

Hepatitis C in the HIV Co-infected Population: Where are we today?

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Disclosures

- Consulting and fees for non-CME/CE services from AbbVie, Merck, and Gilead Sciences.

Learning objectives

- Gain a better understanding of HCV prevalence
- Discuss the impact of HIV infection on liver disease progression
- Discuss the natural history of HCV infection
- Describe HCV treatments and considerations among HIV-HCV population

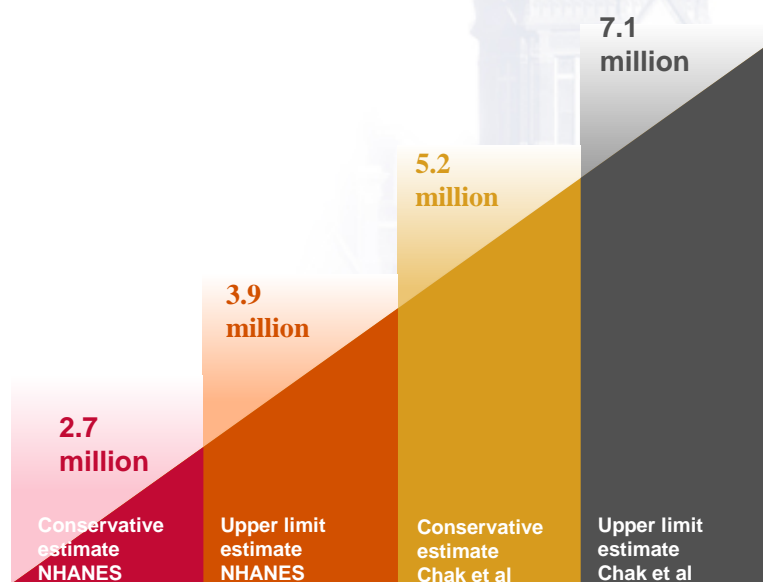
What is hepatitis C?

- An RNA virus known as non-A, non-B hepatitis until it was discovered in 1988
- Hep C Virus (HCV) lives in the liver
- Damages the liver slowly, scars it over decades (fibrosis) and leads to cirrhosis
- Most people with HCV have NO symptoms or physical signs
- First therapy approved in 1991 (interferon injections with ~6% cure rate)
- Scientific advances have made HCV treatment shorter, safer, more effective with cure rates around 95%

The US prevalence of Hepatitis C infection is likely underestimated

- The CDC estimates US prevalence to be 2.7-3.9 million (1%-1.5%)
 - Based on NHANES data, which excludes homeless and incarcerated populations²
- HCV infection prevalence may be as high as ~7 million with inclusion of populations omitted or underrepresented* by NHANES

Estimates of US HCV Infection Prevalence

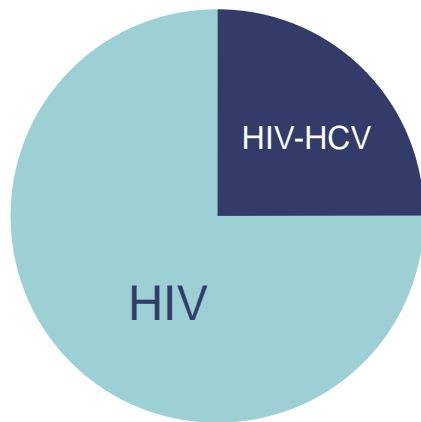


*Homeless, incarcerated, Veterans, active military duty, healthcare workers, nursing home residents, and patients on chronic hemodialysis or with hemophilia who received transfusions before 1992.

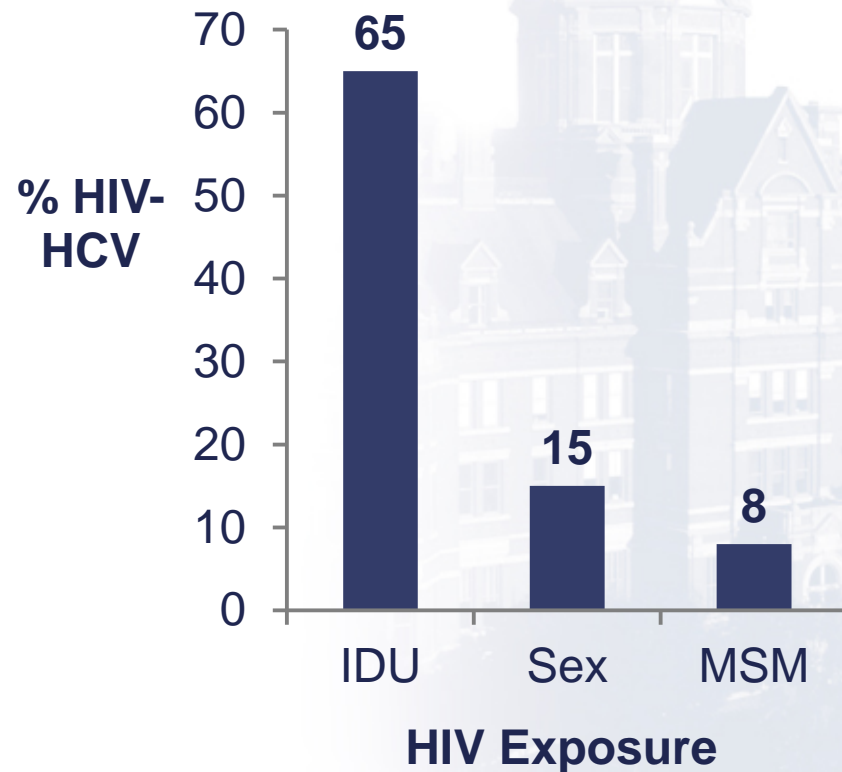
CDC=Centers for Disease Control and Prevention; NHANES=National Health and Nutrition Examination Survey; HCV=hepatitis C virus.

1. Smith BD, et al. *MMWR Recomm Rep.* 2012;61(RR-4):1-32. 2. Armstrong GL, et al. *Ann Intern Med.* 2006;144(10):705-714. 3. Chak E, et al. *Liver Int.* 2011;31(8):1090-1101.

High Prevalence of HCV infection among HIV infected individuals



Prevalence differs by HIV risk group



Hepatitis C Burden

- Hepatitis C virus (HCV) infection is the **leading** cause of cirrhosis, liver cancer, and liver transplantation in US
- Of all persons living with HCV infection, about 75% were born during 1945-1965.
- Persons with chronic hepatitis C infection have an estimated mortality rate 12 times higher than the general population.

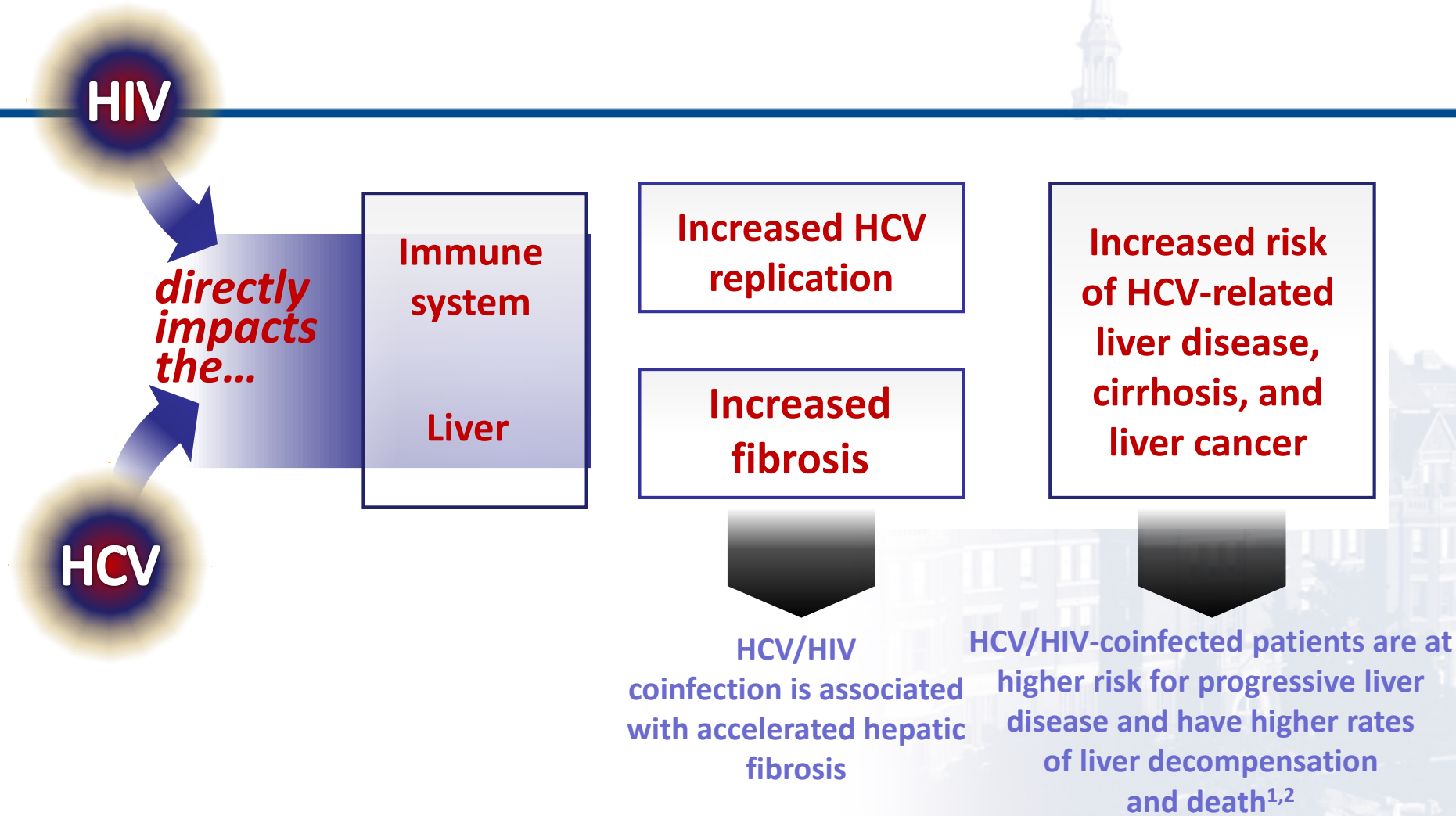
Liver disease remains 2nd leading cause of death in HIV-infected persons in D:A:D

- 33,308 participants from 1999-2008
 - 15.3% with HCV (Ab or RNA+)
 - 11.5% HBV (prior/active)
- 2482 deaths
 - 29.9% AIDS-related
 - 13.7% liver-related
 - 11.6% CVD-related
- Rates highest in CD4<100 cells/mm³

D:A:D study, *AIDS* Jun 2010 24(10)

A mostly European database called DAD (the Data collection on Adverse events of anti-HIV Drugs) has enrolled more than 33,000 HIV positive people in an attempt to try to find out more about uncommon side effects. The *DAD study* is currently ongoing.

Impact of HIV Infection on Chronic HCV

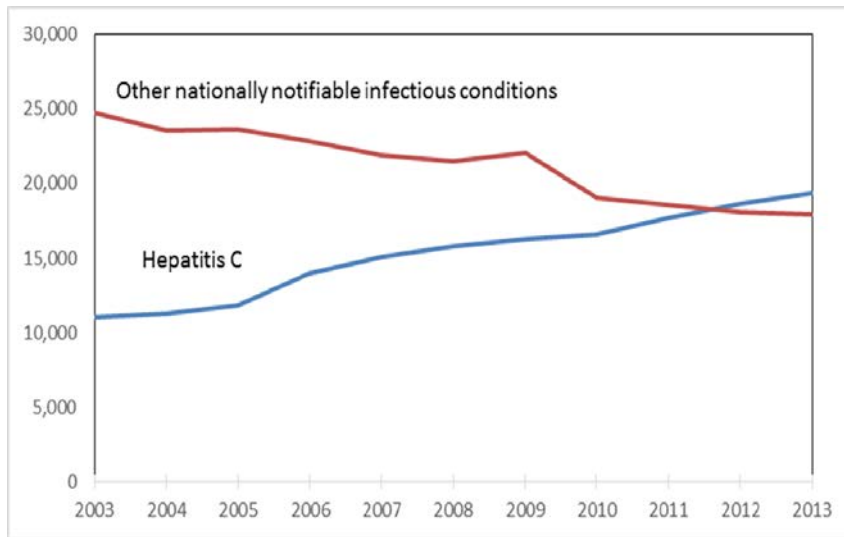


1. Chen JY, et al. *Nat Rev Gastroenterol Hepatol*. 2014;11:362-371.

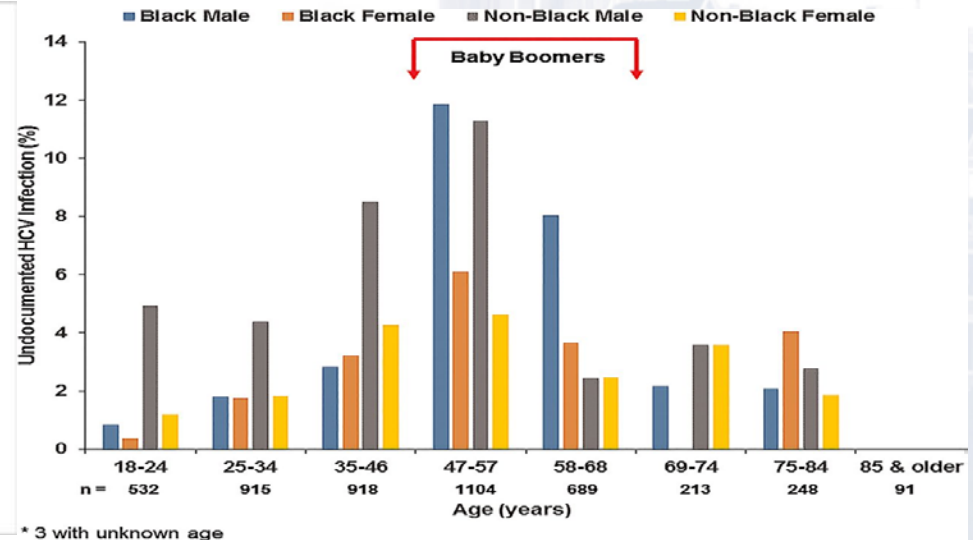
2. CDC. Hepatitis C Virus and HIV Coinfection. http://www.cdc.gov/IDU/hepatitis/hepc_and_hiv_co.pdf. Accessed August 18, 2015.

Hepatitis C is a leading and preventable cause of morbidity and mortality in the United States

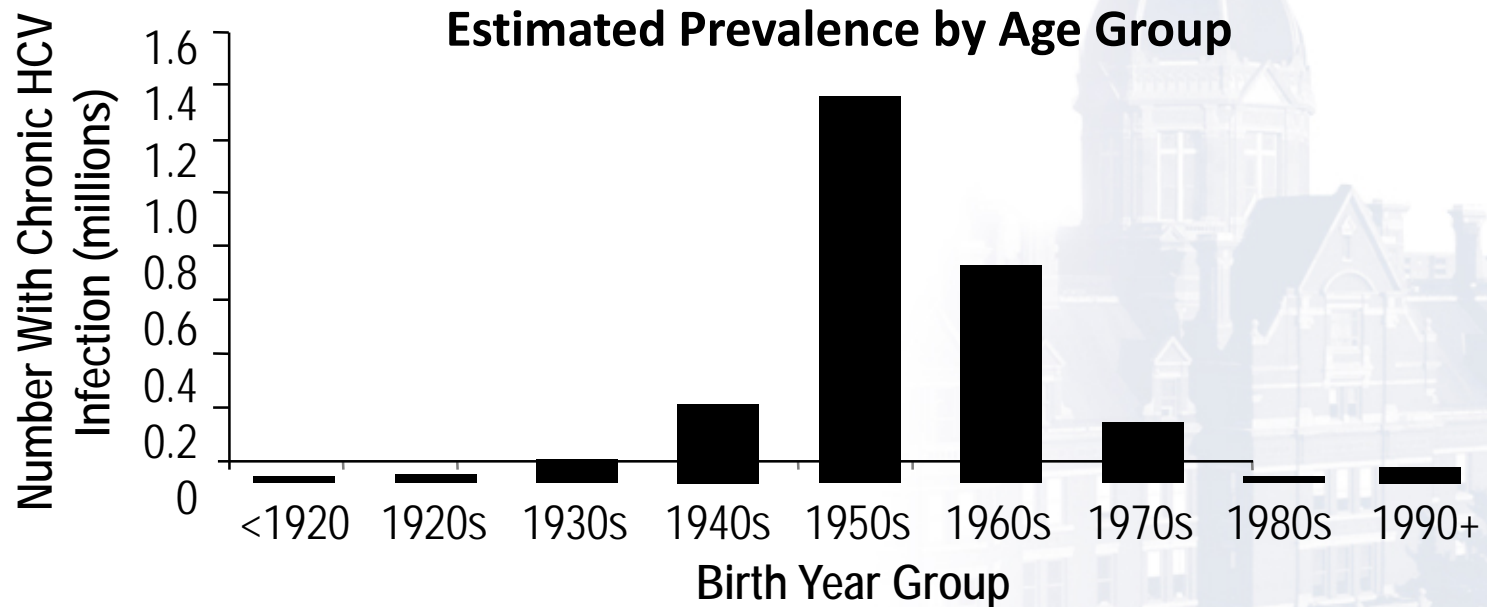
HCV causes more deaths in the US than HIV and 59 other CDC reportable infectious conditions



14% of persons presenting to the Johns Hopkins ED have undiagnosed hepatitis C



Baby Boomers (Born 1945-1965) & HCV



- **Up to 75% of people with HCV in the US are undiagnosed**
- **An estimated 35% of undiagnosed baby boomers with HCV currently have advanced fibrosis (F3-F4, bridging fibrosis to cirrhosis)**

1. Centers for Disease Control and Prevention. *MMWR*. 2012;61:1-18; Adapted from Pyenson B, et al. *Consequences of Hepatitis C Virus (HCV): Costs of a baby boomer Epidemic of Liver Disease*. New York, NY: Milliman, Inc; May 18, 2009. <http://www.milliman.com/expertise/healthcare/publications/rr/consequences-hepatitis-c-virus-RR05-15-09.php> Milliman report was commissioned by Vertex Pharmaceuticals; 3. McGarry LJ et al. *Hepatology*. 2012;55(5):1344-1355.

A Silent Killer

Hepatitis C infection is usually asymptomatic and often goes undiagnosed unless:

- Patient enters primary care for unrelated medical issues and consequent blood panels reflect elevated enzymes
- End stage liver disease or liver cancer has occurred and symptoms present
- HCV screening and testing occurs based on risk behaviors or birth cohort

Screening for Hepatitis C Infection

The CDC & USPSTF recommend:

- Screening for HCV infection in persons at elevated risk for infection.
- Offering one time screening for HCV infection to adults born between 1945 and 1965.

Some experts recommend screening everyone at least once for both HIV and HCV.

WHO to test for HCV?

- Birth Cohort: born between 1945 – 1965
- Ever IDU (annual for active IDU)
- Ever intranasal drug use
- Tattoo (unregulated)
- All HIV+ (annual for MSM living with HIV)
- Ever Incarcerated
- Hemodialysis, ever
- Blood transfusion or products, organ recipients, prior to July 1992
- Clotting factor concentrates before 1987
- Needlestick / occupational exposure
- Children born to HCV+ woman
- Unexplained chronic liver disease, elevated ALT
- MSM and high number of sex partners, sex while using methamphetamine

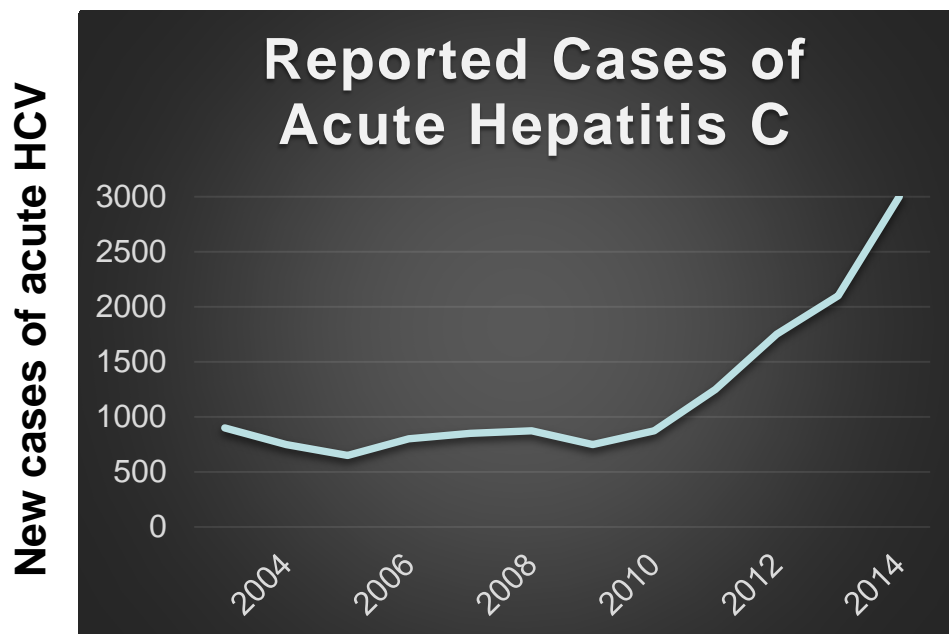
Limited effectiveness of risk-based testing strategies

- **Of the estimated 3.2 to up to 5.2 million persons living with HCV infection in the US, 45%–85% are unaware of their infection status**
- **Barriers to risk-based testing**
 - Inadequate health insurance coverage
 - Asymptomatic
 - Limited access to regular health care
 - Providers lack knowledge about HCV
 - Stigma and poor recall of risk factors for exposure, including drug use and sexual encounters

Emerging trends in transmission

- Rising rates (22.3%) of HCV infection among young people who inject drugs
- Iatrogenic transmission (healthcare exposure)
- Sexual transmission of HCV amongst HIV-infected and HIV-uninfected men who have sex with men (MSM)

Acute Cases of HCV: Emerging Epidemic



New cases of acute HCV infection increased dramatically starting in 2010, primarily occurring in younger Caucasians living in non-urban areas.¹

Most new cases began with abuse of prescription opioid drugs, and then transitioned to often cheaper and more readily available injectable heroin.²

Based upon analysis of cases reported, the CDC believes almost 30,000 acute HCV infections are now occurring yearly.³

1. Centers for Disease Control and Prevention. Division of Viral Hepatitis. Viral hepatitis surveillance 2013.

2. Zibbell. MMWR Morb Mortal Wkly Rep. 2015. 3. Klevens. Am J Public Health. 2014.

Opportunities for HCV transmission during injection drug use



HCV prevention and counseling messages

- Prevent infection: dental, shaving equipment, nail clippers – no sharing. Prevent blood contact by covering cuts/wounds.
- Harm reduction for drug use: ALL “works” including syringe, rinse water, cotton, cooker – straws, pipes, spoons – ALL
- Link to substance use treatment. Support reduction in use.
- Sex: HIV+ and or presence of other STI can facilitate transmission, multiple sex partners, use barrier protection. Highest risk is condomless anal sex with ejaculation between HIV+ men. Heterosexual risk low, increases with multiple partners.

Screening & Testing for HCV

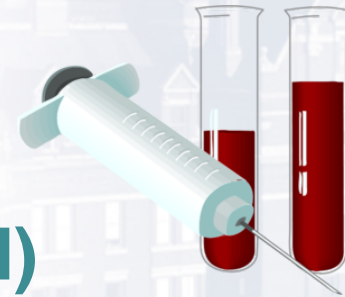
Diagnosing Hepatitis C infection is a 2 step process

1) Anti-HCV (antibody)

- Non reactive (negative)
- Reactive (positive)

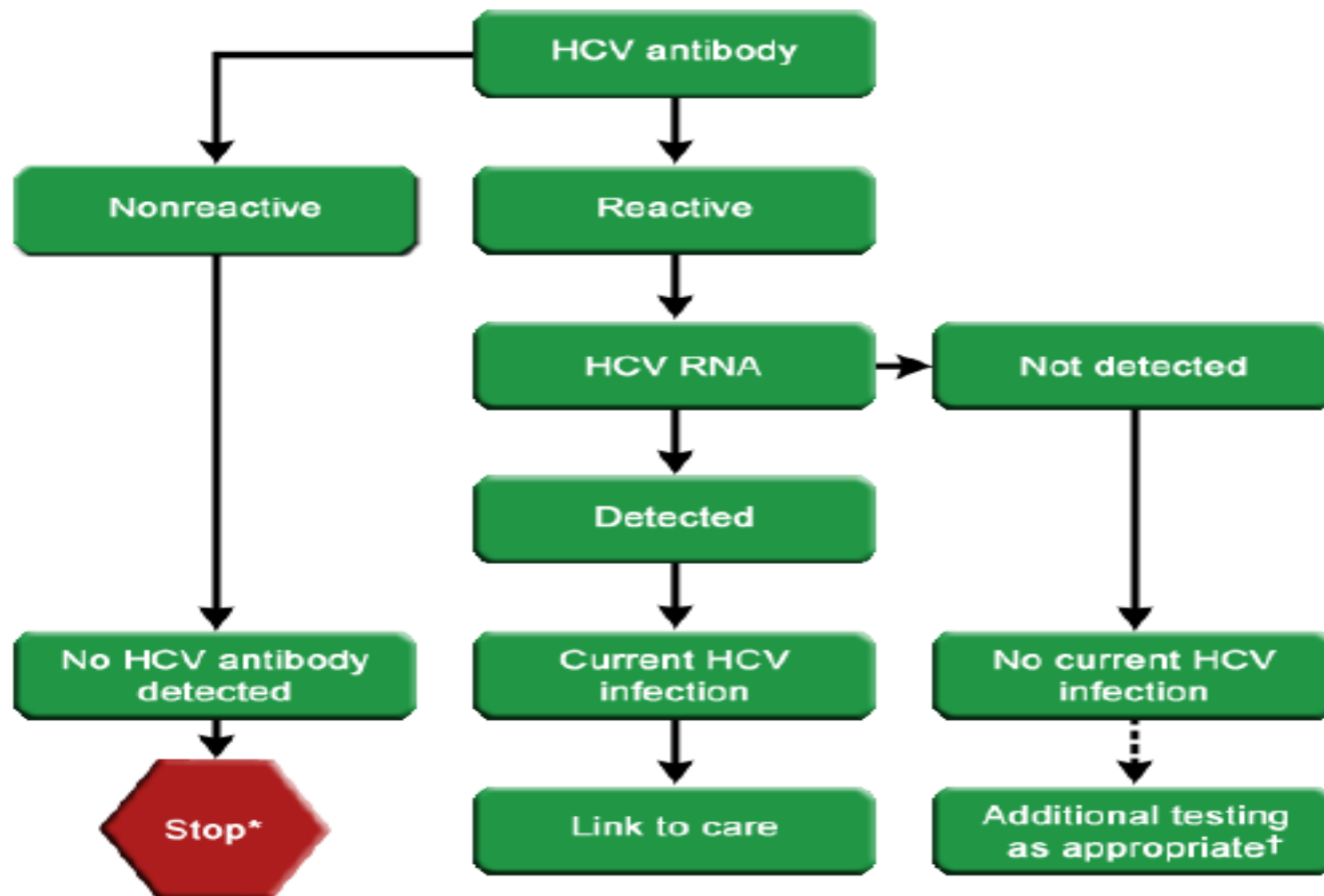
2) HCV RNA (PCR or viral load)

- Not detected
- Detected



Testing to Confirm HCV infection

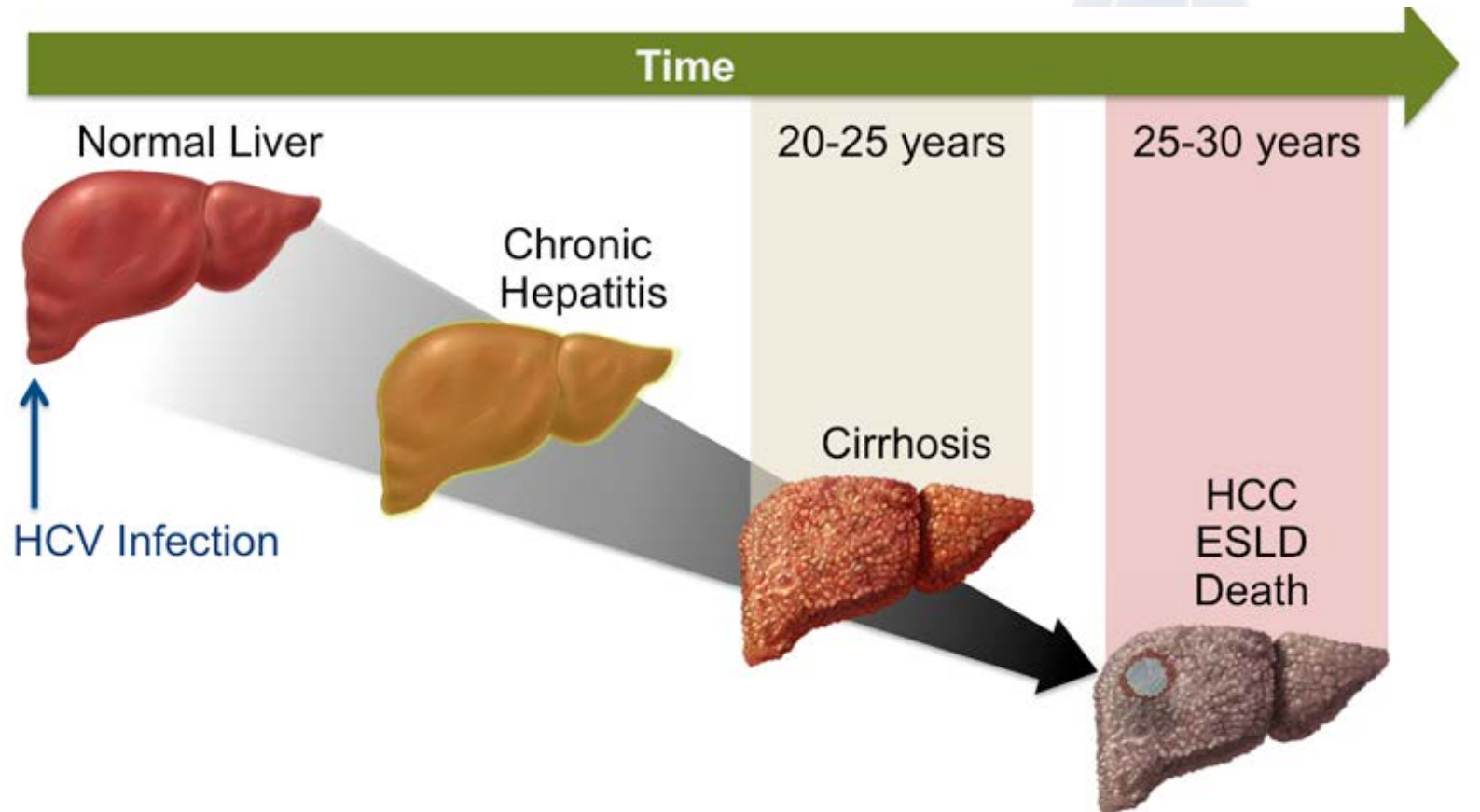
- Positive HCV Ab? → CONFIRM with HCV RNA (test for the virus itself)
- **Chronic vs. Acute HCV**
 1. Those who spontaneously (self) clear HCV will do so within six months of initial infection
 2. Acute infection most likely: recent exposure, symptomatic, documented negative HCV Ab, recent increase in ALT, rapid decline in HCV RNA (virus) over time or low HCV RNA level
 3. CHRONIC HCV infection established by two HCV RNA, six months apart



* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody should be performed. For persons who are immunocompromised, testing for HCV RNA should be performed.

†To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

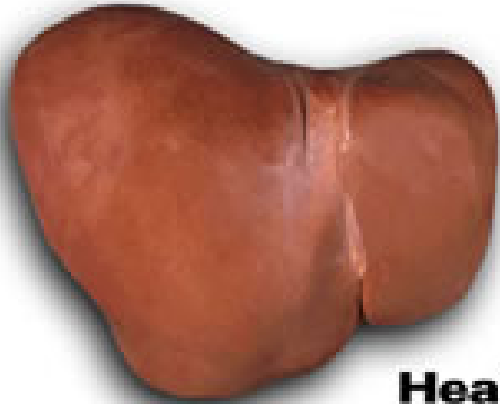
Liver Disease Progression in HCV



Clinical Evaluation

- Blood tests
 - Hep C genotype (1-6)
 - Liver enzymes (ALT, AST)
 - Liver function tests (bilirubin, albumin, prothrombin time)
 - Platelet count
 - Screen for Hep A and Hep B
- Assess degree of fibrosis using fibroscan (liver elastography), blood fibrosis markers or liver biopsy.
- Liver cancer screening for patients with cirrhosis (every six months)
 - Serum alpha-fetoprotein (optional)
 - Hepatic ultrasound

Liver Fibrosis Assessment Tools



Healthy



Cirrhosis

Imaging

- Ultrasound does NOT stage
- May use MR- Elastography to stage

Biopsy

- Traditional method
- Invasive, with associated risks
- May miss areas of scarring

FibroScan (Elastography)

- Measures sound waves to estimate liver stiffness
- Must be fasting >3 hours (no water, no food else score may be falsely elevated)
- Non invasive

FibroSURE, FibroTest

- Blood test, complicated algorithm of several components

FIB4 and APRI

- Quick, easy calculation using commonly available labs (AST, ALT, platelets)

<http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4>

**Clinical role of staging is to
assess for presence or
absence of cirrhosis**

Why is knowledge of cirrhosis important

- Increased risk of hepatic decompensation (development of symptoms)
- Cirrhosis is associated with an increased risk of liver cancer even after HCV cure
 - Screening for hepatocellular cancer every 6 months (life long)
- Cirrhosis may impact HCV treatment regimen and duration
- Esophagogastroduodenoscopy (EGD) may be required to screen for varices

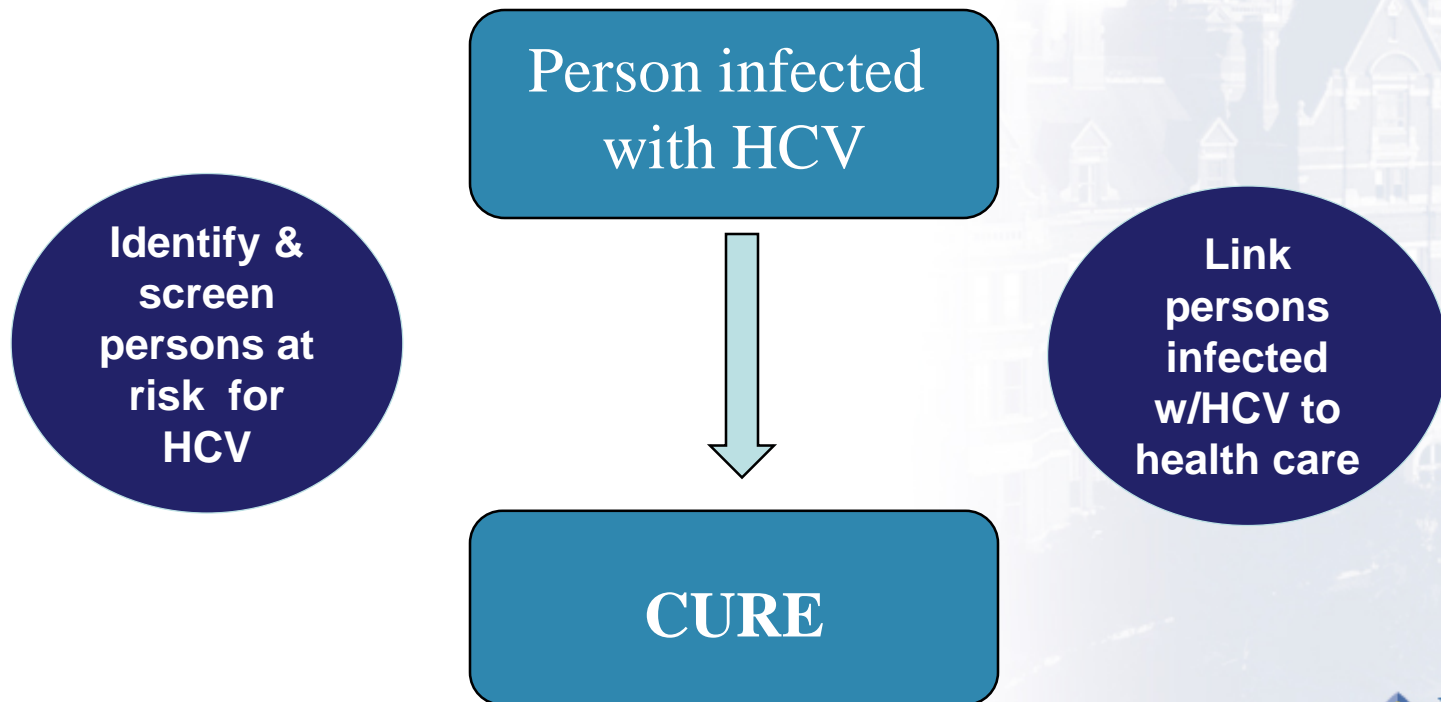
Evaluation of liver disease: Cirrhosis

- Serum markers
 - Low platelets, low albumin
 - Elevated PT/PTT
- Clinical exam
 - Spider nevi (esp. on shoulders)
 - Palmar erythema
 - Ascites
 - Splenomegaly
 - Encephalopathy



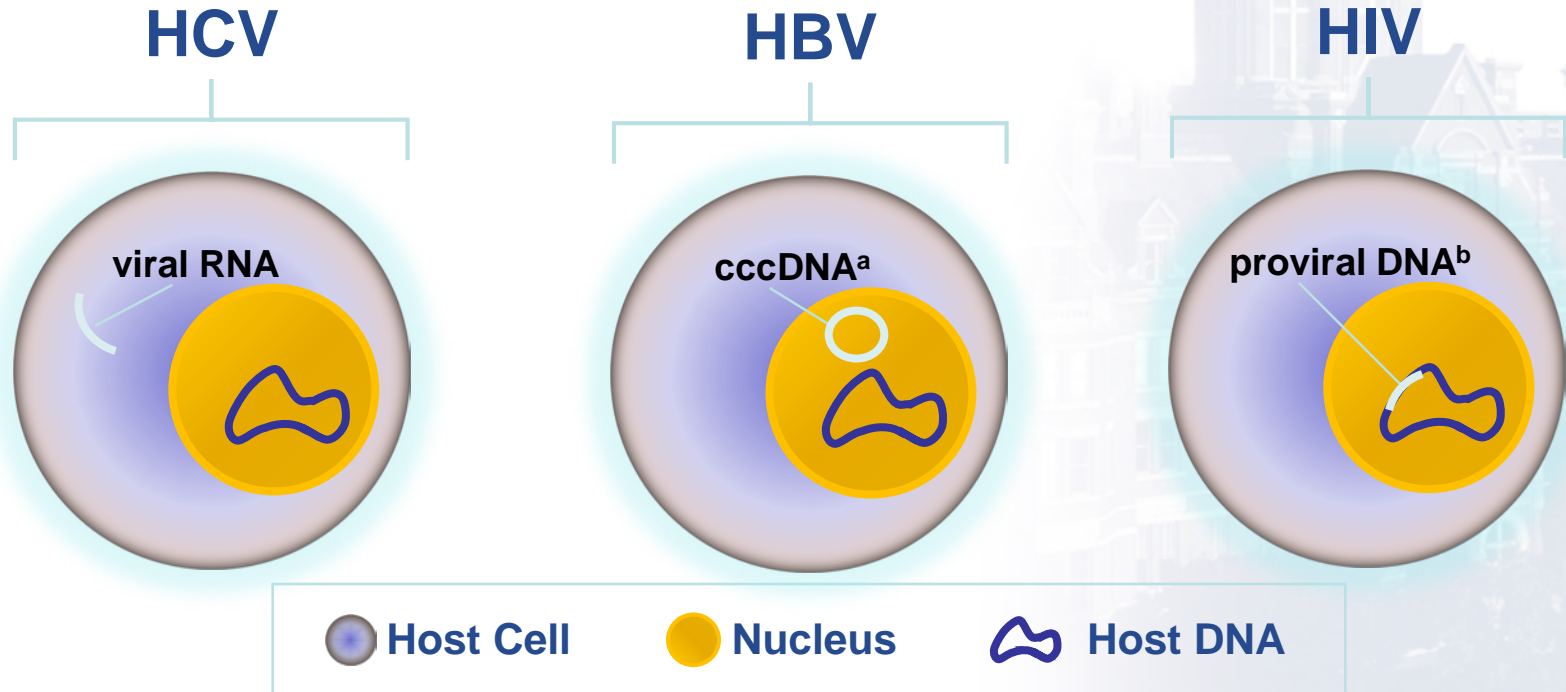
Bridging the Gap to a Cure

Hepatitis C can be cured with all oral therapies in the vast majority (>95%) of patients



HCV Can Be Cured

- Unlike some other chronic diseases, HCV is curable
 - HCV RNA remains in the cytoplasm, while HBV and HIV DNA are incorporated into the nucleus of the cell



^aHBV cccDNA (covalently closed circular DNA): accumulates in hepatocyte nuclei, acting as a template for viral messenger RNA (mRNA) transcription.

^bHIV proviral DNA: integrates into the chromatin of infected cells, acting as the template for the transcription of viral genes.

Soriano V, et al. *J Antimicrob Chemother.* 2008;62:1-4.

Why do we CURE Hepatitis C?

- Reduce spread of HCV
- Reduce illness and death associated with liver disease:
 - End stage liver disease
 - Hepatocellular carcinoma (HCC)
- Health benefits:
 - Decreased liver inflammation
 - Reduced rate of liver fibrosis, possible resolution of fibrosis
 - Improved portal hypertension
 - Reduced extrahepatic manifestations (vasculitis, non-Hodgkin lymphoma)
 - May improve diabetes control, fatigue, overall quality of life



Recommendations for Testing, Managing, and Treating Hepatitis C

Goal of Treatment

- **The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response.**

Rating: Class I, Level A

Recommendations for When and in Whom to Initiate Treatment

- **Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert.**

Rating: Class I, Level A

AASLD/IDSA and DHHS Guidance: HIV/HCV Coinfection

- All pts with HIV should be screened for HCV^[1]
- HCV candidacy nearly universal^[2]
 - HIV coinfection creates unique considerations for pts with HCV, particularly potential drug interactions between HCV and HIV antivirals
- Even with potent HIV ARVs, pts with HIV/HCV coinfection are at increased risk for rapidly progressive liver disease^[2]

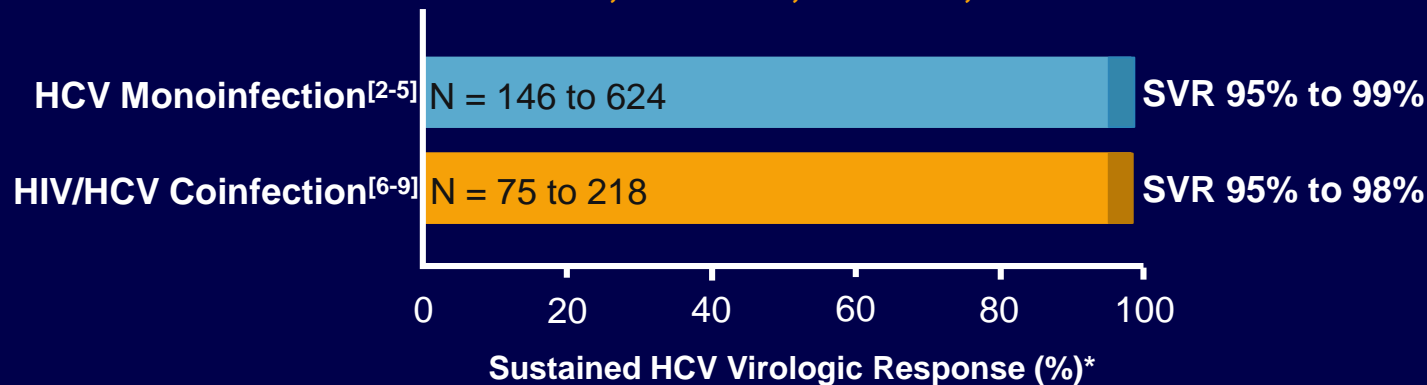
“HIV ARV therapy is not a substitute for HCV treatment”^[2]

Slide credit: clinicaloptions.com

Is HCV Treatment Different in the Setting of HIV/HCV Coinfection?

- Per AASLD/IDSA, treatment in HIV/HCV-coinfected pts should be the same as in HCV monoinfected pts, after consideration of potential drug–drug interactions between DAAs and ARVs^[1]

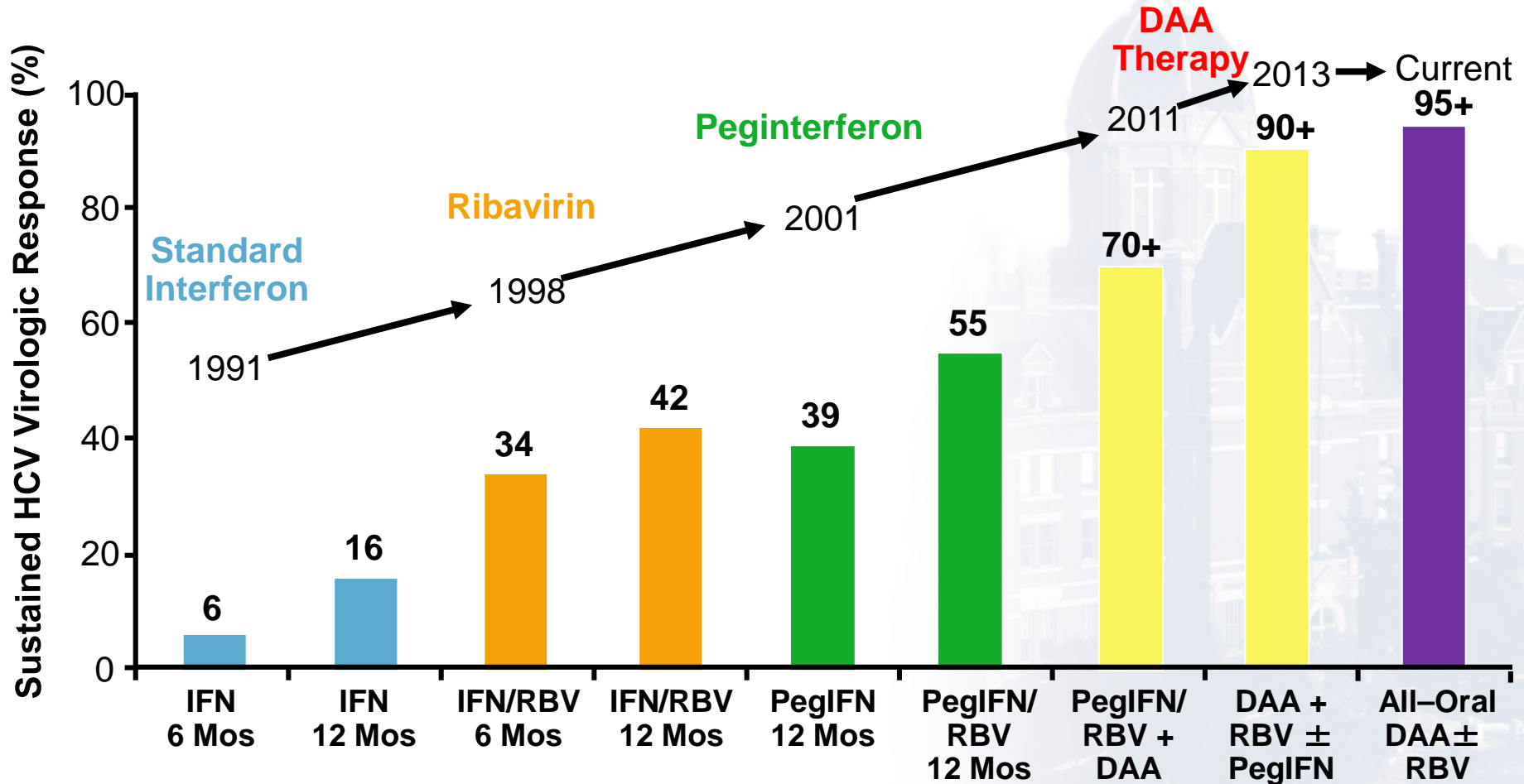
Efficacy Across Separate Studies of GT1-6 HCV Infection With GLE/PIB, GZR/EBR, SOF/LDV, or SOF/VEL



*Most data reported for these studies from treatment-naive pts with GT1/4 HCV infection receiving 12-wk regimens.

Current All-Oral Therapies Highly Effective, Simple, Well Tolerated

All-Oral Therapy



Current All-Oral Regimens for HCV Infection

Regimen	Component Classes	Approved Genotypes
Grazoprevir/elbasvir	Protease inhibitor + NS5A inhibitor	1, 4
Ombitasvir/paritaprevir/ritonavir	Protease inhibitor + NS5A inhibitor	4
Ombitasvir/paritaprevir/ritonavir + dasabuvir	Protease inhibitor + NS5A inhibitor + polymerase inhibitor	1
Sofosbuvir + daclatasvir	Nucleotide polymerase inhibitor + NS5A inhibitor	1, 3
Sofosbuvir/ledipasvir	Nucleotide polymerase inhibitor + NS5A inhibitor	1, 4, 5, 6
Simeprevir + sofosbuvir	Nucleotide polymerase inhibitor + protease inhibitor	1, 4
Sofosbuvir/velpatasvir	Nucleotide polymerase inhibitor + NS5A inhibitor	1, 2, 3, 4, 5, 6

And there's more...

- (Vosevi[®]) one tablet once daily - pangenotypic
- Glecaprevir/Pibrentasivir (Mavyret[™]) three tablets daily - pangenotypic

Factors to consider when preparing for treatment

- Extent and severity of liver disease
- Extrahepatic manifestations (e.g., cryoglobulinemia, nonspecific symptoms)
- Patient readiness
- Drug-drug interactions
- Comorbid HIV or other liver disease (HBV)
- Reinfection risk
- Insurance coverage

HIV/HCV Drug–Drug Interactions

ARV(s)	GLE/PIB	GZR/EBR	SOF/LDV	SOF/VEL	SOF/VEL/VOX
ATV + (RTV or COBI)	X	X	✓*	✓*	X
DRV + (RTV or COBI)	X	X	✓*	✓*	✓*†
LPV + RTV	X	X	✓*	✓*	X
EFV	X	X	✓*	X	X
RPV	✓	✓	✓*	✓	✓
DTG	✓	✓	✓*	✓	✓
RAL	✓	✓	✓	✓	✓
EVG/COBI/FTC/TDF	✓*†	X	X	✓*	✓*†
EVG/COBI/FTC/TAF	✓†	X	✓	✓	✓†
3TC/ABC	✓	✓	✓	✓	✓
TAF	✓	✓	✓	✓	✓
TDF	✓	✓	✓*	✓*	✓*

*Monitor for tenofovir toxicity if used with TDF. †No clinically significant drug interaction per prescribing information; AASLD/IDSA and DHHS guideline recommend monitoring liver enzymes owing to lack of clinical safety data.

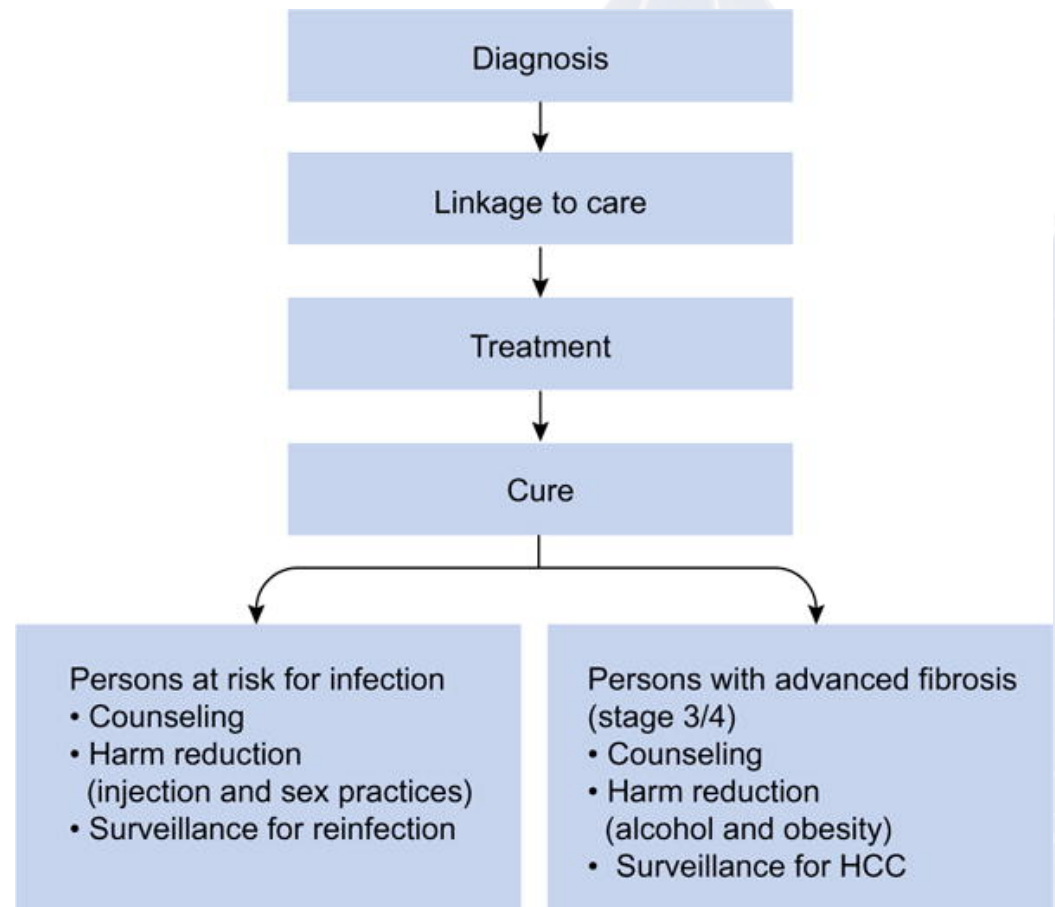


Sustained Virologic Response (SVR) or CURE

- The goal of antiviral therapy for hepatitis C is a sustained virologic response, defined as a negative HCV RNA level 12 weeks after stopping antivirals
- An SVR is durable, can reverse hepatic inflammation and fibrosis, and can reduce the chance of dying from hepatitis C by at least 60%.

The HCV care continuum does not end in viral cure

- HCV reinfection is possible
 - No vaccine
- Liver disease does not reverse in 12 weeks
 - Liver cancer risk persists



Post-HCV cure

- **Reinfection**
 - Harm reduction
 - Persons remain HCV EIA + (don't retest)
 - Consider HCV RNA at least once annually in persons at risk
- **Liver disease**
 - NAFLD – weight
 - Alcohol
- **Cancer in persons with advance fibrosis/cirrhosis**
 - Liver ultrasound recommended every 6 months ± AFP

Patient- and community-centered HCV care: ID Specialty Clinic established January 2015



- **Diagnosis**
 - Free HCV testing in the clinic and community
- **Linkage to care**
 - Walk-in clinic and community outreach
 - Patient navigators, Case managers, PSCs, CMAs and Community partners
- **HCV treatment**
 - Focus on treatment access and adherence to achieve HCV cure
 - Collaborative team: JH Pharmacy, Pharmacists, Nurses and Providers
 - Innovative protocol: Intensity of support is based on the “stoplight” color
- **Cure Club**
 - Every Friday afternoon



2015 to 2017: 2,130 persons cured

Johns Hopkins HCV program

HCV treatment prescribed	3,092 patients
Non-adherence	< 1%
Discontinue due to AEs	< 1%
Lost to follow-up	1%
Virologic failure	1.8%
Outcome pending	26%
HCV cure	
Johns Hopkins Specialty Clinic	97%
US National average including the VA	92%

Take Home Messages

- Hep C causes progressive liver disease Hep C is usually asymptomatic and easy to ignore
- Older individuals are at higher risk for HCV related liver failure, liver cancer and liver related death
- Encourage Hep C screening and tight linkage to care to an experienced treater
- Hep C is curable and treatments are highly effective
- Hep C progresses more rapidly in HIV but treatment outcomes are similar
- Successful treatment requires a multidisciplinary team

The Case of Sam

- Sam, 62 yo AAM presents to JHH ED with ankle swelling (DOB 2/2/1954)
- He has high blood pressure, he's overweight, and sees his primary care provider every 3-6 months
- He is offered a Hep C screening test for the first time
 - Hep C antibody test reactive
 - HCV RNA (viral load) 8,000,000 IU/mL
- He is promptly linked to care in the John G. Bartlett Specialty Practice

The Case of Sam

- Sam feels very anxious since learning of his Hep C diagnosis. He's afraid to tell his family. He comes to clinic and asks:
 - *How did I get Hep C when I feel fine?*
 - *Why was I not tested before? I see my doctor and have blood drawn every few months.*
 - *Can I still play with my grandchildren or will they get Hep C?*
 - *Am I going to die from Hep C?*
 - *I can't afford medicine to treat Hep C. I heard it costs thousands of dollars.*
- How would you respond to his questions?

The Case of Sam

- His evaluation reveals
 - Fibroscan 12.2 kPa- cirrhosis
 - Liver function tests within normal range
 - Abdominal ultrasound shows no liver mass
- You recommend treatment for 12 weeks and he is promptly approved for medication with a \$5 copay.
- He will return to clinic for a medication initiation visit to fully prepare for what is expected to be a successful course of treatment.

The Case of Sam

- What if Sam had HIV and HCV co-infection?
 - Careful consideration for drug-drug interactions between HIV and HCV antivirals is needed
 - Otherwise, assessment, treatment and cure rates are similar

Thank you for your time!

Questions, referrals, consultations?

Call 443-997-1900 option 3

New Patient Walk-ins: Mon-Fri 8:00-3:00

John G. Bartlett Specialty Practice

Park Building

1717 E. Monument Street

Corner of E. Monument and N. Broadway