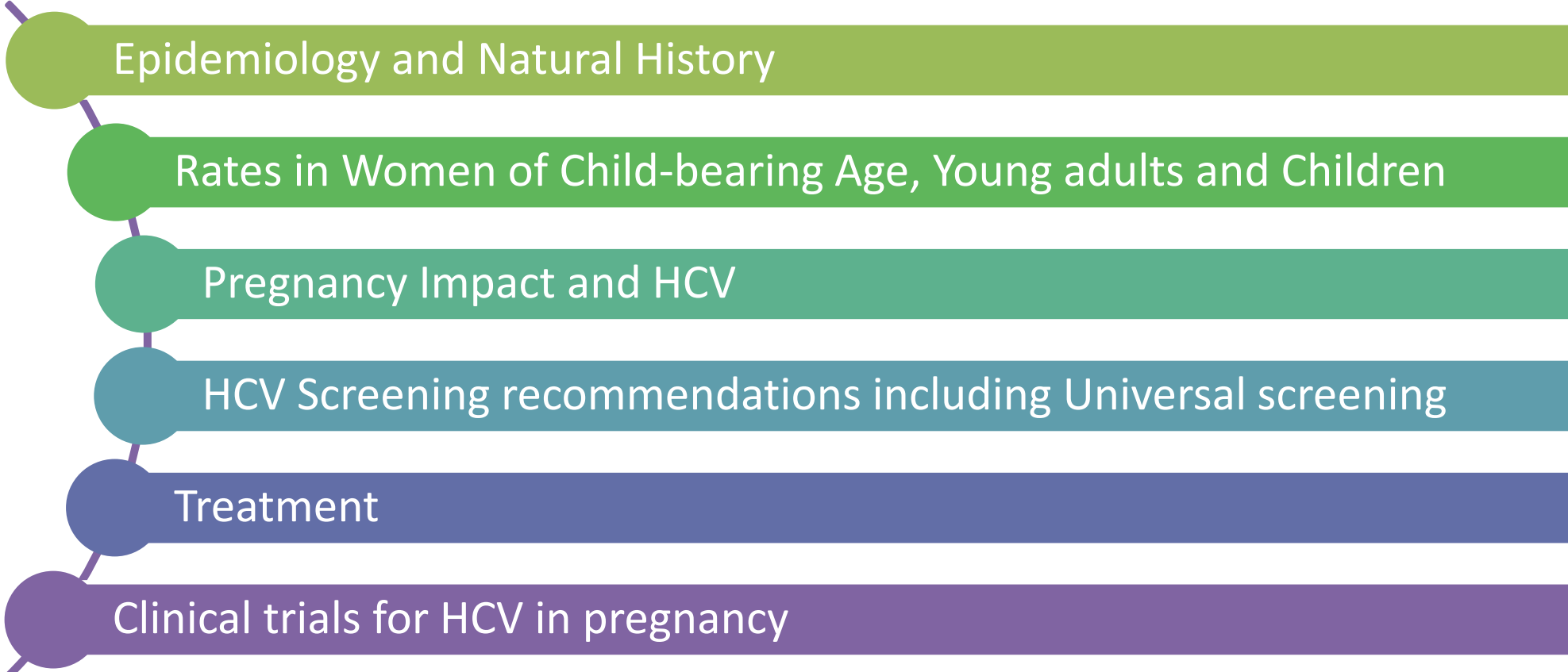




Hepatitis C and Pregnancy

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HCV AND PREGNANCY OBJECTIVES



Epidemiology and Natural History

Rates in Women of Child-bearing Age, Young adults and Children

Pregnancy Impact and HCV

HCV Screening recommendations including Universal screening

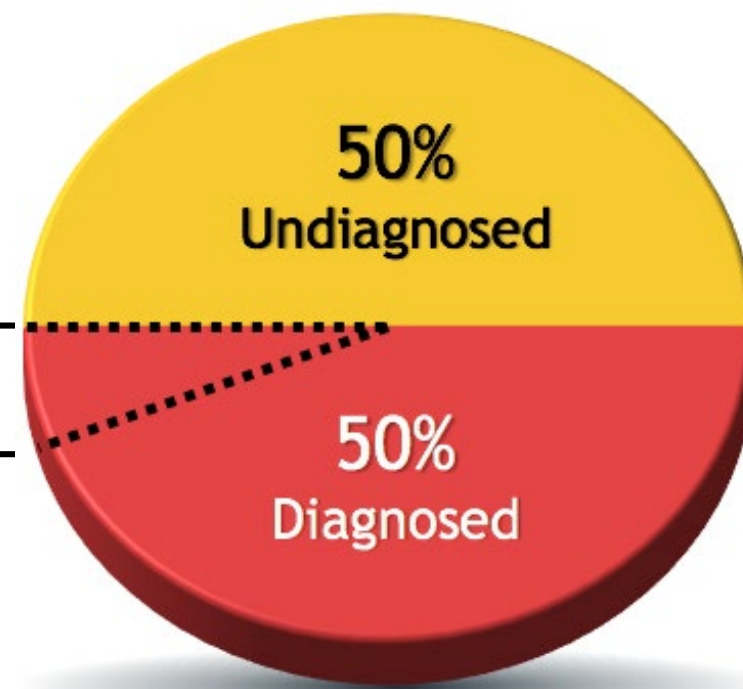
Treatment

Clinical trials for HCV in pregnancy

Epidemiology

- Approximately 3.5 million people in the United States are chronically infected with HCV (1.3%)^{1,a}
 - Including populations excluded from NHANES (e.g., the incarcerated, homeless, institutionalized, and those living on Native American reservations) brings the total estimate to 4.6 million²
- Seroprevalence is higher in¹
 - 1945-1965 birth cohort (3.5%)
 - Non-Hispanic blacks (2.2%)
 - Males (1.9%) vs females (1.1%)
- Approximately 9% of all diagnosed individuals have been successfully treated^{3,b}

About
9%
of all diagnosed
persons
successfully
treated



NHANES=National Health and Nutrition Examination Survey.

^aNHANES data as of 2010.

^bNHANES data, 2001-2008.

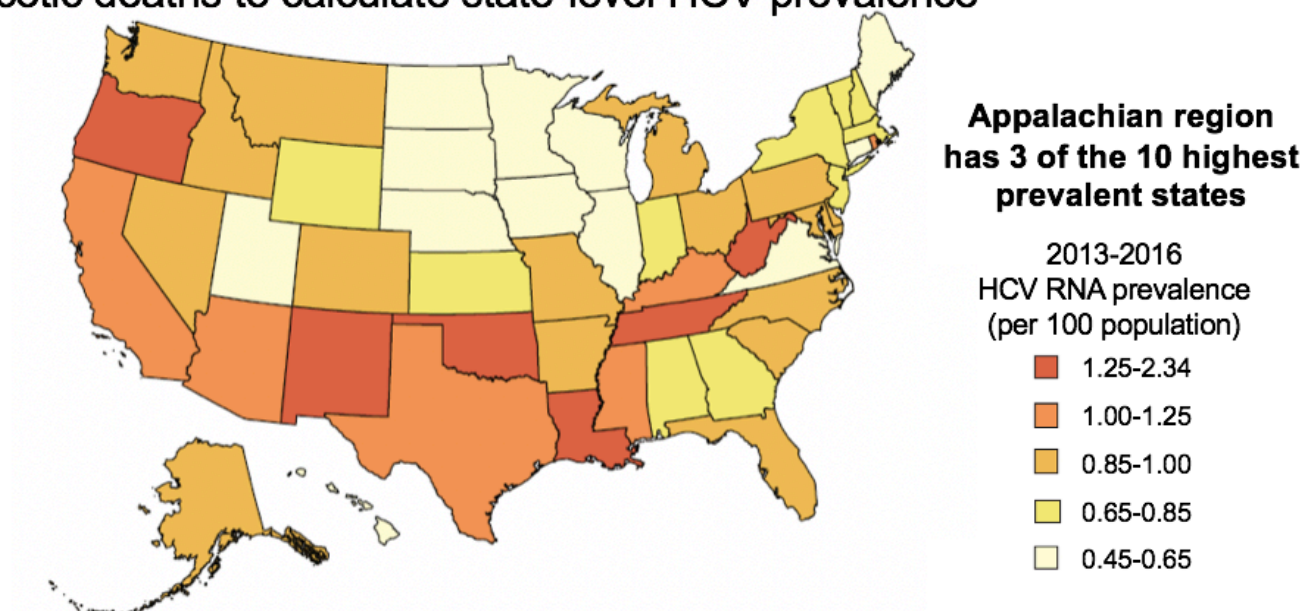
1. Ditah I, et al. *J Hepatol*. 2014;60:691-698.

2. Edlin BR, et al. *Hepatology*. 2015;62:1353-1363.

3. Yehia BR, et al. *PLoS ONE*. 2014;9:1-7.

Prevalence of Chronic HCV in the United States

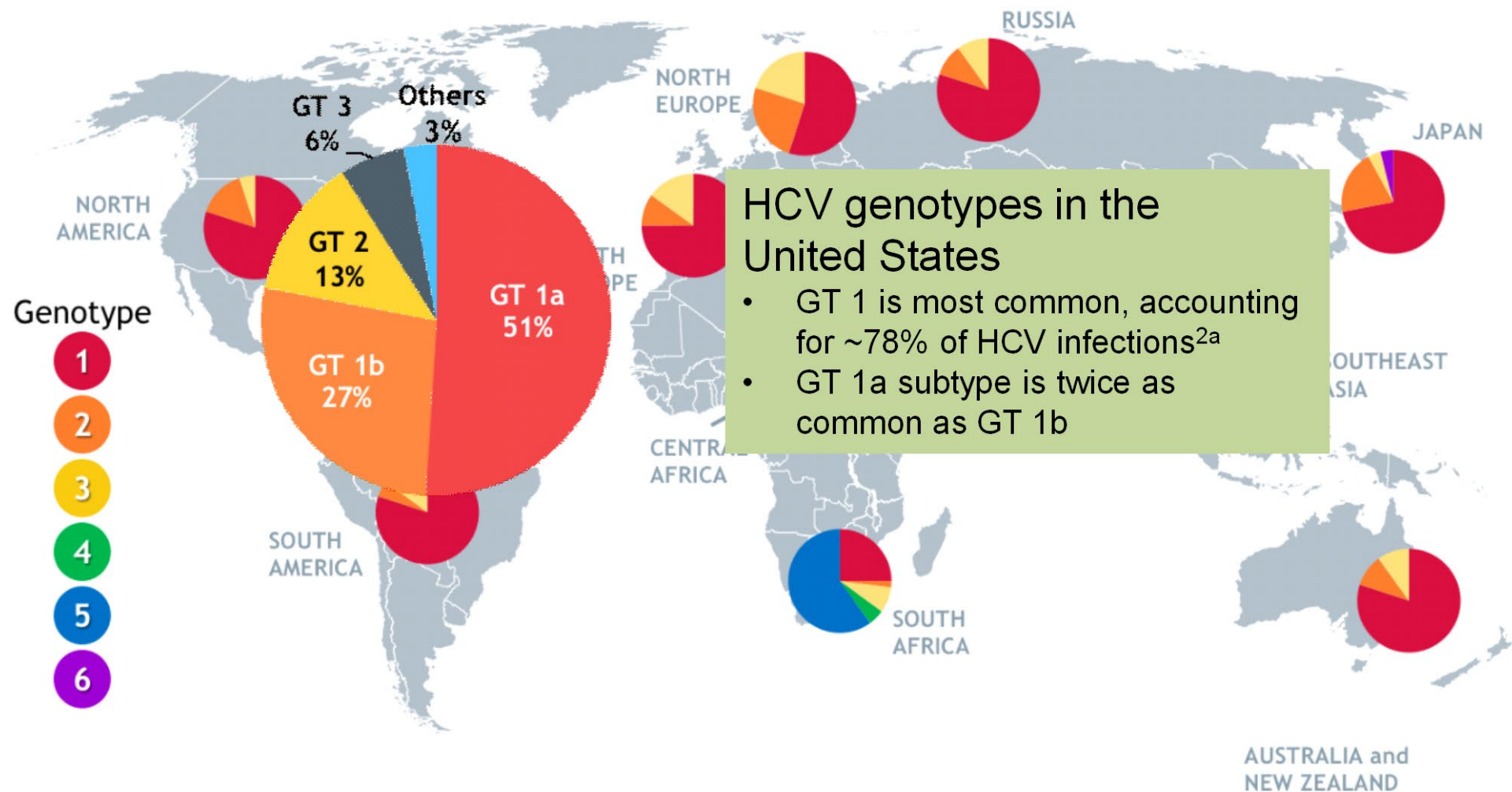
Analysis of NHANES HCV prevalence and National Vital Statistics System (NVSS) HCV and narcotic deaths to calculate state-level HCV prevalence



- Estimated national prevalence of current HCV infection (RNA positive) = 1% (2.4 million persons)*
- Half of prevalent infections occur in 9 states and District of Columbia:
 - Alaska, Arizona, DC, Kentucky, Louisiana, New Mexico, Oklahoma, Oregon, Tennessee, and West Virginia

There is substantial variation in HCV prevalence among states, with the US west and Appalachian region containing more high-burden states

HCV Genotypes by Geographic Region



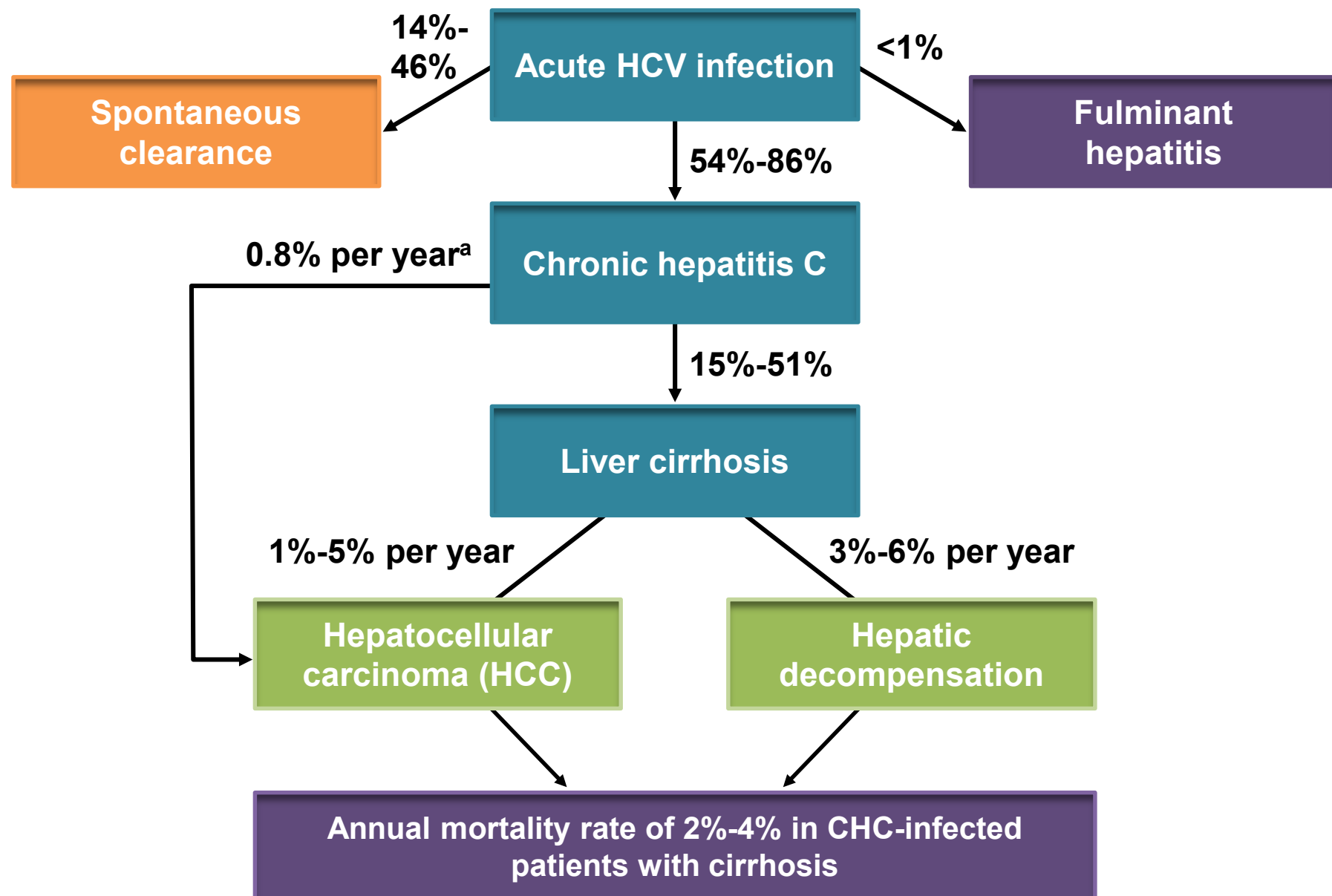
GT=genotype.

^aDerived from HCV RNA-positive participants in NHANES III conducted 1988 to 1994 (N=275).

1. World Gastroenterology Organisation. Diagnosis, management and prevention of hepatitis C. 2013.

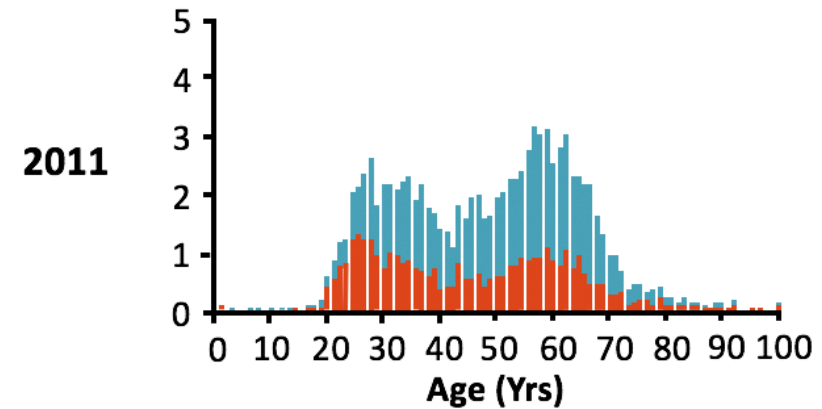
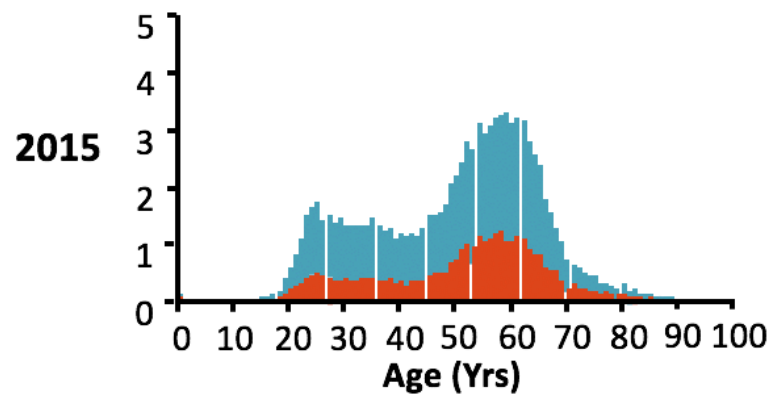
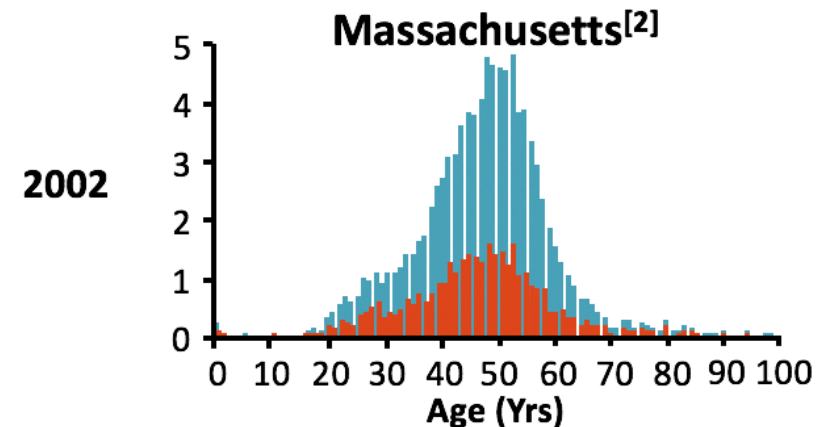
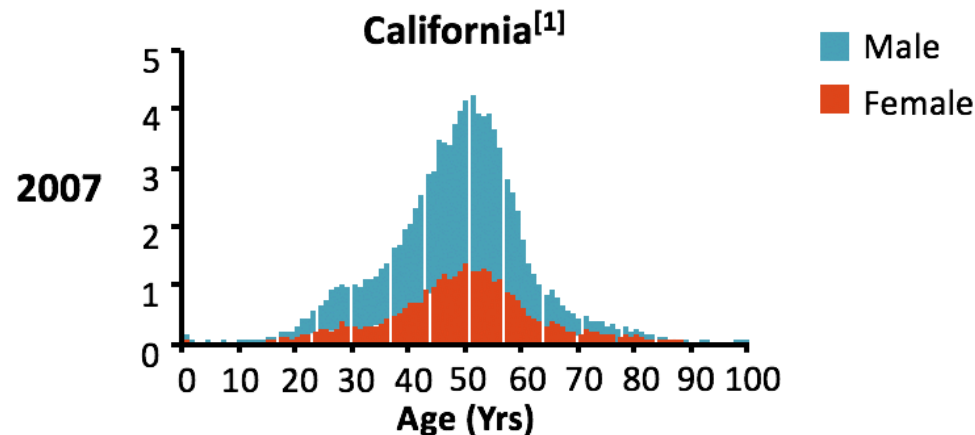
2. Nainan OV, et al. *Gastroenterology*. 2006;131:478-484.

Natural History of HCV Infection



^a0.8% of those with CHC may develop HCC without having developed cirrhosis.

Changing Epidemiology of HCV in the US: Percentage of Newly Reported Cases by Age Group



1. California Department of Public Health. Chronic hepatitis C infections in California: cases newly reported through 2015. June 2017.

2. Kim. J Infect Dis. 2013;207(Suppl 1):S1.

Slide credit: clinicaloptions.com

Increasing HCV Burden in Young Adults in the US

Young adults > Baby Boomers	Population Totals	Young Adult is on incline	Population Totals	Young Adults = Baby Boomers	Population Totals
Pennsylvania	12,784,227	California	39,250,017	Michigan	9,928,300
Ohio	11,614,373	Florida	20,612,439	Wisconsin	5,778,708
Massachusetts	6,811,779	New York	19,745,289	Colorado	5,540,545
Indiana	6,663,053	Virginia	8,411,808	Connecticut	3,576,452
Kentucky	4,436,974	Washington	7,228,000		
Arkansas	2,998,248	Arizona	6,931,071		
New Mexico	2,081,015	Louisiana	4,681,666		
West Virginia	1,831,102	Oregon	4,093,465		
Maine	1,331,479	Iowa	3,134,693		
North Dakota	757,952	Utah	3,051,217		
Vermont	624,594	South Dakota	865,454		
Total population	51,894,796	Total population	118,065,119	Total population	24,824,005

11 States have rates of HCV infection in young adults surpassing that of Baby Boomers

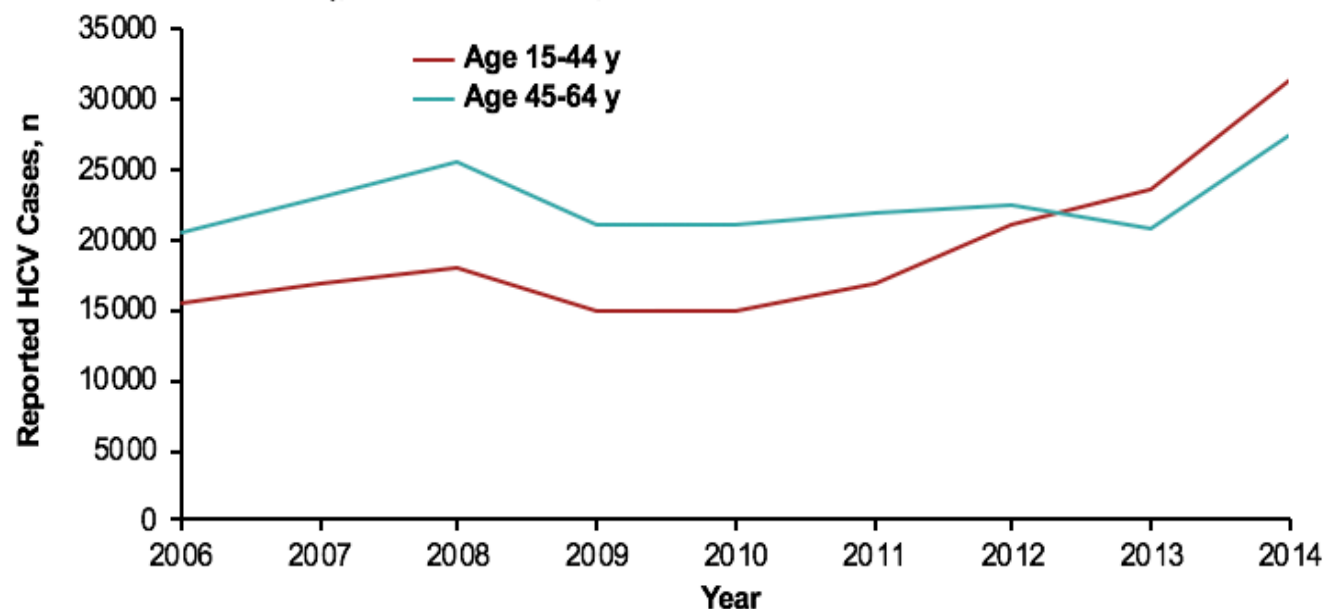
Fraction of US population – 76%; Total population 20-39 = 66,249,672; Total females 20-39 = 32,733,899

Morse, A et al Making the case for universal screening for pregnant women for hepatitis C; one state at a time. Gastroenterology May 2018 Vol 154 (6)

Rates of HCV are Increasing in Women of Child-bearing Age

Number of reported cases of HCV infection among women aged 15-44 years and 45-64 years in the United States, 2006-2014.

Ly, K. et al Ann Intern Med. 2017;166:775-782. doi:10.7326/M16-2350



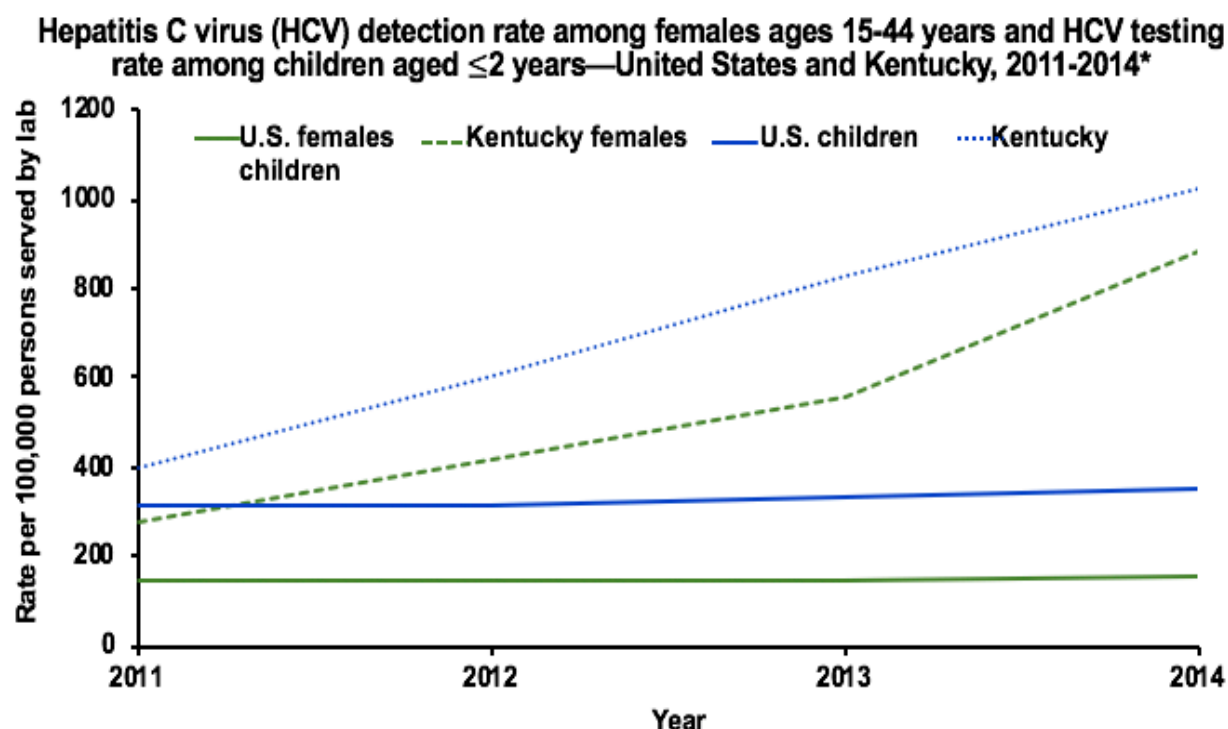
Among women 15-44:

- Acute cases increased 3.4 fold
- Past or present cases increased 2 fold
- In 2013, rates surpassed older women

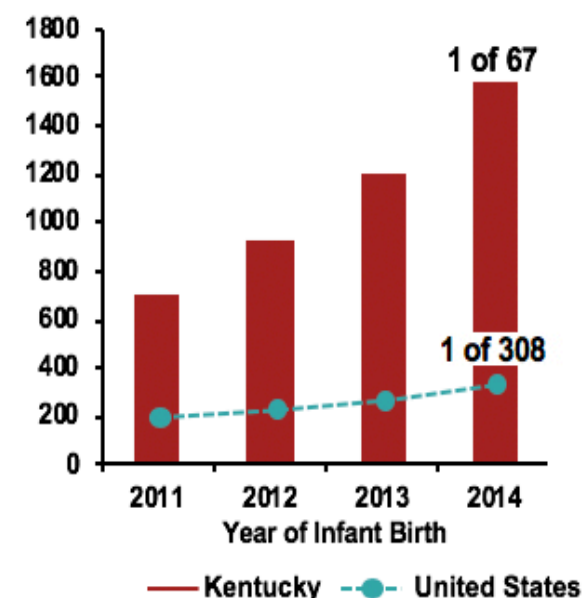
Centers for Disease Control and Prevention, National Notifiable Surveillance System, HCV, Hepatitis C virus
Ly, K. et al Ann Intern Med. 2017;166:775-782. doi:10.7326/M16-2350
Gilead

Changing HCV Prevalence Among Pregnant Women

- During 2009–2014, HCV infection present at the time of delivery among pregnant women from states reporting HCV on the birth certificate increased 89%, from 1.8 to 3.4 per 1,000 live births
- The highest infection rate in 2014 (22.6 per 1,000 live births) was in West Virginia; the rate in Tennessee was 10.1.¹



Infants Born to HCV Infected Women: Kentucky, United States, 2011-2014



1. MMWR / May 12, 2017 / Vol. 66 / No. 18
 2. MMWR . 65(28):705-10, 2016 Jul 22
 Gilead Pharmaceuticals

HCV Rates are Increasing Amongst Pregnant Women in the US

- Hospital discharge data from the Nationwide Inpatient Sample, the largest all-payer hospital inpatient care database in the US provides nationally representative estimates.
- Pregnancy hospitalizations with the following diagnoses were identified:

Characteristic	2002 through 2004		2005 through 2007		2008 through 2010		Total	
	n	Rate ^a	n	Rate ^a	n	Rate ^a	n	Rate ^a
Hepatitis B	11,740	0.85	13,902	0.97	14,022	1.05	39,664	0.96
Hepatitis C	17,114	1.25	24,687	1.72	28,567	2.13	70,367	1.70
Gallbladder disease/cholelithiasis	59,341	4.32	65,748	4.59	67,850	5.06	192,940	4.65
Liver disorders of pregnancy ^b	82,066	5.97	96,082	6.71	119,505	8.91	297,653	7.18
Chronic and alcohol-related liver disease	2758	0.20	4100	0.29	5714	0.43	12,571	0.30
Biliary tract disease	14,552	1.06	22,423	1.57	32,371	2.41	69,346	1.67
HELLP syndrome	10,854	0.79	12,340	0.86	16,171	1.21	39,365	0.95

For hepatitis C, there were significant increases in the rates for 2005 through 2007 and 2008 through 2010 compared to the referent time period (2002 through 2004)

HELLP, hemolysis, elevated liver enzymes, low platelet count.

^a Per 1000 pregnancy hospitalizations;

^b Includes acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, icterus gravis pregnancy, necrosis of liver of pregnancy, and hepatorenal syndrome following delivery.

Original Articles

Increasing Prevalence of Hepatitis C among Hospitalized Children Is Associated with an Increase in Substance Abuse

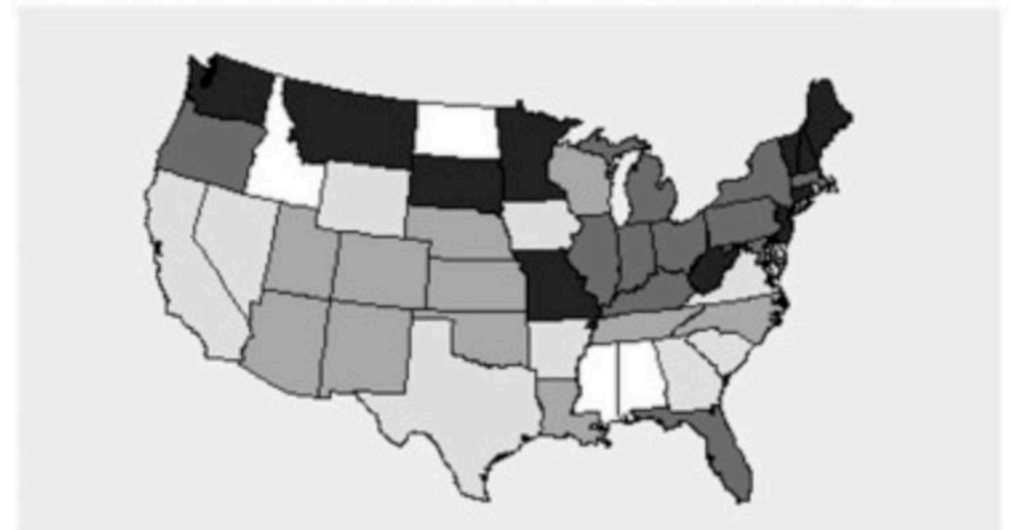
A. Sidney Barritt IV MD, MSCR¹, Brian Lee MPH, PhD², Thomas Runge MD, MPH¹, Monica Schmidt MPH, PhD³, Ravi Jhaveri MD⁴  

A: Hepatitis C Hospitalizations



Rate  0.0-1.14  1.15-2.63  2.64-4.15  4.16+  NA

B: Substance Abuse Hospitalizations



Rate  18.40-32.23  32.34-45.53  45.54-62.98  62.99+  NA

Global Call for HCV Elimination

- WHO vision: *“A world where viral hepatitis transmission is stopped and everyone has access to safe, affordable, and effective treatment and care”*

2030 Targets

90% Diagnosed

80% Treated

65% Reduced mortality

- **Feasible** by scaling up **key interventions**:

- Hepatitis B vaccination and treatment
- Safe injection practices and safe blood
- Harm reduction for PWID
- Safer sex (including condom promotion)
- Hepatitis C cure

- **US HBV/HCV Elimination Strategy** developed by National Academies of Sciences, Engineering, and Medicine: **“elimination” = 90% reduction in incidence by 2030**

WHO. Draft WHO Global Hepatitis Strategy, 2016-2021.

NASEM. A national strategy for the elimination of hepatitis B and C. Washington, DC: The National Academies Press; 2017.



Slide credit: clinicaloptions.com

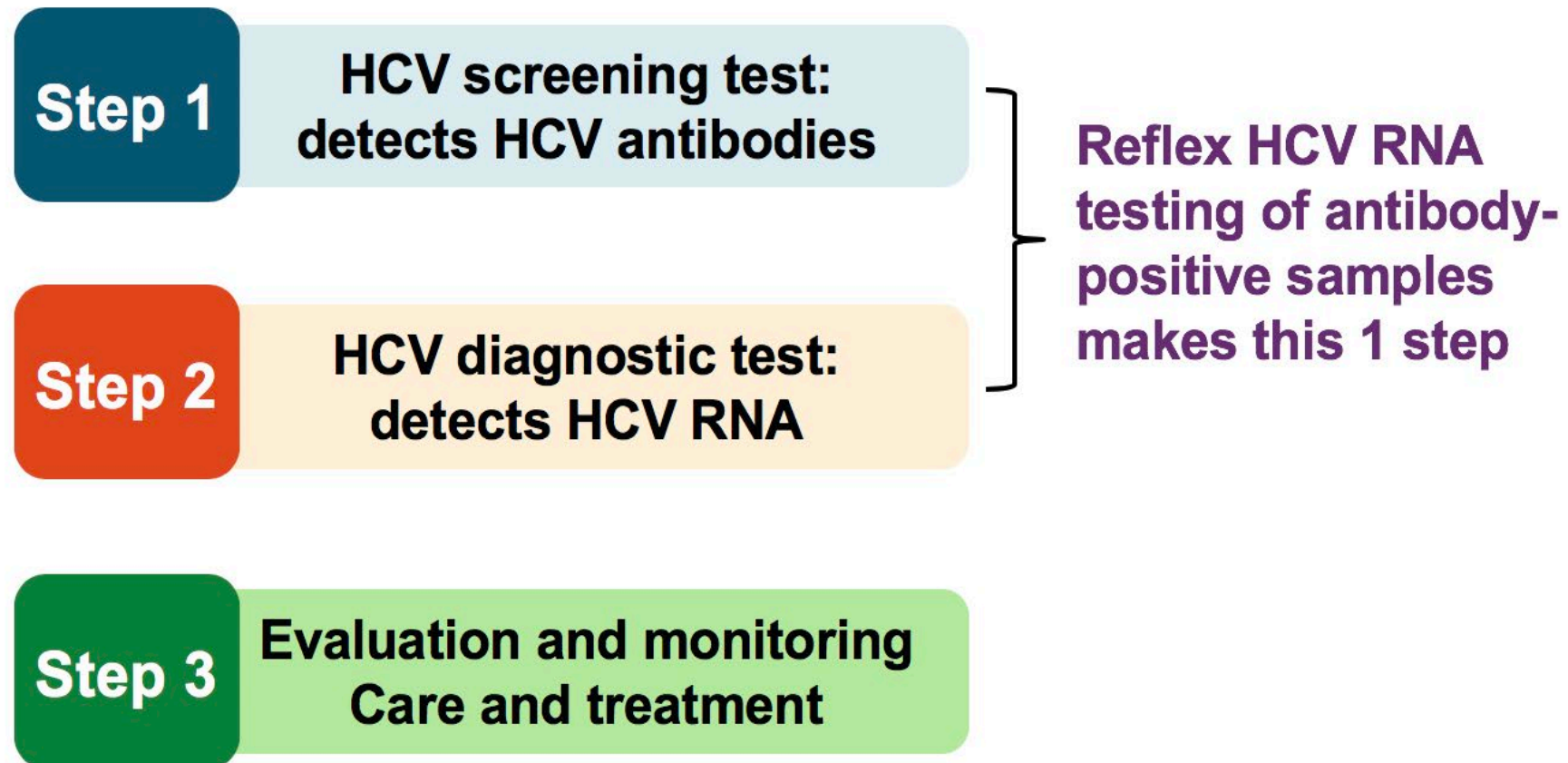
US Progress Toward HCV Elimination Goals

- 12 countries are currently on track to achieve 2030 HCV elimination goals:
 - Australia, Egypt, France, Georgia, Iceland, Italy, Japan, Mongolia, the Netherlands, Spain, Switzerland, and United Kingdom
 - **The United States is NOT among them**
 - **We are missing in important population for elimination efforts by not expanding treatment further to PWID population**

http://polarisobservatory.org/polaris_view/hepC.htm

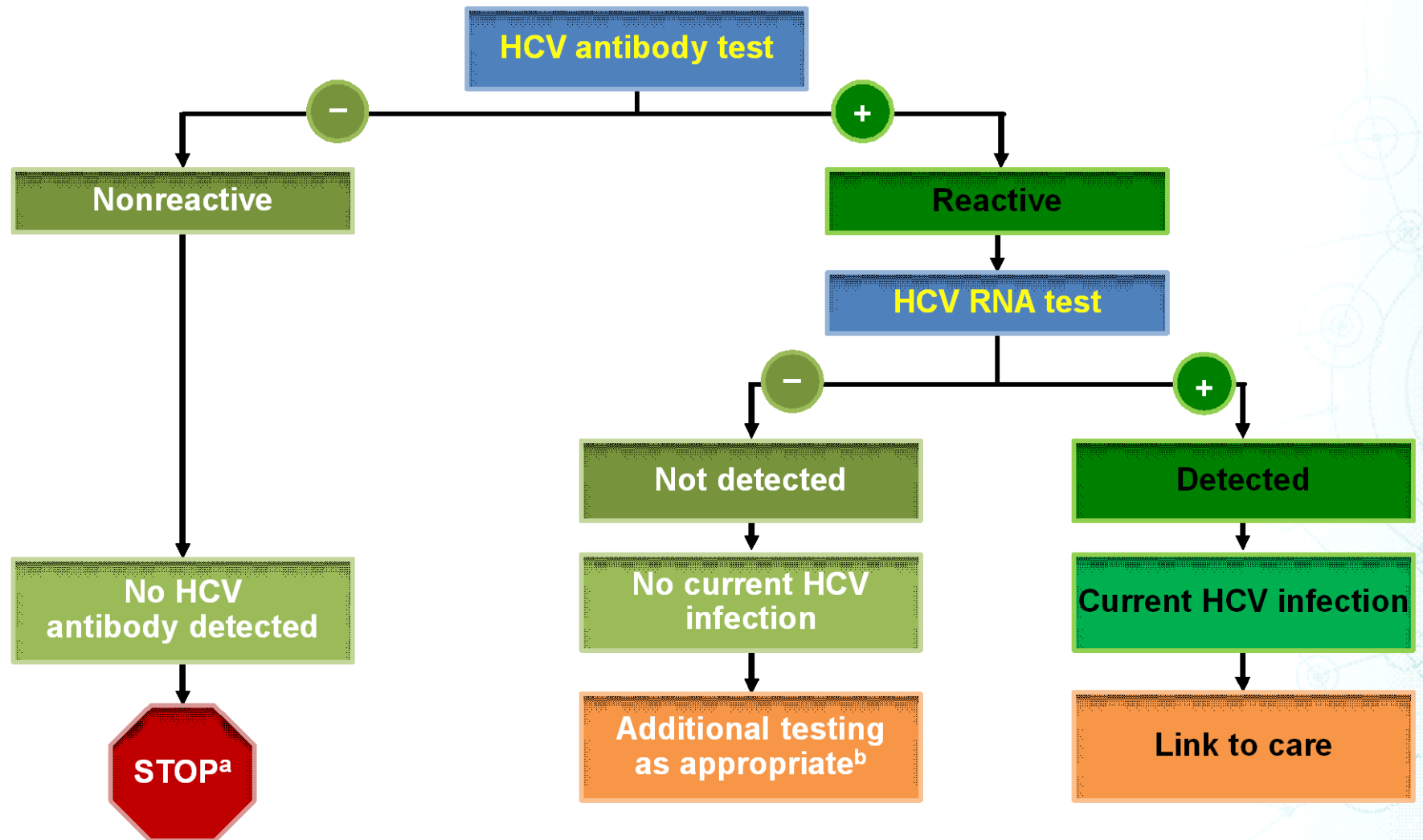
Slide credit:  clinicaloptions.com

Reflexive HCV RNA Testing Overcomes the Gap in Confirming Chronic HCV Infection



Slide credit:  clinicaloptions.com

Recommended Testing Sequence for HCV Screening and Diagnosis



^aFor persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

^bTo 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.

Adapted from CDC. *MMWR*. 2013;62:1-4.

Universal Screening



HCV Guidance: Recommendations for
Testing, Managing, and Treating
Hepatitis C



HCV in Pregnancy

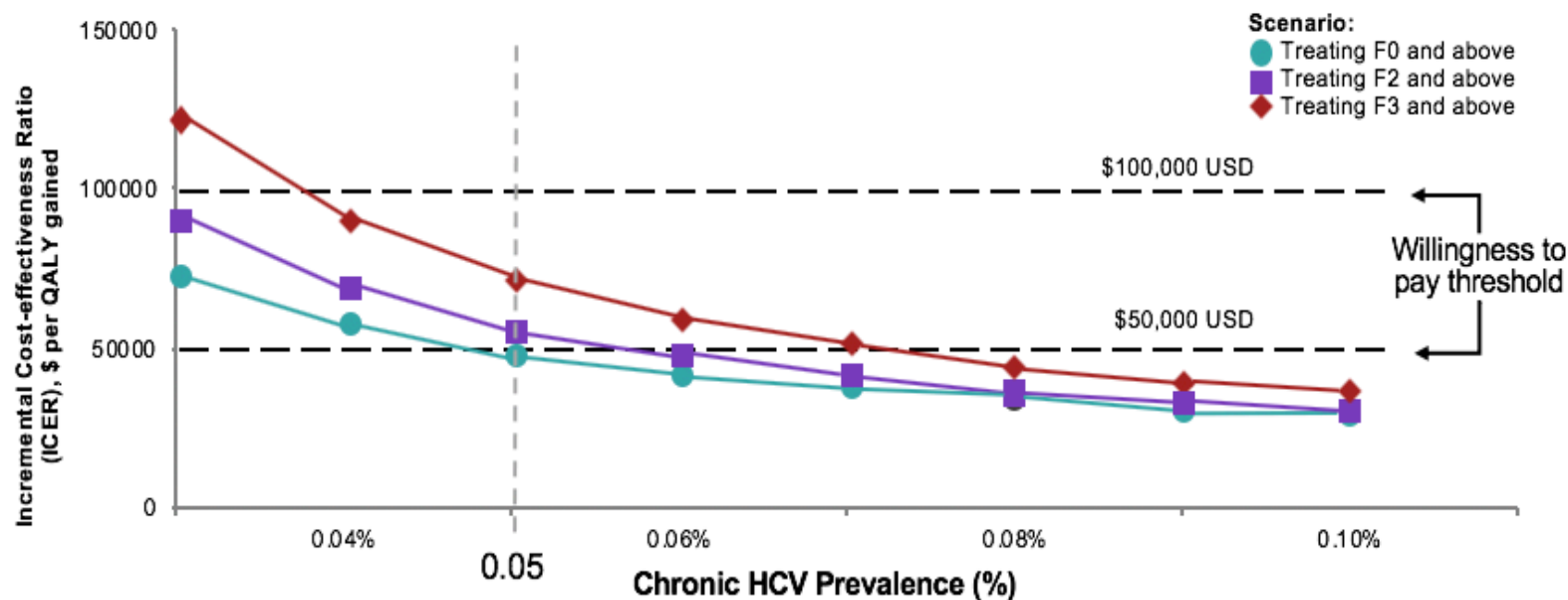
Testing

Recommendation for Universal Hepatitis C Screening in Pregnancy	
RECOMMENDED	RATING ⓘ
All pregnant women should be tested for HCV infection (see Recommendations for Initial HCV Testing and Follow-Up), ideally at the initiation of prenatal care.	IIb, C

<https://www.hcvguidelines.org/unique-populations/pregnancy>

Cost-effectiveness and Impact of Hepatitis C Virus Screening of Pregnant Women in the United States ‡

IMPACT OF HCV CHRONIC PREVALENCE ON ICERs OF SCREENING PREGNANT WOMEN COMPARED TO NO SCREENING



- Screening the estimated 5.04 million pregnant women in 2018 would result in detection and treatment of an estimated 33,000 women
- Screening of pregnant women was cost-effective in settings with chronic prevalence among pregnant women at or above 0.05-0.08%

Chaillon et. al. AASLD, 2018, #SAT-984

HCV & Pregnancy – The Future.....

- **Universal screening** – near future nation wide
 - UUMC – July 1, 2019
- **Treatment** during pregnancy – a bit down the road

Transmission

- 1% to 2.5% of pregnant women are infected with HCV
- Mother-to-child HCV transmission (MTCT) ~ 5%
 - overall rate is estimated between 5-10%. - risk exists and is not on the radar of many providers
 - Higher viremia may increase risk of vertical transmission
 - in utero
 - Peripartum
- MTCT rates in co-infection with HIV carries a 10% risk

Impact of Pregnancy in HCV

- Down-regulation of maternal immune response
 - ↓ALT
 - ↑HCV RNA
- Antifibrotic effects of estrogens = beneficial impact in pregnancy
- Spontaneous viral clearance should be consider in post partum period when being assess for treatment

Impact of HCV on Pregnancy Outcomes

- Poor birth outcomes:
 - Fetal growth restriction
 - Low birth weight (LBW)
 - Congenital anomalies
 - Preterm delivery
- Gestational DMs
- Feeding difficulties
- Adverse neonatal outcomes
 - Cephalohematoma
 - Brachial plexus injury
 - Fetal distress
 - Intraventricular hemorrhage
 - Neonatal seizures

Impact of HCV on Pregnancy Outcomes

- Intrahepatic cholestasis of pregnancy (ICP)
 - Overall incidence: 0.2% - 2.7%
 - 20 folds higher the HCV-infected pregnant women
- HCV + Cirrhosis + pregnancy = high risks of bleeding and death

Considerations

- Invasive testing: Counsel about risks of vertical transmission
 - Amniocentesis is rec over chorionic villus sampling
- Internal fetal monitoring, prolonged rupture of membranes and episiotomy should be avoided
- Modes of delivery: C-section is **not** recommended for sole indication of HCV
- Breastfeeding should **not** be discouraged

TABLE 1. PREGNANCY FEATURES THAT MAY IMPACT PERINATAL TRANSMISSION OF HCV DURING PREGNANCY AND POSTDELIVERY*

Pregnancy Considerations	Studies; # of Women	Number of Women	Strength of Evidence	Summary of Findings	SMFM Recommendation
Elective C-section versus vaginal delivery	4 cohort studies ^(30,54-56)	2,080	Low	No differences, but trends in opposite directions in highest-quality studies	Do not recommend C-section solely for indication of HCV
All C-section versus vaginal delivery	11 cohort studies ^(24,27,31,57-64)	2,308	Moderate	No association	
Amniocentesis and CVS	3 cohort studies ^(30,54,56)	928	Insufficient	Inconsistent, but one good quality study (OR, 6.7; 95% CI, 1.1-36.0)	Counsel patients on potential risks of amniocentesis and CVS
Prolonged ROM	2 cohort studies ^(30,31)	245	Low	Yes with >6 hours (OR, 9.3; 95% CI, 1.5-1.8)	Active labor management if prolonged ROM to expedite delivery
Breastfeeding	15 cohort studies ^(24,27,30,31,54,55,59,62-69)	2,971	Moderate	No association between breastfeeding and risk for transmission	Do not discourage breastfeeding based on positive HCV status

<https://aasldpubs.onlinelibrary.wiley.com/doi/epdf/10.1002/hep4.1282>

Babies Born to HCV Positive Women

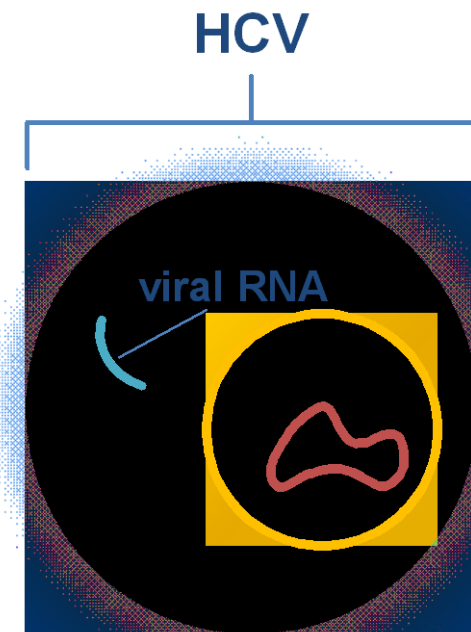
- Screening (American Academy of Pediatrics and CDC rec)
 - Anti-HCV antibodies at >18 months or
 - HCV RNA on two occasions in infants > 1 month
- Treatment
 - Approved for children > 12yo
 - ongoing trials, down to 3 yrs of age, with FDA approval soon

Improvements in HCV Treatment

- Direct Acting Antivirals (DAAs)
 - Glecaprevir/pibrentasvir (*Mavyret*)
 - x 8 weeks (16 weeks if cirrhotic)
 - Sofosbuvir/ledipasvir (*Harvoni*)
 - x 8 weeks
 - Sofosbuvir/velpatasvir (*Epclusa*)
 - x 12 weeks

HCV Can Be Cured

- Unlike HIV and HBV, HCV is curable^a
 - HCV RNA remains in the cytoplasm and does not integrate into host DNA¹
- HCV is highly genetically variable due to its:
 - High replication rate: On average, 1.3×10^{12} HCV virions are produced in each infected individual per day²
 - High mutation rate: The HCV polymerase lacks a proofreading function and is error prone³

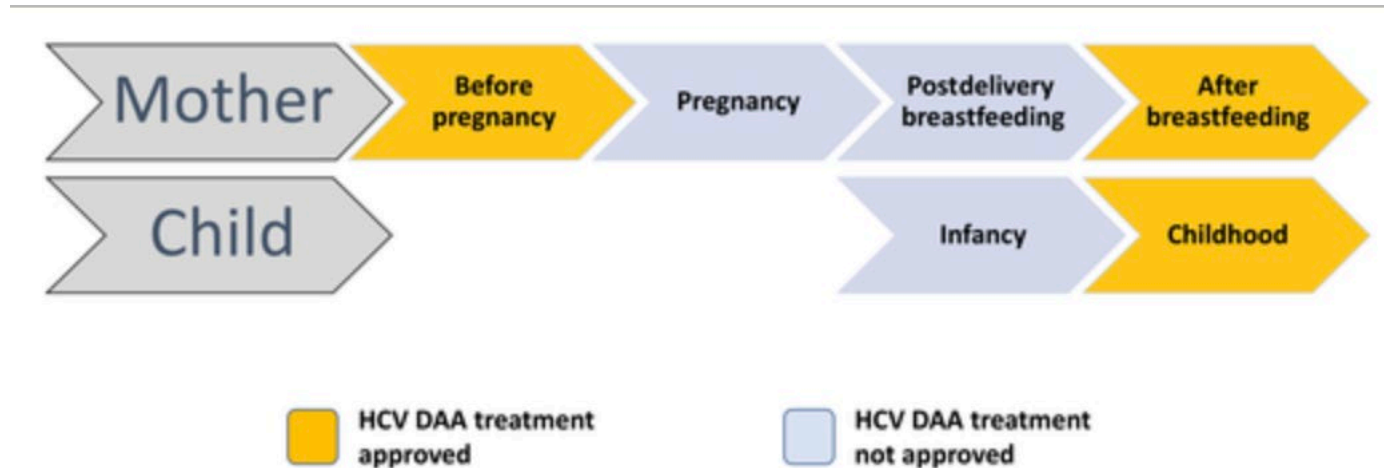


HBV=hepatitis B virus; HIV=human immunodeficiency virus;

^aCure, also known as SVR, is defined as no detectable HCV in the blood at 12 or more weeks after therapy is complete.⁴

1. Soriano V, et al. *J Antimicrob Chemother.* 2008;62:1-4.
2. Neumann AU, et al. *Science.* 1998;282:103-107.
3. Brown NA. *Expert Opin Investig Drugs.* 2009;18:709-725.
4. AASLD/IDSA. Recommendations for testing, managing, and treating hepatitis C. <http://hcvguidelines.org>. Accessed March 3, 2016.

Treatment



- Antiviral therapies (DAAs) are not approved for use in pregnant women
- Abstain from alcohol
- Linkage to care for treatment

DAAAs in Pregnancy

- Clinical trials with DAAs
 - Australia, large study with the use of sofosbuvir x 12wk – ongoing
 - India, developing protocols
 - University of Pittsburgh/ Magee Womens Research Institute, safety and efficacy
- DAA pregnancy rating seems to be similar to antivirals (acyclovir, tenofovir)
 - Preclinical animal data does not support any notable toxicity
 - Wide pharmacokinetics range should not require dose change

A PHASE ONE STUDY OF LEDIPASVIR/SOFOSBUVIR IN PREGNANT WOMEN WITH HEPATITIS C VIRUS



Catherine A. Chappell, Elizabeth E. Krans, Katherine Bunge, Ingrid Macio, Debra Bogen, Kimberly K. Scarsi, Leslie A. Meyn, Sharon L. Hillier



Primary Objective

To define the safety of and virologic response to ledipasvir 90 mg-sofosbuvir 400mg (LDV/SOF) therapy in pregnancy

Hypothesis

Ledipasvir 90mg-sofosbuvir 400mg (LDV/SOF) therapy will be safe and effective in pregnant women

Study design

Started tx 23-24 weeks gestation, 9 enrolled, 8 completed therapy

Conclusion

100% of participants were cured of HCV and all infants are negative to date.

Catherine A. Chappell, Elizabeth E. Krans, Katherine Bunge, Ingrid Macio, Debra Bogen, Kimberly K. Scarsi, Leslie A. Meyn, Sharon L. Hillier. Presented data at CROI 2019.

Summary

- Changing epidemiology of HCV
- Goal - Eradicate the virus
- Screening.
 - Family planning: screen before
 - Pregnancy: universal screening
 - Children: screen
- Impact the HCV cascade of care

CME

Pregnancy Care ECHO

Event code: **193126**

HCV ECHO

Event code: **193058**

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