HEPATITIS C : RECENT ADVANCES IN SCREENING & MANAGEMENT

6/27/2014

“C” Stands for Cure….

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DISCLOSURES

Grant Support

- Gilead

- I will be discussing off-label use of medications

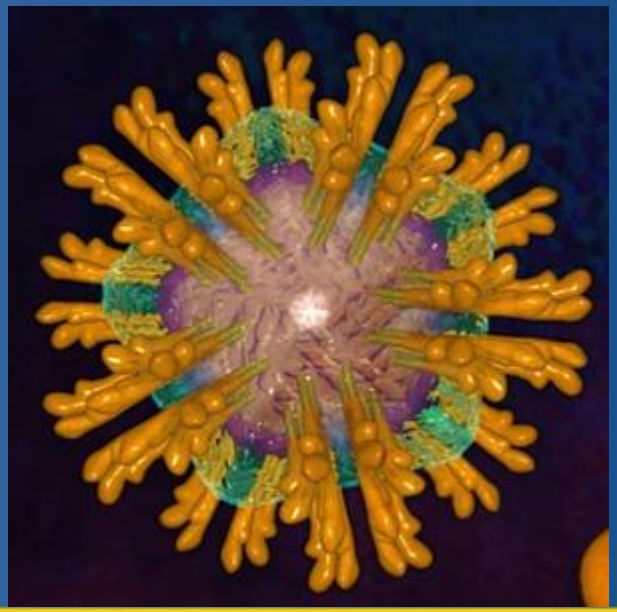
OUTLINE

- Epidemiology
- Screening guidelines
- Natural history and assessment
- Extra-hepatic manifestations
- Treatment strategies

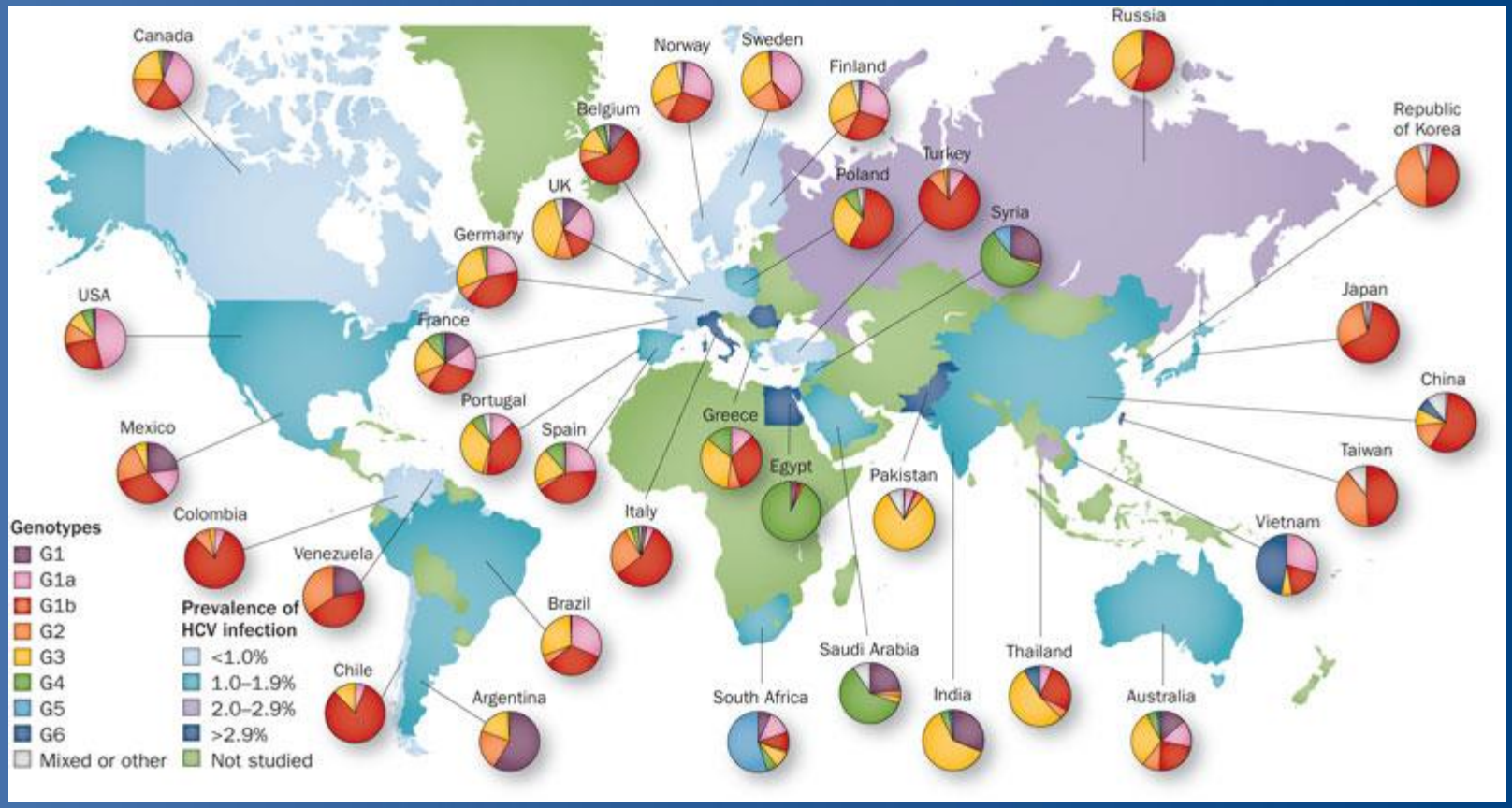
VIROLOGY
HEPATITIS C VIRUS (HCV)

Member of flaviviridae family

- Six genotypes and subgenotypes
  - vary by region
  - important predictor of treatment response



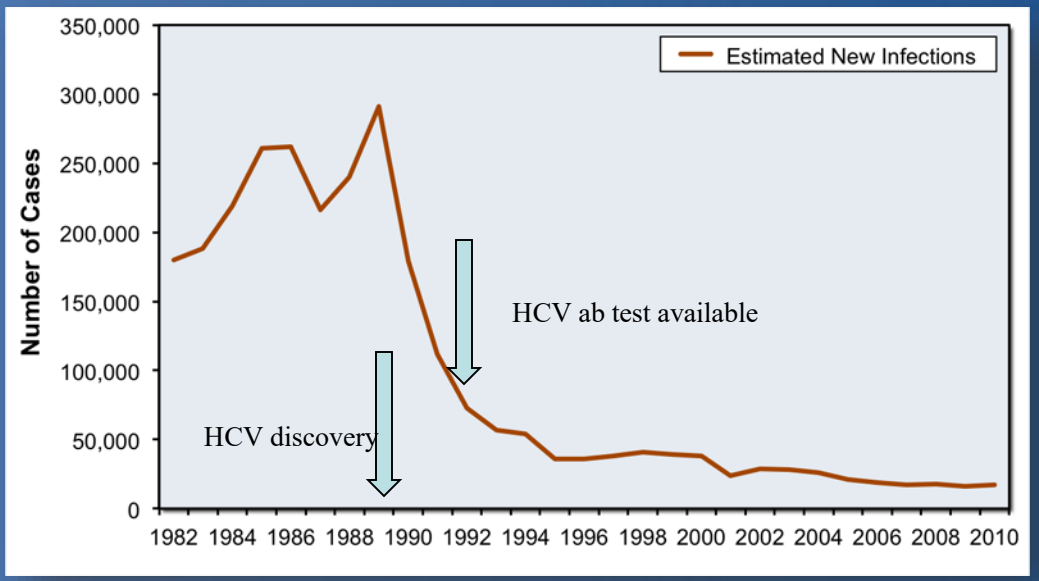
GLOBAL BURDEN OF HCV

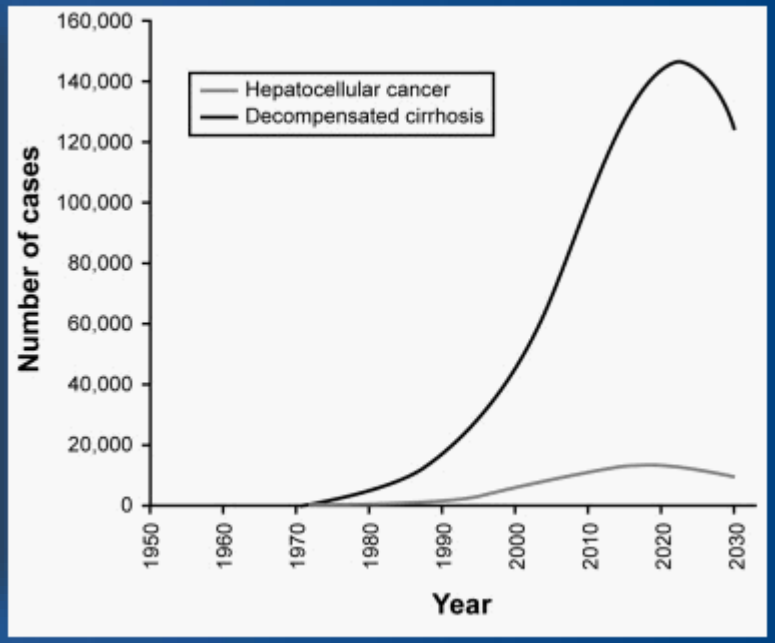


170 million chronically infected

3 – 4 million new infections/year

TRENDS OF HCV – ASSOCIATED DISEASE IN THE US

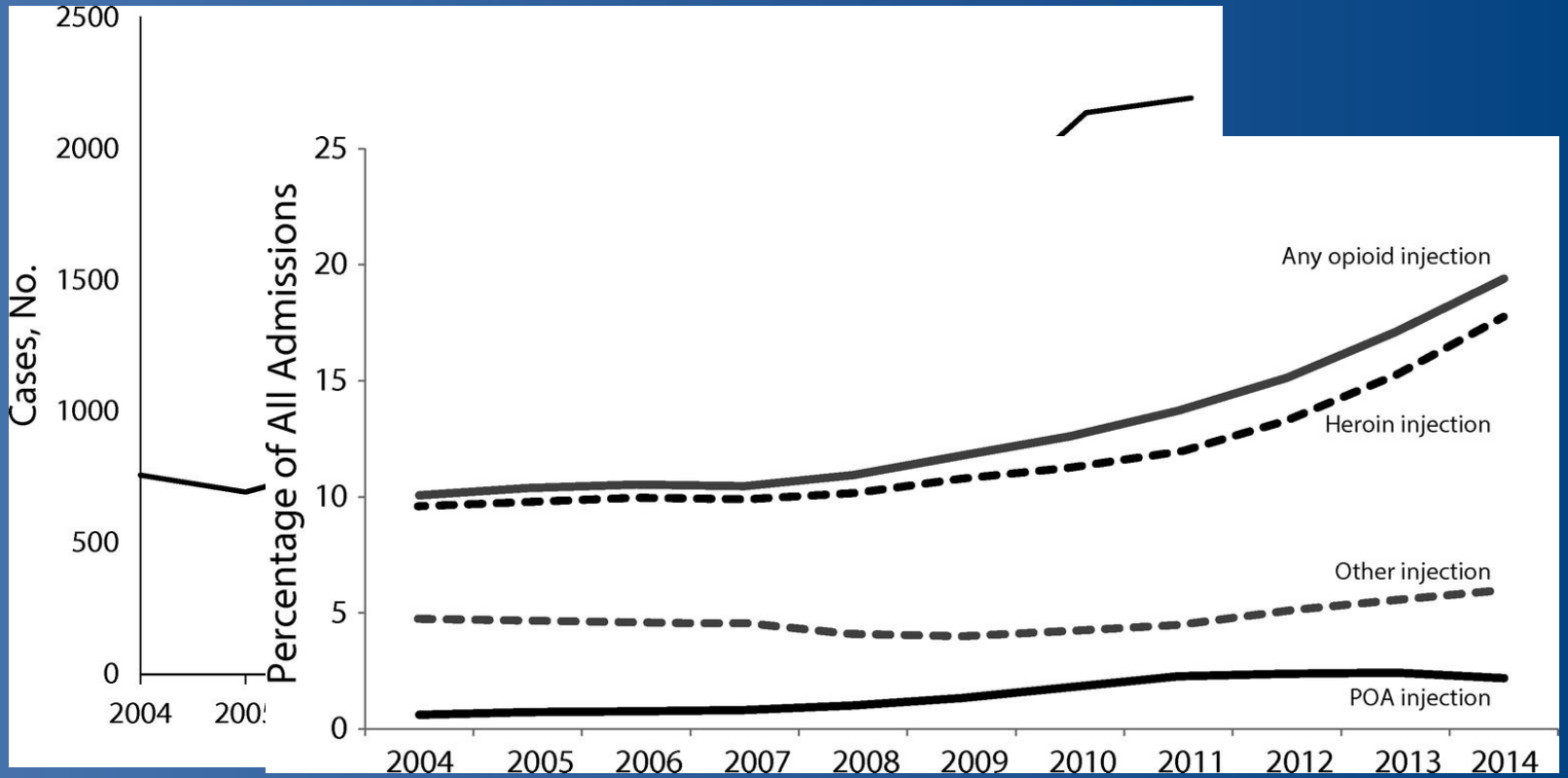




Peak incidence in early 90's

Currently experiencing "maturation" of this peak

RECENT TRENDS IN HCV INCIDENCE (US)



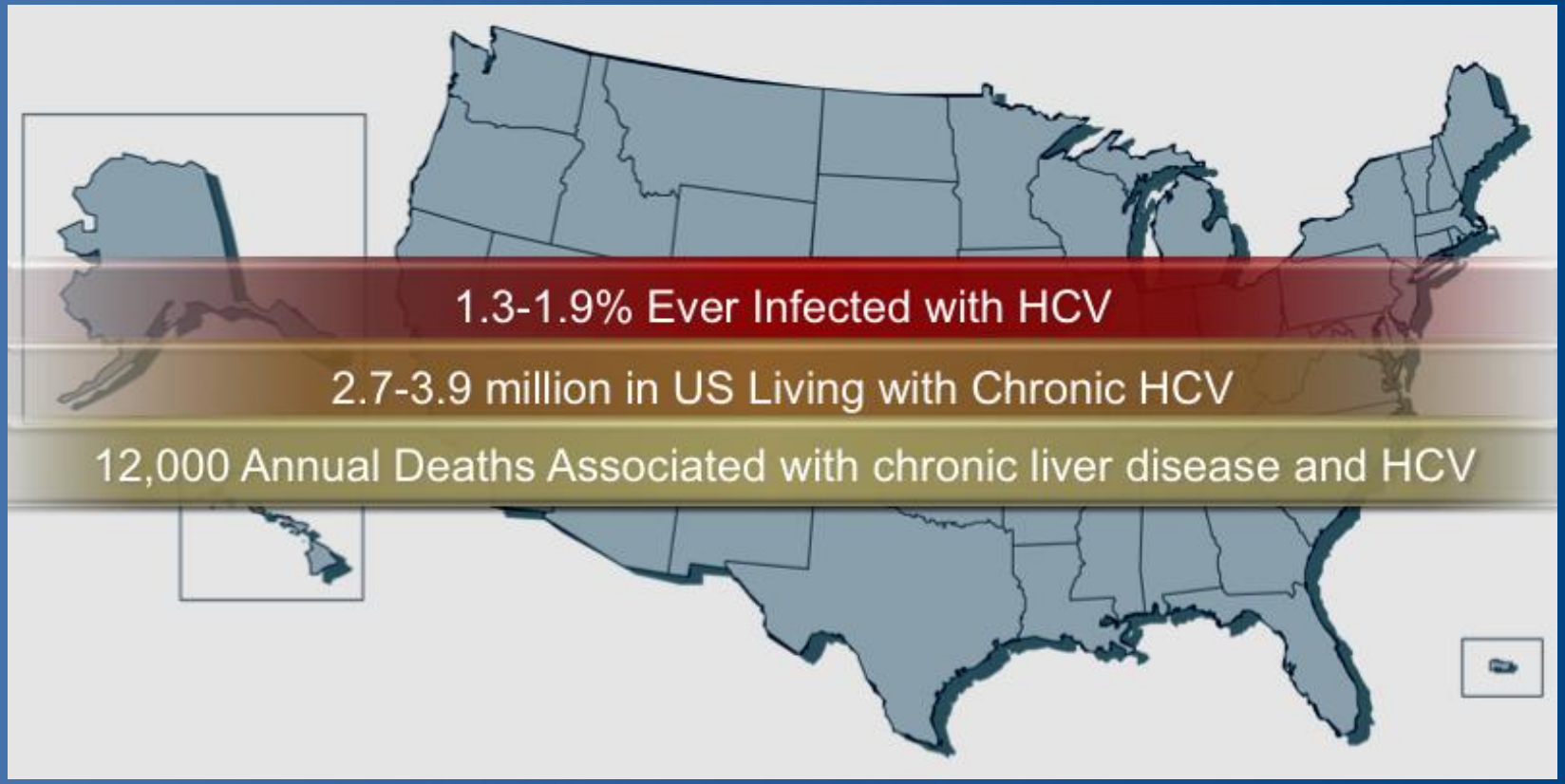
Zibbell JE Am J Public Health 2018

ALARMING TRENDS….,

- New infections ballooned nationally from 850 (2010) to 2,436(2015)
  - highest rates among 20-29 year-olds, who inject drugs,
  - CDC estimates true number is much higher 34,000 new infections nationally for 2015

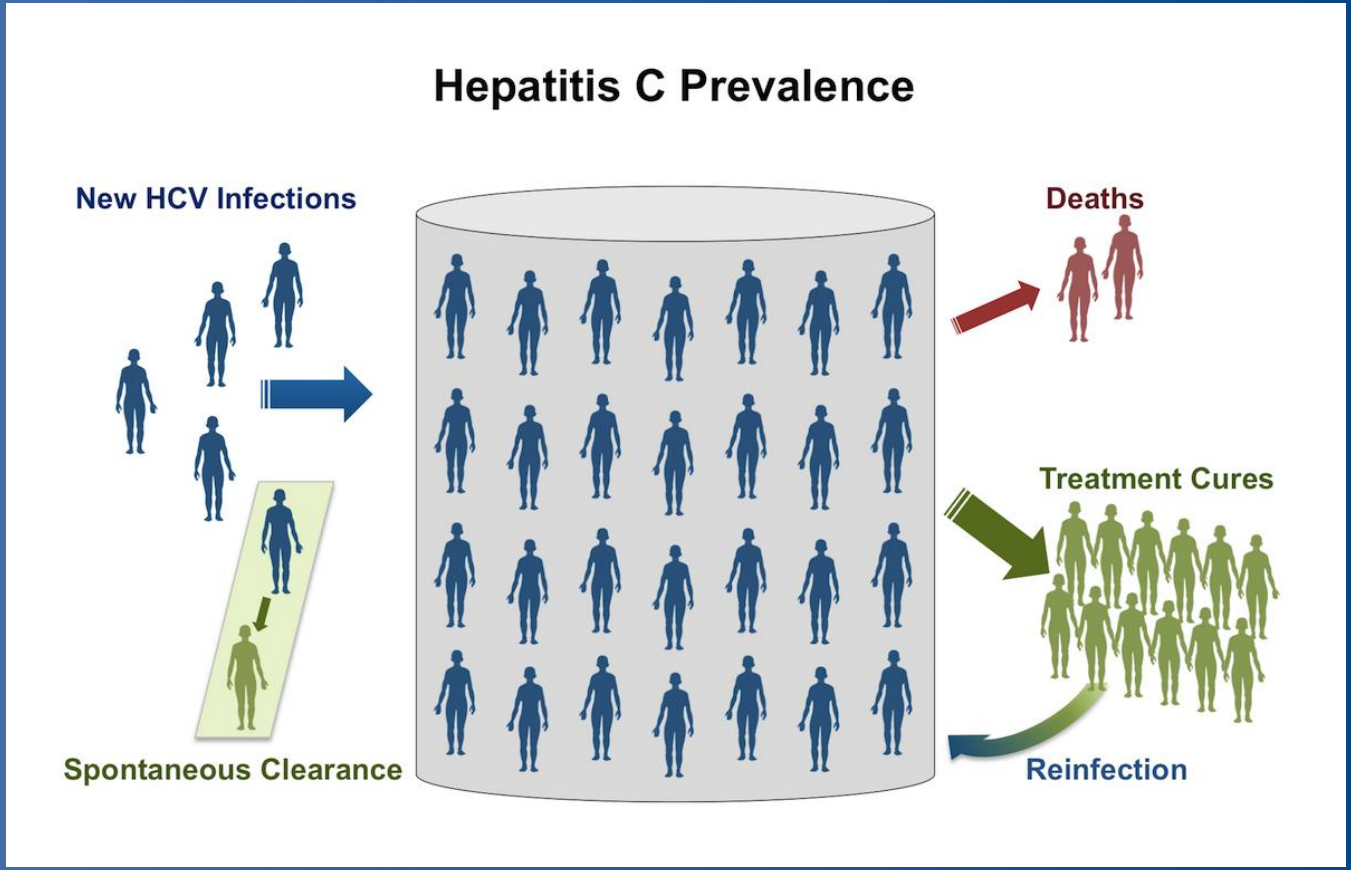
HCV BURDEN IN THE US

JOHNS HOPKINS MEDICINE



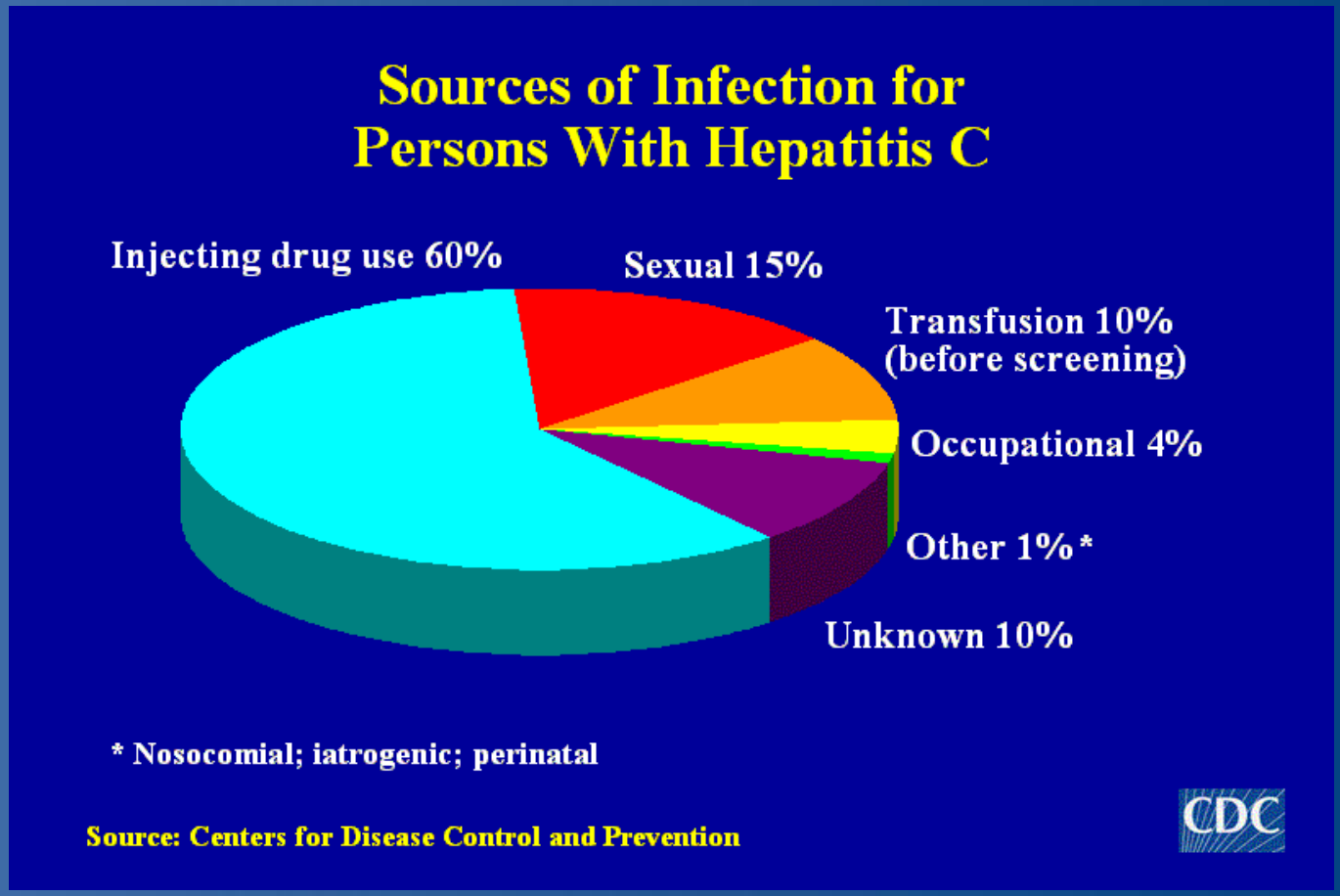
Hajarizadeh B. Nature Reviews Gastroenterology & Hepatology 2013 ;**10**, 553-562

DYNAMICS OF HCV PREVALENCE IN THE US



Source: Illustration by David H. Spach, MD

RISK FACTORS FOR HCV



CHRONIC HCV INFECTION HAS SERIOUS CLINICAL CONSEQUENCES

CHRONIC LIVER DISEASE ~60%–70%
of patients with HCV[1]

CIRRHOSIS 5%–20%
of patients infected with HCV over 20–30 years[1]

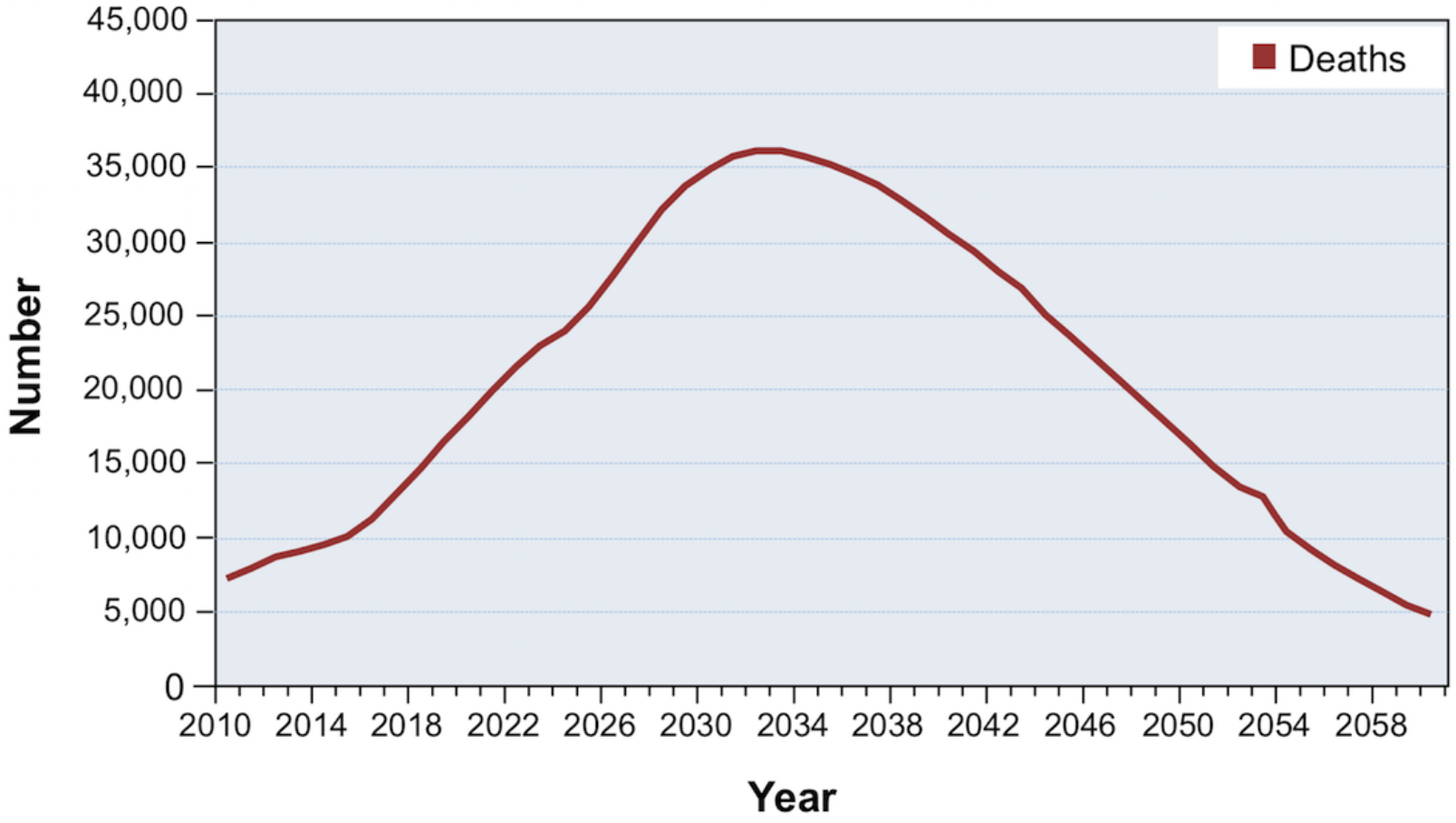
HEPATOCELLULAR CARCINOMA
~1%–5% annually in HCV-related cirrhosis[3]

LIVER TRANSPLANT 40% of all liver transplants are HCV-related. HCV is #1 cause of liver transplant[2]

DEATH ~1%–5%
of HCV-infected patients will die from the consequences of chronic HCV infection[1]

1. CDC. Hepatitis C. general information. (Publication No. 21-1075.) 2. Wiesner RH, et al. *Liver Transpl*. 2003;9(11 Suppl 3):S1-S9.
3. EASL Clinical Practice Guidelines: *J Hepatol*. 2014;60:392-420.

PROJECTED DEATHS FROM HEPATITIS C



WHY SHOULD WE CARE ?

TWO REASONS….

1. Hepatitis C is a major contributor to death and disease worldwide
2. It is now CURABLE

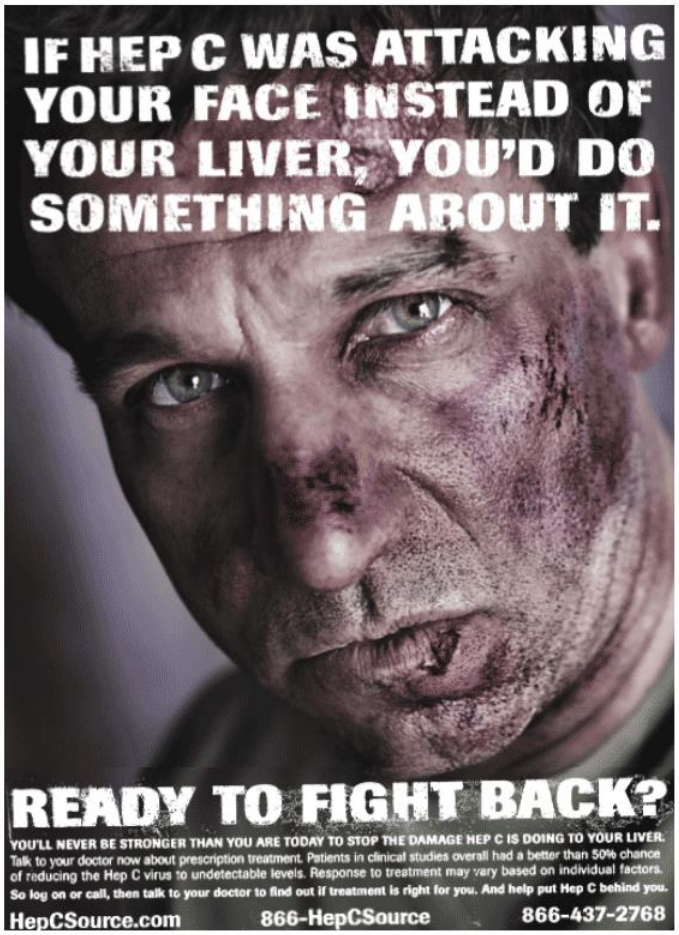
HIV
Genetic material, stored
in the host cell nucleus, integrates into host DNA[2]

T-Cell

HCV
After binding, HCV RNA remains in cytoplasm and is a target for host cell antiviral mechanisms[1,3]

Hepatocyte

HEPATITIS C IS A SILENT DISEASE…

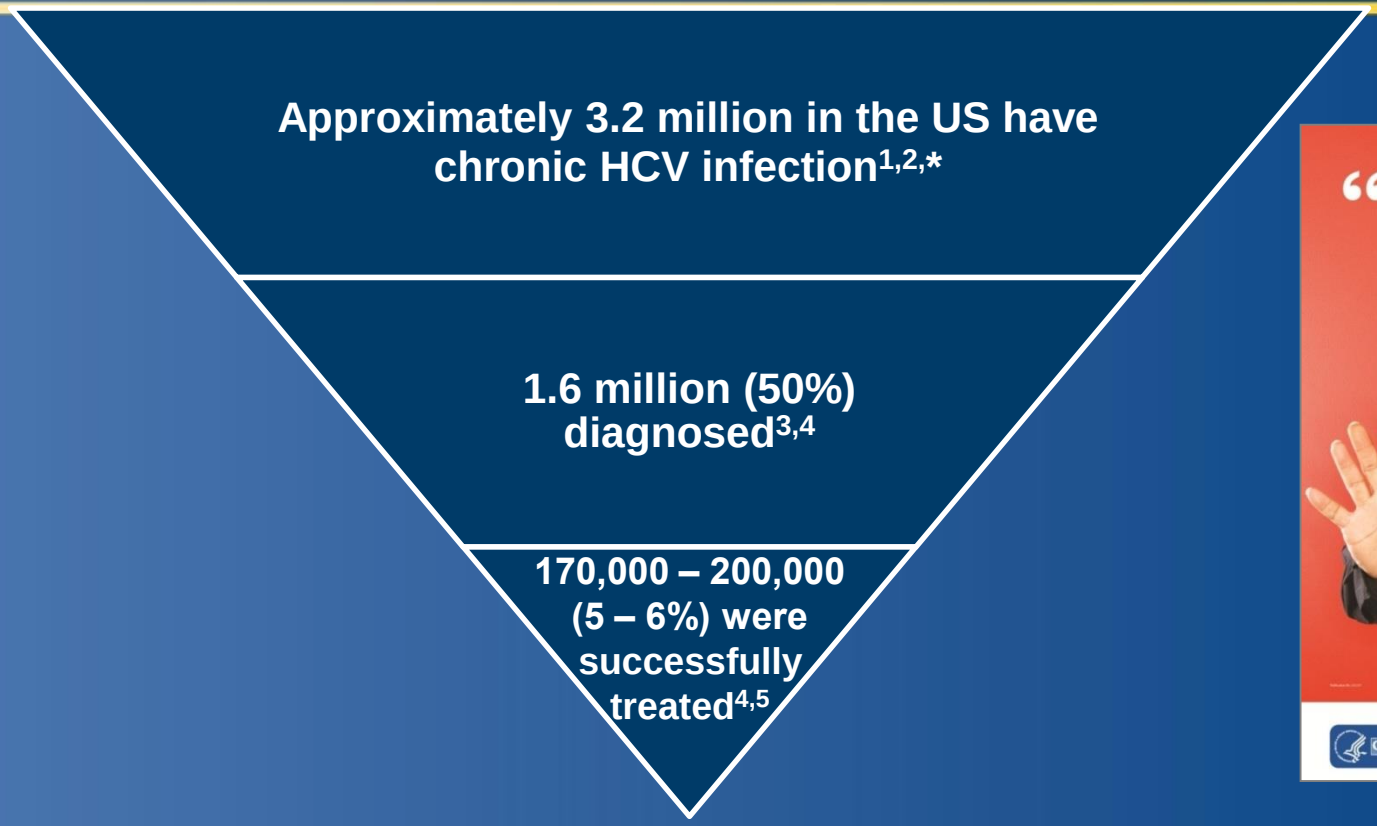


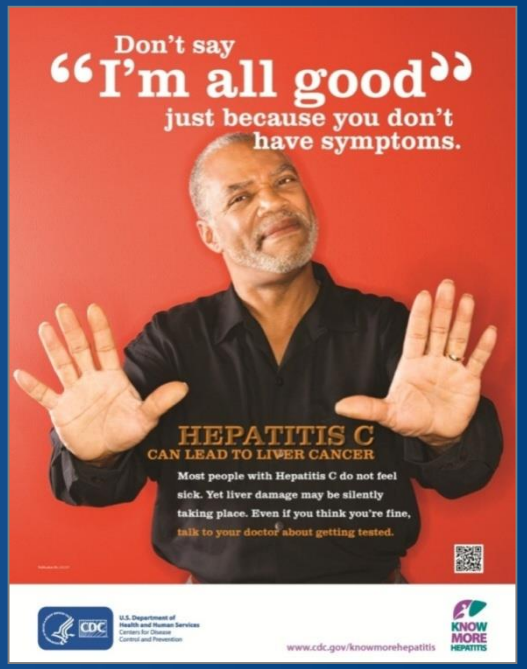
- **Only 50% have symptoms in early stages**

Main symptoms

- **Fatigue**
- **Nonspecific aches**
- **Depression**

Current Estimates Show a Significant Gap in HCV Care





*Prevalence estimate based on NHANES data from 1999 through 2002.[1,2] NHANES data underestimate the actual prevalence of HCV in the US by not accounting for incarcerated, homeless, hospitalized, nursing home and active military duty populations.[6,7]

1. Armstrong GL, et al. *Ann Intern Med.* 2006;144:705-714.
2. http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm.
3. Denniston MM, et al. *Hepatology.*2012;55:1652-1661.
4. Holmberg SD, et al. *New Engl J Med.* 2013;1859-1861.
5. Moorman AC, et al. *Clin Infect Dis.* 2013;56:40-50.
6. Chak E, et al. *Liver Int.* 2011;31:1090-1101.
7. Smith BD, et al. *MMWR Recomm Rep*. 2012;61(RR-4):1-32.
8. www.cdc.gov/knowmorehepatitis/.

HCV SCREENING STRATEGIES

- Risk-based (CDC 1998)
  - Blood products before 1992
  - Intravenous drug use
- Limitations:
  - Providers reluctant to ask about risk factors
  - Patients reluctant to disclose risk

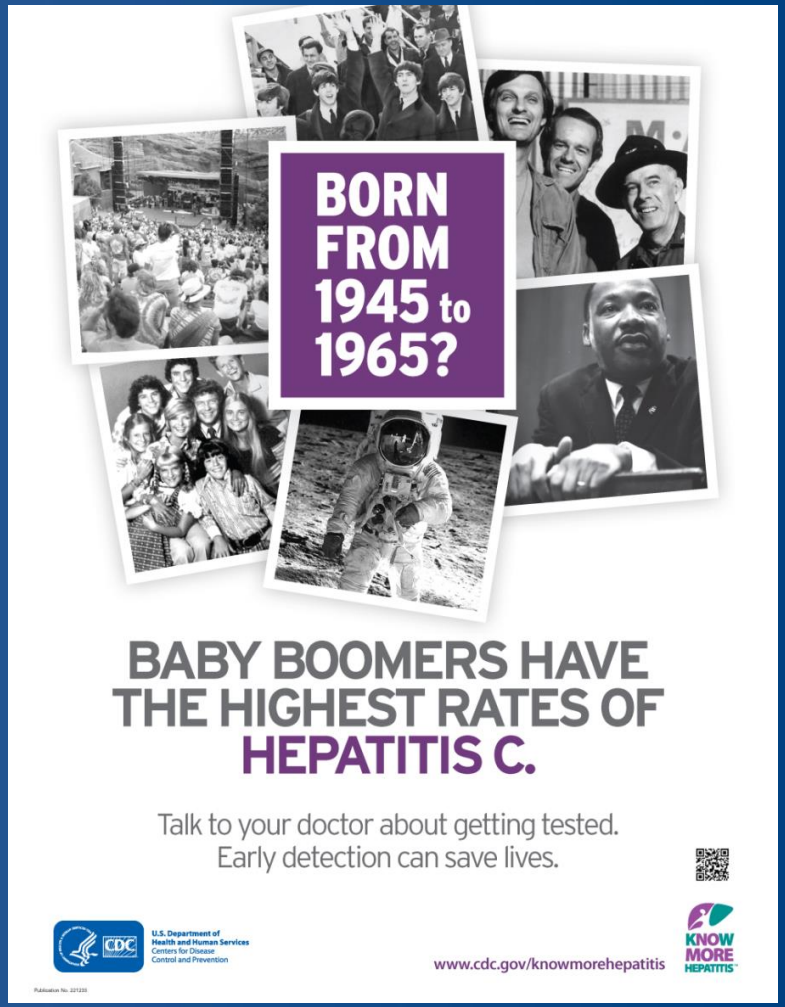
45-60% UNAWARE OF INFECTION

2012 CDC Recommendations for Birth Cohort Screening

- Recommendation 1
  - Adults born from 1945 to 1965 should receive one-time testing for HCV without prior ascertainment of HCV risk

    Grade: strong recommendation
    Evidence: moderate-quality
- Recommendation 2
  - All persons identified with HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions as indicated

    Grade: strong recommendation
    Evidence: moderate-quality



Smith BD, et al. *Ann Intern Med*. 2012;157:817-822.

Updated USPSTF HCV Screening Recommendations (2013)

Risk Assessment:*

- Those at high risk for HCV infection:
  - Most important risk factor is past or current injection drug use
  - Additional risk factors include:
    - Receiving a blood transfusion before 1992
    - Long-term hemodialysis
    - Being born to an HCV-infected mother
    - Incarceration
    - Intranasal drug use
    - Getting an unregulated tattoo, and other percutaneous exposures
- Adults born between 1945 and 1965 ("Baby Boomers")

*Grade B recommendation for persons at high risk for infection and adults born between 1945 and 1965.

Moyer VA; on behalf of the USPSTF. *Ann Intern Med*. 2013 Jun 11. [Epub ahead of print].

Updated USPSTF HCV Screening Recommendations (2013)

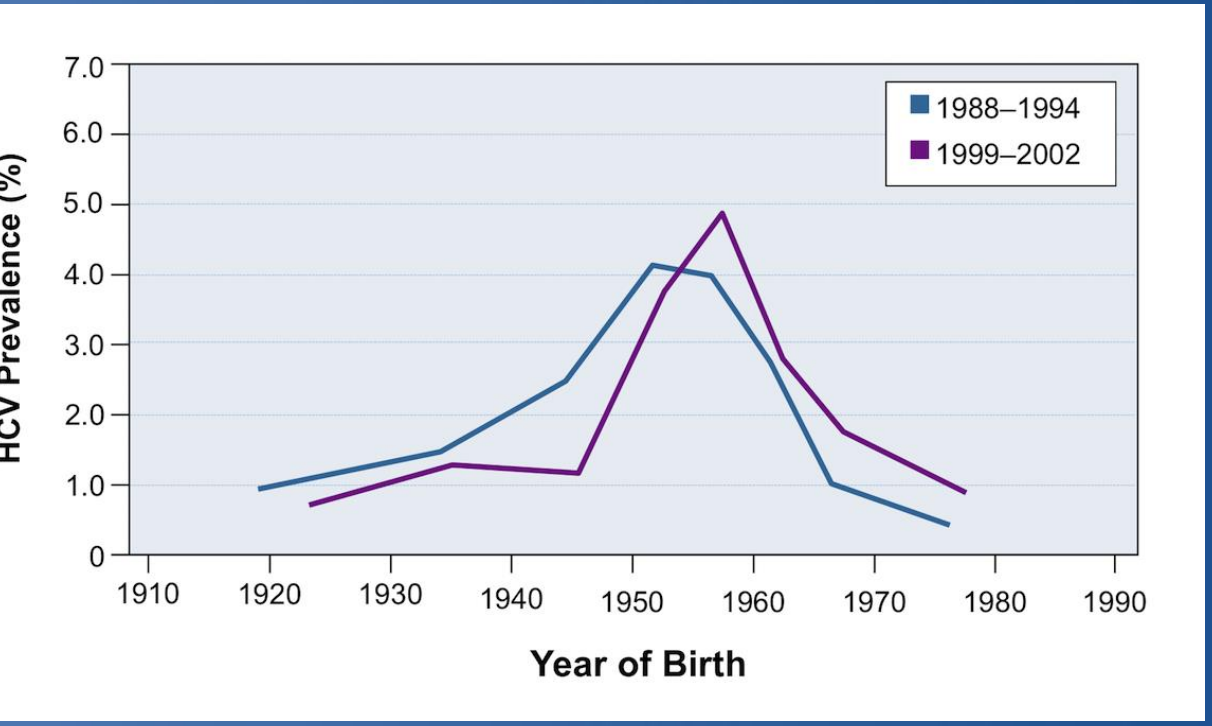
- USPSTF Grade B recommendations regarding HCV screening[1]:
  - Those at high risk for HCV infection
  - Those born from 1945 to 1965 (one-time screening of "Baby Boomers," regardless of risk

  The USPSTF gave this recommendation a Grade B[1]:
  - Grade B means there is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial
- The Affordable Care Act[1,2]:
  - Requires non-grandfathered private health plans to cover clinical preventive services given an A or B Grade by USPSTF without cost sharing
  - Provides incentives for Medicaid programs to cover these services

USPSTF=United States Preventive Services Task Force.

1. Moyer VA; on behalf of the USPSTF. *Ann Intern Med*. 2013 Jun 11. [Epub ahead of print];
2. Ngo-Metzger, Q et al. *Ann Intern Med*. 2013 Jun 11. [Epub ahead of print].

RATIONALE FOR BIRTH COHORT SCREENING



- Two of three Americans with HCV were born between 1945-1965
  - 5 times higher prevalence than others
  - 75% of all HCV + adults
  - 72% of HCV – related mortality

COST EFFECTIVENESS OF BIRTH COHORT SCREENING

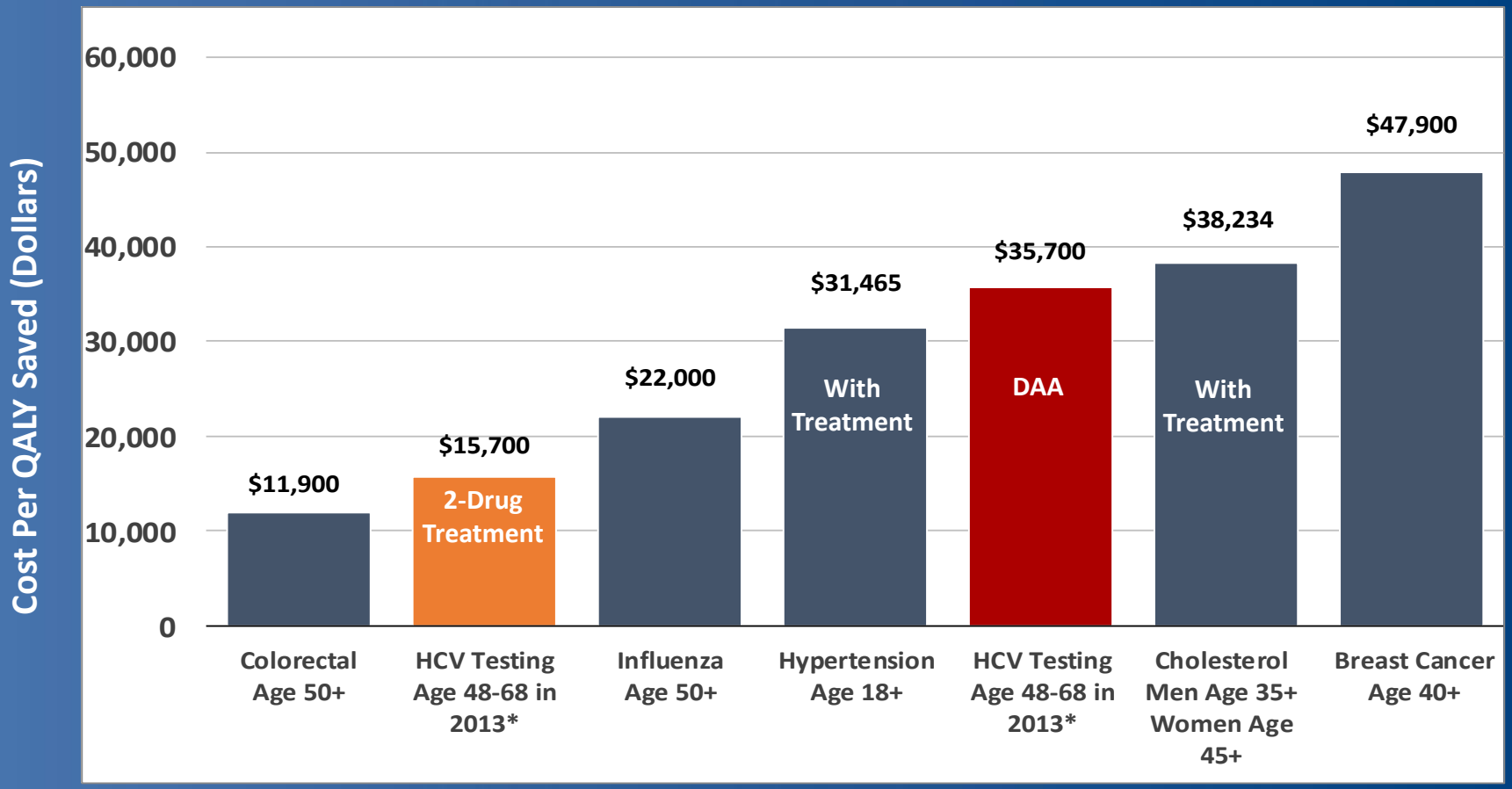
- Six studies with prior therapies all favorable
- First study examining all-oral DAA
  - ICER* sensitive to fibrosis stage
    - $13K for cirrhosis - $173,800 for F0 per QALY **
  - ICER for new treatments $31k -$35 K per QALY

*Incremental cost effectiveness ratio

**Quality Adjusted Life Year

Rein DB, Clin Inf Dis 2015;61:157-168

Cost-Effectiveness of HCV Testing vs Other Routine Preventive Services



*Birth cohort testing, 1945-1965.
2-drug treatment=PegIFN+RBV; 3-drug treatment=PegIFN+RBV+PI.QALY=quality-adjusted life-year.
www.prevent.org/National-Commission-on-Prevention-Priorities/Rankings-of-Preventive-Services-for-the-US-Population.aspx.

Hepatitis C Virus
Host Production of HCV Antibodies

- HCV infects cell
- HCV proteins expressed on surface of hepatocytes
- Antibodies to HCV proteins produced by host
- HCV antibodies DO NOT convey immunity

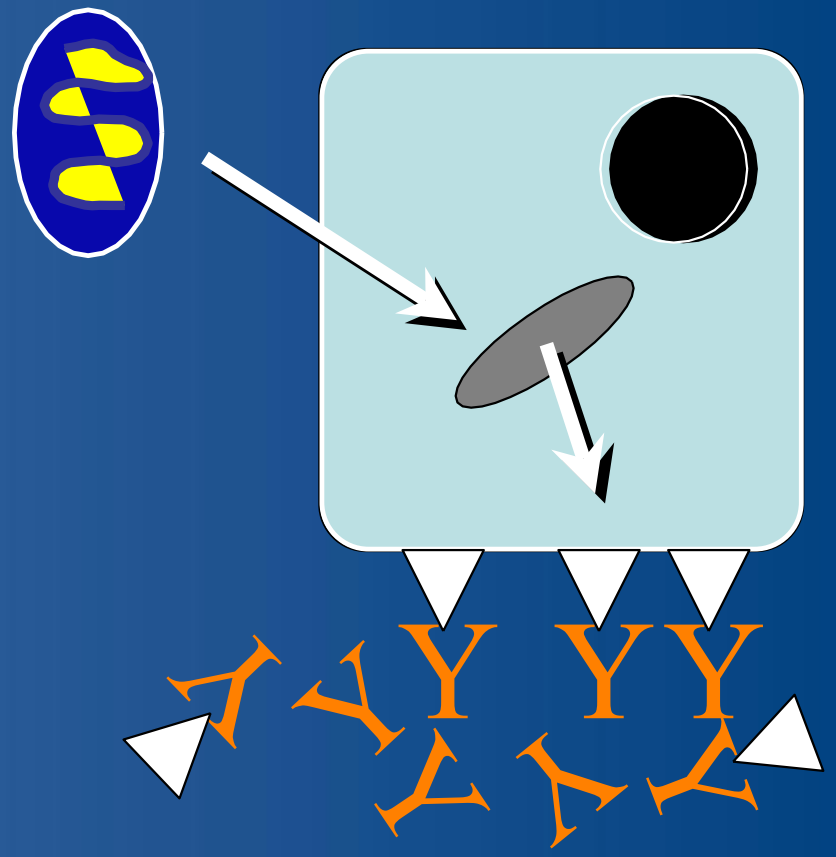
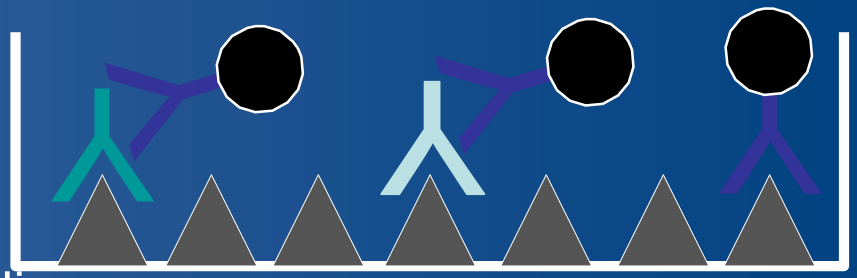


Illustration by Mitchell L. Shiffman, MD.

Testing for Hepatitis C Virus
Anti-HCV Antibodies



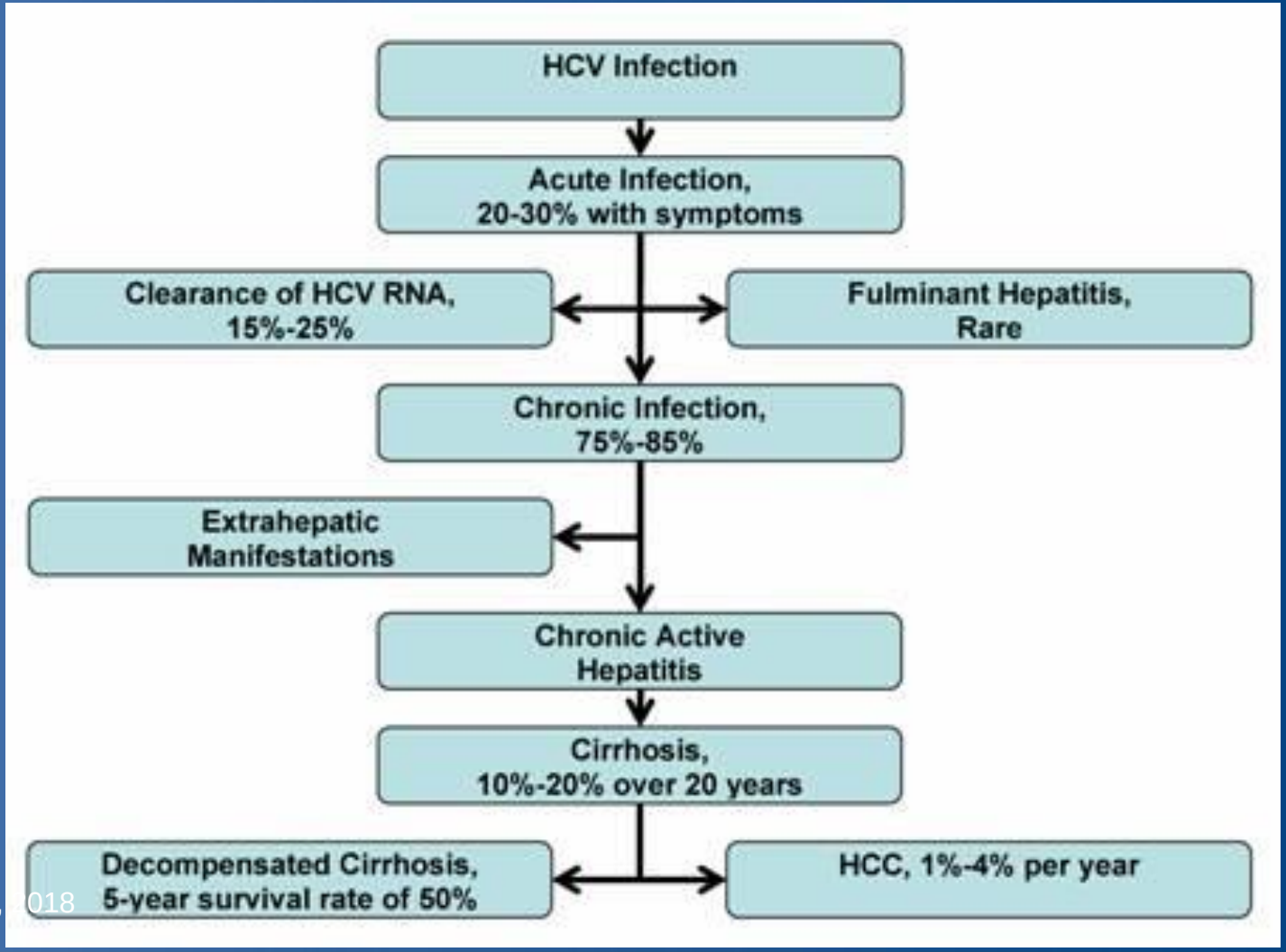
- ELISA screening test
  - Sensitivity: 97%
  - Detects circulating HCV antibodies
- False positive reactions may occur
  - Cross-reacting circulating antibodies
  - Nonspecific binding of anti-HCV antibodies
- Positive predictive value
  - 95% with risk factors and elevated ALT
  - 50% without risk factors and normal ALT

Illustration by Mitchell L. Shiffman, MD.

HCV
LINKAGE TO CARE

- Essential next step after identification of infection
- Implies access to specialized care
  - Assessment of natural history
  - Staging of liver disease
  - Triage to therapy

NATURAL HISTORY OF HCV

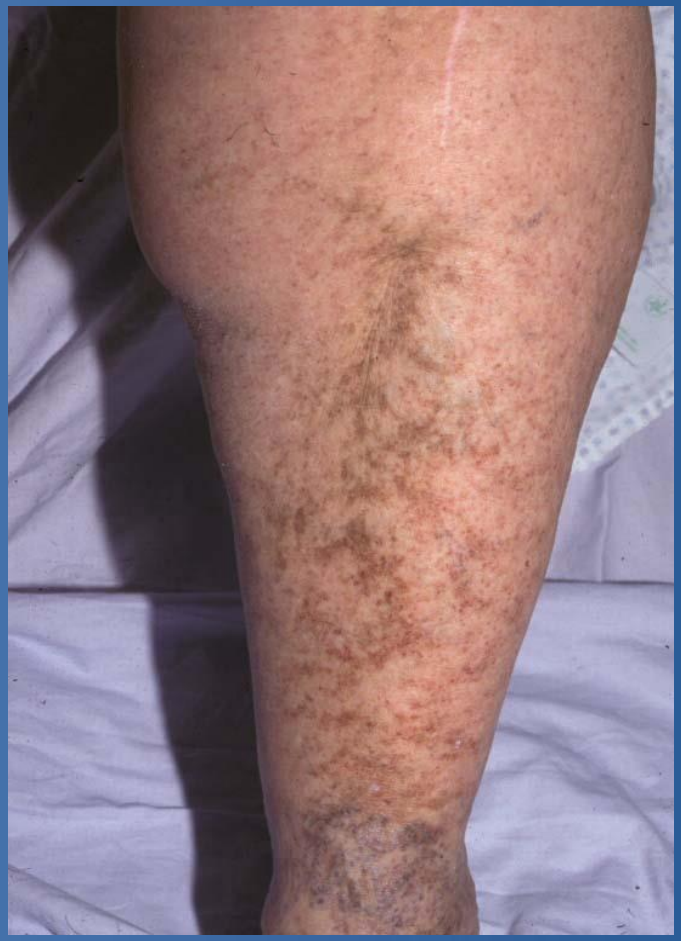


Chronic Hepatitis C Virus
Extrahepatic Manifestations

JOHNS HOPKINS MEDICINE

- Nonspecific antibodies
- Essential mixed cryoglobulinemia
- Glomerulonephritis
- Porphyria cutanea tarda
- Leukocytoclastic vasculitis
- Mooren’s corneal ulcer
- Non-Hodgkin’s lymphoma
- Autoimmune thyroiditis
- Diabetes mellitus
- Sjögren’s syndrome

HCV and Cryoglobulinemia Leukocytoclastic vasculitis



- Occurs in dependent areas
- Deposition of cryoglobulins in small capillaries
- Ulcerations may develop
- Pruritic

HCV and Cryoglobulinemia
Manifestations

- Dermatitis (dependent areas)
- Vasculitis
- Myalgias (fibromyalgia?)
- Arthralgias (RA and/or ANA positive)
- Membranoproliferative glomerulonephritis
- Neuropathy
- Chronic fatigue syndrome (?)

HCV THERAPY
DAWN OF A NEW ERA ?

Editorial | 21 February 2012

Hepatitis C: The End of the Beginning and Possibly the Beginning of the End

Harvey J. Alter, MD; and T. Jake Liang, MD

AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES (AASLD)/INFECTIOUS DISEASE SOCIETY OF AMERICAL I(DSA) GUIDELINES

JOHNS HOPKINS MEDICINE

Goal of treatment

The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by an SVR.

Rating: Class I, Level A

GOALS OF HCV THERAPY

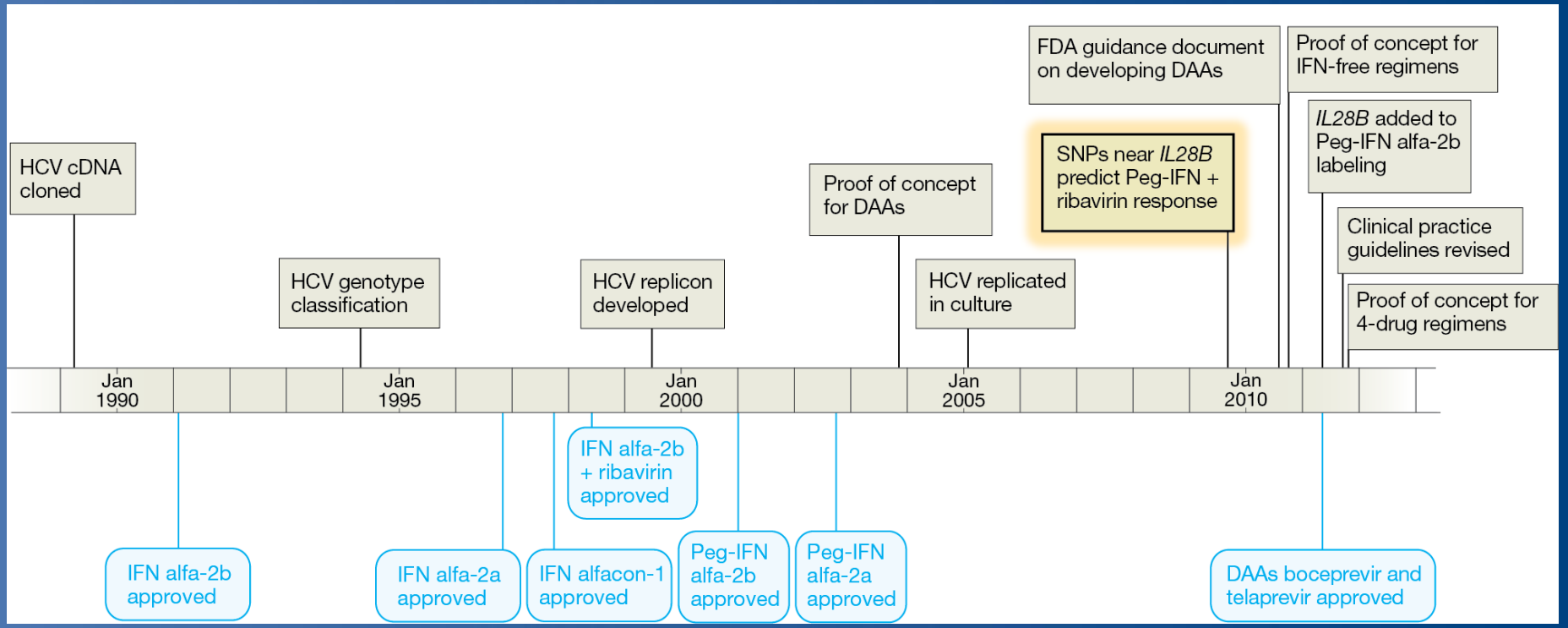
- Suppress viral RNA
- Improve liver histology
- Normalize liver biochemical tests
- Achieve sustained virological response

SVR = CURE

No viral reservoir (unlike HIV/HBV)

Hence : no reactivation

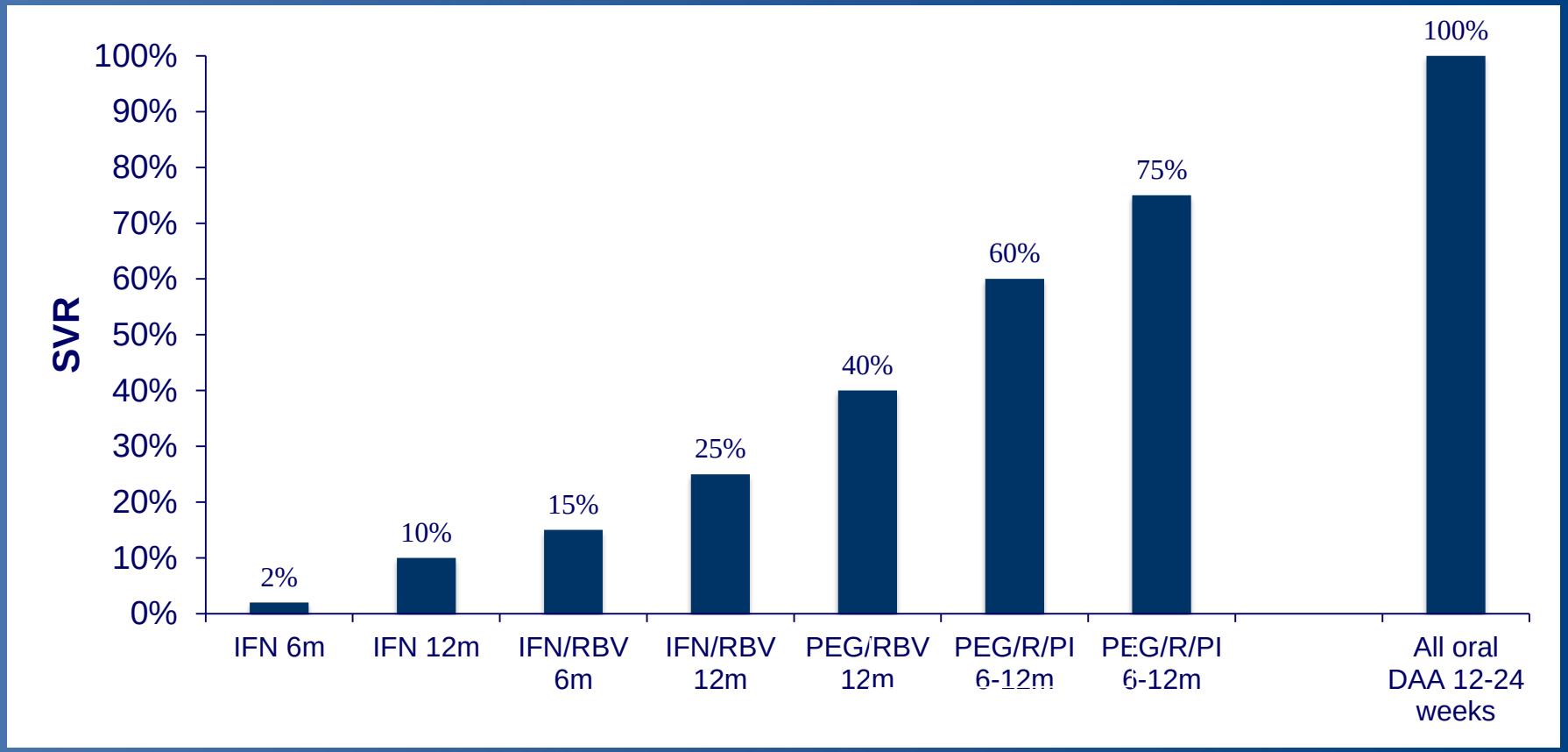
BENCH RESEARCH IN HCV PARALLELS DRUG DEVELOPMENT



EVOLUTION OF THERAPY IN HCV GT1

JOHNS HOPKINS MEDICINE

1990 1999 2001 2011 2015



Multiple antiviral targets are available

JOHNS HOPKINS MEDICINE

DNA-directed RNA interference (ddRNAi)

TT-034 via Adeno-Associated Virus vector

Entry inhibitors

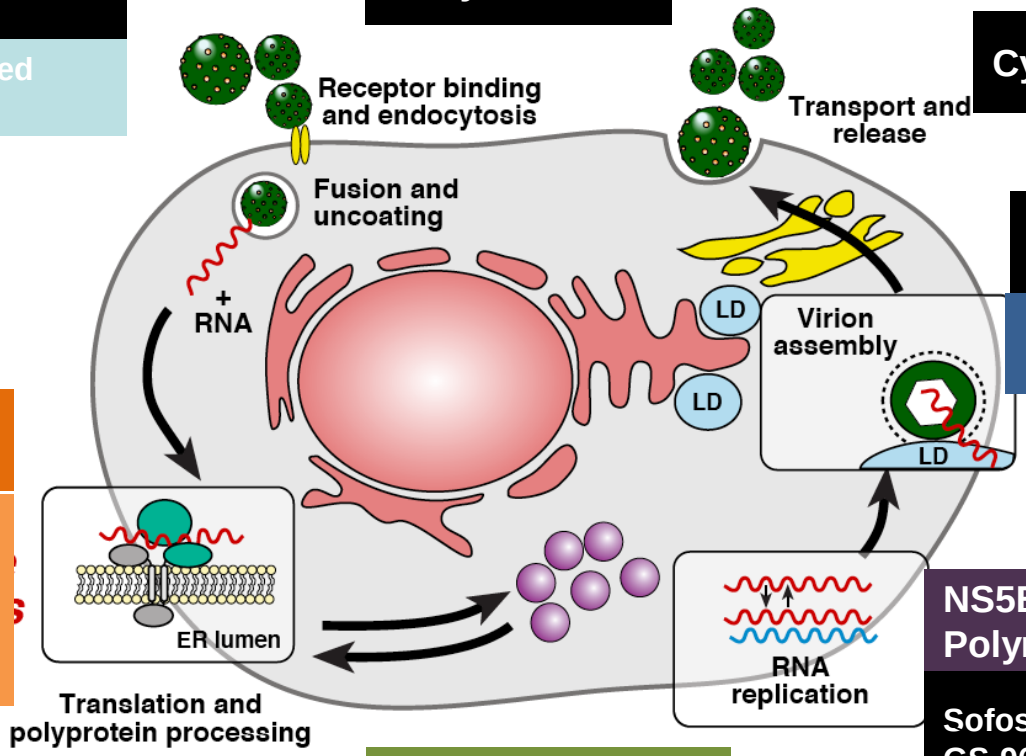
Cyclophylin Inhibitors

Antisense oligonucleotides

Miravirsen (miR-122)

NS3/4 Protease Inhibitors

Simeprevir (SIM)
Asunaprevir
ABT-450/ritonavir (r)
GS-9451



NS5B Polymerase Inhibitors

Sofosbuvir (SOF)
GS-9669
BMS-325
Dasabuvir

NS5A Inhibitors

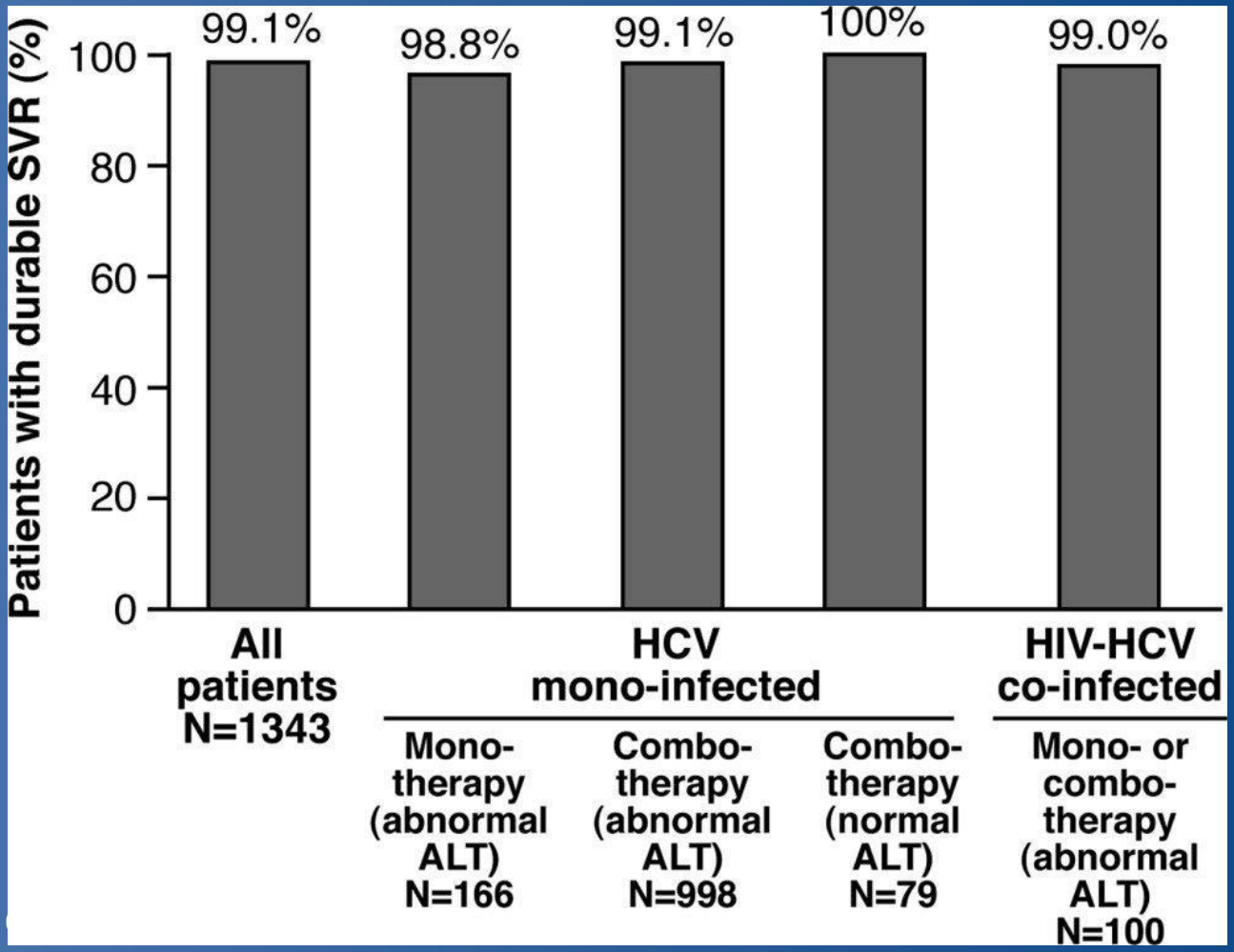
Ledipasvir (LDV)
Ombitasvir
Daclatasvir (DCV)
MK-8742

Antiviral AII –Oral Therapies CurrentlyAvailable

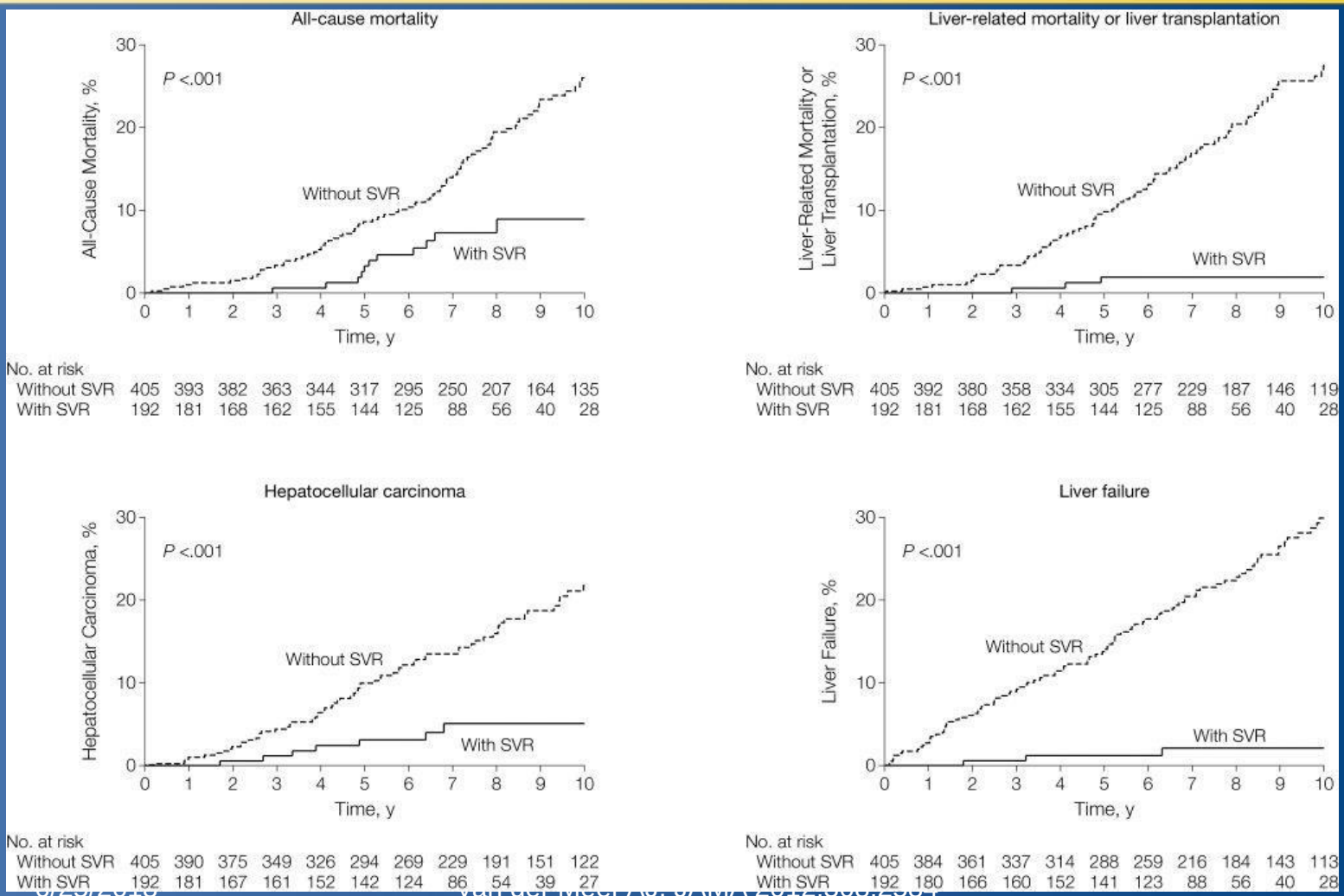
Regimen	Classes	Approved GT	SVR Rates
Sofosbuvir+ribavarin	Nucleotide polymerase inhibitor +nucleoside analogue	1,2,3,4	84%
Sofosbuvir+simeprevir	Nucleotide polymerase inhibitor+protease inhibitor	1,4	83-94%
Sofosbuvir/ledipasvir	Nucleotide polymerase inhibitor+NS5A inhibitor	1,4,5,6	93-99%
Paritaprevir/ritonavir/ ombitasvir/dasabuvir	Protease inhibitor+NS5A inhibitor	1	92-96%
Sofosbuvir+daclatasvir	Nucleotide polymerase inhibitor+NS5A inhibitor	1,3	86%-96%
Grazoprevir/elbasvir	Protease inhibitor+NS5A inhibitor	1,4	92-94%
Sofosbuvir/velpatasvir*	Nucleotide polymerase inhibitor+NS5A inhibitor	Pangenotypic	97-100%
Glecaprevir/ pibrentasvir	Protease inhibitor+NS5A inhibitor	Pangenotypic	98-100

POST TREATMENT CARE

Sustained virological response 12 = CURE

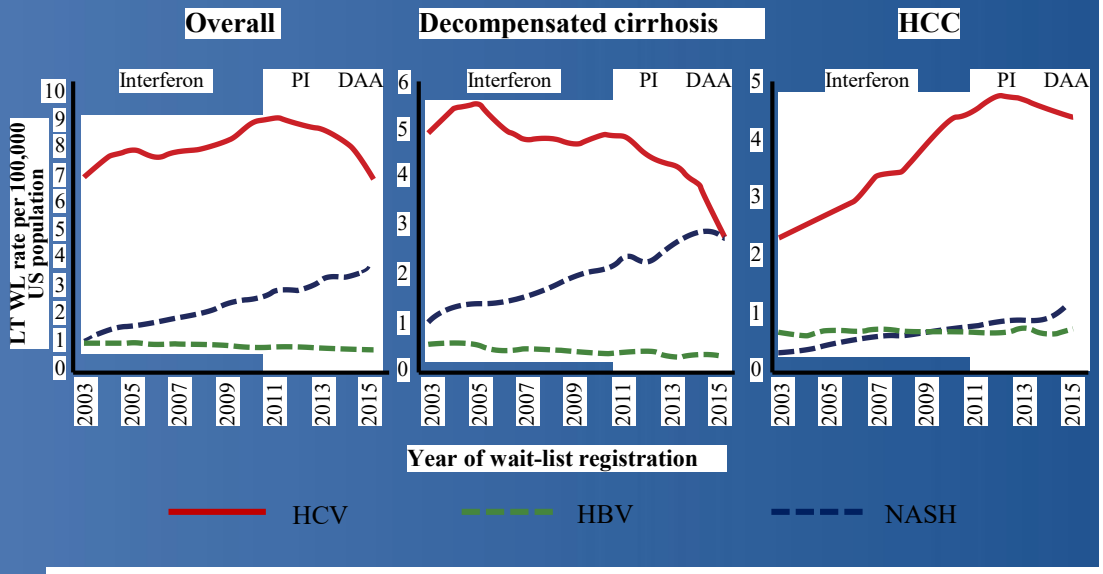


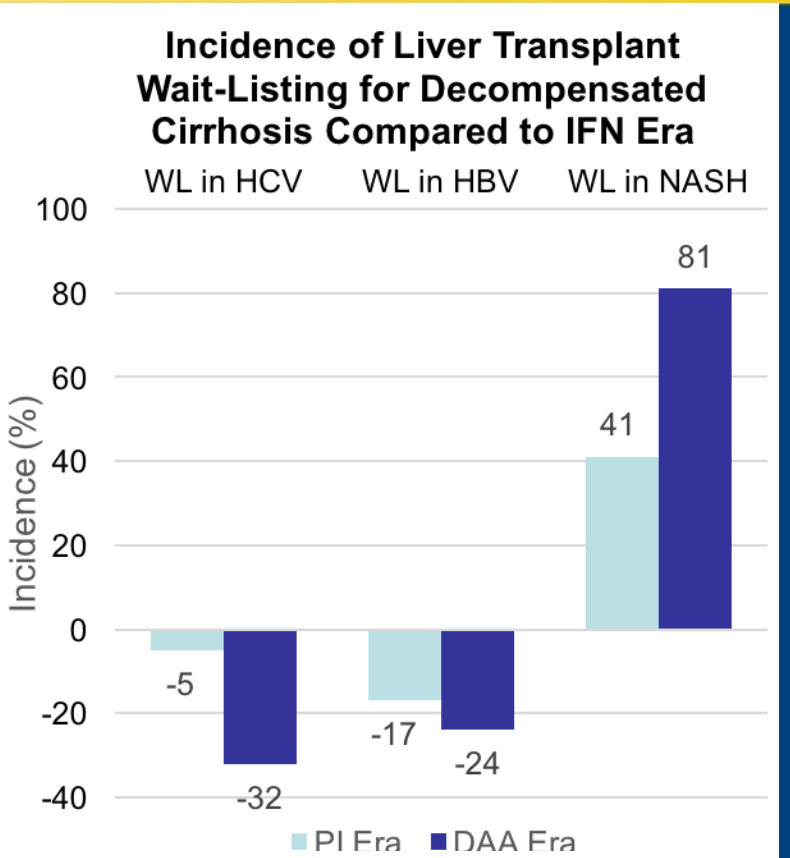
SVR RESULTS IN IMPROVED OUTCOMES



Reduction in Liver Transplant Waitlist in the Era of HCV DAAs

Cohort study of 47,591 adults wait-listed for liver transplant (LT WL) using the Scientific Registry of Transplant Recipients database from 2003–2015





The rate of liver transplant wait-listing for HCV secondary to decompensated cirrhosis has decreased by 32% in the era of DAA therapy as compared to the IFN era and is now equal to that of NASH

Flemming JA et al Hepatology 2016;65(3):804-812.

MONITORING CURED PATIENTS

- HCV provider should check HCV RNA until 24 weeks after treatment (SVR24)
- No standard guidelines for further monitoring
  - Check HCV RNA if change in clinical condition
- HCV antibody remains positive for life
  - not protective
- If underlying cirrhosis/ advanced fibrosis
  - Needs surveillance for HCC / varices

WHO RESOLUTION 2017
Elimination of viral hepatitis by 2030

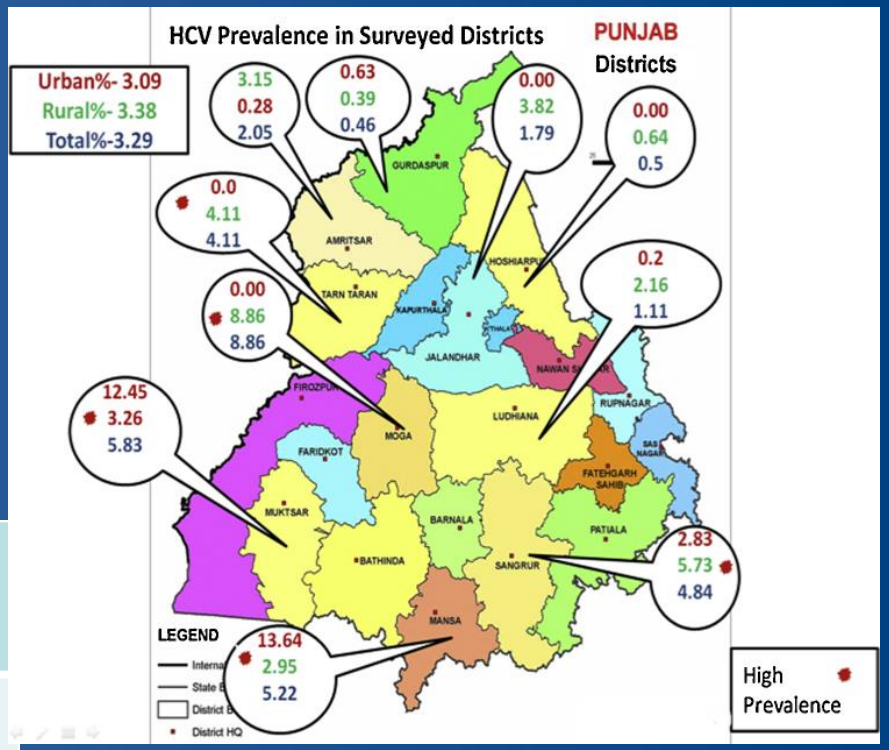
- 90% reduction in HCV incidence is possible by 2030
  - Depends on diagnosing at least 110,000 cases / year until 2020
  - 89,000 cases/year 2020-24
  - 70,000 cases/ year 2025-2030

– NASEM report 2017

ESSENTIAL INTERVENTIONS

- Improve treatment access
  - Universal availability of DAA
  - Build capacity to treat in primary care settings
- Expanded access to syringe exchange and opioid agonist therapy
  - PWID account for 75% of new cases

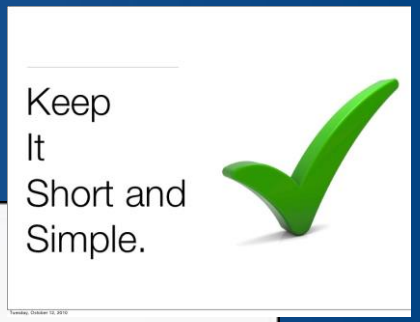
HEPATITIS C IN INDIA



Cost of Sofosbuvir		Per tablet (400 mg)		24 weeks treatment
USA		**1000 $** 67,000 Rupees		11.4 million Rupees
India		660 Rupees		1.2 lakh Rupees

Dhiman et al.
J Clin Exp Hepatol Sep 2016

WHAT IS ON THE HORIZON ?



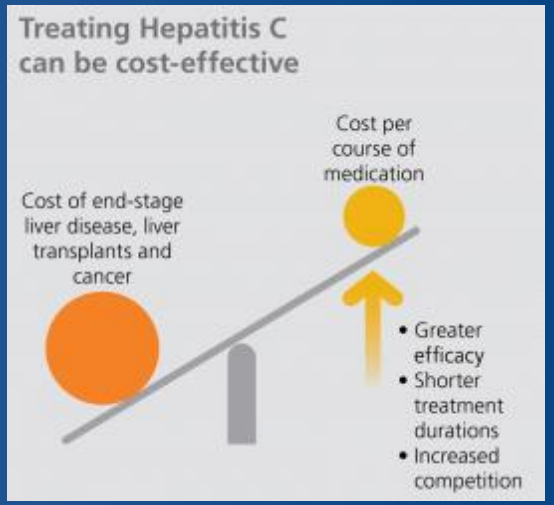
- Pan genotypic regimens
- Short duration
- High barrier to resistance
- Affordable and accessible

CHALLENGES IN HCV MANAGEMENT

- Cost of treatment

  $92 k / course

- Viral resistance
- Effective screening
- Linkage to care



SUMMARY

- Hepatitis C is widely prevalent but mainly unrecognized
- Untreated HCV has serious consequences
- Current guidelines endorse screening all baby boomers and those with risk factors

SUMMARY

- All-oral therapies now standard of care
- Ribavirin necessary for some, not all
- Cirrhosis requires longer duration of therapy, especially in treatment experienced subjects

TAKE HOME POINT

- HEPATITIS C IS A CURABLE DISEASE
- TREATMENT SHOULD BE OFFERED TO ALL THOSE INFECTED