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CHRONIC VIRAL HEPATITIS C

by Adela Turcanu

Chronic viral hepatitis C is defined as necroinflammatory disease of the liver caused by persistent infection (>6 month) with hepatitis C virus.

EASL Clinical Practice Guidelines. Management of hepatitis C virus infection. J Hepatol 2014; vol.60:392–420

EPIDEMIOLOGY OF HCV

- Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide.
- It is estimated that approximately 130–210 million individuals, i.e. 3% of the world population, are chronically infected with HCV.
- Between 7.3 and 8.8 million people are infected with HCV in the European Union, i.e. twice as many as an estimate made in 1997.
- Overall, HCV prevalence across Europe ranges between 0.4% and 3.5%, with wide geographical variation and higher rates in the south and the east
- The prevalence varies markedly from:

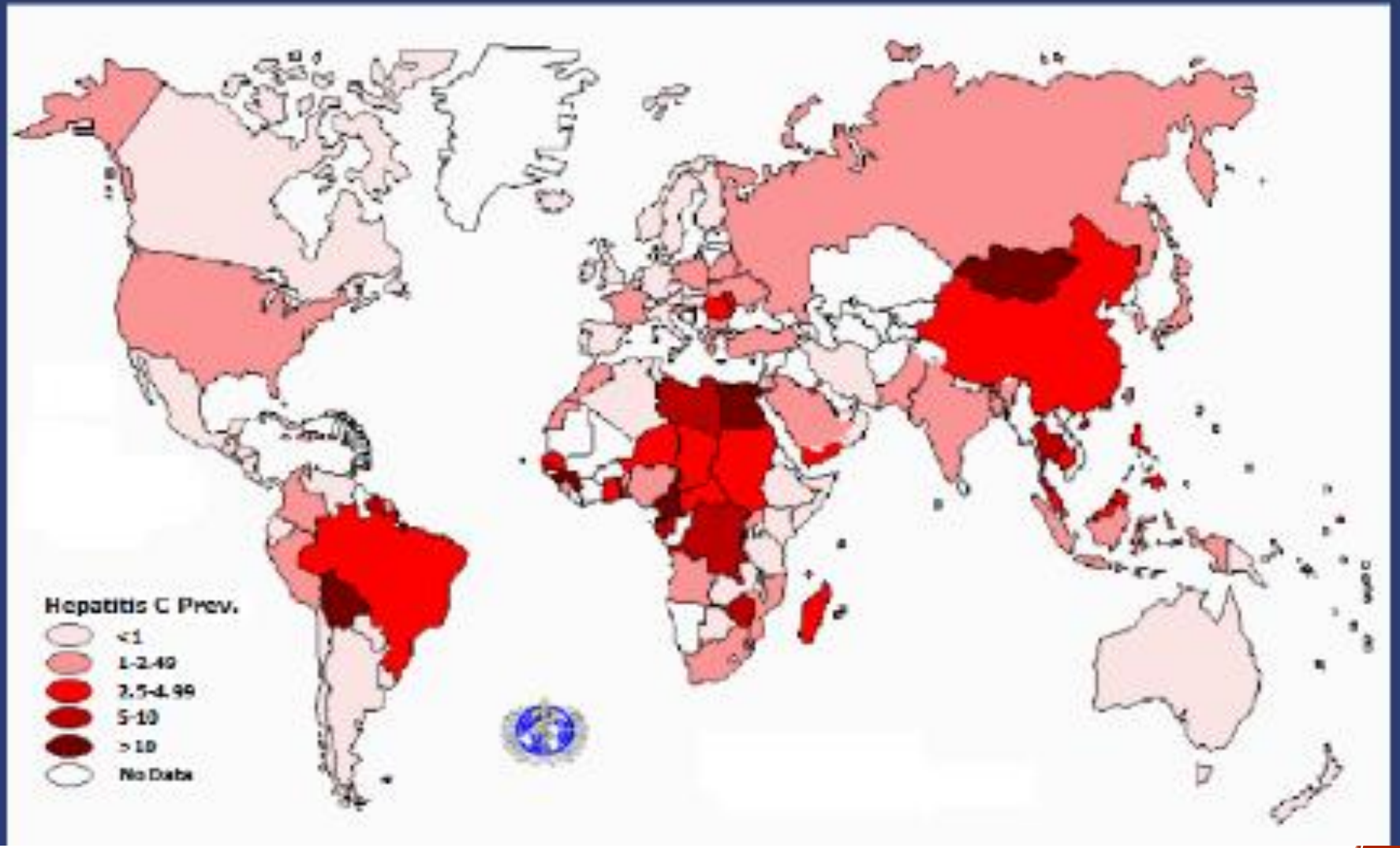
✓ *low* (< 2.5%) in North America, Europe, Australia and Far East,

✓ *intermediate* (2.5% to 10%) in some Mediterranean countries, South America, Africa and Middle East,

✓ *high* (>10%) *prevalence* areas in Egypt, Burundi, Gabon, Cameroon, Rwanda, Guinea, Bolivia, Mongolia with an steady North-South increasing trend.

EASL Clinical Practice Guidelines. Management of hepatitis C virus infection. J Hepatol 2011;55:245–264.
Lavanchy D. Evolving epidemiology of hepatitis C virus. Clin MicrobiolInfect 2011;17:107–115

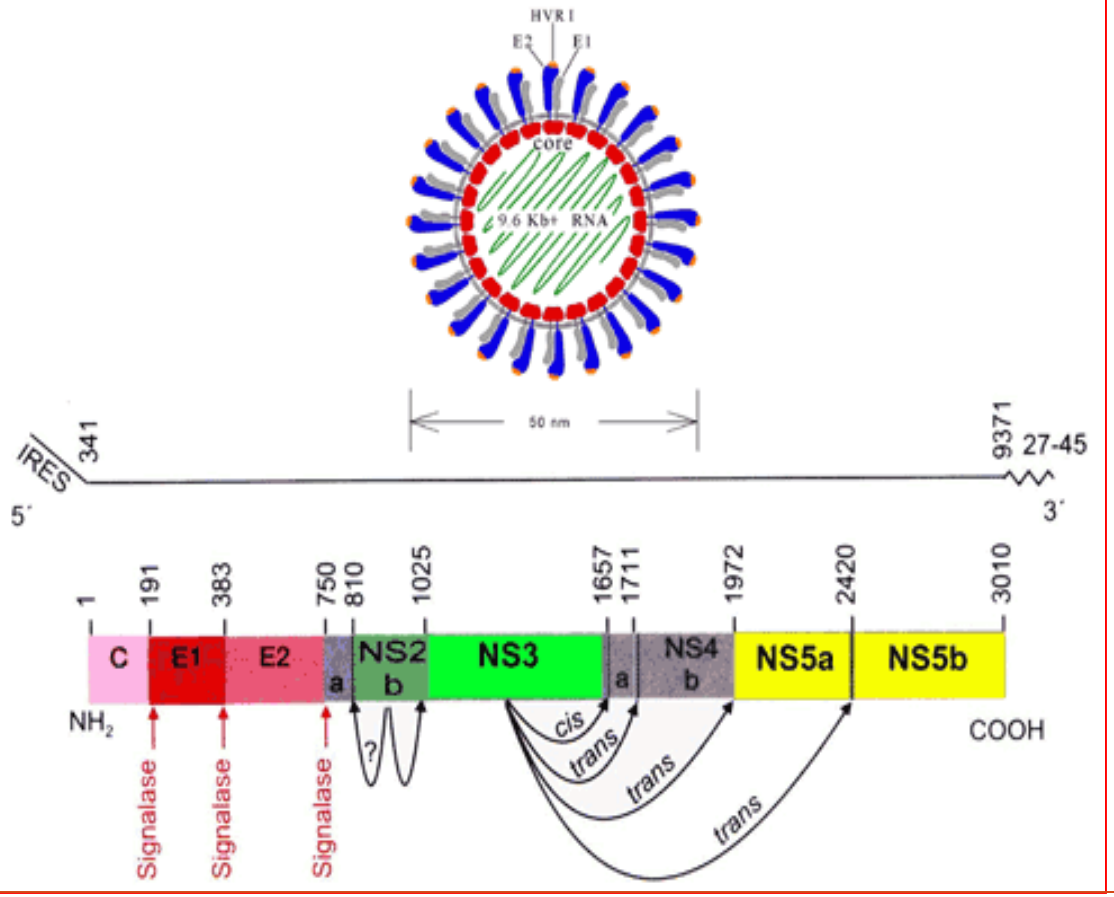
Global prevalence of hepatitis C



THE PEOPLE WITH RISK FOR HCV INFECTION

- Current or former injection drug users, including those who injected only once many years ago
- Recipients of clotting factor concentrates made before 1987, when more advanced methods for manufacturing those products were developed
- Recipients of blood transfusions or solid organ transplants before July 1992, when better testing of blood donors became available
- Chronic hemodialysis patients
- People with known exposures to HCV, such as
  - ✓health care workers after needle sticks involving HCV-positive blood
  - ✓recipients of blood or organs from a donor who tested HCV-positive
- People with HIV infection
- Children born to HCV-positive mothers

STRUCTURE OF VHC



HCV is the sole member of the genus Hepacivirus that belongs to the Flaviridae family.

The HCV genome is a single-stranded positive-sense RNA molecule of approx. 9600 bases length.

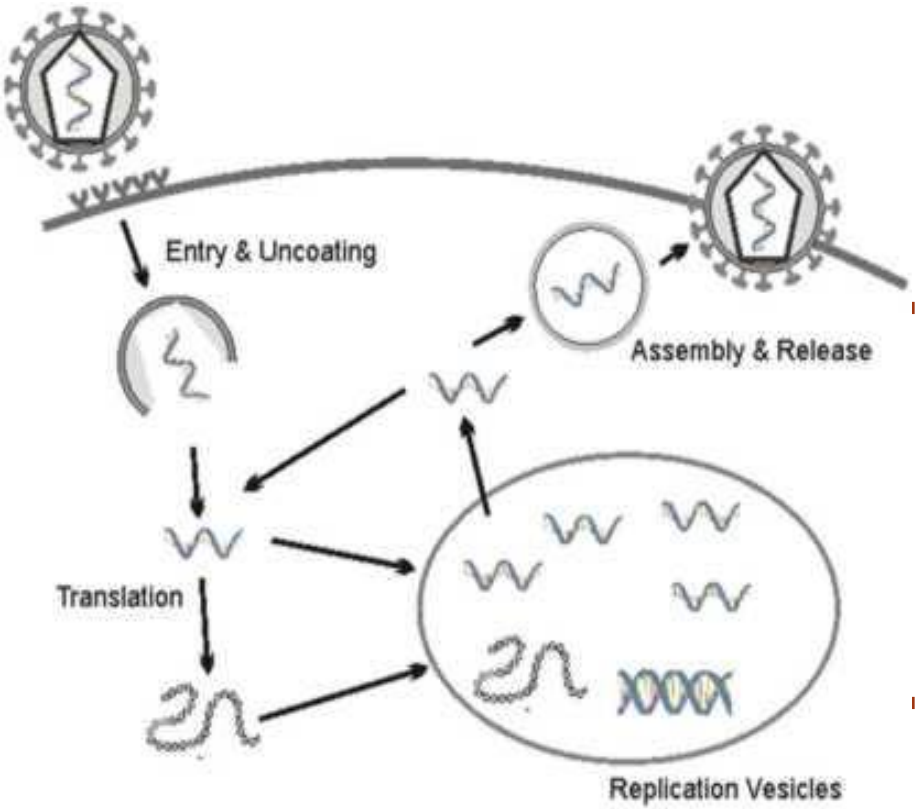
HCV circulates in various forms in the serum of an infected host, including:

- virions bound to very–low-density lipoproteins and low-density lipoproteins, which appear to represent the infectious fraction;
- virions bound to immunoglobulins;
- free virions.

- The structural proteins include the core (C), which forms the viral nucleocapsid, and the envelope glycoproteins E1 and E2. They are released by host-cell signal peptidases.
- The nonstructural (NS) proteins NS2 to NS5B are involved in polyprotein processing and viral replication.

Francois Penin, Jean Dubuisson et al. Structural biology of hepatitis C virus J Hepatology, 2004

Replication of VHC



- Hepatitis C virus (HCV) entry is the first step of interactions between virus and the target cell that is required for initiation of infection.
- The virus linked to its receptor complex, internalize and then nucleocapsid is released into the cytoplasm. The virus is decapsidated, and the genomic HCV RNA is used both for polyprotein translation and replication in the cytoplasm.
- Because HCV tends to circulate in relatively low titer, 1000 - 10^7 virions/mL, visualization of virus particles, estimated to be 40–60 nm in diameter, remains difficult. Still, the replication rate of HCV is very high, 10 trlions virions per day; its half-life is 2.7 hours.
- HCV does not replicate via a DNA intermediate, it does not integrate into the host genome.

An overview of HCV molecular biology, replication and immune responses.
Usman A Ashfaq, Tariq Javed, Sidra Rehman J Virology 2011, 8;161
D. Clausznitzer, N. Sulaimanov, M. Binder, V. Lohmann, R. Bartenschlager, L. Kaderali , 2011. *Systembiologie der Hepatitis C-Virus-Wirts-Interaktionen.* Laborwelt 6:13-15

TRANSMISSION ROUTES OF VHC

- *Intravenous drug use*. Since the most efficient transmission route of hepatitis C virus is percutaneous exposure, it is not surprising that intravenous needle sharing drug users show high infection rates, that may be as high as 90% when HIV co-infected drug addicts are considered .
- *Non-intravenous recreational drug exposure*. Increasing evidence is accumulating that HCV may also cross the nasal mucosa and infect subjects chronically using inhalatory recreational drugs, such as cocaine, by the sharing of inhalatory instrumentation, favored by the frequent bleeding of the nasal mucosa occurring in these individuals
- *Accidental exposure*. The risk of HCV infection after accidental needle stick exposure has been reported to range between 0.2% to 10%, depending on various factors including hollow-bore needles, percutaneous exposure, high HCV viral load or HIV co-infection of the index case .

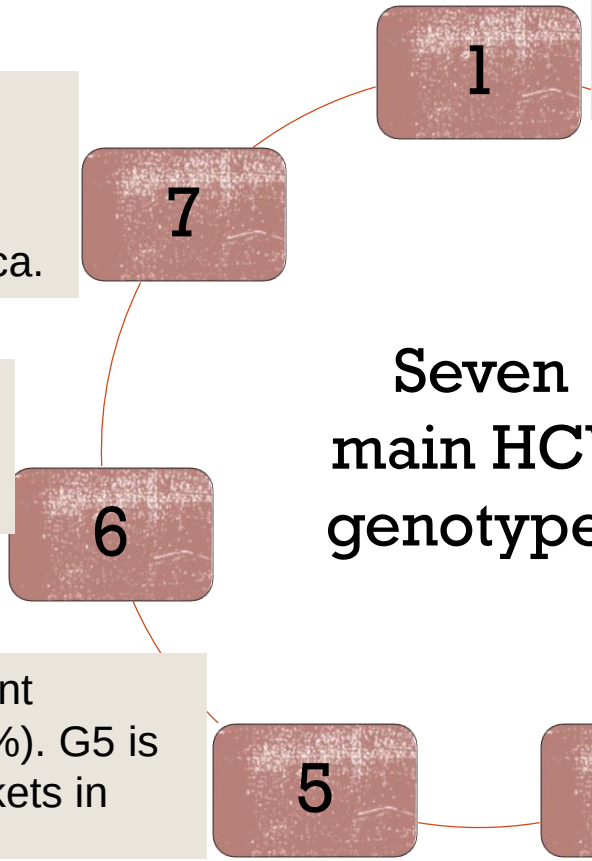
TRANSMISSION ROUTES OF VHC

- *Healthcare procedures*. Exposure to unsafe healthcare practice, including hemodyalisis, has been reported to be one of the most important risk factors associated with HCV infection, even in western countries .
- *Mother to child vertical transmission*. Mother-to-child vertical transmission of HCV is reported to occur in 4.3% of cases, mostly in the late intrauterine period, at delivery or in the peri-natal period. The role of elective cesarean section to reduce mother-to-child transmission rates is debated and controversial.
- *Sexual exposure*. The efficiency of the sexual transmission of HCV has been the subject of extensive debate and it is generally considered to be very low.
- around 10%, no definite exposure source may be identified

EASL Clinical Practice Guidelines. Management of hepatitis C virus infection. J Hepatol 2014; vol.60:392–420


Body Piercing
Mother to Baby Transmission
Tattooing
Causes
of
Hepatitis C
Blood Transfusion

GENOTYPES FROM HCV



G1is the most prevalent genotype worldwide. G1a is the prevalent type in the USA and G1b – in Europe, Asia.

G2 and G3 are found with significant prevalence in many countries in North and South America, Europe and Asia.

G4 accounts for around 90% of HCV infections in Egypt and other 10-20% -in worldwide.

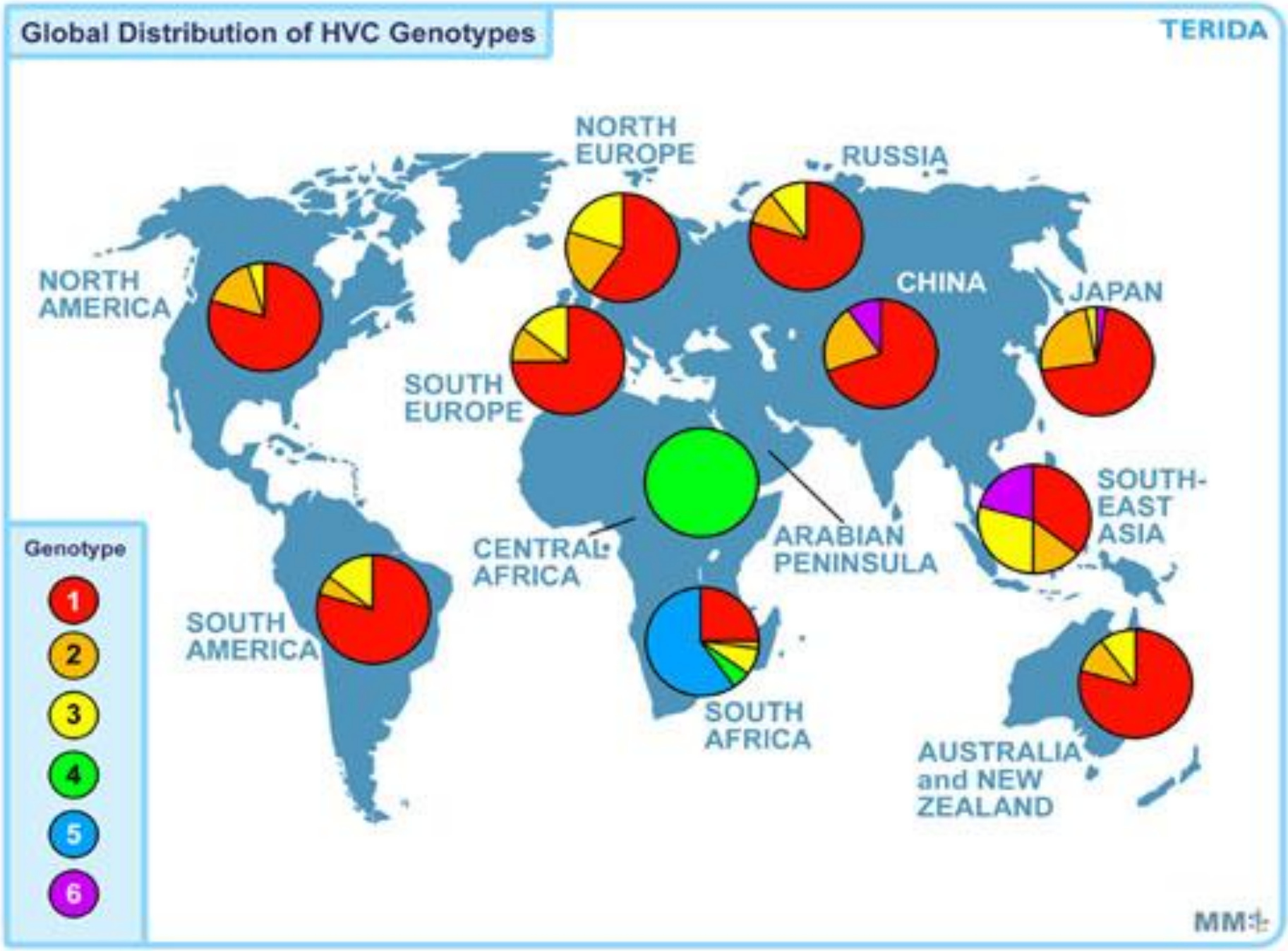
G5 is the most prevalent genotype in Africa (40%). G5 is emerging in small pockets in Syria, Europe.

G6 is rare, identified predominant in Asia (except China).

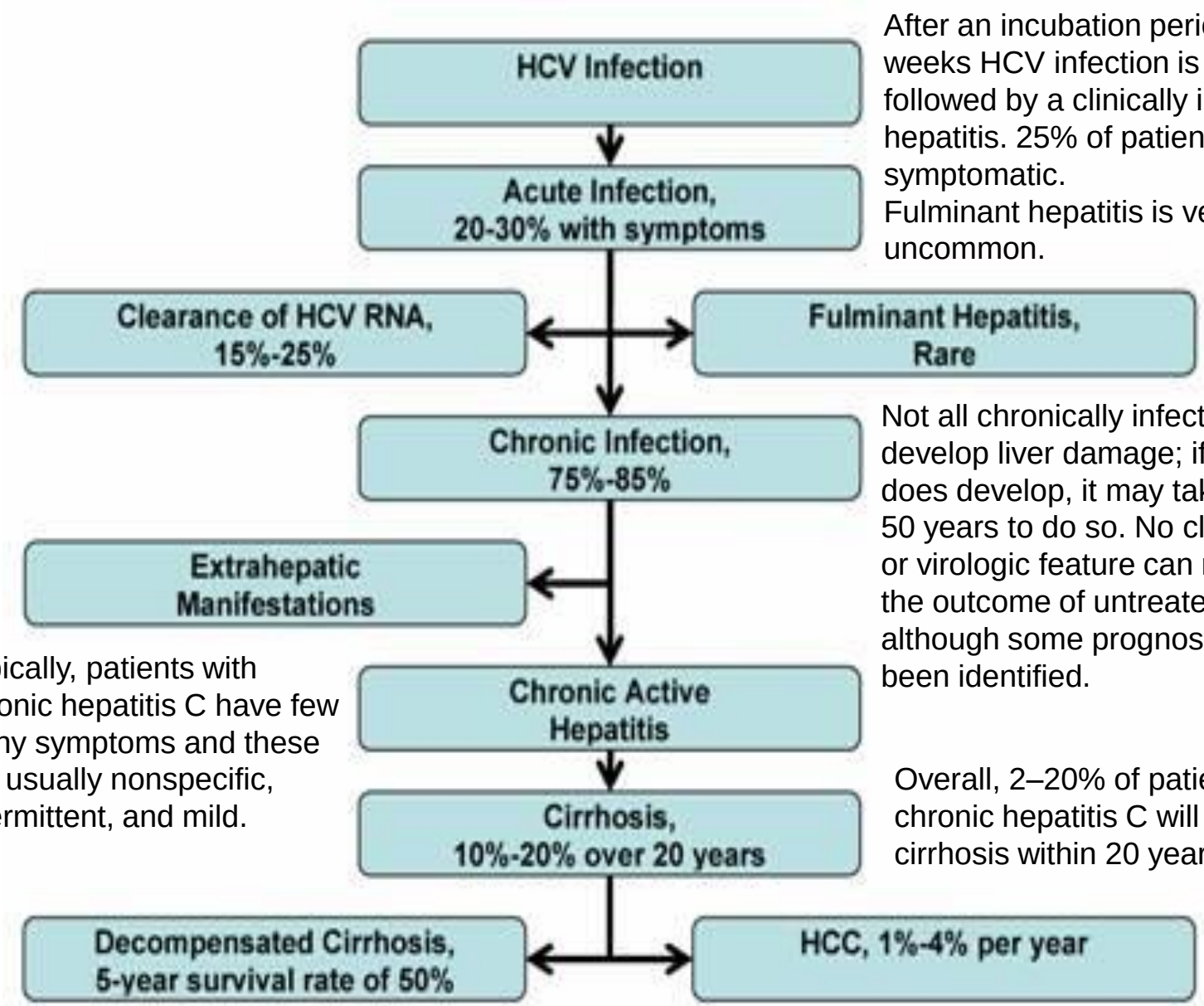
G7 was identified in patients from Canada and Belgium, possibly infected in Central Africa.

All currently recognized HCV genotypes are hepatotropic and pathogenic. However, it has been suggested that different genotypes do vary in their infectivity and pathogenicity, thereby influencing the rate of progression to cirrhosis and the risk of HCC.

Jane P. Messina et.al Global distribution of hepatitis C virus genotypes, Hepatology, vol.61, issue 1, 2014


Global Distribution of HVC Genotypes
TERIDA
NORTH EUROPE
RUSSIA
NORTH AMERICA
CHINA
JAPAN
SOUTH EUROPE
SOUTH-EAST ASIA
CENTRAL AFRICA
ARABIAN PENINSULA
SOUTH AMERICA
SOUTH AFRICA
AUSTRALIA and NEW ZEALAND
Genotype
1
2
3
4
5
6
MM

NATURAL HISTORY OF INFECTION WITH VHC



After an incubation period of 3–12 weeks HCV infection is usually followed by a clinically inapparent hepatitis. 25% of patients are symptomatic.
Fulminant hepatitis is very uncommon.

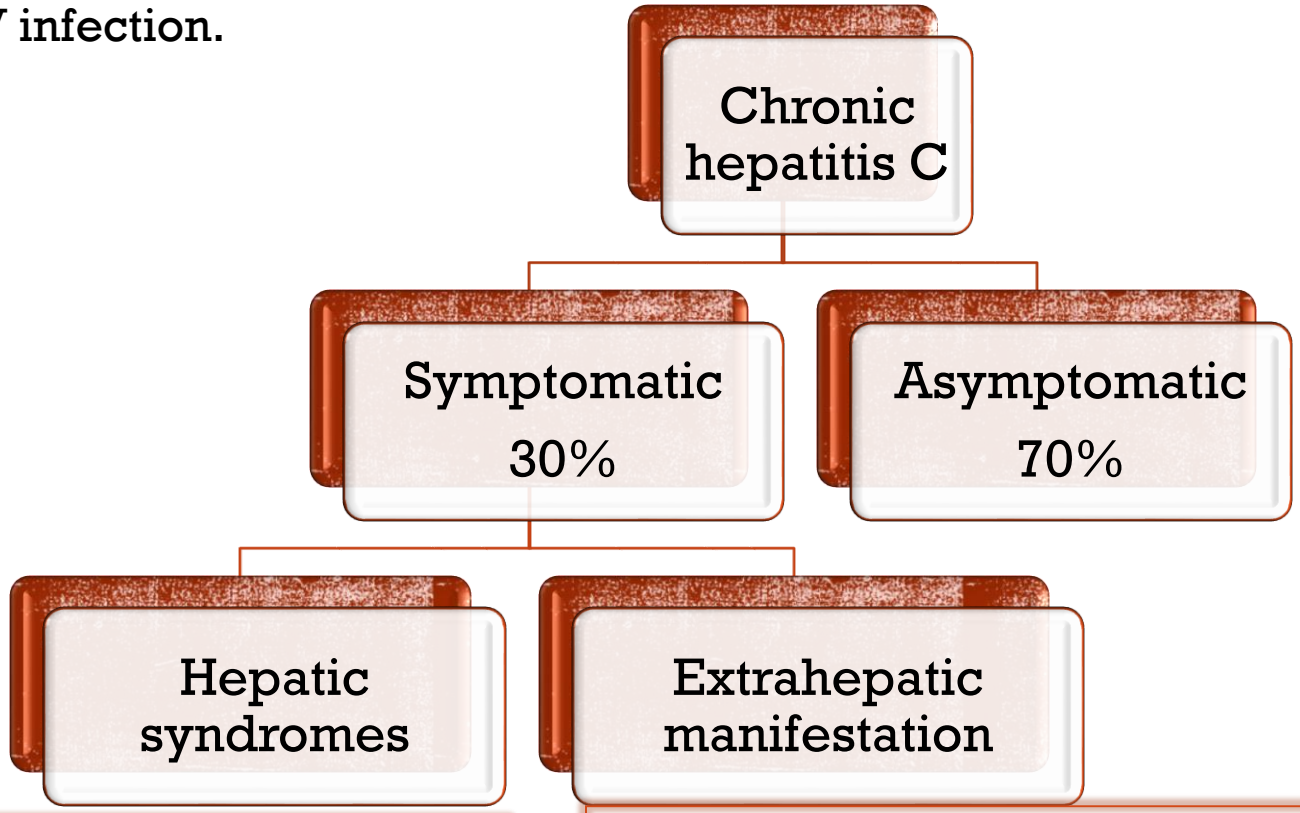
Not all chronically infected people will develop liver damage; if liver damage does develop, it may take from 10 to 50 years to do so. No clinical, serologic, or virologic feature can reliably forecast the outcome of untreated HCV infection, although some prognostic factors have been identified.

Typically, patients with chronic hepatitis C have few if any symptoms and these are usually nonspecific, intermittent, and mild.

Overall, 2–20% of patients with chronic hepatitis C will develop liver cirrhosis within 20 years.

CLINICAL MANIFESTATION OF CHRONIC HEPATITIS C

Most people with chronic HCV infections remain asymptomatic for years, although some individuals will experience fatigue, depression, and other extrahepatic manifestations of HCV infection.

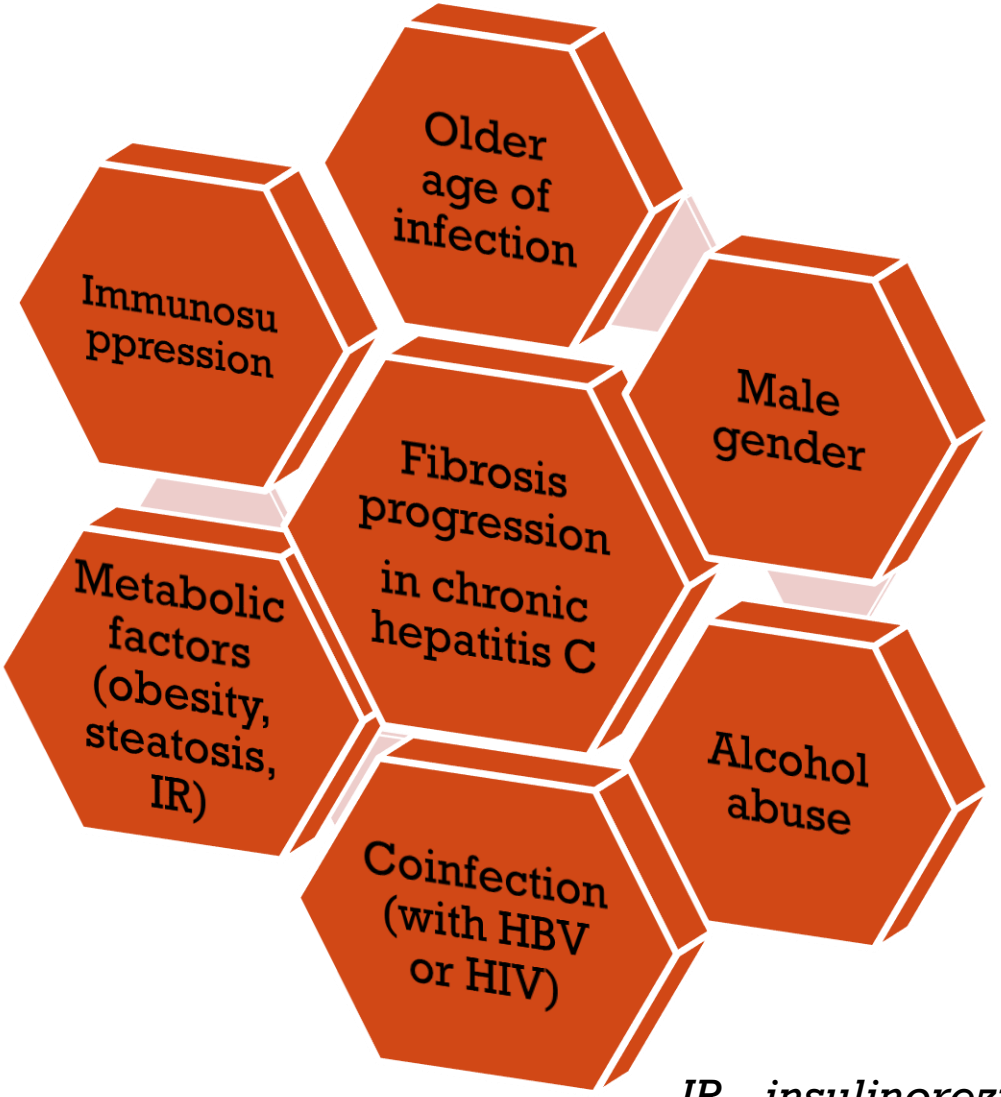


- neurasthenic syndrome (fatigue, depression);
- pain syndrome (abdominal, muscul. pain)
- dyspeptic syndrome
- icteric sindrome

- Reumathological manifestation
- Dermatological and ocular disorder
- Endocrine and renal syndromes
- Hemathological and vascular disord.
- Autoimmune disorder

COFACTORS FOR FIBROSIS PROGRESSION

- Tobacco smoking may increase inflammation and accelerate fibrosis.
- Daily cannabis use has been associated with more advanced liver fibrosis.
- Coffee consumption is associated with lower inflammatory activity, less advanced fibrosis
and reduced risk of developing HCC.



IR - insulinorezistance

EXTRAHEPATIC MANIFESTATIONS ASSOCIATED WITH HEPATITIS C VIRUS

- ❑Several extrahepatic manifestations associated with HCV infection may significantly affect its morbidity and mortality
- ❑Mixed cryoglobulinemia is almost always the result of HCV infection and affects approximately one half of HCV-infected patients
  - ✓Patients often present with a typical triad of symptoms consisting of fatigue, arthralgias, and palpable purpura
  - ✓Successful treatment of HCV infection with antivirals leads to a decrease of cryoglobulin levels in serum and to the remission of cryoglobulin-related symptoms and pathologic lesions
- ❑Type 2 diabetes is more frequent in chronic HCV infection than in HBV infection
  - ✓Successful antiviral treatment of chronic hepatitis C in the absence of overt diabetes leads to a reduced incidence of type 2 diabetes by approximately two thirds

Sene D, Limal N, Cacoub P. Hepatitis C virus-associated extrahepatic manifestation: a review.Metab Brain Dis. 2004 Dec;19(3-4):357-81.

White DL, Ratziu V, El-Serag HB. Hepatitis C infection and risk of diabetes: a sistematic review and meta-analysis. J Hepatol. 2008 Nov;49(5):831-44. doi: 10.1016/j.jhep.2008.08.006. Epub 2008 Aug 21.

DIAGNOSIS FOR CHRONIC HEPATITIS C

Initial evaluation of patients with HCV-suspected	**Laboratory studies**
Medical history: • Identifying risk factors for HCV acquisition • Alchol history (use AUDIT, CAGE questionnaire) • Injection drug use history Physical examination: • Hepatic and extra hepatic signs • Complications of HCV	General laboratory evaluation Biochimical syndromes: • Cytolitical • Cholestatic • Hepatoprive • Immuno-inflamathory Serological markers • Antibodies anti HCV type: IgG, IgM • HCV RNA level • HCV genotype IL-28B testing

SEROLOGICAL MARKERS IN HCV

Screening tests are tests that are used to diagnose a condition or disease among individuals not known to have the disease. They are is particularly useful for individuals who have risk factors for the condition or disease.

The first step in screening for HCV infection is to test blood for the antibody to HCV using an **enzyme immuno-assays (EIAs)**.
If the EIA test is **negative** (does not find the antibody), the patient is assumed to be free of HCV. It takes several weeks (up to six months) for antibodies to develop after the initial infection with HCV, so this screening test may miss a few newly-infected individuals.
The EIA screening tests are very good (specific); if the test is **positive** the probability of having HCV infection is greater than 99%.

Recombinant immunoblot assay (RIBA) is used to confirm the positive results of EIAs since occasionally a positive EIA is a false positive, that is, the test is positive when HCV is not present. Although the direct detection of HCV RNA (HCV PCR) also is widely used to confirm the HCV infection, RIBA is still useful to differentiate false positive results in the few individuals whose immune systems have eliminated the virus but still have antibodies left over from the resolved infection.

SEROLOGICAL MARKERS IN HCV

HCV RNA testing is more sensitive (that is, will detect more cases) than the conventional EIA testing in this setting. The reason for this greater sensitivity is that it may take a person several weeks after exposure to HCV to develop the antibodies, whereas HCV RNA becomes detectable one to three weeks after exposure.

A single negative test for RNA does not mean that there is no infection because the virus may appear in the blood intermittently or may exist in small amounts.

Anti-HCV (ELISA/EIA)	Anti-HCV (RIBA)	HCV RNA	Interpretation
Negative	Negative	Negative	No infection
Positive	Positive	Positive	Ongoing infection
Positive	Positive	Negative	Past or current infection. Additional or repeat testing should be done to exclude fluctuating or low levels of viremia.
Positive	Negative	Negative	False positive ELISA; no infection
Positive	Indeterminate	Negative	Situation unclear, consider additional testing
Negative	Negative	Positive	New (acute) HCV infection or chronic HCV infection in an immunocompromised person unable to make adequate antibodies.

ASSESSMENT THE STAGE OF FIBROSIS IN HCV

Liver biopsy:

- can provide information on current status of liver injury and help guide therapeutic hepatitis C management decisions;
- can characterize features useful in diagnosing and treating co-existing liver diseases;
- can help reveal advanced fibrosis/cirrhosis that would necessitate routine cancer surveillance

Noninvasive markers:

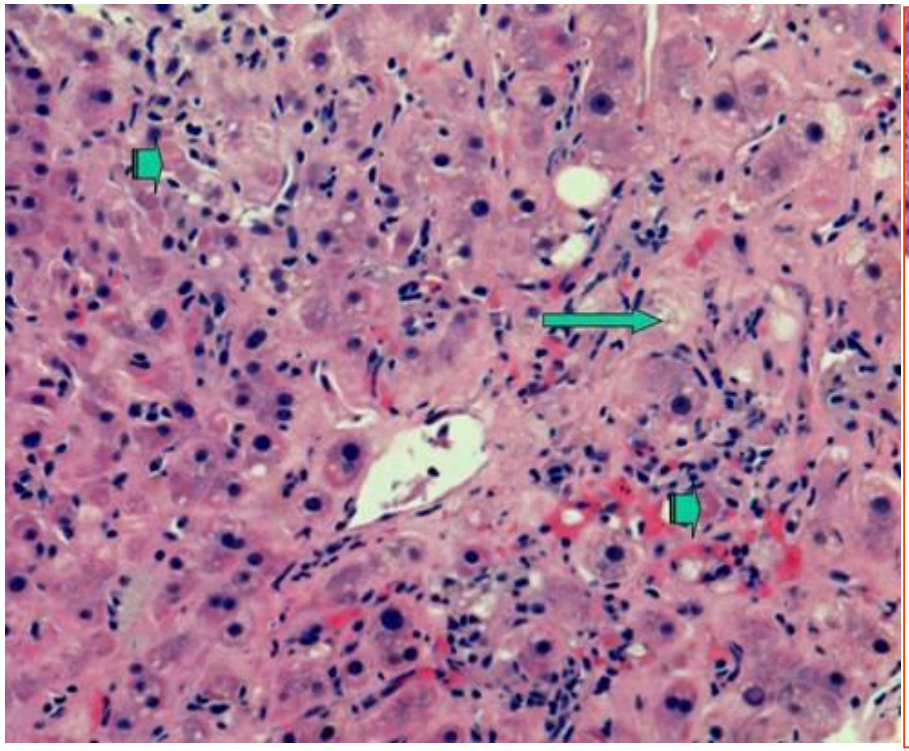
APRI, FIB4

FibroSure, FibroTest (utilizes a proprietary algorithm that includes patient age and gender along with a composite of six biochemical markers associated with hepatic fibrosis: alpha-2-macroglobulin, haptoglobulin, GGT, apolipoprotein A1, total bilirubin, and ALT)

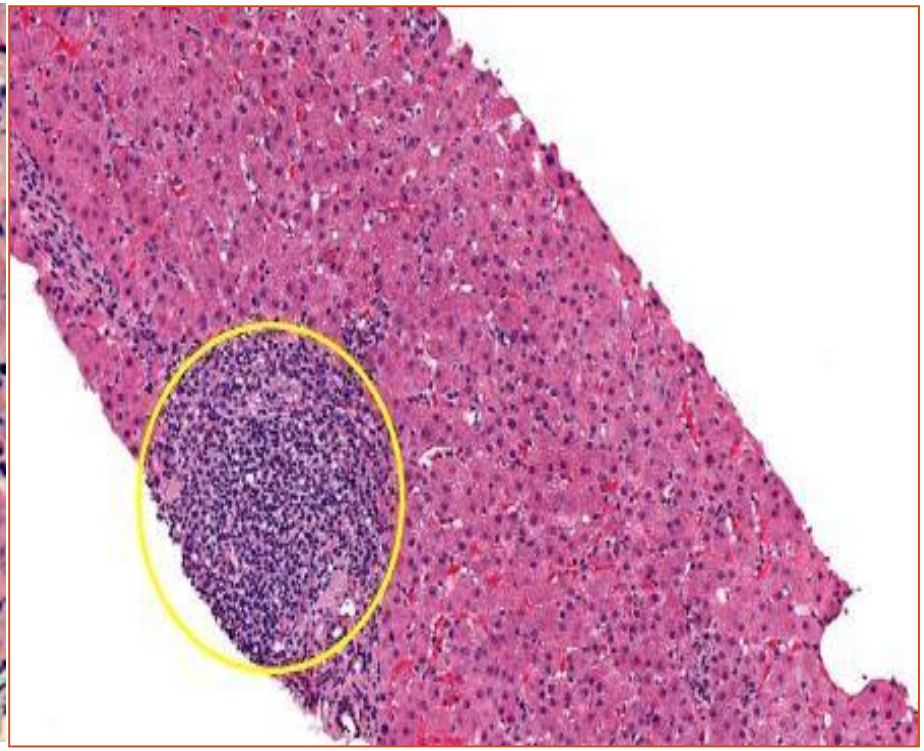
Elastography (Fiboscan) The test is performed using an ultrasound transducer probe that is mounted on the axis of a vibrator. Vibration is transmitted toward hepatic tissue, the vibrations are followed by pulse echo, and their velocities are measured which correlates directly with liver stiffness.

Hepatic ultrasound

LIVER BIOPSY IN CHRONIC HEPATITIS C



In chronic HCV can see centrilobular cholestasis causing feathery degeneration of hepatocytes (long arrow). In addition, there are foci of parenchymal necrosis including acidophilic bodies



Hepatitis C typically has distinctly nodular lymphocytic aggregates in portal areas

THERAPY OF CHRONIC HEPATITIS C

The 2 goals of treatment of chronic hepatitis C are as follows :

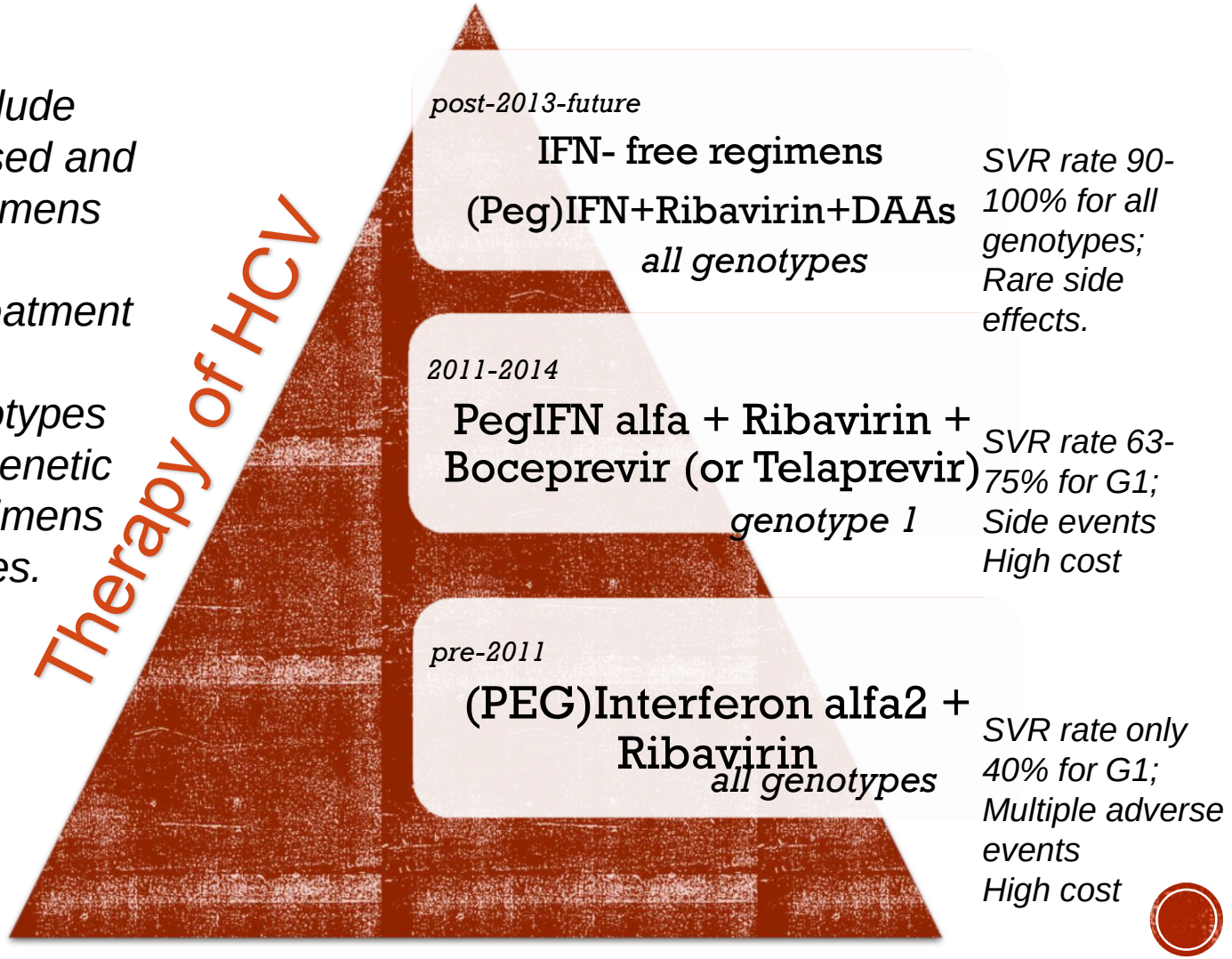
- To achieve sustained eradication of HCV (sustained virological response)
- To prevent progression to cirrhosis, hepatocellular carcinoma (HCC), and decompensated liver disease necessitating liver transplantation.

Indications from antiviral therapy:

- HCV RNA positive in serum,
- Liver biopsy showing chronic hepatitis with significant fibrosis (bridging fibrosis or higher),
- Compensated liver disease (total serum bilirubin <1.5 g/dL; INR 1.5; serum albumin > 3.4, platelet count 75,000/mm3 and no evidence of hepatic decompensation [hepatic encephalopathy or ascites]),
- Acceptable hematological and biochemical indices (hemoglobin 13 g/dL for men and 12 g/dL for women; neutrophil count 1500 /mm3 and serum creatinine >1.5 mg/dL,
- Willing to be treated and to adhere to treatment requirements,
- No contraindications.

STRATEGIES OF ANTIVIRAL THERAPIES IN HCV

- *HCV treatment include both interferon-based and interferon-free regimens*
- *Selection of the treatment regimens will be influenced by genotypes of HCV, potency, genetic barrier, dosing regimens and adverse profiles.*



(PEG)INTERFERON ALFA AND RIBAVIRIN

Dosage: Peginterferon alfa-2b, is administrated of **1.5 g/kg/week** dosed according to body weight. **Peginterferon alfa-2a** is administered at a fixed dose of 180 g/week.

The dose of **ribavirin** is: 800 mg for patients 65 kg; 1,000 mg for patients weighing 65 to 85 kg; 1,200 mg/ weighing 85-105 kg; and 1,400 mg for patients >105 kg.

Duration of therapy: genotype 1,4,6 should be treated for 48 weeks with Peginterferon alfa + weight-based ribavirin. genotypes 2 and 3 could be treated with Peginterferon alfa + low dose ribavirin (800 mg) for 24 weeks.

Pegylated IFN-α/ribavirin containing regimens is absolutely contraindicated in:

- uncontrolled depression, psychosis or epilepsy;
- pregnant women or couples unwilling to comply with adequate contraception;
- severe concurrent medical diseases and comorbidities including retinal disease, autoimmune thyroid disease; autoimmune hepatitis,
- decompensated liver disease.

The use of pegylated IFN-α is not recommended in patients with absolute neutrophil counts <1500/mm3 and/or platelet counts ≤90,000/mm.

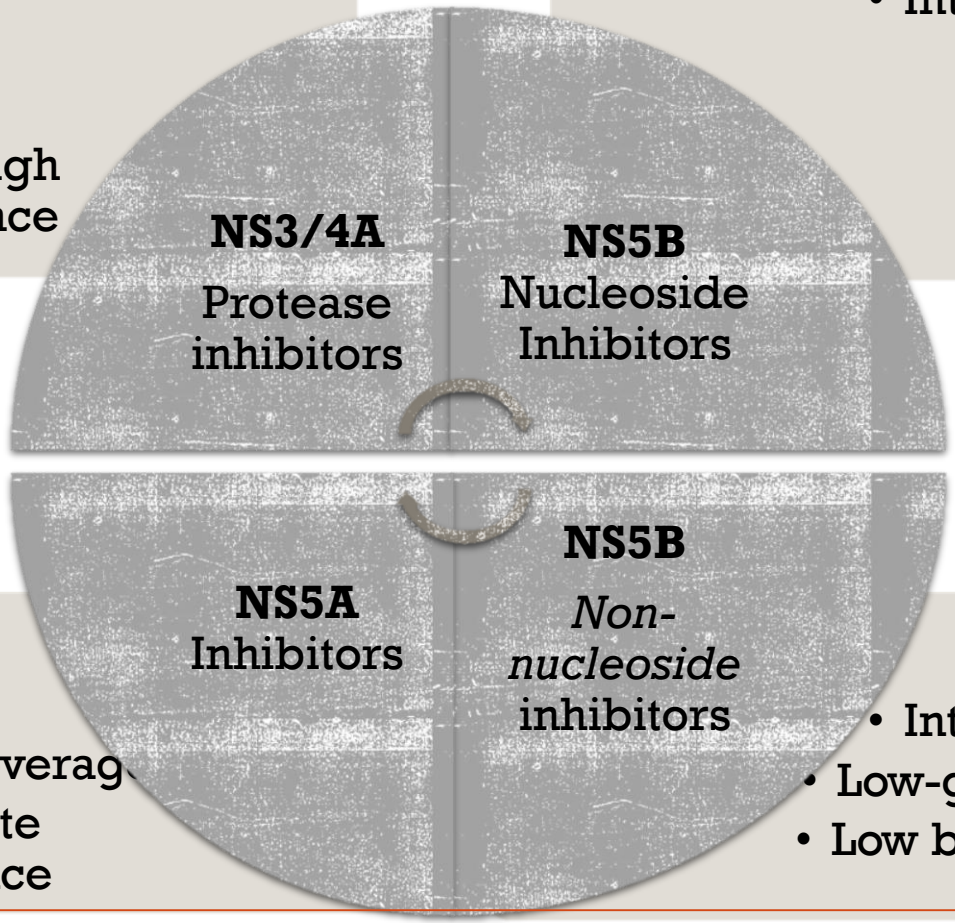
DIRECT-ACTING ANTIVIRAL AGENTS (DAA)

- High potency
- Multi-genotypic coverage
- Intermediate to high barrier to resistance

Boceprevir
Telaprevir
Asunaprevir
Simeprevir
Danoprevir

- Intermediate potency
- Pan-genotypic coverage
- High barrier to resistance

Sofosbuvir
Mericitabine
IDX-184



- High potency
- Multigenotypic coverag
- Low to intermediate barrier to resistance

Daclatasvir
Ledipasvir
ABT-267
PPI-678 etc

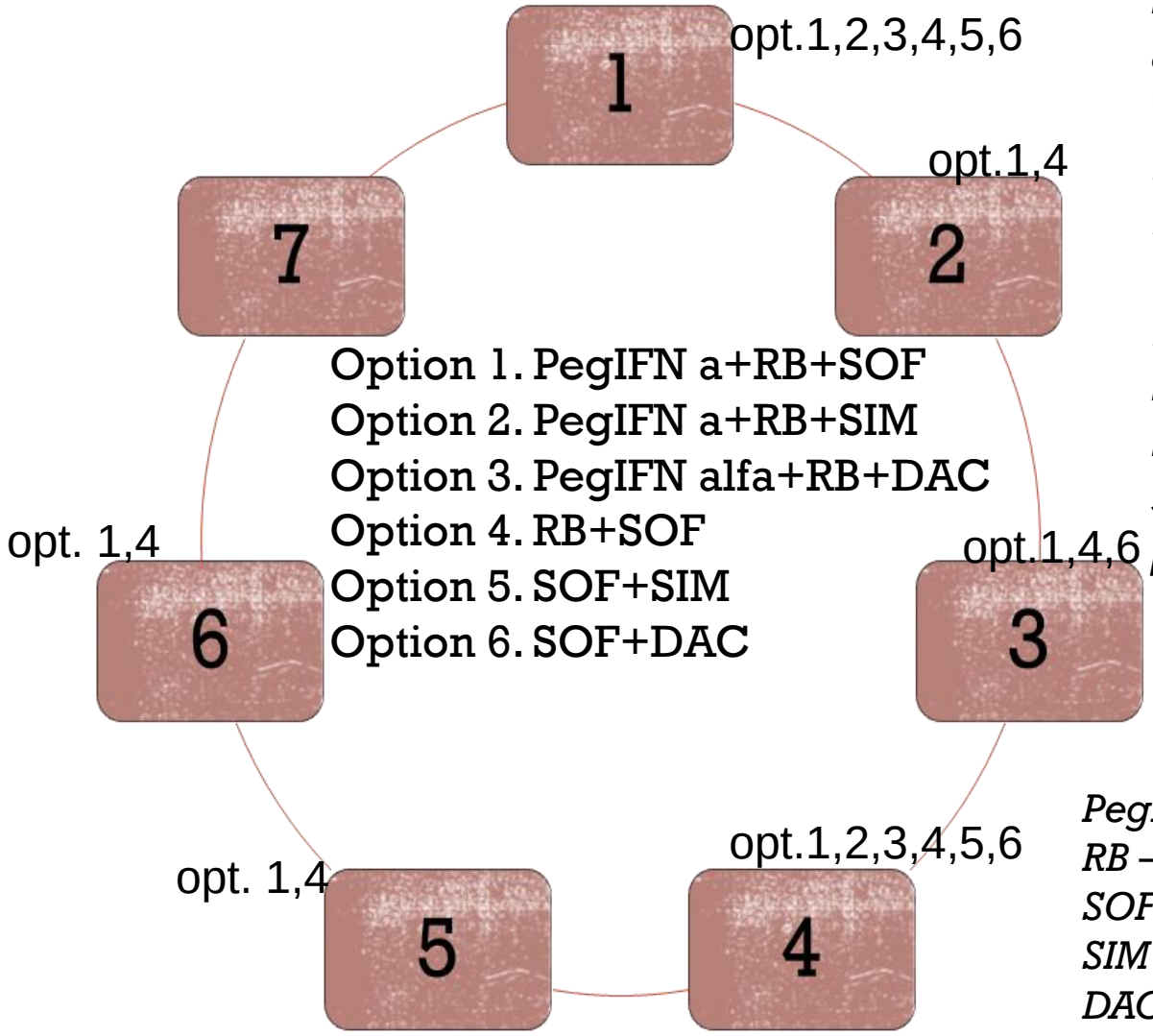
- Intermediate potency
- Low-genotypic coverage
- Low barrier to rezistance

Setrobuvir
Tegobuvir
BI-207127
ABT-333 etc

The combination of:

- ✓ ritonavir-boosted paritaprevir (paritaprevir/r,
- ✓ ombitasvir and dasabuvir
- ✓ SOF-ledipasvir (LDV) fixed-dose combination

THERAPY OF CHRONIC HEPATITIS C



Six treatment options (varying in function of genotypes) are available for patients infected with HCV, including IFN/ribavirin-containing and IFN-free ones.

IFN-free therapy is a major milestone in liver disease that not only eliminates the IFN side effects but it expands patient eligibility for treatment

PegIFN a – PegInterferon alfa 2a, 2b
RB – Ribavirin weighing dose
SOF – Sofosbuvir 400 mg/per day
SIM – Simeprevir 150 mg/per day
DAC – Daclatasvir 60 mg/per day

MONITORING OF TREATMENT EFFICACY

Monitoring of treatment efficacy is based on repeated measurements of HCV RNA levels. A real-time PCR-based assay with a lower limit of detection of <15 IU/ml should be used to monitor HCV RNA levels during and after therapy.

- HCV RNA should be measured at baseline and at weeks 4, 12, 24, 48 and 12 or 24 weeks after the end of therapy – for patients treated with double therapy: **PegIFN** alfa 2 a + **Ribavirin**.
- HCV RNA should be measured at baseline and at weeks 4, 12 (end of treatment), and 12 or 24 weeks after the end of therapy – for patients treated with triple therapy: **PegIFN** + **RB+SOF**.
- HCV RNA should be measured at baseline and at weeks 4, 12, 24 (end of treatment), and 12 or 24 weeks after the end of therapy – for patients (treatment-naïve and prior relapser) treated with triple therapy: **PegIFN** + **RB+SIM**.
- HCV RNA should be measured at baseline and at weeks 4, 10, 24 (end of treatment), and 12 or 24 weeks after the end of therapy – for patients treated with triple therapy: **PegIFN** + **RB+DAC**.
- HCV RNA should be measured at baseline, week 2 (assessment of adherence), week 4, week 12 or 24 (end of treatment), and 12 or 24 weeks after the end of therapy – for patients treated with an Interferon-free regimen (**SOF+SIM**; **SOF+DAC** with/without RB; **SOF+RB**).

PRIMARY PREVENTION STRATEGIES

Primary prevention activities can reduce or eliminate potential risk for HCV transmission from

a) blood, blood components, and plasma derivatives;

b) such high-risk activities as injecting-drug use and sex with multiple partners; and

c) percutaneous exposures to blood in health care and other (i.e., tattooing and body piercing) settings.

Immunization against HCV is not available; therefore, identifying persons at risk but not infected with HCV provides opportunity for counseling on how to reduce their risk for becoming infected.

HCV can survive on environmental surfaces at room temperature for at least 16 hours but not longer than 4 days.

CDC. Recommendations for prevention and control of hepatitis C virus infection and HCV related chronic diseases. MMWR, October 16, 1998, vol 47, No RR-19

SECONDARY PREVENTION

- Secondary prevention activities can reduce risks for chronic disease by identifying HCV-infected people through diagnostic testing and by providing appropriate medical management and antiviral therapy.
- Identification of persons at risk for HCV infection provides opportunity for testing to determine their infection status, medical evaluation to determine their disease status if infected, and antiviral therapy, if appropriate.
- Identification also provides infected people opportunity to obtain information concerning how they can prevent further harm to their liver and prevent transmitting HCV to others.

SECONDARY PREVENTION

Individual institutions should establish policies and procedures for HCV testing of persons after percutaneous or permucosal exposures to blood and ensure that all personnel are familiar with these policies and procedures

Postexposure follow-up of health-care, emergency medical, and public safety workers for hepatitis C virus (HCV) infection:

- For the source, baseline testing for anti-HCV.
- For the person exposed to an HCV-positive source, baseline and follow-up testing including
  - ✓ baseline testing for anti-HCV and ALT activity; and
  - ✓ follow-up testing for anti-HCV (e.g., at 4–6 months) and ALT activity. (If earlier diagnosis of HCV infection is desired, testing for HCV RNA may be performed at 4–6 weeks.)
- Confirmation by supplemental anti-HCV testing of all anti-HCV results reported as positive by enzyme immunoassay.

CDC. Recommendations for follow-up of health-care workers after occupational exposure to hepatitis C virus [Notice to Readers]. MMWR 1997;46:603–6