

# Update Hepatitis C 2018

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# Conflict of Interest Disclosure Statement

None.

# Goals for this Presentation

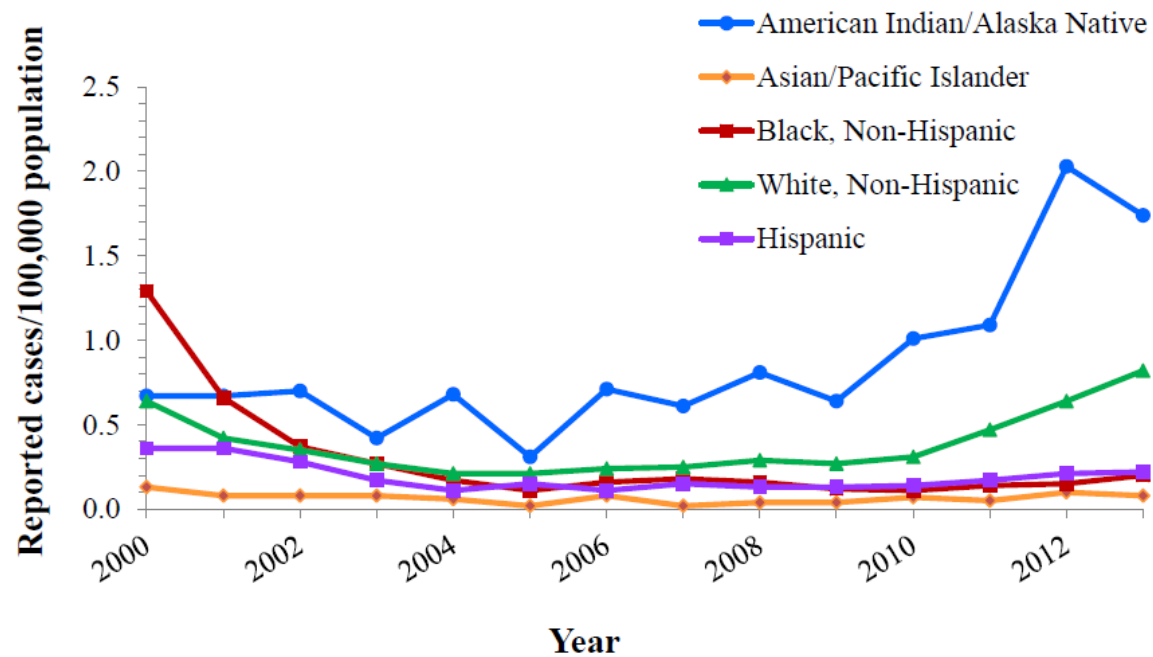
- \* Epidemiology of HCV in Alaska
- \* Understand who should be screened to detect chronic HCV infection based on recommendations from the CDC
  - \* Screening beyond the current recommendations
- \* Understand Natural history of HCV
- \* Understand recommendations for screening for hepatocellular carcinoma (HCC) in HCV

# The Two Epidemics of Hepatitis C in the USA and Alaska

- \* Epidemic in the 1960's, 1970's and Early 1980's
  - \* Related to heavy IDU use, unscreened blood transfusions, unregulated tattooing and lack of universal precautions before HIV
- \* Current epidemic since 2010 from recent surge in injection opioid and other drug use
  - \* Up to 90% of IDU will acquire HCV infection within one year of starting

# Increases in Reported cases Acute Hepatitis C in U.S

Figure 4.4. Incidence of acute hepatitis C, by race/ethnicity — United States, 2000-2013



Source: CDC, National Notifiable Diseases Surveillance System.

2010 to 2013

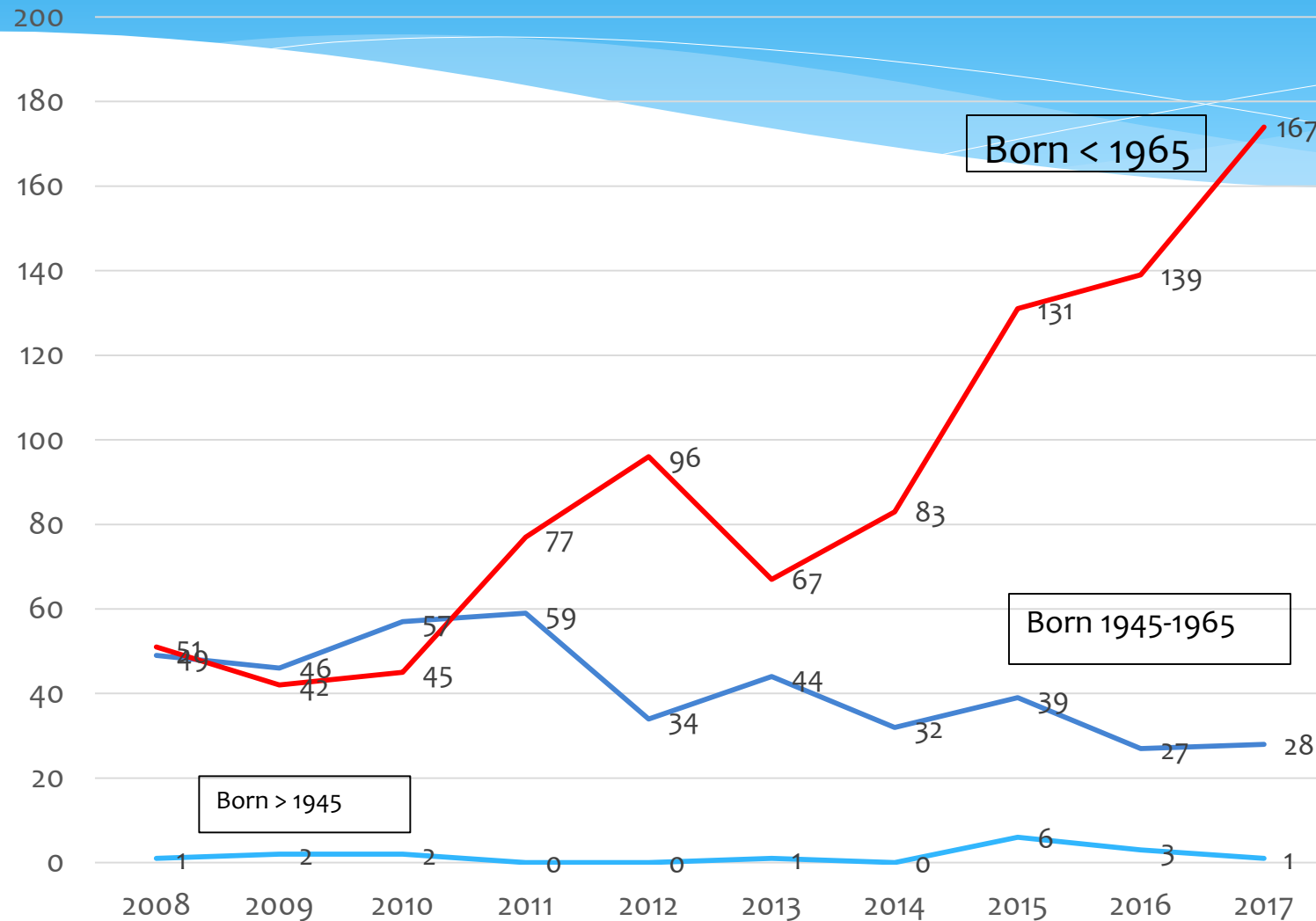
Overall **2.5X**  
increase

**2.7X** increase  
amongst 20-29 year  
olds

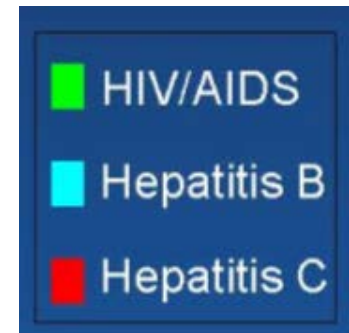
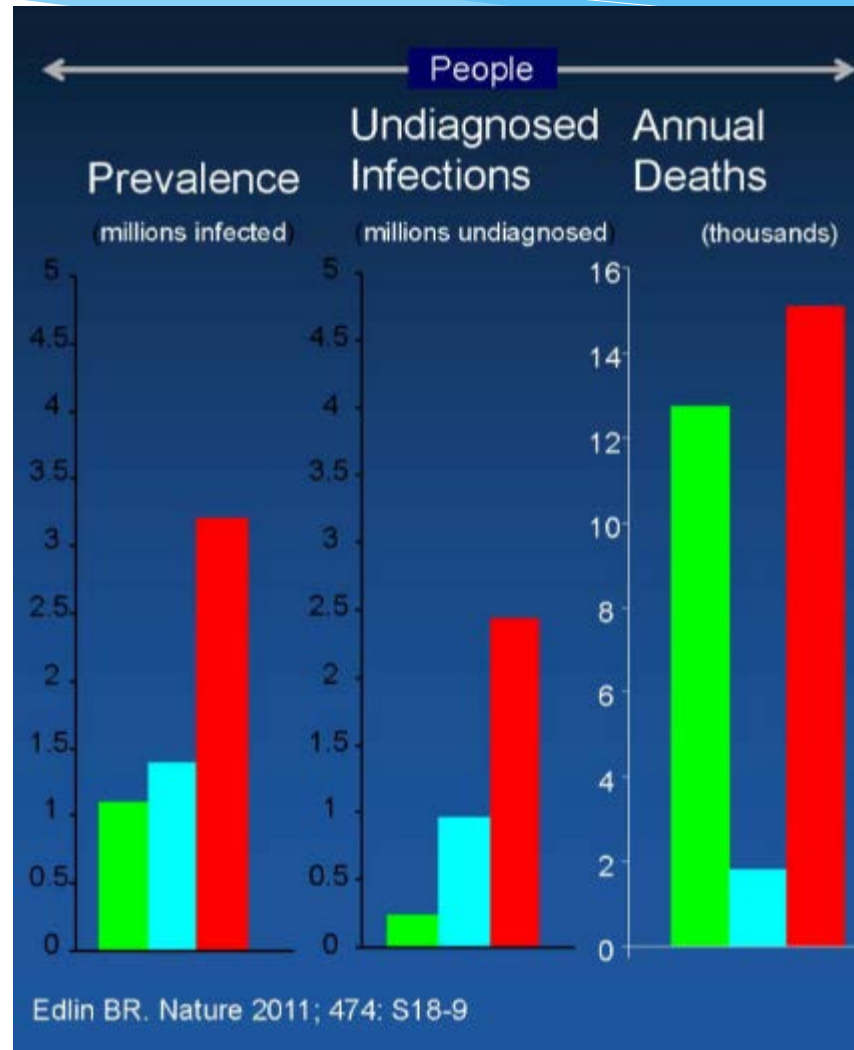
2012 to 2013

**86.2%** increase  
among American  
Indian/Alaska Native  
persons

# Hepatitis C On the Rise: Data from ANTHC

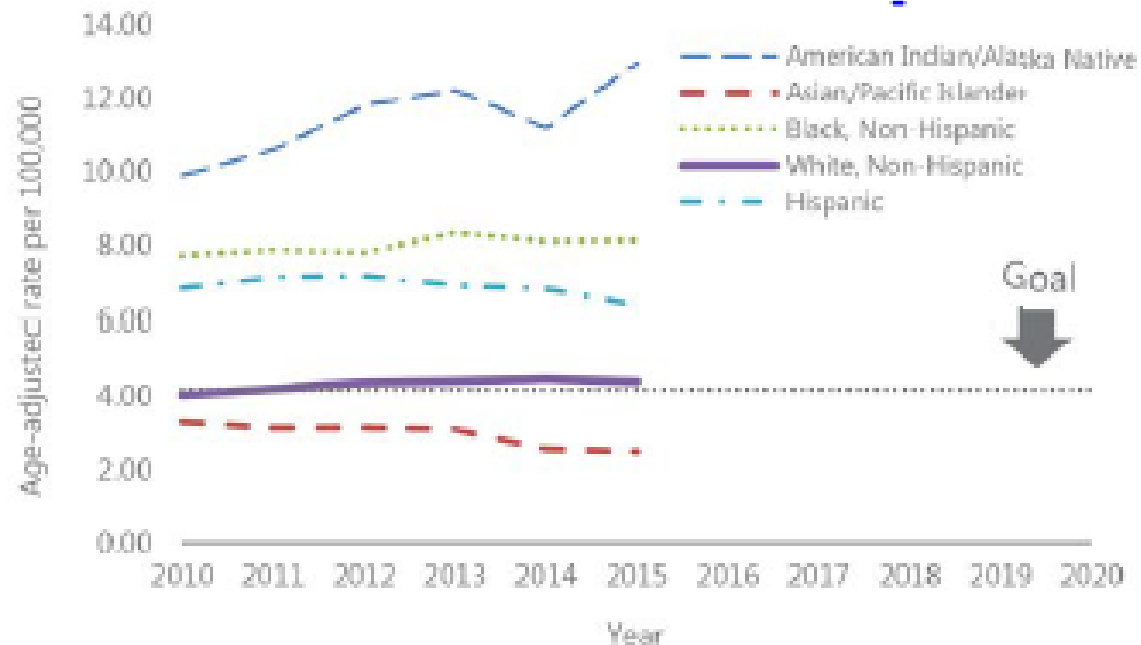


# Burden of Hepatitis C



## Age-adjusted rate\* of HCV-related deaths,<sup>†</sup> by

## race/ethnicity<sup>‡</sup>



American Indians/Alaska Natives have the highest death rates of all racial/ethnic populations, and rates for this group increased by 16% from 2014 to 2015. Death rates are also elevated for non-Hispanic black and Hispanic persons compared with other populations.

Source: CDC, National Vital Statistics System<sup>1,2</sup>

\*Rates for sex and race/ethnicity are age-adjusted per 100,000 U.S. standard population in 2000.

<sup>†</sup>Cause of death is defined as the underlying cause of death or one of the multiple causes of death and is based on the International Classification of Disease, 10th Revision (ICD-10) codes B17.1 and B18.2.

<sup>‡</sup>2 deaths in 2010, 1 death in 2011, 2 deaths in 2012, 2 deaths in 2013, 5 deaths in 2014, and 1 death in 2015 are not represented due to missing age data.

<sup>§</sup>65 deaths in 2010, 73 deaths in 2011, 126 deaths in 2012, 111 deaths in 2013, 142 deaths in 2014, and 157 deaths in 2015 are not represented due to missing race/ethnicity data.



# Hepatitis C Prevalence

- \* In 2010 an estimated 3-4 million persons in US were living with hepatitis C
  - \* 1.6% overall prevalence
  - \* 3.25% are born between 1945-1965 (baby boomers)
- \* This estimate does not include persons infected in current Opioid epidemic

# Estimate of HCV Infected Persons in State of Alaska

- \* Number on non duplicate names in Alaska State database: >20,000 anti-HCV positive
- \* Due to the opioid epidemic, the influx of persons with new HCV diagnosis far outstrips number of persons with HCV who have been treated and cured

# 2010 Institute of Medicine Report on Chronic Viral Hepatitis in the US

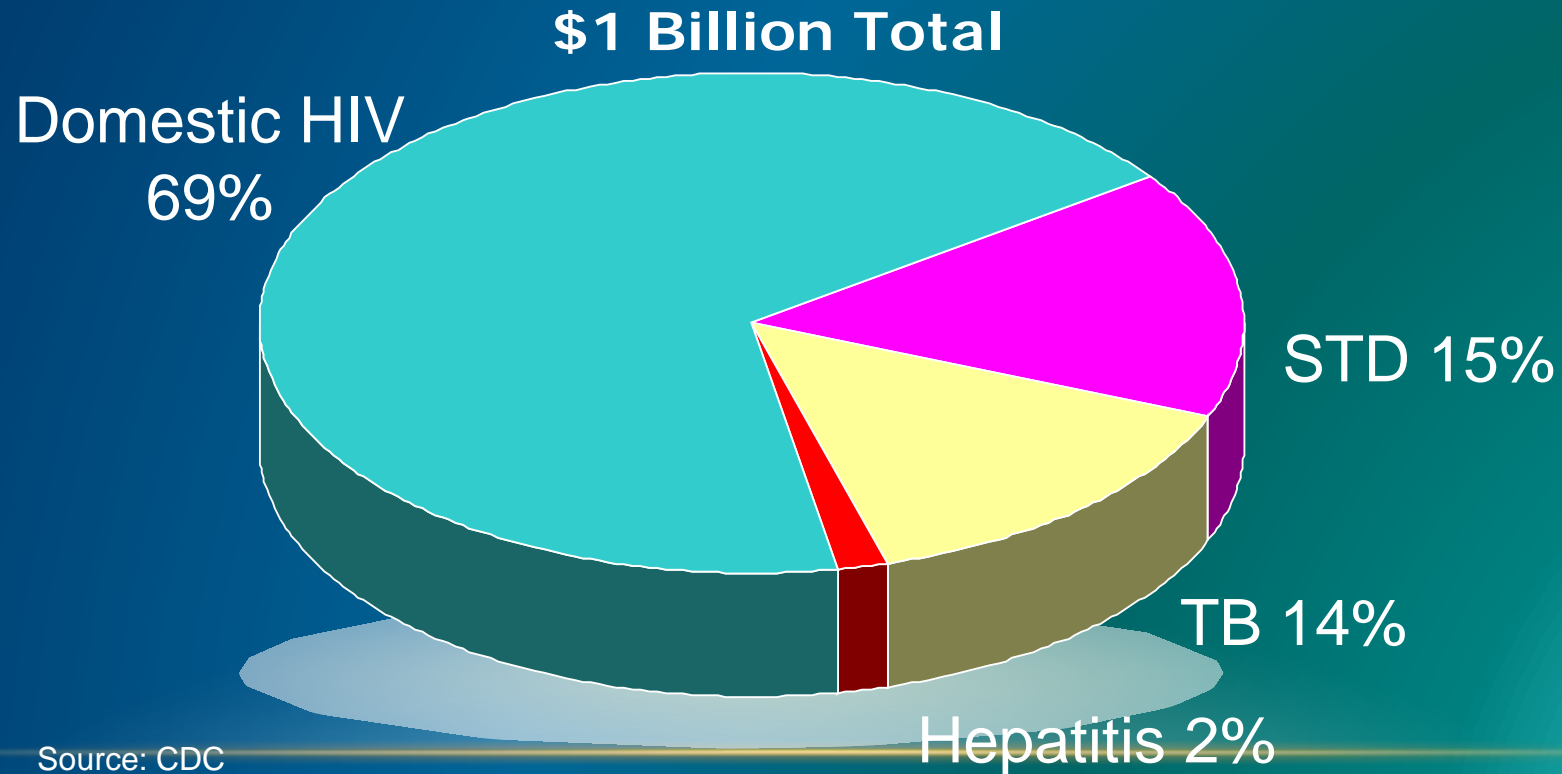
- \* Incidence of liver cancer is rising in US
- \* Deaths attributable to hepatitis B and hepatitis C exceeded deaths due to HIV/AIDS
  - \* 15,000 per year for hepatitis versus 14,000 per year for HIV
  - \* Deaths due to viral hepatitis B and C; these kill more people than all other chronic infectious diseases in the USA combined
- \* Studies showed that current data on hepatitis B and C underestimated the true prevalence and impact of these infections
- \* Preventive measures and medications for effective treatment were now available

# 2016/2017 National Academy of Science and Medicine Report

- \* Hepatitis C could now be easily cured with DAA
- \* Not much progress made on baby boomer screening
- \* Lot's of talk, but little new initiatives have stemmed the spread from opioid epidemic
- \* Lot's of discussion but so far Federal, State and Local government resources not forthcoming

# LACK OF PUBLIC RESOURCE ALLOCATION

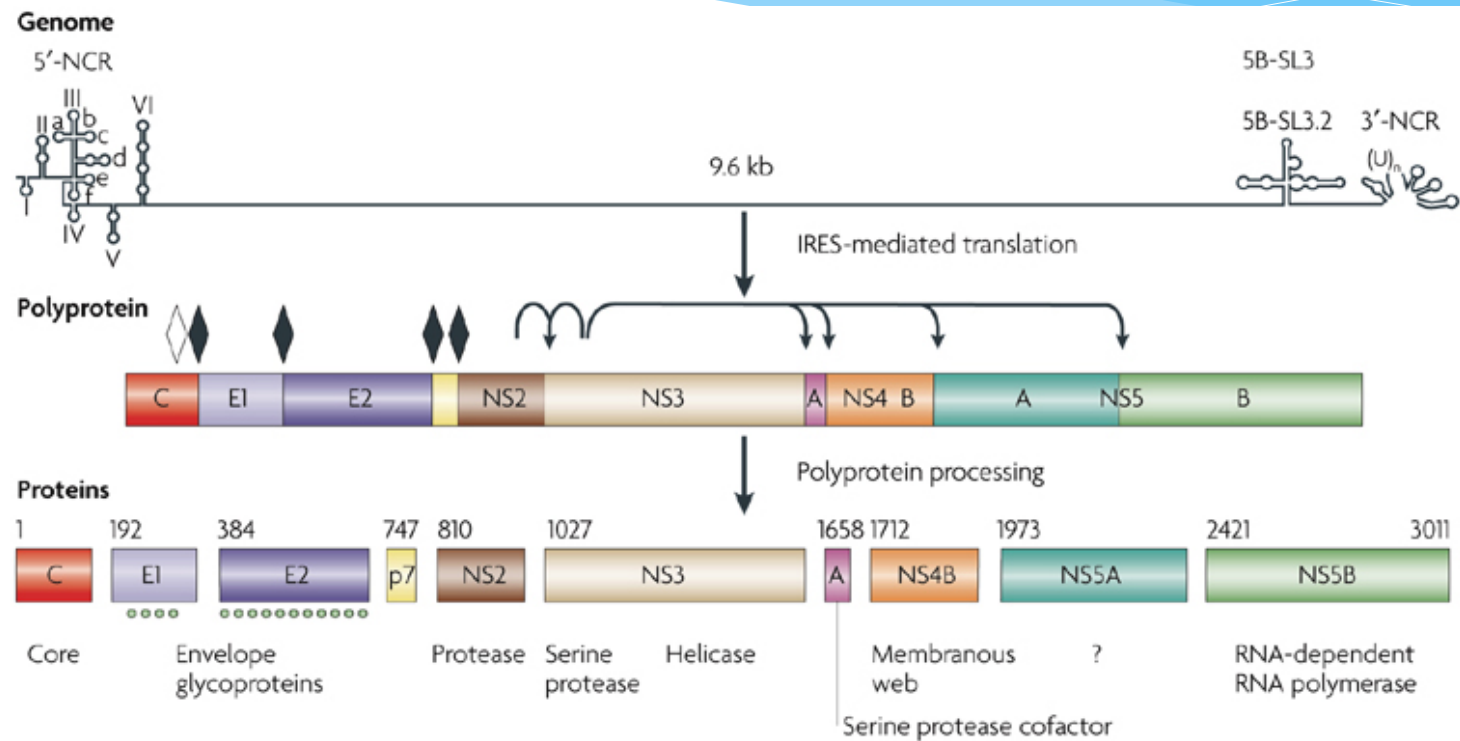
National Center for HIV/AIDS, Viral Hepatitis, Sexually Transmitted Disease, and Tuberculosis Prevention Funding



# HCV Virology

- \* Single stranded RNA virus: 9.6 base pairs
  - \* Identified in late 1980's
  - \* Reliable HCV antibody test became available in 1992
- \* Six major genotypes, > 80 subtypes
- \* Genome codes for 3 structural and 7 nonstructural proteins
- \* Very rapidly mutating virus especially in structural protein areas and vaccine development has been elusive

# Hepatitis C Translation

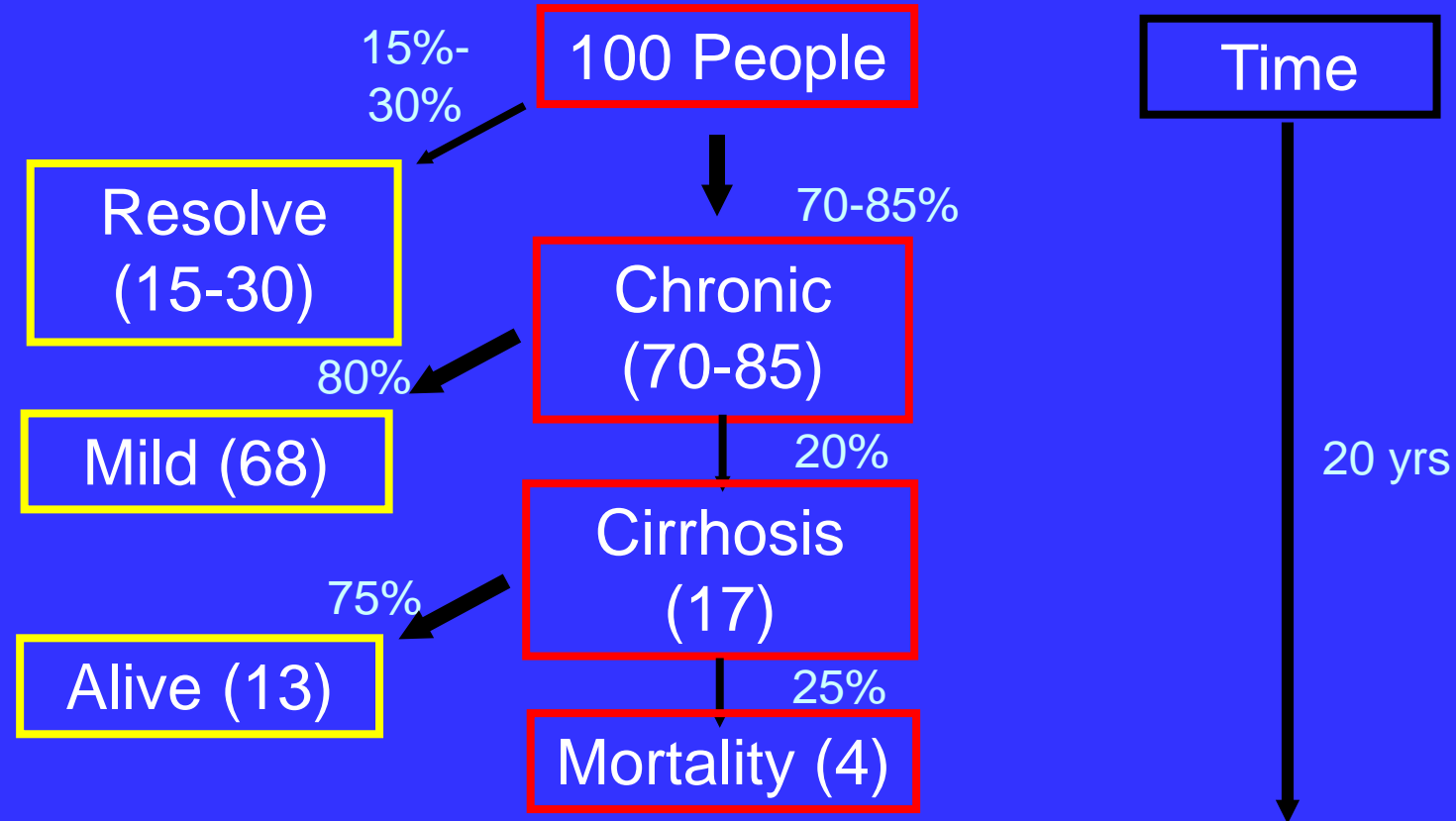


# HCV: Modes of Transmission & Persons to screen

- \* Contaminated Needles:
  - \* Injection drug use: Accounts for > 90% of new infections in US
  - \* Unsafe medical procedures: Developing world
  - \* Sexual: Rare in monogamous heterosexual couples
    - \* Rectal intercourse is a risk factor
- \* Transfusion/Organ transplant before 1992
- \* Perinatal: ~ 5%; 15%-20% with HIV
- \* Other less certain: tattooing, snorting cocaine, sharing tooth brushes/razors, body piercing, incarceration, men who have sex with men
- \* Baby Boomers born 1945-1965 (3.5%+)



# Natural History of HCV Infection



Leading Indication for Liver Transplant in US  
Adapted from Alter HJ

# Extrahepatic Manifestations of Chronic HCV Infection

- \* B cell lymphoma, non Hodgkin's & Myeloma
- \* Glomerulonephritis
- \* Mixed Cryoglobulinemia
- \* Recent published and unpublished studies have shown increased mortality due to
  - \* Atherosclerosis: Cardiovascular disease and stroke
  - \* Diabetes
  - \* Certain cancers (Pancreas, Renal cell)
  - \* Genitourinary and renal disease
  - \* Two recent studies show persons with HCV die at an average age of 59 vs. 72 years for the general US population

# Risk Factors Associated with Progression of HCV

- \* Heavy alcohol usage: Strongest factor
- \* Male sex
- \* Diabetes or hepatic steatosis
- \* Older age at time of infection
- \* HCV genotype 3
- \* Co-infection with HIV or HBV
- \* Not associated:
  - \* Viral load
  - \* Presence of Anti-HBc without HBsAg

# Adverse Outcomes Following Liver Biopsy Among Alaska Native (AN) HCV Cohort

## Patient Population

412 Persons with liver biopsy completed between 1995 and 2012

68% (n = 282) with mild/moderate fibrosis

21% (n = 87) with severe fibrosis

10% (n = 43) with cirrhosis

# Adverse Outcomes Following Liver Biopsy Among AN HCV Cohort

Average age at time of liver biopsy 43.3 years

51% (n = 211) females: 49% (n = 201) males

Followed an average of 7.7 years

## Adverse Outcomes

- End stage liver disease

- Hepatocellular carcinoma

- Liver-related death

# Risk of Developing End Stage Liver Disease (Liver Failure) from Time of Liver Biopsy by Fibrosis Stage

Outcome	Time Period				
		None/Mild (Ishak 0-1) (n = 150)	Moderate (Ishak 2) (n = 131)	Severe (Ishak 3-4) (n = 88)	Cirrhosis (Ishak 5-6) (n = 38)
ESLD	3-Year	0.7% (0.1, 4.6) (n = 122)	2.5% (0.8, 7.7) (n = 102)	8.7% (4.2, 17.5) (n = 63)	27.7% (15.8, 45.6) (n = 22)
	5-Year	1.7% (0.4, 6.8) (n = 95)	7.9% (4.0, 15.2) (n = 86)	16.4% (9.6, 27.2) (n = 51)	49.0% (33.0, 67.7) (n = 16)
	7-Year	5.1% (2.1, 12.1) (n = 78)	10.2% (5.6, 18.2) (n = 71)	23.9% (15.2, 36.4) (n = 40)	74.1% (56.4, 88.9) (n = 9)
	10-Year	8.4% (4.0, 17.3) (n = 49)	19.0% (11.6, 30.3) (n = 42)	39.3% (27.6, 53.9) (n = 25)	
	# of Cases	12	20	31	26

# Risk of Developing HCC from Time of Liver Biopsy by Fibrosis Stage

Outcome	Time Period	Fibrosis Stage			
		None/Mild (Ishak 0-1) (n = 150)	Moderate (Ishak 2) (n = 131)	Severe (Ishak 3-4) (n = 88)	Cirrhosis (Ishak 5-6) (n = 38)
HCC	3-Year	0.0% (0.0, 3.2) (n = 118)	0.0% (0.0, 3.4) (n = 103)	1.1% (0.2, 7.7) (n = 65)	3.3% (0.5, 21.4) (n = 25)
	5-Year	1.0% (0.1, 6.9) (n = 95)	1.0% (0.1, 6.6) (n = 87)	1.1% (0.2, 7.7) (n = 54)	13.4% (4.4, 36.7) (n = 16)
	7-Year	1.0% (0.1, 6.9) (n = 81)	2.3% (0.6, 9.1) (n = 72)	6.0% (1.9, 18.2) (n = 42)	35.0% (16.5, 64.4) (n = 11)
	10-Year	1.0% (0.1, 6.9) (n = 52)	4.6% (1.4, 4.8) (n = 44)	8.4% (3.1, 21.6) (n = 27)	
	# of Cases	2	4	7	9

# Risk of Developing Liver Related Death (LRD) or Transplant from Time of Liver Biopsy by Fibrosis Stage

Outcome	Time Period				
		None/Mild (Ishak 0-1) (n = 150)	Moderate (Ishak 2) (n = 131)	Severe (Ishak 3-4) (n = 88)	Cirrhosis (Ishak 5-6) (n = 38)
LRD	3-Year	0.0% (0.0, 3.2) (n = 120)	0.0% (0.0, 3.4) (n = 103)	1.4% (0.2, 9.6) (n = 66)	8.7% (2.9, 24.8) (n = 28)
	5-Year	0.0% (0.0, 3.2) (n = 95)	1.0% (0.2, 7.5) (n = 86)	4.7% (1.5, 13.9) (n = 54)	15.8% (6.8, 34.1) (n = 22)
	7-Year	1.2% (0.2, 8.1) (n = 78)	1.0% (0.2, 7.5) (n = 75)	6.9% (2.6, 17.6) (n = 43)	23.4% (11.8, 43.4) (n = 16)
	10-Year	1.2% (0.2, 8.1) (n = 49)	2.6% (0.6, 10.0) (n = 45)	12.1% (5.4, 25.6) (n = 29)	
	# of Cases	1	4	13	19



# Assessing Fibrosis Stage in Persons with Chronic HCV: Why is this important

- \* Fibrosis stage was important in the past for obtaining 3<sup>rd</sup> party payer support for DAA
  - \* Medicaid and most insurers in Alaska no longer require this
- \* Fibrosis remains important to identify those persons with advanced fibrosis or cirrhosis (F3-F4)
  - \* Appearance of HCC may occur in persons with a pre-existing malignancy in first 1-2 years
    - \* Highest risk in persons whose AFP does not fall to normal after SVR
  - \* In general, in persons cured of HCV the future risk of HCC does decrease up to 75% over the following 5 to 10 years but they are still at risk and need regular surveillance

# Surveillance for HCC in Persons with HCV with Advanced Fibrosis or Cirrhosis

- \* Liver Ultrasound and AFP every 6 months indefinitely
- \* Best chance of identifying small tumors that can be cured by ablation, surgery or transplantation
- \* Persons with concurrent non-alcoholic fatty liver or moderate to heavy users of alcohol need clinical follow-up at least yearly
- \* In these persons liver disease can progress after HCV cure, albeit likely at a slower rate

# How Can the Incidence and Prevalence of HCV in the US be Reduced in the Near Future? CDC and IOM recommendations

- \* Enhanced screening of high risk groups
- \* Risk reduction:
  - \* Counseling and availability of clean needles
  - \* Alcohol and drug rehabilitation

# Treatment Beyond the Traditional Venues

- \* Treatment of infected persons
  - \* Treating persons in private clinics
  - \* Treating incarcerated persons
  - \* Treating persons in drug rehab programs, needle exchange programs, safe injecting and other non-traditional sites
  - \* Treatment as prevention
- \* No Vaccine on horizon for decade or more

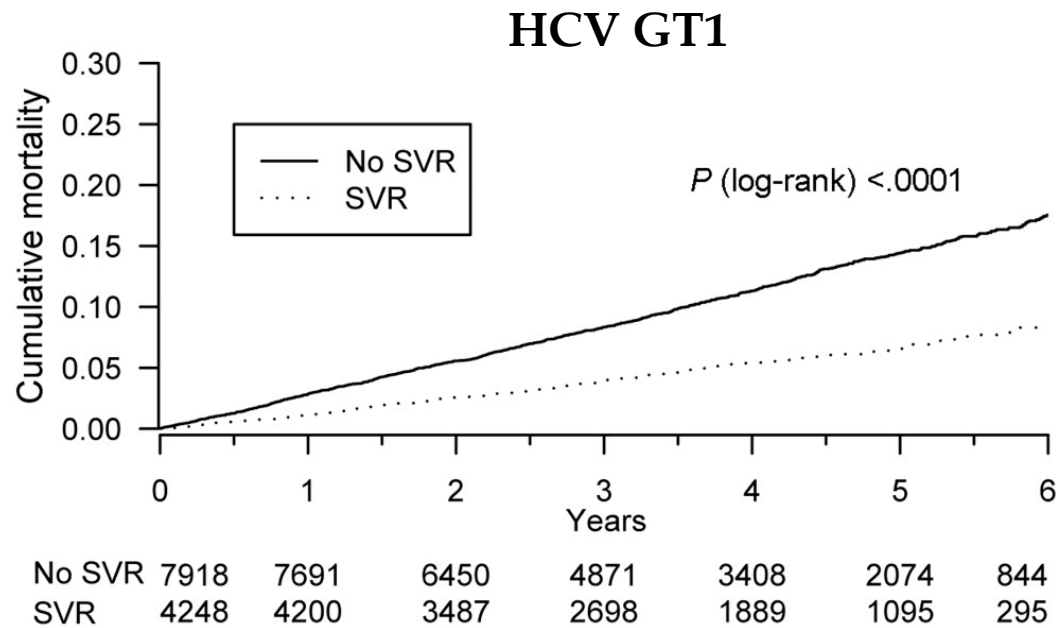
# Coffee Consumption and HCV

- \* HALT-C trial serial liver biopsies q. 2 years
- \* Coffee consumption  $\geq$  3 cups/day associated with:
  - \* Significantly reduced fibrosis (Hepatology 2009;50:1360-9)
  - \* Significantly better response to Peg IFN+RBV (Freedman Gastroenterology 2011;140:1961-9)
- \* Quantity of coffee consumption associated with decreased risk of HCC (Hepatology 2008;48:129-36)

# Why Treat HCV?

- \* Sustained virologic response (SVR) is associated with viral eradication:  $\leq 1\%$  have HCV RNA in serum, PBMC or liver tissue on long-term f/u (Swain MG Gastroenterology 2010;139:1593-1601)
- \* After SVR, risk of developing decompensated cirrhosis greatly reduced
- \* After SVR, regression of cirrhosis if present occurs (Mallet Ann Int Med 2008;149:399-403)
- \* Risk of HCC in those with cirrhosis reduced

# An SVR Reduces Risk of All-Cause Mortality in Patients With Hepatitis C



- \* 12,166 VA patients
- \* 95% male
- \* Estimated 10% with cirrhosis at baseline
- \* No biopsy data
- \* Similar findings for GT2 and GT3

# 10 year outcomes for patients +/- SVR

Outcome	SVR	No SVR	HR
Liver Failure	2.4%	31.7%	13
HCC	5.3%	23.1%	4.3
Liver related death	2.1%	27.5%	13
10 year overall mortality	9.8%	23.0%	2.3

**P < 0.001 for all comparisons**



From: **Association Between Sustained Virological Response and All-Cause Mortality Among Patients With Chronic Hepatitis C and Advanced Hepatic Fibrosis**

JAMA. 2012;308(24):2584-2593. doi:10.1001/jama.2012.144878

**Table 2.** Clinical Events According to Treatment Response

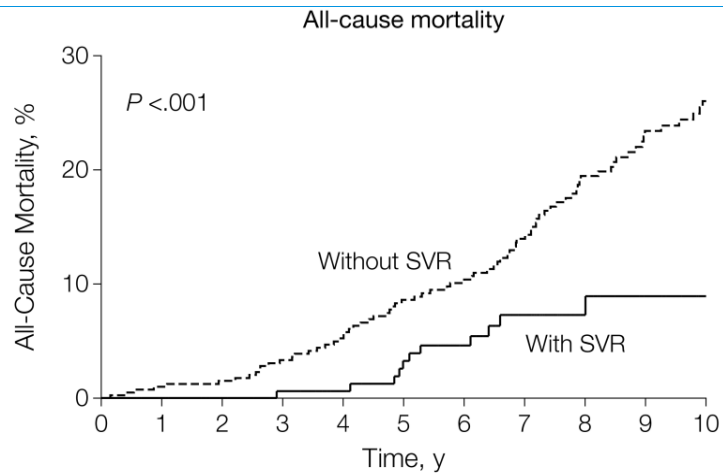
Outcomes	With SVR			Without SVR			P Value <sup>b</sup>
	Events, No.	Observation Period, Person-Years	Rate per 100 Person-Years (95% CI)	Events, No.	Observation Period, Person-Years	Rate per 100 Person-Years (95% CI)	
Any event <sup>a</sup>	18	1260	1.43 (0.77-2.09)	169	2921	5.79 (4.91-6.66)	<.001
All-cause mortality	13	1283	1.01 (0.46-1.56)	100	3410	2.93 (2.36-3.51)	<.001
Liver-related mortality or liver transplantation	3	1283	0.23 (<0.01-0.50)	103	3120	3.20 (2.58-3.82)	<.001
Hepatocellular carcinoma	7	1270	0.55 (0.14-0.96)	76	3222	2.63 (1.83-2.89)	<.001
Liver failure	4	1271	0.31 (<0.01-0.62)	111	3066	3.62 (2.95-4.29)	<.001

Abbreviation: SVR, sustained virological response.

<sup>a</sup>Any event is the composite of all analyzed outcomes, to which only the first event contributed in case of multiple events in an individual patient.

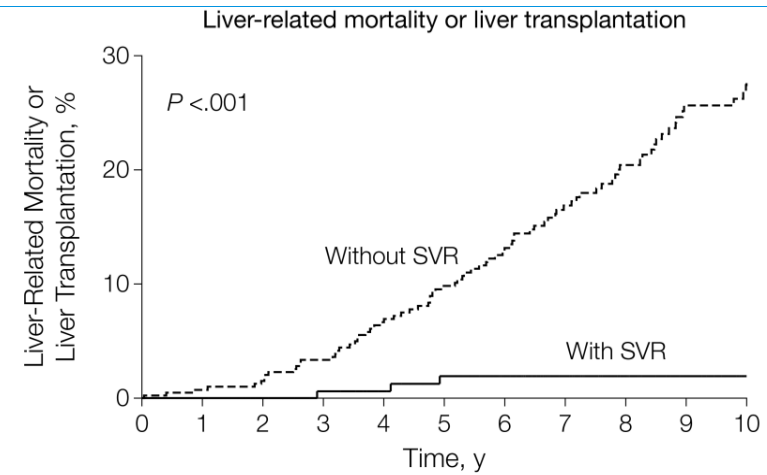
<sup>b</sup>P value is based on unadjusted Cox proportional hazards regression analyses, including SVR as a time-dependent covariate.

**Figure Leg**



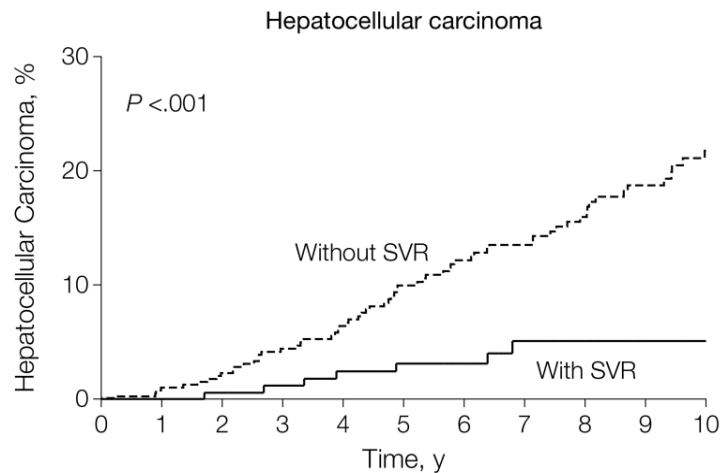
No. at risk

Without SVR	405	393	382	363	344	317	295	250	207	164	135
With SVR	192	181	168	162	155	144	125	88	56	40	28



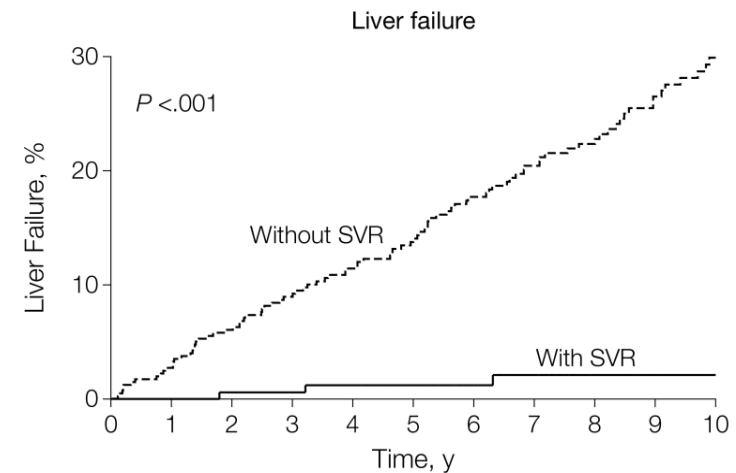
No. at risk

Without SVR	405	392	380	358	334	305	277	229	187	146	119
With SVR	192	181	168	162	155	144	125	88	56	40	28



No. at risk

Without SVR	405	390	375	349	326	294	269	229	191	151	122
With SVR	192	181	167	161	152	142	124	86	54	39	27



No. at risk

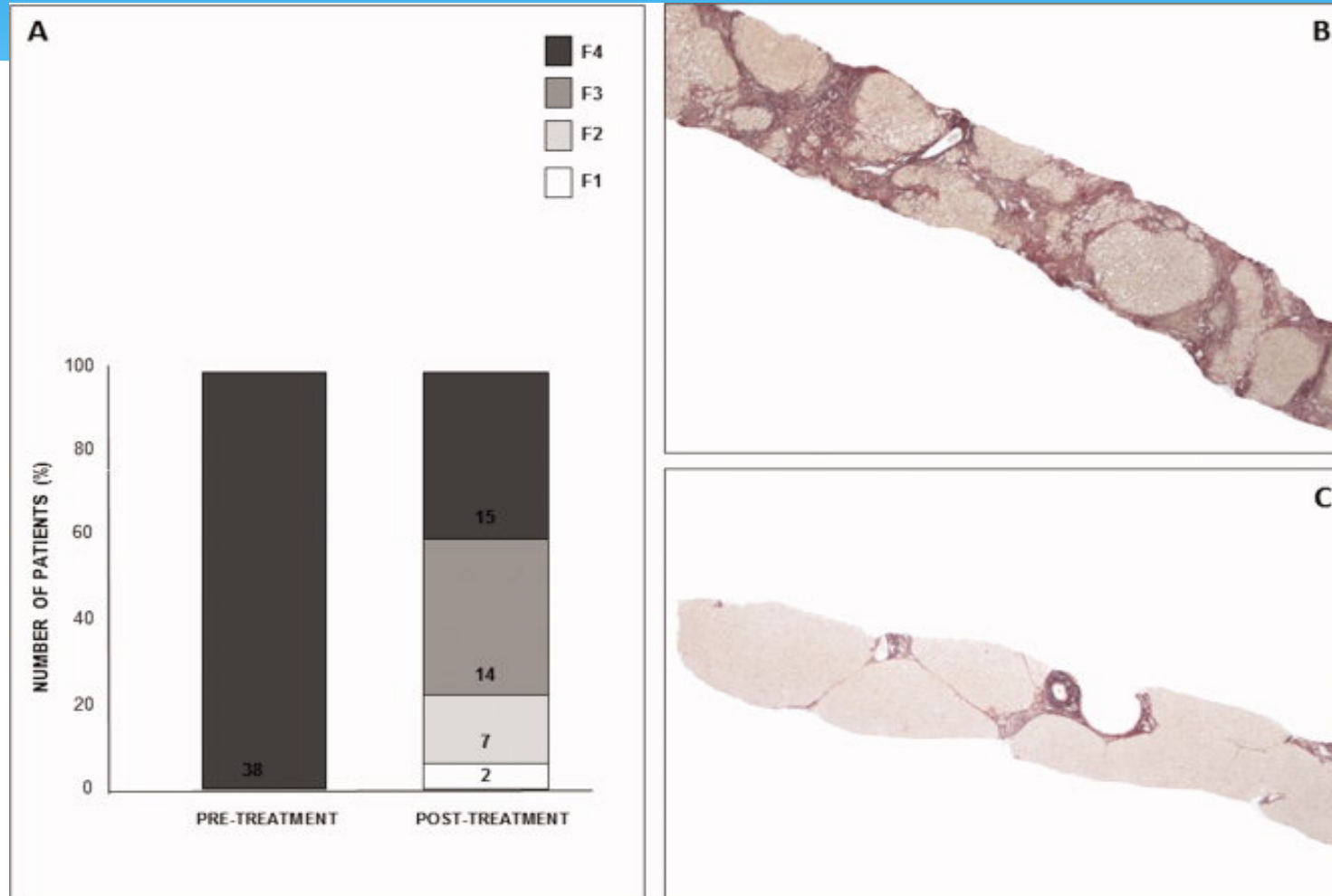
Without SVR	405	384	361	337	314	288	259	216	184	143	113
With SVR	192	180	166	160	152	141	123	88	56	40	28

From: Association Between Sustained Virological Response and All-Cause Mortality Among Patients With Chronic Hepatitis C and Advanced Hepatic Fibrosis  
 JAMA. 2012;308(24):2584-2593.

# Good News: Early Cirrhosis Can be Completely Reversed!

- \* Remove the cause of cirrhosis and reversal will take place over about 10 years
  - \* HBV: Antiviral medication (tenofovir)
  - \* HCV: Treat and cure
  - \* Alcohol: Stop drinking alcohol
- \* Even 30% to 50% of persons with decompensated cirrhosis will become compensated (look normal clinically and by LFT) after proper treatment

## A morphometric and immunohistochemical study to assess the benefit of a sustained virological response in hepatitis C virus patients with cirrhosis



### Hepatology

Volume 56, Issue 2, pages 532-543, 2 JUL 2012 DOI: 10.1002/hep.25606  
<http://onlinelibrary.wiley.com/doi/10.1002/hep.25606/full#fig1>

# Conclusions

- \* Chronic HCV is a progressive disease that leads to cirrhosis over 20-40 years in at least half of infected persons
- \* HCV also increases risk of extrahepatic diseases as it is a chronic inflammatory state including stroke, coronary artery disease and diabetes
- \* Cure of HCV reduces the risk of liver complications in those with advanced liver disease and likely eliminates development of cirrhosis or HCC in those with mild to moderate liver fibrosis
  - \* As a provider you'll experience lots of “high fives and hugs” after curing your patients
- \* Enhanced screening for infected persons and universal treatment can greatly impact the future development of liver related death and costs