Evolving Clinical and Virological Perspectives on Hepatitis B and C: A Critical Review

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ABSTRACT

The hepatitis B virus (HBV) and hepatitis C virus (HCV) are among the leading causes of chronic liver diseases worldwide. The two viruses, with or without complications such as cirrhosis and liver cancer, are responsible for a large part of the illness and death globally, directly or indirectly. Despite the fact that the scientific world has made huge advances in their diagnosis and treatment, HBV and HCV continue to pose a formidable challenge to health of communities around the world. The current paper seeks to comprehensively and comparatively describe the clinical and virological aspects of HBV and HCV including their epidemiology, pathogenesis, transmission, diagnosis, and therapy. Being a DNA virus, HBV can exist in the form of covalently closed circular DNA (cccDNA) which the cell nucleus can keep as a reservoir, and this persistence makes it possible that restoring a patient completely free of virus may not be achieved, and long-term treatment with antiviral drugs will be necessary in order to maintain a low level of viral load. On the other hand, HCV is an RNA virus and since does not have a stable intracellular reservoir it can be almost completely eradicated in most of cases by the use of direct-acting antivirals (DAAs). Such major differences have resulted the two viruses being targeted for very different prevention and treatment approaches. For instance, there is a highly effective vaccine against HBV while there is not yet a vaccine against HCV.This paper also discusses the major problems in disease control today such as underdiagnosis, restriction of treatment availability, and difficulties in the global elimination of viral hepatitis. By reviewing state-of-the-art knowledge and drawing attention to the main differences between HBV and HCV, the present work demonstrates that there is a great need for specific interventions, better healthcare services, and ongoing research to meet the target of eliminating viral hepatitis as a public health threat.

Keywords: Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Viral Hepatitis, Chronic Hepatitis, cccDNA,

INTRODUCTION

Contrarily, hepatitis B (HBV) and hepatitis C (HCV) are the primary etiologies of fatal liver diseases globally. In fact, these microorganisms are leading to almost 1.4 million deaths mostly because of cirrhosis and hepatocellular carcinoma (HCC) and are responsible for over 300 million people being infected chronically (CDC, n.d.-c). Nevertheless, even when HBV and HCV attack the same cell type (hepatocytes) and may cause the same clinical outcomes, these two viruses differ biologically, thus different clinical as well as public health approaches are required. The difference between these two viruses is clearest in their medical treatments. HBV, a DNA virus of the Hepadnaviridae family, creates a permanent nuclear reservoir of covalently closed circular DNA (cccDNA) from where it has not been removed by antiviral therapies (Revill et al., 2019; StatPearls, n.d.-a). Therefore, treatment is almost viral suppression by nucleos(t)ide analogues, a therapy which will most probably be continued for the patient's entire life (Hepatitis B Foundation, n.d.-b; PMC, 2015a). Still, a reliable and effective prophylactic vaccine is already available and can be the source of strong primary prevention (Hepatitis B Foundation, n.d.-a; WHO, n.d.-a). On the other hand, HCV is an RNA virus of the Flaviviridae family and is not linked to the stable nuclear reservoir. Nowadays, this shortcoming is made up for by direct-acting antivirals (DAAs), which in a short time of

therapy can cure more than 95% of the cases (CDC, n.d.-a; University of Washington, n.d.-b). Nevertheless, the absence of a vaccine means that there will always be new infections (Bailey et al., 2019).

Hence, the question arises that which is more important? To have a vaccine for HBV but no cure or to have a cure for HCV but no vaccine? This "therapeutic divide" delineates the battle against these viruses as well as shows the need for different strategies for each. Insufficient screening, diagnostics, and care access make these viruses, and particularly HBV and HCV, still a major health problem that results in the slow pace of reaching the World Health Organization's (WHO) objective of viral hepatitis eradication by 2030 (Lazarus et al., 2022; WHO, n.d.-b). Focusing review issues on clinical and virological aspects of HBV and HCV illustrates the intent to be both inclusive and critical of the changes occurring over time. A comparative review of their epidemiology, pathophysiology, diagnostic methods, treatment, and preventive measures will reveal not only the differences in problems but also the new common directions of these two issues for achieving global elimination goals.

METHODOLOGY

The present research is designed as a narrative literature review, aimed at providing a brief description of clinical and virological understandings of hepatitis B and hepatitis C which are still evolving. A thorough literature search was carried out through a range of electronic databases including PubMed, Google Scholar, ScienceDirect as well as official channels like WHO and CDC.

The appropriate literature was searched by combining different keywords such as, "Hepatitis B virus, " "Hepatitis C virus, " "viral hepatitis, " "HBV pathophysiology, " "HCV treatment, " "direct-acting antivirals, " and "cccDNA." The search was mostly directed towards the availability of recent references to maintain the currency of scientific data.

Inclusion Parameters

The articles were selected considering the following aspects:

- Research articles that are reviewed by peers, guidelines for clinical practices, and trustworthy reports
- The ones which are focused on epidemiology, pathophysiology, diagnosis, finding cures, or prevention of HBV and HCV
- Works published in English
- Most recent and pertinent literature reflecting present features

Exclusion Parameters

- Repeated studies
- Publications with very limited or not trustworthy data
- Non-scientific sources such as blogs or opinion-based content

The first set of collected data being titles and abstracts were screened which resulted in the extraction of appropriate articles for the full-text screen. The information acquired from the selected studies was painstakingly evaluated and divided into several thematic groups. The information drawn from different sources was cross-checked and combined so as to guarantee the correctness of data and fairness in interpretation.

Adopting this research strategy, a well-organized and comparative paper was written which outlines the principal clinical and virological features of hepatitis B and C.

Hepatitis B Virus (Hbv)

Hepatitis is associated with liver inflammation, the liver being one of the largest and most vital organs in the body, which among other things, is responsible for key metabolic, synthetic, and detoxification processes (Cleveland Clinic, n.d.). The swelling can be different depending on the source, for instance, it can be caused by toxins, alcohol, and the body's own immune system; however, viruses are a major etiology of the inflammations globally (CDC, n.d.-e). Hepatitis B is a unique, a little complicated, and a very serious situation in which the liver becomes inflamed due to infection with the Hepatitis B Virus (HBV) (Mayo Clinic, n.d.-b). The clinical course of the disease is like a coin having two sides; it represents an acute, self-limiting episode or can become a chronic, lifelong infection. It is the chronic form of the disease that is responsible for leading to the worst consequences of the disease, such as scarring of the liver and liver cancer (Mayo Clinic, n.d.-b; StatPearls, n.d.-a).

Epidemiology And Public Health Concern

Among viral hepatitis, which in total affect over 300 million people, HBV is one of the major contributors to the problem and thus is an infection with hepatitis B virus, which is a significant global health threat (CDC, n.d.-c). According to the most recent WHO report (2022), more than 254 million people are living with HBV on a long-term basis, and the number of new infections each year is close to 1.2 million (WHO, n.d.-a). Thus, HBV is still a major cause of death globally leading to over one million deaths annually and the main reason being complications such as liver cirrhosis and hepatocellular carcinoma (CDC, n.d.-c; WHO, n.d.-a). The epidemiological situation of HBV is changing as the highest prevalence of chronic infection can be observed in the WHO Western Pacific and African Regions, which together account for the vast majority of the global cases (WHO, n.d.-a). HBV is considered a leading cause of liver cancer worldwide, and even though a secure and very efficient preventive vaccine has been available for quite some time, a large proportion of the infected individuals remain undiagnosed and unmanaged (CDC, n.d.-d). This diagnostic gap leads to millions of people who do not know that they are infected and therefore they do not have access to the care that could stop the disease from progressing and at the same time, it allows the continuous spread of the virus within the communities (U.S. Department of Health & Human Services, n.d.).

Acute vs. Chronic Infection

The clinical outcome of an HBV infection depends on the host immune system's ability to clear the virus. An acute HBV infection is a short-term disease that happens within the first six months after the exposure. In more than 95% of the cases of immunocompetent adults, the immune system makes a successful attack that eliminates the virus, and the patient recovers completely and gets immunity for life (Bertoletti & Ferrari, 2021; StatPearls, n.d.-a).

On the other hand, a chronic HBV infection is a condition that arises when the immune system does not get rid of the virus. This condition is characterized, by the presence of Hepatitis B surface antigen (HBsAg), a major viral protein, in the patient's blood for six months or more (B Positive, n.d.). Whether an acute infection will become chronic is not a matter of chance; rather, it is almost entirely determined by the age at which the infection is acquired. The age-dependent outcome of the infection is the single most influential factor in the worldwide pattern of chronic hepatitis B (Liang, 2006; MedCrave, 2017). For instance, if the infection occurs during infancy or early childhood, especially through mother-to-child (vertical) transmission, then the child will develop chronic infection in around 95% of the cases. Meanwhile, if the infection is acquired in adulthood, the odds of it progressing to chronic will be less than 5% (WHO, n.d.-a).

The huge gap in the infection consequences between different ages of the patients serves as an argument for the worldwide public health measures targeted at HBV (Liang, 2006). Newborn or young child's immune system, which is still developing, usually does not reject the virus but rather completely tolerates it and hence, allows HBV to get

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a permanent residence in the body and thus, the infection lasts for a lifetime (Bertoletti & Ferrari, 2021). The biological facts in question turn the global infant vaccination program, and especially, the provision of a birth dose within 24 hours of life, into a very important, life-changing intervention rather than a regular vaccination (Hepatitis B Foundation, n.d.-a). The purpose of the birth dose is to evoke an immune reaction that will safeguard the infant before his/her immune system becomes tolerant to the virus, thus, the vertical transmission loop that is the main cause of the global chronic HBV reservoir will be broken (CDC, n.d.-d; WHO, n.d.-a).

Etiology and Pathophysiology of HBV

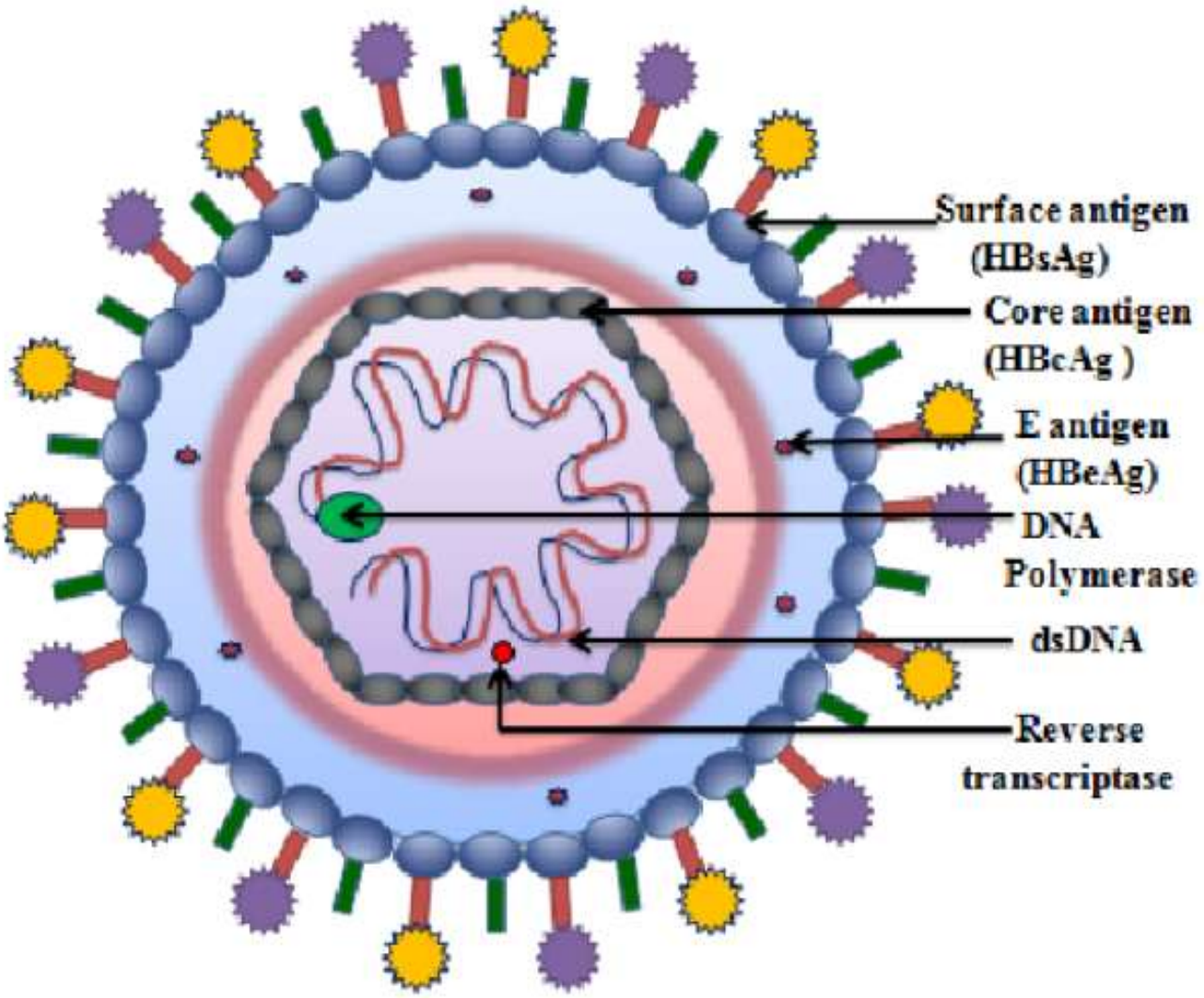

Figure 1: Structure of hepatitis B virus (HBV)

The main cause of Hepatitis B is a disease caused by a Hepatitis B virus (HBV) that is a member of the biologic class of viruses, which are the Hepadnaviridae family. The fully assembled, biologically active particle is called the 'Dane particle' named after the scientist who found it. It is a concentric, two-shelled, globular assembly of about 42 nanometers in diameter (StatPearls, n.d.-a).

The virus has a complicated architecture. It has an external lipid envelope with some viral surface proteins embedded in it, which are generally termed the Hepatitis B surface antigen (HBsAg). This antigen is extraordinarily over-produced during virus replication and is also released into the blood, as non-infective spheres and filaments; thus,

it is the substance on which the main diagnostic blood test is based (B Positive, n.d.; PMC, 2015b). An icosahedral nucleocapsid or core made up of the Hepatitis B core antigen (HBcAg) is what is under the envelope. This core unit not only holds the viral genome but also contains the viral DNA polymerase, which is an enzyme with reverse transcriptase activity (StatPearls, n.d.-a). The viral genome is in fact, very different from other genomes; it is a tiny, relaxed circular, partially double-stranded DNA of about 3.2 kilobases (StatPearls, n.d.-a). What is more, the genome is a very good one: it has four overlapping open reading frames (ORFs) for proteins which are encoded by one and the same genetic sequence: the S gene that encodes the surface proteins, the C gene for the core and 'e' antigens, the P gene for the polymerase, and the X gene for the regulatory X protein (StatPearls, n.d.-a; WHO, n.d.-c).

The Viral Lifecycle: Hepatocyte Entry, Replication, and the Persistence of cccDNA

The HBV lifecycle is a hepatotropic one in which the virus goes after the liver cells (hepatocytes) and multiplies there. The virus, after being in the blood, goes to the liver where the S1 domain of the HBsAg protein of the viral envelope binds with a very specific receptor on the surface of hepatocytes that is called Sodium taurocholate co-transporting polypeptide (NTCP) (Exploration Pub, 2020; Urban et al., 2021). The virus gains entry into the cell through this binding interaction. After the virus is internalized, the viral nucleocapsid is taken to the cell nucleus. Alongside viral polymerase, the cell polymerase completes the synthesis of the partially double-stranded DNA genome, which is then ligated by host enzymes to produce a very stable, independent circular DNA molecule. This molecule is known as covalently closed circular DNA (cccDNA) (Revill et al., 2019).

This cccDNA acts as the viral minichromosomal and is the main source for transcription of viral mRNAs by the host cell's RNA polymerase. All mRNAs are then transported to the cytoplasm, where they are translated into viral proteins (Revill et al., 2019; StatPearls, n.d.-a).

A critical point for replication is the encapsulation of pregenetic RNA (pgRNA), a specific mRNA, together with viral polymerase, inside the newly made core particles. In these immature capsids, the polymerase, by its reverse transcriptase activity, synthesizes the DNA genome by using the pgRNA as a template (StatPearls, n.d.-a). After that, the DNA-containing nucleocapsids are either enveloped and secreted from the cell as new infectious virions or they can be recycled back to the nucleus to replenish the pool of cccDNA (Revill et al., 2019). The presence of the cccDNA reservoir in the nuclei of long-lived hepatocytes is the major reason why antiviral therapy fails to cure the infection completely (PMC, 2015a). These drugs do not allow the elimination of cccDNA hence the virus can return if the drug is stopped, though they are able to block the reverse transcriptase step very efficiently, thereby ruling out new virus formation (Hepatitis B Foundation, n.d.-b; Viral Hepatitis and Liver Disease, n.d.-a).

Modes of Transmission: Vertical, Horizontal, Sexual, and Parenteral Routes

HBV spreads when blood, semen, or other body fluid containing the virus of an infected person is introduced into the body of a percutaneous exposure means the virus enters the body through the skin, while mucosal exposure is a contact with the mucus membrane, and non-intact skin exposure means the virus comes in contact with a skin area that has cuts, abrasions, or other lesions. The virus is extremely resistant and can still infect a person if it is picked up from a contaminated surface that has been there for seven or more days without any disinfection. This is one of the reasons why it can spread so fast. It should also be kept in mind that HBV cannot be transmitted through by individuals to other members of the family in the same household. Transmission via sharing food and water is also impossible (U.S. Department of Health & Human Services, n.d.). The main sources of transmission are divided into the following categories:

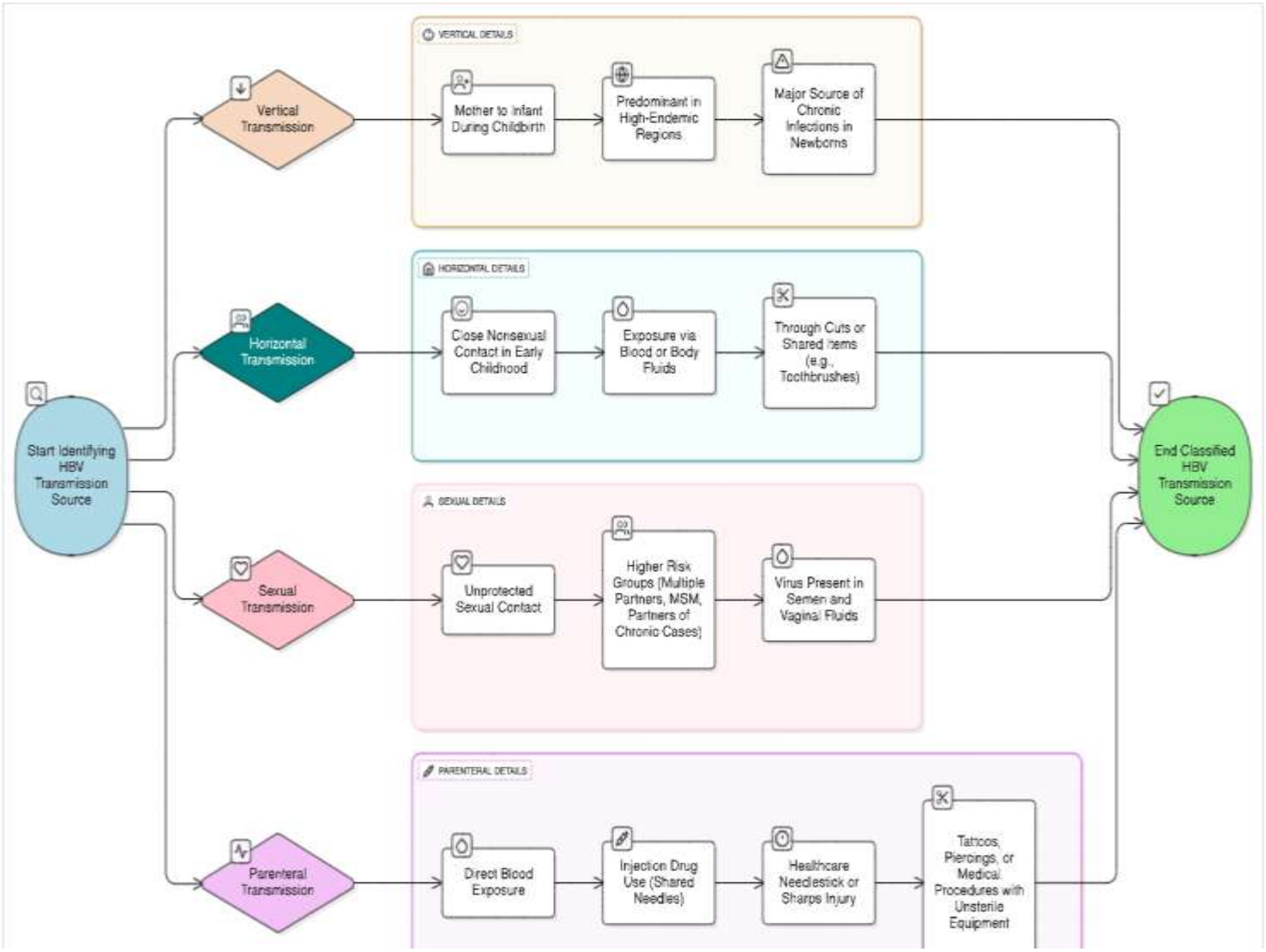

Figure 2: Modes of transmission of HBV virus

The combination of the virus's environmental stability and the persistence of its cccDNA template in the host creates a uniquely formidable challenge (Revill et al., 2019). The virion's ability to survive for a week outside the body means that prevention strategies must extend beyond managing direct fluid exposure to include stringent infection control in healthcare, meticulous household hygiene, and the regulation of cosmetic industries like tattooing and piercing (CDC, n.d.-d). Concurrently, the internal persistence of cccDNA dictates the clinical management paradigm (Mayo Clinic, n.d.-c). Because the viral "master copy" cannot be eliminated, the goal of therapy shifts from eradication to long-term suppression, often requiring lifelong medication (Hepatitis B Foundation, n.d.-b). This has profound implications for patient adherence, the potential for long-term drug side effects, and the overall economic burden of the disease (PMC, 2010). These two virological properties are thus the root causes of the distinct public health and clinical strategies that define the global response to HBV (CDC, n.d.-d; WHO, n.d.-a).

Clinical Manifestations and Complications: Symptomatology of Acute and Chronic HBV Infection

One of the most important aspects of HBV infection is the fact that it is frequently subclinical or asymptomatic, especially in early stages and in infants. A large number of newly infected people do not make any attempts to find out that they are infected (Mayo Clinic, n.d.-b).

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Symptoms of acute hepatitis B usually appear one to four months after the initial viral contact. The time of the disease may be anywhere from two weeks to five months, the clinical presentation is mostly non-specific and flu-like. Typical signs and symptoms are (Mayo Clinic, n.d.-b; StatPearls, n.d.-a):

- Extremely low energy and feeling weak
- Fever
- Loss of appetite, nausea, and vomiting
- Abdominal pain, particularly in the right upper quadrant which is the area of the liver
- Joint pain (arthralgia)
- Urine with dark color and stools with a light color
- Jaundice, that is, yellowing of the skin and the whites of the eyes, caused by high levels of bilirubin

Through chronic hepatitis B, the patient exhibits symptoms that develop slowly and quietly most of the time. The biggest percentage of people who have chronic HBV do not experience any symptoms for a considerable number of years, even for a couple of decades, and probably think that they are in a good state of health. Usually, symptoms are noticed only after the virus has done extensive and very often permanent damage to the liver. In the case when the chronic phase symptoms appear, they can be characterized as constant tiredness and mild, intermittently recurrences of symptoms from the acute phase (Mayo Clinic, n.d.-b; StatPearls, n.d.-a).

The Natural History of Chronic Hepatitis B: Clinical Phases

The chronically infected hepatic HBV condition is not a fixed situation but rather a fluid one. It goes through different stages. These stages are actually the result of a play between the viral replication level (measured by HBV DNA and HBeAg status) and the immune response of the host (serum ALT levels). Knowledge of these stages is vital for making prognosis and the associated therapy decisions, especially antiviral ones (University of Washington, n.d.-a).

- Phase 1: HBeAg-positive Chronic Infection (former "Immune-Tolerant Phase"): This phase is typically found in individuals who got their infection either at birth or during early childhood. Very high viral load and HBeAg positivity characterize the phase, but serum ALT levels keep on being normal. It appears that the immune system of the host "tolerates" the virus, thus liver inflammation and liver fibrosis remain minimal or at a very low level although viral replication is high (Bertoletti & Ferrari, 2021; University of Washington, n.d.-a).

- Phase 2: HBeAg-positive Chronic Hepatitis (formerly "Immune-Active" or "Immune-Clearance Phase"): The immune system is shown here as being capable of recognizing and therefore killing the HBV-infected hepatocytes. This is also confirmed by the presence of increased and sometimes fluctuating ALT levels, which are inflammatory markers of the liver, thus indicating that the liver is actively inflamed. The virus is still replicating at a high rate and the HBeAg is positive. This stage goes along with continuous liver destruction and thus is usually the time when doctors start antiviral treatment (University of Washington, n.d.-a; Viral Hepatitis and Liver Disease, n.d.-a).

- Phase 3: HBeAg-negative Chronic Infection (former "Inactive Carrier State"): Following the immune-active phase, the loss of HBeAg and appearance of antibodies to HBeAg (anti-HBe) may mark this phase. It is characterized by extremely low or even undetectable levels of HBV DNA together with ALT levels that are

normal and stable over time. Patients in this stage have a significantly lower risk of disease progression; however, still, the possibility of reactivation remains (B Positive, n.d.; University of Washington, n.d.-a).

- Phase 4: HBeAg-negative Chronic Hepatitis (Reactivation Phase): A reactivation of HBV could happen to an inactive carrier indifference, which means that the virus is replicating at a minimum level. When this occurs, the HBV DNA levels are on the rise and at the same time ALT is also high though HBeAg is absent in such a case. Most of the time, this reactivation is attributed to the presence of mutations in the precore or core promoter regions of the viral genome that consequently lead to the cessation of HBeAg production. This stage is very likely to be followed by a progression towards cirrhosis and liver cancer (University of Washington, n.d.-a).

Long-Term Sequelae: Progression to Cirrhosis, Hepatocellular Carcinoma (HCC), and End-Stage Liver Disease

Untreated chronic hepatitis B continues to be one of the major factors leading to severe and fatal liver diseases. As the immune system causes inflammation to fight the virus, the liver tissue is being destroyed step by step, the patient eventually faces a whole series of complications. The experts estimate that 15% to 25% of the people with a chronic infection will be burdened with liver pathology during their lifetime (WHO, n.d.-a). First and foremost, long-term complications may include:

- Cirrhosis: It is an effect of the situation, when the liver is inflamed for a long time and the condition is kept very persistent. The damaged liver tissue has been replaced with scar tissue (fibrosis), which has destroyed the liver's structure and rendered it unable to function properly. Cirrhosis is an essential source of risk for other very serious problems that can happen in HBV patients (Mayo Clinic, n.d.-b; StatPearls, n.d.-a).

- Hepatocellular Carcinoma (HCC): In fact, chronic HBV infection is ranked among the top risk factors leading to liver cancer of primary origin worldwide (Mak et al., 2020). One of the most alarming and dangerous characteristics of the HBV is that it has the potential to cause cancer directly. The virus can integrate its genetic material to the genome of the infected liver cell, which eventually leads to disruption of the cellular normal processes and cancer induction directly (Mak et al., 2020; StatPearls, n.d.-a). This is to say that, unlike hepatitis C, in which cancer normally occurs in the already cirrhotic liver, HBV can cause HCC in patients without cirrhosis (Hepatitis B Foundation, n.d.-c). The biological difference between these two has deep clinical consequences, as it requires a different and much wider approach in monitoring liver malignancy in HBV patients. Thus, screening for HCC (for example, liver ultrasound) can only be restricted to those with cirrhosis; it has to be broadened to cover more patients with other risk factors such as age, viral activity, and family history (Mak et al., 2020).

- Liver Failure (Decompensation): The progression of cirrhosis can lead to liver failure in an individual. This is a complicated scenario in which the liver is unable to carry out its vital functions. Sometimes, this may be shown by acute liver failure, whereas mostly it is a situation of decompensated cirrhosis with signs such as ascites (the build-up of fluid in the belly), variceal bleeding, and hepatic encephalopathy (brain dysfunction). At this point, a liver transplant may be the only way to keep the patient alive (Mayo Clinic, n.d.-a; StatPearls, n.d.-a).

- Other Conditions: Besides that, chronic HBV infection has also been linked with the development of extrahepatic conditions, such as some types of kidney disease (glomerulonephritis) and inflammation of blood vessels (vasculitis) (StatPearls, n.d.-a).

Diagnosis and Monitoring: Biomarkers of Liver Injury: Interpreting Liver Function Tests (LFTs)

The initial part of the evaluation for a patient with suspected viral hepatitis is usually a set of blood tests that are often called liver function tests (LFTs). In fact, most of these tests should be regarded as markers of liver injury or

inflammation rather than actual function tests since they show aspects of damage to the liver cells (AASLD, n.d.; Cleveland Clinic, n.d.). The aminotransferases are the most significant of these for hepatitis B:

- Alanine Aminotransferase (ALT): An enzyme that is essentially related to the liver. When liver cells are damaged, ALT is mixed with blood, so it is a very specific factor for liver damage. Normal levels are quite often from 7 to 55 units per liter (U/L) (AASLD, n.d.; StatPearls, n.d.-b).

- Aspartate Aminotransferase (AST): This enzyme is a derivative of the liver as well, but the tissues of the heart, skeleton muscle, and the production of red blood cells may also implicate. Therefore, its increase is less indicative of liver disease than that of ALT. Normal levels are for the most part from 8 to 48 U/L (AASLD, n.d.; StatPearls, n.d.-b).

When viral hepatitis is considered, most of the damage is of hepatocellular type which means that the ALT and AST levels are very much higher than those of other liver enzymes such as alkaline phosphatase (ALP) and markers like bilirubin (AASLD, n.d.). The extent and duration of ALT elevation are playing a very important role in the chronic HBV diagnosis process and they are the main factors in determining the time for antiviral therapy (University of Washington, n.d.-a).

Serological Markers: A Detailed Guide to the HBV Panel

The definitive diagnosis of an HBV infection is based on a panel of serological tests that identify the specific viral antigens (the parts of the virus) and the antibodies produced by the host's immune system. The interpretation of the combination of these markers is what determines the infection status (acute, chronic, or resolved) and the immune status (susceptible or immune) of the individual most accurately (B Positive, n.d.; Michigan Department of Health and Human Services, n.d.).

Essentially, the serology panel for HBV consists of the following components:

- HBsAg (Hepatitis B Surface Antigen): This is the main indicator of one active infection. The detection of HBsAg in the blood means that the person is infected with HBV right now, and thus, the infection is potentially transmissible. After exposure, the marker is the first to be detected (within 1 to 10 weeks). When the indicator is still found after six months, HBV infection is considered to be of the chronic type (B Positive, n.d.; PMC, 2015b).

- Anti-HBs (Antibody to HBsAg): This should be a neutralizing antibody since it gives protection. Finding one's presence means that the body is immune to HBV. The immunity may come from a complete vaccination program or recovery after a past infection that has been solved. After vaccination, this is the only marker that can be detected (B Positive, n.d.; Hepatitis B Foundation, n.d.-a).

- Total Anti-HBc (Total antibody to HBcAg): This antibody is directed against the core antigen of the virus. Its presence essentially means that the person has been infected with HBV at some point, may be currently or in the past. It is not a protective antibody and is usually retained for life after the infection. It is an indicator of the virus contact (B Positive, n.d.; Song, 2016).

- IgM Anti-HBc (IgM class antibody to HBcAg): This is an anti-HBc specific class that is associated with the early phase of an infection and only one. The presence of this antibody is the main criterion in the detection of a recent or acute infection (typically within the last six months). A chronic infection is differentiated from an acute one by this marker (B Positive, n.d.; Michigan Department of Health and Human Services, n.d.).

- HBeAg (Hepatitis B e antigen): Being a protein of the viral core, HBeAg is an indicator of vigorous viral replication and, thus, high infectivity. Its presence is associated with high levels of HBV DNA in the blood (B Positive, n.d.; University of Washington, n.d.-a).

- Anti-HBe (Antibody to HBeAg): The obtaining of this antibody (the disappearance of HBeAg is usually accompanied by a process called seroconversion) in general, indicates a change to a state of less viral replication and thus, low infectivity (B Positive, n.d.; University of Washington, n.d.-a).

Molecular Diagnostics: The Role of HBV DNA Quantification (Viral Load)

In addition to serology, molecular tests that quantify viral genetic material are very important in the case of chronic HBV. Quantitative HBV DNA testing, or in short measuring the viral load, is the most direct way to know the replication of the virus. The level of HBV DNA is instrumental in helping to achieve, diagnose, and treat several important medical decisions. (Viral Hepatitis and Liver Disease, n.d.-a):

- Monitoring Disease Activity: Viral load level is one of the most significant indicators that can forecast how severe the liver disease will be. According to the studies, patients with high viral loads have twice the risk of liver disease, cirrhosis, or HCC development.

- Treatment Decisions: The amount of HBV DNA is a decisive factor together with ALT levels and fibrosis stage in the indication of antiviral therapy initiation.

- Assessing Treatment Response: The main treatment goal is the reduction of HBV DNA to a level that is undetectable or the total elimination of HBV DNA from the biological sample, and this is generally what treatment effectiveness is based on.

Diagnostic Algorithms and Interpretation of Serological Patterns

A full diagnosis of hepatitis B is normally done by looking at the serological panel pattern results rather than a single test. The CDC is now advising a one-time screening all adults with a triple panel of tests including HBsAg, anti-HBs, and total anti-HBc to detect hepatitis B infection (CDC, n.d.-e). A single blood sample is sufficient to know the complete HBV profile of an individual.

Different common serological patterns along with their interpretations are presented in the table below. This table is an aid tool to healthcare professionals to understand complicated lab results and then convert them into a clear clinical diagnosis. Understanding differences between states such as acute infection, chronic infection, and immunity due to vaccination or natural infection is essential for the correct management, counseling of the patient, and public health measures implementation (B Positive, n.d.; Michigan Department of Health and Human Services, n.d.).

Table 1: Diagnostic algorithms and interpretation of hepatitis B virus serological patterns

HBsAg	Total anti-HBc	IgM anti-HBc	Anti-HBs	Interpretation
--	--	--	--	Susceptible: Not immune and never infected. Vaccination is advised.
+	+	+	--	Acute Infection: A recent HBV infection
+	+	--	--	Chronic Infection: Infected with HBV for longer than six months is considered a chronic infection. Calls for additional assessment and observation

--	+	--	+	Immune due to Natural Infection: Has recovered from an infection and is shielded from new infections
--	--	--	+	Immune because of Vaccination: Vaccination has successfully protected against HBV infection. No indication of a previous infection

Treatment and Prevention: Goals of Chronic Hepatitis B Therapy

- The comprehensive diagnosis is not achieved through a single test but rather through understanding the pattern of results from the serological panel. The U.S. Centers for Disease Control and Prevention (CDC) presently suggests that all adults should be screened once for hepatitis B by a triple panel that includes HBsAg, anti-HBs, and total anti-HBc (CDC, n.d.-e). This method makes it possible to fully depict a person's HBV condition from one blood sample.

- The treatment of chronic hepatitis B has changed dramatically and now includes definite therapeutic objectives to enhance the patient's clinical outcome in the long run. Because the available medicines cannot remove the persistent cccDNA completely, the overall aim is not to achieve a sterilizing cure but rather a functional cure or control of the virus (Revill et al., 2019; Viral Hepatitis and Liver Disease, n.d.-a).

- The most important long-term goals of treatment are those of preventing the clinical progression of the disease, i.e. to lower the risk of cirrhosis, liver failure, hepatocellular carcinoma (HCC), and consequently, reduce liver-related mortality and increase patient survival (Hepatitis B Foundation, n.d.-b; Viral Hepatitis and Liver Disease, n.d.-a).

- Treatment moves towards immediate and intermediate goals (University of Washington, n.d.-a; Viral Hepatitis and Liver Disease, n.d.-a) in order to realize these long-term effects of therapy:

- Virologic Suppression: The main immediate goal is to attain a continuous suppression of viral replication as evidenced by the reduction of serum HBV DNA levels to the minimal value possible and, ideally, below the detection limits.

- Biochemical Remission: The aim of the treatment is, at the same time, to normalize serum ALT levels. This represents a biochemical remission which is an indirect way of hepatic inflammation being absent.

- Serologic Response: The intermediate point of treatment in initially HBeAg-positive patients is to bring about the disappearance of HBeAg and consequent development of anti-HBe (HBeAg seroconversion). This indicates a state of viral replication at a lower level.

- Functional Cure: The loss of HBsAg, with or without the formation of anti-HBs, is, in fact, the rare yet desirable kind of therapeutic endpoint, i.e., the so-called "functional cure". It implies the best prognosis in the long term.

Pharmacological Interventions: Nucleos(t)ide Analogues and Pegylated Interferon

The choice of starting chronic HBV therapy is complicated as well as different for each person. Treatment is not advised for all infected people, e.g., those in the immune-tolerant or inactive carrier phases. As a rule, those suffering from hepatitis which is going to get worse and has been proven by a combination of high HBV DNA levels, ALT persistently elevated, and/or at least moderate liver inflammation or fibrosis by non-invasive tests or liver biopsy, are considered for therapy (University of Washington, n.d.-a).

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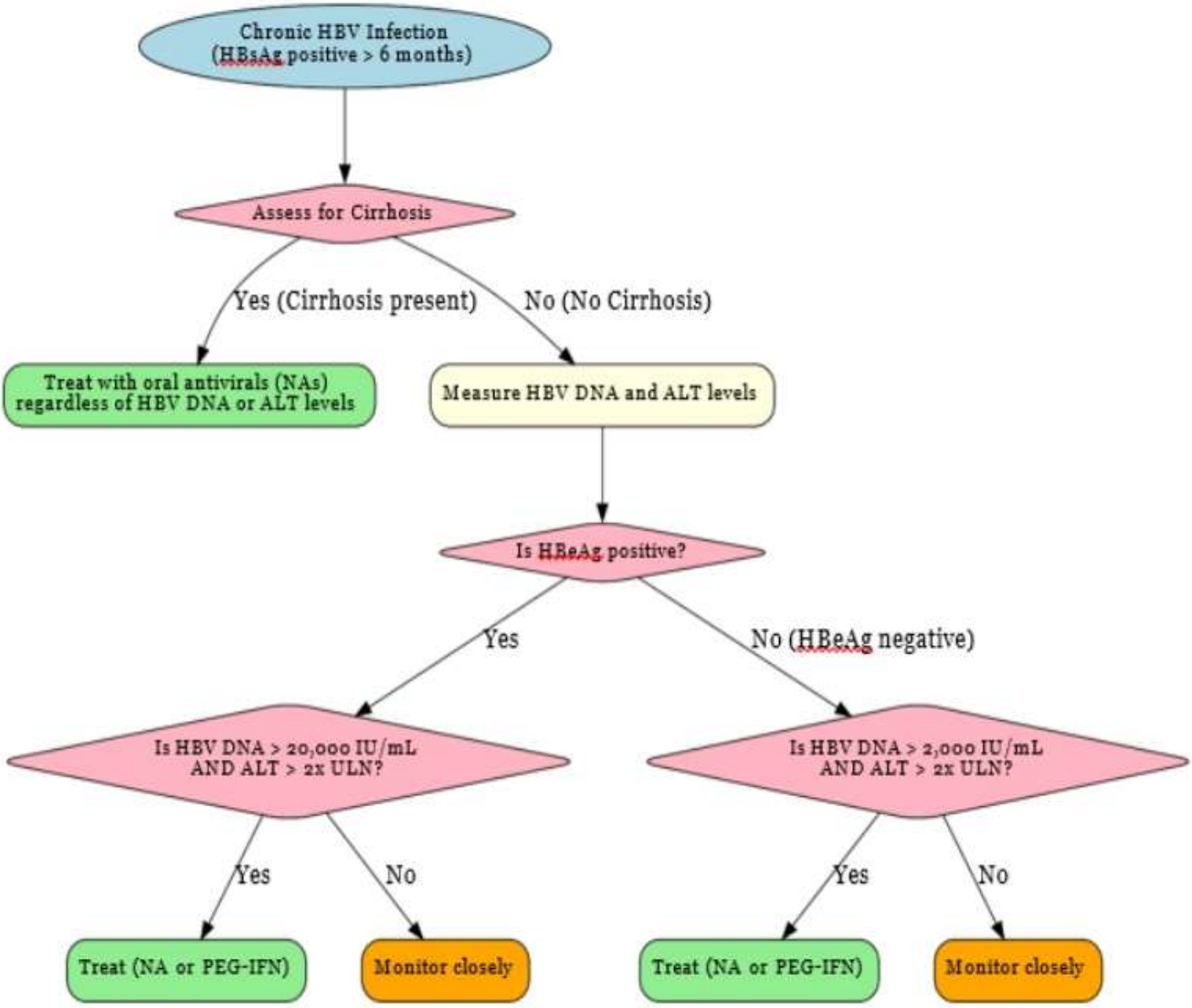

Figure 3: Chronic HBV treatment decision flowchart for non-cirrhotic patients.

The therapy of chronic hepatitis B is grounded in pharmaceutics of two main drug classes:

- Nucleos(t)ide Analogues (NAs): NAs are one of several oral antiviral drugs and also form the basis of contemporary HBV therapy. They shut down the HBV polymerase enzyme, particularly its reverse transcriptase activity, by one step in the process of viral replication in the enzyme is inhibited. Hence, HBV DNA levels get a very potent and fast reduction (PMC, 2015a; PMC, 2022). NAs are known for their good tolerance and effectiveness in virus suppression. Nevertheless, they do not allow eradication of cccDNA, thus treatment can be a long-term one, most probably lifelong, in order to keep viral suppression and avoid relapse (PMC, 2015a; Viral Hepatitis and Liver Disease, n.d.-a).

- Pegylated Interferon (PEG-IFN): This drug is one which regulates the immune system and is given a single dose under the skin. In contrast with NAs that harm the virus directly, interferon uses the host's reworked and

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume XI Issue III March 2026

strengthened immune system for the recognition and clearance of HBV-infected cells (Hepatitis B Foundation, n.d.-b; Viral Hepatitis and Liver Disease, n.d.-a). PEG-IFN's greatest benefit is its being administered for a limited period (usually 48 weeks), and thus, the chance of a lasting immune control of the virus even after the discontinuation of therapy. However, it also comes with a lower virologic response rate than NAs, and the side effects are numerous, among which are flu-like symptoms, fatigue, depression, and bone marrow suppression. For this reason, it is mainly employed in patients who meet specific criteria, like young people with the active form of the disease who intend to forego treatment of indefinite duration (Hepatitis B Foundation, n.d.-b; Viral Hepatitis and Liver Disease, n.d.-a).

Deciding on one of these drugs strategies means having two mutually exclusive options on the table.

Firstly, NAs assure a very strong and almost complete viral suppression but on the other hand, the patient must continue treatment for an indefinite period thus, there are issues related to treatment adherence and safety in the long run (PMC, 2022). Secondly, one could consider PEG-IFN as an alternative promising a limited duration of treatment and the likelihood of a durable, immune-mediated response, but the extra-package here is that the treatment is very toxic to the patient and the chance of success is much lower (Viral Hepatitis and Liver Disease, n.d.-a).

This situation is at the core of a highly personal treatment decision where the patient's virologic profile, liver disease severity, age, comorbidities, and personal preferences need to be taken into account simultaneously (University of Washington, n.d.-a).

Table 2: Characteristics and comparison of nucleos(t)ide analogues and pegylated interferon

Therapy Class	Agent(s)	Administration	Typical Duration	Key Advantages	Key Disadvantages / Common Side Effects
Nucleos(t)ide Analogues (NAs)	Entecavir (ETV), Tenofovir disoproxil (TDF), Tenofovir alafenamide (TAF)	Oral (one pill each day)	Long-term, frequently lifetime,	Strong suppression of viruses, good tolerability, and low resistance rates (for first-line medicines	Does not remove cccDNA, necessitating ongoing treatment; may cause problems with bone density and kidney function (TDF)
Pegylated Interferon (PEG-IFN)	Peginterferon alfa-2a	Weekly subcutaneous injection	Limited (usually 48 weeks),	Limited treatment time; possibility of long-term immunological control loss and HBsAg reduction	notable adverse effects (fatigue, depression, flu-like symptoms, and cytopenias); a decreased rate of virologic response in comparison to NAs

Prevention: The Central Role of Vaccination and Post-Exposure Prophylaxis

Due to the complicated nature of chronic HBV treatment, prevention should be considered as the best way to neighbour this disease (CDC, n.d.-d).

- Vaccination: Most important in the prophylaxis against HBV is firstly a vaccination. Hepatitis B vaccine is an extremely safe and efficient recombinant vaccine, which provides long-term, probably lifelong, protection against the infection (Hepatitis B Foundation, n.d.-a). Therefore, it is regarded as the first "anti-cancer" vaccine because it prevents one of the leading causes of liver cancer (WHO, n.d.-a). The CDC identifies vaccination at birth as a must for all infants, next for children and adolescents up to 18 years of age who have not been vaccinated yet, and lastly for all adults aged 19-59 years. Also, adults aged 60 and above with risk factors are recommended to be vaccinated (CDC, n.d.-d; Hepatitis B Foundation, n.d.-a).

- Post-Exposure Prophylaxis (PEP): PEP through timely intervention can avert infection for unvaccinated or partially vaccinated individuals with a known exposure to HBV. In case of a Hepatitis B immune globulin (HBIG) introduction, it can provide an immediate passive immunity, and at the same time, the first dose of the hepatitis B vaccine can be given. It is less than 24 hours after the exposure that such a combination works best to counteract the isolation of the pathogens and their neutralization as well as the beginning of the immunization process (CDC, n.d.-d; U.S. Department of Health & Human Services, n.d.).

- Prevention of Perinatal Transmission: Stopping mother-to-child transmission is considered as the essential aim of the public healthcare system. Maternally universal screening of HBsAg is performed with the help of a multidisciplinary plan that also administers HBIG and the first dose of the hepatitis B vaccine to infants within 12-24 hours after birth followed by completion of the full vaccine series (Bailey et al., 2019). By way of illustration, mother to an HBV infection with high HBV DNA levels can decrease the chance of a baby's getting the virus significantly if she treated her last trimester with an antiviral drug (usually tenofovir) (WHO, n.d.-a).

Hepatitis C Virus (Hcv)

Hepatitis C is a liver inflammation condition caused by the Hepatitis C Virus (HCV). The disease is called an "epidemic without a face" as most of the infected people do not show symptoms for a very long time, often for several decades. In most cases, they find out that they are infected only when it is diagnosed through routine tests or when they see the signs of the advanced liver diseases such as cirrhosis (CDC, n.d.-a; Mayo Clinic, n.d.-c). This dangerous feature makes it a serious problem of public health. The WHO estimated that, in 2019, 58 million people were living with chronic HCV infection globally, and there were almost 1.5 million new cases each year (CDC, n.d.-a; WHO, n.d.-b).

Epidemiology and High-Risk Population

Hepatitis C is a severe public health challenge and accounts for a significant number of liver transplants and incidences of liver cancer (hepatocellular carcinoma) in many areas of the world (CDC, n.d.-a). The infection is mostly spread through contaminated blood exposure (Elsevier, 2019). Consequently, the disease's epidemiology is directly dependent on behaviors and exposures that result in blood-to-blood contact (PMC, 2010). In wealthy countries, the most significant cause of HCV transmission is the sharing of contaminated needles, syringes, and other equipment for injection drug use without proper sterilization (WHO, n.d.-a; American Society for Microbiology, 2016). Besides that, the following groups are at a higher risk of infection: (CDC, n.d.-a; HIV.gov, n.d.)

- Those who underwent blood transfusions or solid organ transplants before 1992, i.e., the time when screening of the blood supply for HCV was not yet routinely done

- Workers in the healthcare and public safety sectors who have been incidentally pricked by a needle or other sharps in a situation involving exposure to blood and have suffered injuries to the workplace.

- People living with HIV, as a result of shared transmission routes.

- Men who have sex with other men, particularly those involved in high-risk sexual behaviors.
- Children born to mothers infected with HCV.

The High Propensity of Chronicity

One of the main characteristics of the HCV infection is the very high chance of it being persistent after the short initial, acute phase. Unlike HBV infection acquired in adulthood which is generally resolved, acute HCV infection leads to a chronic, lifelong infection in most cases (CDC, n.d.-a). The figures put the proportion of individuals infected with HCV who will not only fail to clear the virus on their own but also develop chronic hepatitis C at more than half and even up to 75-85%, if they are not given any treatment (Mayo Clinic, n.d.-c; PMC, 2010). Only a very small percentage, roughly 15-30% of cases, achieve spontaneous viral clearance (CDC, n.d.-a).

The predominance of asymptomatic clinical course along with an extremely high chronicity rate in this disease entity pose an ideal situation for a silent public health problem to develop (CDC, n.d.-a). It allows for the existence of a large reservoir of chronically infected individuals in the population, of whom a considerable number are not aware of their infection. These people are susceptible to liver disease progression and can in turn infect others without being aware of it (CDC, n.d.-e). The biological truth of the matter renders the strategy of waiting for patients with symptoms to present as basically ineffective. Rather, it calls for a proactive public health strategy that revolves around population-based screening to uncover this silent reservoir of infection well before the occurrence of irreversible liver damage (CDC, n.d.-a). The CDC recommendation for one-time universal HCV screening for all adults along with targeted screening for high-risk groups is most fundamentally explained by this argument (CDC, n.d.-e).

The Hepatitis C Virus: An RNA Virus of the Flaviviridae Family

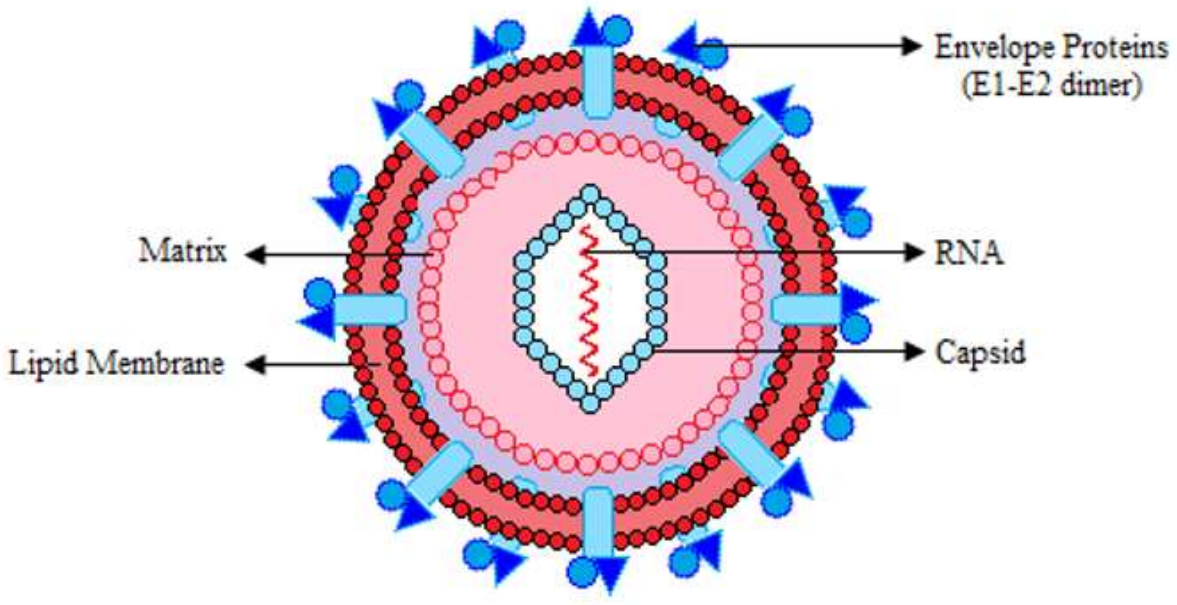

Figure 4: Chronic HBV treatment decision flowchart for non-cirrhotic patients

Hepatitis C is mainly the result of HCV, which is a tiny, enveloped, positive-sense single-stranded RNA virus. It shares the genus Hepacivirus of the Flaviviridae family with the viruses causing dengue fever and yellow fever (MDPI, 2023).

The HCV genome is a little less than 10 kilobases long and comprises only one large open reading frame. The frame encodes a single polyprotein of approximately 3000 amino acids. The polyprotein is later divided by proteases from both the host and the virus into ten different proteins. Three of these are structural proteins (the core protein, the protein that makes the viral capsid, and two envelope glycoproteins, E1 and E2) and seven non-structural (NS) proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B). These non-structural proteins are the ones to form the viral replication complex and, thus, they are the foremost targets of the newly introduced, extremely potent direct-acting antiviral agents (MDPI, 2023; Oxford Academic, 2012).

Genetic Diversity: Genotypes, Subtypes, and Implications for Treatment

One of the main features of HCV is its extremely diverse genetic makeup. The virus's RNA-dependent RNA polymerase is without a proofreading function, a fact that explains its very high mutation rate during replication (Frontiers in Microbiology, 2018). Because of this, HCV is classified as having at least eight different major genotypes (1 to 8) and a large number of subtypes (e.g., 1a, 1b, 2a, 3a) (Mayo Clinic, n.d.-b; Mayo Clinic Labs, n.d.).

The genetic variation of the virus also influences the disease significantly. The genotype of the patient's virus was, for example, one of the most important factors used to predict the treatment outcome of interferon-based therapies (Oxford Academic, 2012). Now, when broad-spectrum direct-acting antivirals (DAAs) are available, which can cure almost any genotype, a genotype test is still considered useful in patient management (University of Washington, n.d.-b). The genotype determination can serve as a tool for the healthcare provider in deciding the optimal DAA regimen, the required therapy duration, and the likelihood of drug resistance (University of Washington, n.d.-b; Viral Hepatitis and Liver Disease, n.d.-b).

Modes of Transmission: The Primacy of Parenteral Exposure

HCV is known to be transmitted through contaminated blood. Its transmission usually happens when infectious blood is introduced directly into the body through the skin (Elsevier, 2019).

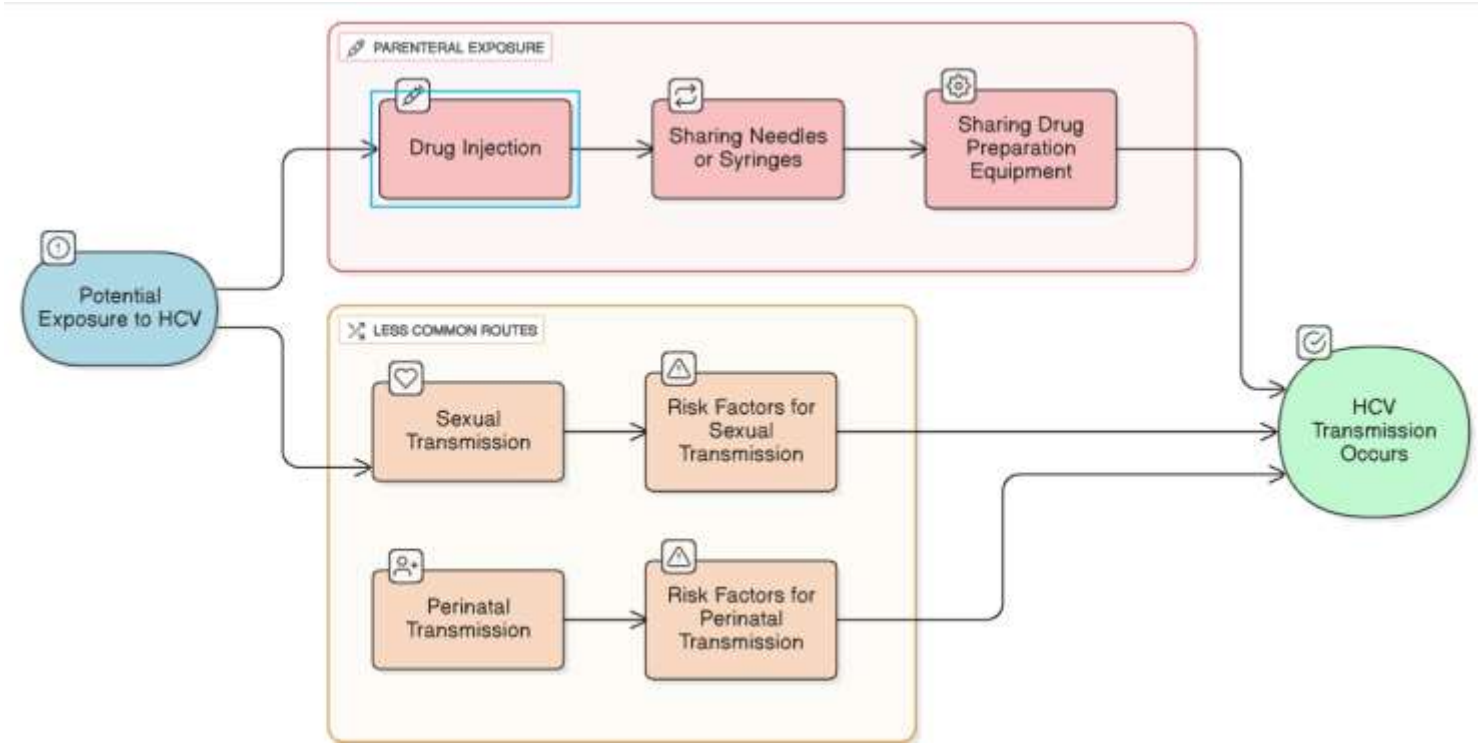

Figure 5: Modes of transmission of HBV virus.

The most basic underlying virology of HCV not only governs its clinical features but also determines its therapeutic sensitivity capabilities. It is an RNA virus with a single polymerase that is prone to errors, and at a very high rate, it produces vast genetic variations that allow it to escape the immune system, and as a result, have complicated treatment for a long time (Frontiers in Microbiology, 2018). But this is only its extreme weakness. Unlike HBV, HCV does not locate its stable latent viral reservoir such as cccDNA in the nucleus of the host cell; rather its whole replication cycle takes place in the cytoplasm (MDPI, 2023). So, if viral replication is completely and regularly prevented, the virus is eliminated from the patient's body. There is no hidden source from which it can grow again (CDC, n.d.-a). This biological fact is the main reason why HCV is termed a curable disease with DAAs that are very efficient in blocking the replication enzymes that are the most important (University of Washington, n.d.-b). The "sloppy" manner in which the virus replicates and the absence of a persistent nuclear form make it an ideal candidate for complete eradication (CDC, n.d.-a; MDPI, 2023).

Clinical Manifestations and Complications: The Asymptomatic Nature of Acute and Chronic HCV Infection

The clinical course of both acute and chronic HCV infection is characterized by the absence of recognizable symptoms in most patients. The subclinical condition is mainly responsible for the fact that the diseases are incompletely diagnosed and thus, the patients remain undetected for a long time (CDC, n.d.-a; Mayo Clinic, n.d.-c). Their manifestation is usually 2 to 12 weeks after exposure in the case of acute HCV infection if symptoms do occur. The symptomatology is mostly cheap, nondescript, and they cannot be differentiated from other types of acute viral hepatitis.

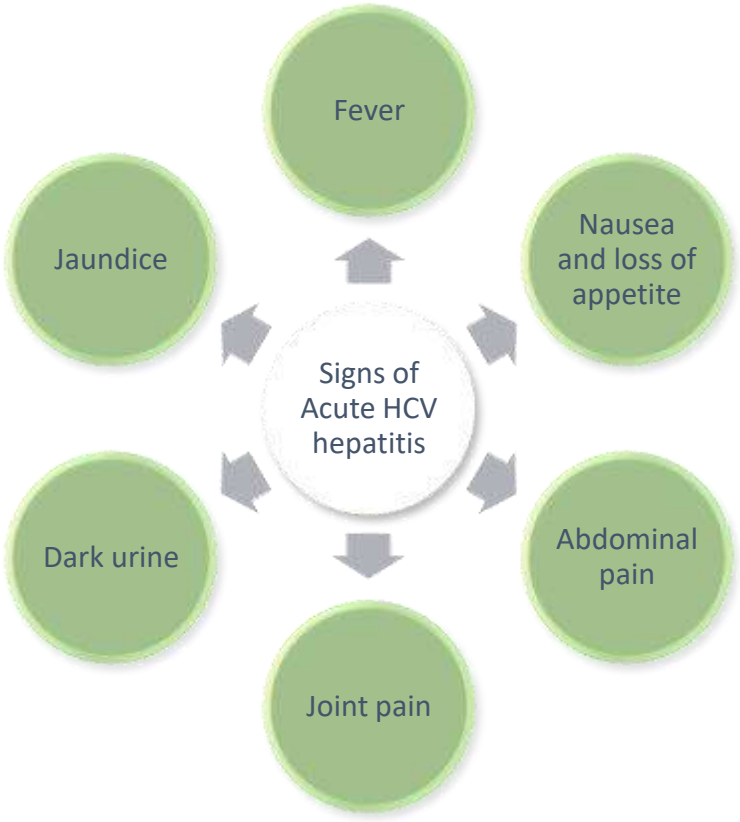

Figure 6: Diagram showing symptoms of acute hepatitis C virus (HCV) infection.

The majority of individuals with chronic HCV infection do not exhibit any symptoms at all and may only experience nonspecific symptoms such as chronic fatigue or depression, which can last for 20 years or more (Viral Hepatitis and Liver Disease, n.d.-a). Usually, the appearance of specific, clear symptoms is indicating that the virus has

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already caused significant liver damage of an advanced stage. The symptoms and signs of decompensated cirrhosis are those, and the patients may present with the following (CDC, n.d.-a; Mayo Clinic, n.d.-c).

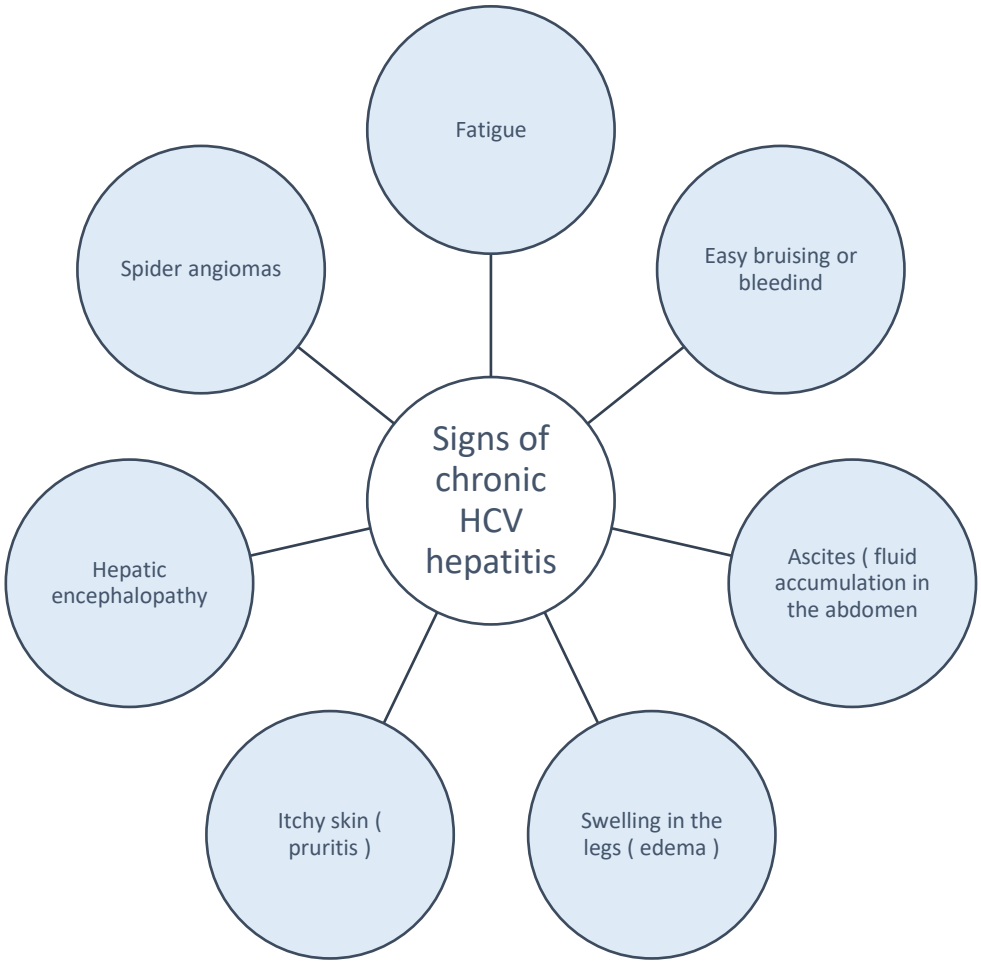

Figure 7: Diagram showing symptoms of chronic hepatitis C virus (HCV) infection.

Progressive Liver Disease: Fibrosis, Cirrhosis, and Hepatocellular Carcinoma

The persistent inflammation caused by chronic HCV infection will gradually, but surely, progress to fibrosis which is the scarring of the liver tissue. Eventually, this can go as far as severe, liver diseases that are not reversible (CDC, n.d.-a).

- Fibrosis and Cirrhosis: It is predicted that within a timeframe of 10 to 20 years, the development of cirrhosis, which is advanced, widespread scarring of the liver that greatly reduces its function, will occur in about 5% to 25% of the individuals suffering from chronic HCV (CDC, n.d.-a; Ioannou et al., 2020).

- Hepatocellular Carcinoma (HCC): Among all factors, cirrhosis is the one that contributes the most to the occurrence of primary liver cancer in patients with HCV (Ioannou et al., 2020). The annual risk for persons with HCV-related cirrhosis to get hepatocellular carcinoma is from 1 to 4% (CDC, n.d.-a). Due to this strong association, HCC monitoring becomes a necessity and a major part of the treatment protocol for HCV patients who have cirrhosis (CDC, n.d.-a).

Extrahepatic Manifestations of Chronic HCV

Long-term HCV infection has been classified as a systemic disease, which can impair several other organ systems next to the liver. The repeated infection of the virus can cause chronic immune system activation and inflammation, which is the main reason for the exophytic manifestations (CDC, n.d.-a). The acknowledgment of these disorders expands the reason of treating and curing HCV as the pros of viral elimination reach well beyond just liver health. Getting rid of the infection can be a way to the improvement or even disappearance of these body-wide disorders (CDC, n.d.-a; Ioannou et al., 2020). Frequent extrahepatic conditions linked to chronic HCV are (CDC, n.d.-a; Mayo Clinic, n.d.-c):

1. Essential Mixed Cryoglobulinemia: Disorder in which abnormal antibodies (cryoglobulins) precipitate in low temperatures, thus causing inflammation of small blood vessels (vasculitis).

2. Kidney Disease: Membranoproliferative glomerulonephritis, which is a type of renal impairment, is the most prominently associated with chronic hepatitis C.

3. Metabolic Disorders: Chronic HCV is found to be associated with elevated risk of insulin resistance and type 2 diabetes mellitus.

4. Dermatologic Conditions: PCT a disease that causes blistering of the skin on the areas exposed to the sun, is highly correlated with HCV.

5. Hematologic Malignancies: The association with the elevated risk of the occurrence of some specific types of B-cell non-Hodgkin's lymphoma is definitely strongly established.

Diagnosis and Monitoring: Biomarkers of Liver Injury: ALT/AST Patterns in HCV

After hepatitis B, one of the main indicators of an inflammatory process in the liver in HCV infection is the measuring of serum aminotransferases, mainly ALT and AST (AASLD, n.d.). Elevated enzymatic levels signal liver cell damage. Nevertheless, in long-lasting HCV, ALT levels may vary dramatically within a certain period, and even half of these patients can have a constant normal ALT level and still viral replication and liver fibrosis progression co-exist (PMC, 2005). What is more, a normal ALT level cannot exclude the presence of chronic HCV or advanced liver disease (CDC, n.d.-a).

The Two-Step Diagnostic Process: Antibody Screening and RNA Confirmation

The diagnosis of hepatitis C is a two-step sequential process that initially aims to find people who have already been in contact with the virus, and then it determines exactly those who have a current ongoing infection. This is because the process is very significant as some percentage of infected people will clear the virus on their own but will still be antibody-positive for life (CDC, n.d.-a; University of Washington, n.d.-b).

Step 1: Screening with an Anti-HCV Antibody Test. The first stage is always a serological screening test of the blood and more commonly a typical enzyme immunoassay (EIA) that detects the presence of antibodies to HCV. A positive (or reactive) result is an indication that the person has been exposed to HCV and that this happened at least once. Nevertheless, it does not distinguish between a currently active infection, a past infection that has resolved, or, in rare cases, a false-positive result. Present-day third-generation EIAs are very sensitive and specific, with accuracy rates of about 99% (Oxford Academic, 2012; University of Washington, n.d.-b).

Step 2: Confirming an HCV RNA Test. Antibodies in the blood after an HCV infection signal the need for a follow-up molecular test in the case of an individual to locate the virus ribonucleic acid (RNA). Hence, the finding of HCV RNA in the blood is definitive proof that the virus is reproducing and the patient is infected with a new, active infection.

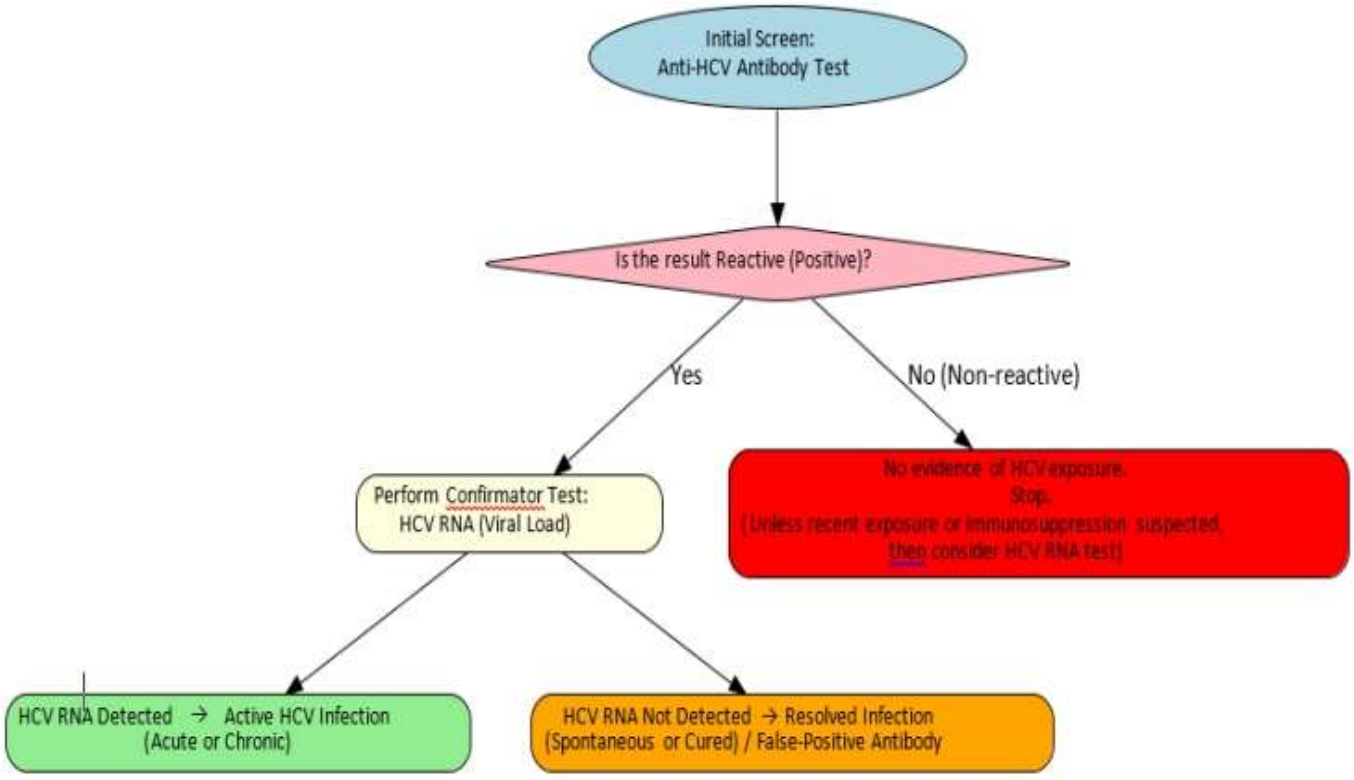

Figure 8 : HCV diagnostic interpretation flowchart

The shift in diagnostic policy from using RIBA as a confirmatory test for antibodies to the presently standard mandatory RNA confirmation is indicative of a deeper understanding of the disease natural history (Oxford Academic, 2012). It is the most explicit recognition that an antibody test, which shows that the person has been exposed, is not an indication of active disease (PMC, 2005). The two-step model is very important in the case of identification of about 15-30% of people who get rid of the virus on their own, thus, it avoids those who are falsely diagnosed as having a chronic disease and it makes sure that the treatment is only given to those who have actively replicating virus (CDC, n.d.-a; University of Washington, n.d.-b).

Molecular Diagnostics: HCV RNA Quantification and Genotyping

Molecular testing is the main method for confirming an HCV infection and planning its treatment (Mayo Clinic Labs, n.d.; University of Washington, n.d.-b).

- HCV RNA Testing: These procedures that employ nucleic acid amplification methods such as polymerase chain reaction (PCR) or transcription-mediated amplification (TMA), are extremely sensitive. They are able to identify the viral RNA in the blood as early as 1 to 2 weeks after the infection, which is much earlier than the antibody can be detected (this period is referred to as the "serologic window") (Mayo Clinic Labs, n.d.; Oxford Academic, 2012).

- Qualitative: Tests indicate the detection of something, e.g., anti-gen or anti-body, hence "detected" or "not detected" results, which, in our case, mean that the presence or absence of active infection has been confirmed (University of Washington, n.d.-b).

- Quantitative: Tests show the amount or concentration of a virus in the blood (the viral load). It is expressed in international units per milliliter (IU/mL). This is done initially to determine the viral load before the treatment and, most importantly, to verify the absence of the virus (SVR) after the treatment is over (Mayo Clinic Labs, n.d.; University of Washington, n.d.-b).

- HCV Genotyping: The first thing to be clear about is that determining the exact genotype of the hepatitis virus is just one of the steps in the elaborated pre-treatment workup. The doctor uses this information to choose the most suitable DAA regimen for the patient and predict the time required for his therapy (University of Washington, n.d.-b).

Differentiating Active from Resolved Infection

Their combination of antibody and RNA test results clearly and unequivocally mark the HCV status of a patient (CDC, n.d.-a; University of Washington, n.d.-b):

- Positive Anti-HCV and Positive HCV RNA: This pattern identifies an active (current) HCV infection. The patient is in need of further medical examination and should be evaluated for the administration of antiviral therapy (CDC, n.d.-a).

- Positive Anti-HCV and Negative HCV RNA: This is a situation of infections cleared from the past. The individual has been exposed to HCV but does not carry the virus presently, either by a spontaneous viral clearance or a successful therapeutic cure. They are not a source of infection and do not need treatment (CDC, n.d.-a; University of Washington, n.d.-b).

- Negative Anti-HCV and Positive HCV RNA: This represents a very rare pattern which is also very significant, and it can be detected during the acute phase of a newly acquired infection without the presence of antibodies. The immune response to a recent high-risk exposure scenario accompanied by the typical symptoms of acute hepatitis, would be grounds for this diagnostic hypothesis (Oxford Academic, 2012; University of Washington, n.d.-b).

The Paradigm Shift in Treatment: The Era of Direct-Acting Antivirals (DAAs)

With the introduction of Direct-Acting Antivirals (DAAs) the treatment of hepatitis C has been fundamentally changed in a revolutionary way. These are oral drugs that directly attack and prevent the Hepatitis C Virus (HCV) replication cycle proteins. DAAs inhibit protein functions of the HCV nonstructural proteins that are indispensable for the replication cycle (CDC, n.d.-a; MDPI, 2023).

What this means is quite literally a paradigm shift from the less tolerated and less efficacious interferon-based treatment of the old times (Oxford Academic, 2012). Modern DAA regimens are defined by (CDC, n.d.-a; University of Washington, n.d.-b):

- High Efficacy: Cure rates are more than 95%.

- Excellent Tolerability: Side effects are mostly of a mild nature and occur rarely.

- Convenience: The patient needs to take the medication only once a day and it is in pill form.

- Short Duration: The standard course of treatment is only 8 to 12 weeks long.

Table 3 : Comman pangenotypic direct-acting antiviral (DAA) regimens for hepatitis C virus

Trade Name	Name or names that Are generic	Target(s)/Class(es)	Average Time
Epclusa®	Sofosbuvir / Velpatasvir	NS5B Polymerase Inhibitor + NS5A Inhibitor	12 weeks
Mavyret®	Glecaprevir / Pibrentasvir	NS3/4A Protease Inhibitor + NS5A Inhibitor	8 weeks
Vosevi®	Sofosbuvir / Velpatasvir / Voxilaprevir	NS5B Polymerase Inhibitor + NS5A Inhibitor + NS3/4A Protease Inhibitor	12 weeks

The Goal of Therapy: Achieving Sustained Virologic Response (SVR) as a Virological Cure

The main purpose of HCV medication is to achieve a Stable Virologic Response (SVR). They call SVR a situation in which HCV RNA is undetectable in the blood by a test performed 12 weeks after the end of antiviral treatment (the time point is also known as SVR12) (CDC, n.d.-a; University of Washington, n.d.-b).

SVR is a virological cure. The idea of a viral cure corresponds to the very low virus levels in the body or the complete elimination of the virus from the body (CDC, n.d.-a). A cure is accompanied by a wide range of benefits: It stops the progression of liver disease, may bring back the liver fibrosis set to disappear, and even reduces considerably the risk of primary liver cancer as well as liver-related death (Ioannou et al., 2020).

The amazing success of DAAs has in essence altered the outlook for people with chronic hepatitis C, making it a curable condition rather than a chronic one (CDC, n.d.-a). The main problem is no longer the lack of an effective drug but the huge logistical, social, and economic challenges of finding those millions of people who are undiagnosed and then linking them to treatment (Lazarus et al., 2022). Thus, the issue has shifted from clinical pharmacology to public health logistics, i.e., how to create a successful "cascade of care" that takes individuals through screening, diagnosis, and treatment completion efficiently (Lazarus et al., 2022; University of Washington, n.d.-b). This means taking steps beyond the stigma against the virus, getting in contact with the marginalized groups and the risky populations, and dealing with healthcare access and cost (CDC, n.d.-a; Lazarus et al., 2022).

Prevention Strategies in the Absence of a Vaccine

A critical difference between HBV and HCV is that there is no preventive vaccine for hepatitis C (Bailey et al., 2019; WHO, n.d.-b). Consequently, preventing new HCV infections depends solely on behavioral and environmental measures that aim at not coming into contact with infected blood (CDC, n.d.-a). Essential prevention methods include (CDC, n.d.-a; Elsevier, 2019):

- Harm Reduction for People Who Inject Drugs: It is the most important prevention measure in many places. It consists of assuring that a new, sterile needle and a new syringe are used for each injection and that no drug prep sharing is done at the same time. It is possible to try to convince drug users through syringe services programs (SSPs) that they should not share the equipment they use for their injections.

- Infection Control in Healthcare Settings: Prevention of disease transmission by carrying out universal precautions to the letter, safe injection practices, and the disinfection of instruments for medical and dental procedures through the use of autoclaves are necessary measures for killing the microorganisms which cause the disease and hence, preventing the spread in the medical field.

- Screening of the Blood Supply: Routine screening for HCV of all blood, tissue, and organ donors has led to the near elimination of such a source of infection in the regions where the screening is carried out (PMC, 2010).

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- Safer Sex Practices: Although sexual transmission is not very probable, the use of condoms may decrease the risk of that mode of transmission, especially for those individuals who belong to high-risk groups, like men who have sex with men and HIV-positive people.

- Avoiding Sharing of Personal Items: Everyone ought not to share any personal things which may have been contaminated with blood such as razor, toothbrush, and nail clipper.

Comparative Analysis And Concluding Insights

A Comparative Overview of HBV and HCV

Both HBV and HCV are bloodborne viruses that result in hepatitis and have the potential to progress to chronic liver disease; however, they are different pathogens in a fundamental way. Their different virology, epidemiology, and clinical behavior determine that the prevention, diagnosis, and treatment of these diseases should be very different (CDC, n.d.-b; Hepatitis B Foundation, n.d.-c).

Epidemiological Comparison of HBV and HCV

Table 4 : Epidemiological comparisons of HBV and HCV

Feature	Hepatitis B Virus (HBV)	Hepatitis C Virus (HCV)
Global Prevalence Estimate (2022)	254 million individuals	50 million individual
Estimated New Infections Per Year (2022)	1.2 million individual	1 million individual
Estimated Deaths Per Year in 2022	~1.1 million individual	~242,000 individual
Principal Worldwide Transmission Path	From mother to kid, or perinatal	Parenteral (using drugs by injection)
Persistent Infection Risk	Age-dependent: 5% in adults, approximately 95% in newborns	High for all ages: 60-85%
Availability of Vaccines	Indeed, it is both secure and efficient	No

Contrasting Transmission Dynamics, Infectivity, and Risk Factors

Primary Transmission Routes: Different factors influence the major ways by which the diseases are spread in different parts of the world. In the case of HBV, the dominant route all over the planet is vertical transmission from mother to child at the time of delivery, so the high rate of chronic infection in local populations is what mainly results from this kind of transmission (PMC, 2015b; CDC, n.d.-d). The major cause of HCV is parenteral exposure by means of injection drug use in most developed countries (CDC, n.d.-a; PMC, 2010).

- Infectivity and Stability: Comparing to which HCV is, HBV is a much more infectious agent, hence the virus is estimated to be five to ten times more infectious than HCV (Hepatitis B Foundation, n.d.-c). One of the reasons for that is the impressive stability of the HBV virion, which is able to live and remain infectious on environmental surfaces for at least a week (Exploration Pub, 2020). On the other hand, the HCV virion is very sensitive and easily destructible (Elsevier, 2019).

- Sexual Transmission: The sexual transmission risk for HBV is several times higher than that for HCV. The sexual transmission of HCV is possible; however, it is an extremely rare case, whereas it is a significant way of transmission for HBV in non-immunized populations (Hepatitis B Foundation, n.d.-c; U.S. Department of Health & Human Services, n.d.).

Divergent Paths to Chronicity and Disease Progression

- Risk of Developing Chronic Infection: This is probably the most important epidemiological difference. The risk for an HBV infection to become chronic is almost solely dependent on age at exposure whereby it is very high in infants (~95%) and extremely low in adults (<5%) (WHO, n.d.-a). On the other hand, HCV is highly likely to become a chronic infection independent of the age of acquisition with 75-85% of all acute infections evolving to the chronic stage (CDC, n.d.-a).

- Pathogenesis of Liver Cancer (HCC): The two viruses differ in the ways that they eventually lead to liver cancer. HBV is a DNA virus that can fuse its genetic material with that of the host hepatocyte making it directly oncogenic (Mak et al., 2020). As a result, HCC associated with HBV may arise from a non-cirrhotic liver (Hepatitis B Foundation, n.d.-c). HCV is an RNA virus and hence, it does not incorporate into the host genome. The cancer-causing agent is inflammation from the chronic infection that eventually leads to cirrhosis. Therefore, HCC due to HCV is virtually always from a liver that is severely scarred with cirrhosis (CDC, n.d.-a; Ioannou et al., 2020).

The Therapeutic Divide: A Clash of Strategies

From the viewpoint of clinical management, the most significant difference between HBV and HCV is their therapeutic endpoints. In the case of HCV, the aim is an unequivocal cure, whereas for HBV, it is sustained long-term suppression (Hepatitis B Foundation, n.d.-c; Medical News Today, 2021). This is not a difference of ambition but a difference of their fundamental virology as a direct consequence. In fact, HCV, being an RNA virus, replicates only in the cytoplasm, therefore, it is the eradication of the virus from the body if the replication is stopped by Direct-Acting Antivirals (DAAs) (CDC, n.d.-a; MDPI, 2023). On the other hand, HBV sets up a stable cccDNA reservoir in the nucleus of liver cells, the viral stronghold that is currently out of the reach of nucleos(t)ide analogues (Revill et al., 2019; StatPearls, n.d.-a).

The gap between these two therapeutics has resulted in different clinical and public health issues altogether. HBV treatment is a daily oral drug therapy that patients need to stick to for life. Patient adherence, drug side effects over a long period, and the high cost of an indefinite therapy are raised as issues due to this (PMC, 2022). The clinical argument is that of continued control against the risk of disease progression (University of Washington, n.d.-a). The argument for HCV has changed. The presence of a short, well-tolerated, and highly efficient cure (SVR rates >95%) has changed the challenge from a pharmacological one to a public health one: how to find and get care for the millions of people who are asymptomatic but are infected before they develop irreversible liver damage (Lazarus et al., 2022). Therefore, the HBV-related debate is about when and whom to treat for a lifetime, whereas the HCV-related debate is about how to find and treat everyone to achieve a cure (Lazarus et al., 2022; University of Washington, n.d.-a).

Prevention and Treatment: The Dichotomy of Vaccination vs. Curability

The differences in the prevention and treatment of these diseases directly result from the distinct biological characteristics of the viruses (Hepatitis B Foundation, n.d.-c).

- Prevention: There is a safe and very effective vaccine for hepatitis B, which makes it a vaccine-preventable disease. This is the basis of worldwide HBV control (CDC, n.d.-d). For hepatitis C, there is no vaccine available (Bailey et al., 2019; WHO, n.d.-b).

- Treatment Outcome: The main point of the treatment and the result are essentially different. In the case of chronic HBV, treatment is suppressive. Present antiviral medications are able to viral replication can control effectively but they do not remove the persistent cccDNA source, thus a therapy that is often lifelong is usually needed (Hepatitis B Foundation, n.d.-b; PMC, 2015a). In chronic HCV, treatment is curative. Almost all patients

(more than 95%) can achieve a sustained virologic response (SVR) on the use of modern DAA regimens, thereby the virus can be totally eliminated from the body (CDC, n.d.-a; University of Washington, n.d.-b).

Management of HIV/HBV and HIV/HCV Coinfections

Because of the common ways infections are spread—sexual contact and injection drug use—co-infection with the Human Immunodeficiency Virus (HIV) is a substantial clinical problem for patients with viral hepatitis (HIV.gov, n.d.). According to the study, the presence of HIV negatively affects the natural progression of both HBV and HCV. Among the coinfected individuals, the liver fibrosis development is quicker, the possibility of going to cirrhosis and terminal liver disease is elevated, and the liver-related mortality rate is increased (HIV.gov, n.d.). It is estimated that liver disease, much of it caused by HBV or HCV, has become one of the major non-AIDS-related death sources among people living with HIV (HIV.gov, n.d.).

The treatment of coinfection aims at a concerted and specialist method. In the condition of HIV/HBV coinfection, most of the standard antiretroviral drugs for HIV therapy (for example tenofovir and lamivudine) are also two of the powerful HBV inhibitors (HIV.gov, n.d.). Thus, it is possible to treat both viruses with a single regimen. Yet, the treatment requires a careful plan because interruption or replacement of an HIV treatment with an HBV-active HIV regimen may lead to a severe hepatitis B flare (HIV.gov, n.d.). Concerning HIV/HCV coinfection, the newest DAA regimens have been proven to have the same safety and efficacy profiles in HCV/HIV co-infected patients as in HCV-monoinfected patients, with a cure rate of more than 95% (CDC, n.d.-a). HCV elimination in the HIV population is considered essential to alleviate their liver disease risk (HIV.gov, n.d.).

Challenges In Global Elimination Efforts

The World Health Organization has set very ambitious objectives for the eradication of viral hepatitis as a public health problem by 2030 (WHO, n.d.-b). Nevertheless, there are still a lot of issues that need to be solved. The biggest barrier, as it were, is the huge number of people with whom HBV or HCV infections have been transmitted and yet they are not diagnosed and unaware of their infection (CDC, n.d.-c). Therefore, it is of utmost importance to test on a large scale and bring more people to the diagnosis stage. In the case of HBV, this should be accompanied by a wider range of access to and use of the vaccine for the birth dose and the full immunization of infants (CDC, n.d.-d; WHO, n.d.-a). The problem with HCV is how to get the millions of people who have not been diagnosed to be treated with the DAA therapy that can cure them (CDC, n.d.-a; Lazarus et al., 2022). This is extremely challenging due to the fact that there are marginalized and difficult-to-reach populations, such as people who inject drugs. Even now, the prices and limitation of diagnostic tests and drugs for low- and middle-income countries are a huge obstacle to incurring in these regions (Lazarus et al., 2022).

The Horizon: Research Towards an HBV Cure and an HCV Vaccine

The future viral hepatitis control will be based on scientific advances which can close the gaps in prevention and treatment that exist today. The research priorities for HBV and HCV differ as they are based on the biological differences of the two viruses (Revill et al., 2019; Bailey et al., 2019).

- The Quest for an HBV Cure: The main objective of HBV research is to provide a completely sterilizing cure. This is a challenging therapeutic problem that depends largely on ways of either removing the cccDNA or ensuring that it is permanently inactivated since cccDNA is the form of the virus that resides in the nucleus of infected cells (Revill et al., 2019). Several drug candidates are being tested in the current pipeline, including those which prevent the formation of cccDNA, drugs which dissolve the viral capsid and thus prevent the viral pool from being replenished, and various immunotherapies which are designed to activate and stimulate the host immune response so that it recognizes and attacks cells undergoing viral infection (Bertoletti & Ferrari, 2021; Revill et al., 2019).

- The Development of an HCV Vaccine: In the case of hepatitis C, where the cure is already very effective, the next big challenge is the prevention of the disease (Bailey et al., 2019). The introduction of a preventive vaccine is a main goal from the public health perspective to break the infection cycle, thus mainly targeting the high-risk groups (Bailey et al., 2019). The main scientific issue to the development of an HCV vaccine is that the virus has a very wide genetic variability and it can mutate very quickly to avoid the immune response (Bailey et al., 2019; Frontiers in Microbiology, 2018).

This divided approach to research priorities summarizes the two diseases. In case of HBV, the medical community is searching for a drug that will bring about a complete cure instead of a lifelong suppression regimen (Revill et al., 2019). On the other hand, for HCV, the community is seeking preventive means so that they can stop treating the infections and instead start preventing them (Bailey et al., 2019). The different virology of the two viruses determines their clinical reality which, in turn, influences the public health strategy and shows the way for the coming scientific discoveries (Lazarus et al., 2022; Revill et al., 2019).

Knowledge Gaps And Future Perspectives

While the understanding and management of hepatitis B and C have progressed impressively, there are still considerable knowledge gaps and clinical issues that need to be resolved. It is very important to deal with these problems in order not only to meet WHO 2030 elimination goals but also to enhance patient outcomes in the long term (Lazarus et al., 2022; Revill et al., 2019).

For Hepatitis B (HBV):

The main obstacle is the ever-present covalently closed circular DNA (cccDNA) that makes it impossible to have a sterilizing cure by the use of current nucleos(t)ide analogues (NAs). Some of the most important unknowns and future research directions are (Revill et al., 2019):

1. Eliminating or Silencing cccDNA: The cellular pathways that support cccDNA stability, transcription, and degradation are barely studied (Revill et al., 2019). The area of research in the future is focused on the novel agents such as:

- Capsid Assembly Modulators that alter the structure of nucleocapsid and stop the process of cccDNA renewal (Revill et al., 2019).

- CRISPR/Cas9-based gene editing technology to pinpoint and break the cccDNA minichromosome directly (Revill et al., 2019).
- Small molecule inhibitors that bind to host factors which are indispensable for cccDNA maintenance (Revill et al., 2019).

2. Restoring Host Immune Control: When HBV becomes chronic, the immune system is exhausted. One of the possible ways of achieving this is maybe the combination therapy of direct-acting antivirals with immunotherapies which aim to restore T-cell and B-cell responses to normal levels. The invention of therapeutic vaccines and checkpoint inhibitors is a potential, albeit difficult, next step (Bertoletti & Ferrari, 2021).

3. Biomarkers for Cure and Disease Progression: There is an urgent and sensitive call for reliable biomarkers besides HBsAg to forecast functional cure, locate patients most vulnerable to HCC even when viral suppression is maintained, and keep track of treatment in new clinical trials (Mak et al., 2020).

4. Learning from Hepatitis D (HDV): The justification of the NTCP receptor as a therapeutic target comes from the recent FDA approval of bulevirtide, an HDV entry inhibitor. The achievement of this milestone opens up a

new paradigm for studying entry and spread inhibition strategies that could be utilized for HBV mono-infection as well (Urban et al., 2021).

For Hepatitis C (HCV):

Although cure is available, several obstacles are still in place:

1. Mechanisms of Liver Disease Regression Post-Cure: The changes in liver tissue over a long period after the achievement of SVR are not very clear. There are still a lot of questions related to the processes and the extent of fibrosis regression, the risk of HCC in patients with advanced fibrosis even after SVR, and the treatment of persistent portal hypertension (Ioannou et al., 2020).

2. The Elusive HCV Vaccine: The main reason for the failure of the vaccine development is the high genetic variability of HCV. A preventive vaccine is indispensable to avoid reinfection in populations at high risk and to reach the goal of total eradication. The next generation of vaccines are investigating the use of immunogens targeting conserved epitopes and new vaccine platforms (Bailey et al., 2019).

3. Global Access and Implementation Science: The main gap is no longer that of therapy but of logistics. Implementation science should be the focus of research: how to develop cost-effective point-of-care diagnostic tools, how to simplify treatment algorithms for primary care, and how to come up with efficient care models for the reach of the marginalized populations, e.g., people who inject drugs and those in resource-limited settings (Lazarus et al., 2022).

4. Unveiling the Viral Lifecycle: Although DAAs are very efficient, a detailed understanding of the HCV lifecycle, and particularly the identification of host-virus interactions that may serve as future drug targets, is still an area of intensive research (MDPI, 2023).

DISCUSSION

Hepatitis B and C are severe problems of global health, even though they differ in terms of virology and require completely different clinical and population health policies. HBV creates a stable cccDNA reservoir, which is characterized by the fact that the existing treatments can only suppress the virus and not cure it. Nonetheless, the HBV infection can be prophylactively avoided by a vaccine that is generally available. On the other hand, HCV is a non-nucleus RNA virus, which is of high curability using direct-acting antivirals (DAAs). Nonetheless, a shortage of an HCV vaccine and the inability to get diagnostics are also important challenges. As part of the World Health Organization 2030 elimination prospects, any future efforts should focus on the development of an effective HBV sterilising cure, the creation of an effective HCV vaccine, and a significant increase in the access of testing and treatment globally.

CONCLUSION

Hepatitis B and hepatitis C are still big problems around the world despite the fact that people have learned a lot about them and how to help those who have them. In this article, we explain the main differences biologically and clinically that actually guide how the two diseases are prevented and treated. For example, HBV can continue since the cccDNA is very stable which is why it is necessary to do viral suppression over a long period. On the other hand, since HCV does not have a stable intracellular reservoir, it can be completely eliminated by way of direct-acting antivirals.

Big strides have been made in both areas: an effective HBV vaccine has greatly decreased the spread of the virus; at the same time, the discovery of potent antiviral drugs has transformed HCV from a lifelong illness to one that can

be cured in the majority of cases. Yet, there exist major challenges such as limited access to diagnostics and treatment, no vaccine for HCV, and no definite cure for HBV.

What's going to be important is not only getting better at the global screening of patients and making antiviral therapies affordable but also helping in the research for a functional cure of HBV and development of a vaccine for HCV. Only together as a coordinated, cross-disciplinary team including clinical innovations, public health strategies, and policy-level changes can we really meet the WHO goal of excluding viral hepatitis.

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