AETC AIDS Education & Training Center Program Southeast

Hepatitis C Virus:
Fresh Take Gone Stale?

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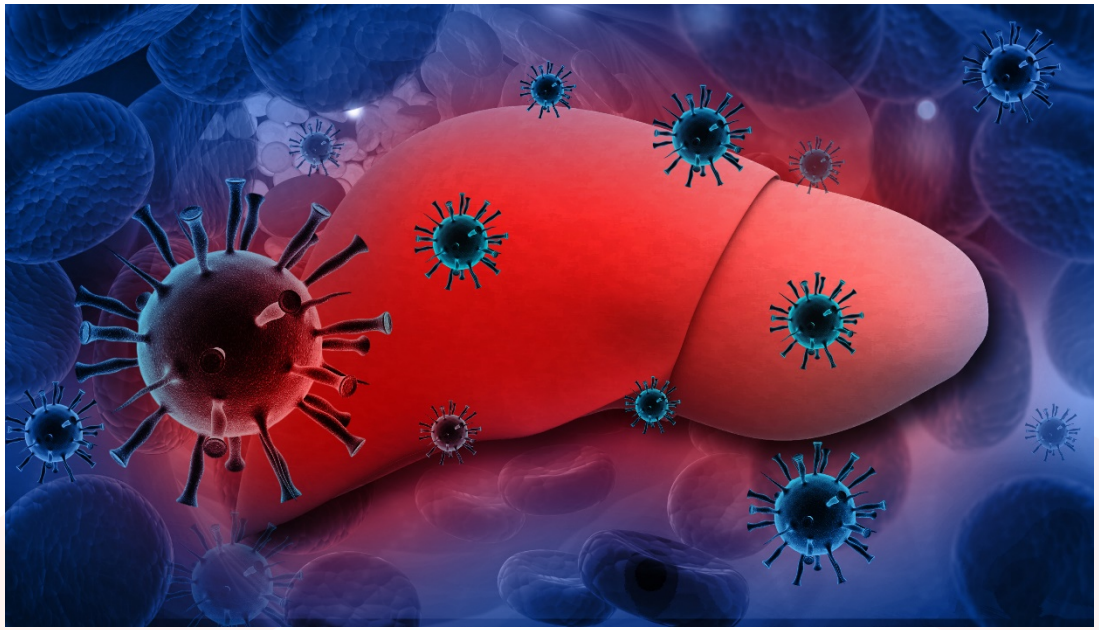
Disclosures

- Dr. Chastain receives grant/research support from Gilead Sciences, Inc.:
  - Site investigator for HIV/HCV SWITCH Registry Study
  - Key faculty personnel for Gilead FOCUS HCV Screening Program through Vanderbilt University Medical Center Emergency Department

Objectives

At the end of this lecture, the learner will be able to:

- Review trends in epidemiology of hepatitis C virus (HCV)
- Understand the indications for screening for HCV
- Identify the clinical manifestations of HCV
- Discuss the principles of and indications for treatment of HCV



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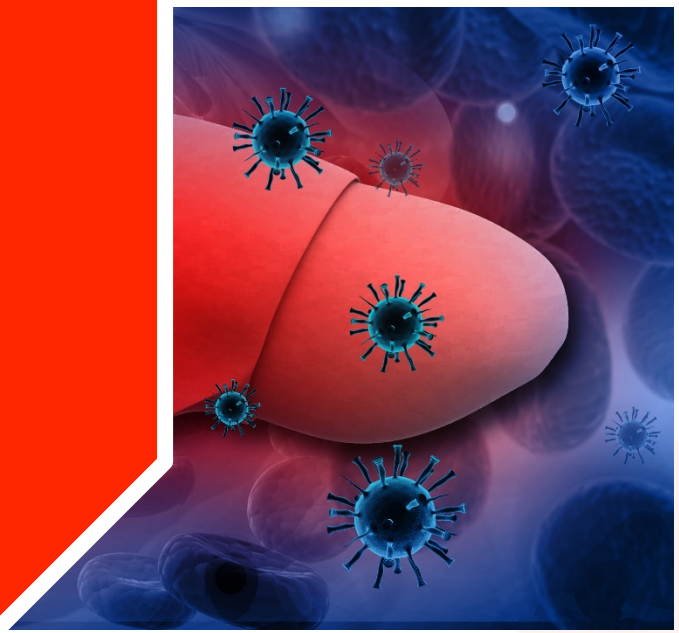
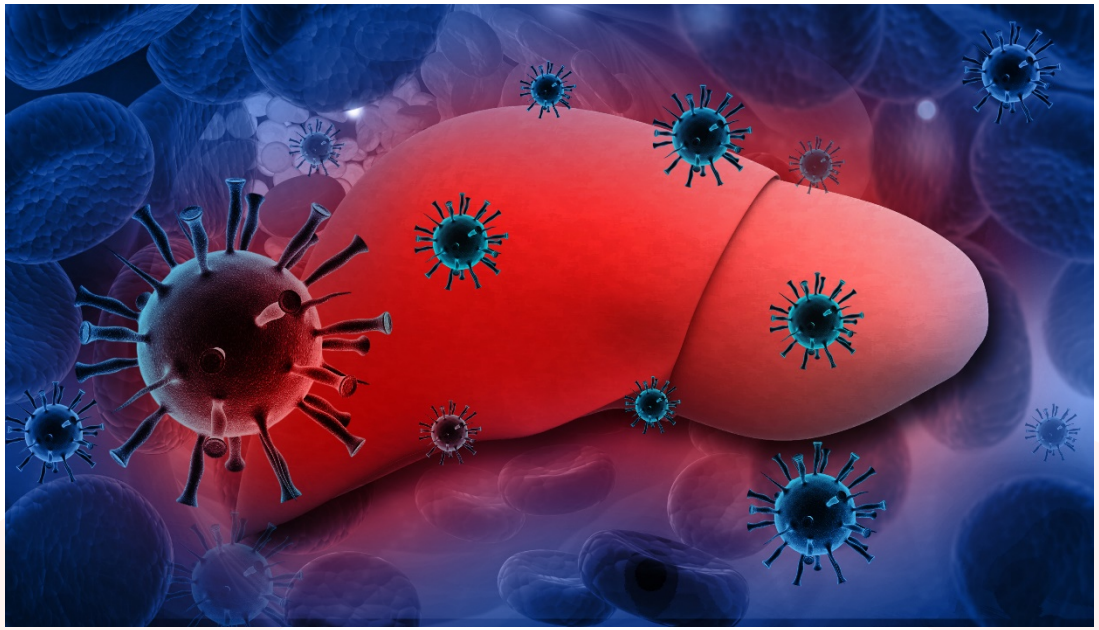


My "Real" Objectives

At the end of this lecture, the learner will:

- Recognize that HCV remains a major public health and individual health concern.
- Identify interventions related to HCV within his/her practice and/or community.
- Commit to a personal change re: the HCV continuum of care.



Outline

- Yesterday's News (i.e. Why We Were Excited)
- The Stale Take (i.e. The Party Line)
- A Call To Action (i.e. The Opportunities Abound)
- That Which Still Remains (i.e. Work To Do)

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Audience Response #1: Word Cloud

- What words do you associate with hepatitis C?

Audience Response #2: Word Cloud

- What words do you associate with hepatitis C treatment?

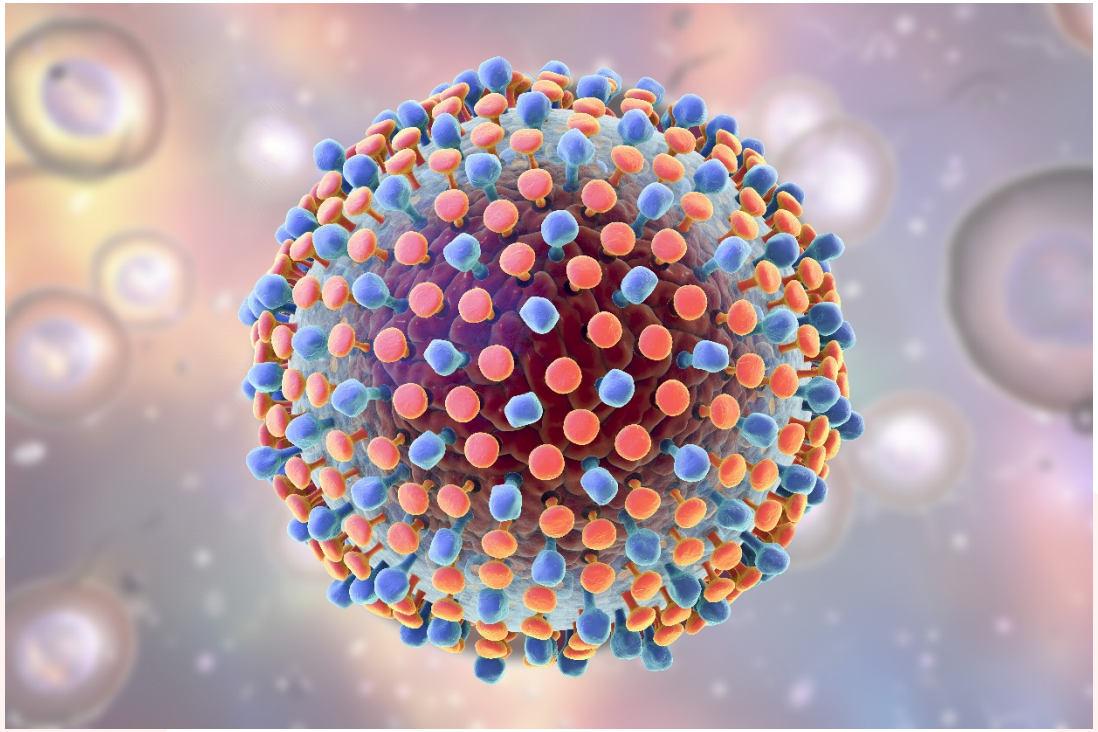
Hepatitis

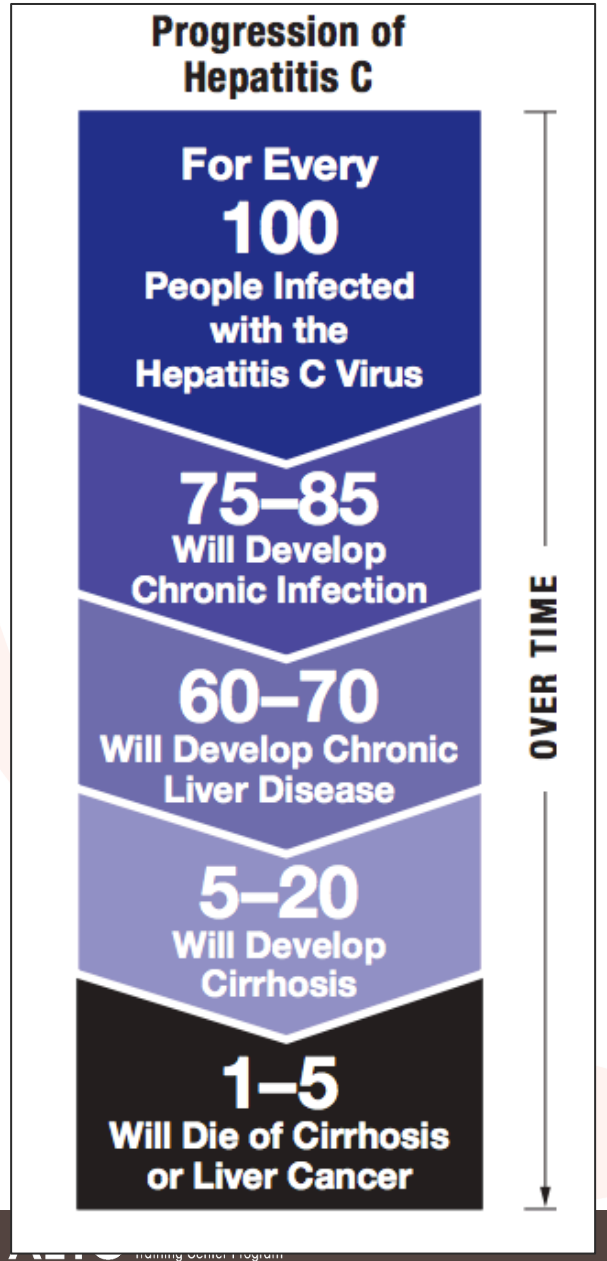
- Hepatitis = inflammation of the liver

- Differential Diagnosis:
  - Hepatitis viruses
    - Hepatitis A (HAV)
    - Hepatitis B (HBV)
    - **Hepatitis C (HCV)**
  - HIV
  - Cytomegalovirus (CMV)
  - Alcohol
  - Drug and/or supplement toxicity
  - Obesity [leading to non-alcoholic fatty liver disease (NAFLD)]
  - Genetic disorders

Hepatitis C Virus (HCV)

- Single-strand, positive sense RNA flavivirus
- Spread through blood and body fluids
- Predominantly infects liver cells
- No latent reservoir
  - I.e. no integration with host DNA as with HIV
  - I.e. no covalently closed DNA within host cells
  - I.e. can be eradicated/cured



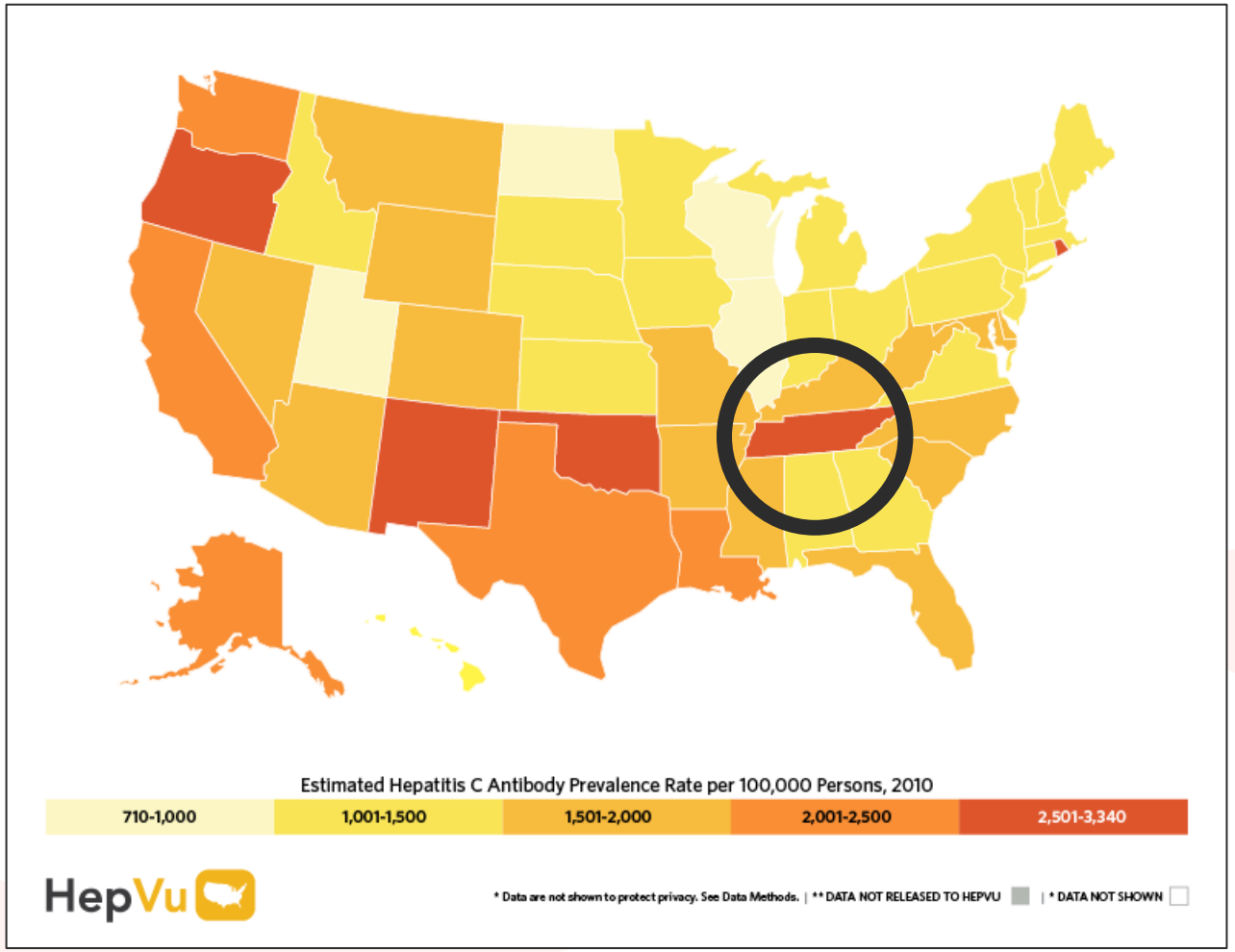


HCV Epidemiology & Natural History

- Epidemiology
  - 2.3-6 million Americans infected with HCV
  - Peak rates of decompensated cirrhosis and hepatocellular carcinoma 2020 in some estimates.
  - Peak mortality peak in 2034 per other estimates.
- Natural history
  - Minority develop advanced liver disease
  - Cirrhosis usually takes years to develop in the absence of comorbidities
  - Timeline may be accelerated by comorbidities, including alcohol use, HBV, HIV, insulin resistance, and/or obesity

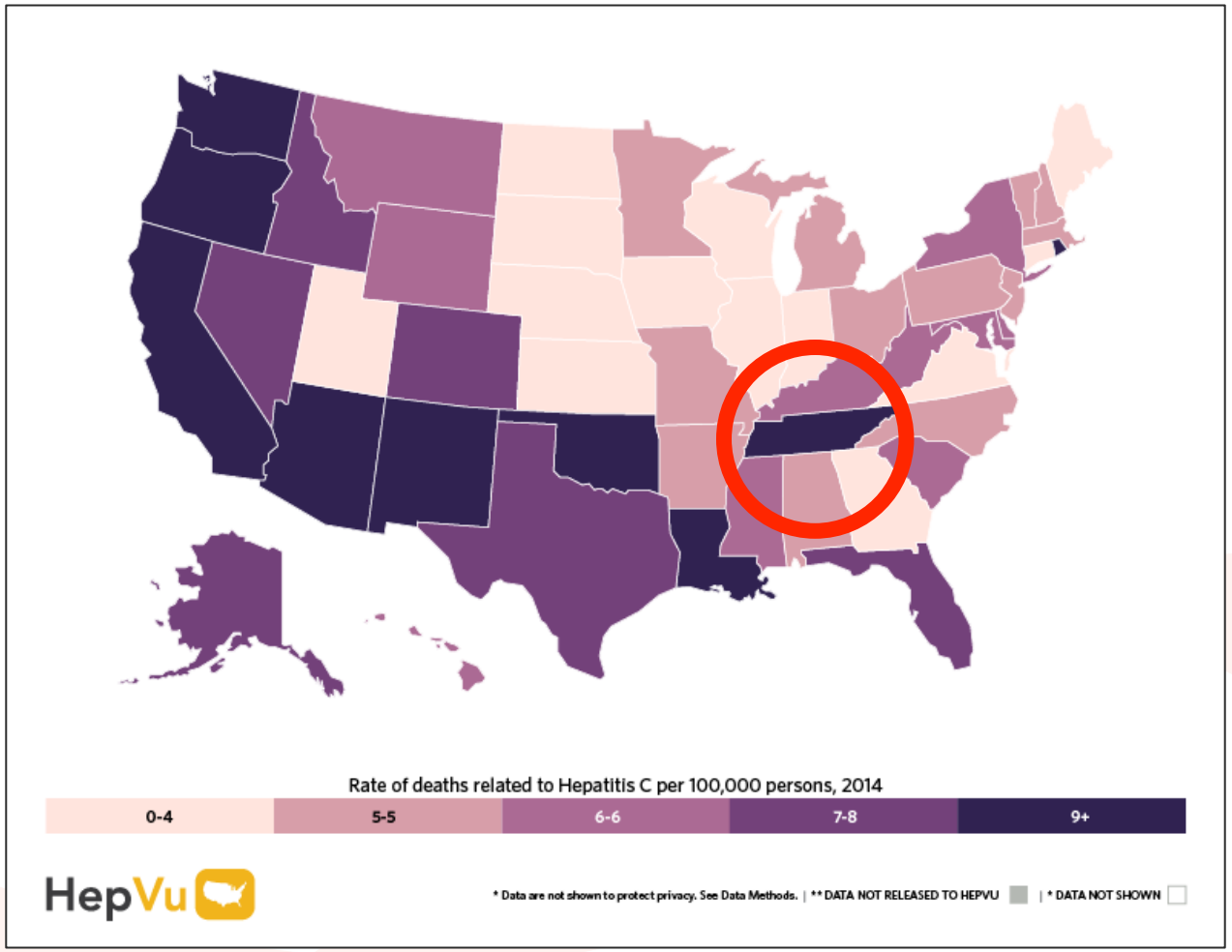
Davis GL et al. *Gastroenterology* 2010. // Ditah I et al *J Hepatol* 2014. // Edlin BR et al *Hepatology* 2015. // Rein DB et al *Dig & Liver Disease* 2011. // www.cdc.gov/hepatitis/HCV

Estimated HCV Ab Prevalence Rate / 100,000 persons



HepVu (www.hepvu.org). Emory University, Rollins School of Public Health.

Rate of Deaths Related to HCV per 100,000 persons



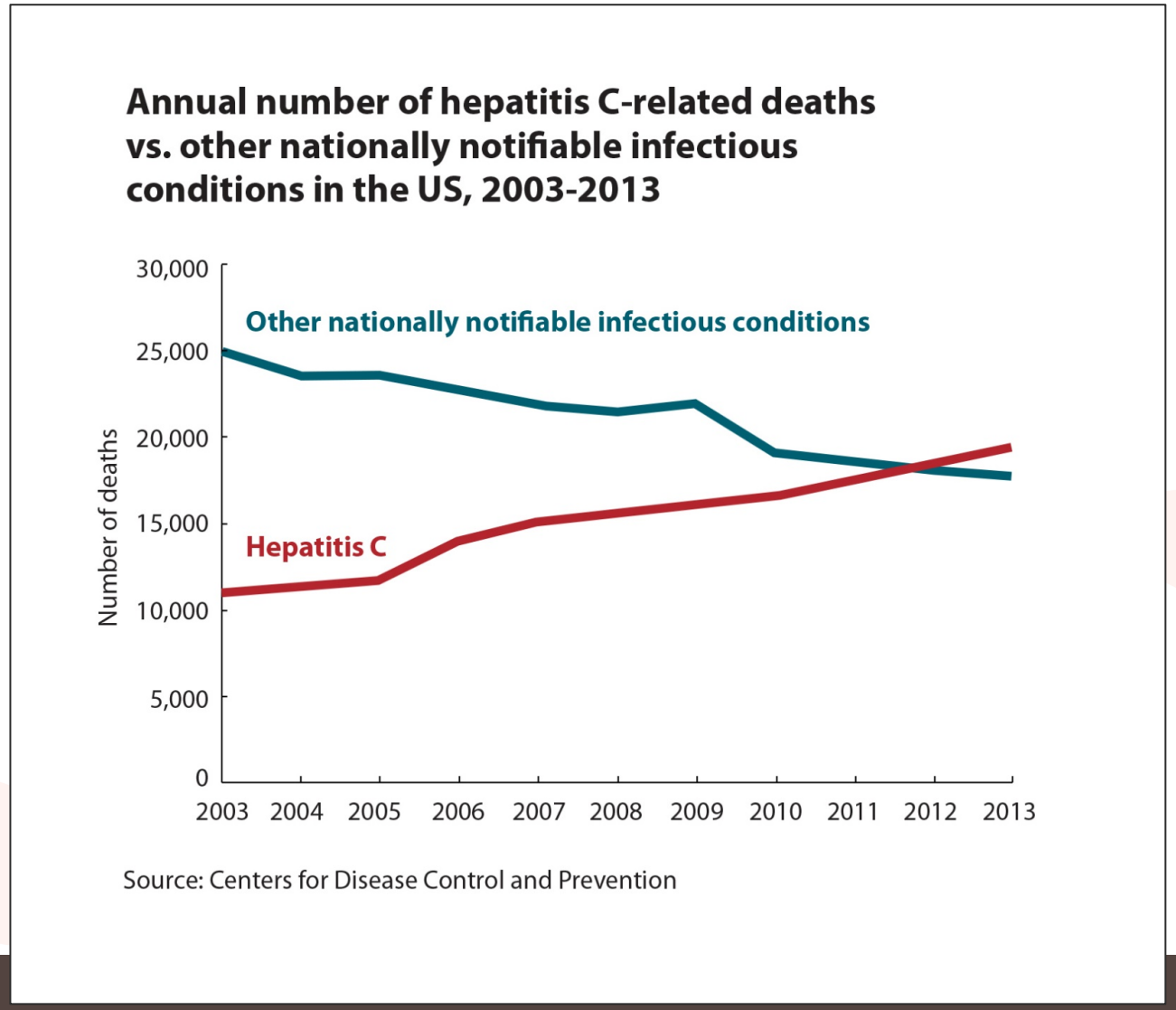
HepVu (www.hepvu.org). Emory University, Rollins School of Public Health.

Audience Response

- Which disease(s) kill more Americans each year?

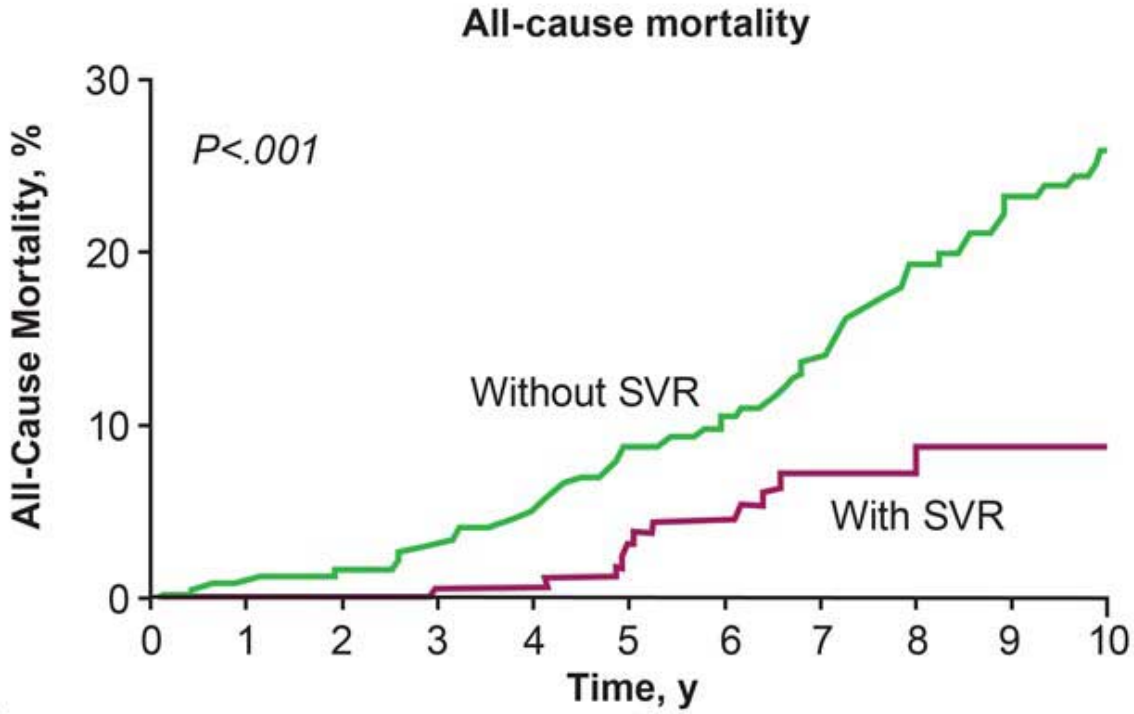
A. HCV
B. All other reportable infections that the CDC tracks (including HIV, TB, and hepatitis B)

HCV and Mortality in the USA



Ly KN et al. *Clin Infect Dis* 2016.

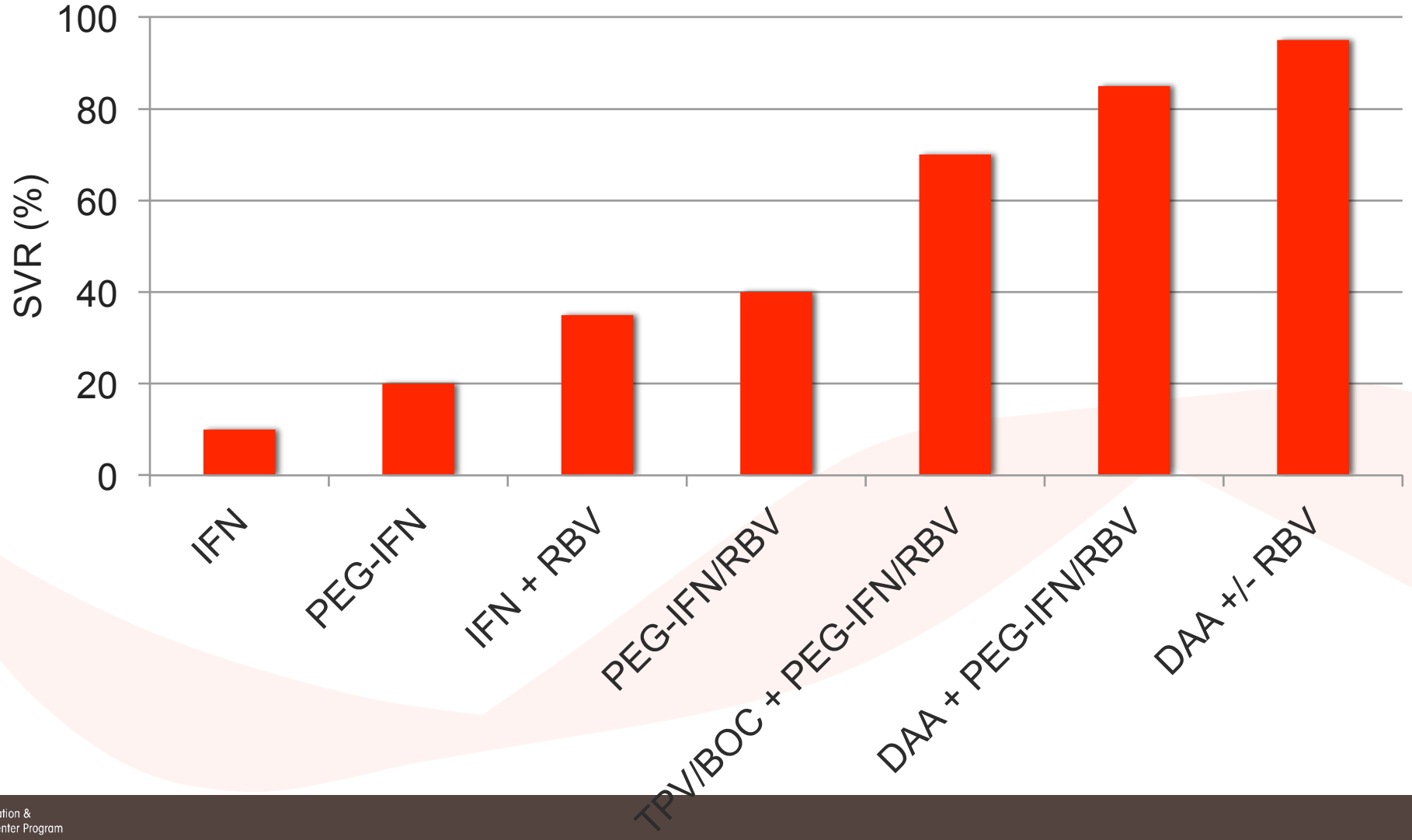
Effective Treatment Will Significantly Reduce Mortality from HCV Infection[14]



No. at risk											
Without SVR	405	393	392	363	344	317	295	250	207	164	135
With SVR	192	181	168	162	155	144	125	88	56	40	28

van der Meer AJ et al. JAMA. 2012

Treatment Response in Direct Acting Antiviral (DAA) Era



Slide courtesy of and adapted from Dr. Susanna Naggie

HCV Approved Agents

FDA Approved Therapies Through 2010

Interferon (1986)
Ribavirin (1998)
Pegylated Interferon (2001)

Since Then

Telaprevir (2011)
Boceprevir (2011)
Simeprevir (2013)
Sofosbuvir (2013)
Ledipasvir (2014)
Paritaprevir (2014)
Ombitasvir (2014)
Dasabuvir (2014)
Daclatasvir (2015)
Elbasvir (2016)
Grazoprevir (2016)
Velpatasvir (2016)
Voxilaprevir (2017)
Glecaprevir (2017)
Pibrentasvir (2017)

HCV Therapies: The Past, Present, and Future

Pre-2011	July 2011	Nov-Dec 2013	Oct-Dec 2014	July 2015	Jan-Jun 2016	July-Aug 2017
IFN	IFN	IFN	IFN	IFN	IFN	IFN
PEG-IFN	PEG-IFN	PEG-IFN	PEG-IFN	PEG-IFN	PEG-IFN	PEG-IFN
RBV	RBV	RBV	RBV	RBV	RBV	RBV
	Telaprevir	Telaprevir	~~**Telaprevir**~~	~~Telaprevir~~	~~Telaprevir~~	~~Telaprevir~~
	Boceprevir	Boceprevir	Boceprevir	~~**Boceprevir**~~	~~Boceprevir~~	~~Boceprevir~~
		Simeprevir	Simeprevir	Simeprevir	Simeprevir	Simeprevir
		Sofosbuvir	Sofosbuvir	Sofosbuvir	Sofosbuvir	Sofosbuvir
			Ledipasvir	Ledipasvir	Ledipasvir	Ledipasvir
			Paritaprevir	Paritaprevir	Paritaprevir	Paritaprevir
			Ombitasvir	Ombitasvir	Ombitasvir	Ombitasvir
			Dasabuvir	Dasabuvir	Dasabuvir	Dasabuvir
				Daclatasvir	Daclatasvir	Daclatasvir
					Elbasvir	Elbasvir
					Grazoprevir	Grazoprevir
					Velpatasvir	Velpatasvir
						Voxilaprevir
						Glecaprevir
						Pibrentasvir

FDA Approved HCV Therapies

Nonspecific Antivirals

Interferon (IFN)
Ribavirin (RBV)
Pegylated Interferon (PEG-IFN)

NS3/4 Protease Inhibitors

Telaprevir (TPV)
Boceprevir (BPV)
Simeprevir (SMV)
Paritaprevir (PTV)
Grazoprevir (GZP)
Voxilaprevir (VOX)
Glecaprevir (GLE)

NS5A Inhibitors

Ledipasvir (LDV)
Ombitasvir (OBV)
Daclatasvir (DCV)
Elbasvir (EBV)
Velpatasvir (VEL)
Pibrentasvir (PIB)

NS5B Polymerase Inhibitors

Sofosbuvir (SOF)
Dasabuvir (DBV)

Goals for HCV Therapy

- Interferon-free
- Ribavirin-free
- Improved efficacy overall
- Improved efficacy for subgroups (i.e. black, HIV/HCV)
- Decreased side effects
- Minimal drug-drug interactions
- Increased genotype options (including pangenotypic)
- Options in renal impairment
- Retreatment options
- Lower prices
- Accessibility for all

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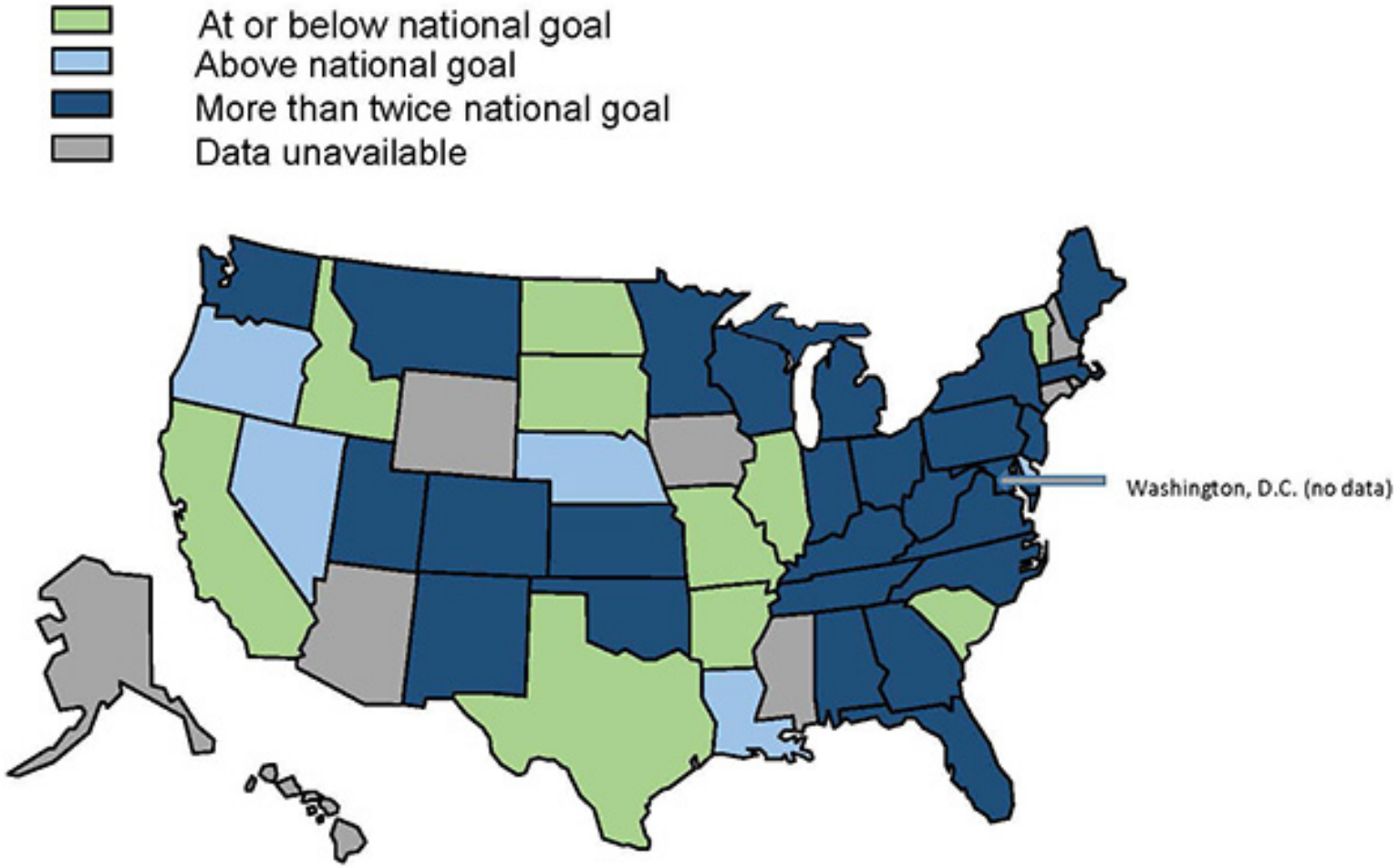
What Hasn't Changed?

- Rate of New Infections
- Treatment Options
- Treatment Capacity

Map 4.1. 2015 State Acute Hepatitis C Incidence Compared to Healthy People 2020 National Goal*

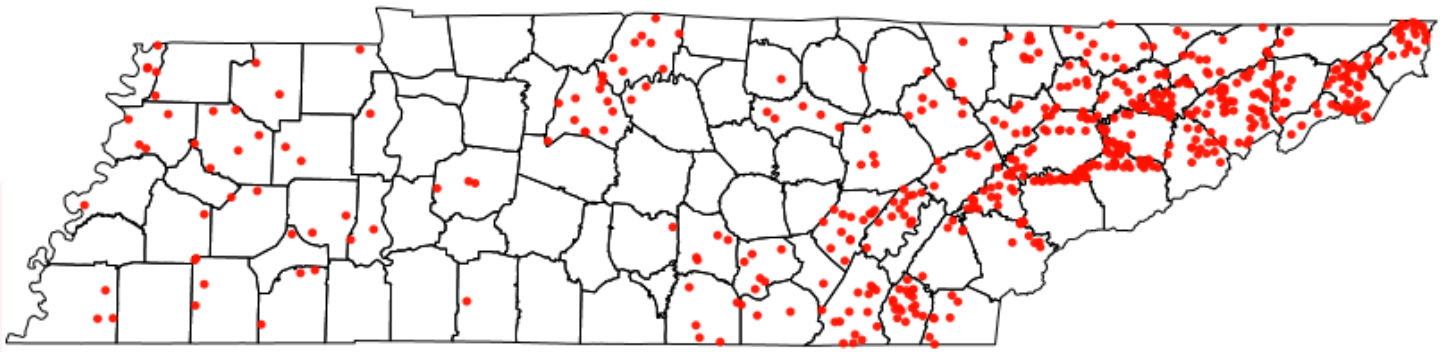


Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)

*National goal: 0.25 cases/100,000 population

Reported Cases of Acute HCV in Tennessee

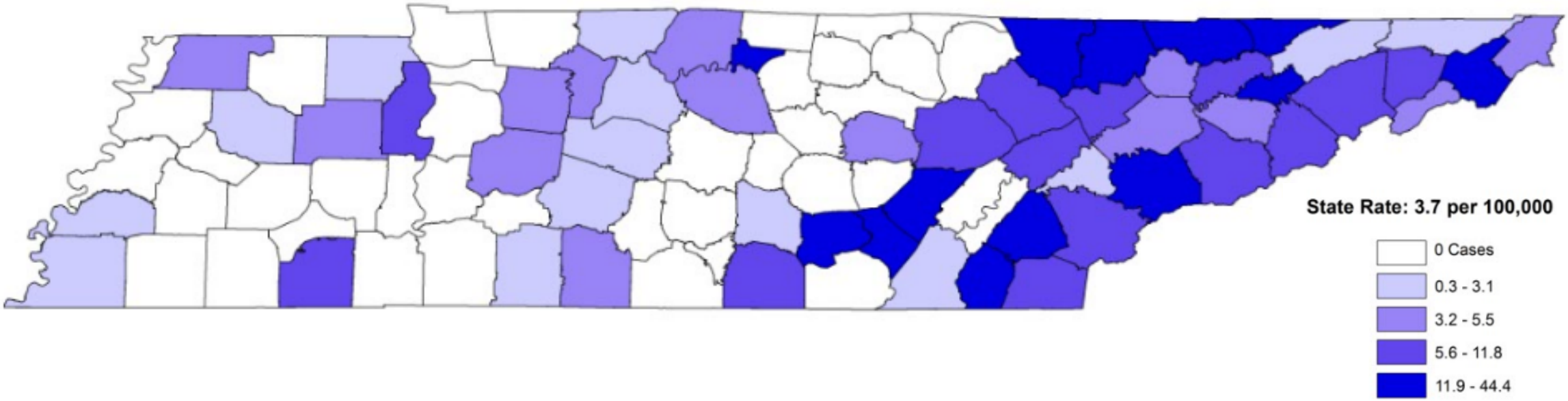
		2011	2012	2013	2014	2015	2016
US	case rate	0.4	0.6	0.7	0.7	0.8	1.0
	cases	1,229	1,778	2,138	2,194	2,436	2,967
TN	case rate	1.3	2.0	1.5	1.9	2.6	2.3
	cases	85	129	96	120	165	146
	rank	**4th**	**4th**	**6th**	**5th**	**4th**	**5th**



http://www.cdc.gov/hepatitis/statistics/2015surveillance/pdfs/2015hepsurveillancerpt.pdf

* per 100,000 population

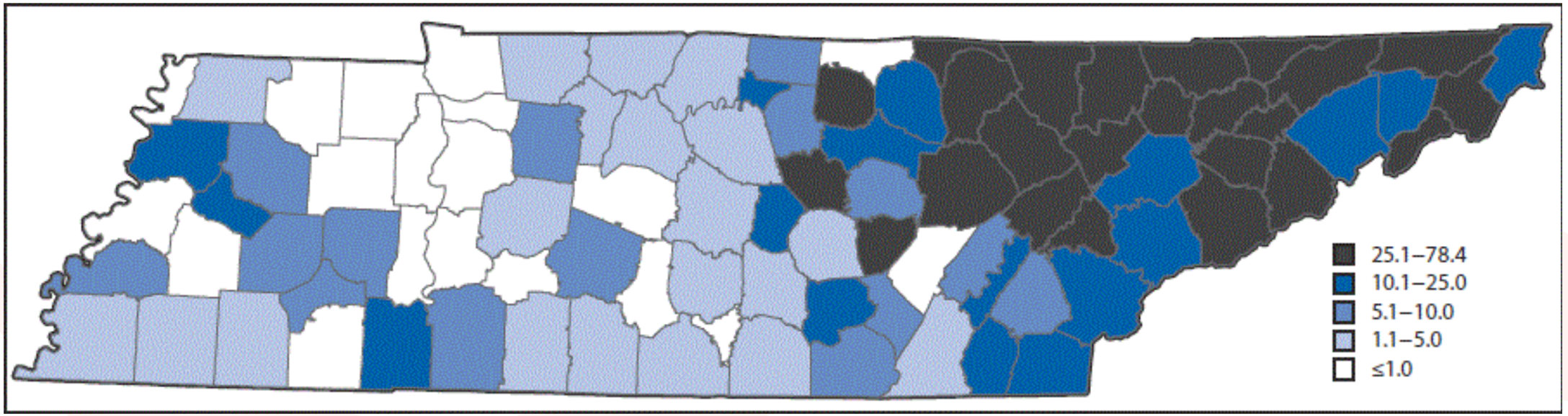
Distribution of Acute HCV Case Rates in TN (2016)



Tennessee NBS, accessed February 10, 2017
Tennessee eHARS, accessed June 30, 2017
Population Source, American Community Survey 2011-2015 County Averages

Pregnant Women and HCV Cont.

Rate of HCV Among Pregnant Women Per 1000 Live Births in US and TN



Patrick SW et al. *MMWR* 2017.

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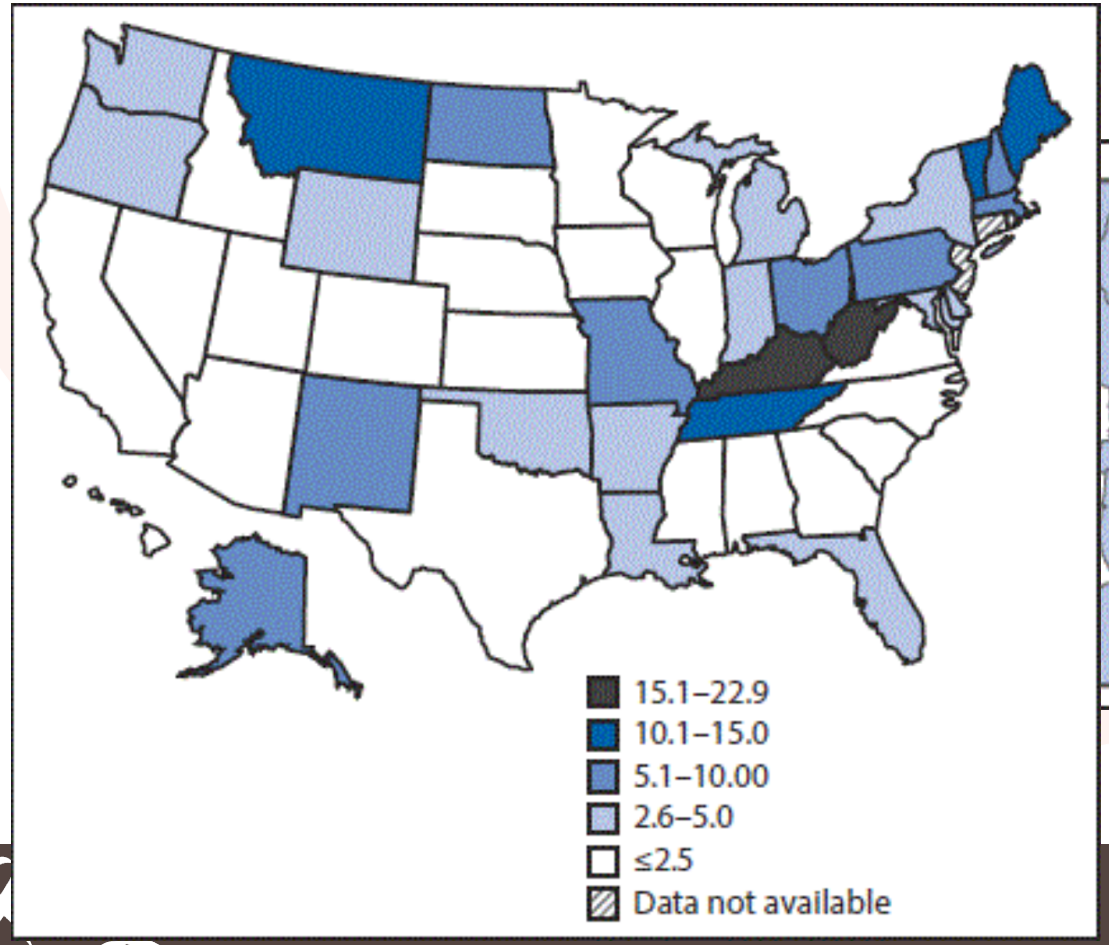

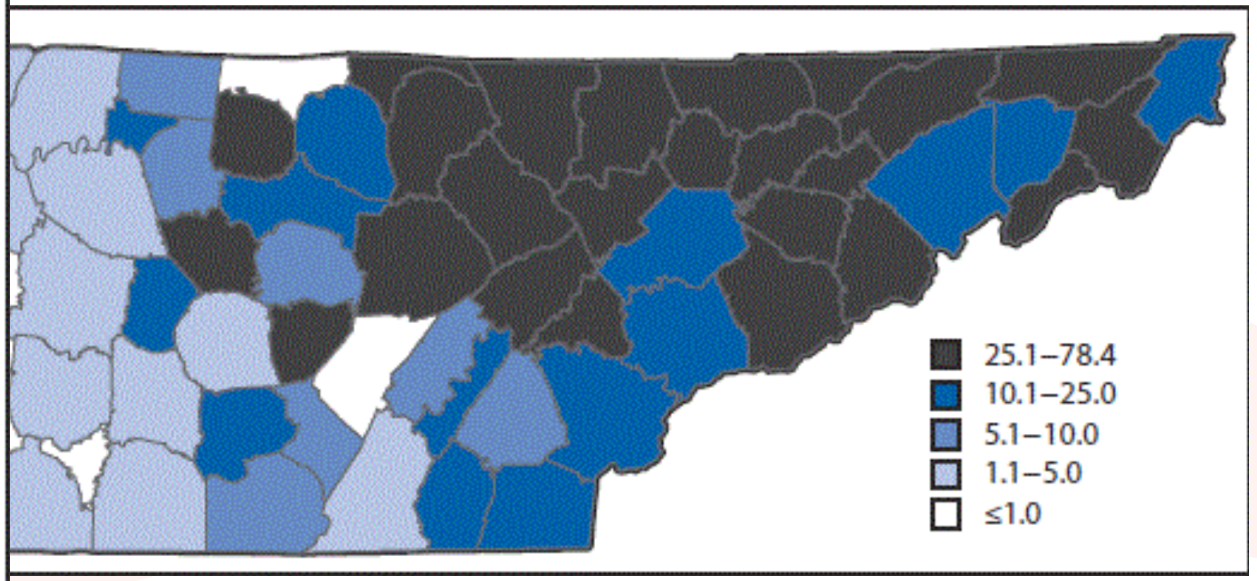

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HCV Therapies: The Past, Present, and Future

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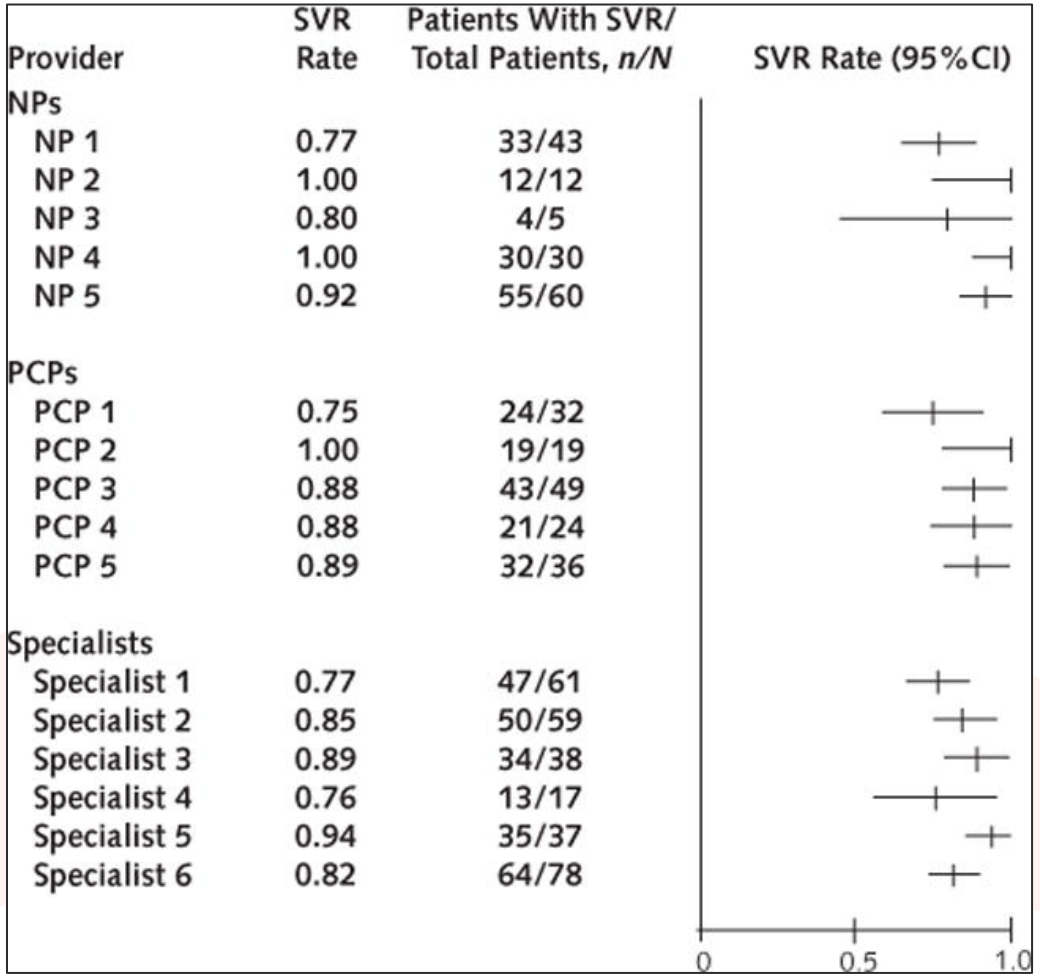
						Glecaprevir	
						Pibrentasvir	

Treatment Capacity

- Providers with HCV training can deliver excellent cure rates in community practice
  - Nonrandomized open-label clinical trial
  - Included NPs, PCPs, and Specialists
  - 600 patients
  - SVR 89.3% vs. 86.9% vs. 83.8% (with specialists LOWEST)
- Uptake among non-specialist providers remains low to date



Kattakhuzy S et al. *Ann Intern Med* 2017.

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Manifestations of HCV

- Acute HCV
  - Fever
  - Fatigue and anorexia
  - Nausea and vomiting
  - Abdominal pain
  - Jaundice, dark urine, and clay-colored stools
  - Arthralgias
- Chronic HCV
  - Often asymptomatic
  - Associated with fatigue, insomnia, depression, and mental status changes
  - Associated with extrahepatic manifestations including vasculitis and renal disease
  - Long-term outcomes include cirrhosis, liver failure, and hepatocellular carcinoma

Immune-related extrahepatic manifestations

- Mixed cryoglobulinemia
- Cryoglobulinemic vasculitis
- B-cell NHL
- Sicca syndrome
- Arthralgia/myalgia
- Autoantibody production (i.e. cryoglobulins, rheumatoid factor, and antinuclear, anticardiolipin, antithyroid and anti-smooth muscle antibodies)
- Polyarteritis nodosa
- Monoclonal gammopathies
- Immune thrombocytopenia

Inflammatory-related extrahepatic manifestations

- Type 2 diabetes mellitus type 2
- Insulin resistance
- Glomerulonephritis
- Renal insufficiency
- Fatigue
- Cognitive impairment
- Depression
- Impaired quality of life
- Polyarthritis/fibromyalgia
- Cardiovascular disorders (i.e. stroke, ischemic heart disease)

Cacoub P et al. *Ther Adv Infect Dis* 2016.

How Does HCV Treatment Impact Major Extrahepatic Outcomes?

- Cumulative 8-year outcomes for patients with SVR resulted in decreased risk of :
  - Acute coronary syndrome (HR 0.77)
  - Ischemic stroke (HR 0.62)
  - ESRD (HR 0.15)
- Cumulative ~5-year outcomes for cirrhotic patients with SVR resulted in decreased risk of:
  - Major adverse cardiovascular event (HR 0.35)

Hsu Y-C et al. *Gut* 2015. //
Cacoub P et al. *Am Heart Journal* 2018.

HCV, Extrahepatic Disease, and Quality of Life

- HCV SVR results in the following:
  - Remission in cryoglobulinemia
  - Treatment response in B cell lymphoma
  - Improved insulin resistance
  - Reduced incidence of diabetes
  - Improved health-related quality of life and related work productivity

Cacoub P et al. *Gut* 2018. // Younossi ZM et al. *AASLD The Liver Meeting 2017* Abstract 64.

HCV Cure and Health

- Lower liver-related and all-cause mortality
- Improved outcomes of non-hepatic conditions
- Increased quality of life and work productivity

- Treatment is recommended for **ALL** patients with chronic HCV (except those with short life expectancies due to unrelated causes)

Smith-Palmer J et al. *BMC Inf Dis* 2015. // Nahon P et al. *Gastroenterology* 2017. // www.hcvguidelines.org.

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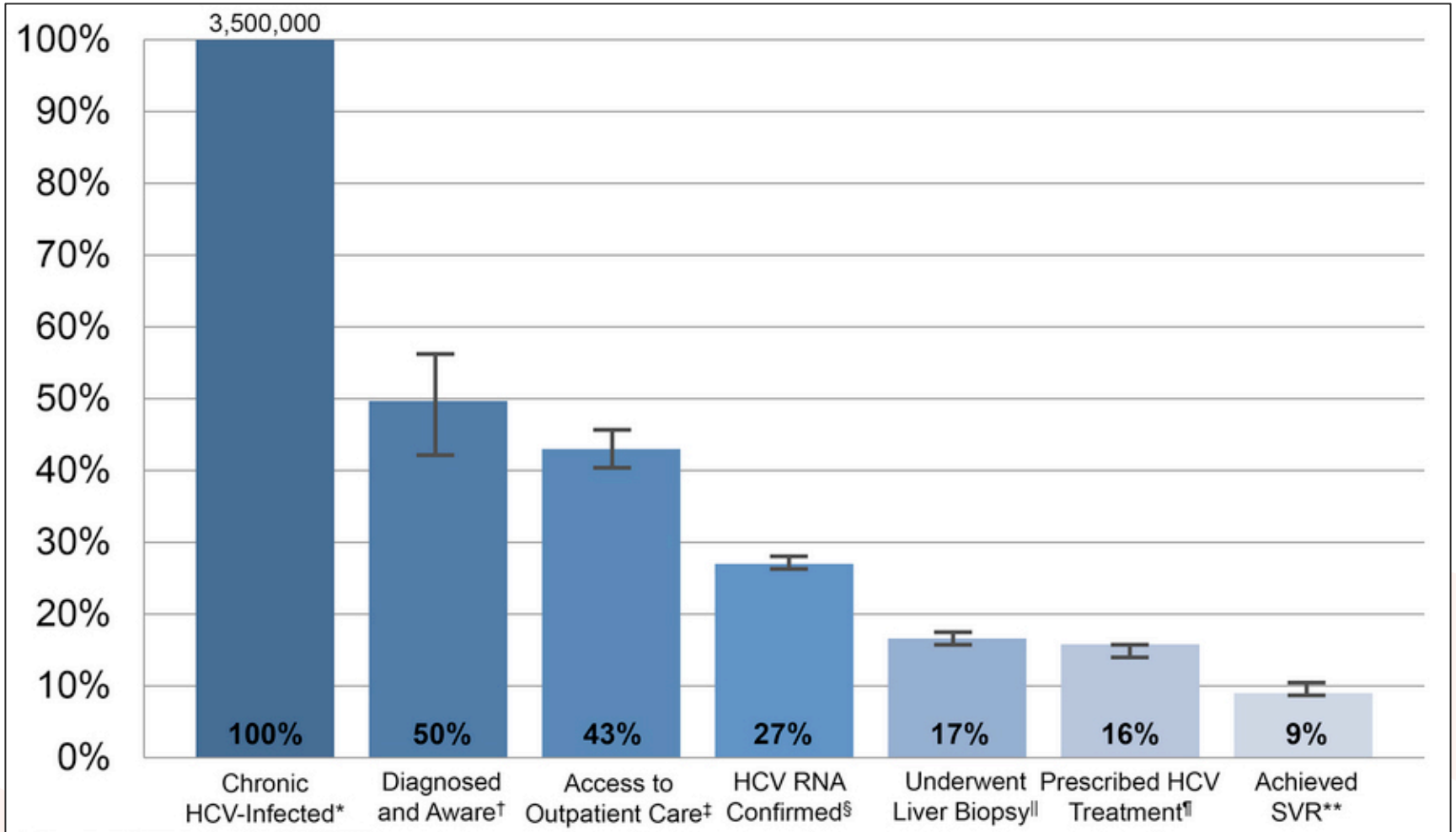
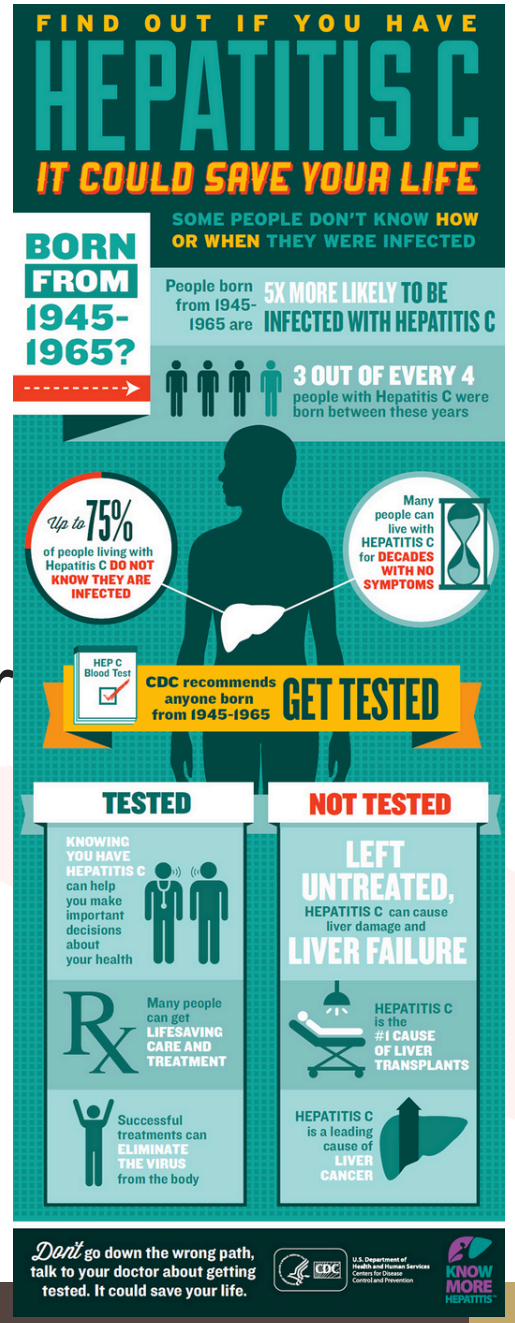


* Chronic HCV-Infected; N=3,500,000.
† Calculated as estimated number chronic HCV-infected (3,500,000) x estimated percentage diagnosed and aware of their infection (49.8%); n=1,743,000.
‡ Calculated as estimated number diagnosed and aware (1,743,000) x estimated percentage with access to outpatient care (86.9%); n=1,514,667.
§ Calculated as estimated number with access to outpatient care (1,514,667) x estimated percentage HCV RNA confirmed (62.9%); n=952,726.
|| Calculated as estimated number with access to outpatient care (1,514,667) x estimated percentage who underwent liver biopsy (38.4%); n=581,632.
¶ Calculated as estimated number with access to outpatient care (1,514,667) x estimated percentage prescribed HCV treatment (36.7%); n=555,883.
** Calculated as estimated number prescribed HCV treatment (555,883) x estimated percentage who achieved SVR (58.8%); n=326,859.
Note: Only non-VA studies are included in the above HCV treatment cascade.

Yehia BR et al. *PLoS One* 2014.

Who is at Risk for HCV?

- IV drug users
- Tattoo/piercing recipients
- Blood/clotting protein recipients prior to 1992
- Mother-to-child transmission from HCV+ mother
- Hemodialysis patients
- People with HIV
- Occupational exposures
- Born between 1945-1965 (“baby boomers”)



Diagnostics Review

- HCV Antibody
  - Tests for ***exposure***
  - Near 100% sensitivity once >6 months after infection
- HCV RNA
  - Tests for ***active infection***
  - ~20% of patients spontaneously clear HCV
- HCV Genotype
  - Defines genetic subtype for prognostic information and treatment guidance

Diagnose

- Remember those at risk
- Implement screening program within your work setting
- Educate other colleagues re: risk and need for screening

Linkage to Care

- Identify treating physicians in your area
- Consider developing treatment capacity within your practice
- Contact for options/questions:
  - Cody Chastain @ cody.a.chastain@VUMC.org
  - Kimberly Gill, TN Department of Health @ kimberly.gill@tn.gov

Evaluation

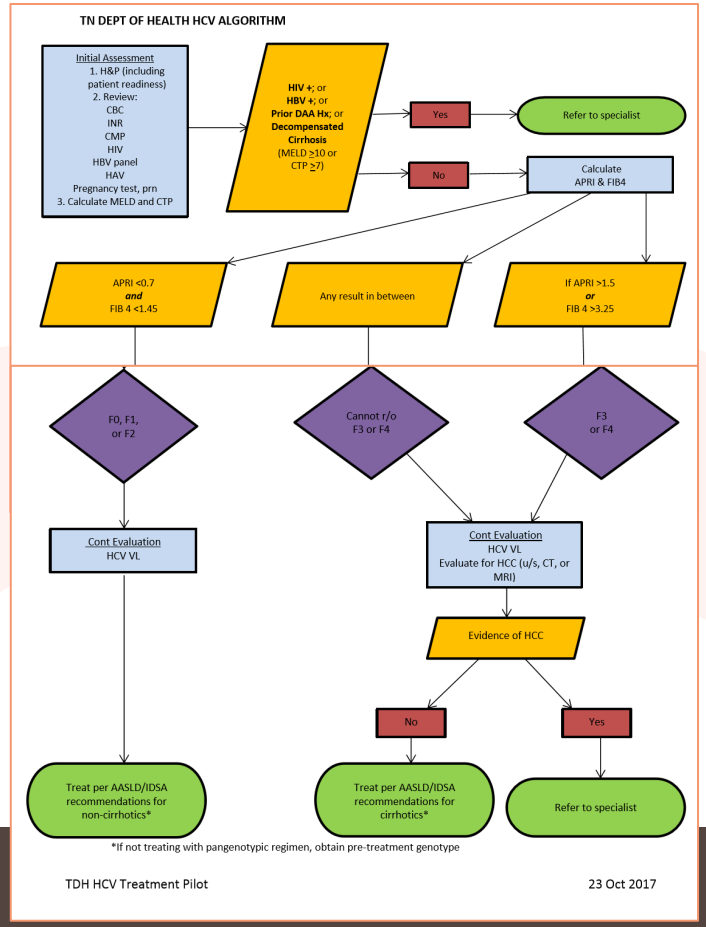
- Assist in medical evaluation
- Utilize available resources for education and clinical care
- Ensure access to provider that prescribes HCV treatment

INVITED ARTICLE VIRAL HEPATITIS
Camilla S. Graham, Section Editor

Evaluation of the Hepatitis C Virus–Infected Patient: The Initial Encounter

Norbert Bräu[1,2]
[1]Divisions of Liver Diseases and Infectious Diseases, Mount Sinai School of Medicine, New York, and [2]Bronx VA Medical Center, Bronx, New York

Clinical Infectious Diseases 2013;56(6):853–60
Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2012.
DOI: 10.1093/cid/cis957
VIRAL HEPATITIS • CID 2013:56 (15 March)



Treatment

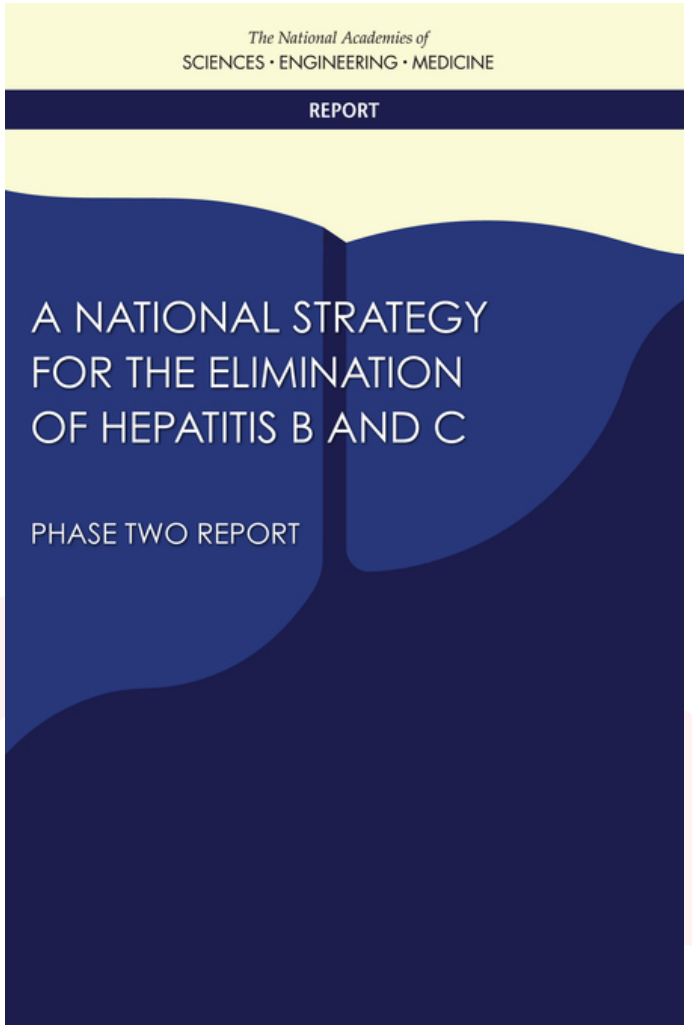
- Three medications now are used for the vast majority of infections
  - Glecaprevir/pibrentasvir can be used in ALL genotypes for 8 weeks (in patients without cirrhosis and without prior treatment) or 12 weeks
  - Sofosbuvir/velpatasvir can be used in ALL genotypes for 12 weeks
- Few adverse effects
- Minimal monitoring requirements
- Prescriber restrictions decreasing nationally

“The Committee's Conclusions Regarding Targets for Hepatitis C Elimination”

- “A 90 percent reduction in incidence of hepatitis C (relative to the 2015 incidence carried forward) is possible in the United States by 2030. Meeting this goal will require treatment without restrictions on severity of disease and a consistent ability to diagnose new cases, even as prevalence decreases.”

- “The same levels of diagnosis and treatment would reduce mortality from hepatitis C in 2030 to 65 percent relative to 2015, and avert 28,800 deaths by 2030.”

- “Meeting these targets depends on diagnosing at least 110,000 cases a year until 2020, almost 89,000 a year between 2020 and 2024, and over 70,000 each year between 2025 and 2030.”



The Path to Elimination: An ID Physician's View

- Enhanced public health surveillance
- Expansion of access to prevention services
- Expansion of screening
- Removal of barriers to treatment
- National coordination of surveillance, research, and capacity

Kim A. *Clin Infect Dis* 2017.

Make A Change!

- New diagnostic testing makes it easier to assess HCV than ever before.
- New therapies have streamlined approach to HCV treatment.
- Multiple training resources available for provider education for those interested in treating HCV directly.
- Email me!
  - Cody.A.Chastain@VUMC.org

Summary

- HCV is a major cause of morbidity and mortality in our country, region, and state.
- Treatment of HCV can improve many patient outcomes.
- New treatments are well tolerated and dramatically effective.
- Screening, diagnosis, and treatment are critical to impacting the HCV epidemic.
- You can make an impact!

Thank You!

Questions?

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