Port Said University

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Evaluation of Sofosbuvir as Anti-Virus C Agent

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Introduction

About Viruses

❖ Structure and Function

Viruses are small obligate intracellular parasites, which by definition contain either a RNA or DNA genome surrounded by a protective, virus-coded protein coat. Viruses may be viewed as mobile genetic elements, most probably of cellular origin and characterized by a long co-evolution of virus and host. For propagation viruses depend on specialized host cells supplying the complex metabolic and biosynthetic machinery of eukaryotic or prokaryotic cells. A complete virus particle is called a virion. The main function of the virion is to deliver its DNA or RNA genome into the host cell so that the genome can be expressed (transcribed and translated) by the host cell. The viral genome, often with associated basic proteins, is packaged inside a symmetric protein capsid. The nucleic acid-associated protein, called nucleoprotein, together with the genome, forms the nucleocapsid. In enveloped viruses, the nucleocapsid is surrounded by a lipid bilayer derived from the modified host cell membrane and studded with an outer layer of virus envelope glycoproteins [1]

A virus structure can be one of the following: icosahedral, enveloped The most well known examples of enveloped viruses are the influenza virus, Hepatitis C and HIV) , complex or helical .[2]

Virus Structure

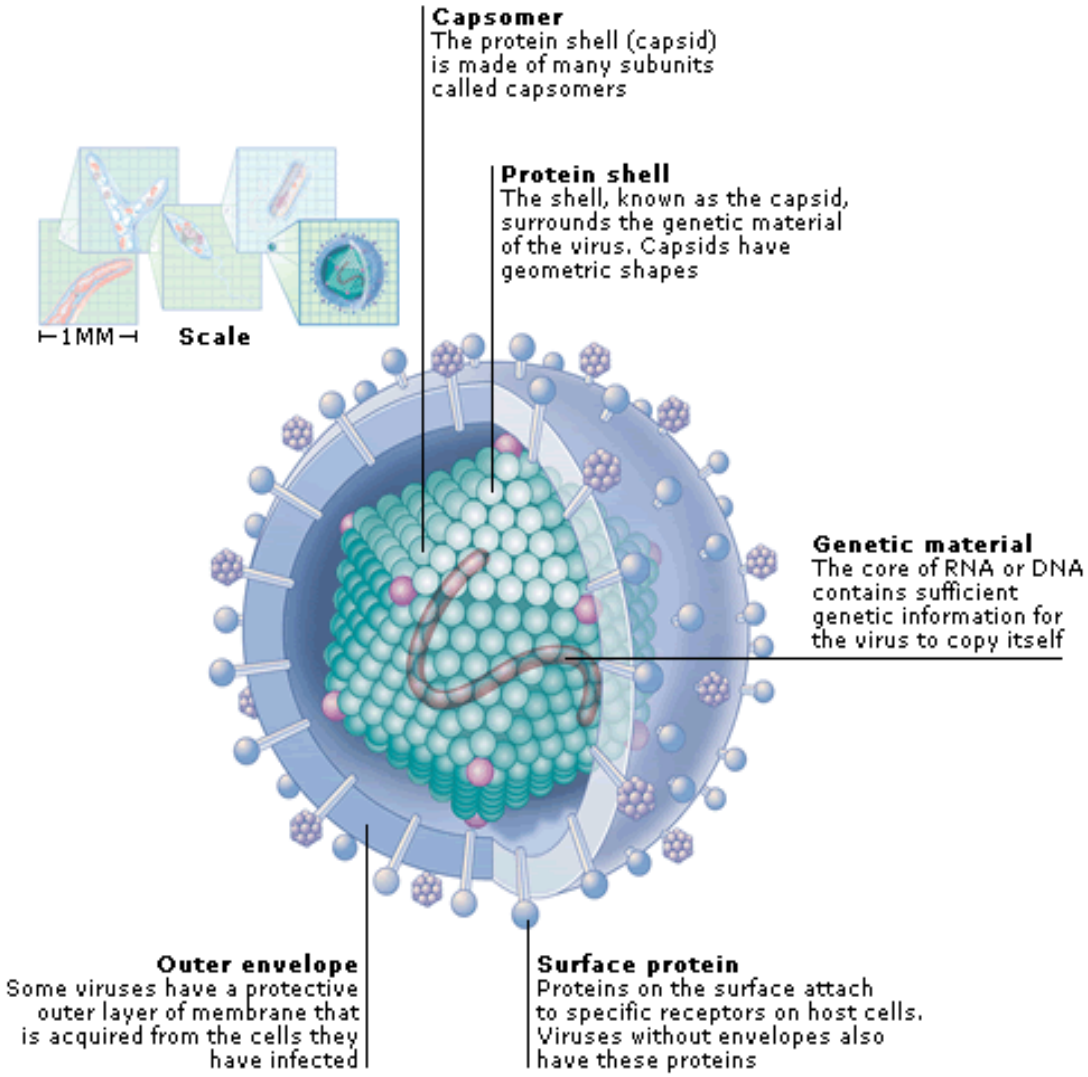


Figure (1)

The structure of Virus [3]

Hepatitis is an inflammation of the liver, most commonly caused by a viral infection. There are five main hepatitis viruses, referred to as types A, B, C, D and E. These five types are of greatest concern because of the burden of illness and death they cause and the potential for outbreaks and epidemic spread. In particular, types B and C lead to chronic disease in hundreds of millions of people and, together, are the most common cause of liver cirrhosis and cancer [4].

Hepatitis A and E are typically caused by ingestion of contaminated food or water. Hepatitis B, C and D usually occur as a result of parenteral contact with infected body fluids. Common modes of transmission for these viruses include receipt of contaminated blood or blood products, invasive medical procedures using contaminated equipment and for hepatitis B transmission from mother to baby at birth, from family member to child, and also by sexual contact [5].

The prevalence of HCV infection varies throughout the world. For example, Frank et al reported in 2000 that Egypt had the highest number of reported infections.[6] This led to a mean prevalence of HCV antibodies in persons in Egypt of 22%.

In the United States, the incidence of acute HCV infection has sharply decreased during the past decade. Its prevalence remains high (approximately 2.7 million Americans), however, because chronic hepatitis C (CHC) infection develops in approximately 75% of patients after acute infection.

According to the US Centers for Disease Control and Prevention (CDC), an estimated 1.8% of the US population is positive for HCV antibodies. Because 3 of 4 seropositive persons are also viremic, this corresponds to an estimated 2.7 million people with active HCV infection nationwide.

Infection due to HCV accounts for 20% of all cases of acute hepatitis, an estimated 30,000 new acute infections, and 8000-10,000 deaths each year in the United States. HCV has rapidly surpassed HIV as a cause of death in the US. An examination of nearly 22 million death records over 9 years revealed an HCV mortality rate of 4.58 deaths per 100,000 people per year and an HIV mortality rate of 4.16 deaths per 100,000 people. Almost 75% of HCV deaths occurred among adults between the ages of 45 and 64.[6]

Most patients infected with HCV have chronic liver disease, which can progress to cirrhosis and hepatocellular carcinoma (HCC). Chronic infection with HCV is one of the most important causes of chronic liver disease, according to a report by Davis et al, the most common indication for orthotopic liver transplantation (OLT) in the United States.[7]

Most patients with acute and chronic infection are asymptomatic. Patients and health care providers may detect no indications of the conditions for long periods; however, chronic hepatitis C infection and chronic active hepatitis are slowly progressive diseases and result in severe morbidity in 20-30% of infected persons. Astute observation and integration of

findings of extra hepatic symptoms, signs and disease are often the first clues to underlying HCV infection.[6]

Hepatitis C is a liver disease caused by the hepatitis C virus, the virus can cause both acute and chronic hepatitis infection, ranging in severity from a mild illness lasting a few weeks to a serious, lifelong illness [4]

Acute infection may occur with limited or no symptoms, or may include symptoms such as jaundice (yellowing of the skin and eyes), dark urine, extreme fatigue, nausea, vomiting and abdominal pain [8]

Although acute hepatitis C virus (HCV) infection is usually mild, chronic hepatitis results in at least 75% of patients. [9] While liver enzyme levels may be in the reference range, the presence of persistent HCV-RNA levels discloses chronic infection. Biopsy samples of the liver may reveal chronic liver disease in patients. Cirrhosis develops in 20-50% of patients with chronic hepatitis C infection. Liver failure and hepatocellular carcinoma can eventually result. Hepatocellular carcinoma occurs in 11-19% of patients.

Hepatitis C is found worldwide. The most affected regions are Africa and Central and East Asia. Depending on the country, hepatitis C infection can be concentrated in certain populations (for example, among people who inject drugs) and/or in general populations. There are multiple strains (or genotypes) of the HCV virus and their distribution varies by region.

Hepatitis C virus is a blood borne virus and the most common modes of infection are through unsafe injection practices, inadequate sterilization of medical equipment and the transfusion of unscreened blood and blood products [4].

Hepatitis C is transmitted or spread when the blood from a Hepatitis C infected person enters the bloodstream of someone who is not infected. Today, most people become infected with HCV by sharing needles or other equipment to inject drugs. Before 1992, when screening donated blood and organs for Hepatitis C was not standard in the United States, the disease was commonly spread through blood transfusions and organ transplants.

Hepatitis C can be transmitted through sex between a man and a woman, but the risk is low. Therefore, condoms are not routinely recommended for monogamous, heterosexual couples. The risk of Hepatitis C transmission is higher with unprotected anal sex between two men; using condoms will decrease this risk. All people with multiple sex partners should use condoms to reduce the risk of getting Hepatitis C and/or HIV.

Hepatitis C may be spread if there is a breakdown in the skin or lining of the mouth. Therefore, sharing of toothbrushes, razor blades and nail clippers is not recommended. [10]

Hepatitis C transmission is not contagious. You cannot get or give, Hepatitis C by: Kissing , Hugging, Holding hands ,Casual contact , Sneezing ,Coughing, Sharing eating utensils ,Sharing food or drink or Breastfeeding (unless nipples are cracked and bleeding) . [10]

Antiviral medicines can cure approximately 90% of persons with hepatitis C infection, thereby reducing the risk of death from liver cancer and cirrhosis, but access to diagnosis and treatment is low. There is currently no vaccine for hepatitis C, however research in this area is ongoing.

The incubation period varies from 2-26 weeks. Liver enzyme tests may range from being elevated to being normal for weeks to as long as a year. The virus is in the blood and may be causing liver cell damage, and the infected person can transmit the disease to others. [11]

Sofusbuvir has pangenotypic HCV activity, but FDA approval for genotypes 1, 2, 3, and 4. Sofosbuvir is effective in treatment-naive and treatment-experienced patients, including those with HIV-coinfection, compensated cirrhosis, or hepatocellular carcinoma meeting Milan criteria awaiting liver transplantation. Sofosbuvir has been studied in a wide range of populations including persons 65 and older, persons with mild to moderate renal impairment. Sofosbuvir is used in clincial practice with other approved agents, including simeprevir or daclatasvir.

Sofosbuvir has been a breakthrough new medication for the treatment of patients with chronic hepatitis C. Sofosbuvir has a number of ideal properties, including pangenotypic activity, once daily dosing, no meal restrictions, few adverse effects, minimal drug-drug interactions, high genetic barrier to resistance, good safety and efficacy in patients with advanced liver disease, and excellent sustained virologic response rates in patients with unfavorable baseline characteristics. In the new AASLD-

IDSA hepatitis C guidelines, the combination of sofosbuvir plus peginterferon plus ribavirin is the recommended regimen for patients with genotype 1,4,5, and 6 infection. In addition, for patients ineligible to receive interferon, sofosbuvir plus simeprevir (with or without ribavirin) is recommended, but this combination is not an FDA-approved regimen. For patients with genotype 2 or 3, the combination of sofosbuvir plus ribavirin is recommended. The use of sofosbuvir in combination with ribavirin provides the first FDA approved all oral therapy for hepatitis C. Of note, the activity against genotype 3 appears less than with genotype 2 and treatment of genotype 3 infection requires a longer all-oral course of treatment than with genotype 2. Sofosbuvir currently has a major role in the treatment of chronic HCV infection, but the extraordinarily high cost has served as a major barrier for more widespread use and treatment of persons with chronic HCV infection [12].

But there's some very good news, in the last few years, we have witnessed extraordinary progress in developing new drug treatments for hepatitis C. Sofosbuvir (Sovaldi) and sofosbuvir combined with ledipasvir (Harvoni) are two well-known examples of these new drug therapies. Another new combination drug, sofosbuvir and velpatasvir, which was recently described in *The New England Journal of Medicine*, is extremely effective against most forms of hepatitis C virus and will become the standard therapy when this combination is approved by the FDA [13]

Sofosbuvir is indicated for treatment of patients with chronic HCV

- Genotype 1 or 4: sofosbuvir plus peginterferon-alfa plus ribavirin for 12 weeks
- Genotype 2: sofosbuvir plus ribavirin for 12 weeks

- Genotype 3: sofosbuvir plus ribavirin for 24 weeks

For patients with genotype 1 HCV who are not eligible to receive interferon: sofosbuvir plus ribavirin for 24 weeks can be considered.

For patients with HCV and hepatocellular carcinoma awaiting liver transplantation: sofosbuvir plus ribavirin for a duration of up to 48 weeks or until liver transplantation, whichever occurs first [12].

Hepatitis C

Hepatitis C is an infectious disease affecting primarily the liver, caused by the hepatitis C virus [14]. HCV is the major agent of chronic liver disease worldwide, affecting an estimated 3% of the population [15] .

It is difficult for the human immune system to eliminate hepatitis C from the body, and infection with hepatitis C usually becomes chronic. Chronic infection with hepatitis C damages the liver and can cause liver failure, when the virus first enters the body there usually are no symptoms, so this number is an estimate. Up to 85% of newly-infected people fail to eliminate the virus and become chronically infected. In the U.S., more than three million people are chronically infected with hepatitis C. Infection is most commonly detected among people who are 40 to 60 years of age, Hepatitis C infection is the leading cause of liver transplantation in the U.S. and is a risk factor for liver cancer [16] .

Epidemiology

Hepatitis C virus (HCV), is the most widespread blood carried disease in the US, with an estimated 3.2 million persons chronically infected [17]. Globally, 130-150 million have chronic infection [18]. Unfortunately, 50% of those infected are unaware [19].

Hepatitis C virus (HCV) causes both acute and chronic infection. Acute HCV infection is usually asymptomatic, and is only very rarely associated with life-threatening disease. About 15–45% of infected persons spontaneously clear the virus within 6 months of infection without any treatment.

The remaining 55–85% of persons will develop chronic HCV infection. Of those with chronic HCV infection, the risk of cirrhosis of the liver is 15–30% within 20 years.

Egypt has the highest prevalence of hepatitis C virus (HCV) in the world, estimated nationally at 14.7%. Our study's objective was to delineate the evidence on the epidemiology of HCV infection among the different population groups in Egypt, and to draw analytical inferences about the nature of HCV transmission in this country [20].

We identified 150 relevant records, four of which were incidence studies. HCV incidence ranged from 0.8 to 6.8 per 1,000 person-years. Overall, HCV prevalence among pregnant women ranged between 5-15%, among blood donors between 5-25%, and among other general population groups between 0-40%. HCV prevalence among multi-transfused patients ranged between 10-55%, among dialysis patients between 50-90%, and among other high risk populations between 10% and 85%. HCV prevalence varied widely among other clinical populations and populations at intermediate risk. Risk factors appear to be parenteral anti-schistosomal therapy, injections, transfusions, and surgical procedures, among others. Results of our time trend analysis suggest that there is no evidence of a statistically significant decline in

Antiviral medicines can cure approximately 90% of persons with hepatitis C infection, thereby reducing the risk of death from liver cancer and cirrhosis, but access to diagnosis and treatment is low. There is currently no vaccine for hepatitis C, however research in this area is ongoing

What causes of hepatitis C?

HCV is caused by a virus transmitted through blood-to-blood contact.[10]

A virus is a microscopic, infectious particle that contains nucleic acid (genetic instruction DNA or RNA). HCV is an RNA virus. Viruses lie in a dormant state until entering the living cell of a host, where it will then hijack the cell's hardware to replicate itself.

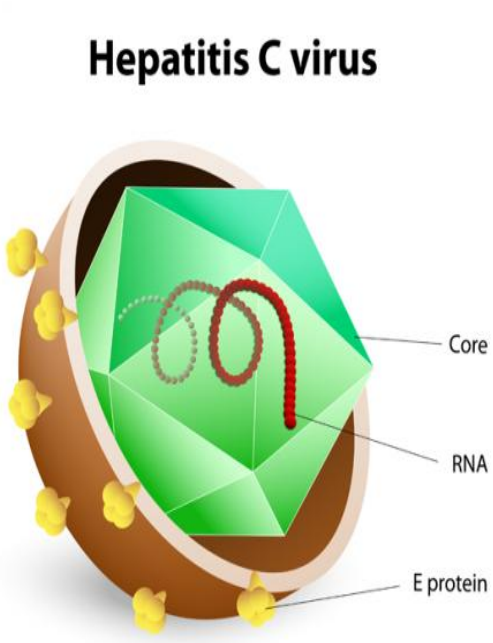


Figure (2)

Hepatitis C is an RNA virus - a virus that has RNA (ribonucleic acid) as its genetic material [21].

Research suggests that chronic HCV infection consists of millions, or billions of actual viruses circulating within the body. At least six distinct HCV genotypes (named 1-6) and 70 subtypes have been identified [22].

HCV is not transmitted through casual contact, respiratory droplets, sharing food, kissing, or through mosquito bites. [23]

For a blood-to-blood infection to occur, blood from an infected person must enter the body of someone who is not infected. By far, the biggest risk factor for becoming infected with HCV is injectable drug use; specifically sharing needles or equipment used to inject drugs. [24]

A speck of blood so small that it is not viewable to the naked eye can carry hundreds of hepatitis C virus particles. Cleaning with alcohol or rinsing with soap and water, even letting the needle and syringe air-dry for several days will not kill the virus.

Once it is injected into the body, even if on only one occasion, exposure has occurred and infection is quite possible. Around 30% of persons who inject drugs are infected with HCV within the first two years of using. After five years of IDU, 90% of users will be infected. [25]

Simple facts about Hepatitis C

Being infected with hepatitis C (HCV) does not necessarily mean that liver disease will occur. What's more, it can take several years—decades, in many cases—for hepatitis C to cause life-threatening liver disease.

Soon after HCV enters the body, it infects cells in the liver called hepatocytes. Only a small number of people (about 25 percent) actually experience symptoms of infection, such as fatigue, decreased appetite, nausea or jaundice (yellowing of the skin and eyes). However, the majority of people infected with hepatitis C have an increase in liver enzymes—such as alanine

aminotransferase (ALT)—that can be detected by a simple blood test. An increase in ALT means that some liver cells are damaged by the HCV infection.

About 15 to 25 percent of people infected with HCV are able to clear the virus from their bodies, usually within six months after becoming infected. Infants and young women are more likely to clear hepatitis C spontaneously. However, the majority of people infected with HCV have "chronic" hepatitis C—an infection that can stay with them for life unless they are treated.

About 15 percent of people with chronic hepatitis C will maintain normal liver enzymes, even though HCV can be detected in their livers and in their blood. Although they usually don't develop progressive liver disease or experience symptoms of the infection, people with normal ALT levels are still at risk for liver damage from HCV. The remainder of people with chronic hepatitis C will go on to experience some signs and symptoms of liver disease, such as fatigue, nausea, muscle aches and abdominal discomfort. [26]

Approximately 70% - 80% of HCV-infected patients fail to clear the virus and develop CHC infection, which is a risk factor for liver diseases such as fibrosis, cirrhosis, and hepatocellular carcinoma [27] [28] . In addition to its hepatic manifestations, CHC infection is associated with extrahepatic manifestations occurring in multiple organ systems, including the hematologic , renal , dermatologic, endocrine and rheumatologic systems. Among the endocrine disorders, thyroid disorders are the most common and the thyroid is one of the principal

target organs for extrahepatic manifestations in HCV-infected patients [29]. The liver plays an important role in the metabolism of THS, as it is the most important organ in the peripheral conversion of tetraiodothyronine (T4) to triiodothyronine (T3) by type 1 deiodinase [27] [30]. Moreover, the liver is involved in thyroid hormone conjugation and excretion, as well as the synthesis of thyroid binding globulin [27] [31]. T4 and T3 regulate the basal metabolic rate (BMR) of all cells, including hepatocytes, and thereby modulate hepatic function. The liver metabolizes the THs and regulates their systemic endocrine effects. Thyroid diseases may perturb liver function; liver disease modulates thyroid hormone metabolism; and a variety of systemic diseases affect both organs [32] . There are clinical and laboratory associations between thyroid and liver diseases. Patients with chronic liver disease may have thyroiditis, hyperthyroidism, or hypothyroidism. Patients with subacute thyroiditis or hyperthyroidism may have abnormalities in liver function tests, which return to normal as the thyroid condition improves [32]. HCV is known to be responsible for both hepatic and extrahepatic diseases. The most frequent and clinically important endocrine extrahepatic diseases are thyroid disorders and type 2 diabetes mellitus [33] .

About 5 to 20 percent of people infected with HCV will develop cirrhosis—a scarring of the liver that results from widespread fibrosis (liver cell damage). This usually occurs over a 20-to-30-year period of HCV infection. Progression to cirrhosis may be accelerated in people who are older, obese or immune-suppressed (such as people who are coinfected with HIV*). Heavy alcohol use can also speed up liver disease, notably in men who drink more than 50 grams of alcohol a day (5 drinks) and women who consume more than 30 grams of alcohol a day (3 drinks).

Although cirrhosis is not always life-threatening, it can affect the way the liver works and it does increase the risk of liver cancer. Between 1 and 5 out of 100 HCV infections will die from the consequences of chronic HCV infection, notably liver cancer or liver failure.

In other words, of every 100 people infected with the hepatitis C virus, about

- 75 to 85 people will develop chronic hepatitis C virus infection; of those,
- 60 to 70 people will go on to develop chronic liver disease,
- 5 to 20 people will go on to develop cirrhosis over a period of 20 to 30 years, and
- 1 to 5 people will die from cirrhosis or liver cancer.

Hepatitis C may increase the risk of dying early from other diseases, such as cancer and cardiovascular disease. On average, people with HCV die 15 years earlier than the general population. However, people who are cured of HCV before they reach cirrhosis, have an average life expectancy.

Transmission

The hepatitis C virus is a blood borne virus. It is most commonly transmitted through:

- injecting drug use through the sharing of injection equipment
- in health care settings due to the reuse or inadequate sterilization of medical equipment, especially syringes and needles
- the transfusion of unscreened blood and blood products

- HCV can also be transmitted sexually and can be passed from an infected mother to her baby, however these modes of transmission are much less common.[34]
- Tattooing or Piercing The CDC notes that infectious diseases like hepatitis C can be transmitted through unregulated settings that provide tattooing, body piercing, or body art.

Commercially licensed tattooing businesses are generally thought to be safe. However, more informal settings that offer tattooing or piercing services may not have adequate safeguards to help avoid the spread of infections [35]

❖ Blood Transfusion/Receipt of Blood Products

Early case-control studies of patients with newly acquired, symptomatic non-A, non-B hepatitis found a significant association between disease acquisition and a history six months prior to illness of blood transfusions, injection drug use, health care employment with frequent exposure to blood, personal contact with others who had hepatitis, multiple sexual partners or low socioeconomic status. [36][37] Today, HCV is rarely transmitted by blood transfusion or transplantation of organs due to thorough screening of the blood supply for the presence of the virus and inactivation procedures that destroy bloodborne viruses. In the last several years, blood banks have instituted techniques that utilize nucleic acid amplification of the hepatitis C virus, which will detect the presence of virus even in newly-infected patients who are still hepatitis C antibody-negative. These techniques are estimated to have prevented 56 transfusion-associated HCV infections per year in the U.S. since 1999, and have lowered the current risk of acquiring HCV via transfused blood products to 1 in 2 million. [38]

❖ Injection Drug Use

Injection drug use has been the principal mode of transmission of HCV since the 1970's. In comparison to other viral infections, HCV is more rapidly acquired after initiation of intravenous drug use. [39] In addition, rates of HCV among young injecting drug-users are four times higher than HIV infection. [40] Studies of injection drug users have demonstrated that the prevalence of HCV infection in them is extremely high, with up to 90% having been exposed. [41] In addition, the incidence of new infections is also high, with seroconversion rates of 10-20 percent per year of injecting. [24][43] Duration of injecting is the strongest single predictor of risk of HCV infection among injection drug users. [44]

❖ Sexual Transmission

Sexual transmission of HCV has been controversial. It is believed that HCV can be transmitted sexually, but that such transmission is inefficient. The likelihood of HCV infection increases with the number of lifetime sexual partners. A history of a sexually transmitted disease, sex with a prostitute, more than five sexual partners per year, or a combination of these has been independently associated with positive HCV serology. [45] Distinction appears to exist between the specific sexual behaviors listed above, and stable, monogamous sexual activity, which is rarely associated with HCV transmission. The frequency of HCV transmission between monogamous sexual partners is very low according to most studies. [46][47]

Other Modes of Transmission

❖ *Household Transmission*

The prevalence of HCV among household contacts of people with HCV infection is low. Moreover, the study of HCV transmission among household contacts is complicated by the difficulty in ruling out other possible modes of acquisition. Many of the studies include a small number of nonsexual contacts, and often include children born to mothers with HCV infection. [48] Therefore, it is difficult to determine whether nonsexual, non-blood contact is a route of transmission for HCV.

❖ *Occupational Exposures*

Health care workers who have exposure to blood are at risk of infection with HCV and other bloodborne pathogens. The prevalence of HCV infection, however, is no greater in health care workers, including surgeons, than for the general population. According to the CDC, the average rate of anti-HCV seroconversion after unintentional needlesticks or sharps exposure from an HCV-positive source is 1.8% (range 0%-7%). An Italian study of 4,403 needlesticks among healthcare workers found 14 seroconversions (0.31%). [49] There is an emerging body of literature; however, that close follow-up of health care workers after a needlestick from a patient with chronic HCV, with early interferon and ribavirin therapy for the healthcare worker if they develop HCV viremia but fail to clear within 3-6 months, can be a beneficial management strategy. [50]

Hepatitis C not transmitted by

It’s as important to know how hepatitis C can’t be transmitted as it is to know how you may get the virus. The CDC confirms that you can’t get hepatitis C through:

- eating with utensils shared by someone with hepatitis C
- holding hands, hugging, or kissing someone with hepatitis C
- being near someone with hepatitis C when they cough or sneeze
- breast-feeding (babies can’t get hepatitis C through a mother’s breast milk) [35]

Symptoms and Signs

Acute HCV infection is rarely diagnosed due to the lack of definitive symptoms. It is often referred to as a silent epidemic [51] . The average time from exposure to symptom onset is 4-15 weeks. [52]
During this "acute infection period" - if symptoms are present - they are not considerably different to any other viral syndrome. When symptoms occur, they can include [53]:

- Fever
- Fatigue
- Dark urine
- Clay-colored stool
- Abdominal pain
- Loss of appetite
- Nausea
- Vomiting
- Joint pain

- Jaundice

During the acute phase of hepatitis C, only a small number of people (about 25 percent) actually experience symptoms of infection [54].

HCV becomes chronic when the virus remains in the blood a year after the acute infection period. Unless treated with medication, the infection is lifelong.

Most people have no physical complaints with chronic infection, while some may have ongoing episodes of abdominal pain, persistent fatigue, and aching joints.

After a 25-30 year period, this chronic infection may result in significant scarring (fibrosis) of the liver, which can progress to cirrhosis (complete fibrosis), liver failure, and possibly liver cancer (hepatocellular carcinoma). Frequently it is not until the liver is on the verge of collapse that the damage is apparent. [55]

Many people with chronic hepatitis C have no symptoms of liver disease. That is, they don't necessarily feel or look sick. If symptoms are present, they are usually mild, aren't very specific (some people simply say they're feeling "blah"), and tend to come and go.
These symptoms may include" fatigue", "brain fog," pain in the upper-right portion of the gut, "nausea", "decreased appetite", and "muscle and joint pains".
Some people have more severe symptoms, the degree of symptoms does not correlate with liver damage, so someone with severe symptoms could have minimal liver damage, and vice versa.
If hepatitis C causes serious liver damage or cirrhosis, symptoms may become more prominent. In addition to "fatigue", there may be "muscle

weakness", "bruising", poor appetite , nausea , weight loss, itchy skin, cola-colored urine, gray-colored stools , jaundice (yellow skin and whites of the eyes) , and fluid accumulation in the lower extremities (edema). Some symptoms of advanced cirrhosis are a bloated belly from fluid accumulation (ascites), bleeding from blood vessels in the digestive tract (varices) and confusion (hepatic encephalopathy). [54]

Managing Common Symptoms

❖ Appetite loss

Isn't a common symptom of hepatitis C, so if you are experiencing a loss of appetite, be sure to discuss this with your medical provider. If you are experiencing significant weight loss, your doctor may refer you to a nutritionist or dietician. Tips to help with your appetite:

- Eat small, frequent meals of nutritious, high-calorie foods such as peanut butter, nuts, avocados, protein shakes and smoothies.
- Select a variety of foods. Vary the color, temperature, texture, and type of food you eat.
- Try new foods or ones that you may not have liked in the past.
- Experiment with seasonings and spices.
- Choose foods that are high in calories and protein.
- Add powdered milk or protein powder to regular milk, milkshakes, casseroles, soups, eggs, mashed potatoes, hot cereal and puddings.
- Spread peanut butter or other nut butters on bread, tortillas, waffles, pancakes, fruit, and celery
- Add cooked beans or hard-boiled eggs to soups, casseroles, and pasta.

- Try products designed to promote weight gain, such as nutritional supplements, canned formulas, protein powders, instant breakfast drinks, power bars, and high-calorie puddings.

❖ **Brain fog**

Is the term patients use to describe when it is difficult to think well and be alert. The mind feels like it is shrouded in fog. It can be difficult to concentrate and there can be short-term memory loss. Not everyone with hepatitis C gets brain fog, and those who do have a wide range of experiences. If you do, talk to your medical provider, so other causes of cognitive dysfunction can be ruled out. Be sure to let you doctor know if you take medication, over-the-counter drugs, supplements, or recreational substances. Tips for managing brain fog:

- Engage in physical activity on a daily basis. Exercise is an enemy of brain fog. An ideal goal is to include aerobic exercise, strength training, and stretching.
- Get enough sleep. The average adult needs seven to nine hours of sleep each night.
- Eat a nutritional diet and don't skip meals. Aim for a good balance between all of the basic food groups, including whole grains, proteins, dairy, fruits, vegetables and fats—making sure to keep the fats in your diet to a minimum.
- Drink plenty of water.
- Manage stress. Meditation and relaxation techniques can help you think more clearly.
- Avoid alcohol and other substances that interfere with clear thinking.

- Get organized. Use electronic devices and daily/weekly pill containers to remind you to take your medicine. Record important events in a calendar or journal. You can also use this to keep track of your medical appointments. Use sticky notes to remind yourself of medical appointments and medication schedules.
- Set the alarms on your smart phone, watch, alarm clock, or electronic device to remind you about medication and appointment times.
- Create habits and daily routines.
- Write things down and keep your lists in the same place.
- Do one task at a time. Multi-tasking tends to increase brain fog.

❖ Fatigue

Is one of the most common symptoms of hepatitis C. Fatigue has many causes, so be sure your medical provider has ruled out other medical conditions if you experience these symptoms. Some common causes of fatigue are depression, insomnia, pain, sleep apnea, and thyroid problems. Here are some tips to help with fatigue:

- Get enough sleep. The National Sleep Foundation recommends seven to nine hours of sleep per night for adults. If sleep is a problem, discuss this with your health care provider.
- Light exercise is a good remedy for fatigue. Pick an activity and do it for 10- to 15-minute intervals, two to three times daily. If you are not accustomed to physical activity, start with five-minute intervals and increase gradually. Sample activities include : walking, biking, swimming, dancing, gardening, yoga, and tai chi.
- Vary your activities—do not sit or stand too long.

- Drink plenty of water. According to the Institute of Medicine, men need about 13 cups (3 liters) of total beverages a day,women need about 9 cups (2.2 liters) daily. If you are drinking enough liquids, your urine will be pale yellow or colorless.
- Reduce stress and find ways to relax.
- Take short naps of 20 minutes or less. Don't nap close to bedtime.
- Use caffeine. Coffee and tea may give you a lift, plus coffee may protect the liver. Do not drink caffeinated drinks late in the day, as this may interfere with sleep.

❖ Gastrointestinal Complaints

Some people feel discomfort in the right upper part of the abdomen around the liver area. Since the liver does not have any nerve cells, the discomfort is usually caused by the capsule surrounding the liver, as well as from nearby organs. Always discuss pain with your medical provider, particularly when pain is constant, severe or interferes with your quality of life.

❖ Abdominal discomfort

This may occur with hepatitis C, as well as other causes. Call your medical provider if you have severe or chronic stomach pain. Eat small, frequent meals, as stomach pain may be caused or worsened by hunger.

❖ Nausea

Isn't a common hepatitis C symptom, but it may occur. Hunger can intensify nausea, so eat a cracker or other small piece of food every hour or two. Ginger helps with mild to moderate nausea. Peppermint, chamomile or rasp berry leaf tea may also alleviate nausea. You can also

try to relieve nausea through an acupressure technique by applying pressure to the inside of your wrist, approximately two fingers above the crease where your hand meets your arm. You may also purchase wristbands developed for motion sickness sold in drugstores. If nausea is frequent, persistent, severe, or if you are vomiting, talk to your medical provider.

❖ Muscle and joint aches

Are common symptoms of hepatitis C, pain isn't. Both need medical evaluation. Research tells us that moderate exercise and staying active are the best way to manage physical discomfort. Other tips that may provide relief are:

- Hot baths
- Stretching
- Massage, whether done by a friend, a professional or yourself
- Avoid prolonged sitting or reclining
- Talk to your medical provider about taking over-the-counter pain relievers such as Tylenol (acetaminophen), aspirin, Advil/Motrin (ibuprofen), or Aleve (naproxen) [52].

Screening and diagnosis

Getting tested

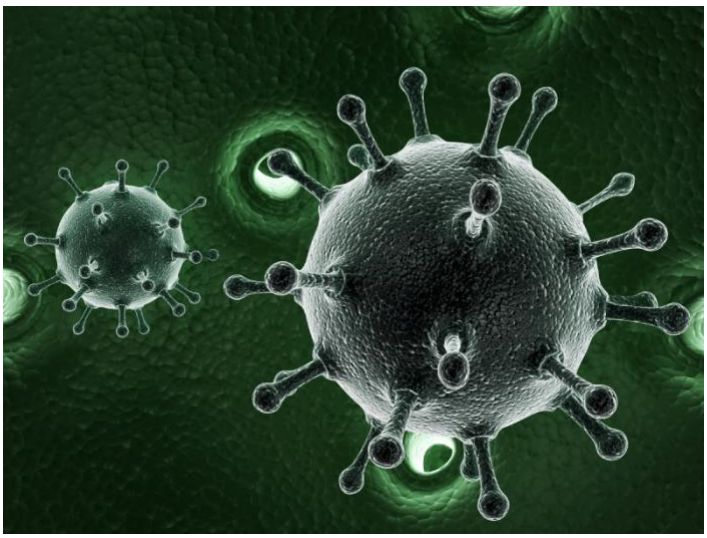
Early diagnosis can prevent health problems that may result from infection and prevent transmission of the virus. WHO recommends screening for people who may be at increased risk of infection.

Populations at increased risk of HCV infection include:

- people who inject drugs
- recipients of infected blood products or invasive procedures in health-care facilities with inadequate infection control practices
- children born to mothers infected with HCH
- people with sexual partners who are HCV-infected
- people with HIV infection
- prisoners or previously incarcerated persons
- people who have used intranasal drugs
- people who have had tattoos or piercings [34]

Tests and diagnosis of hepatitis C

Because of the lack of symptoms of acute HCV infection, it is often overlooked or considered a garden-variety viral illness. Thus, it is rare for the infection to be diagnosed during the acute phase.



Figure(3)

A simple blood test called an HCV antibody screen can test for HCV. [56]

A person infected with HCV produces an immune response, and only 20% will clear the virus on their own. The rest will remain chronically infected, and can unknowingly infect others.

You can get tested for an HCV through a simple blood test called an HCV antibody (or anti-HCV) screen.

If the test is positive for anti-HCV antibodies, a nucleic acid test for HCV RNA is needed to confirm chronic HCV infection because about 15–45% of people infected with HCV spontaneously clear the infection by a strong immune response without the need for treatment. Although no longer infected, they will still test positive for anti-HCV antibodies. There is an FDA-approved rapid test that provides results in 20 minutes. Otherwise, the blood is drawn through a venipuncture and processed at a lab. A negative test means no hepatitis exposure and no infection. A positive test means exposure; it does not prove HCV infection.

All persons who have a positive HCV antibody need a second blood test called HCV RNA (PCR). This test will tell whether the virus is present.

If the test is negative, there is no virus present and, therefore, no chronic infection.[57] If positive, it will measure the amount of virus in the blood (viral load).

A person with a positive PCR should see a liver specialist or other provider who is trained to evaluate and treat chronic HCV infection.

It is important to understand that the positive antibody test will always remain positive, whether or not the virus is still present.

Antibodies to HCV exposure do not mean long-term protective immunity such as a person would receive through a measles vaccine or with chicken

pox infection. There is no permanent immune memory with HCV antibody, a person can certainly get re-infected with a different strain of the virus.

The Center for Disease Control (CDC) has recommended a one-time HCV antibody blood test for these individuals below as they are at the greatest risk of having been exposed to the virus.[57]

- People who had transfusions or organ transplants prior to 1992
- Past/present injectable drug users
- Hemophiliacs
- Long-term hemodialysis patients
- Health care workers after a needle stick exposure
- People with a positive HIV infection
- Individuals that get a tattoo in an unregulated setting
- Those partaking in risky sexual behaviors or sex with a drug user note: the risk of HCV transmission between long-term heterosexual, monogamous partners is 0.07% [58].
- Children born to an HCV-infected mother (the risk of transmission is low, under 5%) [59].
- Those who have been incarcerated
- Individuals with a history of long-term daily alcohol use
- People with unexplained liver disease
- Intranasal (snorting through the nostrils) drug users.

Each individual's primary care provider determines repeat testing.

Once the chronic infection is confirmed the genotype needs to be designated (through a blood test), as it will determine the percentile cure rate, the length of treatment and the treatment protocol.

In terms of infectiousness or aggressiveness, it is not the genotype but rather the overall health of the infected individual and liver that determines if or how quickly damage and possible progression to cirrhosis will occur.

In some instances, a liver biopsy may be recommended, not to confirm the diagnosis, but rather for grading the severity of the disease, staging the degree of fibrosis and evaluating the extent of liver damage.

Although advances have been made, a reliable culture system for HCV is not yet available [60].

Laboratory assays that are available for the diagnosis and management of HCV infection include (i) serologic tests to detect HCV antibodies, (ii) molecular tests to detect and quantitate HCV RNA, and (iii) genotyping techniques. Assays to detect and quantify HCV core antigen have also been developed.

Laboratory studies

The following assays are used for diagnosing and managing Hepatitis C (HCV) infection:

- Serologic assays: These detect a specific antibody to the hepatitis C virus (anti-HCV) in the serum or plasma and are reported as a positive or a negative value

- Molecular assays: These detect viral nucleic acid and can be qualitative or quantitative. Quantification of the virus is reported using international units per milliliter (IU/mL).
- Genotyping assays: These are most useful in epidemiological studies and are clinically used to predict the likelihood of response and duration of therapy; they help to classify the virus into the 6 major genotypes. [61]

❖ SEROLOGIC ASSAYS

- *Enzyme immunoassays (EIAs)*

The initial test used to diagnose HCV is an enzyme immunoassay (EIA) for anti-HCV immunoglobulin G (IgG). The HCV genome encodes a poly protein of 3,011 to 3,033 amino acids that is processed into 10 structural and nonstructural (NS) proteins [61]. Three generations of screening EIAs have been developed to detect antibodies against various epitopes of these proteins

Use of serologic assays:

About 25 to 35% of patients with acute infection who develop symptoms, only 50 to 70% will have detectable antibodies at that time, but 90% will have measurable antibodies after 3 months [62].

Serologic assays detect HCV antibodies that indicate present or previous infection, but they cannot discriminate acute from chronic or resolved infection. Anti-HCV IgM antibodies can be detected in 50 to 93% of patients with acute HCV infections and 50 to 70% of chronic cases, so they are not a reliable indicator of acute infection [63].

Patients with acute hepatitis of uncertain origin and negative hepatitis serology panels should undergo qualitative HCV RNA testing [64]. Occasionally, immunocompromised patients, patients undergoing

hemodialysis, and patients with mixed cryoglobulinemia have false-negative serology results and may require HCV RNA testing for diagnosis [65, 66,67].

Passively transferred maternal anti-HCV antibodies may be detected in the children of HCV-infected mothers for up to 1 year, however, defined diagnostic criteria for HCV RNA detection are not available [68,69].

- **Liver enzymes (ALT and AST)**

Alanine aminotransferase (ALT sometimes listed as SGPT)

ALT is a liver enzyme. When hepatitis C infects the liver, the hepatocytes (liver cells) produce higher-than-normal enzymes such as ALT, indicating inflammation of the liver. When initially infected, ALT may skyrocket to 10 times the normal level. When hepatitis C becomes chronic, ALT usually drops to a lower level, but remains persistently elevated. About two-thirds of people with chronic hepatitis C have continuously elevated ALT levels, reflecting ongoing damage to liver cells. The other third have normal ALT levels, even though they have a detectable HCV viral load. Although most people with HCV and normal ALT will live without any liver-related problems, roughly one-quarter of these people may have progression of liver disease [70].

- Aspartate aminotransferase (AST sometimes listed as SGOT)

AST is also a liver enzyme, which is often elevated in people with chronic hepatitis C. AST levels are usually lower than ALT levels. If cirrhosis occurs, AST levels may be higher than ALT levels, a sign that damage to the liver is worsening. Elevated AST levels may also indicate

excessive alcohol use, drug toxicity and the presence of other medical problems.[70]

❖ Molecular HCV RNA Tests

Molecular diagnostic tests for hepatitis C specifically detect HCV RNA and the process is commonly referred to as a Nucleic Acid Test (NAT) or Nucleic Acid Amplification Test (NAT). The HCV NAT becomes positive approximately 1 to 2 weeks after initial HCV infection. The NAT test has become the gold standard supplemental test for patients who have a positive HCV EIA screening test. The NAT can determine whether a patient with a positive HCV antibody test has current (active) or resolved HCV infection. In addition, the NAT can be used to diagnose individuals with acute HCV infection. The results for the commercially available quantitative HCV RNA assay are given in International Units (IUs) [71].

- **Qualitative and quantitative assay for HCV RNA**

The presence of HCV RNA in plasma defines active infection, and HCV RNA can be detected 1 to 3 weeks postexposure [72].

A single negative HCV RNA assay result does not exclude the possibility of active infection with a transient drop in the level of viremia below the assay's limit of detection [72].

Qualitative HCV RNA: The qualitative HCV RNA tests provide a yes or no answer to whether detectable HCV RNA is present in the sample. The qualitative HCV RNA assays are FDA approved for HCV diagnostic purposes. These tests, however, do not provide a quantitative level of

HCV and are not used for baseline HCV RNA levels or for monitoring response to therapy.

- **HCV Genotyping**

Hepatitis C is divided into six distinct genotypes throughout the world with multiple subtypes in each genotype class. A genotype is a classification of a virus based on the genetic material in the RNA (Ribonucleic acid) strands of the virus. Generally, patients are only infected with one genotype, but each genotype is actually a mixture of closely-related viruses called quasi-species. These quasi-species have the ability to mutate very quickly and become immune to current treatments, which explains why chronic Hepatitis C is so difficult to treat.

Following is a list of the different genotypes of chronic Hepatitis C [73] :

Genotype 1a
Genotype 1b
Genotype 2a, 2b, 2c & 2d
Genotype 3a, 3b, 3c, 3d, 3e & 3f
Genotype 4a, 4b, 4c, 4d, 4e, 4f, 4g, 4h, 4i & 4j
Genotype 5a
Genotype 6a

It is important to find out which hepatitis C genotype you have, because it determines both the type of treatment and the length of treatment, HCV genotype also helps to predict the likelihood of curing HCV. Worldwide, HCV genotype 1 is most common, accounting for 46 percent of cases. In the United States, 75 percent of all HCV infections are genotype 1, genotypes 2, 3 and 4 are less common in the United States, and other genotypes are rare. Genotype 7 was discovered in 2013 and

there is only one known case. It is possible to infected with more than one HCV genotype [74]

Genotype 1 is the most common type of Hepatitis C genotype in the United States and the most difficult to treat. For physicians, knowing the genotype of Hepatitis C is helpful in making a therapeutic recommendation. Individuals with genotypes 2 and 3 are almost three times more likely than individuals with genotype 1 to respond to therapy with alpha interferon or the combination of alpha interferon and ribavirin. Furthermore, when using combination therapy, the recommended duration of treatment depends on the genotype. For this reason, testing for Hepatitis C genotype is often clinically helpful. Once the genotype is identified, it need not be tested again as genotypes do not change during the course of infection [73].

- **HCV Viral Load Testing** (Quantitative HCV RNA)

A health care provider can request a qualitative HCV RNA test to determine if the virus is in a person's bloodstream. A medical provider can also order a quantitative HCV RNA test to figure out a person's HCV viral load (the amount of HCV in a measurement of blood). Various methods are used to detect HCV RNA, including TMA (transcription-mediated amplification), PCR (polymerase chain reaction), and bDNA (branched DNA). Qualitative viral load testing tends to be more sensitive than quantitative testing. Viral load testing using PCR or TMA are more sensitive than bDNA testing.

The HCV viral load is an important laboratory test. Though the HCV viral load test cannot determine if or when someone with hepatitis C will develop cirrhosis or liver failure, it can help determine the length of

treatment needed. HCV viral load testing is also used during treatment to determine how well it is working [73] .

The quantitative HCV RNA test is not FDA-approved for HCV diagnostic purposes. More recently, however, with the introduction of ultrasensitive HCV quantitative RNA assays (that detect as few as 5 copies/ml), the quantitative HCV RNA has achieved a similar level of diagnostic sensitivity as the qualitative assay. In addition, the quantitative HCV RNA assay generates an actual HCV RNA level that may provide useful information as a baseline HCV RNA. Because the sensitivity of the quantitative HCV RNA assays has dramatically improved, many clinicians have utilized the quantitative HCV RNA for diagnostic purposes [71].

Molecular and serologic methods may be used to determine HCV genotypes.

Assessment of hepatitis fibrosis

- **Liver Biopsy**

A biopsy allows experts to examine tissue taken from the liver and determine how healthy the liver is [70].

The role of the liver biopsy in chronic hepatitis C would seem, a liver biopsy provides much information in a small package. It provides for confirmation of the diagnosis, exclusion of other liver diseases, and assessment of the grade and stage of the disease. As such, it can help the clinician advise the patient of the state of their disease, which can, in turn, be used to help decide whether immediate antiviral therapy is warranted, whether some other intervention is needed, or if a period of watchful waiting may be recommended. Furthermore, the usefulness of the liver

biopsy in chronic hepatitis C has received the endorsement of several national and international consensus conferences on the diagnosis and treatment of hepatitis C.[74-77] In addition to its contribution to clinical decision making and clinical investigation, the biopsy can be an essential component of investigations into the cellular and molecular events that underlie histological changes, such as the shortening of telomeres and expression of senescence markers (Tillman et al, [78] this issue). Yet, despite these very positive aspects, the role of the liver biopsy in the evaluation and management of hepatitis C continues to be debated at meetings and in the literature [79-86].

A liver biopsy is often performed on an outpatient basis, usually in a hospital. An ultrasound may be used to identify the best location to make the biopsy. The patient lies quietly on his or her back or slightly to the left side. The area of the skin where the biopsy will be done is carefully cleaned. Then, a local anesthetic agent is used to numb the skin and tissue below. A thin, specially designed needle is inserted through the skin. Liver cells do not have nerves, so technically a liver biopsy would not hurt if doctors could perform a liver biopsy without puncturing the skin, membrane and surrounding tissue.

The physician will instruct the patient to take a deep breath and to hold it for about five seconds. The needle is advanced into and out of the liver. This takes only one or two seconds. A slender piece of tissue is removed with the needle, and is then processed through a laboratory. The entire procedure from start to finish lasts only 15 to 20 minutes. The patient will then be instructed to lie still, sometimes for several hours. There may be some discomfort in the chest or shoulder, but this is usually temporary. In rare cases, the provider conducting the procedure can "nick" a blood vessel, which can result in internal bleeding. It is common to feel mild

soreness in the liver area for a day or two following the procedure. The results of the biopsy are usually available within a week and will be explained to you by your health care provider [70].

Noninvasive Tests of Fibrosis

- **Blood Tests**

Various blood tests directly and indirectly estimate the amount of liver fibrosis. Although the tests vary in accuracy, they are usually good at estimating the degree of fibrosis. Some commonly used blood tests are FibroSpect, FibroSure, and FibroTest [[70].

- **FibroScan**

A newer method, it uses ultrasound and low-frequency elastic waves to measure liver elasticity. FibroScan seems to be as accurate as a liver biopsy. The technician or physician applies gel to the skin and places the probe with a slight pressure on the liver area. The procedure is painless [70]

- **Imaging Studies**

Non-invasive imaging procedures may be used to monitor the health of your liver. The most common is ultrasound, which uses sound waves to produce an image of the liver. Ultrasound is useful for detecting tumors and can potentially detect cirrhosis. If the ultrasound test reveals a tumor, your doctor may want you to have a CT scan or an MRI. The CT scan (computed tomography or CAT scan) is a specialized x-ray that produces a picture of your liver. MRI (magnetic resonance imaging) also takes a picture, but it uses a magnetic field and radio wave pulses to do this. [70]

Prevention of hepatitis C

Because HCV can only be transmitted through blood to infected blood exposure, the number one way to prevent spreading hepatitis C is by not sharing needles, and avoiding all contact with anyone else's blood.

Once identified, those infected with HCV should receive both the hepatitis A and B vaccines, and make lifestyle changes to promote optimum liver health.

Obesity, smoking, diabetes and alcohol consumption can accelerate the rate of liver scarring (fibrosis).[87] It is important that all individuals who are infected with HCV maintain good health. That means:

- No smoking
- Maintaining ideal weight
- Managing co-existing health problems
- Abstaining from all alcohol
- Acetaminophen can be taken under the guidance of the managing provider. Ibuprofen should be avoided.[88]

Treatment of HCV infection

Hepatitis C virus (HCV) infection is curable. In clinical trials, roughly 95 percent of those who took the newest medications were cured. Hepatitis C treatment is easier and shorter than ever before.

When HCV treatment is working, the virus will become undetectable in the blood within four to 12 weeks and will remain that way throughout treatment. People are considered cured when they have achieved a

continuation of this undetectable status for 12 to 24 weeks after completing therapy. This is known as a sustained virologic response (SVR). The chances of HCV returning after 24 weeks of remaining clear of the virus are nearly zero.

Regarding who should be treated, the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America state the following: "Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert."

In the past, acute hepatitis C infections (those that are less than six months) were treated differently than chronic HCV infections. This changed with the availability of new medications. HCV guidelines recommend delaying treating a new infection for a minimum of six months, and allowing time to see if the body will clear HCV on its own. This is called spontaneous clearance. If spontaneous clearance does not occur, then the HCV infection is treated as a chronic one. The prescribed treatment is based on:

- Your HCV genotype (the genetic structure of the virus)
- Your viral load (how much virus is in your blood)
- Your past treatment experience
- If you have cirrhosis
- If you are a liver transplant recipient or on the transplant waiting list
- Your ability to tolerate the prescribed treatment

In some cases, your health insurance plan or drug formulary may determine if you are eligible for treatment, and what drug regimen will be used [70].

The current treatment for chronic hepatitis C is a combination of medications. The choice of medication and duration of treatment depends on the genotype of the virus. Genotype 1a is the most prevalent in the US, and presently there are three recommended treatment options using a certain combination of the medications listed below [89].

- Sofosbuvir
- Paritaprevir
- Ritonavir
- Ombitasvir
- Ribavirin
- Simeprevir
- Dasabuvir.

Direct-acting antivirals (DAAs) are the newest agents available to treat HCV. These medications work by targeting specific steps in the HCV life cycle and disrupting the virus from replicating.

Before the availability of DAAs, the treatment for chronic HCV was lengthy and grueling, with less than ideal cure rates. Now the cure rates are over 90%. The average duration of treatment is 8-12 weeks. The medications are well-tolerated with the most common side effect being headache and fatigue.

Treating chronic HCV early in the disease course before the patient develops complications or progresses to life-threatening circumstances seems unequivocally the most logical choice.

In hepatitis C virus infection, treatment is prevention. Yet, two million persons in the US do not know they are chronically infected.

As we continue with education, risk-based screening, exposure prevention, and the arrival of well-tolerated treatments, the outlook for preventing serious liver complications and curing those who have chronic hepatitis C infection has never been better.

The FDA approved a new medication that is a part of a drug group called polymerase inhibitors. It works by blocking a specific protein the Hepatitis C virus needs to grow. [90] It is called:

Sofosbuvir (brand name SOVALDI)

Figure (4)

Sofobuvir Bottle. [12]

Sofosbuvir (*Sovaldi*) is a nucleotide analog inhibitor of hepatitis C virus NS5B polymerase—the key enzyme mediating HCV RNA replication. Sofosbuvir is a prodrug and after ingestion it is rapidly converted to GS-331007, the predominant circulating drug that accounts for greater than 90% of the systemically active drug. The compound GS-331007 is efficiently taken up by hepatocytes, whereby cellular kinases convert GS-331007 to its pharmacologically active uridine analog 5'-triphosphate form (GS-461203). This triphosphate compound mimics the natural cellular uridine nucleotide and is incorporated by the HCV RNA polymerase into the elongating RNA primer strand, resulting in chain termination. The active form GS-461203 targets the NS5B catalytic site and acts as a non-obligate chain terminator. The active compound (GS-461203) does not inhibit host DNA polymerases, RNA polymerases, or mitochondrial RNA polymerase. [12]

Sofosbuvir, a once-daily pill, was approved to treat HCV genotypes 1, 2, 3 and 4. This was the first drug that allowed genotype 2 and 3 patients to be treated with pills only, offering an interferon-free regimen with ribavirin. The first line therapy for genotype 1 and 4 patients became a 12-week combination regimen with peginterferon and ribavirin. Patients ineligible for interferon could be offered a 24-week regimen of sofosbuvir and ribavirin.

Sofosbuvir was the first HCV drug with the initial FDA approval inclusive of people who had HIV-HCV co-infection.[91]

HCV genotypes are 1 (1a and 1b), 2, 3, 4, 5, and 6. About 75% of the people with HCV in the U.S. have either genotype 1a or 1b. Between 10% – 20% of people with HCV in the U.S. have either genotype 2 or 3.

HCV GENOTYPE 1

- **Harvoni (ledipasvir/sofosbuvir)**
    - Recommended dosage: One tablet (ledipasvir 90 mg/sofosbuvir 400 mg) taken orally once daily with or without food.
    - In clinical trials, the most common side effects observed with treatment for 8, 12, or 24 weeks were fatigue and headache.

- **Olysio (simprevir) plus Sovaldi (sofosbuvir); sometimes given with ribavirin.**
    - Recommended dosage of simeprevir: One 150-mg capsule once a day with food.
    - Recommended dosage of sofosbuvir: One 400-mg tablet once a day with or without food.
    - In clinical trials, the most common side effects observed during 12 weeks of treatment with simprevir/sofosbuvir combination therapy were fatigue, headache, nausea, insomnia, itching, rash and photosensitivity. During 24 weeks of treatment, dizziness and diarrhea were also observed.

HCV GENOTYPE 2

- **Sovaldi (sofosbuvir) plus ribavirin**
    - Recommended dosage of sofosbuvir: One 400-mg tablet once a day with or without food.
    - Ribavirin is a pill taken by mouth with food. The dose is individualized based on your weight.

- Length of treatment is usually 12 or 16 weeks.
- The most common side effects for sofosbuvir/ribavirin combination therapy are fatigue and headache.

HCV GENOTYPE 3

- **Sovaldi (sofosbuvir) plus ribavirin**
  - Recommended dosage of sofosbuvir: One 400-mg tablet once a day with or without food.
  - Ribavirin is a pill taken by mouth with food. The dose is individualized based on your weight.
  - Length of treatment with sofosbuvir/ribavirin combination therapy is usually 24 weeks.
  - The most common side effects for sofosbuvir/ribavirin combination therapy are fatigue and headache.

- **Daklinza (daclatasvir) with Sovaldi (sofosbuvir)**
  - Recommended dosage: Daclatasvir 60 mg with sofosbuvir 400 mg once a day.
  - Length of treatment is 12 weeks.
  - The most common side effects are fatigue and headache

HCV GENOTYPE 4

- **Sovaldi (sofosbuvir) plus ribavirin**
  - Recommended dosage of sofosbuvir: One 400-mg tablet once a day with or without food.
  - Ribavirin is a pill taken by mouth with food. The dose is individualized based on your weight.
  - Length of treatment is usually 24 weeks.

- The most common side effects for sofosbuvir/ribavirin combination therapy are fatigue and headache.

HCV GENOTYPE 5

- **Sovaldi (sofosbuvir) plus ribavirin plus peg-interferon**
  - Recommended dosage of sofosbuvir: One 400-mg tablet once a day with or without food.
  - Ribavirin is a pill taken by mouth with food. The dose is individualized based on your weight.
  - Length of treatment with sofosbuvir/ribavirin/ peg-interferon combination therapy is usually12 weeks.
  - The most common side effects for sofosbuvir/ribavirin/peg-interferon combination therapy are fatigue, headache, nausea, insomnia and anemia.

HCV GENOTYPE 6

- **Harvoni (ledipasvir/sofosbuvir)**
  - Recommended dosage: One tablet (ledipasvir 90 mg/sofosbuvir 400 mg) taken orally once daily with or without food.
  - Length of treatment is usually 12 weeks.
  - The most common side effects are fatigue and headache.

Side effects

Like most drugs, hepatitis C medications may cause side effects. Before 2014, the drugs used to treat chronic hepatitis C virus (HCV) infection had many side effects, some of which were severe. The newest HCV drugs have fewer and milder side effects. Also, treatment lengths are

shorter; less exposure to the medicines reduces the risk of side effects. The majority of people who used the new medicines in clinical trials experienced mild side effects. However, even though the risks are low, it is wise to know about potential side effects before starting a drug, along with tips that may help reduce the risk [70].

Here is a list of common side effects for approved HCV medications. Because most HCV drugs are combined with other medications, review the side effects for the medicines.

❖ Ribavirin

It is prescribed with one or more other HCV medications. In many cases, newer drugs are replacing the need for ribavirin. **Warning**: Ribavirin causes birth defects in animals, so it cannot be used by women who are pregnant or by the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy while taking the drug. As a result, men and women who are having intercourse must use two forms of birth control during HCV treatment and for the next six months afterward, since ribavirin can remain in the bloodstream after people stop taking it.

- Anemia, hemolytic (low red cells)
- Dizziness/lightheadedness
- Fatigue
- Impaired concentration
- Increased heart rate
- Insomnia
- Loss of appetite
- Mood issues (anxiety, depression, irritability, moodiness)
- Nausea

- Rash/itching/dry skin
- Shortness of breath
- Taste perversion (dysgeusia)
- Upset stomach (dyspepsia)
- Weakness
- Symptom of anemia

❖ **Sovaldi (sofosbuvir)** is prescribed with one or more other HCV medications.

- Fatigue
- Headache
- Nausea

Sofosbuvir Mechanism of Action:

Sofosbuvir mechanism of action on molecular level reveals how Sovaldi drug treates and cures Hepatitis C. In order to determine the mechanism of action we must understand how the medicine works on preventing Hepatitis C virus, which is destroying one's liver [91].

Sofosbuvir works by preventing hepatitis C virus from further replicating. Immune system does the rest.

Hepatitis C virus uses genetic material or RNA to generate new viruses – without RNA, there are no new viruses. In fact when virus infests our liver, billions of virus clones are produced every single day. Our immune system is very efficient at eliminating the viruses, but the magnitude of billions of new virus particles every day is too much and it overwhelms

the immune system. Here's where Sofosbuvir comes in to help immune system by decreasing the number of viruses being produced each day.

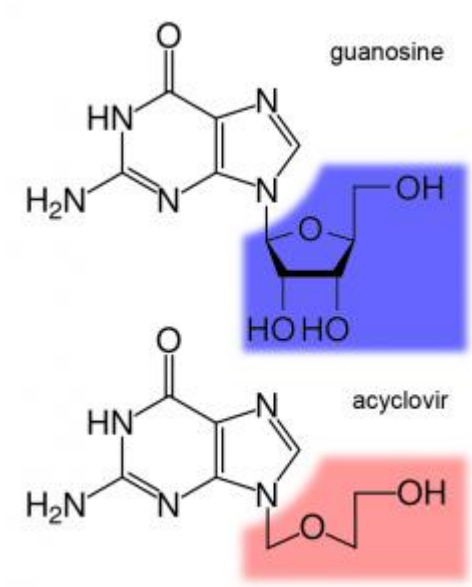
Sovaldi drug prevents the generation of new viral genetic material. This is done by blocking the component that Hepatitis C virus uses to construct genetic material – viral RNA polymerase. Image RNA polymerase as a construction worker that is creating a building – if we eliminate the worker than he will not be able to construct the building. This principle is exactly how Sofosbuvir deals with the virus construction – it inhibits it. The construction is put on hold and immune system comes in like a wrecking ball, smashing the building, or the virus in our case.

Sofosbuvir mechanism of action inhibits viral RNA polymerase by being a defective substrate. Defective substrate is a part of the building that causes the construction halt. This leads to building or virus collapse. Image building the first stage of the building. Then you start using Sofosbuvir – the moment you put the molecule in, the construction cannot continue. In our case, the virus cannot continue to grow – this is the way to fight Hepatitis C virus.

The trick is to convince the virus to take Sofosbuvir inside its structure. If virus knew Sofosbuvir would kill it off, it would never use it. That's why Sofosbuvir has to disguise itself as a useful building block. Virus is using so called nucleosides as a building block. That's why Sofosbuvir disguises itself as a nucleoside.

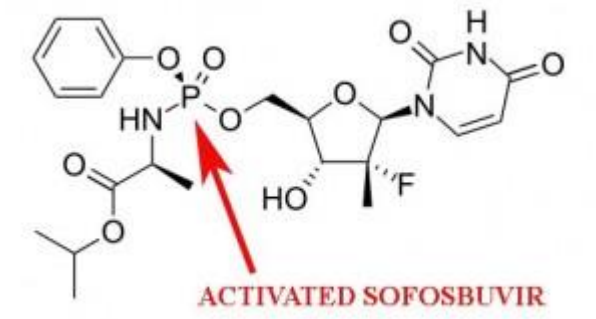
Hepatitis C virus uses nucleoside such as guanosine seen in the picture to build new viruses. Acyclovir, molecule an antiviral drug,on the other hand, is a nucleoside analogue and mimics guanosine. However, if virus instead of guanosine uses acyclovir, the acyclovir will prevent virus from

replicating. In such a way, the Hepatitis C virus is eliminated from the body by immune system.



Acyclovir is a prodrug and has to be turned on to start the treatment. This is done by attaching a phosphate group to -OH group on acyclovir seen on the picture. This, however, takes some time and here the Sofosbuvir has the advantage.

Now let us look at Sofosbuvir molecule below. The problem with previous antiviral drugs is that the activation step took time and were slow. What Sofosbuvir brings to the table is that it is already activated.



As you can see from the molecule, P is already there – the molecule is already activated. In the body, the molecule left of P is separated and

Sofosbuvir can go to work. The major advantage of this is that there is no prior activation needed as with other antiviral drugs.

SOVALDI combination therapy cure rates in clinical studies

SOVALDI is a groundbreaking hepatitis C (Hepatitis C) treatment. Clinical studies have shown that SOVALDI combination therapy can be effective for people with genotypes 1, 2, 3, and 4 [92].

SOVALDI combination therapy is the first all-oral treatment for genotypes 2 and 3.

The table below includes the percentages of patients, in SOVALDI clinical studies, who were cured of the Hepatitis C virus. Cure means the Hepatitis C virus is not detected in the blood when measured 3 months after treatment is completed.

GENOTYPE	DURATION	TREATMENT	CURE RATE
1 OR 4	12 WEEKS	SOVALDI + ribavirin+ peginterferon alfa	90% / 96%
2	12 WEEKS	SOVALDI + ribavirin	93%
3	24 WEEKS	SOVALDI + ribavirin	84%

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