

# You Too Can Treat Hepatitis C

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# Disclosures

None

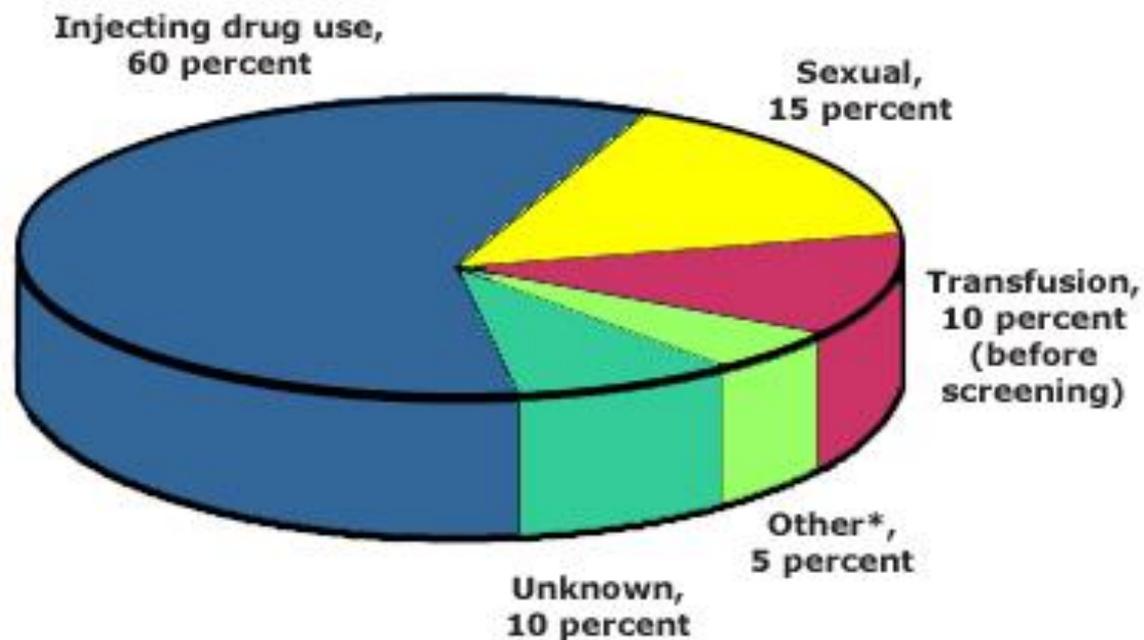
# Objectives

- The Case for Primary Care Rx of HCV
- Review Epidemiology, Staging and Preparation for Treatment
- Legal requirements for treatment, resources of telemedicine specialty consultation
- Clinic treatment model
- Resources for treatment recommendations

# Epidemiology

- ~ 3.5 million living with HCV in U.S.
  - 38% linked to care, 11% treated
- 33,900 New Cases/yr
- 2010 to 2015: 3-Fold increase
- 10-20 times in some homeless populations
- 12-35% of those incarcerated
- LA Study 534 homeless patients: 26.7% HCV-positive (Ab), 46% unaware, 72.6% never received counseling about HCV *Gelberg, 2012*

# HCV Transmission



\* Nosocomial; health-care work; perinatal.  
Centers for Disease Control and Prevention.

## AASLD/IDSA HCV Testing Recommendations

**One-time HCV testing is recommended for persons born between 1945 and 1965, without prior ascertainment of risk (and regardless of country of birth)**

*Rating: Class 1, Level B*

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

### **1. Risk behaviors**

- Injection-drug use (current or ever, including those who injected once)
- Intranasal illicit drug use

### **2. Risk exposures**

- Long-term hemodialysis (ever)
- Getting a tattoo in an unregulated setting
- Healthcare, emergency medical, and public safety workers after needlesticks, sharps, or mucosal exposures to HCV-infected blood
- Children born to HCV-infected women
- Prior recipients of transfusions or organ transplants, including persons who:
  - were notified they received blood from a donor who later tested positive for HCV infection
  - received transfusion of blood or blood components, or underwent organ transplant before July 1992
  - received clotting factor concentrates produced before 1987
- Persons who were ever incarcerated

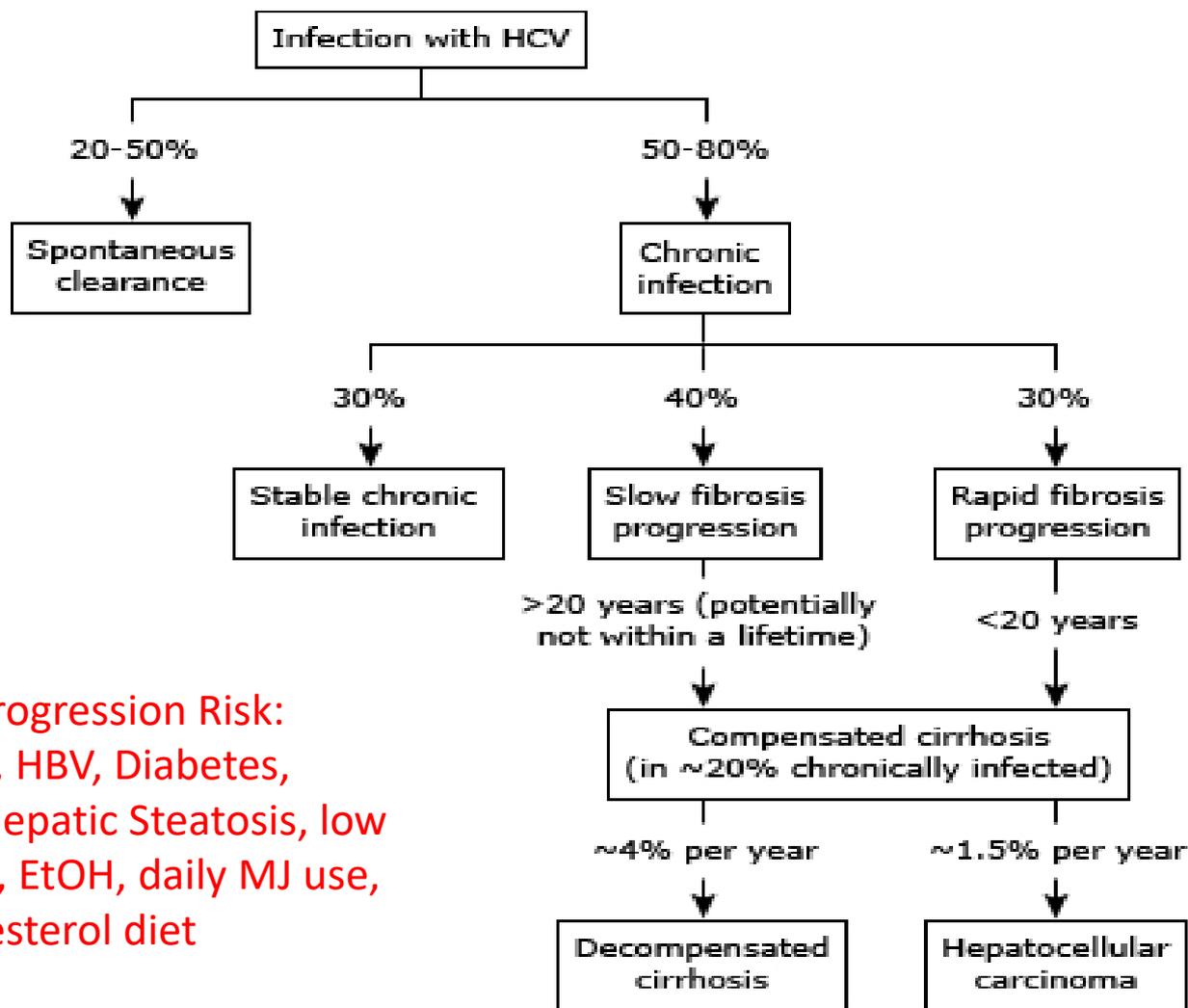
### **3. Other**

- HIV infection
- Unexplained chronic liver disease and chronic hepatitis including elevated alanine aminotransferase levels
- Solid organ donors (deceased and living)

*Rating: Class 1, Level B*

# Sexual Activity Counseling

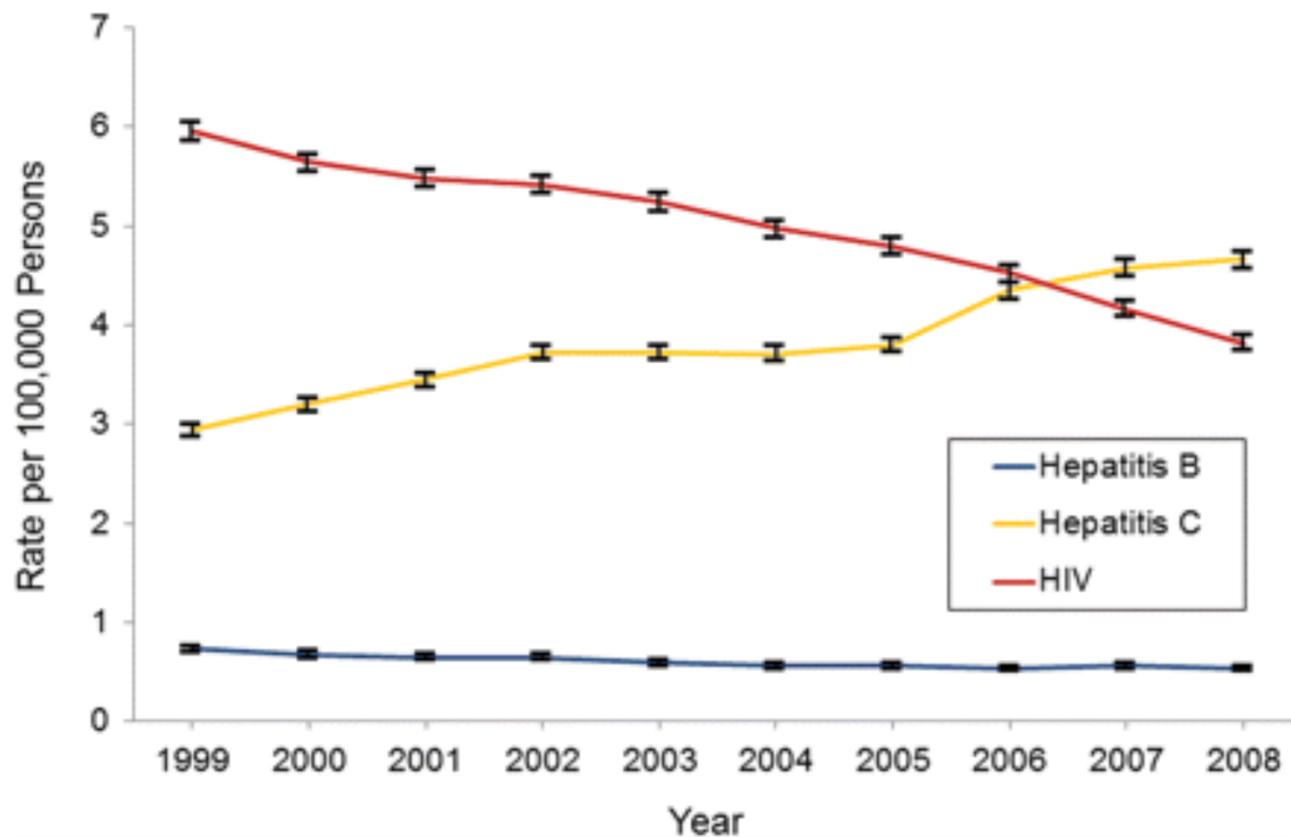
- Risk of heterosexual transmission low. Those in long-term monogamous relationships do not need to alter their sexual practices
- Risk may be substantial for sexual practices that may result in bleeding/mucosal damage
  - use condoms and avoid rough sex.



Greater Progression Risk:  
 Male, HIV, HBV, Diabetes,  
 Obesity, Hepatic Steatosis, low  
 Vitamin D, EtOH, daily MJ use,  
 high cholesterol diet

# Impact of Hepatitis C

- Leading Cause of:
  - End Stage Liver Disease
  - Hepatocellular Carcinoma
  - Liver Transplantation
- Survival Impact
  - 8000-13,000 deaths/year
- Extrahepatic Manifestations
  - Potentially life-threatening, prevented by Rx
  - Renal, hematologic, autoimmune, derm, DM
- QOL, Fatigue, Cognition, Stigma

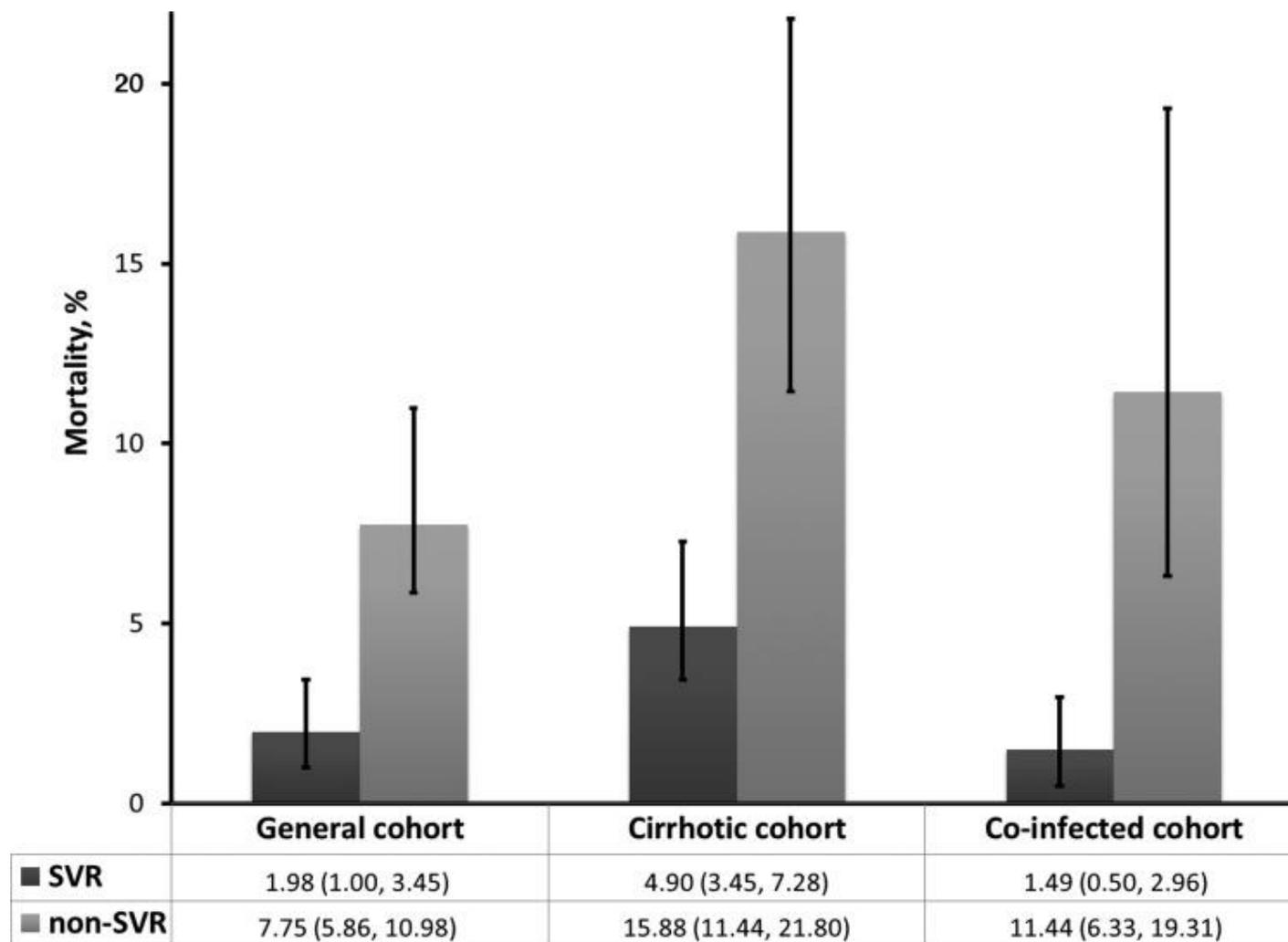


### Mortality Rates 1999-2008

Clin Infect Dis. 2012;55(suppl\_1):S3-S9. doi:10.1093/cid/cis393

# New Era of Treatment: Direct-Acting Antivirals (DAA)

- Shorter duration: 8-12 weeks
- Fewer side effects: Nausea, HA, fatigue
- Higher cure rates
- Guidelines: Rx recommended in all patients
  - exception life expectancy <12 months due to non-related conditions
  - Short life-expectancy due to liver disease—refer to a specialist



Five-year mortality rates (95% confidence interval) for sustained virologic response (SVR) vs non-SVR groups for each cohort. (Simmons, 2015)

# Childs A Rx impact on cirrhosis

- IFN: SVR assoc w/ decreasing Portal Pressures, prevention of varices, decreased hepatic decompensation, and HCC.
- Fibrosis regression does not happen in all patients after SVR even in non-cirrhotics (7-12%)
- If regression occurs it takes a long time. Several studies have shown fibrosis regression at a median of >5 years. In a study by Lens et al, clinical significant portal HTN (HVPG > 6mm/Hg) persisted 6 months post treatment in 86% of patients in spite of good >10mm/Hg reduction

# Childs Class B/C Rx impact

- Limited data from IFN trials  
In registration trials and expanded access trials an initial improvement in 6-month MELD but 15-month deterioration
- 1 study, DAA Rx w/ SVR associated w/ lower portal pressures
  - long term benefit unknown at this point  
*(Afdhal et al, 2016)*

*echo HCV, 2017*

# Rx Impact on Development of HCC

- IFN: clear benefit of 75% reduced HCC risk w/ SVR
- Would suspect this to be higher with DAA since more people getting SVR, data not definitive
- This topic remains controversial. Therefore all cirrhotic patients should be routinely screened for HCC

# Why should PCP Treat HCV?

- Limited access
- Pre-established therapeutic relationships
  - BHCHP Survey: majority of pts most comfortable with PCP Rx
- Access to other care needs
- Skills in engaging disenfranchised patients
- Uncomplicated HCV benefits from treatment
- PCP Rx outcomes with telemedicine consultation:
  - ~ 2X increase in HCV PCR + pts starting Rx (*Mitruka, 2014*)
  - Equally safe and effective in achieving cure (*Arora, 2010*)
- ASCEND Trial: 3-Hour training PCPs vs Providers as safe/effective (*Kattakuzhy, 2017*)

# Barriers to Treatment by PCP

- Patient fear of side effects
- No perceived need for treatment
- State Legal restrictions
- Lack of expertise
- Rapid scientific evolution of care
- Lack of Rx coverage (Pharm assistance options)
- Lack of support staff to process approvals
- High Volume, requires frequent follow-up
- Pioneer Square Process

# Judge orders Washington Medicaid to provide lifesaving hepatitis C drugs for all

Originally published May 28, 2016 at 8:30 pm Updated May 30, 2016 at 7:20 pm

**A federal judge has ordered Washington's Medicaid program to end a 2015 policy that limited expensive drugs that can cure hepatitis C infections to patients with the most severe liver disease.**

The injunction was a response to a [class-action lawsuit filed in February](#) on behalf of two clients of Apple Health — and nearly 28,000 other Medicaid enrollees with hepatitis C.

# WA Legal Restrictions on Rx:

- Prescriber is:
  - A specialist\* in one of the following areas:
    - Gastroenterologist, Hepatologist, HIV, Infectious disease; **OR**
- Prescriber is participating and consulting with Project ECHO or one of the specialists listed above (requires consultation note or documentation of phone call)
- Exceptions possible if training in HCV care or ready access to specialists

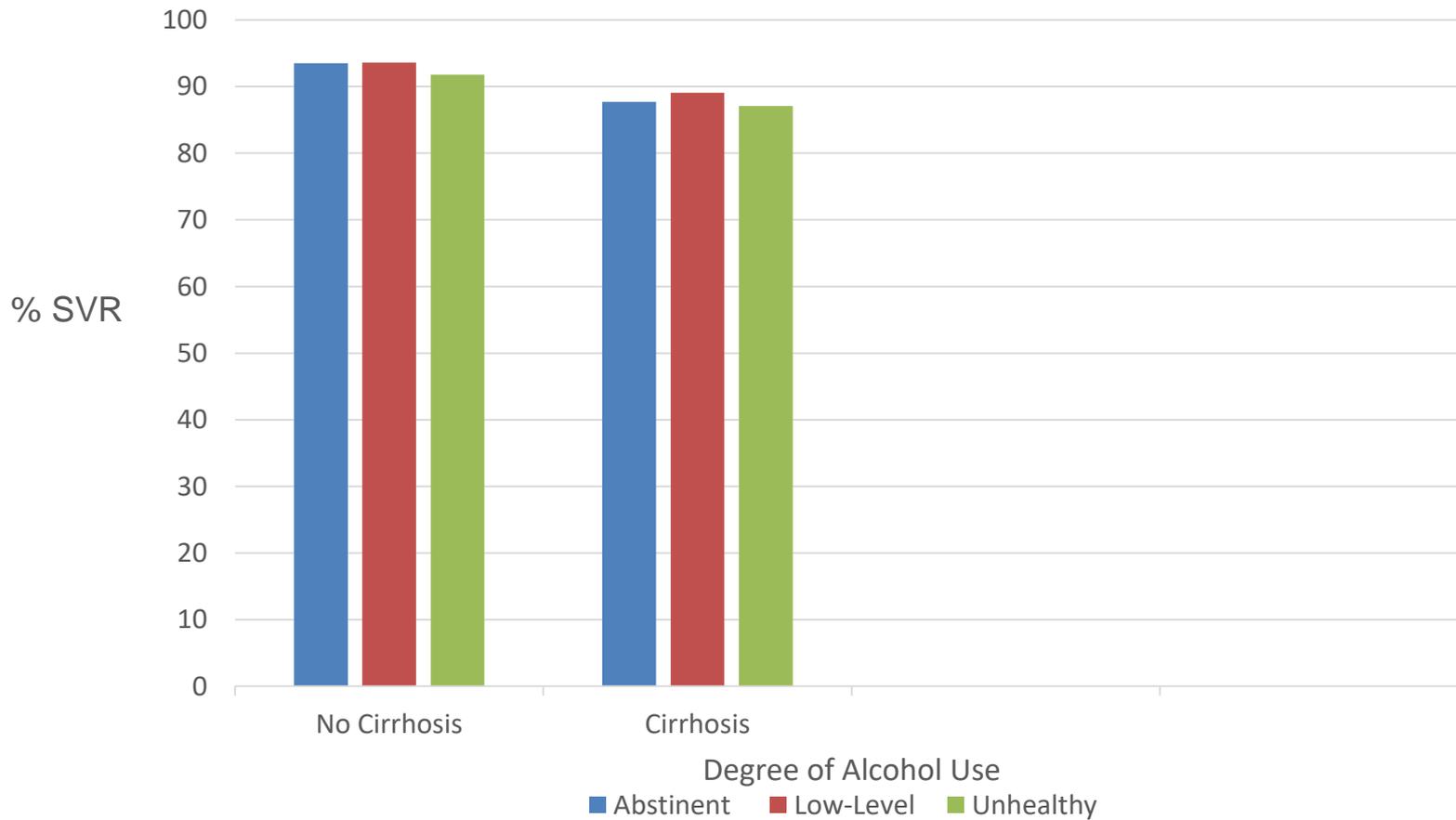
# Telemedicine: ECHO HCV

- Specialty support for PCPs to increase access to best practice management for complex diagnoses
- Set-up/cost--minimal
- ECHO process—who participates, frequency, structure
- ECHO resources
- Option for future independent treatment

# Treatment Selection

- Consistency in follow-up
- Ability to adhere to regimen
- Motivation for treatment
- EtOH use disorders
- Drug use disorders
- Who requires specialty referral?

# Rx Outcomes and Alcohol



*Adapted from Drug And Alcohol Dependence, Vol 169, 2016*

# Treatment of PWID

- Rx often withheld due to perceived
  - Adherence, cost, resistance, reinfection
- Significant public health impact
- High response rates
- Low likelihood of reinfection even with continued use

# Treatment of PWID

- Rx integration in 3 OAT programs: PREVAIL (*Annals, 2019*)
  - Non-blinded RCT: DOT vs Group Therapy vs self-admin,
  - Assessed adherence, Rx completion, SVR
  - High SVR all groups, even with ongoing drug use
  - Drug use did not affect adherence or SVR
  - Rx failures deaths with (-) VL, stopped Rx, lost f/u
- HERO Study: Patient Centered Treatment
  - DOT vs Patient Navigators
  - Rx initiation, adherence, Rx completion, resistance, reinfection

# Specialty Care Considerations

- Childs Class B or C cirrhosis
- Hepatic nodules concerning for HCC
- DAA Treatment failure
- HIV coinfection
- Significant extrahepatic complications
- Renal Failure
- HBV DNA (+)
- If isolated Hep B Core Ab (+), monitor AST, ALT monthly during Rx—risk of reactivation

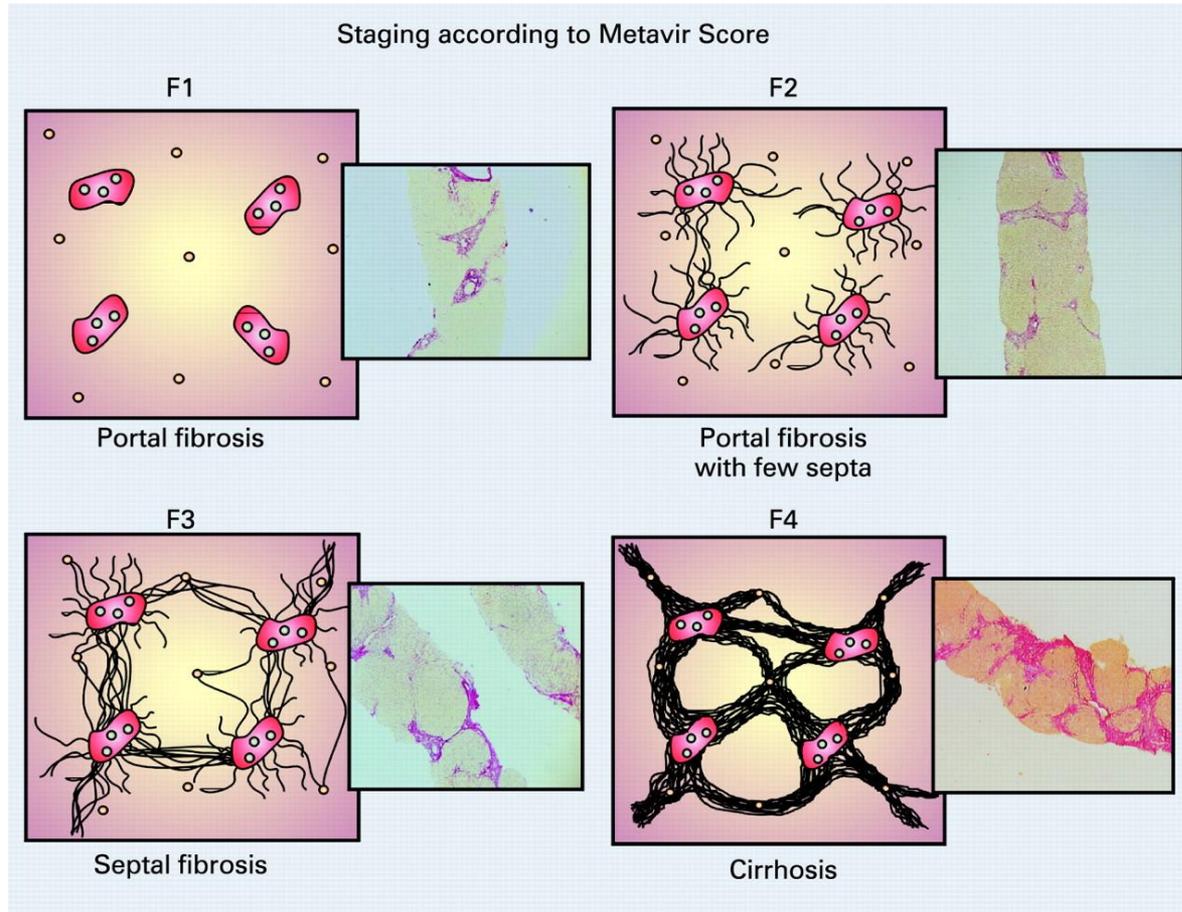
# Preparation for Treatment

- Confirm chronicity of infection at 6 months
- Counsel on infection control
- Screen/Vaccinate for Hep A/B
- Identify Genotype, check baseline labs
- Treatment Naïve or Experienced
- Assess Staging (Review past biopsy, US or CT)
- Imaging & Scoring if advanced fibrosis
- ECHO or specialty consultation
- Refer appropriate patients for specialty care

# Relevance of Staging

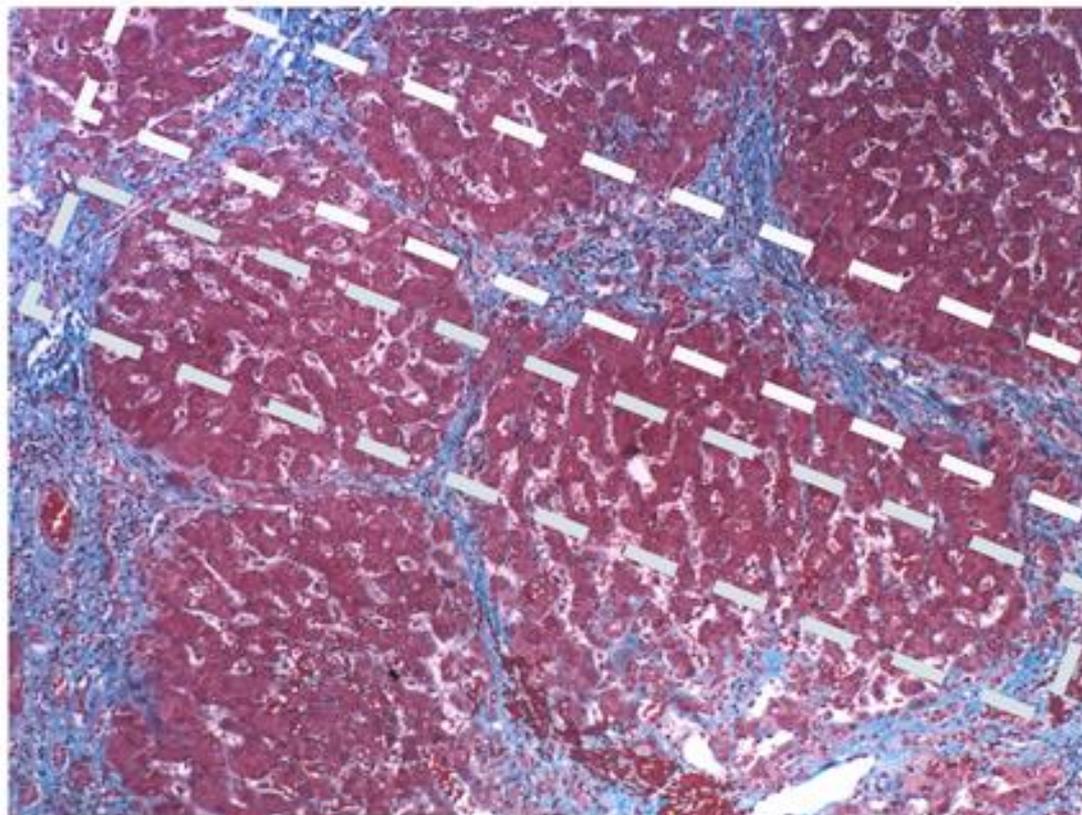
- Informs choice or duration of Rx regimen
- May determine coverage
- Inform need for HCC screening
- Inform need for varices screening
- Inform monitoring or Rx for decompensated cirrhosis

# Fibrosis Stage



## Sampling Error of Liver Biopsy

Fibrosis area: 65%



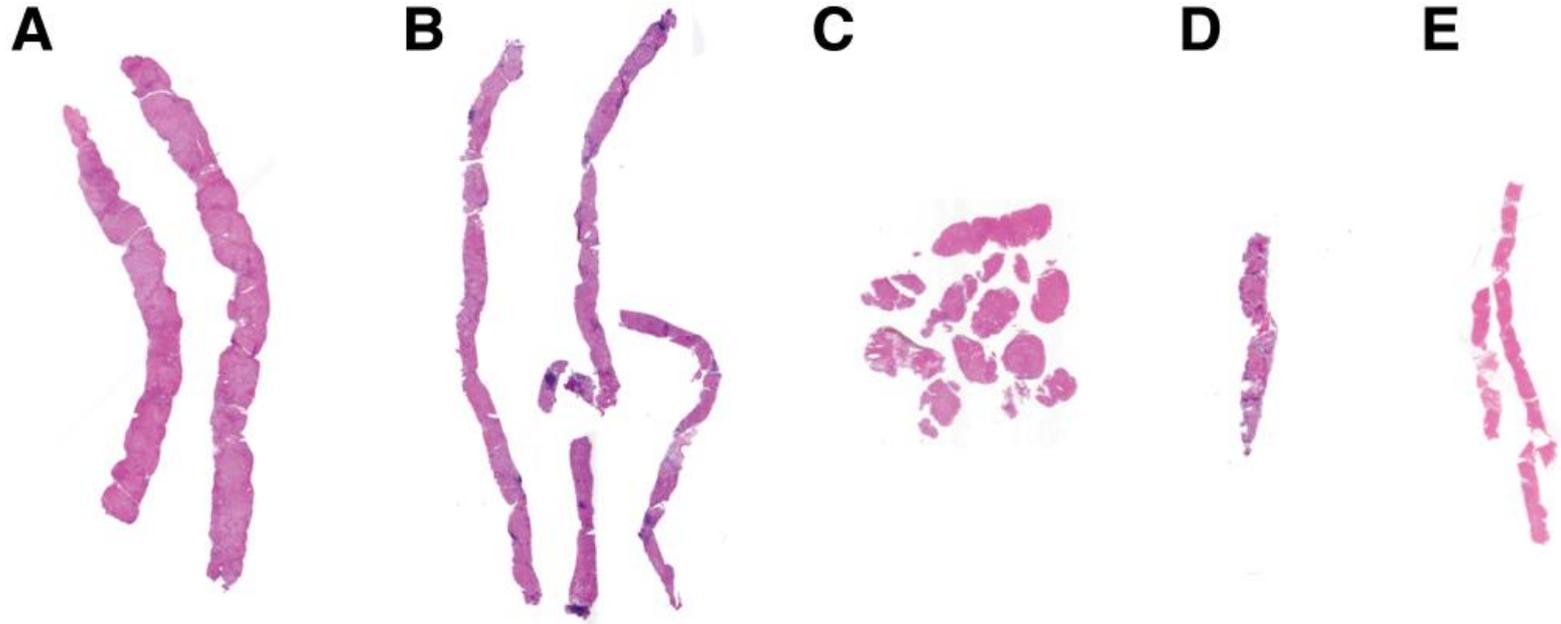
Fibrosis area: 15%

Courtesy of M. Pinzani, Florence

## Liver Biopsy Size in 355 Samples: The Smaller the Piece the Milder the Disease

	Length of specimen		
	> 3 cm	1.5 cm	1 cm
<b>No. Portal Tracts</b>			
complete	22.4 ± 4.9	10.3 ± 2.2	6.4 ± 1.2
<b>Grade</b>			
Mild	49.7%	60.2%	86.6%
Moderate	38.5%	39.1%	17.4%
Severe	11.8%	0.6%	0
<b>Stage</b>			
Mild (F0-1)	59%	68.3%	80.1%
Moderate (F2)	29.8%	24.2%	14.9%
Severe (F3-4)	11.2%	7.4%	4.9%

# Liver Biopsy Optimal:



Optimal: 16G cutting needle, 3 passes, 3 X 1 cm (2 cm acceptable),  
11 portal tracts

*Rockey DC et al. Hepatology 2009;1017-44.*

- A. 2.7 cm, 2 passes 16G cutting needle
- B. 4.8 cm, 3 passes 18G cutting needle
- C. 1.1 cm, 16G suction needle
- D. .5 cm, 18G needle
- E. 1.5 cm, 20G needle



# Non-invasive Fibrosis Staging

- Indirect laboratory markers
  - APRI, Fib-4
  - Good at excluding/confirming fibrosis
  - Indeterminate in mid-range
- Indirect biochemical markers
  - FibroTest: Age, gender, 6 serum markers
- Imaging: US, CT, elastography, fibroscan
- Ideally off EtOH X 3 months prior to staging

# Hepatic Elastography



Sensitivity of 84 - 100% and Specificity of 91 - 96%.

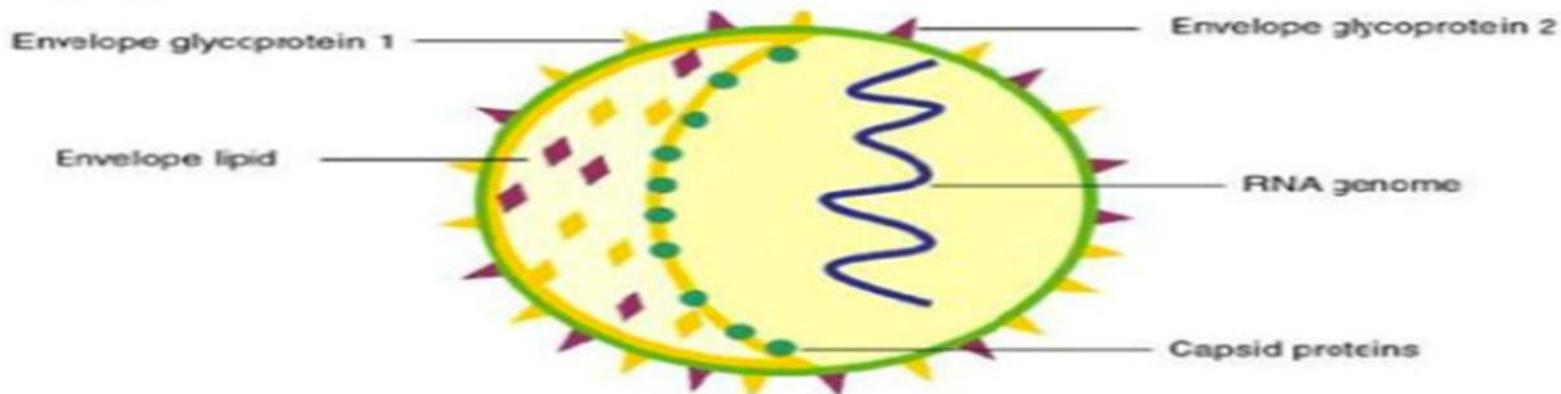
# Staging Low Down

- 2 non-invasive tests:
  - Fibroscan (best) + APRI
  - Fibroscan + FibroTest
  - FibroTest + APRI
- US if suggestion of cirrhosis
- Discordant results that would affect Rx decision
  - Low (F0-2) vs High (F3-4)
  - Consider Fibroscan (if not done) or Biopsy
- Staging those not getting Rx can guide screening

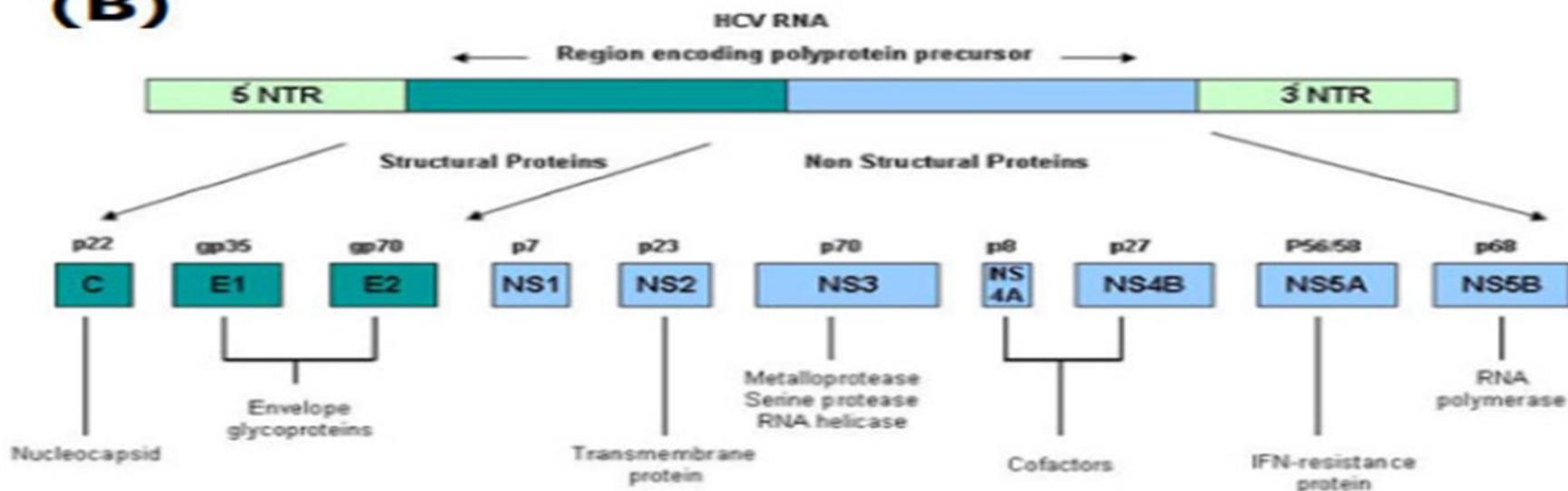
# Hepatitis C Virus

- Single stranded, RNA virus
- Exists as seven genotypes
- 1 a and b, 2, 3, 4, 5 ,6
- Transmitted through blood and sexual contact
- GT 3 Resistant Associated Variants impacts management for cirrhotics
  - Y90 mutation
  - Order RAV testing

**(A)**



**(B)**



# Direct Acting Antivirals

- NS5B Inhibitors (RNA Polymerase Inhibitors)-  
Sofosbuvir, Dasabuvir
- NS5A Inhibitors-Ledipasvir, Ombitasvir,  
Elbasvir, Velpatasvir, Pibrentasvir
- NS3A/4A(Protease Inhibitors)-Simeprevir,  
Paritaprevir, Grazoprevir, Glecaprevir,  
Voxilaprevir

# Direct Acting Antiviral Products

- Harvoni: Ledipasvir/Sofosbuvir
  - 1 tablet once daily
- Mavyret: Glecaprevir/Pibrentasvir
  - 3 tablets once daily, 8-12 weeks
  - Preferred all GT in WA
- Epclusa: Sofosbuvir/Velpatasvir, 12 weeks
- Zepetier: Elbasvir/Grazoprevir
- Vosevi: Sofosbuvir/Velpatasvir/Voxilaprevir

# Drug Interactions

- PPI and Harvoni
- Statin and Mavyret
- HCV Drug Interactions:  
<http://files.ctctcdn.com/f941a670501/a16351c7-423e-4a2a-8c36-59ae9901976c.pdf>

# Post-treatment Management

- SVR monitoring
  - SVR 12 = 12 weeks post-treatment for F0-F3
  - SVR 12, 24 for F4 or HIV Coinfection
- HCC screening US every 6 mo: For F3 and F4
- EGD screening for varices: For F4
  - No EGD if plt > 150K & Liver Stiffness < 20 kPa (*Garcia-Tsao, 2017*)
- Continued HCV screening for those at risk
- Counseling reinfection possible

# Clinical Pearls

- Do not switch insurance during Rx
- Bring meds to the hospital, jail or rehab
- No replacements for lost medications or very difficult to get a lost medication override
- Contraception
- Address HCV status & treatment for partners

# Random Fun Facts

- Low viral load (< 6 million) can indicate mild viral activity or advanced fibrosis with few hepatocytes for HCV to replicate in
- As fibrosis progresses the ALT > AST can “flip” as hepatocytes die (AST has other sources)
- Treatment does not confer immunity, reinfection can occur after spontaneous clearance or SVR—continue screening
- Chronic HCV can spontaneously clear
- Isolated HBV Core Ab—no vaccination indicated
- Email us with any questions

# Hepatitis C Resources

- AASLD Guideline [hcvguidelines.org](http://hcvguidelines.org)
- Hepatitis C Online [hepatitisc.uw.edu](http://hepatitisc.uw.edu)
  - Calculators for APRI, Childs Class, MELD
- EASL Guidelines [easl.eu/research/our-contributions/clinical-practice-guidelines](http://easl.eu/research/our-contributions/clinical-practice-guidelines)
- ECHO Project: [www.echo.unm.edu](http://www.echo.unm.edu)
- [hcvadvisor.com](http://hcvadvisor.com) (EASL web-based Rx recommendations)
- Web-based/Smartphone resources/consultation: [hepcure.org](http://hepcure.org)

# Resources

- HCV Drug Interactions:  
<http://files.ctctcdn.com/f941a670501/a16351c7-423e-4a2a-8c36-59ae9901976c.pdf>
- Patient Access Network Foundation(PAN)  
[www.panfoundation.org](http://www.panfoundation.org)
- Rx Schedule Date Calculator: [Timeanddate.com](http://Timeanddate.com)
- National Viral Hepatitis Action Plan 2017–2020  
<https://www.hhs.gov/sites/default/files/National%20Viral%20Hepatitis%20Action%20Plan%202017-2020.pdf>

# Acknowledgements

- Pioneer Square Clinic Staff
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- 7MB Pharmacists and Technicians

# Appendix Topics

- HCV Screening
- Transmission Counseling
- Accuracy of indirect markers for staging
- Extrahepatic Manifestations
- Rx in PWID—Guideline information
- Post-Rx progression of liver disease
- Random Fun Facts

# Overview of Hepatitis C

Genotype	Geographic area with highest prevalence
<p>1 Most prevalent globally</p>	<p>70 – 75% of all HCV infections in USA North America Asia/Australia/Europe/South America</p>
<p>2</p>	<p>13 – 15% of all HCV infections in USA South America &amp; West Africa</p>
<p>3 2<sup>nd</sup> most prevalent globally</p>	<p>10% of all HCV infections in USA India and parts of South East Asia</p>
<p>4</p>	<p>Egypt, North Africa, sub-Saharan Africa</p>
<p>5</p>	<p>South Africa and some part of Europe</p>
<p>6</p>	<p>China, Korea, Taiwan, Southeast Asia</p>

# Transmission Counseling

- Reinfection possible
- Avoid the new use of injection drugs and stop current use of injection drugs
- Reduce the frequency of injecting
- Use new, sterile needles, syringes, cotton, water, cookers each time you inject
- Do not share or reuse needles or syringes
- Safely dispose of needles and syringes
- Do not reuse or share other injection materials (cookers, cottons, water, drug)
- Receive substance-use treatment and support for safe injection practices

# Pre-treatment Testing

- Genotype, complete metabolic panel, CBC, INR,, Viral load
  - Within past 3 months
- HIV testing within the past year
- HAV and HBV serologies

$$\text{APRI} = \frac{\frac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count (10}^9\text{/L)}} \times 100$$

**Figure 3 - Aspartate Aminotransferase-to-Platelet-Ratio Index (APRI)**

# APRI

- Cut-off  $\leq 0.7$ : Sensitivity 77% for ruling out  $\geq$  F2 stages
- Cut-off  $\geq 2.0$  Specificity 91% (sens 46%), good for ruling in F3-F4,  $\geq 1.5$  threshold used by Medicaid
- Intermediate range (0.7-1.4) results have poor reliability
- Use APRI in combo with 2nd non-invasive test

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count (10}^9\text{/L)} \times \sqrt{\text{ALT (U/L)}}$$

**Figure 4 - Fib4**

The Fib4 represents an easy-to-use test for predicting severe hepatic fibrosis or cirrhosis (*Vallet-Pichard, 2007*)

## FIB-4

- < 1.45: F0-F2 (spec. 80%, sens 74%, NPV 90%)
- > 3.25: F3-F4 (specificity 97%)
- Intermediate ranges not reliable
- Overall accuracy of 86% in avoiding liver biopsy (70% cohort in cut-off ranges)
- Use in combo with 2<sup>nd</sup> non-invasive test

# FibroTest

- Predicts histology based on 6 biochemical tests, age and gender
- haptoglobin,  $\alpha$ 2-macroglobulin, apolipoprotein A1, GGT, bilirubin, ALT
- Costs ~ \$250
- NPV F0-F1 = 85%
- PPV F3-F4 = 76%
- Intermediate values not reliable,
- Cr  $\geq$  1.5: if Fibrosure elevated, may not be accurate

<b>Hepatitis C-Related Extrahepatic Manifestations</b>	
Symptom/Manifestation	Potential HCV-Related Syndrome
Hypertension	Membranoproliferative glomerulonephritis Nephropathy Cryoglobulinemia
Skin disease	Lichen planus Porphyria cutanea tarda Leukocytoclastic vasculitis Cryoglobulinemia vasculitis
Purpura	Cryoglobulinemic vasculitis Leukocytoclastic vasculitis
Distal neuropathic pain	Membranoproliferative glomerulonephritis without cryoglobulin Cryoglobulinemia-Membranoproliferative glomerulonephritis
Renal insufficiency Hematuria	Membranoproliferative glomerulonephritis without cryoglobulin Cryoglobulinemia-Membranoproliferative glomerulonephritis
Lymphadenopathy	Lymphoproliferative disorder
Fever	Cryoglobulinemia Cryoglobulinemic vasculitis Lymphoproliferative disorder
Arthralgia, weakness	Cryoglobulinemia Lymphoma Cryoglobulinemic vasculitis

# AASLD/IDSA Guidelines: Rx in PWID

Ideally, treatment of HCV-infected persons who inject drugs should be delivered in a multidisciplinary care setting with services to reduce the risk of reinfection and for management of the common social and psychiatric comorbidities in this population. Regardless of the treatment setting, recent and active IDU should not be seen as an absolute contraindication to HCV therapy. There is strong evidence from various settings in which persons who inject drugs have demonstrated adherence to treatment and low rates of reinfection, countering arguments that have been commonly used to limit access to this patient population ([Aspinall, 2013](#)); ([Hellard, 2014](#)); ([Grebel, 2011](#)). Indeed, combining HCV treatment with needle exchange and opioid agonist therapy programs in this population with a high prevalence of HCV infection has shown great value in decreasing the burden of HCV disease. Elegant modeling studies illustrate the high return on the modest investment of addressing this often-ignored segment of the HCV-infected population ([Martin, 2013b](#)). These conclusions were drawn before the introduction of the latest DAA regimens. Conversely, there are no data to support the utility of pretreatment screening for illicit drug or alcohol use in identifying a population more likely to successfully complete HCV therapy. These requirements should be abandoned, because they create barriers to treatment, add unnecessary cost and effort, and potentially exclude populations that are likely to obtain substantial benefit from therapy. Scale up of HCV treatment in persons who inject drugs is necessary to positively impact the HCV epidemic in the United States and globally.

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