT-1</td>
<td>LDV/SOF</td>
<td>12 weeks</td>
<td>99% (211/214)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV</td>
<td>12 weeks</td>
<td>97% (211/217)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF</td>
<td>24 weeks</td>
<td>98% (212/217)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV</td>
<td>24 weeks</td>
<td>99% (215/217)</td>
</tr>
<tr>
<td>ION-2^</td>
<td>GT-1</td>
<td>LDV/SOF</td>
<td>12 weeks</td>
<td>94% (102/109)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV</td>
<td>12 weeks</td>
<td>96% (107/111)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF</td>
<td>24 weeks</td>
<td>99% (108/109)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV</td>
<td>24 weeks</td>
<td>99% (110/111)</td>
</tr>
<tr>
<td>ION-3^</td>
<td>GT-1</td>
<td>LDV/SOF</td>
<td>8 weeks</td>
<td>94% (202/215)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV</td>
<td>8 weeks</td>
<td>93% (201/216)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF</td>
<td>12 weeks</td>
<td>95% (206/216)</td>
</tr>
</tbody>
</table>

### “AbbVie 3D Regimen”

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment Regimen</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PEARL-II</strong></td>
<td>GT1b treatment-experienced (N=179)</td>
<td>AbbVie regimen* + RBV (n=88)</td>
<td>97% (85/88)</td>
</tr>
<tr>
<td>(12 weeks)</td>
<td></td>
<td>AbbVie regimen* only (n=91)</td>
<td>100% (91/91)</td>
</tr>
<tr>
<td><strong>PEARL-III</strong></td>
<td>GT1b treatment-naive (N=419)</td>
<td>AbbVie regimen* + RBV (n=210)</td>
<td>99% (209/210)</td>
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<tr>
<td>(12 weeks)</td>
<td></td>
<td>AbbVie regimen* only (n=209)</td>
<td>99% (207/209)</td>
</tr>
<tr>
<td><strong>PEARL-IV</strong></td>
<td>GT1a treatment-naive (N=305)</td>
<td>AbbVie regimen* + RBV (n=100)</td>
<td>97% (97/100)</td>
</tr>
<tr>
<td>(12 weeks)</td>
<td></td>
<td>AbbVie regimen* only (n=205)</td>
<td>90% (185/205)</td>
</tr>
<tr>
<td><strong>TURQUOISE-II</strong></td>
<td>GT1 treatment-naive and treatment-experienced w/ compensated cirrhosis (N=380)</td>
<td>AbbVie regimen* + RBV, 12 weeks (n=208)</td>
<td>92% (191/208)</td>
</tr>
<tr>
<td>(12 &amp; 24 weeks)</td>
<td></td>
<td>AbbVie regimen* + RBV, 24 weeks (n=172)</td>
<td>96% (165/172)</td>
</tr>
<tr>
<td><strong>SAPPHIRE-I</strong></td>
<td>GT1 treatment-naive (N=631)</td>
<td>AbbVie regimen* + RBV (n=473)</td>
<td>96% (455/473)</td>
</tr>
<tr>
<td>(12 weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SAPPHIRE-II</strong></td>
<td>GT1 treatment-experienced (N=394)</td>
<td>AbbVie regimen* + RBV (n=297)</td>
<td>96% (286/297)</td>
</tr>
</tbody>
</table>

* AbbVie Regimen = ABT-450/r/Ombitasvir (150/100/25 mg QD) plus Dasabuvir (250 mg BID)
Genotype 1a is less susceptible than 1b, and Cirrhosis makes both less susceptible.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Noncirrhotic</th>
<th>Compensated Cirrhotic</th>
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<tr>
<td></td>
<td>Regimen</td>
<td>Duration, Wks</td>
</tr>
<tr>
<td>GT1a or 1b</td>
<td>LDV/SOF</td>
<td>12*</td>
</tr>
<tr>
<td>GT1a</td>
<td>OMV/PTV/RTV + DSV + RBV</td>
<td>12</td>
</tr>
<tr>
<td>GT1b</td>
<td>OMV/PTV/RTV + DSV</td>
<td>12</td>
</tr>
<tr>
<td>GT1a</td>
<td>SMV + SOF ± RBV</td>
<td>12</td>
</tr>
<tr>
<td>GT1b</td>
<td>SMV + SOF</td>
<td>12</td>
</tr>
</tbody>
</table>
HCV 1a/1b with prior failed treatment are yet more difficult to treat: Increase duration or add ribavirin

<table>
<thead>
<tr>
<th>Population</th>
<th>Noncirrhotic</th>
<th>Compensated Cirrhotic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regimen</td>
<td>Duration, Wks</td>
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<tr>
<td>Prior PegIFN/RBV</td>
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<tr>
<td>• GT1a or 1b</td>
<td>LDV/SOF</td>
<td>12</td>
</tr>
<tr>
<td>• GT1a or 1b</td>
<td>LDV/SOF + RBV</td>
<td>12</td>
</tr>
<tr>
<td>• GT1a</td>
<td>OMV/PTV/RTV + DSV + RBV</td>
<td>12</td>
</tr>
<tr>
<td>• GT1b</td>
<td>OMV/PTV/RTV + DSV</td>
<td>12</td>
</tr>
<tr>
<td>• GT1a or 1b</td>
<td>SMV + SOF ± RBV</td>
<td>12</td>
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<tr>
<td>Prior SOF</td>
<td></td>
<td></td>
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<tr>
<td>• GT1a or 1b</td>
<td>Defer therapy*</td>
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<tr>
<td>Prior PI</td>
<td></td>
<td></td>
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<tr>
<td>• GT1a or 1b</td>
<td>LDV/SOF</td>
<td>12</td>
</tr>
<tr>
<td>• GT1a or 1b</td>
<td>LDV/SOF + RBV</td>
<td>12</td>
</tr>
</tbody>
</table>
Genotype 2

• Sofosbuvir + Ribavirin for 12 weeks (or 16 weeks in cirrhosis)

Genotype 3

• Sofosbuvir + WB Ribavirin for 24 weeks.
HCV-GT4: recommendations are based on limited data

- LDV/SOF for 12 wks
- OMV/PTV/RTV + RBV for 12 wks
- SOF + RBV for 24 wks
  - Recommended in treatment-experienced and as alternative for treatment-naive pts: SOF + RBV + pegIFN for 12 wks
  - Alternative for treatment-naive pts: SOF + SMV ± RBV for 12 wks
Key Monitoring Guidance

• Before treatment
  • Degree of hepatic fibrosis by noninvasive testing or by biopsy
  • Potential drug–drug interactions (hep-druginteractions.org)

• After treatment
  • If pretreatment Metavir ≥ F3 ultrasound for HCC every 6 mos

• Before and during treatment
  – HCV RNA before treatment and at Wk 4
    – If detectable at Wk 4, assess again at Wk 6 only
  – ALT before treatment and at Wk 4
    – If elevated at Wk 4, assess again at Wk 6 and Wk 8
Summary

• HCV treatment is relatively simple and easy to do.
• Screen by Risk factor and Birth Cohort.
• Remember to look for the LIVER DISEASE.
• Linkage to care: immunizations, prevention, public health measures
• Each Genotype has its own treatment. Just look it up if you cannot remember (.  http://www.hcvguidelines.org)
• Check for Drug-Drug Interactions
• Monitor