

Update Hepatitis C 2020

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ANTHC Liver Disease and Hepatitis Program



**ALASKA NATIVE
TRIBAL HEALTH
CONSORTIUM**

Conflict of Interest Disclosure Statement


- * The LDHP has received two research grants from Gilead Sciences. None of my salary is funded by either of these grants

Goals for this Presentation

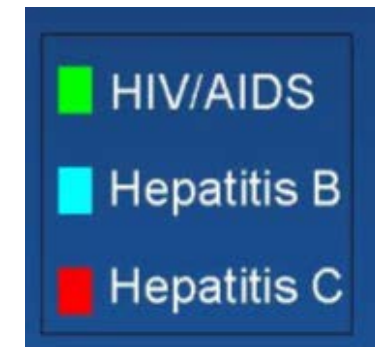
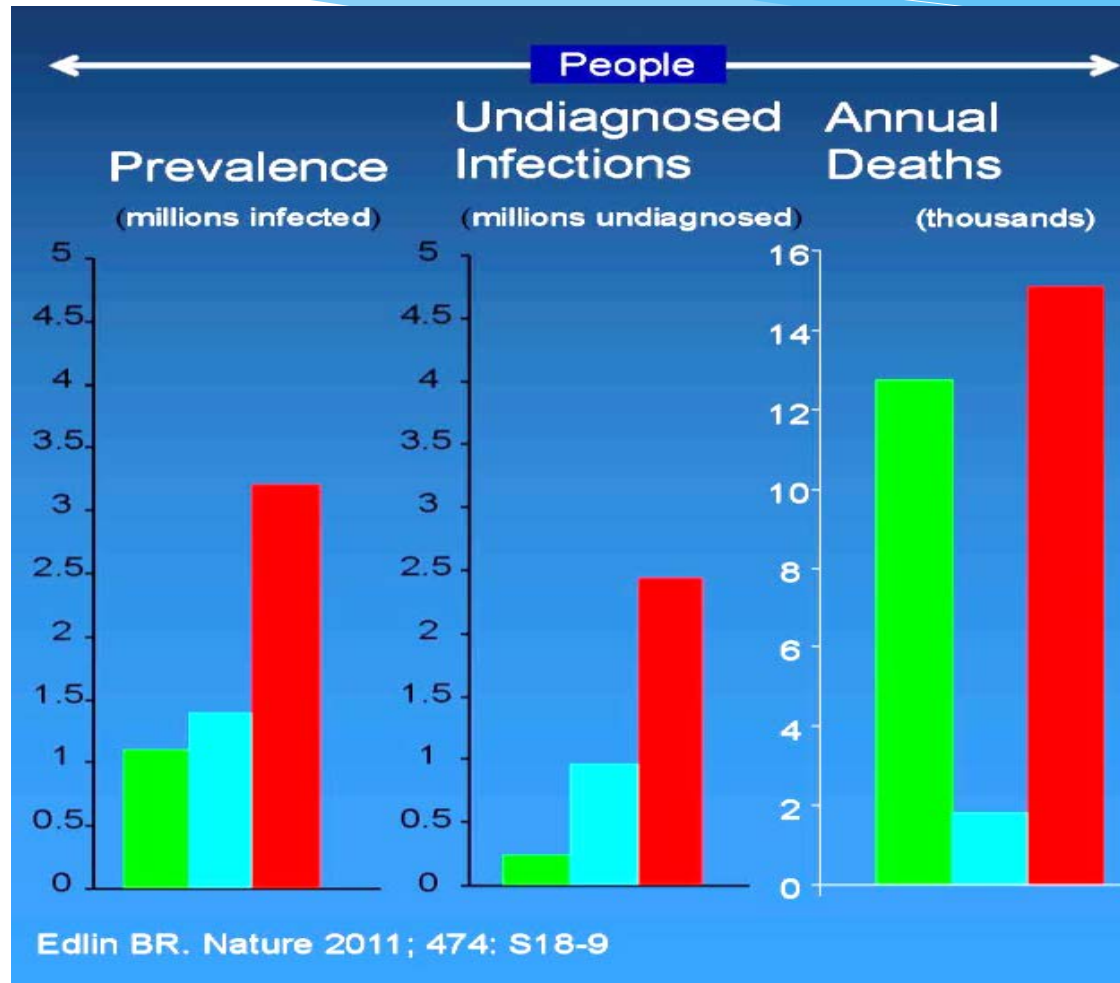
- * Epidemiology of HCV in Alaska
- * Understand who should be screened to detect chronic HCV infection based on recommendations from the CDC & USHSTF
- * Understand Natural history of HCV
- * Understand recommendations for screening for hepatocellular carcinoma (HCC) in HCV

The Two Epidemics of Hepatitis C in the USA and Alaska

- * Epidemic in the 1960's, 1970's and Early 1980's
 - * Related to IDU use, unscreened blood transfusions, unregulated tattooing and lack of universal precautions before HIV
 - * 60%-70% due to IDU
 - * 30%-40% due to lack of universal precautions
- * 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

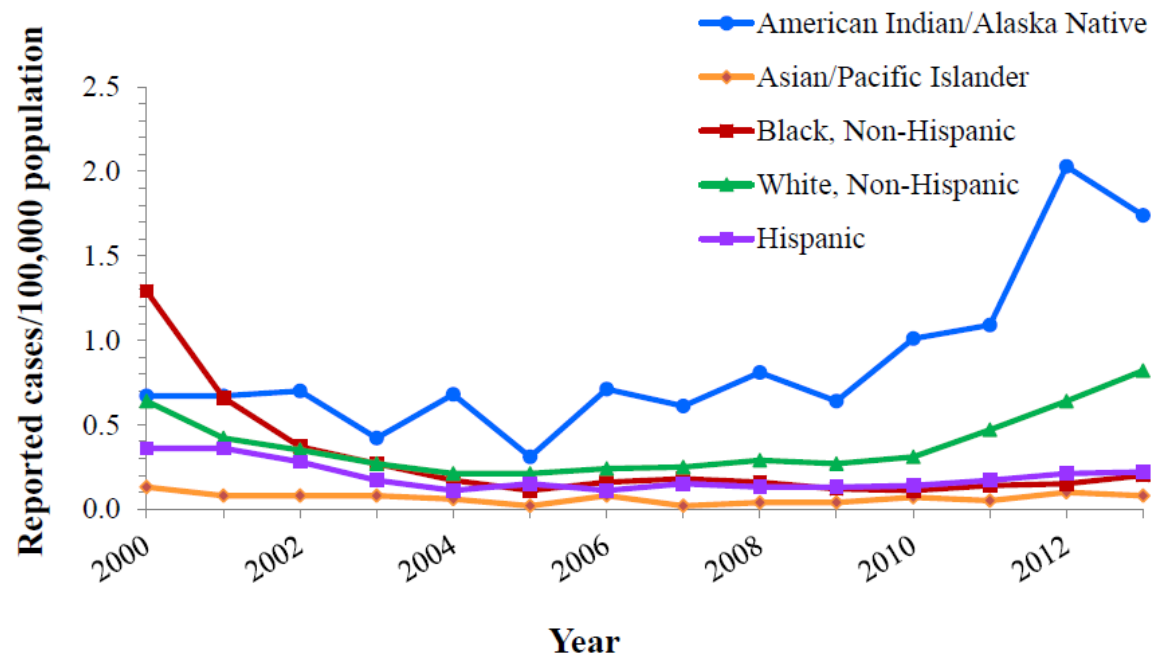
- 
- * Hepatitis C is the most common blood-borne pathogen in the U.S.
 - * More than 3 million Americans are living with HCV with 17,000 new cases identified each year.
 - * It is the leading cause of complications from chronic liver disease.
 - * Prior to COVID-19, it was associated with more deaths than the top 60 reportable infectious diseases in the US combined.
 - * Only 55.6% of adults diagnosed with HCV reported knowing they had hepatitis C.
 - * The highest rates of acute HCV are seen in American Indian/Alaska Native people.

HCV in the US



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

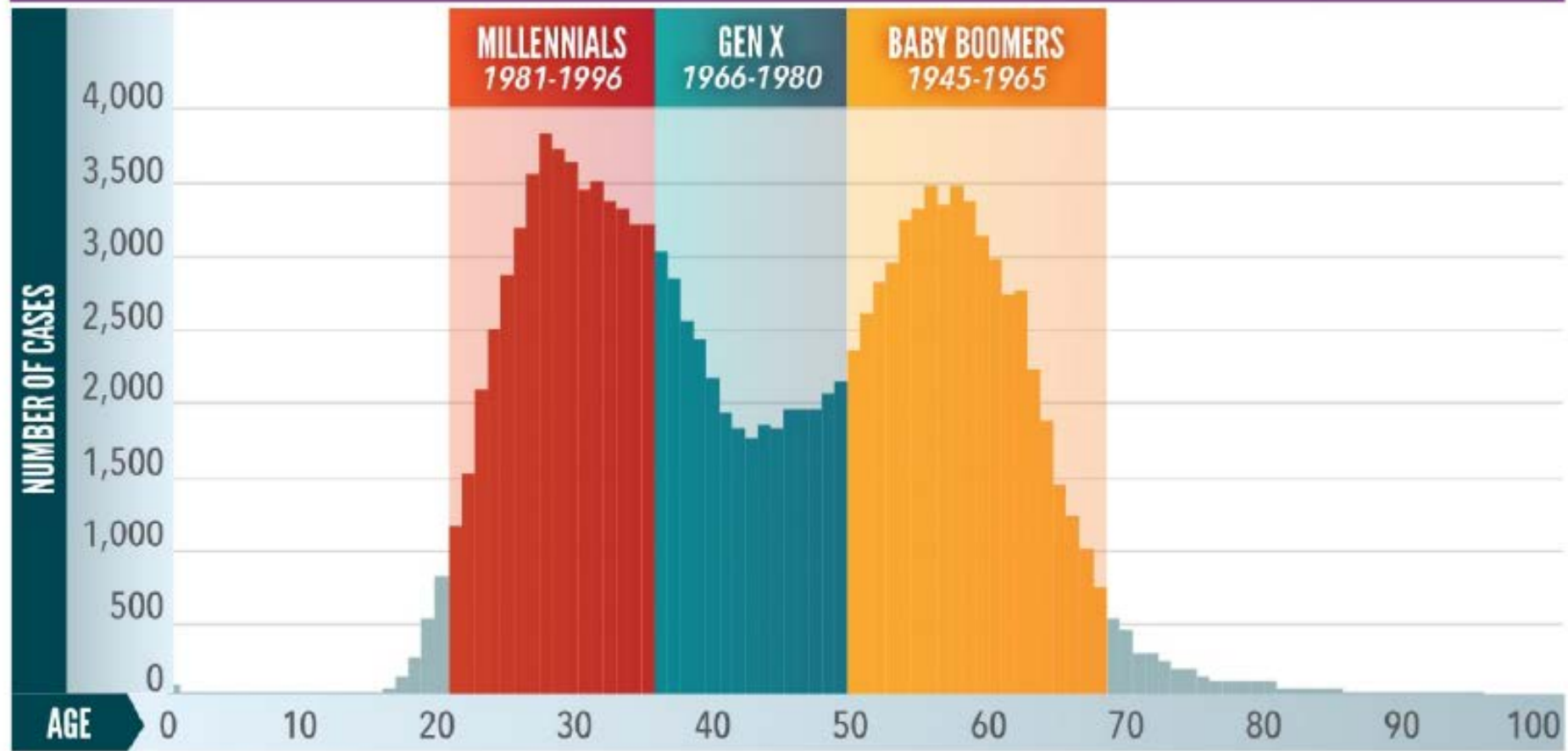
Overall **2.5X**
increase

2.7X increase
amongst 20-29 year
olds

2012 to 2013

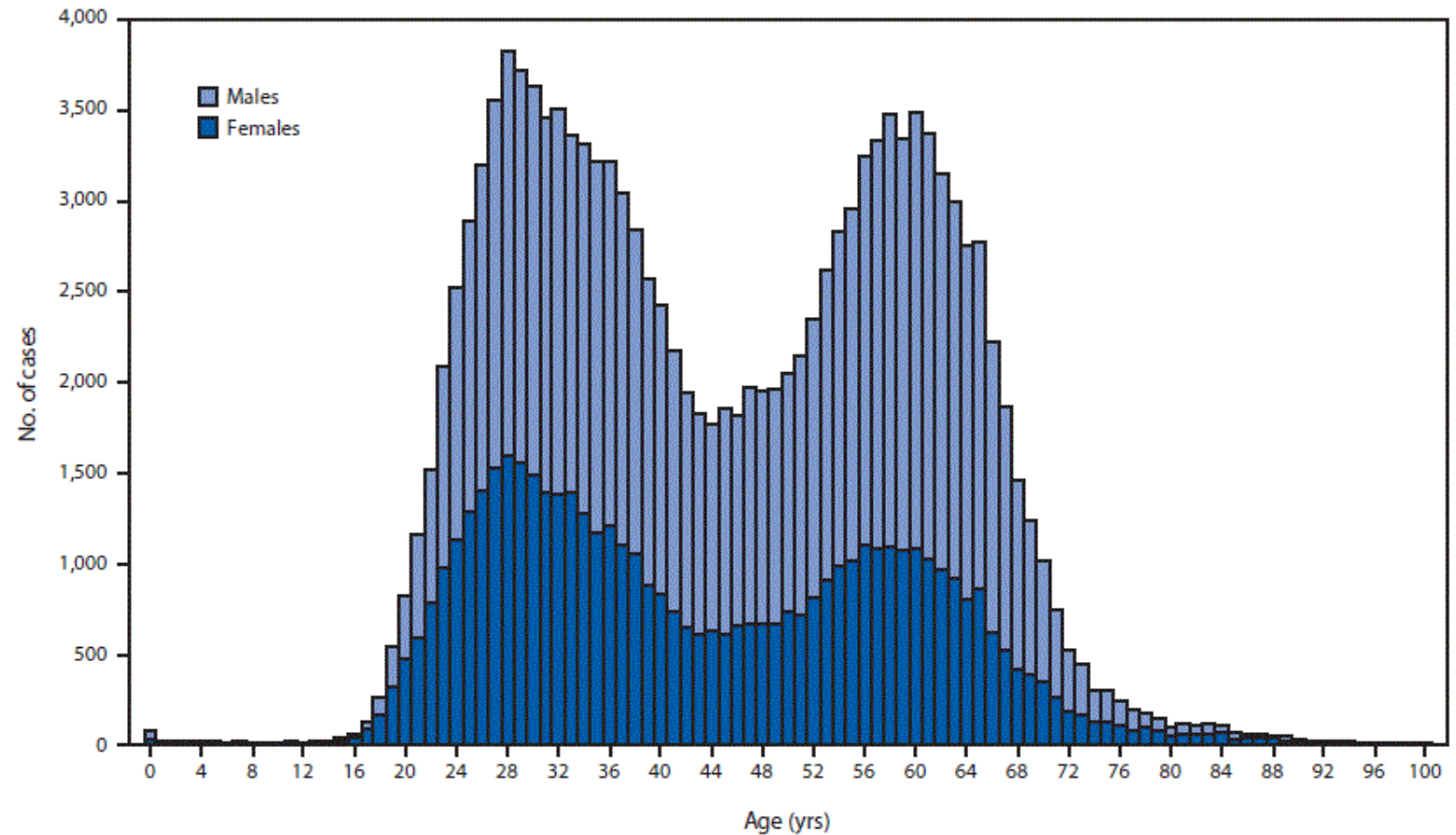
86.2% increase
among American
Indian/Alaska Native
persons

New Reports of Chronic Hepatitis C High in Multiple Generations



SOURCE: National Notifiable Diseases Surveillance System, 2018

Number of Newly Reported Chronic HCV Cases By Sex and Age



Source: National Notifiable Diseases Surveillance System, United States, 2018

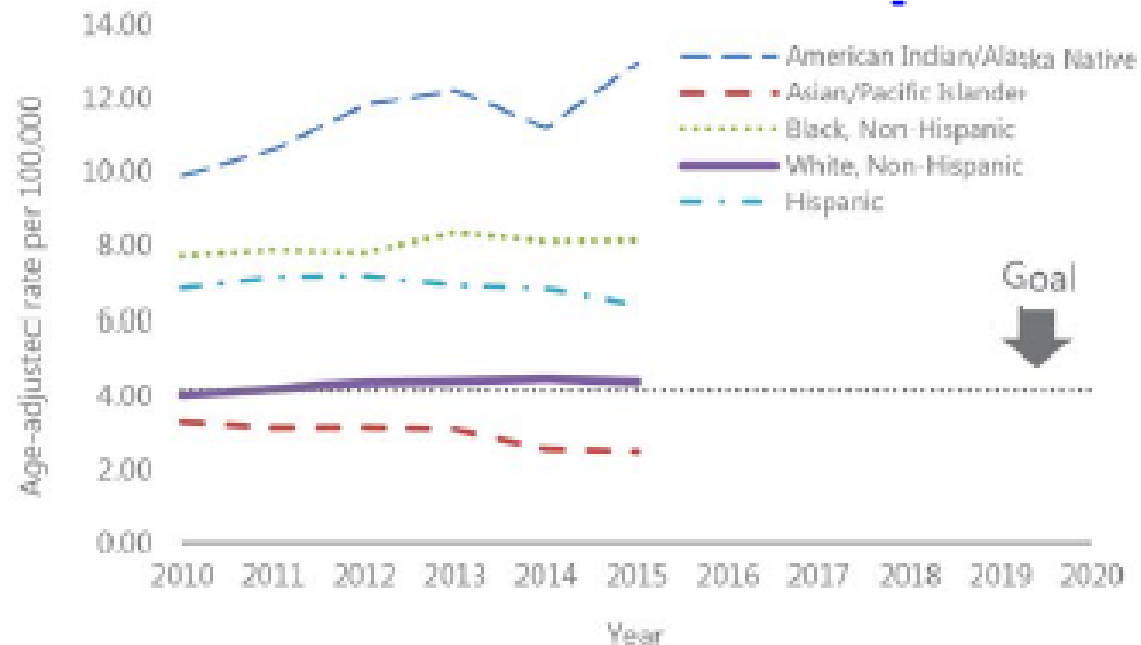
Reported Chronic HCV Cases by Social Generation

Social generation (birth cohort) [¶]	No. (%)	Rate*
Alpha (born after 2012)	176 (0.1)	1.0
Generation Z (born 1997–2012)	3,120 (2.3)	6.1
Millennial (born 1981–1996)	50,160 (36.5)	89.7
Generation X (born 1966–1980)	31,688 (23.1)	66.7
Baby boomers (born 1945–1965)	49,940 (36.3)	79.8
Silent (born 1928–1944)	2,246 (1.6)	—**
Greatest (born 1901–1927)	104 (0.1)	—**

*Cases per 100,000 population

Age-adjusted rate* of HCV-related deaths,[†] by

race/ethnicity[‡]



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^{1,2}

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

[†]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.

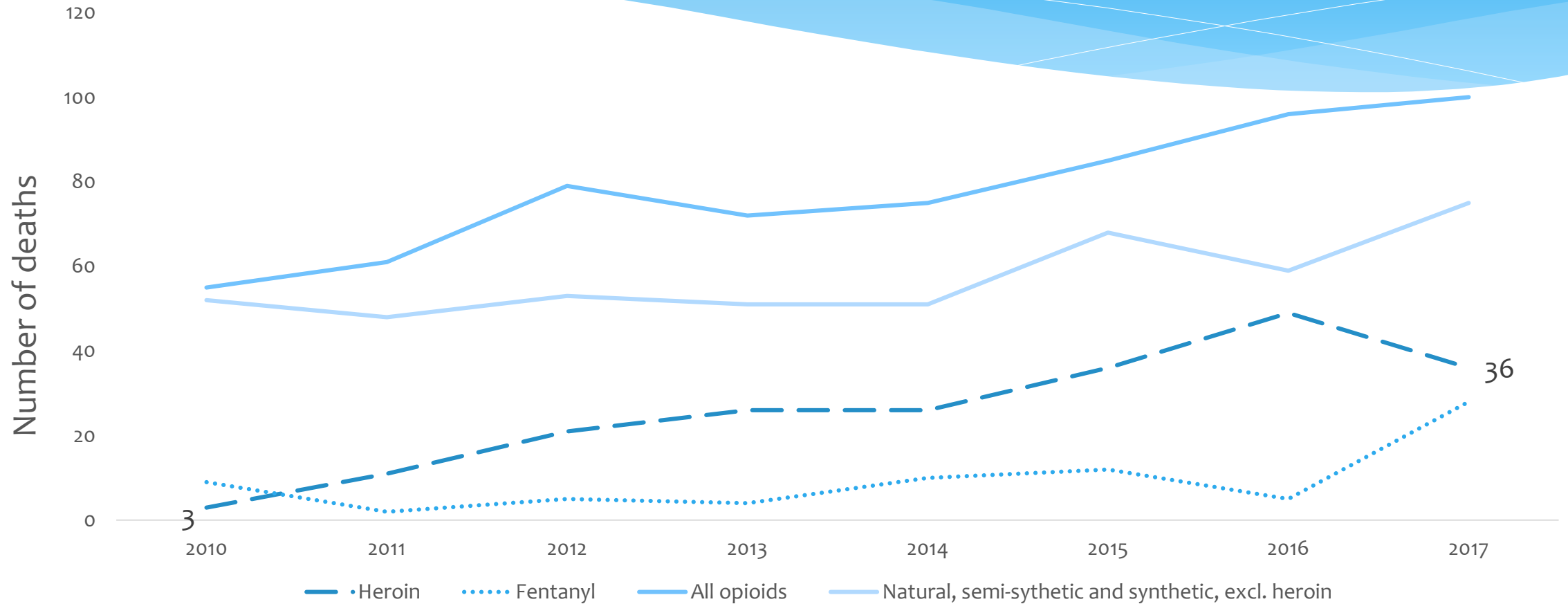
[‡]2 deaths in 2010, 1 death in 2011, 2 deaths in 2012, 2 deaths in 2013, 5 deaths in 2014, and 1 death in 2015 are not represented due to missing age data.

[§]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.

Estimate of HCV Infected Persons in State of Alaska

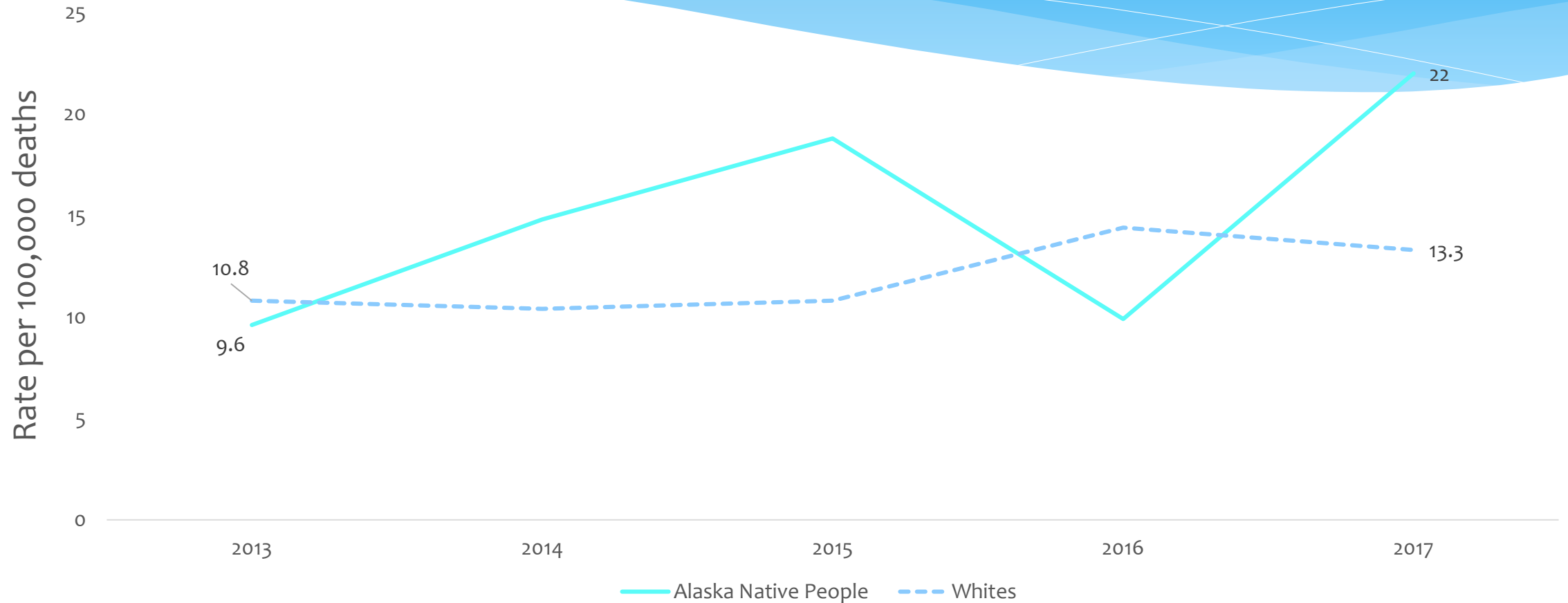
- * Due to the opioid epidemic, the influx of persons with new HCV diagnosis far outstrips number of persons with HCV who have been treated and cured

Number of overdose deaths in Alaska by type of opioid, 2010-2017



Source: Alaska Division of Public Health, Vital Statistics, Mortality

Opioid overdose mortality, rate per 100,000 (Alaska, 2013-2017)



Source: Alaska Division of Public Health, Vital Statistics, Mortality

Opioid overdose mortality in Alaska by race, number of deaths and rate per 100,000, 2013-2017

	2013		2014		2015		2016		2017	
	Deaths	Rate	Deaths	Rate	Deaths	Rate	Deaths	Rate	Deaths	Rate
Alaska Native People	11	9.6	16	14.8	23	18.8	12	9.9	25	22.0
Whites	59	10.8	53	10.4	59	10.8	75	14.4	70	13.3

Note: Rates based on fewer than 20 cases are not statistically reliable and should be used with caution. Number and rate not reported for fewer than 5 cases.

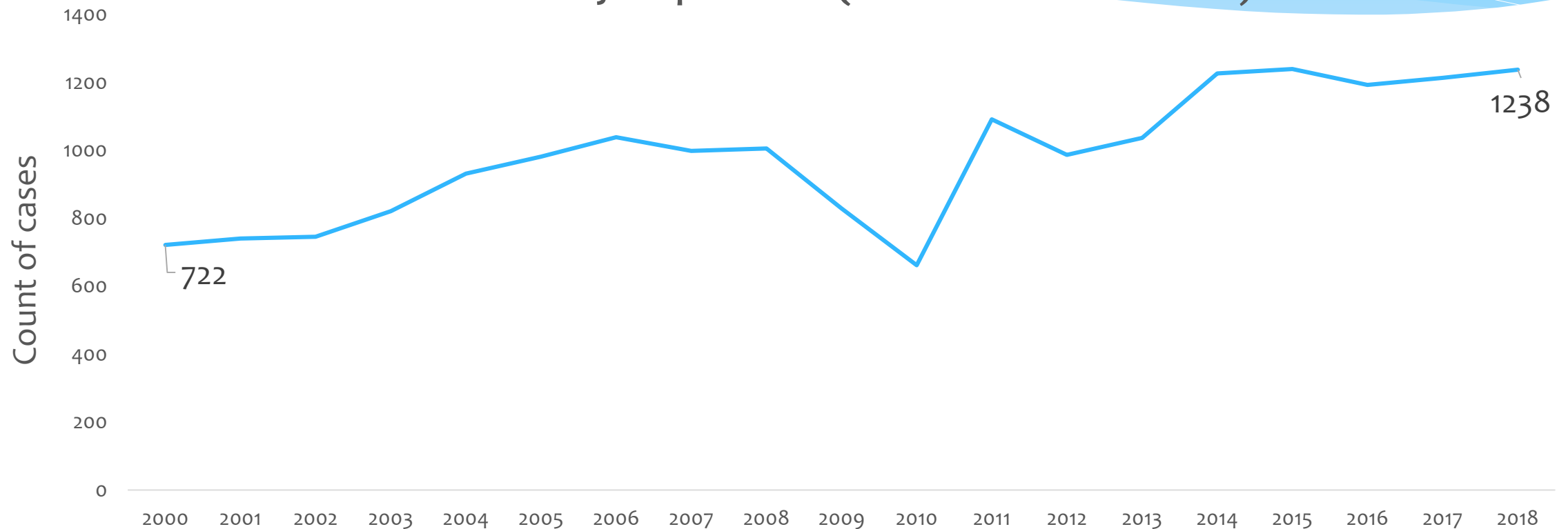
Source: Alaska Division of Public Health, Vital Statistics, Mortality

Opioid Use in Alaska

- * Opioid overdose rates have increased in both Alaska Native and non-Native persons
 - * Rates are consistently higher in Alaska Native than non-Native persons
 - * Fentanyl overdose rates have increased since 2016
 - * Opioid death rates have increased in Alaska Native persons and now exceed rates in non-Native persons
 - * Needle exchange rates have tripled since 2013

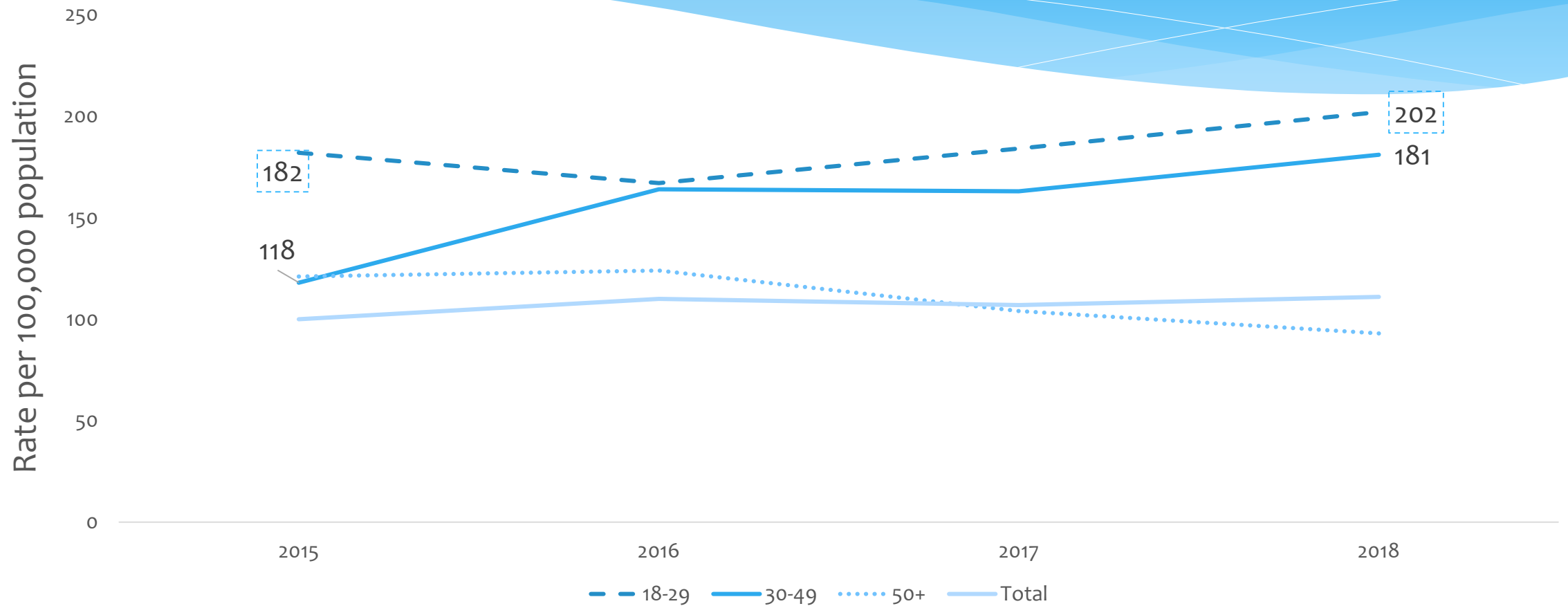
Reported Hepatitis-C cases in Alaska, 2000-2018

Number of newly reported (acute and chronic) cases



SOURCE: Alaska Section of Epidemiology, Alaska Department of Health and Social Services (2019)

Alaska Hepatitis-C rate per 100,000 population by year and age group, 2015-2018

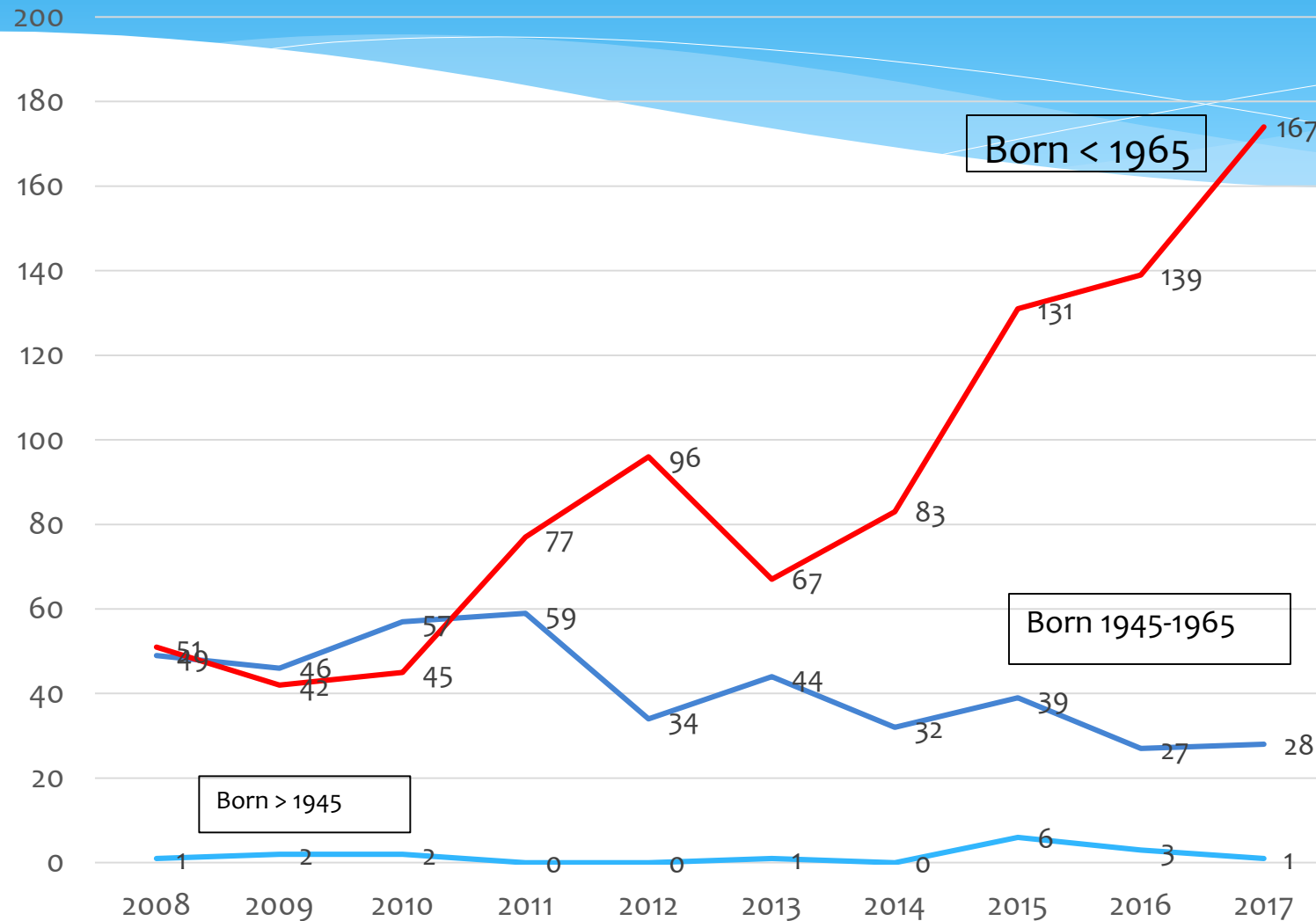


Source: Alaska Division of Public Health, Section of Epidemiology (2019)

Alaska HCV antibody screening and RNA testing, total tests conducted and proportion of positives, week #38, 2019 (September 15-21) and last 12-month period

HCV Antibody screening	Total Tested	Total Positive
Week #2019-38	78	17 (21.8%)
Last 12 month period	5,802	912 (15.7%)
HCV RNA testing		
Week #2019-38	16	11 (68.8%)
Last 12 month period	871	592 (68.0%)

Hepatitis C On the Rise: Data from ANTHC



Where is Hepatitis C Found In Alaska?

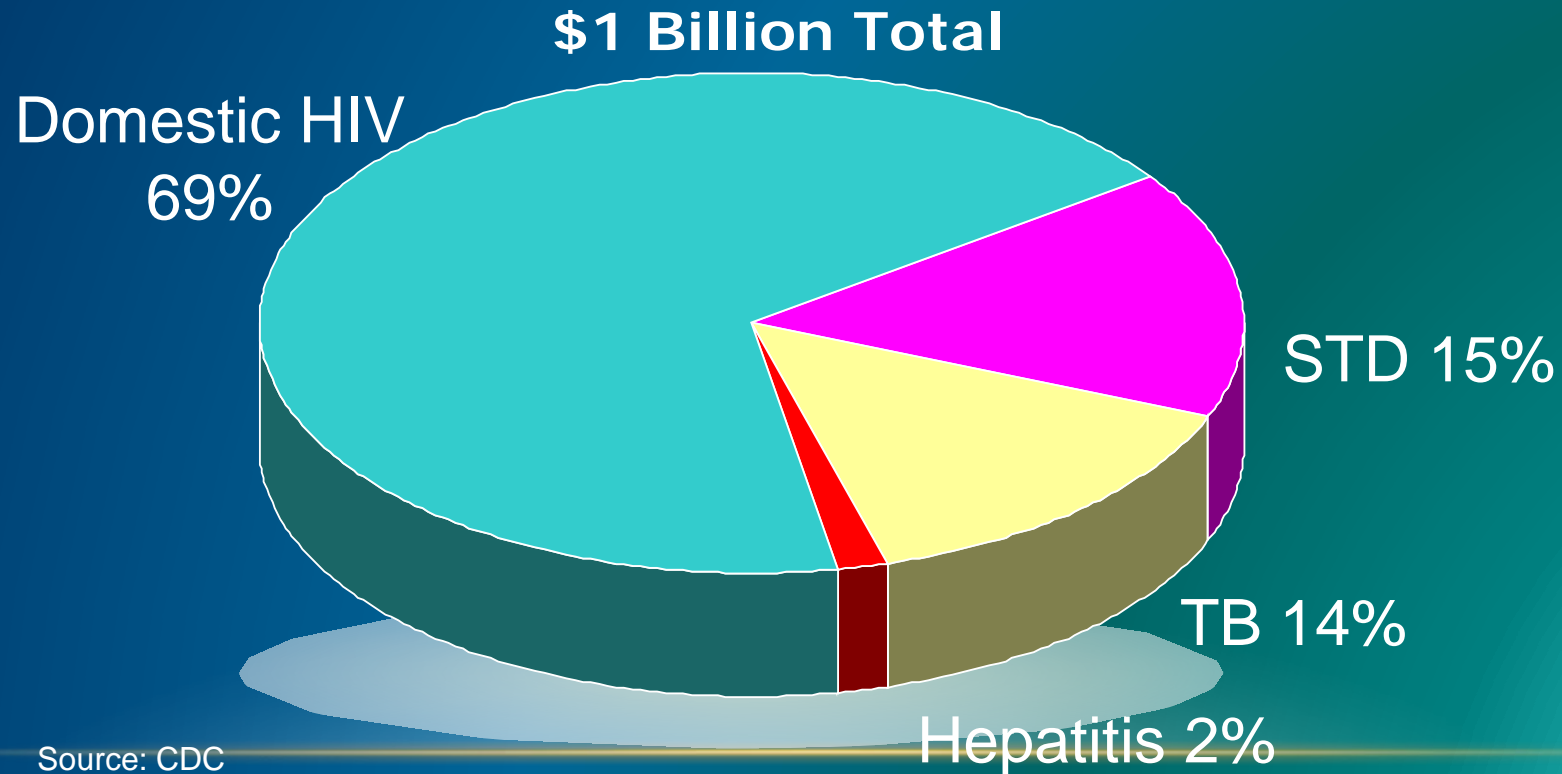


2016/2017 National Academy of Science and Medicine Report

- * Hepatitis C could now be easily cured with DAA
- * Only a little more than half of baby boomer have been screened
- * So far Federal, State and Local government governments have been unable to come up with sufficient recourses for HCV eradication
- * However, the new strategy is for programs to work together on HCV eradication including HIV, STD, medication substitution and behavioral health
- * Strategy: screening for HCV, HIV, HBV at all these sites and treatment onsite or linkage to a care and treatment site after diagnosis

LACK OF PUBLIC RESOURCE ALLOCATION

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



HCV: Modes of Transmission & Persons to screen

- * Contaminated Needles:

- * Injection drug use: Accounts for about 60% to 70% in baby boomers and > 90% of new infections in US
- * Unsafe medical procedures: In baby boomers and in developing world
- * Sexual: Rare in monogamous heterosexual couples
 - * Rectal intercourse is a risk factor

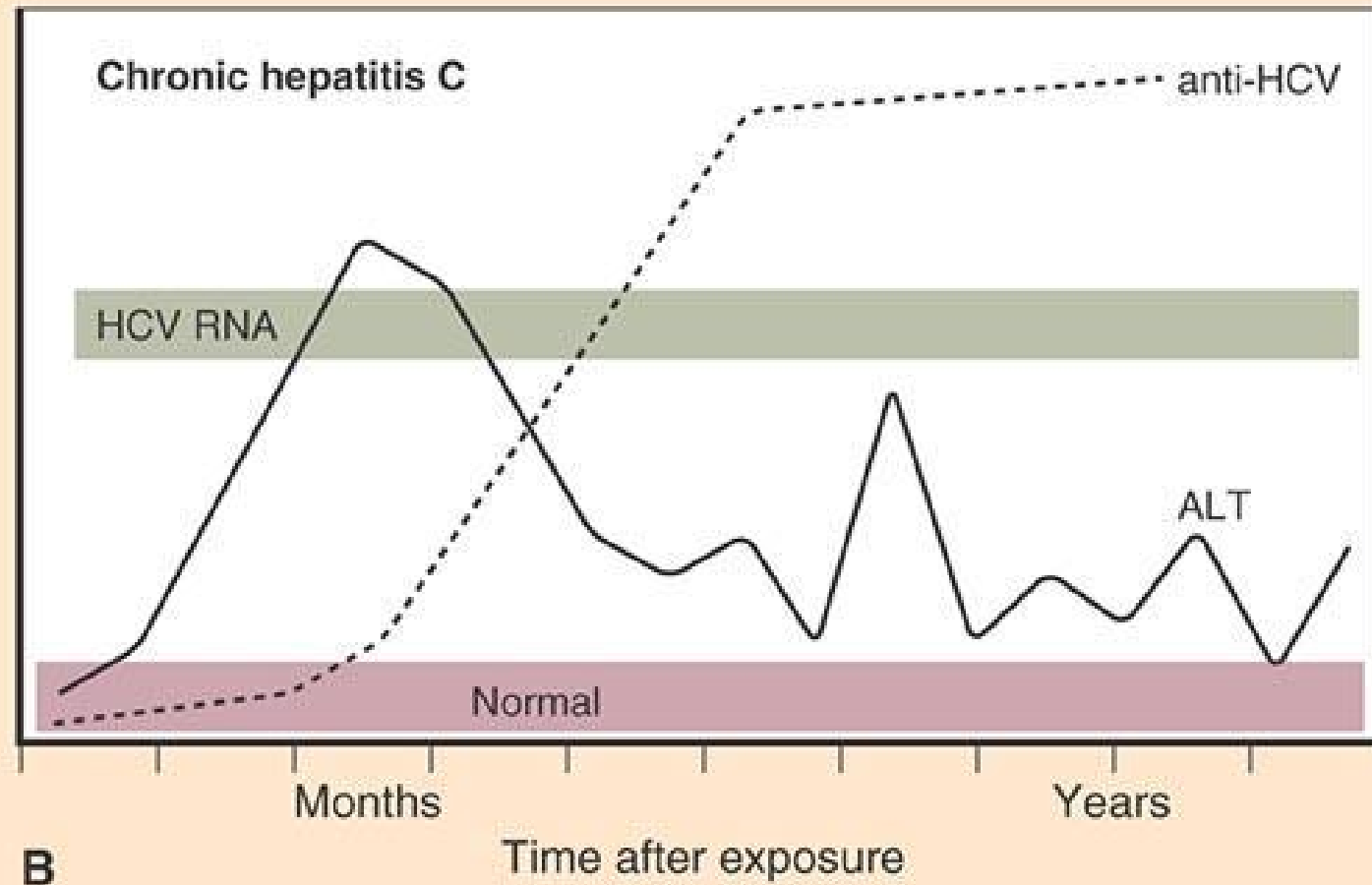
- * Transfusion/Organ transplant before 1992

- * Perinatal: ~ 8 to 10%; 15%-20% with HIV

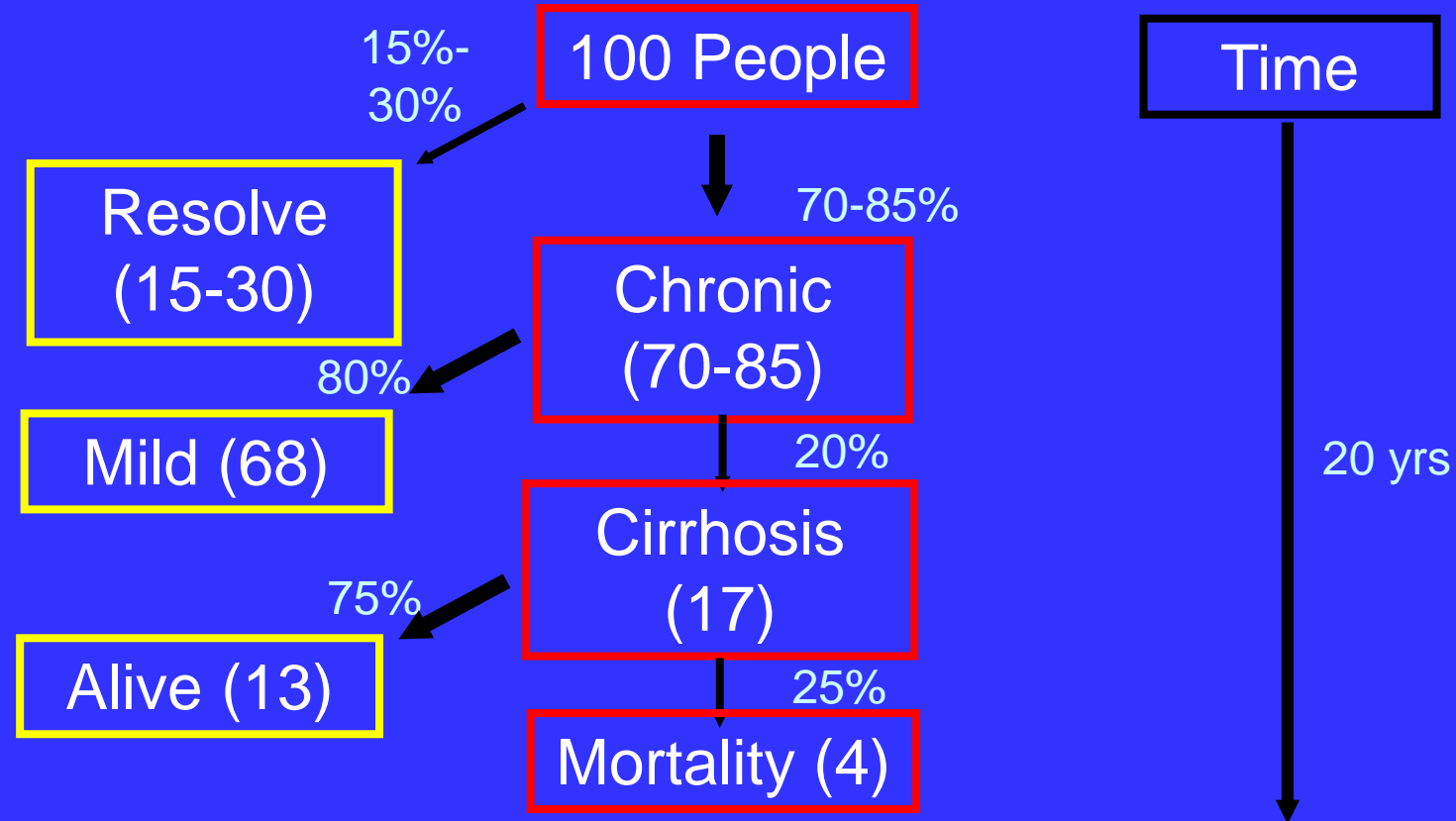
- * Other potential factors: tattooing, snorting cocaine, sharing tooth brushes/razors, body piercing, incarceration, men who have sex with men

- * Baby Boomers born 1945-1965 (3.5% have been exposed)

Serology and HCV RNA in Acute to Chronic Hepatitis C

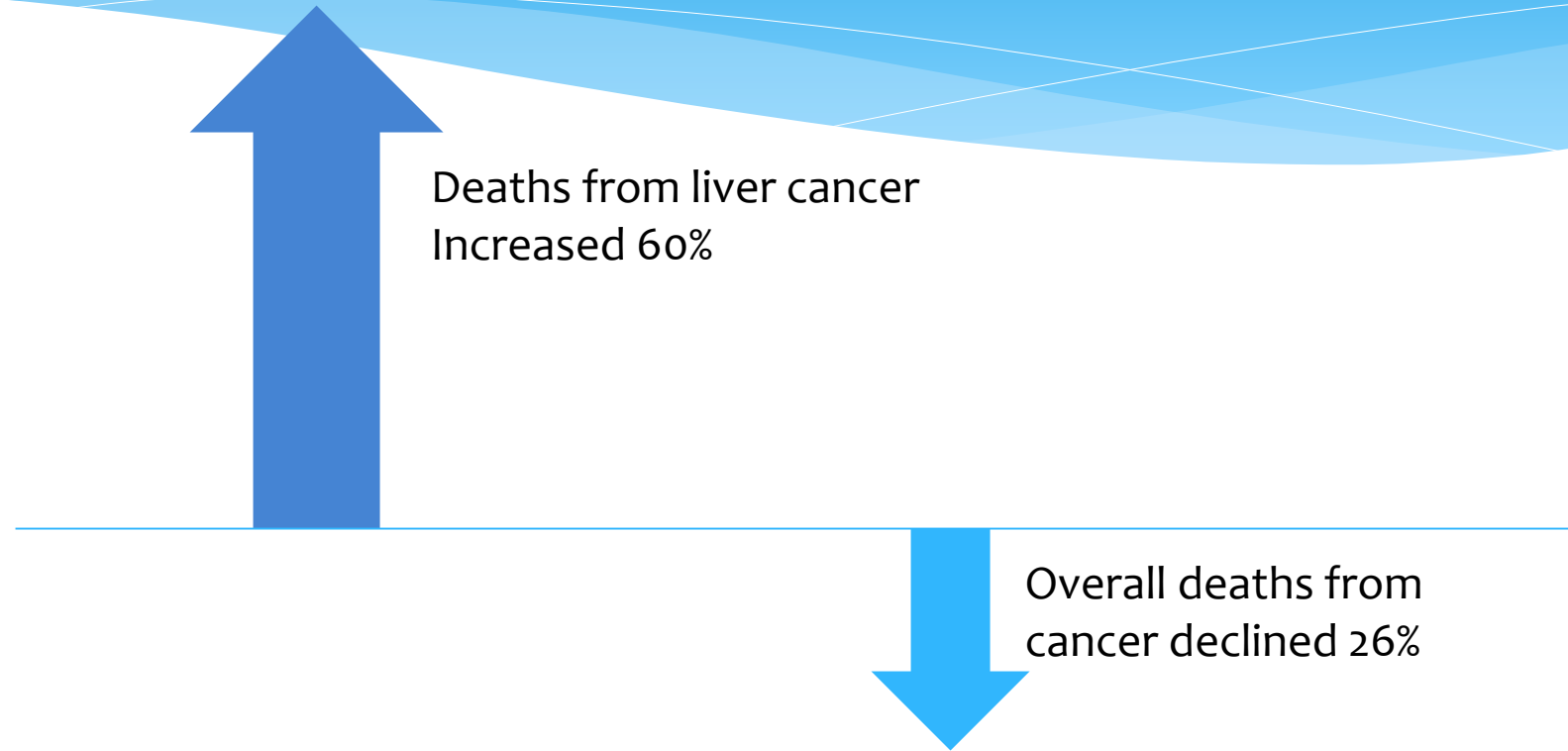


Natural History of HCV Infection



Leading Indication for Liver Transplant in US
Adapted from Alter HJ

Deaths from Cancer, 1990-2015



Source: CDC.gov

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 co-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

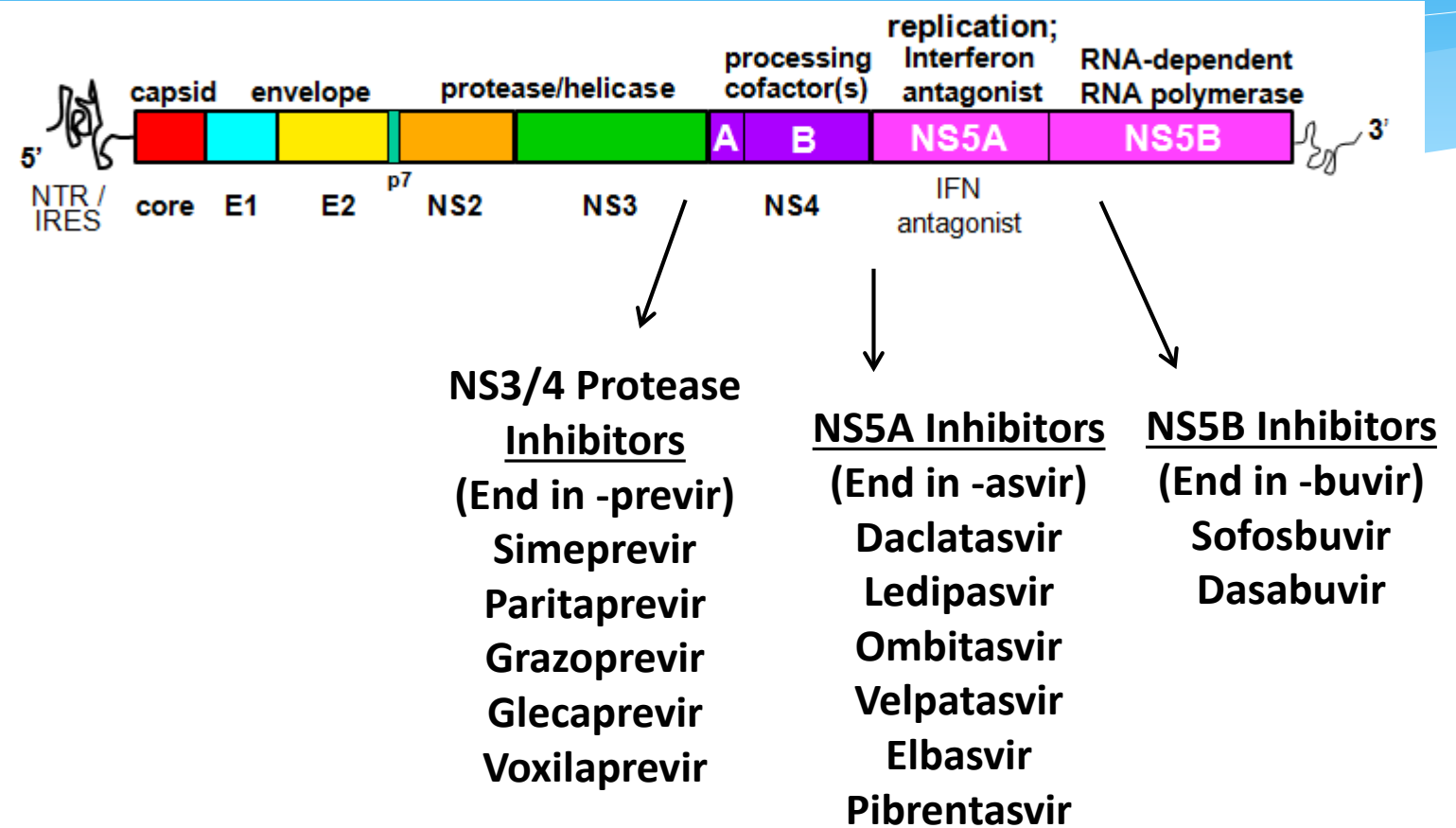
Assessing Fibrosis Stage in Persons with Chronic HCV: Why is this important

- * Medicaid and most insurers in Alaska no longer require fibrosis staging
 - * Persons still using drugs or alcohol can be treated
- * 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 by interferon therapy the future risk of HCC does decrease up to 75% over the following 5 to 10 years
 - * Extent of reduction in rate of HCC has not been determined after DAA SVR
 - * Persons with pre-existing advanced fibrosis or cirrhosis are still at risk and need regular surveillance with AFP and liver US every 6 months

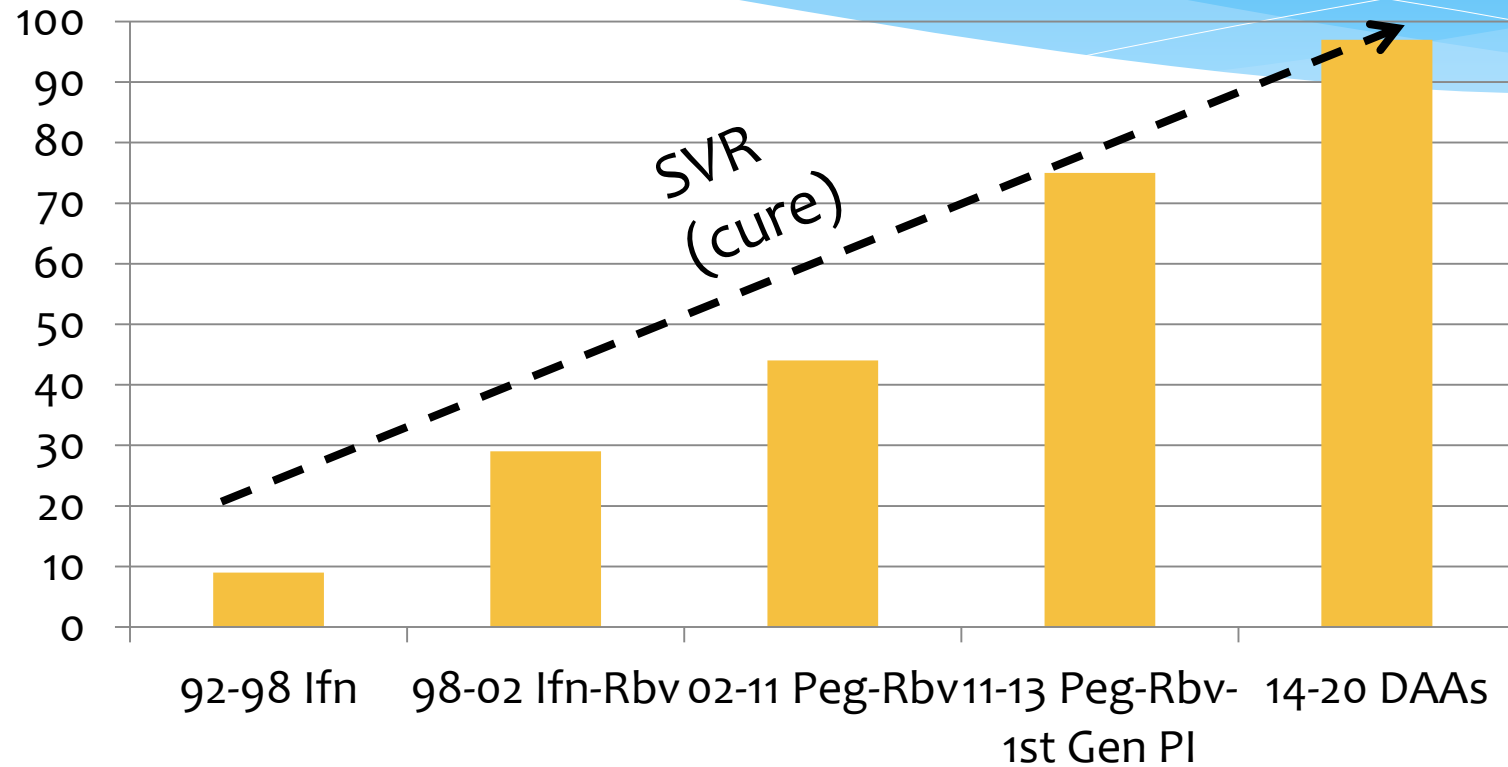
How Can the Incidence and Prevalence of HCV in the US be Reduced in the Near Future? CDC, IHS, AASLD, IDSA and IOM Recommendations

- * USHSTF/CDC now recommend universal screening all adults one time ages 18-79 : Insurers will cover
 - * Baby boomers: ~50% can have advanced fibrosis/cirrhosis
- * Other high risk groups: screen more frequently
 - * IDU
 - * Persons with a history of incarceration
 - * All Pregnant women
- * Risk reduction:
 - * Counseling and availability of clean needles
 - * Alcohol and drug rehabilitation
 - * Diet and exercise to avoid or help those with NAFLD
 - * Coffee

Antiviral Drugs for HCV



HCV Treatment Revolution 2014-present



Current 1ST Line HCV Medication Options

Glecaprevir/pibrentasvir (Mavyret™)

Sofosbuvir/velpatasvir (Epclusa®)

Ledipasvir/sofosbuvir (Harvoni®)



Recommendations for First-line HCV Treatment

Medications	Genotype	Duration in wks no cirrhosis/cirrhosis
Glecaprevir/pibrentasvir	All	8/ 8*
Ledipasvir/sofosbuvir	1, 4, 5, & 6	8** or 12/12
Sofosbuvir/velpatasvir	All	12

- *Compensated cirrhosis, treatment naïve only
- **Genotype 1 patients with no cirrhosis, treatment naïve, with HCV RNA less than < 6 million IU/ml at treatment start, and not co-infected with HIV can be treated with led/sof for 8 weeks

Side Effects

Medications	Headache	Fatigue	Nausea
Glecaprevir/pibrentasvir	18%	15%	12%
Ledipasvir/sofosbuvir	14%	16%	6%-7%
Sofosbuvir/velpatasvir	~22%	~16%	~9%

Every Person can be Treated at no or Minimal Cost to them or THO's

- * Covered by Alaska Medicaid
- * Medicare
- * Private Insurances
- * Require Prior Authorization before Prescription Dispensed
- * Pharmaceutical Assistance Programs to Cover Those Uninsured or Who Cannot Afford Copayments

www.abbvie.com/patients/assistance

www.mysupportpath.com

Put These Drugs on Your Formulary as the are Revenue Generating

Pediatrics

- ❖ Ledipasvir/sofosbuvir (Harvoni) FDA approved as young as age 3 yo
 - ❖ Oral pellets:
 - ❖ ledipsavir 45mg/sofosbuvir 200mg
 - ❖ Oral tabs:
 - ❖ ledipsavir 45mg/sofosbuvir 200mg ledipasvir
 - ❖ Dosage based on weight, treatment duration same as adults
 - ❖ Sofosbuvir + ribavirin \geq age 3 yo for GT 2 and 3
- ❖ Glecaprevir/pibrentasvir (Mavyret) FDA approved as young as 12 yo or in children weighing at least 45 kg
 - ❖ Same dosing and treatment duration as adults

AFTER SVR

- * For those without advanced liver disease
 - * Follow up same as though they were never infected with hepatitis C
 - * Assess for recurrence only if risk factors are present or unexplained elevation of ALT
 - * HCV RNA preferred test as HCV antibody will remain positive
- * Cirrhotic and advanced fibrosis patients
 - Continue HCC surveillance RUQ US every 6 months (consider AFP)

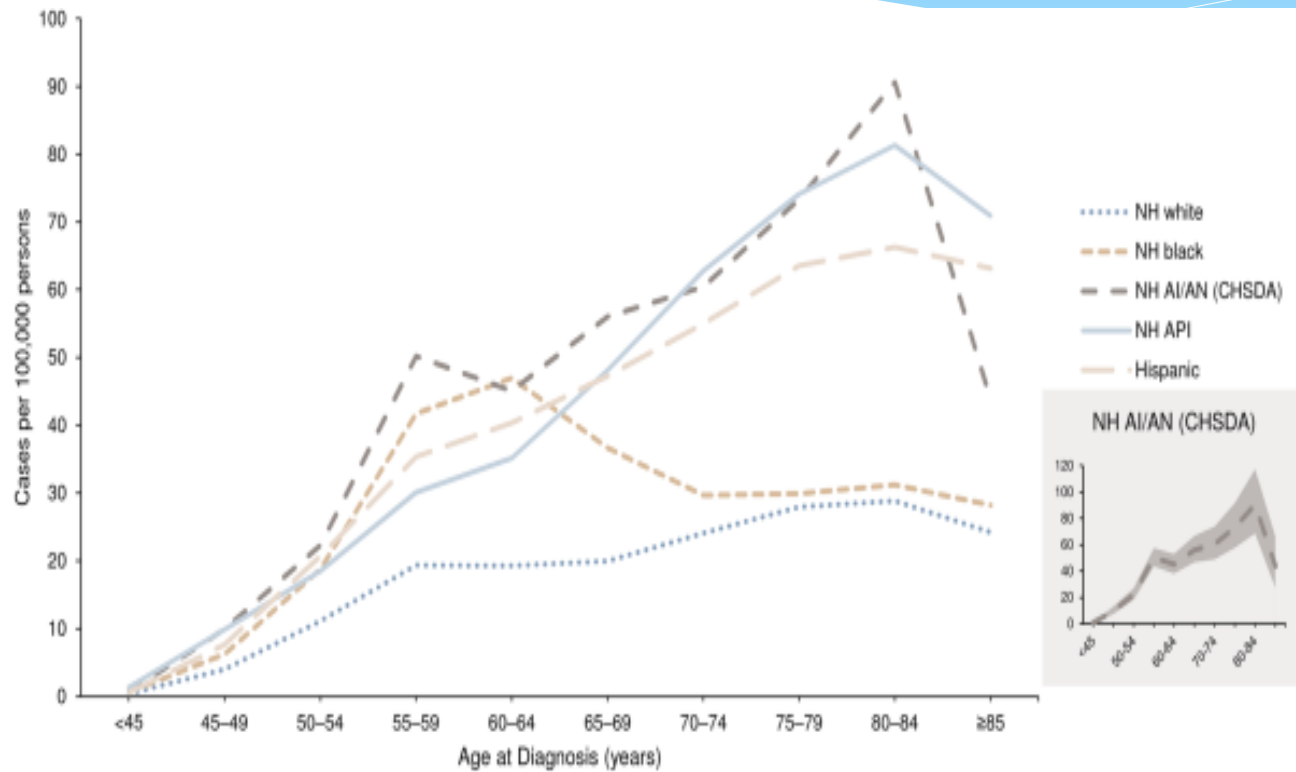
Tools for Prevention of SVR

- * Needle Exchange
- * Treatment of IDU as prevention

Hepatocellular Carcinoma (HCC) in Hepatitis C Cirrhosis

- * The annual risk of HCC in persons with hepatitis C who have cirrhosis is 3-5%/year
- * In those persons with cirrhosis SVR reduces substantially the risk of HCC but does not eliminate it
- * Surveillance with liver Ultrasound and AFP every 6-months is essential to diagnose HCC at a curable state
- * No chemo or immunotherapy for HCC provides a cure or long-term survival, only early detection of small tumors, removal, ablation or transplantation offers the possibility of cure

Annual Report to the Nation on the Status of Cancer, 1975-2012, featuring the increasing incidence of liver cancer

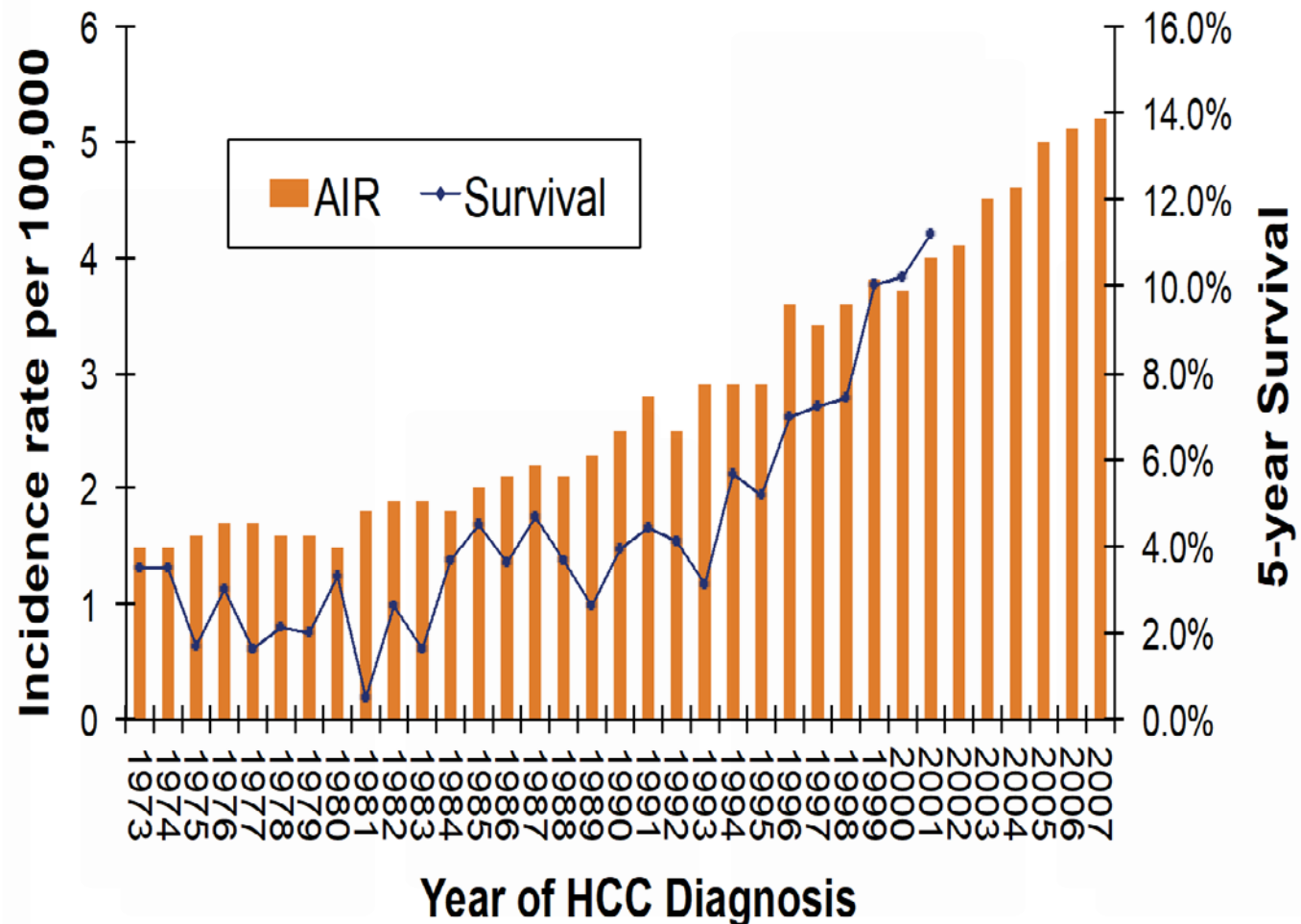


Cancer

9 MAR 2016 DOI: 10.1002/cncr.29936

<http://onlinelibrary.wiley.com/doi/10.1002/cncr.29936/full#cncr29936-fig-0002>

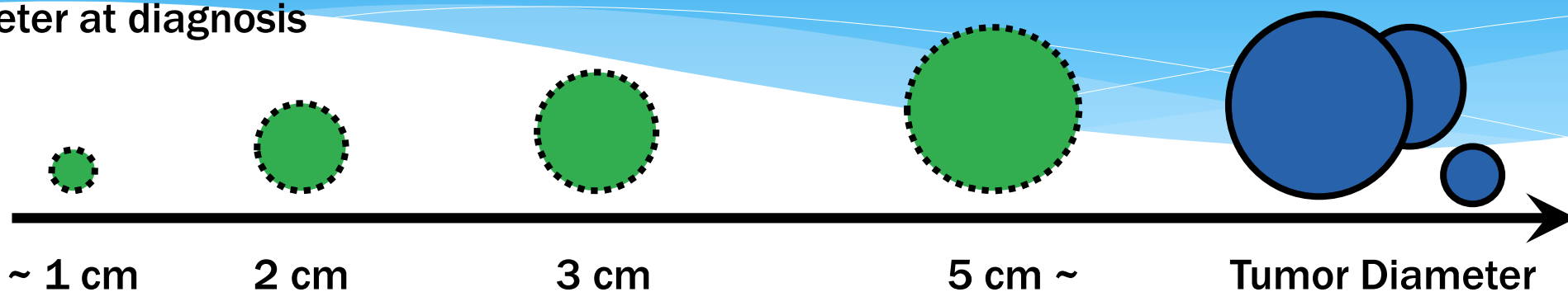
The Incidence and 5-Year Survival of HCC in United States



Why is HCC Surveillance Beneficial?

HCC Treatment Options: Earlier is Better

Tumor Diameter at diagnosis



~ 1 cm

2 cm

3 cm

5 cm ~

Tumor Diameter

Japan
Surveillance

USA Surveillance

USA
referred base
no surveillance

2-4+cm

>5cm

Curative treatment
Resection, Transplantation,
Microwave/RFA

**DEB TACE, TARE, cTACE,
Sorafenib**

**Palliative
treatment**

Ablation demo



rita animation.mpg

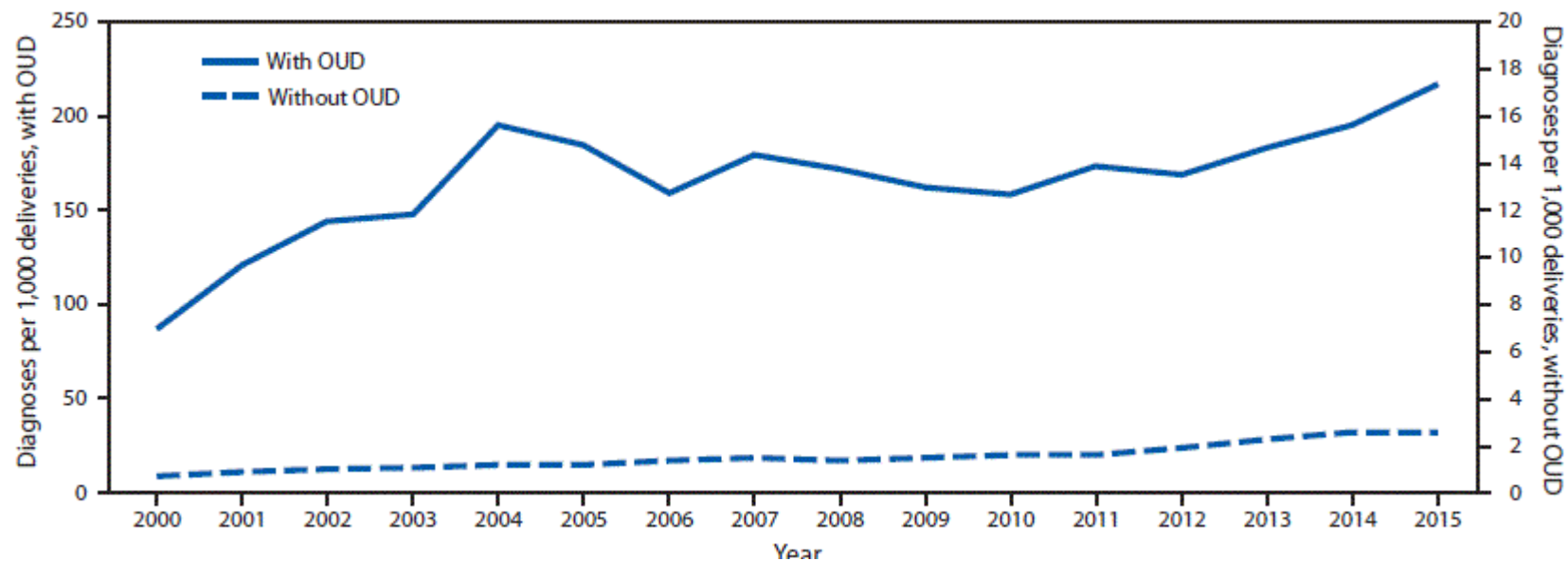
Chemoprevention for HCC

1. Coffee caffeinated
2. Coffee Decaffeinated
3. Coffee Espresso without cream or sugar
4. Aspirin
5. Statins

To Eliminate HCV We Must Screen and Treat Beyond the Traditional Venues

- * Treatment of infected persons: PCP on the frontline
 - * Screening and Treating persons in rural Alaskan Communities
 - * CHAP screening all adults once and high risk persons yearly with rapid finger-stick test and treatment of those HCV RNA+ via telemedicine (one stop shopping in the communities)
 - * Screening and Treating incarcerated persons: now done in Alaska
 - * Treating persons in drug rehab programs, programs serving homeless persons, needle exchange programs, safe injecting and other non-traditional sites
 - * Treatment as prevention
- * No Vaccine on horizon for decade or more

National prevalence* of maternal hepatitis C virus (HCV) infection per 1,000 delivery hospitalizations, by opioid use disorder (OUD) status, 2000–2015



During 2000-2015, rate of HCV infection in pregnancy increased from 0.8/1,000 to 4.1/1,000 live births in opioid users and from 87.4 to 216.9 per 1,000 live births

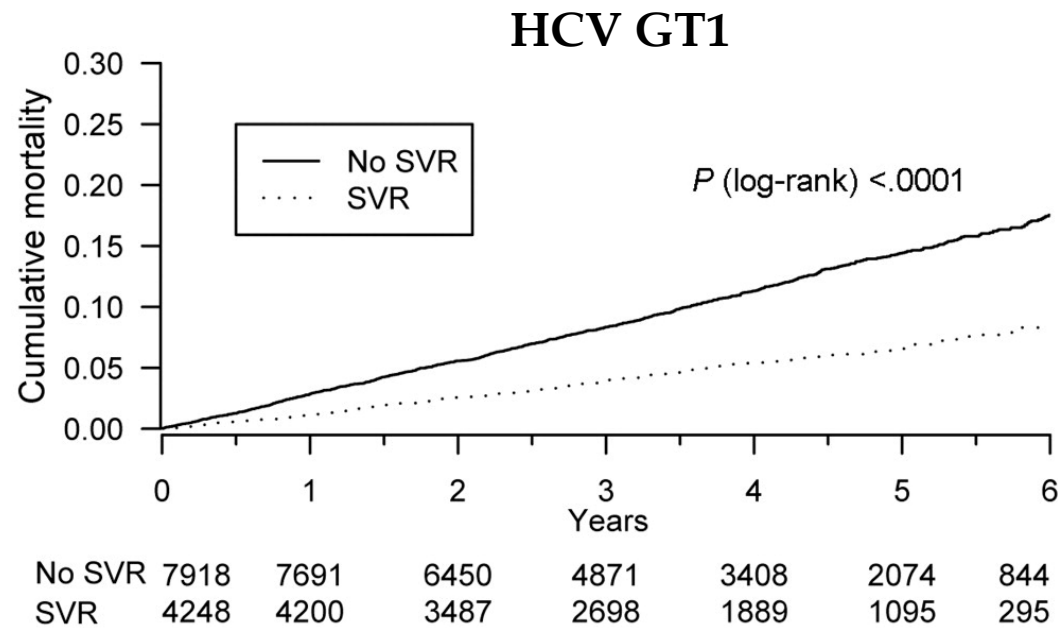
MMWR volume 68 October 4, 2019

Why Treat HCV?

- * Sustained virologic response (SVR) with IFN 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 with IFN, risk of developing decompensated cirrhosis greatly reduced
- * After SVR after IFN, regression of cirrhosis if present occurs (Mallet Ann Int Med 2008;149:399-403)
- * Risk of HCC in those with cirrhosis reduced*

* Most data comes from SFV after interferon-based therapy

An Interferon-based 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 Interferon-Based

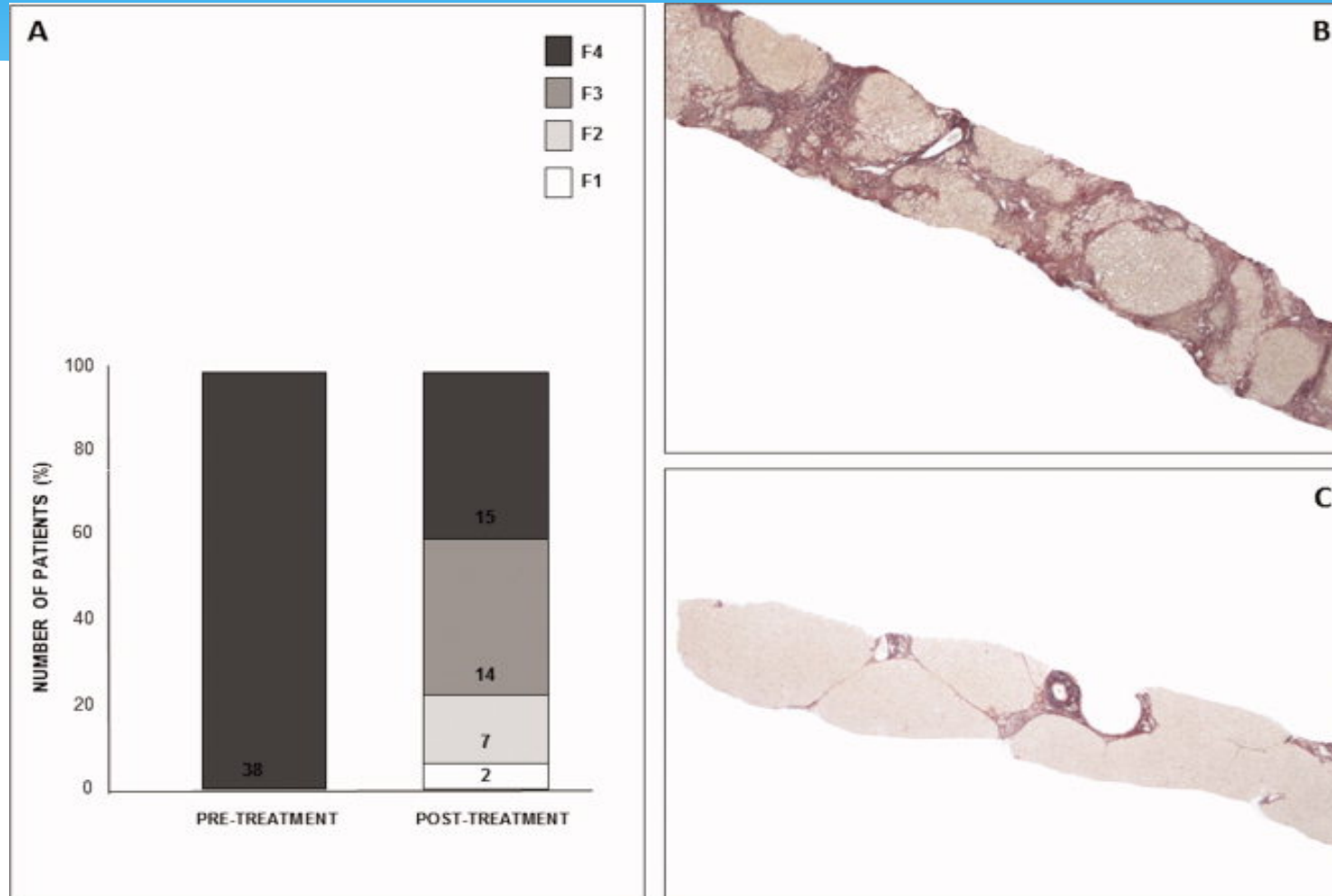
Outcome	SVR	No SVR	HR
Liver Failure	2.4%	31.7%	13
HCC	5.3%	23.1%	4.3
Liver related death	2.1%	27.5%	13
10 year overall mortality	9.8%	23.0%	2.3

P < 0.001 for all comparisons

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

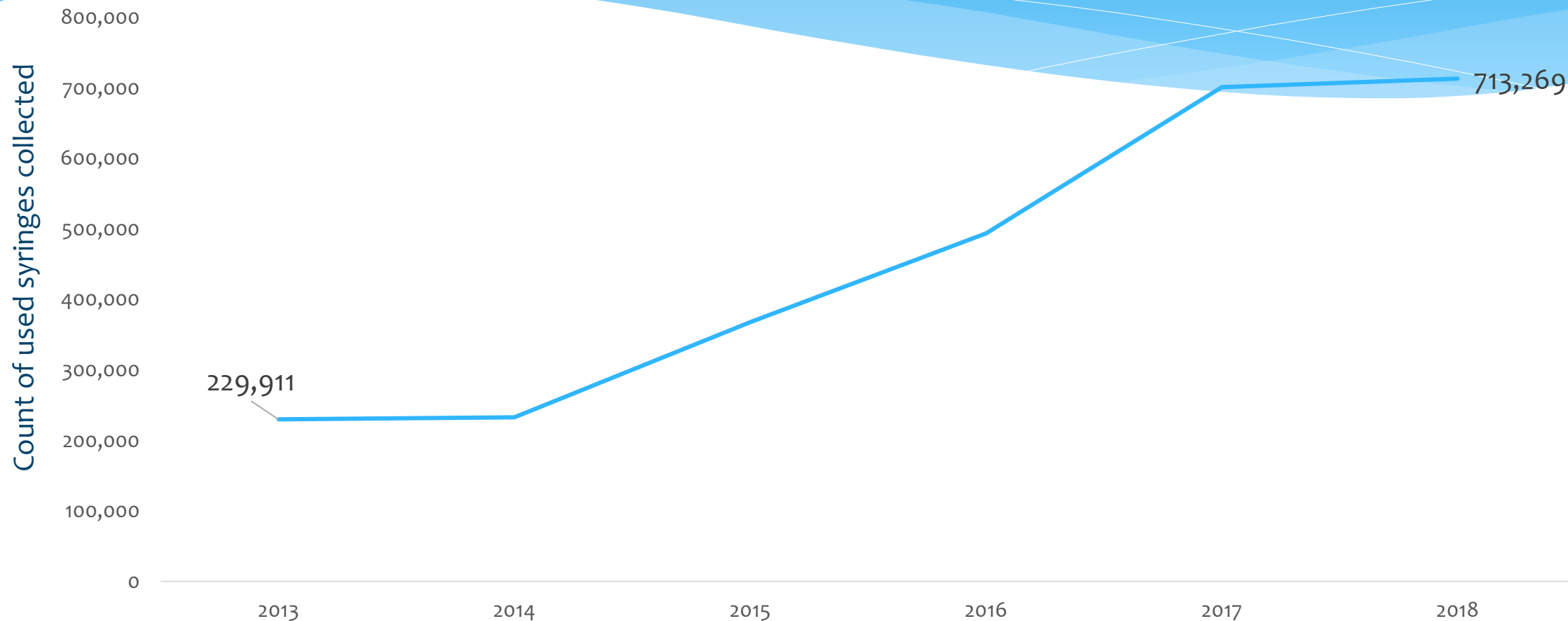
A morphometric and immunohistochemical study to assess the benefit of a sustained virological response in hepatitis C virus patients with cirrhosis



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>

Used syringes collected, Anchorage and Juneau syringe exchange service, 2013-2018



SOURCE: Alaskan AIDS Assistance Association (May 2019), Anchorage, AK

Program for the elimination of HCV

- * Right now a “pipe dream” but actively pursued by the Hepatitis Alaska Working Group (HAWG)
- * Must consist of community wide participation to achieve any measure of success
- * Must include: Screening and Linkage to Care of:
 - * Baby Boomers and at risk adults: Considering expanding to all adults over 18
 - * Drug treatment programs, homeless persons, needle exchange programs
 - * Screening for hepatitis B and C in Prisons
 - * Vaccination for those negative for HBV
 - * Treatment for those positive for HCV
 - * Pregnant females: Alaska Native Medical Center (ANMC) in Anchorage
 - * Emergency Departments

Collaboration with Other Partners in Alaska

- * All Alaska Native Tribal Health Organizations
- * CDC; Arctic Investigations Program and Division of Viral Hepatitis
- * State of Alaska Depts. of Epidemiology, Public Health Nursing and HIV
- * Municipality of Anchorage
- * Anchorage Community Health Center
- * Anchorage Needle Exchange Program
- * Alaska State Prisons
- * University of Alaska, Anchorage
- * University of Washington, Seattle
- * WWAMI Alaska Medical School
- * Private Sector
- * The Hepatitis Alaska Working Group (HAWG)
 - * Meets Quarterly to discuss collaboration on viral hepatitis

HAWG Accomplishments to date

- * Developed a curriculum to train primary care providers to diagnose, estimate the level of liver fibrosis and treat HCV, obtain funding for DAA for their patients and continual follow-up of patients after SVR who have F3-F4 fibrosis
 - * Have put on four half day training programs for providers around the state with CME and documentation that they are now trained to treat HCV without a consult
- * Continuing to update the ANTHC website www.anthc.org/hep for both patients and providers contains information, treatment algorithms and treatment forms for printout
- * Participant in three project ECHOs, Alaska, NW Indian and IHS
- * Conduct a monthly telemedicine accredited CME statewide and beyond for health personal

Ongoing Research on HCV Outcomes after SVR (cure)

- * Current focus of our research is examining the outcome of HCV after cure
 - * Before the introduction of DAA, we have 7-years of baseline longitudinal data on 700 persons with chronic HCV including 450 with staging by liver biopsy.
 - * We plan to compare rates of HCC, liver failure and liver related death/liver transplantation between historical pre-DAA comparison group and those who received DAA over 10 years
 - * We also are conducting a prospective 5-year study on resolution of liver cirrhosis and fibrosis using FibroScan and other non-invasive markers after SVR on 300 participants
 - * Just published Restoration of immune function before and after SVR in collaboration with UAA immunology dept. Results at time of SVR show partial restoration of T cell regs and other immune modulators
 - * We are submitting a grant to examine the same cohort 2 years after SVR

ANTHC Liver Disease & Hepatitis Program

Visit our website:

www.anthc.org/hep

LiverConnect
2nd Tuesdays,
8-9am AK time
CEUs provided



The screenshot shows the website for the Alaska Native Tribal Health Consortium (ANTHC). The header includes the ANTHC logo and navigation links: "Who We Are", "What We Do", "Working with Us", and "Contact Us". A search icon is also present. The main banner features the text "FIND OUT IF YOU HAVE HEPATITIS IT COULD SAVE YOUR LIFE" with a liver icon. Below the banner is the title "Liver Disease & Hepatitis Program" and a mission statement: "Our mission is to conduct activities that will serve to improve the health of Alaska Native and American Indian persons who either have or are at risk of getting viral hepatitis or other liver diseases". The page is divided into four sections with images and text:

- About Our Program**: Image of two people sitting on a beach.
- for Patients**: Image of a man and a woman looking at each other. Text: "Hepatitis is a disease".
- for Providers**: Image of a group of people standing together. Text: "Providing support to patients".
- Hepatitis C Treatment**: Image of a liver with a virus icon.

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
- * Regular 6-month surveillance for HCC can find small curable tumors early