AETC AIDS Education & Training Center Program Southeast

Hepatitis C:
Looking to the Future

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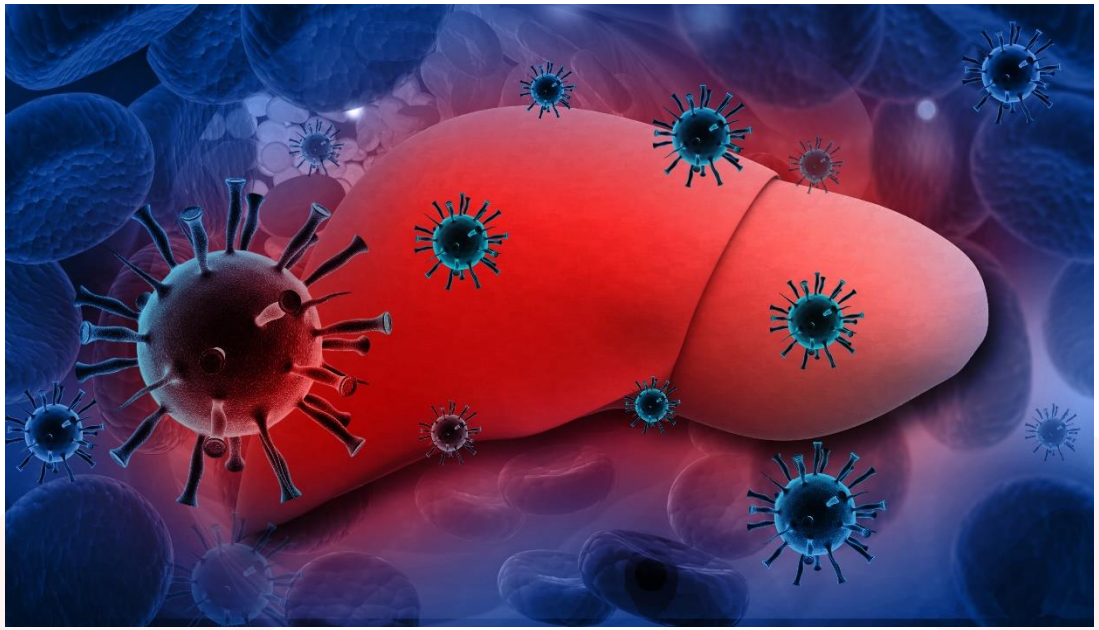
Disclosures

- Research supported by 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:

- Discuss the needs and future options related to hepatitis C virus (HCV) diagnostic testing
- Discuss the past, current, and future landscape for HCV treatment
- Identify challenges and opportunities for HCV control and elimination



Outline

- Diagnostic Testing
- Treatment Landscape
- Elimination

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- **Diagnostic Testing**
- Treatment Landscape
- Elimination

Open Ended

- What are the greatest barriers to effective screening?

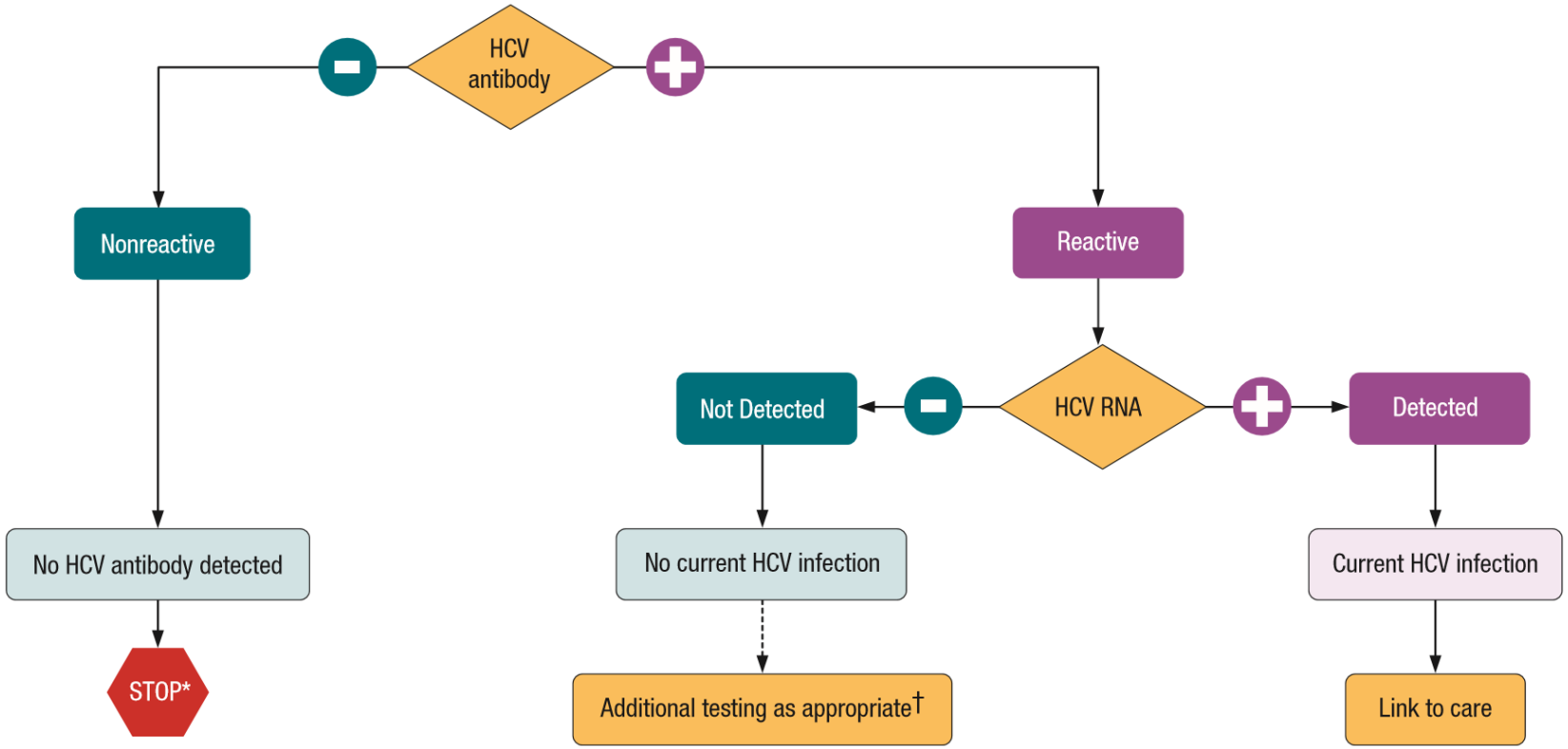
Multiple Choice

- What would help improve diagnostic testing most?

A. Universal screening recommendation
B. Lower cost / better access
C. Point of care confirmatory testing

Recommended Testing Sequence for Identifying Current Hepatitis C Virus (HCV) Infection

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention



* For 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.

† To 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.

Source: CDC. Testing for HCV infection: An update of guidance for clinicians and laboratorians. MMWR 2013;62(18).

Reflex Testing

- Samples with positive antibody are automatically “reflexed” to confirmatory nucleic acid testing
- Performed by both institutional and commercial laboratories
- May require some changes in lab collection and/or automation procedures
- Dramatically improves appropriate confirmation testing

HCV Point of Care Testing

- ELISA-based antibody testing FDA approved since 2010
  - Limited by lack of active infection confirmation
- Future options may include:
  - Venepuncture for RNA
  - Finger-stick capillary whole-blood for RNA
  - Capillary dried blood spot (DBS) testing for RNA
  - HCV core antigen testing

Grebely J et al. *Lancet Gastroenterol Hepatol* 2017. // Saludes V et al. *J Viral Hepat* 2017.

Are Screening Guidelines Adequate?

- Risk factor based screening has inherent weaknesses
  - Patient memory
  - Patient recognition of risk
  - Patient disclosure
  - Provider dependent
  - Provider delivery

- Birth cohort screening may be inadequate in certain locales
  - Baltimore ER
    - 25% of HCV cases were NOT baby boomer, HIV positive, or injection drug use
  - Cincinnati ER
    - 25% of chronic HCV cases were NOT baby boomers

Hsieh Y-H et al. *Clin Infect Dis* 2016. // Lyons MS et al. *Clin Infect Dis* 2016.

Is Universal Screening the Answer?

- Dueling organizational positions in Canada
  - Canadian Liver Foundation recommended expansion of birth cohort screening from 1945-1965 to 1945-1975
  - Canadian Task Force on Preventive Health Care recommended against birth cohort screening
- Debate whether screening is necessary
  - Depends on perspective of population impact)
- Debate whether screening makes a difference
  - Depends on interpretation of natural history data and treatment

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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	Future
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)

Open Ended

- What remains a scientific “need” or “niche” for new HCV therapies?

Multiple Choice

- What would be the greatest improvement to current HCV therapies?

A. Improved efficacy
B. Fewer adverse effects
C. Smaller pill burden
D. Shorter regimen
E. Alternate routes (e.g. IM)

Future Pipeline Outlook

- Fewer drugs in development
- Recent drugs removed from pipeline
  - JNJ-4178 (AL-335/odalasvir/simeprevir) discontinued 9/11/17
  - MK-3682B (grazoprevir/ruzasvir/uprifosbuvir) and MK-3682C (ruzasvir/uprifosbuvir) discontinued 9/29/17
- Uncertain development goals/targets

Shorter Regimens?

- Additional study of shorter regimens ongoing
- How much shorter would make a difference?
  - 6 weeks?
  - 4 weeks?
  - 2 weeks?
- If “cost per cure” remained the same, would this change dynamics?

Outline

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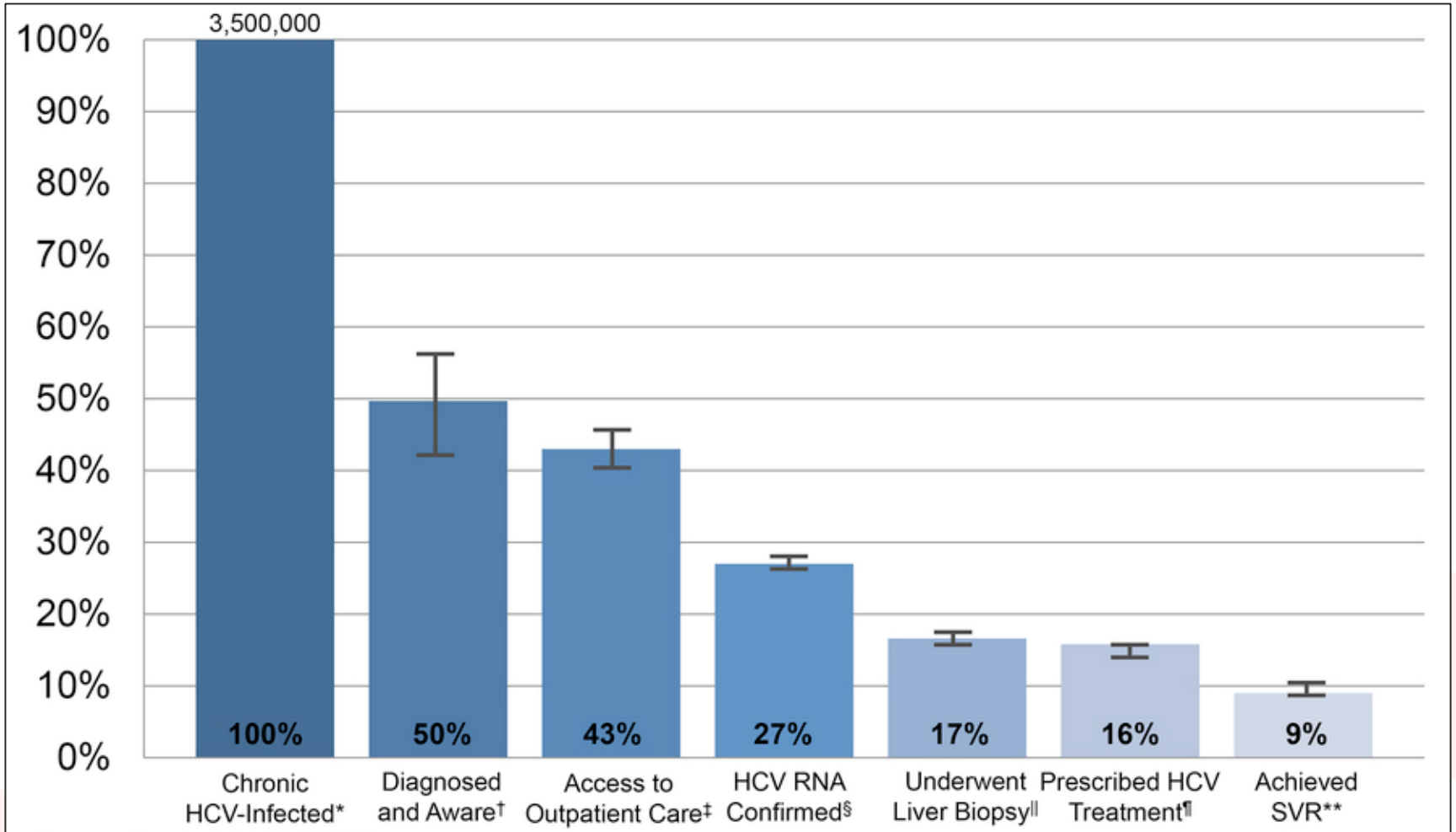


* Chronic HCV-Infected; N=3,500,000.
† Calculated as estimated number chronic HCV-infected (3,500,000) x estimated percentage diagnosed and aware of their infection (49.8%); n=1,743,000.
‡ Calculated as estimated number diagnosed and aware (1,743,000) x estimated percentage with access to outpatient 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.

Word Cloud

- What is required for HCV elimination?

Multiple Choice

- What would help most with HCV elimination?

A. Immunization
B. Universal screening
C. Universal treatment access
D. Coupling medical services (i.e. substance use / psych)

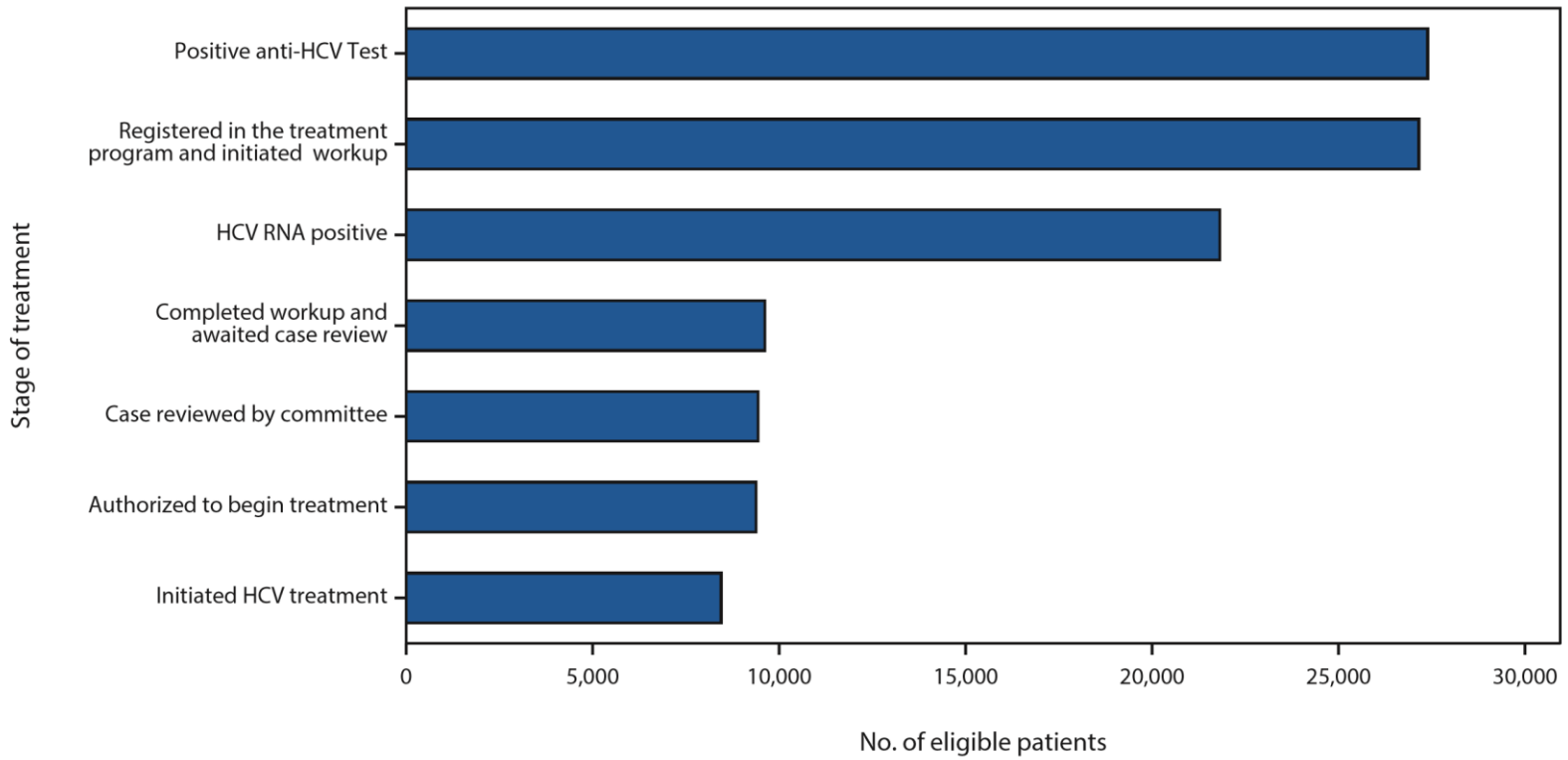
Challenges for HCV Immunization

- Genetically variable
  - At least 6 genotypes, ~50 subtypes
- Limited animal models
  - Chimpanzees and genetically modified mice
- Enrollment of at-risk individuals
  - High risk individuals in developed countries vs. typical risk in developing countries
- Immune markers
  - HCV Ab not helpful for defining protection

Georgia

- Elimination program formally started in 2015
- Multiple levels of commitment:
  - Treatment access
  - Political will
  - Partnership
  - Capacity building
  - National plan
  - Monitoring
  - Provider education
  - Defining burden
  - Disease awareness

FIGURE 3. Cascade of care for hepatitis C virus (HCV)-infected patients — nationwide HCV elimination program, Georgia, April 28, 2015–April 27, 2016*,†



Abbreviation: MOLHSA = Ministry of Labor, Health, and Social Affairs.
* Patients with positive anti-HCV test began treatment at one of 17 provider sites; data from MOLHSA's financial reimbursement system.
† Of the patients who initiated HCV treatment, 162 (1.9%) with different indications have restarted HCV treatment.

Matruka K et al. *MMWR* 2015. // Gvinjilia L et al. *MMWR* 2016.

Australia

- Government commitment of $1 billion Australian dollars (~$720 million US dollars) for initial 5-year program
- Risk-sharing model with pharmaceutical partners
- 33,000 patients with HCV treated in first year
  - Approximately 16% of Australian HCV population
- Integrated treatment programs with other medical condtions as well as enhanced test-and-treat models

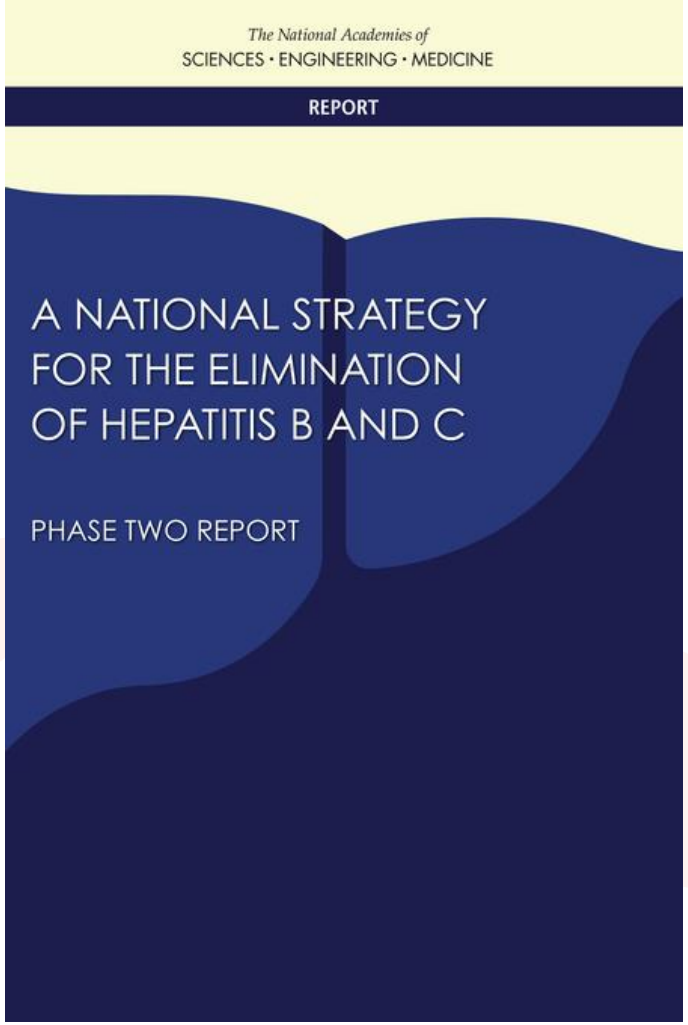
Pedrana AE et al. *Expert Review of Pharmacology* 2017.

In the US? … “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.”



Eliminating HCV as a Public Health Threat: 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.

Thank You!

Questions?

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