

Update on Hepatitis C virus infection

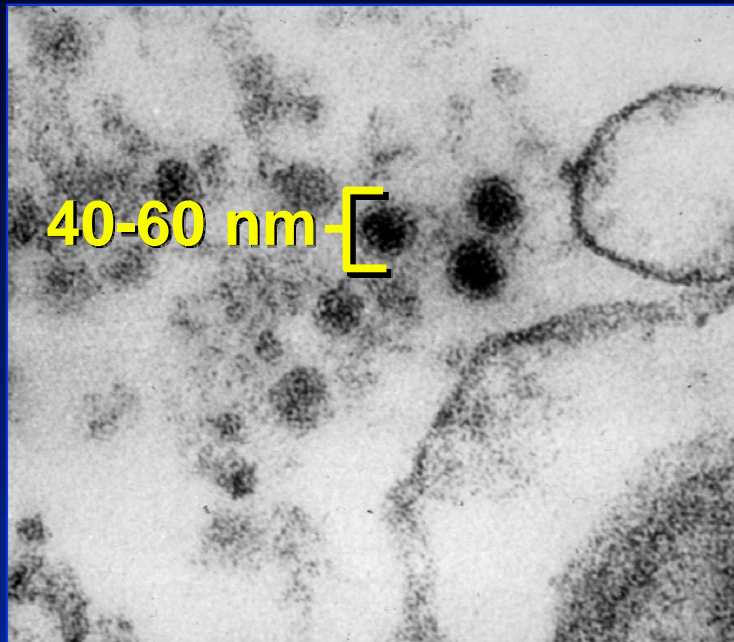
**B-UMCP
Internal Medicine
Academic half-day
November 2016**

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Hepatitis C Virus :

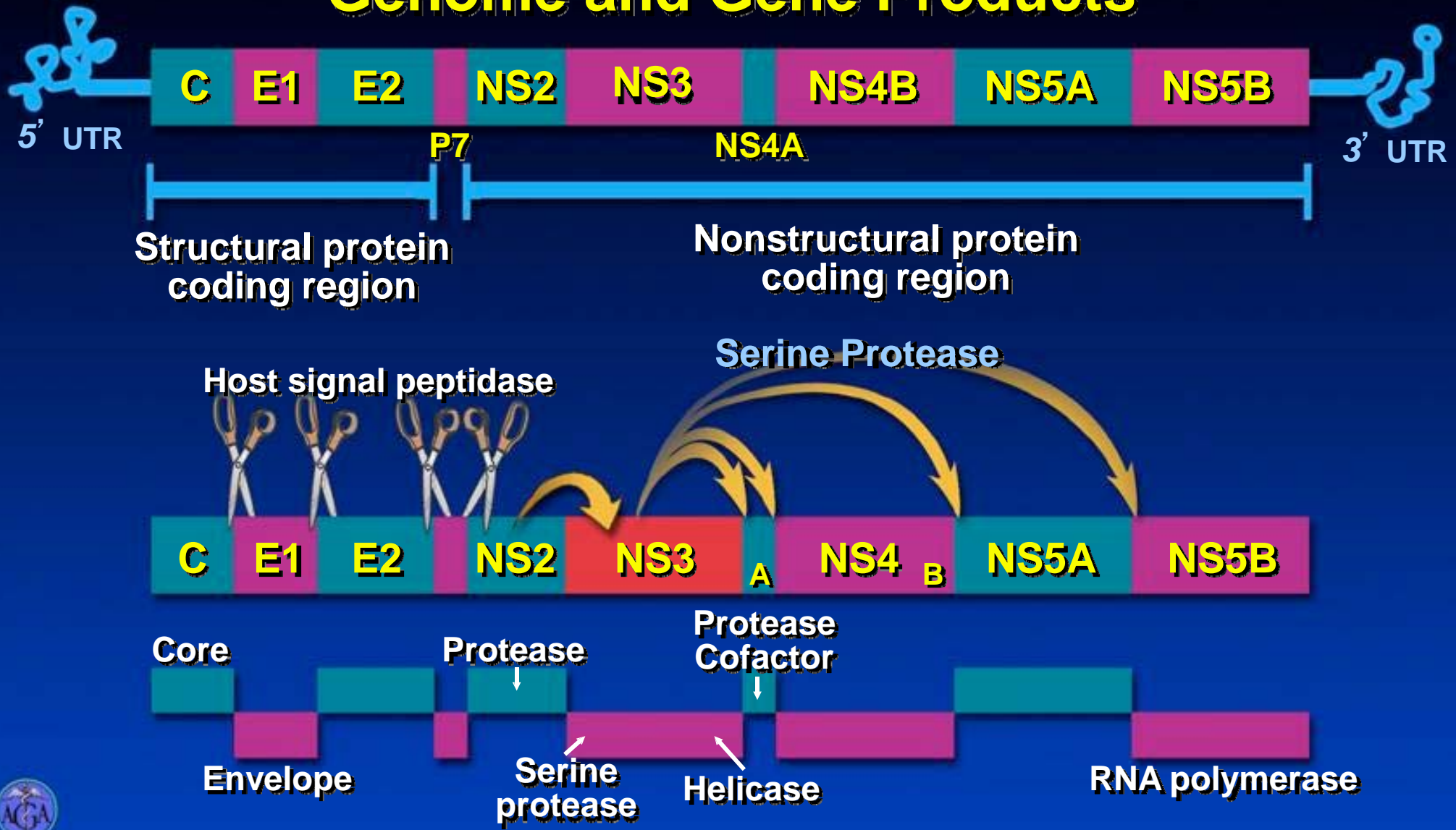
- Structure of the virus
- Historical facts
- Prevalence
- Diagnosis
- Clinical manifestations
- Natural history
- Treatment

Hepatitis C Virus



- Nucleic Acid: 9.6 kb ssRNA
- Classification: *Flaviviridae*, *Hepacivirus*
- Genotypes: 1 to 9
- Enveloped
- In vitro model: primary hepatocyte and T cell cultures; replicon system
- In vivo replication: in cytoplasm, hepatocyte and lymphocyte; human and other primates

Genome and Gene Products



HCV historical facts:

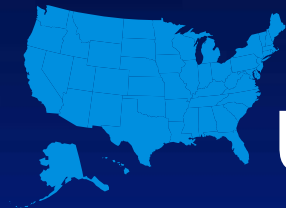
- 1970-80's a chronic type of hepatitis associated with transfusion was recognized
- 1989 the HCV virus was identified
- 1990 blood banks start screening but tests were not perfected until 1992
- 1991 FDA approved first Interferon alpha
- 1998 FDA approved Interferon plus Ribavirin
- 2001 FDA approved Pegylated Interferon
- 2011 FDA approved first direct anti viral agent

HCV - Epidemiology



Worldwide

170 million (3%)



United States

Anti-HCV positive

3.9 million (1.8%)

HCV RNA positive

2.7 million (1.4%)

Alter MJ et al., New Engl J Med 1999; 341:556

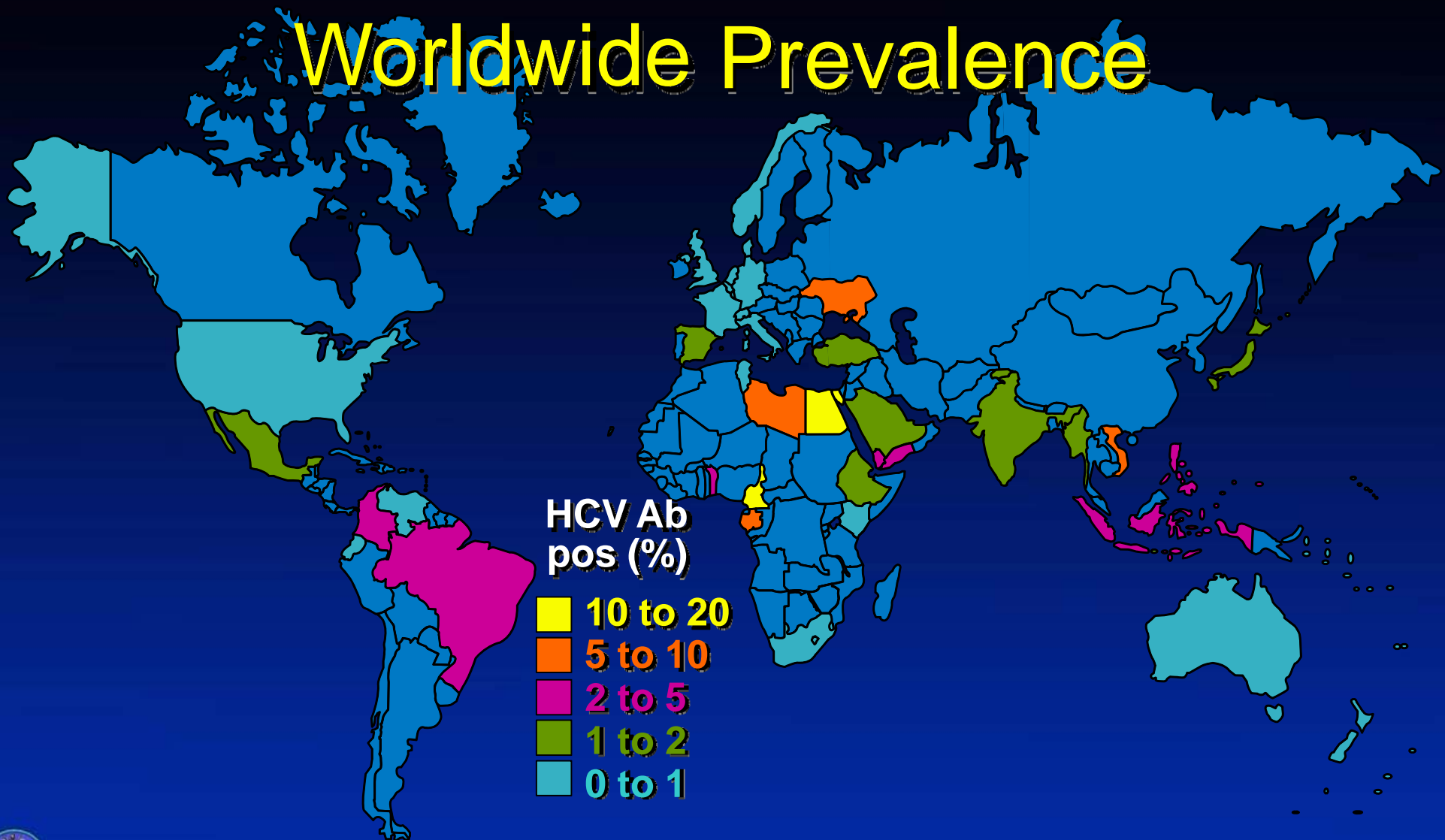
Lavanchy D & McMahon B, In: Liang TJ & Hoofnagle JH (eds.)

Hepatitis C. New York: Academic Press, 2000:185

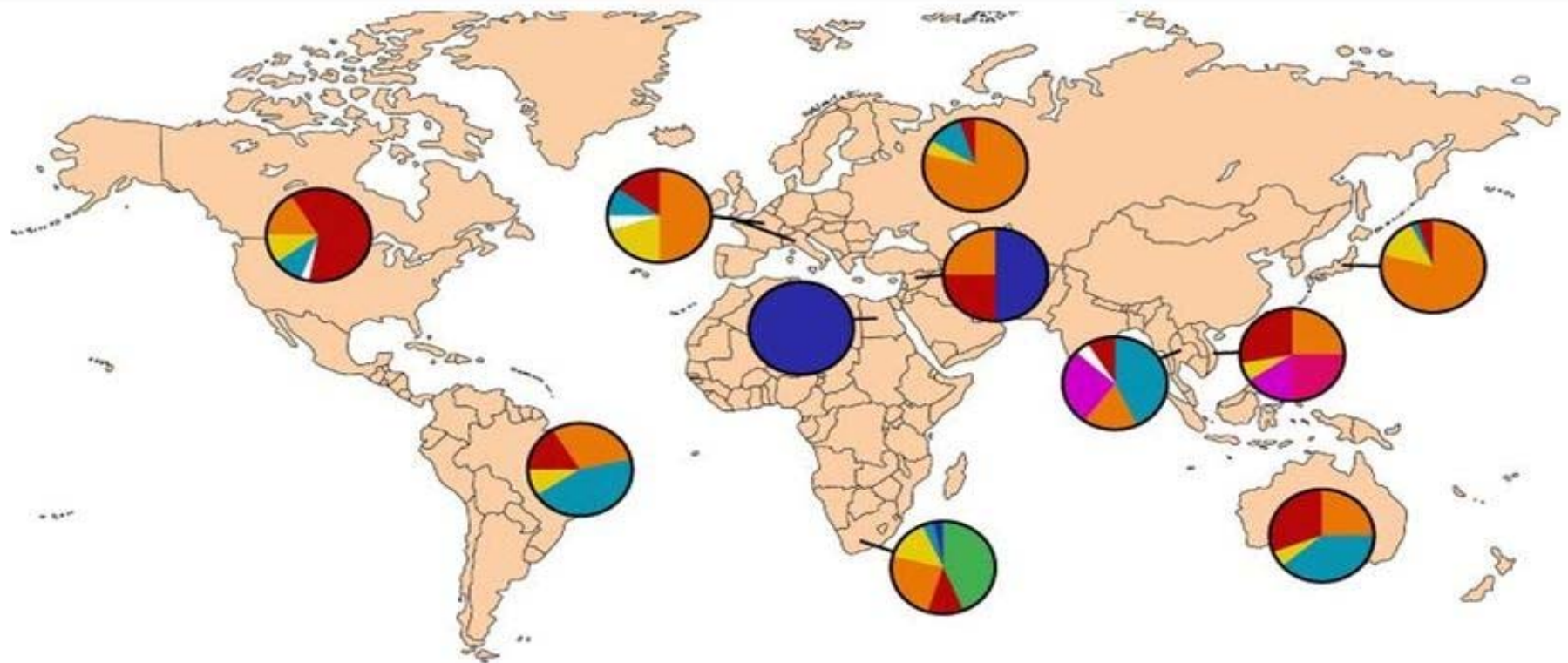


HCV - Epidemiology

Worldwide Prevalence

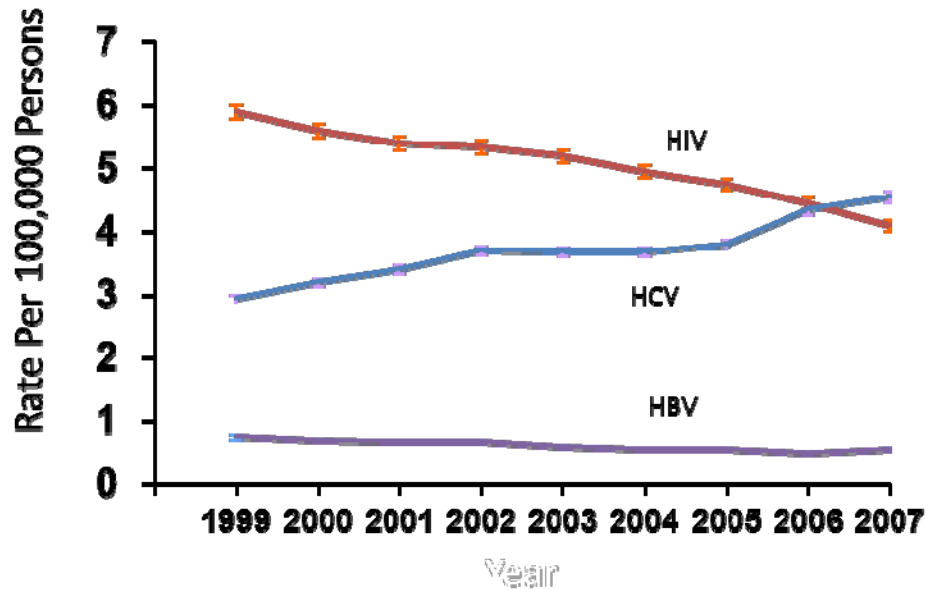


Distribution of hepatitis C genotypes



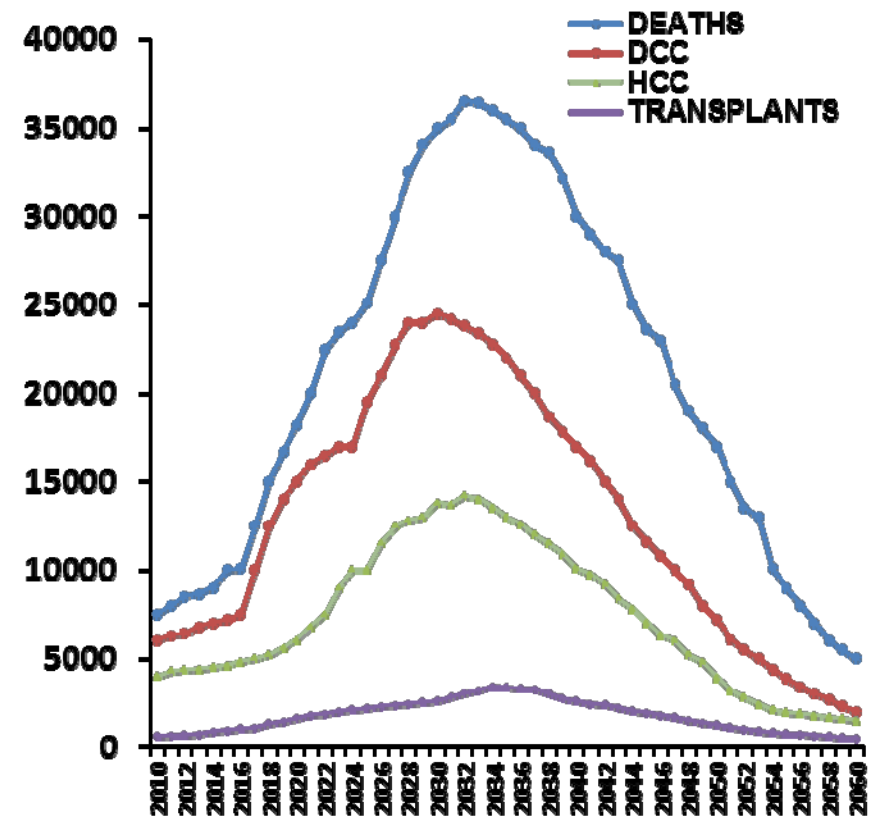
United States: Increased Morbidity and Mortality Due to HCV Now and in the Future

Mortality Rates of HBV, HCV and HIV: 1999-2007¹



By 2007 hepatitis C-associated deaths had overtaken HIV as a cause of mortality in the United States. To achieve declines in mortality similar to those seen with HIV will require new policy directions and commitment to detect and link infected persons to care and successful treatment.

Morbidity and Mortality Predictions²

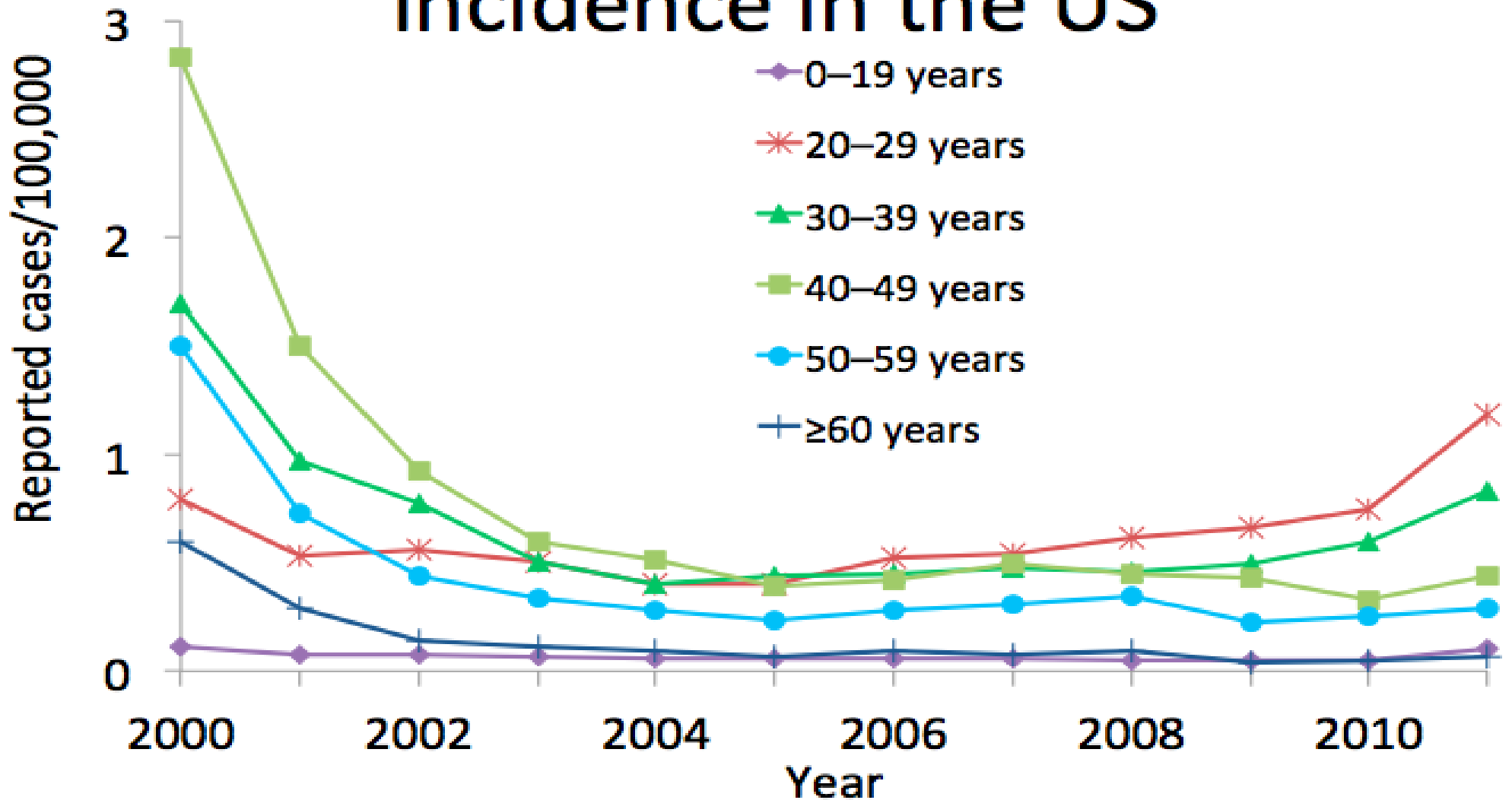


DCC, decompensated cirrhosis

1. Adapted from Ly KN et al. *Ann Intern Med.* 2012;156:271-278.

2. Adapted from Rein DB et al. *Dig Liver Dis.* 2011;43:66-72.

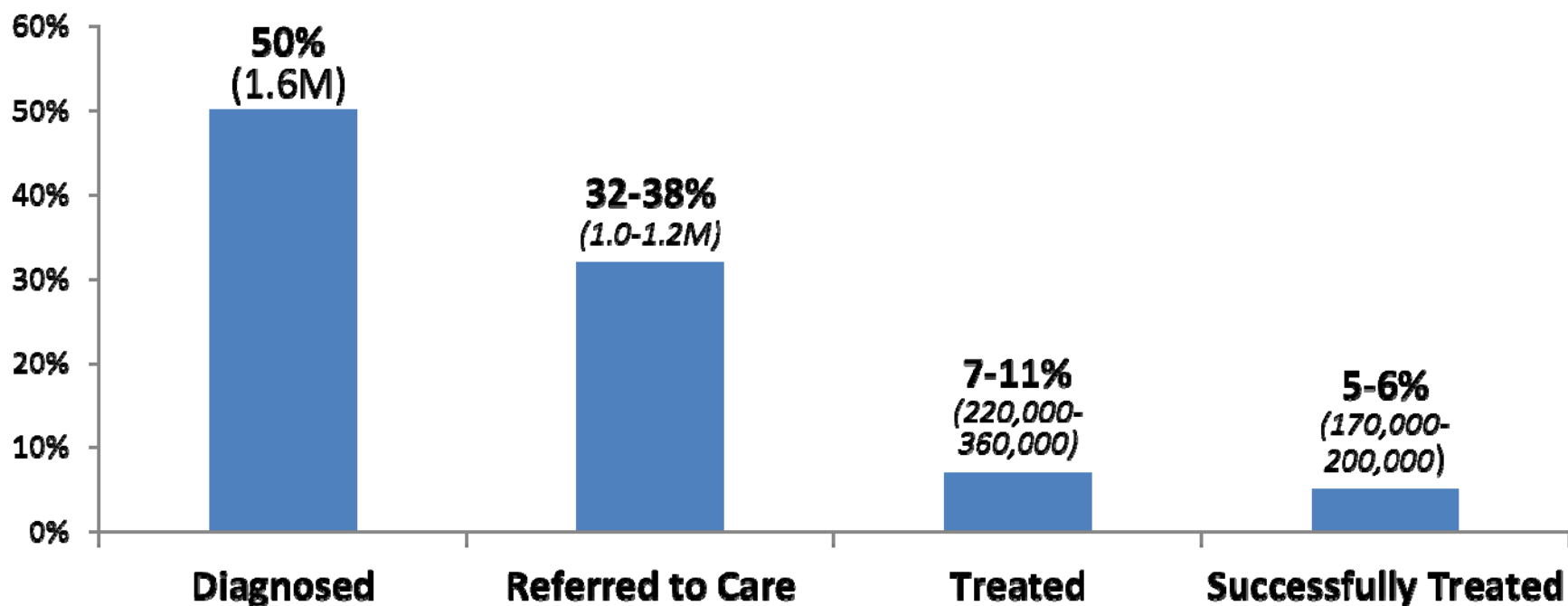
Recent Trend in Acute HCV Incidence in the US



Source: National Notifiable Diseases Surveillance System (NNDSS)

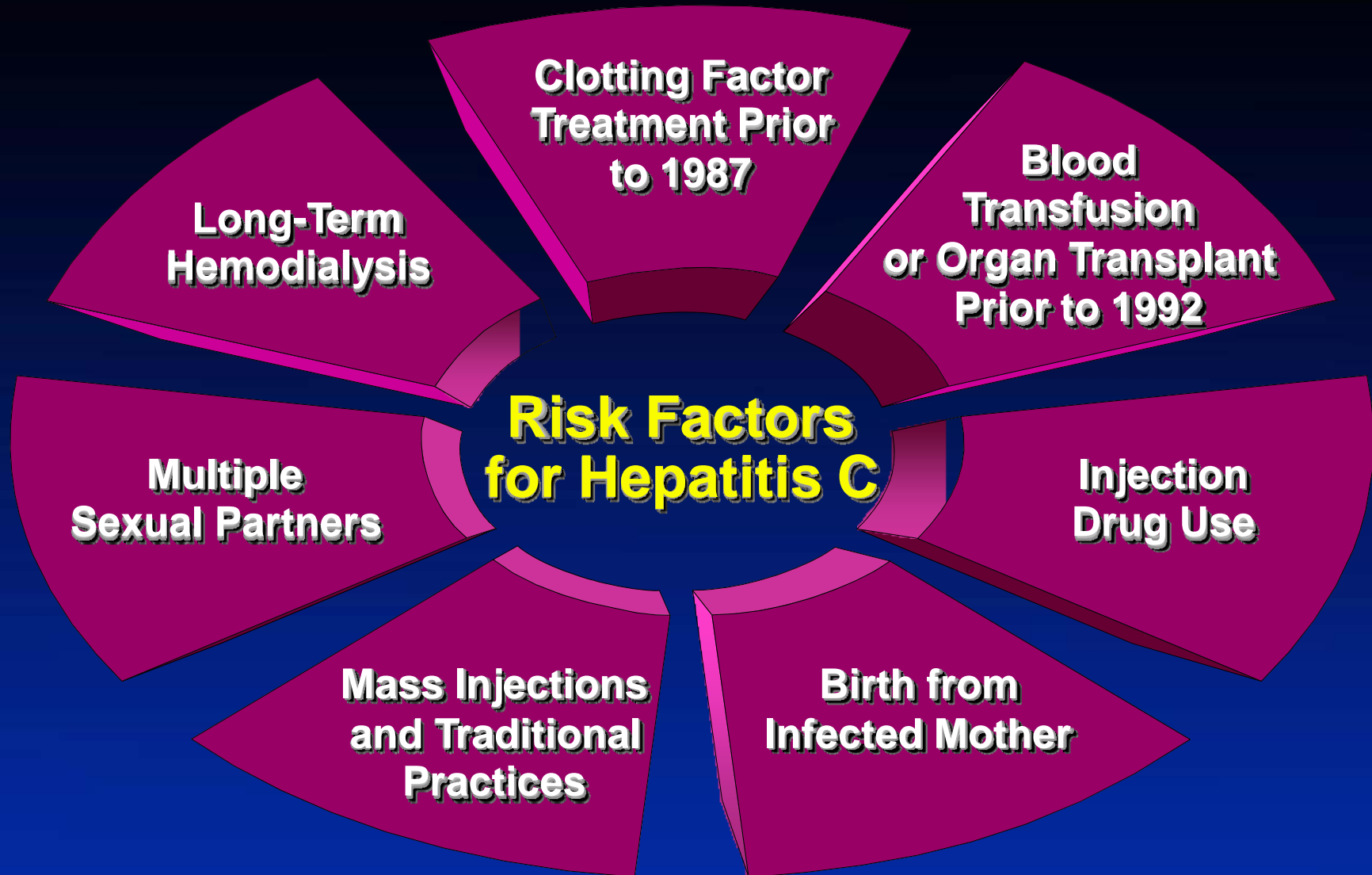
Most Americans With Chronic HCV Have Not Been Diagnosed and Few Have Been Treated

Overall: 3.2 million of U.S. population with chronic HCV



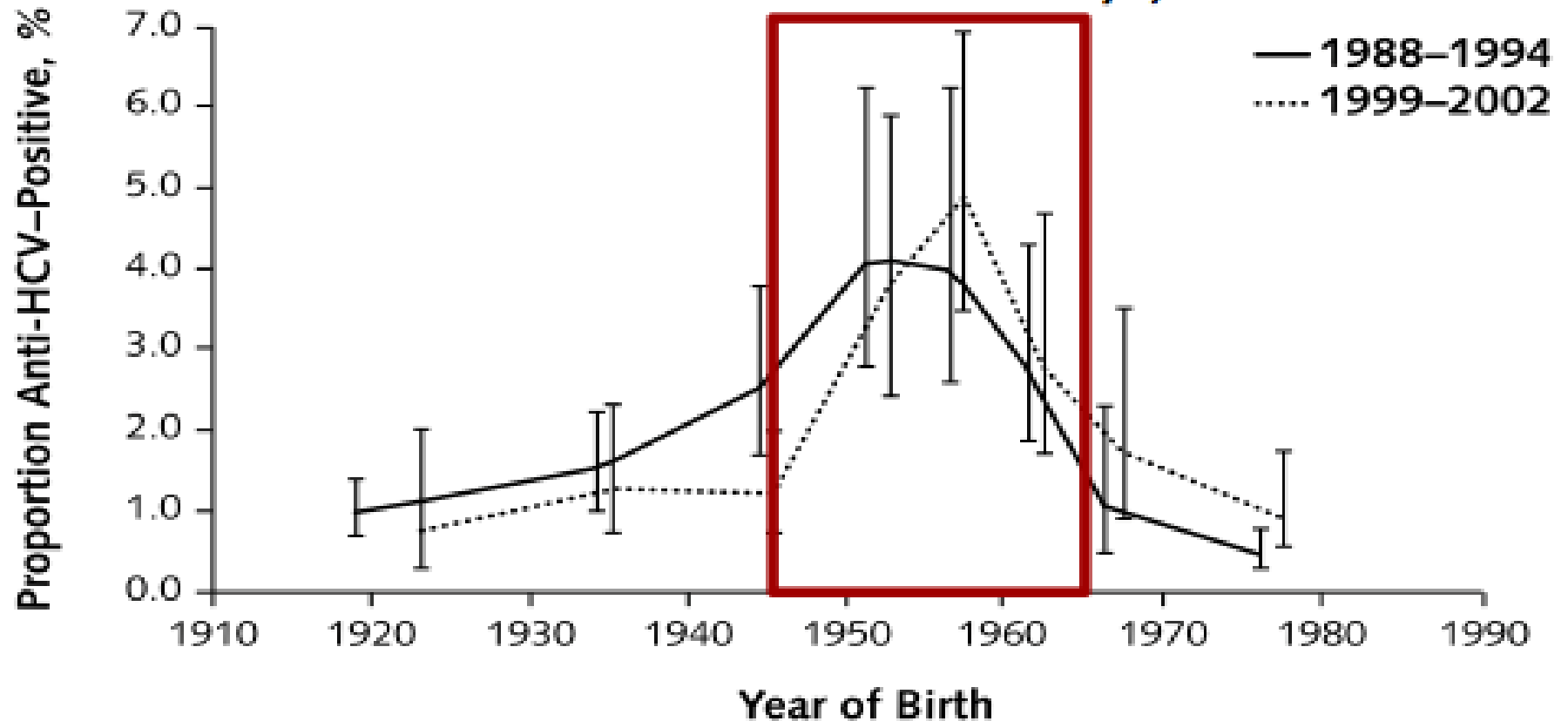
- Limited response to treatment with Interferon
 - Severe side effect profile
 - Multiple contra indications

HCV - Epidemiology



Birth Cohort Screening for HCV

Age-specific HCV Prevalence in US General Population (National Health and Nutrition Examination Surveys)



The CDC and USPSTF recommend offering 1-time screening for HCV infection to adults born between 1945 and 1965.

2 1943 1944 1945 1946 1947 1948 1949 1950 1951 1952 1953 1954 1955 1956 1957 1958 1959 1960 1961 1962 1963 1964 1965 1966 1967

BORN FROM 1945 TO 1965?

AMERICANS BORN DURING THESE YEARS HAVE
THE HIGHEST RATES OF HEPATITIS C.

Talk to your doctor about getting tested. Early detection can save lives.



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

www.cdc.gov/knowmorehepatitis




**KNOW
MORE
HEPATITIS™**

Who should be tested for hepatitis C

Risk factors for HCV

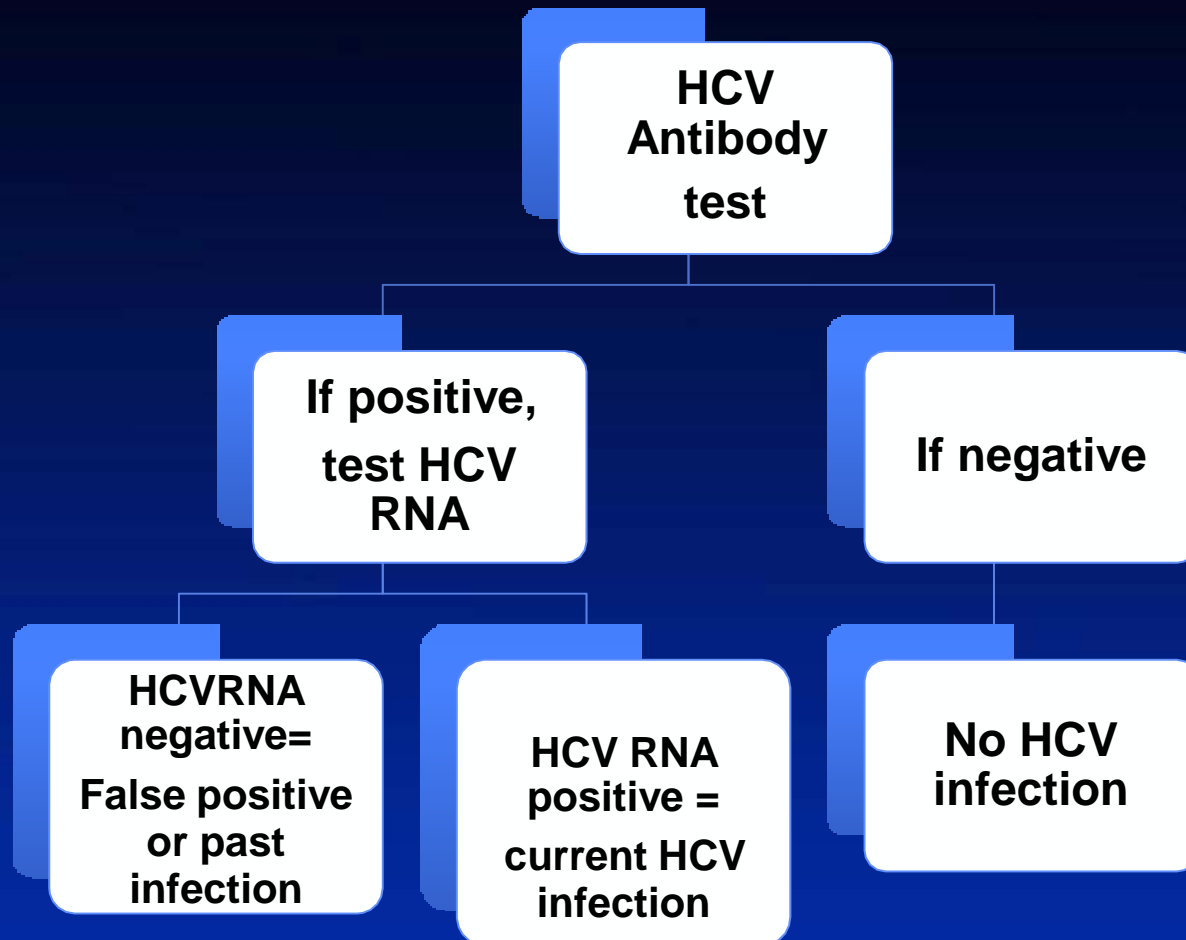
Elevated ALT

Baby boomers

Test for HCV antibody

Extra-hepatic

Diagnostic Tests for HCV



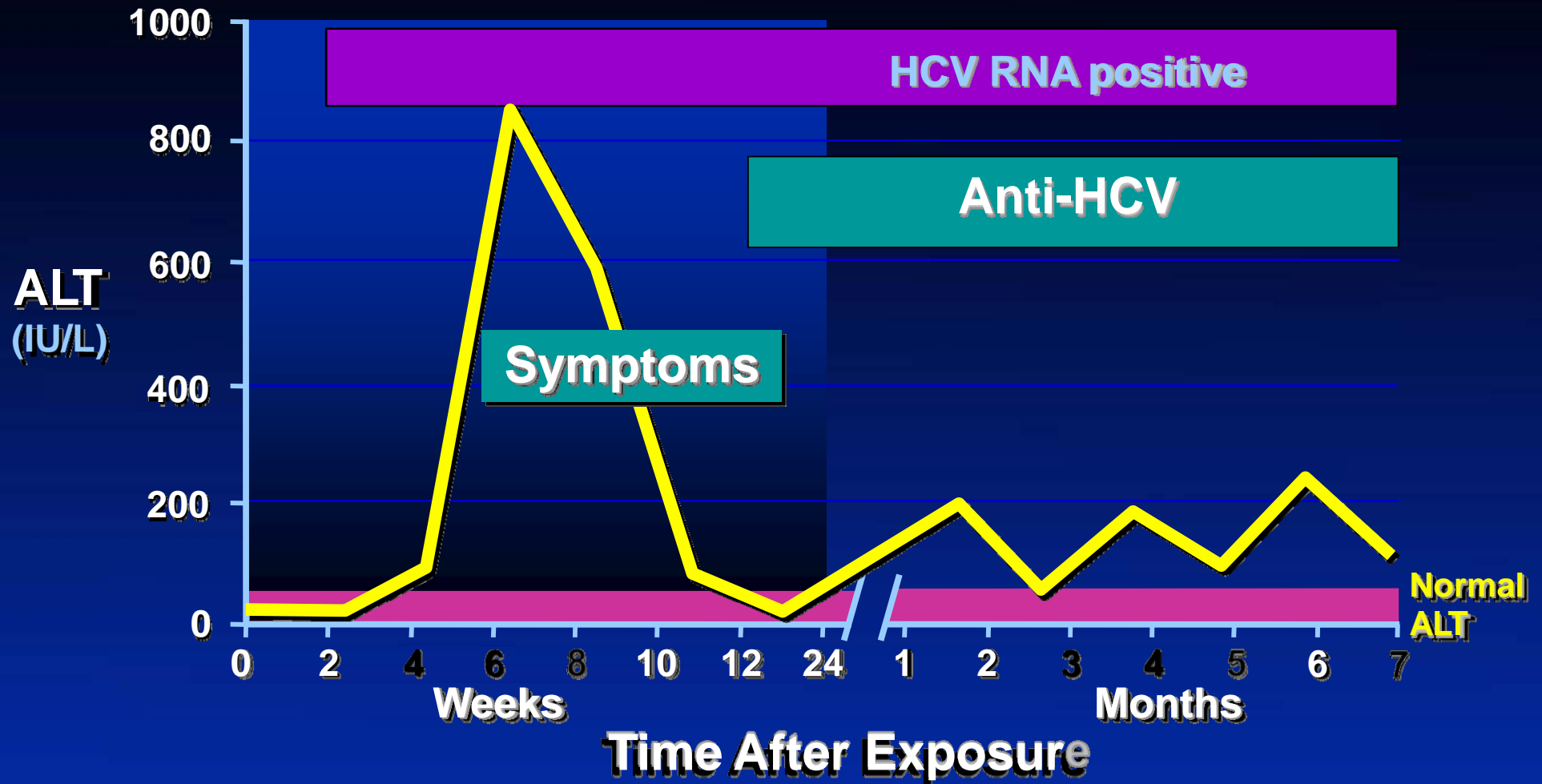
HCV - Diagnosis

Diagnostic Tests

- Hepatitis C antibody test: screening
- Qualitative HCV RNA test: confirmatory
- Quantitative HCV RNA test: monitor treatment
 - Genotype: how to treat and for how long *
 - Liver biopsy: when to treat*

HCV - Diagnosis

Acute HCV Infection



Acute hepatitis C

- **Signs and symptoms:**
 - Asymptomatic (79% of cases)
 - Anorexia, right upper quadrant abdominal pain, with or without jaundice, arthralgia, myalgia, fatigue, weight loss, skin rash and fever.
- **Laboratory tests:**
 - CMP: increased AST, ALT up to thousands, mild increase in ALK phosphatase and GGT, variable increase in bilirubin, decreased albumin
 - Coagulation: prolonged prothrombin time in severe cases.
- **Natural history:** 55 to 85% of the patients will progress to chronic HCV

Chronic hepatitis C

- **Signs and symptoms:**
 - Asymptomatic
 - Fatigue, joint pain, dull right upper quadrant abdominal pain, anorexia, nausea, pruritus, memory loss
- **Laboratory tests:**
 - 1/3 of patients have normal ALT/AST.
 - Mildly increased AST/ALT (50-low hundreds), with typical fluctuation over time.
 - Increased PT and bilirubin, low albumin is seen as the disease progresses to cirrhosis.
- **Natural history:**
 - Remain as chronic hepatitis
 - Progress to cirrhosis and liver failure
 - Patients may develop liver cancer.



Extra hepatic Disorders Associated with Chronic HCV

Hematological	Essential mixed cryoglobulinemia Non-Hodgkin's lymphoma
Renal	Membranoproliferative glomerulonephritis Membranous nephropathy
Dermatological	Porphyria cutanea tarda Leukocytoclastic vasculitis Lichen planus
Autoimmune	Diabetes mellitus * Idiopathic thrombocytopenic purpura



Banner Health®



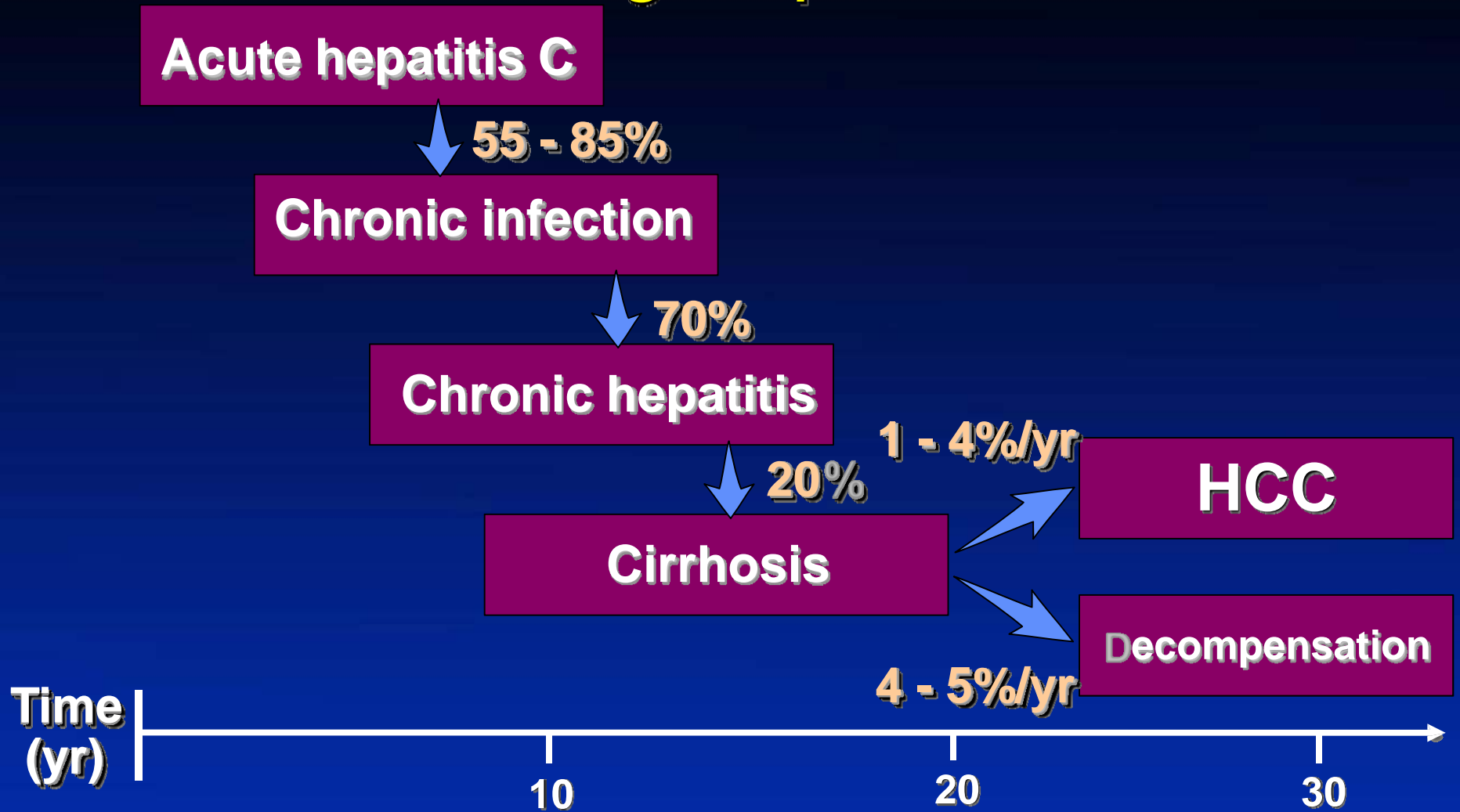
HCV – Extra hepatic manifestations

Liver biopsy or image modalities
HCV as a risk factor for cardiovascular
diseases

- Several small studies and a meta-analysis (Gastroenterology 2016; 150:145-55)
- Increased risk of cardio-vascular related mortality, carotid plaques and cerebrovascular diseases

HCV - Natural History

Outcome Following Hepatitis C Infection



HCV - Natural History

Factors Associated With Fibrosis

Factors Associated With Fibrosis

- Duration of infection
- Alcohol > 50 gm per day
- Age > 40 years at infection
 - Male gender
 - Co-infection
(HBV, HIV)

Poynard T, et al., Lancet 1997; 349:825



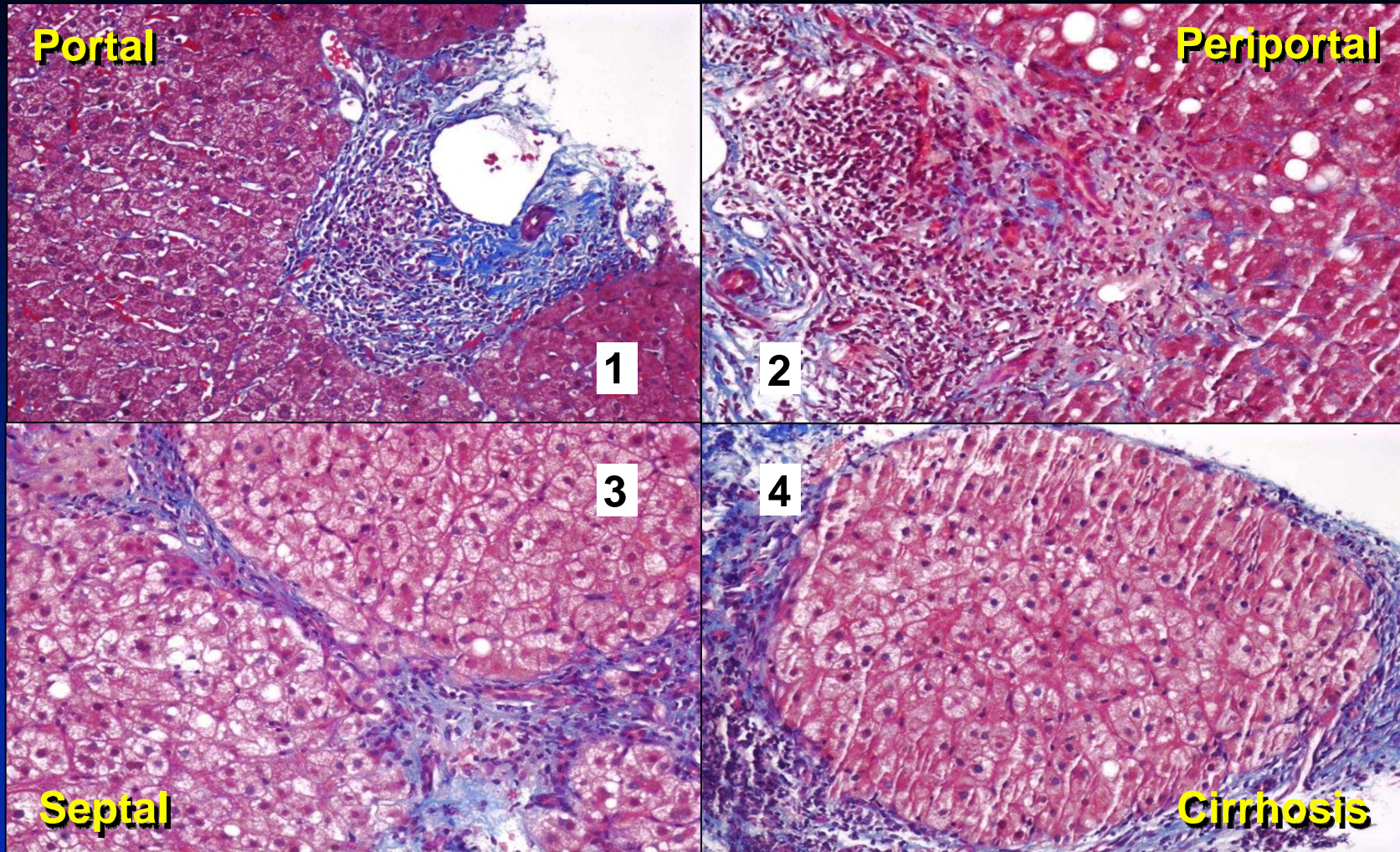
HCV - Diagnosis

Liver biopsy or image modalities

- Degree of fibrosis is most important predictor of prognosis
- Useful in determining need for anti-viral therapy (?)
- Advanced cirrhosis is associated with reduced response to treatment (?)

HCV - Natural History

Stages of Fibrosis In Chronic Hepatitis



Liver Biopsy

X



X

X

X

Evaluation of fibrosis:

- Fibro sure test
- US elastography
- MRI elastography

HCV - Diagnosis

HCV Genotypes

- Six major genotypes found throughout the world (1 to 6).
- In Europe and U.S., 60-70% of patients have genotype 1 infection, followed by genotypes 2 and 3.
- Treatment is different for G 1 and G 2 and 3(?)

Goals of Hepatitis C Treatment

Primary

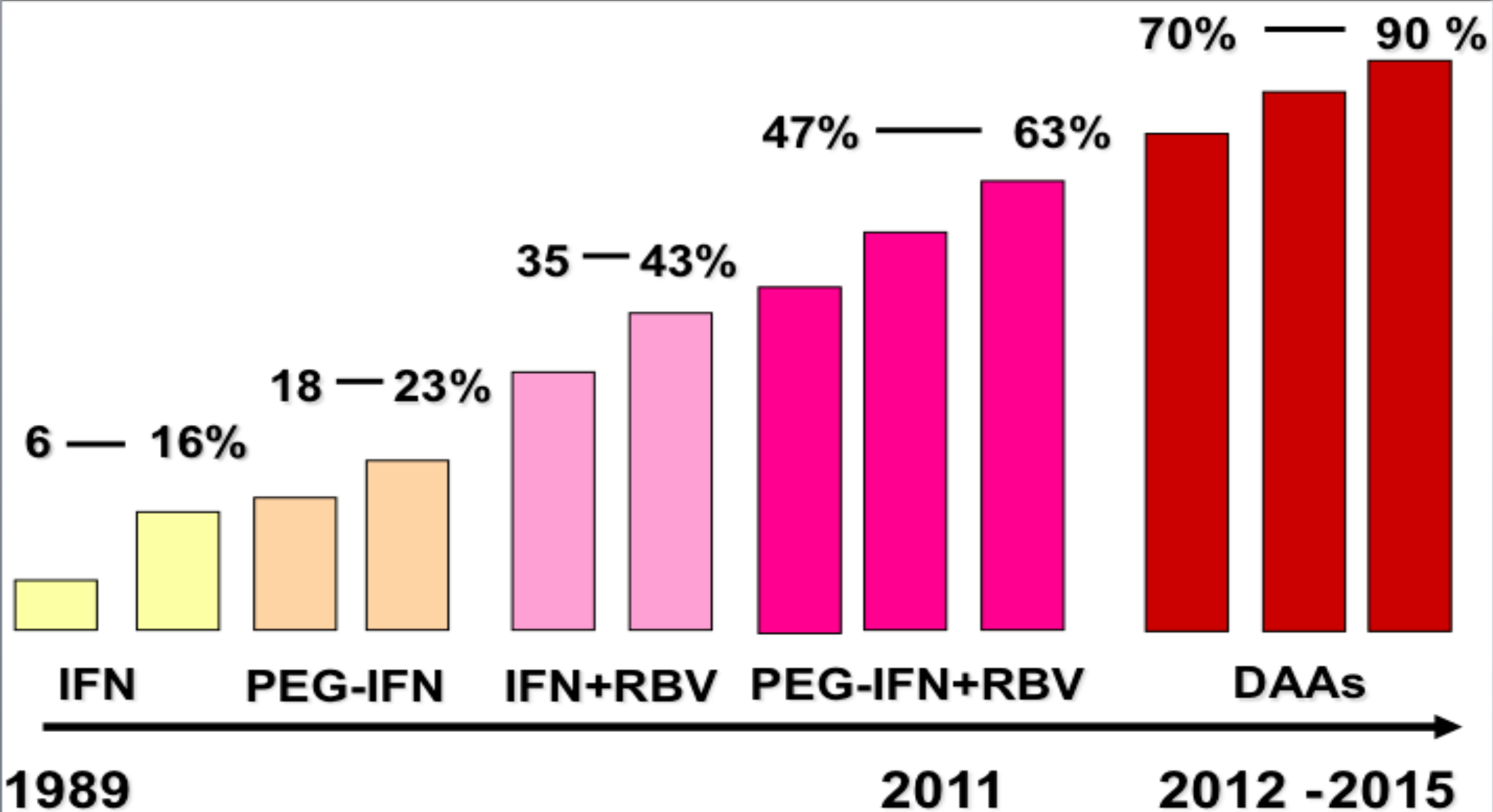
- Eradicate the virus

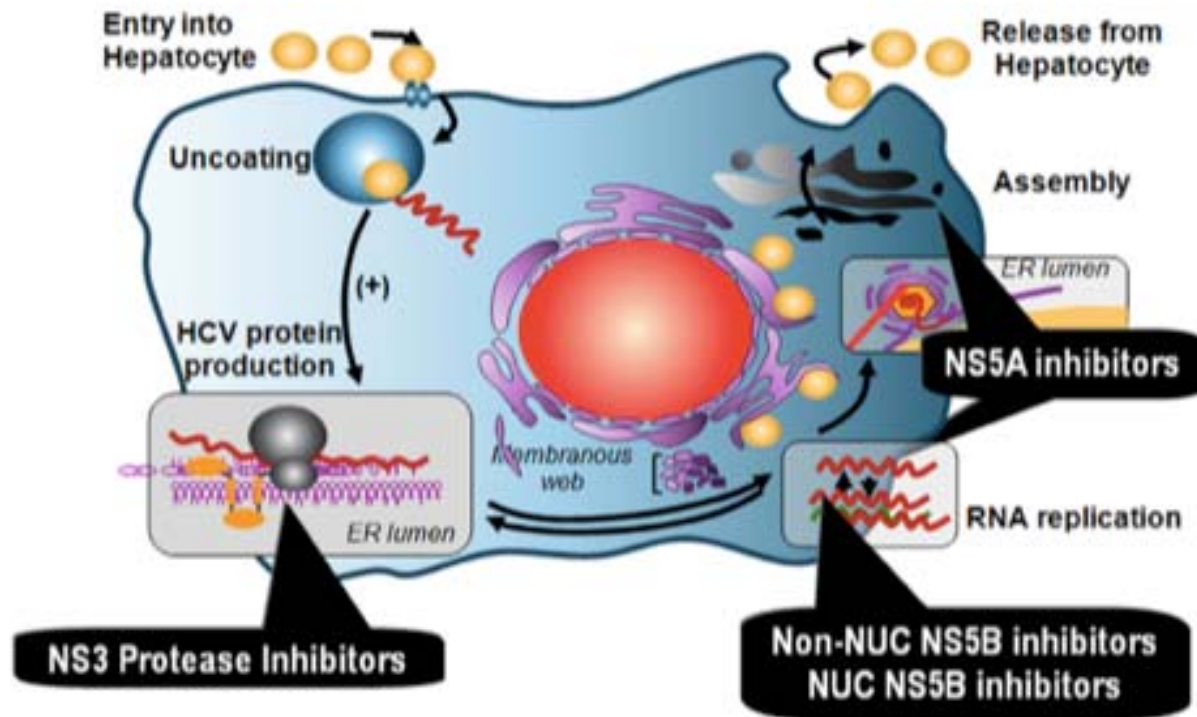
Secondary

- Prevent progression to cirrhosis
- Reduce incidence of HCC
- Reduce need for transplantation
- Enhance survival



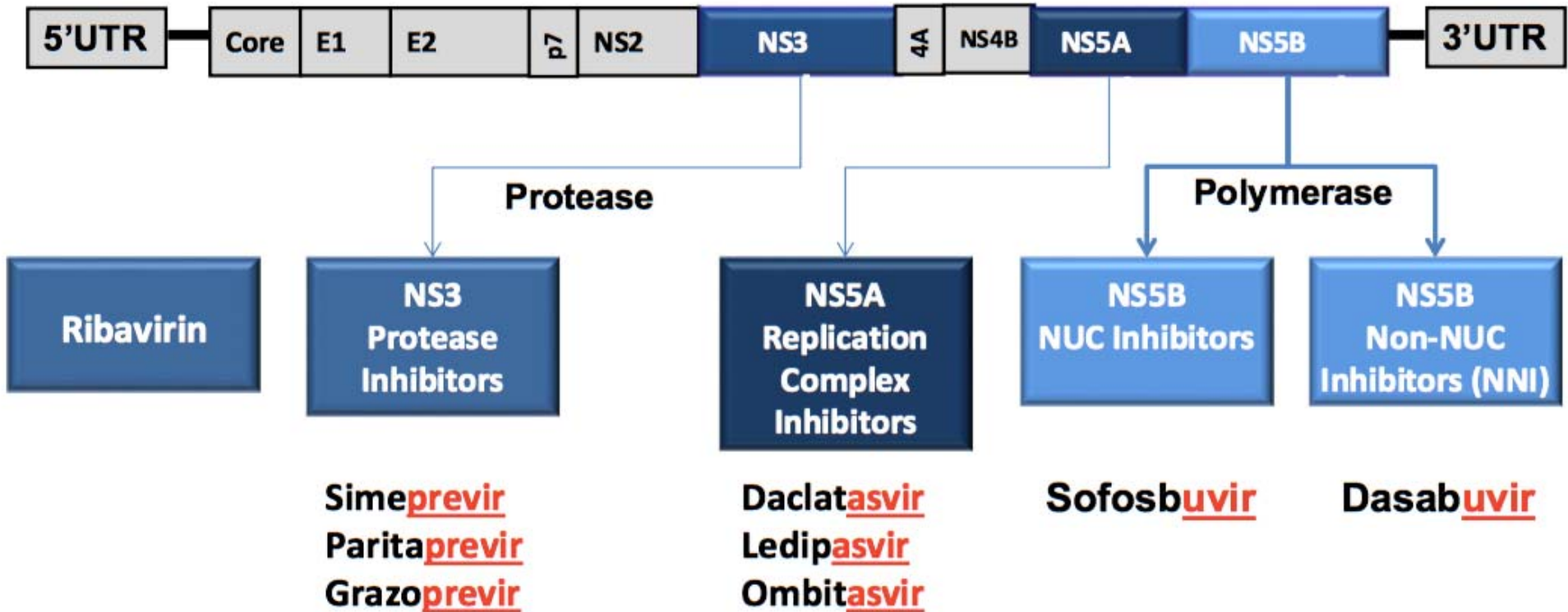
Progress in the Treatment of Hepatitis C





Gane EJ, Agarwal K. Am J Transplant 2014;14:994-1002.

Multiple Classes of Direct-Acting Antiviral Agents



- Combinations of different classes of DAAs:
 - Provide near-universal cure
 - Are generally safe and well-tolerated

Current therapy for HCV Genotype 1 and 4

- 1) Daclatasvir and Sofosbuvir with and w/o Ribavirin for 12 or 24 weeks
- 2) Ledipasvir and Sofosbuvir with and without Ribavirin for 12 or 24 weeks
- 3) Sofosbuvir and Velpatasvir with and w/o Ribavirin for 12 weeks*
- 4) Ombitasvir, Paritaprevir/Ritonavir and Dasabuvir for 12 or 24 weeks, with or w/o Ribavirin
- 5) Simeprevir and Sofosbuvir, with or w/o Ribavirin
- 6) Elbasvir and Grazoprevir with and w/o Ribavirin**



Current HCV therapy: Genotypes 2 and 3

- Sofosbuvir and Ribavirin for 12 weeks or 24 weeks for G 2 and G 3 respectively.
- Sofosbuvir and Daclatasvir for Genotypes 2 and 3 *
- Sofosbuvir and Velpatasvir **

General Concepts About Selecting HCV Regimens to Optimize SVR and Safety

- **Choice of regimen, treatment duration, and use of ribavirin depends on:**
 - **Genotype**
 - **Genotype 1a vs 1b**
 - **Genotypes 2-6**
 - **Prior treatment experience (Naïve vs Experienced)**
 - **PEG-RBV failure**
 - **Prior protease inhibitor failure**
 - **Prior NS5A inhibitor failure**
 - **Prior sofosbuvir failure**
 - **Presence of cirrhosis**
 - **Compensated (CP-A) vs Decompensated (CP-B, CP-C)**
 - ****Presence of baseline resistance-associated variants (NS5A)**
 - **Potential for drug-drug interactions**

Principles of All Oral Regimens for HCV

- **Combine drugs from different classes:**
 - **Hit multiple targets to increase efficacy**
 - **Diminish risk of viral resistance**
 - **Possible strategies:**
 - **Backbone/Anchor drug plus additional agent(s)**
 - **Multiple drugs: When combined achieve superior efficacy than might be predicted by individual drug characteristics**
 - **If done properly:**
 - **Near universal efficacy**
 - **Shortened duration of therapy**
 - **Adverse events have minimal impact on QOL**
-

Resources for DDIs

- AASLD treatment guidelines with regular updates
- Outstanding – University of Liverpool (David Back, Editorial Board, EASL reps); sponsored by Janssen, MSD, Roche, Vertex:
 - <http://www.hep-druginteractions.org>
- FDA:
 - <http://www.fda.gov/Drugs/DrugSafety/>
- Other Online Resources –
 - <http://www.drugs.com/drug-interactions/html>
 - <http://www.merckmedicus.com/pp/us/hep>
 - Epocrates
 - Micromedex, Lexicomp and Others



HCV treatment special populations:

- HIV co-infected patients (pts) can be treated with similar response rate
- Pts with renal failure including those on dialysis can be treated
- Post liver and post kidney transplant pts can be treated with excellent response rate

Hepatitis C in 2016: Treatment Recommendations

- **Patients with HCV infection will achieve near universal cure with currently available regimens**
- **Treatment is safe and well tolerated**
 - **Caution when treating patients with decompensated cirrhosis (protease inhibitors)**
 - **Caution with drug-drug interactions (amiodarone)**
- **Optimizing SVR rates for different clinical scenarios includes lengthening duration of therapy, adding ribavirin, or performing baseline resistance testing**
- **Access to treatment remains the major barrier to improving health outcomes for all patients with HCV**

What is in the pipeline?

- More pan genotypic direct anti-viral agents
- Shorter duration of therapy

HCV summary

- HCV infection is common and can be silent
- In addition to the classic risk factors all baby boomers MUST be tested
- Normal AST and ALT does not exclude HCV
- Untreated HCV may progress to cirrhosis and HCC
- Treatment is now simpler, better tolerated and shorter duration
- Response to therapy is seen in 70 to 90% of the treated patients





Thank you!