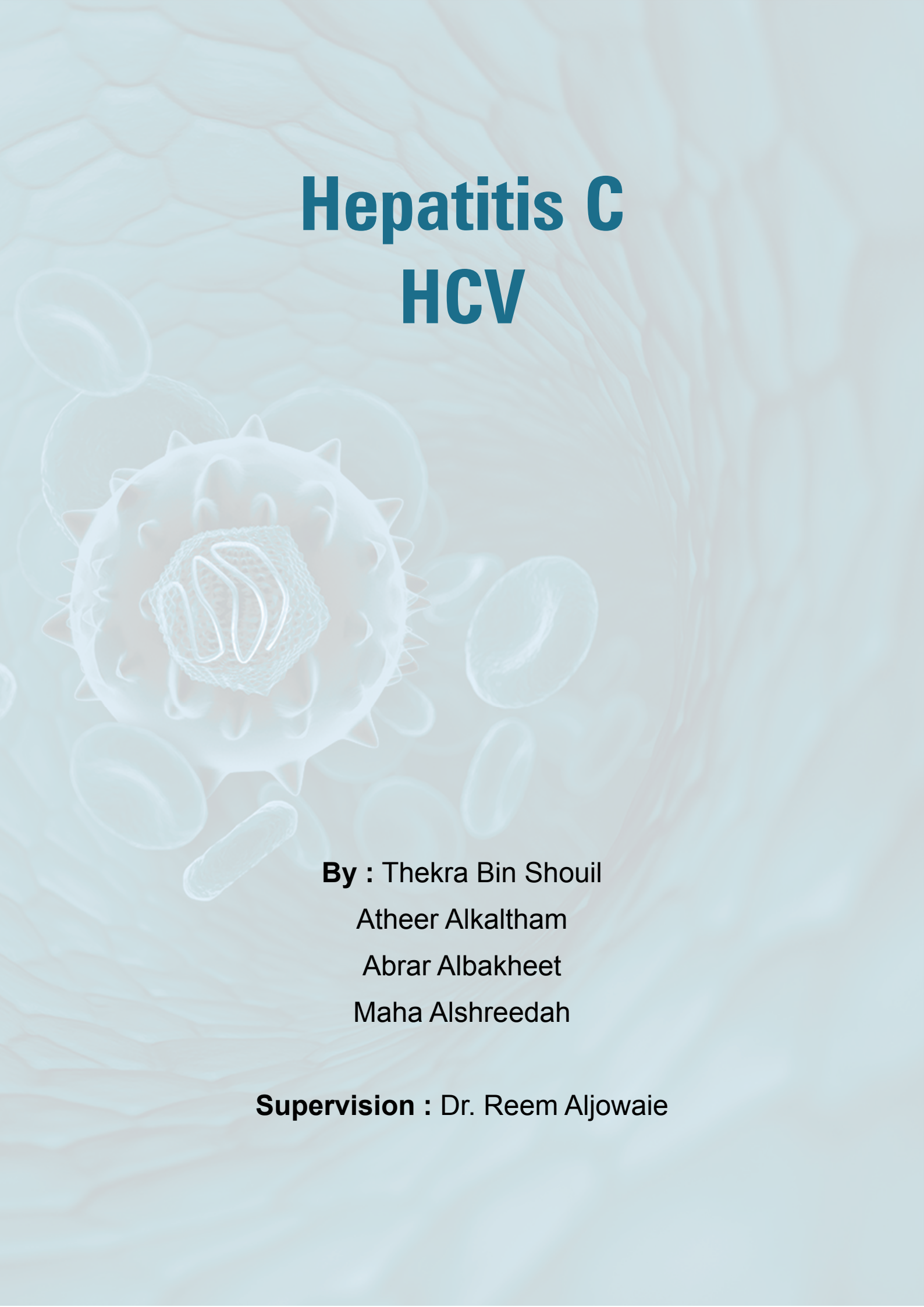
Hepatitis C
HCV



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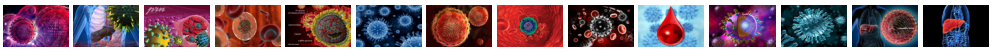

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History of disease

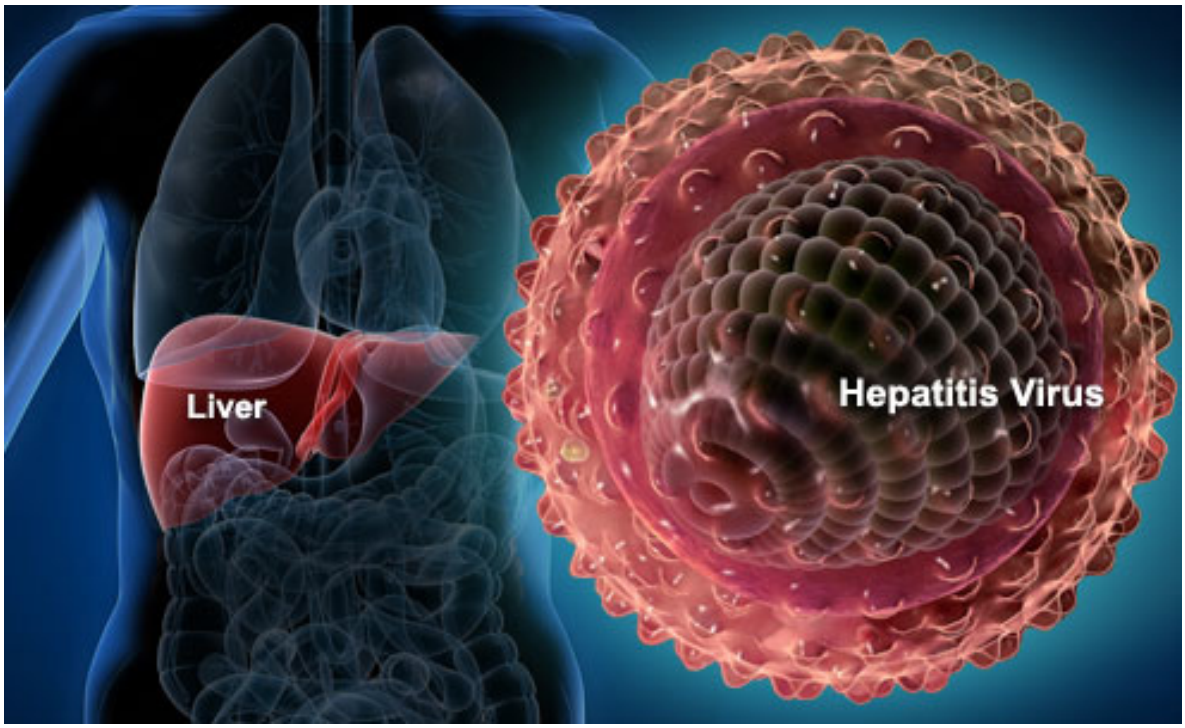
In the mid-1970s, Harvey J. Alter, Chief of the Infectious Disease Section in the Department of Transfusion Medicine at the National Institutes of Health, and his research team demonstrated how most post-transfusion hepatitis cases were not due to hepatitis A or B viruses.

Despite this discovery, international research efforts to identify the virus, initially called non-A, non-B hepatitis (NANBH), failed for the next decade.

In 1987, Michael Houghton, Qui-Lim Choo, and George Kuo at Chiron Corporation, collaborating with Dr. D.W. Bradley at the Centers for Disease Control and Prevention, used a novel molecular cloning approach to identify the unknown organism and develop a diagnostic test.

In 1988, Alter confirmed the virus by verifying its presence in a panel of NANBH specimens. In April 1989, the discovery of HCV was published in two articles in the journal Science.

The discovery led to significant improvements in diagnosis and improved antiviral treatment.



INTRODUCTION

Hepatitis C virus (HCV) is an enveloped virus with a ~ 9.6 kb single-stranded positive sense RNA genome, a member of the *Flaviviridae* family and genus *Hepacivirus*. HCV genome encodes a single polyprotein which is processed co translationally into three structural and seven nonstructural (NS) polypeptides.

HCV core protein forms the capsid, which is surrounded by a lipid bilayer containing the envelope glycoproteins, E1 and E2 on the external surface. These envelope glycoproteins are responsible for initiation of infection in a host cell.

The nonstructural (NS) proteins coordinate the intracellular processes of the virus life cycle. HCV is a major cause of chronic liver disease, with an estimated 180 million people infected worldwide.

Majority of the infected patients (approximately 80 %) develop chronic infection and are at high risk for end stage liver disease progression to cirrhosis and hepatocellular carcinoma (HCC). HCC is a common cancer worldwide and accounts for ~5.6 % of all cancers. It is the fifth common cancer in the world and the third common cause of cancer death.

The incidence of HCC is rising precipitously, primarily as a result of the increasing prevalence of chronic HCV infection and fatty liver disease in the United States. Liver fibrosis is strongly associated with HCC, since approximately 80-90% of HCC cases are arising in cirrhotic livers. HCC development is also linked to alcoholic cirrhosis, nonalcoholic steatohepatitis (NASH). HCV does not integrate into its host genome and has a cytoplasmic life cycle.

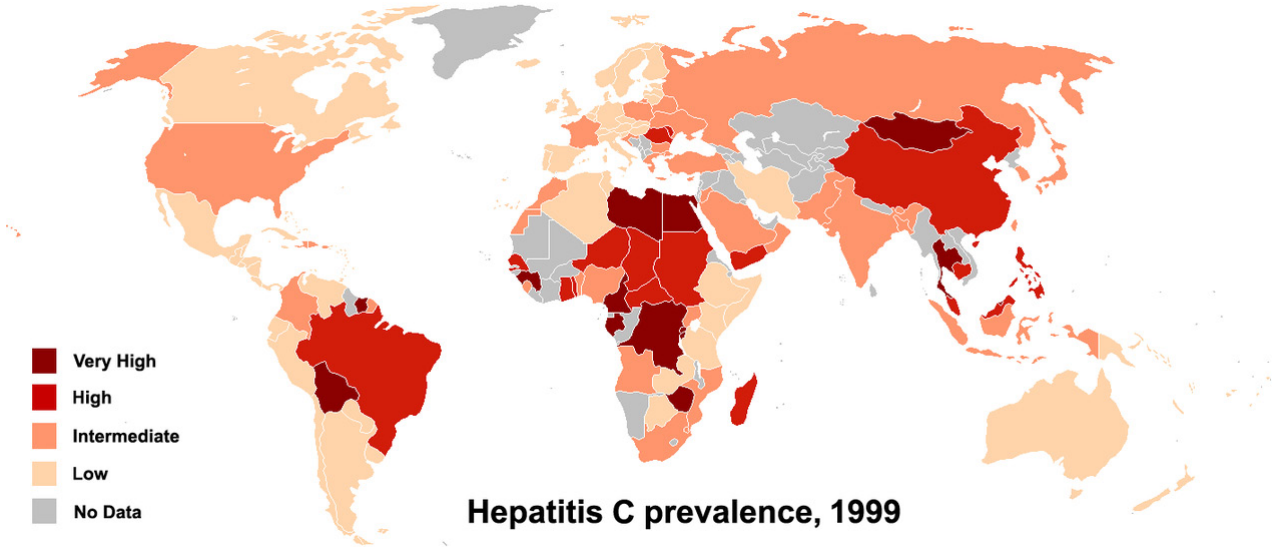
HCC therefore, must involve several indirect mechanisms including the interplay between HCV and host cell genes/proteins for pathological consequences.

(kwon etal., 2014)

Epidemic of disease

It is estimated that 150-200 million people, or ~3% of the world's population, are living with chronic hepatitis C. About 3-4 million people are infected per year, and more than 350,000 people die yearly from hepatitis C-related diseases.

During 2010 it is estimated that 16,000 people died from acute infections while 196,000 deaths occurred from liver cancer secondary to the infection. Rates have increased substantially in the 20th century due to a combination of intravenous drug abuse and reused but poorly sterilized medical equipment.



Hepatitis C prevalence, 1999

Rates are high (>3.5% population infected) in Central and East Asia, North Africa and the Middle East, they are intermediate (1.5%-3.5%) in South and Southeast Asia, sub-Saharan Africa, Andean, Central and Southern Latin America, Caribbean, Oceania, Australasia and Central, Eastern and Western Europe; and they are low (<1.5%) in Asia Pacific, Tropical Latin America and North America.

Prevalence of hepatitis C worldwide in 1999 Among those chronically infected, the risk of cirrhosis after 20 years varies between studies but has been estimated at ~10-15% for men and ~1-5% for women.

The reason for this difference is not known. Once cirrhosis is established, the rate of developing hepatocellular carcinoma is ~1-4% per year. Rates of new infections have decreased in the Western world since the 1990s due to improved screening of blood before transfusion.

In the United States, about 2% of people have hepatitis C, with the number of new cases per year stabilized at 17,000 since 2007.

The number of deaths from hepatitis C has increased to 15,800 in 2008 and by 2007 had overtaken HIV/AIDS as a cause of death in the USA. This mortality rate is expected to increase, as those infected by transfusion before HCV testing become apparent.

In Europe the percentage of people with chronic infections has been estimated to be between 0.13 and 3.26 %.

In England about 160,000 people are chronically infected. Between 2006 and 2011 28,000 about 3%, received treatment.

The total number of people with this infection is higher in some countries in Africa and Asia. Countries with particularly high rates of infection include Egypt (22%), Pakistan (4.8%) and China (3.2%). It is believed that the high prevalence in Egypt is linked to a now-discontinued mass-treatment campaign for schistosomiasis, using improperly sterilized glass syringes.

Epidemic of HIV / HCV

Of the 35 million HIV-infected persons worldwide in 2012 it is estimated that at least 5 million of them had hepatitis C virus infection. Whereas both viruses are transmitted with high efficacy via blood-to-blood contact, HCV is less easily transmitted sexually.

Thus, the prevalence of hepatitis C coinfection within different countries, regions and populations is closely related to the prevalence of blood-borne transmission.

(mainly intravenous drug use) of HIV (Table 1.1).

Table 1.1. - Geographic differences in coinfection rates

	HIV/HCV coinfection rates
Europe, Australia	25%
Belarus, Ukraine	70%
Belgium, Austria, Germany	10-15%
Australia, UK	10-15%
US general population	18-25%
US prison population	65-70%
Chinese blood donors	85%
Thailand	10%
Sub-Saharan Africa	Relatively low

HCV may well be sexually transmitted and should therefore also be taken into account at regular STD screenings. HCV is detected in 4-8% of infants born to HCV-infected mothers. However, in HIV/HCV-coinfected mothers receiving HAART and undergoing cesarean section the risk of HCV transmission is reduced to less than 1%.

The average estimated risk of transmission for hepatitis C in HIV is depicted in Table 1.2.

Table 1.2. - Average estimated risk of transmission for HIV, HCV and HCV/HIV simultaneously

Mode of transmission	HIV	HCV	HCV/HIV coinfection
Perinatal	7-50%	1-7%	1-20%
Sexual contact*	1-3%	<1%	<4%
Needlestick injury	0,3%	<1%	Unknown

*With sexual contact the risk refers to cumulative exposure

Diagnosing HCV in HIV coinfection

The presence of HCV can be confirmed serologically by the detection of antibodies with ELISA testing. Loss of HCV antibodies does not necessarily indicate viral clearance (Cribier

Clinical aspects

Acute hepatitis

After HCV inoculation, there is a variable incubation period. HCV RNA in blood (or the liver) can be detected by PCR within several days to eight weeks. Aminotransferases become elevated approximately 6-12 weeks after exposure (range 1-26 weeks) and they tend to be more than 10-30 times the upper limit of normal. HCV antibodies can be found about 8 weeks after exposure although it may take several months.

However, the majority of newly infected patients will be asymptomatic and have a clinically non-apparent or mild course. Periodic screening for infection may be warranted in certain groups of patients who are at high risk of infection, eg, HIV positive MSM.

Symptoms include malaise, nausea, and right upper quadrant pain. In patients who experience such symptoms, the illness typically lasts for 2-12 weeks. Along with clinical resolution of symptoms, aminotransferases will normalize in about 40% of patients.

Loss of HCV RNA, which indicates a hepatitis C cure, occurs in fewer than 20% of patients. Fulminant hepatic failure due to acute HCV infection may happen in patients with underlying chronic.

Chronic hepatitis

The risk of chronic HCV infection is high. About 75% of patients with acute hepatitis C do not eliminate HCV RNA and progress to chronic infection.

Most of these will have persistently elevated liver enzymes in follow-up. Hepatitis C is considered to be chronic after six months.

Once chronic infection is established, there is a very low rate of spontaneous clearance.

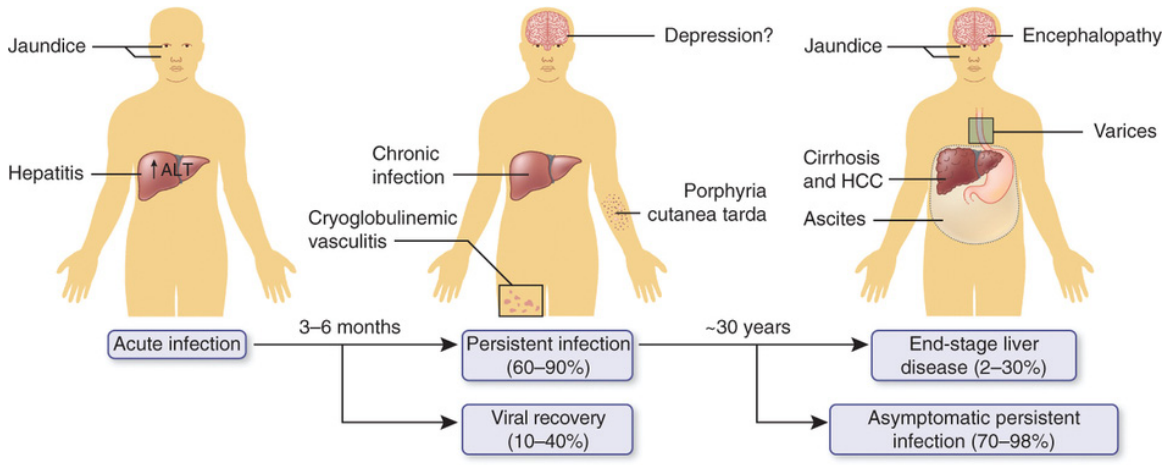
Most patients with chronic infection are asymptomatic or have only mild nonspecific symptoms as long as cirrhosis is not present.

The most frequent complaint is fatigue. Less common manifestations are nausea, weakness, myalgia, arthralgia, and weight loss.

Aminotransferase levels can vary considerably over the natural history of chronic hepatitis C.

Cirrhosis and hepatic decompensation

Complications of hepatitis C occur almost exclusively in patients who have developed cirrhosis. Non-liver-related mortality is higher in cirrhotic patients as well.

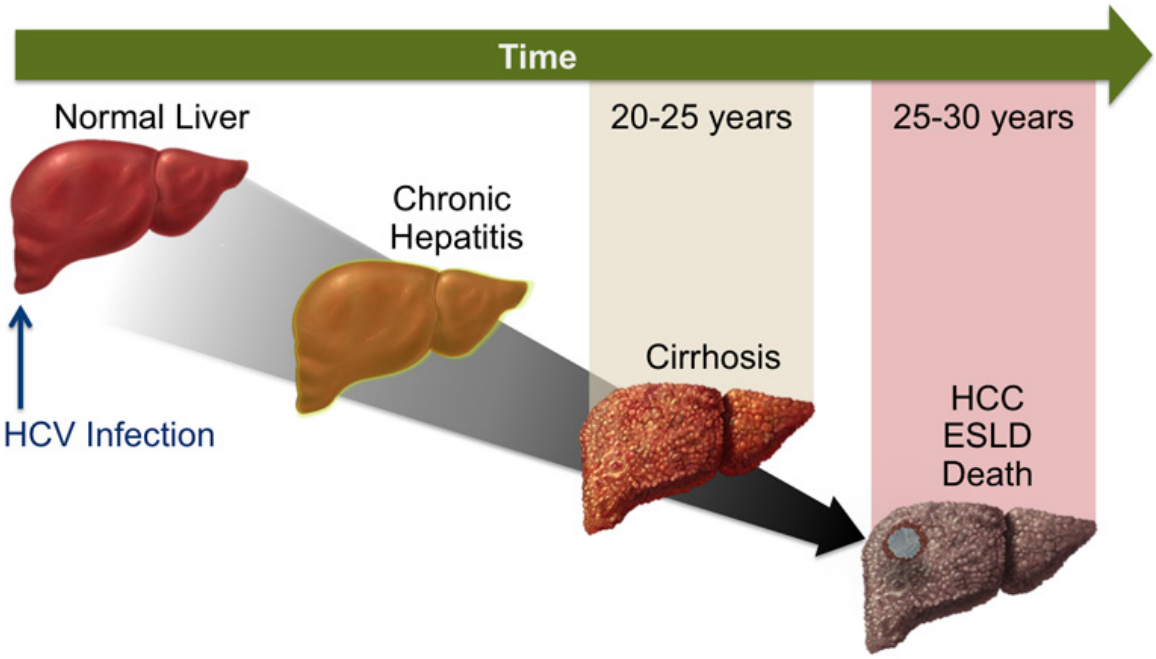


The risk for decompensation is estimated to be close to 5% per year in cirrhotics.

Once decompensation has developed, the 5 year survival rate is roughly 50%.

Liver transplantation is then the only effective therapy.

Hepatocellular carcinoma (HCC) also develops solely in patients with cirrhosis (in contrast to chronic hepatitis B).



Classification of the virus :

Group : IV (+ ss RNA)

Order : Unassigned

Family : Flaviviridae

Genus : Hepacivirus

Species : Hepatitis C virus (HCV)

Structure and Genome :

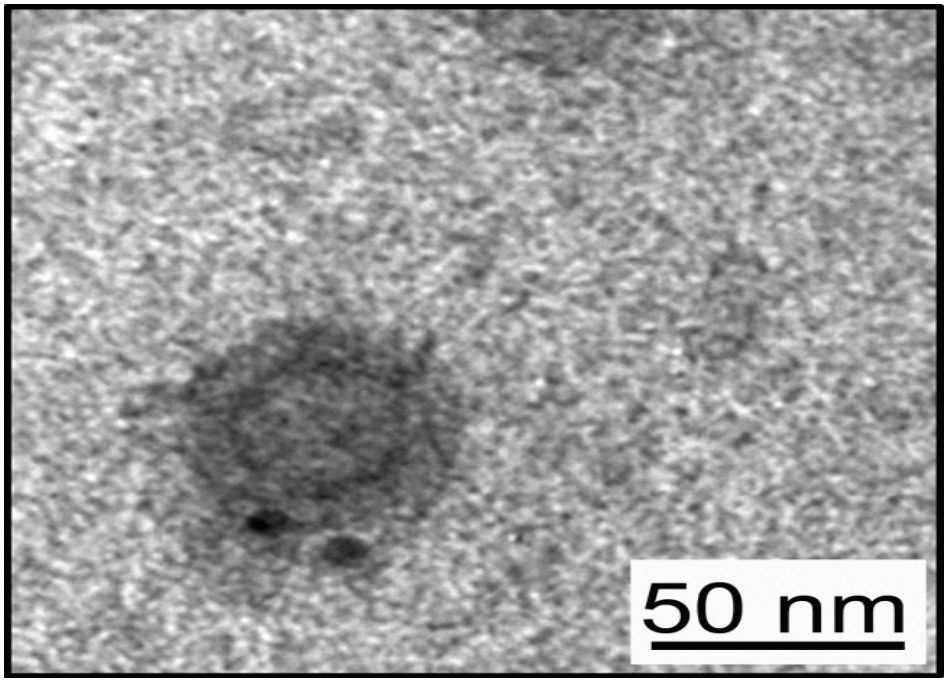
HCV is a small enveloped virus with one single-stranded positive-sense RNA molecule of approximately 9.6 kb. It belongs to the genus hepacivirus, a member of the Flaviviridae family.

The high replication rate of the virus together with the error prone RNA polymerase of HCV is responsible for the large interpatient genetic diversity of HCV strains.

However, the fast growing number of full-length HCV genome sequences will probably lead to even higher numbers of HCV genotypes.

Structural analyses of HCV virions are very limited because for a long time the virus was difficult to cultivate in cell culture Systems, a prerequisite for yielding sufficient virions for electron microscopy.

Moreover, serum-derived virus particles are associated with serum low-density lipoproteins, which makes it difficult to isolate virions from serum/plasma of subjects via centrifugation.



It has been shown that HCV virions isolated from cell culture have a spherical envelope containing tetramers (or dimers of heterodimers) of the HCV E1 and E2 glycoproteins. Inside the virions a spherical structure has been observed representing the nucleocapsid (core) that harbours the viral genome.

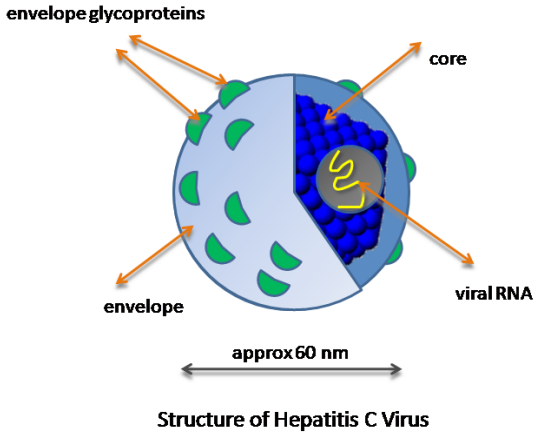


Figure 2.1 Electron micrograph of hepatitis C virus purified from cell culture. Scale: black bar = 50 nanometres

Figure 2.2 Simplified diagram of the structure of the Hepatitis C virus particle

Genome organization

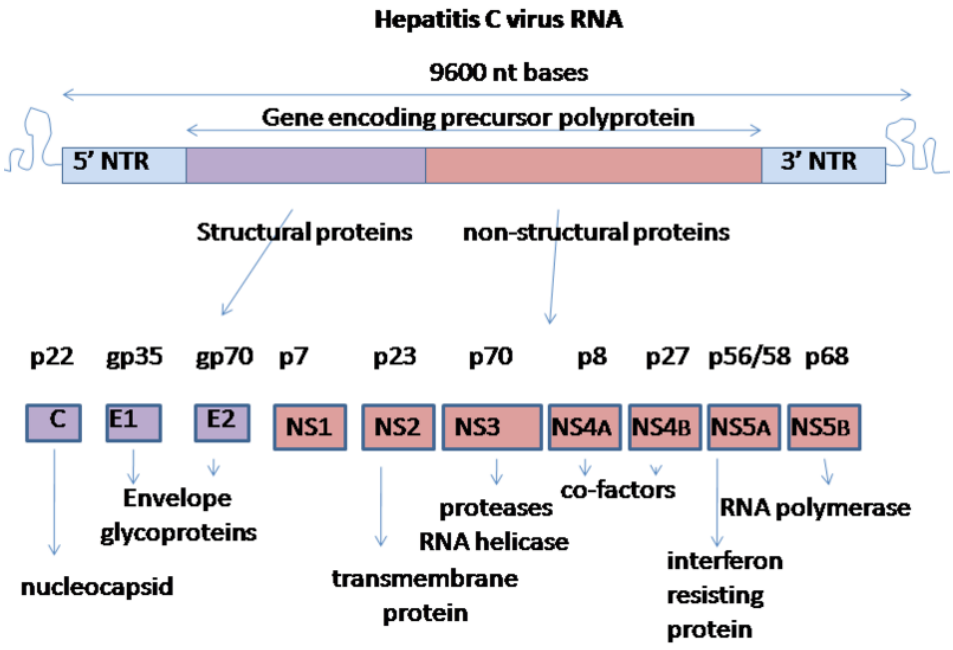
The genome of the hepatitis C virus consists of one 9.6 kb single stranded RNA molecule with positive polarity. Similar to other positive-strand RNA viruses, the genomic RNA of the hepatitis C virus serves as messenger RNA (mRNA) for the translation of viral proteins.

The linear molecule contains a single open reading frame (ORF) coding for a precursor polyprotein of approximately 3000 amino acid residues flanked by two regulatory nontranslated regions (NTR) (Figure 3.1).

Genome organization of Hepatitis C virus Figure 3.1

Table 3.1. - Size and main function of HCV proteins. MW, molecular weight in kd (kilodalton)

Protein	MW	Function
Core	21 kd	Capsid-forming protein. Regulatory functions in translation, RNA replication, and particle assembly.
F-protein or ARFP	16-17 kd	Unknown.
Envelope glycoprotein 1 (E1)	35 kd	Transmembrane glycoprotein in the viral envelope. Adsorption, receptor-mediated endocytosis.
Envelope glycoprotein 2 (E2)	70 kd	Transmembrane glycoprotein in the viral envelope. Adsorption, receptor-mediated endocytosis.
p7	7 kd	Forms an ion-channel in the endoplasmic reticulum. Essential formation of infectious virions.
NS2	21 kd	Portion of the NS2-3 protease which catalyses cleavage of the polyprotein precursor between NS2 and NS3 (Figure 2.1).
NS3	70 kd	NS2-NS3 protease, cleavage of the downstream HCV proteins (Figure 2.1). ATPase/helicase activity, binding and unwinding of viral RNA.
NS4A	4 kd	Cofactor of the NS3-NS4A protease.
NS4B	27 kd	Crucial in HCV replication. Induces membranous web at the ER during HCV RNA replication.
NS5A	56 kd	Multi-functional phosphoprotein. Contains the IFN α sensitivity-determining region (ISDR) that plays a significant role in the response to IFN α-based therapy. Involved in HCV RNA replication, virus assembly and virion release.
NS5B	66 kd	Viral RNA-dependent RNA polymerase. NS5B is an error-prone enzyme that incorporates wrong ribonucleotides at a rate of approximately 10^{-3} per nucleotide per generation.

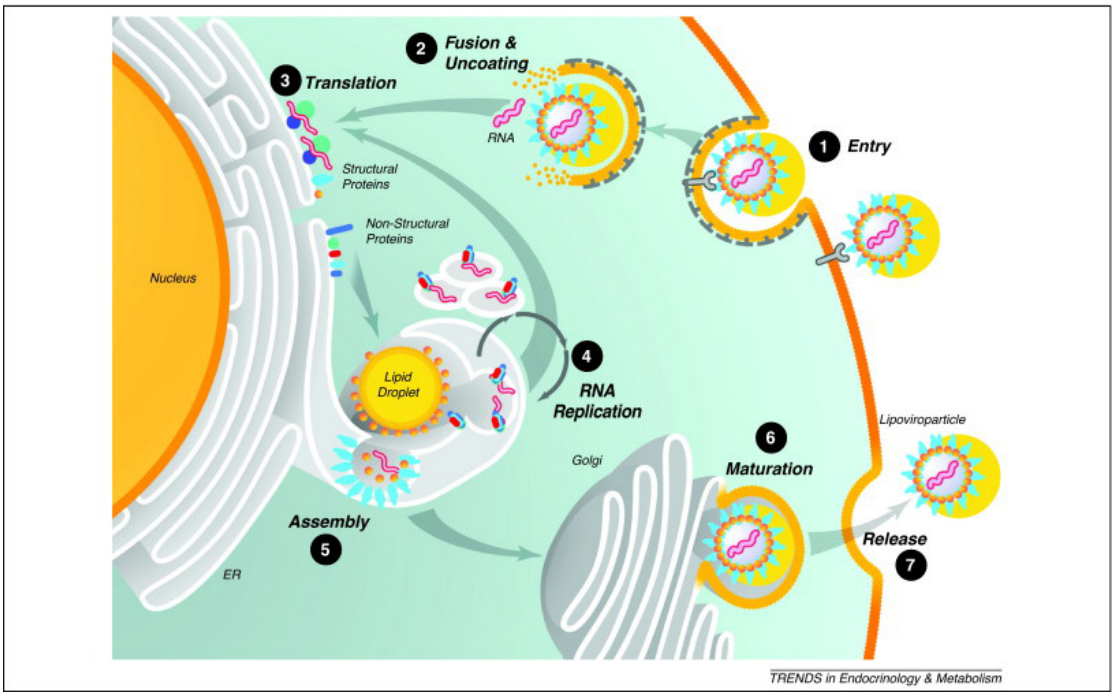


Transmission

Parenteral exposure to hepatitis C is the most efficient means of transmission. The majority of patients infected with HCV in Europe and the United States acquired the disease through intravenous drug use or blood transfusion, which has become rare since routine testing of the blood supply for HCV began.

The following possible routes of infection have been identified in blood donors (in descending order of transmission risk):

- Injection drug use
- Blood transfusion
- Sex with an intravenous drug user
- Having been in jail more than three days
- Religious scarification
- Having been struck or cut with a bloody object
- Pierced ears or body parts
- Immunoglobulin injection



Viral lifecycle

The recent development of small animal models and more efficient in vitro HCV replication systems has offered the opportunity to analyze in detail the different steps of viral replication (Figure 4.1).

Figure 4.1 - Model of the HCV lifecycle. Designations of cellular

HCV +ssRNA, single stranded genomic

HCV RNA with positive polarity; rough ER, rough endoplasmic reticulum;

PM, plasma membrane.

Adsorption and viral entry

A cascade of virus-cell interactions is necessary for the infection of hepatocytes. The precise mechanism of viral entry is complex and still not completely understood. The current model of viral adsorption assumes that HCV is associated with low-density lipoproteins (LDL).

The binding step includes binding of the LDL component to the LDL-receptor (LDL-R) on the cell surface and simultaneous interaction of the viral glycoproteins with cellular glycosaminoglycans (GAG) .This initiation step is followed by consecutive interactions of HCV with scavenger receptor B type I (SR-BI) and the tetraspanin CD81.

Two components of tight junctions, claudin-1 (CLDN1) and occluding (OCLN) have been shown to interact with HCV.

Interaction of HCV with CLDN1 and OCLN seems to induce the internalisation of the virion via clathrin-mediated endocytosis. Finally, it has been shown that two receptor tyrosine kinases (RTKs) and the Niemann–Pick C1-like 1 (NPC1L1) cholesterol uptake receptor are cellular cofactors for HCV entry into hepatocytes.

Subsequent HCV E1-E2 glycoprotein mediation fuses the viral envelope with the endosome membrane.

Despite having identified several host factors that probably interact with the viral glycoproteins, the precise mechanisms of interaction need to be investigated further.

Translation and post-translational processes

As a result of the fusion of the viral envelope and the endosomic membrane, the genomic HCV RNA is released into the cytoplasm of the cell (uncoating). The viral genomic RNA possesses a nontranslated region (NTR) at each terminus. It contains an internal ribosome entry site (IRES) involved in ribosome binding and subsequent initiation of translation.

The synthesized HCV precursor polyprotein is subsequently processed by at least four distinct peptidases.

The cellular signal peptidase (SP) cleaves the N-terminal viral protein's immature core protein, E1, E2, and p7, while the cellular signal peptide peptidase (SPP) is responsible for the cleavage of the E1 signal sequence from the C-terminus of the immature core protein, resulting in the mature form of the core. The E1 and E2 proteins remain within the lumen of the ER where they are subsequently N-glycosylated with E1 having 5 and E2 harbouring 11 putative N-glycosylation sites. The remaining HCV proteins are posttranslationally cleaved by the viral NS2-NS3 and the NS3-NS4A protease, respectively.

HCV RNA replication

The process of HCV RNA replication is poorly understood. The key enzyme for viral RNA replication is NS5B, an RNA-dependent RNA polymerase (RdRp) of HCV. After the RdRp has bound to its template, the NS3 helicase is assumed to unwind putative secondary structures of the template RNA in order to facilitate the synthesis of minus-strand RNA. In turn,

the newly synthesized antisense RNA molecule serves as the template for the synthesis of numerous plus-stranded RNA. The resulting sense RNA may be used subsequently as genomic RNA for HCV progeny as well as for polyprotein translation. Another important viral factor for the formation of the replication complex appears to be NS4B, which is able to induce an ERderived membranous web containing most of the non-structural HCV proteins including NS5B.

Assembly and release

After the viral proteins, glycoproteins, and the genomic HCV RNA have been synthesized, these components have to be arranged in order to produce infectious virions. Viral assembly is a multi-step procedure involving most viral components along with many cellular factors. Recent findings suggest that viral assembly takes place within the endoplasmic reticulum and that lipid droplets are involved in particle formation.

However, the precise mechanisms for the formation and release of infectious HCV particles are still unknown.

Symptoms of HCV

Most people do not notice any symptoms of hepatitis C until the virus has started to damage their liver. Other people have symptoms right away.

Symptoms of hepatitis C can include :

- Feeling tired
- Fever
- Loss of appetite
- Upset stomach
- Nausea and vomiting
- Joint pain

Symptoms of advanced hepatitis C can include :

- Yellowed eyes and skin
- Dark-colored urine
- Light-colored stools
- Easy bruising
- Taking longer forbleeding to stop

Diagnosis

A variety of different tests are used to diagnose hepatitis C. These include :

- HCV Antibody Test
- HCV Viral Load Test or HCV RNA Test
- HCV Genotype / Subtype Test
- Liver Biopsy
-
-

HCV Antibody Tests

When a person is exposed to HCV, the immune system produces proteins called antibodies against the virus. It usually takes the immune system a few weeks to develop enough antibodies to be detected by an antibody test, but it could take as long as six months. There are two commercial antibody tests used to detect HCV antibodies-HCV EIA, (HCV ELISA) and CIA. The most common HCV antibody test is the HCV EIA or ELISA. A positive HCV antibody test will only confirm that someone has been infected with the hepatitis C virus at one time; an HCV RNA viral load test will need to be performed to find out if someone is actively infected with the hepatitis C virus.

The signal-to cut-off ratio was developed to give confidence that an HCV antibody test result is truly positive when an HCV RNA (viral load) test may not be feasible because of the expense or availability. It is important to remember, however, that an HCV RNA test will need to be performed to find out if an individual is currently infected with hepatitis C since some people will spontaneously resolve an acute infection.

In 2011 the FDA approved the OraQuick Rapid Antibody Test that allows for test results to be given after 20 minutes. The FDA also approved the CLIA waiver that allows testing in non-traditional medical environments.

Once people are exposed to hepatitis C, they will retain HCV antibodies for life even if the body is able to eliminate the hepatitis C virus either naturally or the person is cured by medical treatment. It is also important to remember that HCV antibodies do not protect people from infection or re-infection of hepatitis C.

HCV RNA (Viral Load) Tests

A viral load test measures the amount of HCV RNA (genetic material) in the blood. This test is used to confirm active HCV infection and it is also used to guide treatment. There are two types of viral load tests:

- **Qualitative:** Measures the presence of the virus in the blood. This type of test is usually used to confirm initial and chronic infection with HCV. If HCV RNA is detected, a positive result is reported; if HCV RNA is not detected, the test result is negative.

- **Quantitative:** Measures the amount of virus in the blood. This test generally is used for HCV treatment to determine if a patient is responding or has responded to treatment.

Scientific studies have not found any correlation between viral load and disease progression.

A viral load test requires a blood sample.

Genotype / Subtype Test :

There are several strains of hepatitis C called genotypes. These strains are very similar but have enough genetic diversity to classify them into seven major genotypes: 1, 2, 3, 4, 5, 6 and 7. Genotype 1 is the most common genotype (70-75%) in the United States, followed by genotypes 2 and 3 (25-30%). Genotypes 4, 5, 6 and 7 are less prevalent in the United States.

Additionally, a genotype may be further classified into subtypes, such as genotype 1a, 1b, etc. In a study published in 2010 it was found that the genotype distribution in the United States was 62.8% for genotype 1a; 12.4% gen-

otype 3a; 10.9% genotype 1b, and 8.2% for genotype 2b. Other genotypes/ subtypes were found, but the number of patients with the other genotypes was less than 6%.

A genotype / subtype test is generally given to someone who is considering HCV medical treatment and is only performed once since a person's genotype remains the same throughout the course of the disease unless they become re-infected with another genotype. *Genotype and subtype tests require a blood sample.*

Liver Biopsy

Liver biopsies are used to measure the extent of liver damage, including the degree of inflammation, the extent of fibrosis (fibrous tissue), and the general health of the liver. The most common type of liver biopsy is the percutaneous biopsy (through the skin). An ultrasound test might be performed before the procedure to locate the area where the needle is to be inserted and to look for any abnormalities. A medical professional will use a local anesthetic to numb the skin and muscle where the needle will be inserted. A tiny piece of the liver is drawn out through the needle.

The actual procedure to extract the liver specimen only takes a few seconds. After the procedure a patient will be required to lie on their right side (where the needle was inserted) for a few hours so that they can be monitored. About 30-50% of people experience mild to moderate pain. Complications from a liver biopsy rarely occur (1 in 1,000 biopsies or less). If necessary, people can ask their medical professional for a mild tranquilizer before a biopsy and for pain medication after the procedure.

(Franciscus etal., 2015)

The following groups should be tested for HCV :

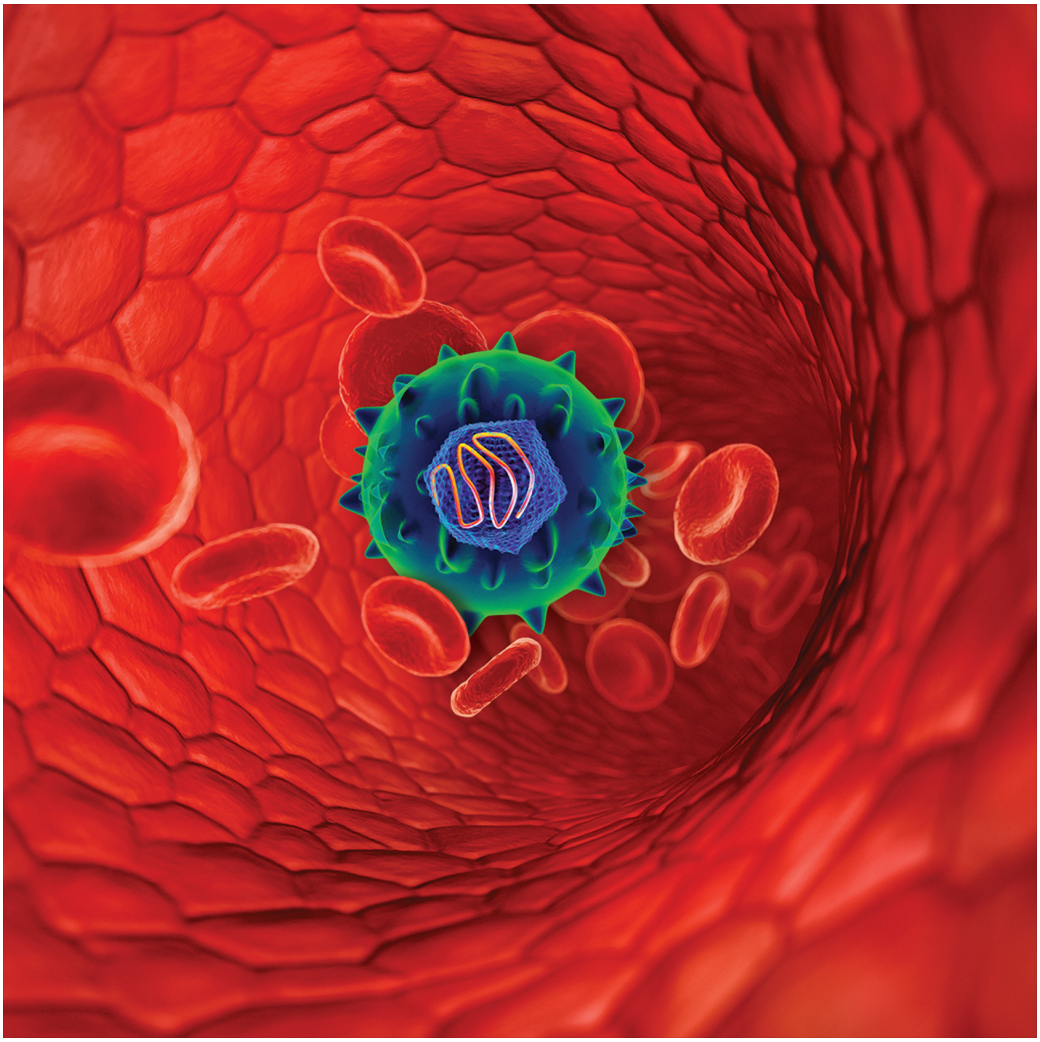
- blood/tissue donors.
- patients on haemodialysis.
- healthcare professionals who intend to pursue a career in a specialty that requires them to perform exposure prone procedures.
- patients with an otherwise unexplained persistently elevated alanine aminotransferase.
- people with a history of injecting drug use.
- people who are human immunodeficiency virus (HIV) positive.
- recipients of blood clotting factor concentrates.
- recipients of blood and blood components, and organ/tissue transplants.
- children whose mother is known to be infected with HCV.
- healthcare professionals following percutaneous or mucous membrane exposure to blood which is, or is suspected to be, infected with HCV.
- people who have received medical or dental treatment in countries where HCV is common and infection control may be poor.
- people who have had tattoos or body piercing in circumstances where infection control procedure is, or is suspected to be, suboptimal.
- people who have had a sexual partner or household contact who is HCV infected.

(*national clinical guideline*., 2013)

Treatment of HCV genotype 4 :

Efficacy of antiviral treatment with PEG-IFN plus ribavirin Overall, data from smaller studies suggest that GT4, 5 and 6 appear easier-to-treat compared to HCV GT1 but the optimal treatment duration is not clear.

In countries where SOF(sofosbuvir) is available, triple therapy of PEG- IFN/ RBV/SOF for 12 weeks is the optimal treatment for GT4-6.



Optimisation of HCV treatment Adherence to therapy :

patients who receive more than 80% of the medication and are treated for more than 80% of the planned duration of treatment are considered adherent. One of the first studies investigating the effect of adherence in PEG-IFN/RBV treatment demonstrated that patients who fulfilled the 80/80 rule had a 63% SVR (sustained viral response) compared to 52% of those with less than 80% adherence.

Another study showed that a cumulative ribavirin dose of more than 60% is important to achieve an SVR. For the triple therapy, adherence to the PI becomes even more important. Reduction of the PI or irregular intake bears the risk of rapid emergence of drug resistance. Dose reduction of the PI is associated with significantly diminished SVR, and is therefore not an option for managing side effects. Thus, the new once-daily DAAs are a step forward in the treatment of HCV infection. An optimal management of PEG- IFN/RBV side effects is essential in order to optimize treatment response.

In the case of anemia, dose reduction of ribavirin is possible and not associated with impaired SVR Another important and new issue is drug interactions that can diminish the effectiveness of the PI or induce toxicity of concomitant medications, which may lead to discontinuation of all drugs. Knowledge about drug interactions is therefore important for the optimal management of patients receiving DAA.

Management of side effects and complications :

Severe side effects may reduce adherence to therapy and may result in dose modifications that result in a less-than-optimal response. IFN, RBV and some of the PI induce side effects that have to be managed, with involvement

of the patient. The IFN-related side effects can be divided into IFN- induced bone marrow suppression, flu-like symptoms, neuropsychiatric disorders, and autoimmune syndromes.

The main problem of RBV is hemolytic anemia. BOC and TLV(Telaprevir) are associated with additional side effects such as rash or dysgeusia and additionally an increase of anemia. SMV and FDV are much better tolerated and importantly not associated with higher rates of anemia. SMV and FDV show an increase in unconjugated bilirubin not related to liver toxicity. FDV requires sun protection; otherwise photosensitivity/phototoxicity can occur more frequently compared to other PIs.

The adverse events in the SOF trials are more or less the PEG-IFN/RBV or RBV side effects. Headache may be more frequent. Overall, side effects result in premature withdrawals from therapy and additional patients require dose modifications during treatment. In trials with dual therapy, the frequency of treatment discontinuations and dose modifications were lower in recent studies, suggesting an improved understanding and management of adverse events. Similar developments can be expected for treatment with PI.

Complication / side effect of using INF as a treatment **:**

Systemic symptoms

Flu-like symptoms, fever, arthralgia and myalgia will usually diminish spontaneously during the first weeks of treatment.

Gastrointestinal disorders. Nausea and loss of appetite, dry mouth.

Weight loss in interferon-based studies is around 6-10% at 48 weeks due to loss of appetite and reduction in calorie intake.

Asthenia and fatigue are frequent complaints that usually increase slowly

in intensity over the first couple weeks of therapy. Asthenia is also reported by patients without marked anemia. In these patients hypothyroidism needs to be excluded.

Treatment in patients without an underlying complication such as anemia, depression or hypothyroidism is difficult. For chronic fatigue, currently available data does not point to specific treatment recommendations.

Cough is frequently reported and is most probably due to edema of the mucosa of the respiratory system.

Advanced, not wellcontrolled asthma bronchiale may be a contraindication for hepatitis C therapy.

Dyspnea is another frequent complaint. Hypothyroidism and hyperthyroidism are seen, possibly due to an interferon-induced thyroiditis or the induction of thyroid antibodies.

Premature termination of interferon-based therapy is usually not necessary.

Psychiatric adverse events

The most common IFN α-induced psychiatric adverse events are outlined in Tables 6.1. Most hepatology trials are only monitored for “major depression” without using depression scales, leading to an underreporting of mild to moderate depressive episodes.

Hematologic and immunologic effects

In general the incidence of serious infections is low (<5%) in patients on interferon-based therapy. In general G-CSF can be used to correct neutropenia, but it has not been studied for this purpose and its use is off-label.

For mild to moderate thrombocytopenia in advanced liver Fibrosis, eltrombopag may be used cautiously.

Skin disorders

Skin disorders such as lichen ruber planus, necrotising vasculitis or porphyrea cutanea tarda are associated with hepatitis C infection. Local skin reactions to the injection of pegylated interferon are common.

Repeated injections at the same site may cause ulcers and should be avoided.

Hair loss is frequent, usually appearing after the first months of therapy and continuing for some weeks after the cessation of therapy but is usually fully reversible, although the structure of the hair may be different after therapy. Alopecia is very rare.

Many other side effects are outlined in Tables 6.2 and 6.3.

Treatment of hepatitis C in special populations :

Patients with acute hepatitis C :

The goal of acute hepatitis C treatment is the prevention of persistent HCV infection. The natural rate of HCV evolution to a chronic state is 50-90%. As a vaccine is not yet available, early treatment of acute HCV infection with IFN is the only option to prevent persistent HCV infection.

Table 6.1. - Incidence of the most reported IFN a-induced psychiatric side effects

	Incidence
Fatigue	40-80%
Sleep disturbances	20-45%
Irritability	20-45%
Cognitive disturbances with impairment of concentration and memory	20-30%
Depressive episodes	20-70%
- Mild	40-70%
- Moderate	20-40%
- Severe	5-20%
Delirium, psychosis	1-3%
Suicidal thoughts	3-10%
Suicidal attempts	0-0.02%

Table 6.2. - What to expect and what to do (I)

Symptom	When/why/ Duration (D)	Treatments	Caution
Flu-like symptoms	Immediately post-IFN injection / D: 3 days	<2 g paracetamol, NSAIDs	Low platelets, liver toxicity
Loss of appetite		Pre-RBV: metoclopramide, domperidone	
Dry mouth	With RBV/ D: May continue post-therapy		
Weight loss	During treatment/ D: On treatment	Reversible on discontinuation	6-10% loss over 48 wks
Anemia, asthenia, fatigue	First few weeks of treatment/ D: Increases over time	Erythropoietin, reduce RBV dosage, red blood cell transfusion, antidepressants, tryptophan, odanestron	
depression			
Hemolytic anemia	RBV	RBV dose reduction RBC transfusion Erythropoetin[7]	
Thrombo-cytopenia	In advanced liver fibrosis	IFN dose reduction Eltrombopag[8]	
Dry skin, itching, eczema, exacerbation of psoriasis	HCV, IFN, RBV	Urea ointments, steroids	Involve dermatologist May continue post-treatment
Hypersensitivity	PEG-IFN		Anecdotal

1. Schaefer 2005. 2. Krauss 2008. 3. Krauss 2001. 4. Valentine 1995. 5. Schaefer & Mauss 2008. 6. Schaefer 2007b; Schaefer 2003; Pariante 2002. 7. Afdahl 2004; Pockros 2004; Shiffman 2007. 8. McHutchinson 2007.

Table 6.2. - What to expect and what to do (II)

Symptom	When/why/ Duration (D)	Treatments	Caution
Hypothyroidism	Can occur at any time	L-thyroxin replacement therapy	
Cough	Edema of resp. mucosa / D: On treatment	Local therapy of fluticasone or budesonide	
Hypothyroidism	IFN / 3-10% reversible on discontinuation	Substitution of thyroid hormone	
Hyper-thyroidism	1-3%	B-blockers, carbimazole	
Psychiatric effects	On IFN, pre-existing[1] or not[6]	SSRIs (citalopram[2], paroxetin) Mirtazapine[3] Nortriptyline[4] Tricyclics (doxepine)	Tricyclics are 2nd choice – interactions and delirium, heart, liver complications
Agitation/ aggression		Antipsychotics (risperidone, olanzapine)	Monitor with psychiatrist
Severe sleep disturbances, irritability,		Benzodiazapines[5], zolpidem, trimipramine	[5]Can induce addiction

Patients with normal aminotransferase levels :

Approximately 30% of patients with chronic hepatitis C maintain persistently normal alanine aminotransferase (ALT) levels despite having detectable HCV RNA in serum. These patients have generally mild liver disease and show a slow progression to cirrhosis. However, up to one third of patients with normal ALT can present with significant liver fibrosis necessitating an effective treatment.

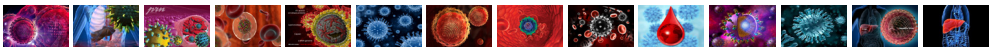
Genotype :

HCV is heterogeneous with an enormous genomic sequence variability due to its rapid replication cycle producing 1012 virions a day and the low fidelity of the HCV RNA polymerase. Seven genotypes (1-7), multiple subtypes (a, b, c…) and most recently a seventh HCV genotype have been characterized. Within one subtype, numerous quasispecies exist and may emerge during treatment with specific antivirals. Because the currently recommended treatment durations and ribavirin doses depend on the HCV genotype, HCV genotyping is mandatory in every patient considering antiviral therapy.

Importantly, GT4, 5, and 6 are very common in areas where chronic hepatitis C is highly prevalent.

For example, HCV GT4 is most prevalent in the Middle East and Egypt where it accounts for >80% of all HCV cases (approximately 34 million people).

HCV GT5 is most prevalent in South Africa, and genotype 6 in Southeast Asia



Moreover, the extent of viral diversification of HCV strains within a single HCV positive individual increases significantly over time resulting in the development of quasispecies.

A very recent study revealed the presence of at least 7 different HCV genotypes and 67 subtypes, respectively.

Recent discoveries :

- New drugs
- NS3/4A protease inhibitors
- Nucleoside analog NS5B polymerase inhibitors (NI)
- Non-nucleoside NS5B polymerase inhibitors (NNI)
- NS5A inhibitors
- Host targeting agents

Prevention

Primary prevention

There is no vaccine for hepatitis C, therefore prevention of HCV infection depends upon reducing the risk of exposure to the virus in health-care settings, in higher risk populations, for example, people who inject drugs, and through sexual contact.

The following list provides a limited example of primary prevention interventions recommended by WHO :

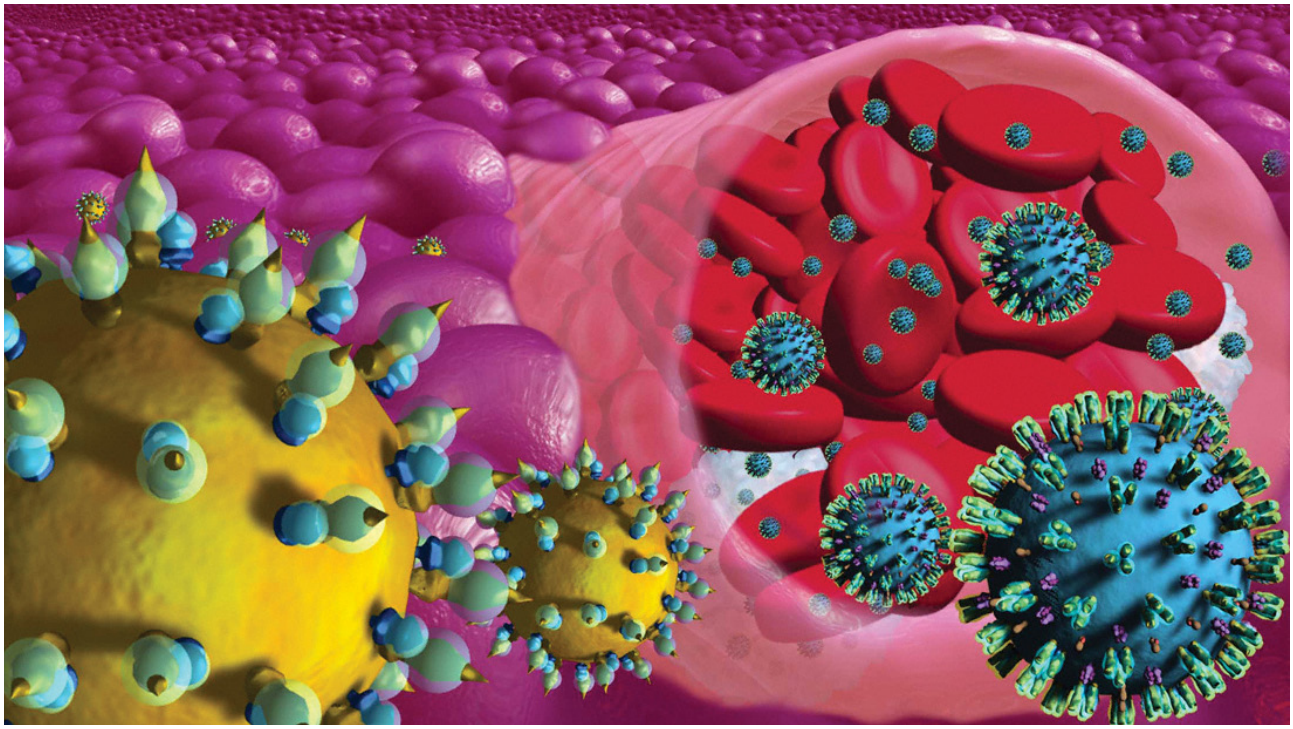
- hand hygiene: including surgical hand preparation, hand washing and use of gloves.
- safe handling and disposal of sharps and waste.

- provision of comprehensive harm-reduction services to people who inject drugs including sterile injecting equipment.
- testing of donated blood for hepatitis B and C (as well as HIV and syphilis).
- training of health personnel
-

Secondary and tertiary prevention

For people infected with the hepatitis C virus, WHO recommends :

- education and counselling on options for care and treatment.
- immunization with the hepatitis A and B vaccines to prevent coinfection from these hepatitis viruses to protect their liver.
- early and appropriate medical management including antiviral therapy if appropriate and regular monitoring for early diagnosis of chronic liver disease.



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