STOP HCC

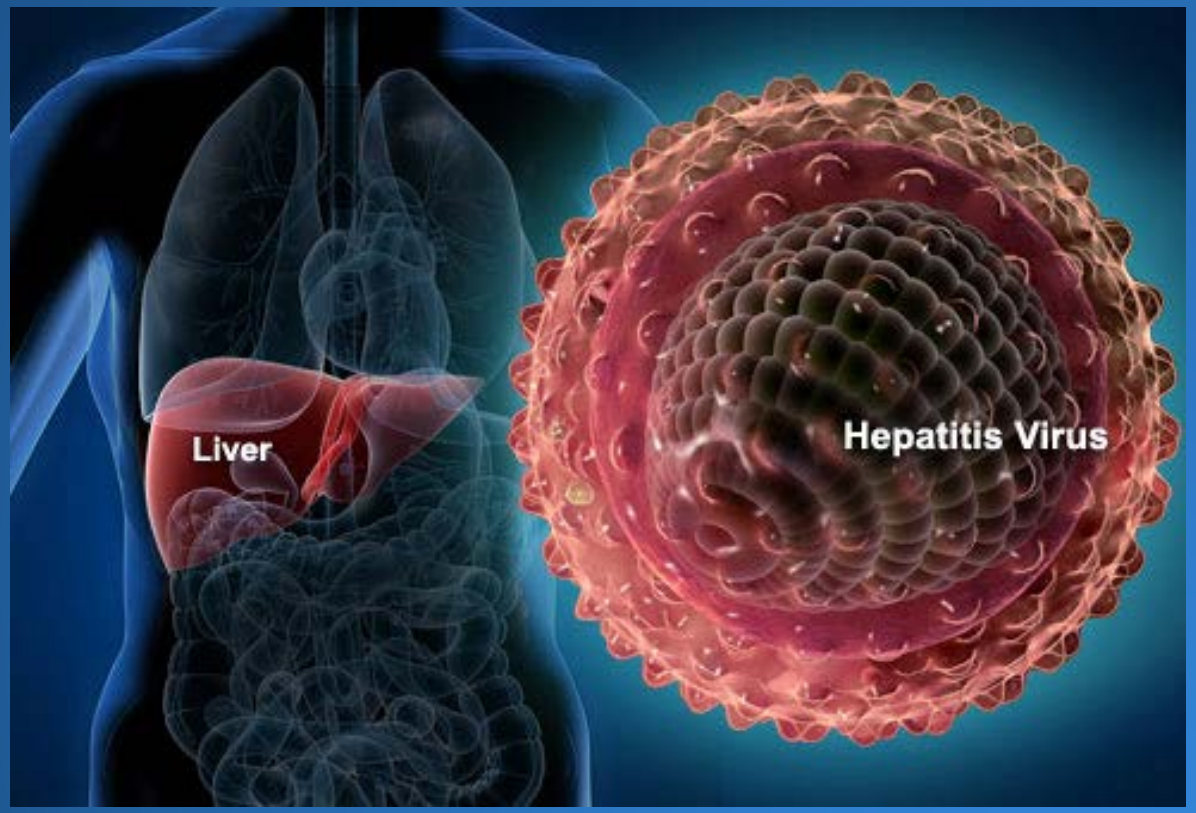
Hepatitis C: From Threat to a Cure

ReACH Center
UT Health San Antonio
and
University of Texas Southwestern Medical Center

Hepatitis C Virus (HCV) Overview

- What is HCV?
- Prevalence
- Effects
- Prevention
- Diagnosis
- Education
- Treatment
- Financial Toxicity

Hepatitis C Virus



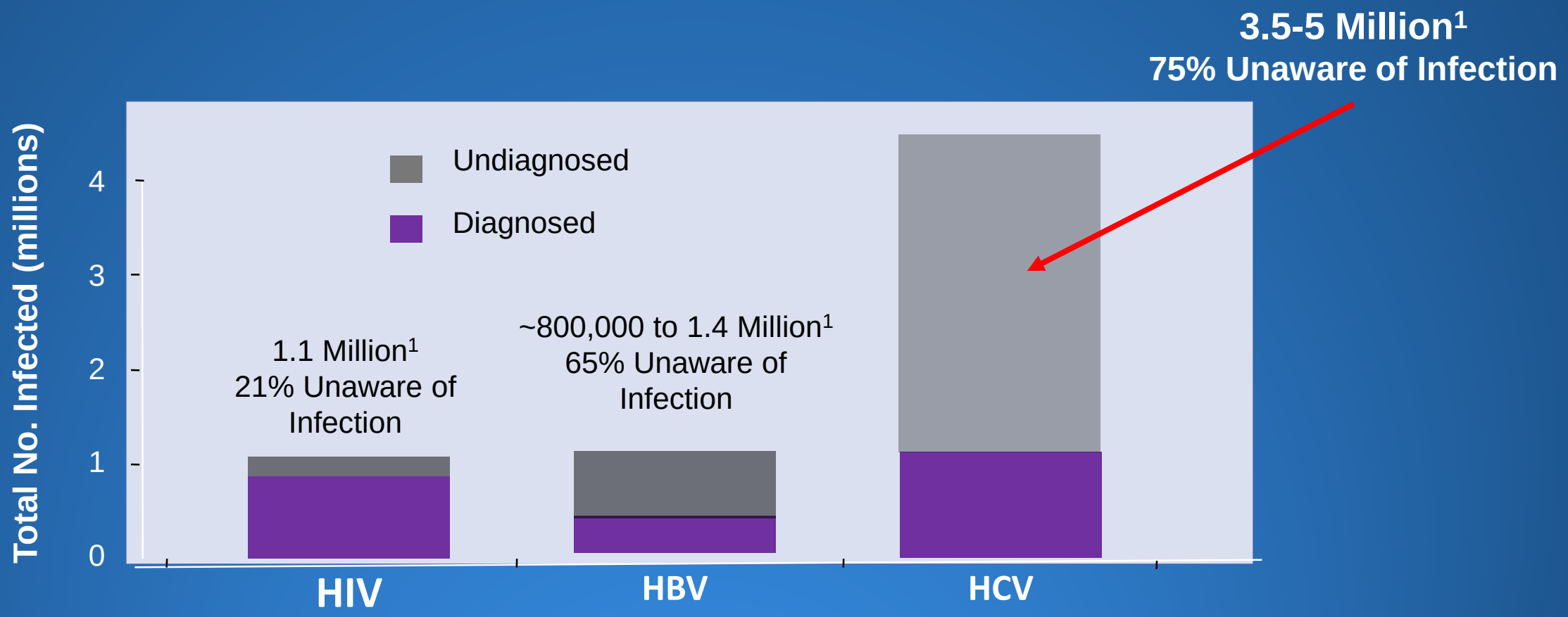
- Flaviviridae group of virus (RNA)- along with Zika
- Discovered in 1989
- Blood borne infection
- Acute infection: short term illness but in 60-85% can lead to
- Chronic infection: long-term, potentially deadly

http://www.webmd.com/hepatitis/ss/slideshow-hepatitis-overview

HCV Prevalence and Incidence

United States and Texas

HCV is Nearly 4 Times More Prevalent than HIV and HBV

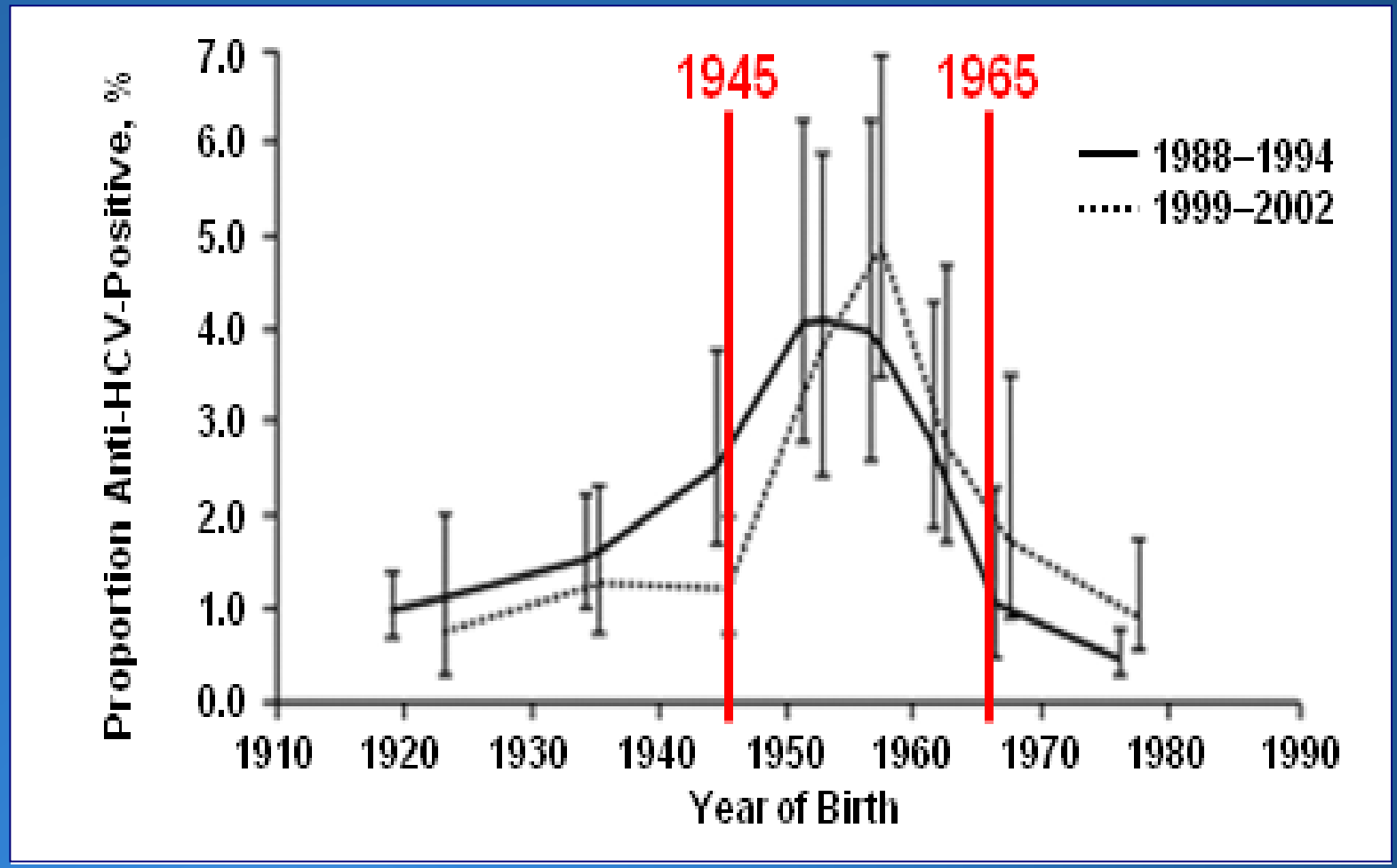


HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus.

1. Institute of Medicine. Washington, DC: The National Academies Press; 2010.
2. Chak E, et al. *Liver Int*. 2011;31(8):1090-1101.

80% of Americans with HCV Born from 1945-1965 (Baby Boomers)

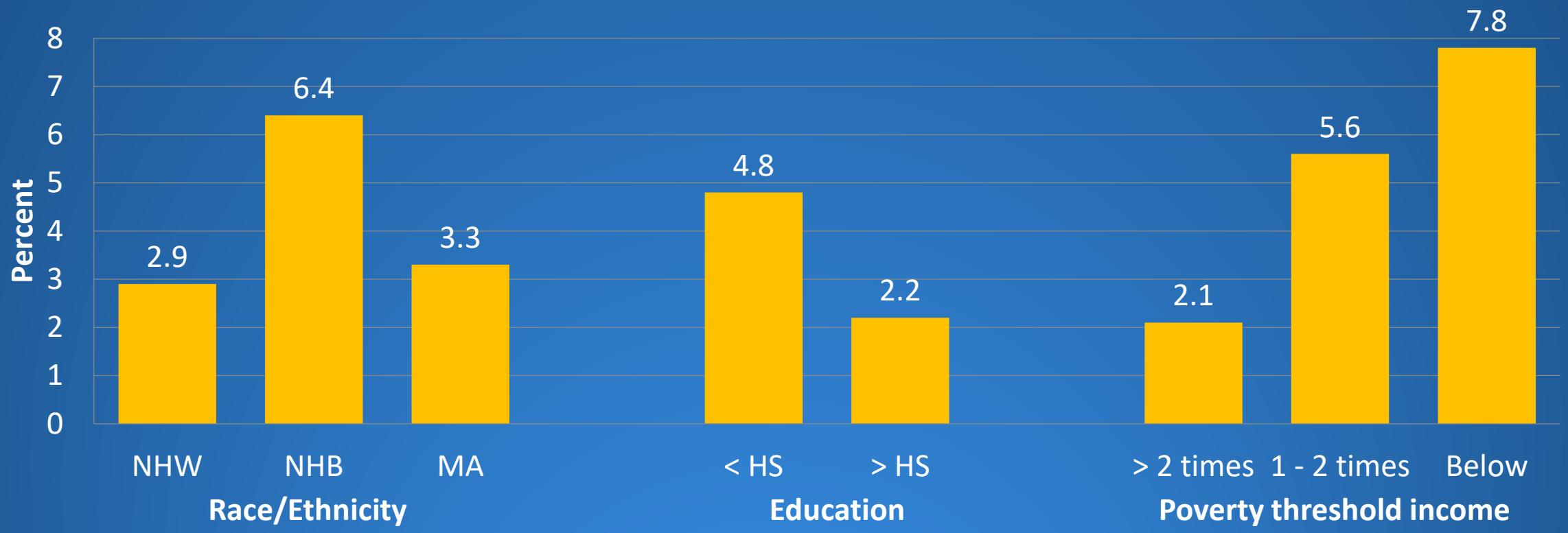
- Reflects high incidence in past
- 5x higher prevalence than other birth cohorts (3.4 vs. 0.5%)
- 73% of HCV mortality



CDC RECOMMENDATION: Screen all individuals born between 1945-1965

Smith. AASLD SF 2011.
Kramer. Hepatology 2011
Ly. An Int. Med 2011

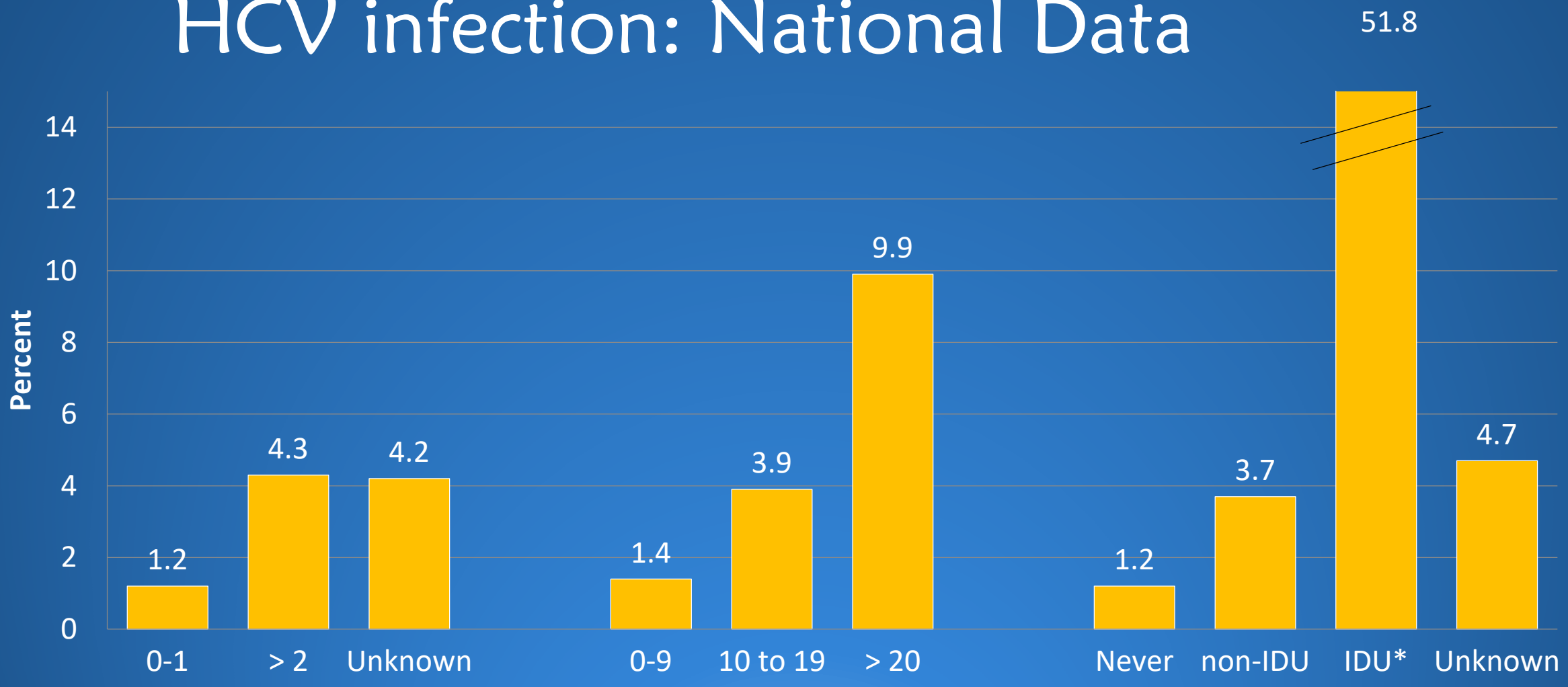
Other Characteristics of Persons with HCV Infection: National Data



NHW: Non-white Hispanic
NHB: Non-Hispanic Black
MA: Mexican American
HS: High School

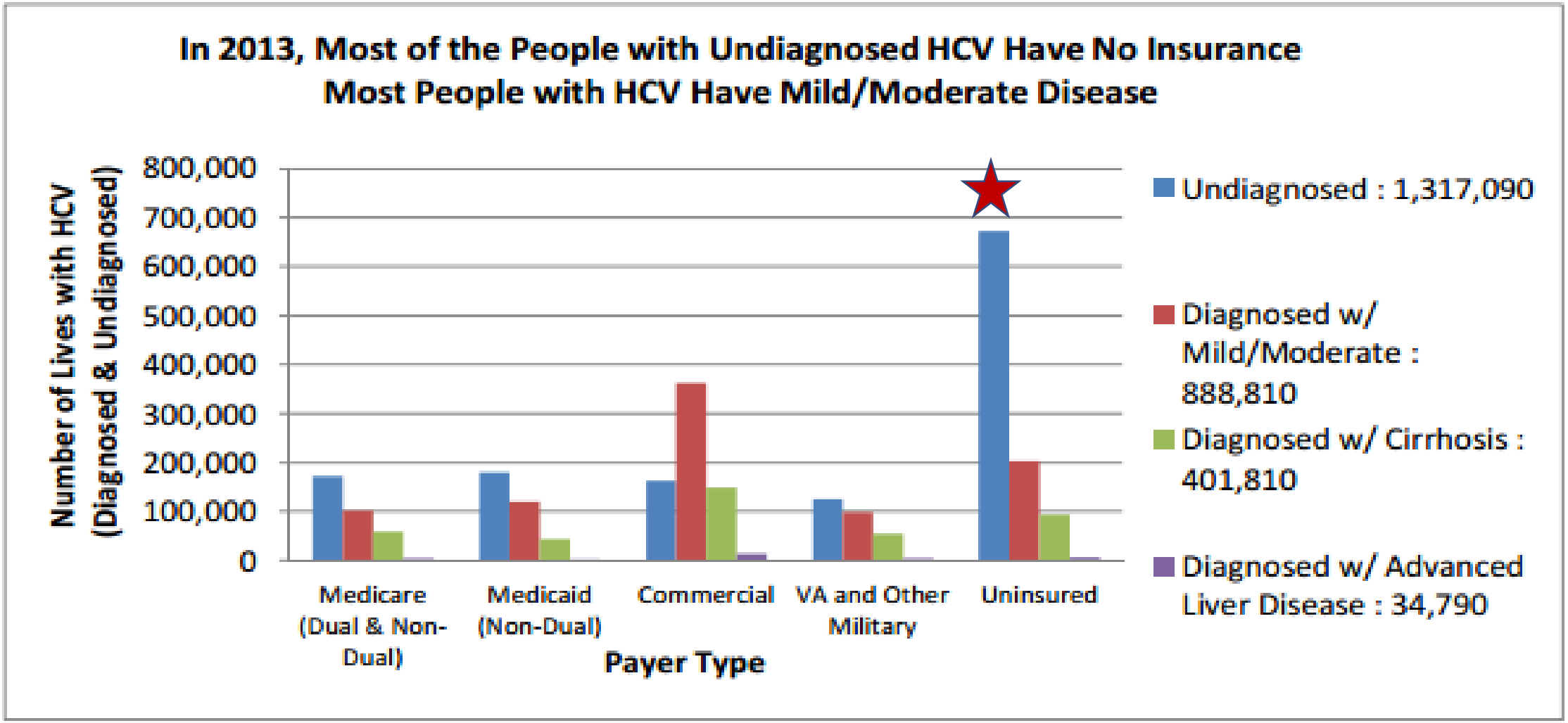
Ditah et al. J Hepatol. 2014;60:691-8.

Other Characteristics of Persons with HCV infection: National Data



Ditah et al. J Hepatol. 2014;60:691-8.

Figure 1: 2013 HCV Population by Disease State and Payer



Source: Authors' analysis of NHANES, MarketScan 2010, Medicare 5% Sample, and Medicaid Contributor data. Does not include prison population.

http://us.milliman.com/uploadedFiles/insight/2013/convergence-of-risk-and-opportunity.pdf

Other Common Risk Factors

- Any injection drug use (even once many years ago)
- Certain medical conditions:
  - Received clotting factor concentrates from before 1987
  - Long-term hemodialysis
  - Persistently abnormal alanine aminotransferase levels (ALT)
  - HIV infection
  - Transfusions or organ transplants before July 1992
- Children born to HCV-positive women

https://www.cdc.gov/hepatitis/hcv/guidelinesc.htm

Chronic HCV in Texas

In 2000, nearly 400,000 Texans (1.79%) were estimated to be chronically HCV+

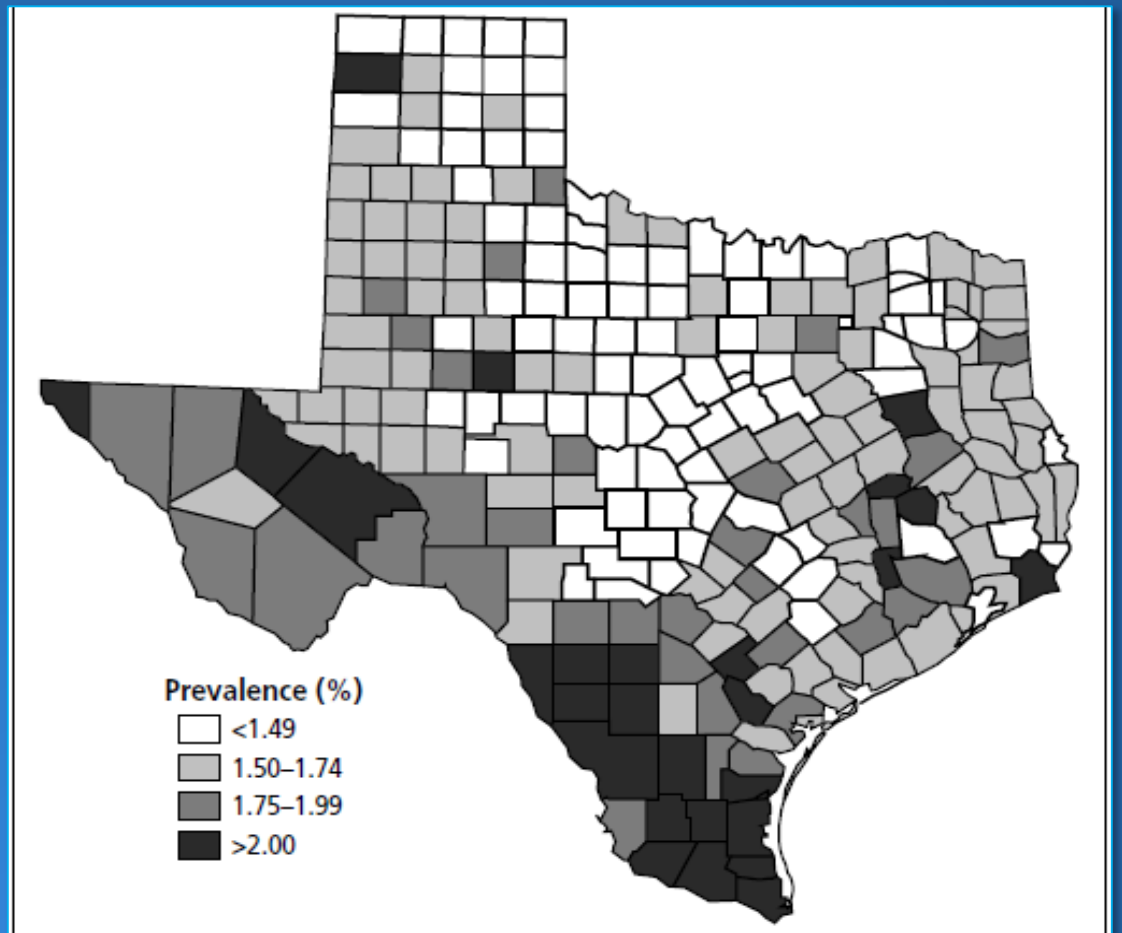


Figure 1. Prevalence rates of chronic hepatitis C virus infection by county in Texas.

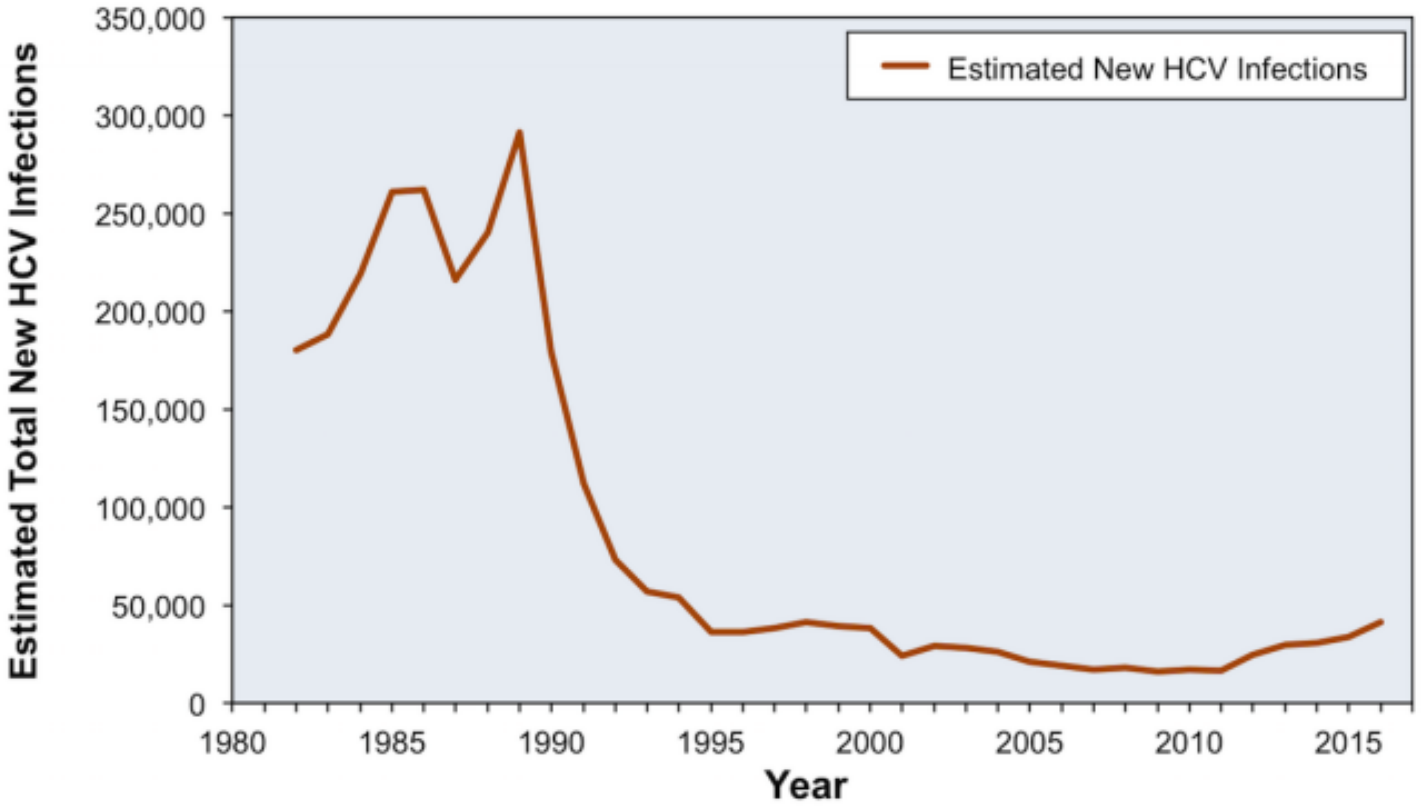
Yalamanchili K. Proc (Bayl Univ Med Cent). 2005 Jan; 18(1): 3–6.

Bad News: Incidence of HCV infection Increasing Again

Figure 1 Hepatitis C Incidence in United States, 1982-2016

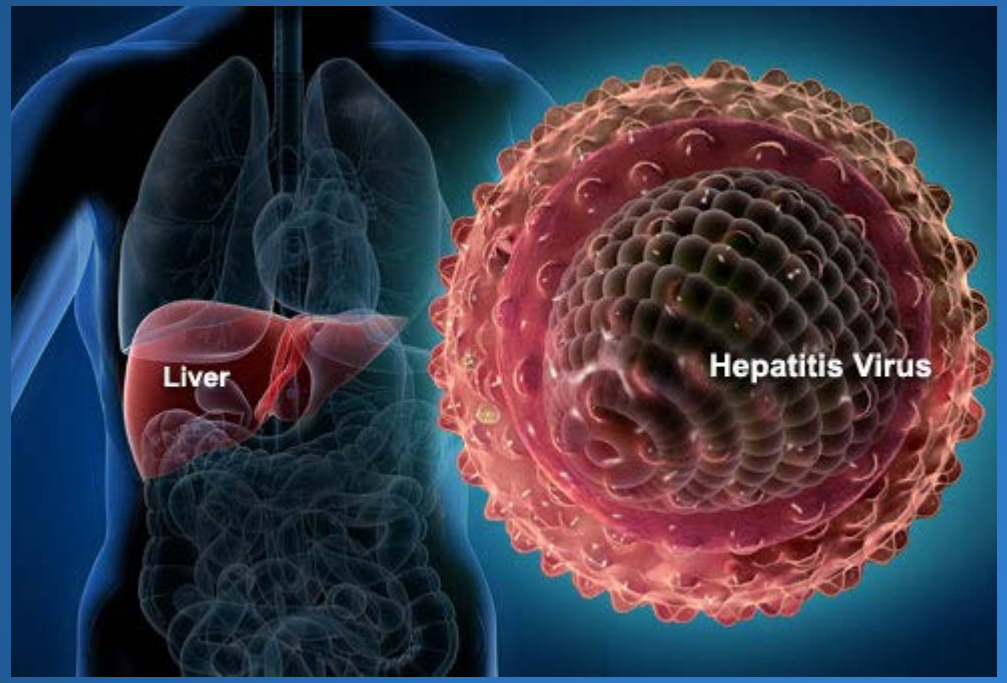
This graphic represents the estimated number of new hepatitis C infections per year.

Source: Centers for Disease Control and Prevention. Division of Viral Hepatitis. Statistics and Surveillance.



Morbidity and Mortality from Hepatitis C

Silent Killer Until Too Late

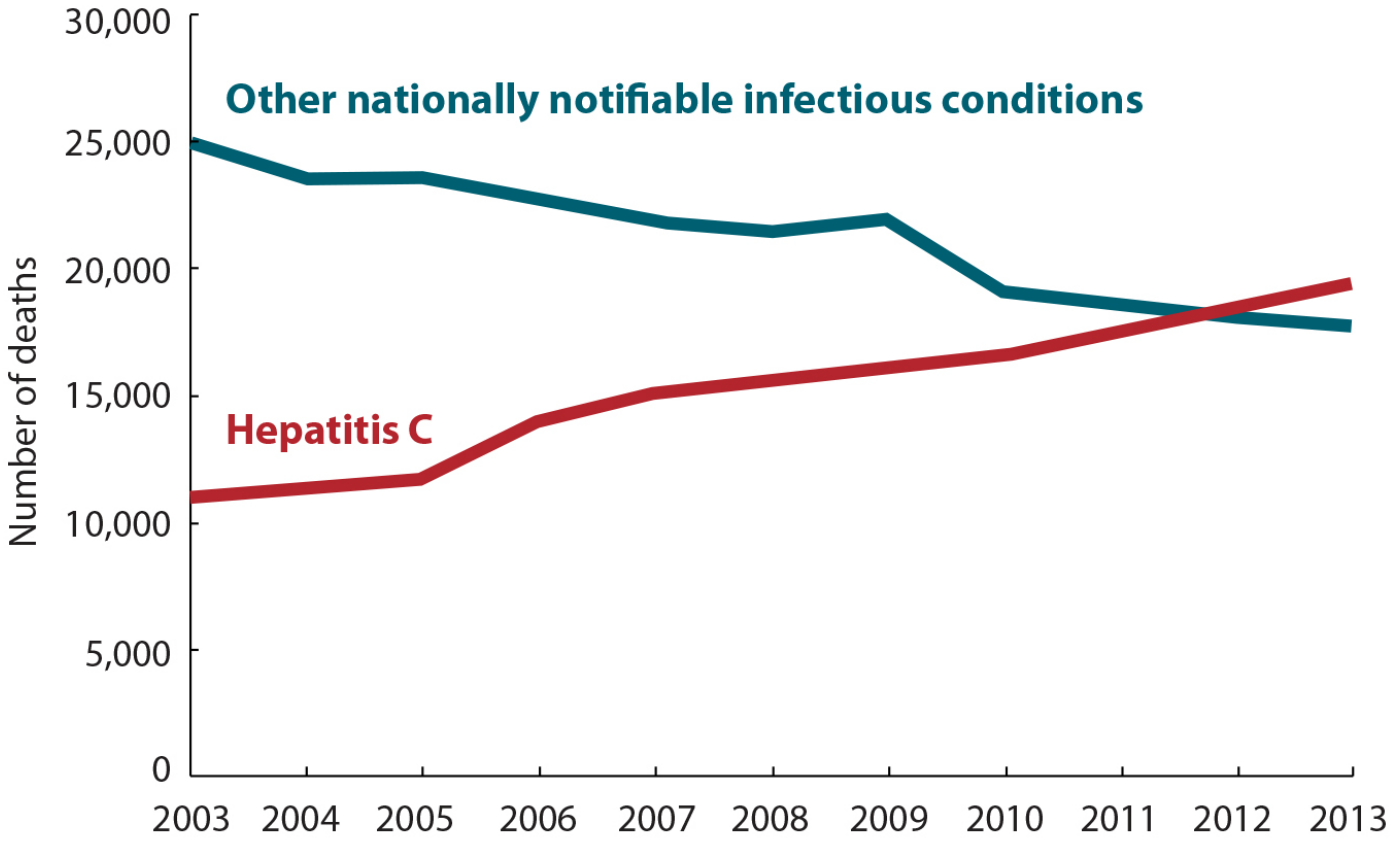


- There is NO vaccine for HCV infection
- Often few or no symptoms for years
- Chronic infection can lead to:
  - Fibrosis (scarring)
  - Cirrhosis (permanent scarring and liver failure)
  - Liver cancer (HCC)

http://www.webmd.com/hepatitis/ss/slideshow-hepatitis-overview

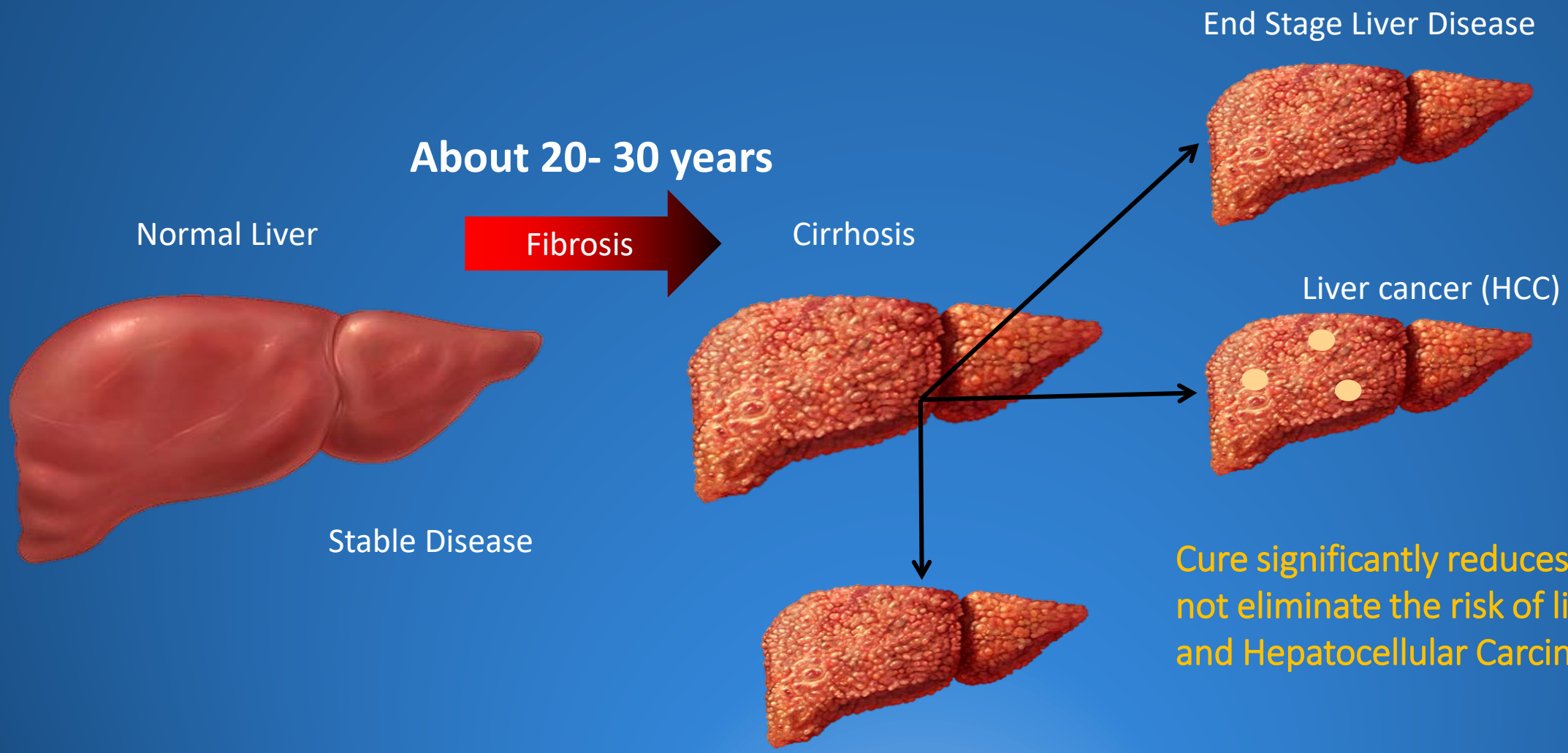
Increasing HCV-related Mortality

Annual number of hepatitis C-related deaths vs. other nationally notifiable infectious conditions in the US, 2003-2013



Source: Centers for Disease Control and Prevention

Time From HCV Infection Until Serious Complications



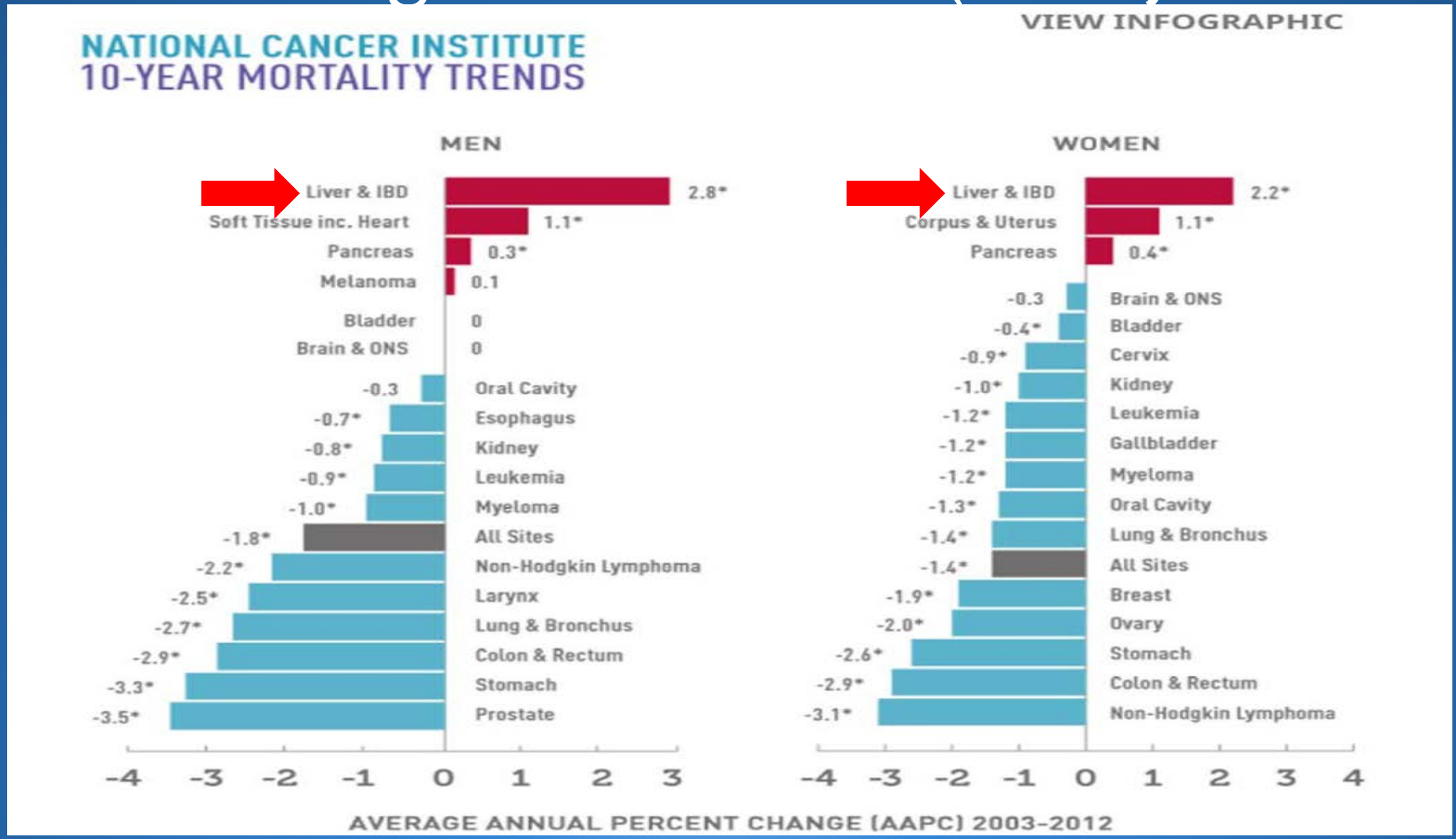
Cure significantly reduces but does not eliminate the risk of liver failure and Hepatocellular Carcinoma (HCC)

Liver Failure

- Significant cause of morbidity and mortality – high demand for health care services
- About 50% of all U.S. liver transplantations result from liver damage from HCV infection at a cost of >$100,000
- Although most persons with HCV will not need a transplant, even a few are very expensive

Picture from: http://www.who.int/patientsafety/education/curriculum/course10_handout.pdf

Increasing Liver Cancer (HCC) in US



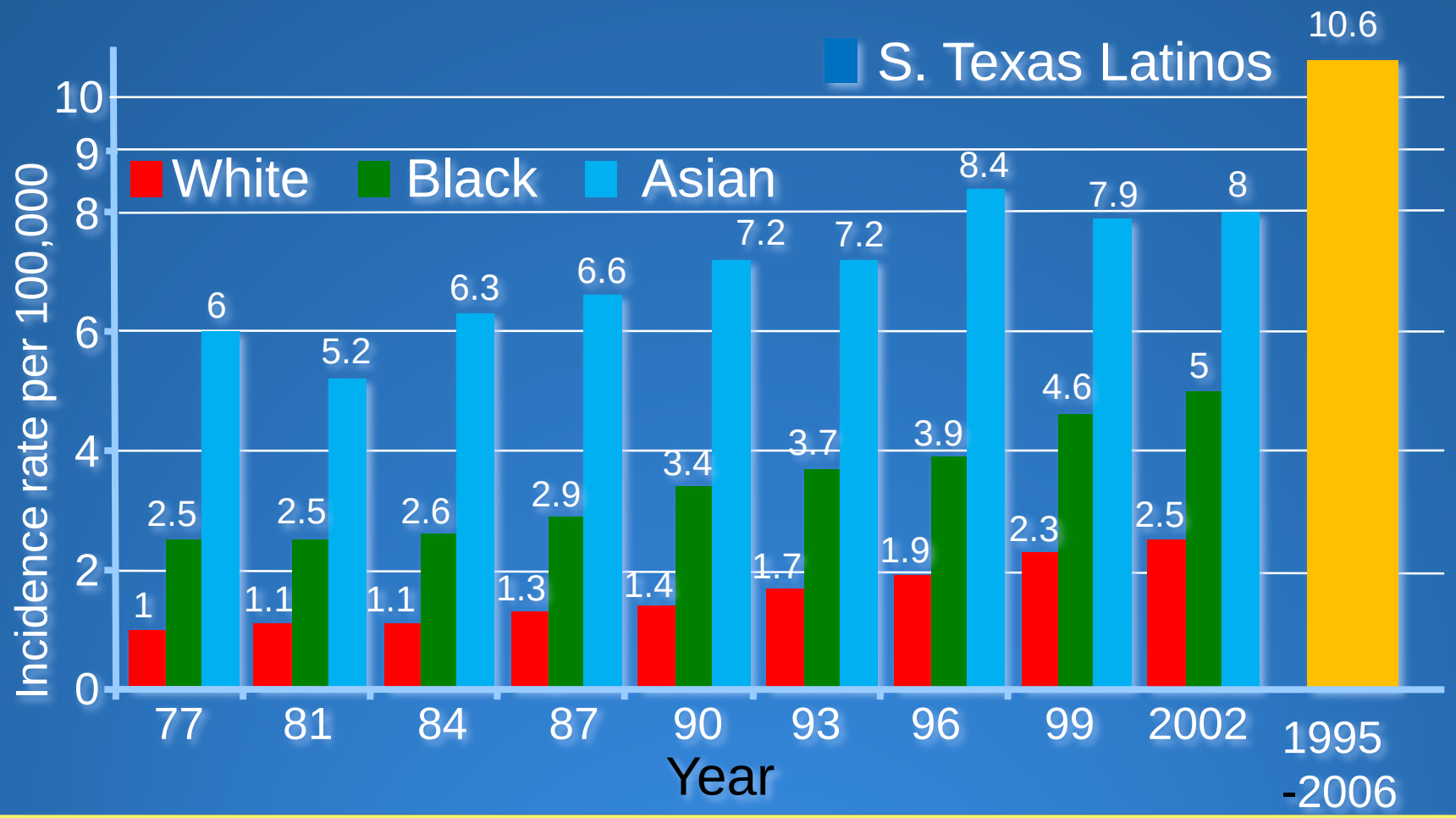
Source: NCI. Report to the Nation on the Status of Cancer 1975-2012 Feb 2016

Hepatitis C and Liver Cancer

- Liver cancer is increasing in the US in contrast to nearly all other cancers
- Hepatitis C is the leading cause of primary liver cancer (hepatocellular carcinoma)
- The incidence of liver cancer for men in Texas has more than doubled from 1995 to 2014 from 7.1 to 16.2/100,000
- In the 2000s, the increase in liver cancer incidence was greatest in Latinos and is especially high in South Texas*

*Ha J et al. Burden of hepatocellular carcinoma among hispanics in South Texas: a systematic review Biomark Res 2017;5:15

Racial-Ethnic Incidence for HCC in U.S. and Latinos in South Texas



Hepatocellular carcinoma related to HCV is the fastest rising cause of U.S. cancer-related deaths.

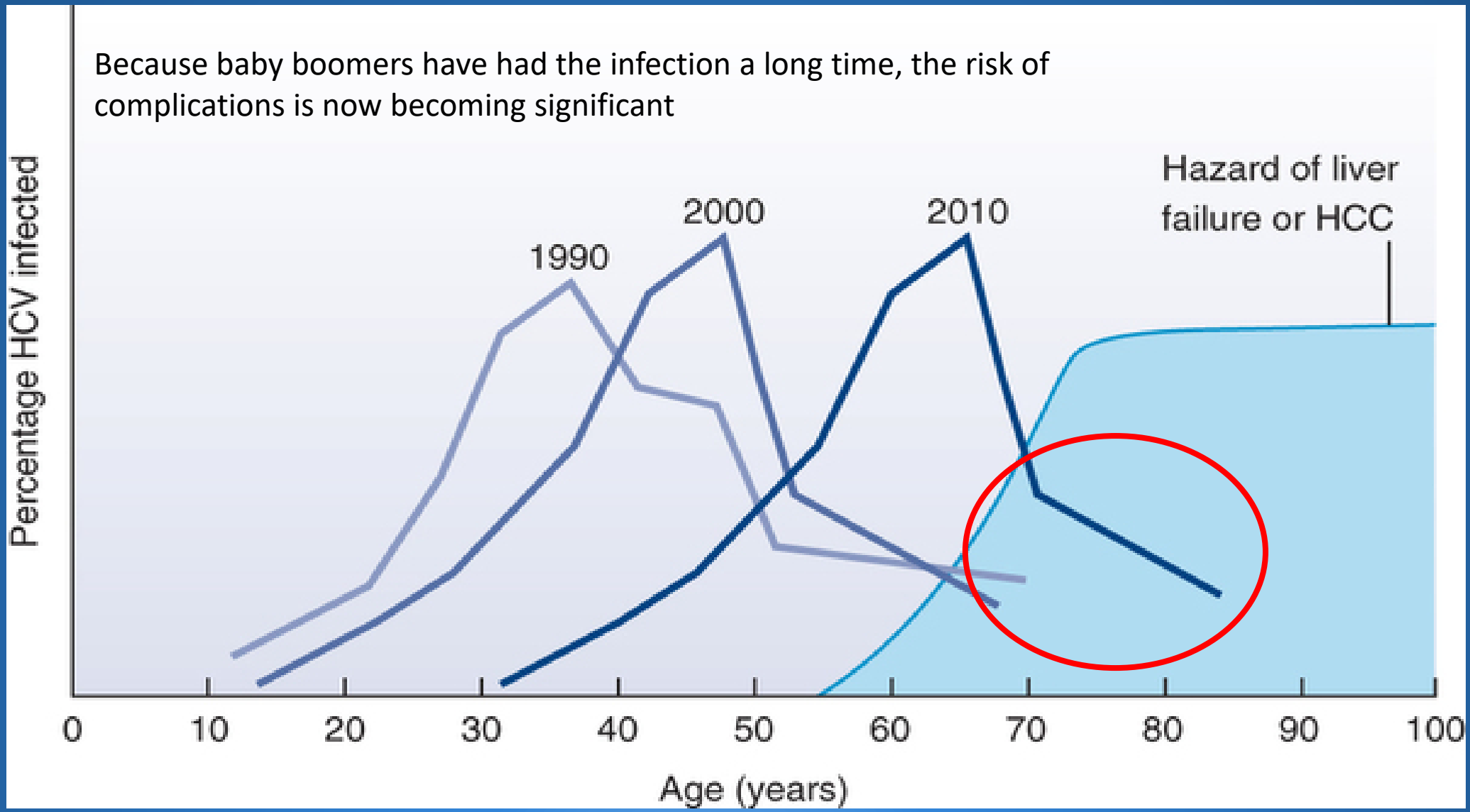
* Per 100,000

Ramirez AG, PLoS One. 2014; 9(6): e99365. El-Serag HB et al, NEJM 2011

Best Option to Prevent HCC

- Treated with surgery, medications or liver transplant
- But poor prognosis with a median survival following diagnosis ranging from 6 to 20 months

Baby Boomers Advanced Liver Disease/HCC

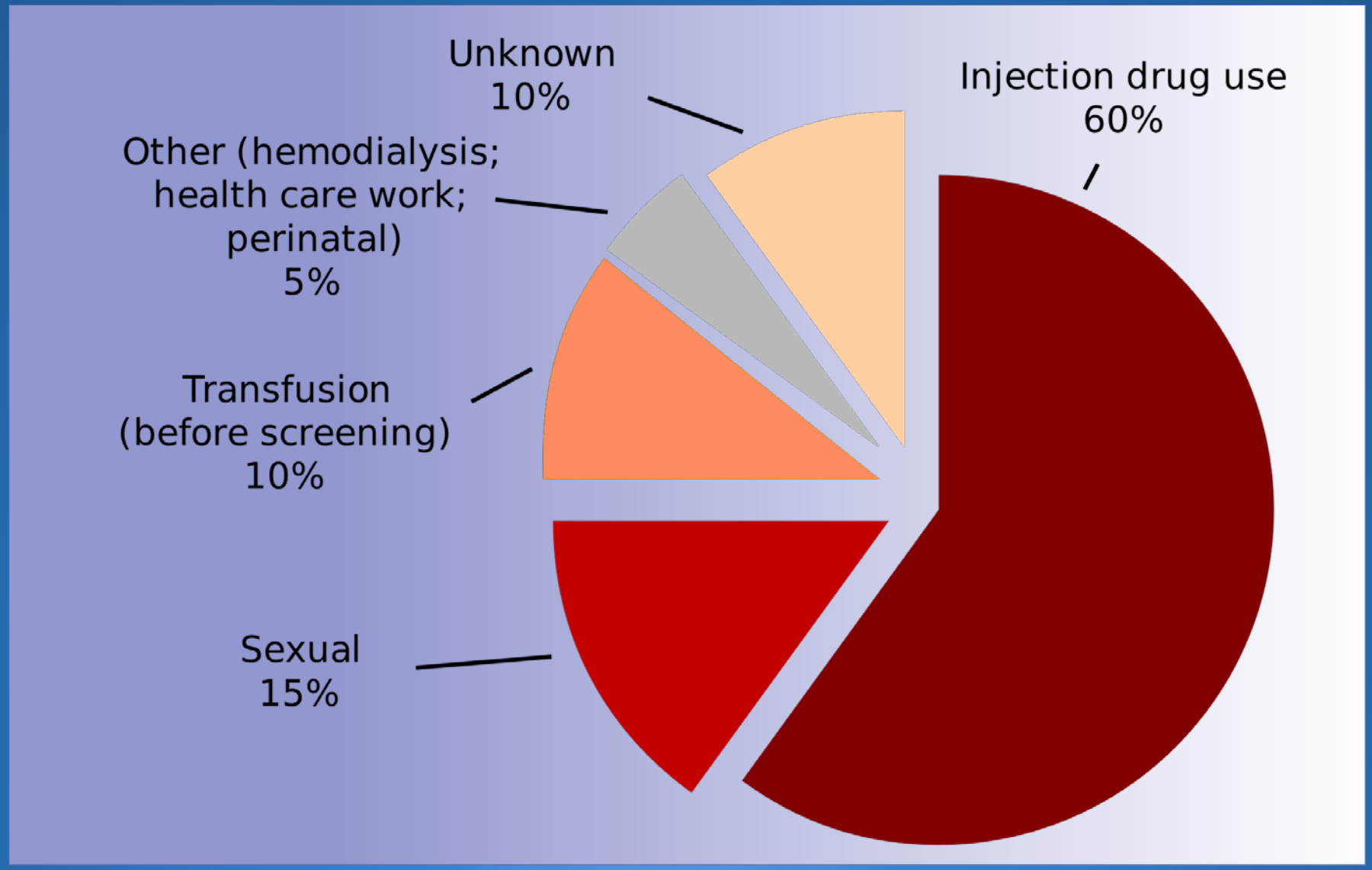


Thomas D. Nature Medicine 2013:19, 850-58

HCV Prevention

USPSTF Recommendations

How is HCV transmitted?



Source: CDC and Prevention

Problem…

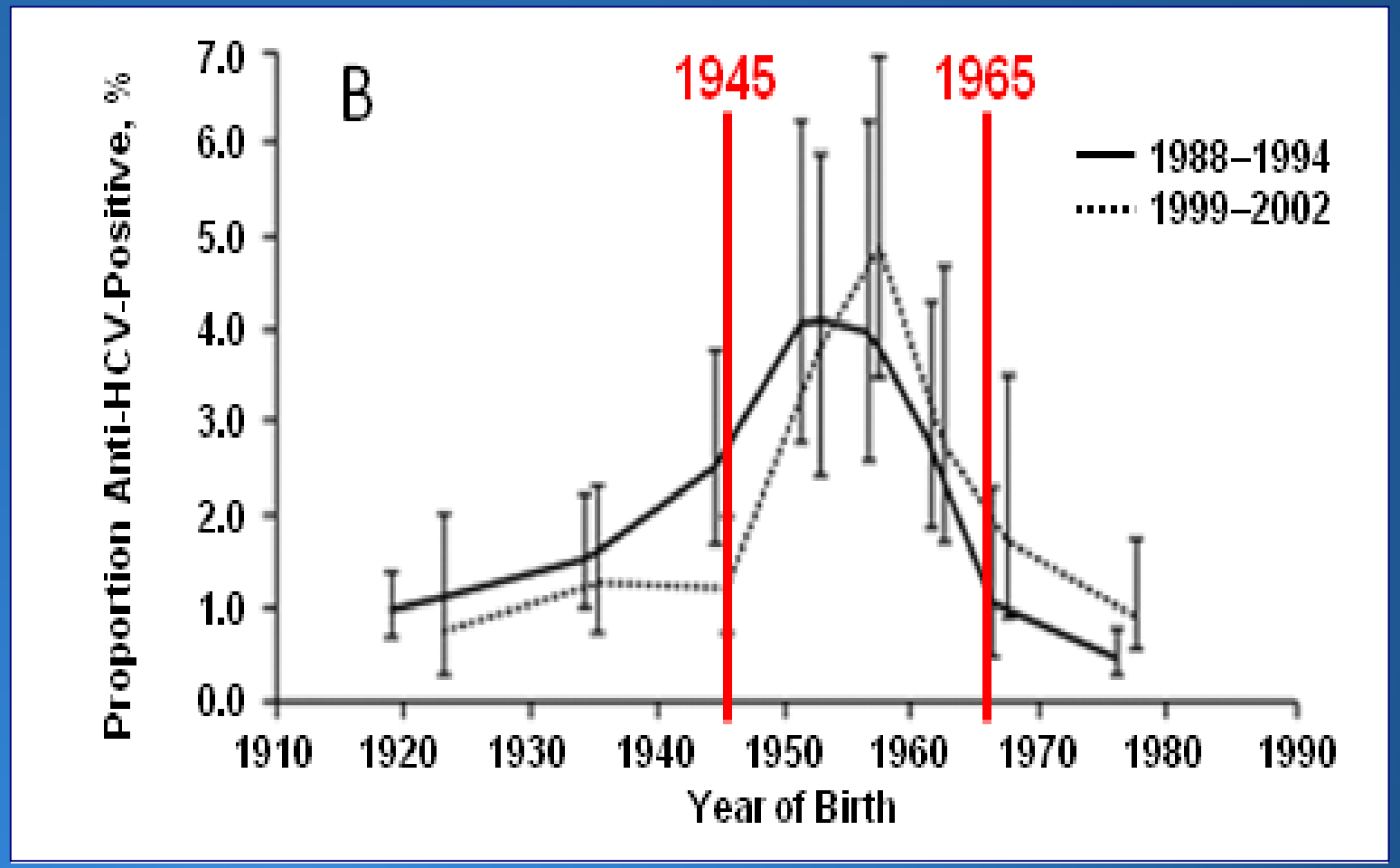
High risk patients not being screened for HCV infection

Reasons:

1. Too complicated
2. 70-80% of people with HCV had no symptoms so no prompt to screen
3. No viable treatment option before 2012

Remember the Baby Boomers?

- 5x higher prevalence than other birth cohorts (3.4 vs. 0.5%)
- 81% of HCV infected adults and 73% of HCV mortality



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Ly. An Int. Med 2011

US Preventive Services Task Force (USPSTF) Guidelines - 2012

- One time screening of all baby boomers (born 1945 through 1965) for HCV infection (USPSTF Rating: Class I, Level B)

Hepatitis C

Testing baby boomers saves lives

3 Million

About 3 million adults in the US are infected with the hepatitis C virus, most are baby boomers.

3 in 4

Up to 3 in 4 people who are infected don't know they have hepatitis C so they aren't getting the necessary medical care.

1945–1965

Baby boomers, anyone born from 1945 through 1965, should get tested for hepatitis C.

Source: CDC Vital Signs, May 2013 | www.cdc.gov/vitalsigns

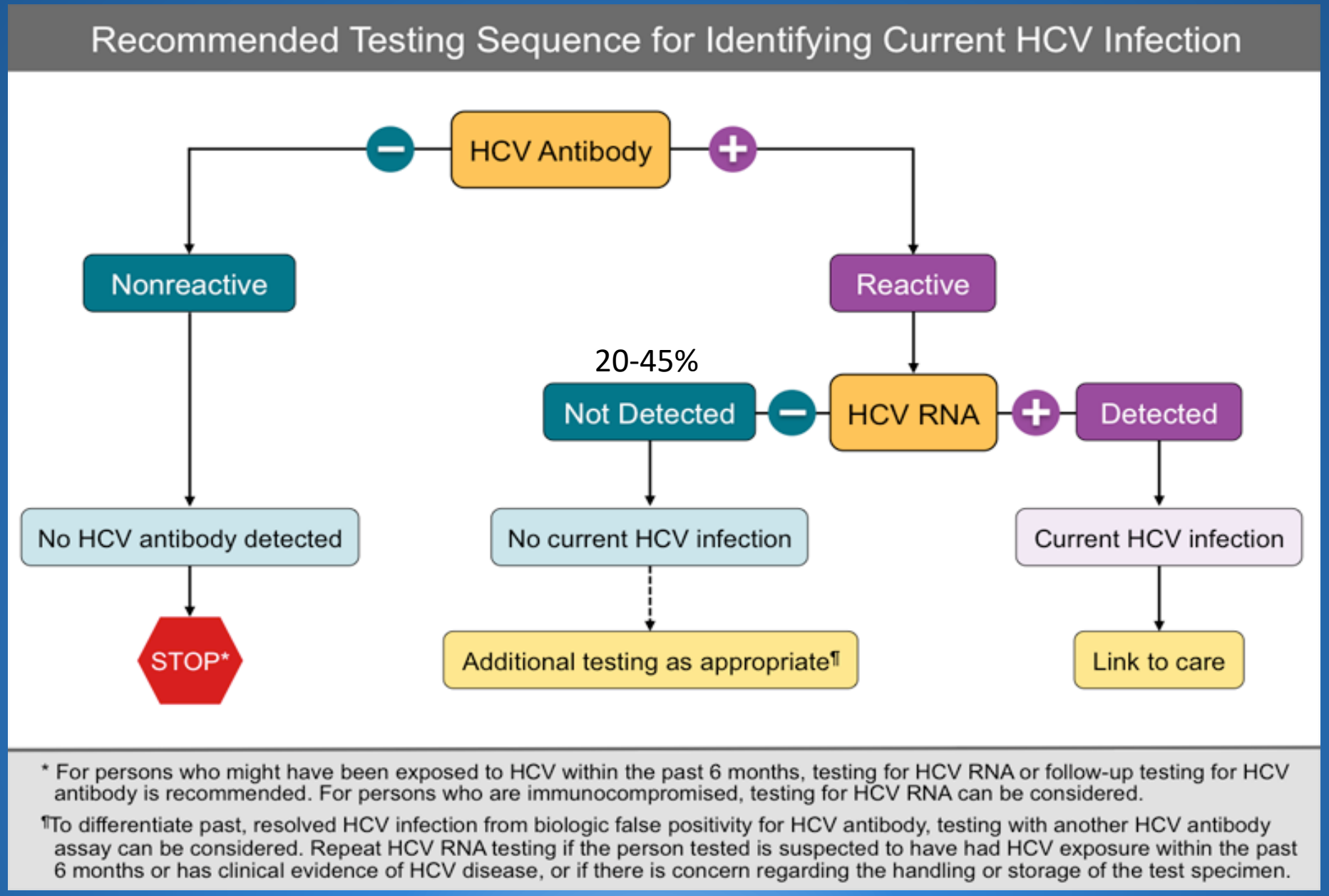
High Risk Groups to Screen

- All baby boomers (once)
- High risk behaviors
  - Injection-drug use (even once) or intranasal drug abuse
  - Tattoo in an unregulated setting
- High Risk Settings
  - Incarceration
  - Healthcare/public safety workers exposed to HCV+ blood
  - Born in a high risk country

Diagnosing HCV

Lab Tests and Risk Measures

Screening Tests for HCV Infection



Laboratory Tests for HCV

- HCV antibody (anti-HCV)
  - Negative
    - Not infected
    - Except if exposure to HCV within the past 6 months in a patient suspected of having liver disease, then **retest**
  - Positive
    - Patient infected at some point with HCV
- HCV RNA to determine if still infected
  - Test for HCV RNA if patient is immunocompromised (may not have anti-HCV)

http://www.hcvguidelines.org/full-report/hcv-testing-and-linkage-care

Diagnosis Codes HCV Screening

Screening

Diagnosis

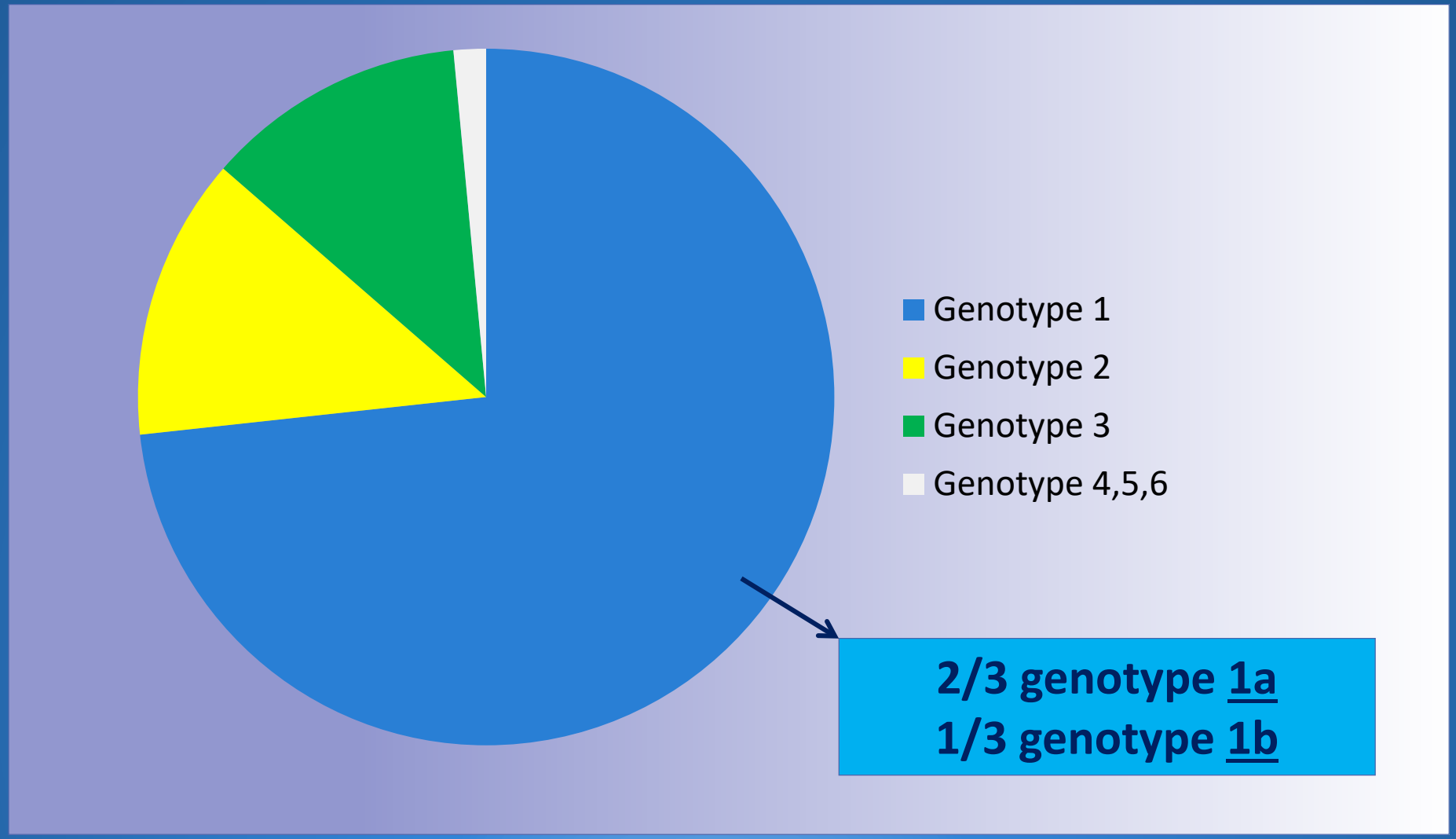
ICD-9-CM (before 2018)	ICD-10-CM
V73.89- Encounter for screening for other viral diseases	Z11.59- Encounter for screening for other viral diseases
070.54- Chronic hepatitis C without mention of hepatic coma 0.70.44- Chronic hepatitis C with hepatic coma	B18.2- Chronic viral hepatitis C
070.70- Unspecified viral hepatitis C without hepatic coma	B19.20- Unspecified viral hepatitis C without hepatic coma
070.71- Unspecified viral hepatitis C with hepatic coma	B19.21- Unspecified viral hepatitis C with hepatic coma
V02.62- Hepatitis C Carrier	Z22.52 Carrier of hepatitis C
070.51- Acute hepatitis C without mention of hepatic coma	B17.10- Acute hepatitis C without hepatic Coma
070.41- Acute hepatitis C with hepatic coma	B17.11- Acute hepatitis C with hepatic coma

CPT codes for HCV Testing

Description	Code
Hepatitis C antibody	86803
Hepatitis C, direct probe technique (qualitative)	87520
Hepatitis C Virus **RNA, amplified probe technique (qualitative)**	87521
Hepatitis C, Quantative PCR (if + for antibody)	87522
Hepatitis C Genotype	87902

Preferred test: Hepatitis C Antibody with Reflex to HCV, RNA, Quantitative PCR

HCV Genotype 1a: Most Common in U.S.



Key Areas for H and P Exam

HISTORY

- Alcohol and/or drug use
- GI bleeding/varices
- Hepatic encephalopathy
- History of cirrhosis or prior biopsy
- Heart and kidney disease – affects drug choice
- HIV infection – faster HCV progression

PHYSICAL EXAM

- Jaundice
- Temporal wasting
- Spider angiomata
- Gynecomastia
- Ascites
- Hepatomegaly or splenomegaly
- Edema
- Asterixis or confusion

Baseline Labs for Evaluation with Chronic Infection

- Basic: CMP, CBC, and INR
- Genotype
  - Including sub-genotype (1a vs. 1b)
- Screen for Hepatitis A and B
  - Consider vaccination if not immune
- HIV screen
- Other considerations:
  - UA (r/o proteinuria)

Indicators of Advanced Disease

- Platelet count
  - Reflects cirrhosis and portal hypertension
  - <170K suspicious and <140K highly suspicious for cirrhosis
- LFTs, Albumin, total bilirubin (TB) and INR
  - AST, ALT and ALK Phosphatase 20 X upper limit of normal
  - Albumin <3.5g/dL or INR or TB >upper limit of normal

Staging Liver Disease

- Liver biopsy has been gold standard but noninvasive evaluation are increasingly used to reduce risk and cost
  - FIB-4 measure
  - Imaging (liver ultrasound or CT)
  - FibroScan (not widely available)
  - FibroSure (Expensive—not widely available)

Calculating FIB-4

Fibrosis-4 (FIB-4) Calculator

The Fibrosis–4 score helps to estimate the amount of scarring in the liver. Enter the required values to calculate the FIB–4 value. It will appear in the oval on the far right (highlighted in yellow).

$$\text{FIB–4} = \frac{\text{Age } (\textit{years}) \; 0 \times \text{AST Level } (\textit{U/L}) \; 0}{\text{Platelet Count } (10^9/\textit{L}) \; 0 \times \sqrt{\text{ALT } (\textit{U/L}) \; 1}}$$

Non-cirrhotic
1.45
3.25
Cirrhotic

Interpretation:
Using a lower cutoff value of 1.45, a FIB–4 score <1.45 had a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4–6 which includes early bridging fibrosis to cirrhosis). In contrast, a FIB–4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis. In the patient cohort in which this formula was first validated, at least 70% patients had values <1.45 or >3.25. Authors argued that these individuals could potentially have avoided liver biopsy with an overall accuracy of 86%.

Source: Sterling RK, Lissen E, Clumeck N, et. al. Development of a simple noninvasive index to predict significant fibrosis patients with HIV/HCV co–infection. Hepatology 2006;43:1317–1325.

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

Liver Disease Stages Based on Scarring

- F0 = no scarring
- F1 = mild fibrosis
- F2 = moderate fibrosis
- F3 = severe fibrosis
- F4 = cirrhosis or advanced fibrosis

Case 1

Case---Mr. Herrera

- 63 yo Hispanic man BMI 31, BP 138/88
- Seen in primary care clinic for hypertension and prediabetes
- Uninsured
- Routine HCV screening = antibody +
- Follow-up HCV RNA = 2,500,000
- No symptoms other than fatigue
- Exam: no hepatosplenomegaly, pedal edema or other evidence of chronic liver disease

Key Points for Patient Counseling

- Reduce risk of transmission to family and other contacts
  - Exposure to blood, rough sex, sharing needles
- Strategies to reduce liver toxicity
  - NO alcohol, herbal meds, avoid high doses of prescription drugs metabolized in liver (eg Tylenol)
- Offer hope and minimize stigma
  - Highly effective treatment options
- Offer support
  - Insurance coverage, access to costly drugs, dealing with substance use

Lab Tests for Mr. Herrera

- ALT 102, AST 65, AP 83
- ALB 4.1, T BILI 0.3,
- WBC 4.71, HGB 12.8, PLT 115,000
- INR 1.1
- HIV negative
- Not immune to HAV or HBV
- HCV genotype 1a
- Ultrasound: surface nodularity and mild coarsening of echotexture without blunting of the liver edge

FIB-4 Calculation

$$\text{FIB-4} = \frac{\text{Age } \textit{(years)}\ \textit{[63]} \times \text{AST Level } \textit{(U/L)}\ \textit{[65]}}{\text{Platelet Count } \textit{(10}^9\textit{/L)}\ \textit{[115]} \times \sqrt{\text{ALT}}\ \textit{(U/L)}\ \textit{[102]}} = 3.53$$

- **This is a high FIB-4 score (likely F3 – advanced fibrosis or even F4 - cirrhosis)**
- FIB-4 score <1.45 a negative predictive value of 90% for advanced fibrosis.
- A FIB-4 >3.25 has 97% specificity and a positive predictive value of 65% for advanced fibrosis or cirrhosis.

Source: Sterling RK, Lissen E, Clumeck N, et. al. Development of a simple noninvasive index to predict significant fibrosis patients with HIV/HCV co-infection. Hepatology 2006;43:1317-1325.

Factors That Can Accelerate HCV-Related Liver Damage

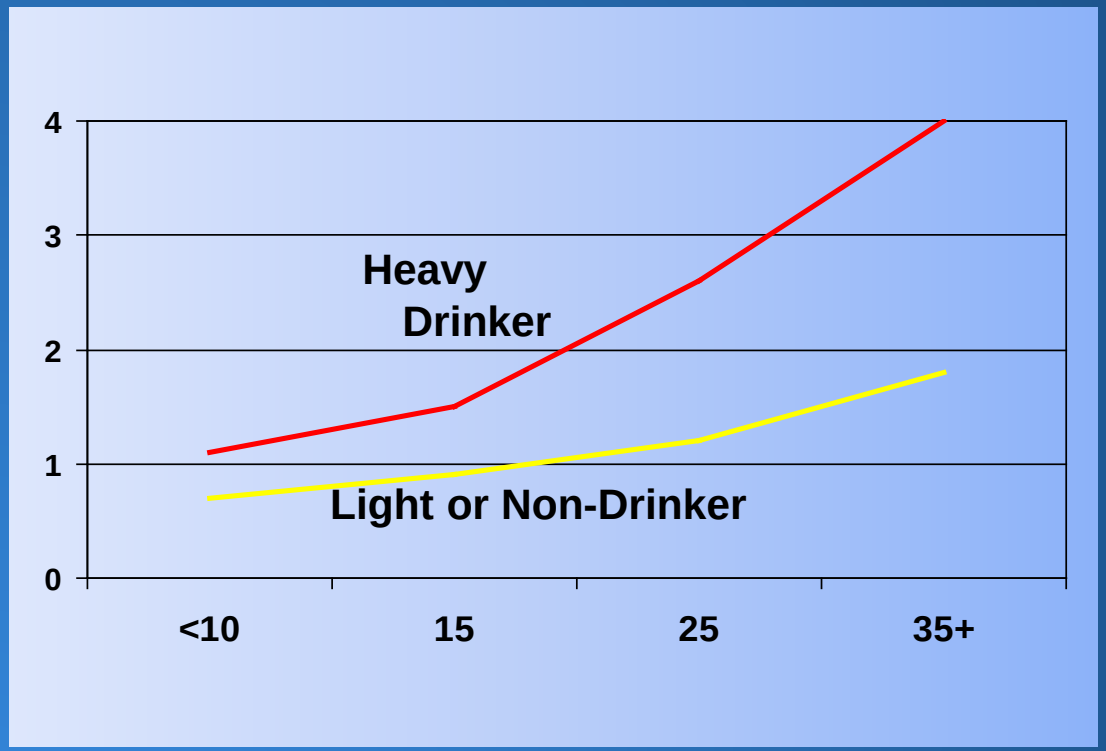
- Alcohol consumption
- HIV
- Co-infection with hepatitis A or B
- Older age (>40 years) at infection
- Metabolic factors such as high cholesterol, obesity, diabetes
- Certain genetic risks

Co-Factors That Worsen Liver Disease in Person With Chronic HCV Infection

- Alcohol adds fuel to the fire

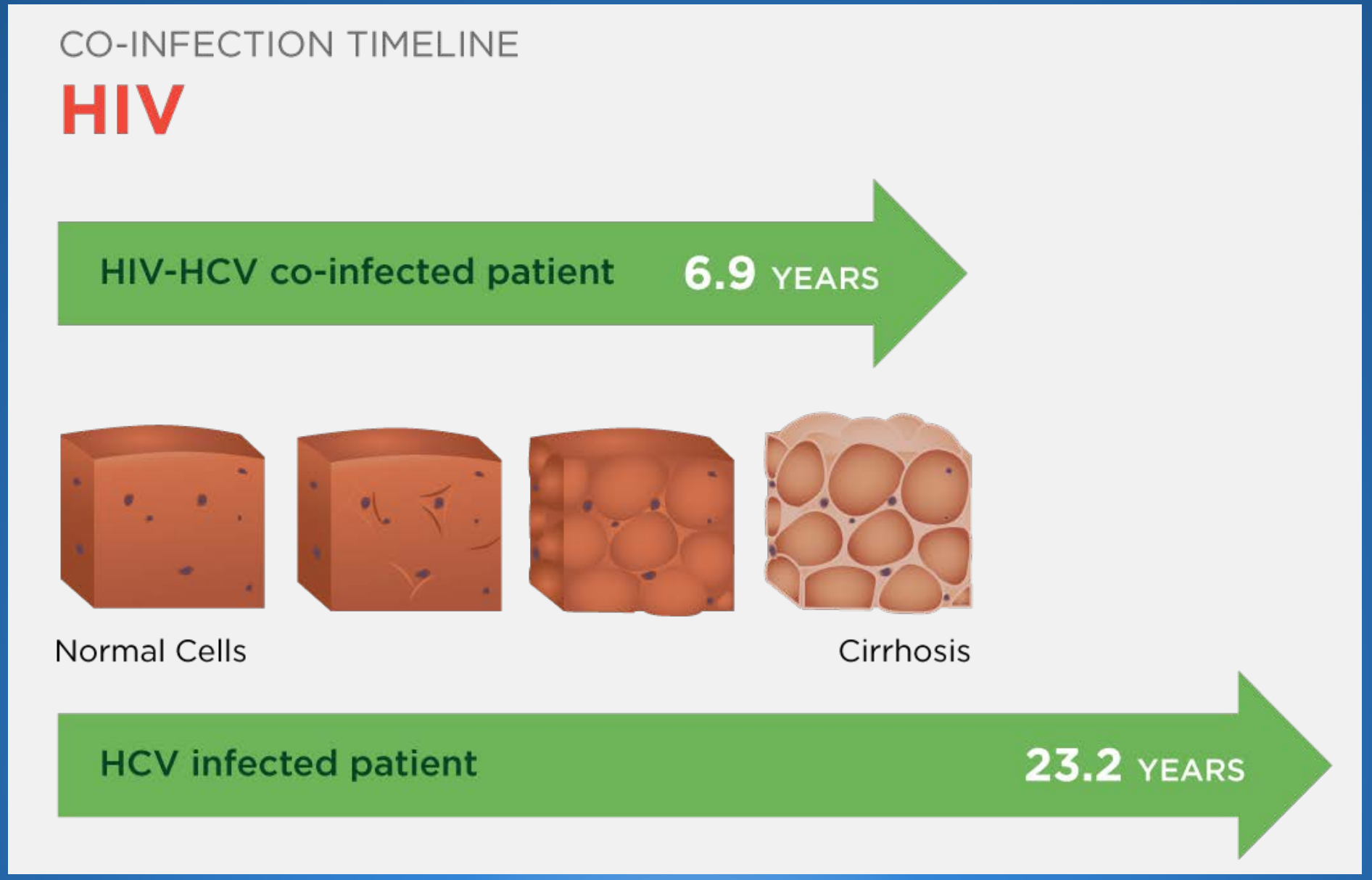
Cirrhosis

No Scarring



Years of Hepatitis C Infection

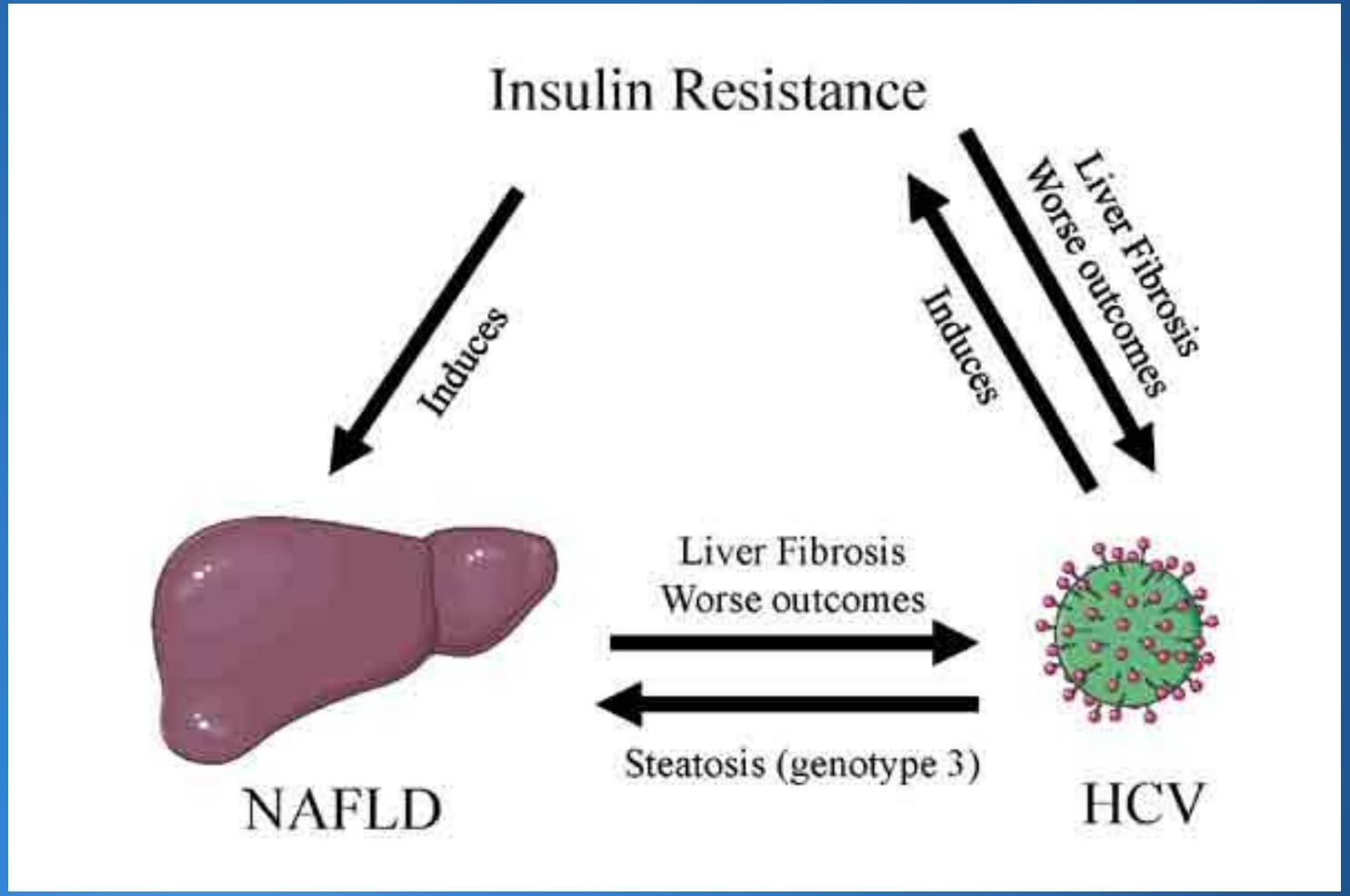
HIV Shortens Time to Cirrhosis



http://hcv.guidelinecentral.com/toolbox/patient-resources/co-infection-timeline-hiv/

Obesity-Related Non-Alcoholic Liver Disease and HCV

- The combination of NAFLD and HCV worsens fibrosis progression and increases risk of developing HCC even further



Goossens et al. Reviews on recent clinical trials. 2014;9.3:204-209

Mr. Herrera's Risks

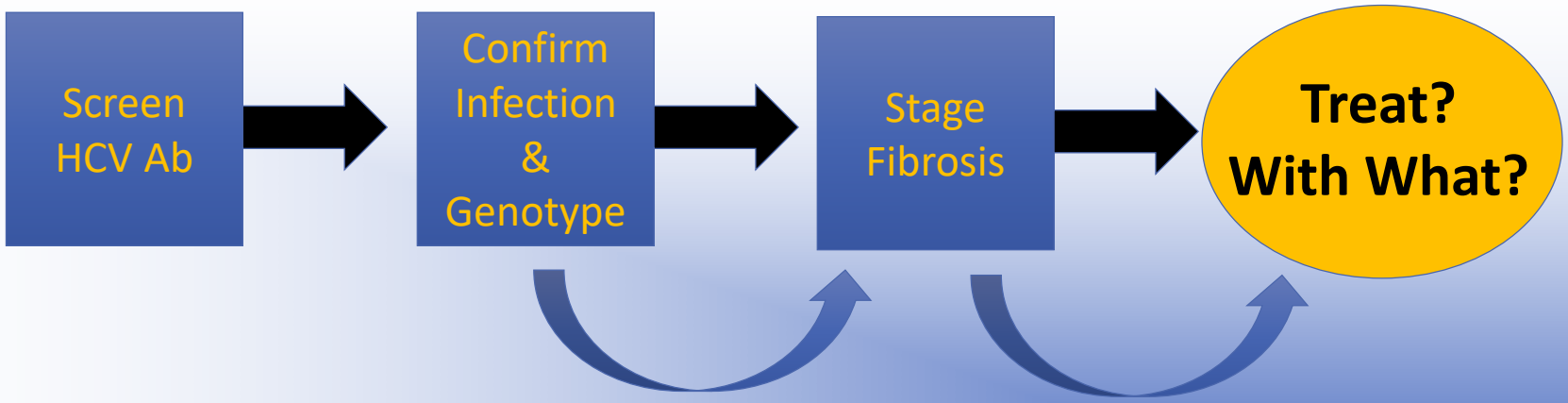
- Negative for HIV
- Not immune to HAV or HBV
- Drinks 3 beers nightly
- Obese but not yet diabetic
- Hispanics have high prevalence of genetic risk (PNPLA3)

Plans for Mr. Herrera

- He has evidence of advanced fibrosis and possibly cirrhosis (F3)
- Screening Brief Intervention for alcohol – goal is none.
  - Some Medicaid programs require abstinence for 3 months
- Obesity can lead to progression of liver disease even after cure of hepatitis C
- Immunize for HAV and HBV
- Apply for Medicaid (unlikely success)
  - When rejected, can still apply for drug assistance program through companies that make anti-HCV drugs

The Good News! Highly Effective Direct-Acting Drugs = Cure

Preparing for HCV Therapy



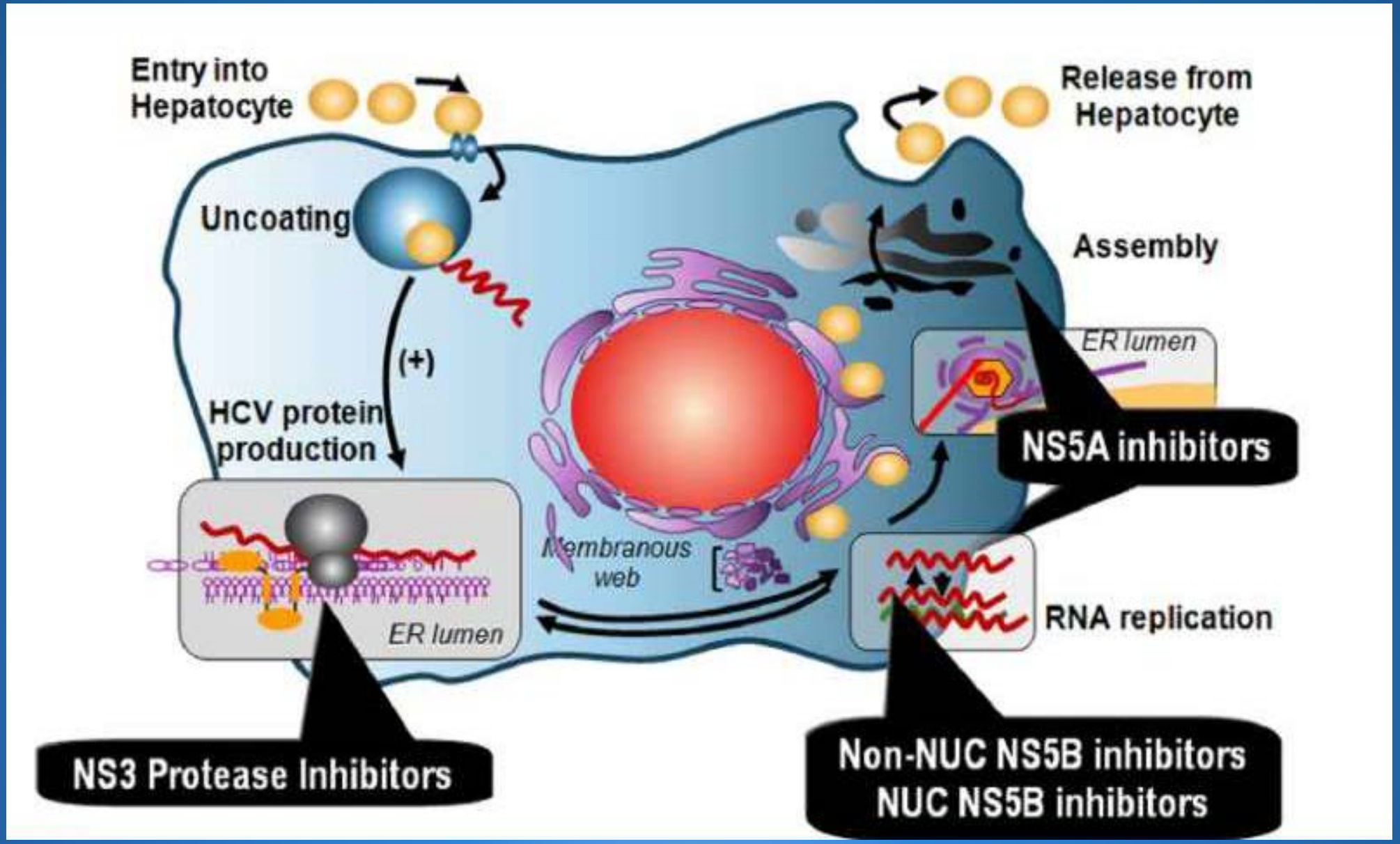
HCV Evaluation and Staging

-Treatment history (interferon therapy or DAA)
-Genotype (1, 2, 3..) and subgenotype (1a vs 1b)
-Imaging
-Viral load (copies/mL)
-Fibrosis score (i.e. Fib-4)
-Drug-drug interactions (DDIs)

Goal of Treatment

CURE!

Direct Acting Antivirals



Gane, E.J., et al. American Journal of Transplantation. 2014;14(5):994-1002.

Commonly Used DAA Therapies

Trade name	Genotype	Treatment	SVR	Common Adverse Effects
Harvoni®	1, 4	12wk	99%	HA, nausea, fatigue
Epclusa®	1-6	12wk	99%	HA, nausea, fatigue
Mavyret®	1-6	8-12wk	98%	HA, nausea, fatigue

Selecting HCV Regimens

- Cure rates >90% even in patients with more advanced fibrosis or cirrhosis
- Most regimens 12 weeks with few side effects
  - But monitor patients with cirrhosis more closely
  - Mild disease can be cured with only 8 weeks
- Choice of regimen and duration
  - New pan-genotypic drugs (less focus on genotype)
  - Presence of cirrhosis
  - Prior HCV treatment (uncommon in most patients)
- Watch for drug-drug interactions

Threats to Achieving a Cure

- Alcohol or substance abuse
- Risk of poor adherence to therapy
  - Evidence of nonadherence to drugs for other diseases (e.g. diabetes)
- Poor social support
- Pregnancy risk
- Unstable mental health
  - But depression no longer a contraindication as for interferon

HCV Cure: Sustained Virologic Response (SVR)

- Check HCV RNA after 12 and 24 weeks post treatment
  - Typically negative at 12 weeks post treatment, though some patients take up to 24 weeks to clear infection
  - An undetectable level at 12 weeks post treatment is generally maintained through week 24

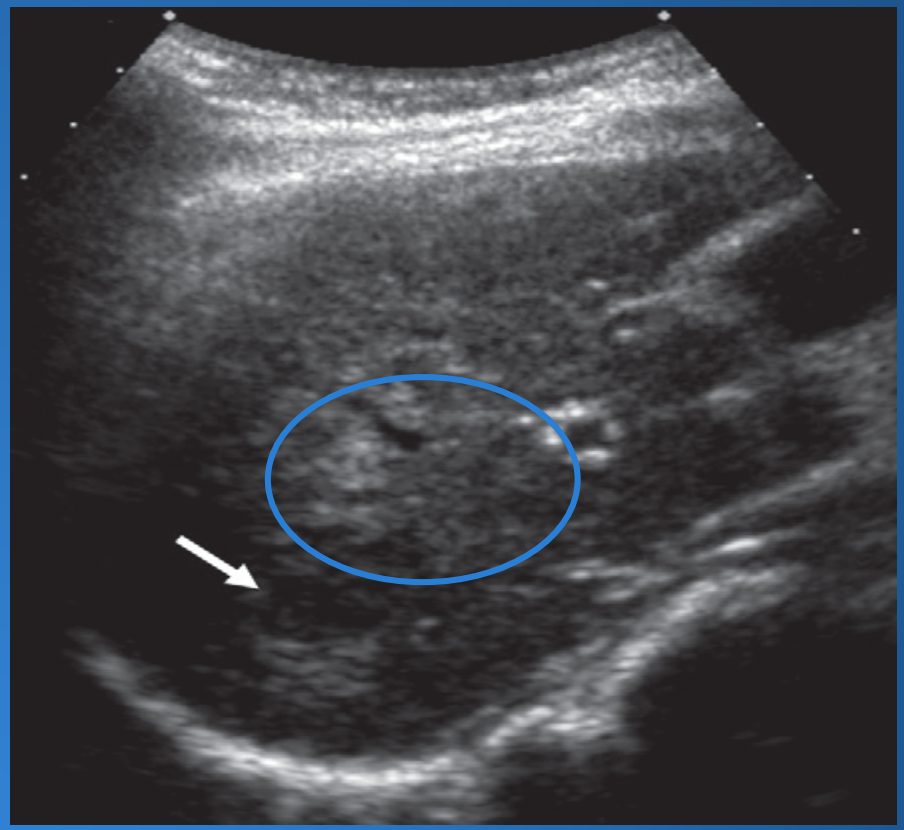
Risk of Hepatocellular Carcinoma (HCC)

- 70% of HCC develops in patients with cirrhosis
- HCC develops in 5-30% of cirrhotics per five years
  - Although reduced, this risk persists after cure
- Ongoing monitoring for HCC necessary every 6 months even after cure for patients with cirrhosis
  - Ultrasound recommended but not clear if alpha fetoprotein adds significantly

Finkelmeier F et al. Liver Cancer 2018;7:190-204

Patients With Cirrhosis
Serial Screening with Ultrasound

- Ultrasound recommended modality for HCC surveillance every 6 months
- Advantages: cheap, safe, readily available, supported by data
- Drawbacks: operator dependent, limited sensitivity, difficult in obese patients
- Masses detected by ultrasound require further characterization with other modalities (CT, MRI)



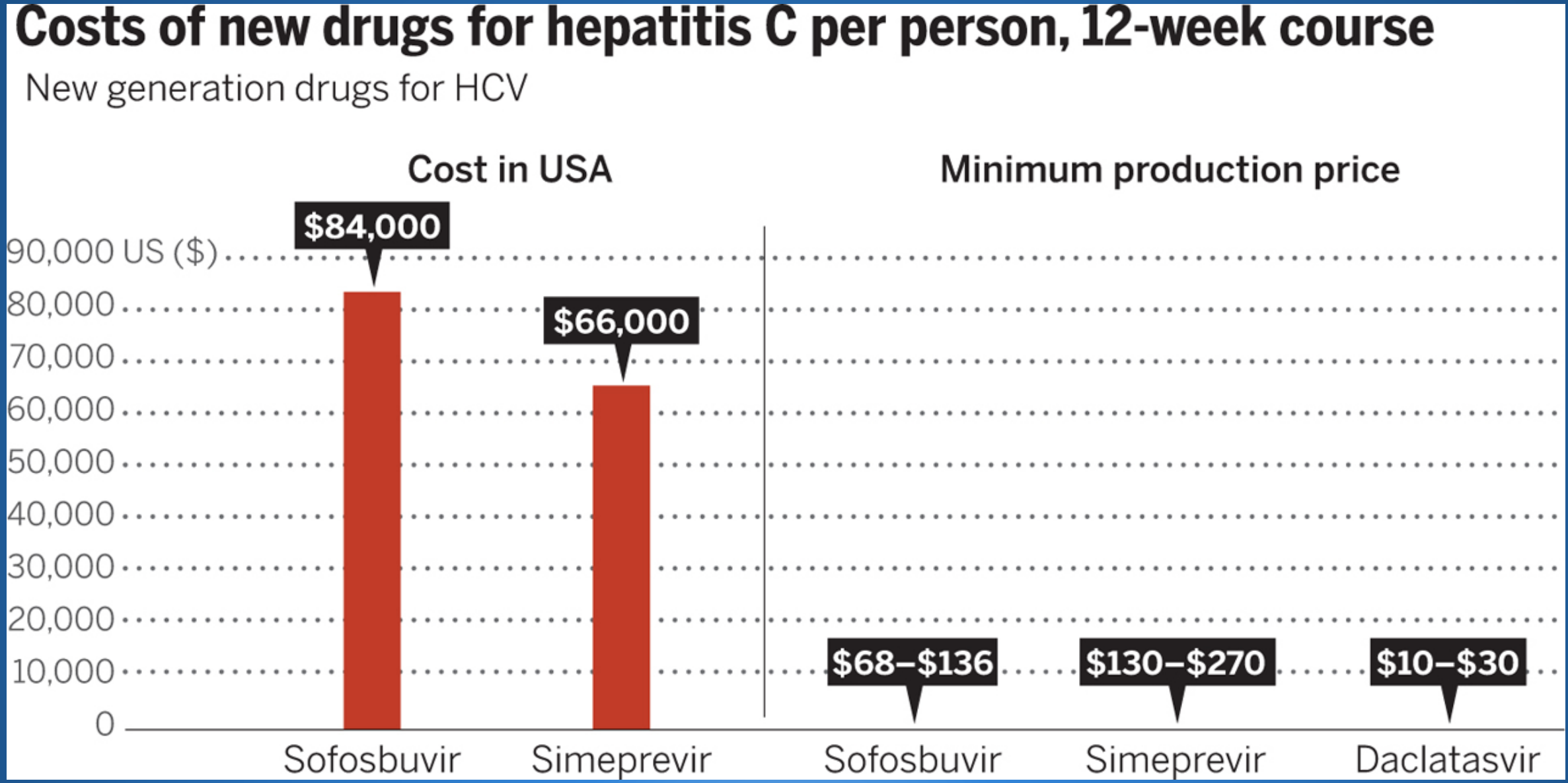
Sonogram shows a small hypoechoic mass

Wilson SR, et al. Radiology 2010

FINANCIAL TOXICITY

Insuring access to treatment and care

Monumental Cost of HCV Drugs



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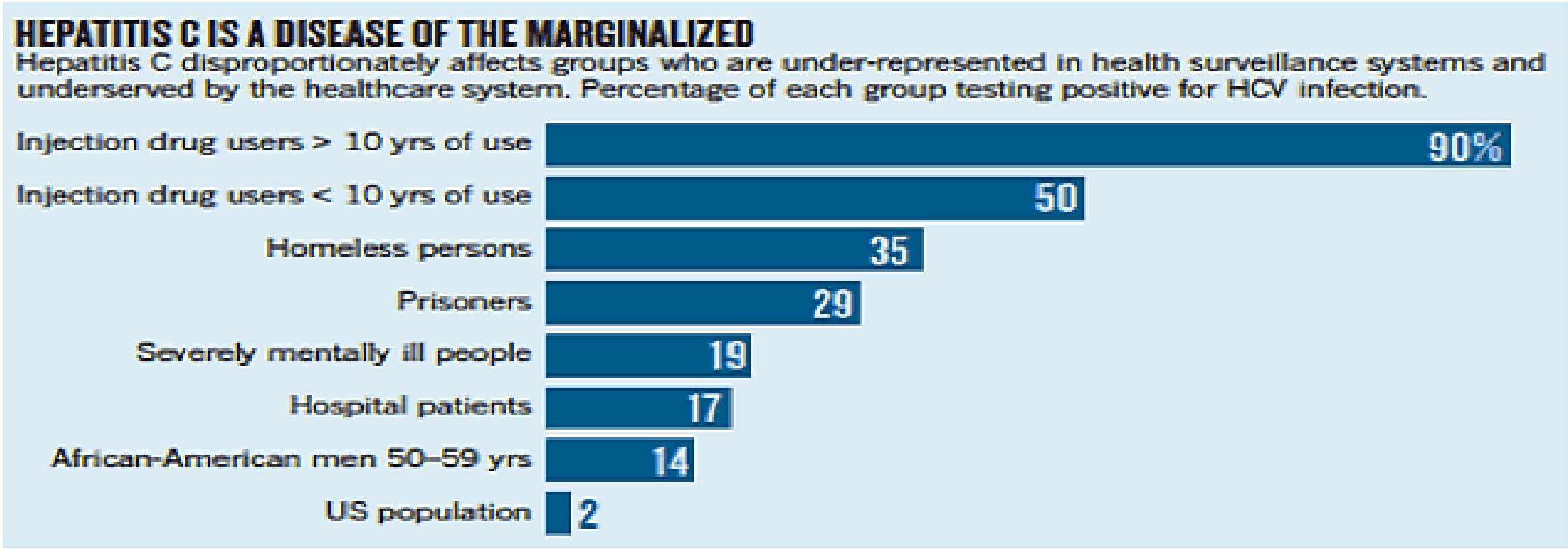
So What's The Problem?



http://www.natap.org/2014/HCV/071614_04.htm

Barriers to HCV Therapy

- Provider
  - Not enough specialists exist to treat the ~3 million patients with chronic HCV
  - Access to specialists limited for uninsured populations
  - Transportation challenges to access specialty care
  - HCV patients report feeling stigmatized by specialty care settings

More Barriers

- Patient
  - Limited knowledge and misinformation about HCV
  - Competing priorities – other diseases, family issues, no $
  - Difficulty accessing healthcare
  - Low perceived health risks for a disease without symptoms
  - Stigma
  - Unwillingness to reduce alcohol or drug use

Solutions?

- Insurance
  - Medicaid restrictive
- Patient Assistance Program
  - For persons who met low income requirements
  - Can be prescribed by a primary care physician
- Hepatologist support may be accessed through ECHO programs or our specialty-office based consult hours
- More and more primary care clinicians are treating and curing HCV successfully!

Summary

- Screen all baby boomers and other risk groups (especially IV drug users) for HCV infection
  - We are here to help make that straightforward
- Diagnose chronic HCV infection and counsel patients with chronic infection
- Evaluate disease stage
- We help you partner with hepatologists to treat patients with chronic HCV

Acknowledgement

- Grant Funder:

Thank You