Hepatitis C virus Academic half day 2017

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Learning Objectives

1. Outline the basic characteristics of the HCV, including its configuration, replication and immunopathogenesis.

2. Describe the epidemiology of HCV, how it is transmitted, and list major risk factors for HCV.

3. Explain how acute and chronic hepatitis C virus infections are diagnosed.

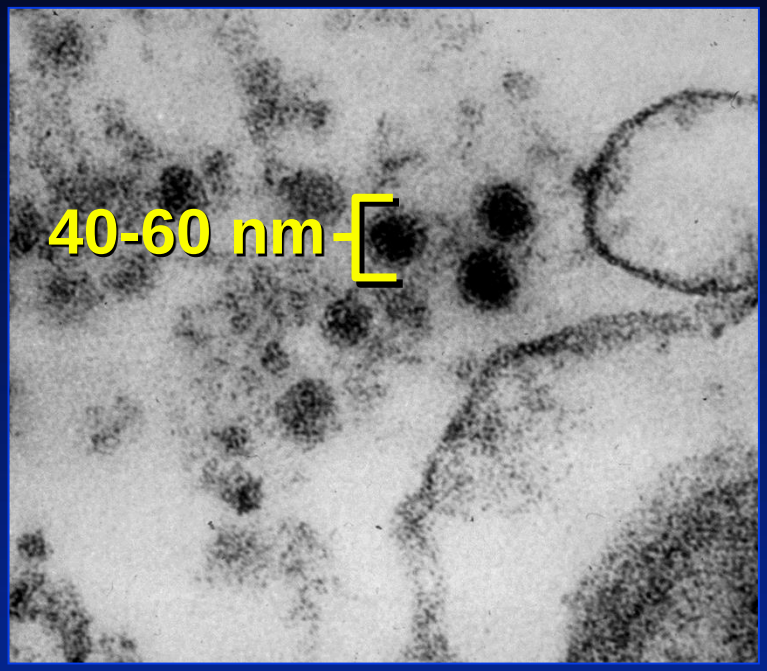
4. Describe the natural history of HCV infection.

5. Outline basic concepts relating to HCV treatment.

Comparative Features

	HAV	HBV	HCV	HEV
Type	RNA	DNA	RNA	RNA
Incubation period (days)	15-50	50-180	14-84	15-60
Acute hepatitis	yes	yes	yes	yes
Can cause chronic hepatitis	no	yes	yes	no
Can cause cirrhosis and primary hepatocellular carcinoma	no	yes	yes	no
Vaccine available	yes	yes	no	no

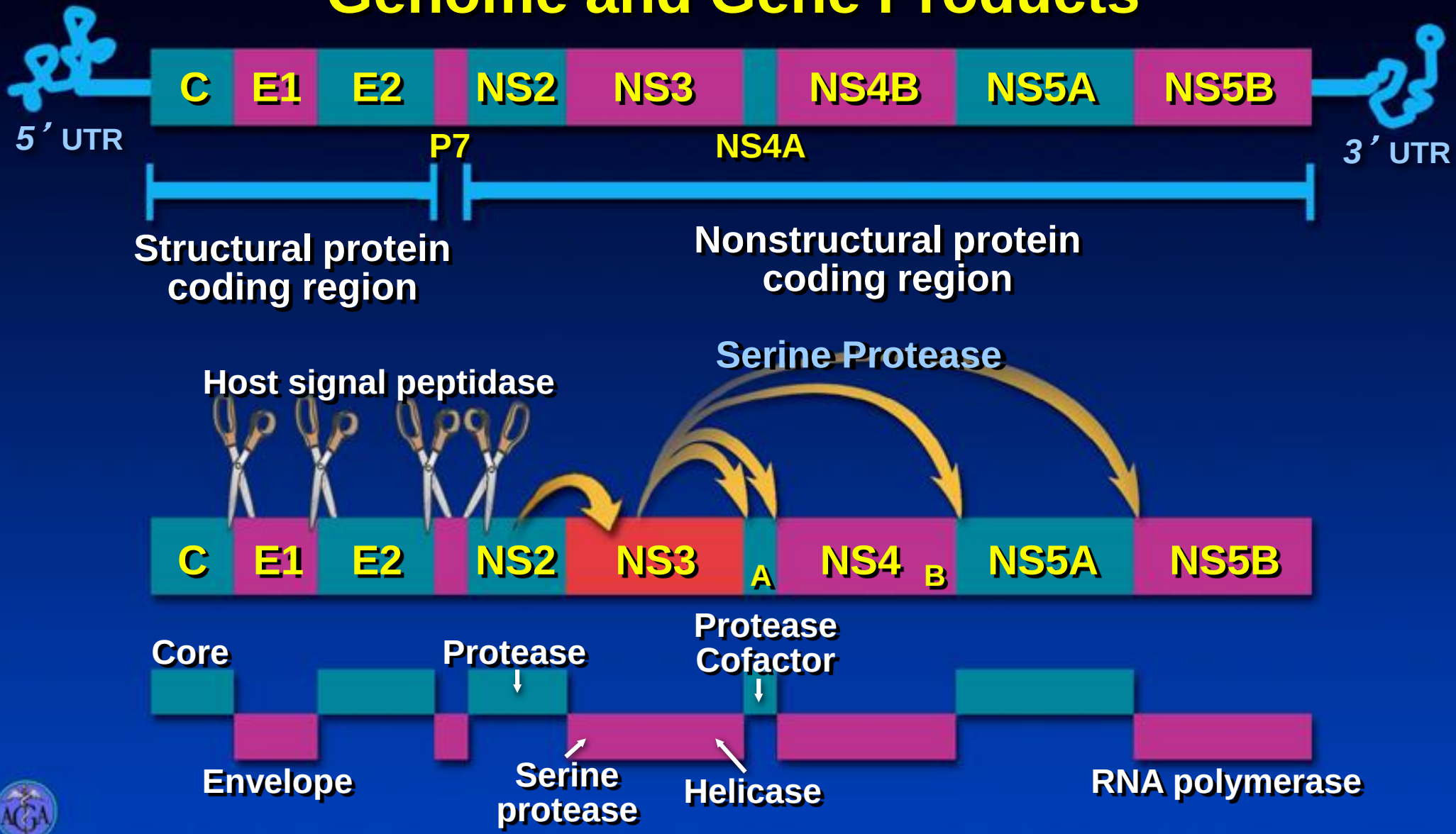
Hepatitis C Virus

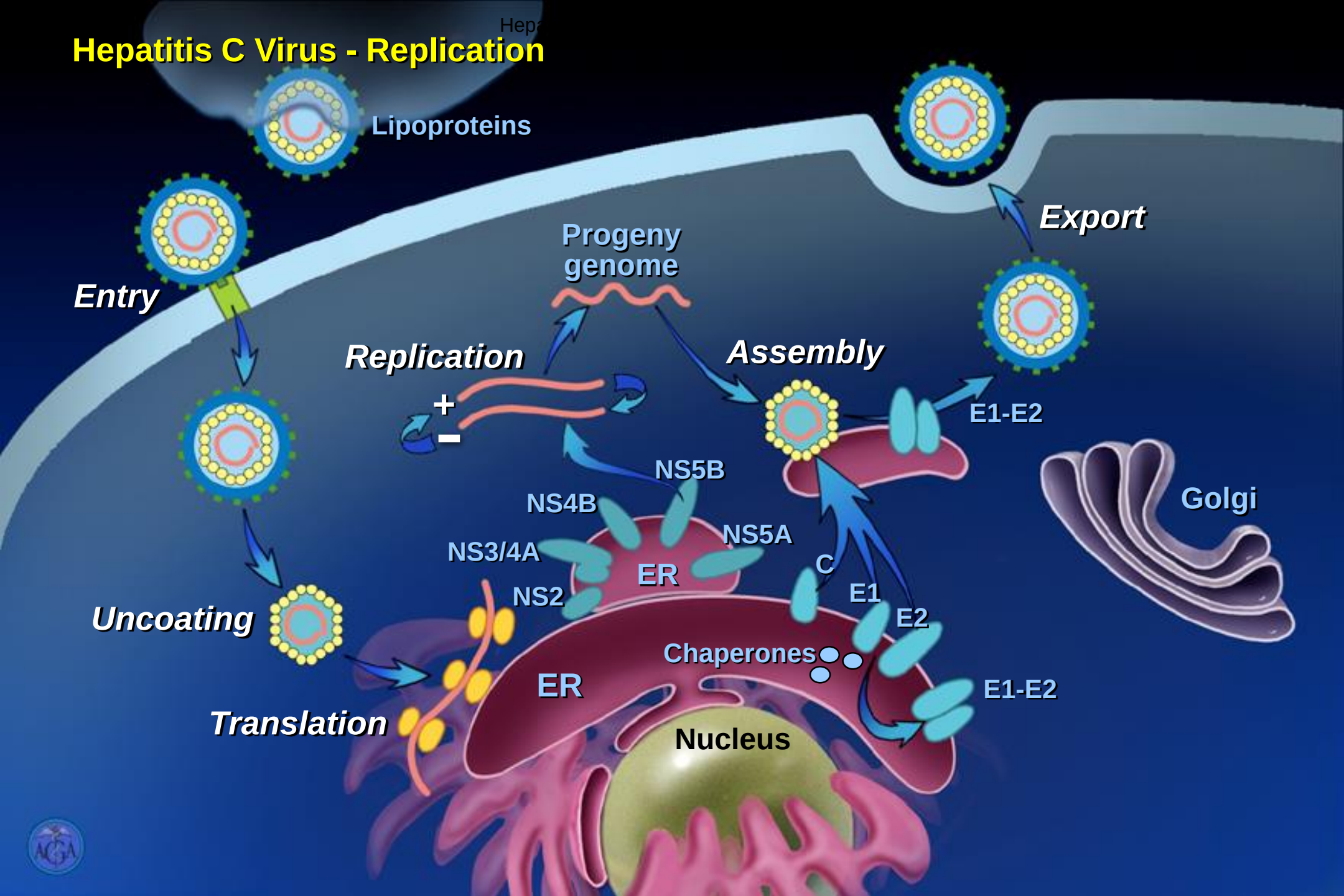


- Nucleic Acid: 9.6 kb ssRNA
- Classification: *Flaviviridae, Hepacivirus*
- Genotypes: 1 to 6*
- Enveloped
- In vitro model: primary hepatocyte and T cell cultures; replicon system
- In vivo replication: in cytoplasm, hepatocyte and lymphocyte; human and other primates

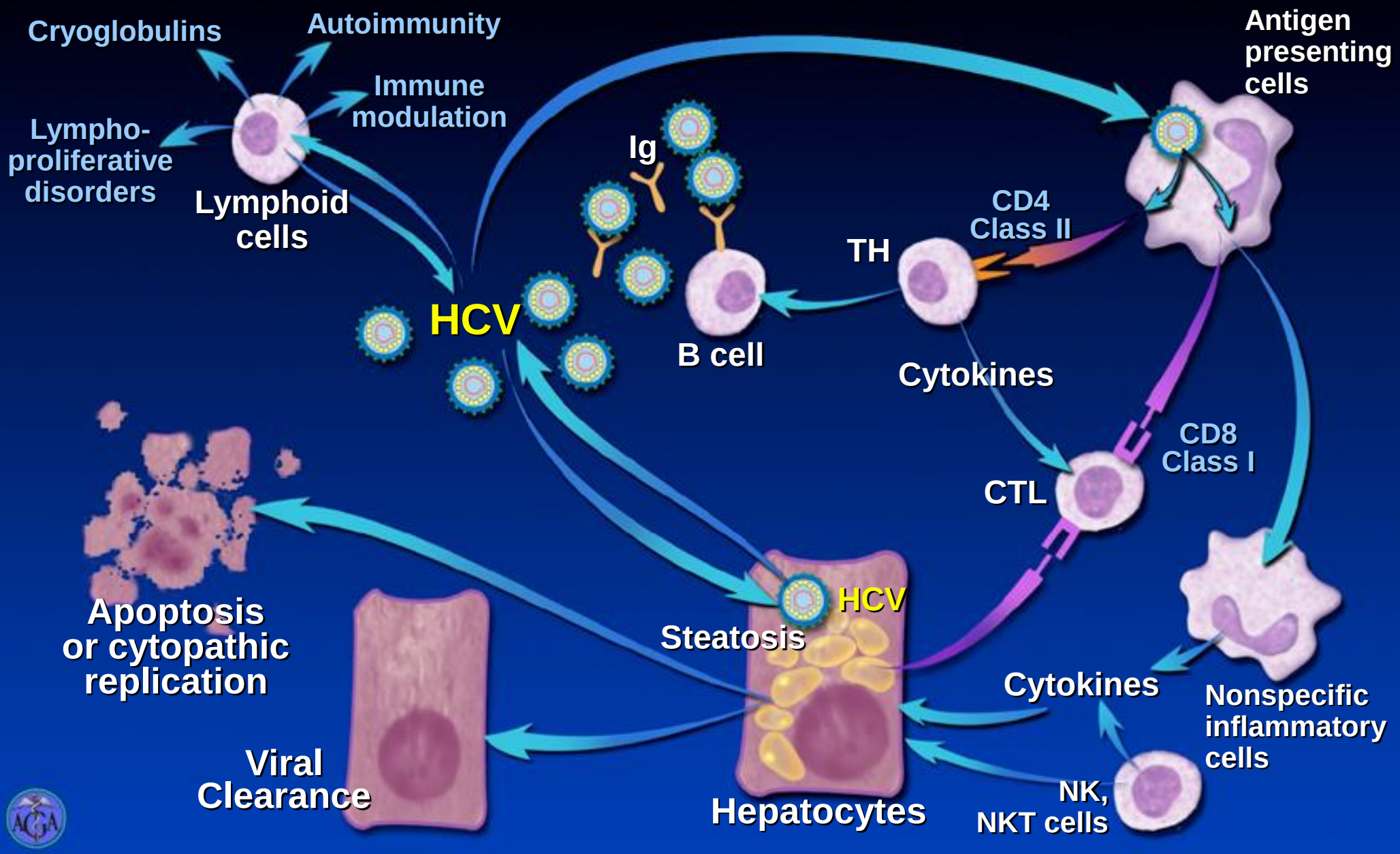
Hepatitis C Virus

Genome and Gene Products




Hepatitis C Virus - Replication
Lipoproteins
Entry
Progeny genome
Export
Replication
Assembly
+
−
E1-E2
NS5B
NS4B
NS5A
NS3/4A
ER
C
E1
E2
NS2
Golgi
Uncoating
Chaperones
ER
E1-E2
Translation
Nucleus

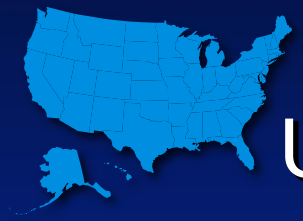
Hepatitis C Virus - Immunopathogenesis



HCV - Epidemiology

Prevalence

Worldwide	170 million (3%)

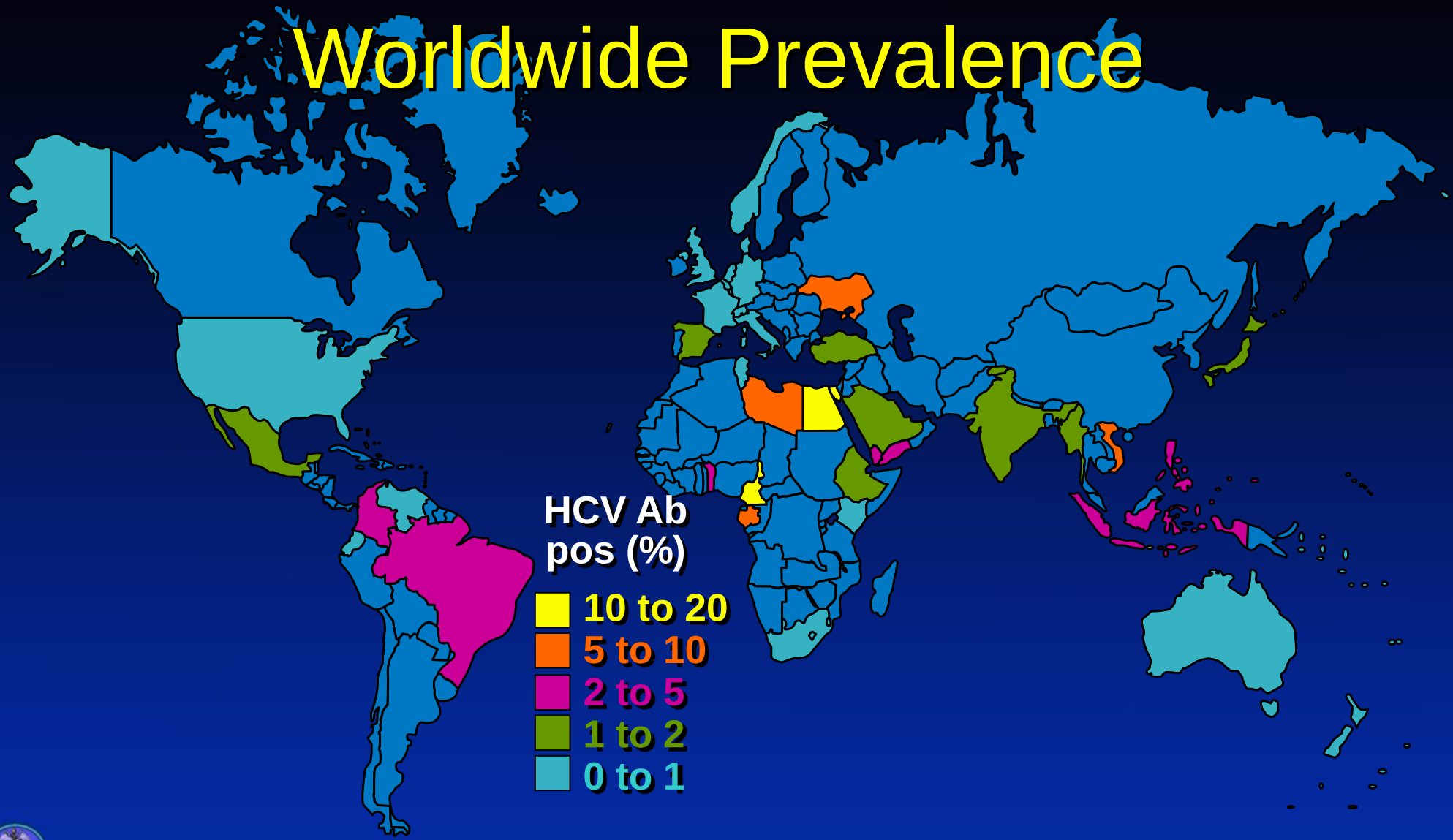


United States		
Anti-HCV positive	3.9 million	(1.8%)
HCV RNA positive	2.7 million	(1.4%)

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

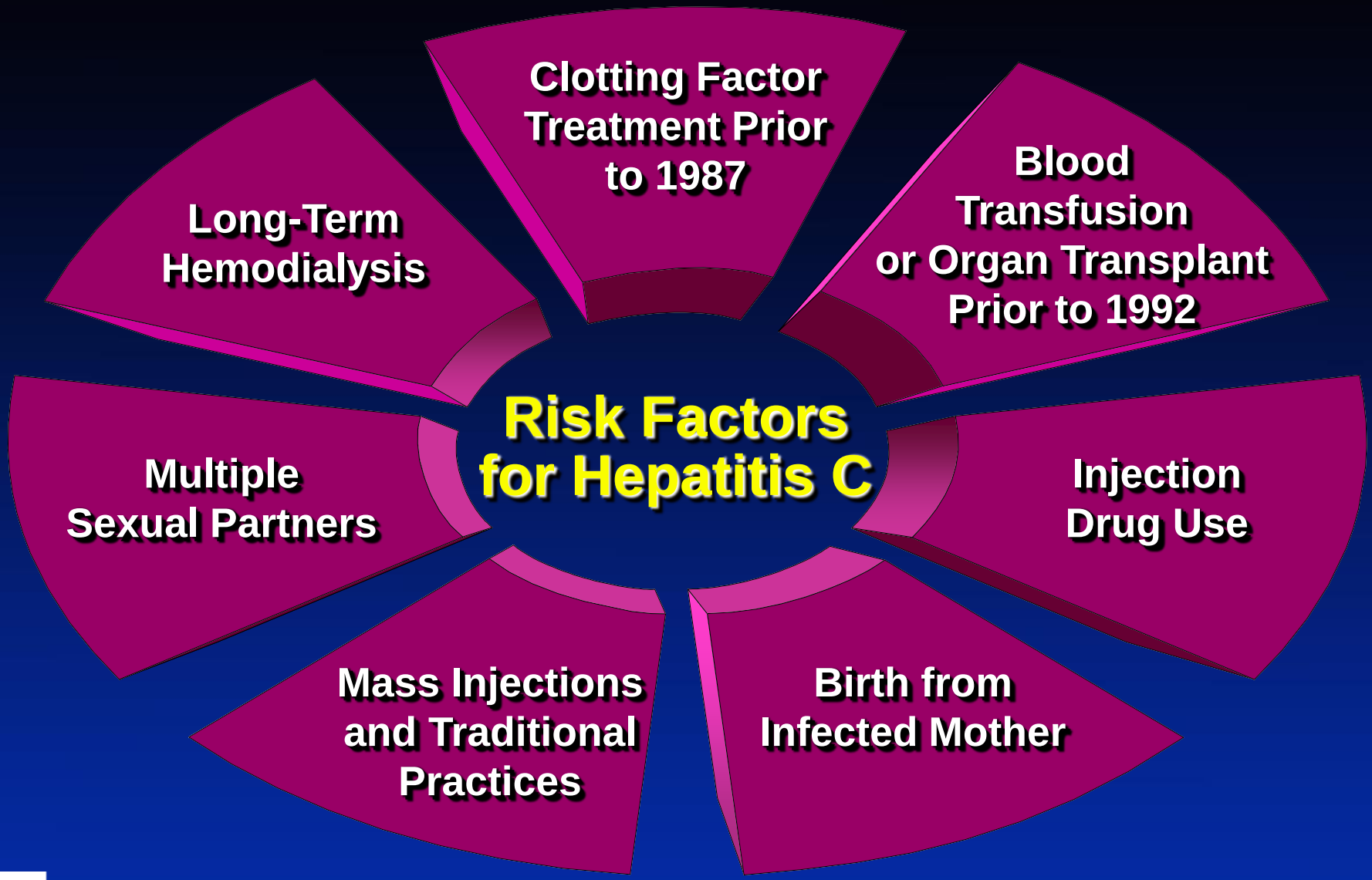
HCV - Epidemiology

Worldwide Prevalence



Heintges, T., Hepatology 1997; 26:521

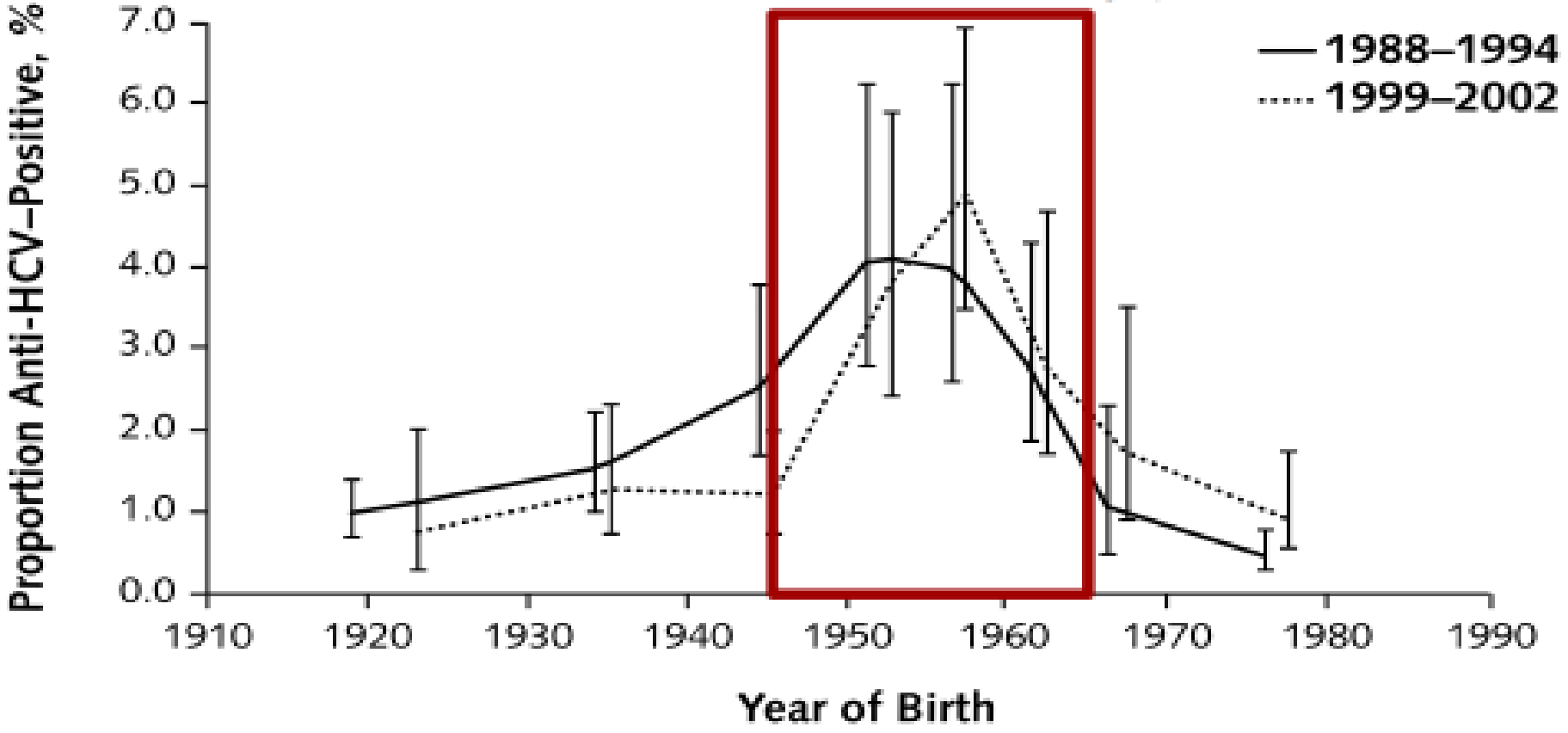
HCV - Epidemiology



Birth Cohort Screening for HCV

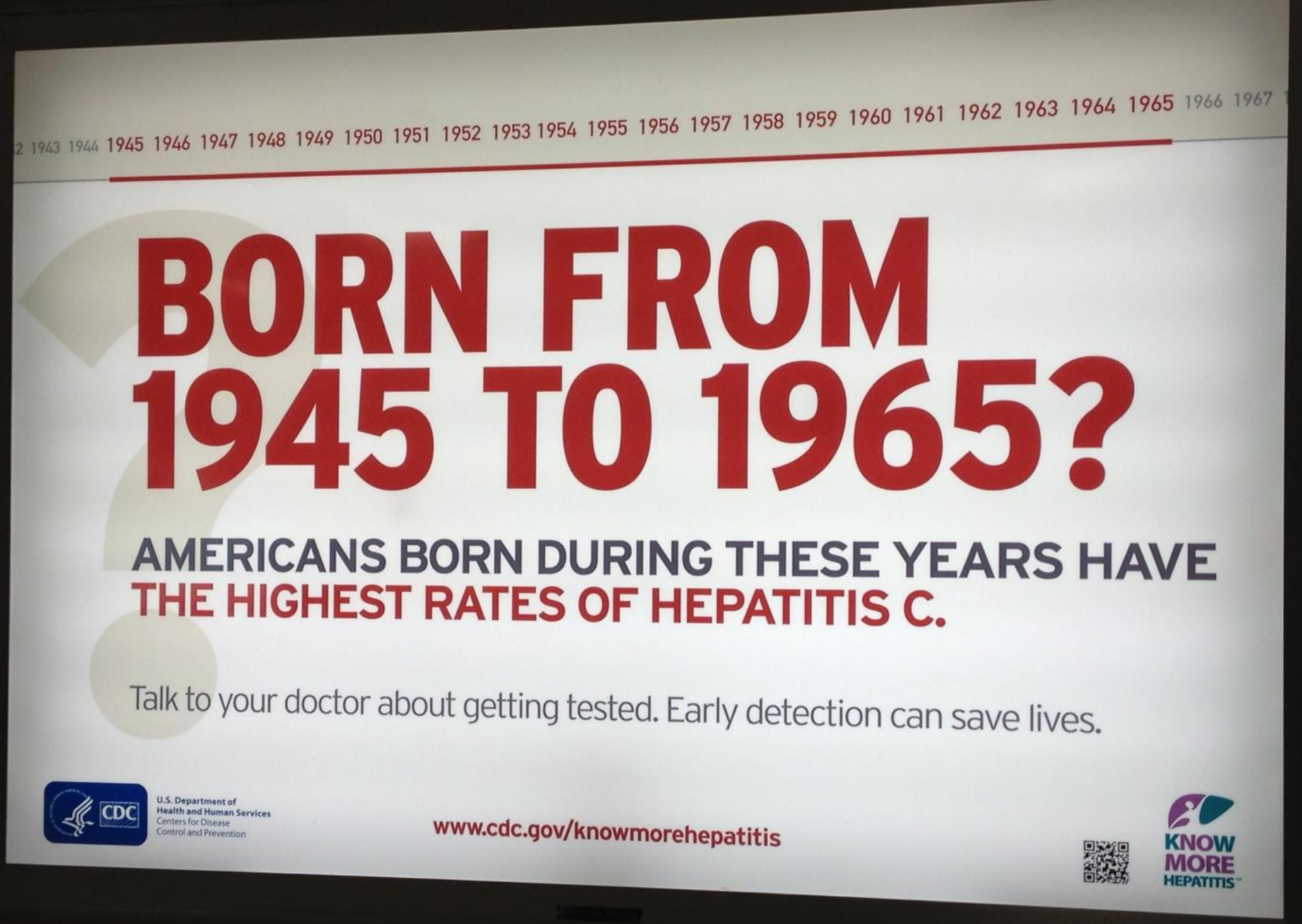
Age-specific HCV Prevalence in US General Population

(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.

Armstrong. Ann Intern Med. 2006;705, Moyer. Ann Intern Med. 2013; online 6/25


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.
CDC
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention
www.cdc.gov/knowmorehepatitis
KNOW MORE HEPATITIS

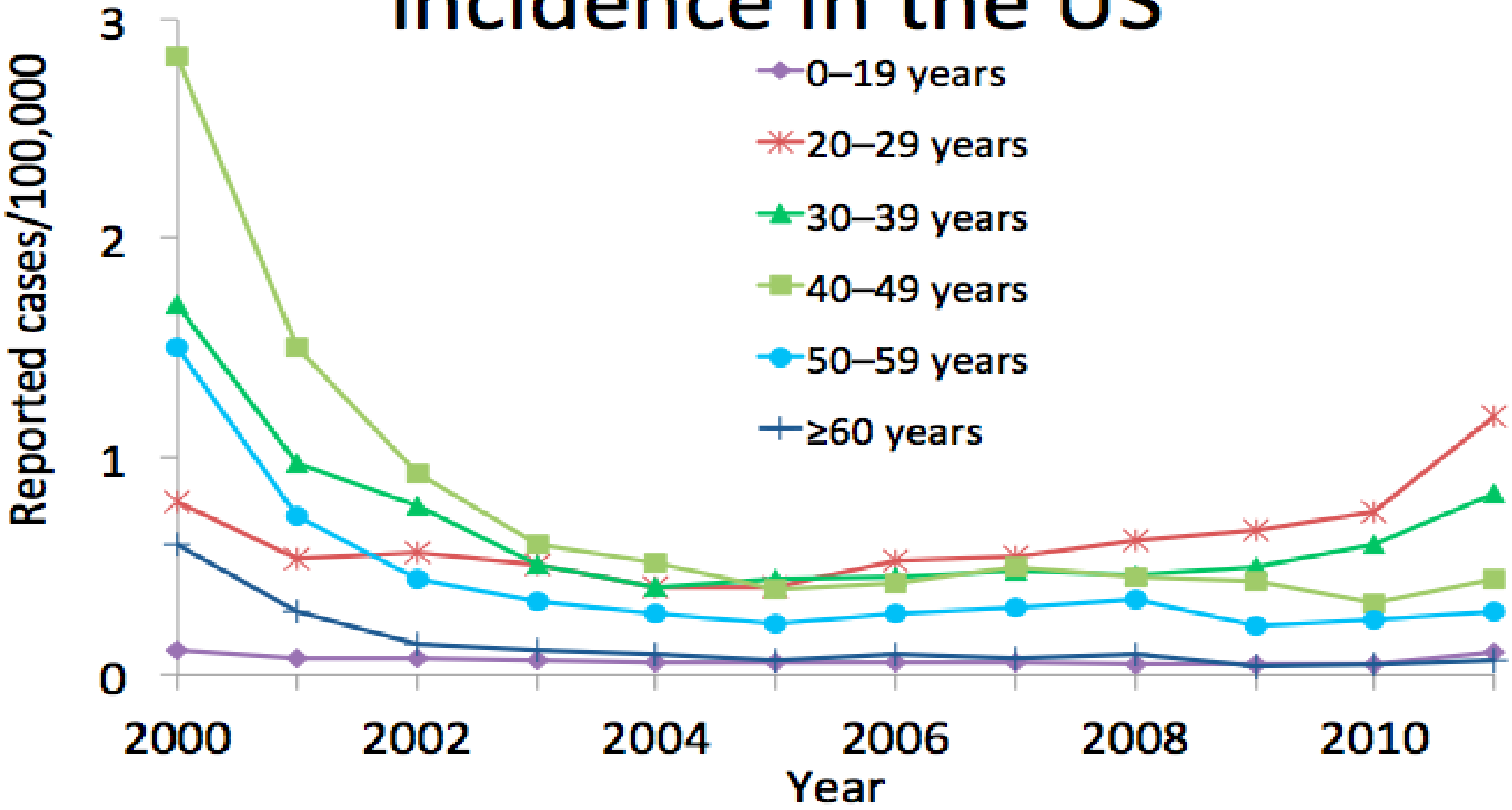
Prevalence In Groups at Risk

Recipients of clotting factors before 1987	75 - 90%
Injection drug users	70 - 85%
Long-term hemodialysis patients	10%
Individuals with ≥ 50 sexual partners	10%
Recipients of blood prior to 1990	5%
Infants born to infected mothers	5%
Long-term sexual partners of HCV positive	1 - 5%
Health workers after random needle sticks	1 - 2%

All baby boomers (1945 to 1964)*

CDC, MMWR 1998;47(No. RR-19):1

Recent Trend in Acute HCV Incidence in the US

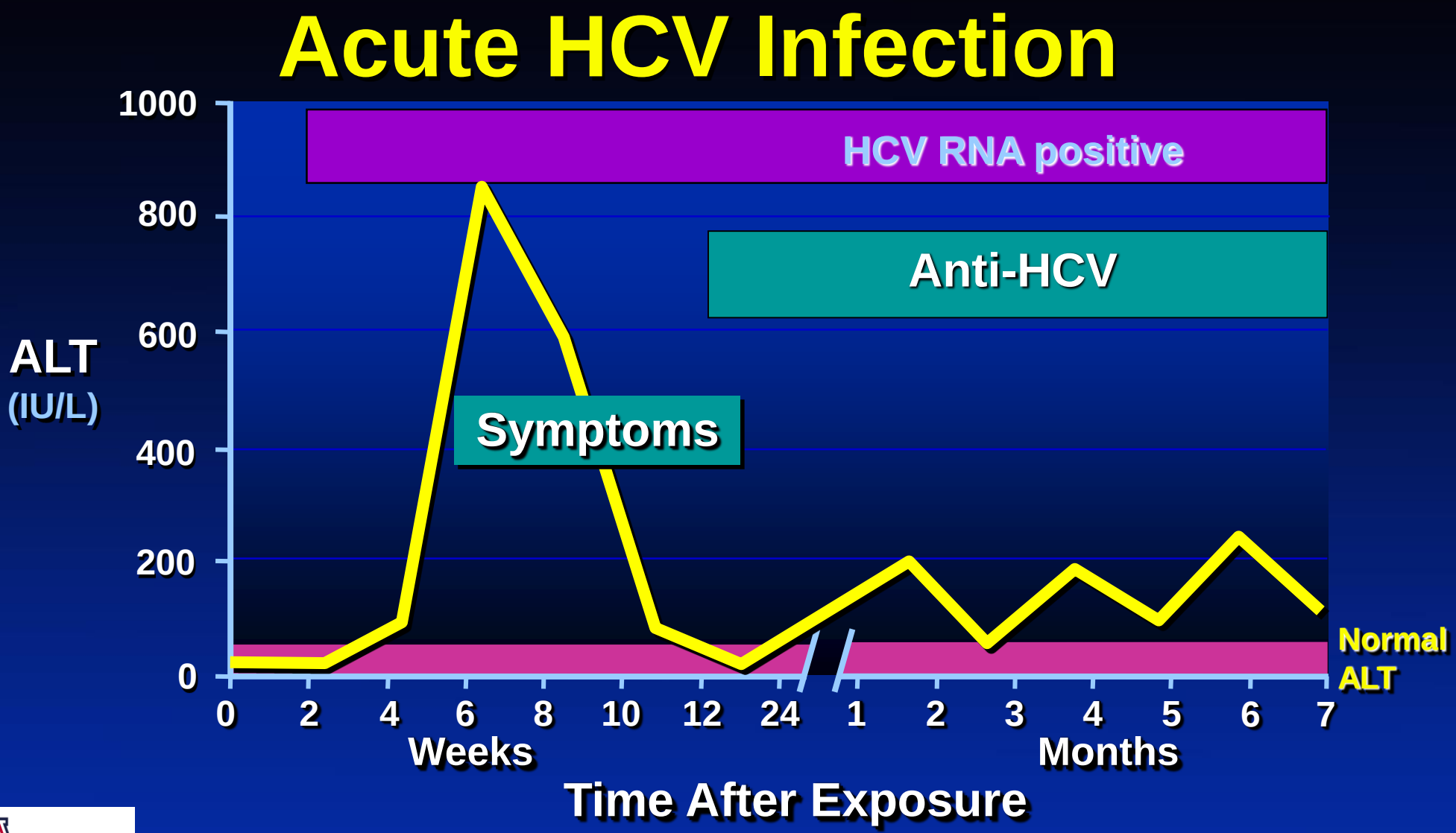


Source: National Notifiable Diseases Surveillance System (NNDSS)

CASE #1:

- A 34 yo female nurse comes to your office 4 weeks after a needle stick accident (the patient had HCV related cirrhosis). She started having fatigue, nausea and occasional vomiting a week ago. She went to an urgent care near her house and had labs: ALT was 750, AST 670, T bili was 2.5 and HCV antibody was negative.
    - What is the most likely cause of her hepatitis?

HCV - Diagnosis



Hoofnagle JH, Hepatology 1997; 26:15S

Banner
University Medicine
Transplant Institute

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, fever.
- Laboratory tests:
  - CMP: increased AST, ALT up to thousands, mild increase in AP 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, join 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.

Case # 2

- A 58 yo Hispanic male came to your office for HCV treatment, he has HCV genotype 1a, never treated, fibro-scan showed fibrosis stage 2/4. His only other medical problem is type II DM on Metformin. He exercises regularly and his BMI is 22. He asks you if the HCV has anything to do with the fact that he developed DM II.

- What do you tell him?

HCV, diabetes and cardiovascular disease

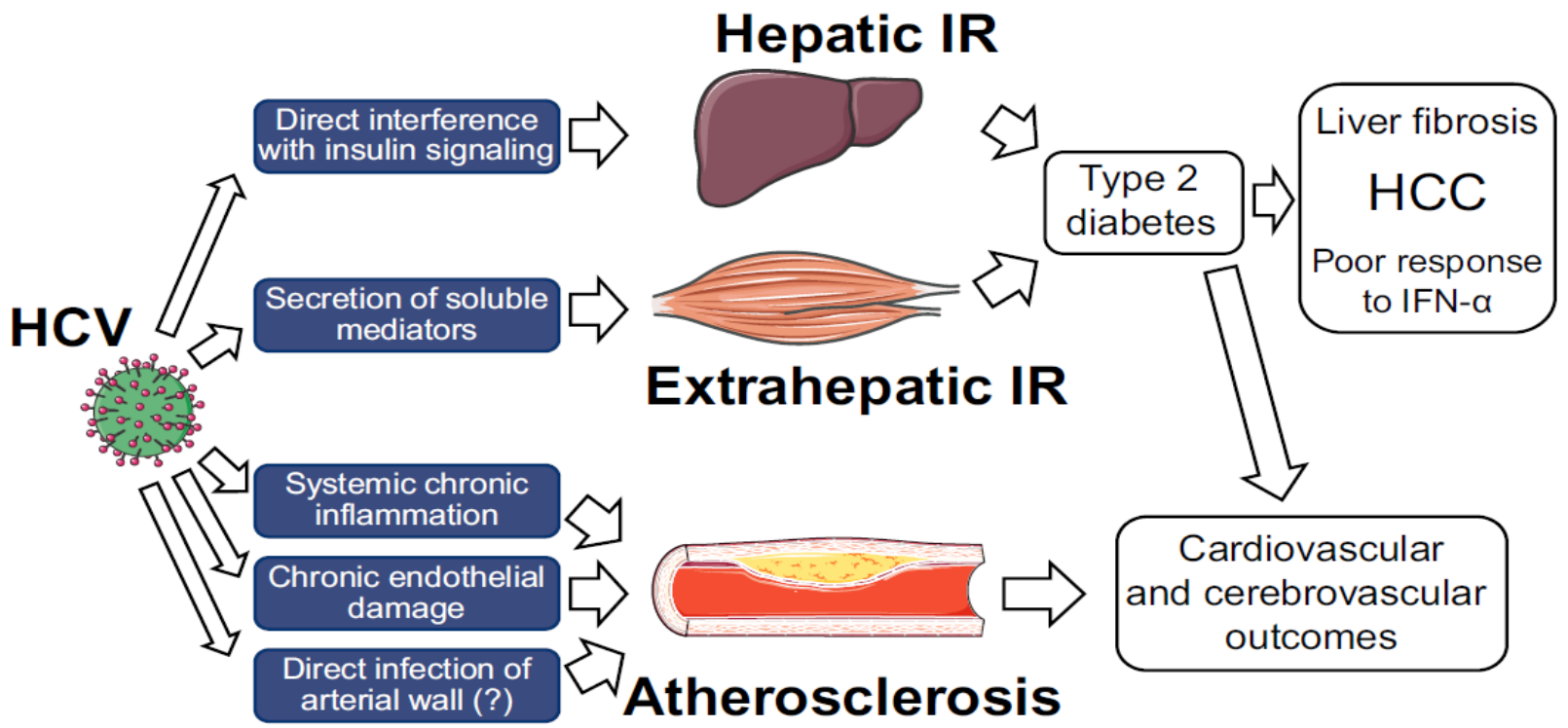
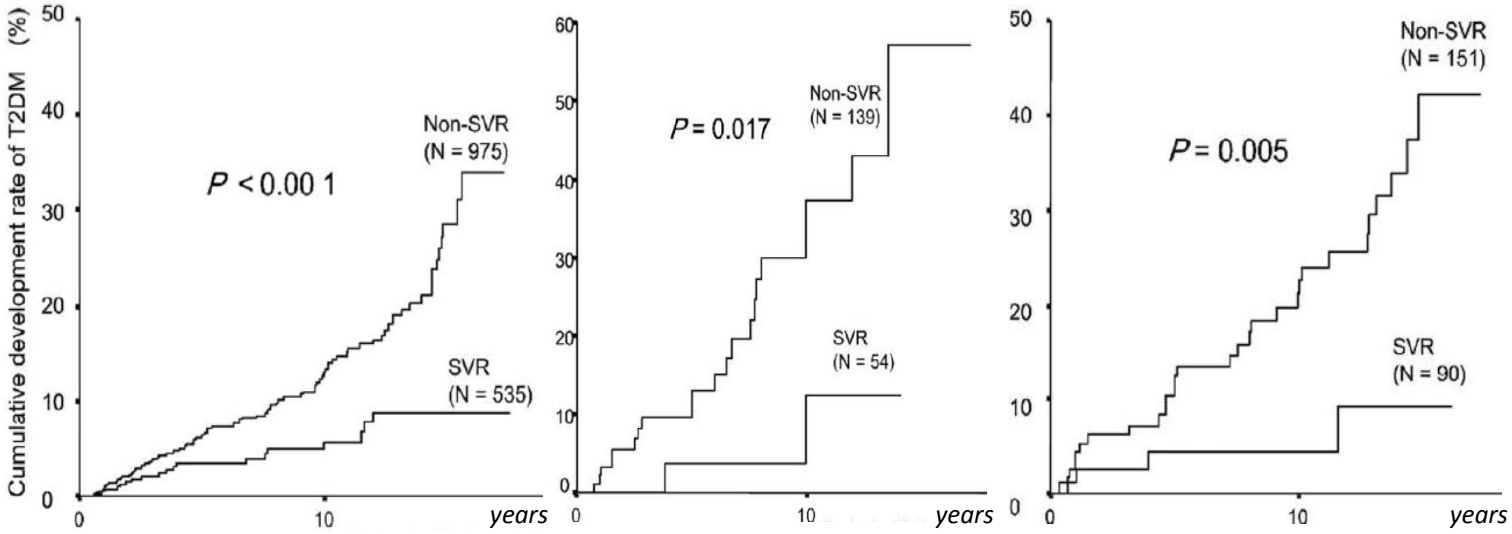


Fig. 2. Tentative mechanisms involved in the pathogenesis of HCV-associated insulin resistance, type 2 diabetes and cardiovascular morbidity.

Negro, J Hepatol 2014; Domont & Cacoub, Liver Int 2016

Cumulative incidence of type 2 diabetes in chronic hepatitis C: SVR vs non-SVR

2842 Japanese non-diabetic pts with chronic hepatitis C (IFN ± RBV): 143 developed DM after 6.4 years: 26/1175 SVR (2.2%) vs 117/1667 non-SVR (7%)



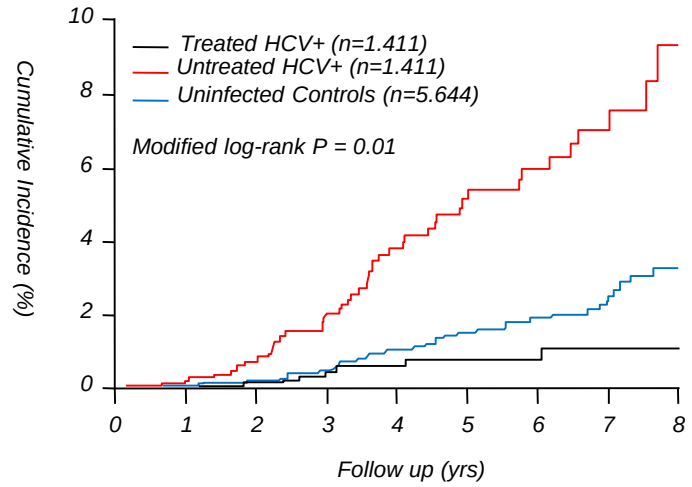
Age >50 years **Cirrhosis** **Pre-diabetes**

SVR is associated with a two-thirds reduction in the risk of developing diabetes

ARASE et al, Hepatology 2009;49:739-744

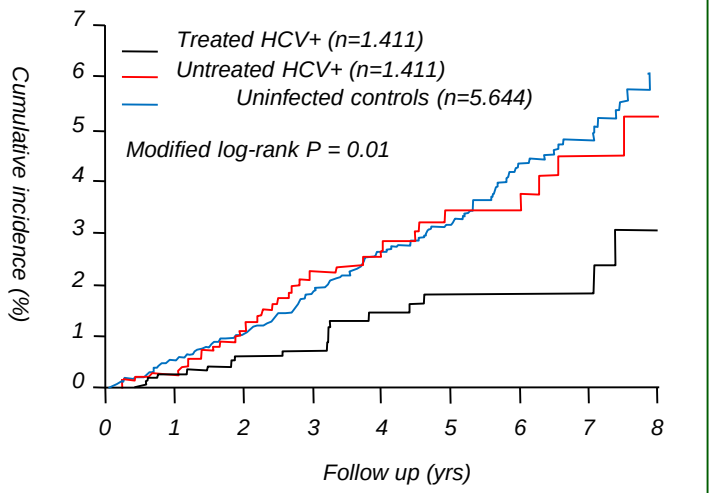
Antiviral therapy for HCV is associated with improved renal and cardiovascular outcomes in diabetic patients

End-stage renal disease (3 cohorts)



N at risk									
Treated	1411	1400	987	755	586	418	303	168	47
Untreated	1411	1388	962	711	530	362	262	152	43
Uninfected	5644	5591	3928	2980	2322	1624	1194	684	201

Ischemic strole (3 cohorts)



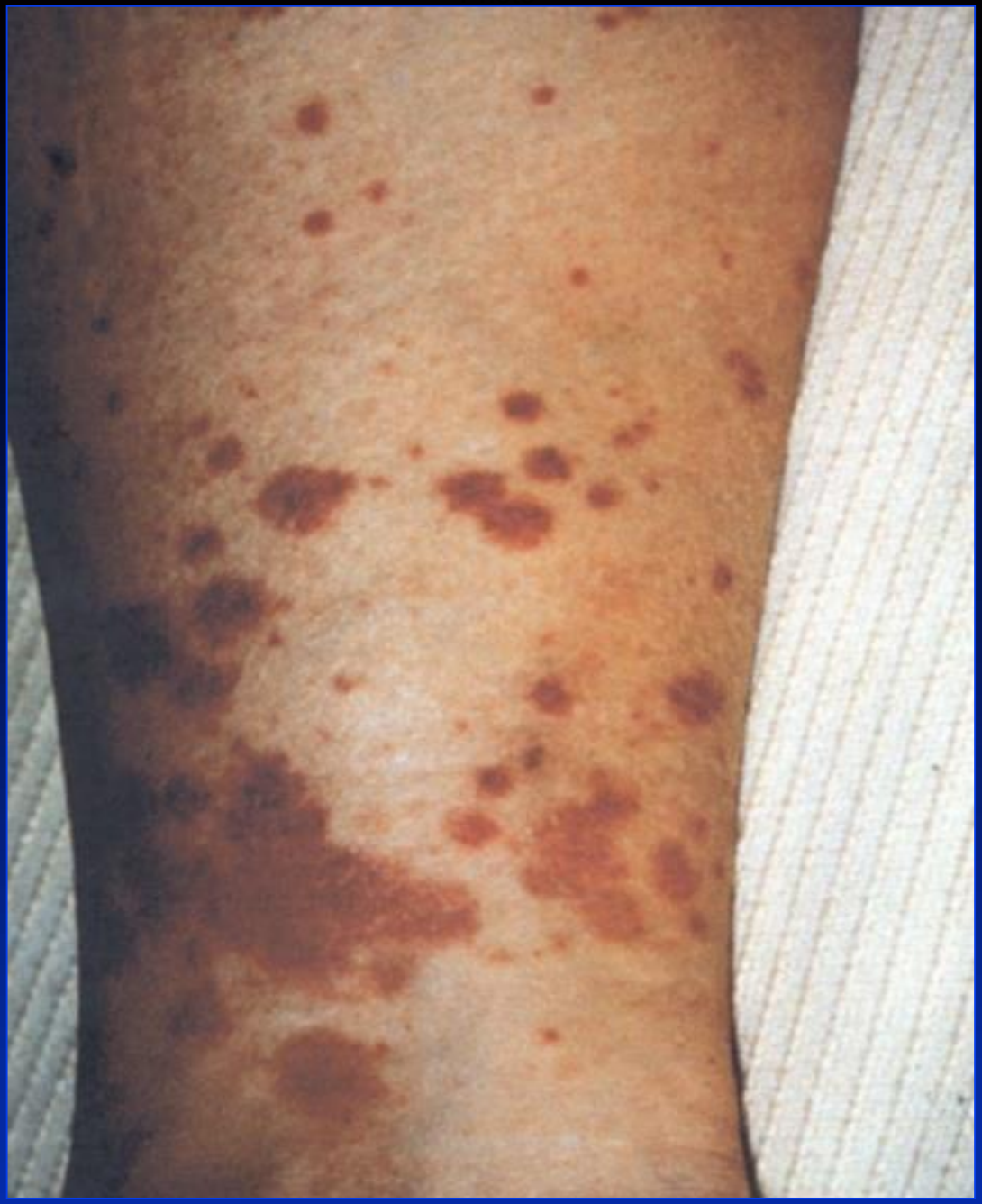
N at risk									
Treated	1411	1397	982	750	579	410	299	164	45
Untreated	1411	1389	961	715	541	367	266	154	47
Uninfected	5644	5566	3899	2944	2283	1602	1161	662	195

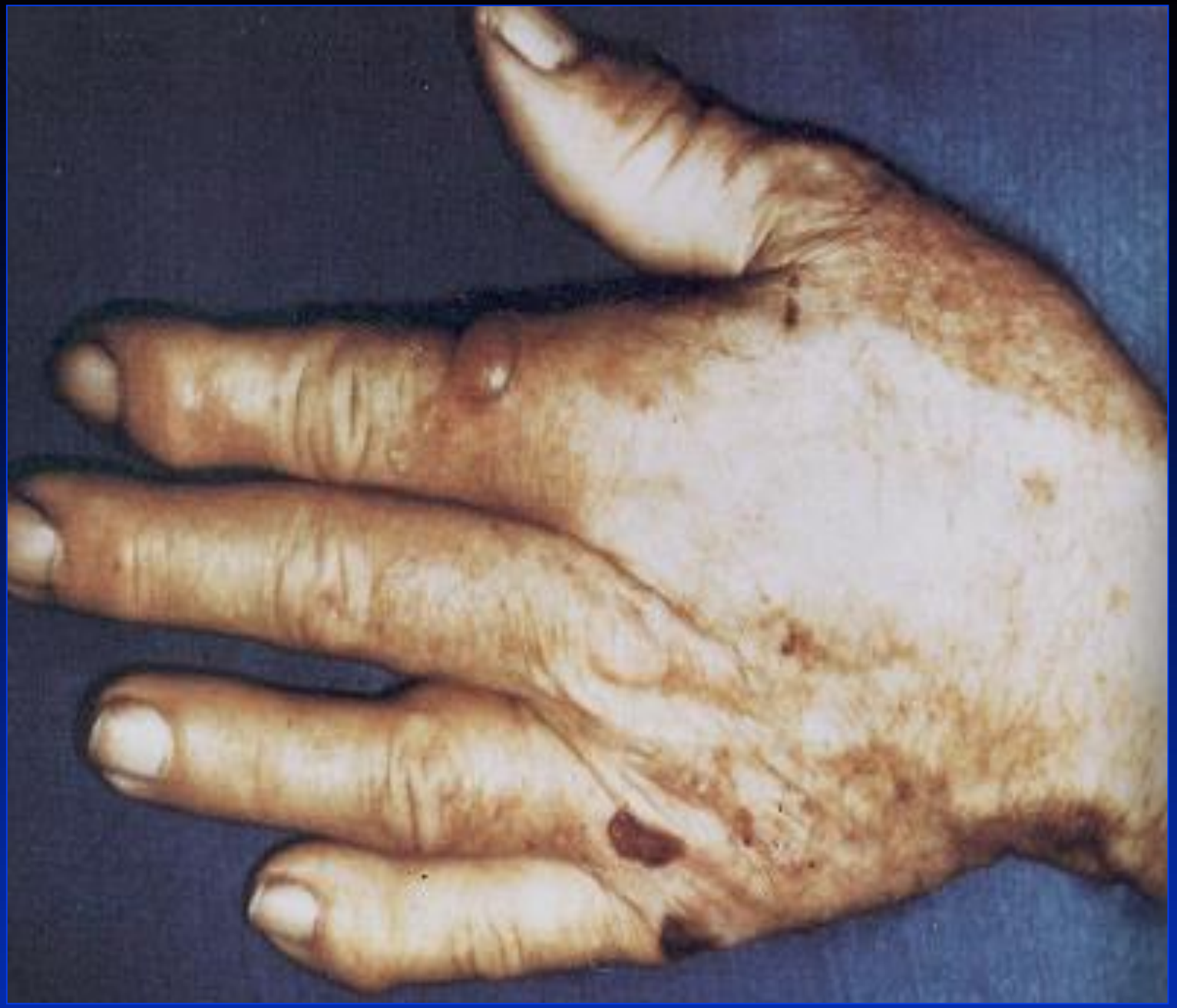
Hsu Y, et al, Hepatology 2014;59:1293–1302

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

Gumber SC and Chopra S., Ann Intern Med 1995;126
Cacoub P, et al., Medicine 2000; 79:47





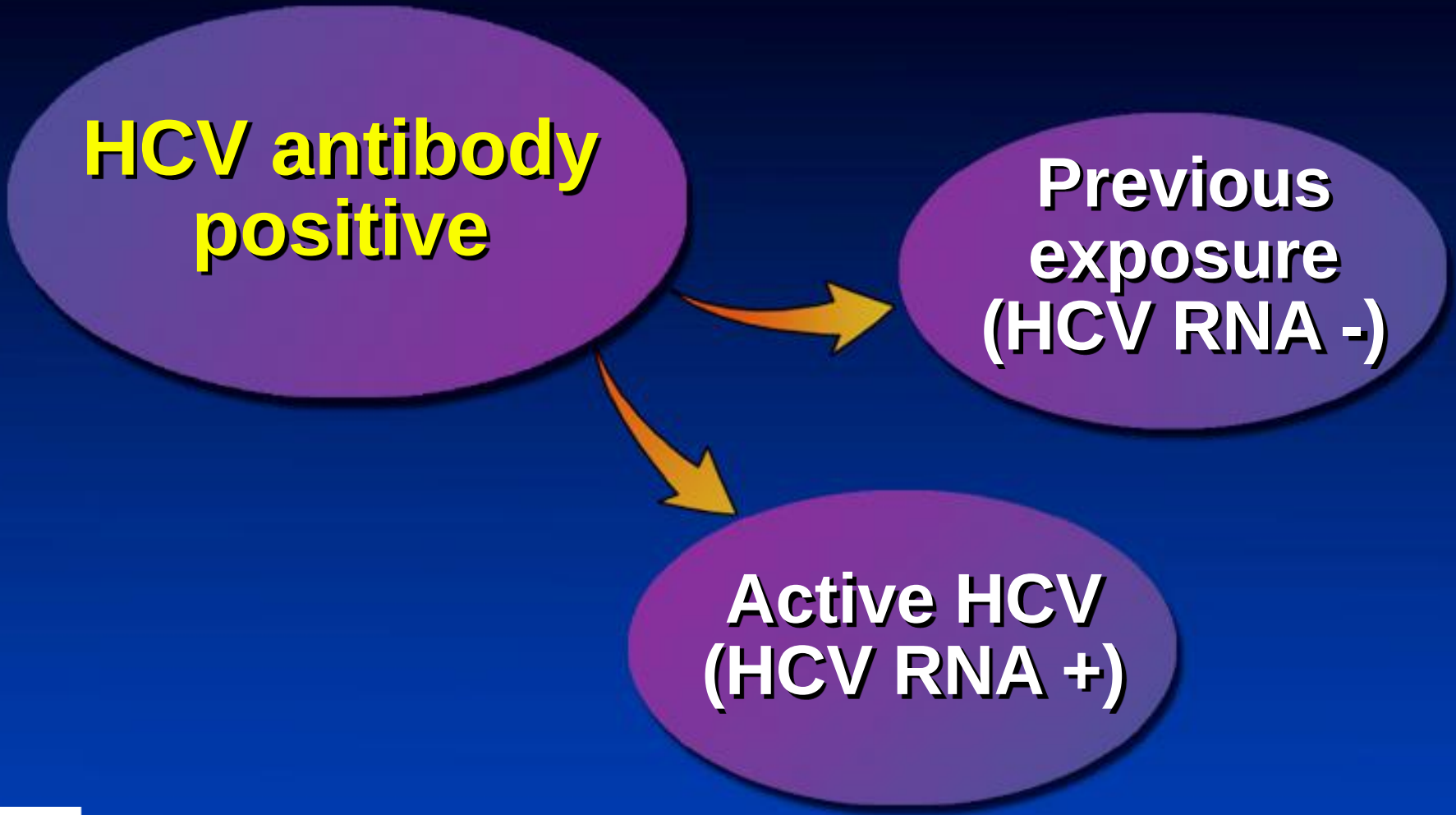
Diagnostic Tests

- Hepatitis C antibody test: screening
- Qualitative HCV RNA test: confirmatory*
- Quantitative HCV RNA test: monitor treatment
- Genotyping: how to treat **

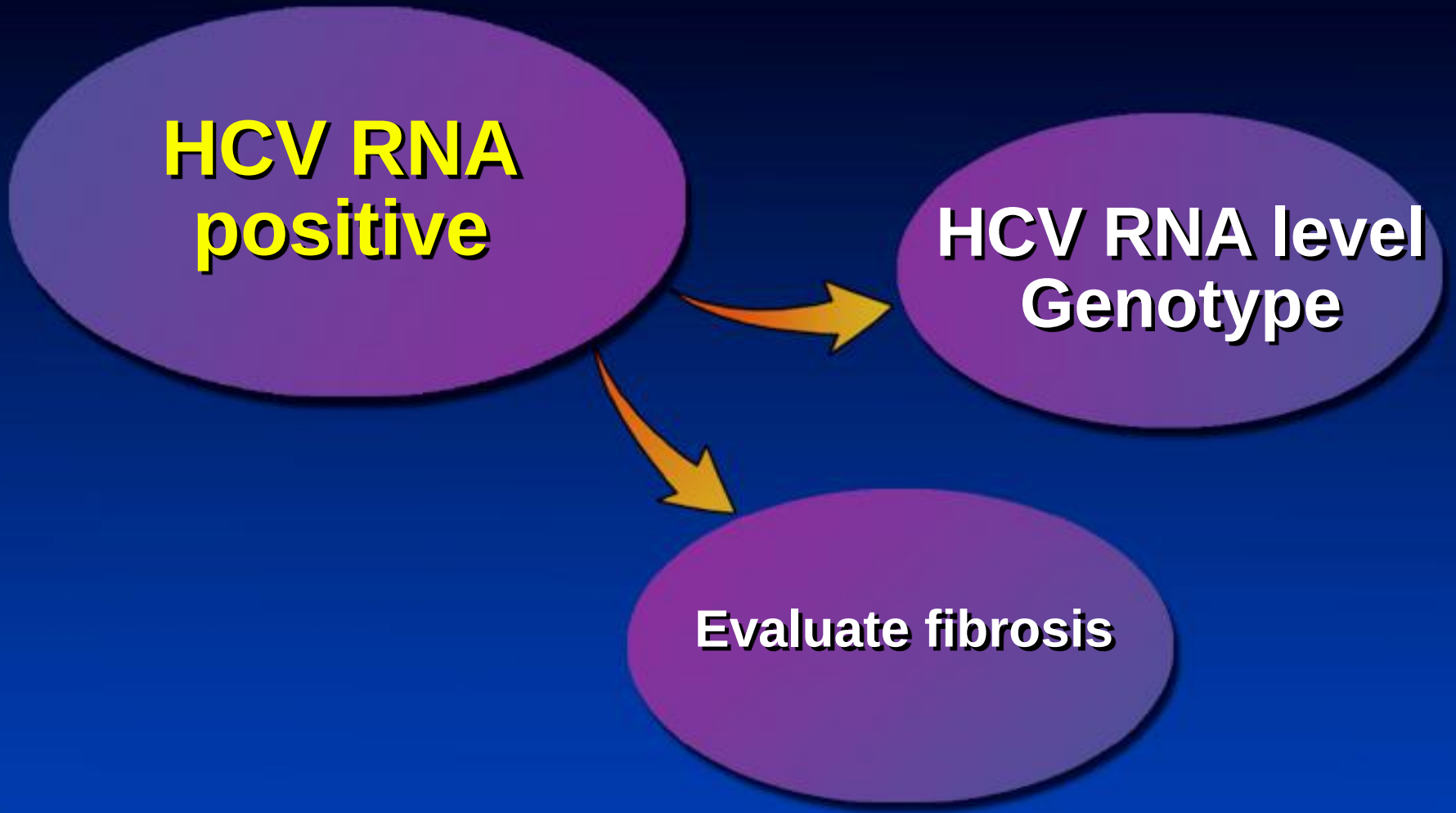
HCV Genotypes

- Six major genotypes found throughout the world (1 to 6)
- In Europe and US 60-70% of patients have genotype 1 infection, followed by genotypes 2 and 3

HCV diagnosis



Pretreatment Evaluation



Evaluation of fibrosis

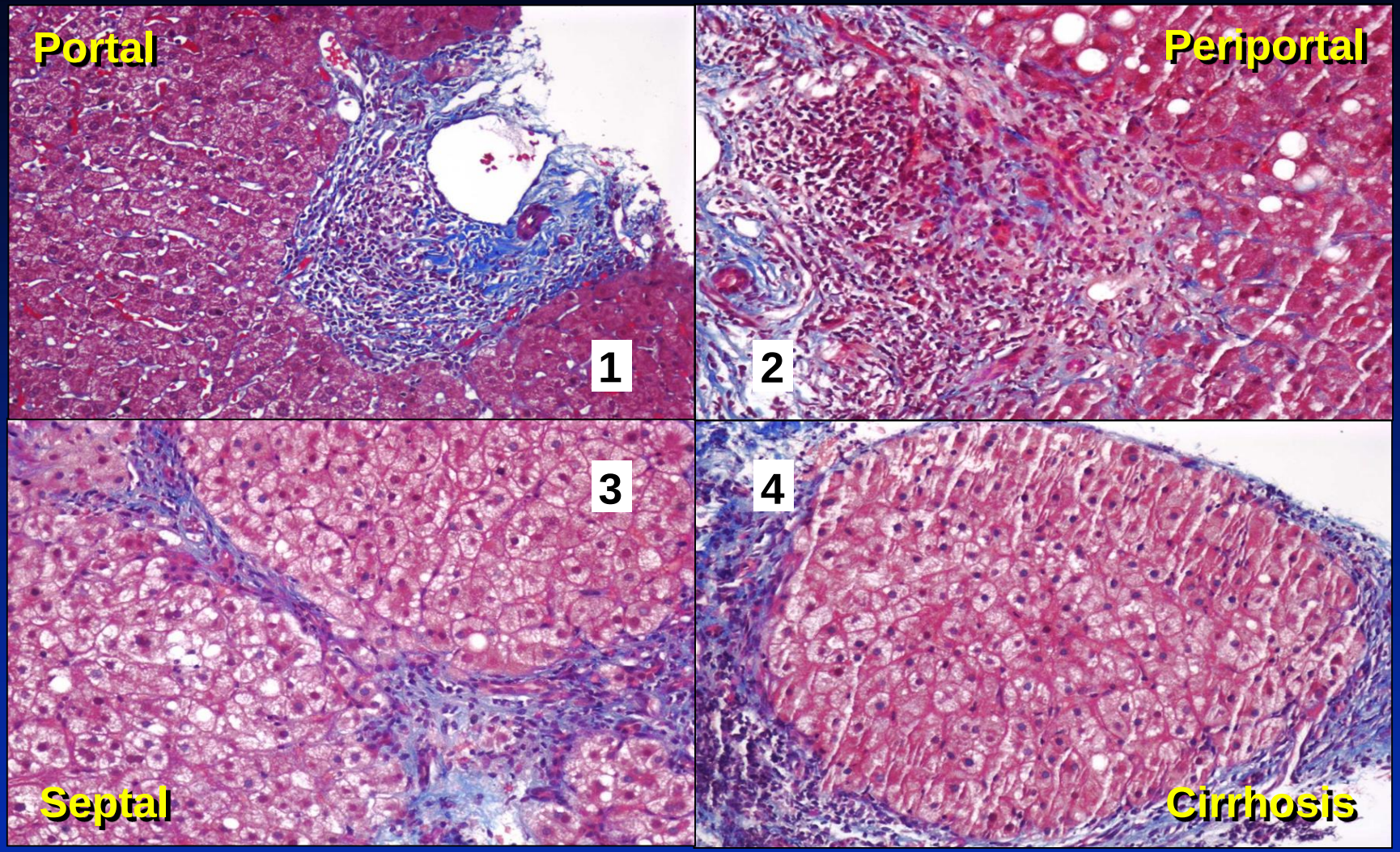
- Serologic tests
- Radiologic tests
  - Transient elastography (Fibro scan)
  - Ultrasound elastography
  - Magnetic Resonance Elastography

Liver Biopsy

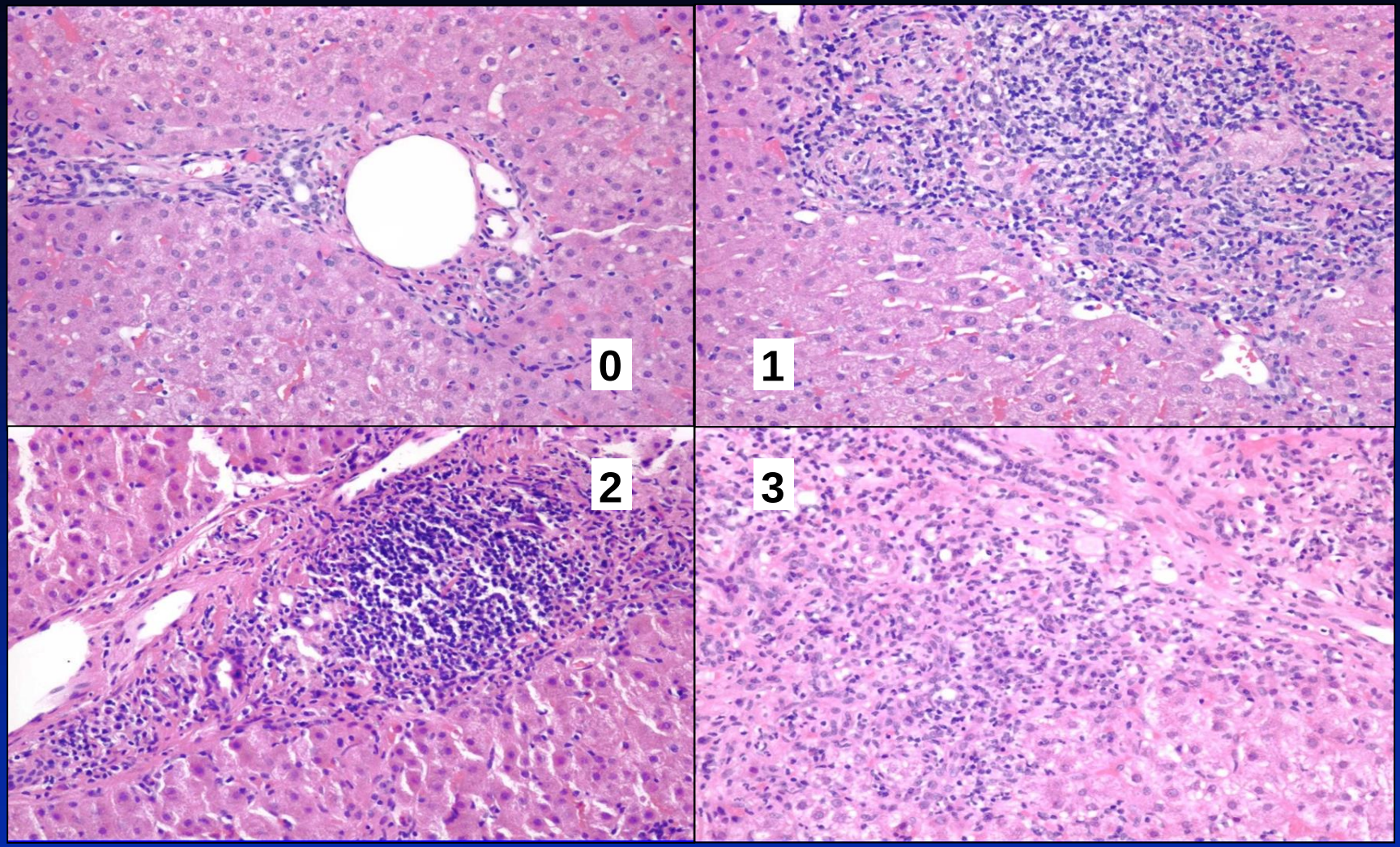
- Degree of fibrosis (stage 1 to 4 or 1 to 6) is the most important predictor of prognosis of HCV
- Advanced cirrhosis is associated with reduced response to treatment

HCV - Natural History

Stages of Fibrosis In Chronic Hepatitis



Grades of Inflammatory Activity in Chronic Hepatitis



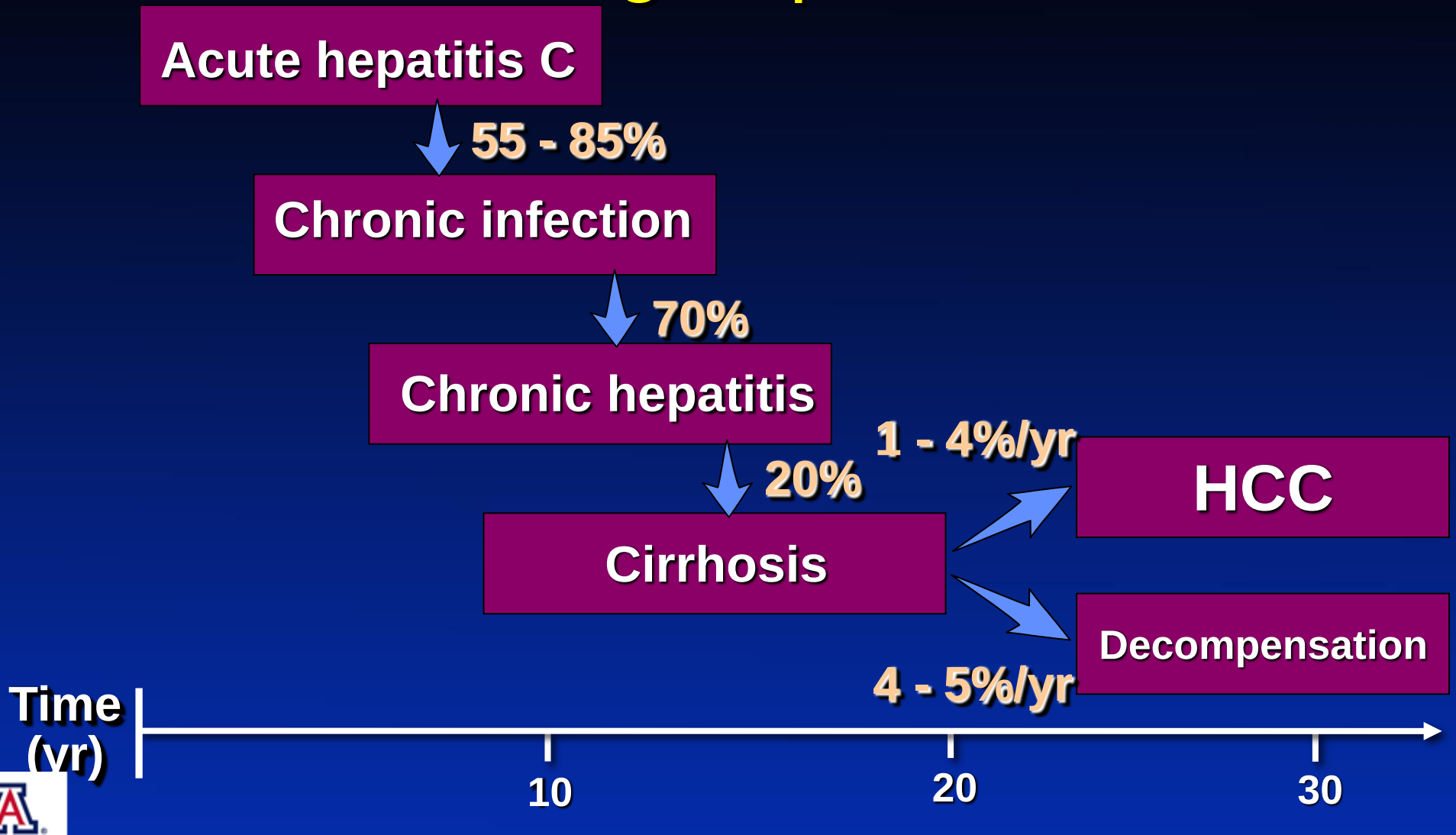
Factors associated with fibrosis progression:

- Duration of infection
- Alcohol > 50 gm per day
- HBV or HIV co-infection
- Age > 40 years at infection
- Male gender

Virological Tests Do Not Predict Natural History of Disease

- No correlation between genotype and progression of disease
- No correlation between HCV RNA level and progression of disease
- No correlation between ALT/AST and the severity of the disease.

Outcome Following Hepatitis C Infection



Goals of Hepatitis C Treatment

Primary

- Eradicate the virus

Secondary

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

1991 FDA approved 1st alpha Interferon

1998 FDA approved interferon alpha plus ribavirin

2001 FDA approved pegylated interferon

2011 FDA approved first direct antivirals agents (DAA) Telaprevir and Boceprevir

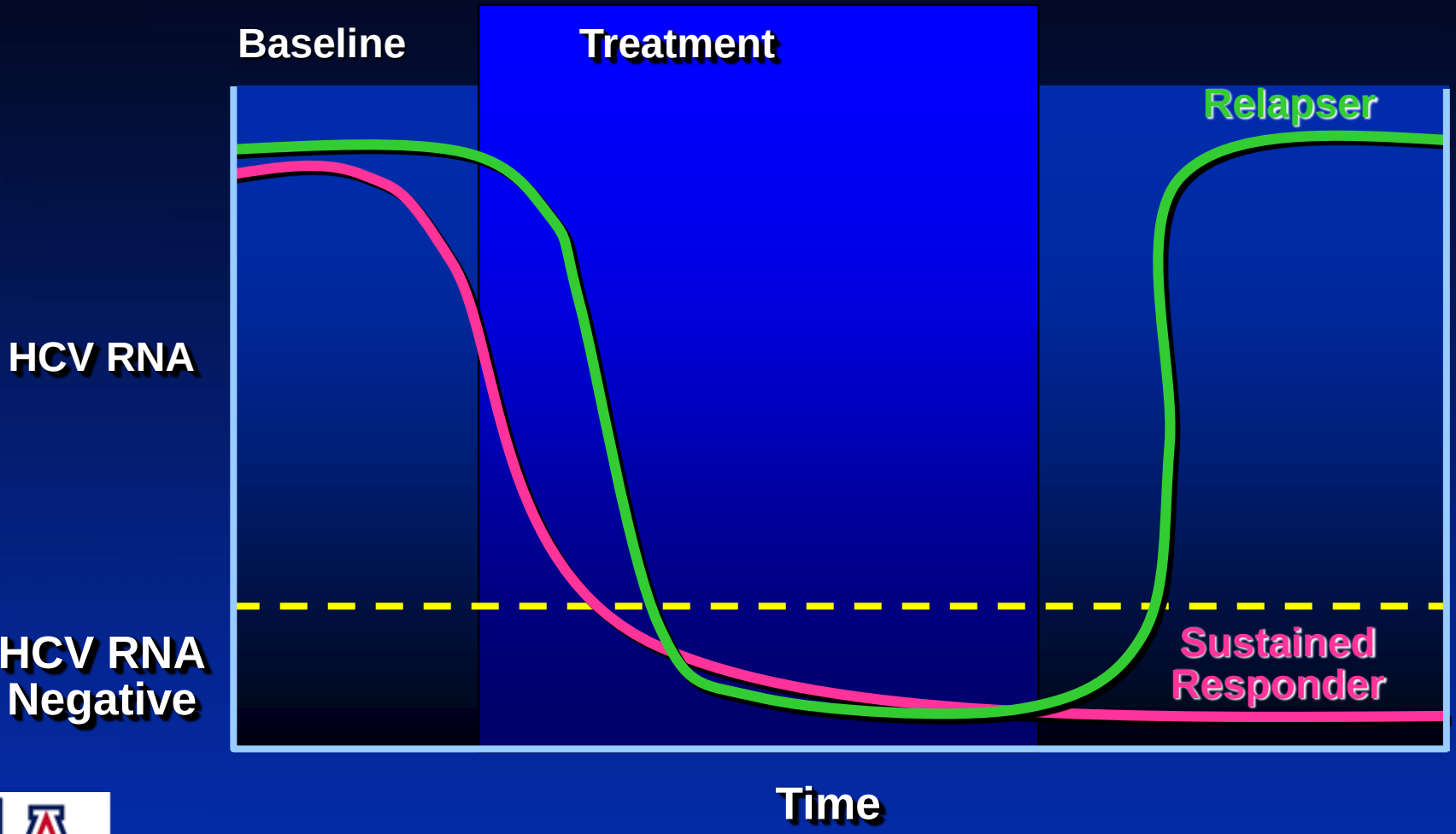
2013 FDA approved second wave of DAA: Simeprevir and Sofosbuvir – a game change in HCV treatment.

2015 FDA approved the first DAA safe for those with renal insufficiency

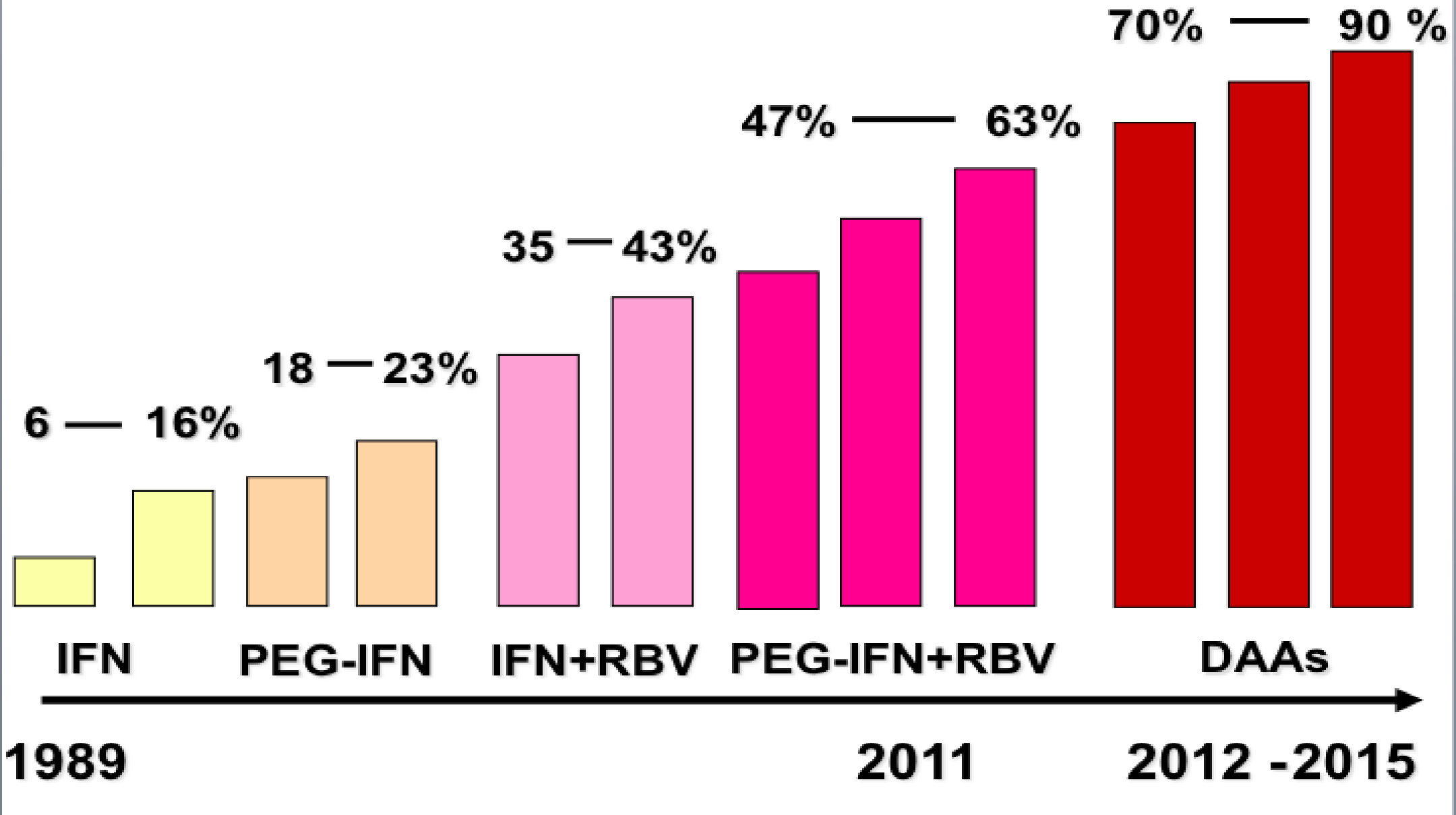
2017 FDA approved DAAs that are pan-genotypic and DAAs for patient who failed earlier DAAs

HCV - Treatment

Historic Patterns of Response to Hepatitis C Treatment

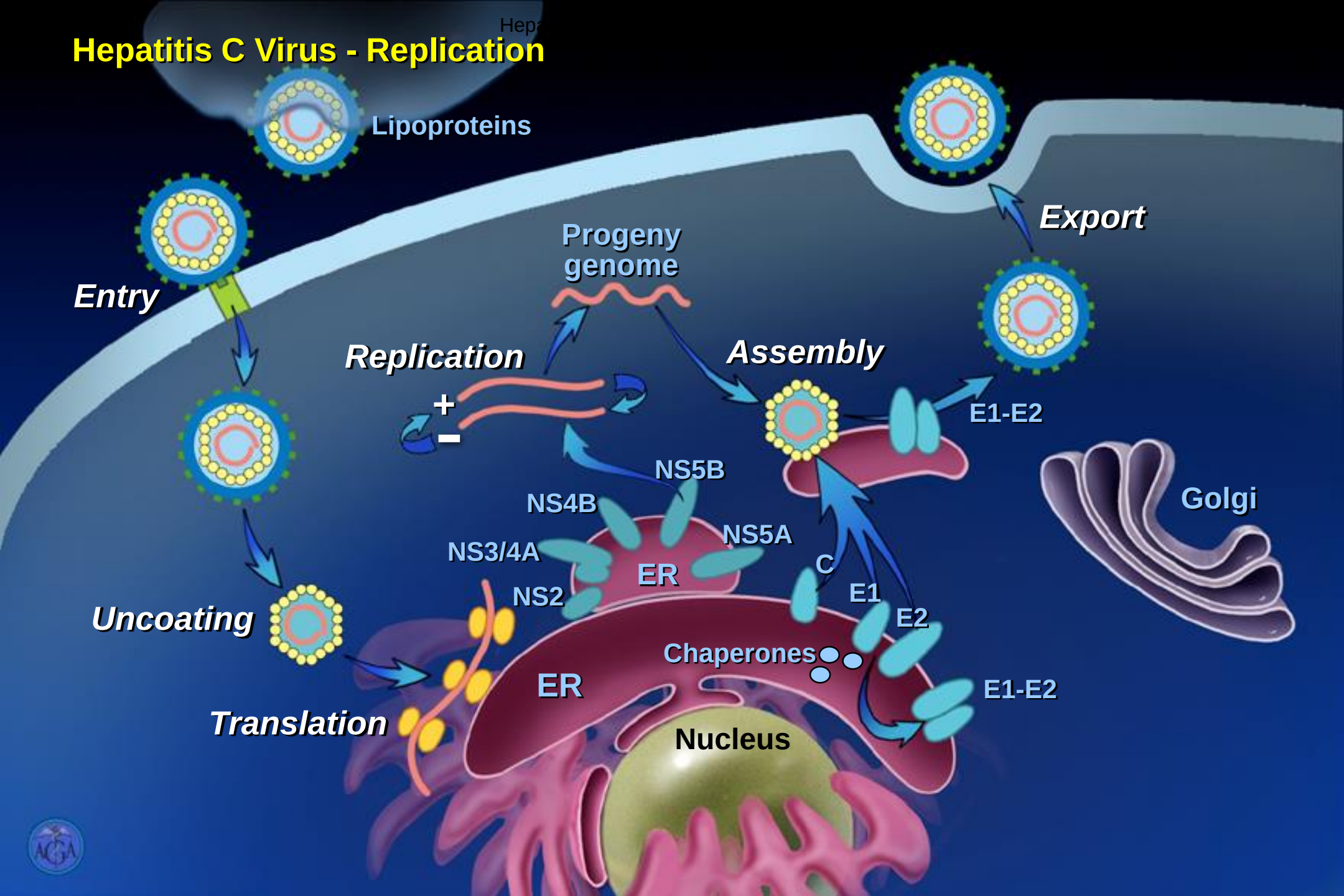


Progress in the Treatment of Hepatitis C



Case # 3:

- Patient with chronic HCV and no cirrhosis comes for an appointment 24 weeks after his last HCV pill. Laboratory tests are normal and HCV RNA remains undetectable.
- What do you tell him about:
  - Relapse risk?
  - Re-infection risk?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E2
NS2
Golgi
Uncoating
Chaperones
ER
E1-E2
Translation
Nucleus

Direct-Acting Antiviral Agents

Ribavirin

Alisporivir

Protease Inhibitors

NS3/NS4A Protease Inhibitors (Post-translation and replication)

Telaprevir
Boceprevir
Simeprevir
Paritaprevir (Ritonavir)**
Grazoprevir***
Voxilaprevir****
Glecaprevir

High potency
Low barrier to resistance

NS5A (Viral replication and assembly)

Ledipasvir*
Ombitasvir**
Daclatasvir
Elbasvir***
Velpatasvir****
Pibrentasvir

High potency
Low to moderate barrier to resistance

Polymerase Inhibitors

NS5B NUC Inhibitors (Post-translation)

Sofosbuvir* and ****

Moderate to high potency
High barrier to resistance

NS5B Non-NUC Inhibitors (Post-translation)

Dasabuvir**

Variable potency and barrier to resistance

Adverse effects & duration of HCV therapy:

- **Ribavirin:** teratogenicity, anemia, skin rash.
- **DAAs:** headache, nausea, diarrhea, abdominal pain, insomnia, elevation of bilirubin.
- **All oral regimens are available for all genotypes**
  - **Highly effective across all genotypes**
  - **Highly effective in non-cirrhotics and cirrhotics**
  - **Duration of treatment is either 8 or 12 weeks**
  - **Combination therapy is the norm**
  - **Cost significantly lower than first regimen approved**

Case # 4

- Patient with HCV Genotype 1a and HCV RNA of 987.000 IU/ml, treatment naïve, comes to see you for HCV. No history of alcohol or drugs. Physical exam is normal. Labs show: normal CBC and CMP except for ALT 90 and AST 67. HAV IgG Ab is positive, HBsAg is positive, HBV DNA is undetectable. You start treatment and his viral load becomes undetectable at week 4.
- At 12 weeks after completion of treatment his HCV RNA remains undetectable but ALT and AST are not at 140 and 135.

  - What is the most likely cause of the AST/ALT elevation?

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Section Contents

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- Genotype 1
- GT1a: No Cirrhosis
- GT1a: Compensated Cirrhosis
- GT1b: No Cirrhosis
- GT1b: Compensated Cirrhosis
- Genotype 2
- No Cirrhosis
- Compensated Cirrhosis
- Genotype 3
- No Cirrhosis
- Compensated Cirrhosis

Home › Treatment-Naive › GT1a ›

Treatment-Naive Genotype 1a Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 1a Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[a] for elbasvir	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are non-black, HIV-uninfected, and whose HCV RNA level is <6 million IU/mL	8 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), with weight-based ribavirin	12 weeks	I, A
Daily simeprevir (150 mg) plus sofosbuvir (400 mg)	12 weeks	I, A
Daily daclatasvir (60 mg)[c] plus sofosbuvir (400 mg)	12 weeks	I, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for patients with baseline NS5A RASs[a] for elbasvir	16 weeks	IIa, B

[a] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

What is the story of HCV treatment, DAA and HCC?

- Treatment of HCV decreases the risk of HCC
- Treatment with DAA does not increase and actually decreases the risk of HCC
- Treatment of HCV related cirrhosis decreases but does not eliminate the risk of HCC

Thank you!