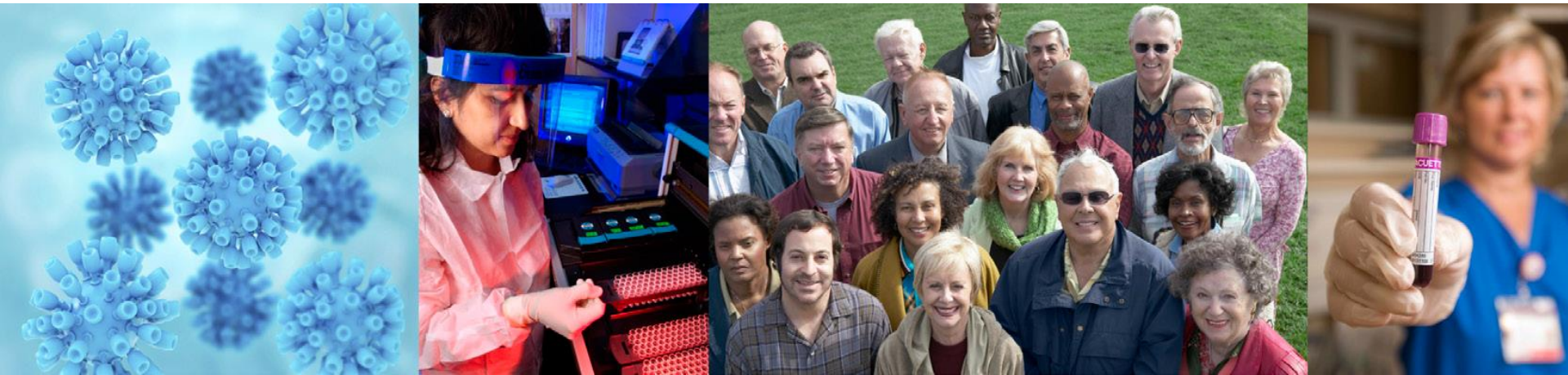


CDC PUBLIC HEALTH GRAND ROUNDS

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



Accessible Version: <https://youtu.be/qn33EWGLjXw>

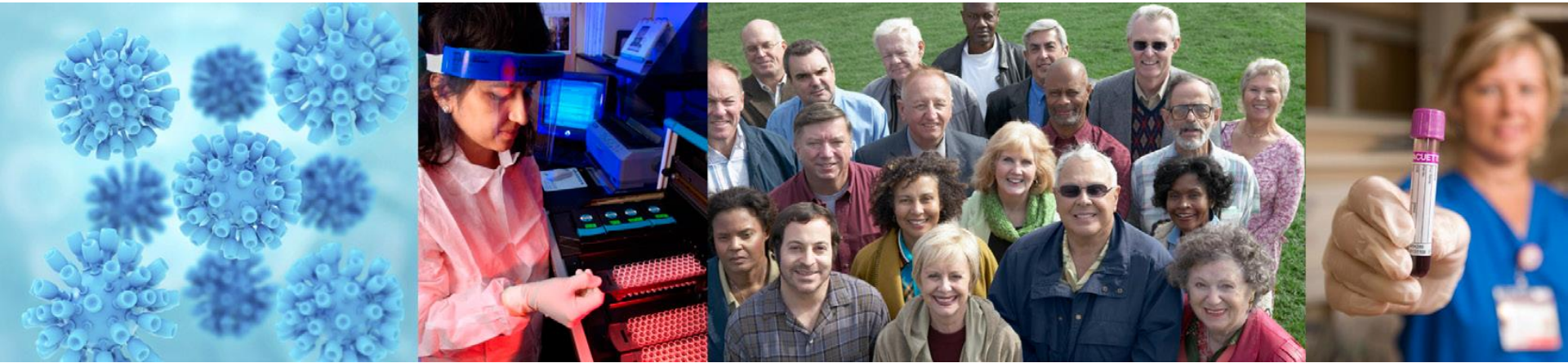
June 17, 2014



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

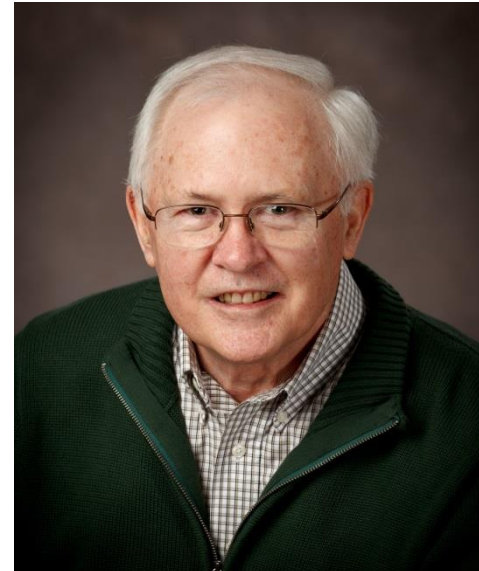


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Key Contributors to the Discovery of HCV



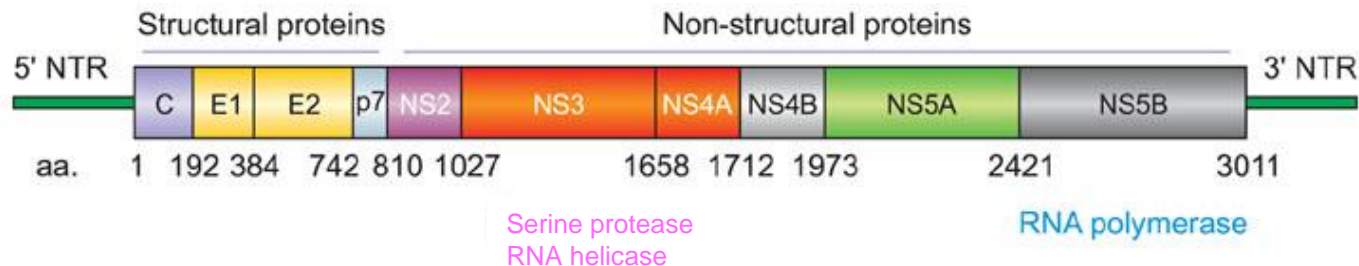
Harvey Alter



Daniel Bradley

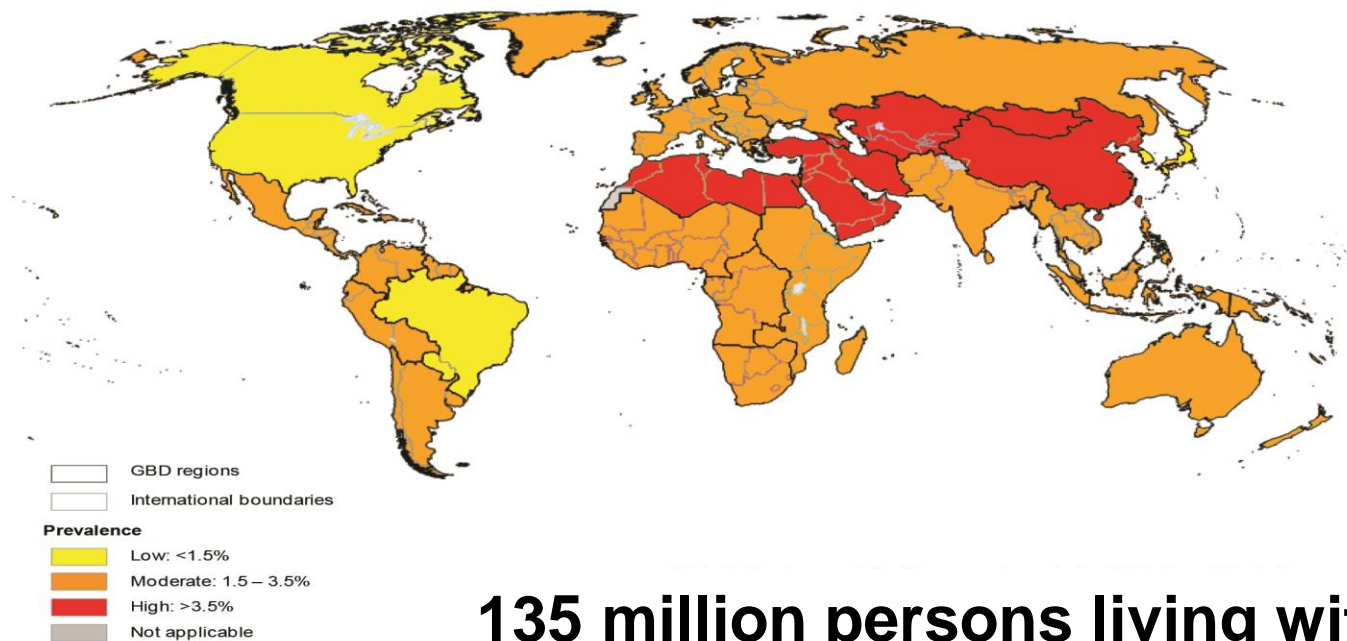
Discovery of Hepatitis C Virus (HCV)

- ❑ 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

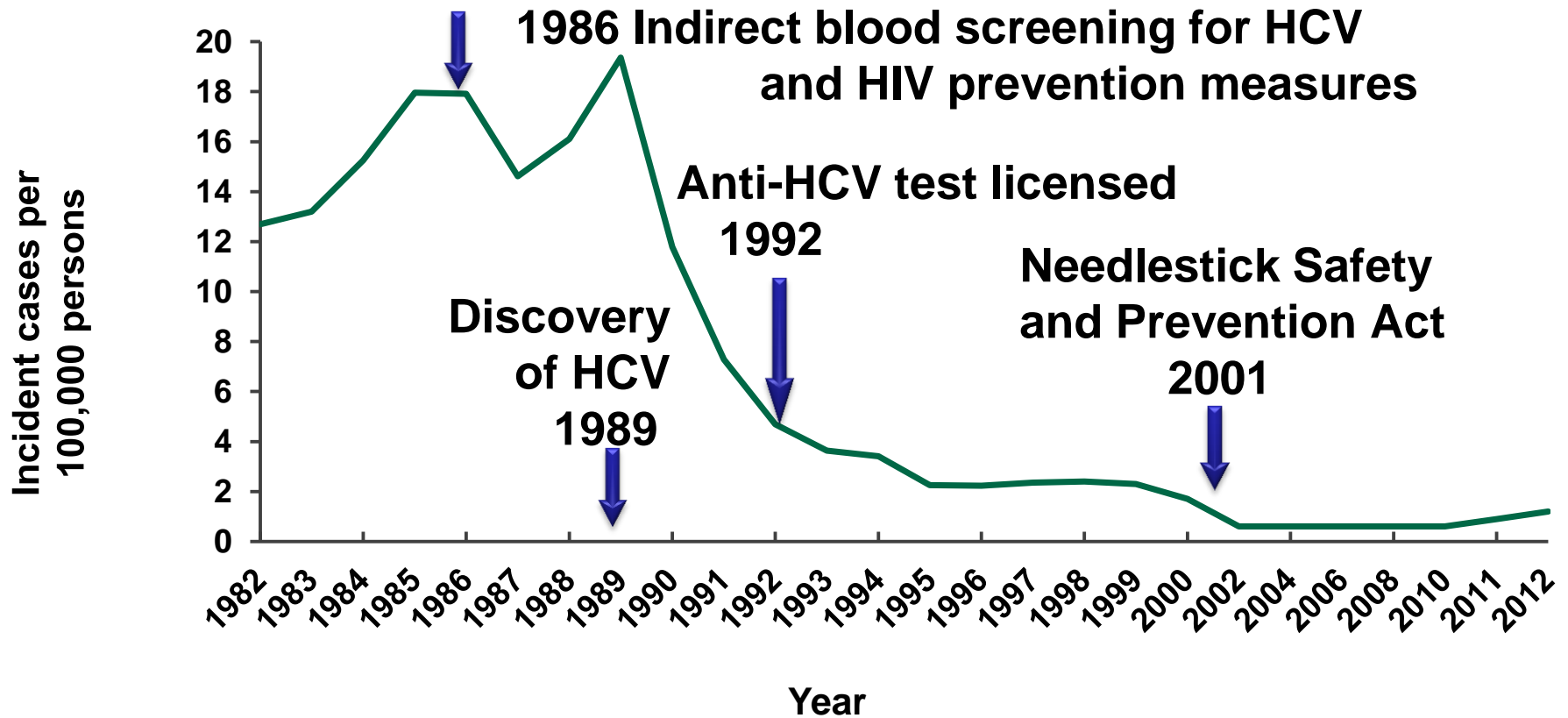
❑ Non-NHANES prevalence estimate

- 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

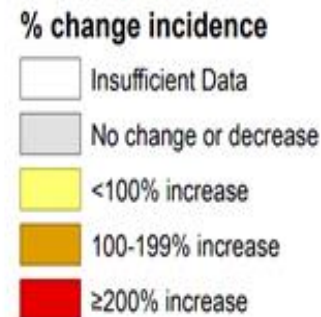
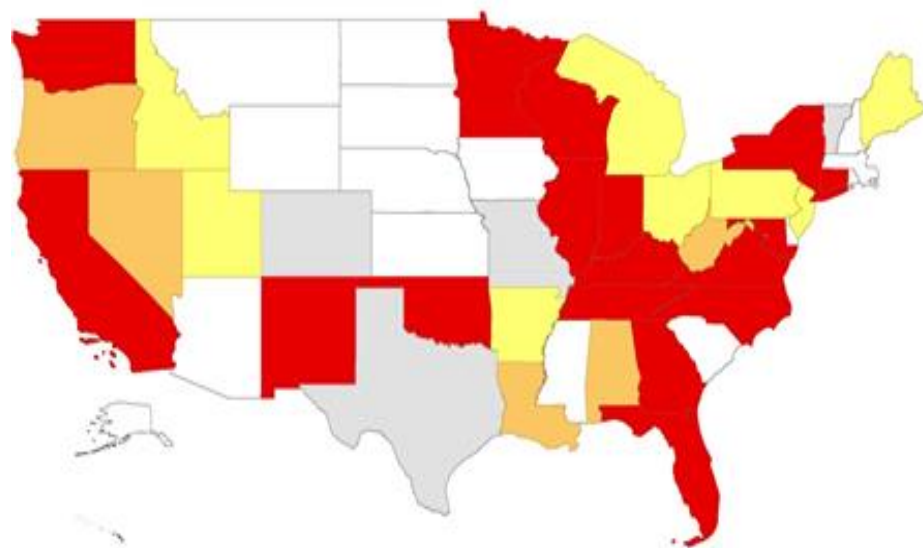
Recent Increases in HCV Infection

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)

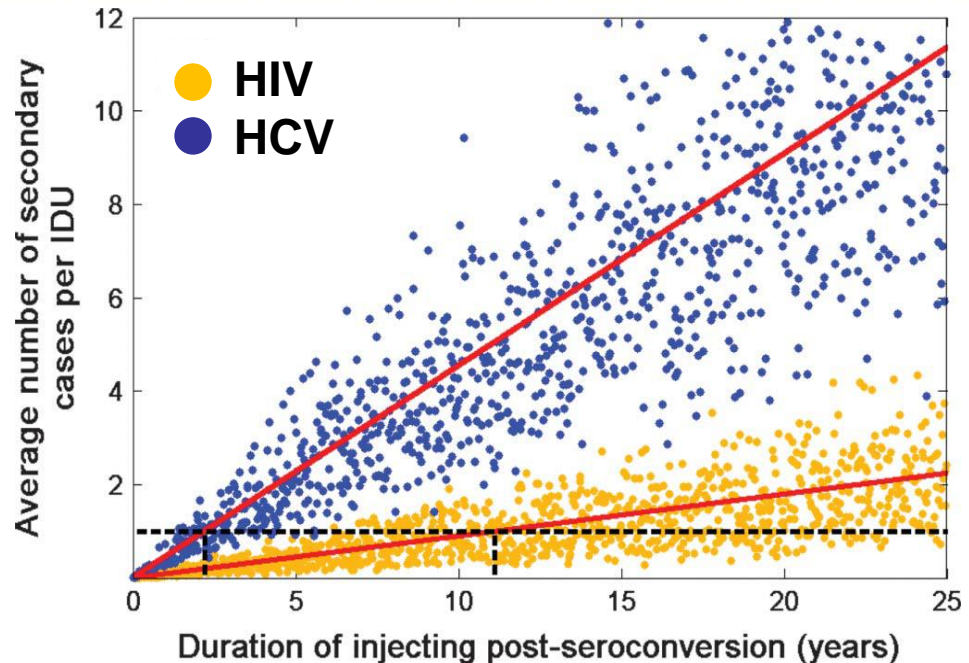
Transmission risks

- 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

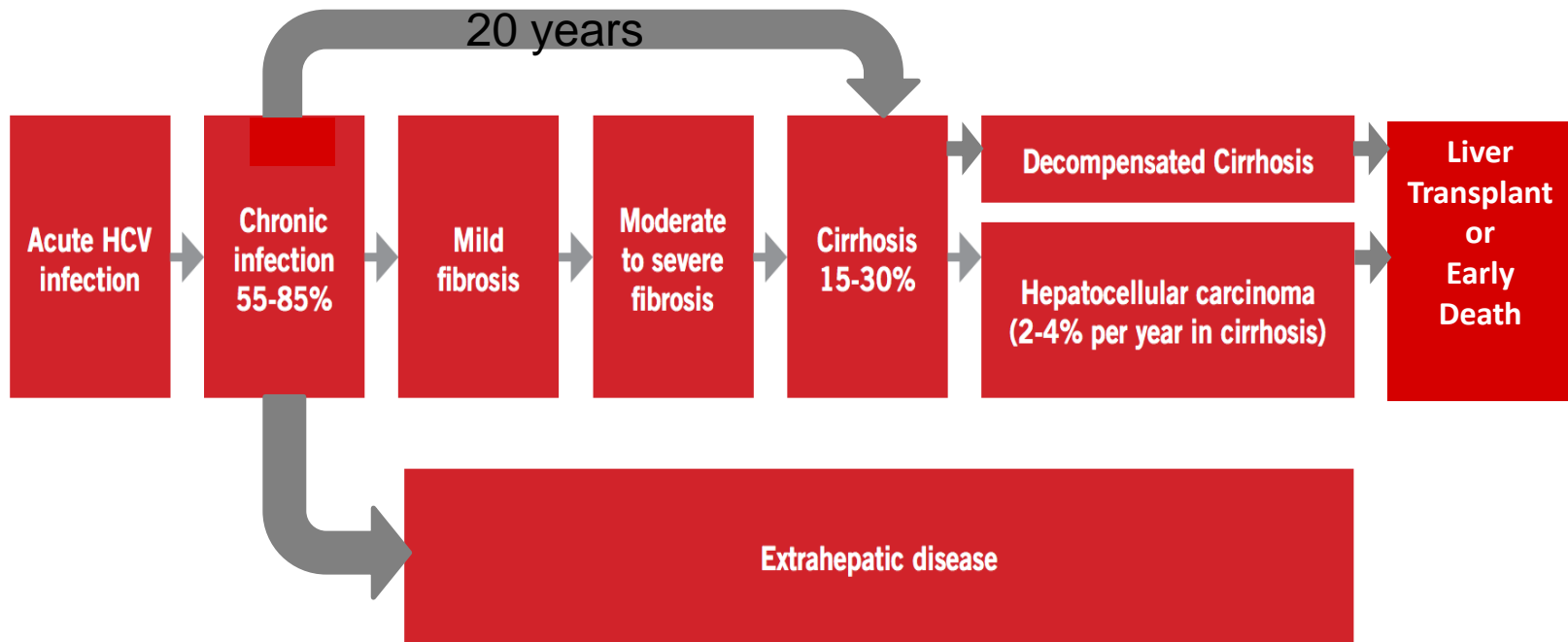
MSM: Men who have sex with men.

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.

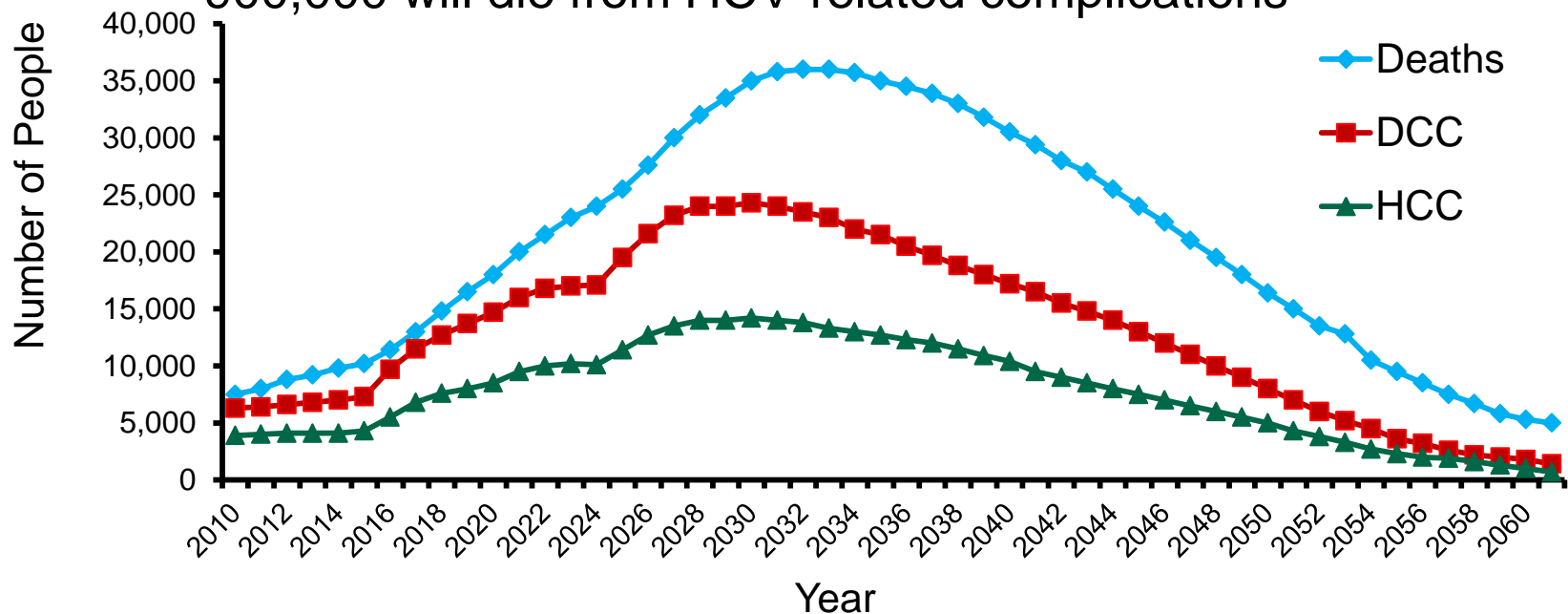
Ly KN, *Clin Infect Dis*. 2014. Mahajan R, *CID* 2014 .

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

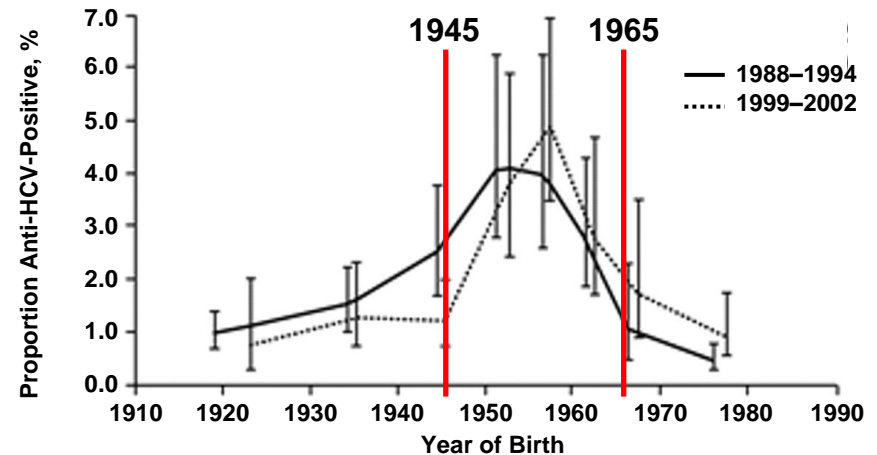
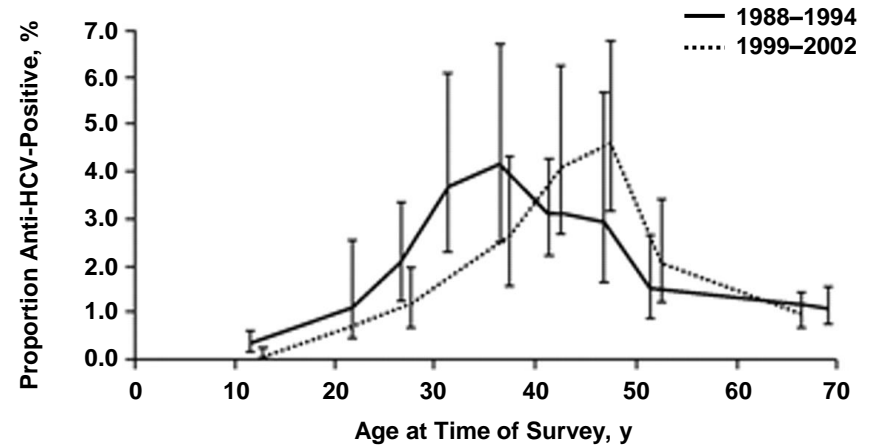


NHANES: Nutritional Health DCC: Liver failure. HCC: Liver cancer.

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

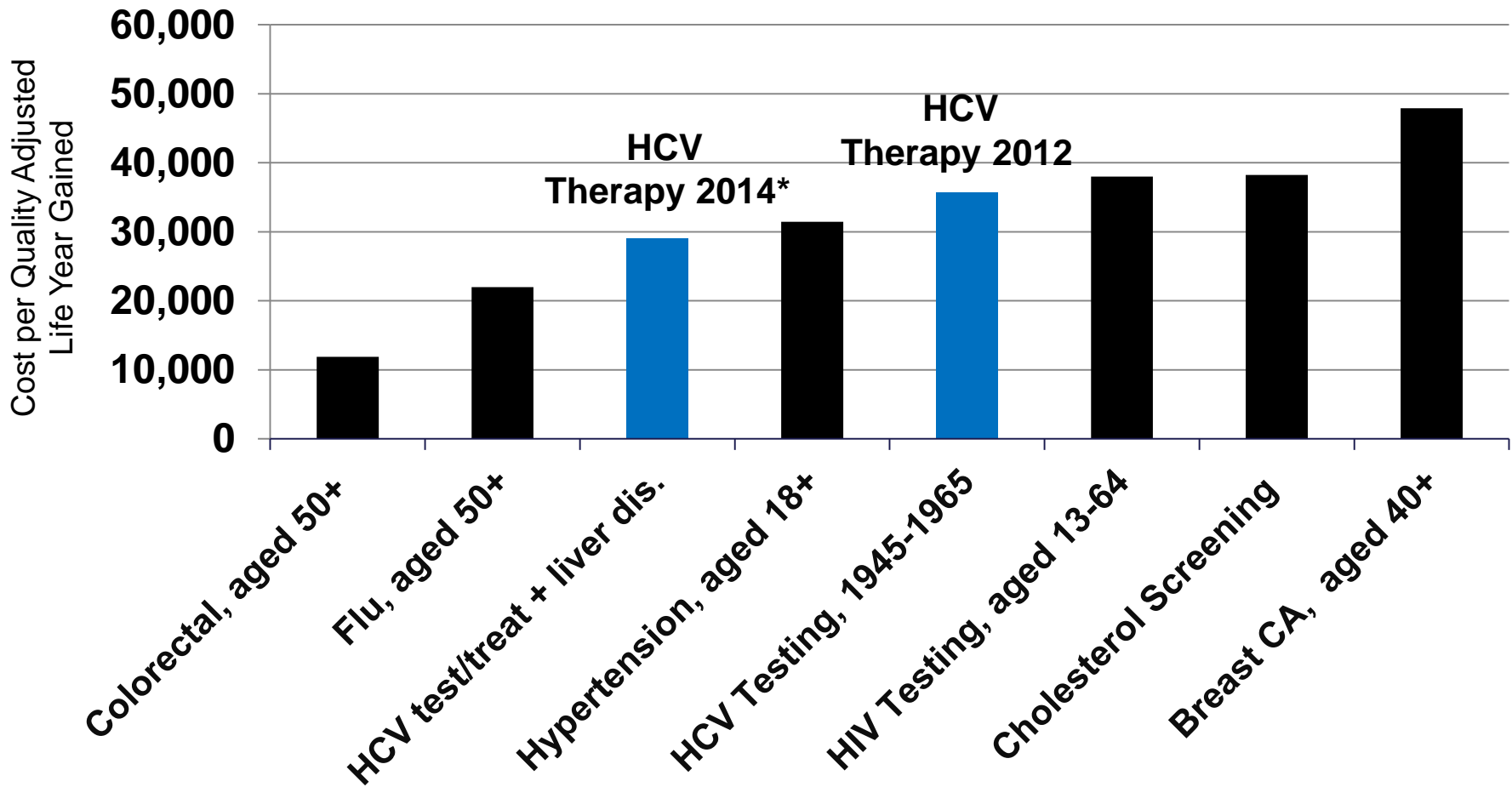
USPSTF: U. S. Preventive Services Task Force. ALT: Alanine transaminase.

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



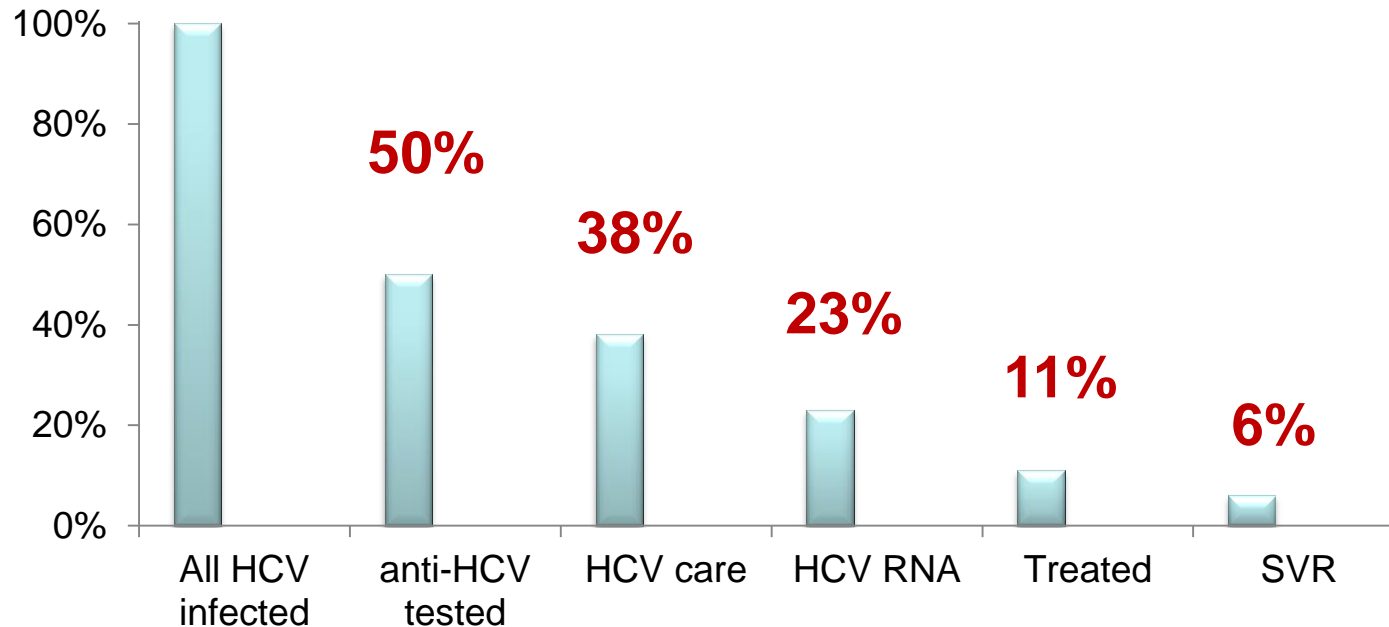
*CDC unpublished data. TVR: Telapavir.

<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.

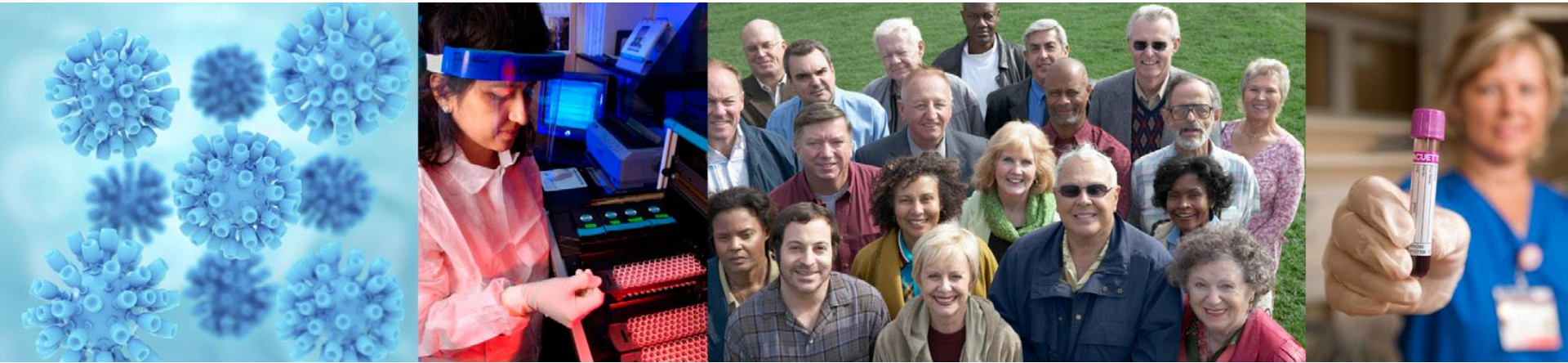
Where Are We Now?

- ❑ **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

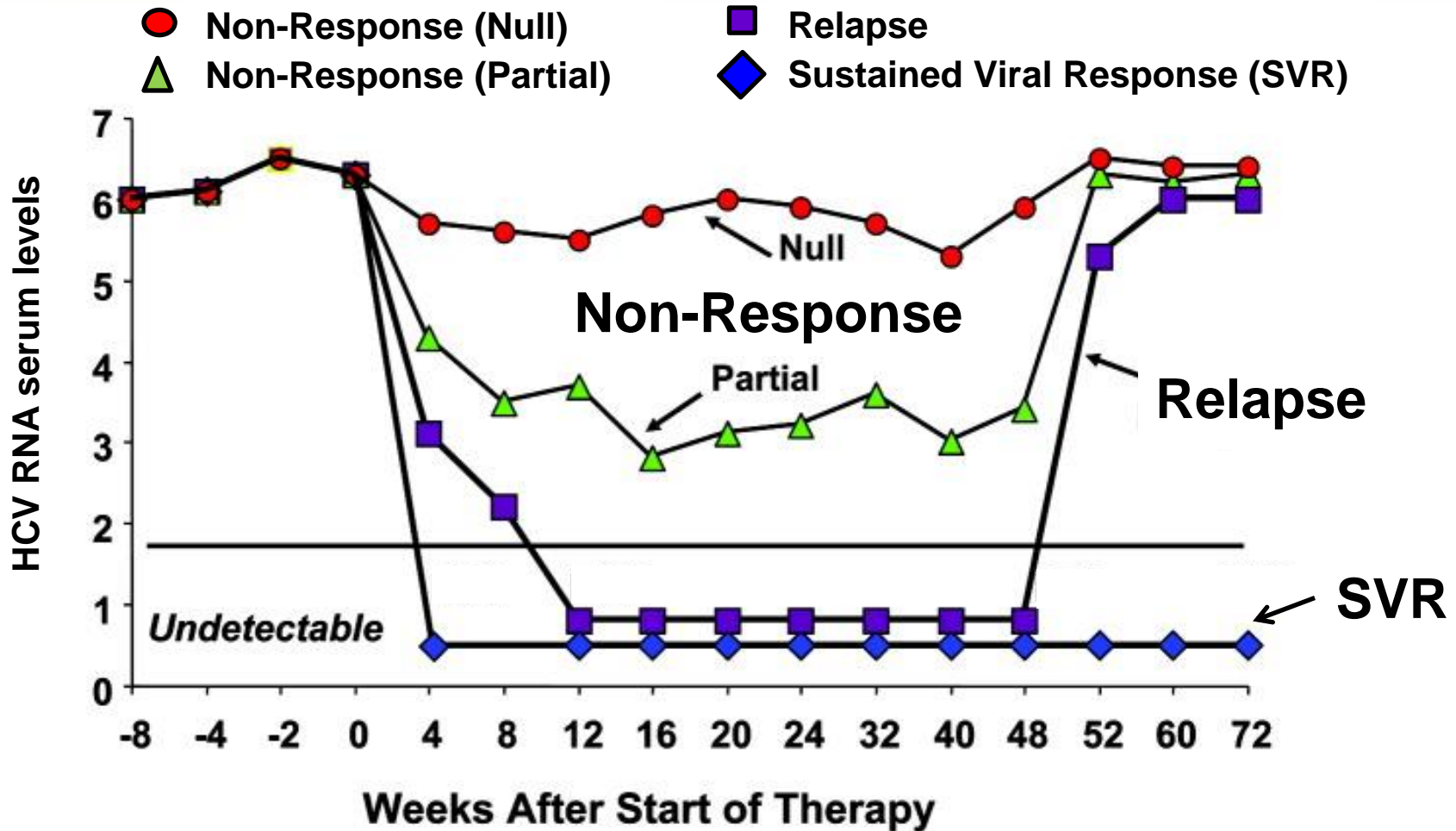
Johns Hopkins School of Medicine



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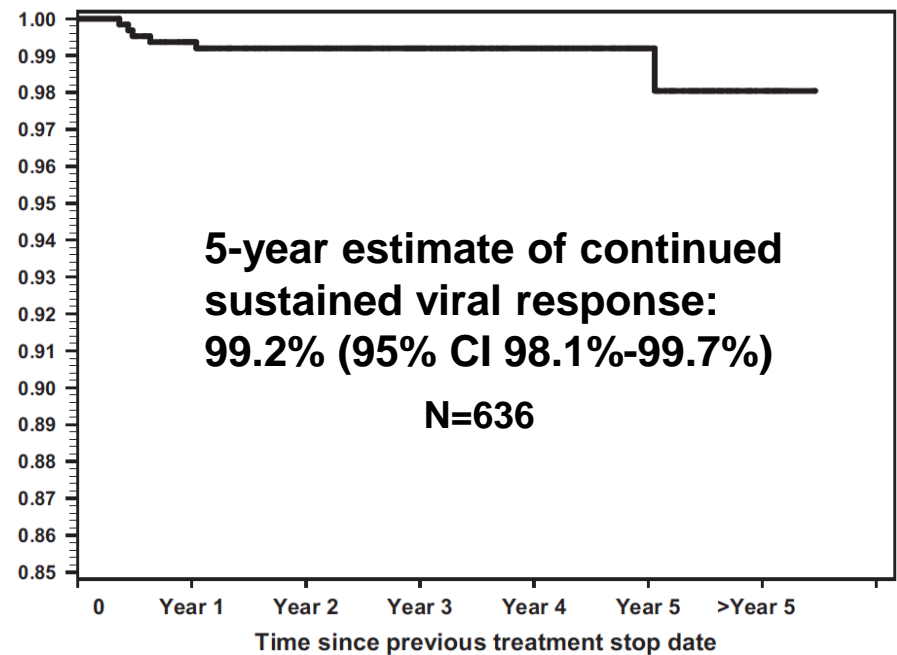
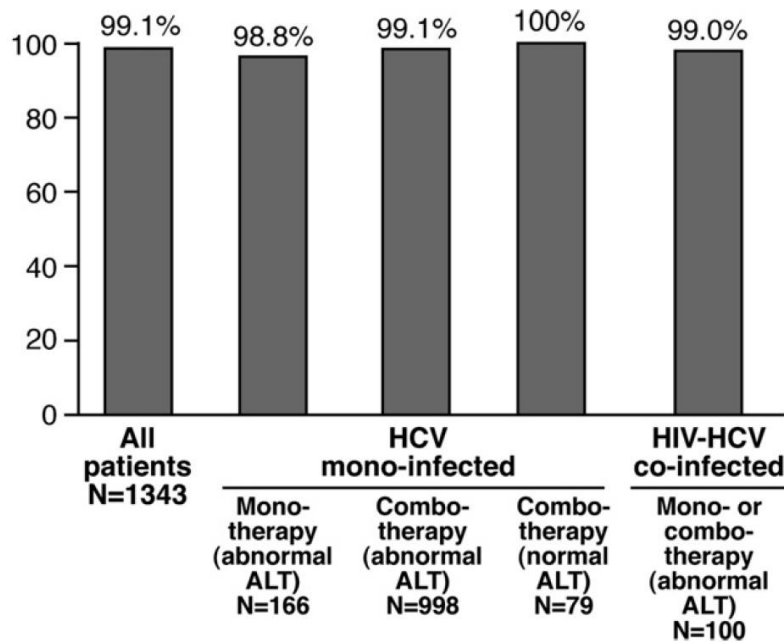
Hepatitis C Treatment Responses

Non-Response, Relapse, Sustained Viral Response



SVR is Considered Cure Reinfection is Uncommon

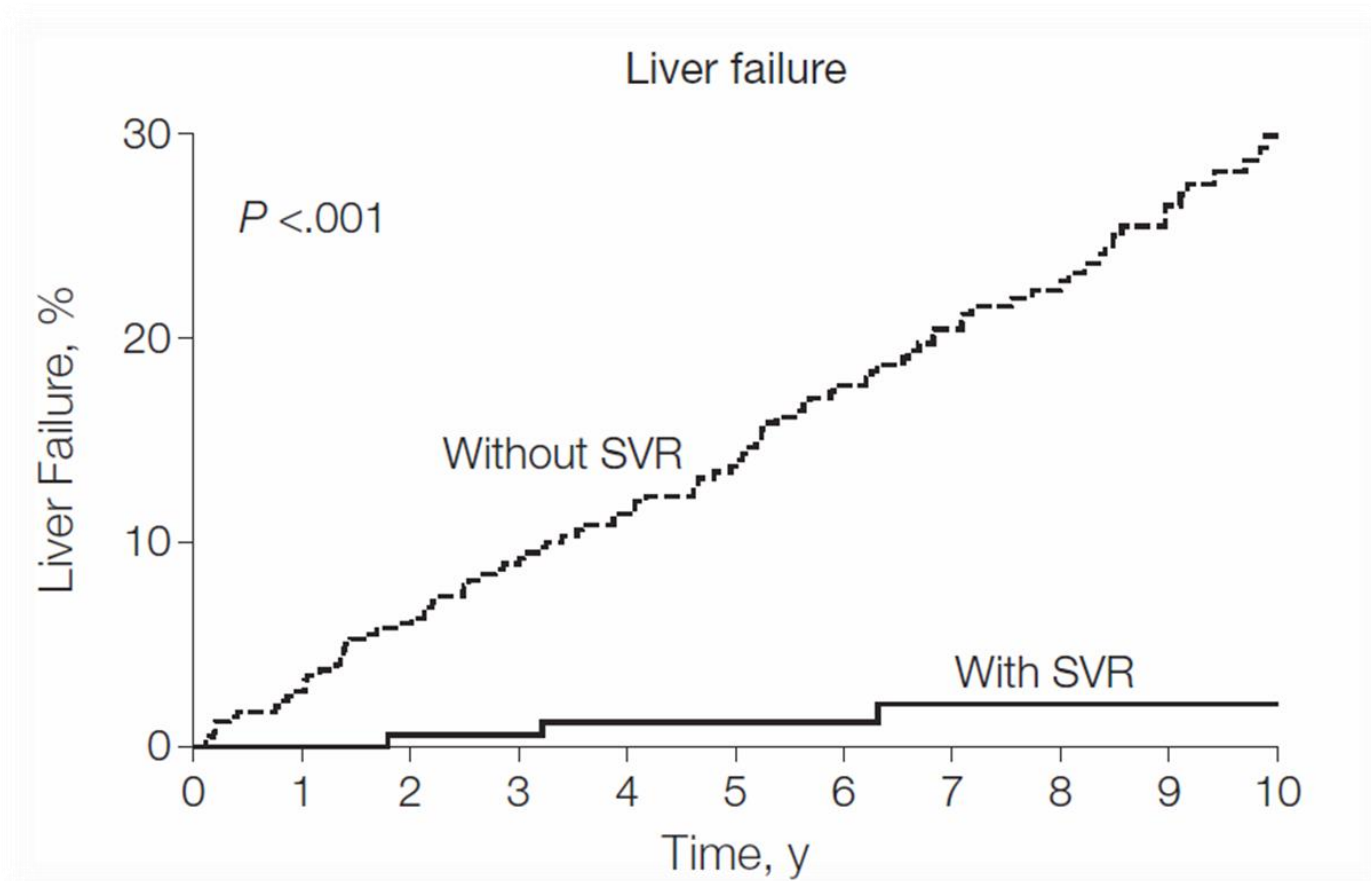
Percent with 5-year SVR



SVR: Sustained viral response

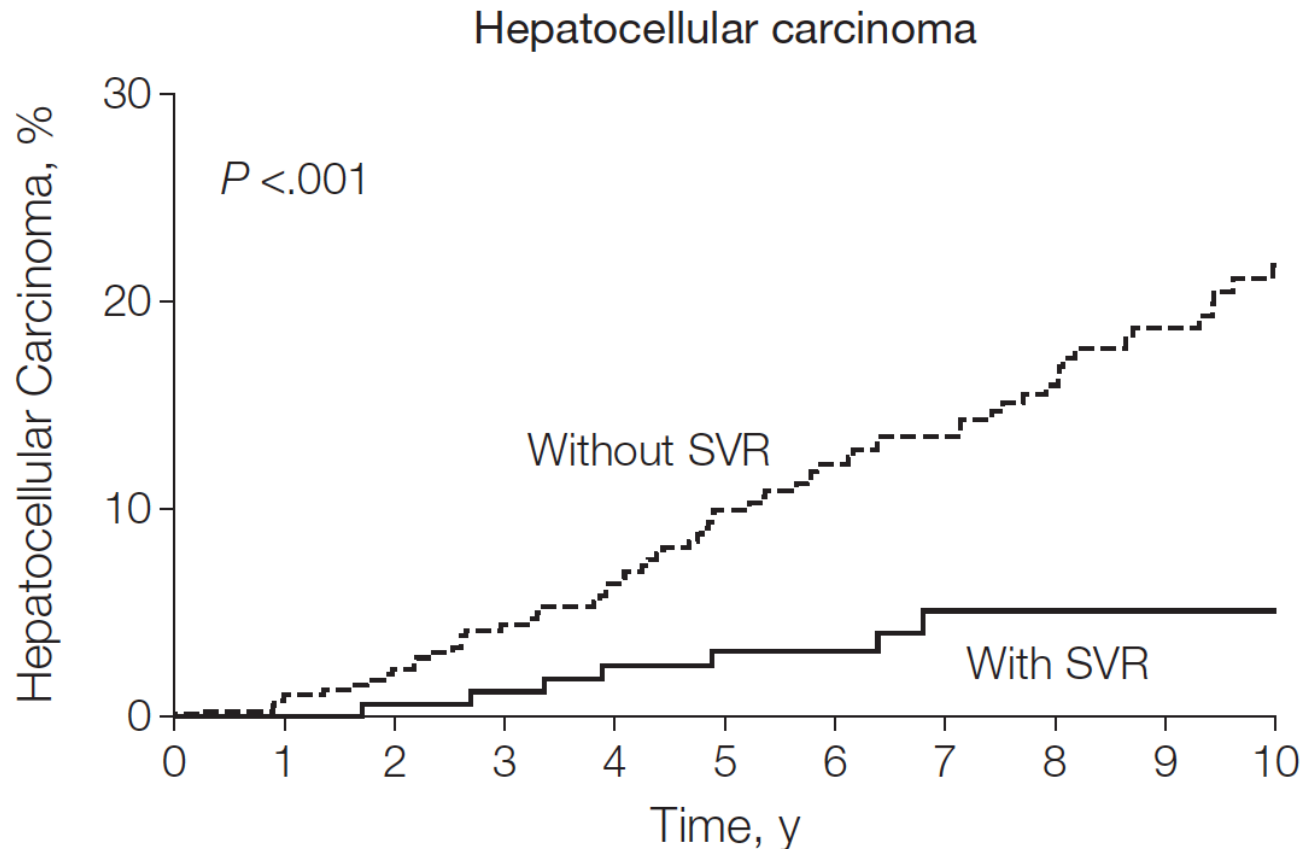
Swain, *Gastro* 2010. Manns, *J Viral Hep* 2014.

SVR is Considered Cure Reduction in Liver Failure



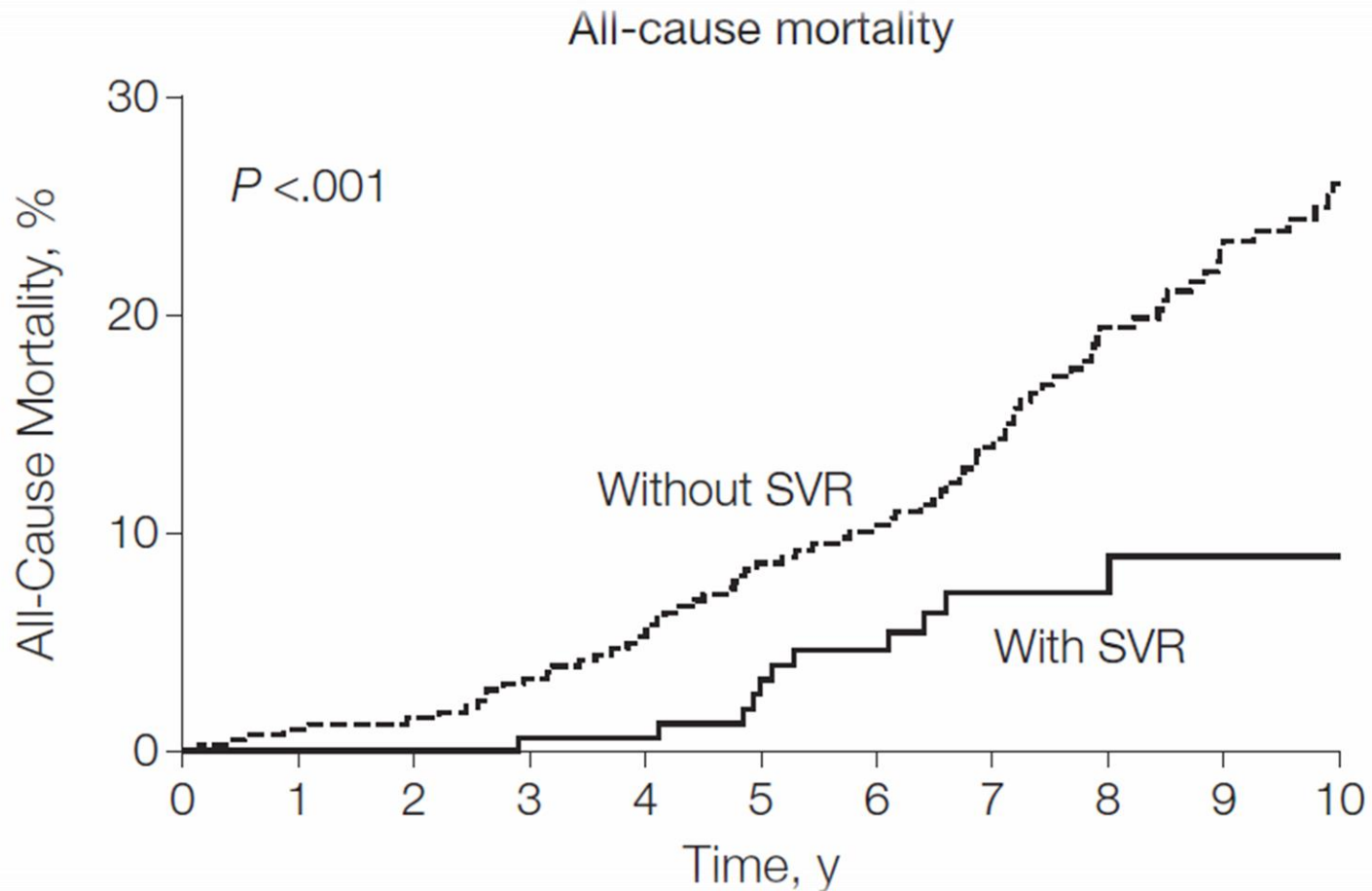
Van der Meer, *JAMA* 2012. Backus, *Clin Gastro* 2011. Imazeki, *Hepatology* 2003. Shiratori, *Ann Intern Med* 2005. Veldt, *Ann Intern Med* 2007. Berenguer, *Hepatology* 2009.

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.

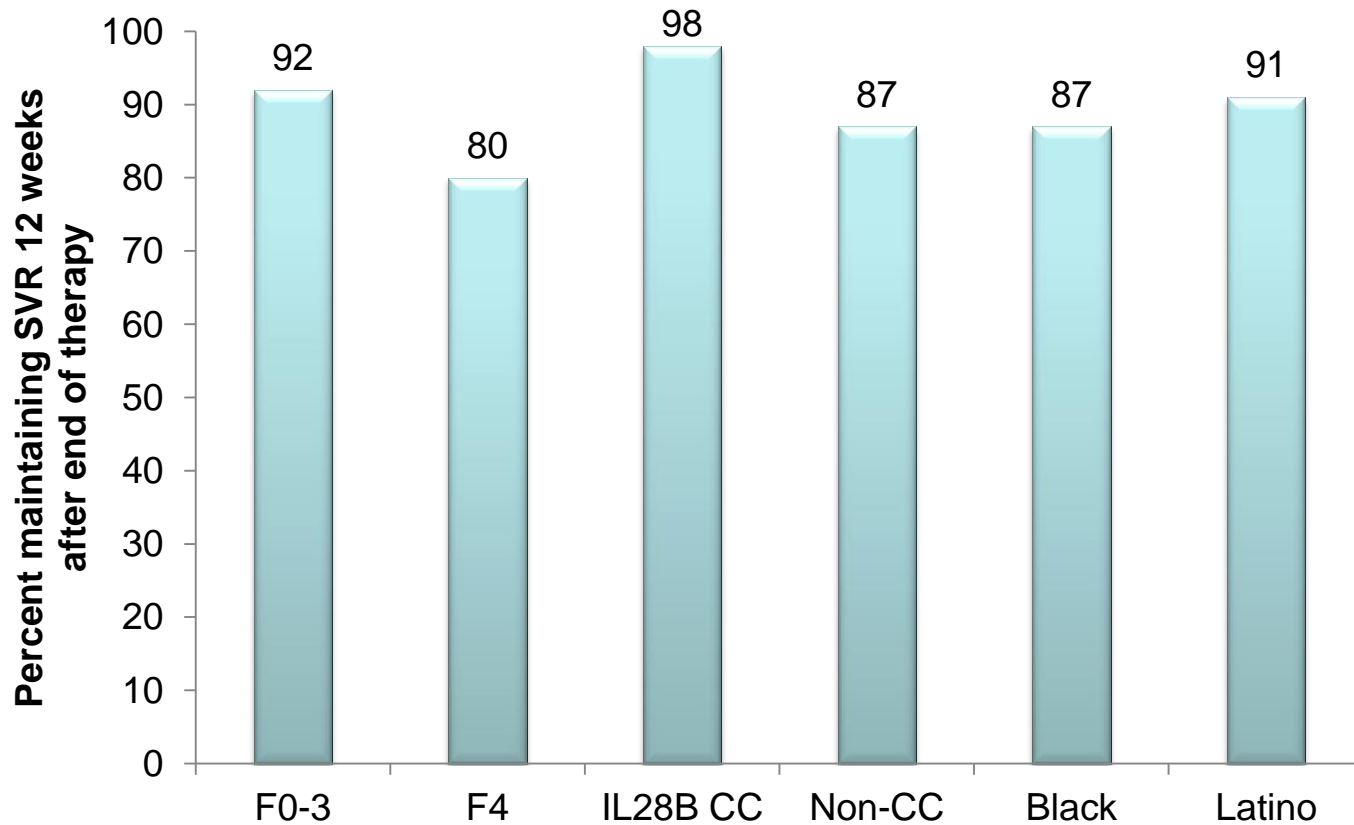
Key Therapeutic Milestones in Reaching the Curative Era of HCV

□ 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

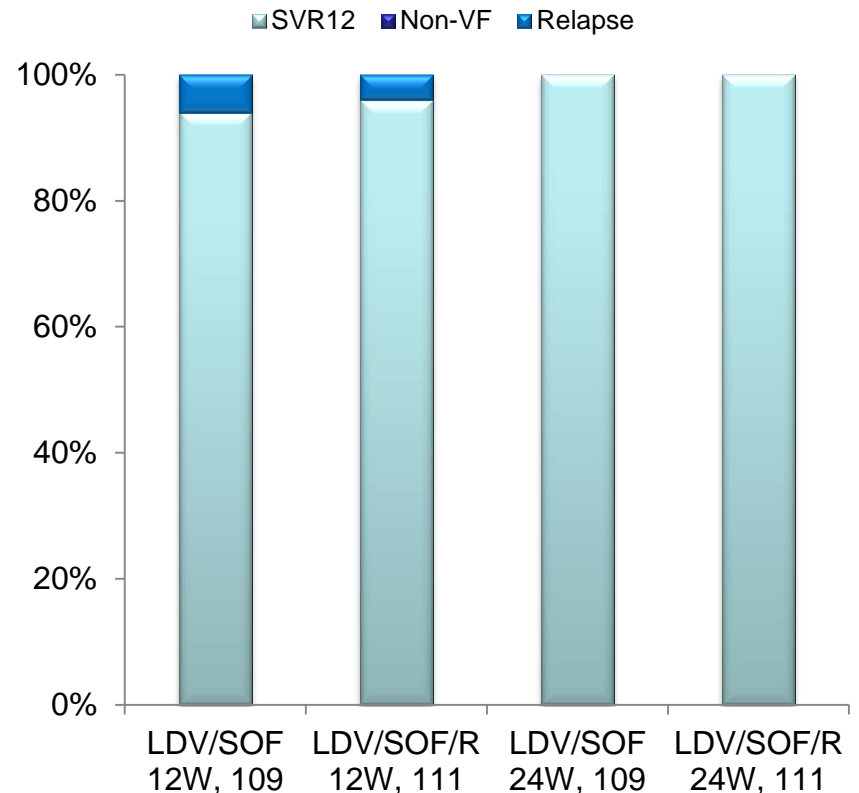
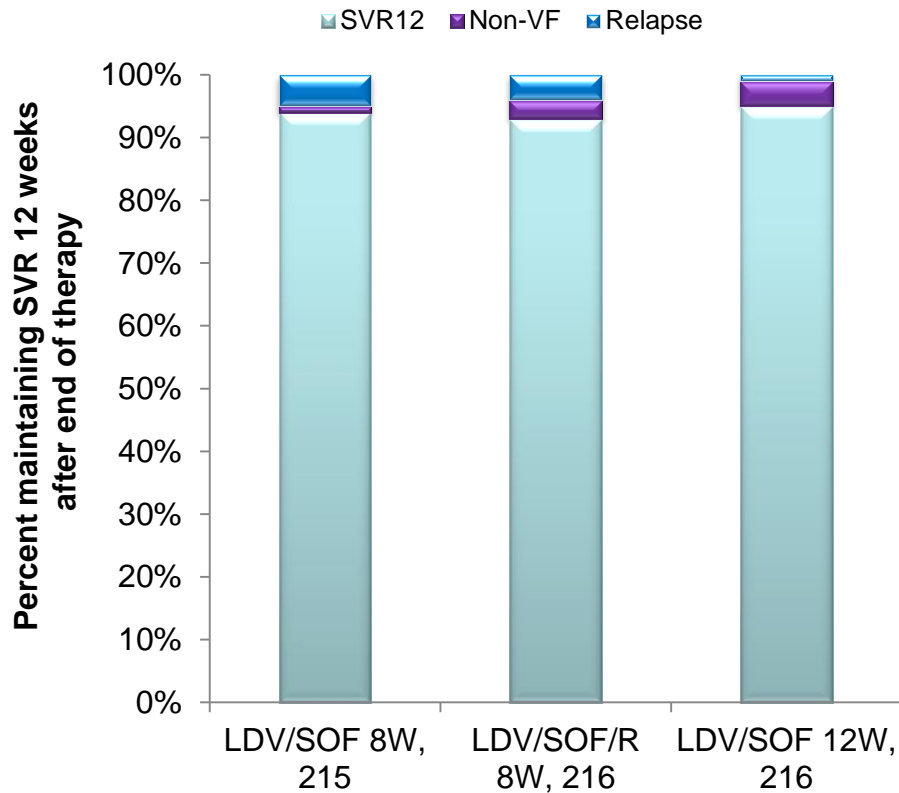


PegIFN; pegylated interferon. F0-3: Stages of liver fibrosis from none to moderate. F4: Severe liver fibrosis. Non-CC: Individuals with either CT or TT IL28-genotype.

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

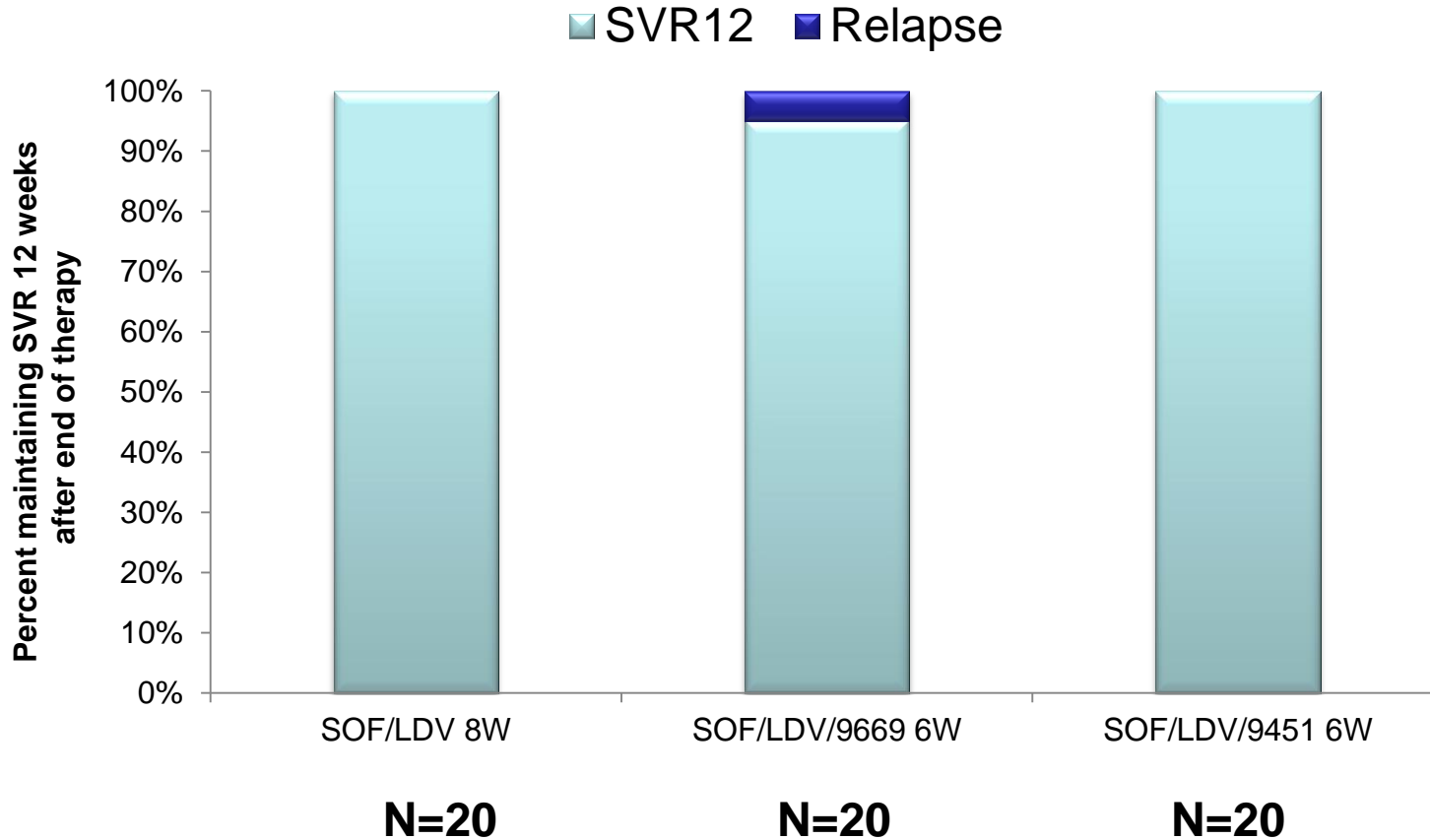
LDV/SOF naive F0-2, naive

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**

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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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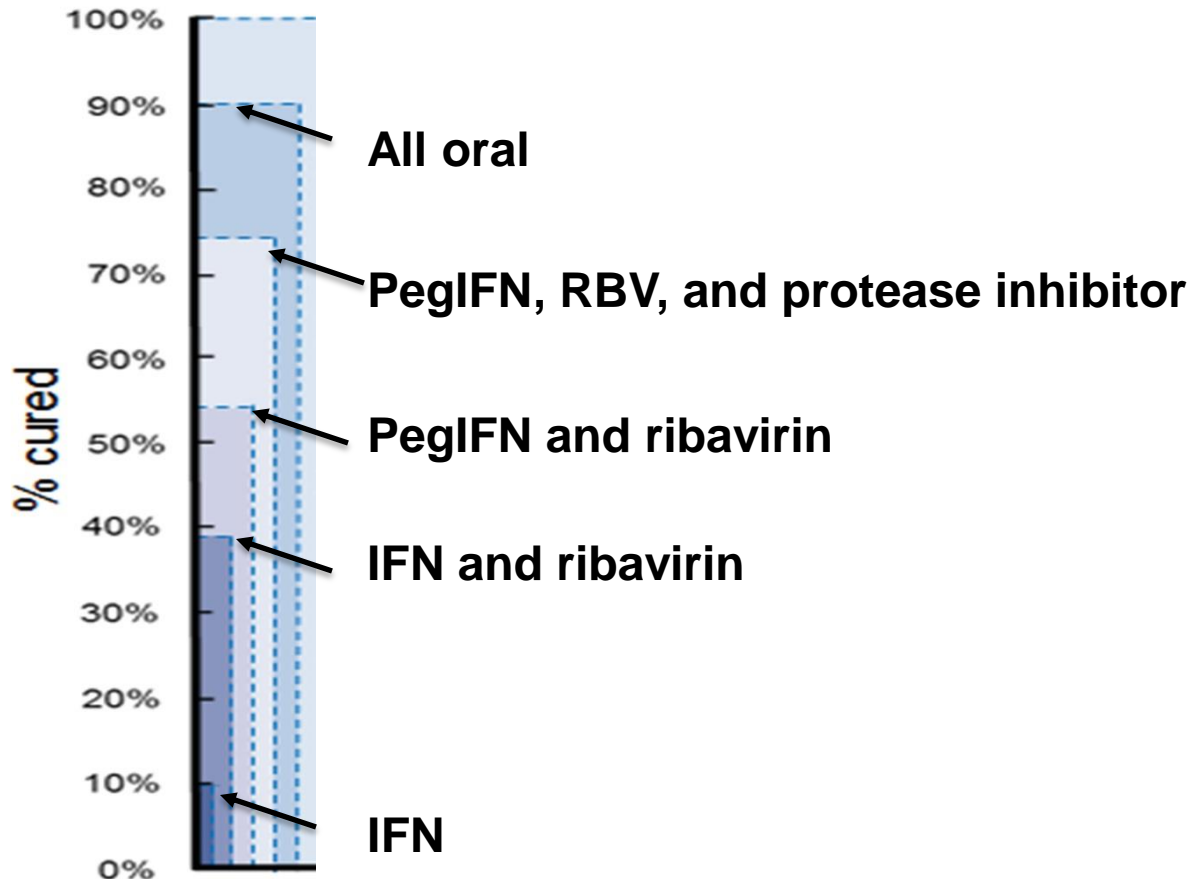
Methods Table 3. Commonly Used Abbreviations and Their Expansions
...
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HCV TESTING AND LINKAGE TO CARE

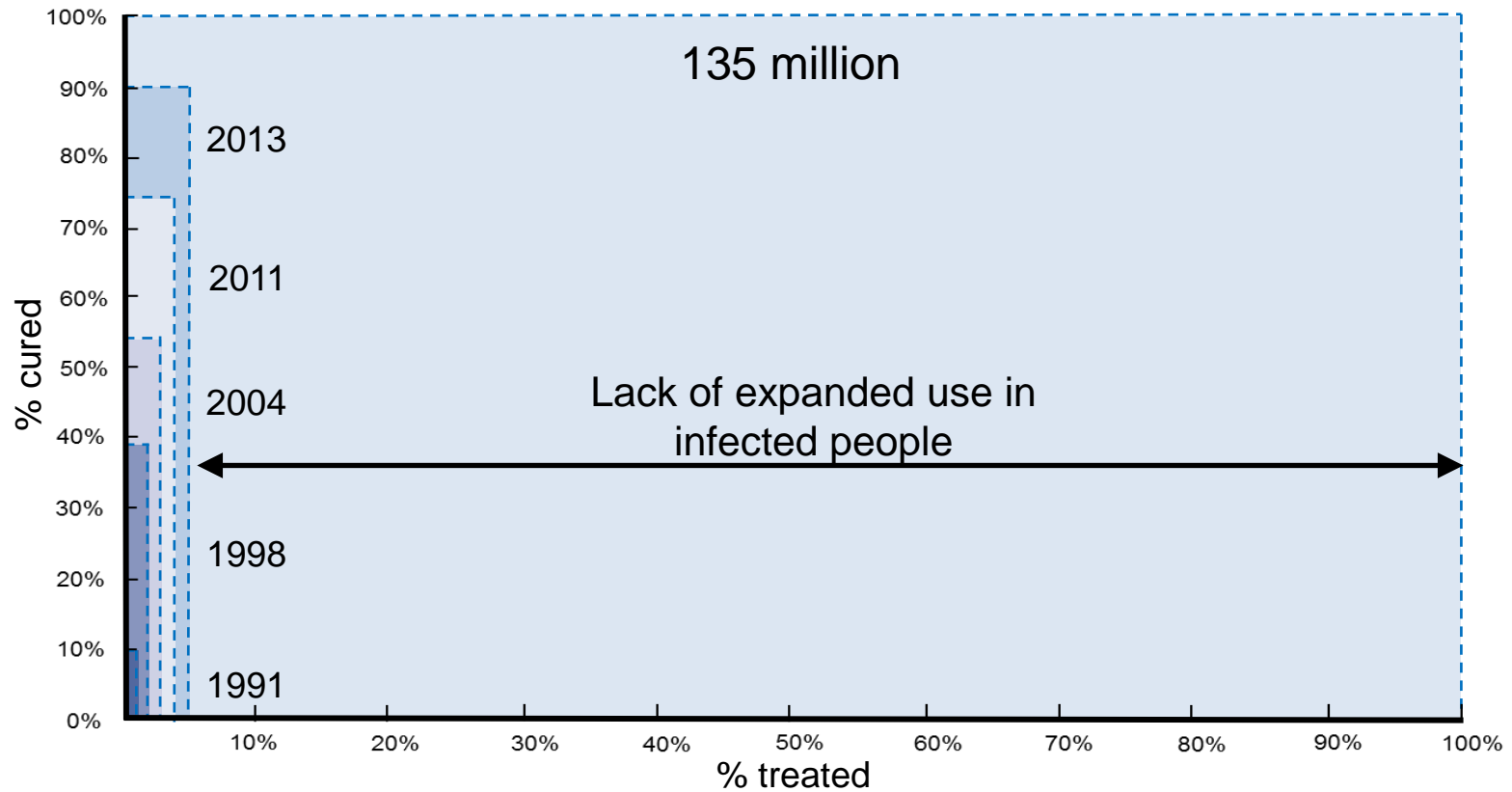
Evaluating the Cost Effectiveness of New Therapies

- ❑ 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



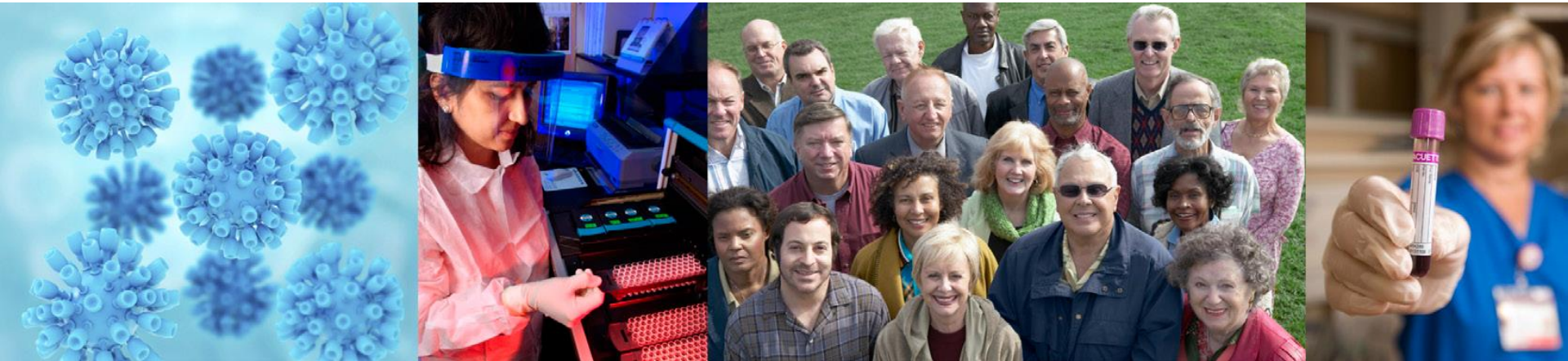
Greater Uptake Will Maximize Potential Global Impact



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



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Essential Goals to Eliminate HCV

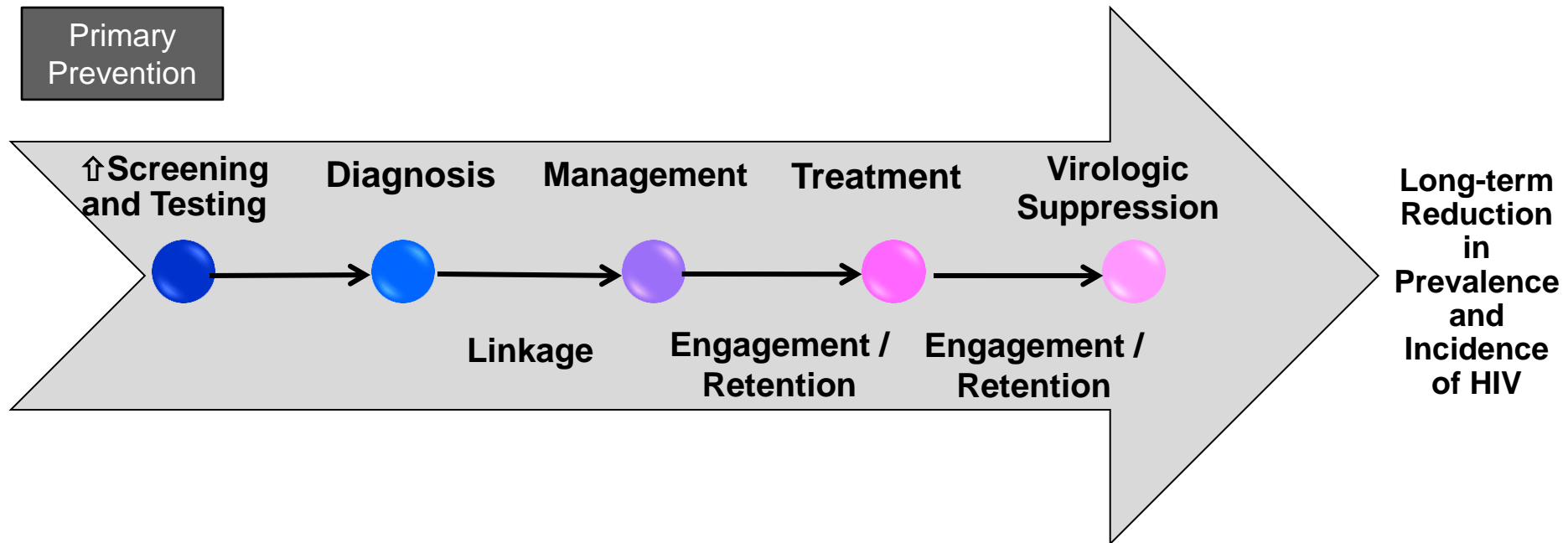
❑ Prevent sequelae of advancing liver disease in those already infected

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

❑ Prevent new or “incident” infections

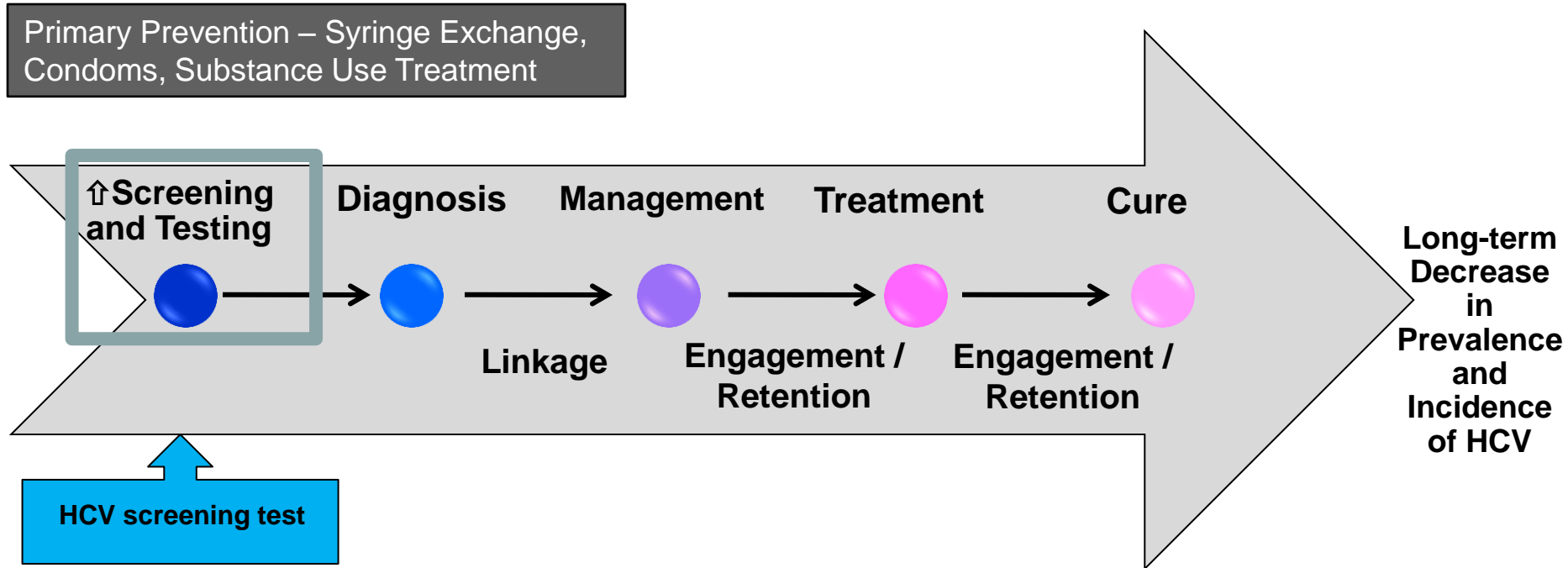
- Persons who inject drugs (PWID)
- Unsafe healthcare practices
- Sexual exposures in immunocompromised individuals

Continuum of Care Model for HIV



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

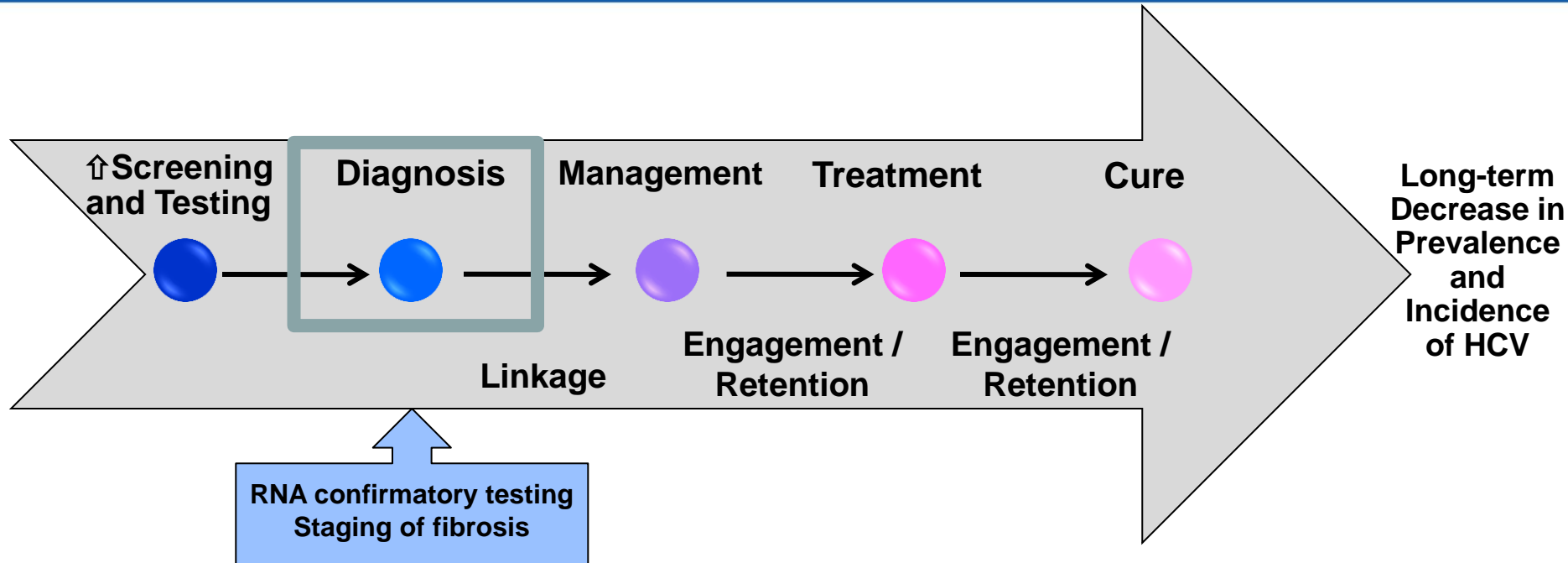
Continuum of Care Model for HCV



- **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.

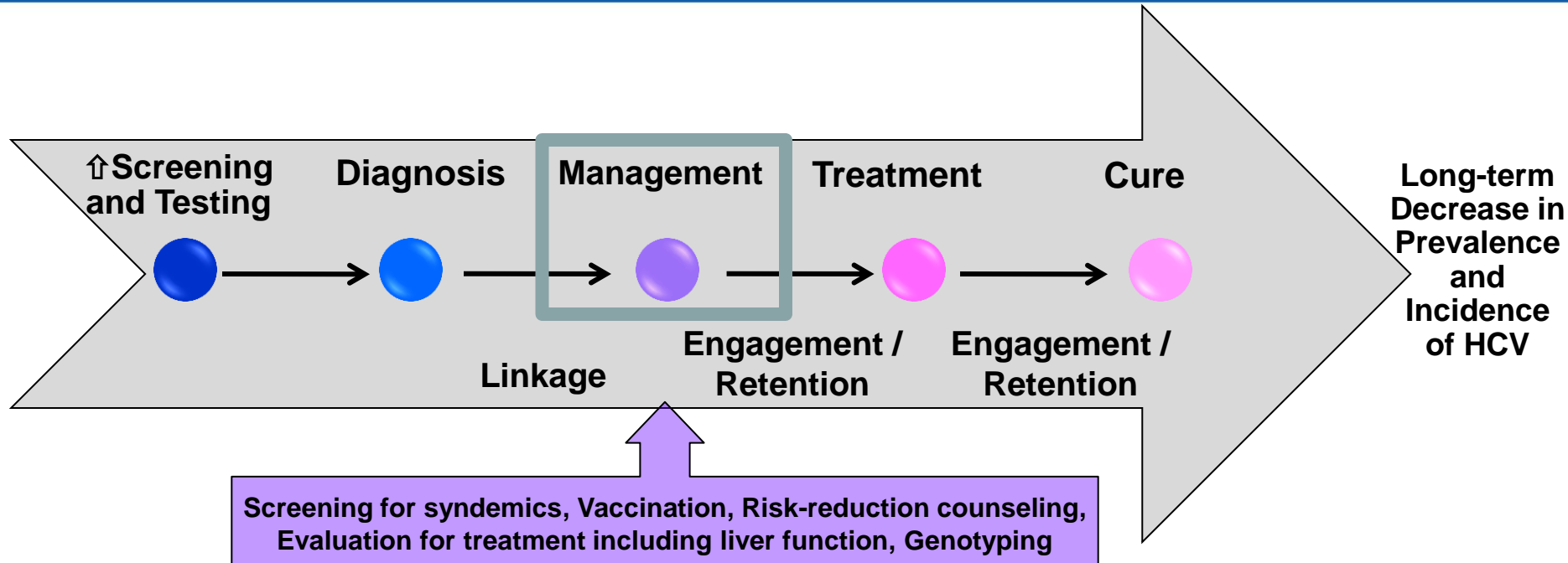
Continuum of Care Model for HCV



- 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

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

Continuum of Care Model for HCV

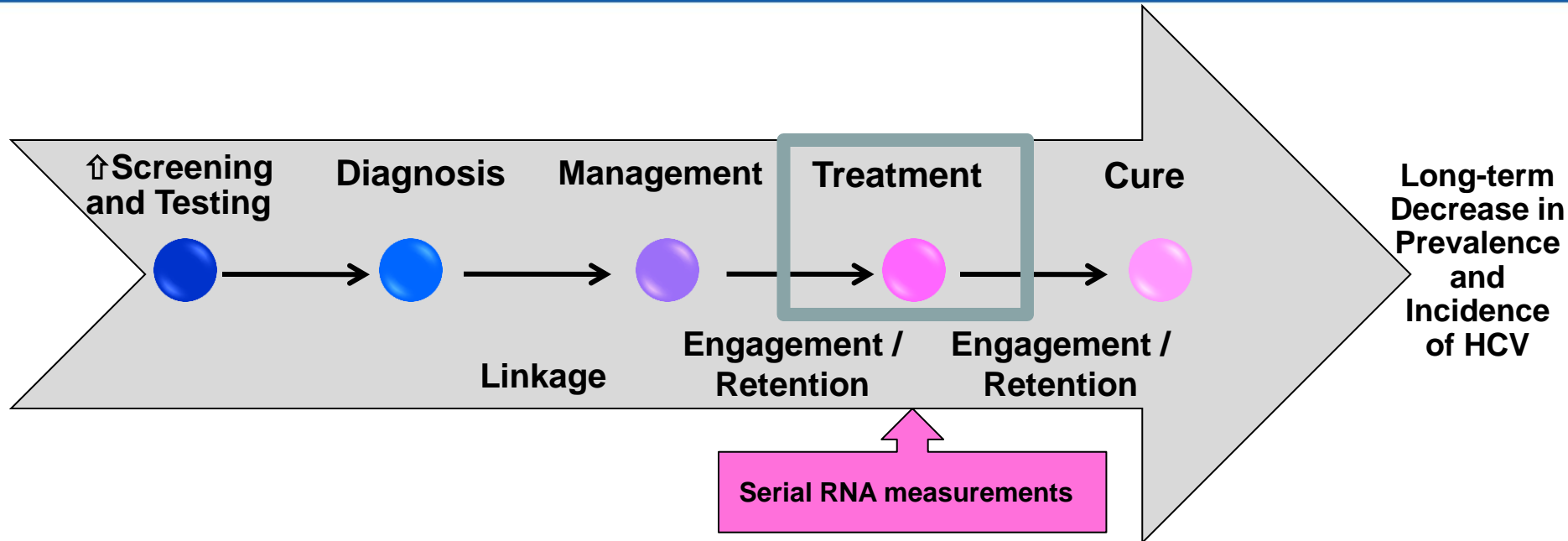


- **Patient management should include referral to substance use disorder treatment and brief alcohol interventions**
- **Healthcare-level systems could track serial ALT to ensure periodic evaluation is done**

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

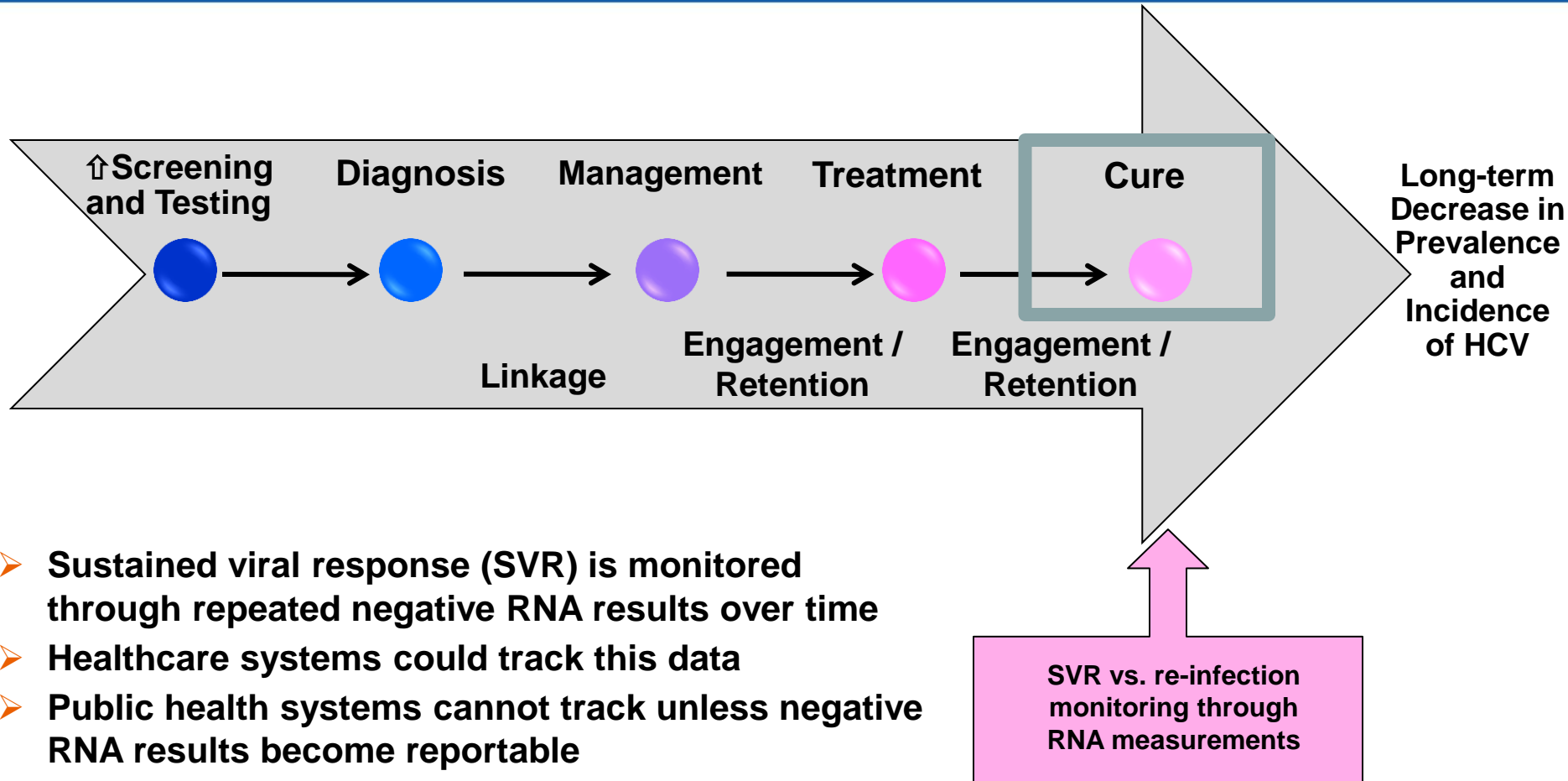


- **Historically, treatment uptake was major barrier**
- **New regimens should improve treatment uptake**
- **New barriers such as cost and access may limit potential impact of new regimens**
- **Interventions could address these new barriers**
- **If negative RNA results were reportable, public health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

SVR: Sustained viral response.

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

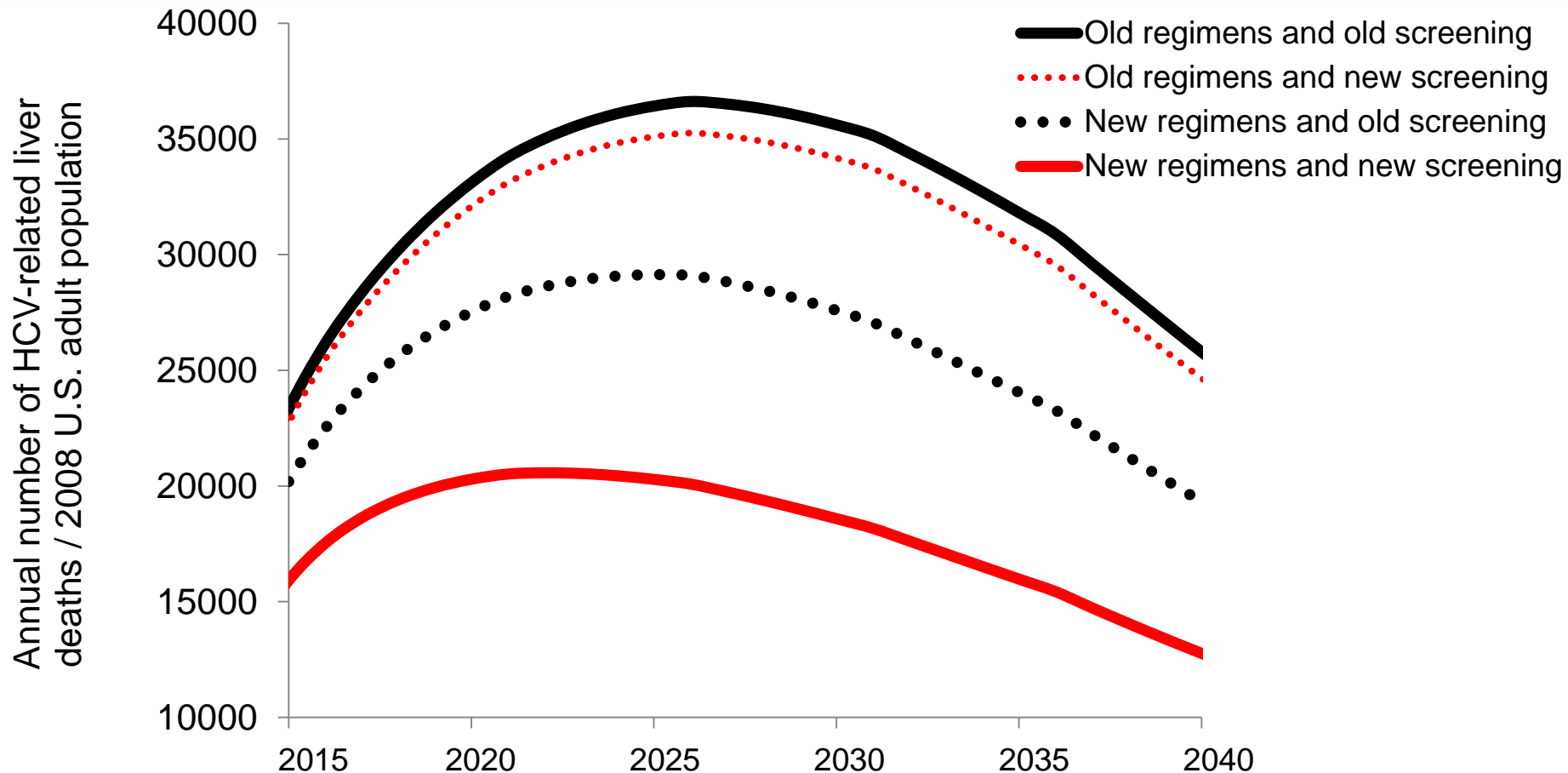
Continuum of Care Model for HCV



- **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**

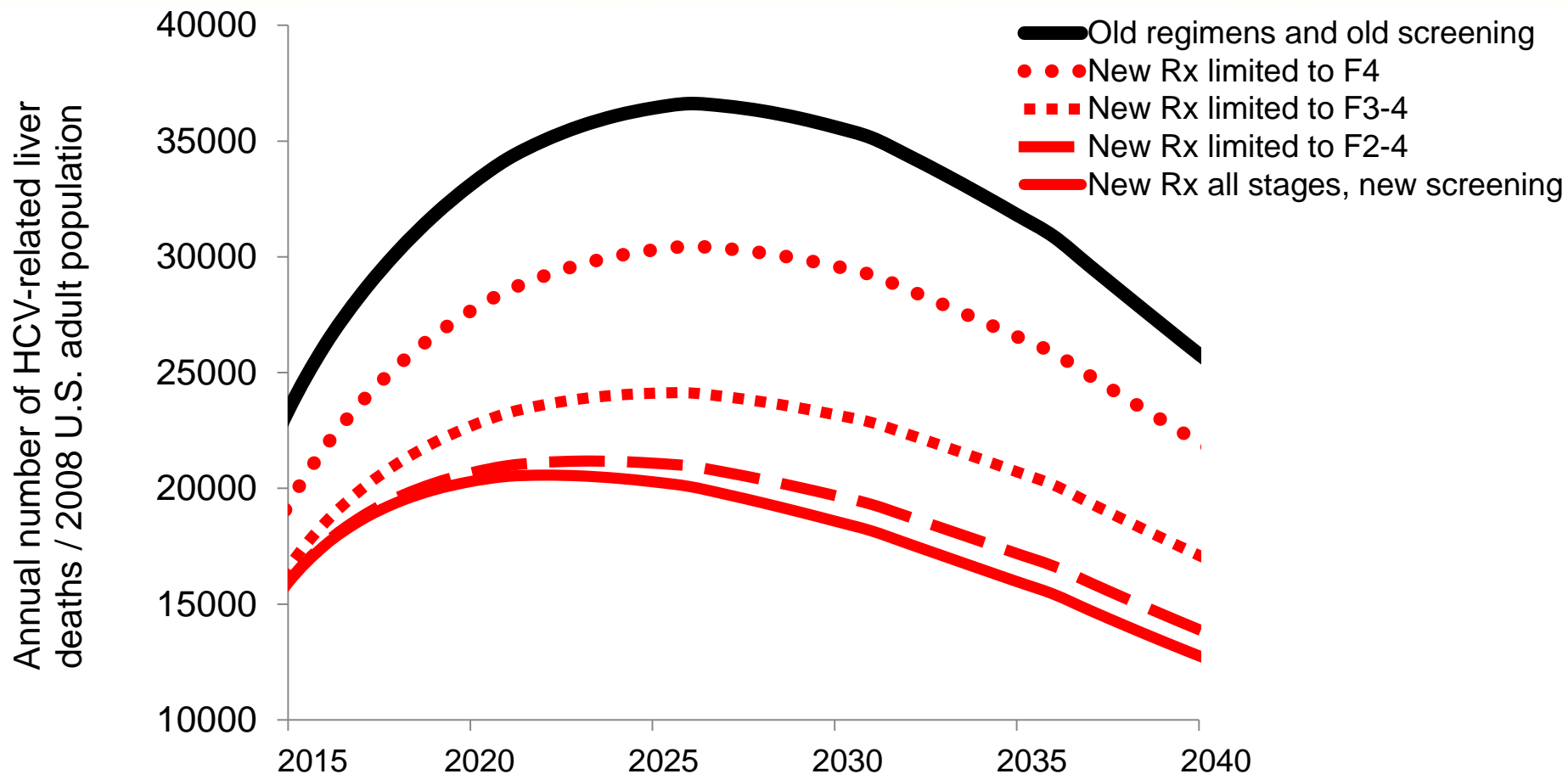
Adapted from: Das M, Conference on Retroviruses and Opportunistic Infections 2014.

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



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

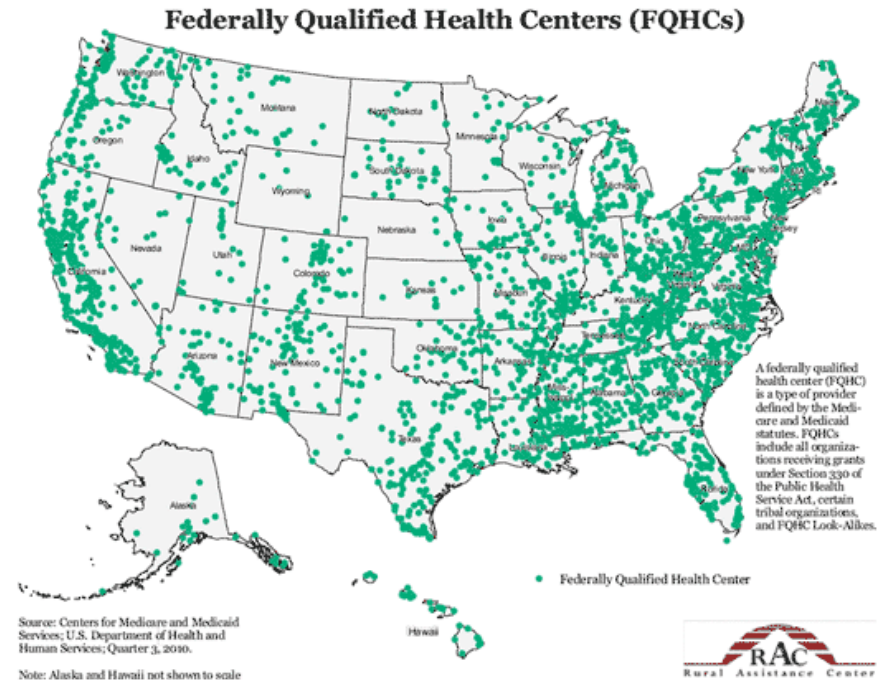
Potential Reduction in HCV-Related Liver Deaths by Treatment Strategy based on Liver Fibrosis



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

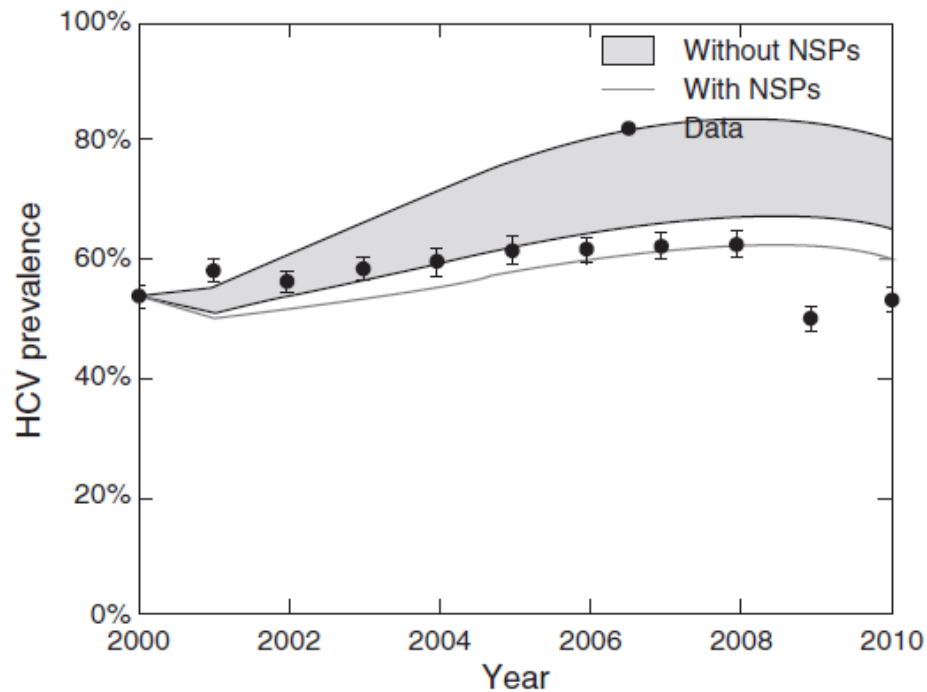
 - Treatment as Prevention (TasP)

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

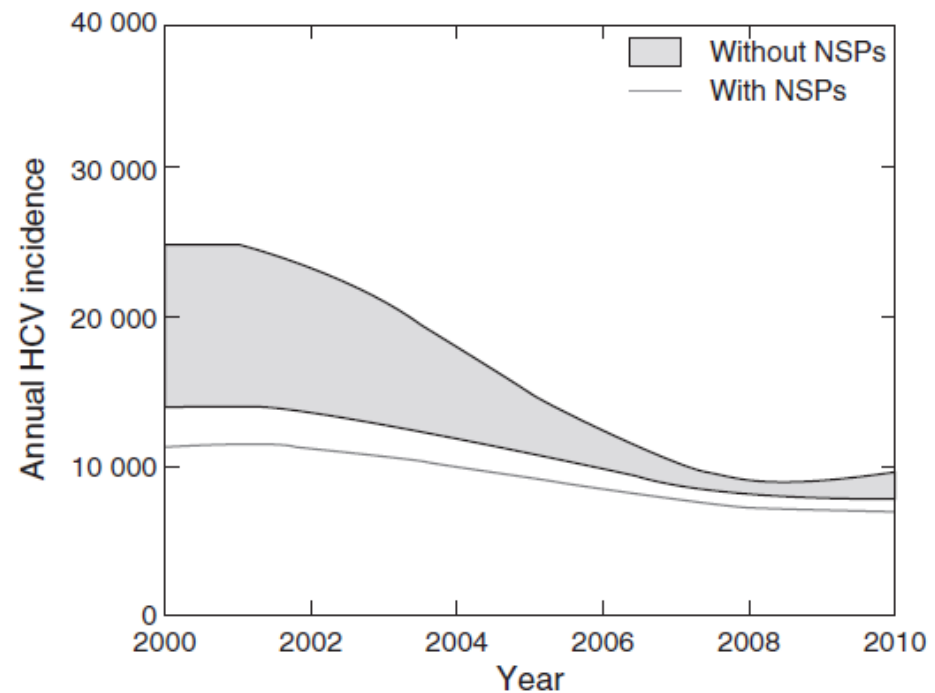
 - Vaccine research
 - Early Phase 2 stages

Syringe Access Programs Impact On HCV Prevalence and Incidence

Impact on Prevalence



Impact on Incidence



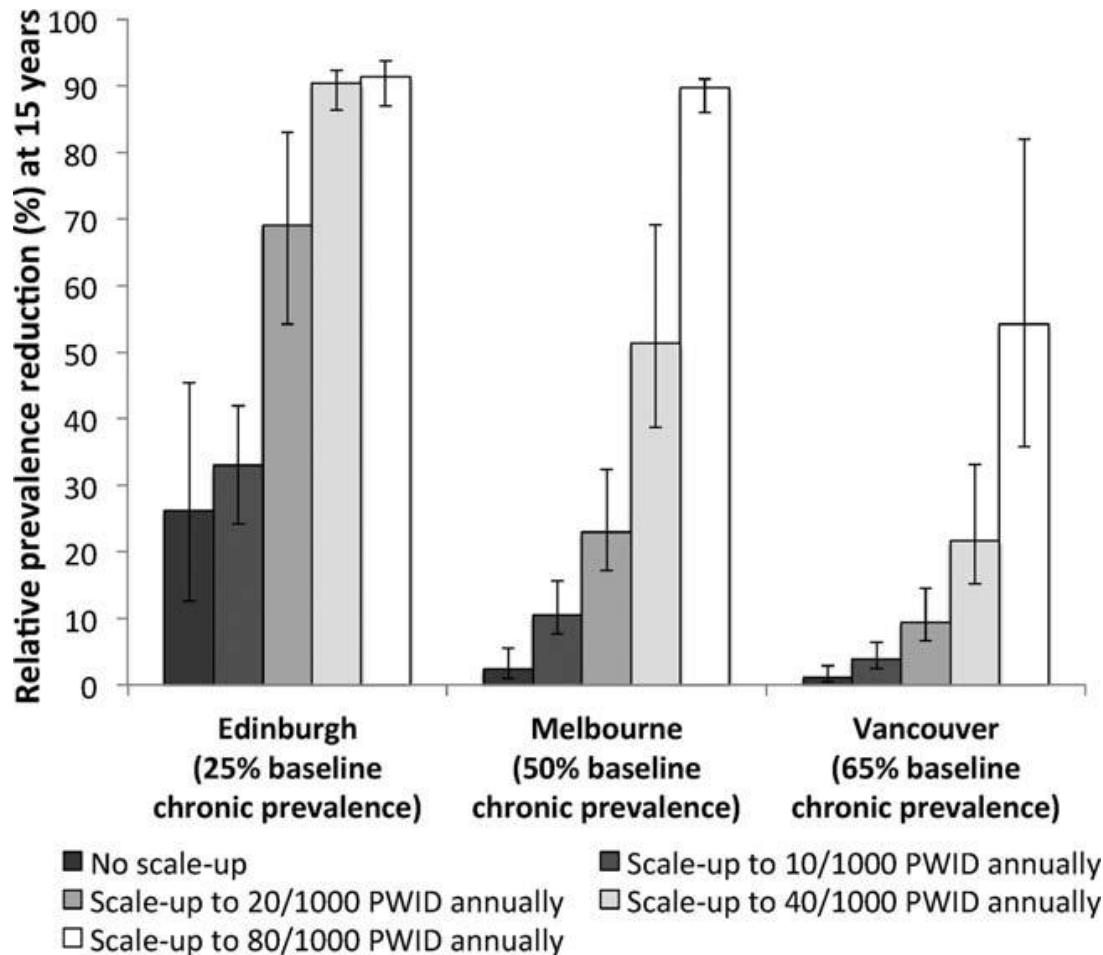
NSP: Needle & syringe program.
Kwon J, *AIDS* 2012.

Treatment as Prevention (TasP) for HCV

- ❑ **Interrupt Secondary Transmission**

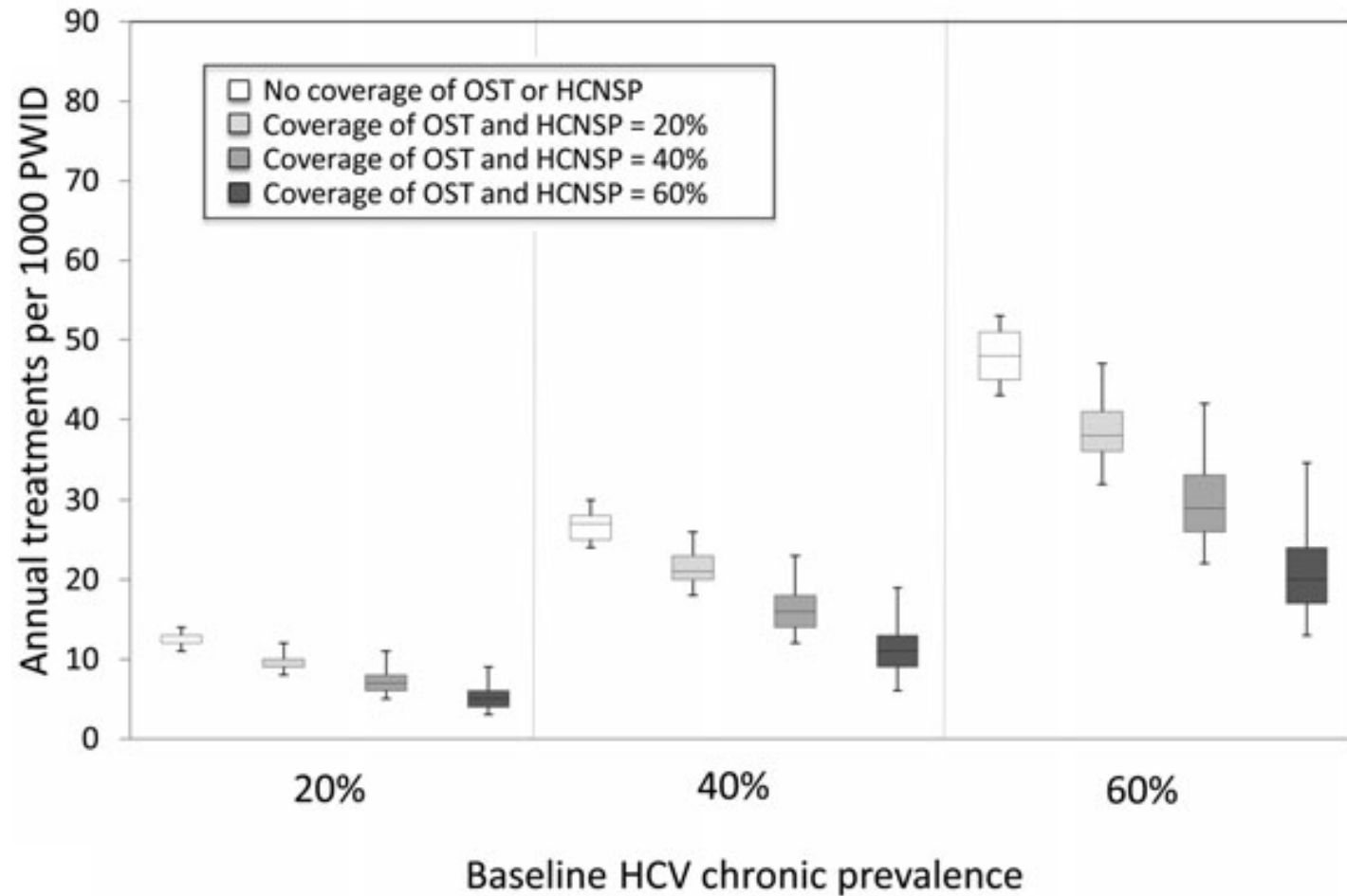
- ❑ **Maximize Impact on Incidence**
 - Target active injectors
 - Social network-based recruitment strategy
 - PWID in high prevalence areas
 - Optimize treatment delivery
 - Patient navigation programs
 - Conditional cash transfer programs
 - Directly observed therapy

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

