AETC AIDS Education & Training Center Program Southeast

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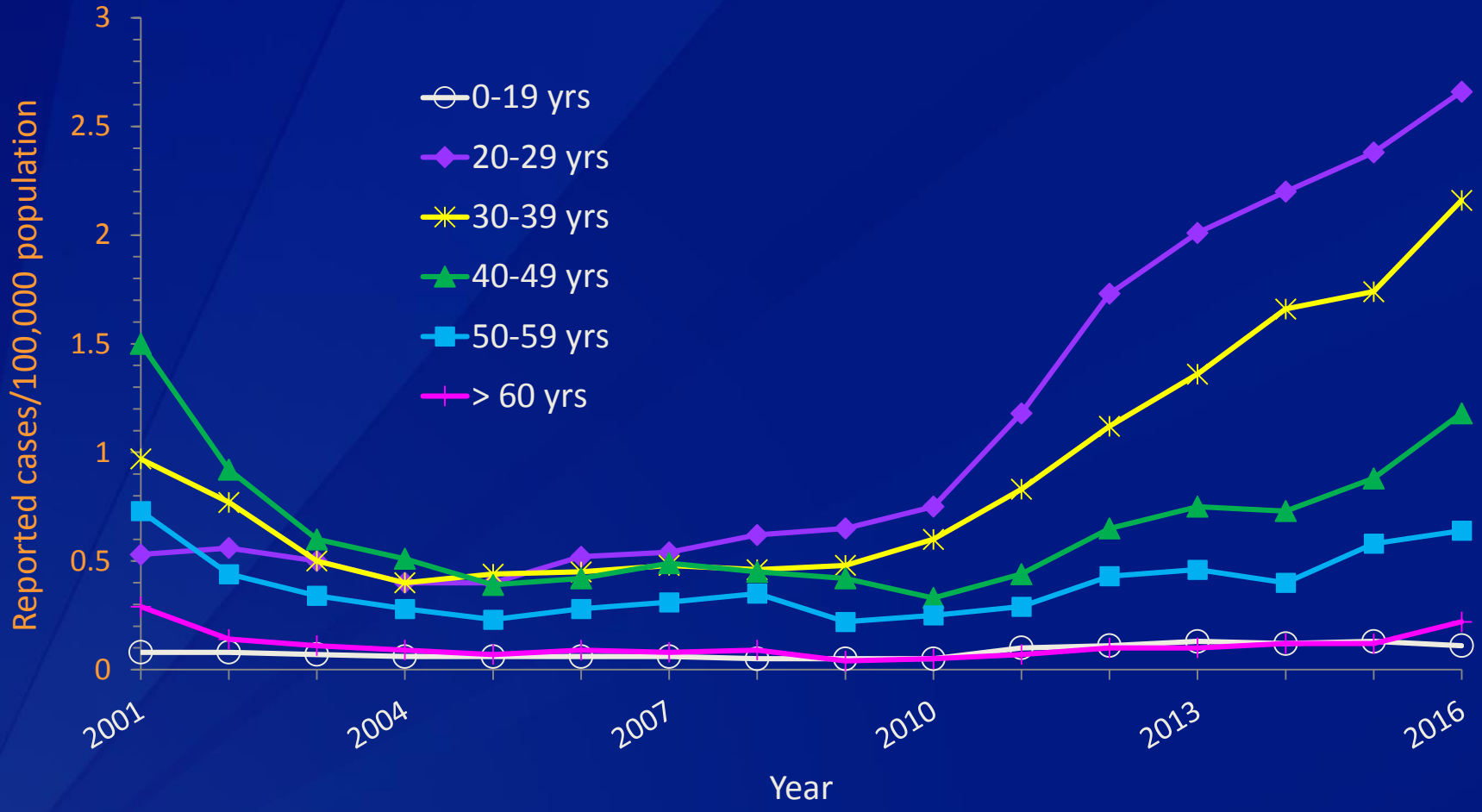
# Disclosures -None

# Opening Remarks

- HCV was discovered in 1989 by scientists at CDC and industry
  - 1990: routine testing of the blood supply began
  - 1998: CDC expands HCV testing recommendations
  - 2007: deaths from HCV surpass HIV
  - 2012: CDC recommends HCV testing of all baby boomers
- Currently in the United States, HCV affects
  - 1 out of 100 persons
  - 1 out of 25 baby boomers
- Of every 100 people infected with HCV, approximately:
  - 75 to 85 will go on to develop chronic infection
  - 10 to 20 will go on to develop cirrhosis over a period of 20 to 30 years

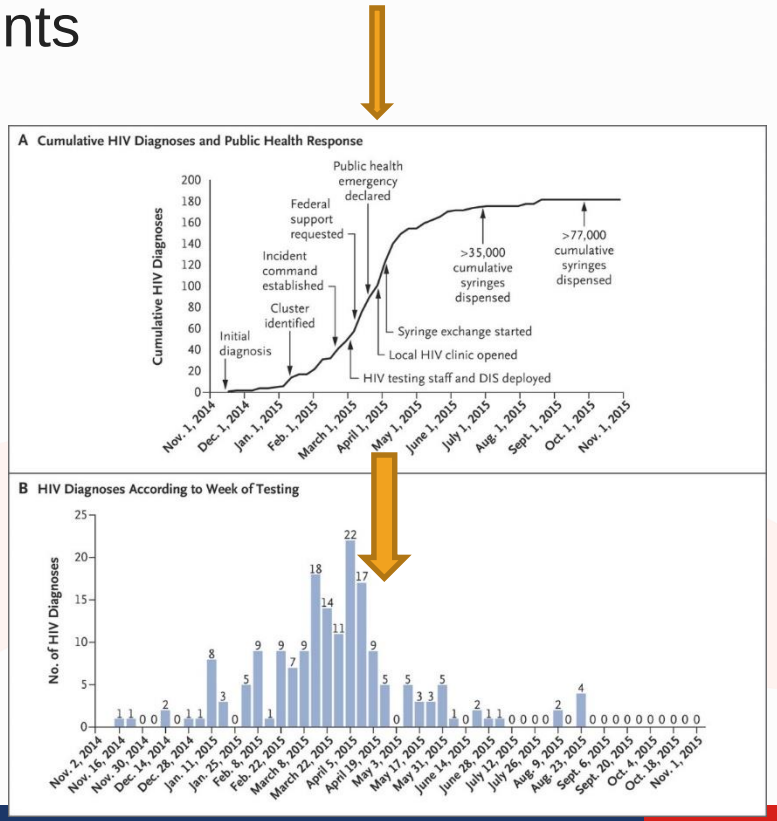
# Figure 4.2. Incidence of acute hepatitis C, by age group — United States, 2001–2016




Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)

# HIV and Hepatitis C Outbreak in Indiana

- November 18, 2014- November 1, 2015
- Scott County- Population-24,000
  - HIV infection- diagnosed in 181 patients
  - 92.3% -coinfected with HCV
  - 87.8% -IV oxymorphone
- Syringe Exchange Program
  - Huge positive impact




Peters PJ et al. N Engl J Med 2016;375:229-239.

# HIV/HCV- 10-30 % co-infection rate

- All patients with HIV should be screened for HCV infection
  - At-risk patients should undergo repeat testing annually(MSM).
- Patients with HCV/HIV coinfection:
  - Counsel to avoid alcohol and to use appropriate precautions
  - Should be screened for active and prior hepatitis B virus by testing
    - Hepatitis B surface antigen (HBsAg)
    - Hepatitis B surface (HBsAb)
    - HBcAb; total or IgG
- Active HBV infection : ART that includes TAF/TDF
- Hep B vaccination
- Hep A vaccination

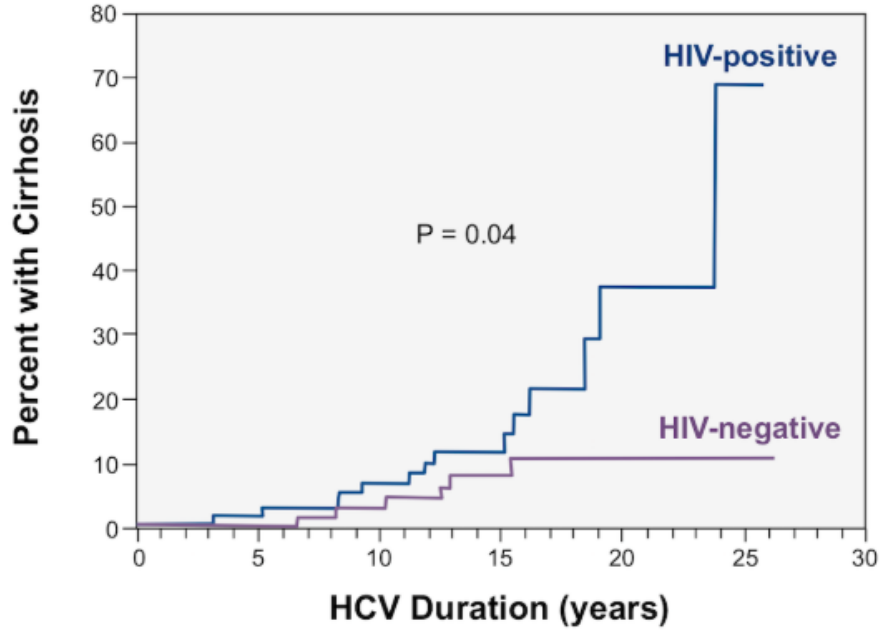



**Figure 1 - Progression to Cirrhosis in Patients with HCV Monoinfection and HIV-HCV Coinfection**
This graph shows accelerated progression to cirrhosis in patients with HIV-HCV coinfection when compared with those with HCV monoinfection.

Source: Di Martino V, Rufat P, Boyer N, et al. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. Hepatology. 2001;34:1193-9.

- Meta-analysis of 8 studies
- **More rapid progression of liver fibrosis in HIV/HCV co-infected patients vs HCV mono-infected patients**
  - Combined adjusted relative risk (RR) of 2.92
    - The RR is higher (6.14) in decompensated liver disease

*Graham CS, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis. 2001*

# HCV Screening: Behaviors, Exposures, and Conditions Associated With Increased Risk of HCV Infection

**General**

Adults born between 1945 and 1965

**Other Medical Conditions**

HIV infection

Sexually active persons about to start PrEP

Unexplained chronic liver disease and chronic hepatitis including persistently abnormal ALT

Solid organ donors (deceased and living)

**Risk Behaviors**

Past or current injection drug use

Intranasal illicit drug use

**Risk Exposures**

Chronic hemodialysis

Getting tattoo in an unregulated setting

Persons with recognized exposures (needle-sticks, mucosal exposures)

Birth to an infected mother

Recipients of transfusions or organ transplants

Recipients of clotting factors (prior to 1991)

Ever incarcerated

AASLD-IDSA. http://www.hcvguidelines.org/full-report-view.

# New USPSTF Recommendation for HCV Screening (Draft Recommendation)

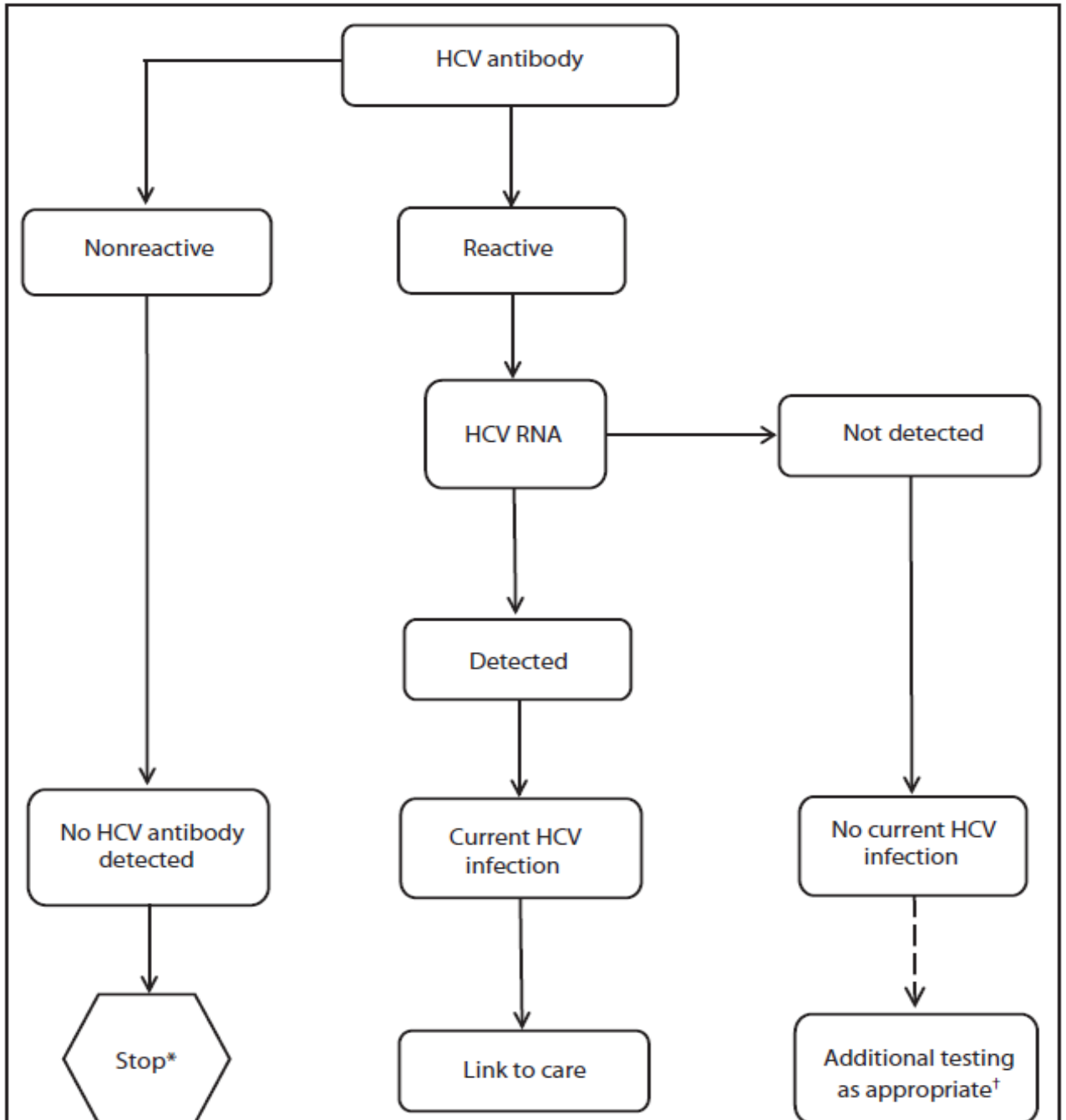
- **Screening for HCV infection in all adults ages 18 to 79 years has substantial net benefit. (Grade B evidence)**
  - Replaces the 2013 USPSTF recommendation
    - Screen persons at high risk
    - And 1-time screening for adults born between 1945 and 1965
- What has changed since the last recommendation in 2013
  - DAA regimens have evolved to shorter duration and improved safety
  - Prevalence of HCV infection has increased in younger persons, and remains relatively high in older adults

USPSTF. https://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement/hepatitis-c-screening1#tab.
Draft comment period expires 9/23/2019.

# Screening in Pregnancy

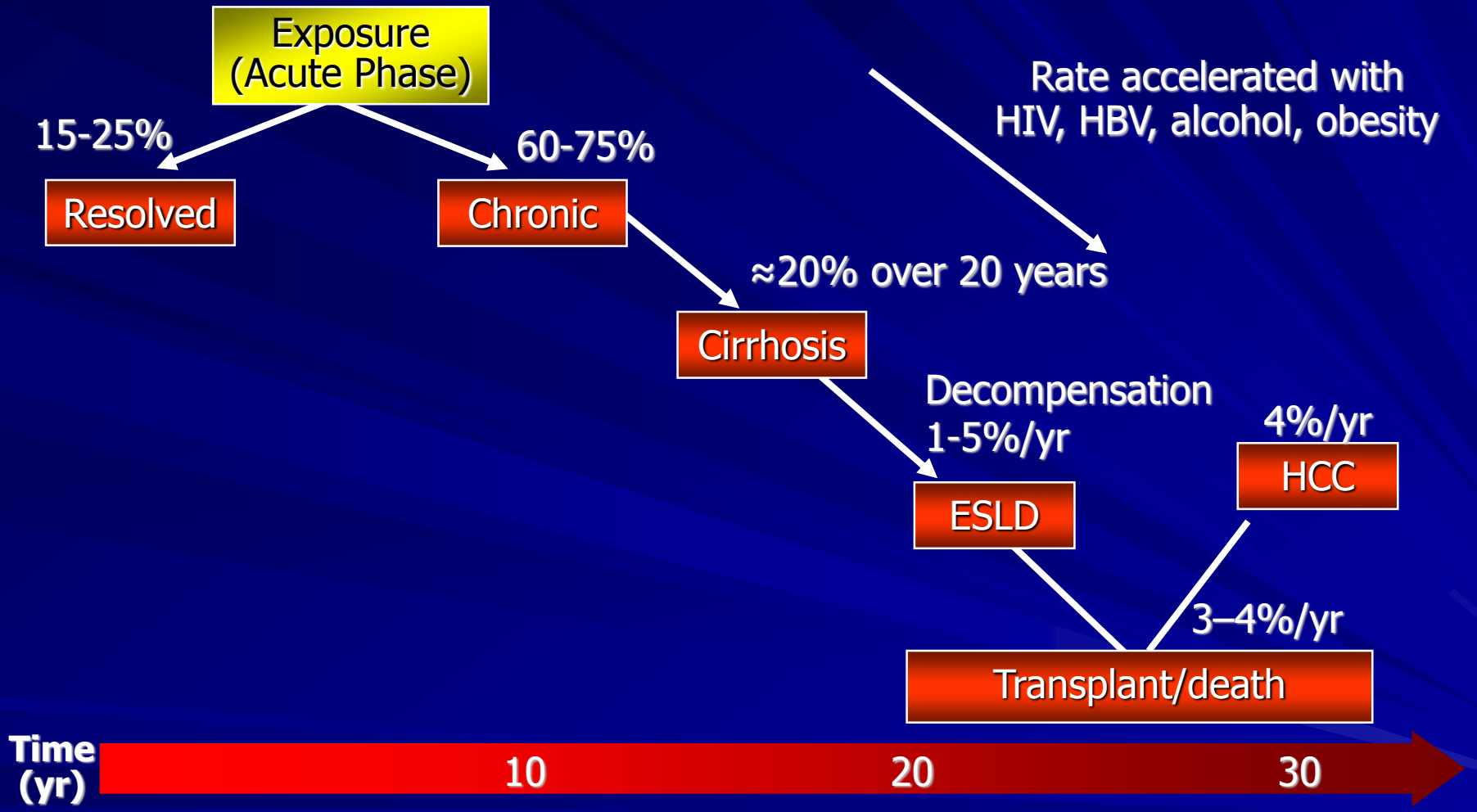
- Not yet routine.
- Rate of vertical transmission
  - HCV mono infected-  6%
  - HIV/HCV co infected- 11%
- Testing of infant
  - HCV RNA is the appropriate test.
- Endorse risk-based HCV screening
    - Centers for Disease Control and Prevention
    - American College of Obstetrics and Gynecology
    - The Society of Maternal-Fetal Medicine
- Endorsement of Universal HCV screening in pregnancy is coming!
  - AASLD-IDSA
  - USPSTF(Draft statement)

**FIGURE. Recommended testing sequence for identifying current hepatitis C virus (HCV infection**




MMWR / May 10, 2013

# Natural History of HCV Infection




HCC = hepatocellular carcinoma

ESLD = end-stage liver disease

Modified from Di Bisceglie A, et al. *Hepatology*. 2000;31:1014-1018.

# Course of HCV

- **Acute infection**
  - An estimated 44,300 acute HCV cases occurred in 2017.
  - HCV antibody can be detected 4-10 weeks after infection.
  - Acute HCV is asymptomatic in 70-80%.
  - 65-75% of persons will develop chronic infection

*Hoofnagle JH. Course and outcome of hepatitis C. Hepatology. 2002;36:S21-9*

- **Cirrhosis**
  - May develop in 20-30% about 20 years after infection
  - Meta analysis of PWID with CHC
    - Estimated time to cirrhosis was 34 years

*Smith DJ;. Int J Drug Policy. 2015;26(10):911–921*

# AASLD-IDSA Guidelines: Management of Acute HCV Infection

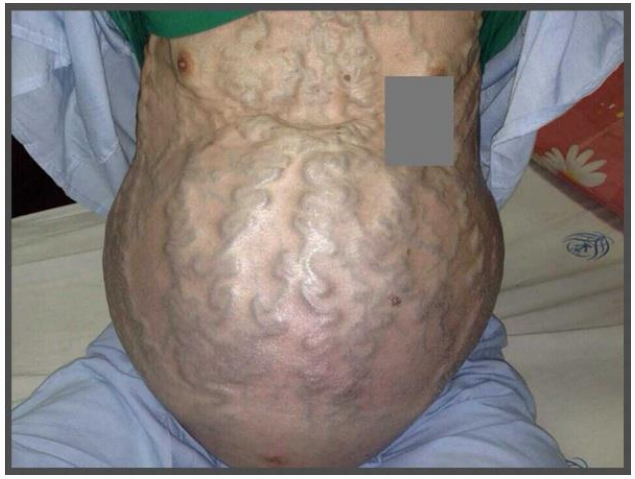
- If delaying treatment initiation is the plan
  - Monitor for spontaneous clearance (minimum of 4-6 months)
  - If decision is made to initiate treatment after 6 months, treat according to recommendations for chronic HCV

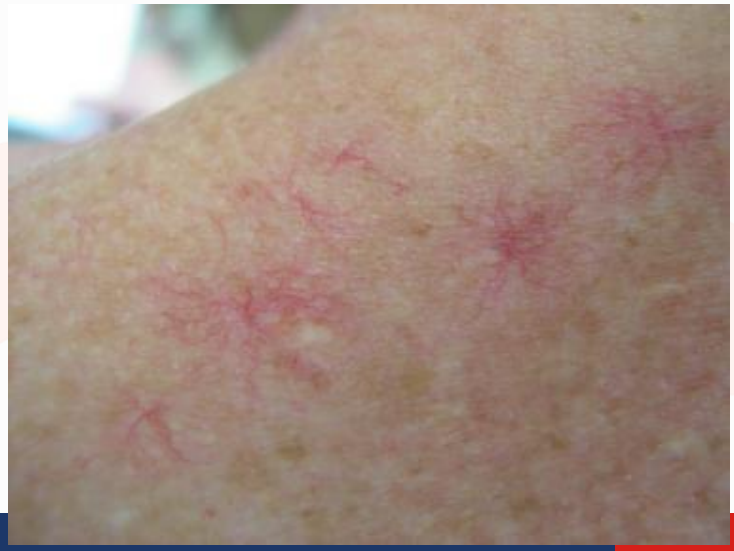
- If initiating treatment during the acute infection period
  - Monitor HCV RNA for at least 12 to 16 weeks before starting treatment
  - Owing to high efficacy and safety, the same regimens that are recommended for chronic HCV infection are recommended for acute infection

AASLD-IDSA. http://www.hcvguidelines.org/full-report-view. Version May 24, 2018.

# Advanced Fibrosis/cirrhosis

- Cirrhosis
  - Palmar Erythema
  - Gynecomastia
  - Spider nevi
  - Thrombocytopenia
- Decompensated cirrhosis
  - Ascites
  - Caput medusa
  - Jaundice
  - Coagulopathy

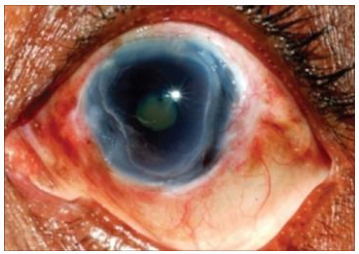


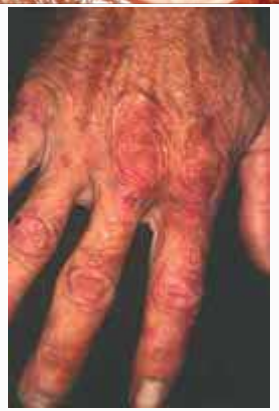


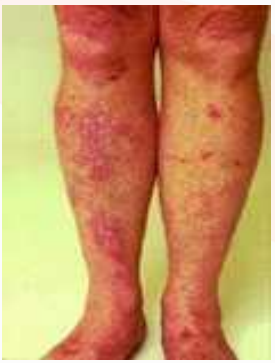
# Extrahepatic Manifestations of Hepatitis C

- Insulin resistance (Diabetes)
- Strokes?
- Hematologic:
  - Mixed cryoglobulinemia

  (10%–25% of HCV patients)
- Renal: Glomerulonephritis
- B Cell Non hodgkins lymphoma
- Sjogren's syndrome
- Dermatologic:
  - Porphyria cutanea tarda
  - Cutaneous necrotizing vasculitis







Management of Hepatitis C. NIH Consensus Statement, 2002.

# Complete Pre-treatment Evaluation

## General Labs

- HIV Antibody
- Hepatitis A(IgG or Total)
- Hepatitis B
  - HBc Ab (IgG or Total)
  - HBsAg
  - HBsAb (quantitative)
- CBC, CMP
- *(Mental health/Adherence)*

## HCV Specific data

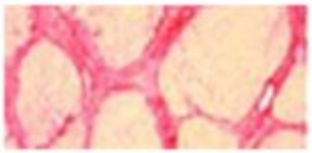
- HCV Genotype & subtype
- HCV RNA
- HCV treatment history
- Liver staging
- Ultrasound
  - To R/O HCC in advanced fibrosis only
- Baseline Resistance Testing
  - Very limited indications

# Genotypes

- **HCV genotype distribution**
  - GT 1 -77.%
  - GT 2- 13%
  - GT 3-12%;
  - GT 4 -1%
  - GT5 and GT6 < 1%
- *Germer JJ,et al: J Clin Microbiol. 2011;49(8):3040–3043.*
- GT3
  - Increase in GT 3 in IVDUs
  - GT3 associated with more cirrhosis and HCC
- *Kanwal F, et al. Hepatology. 2014;60(1):98–105.*

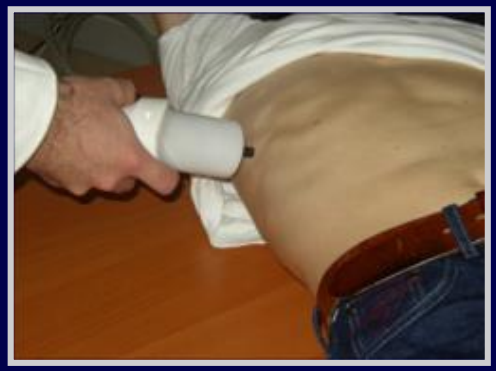
# Staging liver disease

- Degree of inflammation
  - Disease severity
  - Tissue damage

| Appearance | Ishak stage: Categorical description | ISHAK | METAVIR |
|---|---|---|---|
|  | No fibrosis (Normal) | 0 | F0 |
|  | Fibrosis expansion of some portal areas ± short fibrous septa | 1 | F1 |
|  | Fibrosis expansion of most portal areas ± short fibrous septa | 2 | F2 |
|  | Fibrosis expansion of most portal areas with occasional portal to portal(P-P) bridging | 3 | |
|  | Fibrosis expansion of portal areas with marked portal to portal(P-P) bridging as well as portal to central( P-C) | 4 | F3 |
|  | Marked bridging (P-P and/or P-C) with occasional nodules (incomplete cirrhosis) | 5 | |
|  | Cirrhosis, probable or definite | 6 | F4 |

# Staging Liver Fibrosis

| Clinical or Laboratory Tests | | | Imaging |
|---|---|---|---|
| **Invasive[1]** | **Simple[1]** | **Complex[2]** | **Elastography[3]** |
| ▪ **Liver biopsy**<br>▪ **Almost NEVER needed for HCV Rx** | ▪ AST-to-platelet ratio index<br>▪ FIB-4 index | ▪ *FibroSure* | ▪ VCTE *FibroScan*<br>▪ MR elastography<br>▪ ARFI |



1. AASLD/IDSA. HCV Guidelines. April 2017. 2. EASL, et al. J Hepatol. 2015;63:237-264. 3. Barr RG, et al. Radiology. 2015;276:845-861.

Slide credit: clinicaloptions.com

# Commonly used Liver staging modalities

## APRI
## FIB-4

- **APRI**
- AST to PLT ratio index
  - <0.5-low likelihood of fibrosis
  - >1.5: High likelihood of cirrhosis
- **FIB-4**
  - Age, AST, ALT, PLTs.
  - <1.45: Low likelihood of fibrosis
  - >3.25: High likelihood of cirrhosis

## Fibrosure

- **Patented Blood test**
- Measures-
  - alpha-2 macroglobulin, haptoglobin, GGT, ALT, and apolipoprotein A1

## Fibroscan

- **Ultrasound Transient elastography**
  - Non invasive
  - Equally accurate in measuring degree of liver inflammation and fibrosis as biopsy

# AST/Platelet Ratio Index (APRI)

- The lower the APRI (<0.5) the greater the negative predictive value to rule out cirrhosis.
- The higher the APRI (>1.5) the greater the positive predictive value to rule in cirrhosis

| APRI ability to detect significant fibrosis | | |
|---|---|---|
| APRI | Sensitivity | Specificity |
| Cutoff > 0.7 | 77% | 72% |
| Cutoff > 1 | 61% | 76% |
| Cutoff > 2.0 | 46% | 91% |

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

# Fibrosure/Fibrotest

A blood test that uses an algorithm to generate a measure of fibrosis and necro-inflammatory activity in the liver :

Biomarkers:

α2-macroglobulin; haptoglobin; apolipoprotein A1; bilirubin; γ-glutamyl transpeptidase (GGT); ALT; age and gender

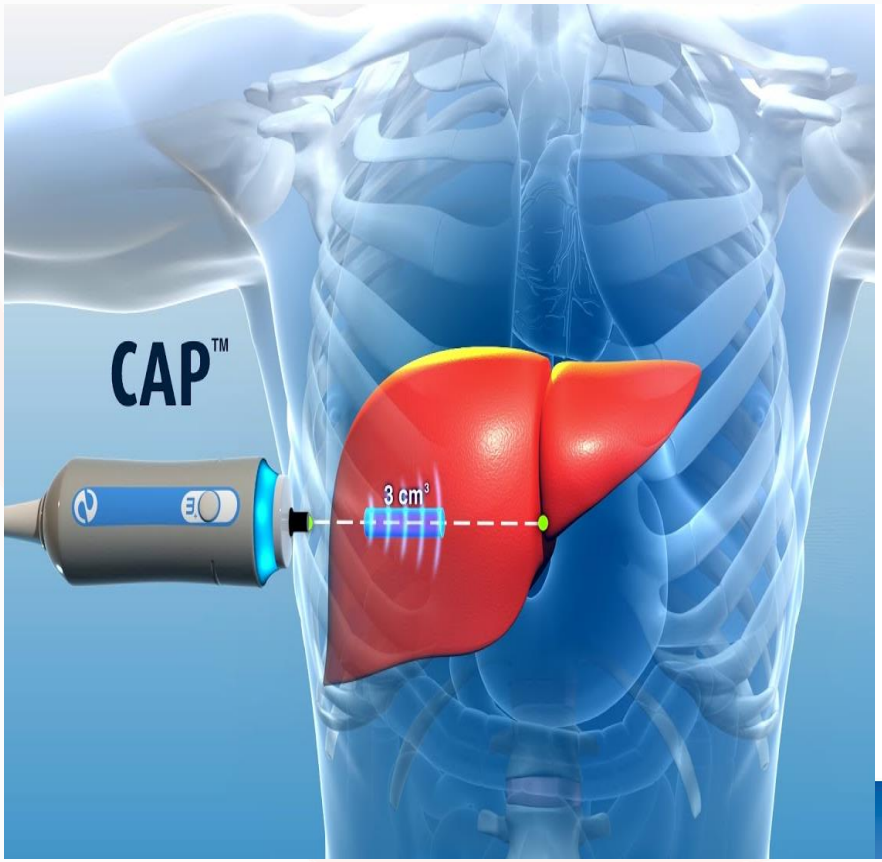
Advanced fibrosis : Sensitivity- 85%, Specificity - 60%

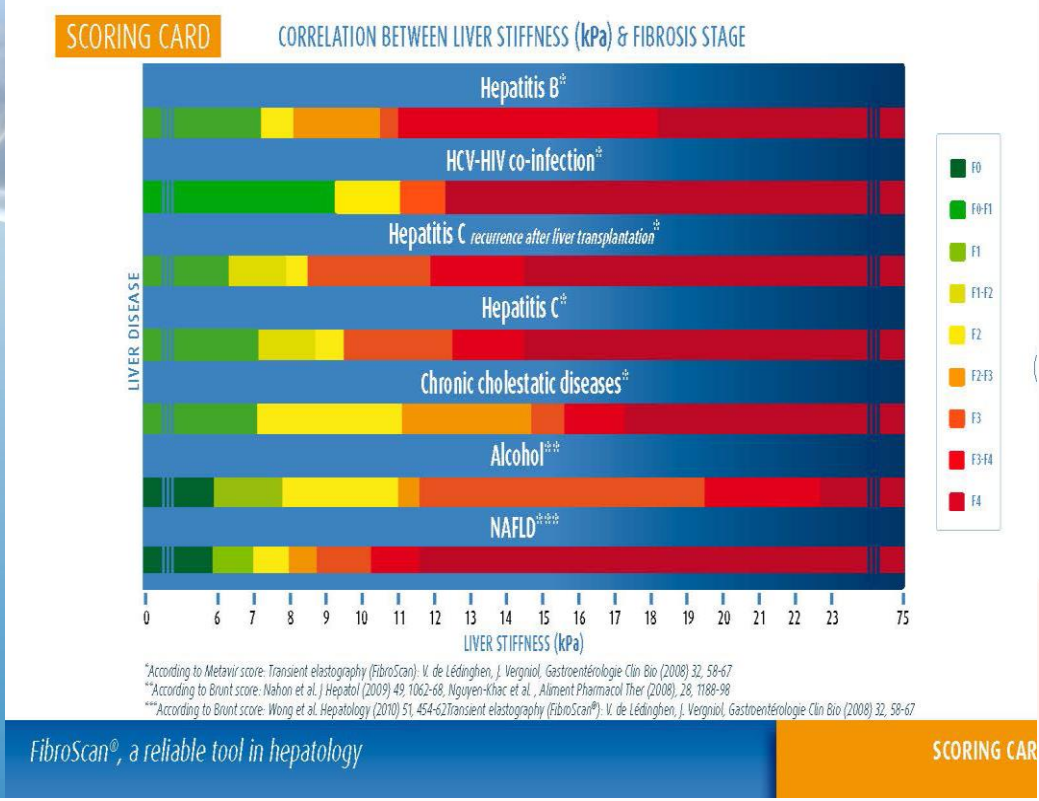
Score > 0.75 is consistent with cirrhosis

Caution in :Gilbert's disease, acute hemolysis, acute liver inflammation, extrahepatic cholestasis, renal insufficiency, post transplantation, or receipt of medications that may cause unconjugated hyperbilirubinemia.

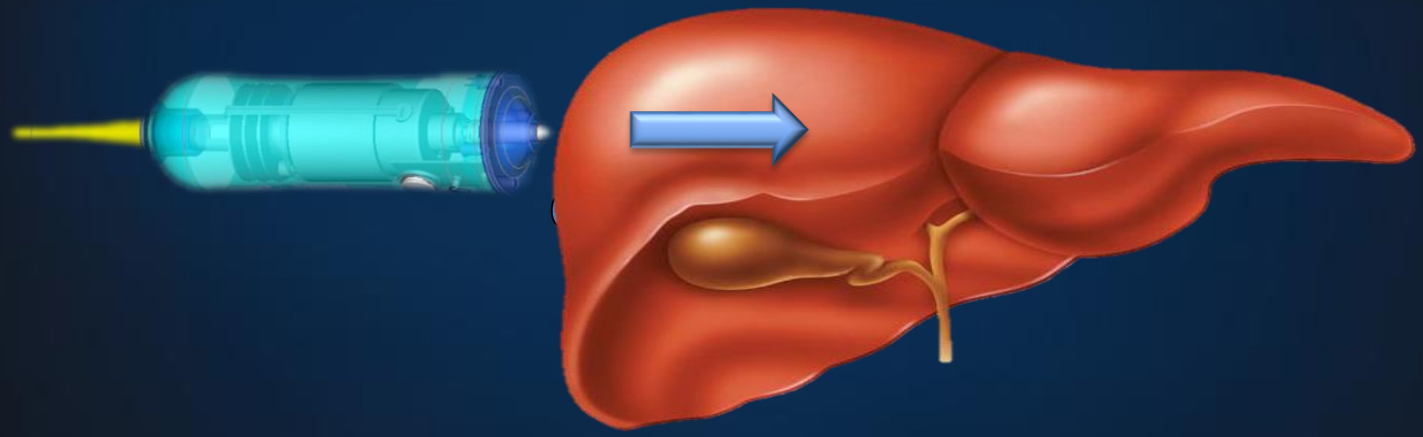
# Fibroscan®: **Transient elastography**

- **Least invasive**



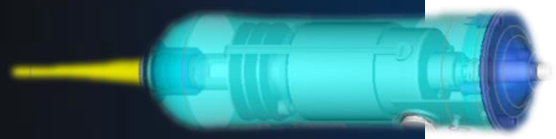



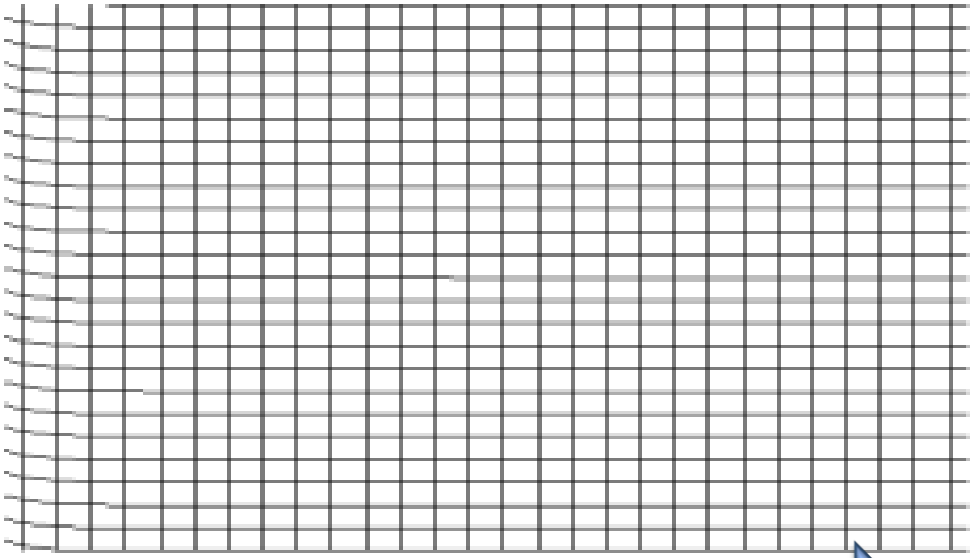
# Mechanical Shear Wave Induction



SANDHILL SCIENTIFIC
a medovations company

# Shear Wave Movement





# Non-invasive assessment of liver fibrosis

None of the non-invasive blood tests are perfect

Liver biopsy is almost never needed unless ruling out other concomitant liver problems

If clinical evaluation, or thrombocytopenia or liver ultrasound point towards cirrhosis or significant fibrosis then treat as such

Better to combine 2 different tests such as:

APRI+ Fibrosure

Or FIB-4 + Fibrosure

Or APRI + Fibroscan

# Ensure Hepatitis B testing is complete

- Evaluation prior to HCV treatment- CHECK ALL THREE
  - HBsAg
  - Hepatitis B c antibody (anti-HBc)- Total antibody or IgG
  - Hepatitis B surface antibody (anti-HBs)
- If a patient is HBsAg +-- check HBV DNA prior to DAA therapy
- If isolated anti-HBc positive- monitor every 4 weeks while on DAA therapy
- There have been a few cases of Hepatitis B “flare ups” while on HCV treatment



http://www.fda.gov/Drugs/DrugSafety/ucm522932.htm

# Hepatitis B Serology

| HBsAg | Total Anti-HBc | IgM Anti-HBc | Anti-HBs | Interpretation |
|---|---|---|---|---|
| Negative | Negative | -- | Negative | Susceptible; offer vaccination |
| Negative | Positive | -- | Positive | Immune due to natural infection |
| Negative | Negative | -- | Positive | Immune due to hepatitis B vaccination |
| Positive | Positive | Negative | Negative | Chronic HBV infection |
| Positive | Positive | Positive | Negative | Acute HBV infection |
| Negative | Positive | -- | Negative | 1. Resolved infection<br>2. Chronic Infection with low level HBsAg<br>3. False-positive anti-HBc; susceptible |

# Recommended Monitoring During Antiviral Therapy

- Clinic visits or telephone contact as clinically indicated
- 4 weeks after starting treatment
  - Creatinine  (eGFR), LFT, (CBC if on Ribavirin)
  - Quantitative HCV viral load
- 12 weeks after completion of therapy
  - Quantitative HCV viral load testing
- More frequent assessment and labs if
  - On Ribavirin ; on elbasvir/grazoprevir; or 4 week labs are abnormal; or HCV viral load is detectable at 4 weeks of Rx
- Stop treatment if 10-fold increase in ALT

# Vaccination

| Hep B vaccine | |
|---|---|
| Engerix B | 3 doses at 0,1 , 6-12 month |
| Heplisav:<br>New hepatitis B vaccine utilizes the CpG 1018 adjuvant | 2 doses at 0 and 1 months |
| **Combination of Hep A and Hep A** | |
| Twinrix | 3 doses at 0,1 and 6-12 months |
| **PPSV23, PCV13, TDaP as appropriate** | |

New recommendations by CDC on February 15, 2019

All persons aged >/= 1 year experiencing homelessness should be routinely immunized against HAV

# CASE PRESENTATIONS

# Case 1 – Dr. Holmes

| Baseline Demographics | | | | | |
|---|---|---|---|---|---|
| **Age:** 30 | **Race:** White | **Gender:** Female | | **Primary Insurance:** Medicaid | |
| **PMH/Comorbidities/Substance Use:** GERD, Smoker | | | | | |
| **Pertinent Clinical Findings:** N/A | | | | | |
| **Weight (kg):** | 80.91 | **Serum Albumin:** | 4.3 | **ALT:** | 31 |
| **Hgb:** | 12.3 | **Total bilirubin:** | 0.3 | **AST:** | 23 |
| **PLT:** | 282 | **INR:** | ----- | **SCr/CrCl:** | 0.52 (202.1) |

# Case 1

| HCV Evaluation | | | | | |
|---|---|---|---|---|---|
| **Ultrasound:** Not done | **CT:** Not done | | | | **MRI:** Not done |
| **Signs of Cirrhosis:** | No | | | | |
| **Staging Modality:** | **Results:** | **Interpretation:** | | **APRI:** | 0.2 |
| **Fibroscan/Transient Elastography:** | ----- | ----- | | **FIB-4:** | 0.44 |
| **Fibrosure:** | 0.04 | F0 | | | |
| **Treatment Naïve?:** | Yes | **If no, previous treatment:** N/A | | **HIV Antibody:** | Negative |
| **HCV Genotype:** | GT 1a | **HCV RNA:** | 510,000 | **HAV \| Total Ab:** | Negative |
| **HBV \| sAb:** | Negative | **HBV \| sAg:** | Negative | **HBV \| Total cAb:** | Non-Reactive |
| **Requested Regimen:** | Mavyret (glecaprevir 300mg/pibrentasvir 120mg) x 8 weeks | | | | |

# Case 1

- Medication List:
  - Omeprazole 20mg QD
  - Ranitidine 300mg HS

- Clinical Considerations:
  - Genotype 1a
  - Treatment naïve,
  - Metavir F0
  - HAV and HBV vaccinations needed

# Recommendations for When and in Whom to Initiate HCV Treatment

- **Treatment is recommended for all pts with chronic hepatitis C infection**
  - Exception: life expectancy likely to be < 6 months despite treatment or transplantation

**Goal of treatment is SVR**

Sustained virological response

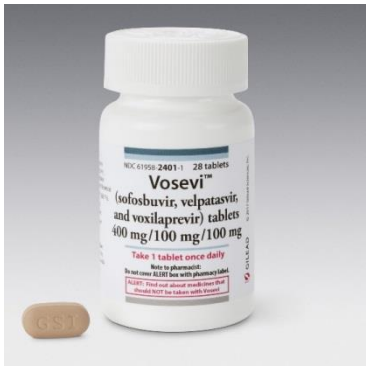
Undetectable HCV viral load 12 weeks after treatment completion

SVR (virologic cure) is defined as the continued absence of detectable HCV RNA for at least 12 weeks after completion of therapy

# Available co-formulated DAAs

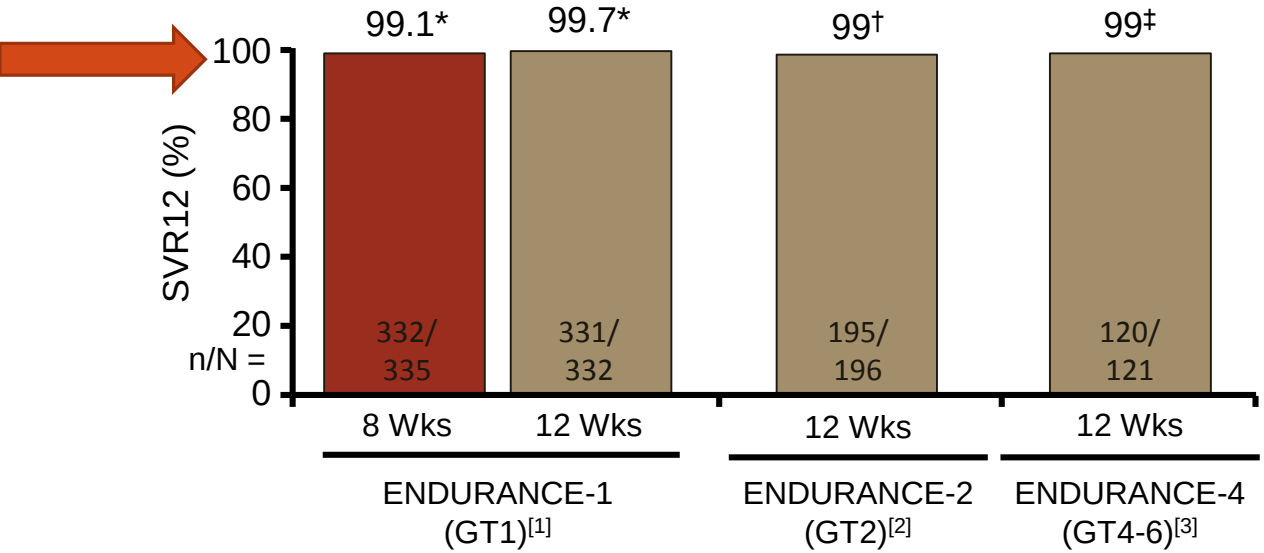




# Mavyret® **treatment naïve** studies: ENDURANCE-1, -2, -4 : Efficacy of GLE/PIB for GT1, 2, 4, 5, 6 HCV

## SVR > 99% regardless of GT or duration of therapy




1 case of on-treatment virologic failure at Day 29 in pt with GT1a HCV infection

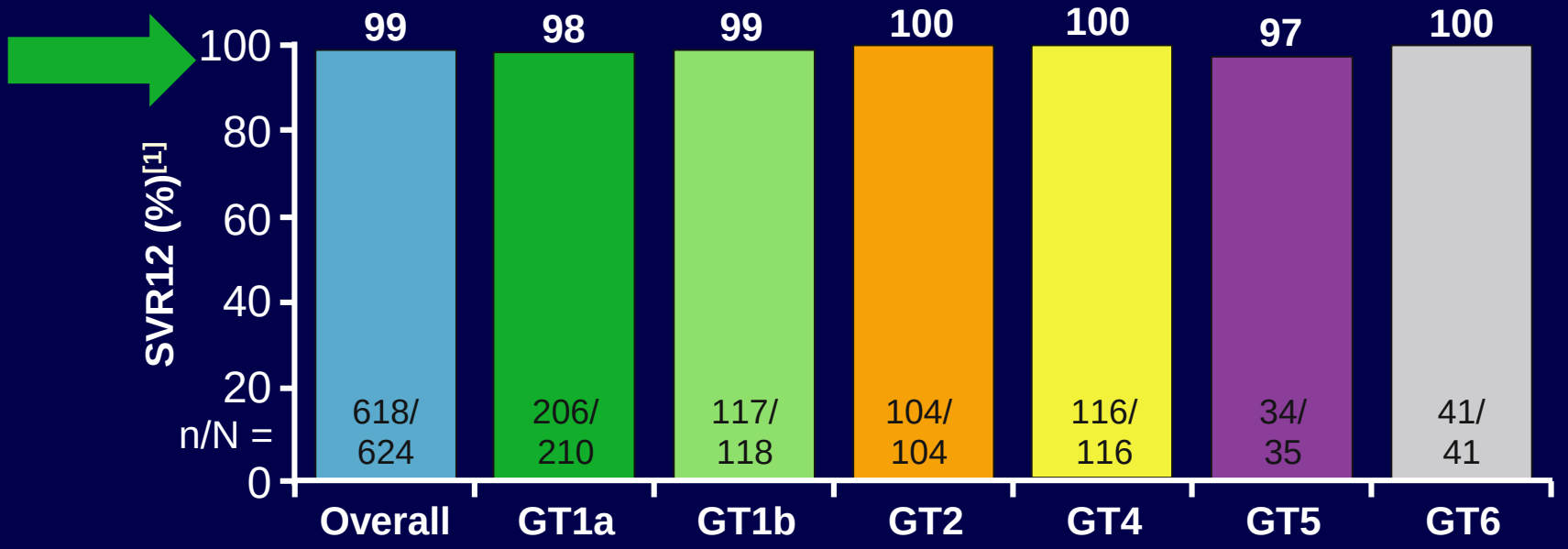
*ITT-PS analysis: included all pts receiving ≥ 1 dose of study drug; excluded pts with HIV coinfection or SOF experience.
†ITT analysis: excluded pts with SOF experience. ‡ITT analysis.

1. Zeuzem S, et al. AASLD 2016. Abstract 253. 2. Kowdley KV, et al. AASLD 2016. Abstract 73. 3. Asselah T, et al. AASLD 2016. Abstract 114.

Slide credit clinicaloptions.com

# ASTRAL-1: SOF/VEL for 12 Wks in GT1, 2, 4, 5, 6 Pts With and Without Cirrhosis

- 19% cirrhosis, 32% treatment experienced
- SVR > 97% regardless of genotype





1. Feld JJ, et al. N Engl J Med. 2015;373:2599-2607.
2. Foster GR, et al. N Engl J Med. 2015;373:2608-2617.


Slide credit: clinicaloptions.com

# Case 1 – Guideline Based Treatment

Recommended and alternative regimens listed by evidence level and alphabetically for:

## Treatment-Naive Genotype 1a Patients Without Cirrhosis

| RECOMMENDED | DURATION | RATING |
|---|---|---|
| Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[a] for elbasvir | 12 weeks | I, A |
| Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b] | 8 weeks | I, A |
| Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) | 12 weeks | I, A |
| 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 <6 million IU/mL | 8 weeks | I, B |
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) | 12 weeks | I, A |



AASLD/IDSA HCV Guidelines. 2018.

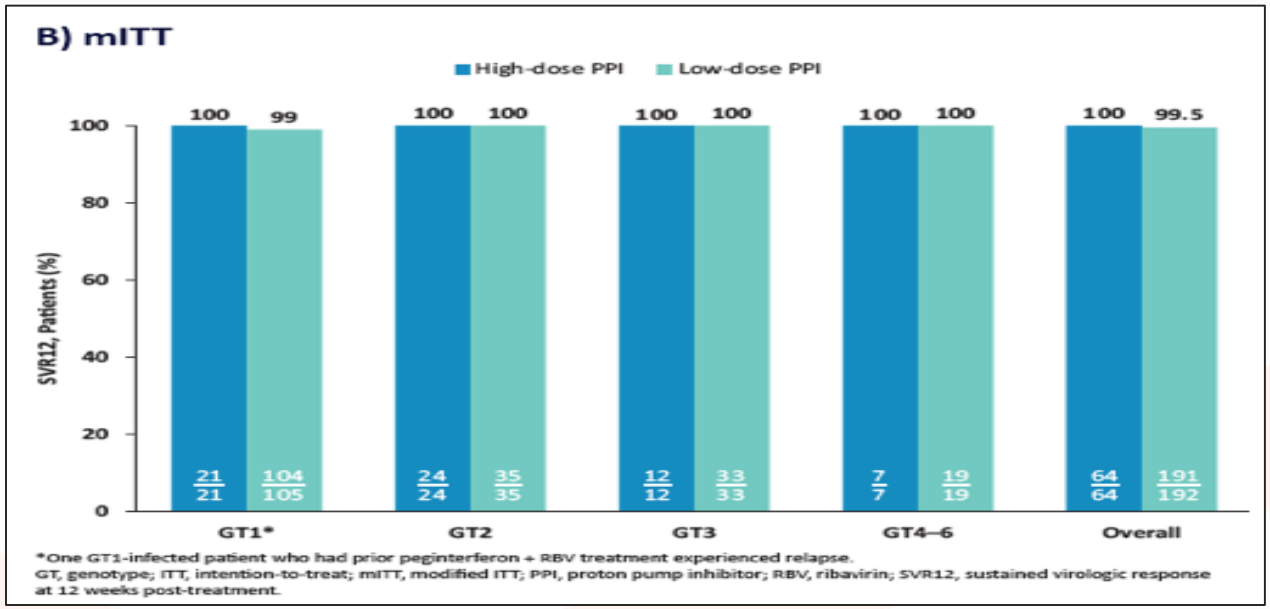
# Case 1 – Drug-Drug Interactions

| | EBR/GZR | GLP/PIB | LED/SOF | SOF/VEL |
|---|---|---|---|---|
| Omeprazole | ◆ | ▲ | ■ | ■ |
| Ranitidine | ◆ | ▲ | ■ | ■ |

- LED/SOF plus omeprazole-
  - Decreased ledipasvir Cmax and AUC by 11% and 4% respectively and increased sofosbuvir Cmax by 12%.
- SOF/VEL with food 4 hours before omeprazole (20mg once daily)
  - Decreased sofosbuvir Cmax by 21%, but increased AUC by 5%;
  - Velpatasvir Cmax and AUC decreased by 33% and 26%, respectively.
- GLP/PIB:
  - The potential for interaction between GLP/PIB and omeprazole and ranitidine is likely to be of weak intensity; additional action/monitoring or dosage adjustment is unlikely to be required.

# Glecaprevir/Pibrentasvir

- Pooled analysis of G/P in 2,369 patients (263 on PPI)
  → mITT SVR12 rate of 97.4%




Flamm, World Congress of Gastroenterology at ACG 2017

# Case 1

- Recommendations :
- All the DAAs will be > 97% effective in eradicating HCV, given the dual antacid therapy and potential for DDIs with Ledipasvir/Sofosbuvir and Velpatasvir/Sofosbuvir agree with:
  - Glecaprevir/Pibrentasvir (Mavyret®) x 8 weeks
  - Not recommending Elbasvir/Grazoprevir as it requires NS5A resistance testing prior to treating GT1a.

# Case 2

| Baseline Demographics | | | | | |
|---|---|---|---|---|---|
| **Age:** 54 | **Race:** White | **Gender:** Female | | **Primary Insurance:** Medicaid | |
| **PMH/Comorbidities/Substance Use:** Smoker (1/2 PPD); Substance Use (h/o IV drug use, last use 2017); Mental Health--schizophrenia, depression | | | | | |
| **Pertinent Clinical Findings:** N/A | | | | | |
| **Weight (kg):** | 85.9 | **Serum Albumin:** | 3.6 | **ALT:** | 42 |
| **Hgb:** | 12.8 | **Total bilirubin:** | 0.4 | **AST:** | 57 |
| **PLT:** | 91 | **INR:** | 1.1 | **SCr/CrCl:** | 0.89 (98) |

# Case 2

| HCV Evaluation | | | | | |
|---|---|---|---|---|---|
| **Ultrasound:** Not done | **CT:** Not done | | | | **MRI:** Not done |
| **Signs of Cirrhosis:** | No | | | | |
| **Staging Modality:** | **Results:** | **Interpretation:** | | **APRI:** | 1.57 |
| **Fibroscan/Transient Elastography:** | ----- | ----- | | **FIB-4:** | 5.22 |
| **Fibrosure:** | 0.73 | F3-F4 | | | |
| **Treatment Naïve?:** | Yes | **If no, previous treatment:** N/A | | **HIV Antibody:** | Negative |
| **HCV Genotype:** | GT 1a | **HCV RNA:** | 3,170,000 | **HAV \| Total Ab:** | Positive |
| **HBV \| sAb:** | Negative | **HBV \| sAg:** | Negative | **HBV \| Total cAb:** | Non-Reactive |
| **Requested Regimen:** | Sofosbuvir/Velpatasvir (Epclusa®) x 12 weeks | | | | |

# Case 2

- Medication List:
  - Citalopram 40mg QD
  - Divalproex ER 250mg TID
  - Lisinopril 20mg QD
  - Quetiapine 100mg QD
  - Trazodone 50mg QD
  - Triamterene/HCTZ 37.5mg/25mg QD

- Clinical Questions
  - Treatment naïve
  - GT 1a
  - Metavir F3-F4
  - HBV vaccination
  - Drug-Drug interactions
  - Thrombocytopenia
  - Concordant Liver Staging

# HCV Elimination Strategy

**HCV elimination in US not feasible without engaging, treating PWID**

- 30.5% of all HCV infections in North America are among people with recent IDU

- PWID
  - Do not seek medical care
  - Isolated, live in poverty, homeless, mental health issues
  - 60% of PWID have a history of incarceration

- PWID- duration of IVDU
  - 20% use intravenous drugs for <5 years
  - 15% use for <10 years
  - 30% are persistent lifelong users of injection drugs

*Degenhardt L, et al: Lancet Glob Health. 2017;5:*
*Genberg BL, et al.. Am J Epidemiol. 2011;173:829-836.*



WHO. Global Health Sector Strategy on Viral Hepatitis, 2016-2021.
NASEM. A national strategy for the elimination of hepatitis B and C. Washington, DC: The National Academies Press; 2017.
Grebely. Addiction. 2019;114:150.

# Opioid Substitution Therapy

- Suboxone®
  - Contains buprenorphine and naloxone
- Buprenorphine
  - partial opioid agonist
  - suppresses craving and withdrawal symptoms
- Naloxone
  - Helps reverse the effects of opioids

No major DDIs with MAT and DAAs

| | EBR/GZR | GLP/PIB | LED/SOF | SOF/VEL | SOF/VEL/VOX |
|---|---|---|---|---|---|
| Buprenorphine | ◆ | ◆ | ▲ | ▲ | ▲ |
| Methadone | ◆ | ◆ | ◆ | ◆ | ◆ |
| Naltrexone | ◆ | ◆ | ◆ | ◆ | ◆ |

# SVR and Reinfection rates in PWID

- SVR Rates:
  - PWID have **similar** SVR rates as patients without a history of IVDU and not receiving OST
- Reinfection rates:
  - Patients who continue to use intravenous opioids
  - 5%-10% annual risk of becoming reinfected with HCV
- The relapse rate back to active drug abuse after completing rehab programs
  - Ranges from 40% - 80%.
  - 10% risk of dying from a narcotic overdose within 3 years


- *Dore GJ, Altice F, Litwin AH, et al. Ann Intern Med. 2016;165:625-634.*
- *Valerio H, et al. Drug Alcohol Depend. 2015;154:125-131*

# Progression of cirrhosis

- NIH -sponsored HALT–C study
  - 220 patients with HCV related cirrhosis
  - Observed for  8 years
- Primary outcome - death, hepatic decompensation, Hepatocellular carcinoma (HCC), or increase in CTP score ≥2
  - Rate of 7.5% per year
  - Patients with a CTP score of ≥7 experienced a death rate of 10% per year.

- *Di Bisceglie AM,et al. N Engl J Med. 2008;359(23):2429-2441.*

# Benefits of SVR

- 3,010 treatment-naive patients from 4 randomized trials
  - Pretreatment and post treatment liver biopsies
  - 10 different interferon-based regimens
- **40% - 73%** who achieved SVR had improvement in liver fibrosis and necrosis.
- Cirrhosis resolved in **49%** of the cases
- Portal hypertension, splenomegaly, and other clinical manifestations of advanced liver disease also improved

*Poynard T, et al. Gastroenterology. 2002;122(5):1303-1313.*

- SVR is associated with
- >70% reduction in the risk of HCC
- 90% reduction in the risk of liver-related mortality and liver transplantation

*Van der Meer AJ, et al. JAMA. 2012;308(24):2584-2593*

# Hepatocellular carcinoma in HCV

- **Hepatocellular Carcinoma**
  - HCV induced HCC is seen in 1- 5% after 30 years
  - HCV accounts for 1/3rd of HCC in the US
  - In cirrhotic patients risk is estimated to be 3.5%/year

  *Younassi et al:Aliment Pharmacol Ther 2014; 39: 518–531*

  - HCC in patients with HCV occurs almost exclusively in patients with advanced stages of hepatic fibrosis or cirrhosis

  *Lok AS, et al, HALT-C Trial Group ; Gastroenterology. 2009*
- Risk factors
  - Age, male sex, black race , smoking, advanced cirrhosis, GT 3, GT1b,co-infection with hep B, DM, Obesity
- AASLD -suggests life long surveillance using ultrasound with or without alpha-fetoprotein every 6 months for patients with advanced fibrosis

# Case 2 – Guideline Based Treatment

Recommended and alternative regimens listed by evidence level and alphabetically for:

**Treatment-Naive Genotype 1a Patients With Compensated Cirrhosis[a]**

| RECOMMENDED | DURATION | RATING |
|---|---|---|
| Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[b] for elbasvir | 12 weeks | I, A |
| Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[c] | 12 weeks | I, A |
| Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) | 12 weeks | I, A |
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) | 12 weeks | I, A |
| **ALTERNATIVE** | **DURATION** | **RATING** |
| Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for patients with baseline NS5A RASs[b] for elbasvir | 16 weeks | IIa, B |

[a] For decompensated cirrhosis, please refer to the appropriate section.

[b] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.

[c] This is a 3-tablet coformulation. Please refer to the prescribing information.



AASLD/IDSA HCV Guidelines. 2018.

# Case 2 – Drug-Drug Interactions

| | EBR/GZR | GLP/PIB | LED/SOF | SOF/VEL |
|---|---|---|---|---|
| Citalopram | ◆ | ◆ | ◆ | ◆ |
| Hydrochlorothiazide | ◆ | ◆ | ◆ | ◆ |
| Lisinopril | ◆ | ◆ | ◆ | ◆ |
| Quetiapine | ■ | ■ | ◆ | ◆ |
| Trazodone | ◆ | ◆ | ◆ | ◆ |
| Valproate | ◆ | ◆ | ◆ | ◆ |

- Quetiapine & EBR/GZR, GLP/PIB – Could lead to increased concentrations of Quetiapine, which has a narrow therapeutic index and unpredictable therapeutic levels at steady state, requiring patients to be monitored closely. Use with caution.
- EBR/GZR – no resistance testing done, not indicated here

# Case 2 – Recommendations

- Guideline Based Therapy:
  - Ledipasvir/Sofosbuvir (Harvoni®) x 12 weeks
  - Sofosbuvir/Velpatasvir (Epclusa®) x 12 weeks
- Lifelong Screening for HCC as he has cirrhosis
- Reconsider Valproic Acid
  - Thrombocytopenia could be due to cirrhosis or valproic acid (1-27% and is dose related)
  - Valproate is also hepatotoxic
- Referral for EGD to screen for varices
- Vaccinate for HBV

# HCV Therapy Highly Effective in HIV/HCV-Coinfected Patients

| | Study | Population | HCV Regimens | SVR12, % |
|---|---|---|---|---|
| **HARVONI** | ION-4 | N = 335; GT1 (98%) or 4 | LDV/SOF 12 wks | **96** |
| | ERADICATE | N=50 | | **100** |
| **ZEPATIER** | C-EDGE CO-INFECTION | N = 218; GT1, 4, 6 | EBR/GZR 12 wks | **96** |
| **EPCLUSA** | ASTRAL-5 | N = 106; GT1-4 | SOF/VEL 12 wks | **95** |
| **MAVYRET** | EXPEDITION-2 | N = 153; GT1-6 | GLE/PIB for 8 wks without cirrhosis or 12 wks with cirrhosis | **98** |
| | ENDURANCE-1 | N=15, GT1 | | **100** |

1. Naggie. NEJM. 2015;373:705. 2. Rockstroh. Lancet HIV. 2015;2:e319.
3. Wyles. Clin Infect Dis. 2017;65:6. 4. Rockstroh. Clin Infect Dis. 2018;67:1010.

AETC AIDS Education & Training Center Program Southeast

**Monthy 1st and 3rd Wednesday and**
**12:00pm-1:00pm EST**
**11:00am-12:00pm CST**
**09:00am-10:00am PST**

**4th Wednesday**
**12:00pm-1:00pm CST**
**01:00pmpm-2:00pm EST**
**10:00am-11:00am PST**

# South East Viral Hepatitis Interactive Case Conference