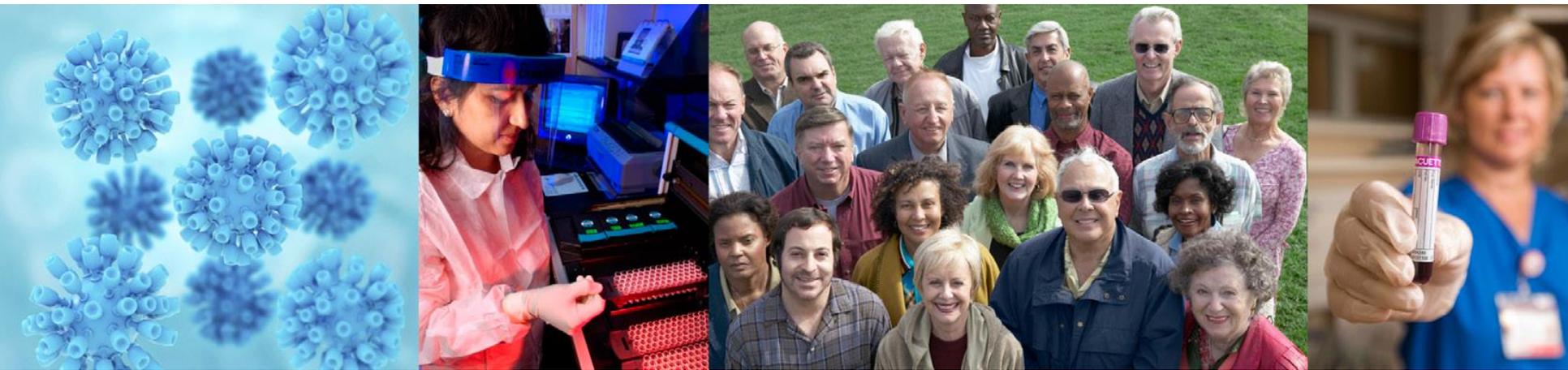


CDC PUBLIC HEALTH GRAND ROUNDS

The 25th Anniversary of the Discovery of the Hepatitis C Virus Looking Back to Look Forward



June 17, 2014



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

The Epidemiology of Hepatitis C

How Did We Get Here?



John W. Ward, MD

Director, Division of Viral Hepatitis

National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention

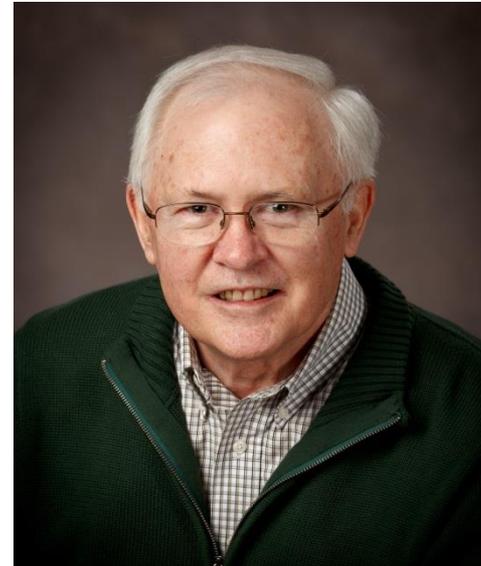


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Control and Prevention

Key Contributors to the Discovery of HCV



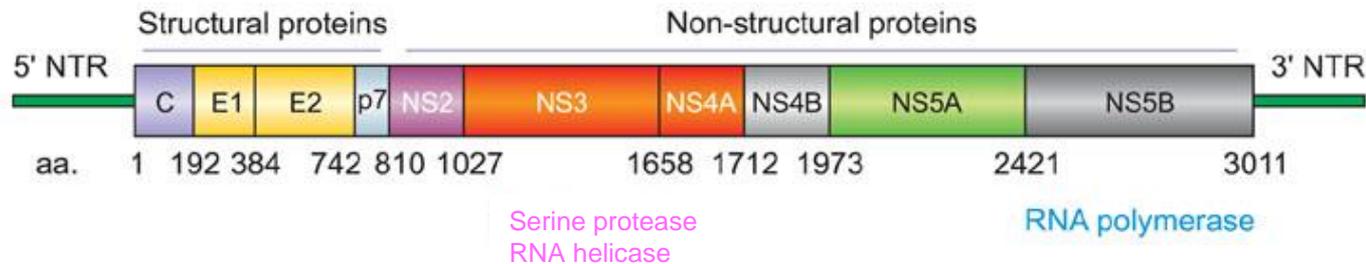
Harvey Alter



Daniel Bradley

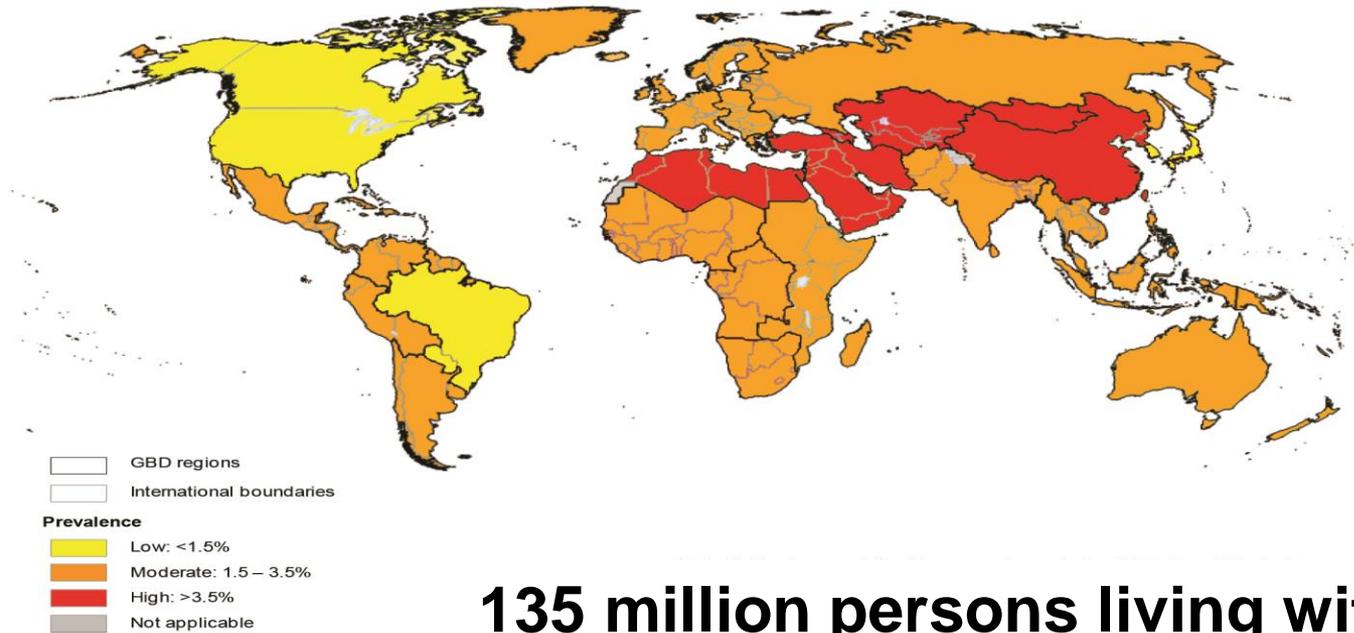
Discovery of Hepatitis C Virus (HCV)

- ❑ Discovered in 1989, RNA virus, family *Flaviviridae*
- ❑ 9,600 nucleotide genome-single polyprotein
 - Structural proteins
 - Non-structural proteins - viral replication and targets of therapy
 - High genetic diversity leads to intra-host variants “quasispecies”
 - 7 major genotypes that predict treatment response
 - Genotype 1 accounts for ~ 70% of infections in US
 - No vaccine candidates for licensure



Lindenbach BD, Fields Virology 2001. Simmonds P, *Hepatology* 1995. Irshad M, *Hepatogastroenterology* 2010. Manos MM, *J Med Virol* 2012.

Global Burden of HCV Infection, 2005



135 million persons living with HCV
500,000 deaths per year

HCV: Hepatitis C virus.

Estimated from: Hanafiah K, *Hepatology* 2012. Lozano R, *Lancet* 2012.

Prevalence of Current HCV Infection Among Persons in the United States

❑ Prevalence in United States ~3 million

❑ NHANES prevalence estimate

- 2.7 million individuals (2.2-3.2 million)
- 1.0% (0.8%-1.2%)
- Civilian, non-institutionalized populations

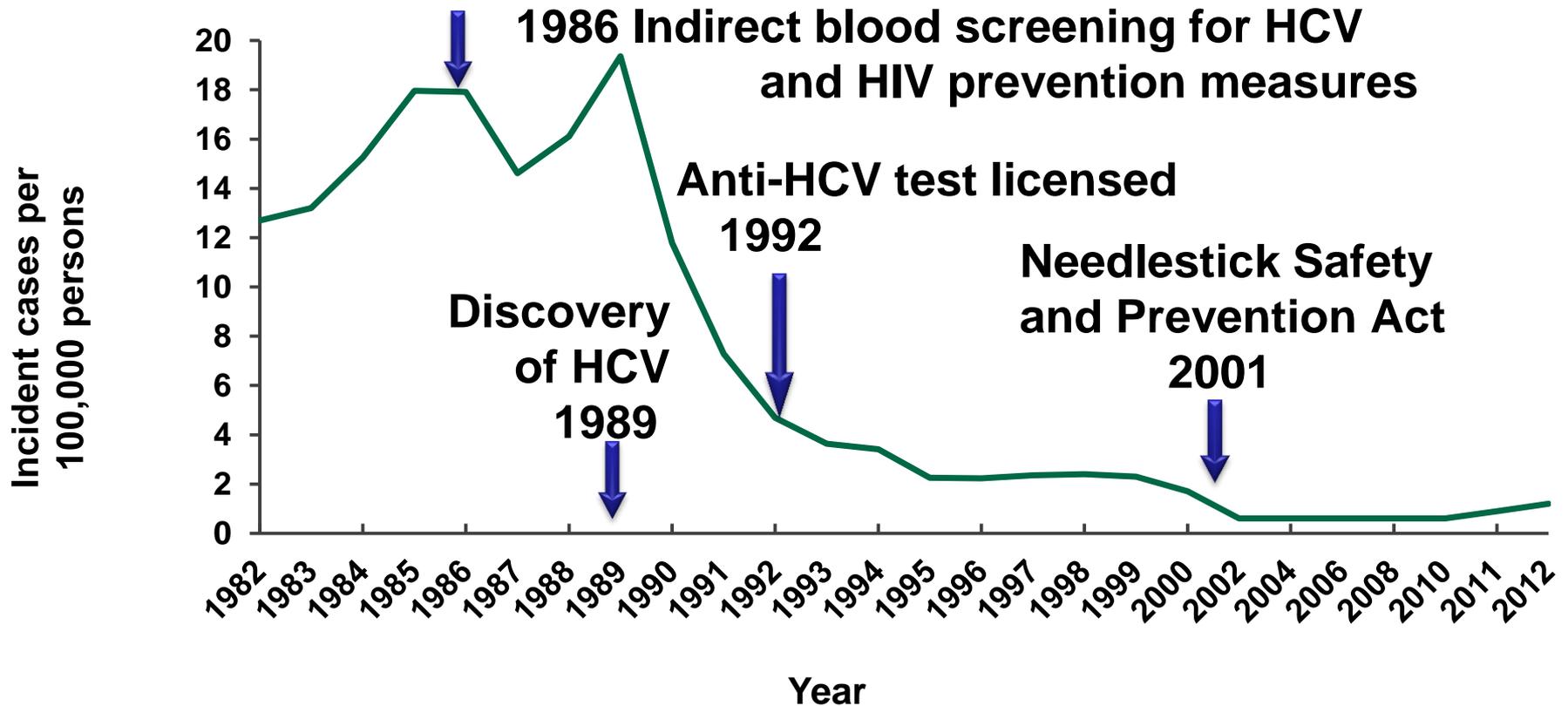
❑ Non-NHANES prevalence estimate

- 360,000-840,000
- 22%-52% of those incarcerated
- Homeless or incarcerated persons

NHANES: National Health and Nutrition Examination Survey.

Denniston M, *Ann Int Med* 2014. Chak E, *Liver Int* 2011.

Impact of Prevention Measures on HCV in United States



22,000 new cases reported in 2012

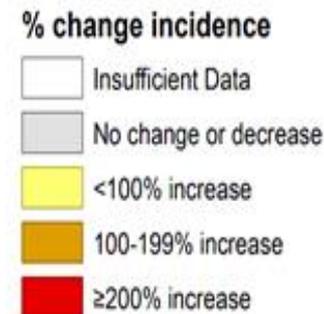
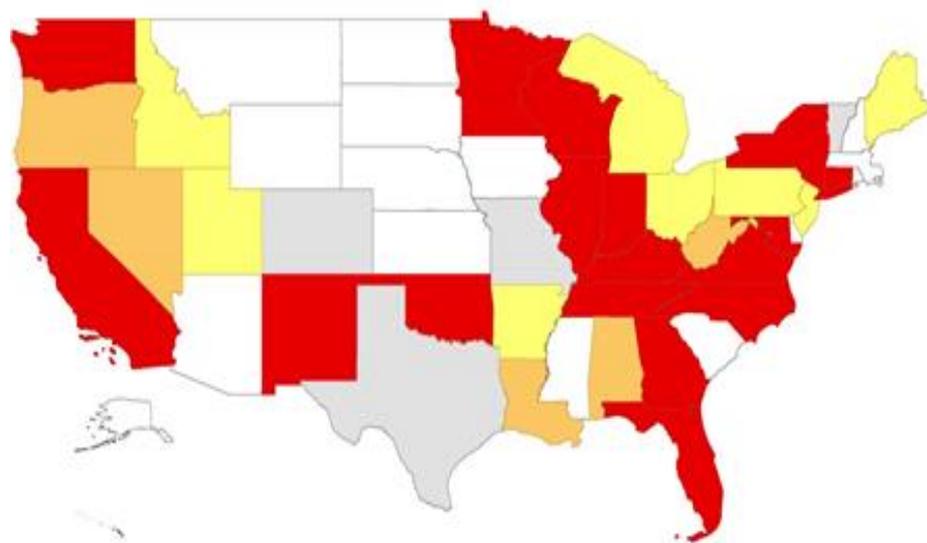
Recent Increases in HCV Infection

Between 2007 and 2012

- 50% increase in case reporting
- 200% increase in 17 states

Risk factors

- ~ 70% persons who inject drugs
- Previous oral prescription narcotic use
- Equally male to female
- Young, ages 18 to 29 years
- Rural and suburban
- White



PWID: Persons who inject drugs.

CDC unpublished data.

HCV Transmission Among Persons Who Inject Drugs (PWID)

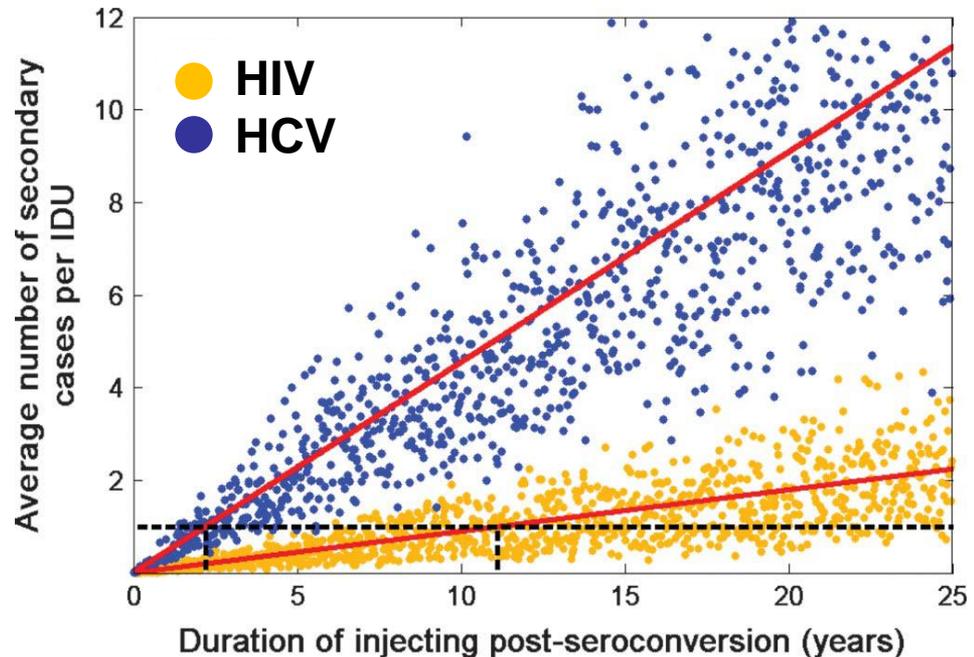
Transmission risks

- Injection duration
- Injection frequency
- Equipment sharing, not just sharing needles

HCV prevalence

- 27 to 51%

Incidence declined in response to harm reduction for HIV (e.g., syringe access programs)



Other Modes of HCV Transmission

- ❑ **Accidental needle stick in healthcare setting**
 - HCV risk is 1.3%, HIV risk is 0.3%
- ❑ **18 healthcare-associated outbreaks from 2008 to 2013**
 - 223 cases involving over 90,550 at-risk persons notified
- ❑ **Non-injecting drug use (e.g., intranasal cocaine use)**
- ❑ **Perinatal-infants born to HCV infected mothers**
 - ~4% risk if mother infected with HCV
 - ~25% risk if mother co-infected with HCV and HIV
- ❑ **Sexual transmission is rare**
 - HIV infected MSM at highest risk
- ❑ **Miscellaneous reported**
 - Unregulated tattooing

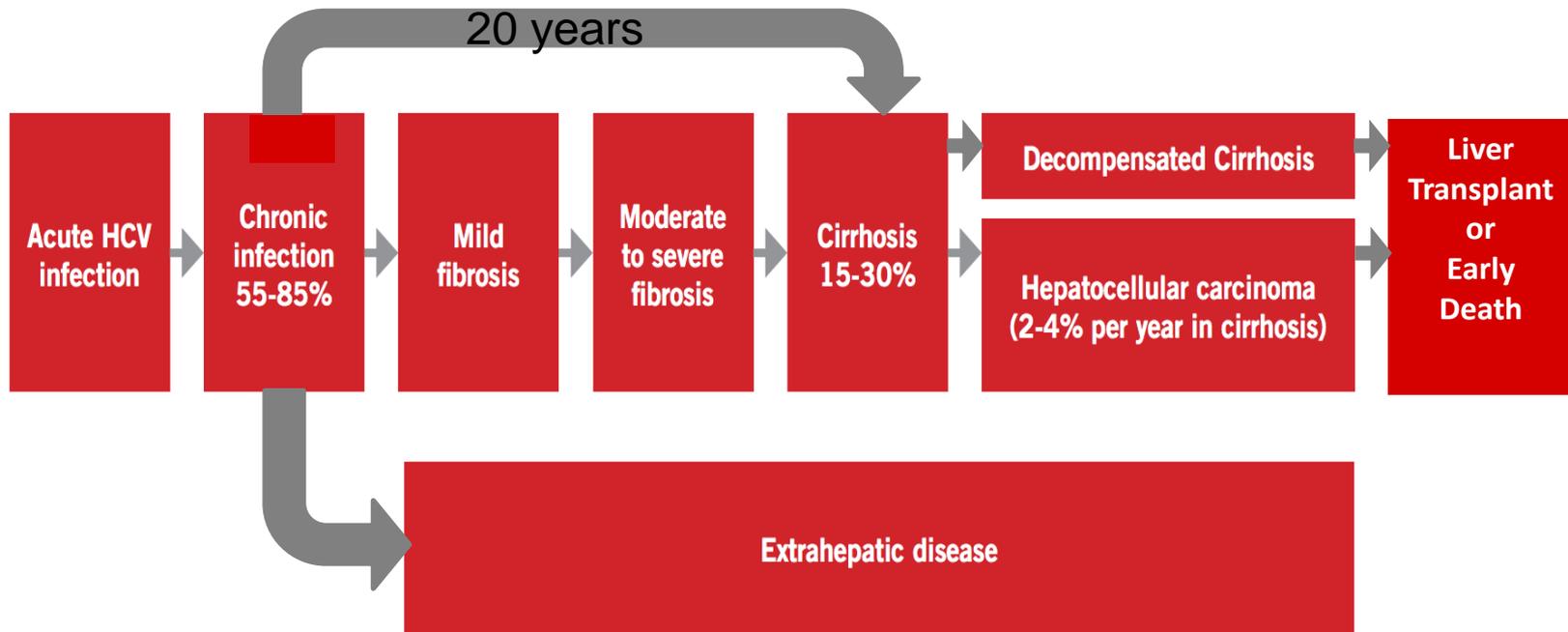
MSM: Men who have sex with men.

Scheinmann, *Drug and Alcohol Dependence* 2006. Weinbaum, *MMWR* 2003. Gough, *BMC Public Health* 2010. Mast, *J Infect Dis*, 2005. Marinovich B, *Sex Transm Infect* 2003. Yaphe S, *Sex Transm Inf* 2012. Bottieau, *Eurosurveillance* 2010. Ackerman Z, *J Viral Hepat* 2000. Tohme RA, *CID* 2012. *MMWR* 2001. CDC/hepatitis.gov

Natural History of HCV Infection

In 20 years, 15-30% progress to cirrhosis

Progression accelerated by HIV, HBV, alcohol use, and fatty liver



HIV: Human immunodeficiency virus. HBV: Hepatitis B virus.

Hepatocellular carcinoma = Liver cancer. Decompensated Cirrhosis = End stage liver disease.

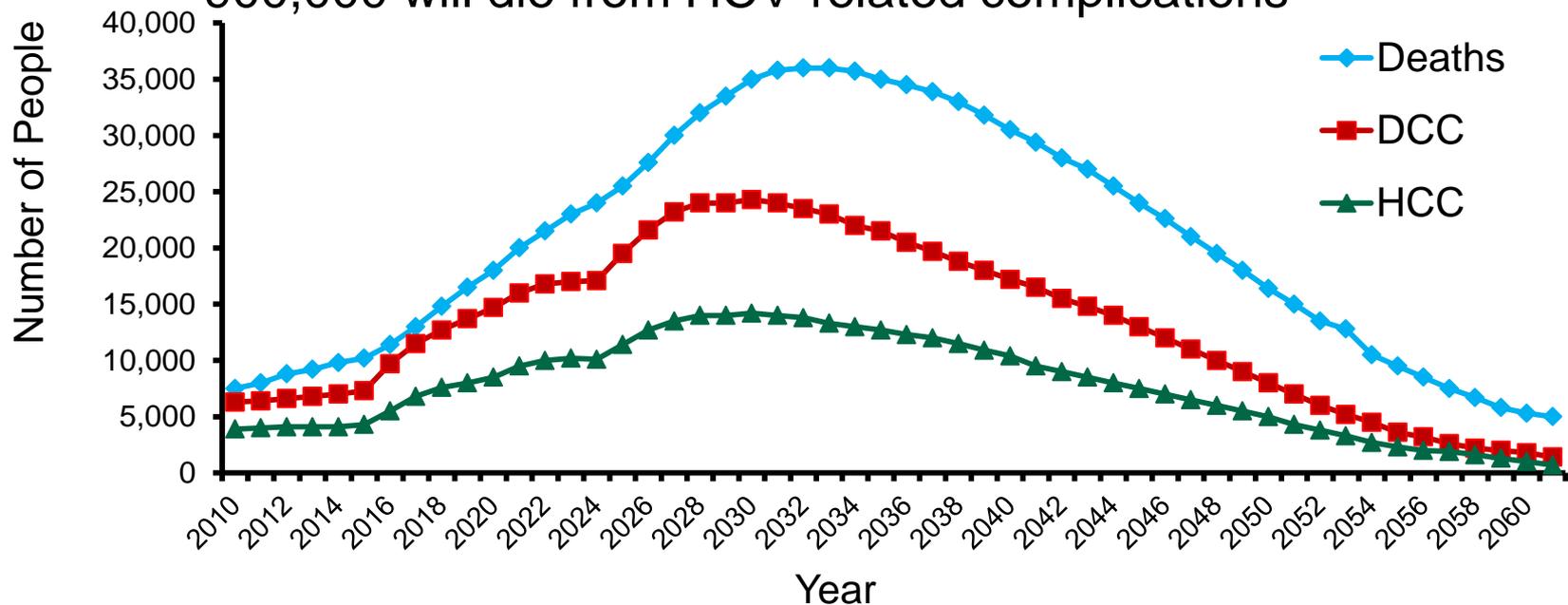
Ly KN, *Clin Infect Dis.* 2014. Mahajan R, *CID* 2014 .

Mortality from HCV is Increasing

- ❑ **From 1999 to 2010, HCV deaths increased by 50%**
 - In 2010, 16,600 deaths
 - Mean age at death was 59 years
- ❑ **Two-fold increased mortality risk**
 - Black non-Hispanic
 - American Indian/Alaskan Natives
- ❑ **Mortality is under estimated**
 - Only 33% of liver-related deaths among HCV infected persons are reported on Vital Records
- ❑ **At least 45-60% are not aware of their HCV infection**

The Silent Growing Burden of Hepatitis C in the United States

- **Of 2.7 million HCV-infected people from NHANES**
 - 1.47 million will develop decompensated cirrhosis (DCC)
 - 350,000 will develop hepatocellular carcinoma (HCC)
 - 900,000 will die from HCV-related complications

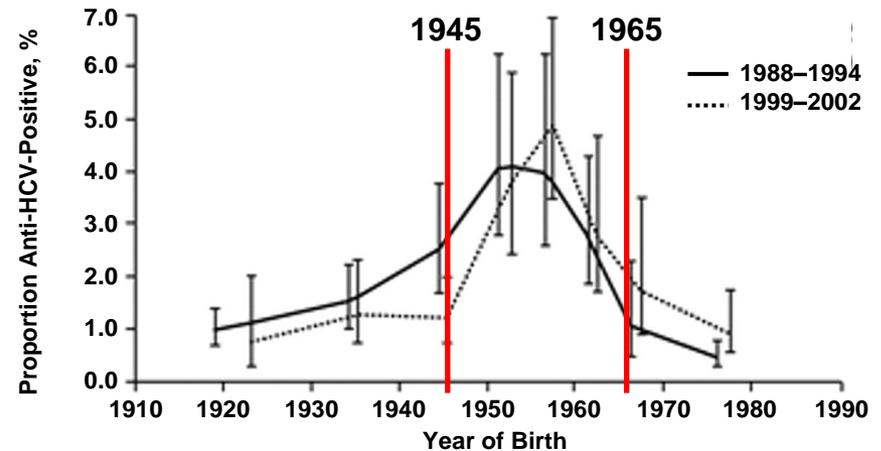
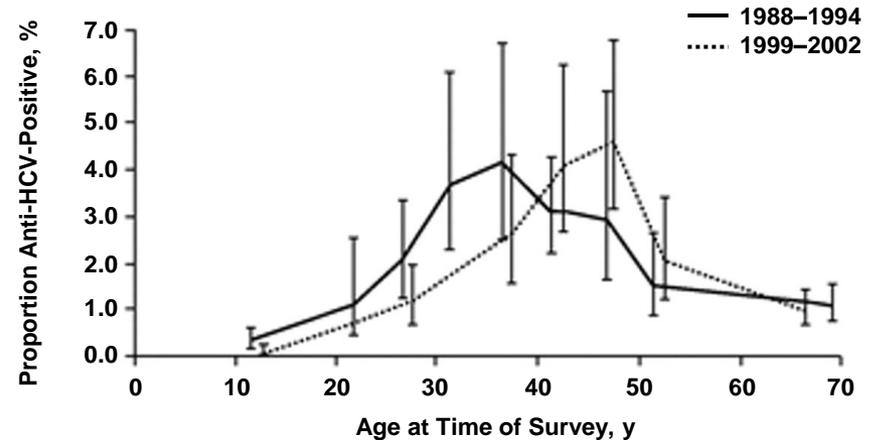


NHANES: Nutritional Health DCC: Liver failure. HCC: Liver cancer.

The Birth Cohort: People Born during 1945 to 1965

□ Historical high incidence

- Six-fold higher prevalence than other US adults 3.39% vs 0.55%
- Of all HCV infected US adults, 81% were born in this cohort
- Of all HCV-related deaths in US, 73% were born in this cohort



One time Testing for HCV for Persons Born 1945-1965

- ❑ **Recommended by CDC in 2012 and USPSTF in 2013**

- ❑ **Screening recommendation is solely based on year of birth, not on risk factors**
 - Clinicians may be reluctant to ask about risks
 - Patients may be reluctant to disclose or may not recall risks

- ❑ **Persons found to be HCV infected need to link to care and treatment**

USPSTF: U.S. Preventive Services Task Force.

MMWR Aug 2012. Moyer VA, *Ann Int Med* 2013. Shehab TM, *J Viral Hepat* 2001. Shehab TM, *Am J Gastroenterol* 2003. Serrante JM, *Fam Med* 2008. Shehab TM, *Hepatology* 1999. Roblin, *Am J Man Care* 2011. Spradling, *Hepatology* 2012. Zapata, *Ann Hepatology* 2010. Napper, *AIDS Behav* 2010. Haley, *Preven Med* 2002. Torrone, *AIDS Pat Care* 2010. Rein D, *Ann Int Med* 2012. Eckman, *CID*, 2013. McEwan, *Hepatology* 2013. McGarry, *Hepatology* 2012. Liu S, *Plos One* 2013.

Continued Risk-based Recommendations for HCV Screening

□ Risk-based screening

- Major risk-past or present injection drug use
- Other risks
 - Received blood/organs prior to June 1992
 - Received blood products made prior to 1987
 - Ever on chronic hemodialysis
 - Infants born to HCV-infected mothers
 - Intranasal drug use
 - Unregulated tattoo
 - History of incarceration
- Medical
 - Persistently elevated ALT
 - HIV

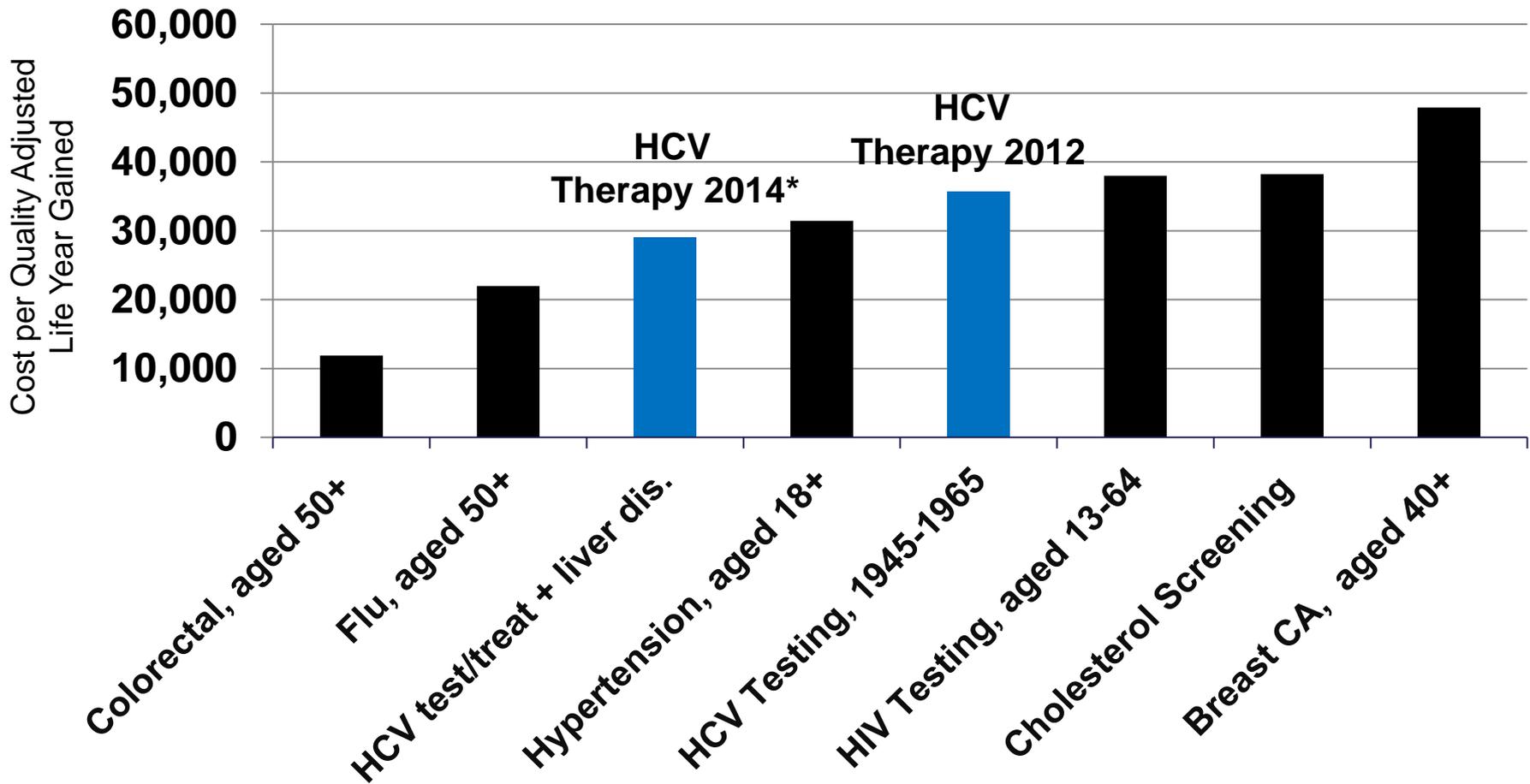
USPSTF: U. S. Preventive Services Task Force. ALT: Alanine transaminase.

MMWR Aug 2012. Moyer VA, *Ann Int Med* 2013.

Benefits of Birth Cohort Testing

- ❑ **The Birth Cohort urgently needs to be identified to allow them the opportunity to be diagnosed and treated**
- ❑ **Reduces risks of all-cause mortality by 50%**
- ❑ **Reduces risks of hepatocellular carcinoma by 70%**

HCV Testing Cost Effectiveness



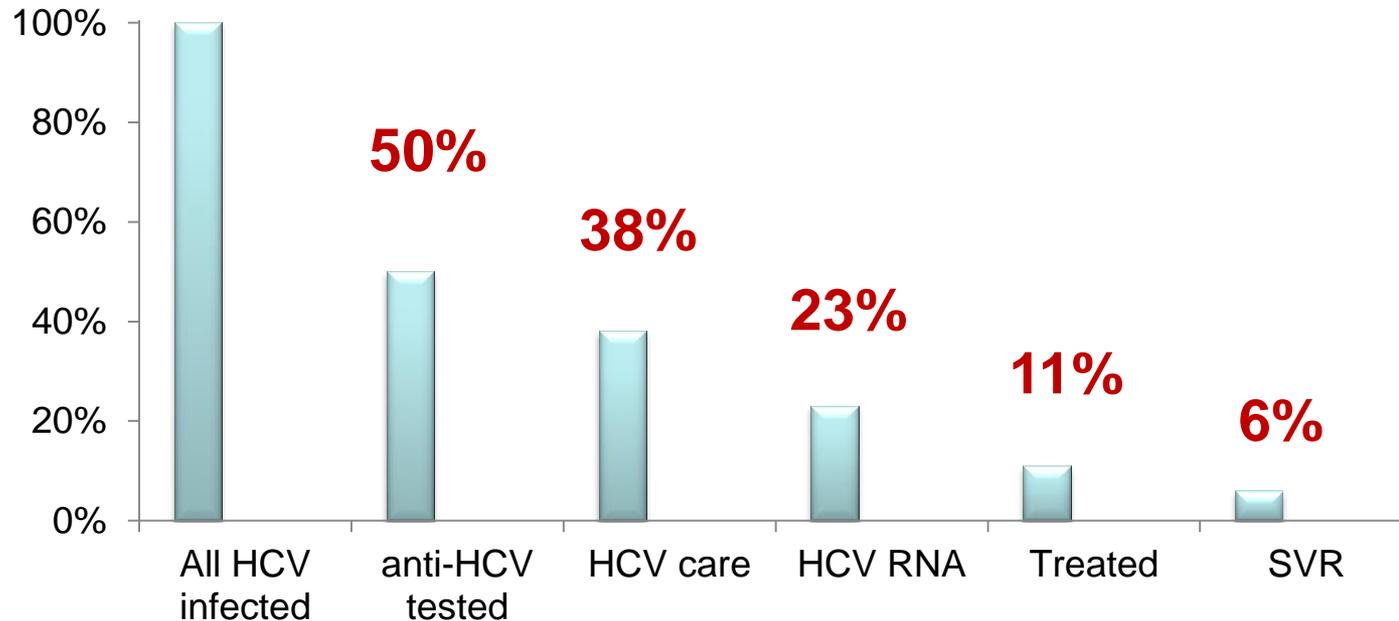
*CDC unpublished data. TVR: Telapavir.

<http://www.prevent.org/National-Commission-on-Prevention-Priorities/Rankings-of-Preventive-Services-for-the-US-Population.aspx>

Rein D, *Ann Int. Med* 2012.

Improving the Continuum of Care for HCV Management

- ❑ ~ 3 million persons living with HCV in the United States
- ❑ Current cure rates need to improve

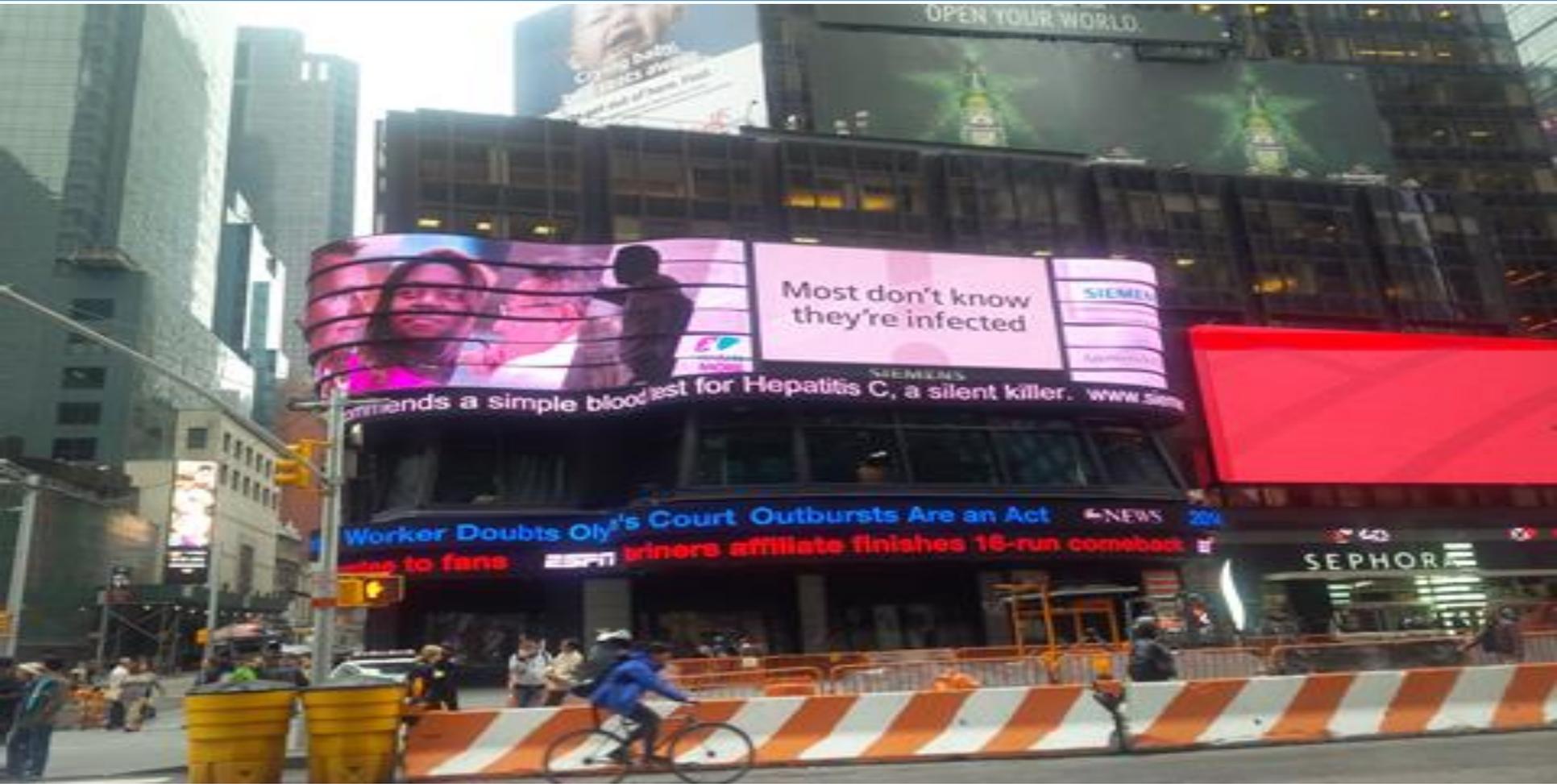


SVR: Sustained viral response. Holmberg S, *NEJM* 2013.

Where Are We Now?

- ❑ **The burden of HCV-related disease is large**
- ❑ **Reports of new HCV infections are increasing**
- ❑ **CDC and USPSTF recommend HCV testing for persons**
 - Born during 1945 to 1965
 - Who inject drugs, past or present
 - Others at risk
- ❑ **At least half of HCV-infected person are unaware of status**
- ❑ **Access to HCV testing, care, and treatment must improve for patients to benefit from advances in therapy**

Know More Hepatitis Campaign Times Square, May 2014



Hepatitis C: The Curative Era



David Thomas, MD

Stanhope Bayne Jones Professor of Medicine

Chief of Infectious Diseases

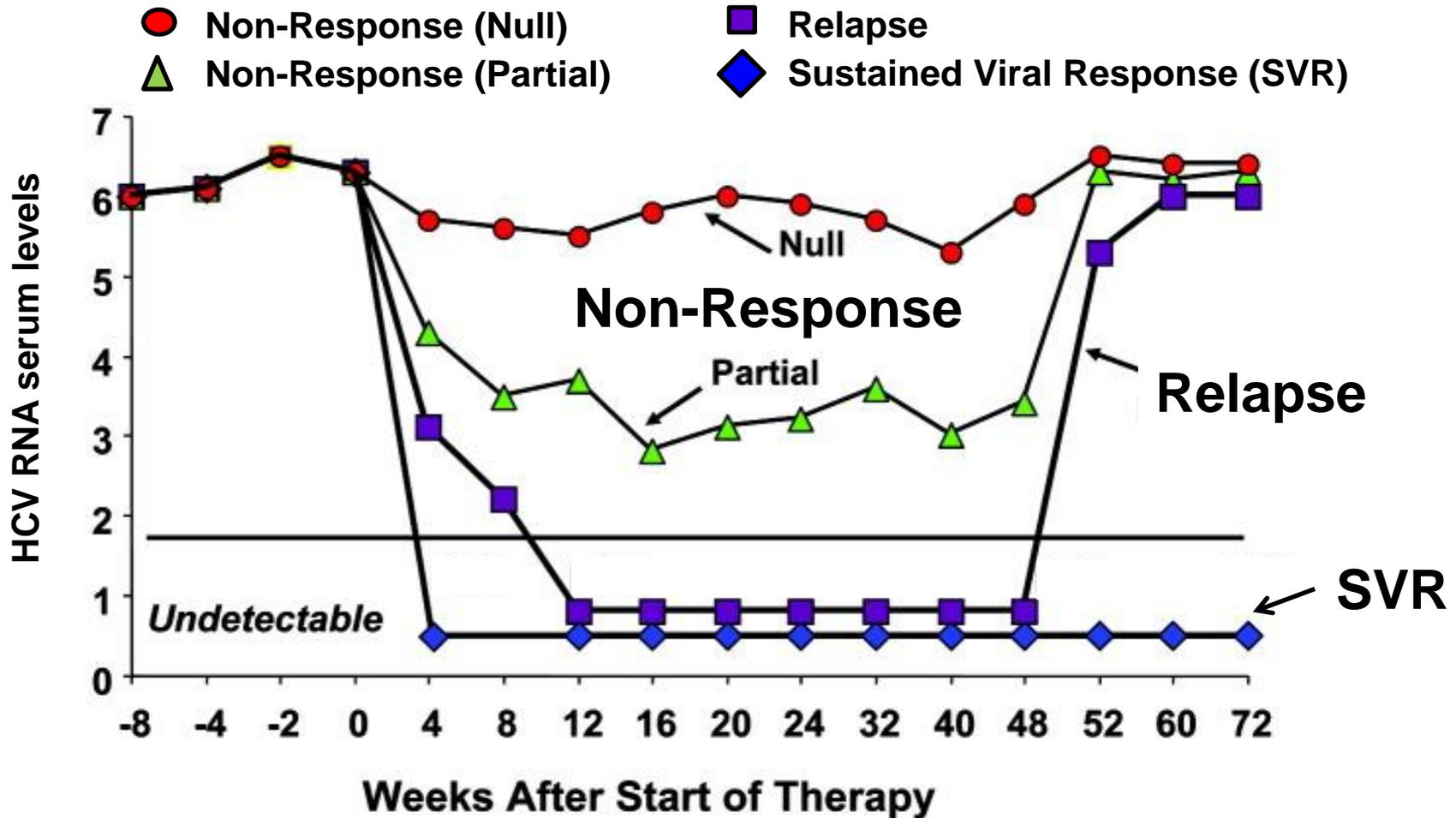
Johns Hopkins School of Medicine



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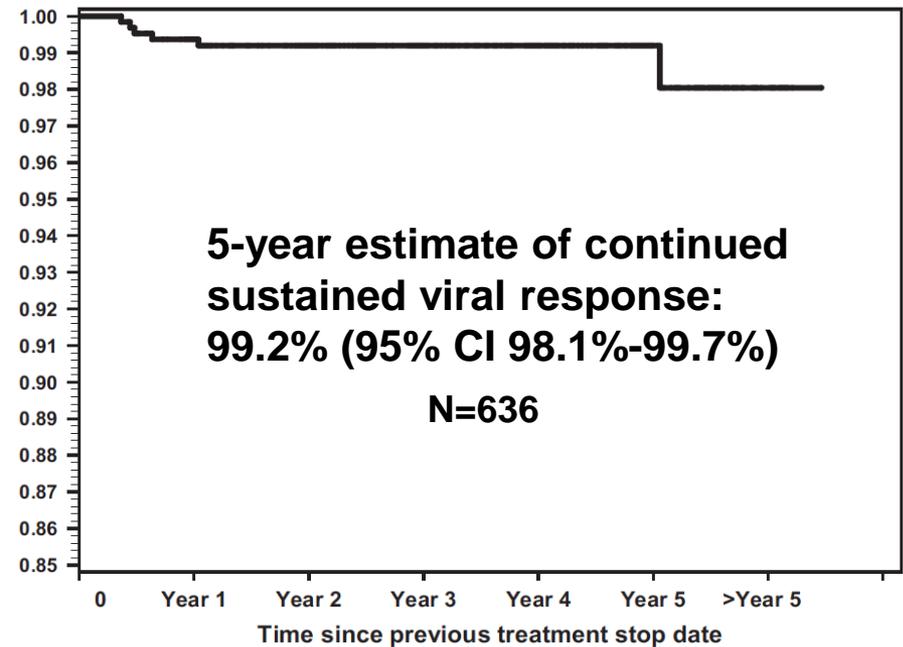
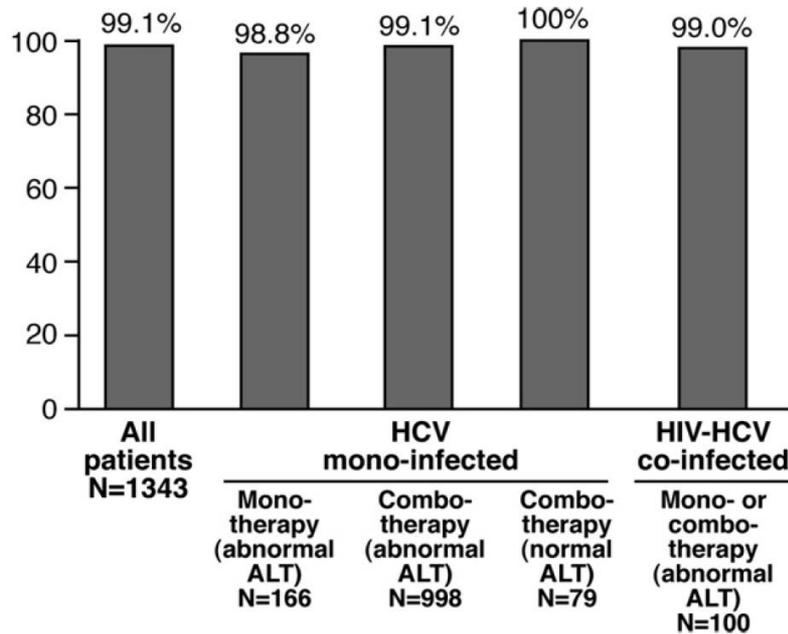
Hepatitis C Treatment Responses

Non-Response, Relapse, Sustained Viral Response



SVR is Considered Cure Reinfection is Uncommon

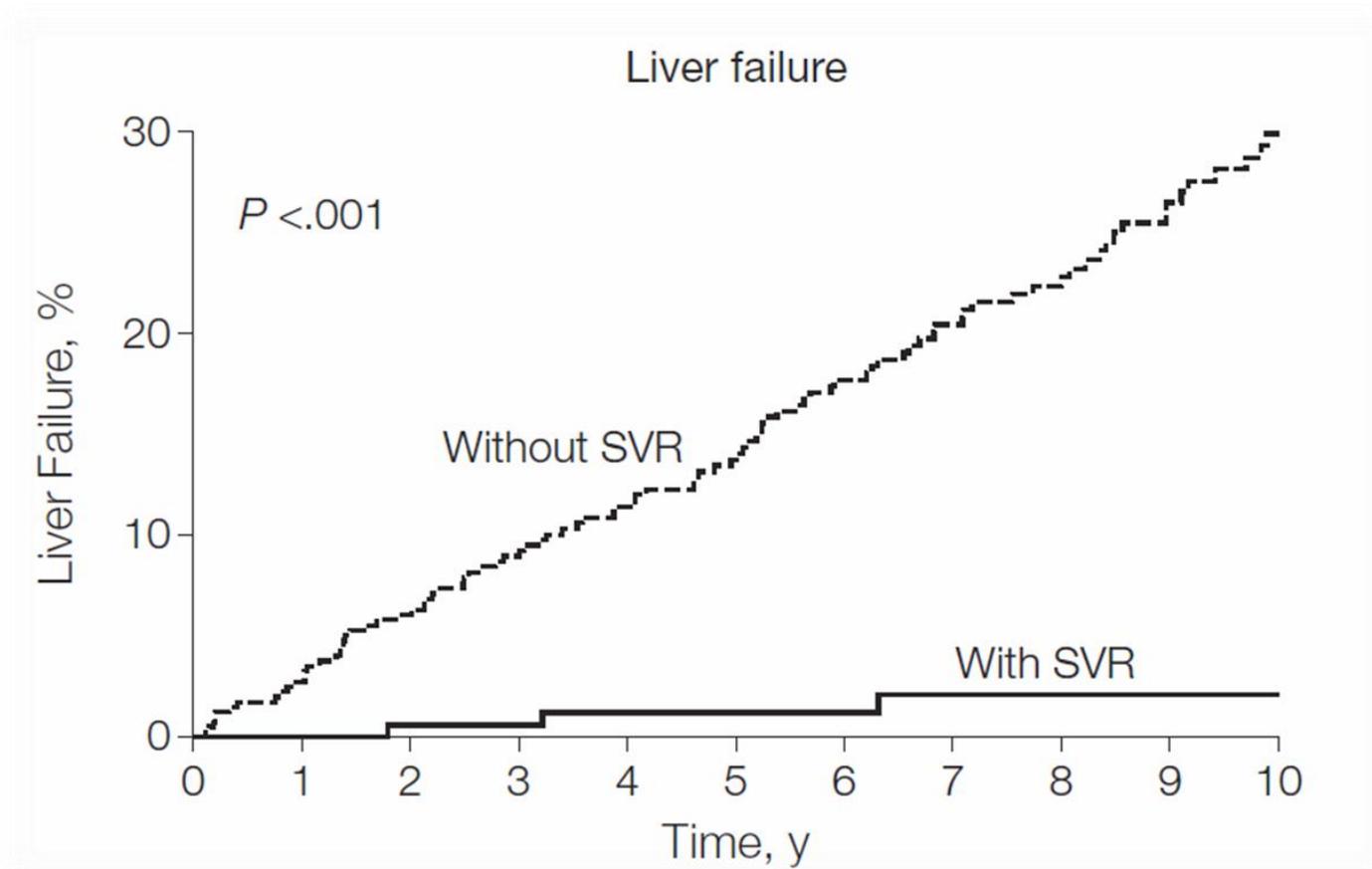
Percent with 5-year SVR



SVR: Sustained viral response

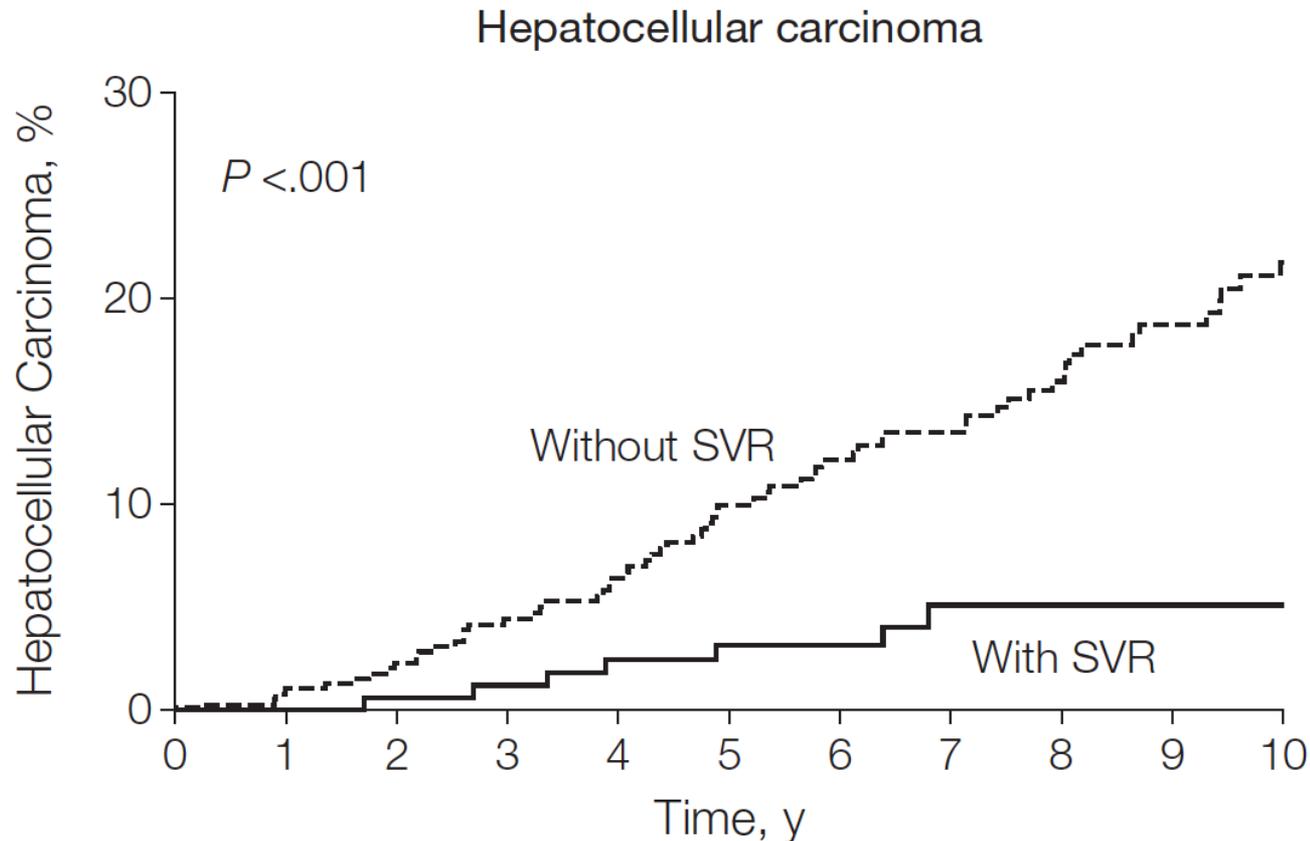
Swain, *Gastro* 2010. Manns, *J Viral Hep* 2014.

SVR is Considered Cure Reduction in Liver Failure



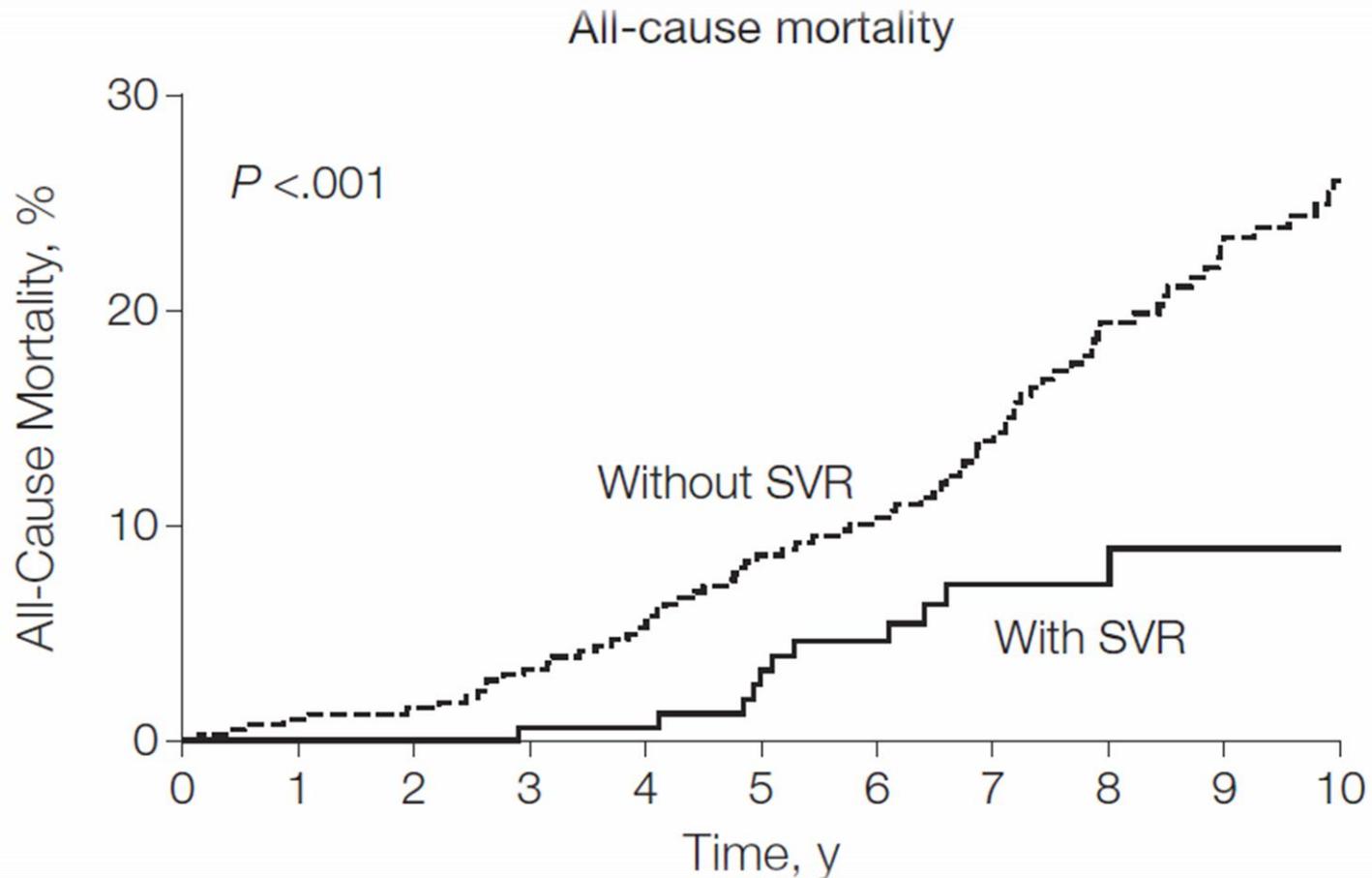
Van der Meer, *JAMA* 2012. Backus, *Clin Gastro* 2011. Imazeki, *Hepatology* 2003. Shiratori, *Ann Intern Med* 2005. Veldt, *Ann Intern Med* 2007. Berenguer, *Hepatology* 2009.

SVR is Considered Cure Reduction in Hepatocellular Carcinoma



Van der Meer, *JAMA* 2012. Backus, *Clin Gastro* 2011. Imazeki, *Hepatology* 2003. Shiratori, *Ann Intern Med* 2005. Veldt, *Ann Intern Med* 2007. Berenguer, *Hepatology* 2009.

SVR is Considered Cure Reduction in All-Cause Mortality



Van der Meer, *JAMA* 2012. Backus, *Clin Gastro* 2011. Imazeki, *Hepatology* 2003. Shiratori, *Ann Intern Med* 2005. Veldt, *Ann Intern Med* 2007. Berenguer, *Hepatology* 2009.

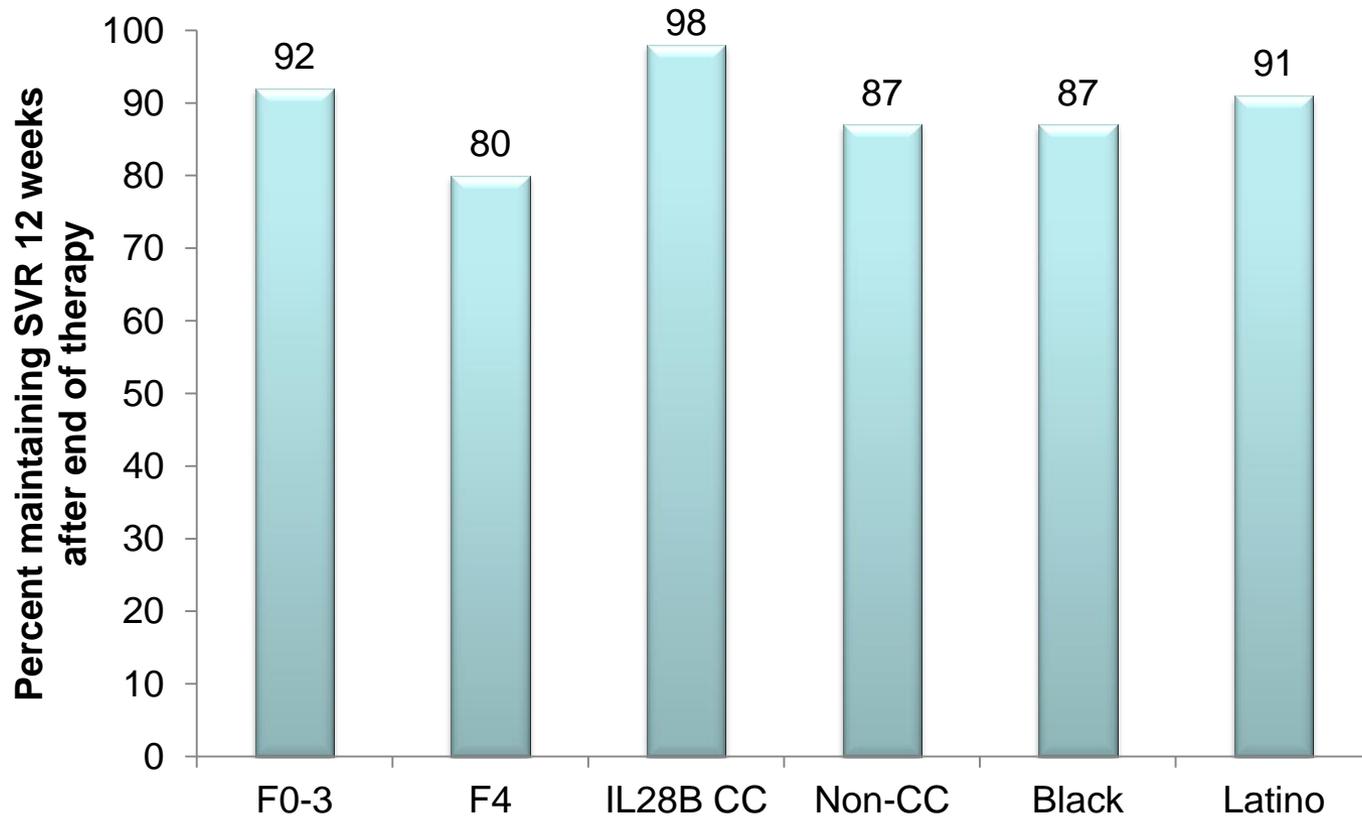
Key Therapeutic Milestones in Reaching the Curative Era of HCV

□ FDA Approval of HCV Treatments

- 1991 Interferon (IFN)
- 1998 IFN and ribavirin
- 2001 Pegylated IFN
- 2011 Boceprevir and telaprevir
- 2013 Sofosbuvir and simeprevir

High Rate of SVR

Sofosbuvir, PegIFN, and Ribavirin for 12 weeks

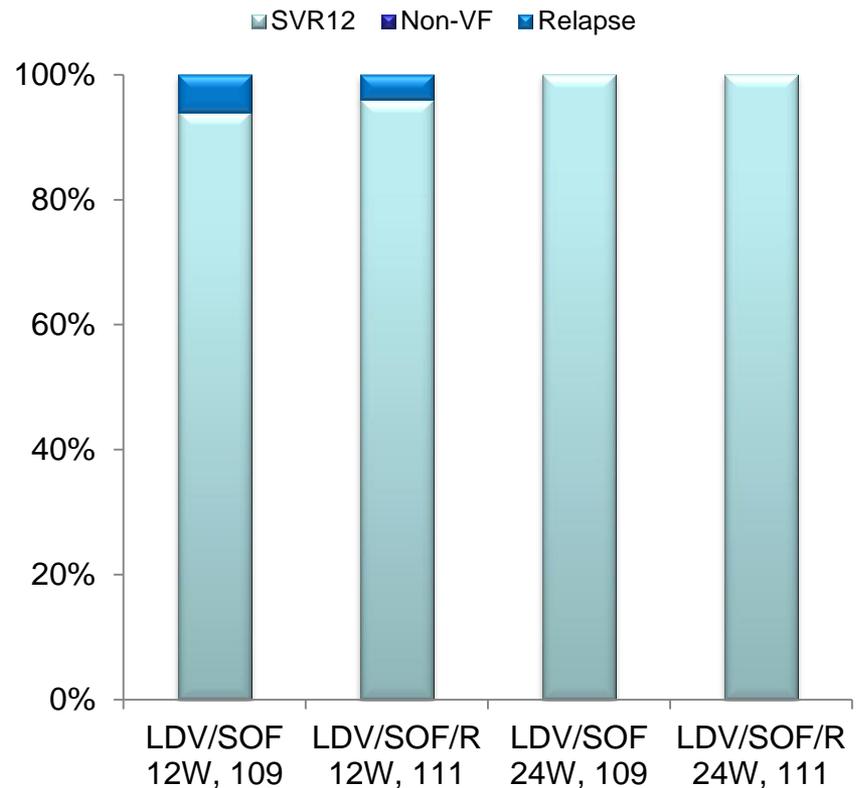
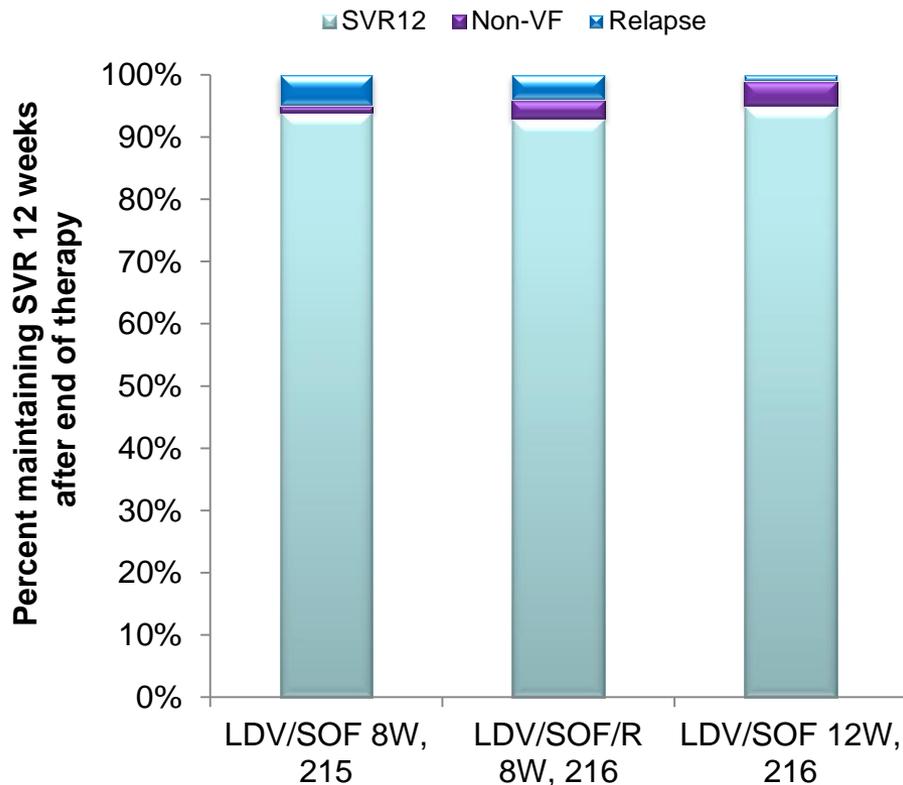


PegIFN; pegylated interferon. F0-3: Stages of liver fibrosis from none to moderate. F4: Severe liver fibrosis. Non-CC: Individuals with either CT or TT IL28-genotype.

High Rate of SVR for Genotype 1 HCV Ledipasvir (LDV) and Sofosbuvir (SOF)

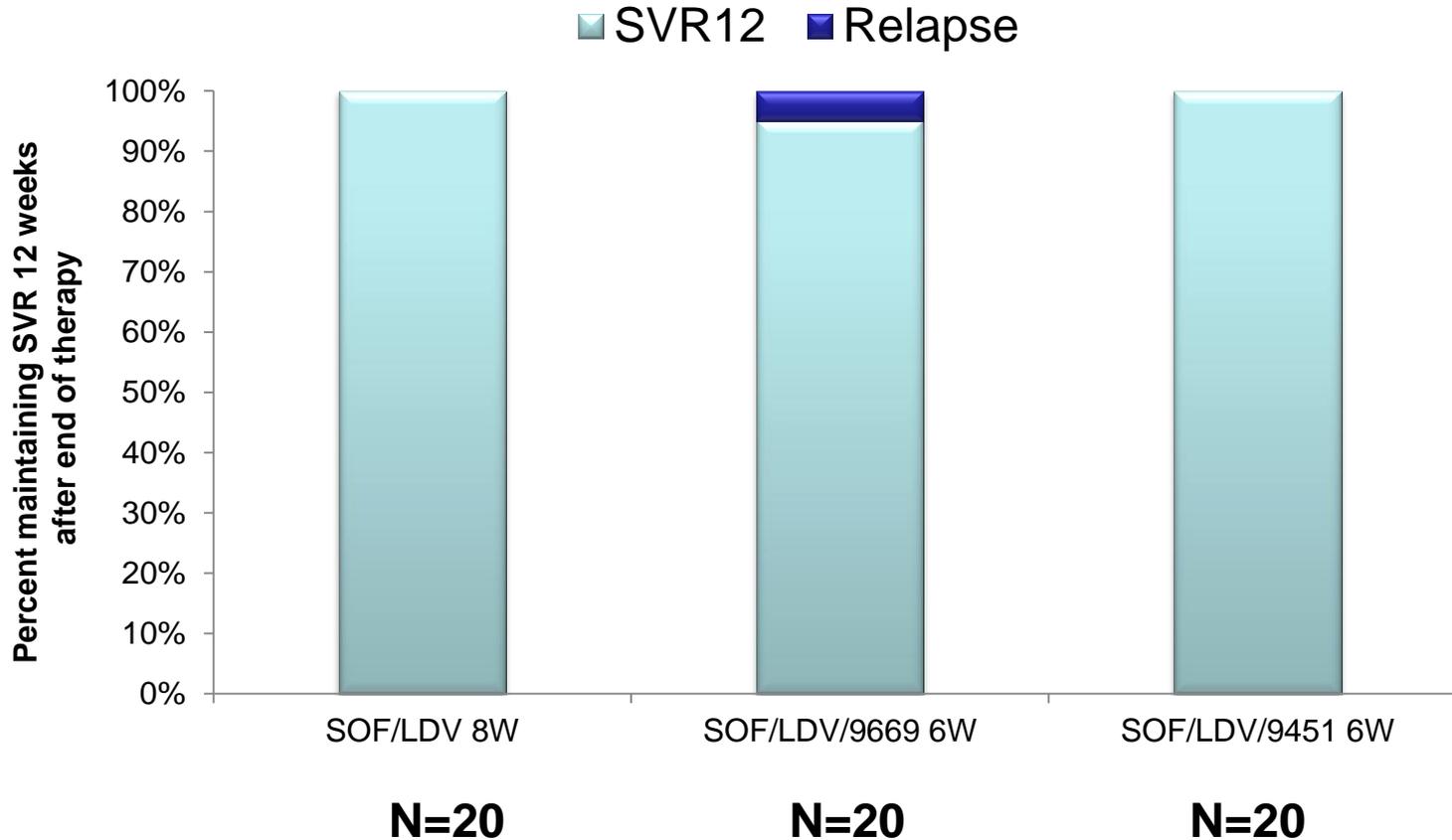
LDV/SOF naive F0-2, naive

LDV/SOF prior treatment, 20% cirrhosis



SVR12: Sustained Viral Response for 12 weeks. Non-VF: Non-virologic treatment failure. 8W: 8 weeks of therapy. 12W: 12 weeks of therapy. 24W: 24 weeks of therapy. R: Ribavirin.

SVR with 6 weeks of Sofosbuvir, Ledipasvir, and GS-9669 or GS-9451



SVR12: Sustained Viral Response at 12weeks. SOF: Sofosbuvir. LDV: Ledipasvir. 8W: 8 weeks. 6W: 6 weeks.

Kohli, Poster 27LB, Conference on Retroviruses and Opportunistic Infections 2014. NCT01431898. NCT01805882.

Fewer Adverse Events with Newer Therapies

Events	Telaprevir, Peg, R n=292	Boceprevir, Peg, R n=205
Serious adverse event (SAE)	132 (45%)	67 (33%)
Premature discontinuation	66 (23%)	54 (26%)
Discontinuation due to SAE	43 (15%)	15 (7%)
Hepatic decompensation	6 (2%)	6 (3%)
Serious rash	14 (5%)	0
Events	LDV-SOF x 8 wk n=215	LDV-SOF RBV x 8 wk n=216
Serious adverse event (SAE)	4 (2%)	1 (<1%)
Discontinuation due to SAE	0	1 (<1%)

Peg=Pegylated interferon. R=Ribavirin. LDV=Ledipasvir. SOF=Sofosbuvir.

Hezode *J Hepatol* 2013. Knowlley, *NEJM* 2014.

Rapid Progress in Interferon-sparing HCV Treatment

□ **Genotype 1**

- *Simeprevir and sofosbuvir (not FDA approved, filed)
- *Sofosbuvir and ribavirin (alternative)
- Sofosbuvir and ledipasvir (filed)
- ABT 450/r, ombitasvir, dasabuvir, +/- ribavirin (filed)
- Daclatasvir and asunaprevir (filed)
- MK5172, MK8742, +/- ribavirin (phase 3)

□ **Genotype 2 and 3**

- *Sofosbuvir and ribavirin

*the individual components of these regimens are already available in June 2014.

Expert Guidelines for HCV Screening, Management and Treatment

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AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES
 **Recommendations for Testing, Managing, and Treating Hepatitis C**

 **IDSA**
Infectious Diseases Society of America

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Full Report Menu

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COMING SOON: In Whom and When to Initiate Treatment
- INITIAL TREATMENT OF HCV INFECTION IN PATIENTS STARTING TREATMENT
- RETREATMENT OF PERSONS IN WHOM PRIOR THERAPY HAS FAILED
COMING SOON: Monitoring Patients Who Are On or Have Completed Therapy
- UNIQUE PATIENT POPULATIONS
COMING SOON: Management of Acute HCV Infection
- REFERENCES
- WEBSITE POLICIES

Full Report

INTRODUCTION
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METHODS
The Guidance was developed by a panel of HCV experts in the fields of hepatology and infectious diseases, using an evidence-based review of information that is largely available to healthcare...
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Methods Table 1. Summary of the Process and Methods for the Guidance Development
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Methods Table 2. Grading System Used to Rate the Level of the Evidence and Strength of the Recommendation for Each Recommendation
Recommendations are based on scientific evidence and expert opinion.
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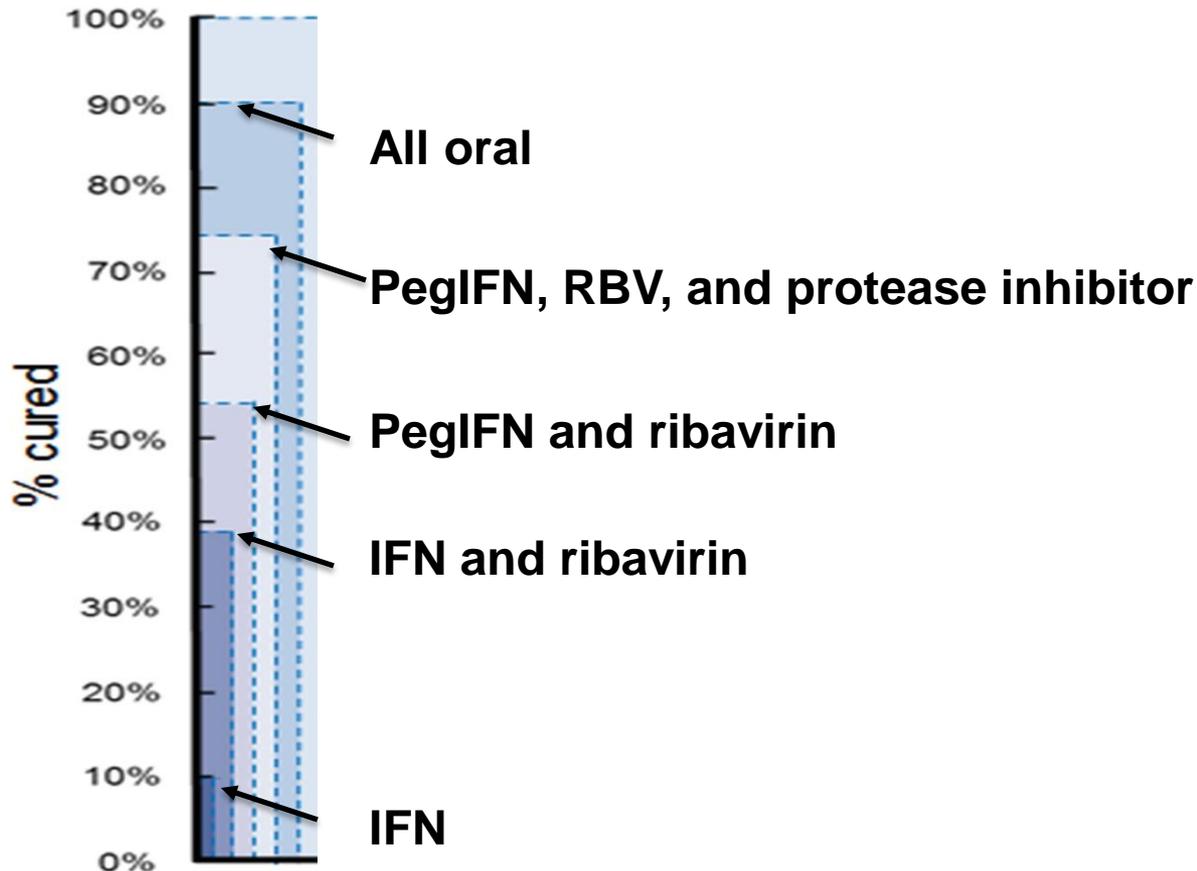
Methods Table 3. Commonly Used Abbreviations and Their Expansions
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HCV TESTING AND LINKAGE TO CARE

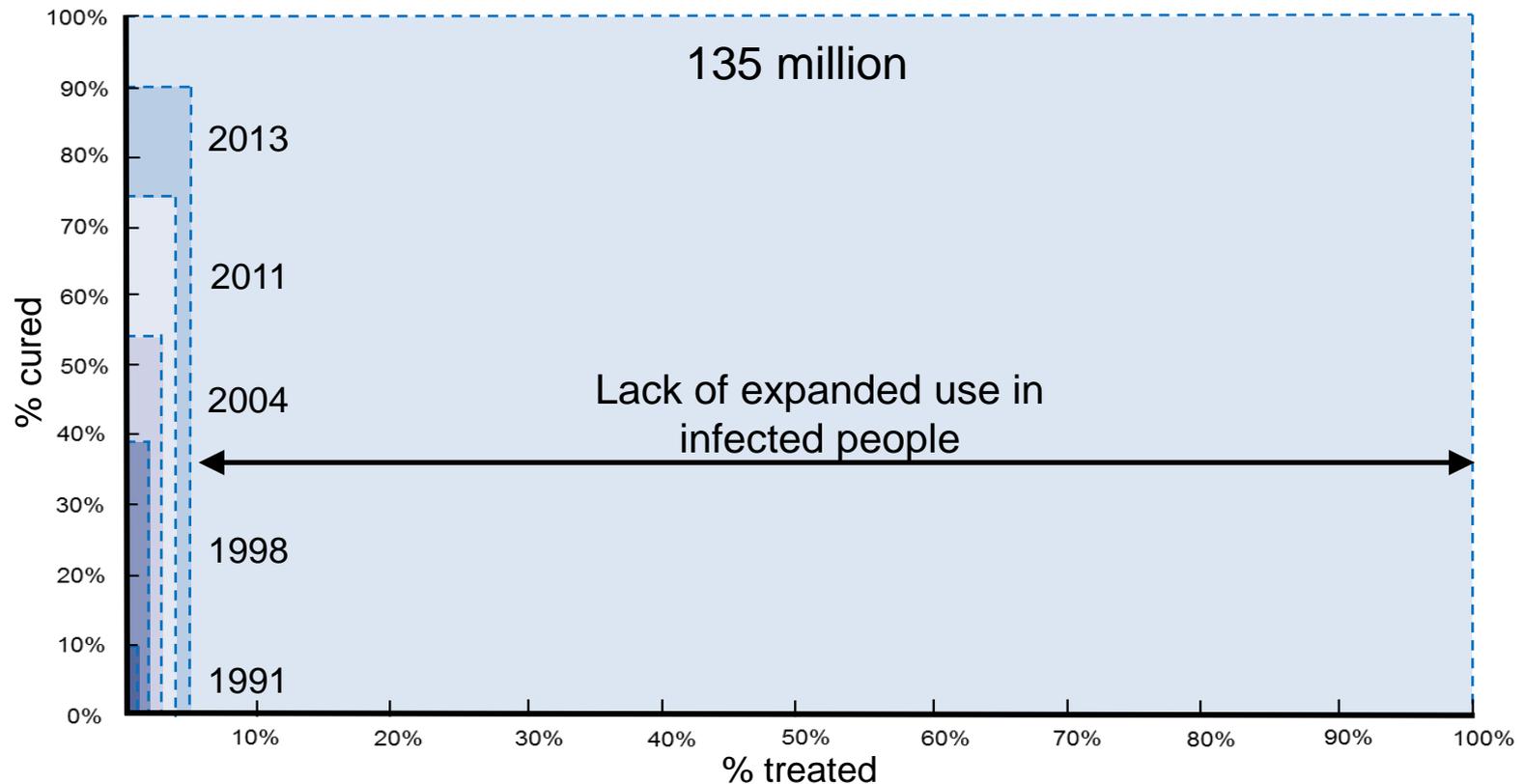
Evaluating the Cost Effectiveness of New Therapies

- ❑ In 2011, average wholesale acquisition costs of drugs alone were \$32,000 to over \$100,000
- ❑ Quality adjusted life years for those regimens considered reasonable
- ❑ New regimens are \$100,000 to \$175,000 in US
- ❑ Incremental cost benefits have been demonstrated
- ❑ Evaluating cost effectiveness of new regimens also has to reflect the increased efficacy of the treatment (cost/cure)

Steady Progress in Treatment Efficacy Has Increased the Proportion of Persons Who Are Cured



Greater Uptake Will Maximize Potential Global Impact



Conclusions: HCV Curative Era

- ❑ HCV can be cured**
- ❑ Curing HCV reduces mortality and morbidity**
- ❑ Curing HCV reduces the risk of HCV transmission**
- ❑ Major challenges to global control are screening and testing and lack of treatment access**

Steps Toward Ending Hepatitis C in the US



Phillip Coffin, MD, MIA

Director of Substance Use Research

San Francisco Department of Public Health

University of California San Francisco



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

Essential Goals to Eliminate HCV

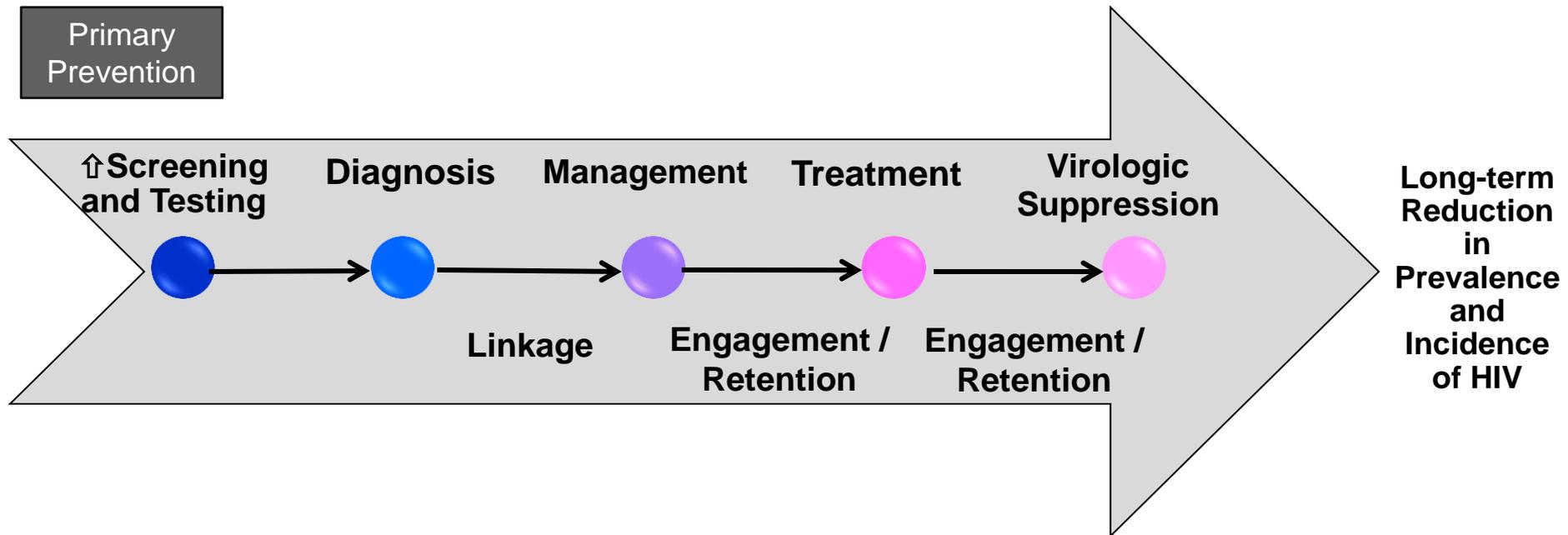
❑ Prevent sequelae of advancing liver disease in those already infected

- Baby Boomers, born 1945-1965
- Many don't know they are infected

❑ Prevent new or “incident” infections

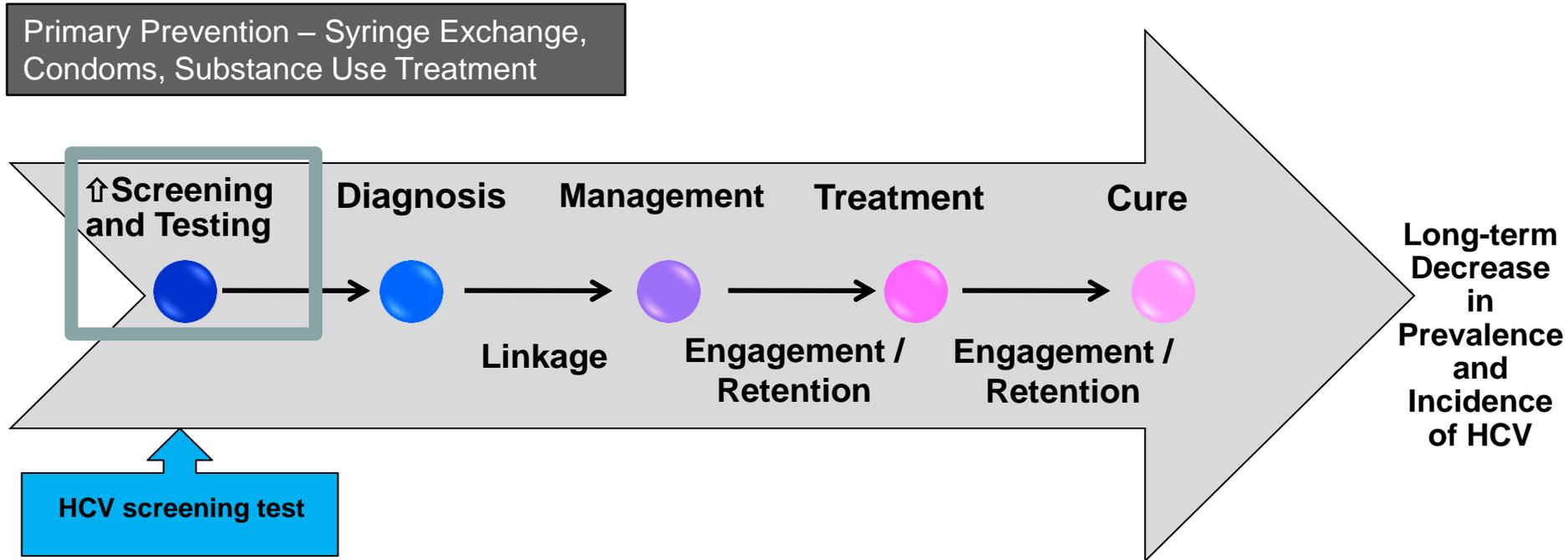
- Persons who inject drugs (PWID)
- Unsafe healthcare practices
- Sexual exposures in immunocompromised individuals

Continuum of Care Model for HIV



Adapted from: Das M, Conference on Retroviruses and Opportunistic Infections 2014.

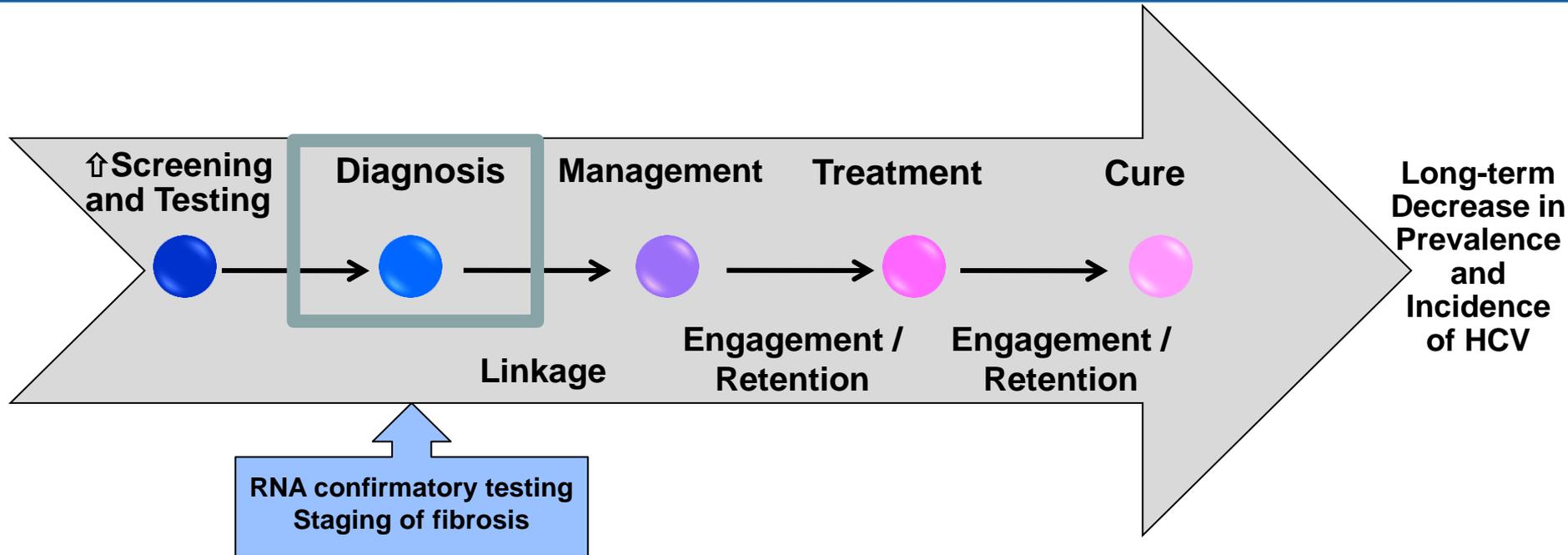
Continuum of Care Model for HCV



- **Screening tests would be opt-out**
- **EHR designed to have automated reminders**
- **Healthcare-level tracking to ensure baby boomers get screened**

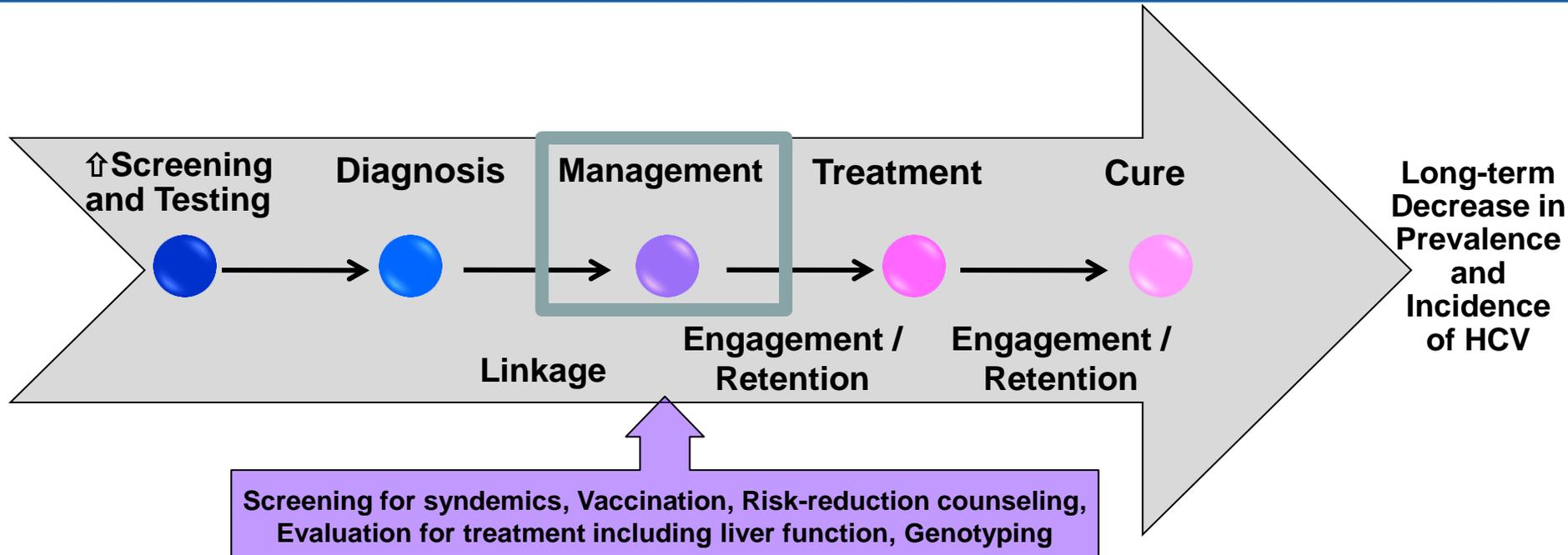
Adapted from: Das M, Conference on Retroviruses and Opportunistic Infections 2014.

Continuum of Care Model for HCV



- Simplify two-step process of screening then RNA confirmatory through reflexive testing
- Healthcare level systems could match positive screens to ensure follow-up testing
- Public health systems cannot track follow-up testing, negative test results not reportable
- Evaluate effectiveness of screening efforts by comparing to stage of fibrosis at diagnosis

Continuum of Care Model for HCV

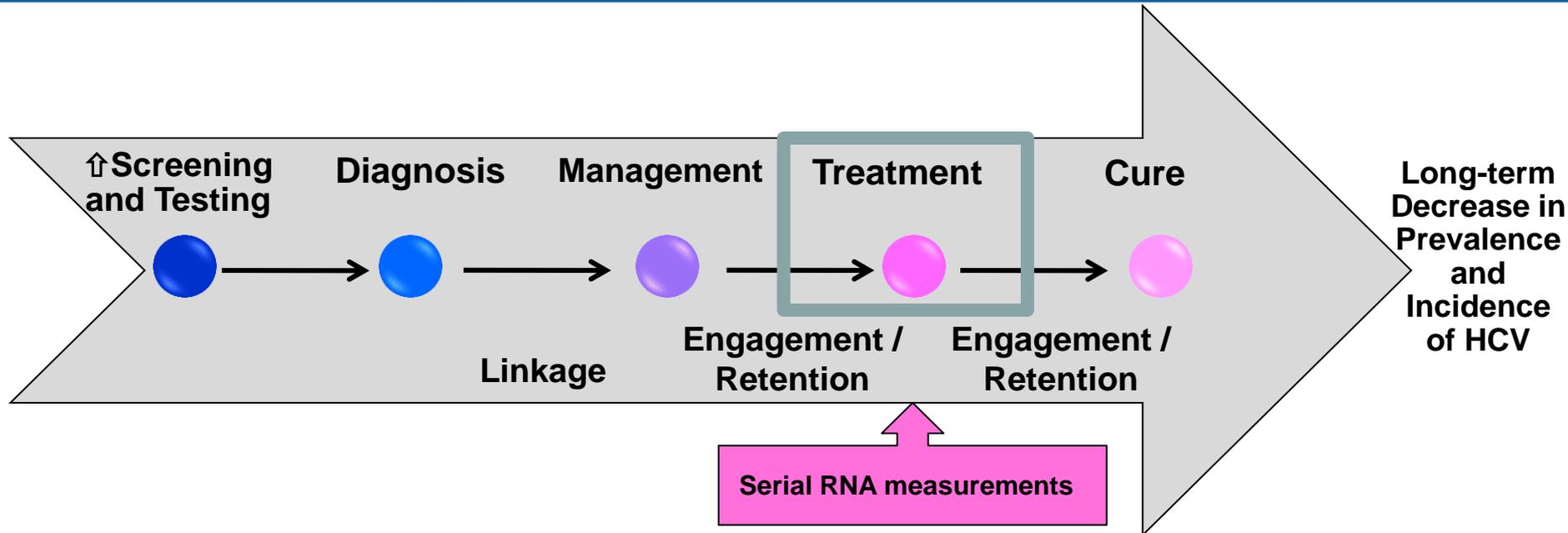


- **Patient management should include referral to substance use disorder treatment and brief alcohol interventions**
- **Healthcare-level systems could track serial ALT to ensure periodic evaluation is done**

ALT: Alanine transaminase. Syndemic infections include Hepatitis A, Hepatitis B and HIV.

Adapted from: Das M, Conference on Retroviruses and Opportunistic Infections 2014.

Continuum of Care Model for HCV

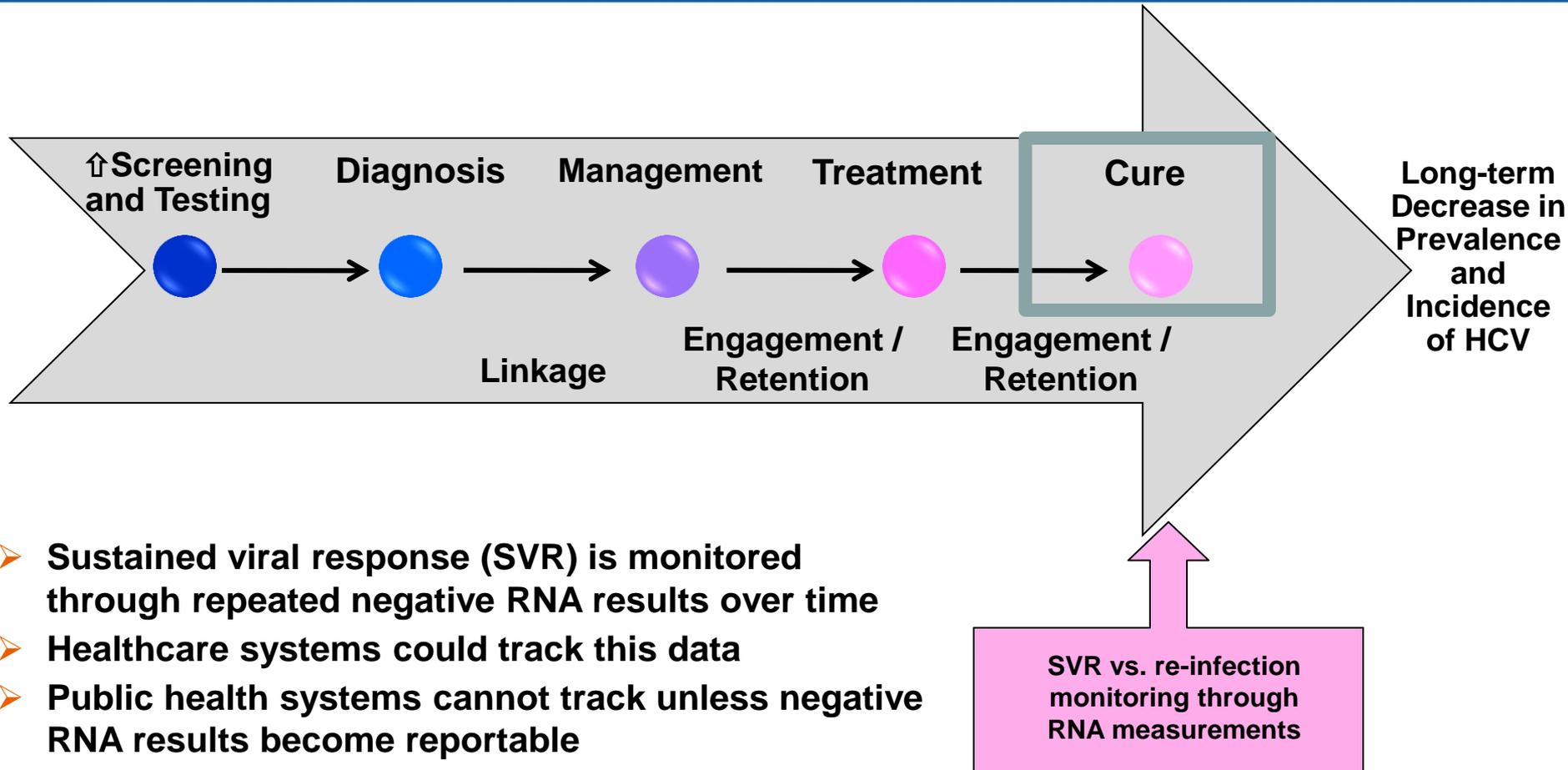


- **Historically, treatment uptake was major barrier**
- **New regimens should improve treatment uptake**
- **New barriers such as cost and access may limit potential impact of new regimens**
- **Interventions could address these new barriers**
- **If negative RNA results were reportable, public health systems could track SVR**

SVR: Sustained viral response.

Adapted from: Das M, Conference on Retroviruses and Opportunistic Infections 2014.

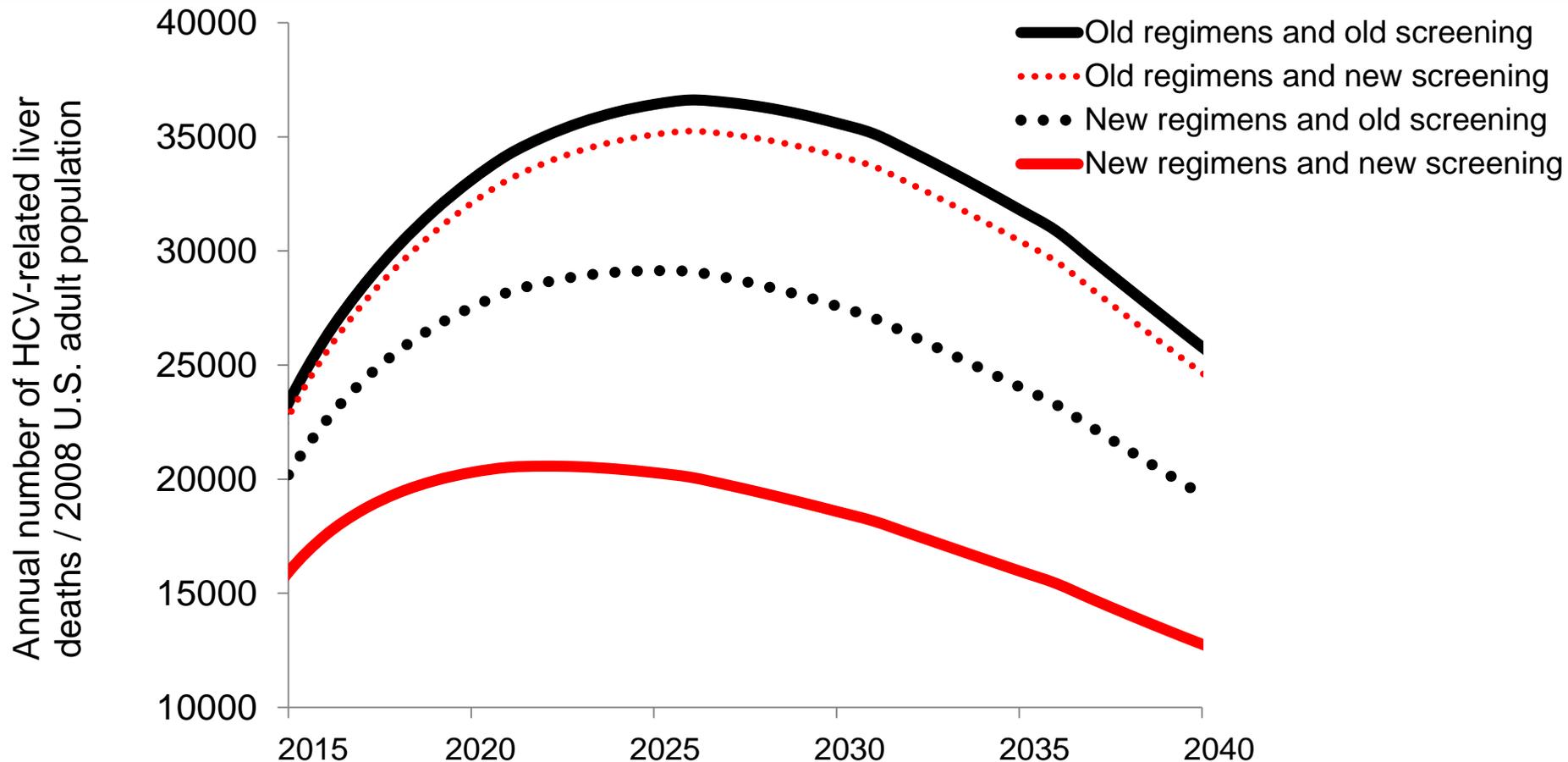
Continuum of Care Model for HCV



- **Sustained viral response (SVR) is monitored through repeated negative RNA results over time**
- **Healthcare systems could track this data**
- **Public health systems cannot track unless negative RNA results become reportable**

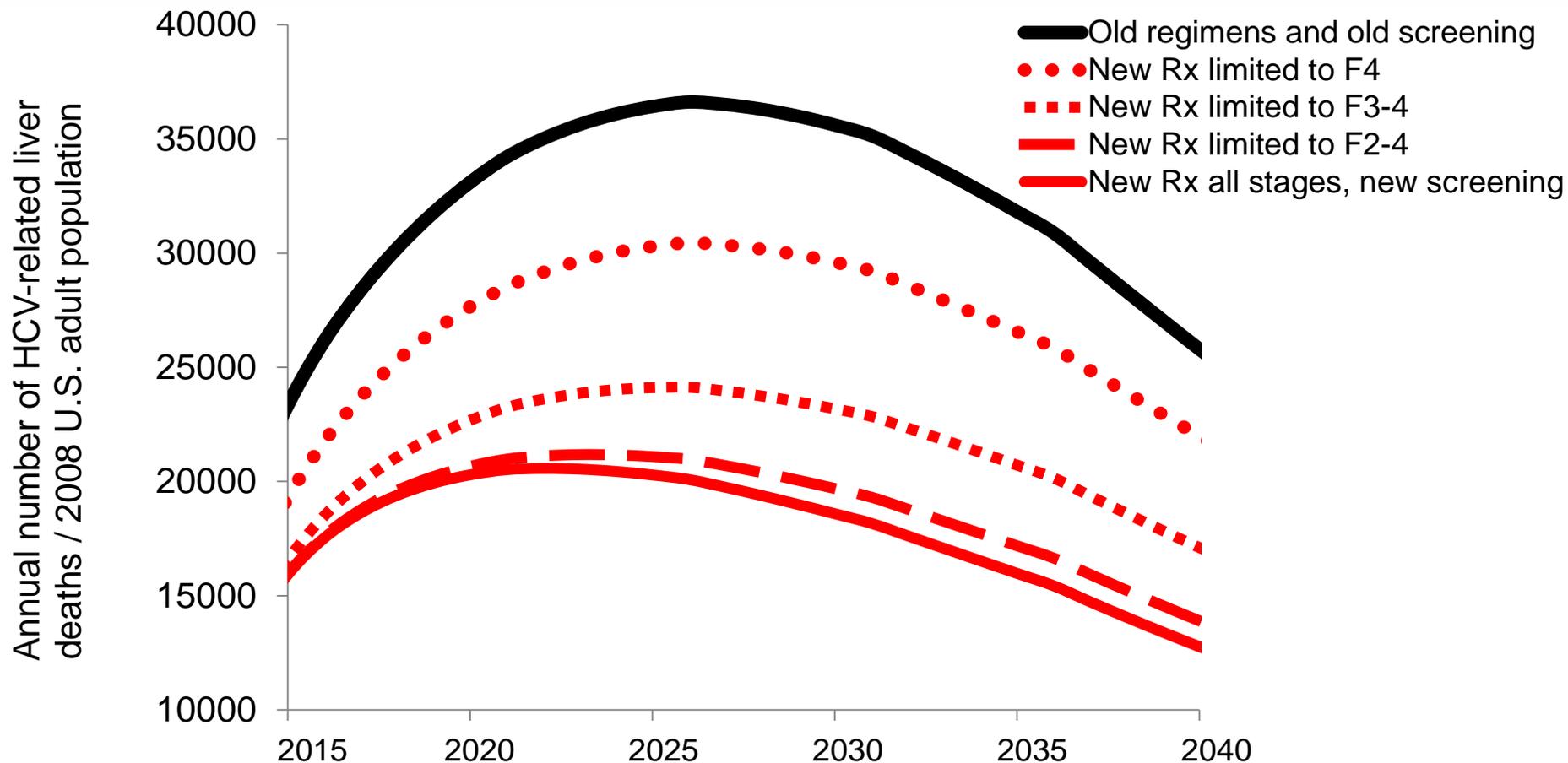
Adapted from: Das M, Conference on Retroviruses and Opportunistic Infections 2014.

Potential Reduction in HCV-Related Liver Deaths from Expanded Screening and Treatment Regimens



Coffin, CID 2012 (modified for new treatment regimens, direct-acting agents).

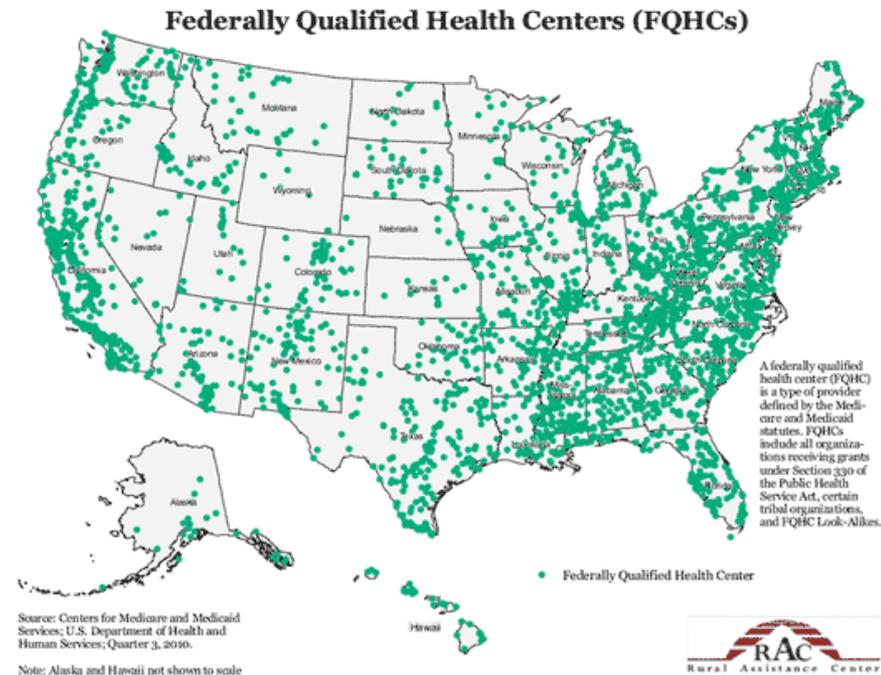
Potential Reduction in HCV-Related Liver Deaths by Treatment Strategy based on Liver Fibrosis



F2-F4: Stages of liver fibrosis including moderate (F2), severe (F3), and cirrhosis (F4)
Coffin, CID 2012 (modified for novel direct-acting agents).

Expanding Treatment in Primary Care to Meet Demand

- ❑ **New therapies are 8-12 weeks, all-oral, with minimal side effects**
- ❑ **HCV specialists**
 - 2,335 US-based AASLD members in 2010
 - Only 5,200 unique prescribers of HCV therapeutics for January-March 2014
- ❑ **Primary care & other providers**
 - 209,000 practicing PCPs in 2010
 - Similar SVR with ECHO support for IFN-based Rx
 - 9,000 IDSA members in 2013



Strategies to Prevent New Infections of HCV

- ❑ **Major risk factor for new infections is IV drug use**
 - Largest numbers of new infections are in PWIDs

- ❑ **Strategies to reduce HCV in PWIDs**
 - Syringe access programs and education programs

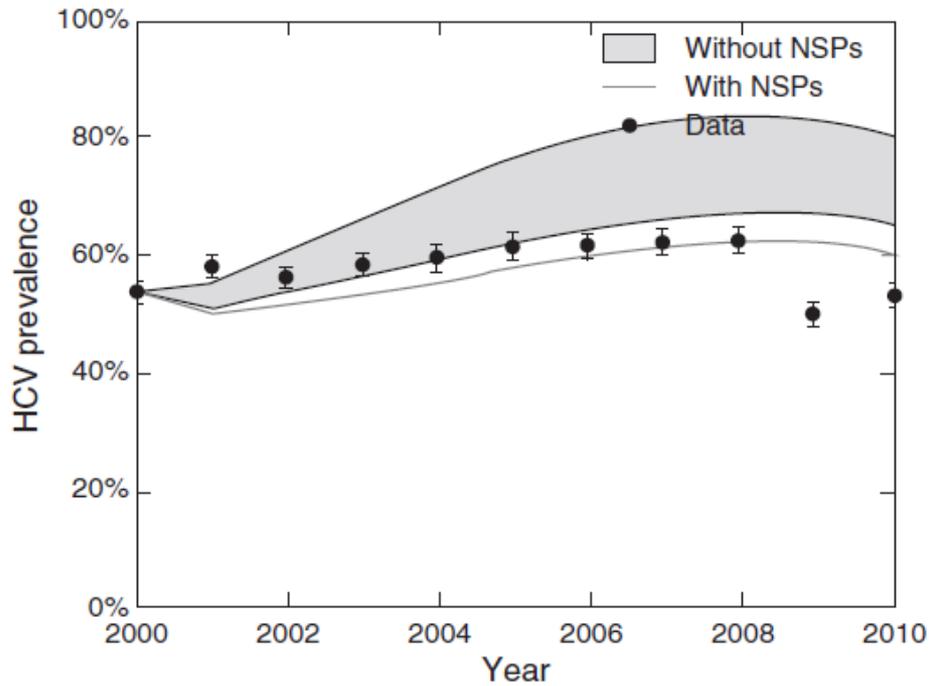
 - Treatment as Prevention (TasP)

 - Medication-assisted treatment for substance use disorder
 - Low threshold methadone treatment programs

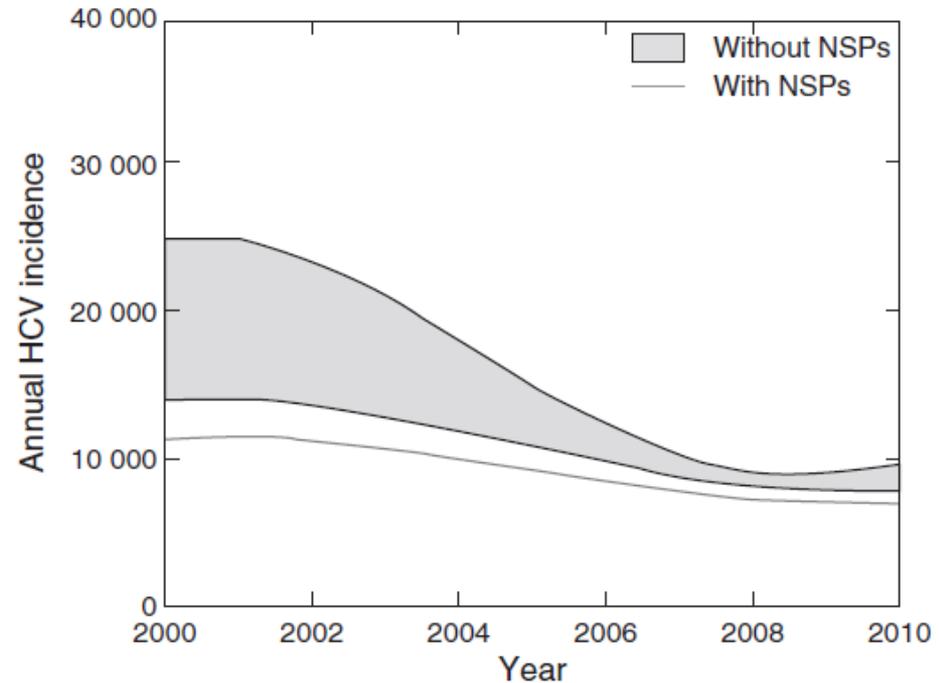
 - Vaccine research
 - Early Phase 2 stages

Syringe Access Programs Impact On HCV Prevalence and Incidence

Impact on Prevalence



Impact on Incidence



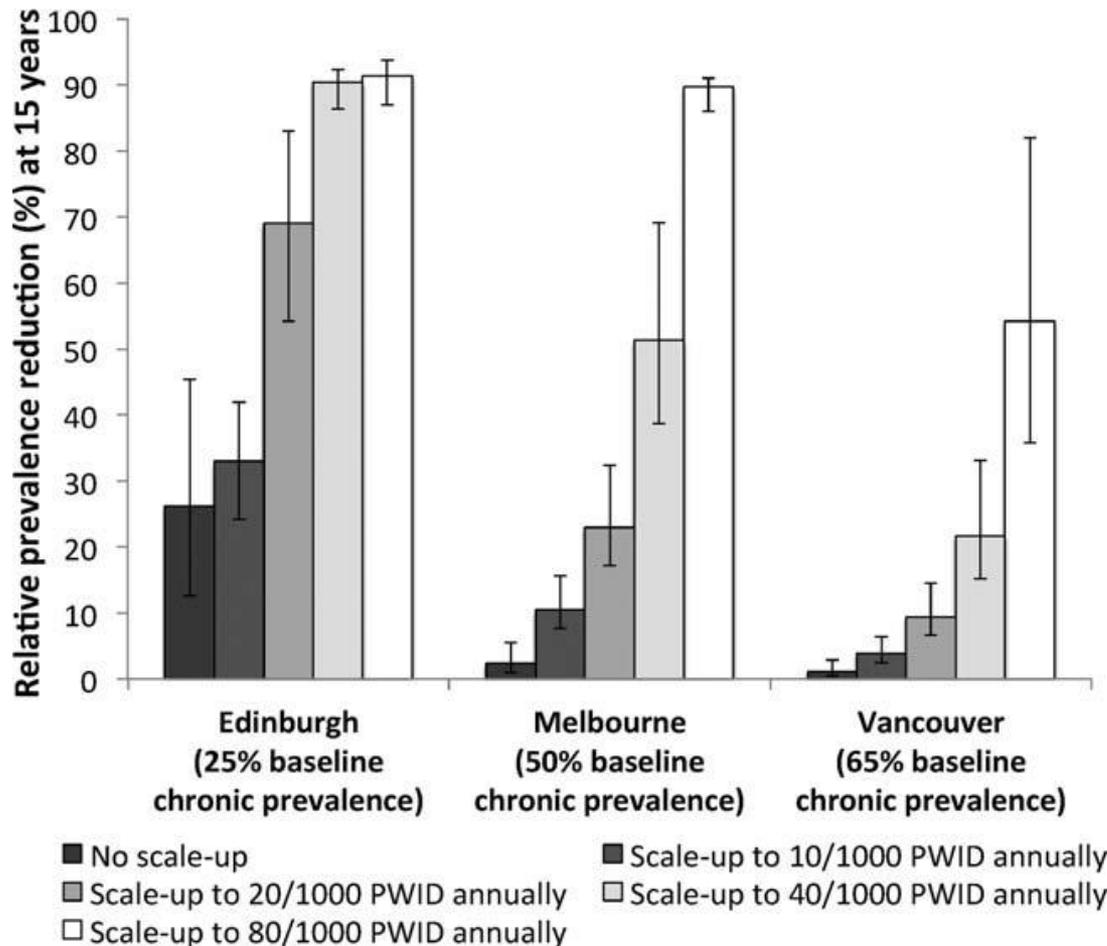
NSP: Needle & syringe program.
Kwon J, *AIDS* 2012.

Treatment as Prevention (TasP) for HCV

- ❑ **Interrupt Secondary Transmission**

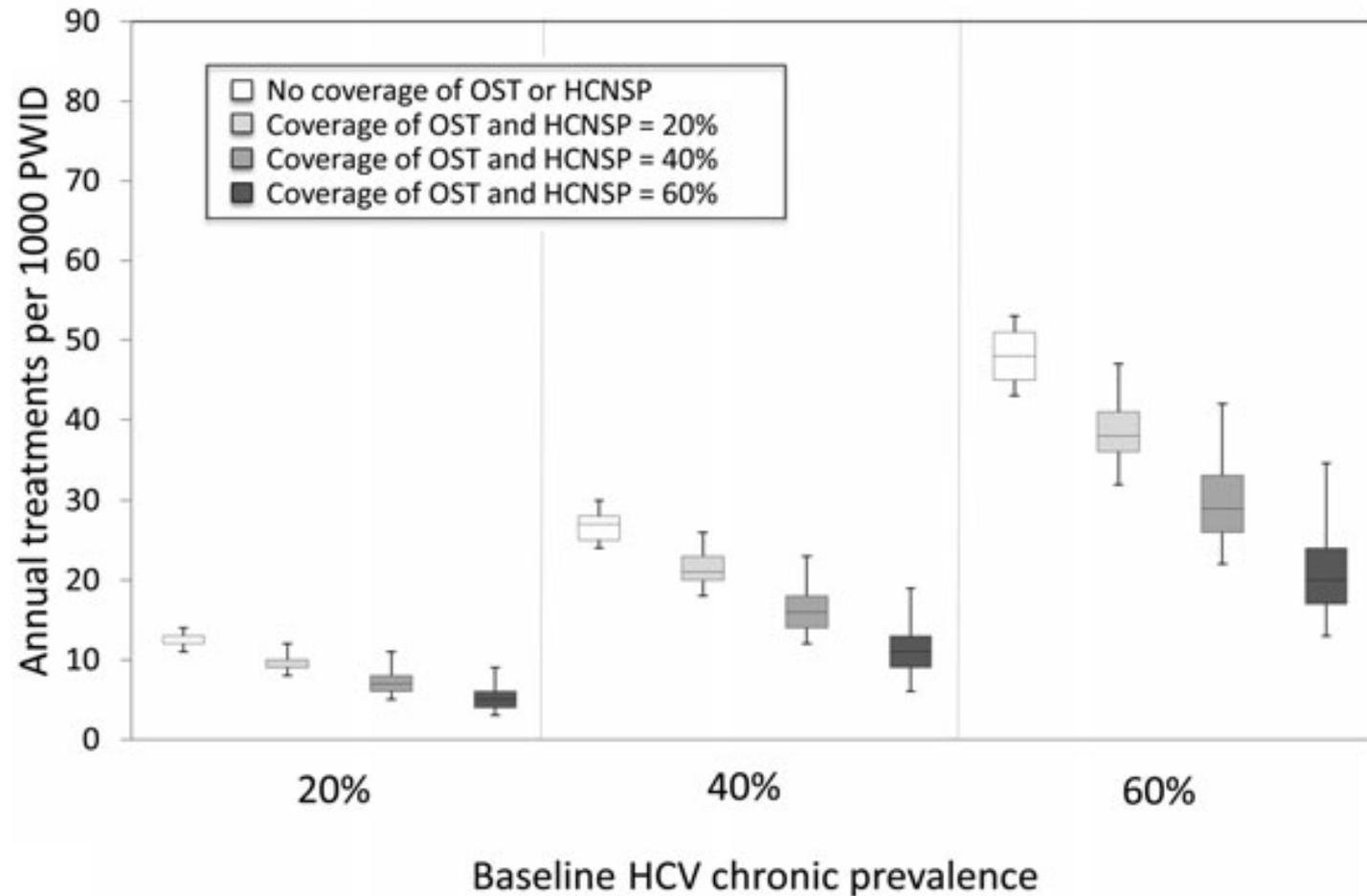
- ❑ **Maximize Impact on Incidence**
 - Target active injectors
 - Social network-based recruitment strategy
 - PWID in high prevalence areas
 - Optimize treatment delivery
 - Patient navigation programs
 - Conditional cash transfer programs
 - Directly observed therapy

Potential Impact of Treatment as Prevention based on Prevalence



- Prevalence in many US cities falls close to 50%-65%
- Treating just 8% of active injectors per year would reduce prevalence by 50% to 90% in 15 years

Value of Comprehensive Prevention: TasP, Syringe Access and Opioid Substitution



TasP: Treatment as prevention. OST: Opioid substitution treatment. HCNSP: Syringe access programming.

Martin, *Clinical Infectious Diseases* 2013.

Concerns and Research Needs for HCV TasP

- ❑ **Acceptability of new treatments to PWIDs**
- ❑ **Impact of acute infection on treatment and transmission**
- ❑ **Drug resistance archiving**
- ❑ **Efficacy of behavioral interventions to reduce reinfection**

To Reduce and Perhaps Eliminate HCV

- ❑ **Increase priority** – widen public recognition of urgency of action
- ❑ **Increase screening** – follow USPSTF recommended screening
- ❑ **Improve testing algorithm** – simplify HCV screening and diagnosis
- ❑ **Enhance surveillance** – change policies to improve utility of data
- ❑ **Expand clinical workforce** – allow for primary care management
- ❑ **Increase treatment availability** – modify treatment regimens
- ❑ **Reduce payer restrictions** – increase number of therapeutics

CDC PUBLIC HEALTH GRAND ROUNDS

The 25th Anniversary of the Discovery of the Hepatitis C Virus Looking Back to Look Forward

