HCV Case Studies and Special Populations

Svenja J. Albrecht, MD MPH
April 29, 2018
Case 1: Diagnosis and Initial Management

• 58 y/o male during routine follow up in primary care inquires about HCV screening.

• Upon further questioning, he reports the following:
  • Recently tested for HIV (negative)
  • No history of liver disease or abnormal liver enzymes
  • Married for 9 years, no history of STDs, no history of sex with men
  • Remote history of intranasal cocaine and inhaled marijuana, but never IVDU
  • No history of blood transfusion or hemodialysis
  • Has one pierced ear that was done 5 years ago in professional shop
  • Has one tattoo that was done in prison 12 years ago
Menti Question #1

All of the following are correct EXCEPT:

A. Even without additional risk factors, his age alone would be an indication for screening
B. His history of incarceration is an indication for screening
C. His drug use is NOT an indication for screening since it was not IV
D. His piercing is NOT an indication for screening since it was in a regulated setting
E. His tattoo is an indication for screening since it was done in prison
Hepatitis C Prevalence is Increased in Baby Boomers

Prevalence of Hepatitis C Antibody Positivity in US Population by Sex by Yr of Birth (NHANES III)[1]
CDC, USPSTF, and AASLD/IDSA HCV Screening Recommendations

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>One-time screening is recommended for persons born between 1945 and 1965 (&quot;baby boomers&quot;), without HCV risk(^{[1-3]}) highest age cohort prevalence (6% men)</td>
</tr>
<tr>
<td>Risk</td>
<td>One-time screening is recommended for persons with these risk factors(^{[1,3]}):</td>
</tr>
<tr>
<td></td>
<td>- History of illicit injection drug use (IDU) or <strong>intranasal illicit drug use</strong></td>
</tr>
<tr>
<td></td>
<td>- History of long-term hemodialysis</td>
</tr>
<tr>
<td></td>
<td>- Receiving a tattoo in an unregulated facility/setting</td>
</tr>
<tr>
<td></td>
<td>- Healthcare workers upon accidental exposure</td>
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<tr>
<td></td>
<td>- Children born to anti-HCV–positive mothers</td>
</tr>
<tr>
<td></td>
<td>- History of transfusion with blood or organ transplantation</td>
</tr>
<tr>
<td></td>
<td>- <strong>Were ever in prison</strong></td>
</tr>
<tr>
<td></td>
<td>- HIV infection</td>
</tr>
<tr>
<td></td>
<td>- Chronic liver disease/hepatitis with unknown cause, including elevated liver enzymes</td>
</tr>
</tbody>
</table>

**Annual screening is recommended for current IDUs and HIV-infected MSM\(^{[3]}\)**

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Menti Question #2

His HCV antibody returns positive. His liver enzymes are completely normal. What do you recommend next?

A. No further testing unless he develops abnormal liver tests
B. Fibrosure and if abnormal, check HCV RNA
C. Fibroscan or ultrasound elastography and if abnormal, check HCV RNA
D. Confirmatory testing with recombinant immunoblot assay (RIBA) now
E. Confirmatory testing with HCV RNA now
Recommended Testing Sequence for Identifying HCV

1. HCV antibody test
   - Reactive
     - HCV RNA test
       - Detected
         - Current HCV infection
           - Provide care or link to care
       - Not detected
         - No current HCV infection
   - Nonreactive
     - Stop

Rapid tests or EIA Ab (20% spontaneously clear)

Qualitative or quantitative Viral load/PCR to confirm chronic HCV is adequate

Will need quantitative PCR and genotype to determine optimal therapy

PCR for diagnosis of acute HCV or for reinfection screening in prior Ab positive

Menti Question #3

His HCV RNA returns at 1,230,000. He feels well and his ROS is negative except for occasional fatigue, chronic LBP and multiple “joint aches”, and seasonal allergies. Since he has no liver related symptoms, he wants to know how else HCV may affect his body. You tell him that HCV has been associated with an increased risk for all of the following EXCEPT:

A. Fatigue and polyarthralgias
B. Allergic rhinitis and seasonal allergies
C. Insulin resistance and Type 2 DM
D. Chronic kidney disease
E. Hypertension and CHF.
Liver Complications Due to HCV Are Continuing to Increase

• Approximately 45% of untreated HCV patients are projected to develop cirrhosis by 2030²

• Patients who develop cirrhosis are at greater risk for developing liver cancer and other liver-related complications³ (even after SVR)

• Over 40% of all liver transplants in US are for HCV

• 50-60% all HCC is 2/2 HCV

• Median life expectancy with HCV = 57 years (20 years less than average US life expectancy)⁴

• Annual deaths from HCV surpassed mortality from 60 other infectious diseases combined (including HIV, pneumococcal disease, and TB) in 2013⁵

HCV Is a Systemic Disease that May Affect Organs Other than the Liver\textsuperscript{1-16}

**Extrahepatic Manifestations**

1. Mixed cryoglobulinemia vasculitis
2. Lymphoproliferative disorders
3. Peripheral neuropathy\textsuperscript{a}
4. Membranoproliferative glomerulonephritis\textsuperscript{a}
5. Insulin resistance
6. Cutaneous manifestations (eg, lichen planus, porphyria cutanea tarda, palpable purpura\textsuperscript{a})

\textsuperscript{a}Secondary to mixed cryoglobulinemia vasculitis
HCV May Increase Risk for Diseases and Conditions Outside the Liver\textsuperscript{1-16}

Associated Extrahepatic Conditions

**INCREASED RISK FOR:**

1. Depression
2. Carotid atherosclerosis/atherothrombosis
3. Type 2 diabetes mellitus
4. Hypertension
5. Congestive heart failure
6. Chronic kidney disease

**POSSIBLE INCREASED RISK FOR\textsuperscript{b}:**

10. Neurologic impairment/disorders
11. Coronary artery disease/ischemic heart disease

\textsuperscript{a}Secondary to mixed cryoglobulinemia vasculitis
\textsuperscript{b}Conflicting or equivocal data from studies

- End-stage renal disease
- Kidney cancer
- Other renal manifestations (e.g., glomerulonephritis, proteinuria)\textsuperscript{a}
- Low bone mineral density (BMD)
- Rheumatologic manifestations (e.g., polyarthralgia, polyarthritis)\textsuperscript{a}
- Fatigue

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HCV Virologic Cure Associated With Improved Outcomes


HR: 0.26 (95% CI: 0.14-0.49; P < .001)
Menti Question #4

He is interested in further evaluation for his HCV. You tell him that you will need to run some additional blood tests and stage his degree of liver fibrosis. Pending those results, you advise him at this time about all the following EXCEPT:

A. Counsel him to avoid alcohol
B. Counsel him to use condoms with his wife
C. Counsel him to avoid sharing his razors or toothbrushes
D. Counsel him that he may need vaccination for Hepatitis A/B
E. Counsel him that he may need vaccination for Pneumococcus
Initial Management for HCV-Infected Individuals

Prevent Hepatitis C Transmission

- Avoid sharing toothbrushes, dental, shaving equipment
- Prevent blood contact; do not donate blood
- Avoid illicit drugs; avoid reusing or sharing drug paraphernalia
- Risk of sexual transmission is low, except for people with HIV, multiple partners, or STIs

Reduce Progression of Liver Disease

- Test for conditions that accelerate fibrosis
  - Hepatitis B and HIV infections
- Evaluate for advanced fibrosis
- Update vaccinations (A/B all, pneumococcal if cirrhotic)
- Avoid alcohol

- Even if not ready for therapy, strongly suggest expert referral or perform counseling, vaccination, fibrosis assessment
- Liver synthetic function tests: AST/ALT, platelets, albumin, tbili, renal function, +/- coags, biopsy or non-invasive staging
  - Baseline ultrasound if F3/F4
  - Low platelets (<100K): Screening EGD for varices

Key Resource: “Pre-treatment Evaluation” check sheet

AASLD-IDSA. HCV Guidelines 2016  Slide modified from CCO
Menti Question #5

Your orders at this visit would likely include all of the following EXCEPT:

A. HBsAg, HBsAB +/- HBcAB
B. HAV IgG or Total Ab
C. HCV genotype
D. Referral for liver biopsy staging
E. Referral for Fibroscan +/- ultrasound elastography staging
HCV Treatment:
Variables that Mainly Determine Treatment Selection

- HCV genotype?
- Presence of cirrhosis?
- Previous HCV therapy?

Helps tailor:
- Treatment options
- Treatment duration
- Need for ribavirin

Other major determinants: Renal function (especially GFR <30; Co-administered medications;
Baseline resistance associated sequences (RAVs) in certain circumstances

Key Resource: www.hcvguidelines.org; modified from CCO
Fibrosis Staging in Hepatitis: What You Need to Know

- **Assess whether pt has advanced disease**
  - **Metavir Stage 0-2**
    - No fibrosis or portal fibrosis
  - **Metavir Stage 3-4**
    - Advanced fibrosis or cirrhosis

- **Monitor for progressive fibrosis**
  - Noninvasive strategies or biopsy
    - APRI (AST platelet ratio index), FIB-4, *FibroSure*
    - *FibroScan*, ultrasound with pSWE

**Determines:**
- Treatment duration
  - Use of ribavirin
- Follow-up after cure

Also: Don’t use NS3 Protease inhibitor (paritaprevir, simeprevir, grazoprevir) with h/o decompensation or CTP 7 or greater; avoid paritaprevir in CTP 5-6 unless close monitoring possible.
Case 2: Treatment Selection

• A 36 y/o Caucasian female with no comorbidities and on no medications is referred after release from drug rehab where she tested positive for HCV. She has never been treated for HCV and has the following results:
  • HIV negative, HBV sAg/cAB/sAB negative, HAV AB negative
  • HCV VL 6,500,000, genotype 1A, RAS testing negative
  • Fibrosure F0, Fibroscan F0-1
  • CBC, BMP, LFTs unremarkable

• You have administered A/B vaccine. She has been abstinent from all drugs and alcohol for 6 months, is not currently sexually active, and wishes to pursue treatment for HCV.
Menti Question #6

Assuming no payer/formulary restrictions, all of the following would be first line regimens (as recommended by AASLD/IDSA guidelines) EXCEPT:

A. LDV/SOF (Harvoni) for 8 weeks
B. GLE/PIB (Mavyret) for 8 weeks
C. SOF/VEL (Epclusa) for 12 weeks
D. PrOD (Viekira XR) for 12 weeks
E. EBR/GZR (Zepatier) for 12 weeks
Where HCV Therapy Stands Now

- Treatment is recommended for all patients with HCV except those with a short life expectancy (from non-liver related causes)
  - Cost and access issues persist but improving
- Long injectable therapy with AEs and frequent monitoring are no longer the case
  - Interferon is gone in the US; ribavirin . . . not quite but mostly
  - Current DAAs extremely well tolerated. Mild headache common with SOF; fatigue with most regimens
  - Anemia may still be concern if RBV needed
- SVR in > 95% of pts with current regimens for most patients
  - Confidence that SVR12 = cure
  - Late relapse beyond 12 wks after EOT exceedingly rare
- “Difficult-to-cure” populations no longer difficult
  - Black race
  - HIV coinfection
  - Cirrhosis
  - Genotype 3
  - Renal disease
- DAA failures were challenge until last year
Approved DAAs From Multiple Classes:

Structural Domain

5'UTR

Core E1 E2 P7 NS2

Nonstructural Domain

3'UTR

NS3 NS4A NS4B NS5A NS5B

Protease

Grazoprevir (GZR)
Paritaprevir/Ritonavir (PTV/RTV)
Simeprevir (SMV)

Protease Inhibitors

E1 E2 P7 NS2

Replication Complex Inhibitors

Daclatasvir (DCV)
Elbasvir (EBR)
Ledipasvir (LDV)
Ombitasvir (OBV)
Velpatasvir (VEL)

NS5A Replication Complex Inhibitors

Sofosbuvir (SOF)

NS5B NUC Inhibitors

Dasabuvir (DSV)

NS5B Non-NUC Inhibitors (NNI)

Ribavirin (RBV)

Polymerase

Voxilaprevir (VOX) in Vosevi
Glecaprevir (GLE) in G/P (Mavyret)

Pibrentasvir (PIB) in G/P

ǁ
Many Options: AASLD/IDSA -Recommended Regimens for HCV as of September 2017

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Approved Genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grazoprevir/elbasvir*</td>
<td>1, 4</td>
</tr>
<tr>
<td>Sofosbuvir/ledipasvir</td>
<td>1, 4, 5, 6</td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir</td>
<td>1, 2, 3, 4, 5, 6</td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir/voxilaprevir (recently approved)</td>
<td>1, 2, 3, 4, 5, 6</td>
</tr>
<tr>
<td>Glecaprevir/pibrentasvir* (recently approved)</td>
<td>1, 2, 3, 4, 5, 6</td>
</tr>
</tbody>
</table>

*Approved in advanced renal insufficiency and dialysis.

- Single- or 3-tablet coformulations, all with daily dosing
- For every genotype, there is an effective treatment
- Newest treatments effective for all genotypes, with cure rates of 95% or higher, even without ribavirin

Additional regimens exist as alternative regimens.
### AASLD Recommended HCV Treatments: DAA-Experienced Patients

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>Previous NS3/4A Experience</th>
<th>Previous NS5B Experience</th>
<th>Previous 1a</th>
<th>Regimen</th>
<th>Treatment Duration</th>
<th>Regimen</th>
<th>Treatment Duration</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GLE/PIB, SOF/LDV, SOF/VEL</td>
<td>GLE/PIB, SOF/LDV, SOF/VEL</td>
<td></td>
<td>GLE/PIB</td>
<td>12 wks</td>
<td>SOF/VEL</td>
<td>12 wks</td>
<td>SOF/VEL</td>
</tr>
<tr>
<td>2</td>
<td>GLE/PIB, SOF/VEL</td>
<td>GLE/PIB, SOF/VEL</td>
<td></td>
<td>GLE/PIB</td>
<td>12 wks</td>
<td>SOF/VEL</td>
<td>12 wks</td>
<td>SOF/VEL</td>
</tr>
<tr>
<td>3, 4, 5, 6</td>
<td>SOF/VEL, VEL</td>
<td>SOF/VEL, VEL</td>
<td></td>
<td>SOF/VEL</td>
<td>12 wks</td>
<td>SOF/VEL</td>
<td>12 wks</td>
<td>SOF/VEL</td>
</tr>
</tbody>
</table>

*Not recommended if also cirrhotic. *Not recommended if genotype 1a. *Not recommended if genotype 1b. If also compensated.

### AASLD Recommended HCV Treatments: DAA-Naive Patients

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>No Cirrhosis</th>
<th>Compensated Cirrhosis</th>
<th>eGFR &lt; 30 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regimen</td>
<td>Treatment Duration</td>
<td>Regimen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>GLE/PIB</td>
<td>8 wks</td>
<td>GLE/PIB</td>
</tr>
<tr>
<td></td>
<td>GRZ/ELB, SOF/VEL</td>
<td>12 wks</td>
<td>GRZ/ELB</td>
</tr>
<tr>
<td>2</td>
<td>GLE/PIB</td>
<td>8 wks</td>
<td>GLE/PIB</td>
</tr>
<tr>
<td></td>
<td>SOF/VEL</td>
<td>12 wks</td>
<td>SOF/VEL</td>
</tr>
<tr>
<td>3</td>
<td>GLE/PIB</td>
<td>8 wks</td>
<td>GLE/PIB</td>
</tr>
<tr>
<td></td>
<td>SOF/VEL</td>
<td>12 wks</td>
<td>SOF/VEL</td>
</tr>
<tr>
<td>4</td>
<td>GLE/PIB</td>
<td>8 wks</td>
<td>GLE/PIB</td>
</tr>
<tr>
<td></td>
<td>GRZ/ELB, SOF/VEL</td>
<td>12 wks</td>
<td>GRZ/ELB</td>
</tr>
</tbody>
</table>

*If pegIFN/RBV naive, nonblack, no HIV, and HCV RNA < 6 million IU/mL. Otherwise, increase to 12 weeks. *Not recommended if both genotype 1a and baseline NS5A resistance to ELB detected. *If also cirrhotic, increase to 12 weeks. *Not recommended if pegIFN/RBV experienced. *Not recommended if pegIFN/RBV naive. *If pegIFN/RBV experienced, must have experienced virologic relapse after pegIFN/RBV.

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**Downloadable Resources**

Treatment-naive

- Initial Treatment of HCV infection
- Treatment-naive Genotype 1
- Treatment-naive Genotype 1a Without Cirrhosis
- Treatment-naive Genotype 1a with Compensated Cirrhosis
- Treatment-naive Genotype 1b Without Cirrhosis
- Treatment-naive Genotype 1b with Compensated Cirrhosis
- Treatment-naive Genotype 2
- Treatment-naive Genotype 2 Without Cirrhosis
- Treatment-naive Genotype 2 with Compensated Cirrhosis
- Treatment-naive Genotype 3
- Treatment-naive Genotype 3 Without Cirrhosis
- Treatment-naive Genotype 3 with Compensated Cirrhosis
- Treatment-naive Genotype 4
- Treatment-naive Genotype 4 Without Cirrhosis
- Treatment-naive Genotype 4 with Compensated Cirrhosis
- Treatment-naive Genotype 5 or 6

Treatment-experienced

- Retreatment of Persons in Whom Prior Therapy Has Failed
- Treatment-experienced Genotype 1
- PEG-IFN/Ribavirin Experienced, Genotype 1a Patients Without Cirrhosis
- PEG-IFN/Ribavirin Experienced, Genotype 1a Patients with Compensated Cirrhosis
- PEG-IFN/Ribavirin Experienced, Genotype 1b Patients Without Cirrhosis
- PEG-IFN/Ribavirin Experienced, Genotype 1b Patients with Compensated Cirrhosis
- NS3 PI + Peg-IFN/Ribavirin Experienced, Genotype 1 Patients Without Cirrhosis
- NS3 PI + Peg-IFN/Ribavirin Experienced, Genotype 1 Patients with Compensated Cirrhosis
- NS5A Experienced Genotype 1 Patients
- Simeprevir Plus Sofosbuvir Experienced, Genotype 1 Patients
- Sofosbuvir plus Ribavirin, with or Without PEG-IFN, Experienced Genotype 1 Patients with or Without Cirrhosis
- Treatment-experienced Genotype 2
- PEG-IFN/Ribavirin Treatment-experienced, Genotype 2 Patients Without Cirrhosis
- PEG-IFN/Ribavirin Treatment-experienced, Genotype 2 Patients with Compensated Cirrhosis
- Sofosbuvir Plus Ribavirin Treatment-experienced, Genotype 2 Patients
- Treatment-experienced Genotype 3
- PEG-IFN/Ribavirin Experienced, Genotype 3 Patients Without Cirrhosis
- PEG-IFN/Ribavirin Experienced, Genotype 3 Patients with Compensated Cirrhosis
- Sofosbuvir Experienced, Genotype 3 Patients
- Treatment-experienced Genotype 4
- PEG-IFN/Ribavirin Experienced, Genotype 4 Patients Without Cirrhosis
- PEG-IFN/Ribavirin Experienced, Genotype 4 Patients with Compensated Cirrhosis
- Treatment-experienced Genotype 5 or 6
# Treatment-Naive Genotype 1a Without Cirrhosis

## Recommended and alternative regimens listed by evidence level and alphabetically for:
### Treatment-Naive Genotype 1a Patients Without Cirrhosis

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>DURATION</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs for elbasvir</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)²</td>
<td>8 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are non-black, HIV-uninfected, and whose HCV RNA level is &lt;6 million IU/mL</td>
<td>8 weeks</td>
<td>I, B</td>
</tr>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ALTERNATIVE</th>
<th>DURATION</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), with weight-based ribavirin</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily simprevir (150 mg) plus sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily daclatasvir (60 mg)² plus sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>I, B</td>
</tr>
<tr>
<td>Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for patients with baseline NS5A RASs for elbasvir</td>
<td>16 weeks</td>
<td>IIa, B</td>
</tr>
</tbody>
</table>

* Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 63 known to confer antisense resistance.
* This is a 3-tablet formulation. Please refer to the prescribing information.
* The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinflection for patients on antiretroviral therapy.

Source: AASLD/IDSA Guidelines. HCVGuidelines.org
Eligibility Criteria for 8-Wk HCV Treatment by Regimen

**GLE/PIB**[1]

- Eligible pts must be
  - Noncirrhotic
  - Treatment-naive with GT1-6

**SOF/LDV**[2-4]

- Eligible pts must be
  - Noncirrhotic
  - Treatment naive with GT1
  - HCV RNA < 6 million IU/mL
  - Nonblack
  - No HIV coinfection
  - EASL: caution if F3 fibrosis

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Slide credit: clinicaloptions.com
Alternate Scenario 1: Genotype

What if she was genotype 2 (or 3) instead?
Essentially two options: GLE/PIB x8 or SOF/VEL x12
  Alternative DAC+SOF x12

Genotype 4 etc?
GT4 similar to GT1 (except 8 week LED/SOF option)
Other GTs have options but are very rare in US
AASLD/IDSA Recommendations for First-line HCV Treatment

<table>
<thead>
<tr>
<th>HCV GT</th>
<th>Regimen</th>
<th>Duration, Wks</th>
<th>No Cirrhosis</th>
<th>Compensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GLE/PIB</td>
<td>8</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>GZR/EBR*</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>SOF/LDV</td>
<td>8 or 12†</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>SOF/VEL</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>2 or 3</td>
<td>GLE/PIB</td>
<td>8</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>SOF/VEL</td>
<td>12</td>
<td>12†</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>GLE/PIB</td>
<td>8</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>SOF/VEL</td>
<td>12</td>
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<td></td>
<td>SOF/LDV</td>
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<td>12</td>
<td>12</td>
</tr>
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<td>5 or 6</td>
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<td></td>
<td>SOF/LDV</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>SOF/VEL</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

*If GT1a, use only if no baseline NS5A elbasvir RASs detected.

†If nonblack, no HIV, and HCV RNA < 6 million IU/mL, 8-wk duration recommended.

‡For GT3, if Y93H RAS detected, add RBV or consider SOF/VEL/VOX.
Alternate Scenario 2: Cirrhosis

What if she was fibrosis stage 4 (cirrhosis)?

Need to assess compensation history/CPT score
First line regimen choices overall similar as long as compensated
BUT: No 8 week options
Avoid certain protease inhibitor containing regimens
Some of the alternative regimens not indicated
Baseline RAS testing (Y93H) in GT3 if planning to use SOF/VEL

Special considerations if decompensated/ Child class B/C
Alternate Scenario 3: Treatment Experienced

What if she had failed previous therapy?

Important to know what prior therapy was

- P/R only
- NS3 (earlier generation protease inhibitors)
- SOF containing DAAs (but no NS5A)
- Current DAAs including NS5A

Until last year, limited choices in the latter, based on resistance testing. Now have effective options even without RAS testing.
Best Two Options for DAA Failures

• GLE/PIB approved for GT1 with NS5A or NS3 inhibitor experience only, not both.
• GLE/PIB approved for GT1-6 with SOF experience\(^1\)
  • AASLD/IDSA only recommends SOF/VEL/VOX for GT3 DAA experienced
• SOF/VEL/VOX approved for GT1-6 with NS5A inhibitor experience and GT1a or GT3 with SOF experience without NS5A inhibitor experience (all regardless of NS3 experience)\(^3\)
  • It works in GT2 and other GT SOF failures, but so does SOF/VEL
  • AALSD/IDSA also recommends for GT1, 3, 4, 5, or 6 with NS5A inhibitor experience with or without NS3 inhibitor experience (i.e., any DAA experience)\(^2\)
• Resistance testing not necessary when using GLE/PIB or SOF/VEL/VOX

Alternate Scenario 4: RAS Testing

What if her baseline RAS test was positive?

When do you test?

- Baseline GT1A if anticipating possible use of Zepatier
  - Must use 16 weeks with RBV if positive
  - Not needed in GT1B
- Select GT3 with certain regimens
- Select prior DAA failure (not needed for most now)
Alternate Scenario 5: HBV Co-Infection

What if her pre-treatment HBsAg was positive?

• Case reports of HBV reactivation in pts treated with various different DAA regimens
  • Possibly due to loss of host immune response to HBV
• 29 confirmed cases of HBV reactivation in HCV DAA recipients November 2013 to October 2016.
  • Most cases occurred within 4-8 wks of HCV DAA initiation
  • 2 deaths, 1 liver transplant
  • 3 reactivations in pts with anti-HBc alone (one receiving rituximab)
• October 2016 FDA issued boxed warning
HBV Testing and Monitoring During HCV DAA Therapy:

- HCV DAA therapy is risk for HBV reactivation (including “occult HBV”)
- Test all pts initiating HCV therapy for HBsAg, anti-HBc, and anti-HBs
  - No HBV markers: VACCINATE (this is not new!)
  - HBV markers present:
    - HBsAg positive
      - HBV DNA detectable
        - HBV DNA meets criteria for treatment in AASLD HBV guidelines
          - Treat with HBV drug
      - HBV DNA low or undetectable
        - Monitor for reactivation; treat if HBV DNA level meets AASLD HBV guideline treatment criteria
    - HBsAg negative; Anti-HBc positive (± anti-HBs)
      - “Insufficient data to provide recommendations”
        - Consider screening for occult viremia

AASLD/IDSA. HCV guidance.

Slide modified from clinicaloptions.com
Alternate Scenario 6: HIV Co-Infection

What if she was HIV co-infected?

**SVR rates similar to mono-infected**
Harvoni not an 8 week option

**DDIs are main concern!**
Discuss reinfection and continue to screen MSMs after SVR
HIV no longer “difficult to treat”

<table>
<thead>
<tr>
<th>Study</th>
<th>HCV/HIV-Coinfected Pts, N</th>
<th>HCV Treatment Naive/Exp’d, n</th>
<th>HCV Genotypes</th>
<th>Regimen</th>
<th>SVR12, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ION-4[1]</td>
<td>335</td>
<td>150/185</td>
<td>1, 4</td>
<td>12 wks’ LDV/SOF</td>
<td>96</td>
</tr>
<tr>
<td>ALLY-2[2]</td>
<td>153</td>
<td>101/52</td>
<td>1, 2, 3, 4</td>
<td>12 wks’ DCV + SOF</td>
<td>97</td>
</tr>
<tr>
<td>C-EDGE CO-INFECTION[3]</td>
<td>218</td>
<td>218/0</td>
<td>1, 4, 6</td>
<td>12 wks’ GZR/EBR</td>
<td>96</td>
</tr>
<tr>
<td>ASTRAL-5[4]</td>
<td>106</td>
<td>75/31</td>
<td>1, 2, 3, 4</td>
<td>12 wks’ SOF/VEL</td>
<td>95</td>
</tr>
<tr>
<td>TURQUOISE-I[5]</td>
<td>31</td>
<td>20/11</td>
<td>1</td>
<td>12 wks’ OBV/PTV/RTV + DSV + RBV</td>
<td>94</td>
</tr>
<tr>
<td>EXPEDITION-2[6]</td>
<td>137</td>
<td>111/26</td>
<td>1, 2, 3, 4, 6</td>
<td>8 wks’ GLE/PIB</td>
<td>99</td>
</tr>
<tr>
<td>ENDURANCE-1[7]</td>
<td>15</td>
<td>10/5</td>
<td>1</td>
<td>8 wks’ GLE/PIB</td>
<td>100</td>
</tr>
</tbody>
</table>


Slide modified from clinicaloptions.com
HCV Medication Interactions With HIV ART

<table>
<thead>
<tr>
<th>HCV Regimen</th>
<th>Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBR/GZR</td>
<td>Do not use with COBI, EFV, ETV, NVP, or any HIV PI</td>
</tr>
<tr>
<td>GLE/PIB</td>
<td>Do not use with ATV, RTV-containing ART regimens, EFV, or ETV</td>
</tr>
<tr>
<td>SOF/VEL</td>
<td>Do not use with EFV, ETV, or NVP</td>
</tr>
<tr>
<td>SOF/VEL/VOX</td>
<td>Do not use with ATV/RTV, EFV, ETV, or NVP</td>
</tr>
<tr>
<td>SOF-based regimens</td>
<td>Do not use with TPV</td>
</tr>
<tr>
<td>OBV/PTV/RTV/DSV</td>
<td>Do not use with DRV, EFV, LPV/RTV, TPV/RTV, ETV, NVP, COBI, or RPV</td>
</tr>
<tr>
<td>OBV/PTV/RTV ± DSV</td>
<td>Do not use in HIV/HCV-coinfected patients not taking ART</td>
</tr>
<tr>
<td>RBV</td>
<td>Do not use with ddl, d4T, or ZDV</td>
</tr>
<tr>
<td>SMV</td>
<td>Do not use with COBI, EFV, ETV, NVP, or any HIV PI</td>
</tr>
</tbody>
</table>

- Interruption of ART to allow HCV therapy is not recommended, but ART switch to allow compatibility with HCV therapy may be performed.

These are only those that are contraindicated, others have effects such as SOF and TDF!

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Triple Nucleotide (SMV/SOF)</th>
<th>Daclatasvir/Sofosbuvir (DCV/SOF)</th>
<th>Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir (PR/OD)</th>
<th>Paritaprevir/Ritonavir/Ombitasvir (PR/O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir/Sofosbuvir (LDV/SOF)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/VEL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir (ELB/GRZ)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glecaprevir/Pibrentasvir (GLE/PIB)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/VEL/VOX</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

- **Ribavirin-boosted telaprevir (TPV)**
  - **Ribavirin-boosted elbasvir (ELB)**
    - Ledipasvir/Sofosbuvir (LDV/SOF)
    - Sofosbuvir/VEL
    - Elbasvir/Grazoprevir (ELB/GRZ)
    - Glecaprevir/Pibrentasvir (GLE/PIB)
    - Sofosbuvir/VEL/VOX
    - **Ribavirin**

- **Elbasvir (ELB)**
  - Ledipasvir/Sofosbuvir (LDV/SOF)
  - Sofosbuvir/VEL
  - Elbasvir/Grazoprevir (ELB/GRZ)
  - Glecaprevir/Pibrentasvir (GLE/PIB)
  - Sofosbuvir/VEL/VOX
  - **Ribavirin**

- **Ribavirin (RIV)**
  - Ledipasvir/Sofosbuvir (LDV/SOF)
  - Sofosbuvir/VEL
  - Elbasvir/Grazoprevir (ELB/GRZ)
  - Glecaprevir/Pibrentasvir (GLE/PIB)
  - Sofosbuvir/VEL/VOX
  - **Ribavirin**

- **Elvitegravir (EVG)**
  - Ledipasvir/Sofosbuvir (LDV/SOF)
  - Sofosbuvir/VEL
  - Elbasvir/Grazoprevir (ELB/GRZ)
  - Glecaprevir/Pibrentasvir (GLE/PIB)
  - Sofosbuvir/VEL/VOX
  - **Ribavirin**

- **Raltegravir (RAL)**
  - Ledipasvir/Sofosbuvir (LDV/SOF)
  - Sofosbuvir/VEL
  - Elbasvir/Grazoprevir (ELB/GRZ)
  - Glecaprevir/Pibrentasvir (GLE/PIB)
  - Sofosbuvir/VEL/VOX
  - **Ribavirin**

- **Cobicistat-boosted elvitegravir (COB)**
  - Ledipasvir/Sofosbuvir (LDV/SOF)
  - Sofosbuvir/VEL
  - Elbasvir/Grazoprevir (ELB/GRZ)
  - Glecaprevir/Pibrentasvir (GLE/PIB)
  - Sofosbuvir/VEL/VOX
  - **Ribavirin**

- **Dolutegravir (DTC)**
  - Ledipasvir/Sofosbuvir (LDV/SOF)
  - Sofosbuvir/VEL
  - Elbasvir/Grazoprevir (ELB/GRZ)
  - Glecaprevir/Pibrentasvir (GLE/PIB)
  - Sofosbuvir/VEL/VOX
  - **Ribavirin**

- **Maraviroc (MVC)**
  - Ledipasvir/Sofosbuvir (LDV/SOF)
  - Sofosbuvir/VEL
  - Elbasvir/Grazoprevir (ELB/GRZ)
  - Glecaprevir/Pibrentasvir (GLE/PIB)
  - Sofosbuvir/VEL/VOX
  - **Ribavirin**

- **Tenofevir (TFV) disodium fumarate**
  - Ledipasvir/Sofosbuvir (LDV/SOF)
  - Sofosbuvir/VEL
  - Elbasvir/Grazoprevir (ELB/GRZ)
  - Glecaprevir/Pibrentasvir (GLE/PIB)
  - Sofosbuvir/VEL/VOX
  - **Ribavirin**

- **Tenofevir (TFV) alafenamide**
  - Ledipasvir/Sofosbuvir (LDV/SOF)
  - Sofosbuvir/VEL
  - Elbasvir/Grazoprevir (ELB/GRZ)
  - Glecaprevir/Pibrentasvir (GLE/PIB)
  - Sofosbuvir/VEL/VOX
  - **Ribavirin**
Alternate Scenario 7: Other DDIs

What if she was taking OTC acid suppressive therapy?

Which one (Tums, H2blockers, PPIs), what dose, how often?

Is it needed?

... taking statins?

... taking anti-epileptics?

... taking herbals? (St John’s Wort, really?)
# DDIs Between Recommended DAAs and Selected Medications

<table>
<thead>
<tr>
<th>Concomitant Medication</th>
<th>DCV</th>
<th>LDV</th>
<th>SOF</th>
<th>EBR/GZR</th>
<th>GLE/PIB</th>
<th>SOF/VEL</th>
<th>SOF/VEL/VOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid-reducing agents*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>Amiodarone</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Azole antifungals*</td>
<td>X†</td>
<td></td>
<td></td>
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<tr>
<td>Calcineurin inhibitors,* cisapride, PDE inhibitors,* other antiarhythmics* or sedatives*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Calcium channel blockers*</td>
<td>X</td>
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<td>Cyclosporine</td>
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<td>X</td>
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<tr>
<td>Digoxin</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Ethinyl estradiol–containing products</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Glucocorticoids*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herbals, St John’s wort, milk thistle</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Statins*</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrolide antimicrobials*</td>
<td>X†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifamycin antimicrobials*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*Some DDIs not class specific; see prescribing information for specific drugs within a class. †Requires DCV dose adjustment.

AASLD/IDSA. HCV guidance. September 2017. FDA GLE/PIB. FDA SOF/VEL/VOX

Slide credit: [clinicaloptions.com](https://clinicaloptions.com)
Key resource: www.hep-druginteractions.org
Alternate Scenario 8: Renal Disease

What if she had stage 3 CKD with GFR 45?

Can use SOF based regimens with GFR above 30

... GFR below 30? ... ESRD +/- HD?

<table>
<thead>
<tr>
<th>HCV GT</th>
<th>Recommended Regimens for Stage 4 or 5 CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a, 1b, 4</td>
<td>▪ EBR/GZR 12 wks</td>
</tr>
<tr>
<td>1, 2, 3, 4, 5, 6</td>
<td>▪ GLE/PIB 8-16 wks*</td>
</tr>
</tbody>
</table>

*Use durations recommended for pts without CKD - based on cirrhosis, previous treatment experience.
AASLD/IDSA HCV Guidance for Stage 4 or 5 Chronic Kidney Disease

- Stage 4 (severe) CKD: eGFR 15-29 mL/min
- Stage 5 (end-stage) CKD: eGFR <15 mL/min

<table>
<thead>
<tr>
<th>HCV GT</th>
<th>Recommended Regimens for Stage 4 or 5 CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a, 1b, 4</td>
<td>▪ EBR/GZR 12 wks</td>
</tr>
<tr>
<td>1, 2, 3, 4, 5, 6</td>
<td>▪ GLE/PIB 8-16 wks*</td>
</tr>
</tbody>
</table>

*Use durations recommended for pts without CKD - based on cirrhosis, previous treatment experience.

Slide credit: clinicaloptions.com

Alternate Scenario 9: Decompensation and Post Transplant

What if she had a history of ascites, encephalopathy, variceal bleed?

What if she had a liver transplant and has recurrent post-transplant HCV?
... a renal transplant?

There are effective treatment options for all of the above, but recommend consultation with specialized transplant team
Alternate Scenario 11: Pregnancy

• What if she were pregnant? ...Thinking about becoming pregnant in the future?

• **89% increase in HCV among women at time of delivery:** 1.8/1000 live births in 2009 to 3.4/1000 live births in 2014
  - Current guidelines do not recommend universal HCV screening in pregnancy

• Mother-to-child HCV transmission rates are 3-5%
• No special precautions regarding MTCT or breastfeeding
• HCV identification during pregnancy key for appropriate follow-up of infants
• Treatment during pregnancy is not recommended at this time
• Treatment of women of reproductive age before becoming pregnant encouraged
Alternate Scenario 12: Acute Infection

What if she tested negative at admission to rehab, had a relapse right before discharge and shared needles with her roommate?

Testing and management for acute HCV:
Based on either exposure or clinical presentation (symptomatic rare)
Need to test with both antibody AND viral (RNA) test at presentation
No pre- or post-exposure prophylaxis recommended at this time
Follow up tests until negative at 6 months

If positive, monitor RNA every 4-8 weeks for 6-12 months
  Consider delaying treatment for 12-16 weeks to allow for spontaneous clearance
  Treat as otherwise if no clearance after 6 months
  All recommended regimens at this time are same as for chronic HCV
Figure. Testing Algorithm for Discrete Recognized Hepatitis C Virus (HCV) Exposure

- **HCV antibody (Ab) negative, HCV RNA negative**
  - No HCV infection

- **HCV Ab positive\(^b\), HCV RNA negative**
  - Prior resolved infection
  - Repeat testing for 6 months to assess for new infection\(^a,b\)
  - Test HCV RNA and HCV Ab\(^b\)

- **HCV RNA positive or seroconversion**
  - Acute HCV infection

- **HCV Ab negative, HCV RNA positive**
  - Acute infection already present
  - Repeat testing to assess for outcome of acute infection\(^b,c\)
  - Monitor HCV RNA and alanine aminotransferase (ALT) for at least 12 weeks
  - HCV RNA negative x 2, 12 weeks apart
  - Spontaneous clearance

- **HCV Ab positive, HCV RNA positive**
  - Prior chronic infection\(^d\)

- **HCV RNA negative and HCV Ab negative, or no seroconversion for 6 months**
  - No HCV infection
  - For prior resolved infection, if HCV RNA remains negative:
    - No HCV infection
  - Counsel on risk reduction
  - Annual testing for high-risk patients

- **HCV RNA positive at 6 months**
  - Chronic HCV infection
  - See initial treatment of chronic HCV infection

---

Exposure

Baseline testing within 48 hours of exposure\(^e\)

48 hours

12 weeks

24 weeks
Reported Number of Acute Hepatitis C Cases: United States 2000-2015

CDC. National Notifiable Diseases Surveillance System.

Slide credit: clinicaloptions.com

Reported Cases/100,000 Population

- 0-19 yrs
- 20-29 yrs
- 30-39 yrs
- 40-49 yrs
- 50-59 yrs
- 60+ yrs

Yr


0 0.5 1.0 1.5 2.0 2.5 3.0
Opioid Epidemic Is Increasing HCV Transmission

• Increase in new HCV infections in the US is primarily among young white adults with injection drug use[1]
  • Has led to increase in mother-to-child transmission[2]

Change in HCV Incidence Among Young PWID, 2006-2012[3]


Slide credit: clinicaloptions.com
Case 3: Post SVR Management

You are seeing a 56 y/o HIV infected patient on Genvoya for follow up after HCV treatment. He is adherent with his ARV and has no specific complaints today. He remains sexually active with casual male partners and reports using condoms inconsistently.

He finished Harvoni x12 treatment 3 months ago. His baseline elastography was F3 and he has no clinical stigmata of liver disease. His last liver ultrasound was 6 months ago and was negative for any suspicious lesions. His liver related enzymes normalized during his HCV treatment.
Menti Question #7

Which of the following do you advise specifically for his HCV follow up?

A. HCV RNA only today; if negative no further HCV F/U
B. HCV RNA today and ultrasound in 6 months
C. HCV RNA and ultrasound today; if both negative no further HCV F/U
D. HCV RNA and ultrasound today; if both negative u/s every 6 months
E. HCV RNA and ultrasound today; if both negative u/s every 6 months and RNA every 12 months
## Recommended Follow-up After Hepatitis C Treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>No advanced fibrosis (Metavir stage F0-F2)</td>
<td>No hepatitis C follow-up</td>
</tr>
<tr>
<td><strong>Advanced fibrosis (Metavir stage F3 or F4)</strong></td>
<td>Twice-yearly ultrasound surveillance for hepatocellular carcinoma</td>
</tr>
<tr>
<td></td>
<td>– If compensated cirrhosis (F4) also test for varices using baseline endoscopy</td>
</tr>
<tr>
<td><strong>Ongoing hepatitis C risk</strong> or unexplained hepatic dysfunction</td>
<td>Test for recurrence or <strong>reinfection</strong> with quantitative hepatitis C RNA assay</td>
</tr>
<tr>
<td><strong>Persistently abnormal liver tests</strong></td>
<td>Test for other causes of liver disease</td>
</tr>
<tr>
<td>No virologic cure</td>
<td>Test for disease progression every 6-12 mos with hepatic function panel, CBC, and INR</td>
</tr>
<tr>
<td></td>
<td>Consider retreatment options</td>
</tr>
</tbody>
</table>

HCV Reinfec3on Over 5 Yrs by Study Popula3on

Counsel all on reinfection risk and prevention/risk reduction!
Counsel all on AB persistence but not protective!

---

Recent German cohort:
25% reinfection in HIV + MSM (vs 13-15% IVDA, <1% prior transfusion)

Counsel all on reinfec3on risk and preven3on/risk reduc3on!
Counsel all on AB persistence but not protective!

Remember to continue screening active IVD/nasal cocaine users and HIV positive MSM (annually, must use PCR)


Slide modified from clinicaloptions.com
Thank You! Questions?
Future: Goal Is Elimination of Hepatitis C Infection

2030 WHO Targets
90% Diagnosed
80% Treated
65% Reduced Mortality