Hepatitis C Management and Treatment

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Infectious Diseases and Clinical Microbiology

Discovery of Hepatitis C

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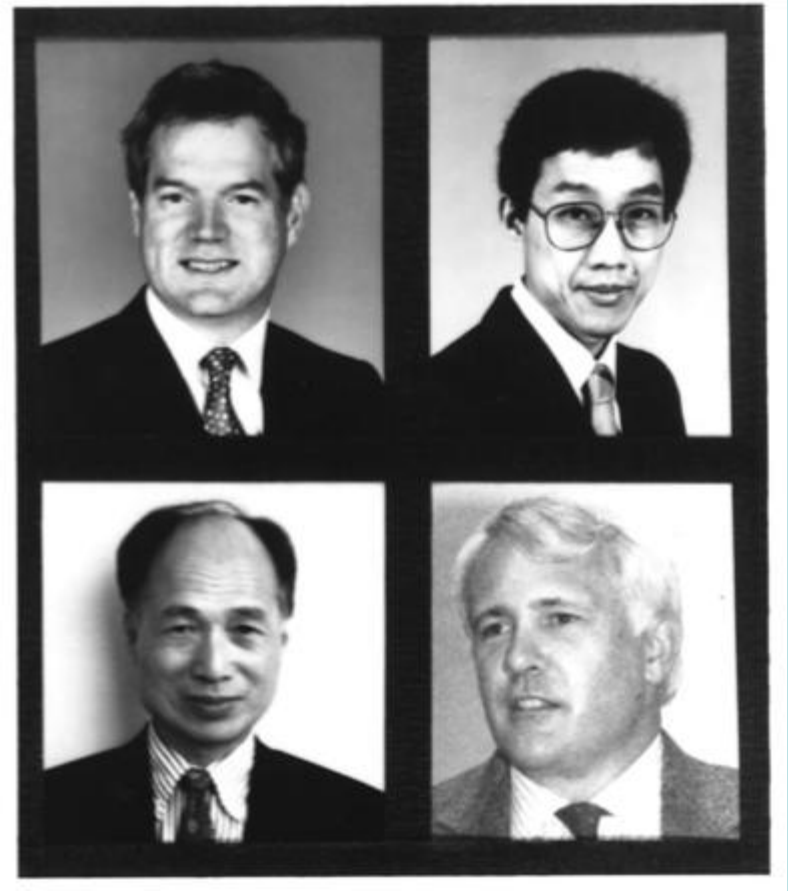

Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989

1. M. Houghton
2. Q-L Choo
3. G. Kuo
4. D. Bradley

Key facts

- Hepatitis C: the virus can cause both acute and chronic hepatitis infection,
- The hepatitis C virus is a bloodborne
- 130–150 million people globally have chronic hepatitis C infection.
- A significant number of those who are chronically infected will develop liver cirrhosis or liver cancer.
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Key facts

- 350 000 to 500 000 people die each year from hepatitis C-related liver diseases.
- Antiviral treatment is successful in 50–90% of persons treated, depending on the treatment used, and has also been shown to reduce the development of liver cancer and cirrhosis.
- There is currently no vaccine for hepatitis C, however research in this area is ongoing.

Chronic HCV Infection Ultimate Therapeutic Goals

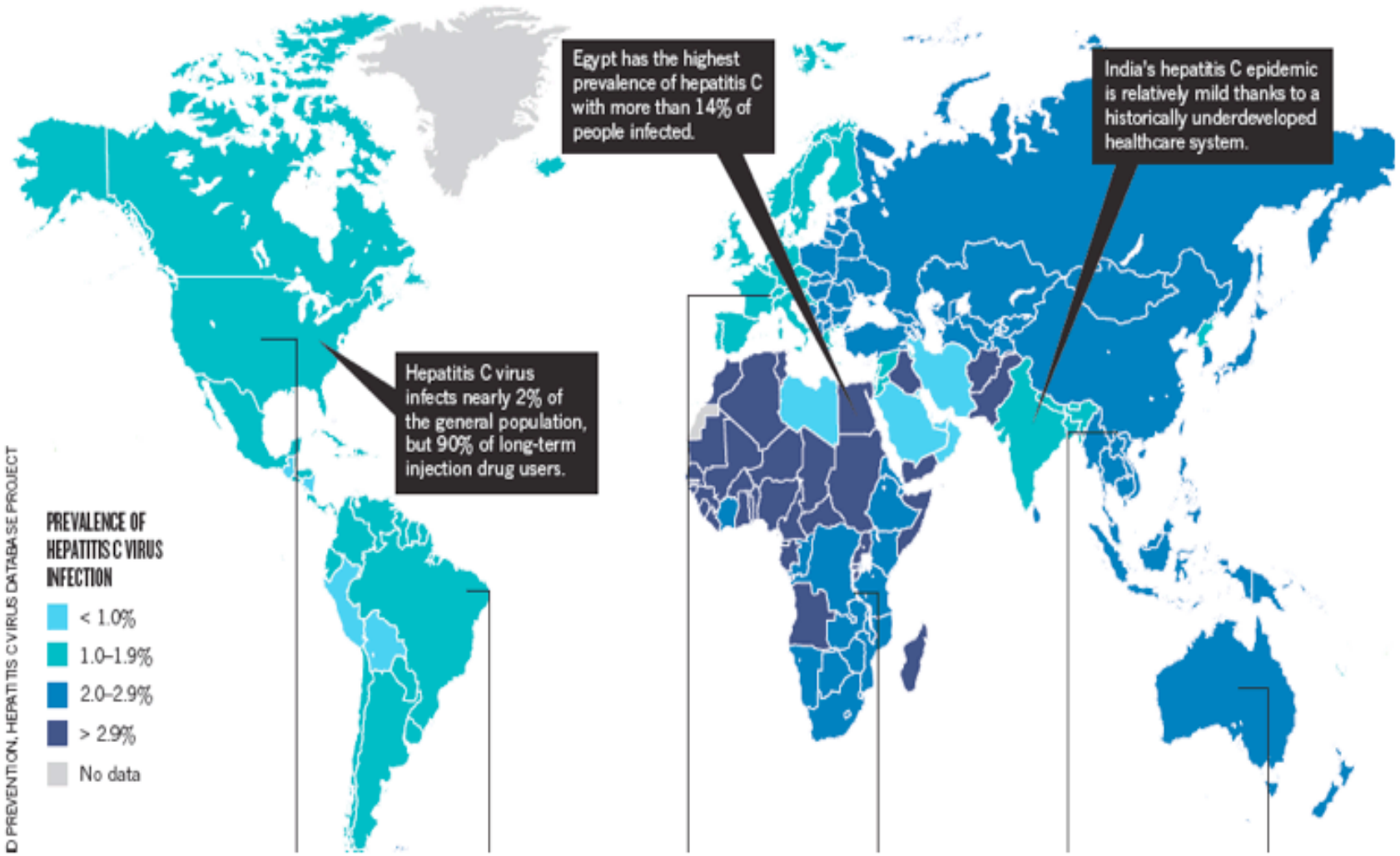
- HCV as not vaccine-preventable disease
- Safe and effective pharmacological cure for acute and chronic HCV infections resulting in:
  - Termination of hepatic and extrahepatic disease(s)
  - Prevent hepatic fibrosis
  - Reduction in incidence of associated diseases:
    - HCC

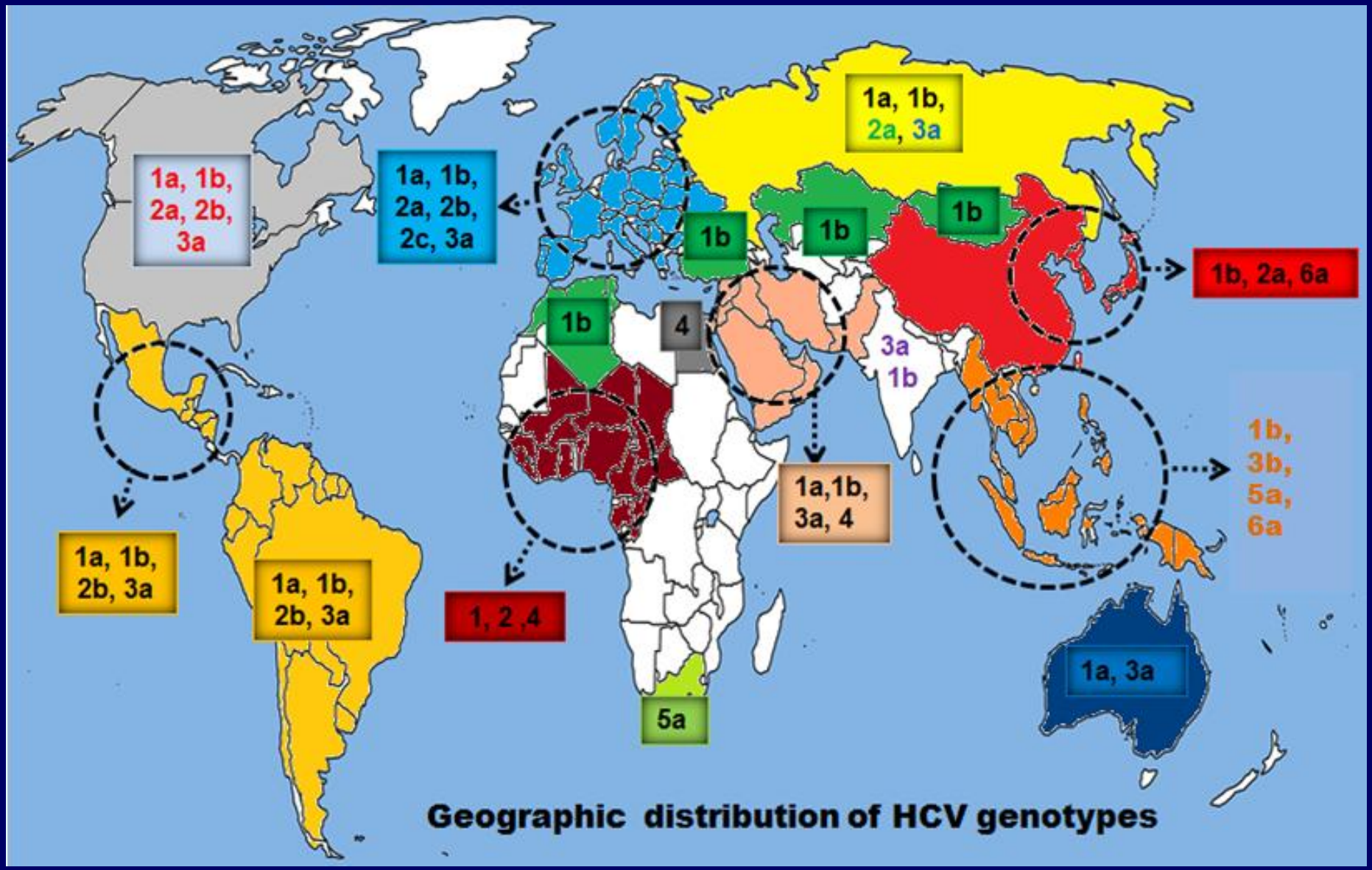
Geographical distribution

- Hepatitis C / worldwide. The most affected regions are Central and East Asia and North Africa.
- The hepatitis C epidemic can be among people who inject drugs
- There are multiple strains (or genotypes) of the HCV virus and their distribution varies by region.

THE SPREAD OF HCV

The hepatitis C virus reaches across the globe with highest prevalence in north Africa and south Asia. A major challenge is tailoring treatments and vaccines to the various viral genotypes which affect treatment response.




1a, 1b,
2a, 3a
1a, 1b,
2a, 2b,
3a
1a, 1b,
2a, 2b,
2c, 3a
1b
1b
1b
1b, 2a, 6a
1b
4
3a
1b
1b,
3b,
5a,
6a
1a,1b,
3a, 4
1a, 1b,
2b, 3a
1a, 1b,
2b, 3a
1, 2 ,4
5a
1a, 3a
Geographic distribution of HCV genotypes

Risk Factors for HCV

- Injection drug use (60%)
- Blood transfusion before 1992/1996 TR/CY
- Multiple sex partners
- Iatrogenic (hemodialysis, re-use of vials, etc)
- Intranasal cocaine
- Piercing, tattooing, scarification
- Unknown (10%)

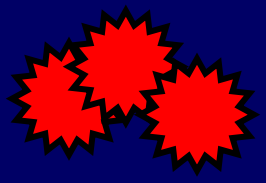
HCV and Health Care Workers

- 600,000-800,000 needlestick injuries occur each year
- Prevalence in Public Safety workers 1.3-3.2%
- Prevalence in Scottish HCW 0.28%

- Risk of HCV from a needlestick estimated to be 2.7-6%

- Multiple reported cases of transmission from HCW to patients
- Risk of HCV+ surgeon transmitting it a patient estimated at 1 in 1,750-16,000 procedures

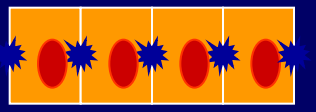
HCV Pathogenesis
Infection versus Disease



HCV

Infects different cells

Hepatocytes



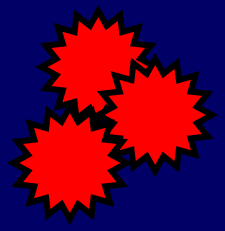
Lymphocytes

B cells

T cells

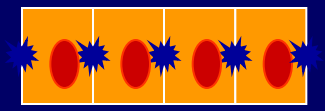
Other Tissues:

Pancreas, Adrenal gland, Bone Marrow



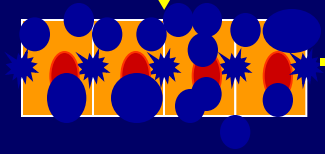
HCV

Not cytopathic for hepatocytes



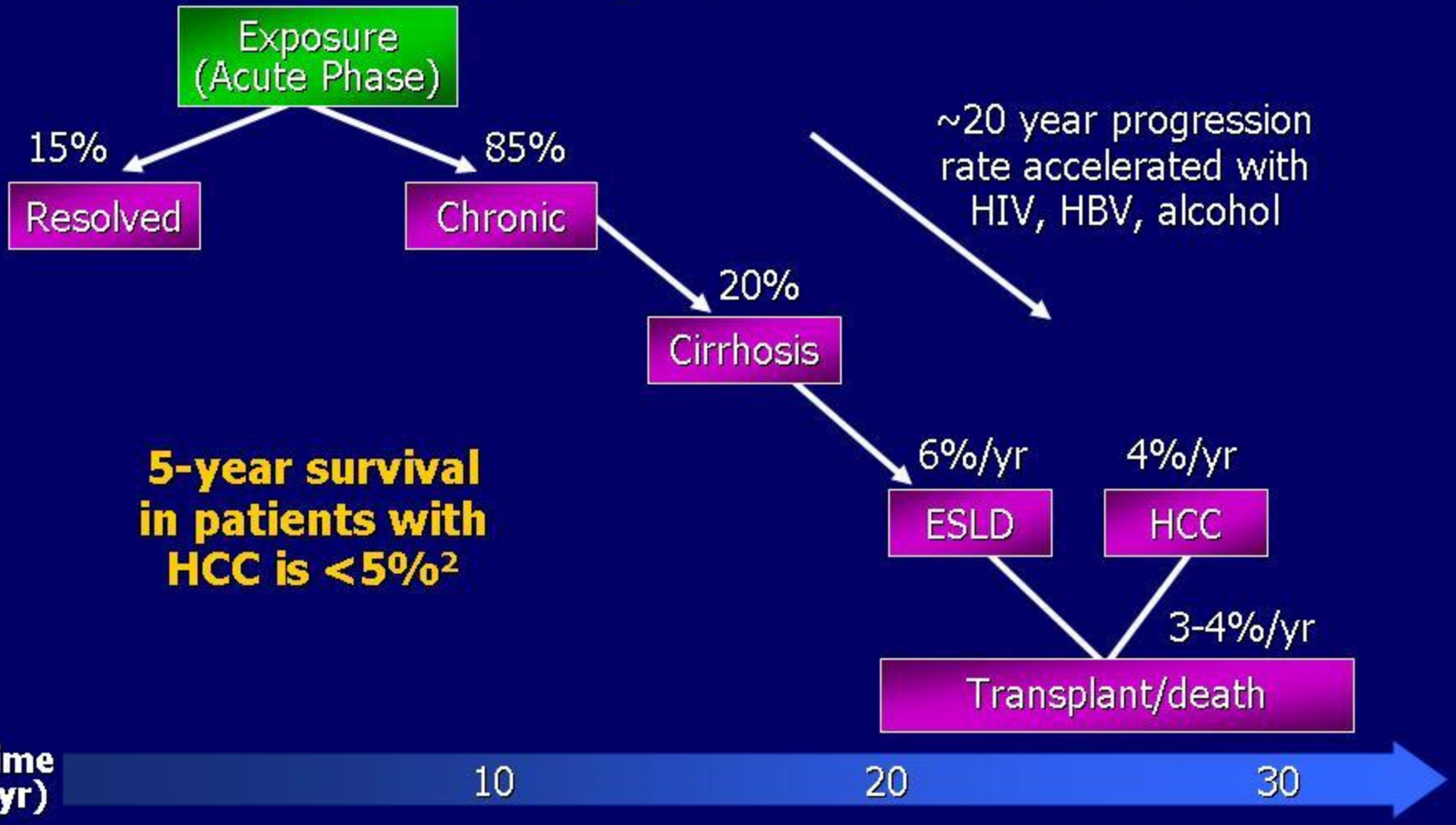
Immune Response

Minimal Fibrosis



Advanced Fibrosis

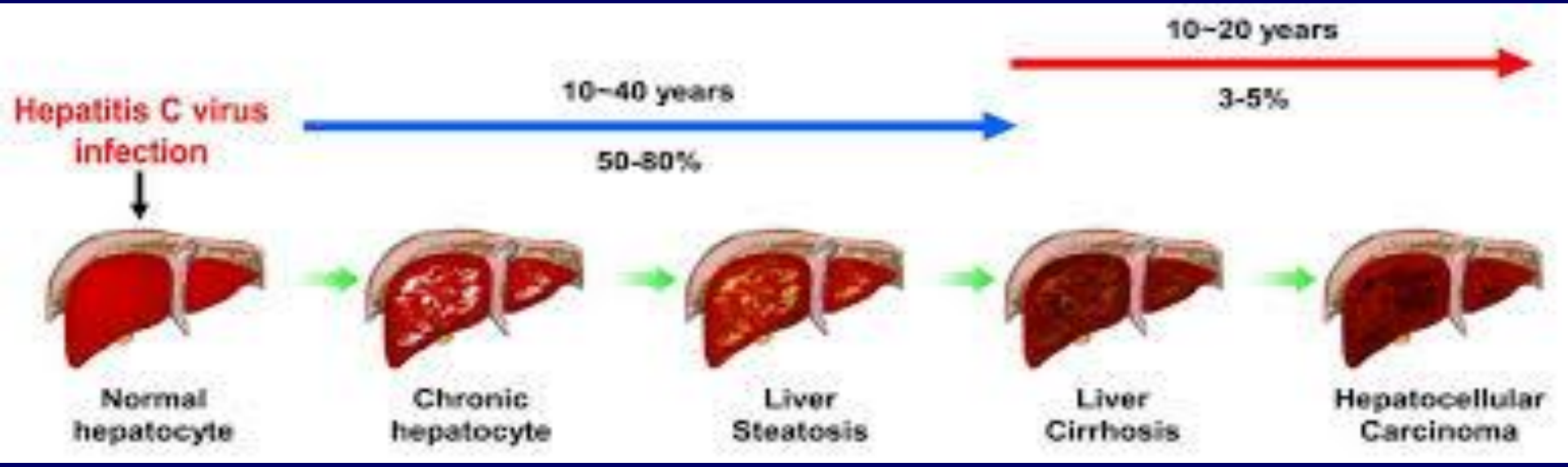
Natural History of HCV Infection

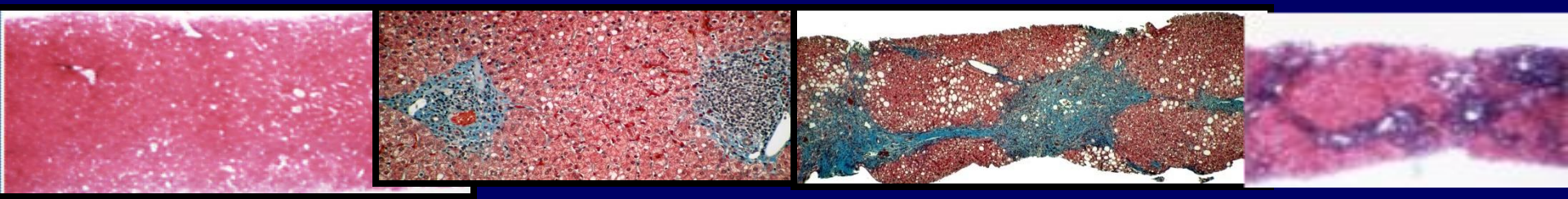


HCC = hepatocellular carcinoma

ESLD = end-stage liver disease

DiBisceglie et al. *Hepatology*. 2000;31(4):1014-1018.


10–20 years
3-5%
10–40 years
50-80%
Hepatitis C virus infection
Normal hepatocyte
Chronic hepatocyte
Liver Steatosis
Liver Cirrhosis
Hepatocellular Carcinoma



Utility of the Liver Biopsy and Noninvasive Tests of Fibrosis

- **There are three primary reasons for performing a liver biopsy:**
  1. it provides helpful information on the current status of the liver injury,
  2. it identifies features useful in the decision to embark on therapy,
  3. and it may reveal advanced fibrosis or cirrhosis that necessitates surveillance for hepatocellular carcinoma (HCC) and/or screening for varices.

Non-invasive tests

- ‘Painless’
- Frequent sampling possible
- Accurate at separating mild fibrosis from cirrhosis
- ?enough degree of separation to show progressive changes

Fibrosis stage assessment is more important than which test or technique you use ……..

Staging of fibrosis in chronic viral hepatitis

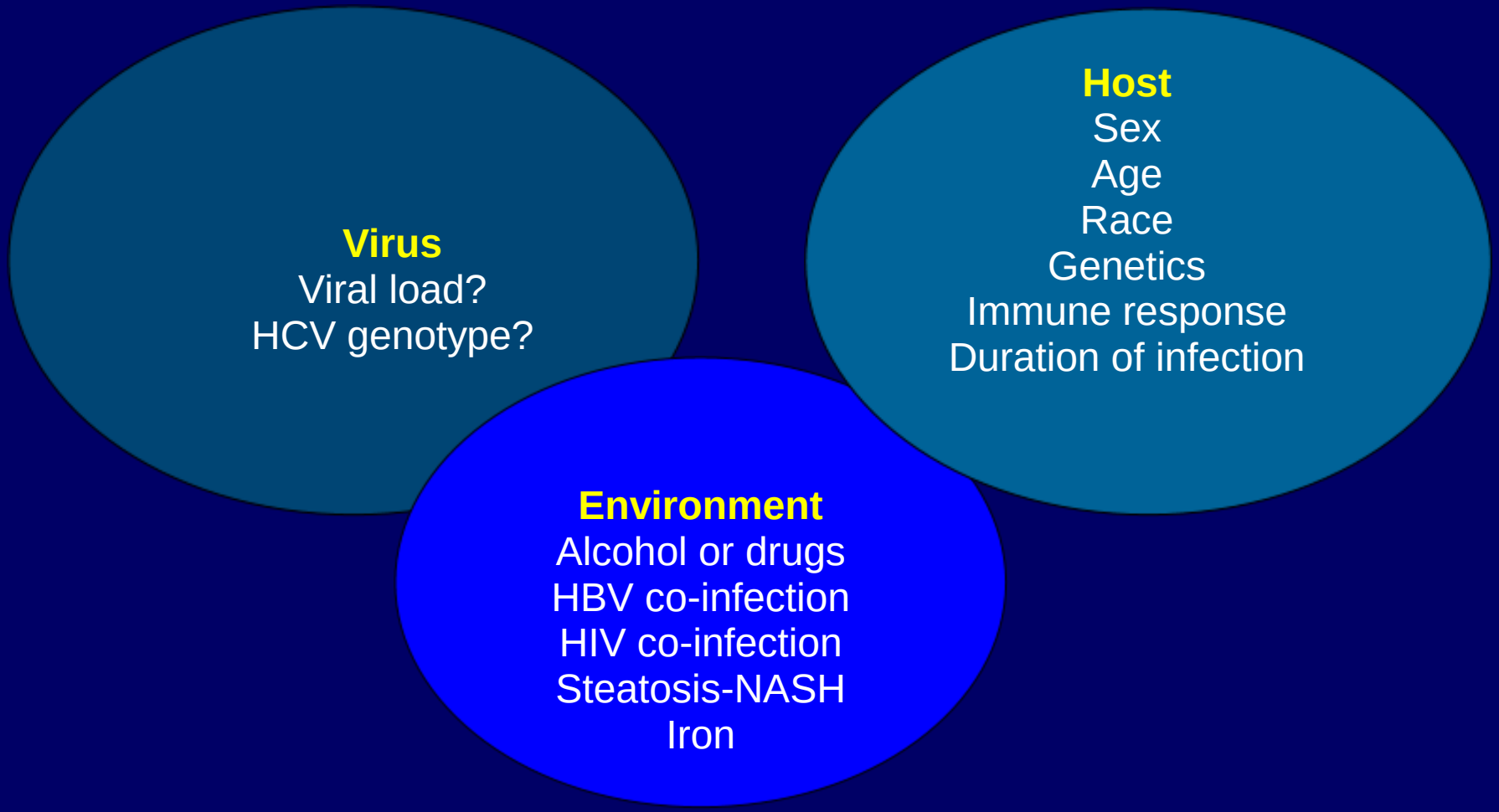
Definition		Fibrous		Numerous Bridges or	
IASL	No Fibrosis	Mild Fibrosis	Moderate Fibrosis	Severe Fibrosis	Cirrhosis
Metavir	F0	F1	F2	F3	F4
					

Goodman Z et al. J Hepatol 2007;47:598-607

Does chronic Hepatitis C affect only the liver?

- A small percentage of persons with chronic HCV infection develop medical conditions due to Hepatitis C that are not limited to the liver. These conditions are thought to be attributable to the body's immune response to HCV infection. Such conditions can include
  - Diabetes mellitus,
  - Glomerulonephritis,
  - Essential mixed cryoglobulinemia
  - Porphyria cutanea tarda,
  - Non-Hodgkins lymphoma,

Factors That May Influence the Progression of HCV Infection



Alberti A, et al. J Hepatol. 1999;31(suppl 1):17-24.

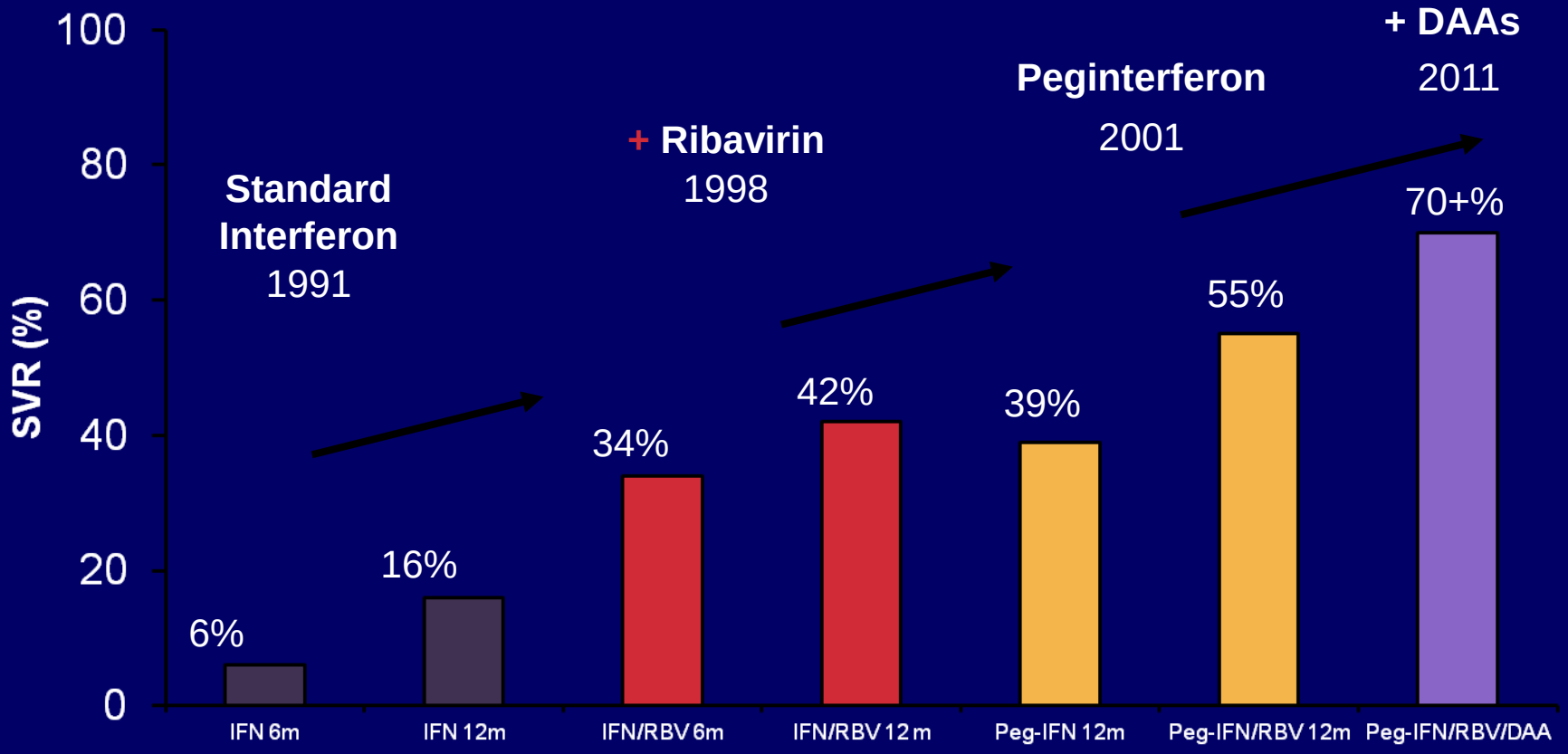
Is it necessary to do viral genotyping when managing a person with chronic Hepatitis C?

- There are at least six known genotypes and more than 50 subtypes of HCV, genotype information is helpful in defining the epidemiology of Hepatitis C and in making recommendations regarding treatment. Knowing the genotype can help predict the likelihood of treatment response and, in many cases, determine the duration of treatment.
- Once the genotype is identified, it need not be tested again; genotypes do not change during the course of infection.

What should be done for a patient with confirmed HCV infection?

- HCV-positive persons should be evaluated for presence of chronic liver disease,
  - including assessment of liver function tests,
  - evaluation for severity of liver disease
  - possible treatment,
  - determination of the need for Hepatitis A and Hepatitis B vaccination.

Milestones in Therapy of CHC: Average SVR Rates from Clinical Trials



Adapted from US Food and Drug Administration,
Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring MD.

HCV - Treatment

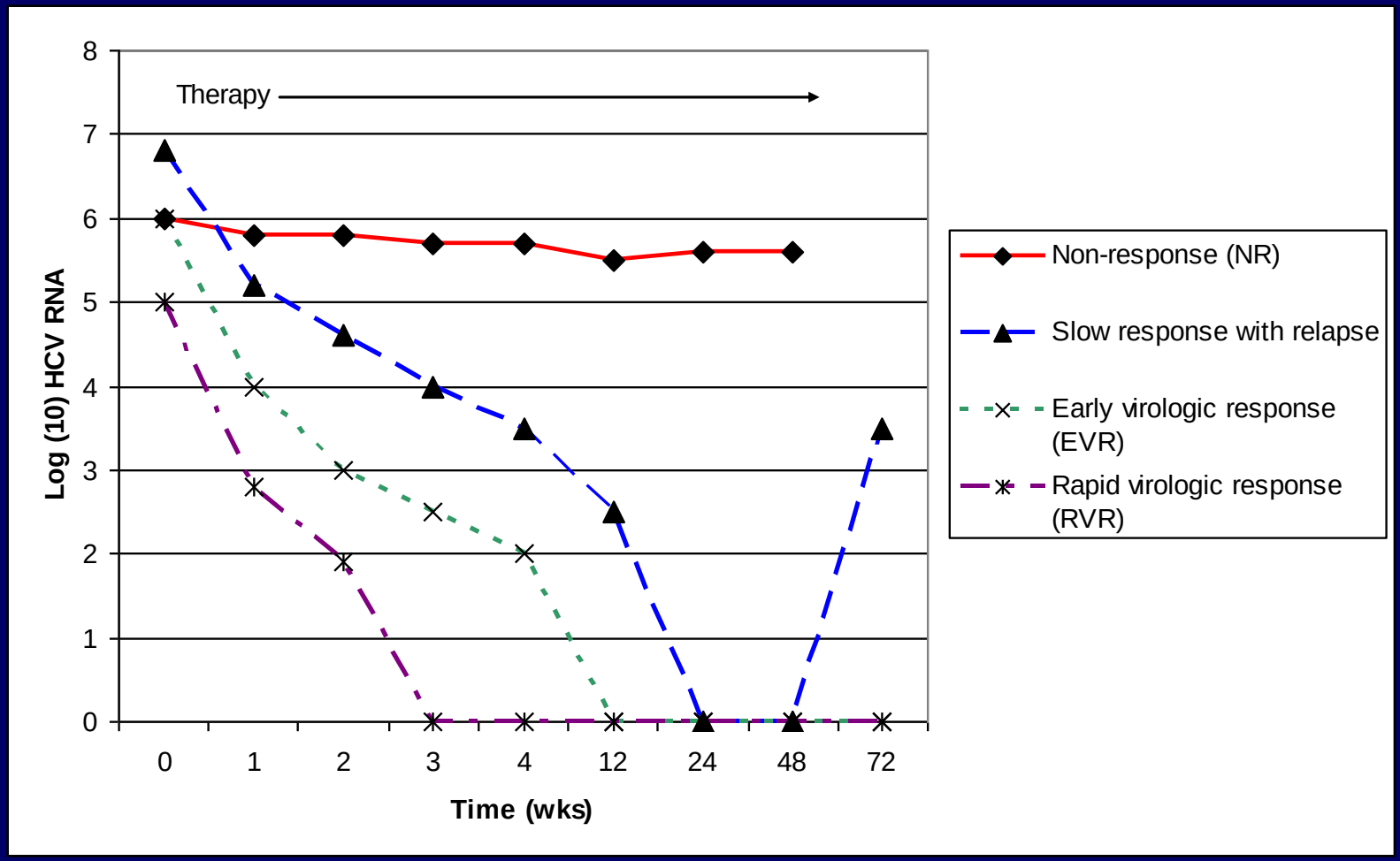
- **Indications for treatment**

Recommended	Not recommended	Unclear
Detectable HCV RNA **•Persistently elevated ALT** **•Abnormal liver biopsy showing portal or bridging fibrosis, or at least moderate inflammation**	**Persistently normal ALT** **•Advanced or decompensated cirrhosis** **•Excessive alcohol use** **•Active drug use** **•Contraindications to treatment**	**•Compensated cirrhosis** **•Elevated ALT but normal liver histology**

HCV – Pretreatment Workup

- History and Physical Exam
- Psychiatric history/evaluation
- Blood counts
- Chemistry panel
- Liver panel, including PT
- TFTs
- HCV genotype
- HCV RNA
- AFP; ?liver imaging
- Liver biopsy

The importance of viral kinetics



Scott J and Gretch DR. *JAMA* 2007.

Kinetics and SVR
GT 1 (Pegasys + RVN)

Time	HCV RNA status			
Wk 4	Neg	<2 log	<2 log	Any
Wk 12	Neg	Neg	>2 log	Any
Wk 24	Neg	Neg	Neg	Pos
SVR	**91%**	**60%**	**43%**	**2%**

Ferenci P. J Hepatol 2005; 43:425-33

Who to treat ?

Table 10. Characteristics of Persons for Whom Therapy Is Widely Accepted

- Age 18 years or older, and
- HCV RNA positive in serum, and
- Liver biopsy showing chronic hepatitis with significant fibrosis (bridging fibrosis or higher), and
- Compensated liver disease (total serum bilirubin $<$1.5 g/dL; INR 1.5; serum albumin $>$3.4, platelet count 75,000 mm and no evidence of hepatic decompensation (hepatic encephalopathy or ascites), and
- Acceptable hematological and biochemical indices (Hemoglobin 13 g/dL for men and 12 g/dL for women; neutrophil count 1500 /mm^3 and serum creatinine $<$1.5 mg/dL, and
- Willing to be treated and to adhere to treatment requirements, and
- No contraindications (Table 12)

HCV - Treatment

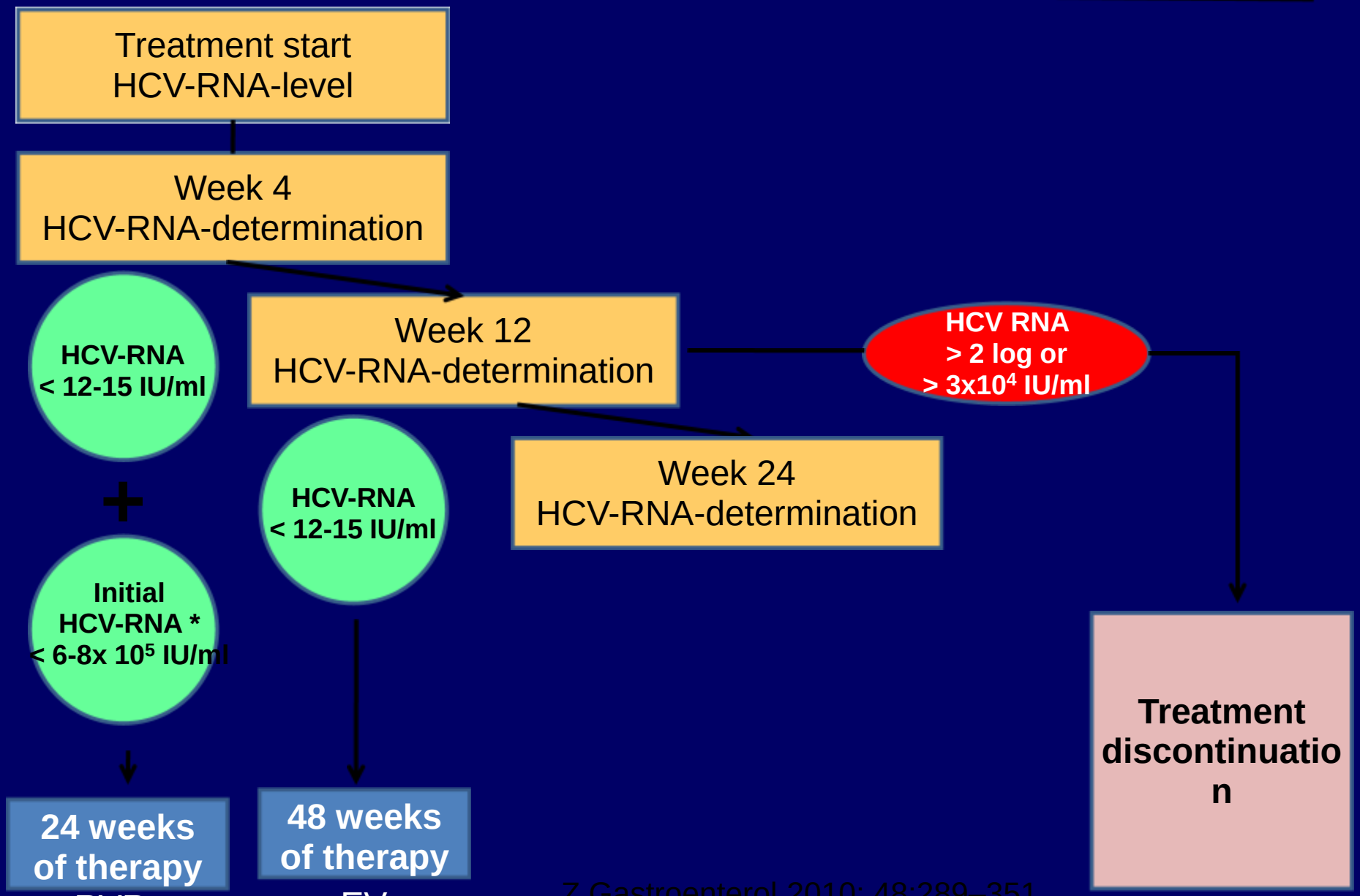
- **Predictors of a Favorable Response**
  - **Genotype 2 or 3**
  - **Low HCV Viral Load (<2 million)**
  - **No or only portal fibrosis**
  - **Female gender**
  - **Age ≤ 40 years**

  - **Role of gender not an independent factor if controlled for body weight**

Is it necessary to do viral genotyping when managing a person with chronic Hepatitis C?

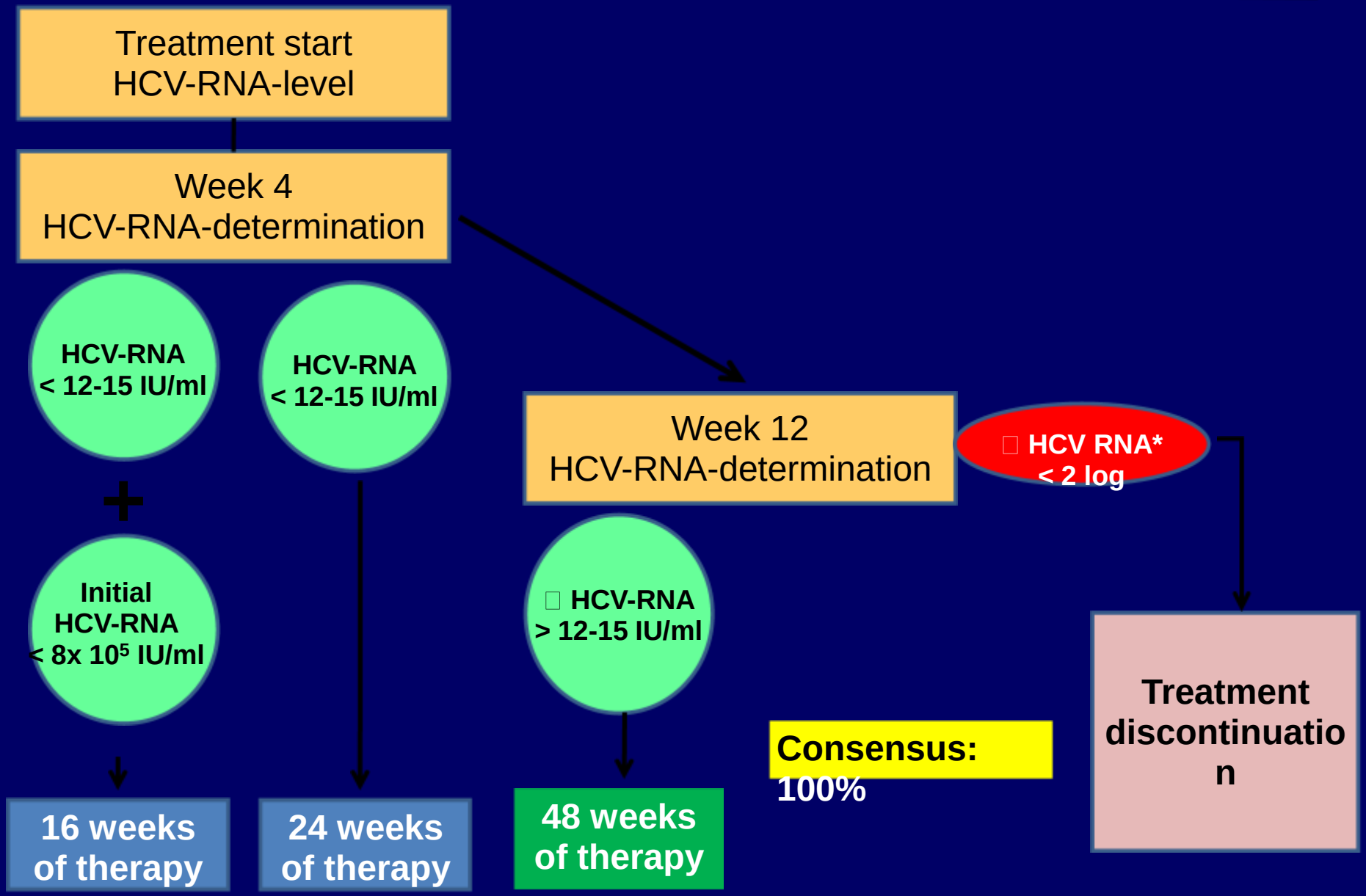
- Patients with genotypes 2 and 3 are almost three times more likely than patients with genotype 1 to respond to therapy with the combination of alpha interferon and ribavirin
- When using combination therapy, the recommended duration of treatment depends on the genotype. For patients with genotypes 2 and 3, a 24-week course of combination treatment is adequate, whereas for patients with genotype 1, a 48-week course is recommended.

Standard therapy in HCV genotyp 1/4



Z Gastroenterol 2010; 48:289–351

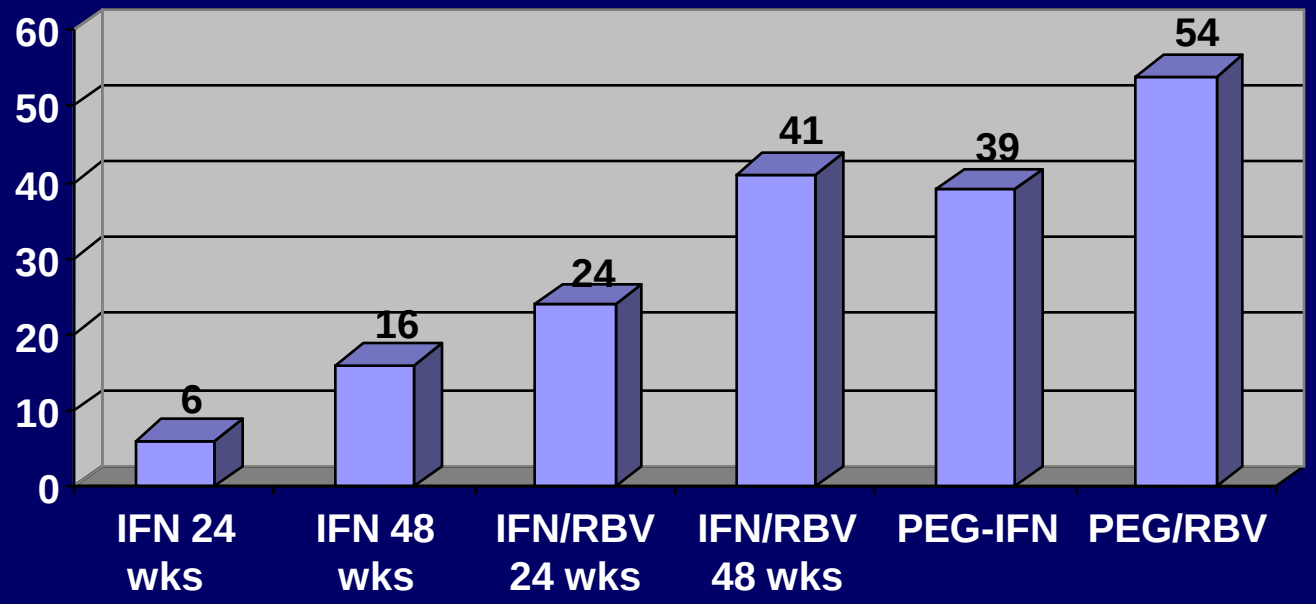
Standard therapy in HCV genotyp 2/3



Z Gastroenterol 2010; 48:289–351

HCV – Treatment (non-HIV Patients)

Sustained Virologic Response Rates



Source: Multiple randomized controlled trails

DAA

- Until recently, the mainstay of treatment for chronic hepatitis C virus (HCV) infection has been pegylated interferon and ribavirin, with possible addition of boceprevir (Victrelis™) and telaprevir (Incivek™) (both protease inhibitors) for HCV genotype 1 infection.

DAA

- After given for 24-48 weeks, this treatment resulted in a sustained virologic response (a marker for cure), defined as undetectable HCV RNA in the patient's blood 24 weeks after the end of treatment in 50%–80% of patients (with higher SVR among persons with HCV genotype1,

Sofosbuvir

- Sofosbuvir (Sovaldi™) is a nucleotide analogue inhibitor of the hepatitis C virus (HCV) NS5B polymerase enzyme, which plays an important role in HCV replication. It is taken orally once a day at a 400-mg dose.
- The drug is approved for two chronic hepatitis C indications:

Sofosbuvir

- 1-In combination with pegylated interferon and ribavirin for treatment-naïve adults with HCV genotype 1 and 4 infections, and in combination with ribavirin for adults with HCV genotypes 2 and 3 infection.
- 2-The first approval of an interferon-free regimen for the treatment of chronic HCV infection.