Vaccines, Drug Development, and Novel Therapeutic Strategies for Hepatitis: Current Advances and Future Perspectives

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Abstract

Despite remarkable progress in prevention and treatment, hepatitis is still one of the main drivers of chronic liver disease, liver cirrhosis and hepatocellular carcinoma and is a big public health problem worldwide. The hepatitis viruses A, B, C, D and E are responsible for the occurrence of viral hepatitis in millions of people and are a significant cause of morbidity and mortality worldwide. Vaccination has been found to be very effective in preventing hepatitis A and B infections, and vaccination is not licensed for use in hepatitis C or used widely enough in hepatitis E. At the same time, there has been great advancement in antiviral drug development, including nucleotide analogues, pegylated interferons and direct-acting antivirals, which have greatly improved clinical outcomes, especially in the treatment of chronic hepatitis B and C. However, there are several issues that need to be addressed including the high cost of healthcare, accessibility of treatment, partial functional cure, persistent viral reservoirs, and antiviral resistance, which requires innovative therapeutic strategies. New technologies, such as therapeutic vaccines, gene editing via CRISPR/Cas systems, RNA interference, monoclonal antibodies, immune modulators, and host-targeted treatment and drug delivery via nanotechnology have the potential to improve antiviral efficacy and sustained viral eradication. Additionally, advancements in AI, computational drug discovery, pharmacogenomics, and precision medicine are driving the discovery of new drug targets, optimization of drug interventions, and the personalized treatment strategies. This review will provide a comprehensive overview of the current status of hepatitis vaccines, recent developments in antiviral drug discovery, and new developments in therapeutic innovations. It also highlights the current clinical trials, translational research, key challenges and future directions towards the global target of hepatitis elimination. Together, these

advances demonstrate the exciting possibilities for multidisciplinary care in the prevention, treatment, and long-term clinical outcomes of patients with viral hepatitis.

Keywords: Viral hepatitis; Hepatitis vaccines; Antiviral drug development; Therapeutic vaccines; Gene editing; Precision medicine.

1. Introduction

1.1 Global Burden of Viral Hepatitis

Viral hepatitis is among the most important causes of morbidity and mortality due to infectious diseases in the world and a significant public health problem. It includes infections with five hepatotropic viruses: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV). Although all of these viruses have the ability to cause liver inflammation, they vary in their epidemiology, clinical consequences and method of transmission, and all play major roles in acute and chronic liver disease. HBV and HCV are the major causes of chronic infection while HAV and HEV are the main causes of acute hepatitis. The most serious form of viral hepatitis is caused by HDV, which depends on the presence of HBV for its replication, and has been shown to significantly accelerate the progression of liver disease [1, 2]. The World Health Organization (WHO) Global Hepatitis Report 2024 estimates that about 304 million people were infected with chronic hepatitis B or C in 2022. Of these, an estimated 254 million people were chronically infected with the HBV virus and 50 million people were infected with the HCV virus. Although there are highly effective vaccines to prevent HBV infections and effective antiviral drugs to treat HCV, viral hepatitis accounted for an estimated 1.3 million deaths, making it the 2nd most important infectious cause of death in the world in 2022, behind tuberculosis [1, 6].

Despite a few advancements, the impact of viral hepatitis on mortality remains on the rise due to the high number of people who are not diagnosed or treated. In 2022, there were 1.3 million deaths related to hepatitis, of which almost 83% were due to hepatitis B and about 17% were due to hepatitis C. The long-term effects of chronic viral hepatitis, leading to liver cirrhosis and/or liver failure and hepatocellular carcinoma (HCC), account for most of the mortality [1, 6]. The distribution of the burden of viral hepatitis is not the same in all geographical areas. Chronic HBV infection is very endemic in the WHO African Region and Western Pacific Region, with prevalence often being above 6%. HCV infection, on the other hand, is common in Eastern Europe, Central Asia, North Africa and the Middle East. Both HAV and HEV continue to be endemic in countries that have inadequate sanitation and access to safe drinking water, including in South Asia and sub-Saharan Africa. Socioeconomic factors, vaccination rates, health care facilities, and infection-control measures are important factors that shape these regional differences [1, 2]. In very endemic areas, transmission of HBV infection frequently occurs during infancy or childhood, and is the most common chronic viral

infection in the world. In many countries in the developing world, the most important mode of transmission is from mother to child at birth, resulting in lifelong infection in most of those infected. Chronic HBV infection is a significant risk factor for liver fibrosis, cirrhosis and HCC, and is responsible for a large percentage of liver cancer cases globally [1, 7]. HCV infection is also a major contributor to the burden of chronic liver disease in the world. Chronic HCV infection is estimated to affect 50 million people globally, particularly among people who inject drugs, recipients of un-screened blood transfusions, long-term hemodialysis patients and individuals who are exposed to unsafe healthcare practices. While DAA therapy has cured more than 95% of people infected, access to DAA therapy is limited due to insufficient diagnosis, high treatment costs in some areas, and inadequate access to healthcare [1, 2].

Unlike HBV and HCV, hepatitis A and E infections are usually acute and self-limited, and do not give rise to chronic liver disease. However, these infections are still a public health problem, and they are the cause of regular outbreaks of infections caused by contaminated water and food. The mortality rate in pregnant women may be up to 20-30% in the third trimester of pregnancy, because of fulminant hepatic failure, which is especially dangerous during pregnancy in pregnant women [2, 8]. Hepatitis D is estimated to impact 12–20 million people worldwide and is only seen in people who are already infected with HBV. HDV infection has been shown to markedly shorten the course of the disease and to be associated with an increased risk of cirrhosis and hepatocellular carcinoma when compared to HBV infection alone. Therefore, HDV is considered to be the most virulent and active type of chronic viral hepatitis [2, 7]. High percentage of undiagnosed infections is another important factor in the burden worldwide. According to estimates from WHO, only a minority of people with chronic HBV or HCV infection has ever known they were infected and even fewer receive appropriate antiviral treatment. Victim's survival is affected by delayed diagnosis that allows continued viral transmission and the risk for the development of advanced liver disease before medical intervention [1, 6]. Viral hepatitis has significant economic impacts. There is a significant expense associated with diagnostic testing, antiviral therapy, hospitalization, liver transplantation, and cirrhosis and liver cancer management associated with healthcare systems. The socioeconomic impact is further elevated by indirect costs such as loss of productivity, disability and premature death, and loss of quality of life; especially in low- and middle-income countries where healthcare resources are limited [1].The Global Health Sector Strategy on HIV, Viral Hepatitis and Sexually Transmitted Infections 2022-2030 was adopted by WHO to end viral hepatitis as a public health threat by 2030, recognising the vast and immense burden of viral hepatitis globally. Its goal is to scale up vaccination, screening, and access to antiviral treatment, harm-reduction services and enhance public health surveillance to achieve 90% reduction in new infections and 65% reduction in mortality related to hepatitis. In recent times however, the world has not been on track with achieving the elimination targets, thus, the need for intensified global efforts and increased investment in prevention and control

of hepatitis is necessary [2, 7]. In summary, viral hepatitis remains a public health problem that continues to cause hundreds of millions of people worldwide to suffer and die from preventable liver disease. Despite significant advances in vaccines, diagnostics and antiviral medication, a lack of access to health services, diagnosis and treatment of Ebola remains significant. Building up public health systems, increasing screening and access to treatment services and raising awareness are critical to lowering the global burden of viral hepatitis [1, 7].

1.2 Epidemiology and Disease Distribution

The viral hepatitis is one of the biggest public health issues with millions of people impacted globally. Hepatitis viruses have different epidemiology in various geographic areas, depending on socioeconomic status, sanitation, vaccination coverage, and the health care infrastructure. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the major causes of chronic liver disease, and hepatitis A virus (HAV) and hepatitis E virus (HEV) cause acute infections primarily with regard to poor sanitation. Hepatitis D virus (HDV) is only found in people who have already been infected with HBV and makes the infection worse [1, 2]. In 2022, the World Health Organization (WHO) estimates there were 304 million people with chronic HBV or HCV infection (254 million chronically infected with HBV and 50 million HCV). Global annual mortality rate from liver cirrhosis and hepatocellular carcinoma (HCC) is around 1.3 million [1]. HBV is more common in Africa and the Western Pacific regions, and HCV is more common in Eastern Europe and Central Asia, North Africa and the Middle East. HAV and HEV are endemic in underdeveloped regions in the countries where sanitation is poor. HBV prevalence in India ranges between 2-4% and HCV prevalence is 0.5-1.5% in the general population. Healthcare workers, individuals with blood transfusion history, patients with hemodialysis, individuals who use injection drugs and new-borns of HBV-infected mothers are at high risk [2, 6, 7]. Viral transmission varies, depending on the virus. HAV and HEV have been mainly transmitted by fecal-oral route via contaminated food and water while HBV, HCV and HDV are transmitted by infected blood, unsafe injections, sexual contact and vertical transmission from mother to child [2, 6].

1.3 Classification of Hepatitis Viruses (HAV, HBV, HCV, HDV, and HEV)

The five hepatitis viruses belong to different viral families and possess distinct genomic characteristics, transmission routes, and disease outcomes [2, 8]**.**

Table 1: Classification of Hepatitis

Virus	Family	Genome	Transmission	Chronic Infection	Vaccine
HAV	Picornaviridae	ssRNA (+)	Fecal–oral	No	Yes

HBV	Hepadnaviridae	Partially dsDNA	Blood, sexual, perinatal	Yes	Yes
HCV	Flaviviridae	ssRNA (+)	Blood	Yes	No
HDV	Kolmioviridae	Circular ssRNA	Requires HBV	Yes	Prevented by HBV vaccine
HEV	Hepeviridae	ssRNA (+)	Fecal–oral	Rare (mainly immunocompromised)	Limited availability

HAV leads to acute self limiting hepatitis and life-long immunity following infection. HBV is a DNA virus that can integrate into the host genome, leading to chronic hepatitis, cirrhosis, and HCC. HCV belongs to the RNA viruses, which are very variable and difficult to vaccine. HDV is defective virus which can replicate only in the presence of HBV surface antigen (HBsAg) and is linked to severe liver disease. HEV typically results in acute hepatitis, however, it can result in chronic infection in immunocompromised individuals and lead to severe disease in pregnant women [1, 2, 8].

1.4 Clinical Manifestations and Disease Progression

The clinical features of viral hepatitis include asymptomatic infections to fulminant hepatic failure. The incubation period for HAV is 2-6 weeks, and for HBV is 6 weeks – 6 months. Symptoms include fatigue, fever, nausea and vomiting, loss of appetite (anorexia), abdominal pain, dark urine, pale stools and jaundice [2, 6]. Acute infections with HAV and HEV are generally self-limited, and do not lead to long-term problems. Hepatitis B virus (HBV) and hepatitis C virus (HCV), on the other hand, are often chronic when young children or immunocompromised patients are infected. Progressive liver fibrosis, cirrhosis, portal hypertension and eventually hepatocellular carcinoma occurs as a result of chronic inflammation [2, 6]. HDV infection leads to the most severe hepatitis and likely to the most rapid liver fibrosis and liver failure. Viral load, host immune responses, alcohol intake, obesity, diabetes and HIV co-infection affect disease progression [8, 6]. Diagnosis includes liver function tests (ALT, AST), serological markers (HBsAg, anti-HCV antibody), molecular detection (PCR) and liver imaging and/or biopsy, if needed. Complications and mortality are significantly decreased with early diagnosis and antiviral treatment [2, 6].

1.5 Socioeconomic and Healthcare Impact

Viral hepatitis is a major socio-economic problem for individuals, health care systems and countries. The cost of health care is increased by the cost of diagnosis, anti-viral medication(s), hospitalization, liver transplantation, and chronic care of cirrhosis and liver cancer. Indirect costs include loss of productivity, absenteeism, disability, early death and decreased quality of life. Slow treatment in LMICs leads to poor treatment outcomes partly due to low health facilities, unavailability of public awareness, and lack of access to diagnostic services [10]. With the help of prevention, vaccination, testing, and treatment programs, the WHO estimates that the potential for millions of deaths and huge economic gains are possible. Universal HBV vaccination, blood safety measures, infection-control measures and public awareness campaigns are among the most cost-effective public health measures [1, 10]

1.6 Need for Improved Vaccines and Therapeutic Strategies

There are effective vaccines available for HAV and HBV, but as yet no licensed vaccine is available for HCV, and access to HEV vaccines is limited. Moreover, HBV vaccines stop infection but cannot cure chronic HBV infection. Thus, better vaccines and therapeutic strategies are still needed to reach the global hepatitis elimination goals [1, 2]. There are effective antiviral treatments to suppress HBV replication and cure HCV infections with DAAs (direct-acting antivirals) that cure the majority of HCV infections (more than 95% efficient). There are some drawbacks to these treatments such as drug resistance, high cost for some treatment centers, difficult access to treatment, and absence of clearance of covalently closed circular DNA (cccDNA) in HBV infection [9, 8]. Therapeutic HBV vaccines, immune checkpoint inhibitors, RNA interference (RNAi), antisense oligonucleotides, CRISPR/Cas9-mediated genome editing, and monoclonal antibodies, and nanoparticle-based drug delivery systems are recent breakthroughs. These pioneering methods are designed to produce an effective cure of chronic HBV infection, and to enhance therapeutic outcomes for those with severe liver disease [11, 12]. The WHO Global Health Sector Strategy has a bold goal of ending viral hepatitis as a public health threat by 2030, a goal that can be achieved by cutting new infections by 90% and deaths from viral hepatitis by 65%. To meet these goals, more vaccination efforts are needed, screening should be rolled out even at the most basic level, low-cost antiviral drugs should be developed, better surveillance is required, and further research is necessary to create new vaccines and novel antiviral drugs [2, 11].

2. Virology and Pathogenesis of Hepatitis

The liver inflammation, known as hepatitis, may be caused by any of five major hepatotropic viruses: Hepatitis A virus (HAV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), Hepatitis D virus (HDV), and Hepatitis E virus (HEV). The virus genome organization, replication strategies, mode of transmission, and pathogenic mechanisms are different. The acute, self-limited infections are generally caused by HAV and HEV, while HBV, HCV and HDV are often chronic infections that can lead to liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC). Viral replication and host immune response are the two factors that play a role in infection outcome [1, 2].

2.1 Structure and Genome Organization of Hepatitis Viruses

The five hepatitis viruses are structurally and genomically different viruses that belong to different families. The viruses are non-enveloped, positive sense, single-stranded RNA viruses that are primarily transmitted via the fecal-oral route and are known as HAV and HEV. HBV is an almost full double-stranded DNA virus of the Hepadnaviridae family, while HCV is an enveloped positive-sense RNA virus of Flaviviridae family. A defective single-stranded circular RNA virus, HDV needs the HBV surface antigen (HBsAg) for its replication and assembly [2, 13]. HBV has four overlapping open reading frames (ORFs) encoding surface (S), core (C), polymerase (P), and X proteins. There is one ORF in HCV and it codes for a poly protein that is later processed into structural and non-structural proteins. HEV has three large ORFs that are associated with replication and capsid assembly. Variations in genome organization lead to the differences in viral replication, persistence and disease severity [2, 14].

2.2 Viral Life Cycle and Replication Mechanisms

Receptor-mediated endocytosis and membrane fusion are the initial steps in viral entry into hepatocytes: the viral life cycle starts with viral attachment to specific receptors on the hepatocyte cell surface. Once inside, viral genome enters cytoplasm or nucleus (depending on virus) HBV replicates by reverse transcription of covalently closed circular DNA (cccDNA), while HCV, HAV and HEV replicate directly in the cytoplasm by viral RNA-dependent RNA polymerase [13, 9]. After genome duplication, viral proteins are produced, virions are assembled and released to infect adjacent hepatocytes. HDV cannot replicate itself without the help of HBV, thus dependent for its envelope proteins. Persistent infection and disease progression, especially in chronic hepatitis B and C infections, are related to efficient viral replication [13, 9].

2.3 Host Immune Response to Hepatitis Infection

Innate and adaptive immunity are mechanisms of the immune response to hepatitis viruses. The innate immune cells such as macrophages, dendritic cells, Kupffer cells, and natural killer (NK) cells are able to recognize viral components via pattern recognition receptors and trigger antiviral cytokines like interferons (IFN-α and IFN-β) [2, 15]. Adaptive immunity involves activation of $CD4^+$ helper T cells, $CD8^+$ cytotoxic T lymphocytes, and B cells. Antibodies produced by B cells prevent reinfection and virus-specific $CD8^+$ T cells kill infected hepatocytes. Acute infections of HAV and HEV are generally self-limited by a powerful and coordinated immune response. But, weak or fatigued T-cell responses are responsible for chronic HBV and HCV infections [9, 15].

2.4 Mechanisms of Immune Evasion

Hepatitis viruses have developed several ways to escape host immunity and achieve persistent infection. HBV is able to persist in the hepatocyte nuclei as stable cccDNA even when the patients receive antiviral therapy. HBV X protein also disrupts the antiviral signaling pathways in the host and blocks interferon response [9, 16]. The RNA polymerase of HCV is prone to errors and, therefore, produces many variants that are capable of evading immune response. The viral proteins suppress antigen presentation, disrupt cytokine production and function of t-cells. HDV also contributes to immune dysregulation in the presence of HBV, leading to increased liver damage [15, 16].

2.5 Molecular Basis of Liver Injury and Disease Progression

Major cause of liver damage in viral hepatitis is not viral toxicity itself, but rather host immune response. Activated CD8+ T cells kill infected hepatocytes and chronic inflammation activates hepatic stellate cells to produce collagen and other extracellular matrix proteins which cause liver fibrosis [15, 17]. Chronic inflammation leads to oxidative stress, production of cytokines and repeated hepatocyte regeneration, which finally leads to cirrhosis and an elevated risk of hepatocellular carcinoma. HBV integration into the host genome and expression of HBx protein have been directly shown to play a role in carcinogenesis, while HCV promotes cancer by inducing chronic inflammation, oxidative stress and genetic instability [9, 17].

2.6 Biomarkers for Diagnosis and Disease Monitoring

Serological, molecular and biochemical markers are the tools that are needed to make accurate diagnosis and monitoring of viral hepatitis. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are liver enzymes that suggest hepatocellular damage. Liver function is evaluated by bilirubin, albumin and prothrombin time [2, 11]. HBsAg, HBeAg, anti-HBs, anti-HBc, anti-HCV antibodies, anti-HAV IgM, anti-HEV IgM and anti- HDV antibodies are virus-specific serological markers. The molecular methods like quantitative PCR are able to quantify HBV DNA, HCV RNA and HDV RNA, which offer information on the viral load and treatment response. Over the last few years, more sophisticated biomarkers such as hepatitis B core-related antigen (HBcrAg), hepatitis B surface antigen quantification (qHBsAg), and liver fibrosis markers (FibroScan®, APRI and FIB-4 index) have been increasingly used in disease monitoring and prognosis [9, 11].

3. Current Vaccines Against Hepatitis

Vaccination is the most powerful tool for preventing viral hepatitis and to decrease the burden of viral hepatitis worldwide. HeA and HeB vaccines are safe and highly effective; and there is a licensed vaccine available for HEV, though it is currently only available in China. Although it is a great achievement in vaccination programs, there are no licensed vaccines available for hepatitis C virus (HCV) or hepatitis D virus (HDV). Hepatitis related morbidity and mortality have been significantly reduced thanks to global immunisation programmes, especially among children and high-risk groups [1, 2].

3.1 Hepatitis A Vaccines

Inactivated whole-virus vaccines that are long lasting against HAV infection are used for hepatitis A vaccines. They are recommended for children, travelers to endemic regions, health care workers and people with chronic liver disease. Administered as a 2 dose schedule, vaccination achieves protective antibody levels in >95% of the vaccinees and confers immunity for 20 years or more [2, 18].

3.2 Hepatitis B Vaccines

Hepatitis B vaccines are made from hepatitis B surface antigen (HBsAg) that is a recombinant vaccine. They are given in three doses and research has shown that they cause an antibody protection response in more than 95% of healthy children, infants, and adults. The transmission of HBV, chronic infection, cirrhosis and HCC has been significantly reduced in the world as a result of universal infant vaccination and timely administration of the birth dose [1, 11].

3.3 Combination Hepatitis A and B Vaccines

HAV + HBV vaccines are combination vaccines that give protection against both infections at the same time. These vaccines decrease the number of immunizations, enhance vaccination adherence and are recommended for adults who have an increased risk of exposure to hepatitis, such as health care providers, travellers, and patients with chronic liver disease [18, 19].

3.4 Hepatitis E Vaccines: Current Status

Currently, recombinant HEV vaccine HECOLIN® is only licensed in China and has shown high efficacy against the prevention of HEV infection. While some clinical trials have demonstrated its immunogenicity and safety, the vaccine has not been widely used in the world due to limited availability and insufficient data on its use in pregnant women and immunocompromised people [2, 20].

3.5 Vaccine Immunogenicity and Safety

The current vaccines for hepatitis show very good immunogenicity and safety. Most immunized people develop protective antibody responses and serious adverse effects are very rare. Common side effects include mild reactions in the area, fever, and pain at the injection site. Higher doses or antibody testing after vaccination may be necessary for immunocompromised persons and older adults to assure sufficient immune protection [2, 11].

3.6 Global Immunization Strategies and Recommendations

The World Health Organization (WHO) has called for universal hepatitis B vaccination—every infant, including one dose at birth within 24 hours of birth, and completing the vaccination series. Vaccinations against Hepatitis A are recommended for endemic countries and for high-risk groups. Global strategies to prevent hepatitis depend on national immunization programmes, measures to protect the blood supply, infection control and public awareness campaigns. These interventions contribute to WHO's Hepatitis Elimination target for 2030 [1, 2].

3.7 Limitations of Existing Vaccines

But there are a number of limitations of existing hepatitis vaccines. No licensed vaccines exist for HCV, HDV, or the HEV vaccine is limited and available throughout the world. HBV vaccines are available for humans, and they prevent infection, but do not cure chronic HBV infection or eliminate covalently closed circular DNA (cccDNA). Elderly people, immunocompromised and chronic kidney disease patients may also have a diminished response to vaccinations. The restrictions underline the importance of developing more effective vaccines that provide greater protection, have enhanced immunogenicity, and have therapeutic properties [11, 9].

4. Emerging Vaccine Technologies

4.1 mRNA Vaccines

The hepatitis mRNA vaccines are a promising vaccination platform for prevention and treatment of hepatitis. These vaccines are made by loading synthetic mRNA containing viral antigens into host cells, which express the antigens and trigger humoral and cellular immune responses. The development of mRNA technology for the COVID-19 has propelled its development for the hepatitis viruses, especially HBV and HCV. Its benefits include speed of development, its high immunogenicity, ease of scalability and versatility of emerging viral variants. However, there are many issues that need to be overcome including the stability of the mRNA and freezing storage [21, 22].

4.2 DNA Vaccines

DNA vaccines involve the injection of a plasmid DNA encoding hepatitis viral antigen that is taken up by cells in the host and translated into protein that produces immune response. The are stable, economical and able to cause persistent cellular immunity. In the case of HBV and HCV, encouraging results have been obtained in preclinical studies, with the need to optimize these vaccines for human use by using more efficient delivery systems such as electroporation, nanoparticle carriers etc. [23, 24].

4.3 Viral Vector-Based Vaccines

Viral vector vaccines rely on the use of viruses, genetically modified to carry viral genes into the host cells, such as adenoviruses or modified vaccinia Ankara (MVA). These vectors efficiently induce robust $CD4^+$ and $CD8^+$ T-cell responses along with antibody production. There are a number of viral vector vaccines currently in clinical trials for the therapeutic treatment of chronic HBV and HCV infections. Important limitations are pre-existing immunity to viral vectors and manufacturing complexity [25, 26].

4.4 Protein Subunit Vaccines

Protein subunit vaccines do not contain whole viruses but do contain purified viral proteins or recombinant antigens that are derived from the virus. They have very good safety profiles and are not prone to infection, and have been used to successfully produce licensed vaccines for HBV. The ongoing research is to boost immunogenicity through the use of new adjuvants and nanoparticles for delivery to increase protection against the various strains of the hepatitis viruses [18, 27].

4.5 Virus-Like Particle (VLP) Vaccines

Virus-like particles, also known as VLPs, are self-assembled viral structural proteins that resemble real viruses, but do not contain the genetic material needed to replicate. VLP vaccines are excellent safety, highly effective humoral and cellular immunizing vaccines. Currently, VLP technology is already being used in the development of HBV vaccine, and current studies are also exploring the use of VLP technology in the development of HCV and HEV vaccines due to its promising immunogenic potential [28, 29].

4.6 Peptide-Based Vaccines

Peptide vaccines are synthetic versions of viral epitopes that are able to trigger specific immune responses. They are very specific, readily available and have good safety profiles. Peptide vaccines are however, not highly immunogenic and need to have a knowledge of the correct delivery systems and powerful adjuvants to work. The use of immunoinformatics has led to the identification of conserved regions of the hepatitis virus for development of next-generation peptide vaccines [30, 31].

4.7 Therapeutic Vaccines for Chronic Hepatitis B and C

Therapeutic vaccines are aimed at triggering immune responses in those who are already infected, in contrast to prophylactic vaccines. The idea of these vaccines is to help restore exhausted T-cell function, decrease viral load and achieve functional cure, especially chronic HBV infection. There are several types of therapeutic vaccine platforms currently being evaluated in the clinic: DNA vaccines, viral vectors, mRNA vaccines, peptide vaccines and dendritic cell-based vaccines. Therapeutic vaccines in combination with antiviral drugs and immune checkpoint inhibitors might have a better therapeutic efficacy [32, 33].

4.8 Universal Hepatitis Vaccine Development

Universal hepatitis vaccines are designed to be broadly protective against multiple hepatitis virus genotypes or even against different hepatitis viruses, targeting highly conserved hepatitis virus epitopes. The development of the reverse vaccinology, structural biology, artificial intelligence and immunoinformatics has facilitated the identification of conserved antigens for the development of universal vaccine design. While development of a universal vaccine is still in its infancy, potentially the vaccine could have a substantial impact on the global burden of viral hepatitis and would make immunization programmes easier [22, 34].

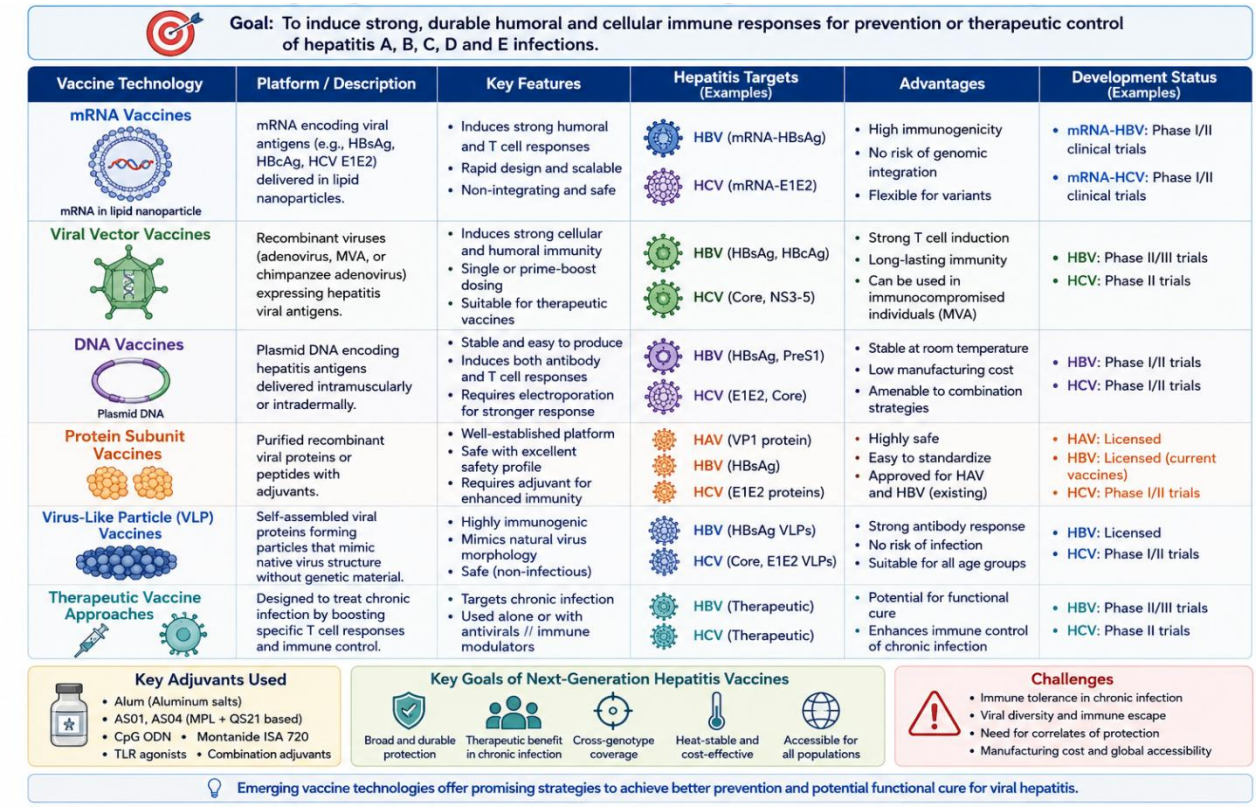

Figure 4.1: Emerging Vaccine Technologies for Viral Hepatitis

5. Current Pharmacological Management of Hepatitis

5.1 Treatment of Hepatitis A

Hepatitis A is a self-limited infection and there is no antiviral treatment available. Treatment is supportive, with adequate fluids, nutrition, rest, and symptomatic relief from fever, nausea and vomiting. Only those patients with severe dehydration, acute liver failure or fulminant hepatitis need hospitalization. The best prevention is still vaccines and post-exposure prophylaxes using hepatitis A vaccine or immunoglobulin [35, 36].

5.2 Current Therapy for Chronic Hepatitis B

The main objective of chronic hepatitis B (CHB) treatment is to control disease progression with suppression of HBV replication and to lower the risk of cirrhosis and HCC. Nucleos(t)ide analogues like tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), and entecavir are used as first-line therapies, and all have a high genetic barrier to resistance. Selected patients may also be treated with pegylated interferon-α due to its immunomodulatory activity and ability to achieve functional cure. Antiviral treatment is usually necessary for a long time [9, 11, 1].

5.3 Direct-Acting Antiviral Therapy for Hepatitis C

Hepatitis C treatment has been transformed by the advent of direct-acting antivirals (DAAs). They are administered orally and inhibit viral proteins such as NS3/4A protease, NS5A and NS5B RNA polymerase, which gives sustained virological response (SVR) rates greater than 95%. These are

commonly used regimens: sofosbuvir/velpatasvir and glecaprevir/pibrentasvir, which treat a variety of HCV genotypes and are typically given for 8-12 weeks and are well tolerated [9, 37, 38].

5.4 Management of Hepatitis D Infection

Hepatitis D virus (HDV) infection is only seen in those who are already infected with HBV. Treatment involves anti-HBV drugs (such as nucleos(t)ide analogues) to suppress replication of HBV, but these drugs are not very active against HDV itself. However, pegylated interferon (IFN)-α is still considered as the cornerstone for the treatment of chronic HDV infection. Recently, an entry inhibitor that targets sodium taurocholate co-transporting polypeptide (NTCP) receptor, bulevirtide, has been identified as a potential treatment for chronic hepatitis D (Hepatitis D) [39, 40].

5.5 Management of Hepatitis E Infection

Acute attacks of Hepatitis E are self-limited and supportive care is all that is needed. No antiviral treatment is recommended for most people with HEV infection, unless there is a chronic infection in an immunocompromised person, who may require treatment with ribavirin. Withdrawal of immunosuppressive therapy also can help promote viral clearance. Sometimes fulminant hepatic failure may require liver transplantation [41, 42].

5.6 Supportive Care and Liver Transplantation

Supportive management in all viral hepatitis is very important and involves maintaining hydration, electrolyte balance, nutrition support, avoiding alcohol/intoxicant drugs and regular monitoring of liver function. Orthotopic liver transplantation is the definitive treatment for irreversible liver failure, and is indicated in patients with acute liver failure, decompensated cirrhosis and end-stage liver disease. Transplanted patients need to take immunosuppressive drugs for life [43, 44].

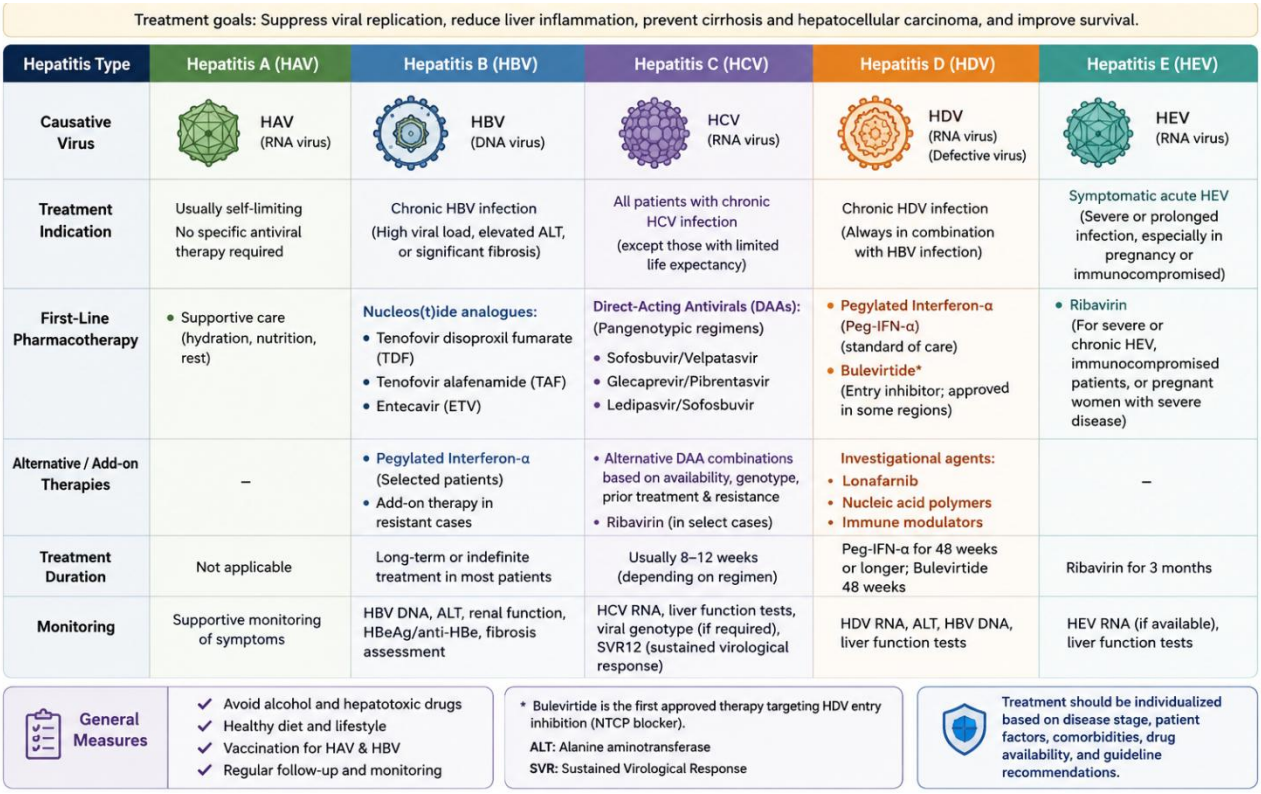

Figure 5.1: Current Pharmacological Management of Viral Hepatitis

Table 5.1: Current Pharmacological Management of Viral Hepatitis

Hepatitis Virus	First-Line Treatment	Main Therapeutic Goal	Current Status	References
HAV	Supportive care	Symptom relief and recovery	No specific antiviral	[35-40]
HBV	Tenofovir, Entecavir, Peg-IFN-α	Viral suppression and prevention of cirrhosis	Standard therapy	
HCV	Direct-acting antivirals (DAAs)	Sustained virological response (SVR)	Curative therapy	
HDV	Peg-IFN-α, Bulevirtide	Suppress HDV replication	Emerging targeted therapy	
HEV	Supportive care; Ribavirin (chronic cases)	Viral clearance	Mainly supportive	

Liver Failure	Liver transplantation	Restore liver function	Definitive treatment	

6. Drug Development Strategies for Hepatitis

6.1 Identification of Novel Drug Targets

Effective antiviral drugs development targets viral and host targets associated with viral entry, viral replication, viral assembly and viral immune evasion. With the new techniques of genomics, proteomics and structural biology, and the current advancement of artificial intelligence, novel therapeutic targets have been identified, especially for chronic HBV and HCV infections [33, 45].

6.2 Viral Entry Inhibitors

Viral entry inhibitors are the drugs which block the interaction of the viral surface proteins with the host cell receptor and thereby prevent the entry of the hepatitis viruses into the hepatocytes. Bulevirtide is the first approved entry inhibitor for chronic hepatitis D as well as blocking the entry of HBV into liver cells by targeting the sodium taurocholate co-transporting polypeptide (NTCP) receptor. Liver transplantation offers a good opportunity to consider entry inhibitors to prevent new infection and reinfection [39, 46].

6.3 Polymerase Inhibitors

Polymerase inhibitors are drugs that inhibit the replication of the viral genome by blocking the polymerase enzymes of the virus. HBV: Nucleos(t)ide analogues (e.g., tenofovir and entecavir) act as reverse transcriptase/DNA polymerase inhibitors; HCV: Sofosbuvir is an NS5B RNA-dependent RNA polymerase inhibitor. These agents are active in reducing viral replication and hence have better long-term clinical outcomes [9, 11].

6.4 Protease Inhibitors

Protease inhibitors inhibit viral proteases that are used to convert viral polyproteins into functional proteins necessary for viral replication. Direct-acting antiviral (DAA) regimens that contain NS3/4A protease inhibitors (glecaprevir, grazoprevir, and voxilaprevir) are essential to the treatment of HCV, yielding sustained virologic response rates of >95% [37, 47].

6.5 Capsid Assembly Modulators

Capsid assembly modulators (CAMs) disrupt the assembly of hepatitis B virus (HBV) nuclecapsid and inhibit viral replication and a decrease in the production of infectious virion. Several CAMs such as ABI-H0731 and JNJ-56136379 are currently being investigated in clinical trials and could be used in combination with existing antiviral treatment for a functional cure in HBV [48, 49].

6.6 cccDNA Targeting Strategies in HBV

cccDNA is a persistent viral reservoir which is regarded as the cause of chronic HBV infections. New therapies target the elimination and/or silencing of cccDNA with the use of gene editing technology (CRISPR/Cas9), RNA interference (RNAi), antisense oligonucleotides, epigenetic modifiers, and

gene silencing technologies. These strategies will likely be key to new HBV cure therapies in the future [50, 51].

6.7 Host-Targeted Antiviral Therapies

Host-targeted antiviral treatments will interfere with host cellular pathways that are necessary for the virus to replicate, instead of inhibiting proteins found in the virus. These include immune modulators, Toll Like Receptor (TLR) agonists, interferons, checkpoint inhibitors and metabolic pathway inhibitors. The treatment of host factors decreases the chance for viral resistance and may improve antiviral immunity [16, 52].

6.8 Combination Antiviral Therapy

Combination antiviral therapy involves the use of antiviral agents that act on different targets to increase antiviral efficacy and reduce drug resistance and enhance treatment outcomes. Current treatment of HCV is based on triple drug combinations of direct acting antiviral agents targeting NS3/4A protease, NS5A and NS5B polymerase. For HBV, future therapeutic strategies are anticipated to be the use of nucleos(t)ide analogues, capsid assembly modulators, RNA interference, therapeutic vaccines and immune-based therapies for a functional cure [33, 53].

7. Novel Therapeutic Strategies

7.1 RNA Interference (RNAi)-Based Therapeutics

A new therapeutic technology being developed is RNA interference (RNAi), involving the use of small interfering RNAs (siRNAs) to selectively target viral messenger RNA, which leads to a decrease of hepatitis B virus (HBV) protein synthesis and viral replication. The use of RNAi-based therapeutic agents like viridian (VRC-01) and JNJ-3989 has been shown to significantly lower the level of hepatitis B surface antigen (HBsAg) in clinical trials and are being explored for inclusion in functional cure strategies [16, 33].

7.2 Antisense Oligonucleotide Therapy

Antisense oligonucleotides (ASOs) are short synthetic sequences of nucleic acids designed to hybridize to complementary mRNA from a virus to block protein synthesis or to promote its degradation. When used in combination with antiviral therapy, in chronic HBV infection ASOs are effective in lowering the production of viral antigens and can improve host immune responses as well [33, 54].

7.3 CRISPR/Cas Gene Editing Technology

CRISPR/Cas technology has been found to have a wide potential to edit viral DNA with precision and has already demonstrated significant promise in the ability to remove the most abundant reservoir for HBV, covalently closed circular DNA (ccDNA). Presently, the use of CRISPR-based therapies is still in the preclinical stages but could offer a route to the complete eradication of chronic HBV infection [16, 50].

7.4 Therapeutic Monoclonal Antibodies

The therapeutic monoclonal antibodies specifically inhibit the binding of viral antigen or host immune molecule to neutralize infection and boost antiviral immunity. Hepatitis B surface antigen (HBsAg) neutralizing antibodies are being investigated as a second line treatment to enhance viral clearance and limit disease progression [16, 9].

7.5 Immune Checkpoint Inhibitors

Immune checkpoint inhibitors reverse the dysfunction of virus-specific T-cells by inhibiting inhibitory receptors like programmed cell death protein-1 (PD-1). These agents could enhance antiviral immunity in chronic hepatitis B, and are under investigation in conjunction with anti-viral agents and therapeutic vaccines [16, 9].

7.6 Adoptive T-Cell Therapy

The technology for adoptive T cell therapy is based on the transfer of virus-specific or genetically engineered T cells that are capable of binding to and killing infected hepatocytes. The results of this personalized immunotherapy have been promising in experimental studies and could be a useful strategy for chronic HBV treatment [16, 50].

7.7 Cytokine and Immune Modulator Therapy

Hepatitis viruses are stimulated by innate and adaptive immune system by using cytokines and immune modulators such as interferon α, toll-like receptor (TLR) agonist and other immune stimulators. These therapies could enhance the control of the virus, and are being investigated to be combined with other antiviral therapies [16, 33].

7.8 Stem Cell Therapy and Regenerative Medicine

The purpose of stem cell therapy is to help regenerate liver tissue, regenerate hepatocytes and restore liver function in HIV patients with severe liver disease that is caused by hepatitis. MSCs have been demonstrated to have anti-inflammatory, immunomodulatory, and regenerative effects in early clinical trials, but additional large-scale trials are needed to confirm their long-term safety and effectiveness [9, 55].

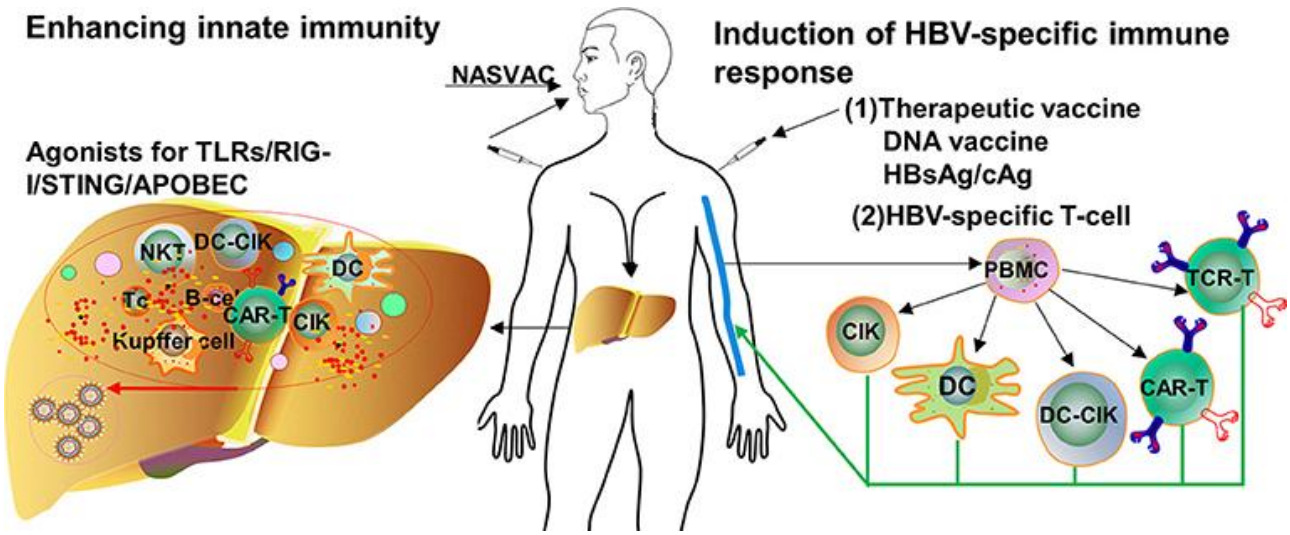

Figure 7: Novel Therapeutic Strategies for Viral Hepatitis

8. Nanotechnology-Based Drug Delivery

8.1 Lipid Nanoparticles

Lipid nanoparticles (LNPs) are one of the most advanced nanocarriers for the delivery of hepatitis therapy and vaccines. They shield nucleic acids from enzyme degradation, promote cell uptake and direct drugs to the hepatocyte cell. LNPs have also proven to be effective for delivering mRNA vaccines and RNA interference (RNAi)-based therapeutics to achieve high transfection efficiency and better therapeutic effects in chronic hepatitis B [56, 57].

8.2 Polymeric Nanoparticles

Polymeric nanoparticles are biodegradable nanoparticles that are made of natural or synthetic polymers like poly(lactic-co-glycolic acid) (PLGA) and chitosan. These systems offer controlled drug release, improved drug stability and bioavailability. They are extensively studied for delivery of antiviral drugs, nucleic acids and therapeutic proteins in the treatment of hepatitis [57, 58].

8.3 Liposomes and Nanoemulsions

Liposomes are vesicles of phospholipids that can include both hydrophilic and lipophilic drugs, while nanoemulsions are stable nano-sized oil–water dispersions. These both have a beneficial effect on enhancing the solubility of the drug, extend circulation time, and improve liver-specific drug delivery, and decrease systemic toxicity. They are also being investigated as the means for delivering genes and as vaccine adjuvants [58, 59].

8.4 Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are physiologically compatible solid lipids, which offer excellent drug stability, sustained drug release and reduced toxicity. SLNs are useful as carriers of antiviral drugs to enhance their oral bioavailability and to target the hepatic delivery, thus offering potential for the treatment of chronic hepatitis [57, 59].

8.5 Targeted Hepatic Drug Delivery

This is a specific hepatic drug delivery.

Ligand functionalized nanocarriers are used for targeted hepatic drug delivery that selectively bind the receptors expressed on hepatocyte, e.g., asialoglycoprotein receptor (ASGPR). This targeted approach will lead to higher liver accumulation of the drug, better antiviral activity, less off-target toxicity, and less effects in the systemic circulation [56, 60].

8.6 Nanocarriers for Gene and Vaccine Delivery

Nanocarriers have emerged as significant platforms for use in delivering DNA, mRNA, siRNA, CRISPR/Cas systems, and recombinant vaccine antigens. They are involved in protecting the genetic material from degradation, enhancing the transport of genetic material into the cell, and creating strong immune responses. Nanotechnology-based delivery systems are anticipated to be significantly involved in developing new-generation of vaccines against hepatitis and gene therapy [56, 57, 60].

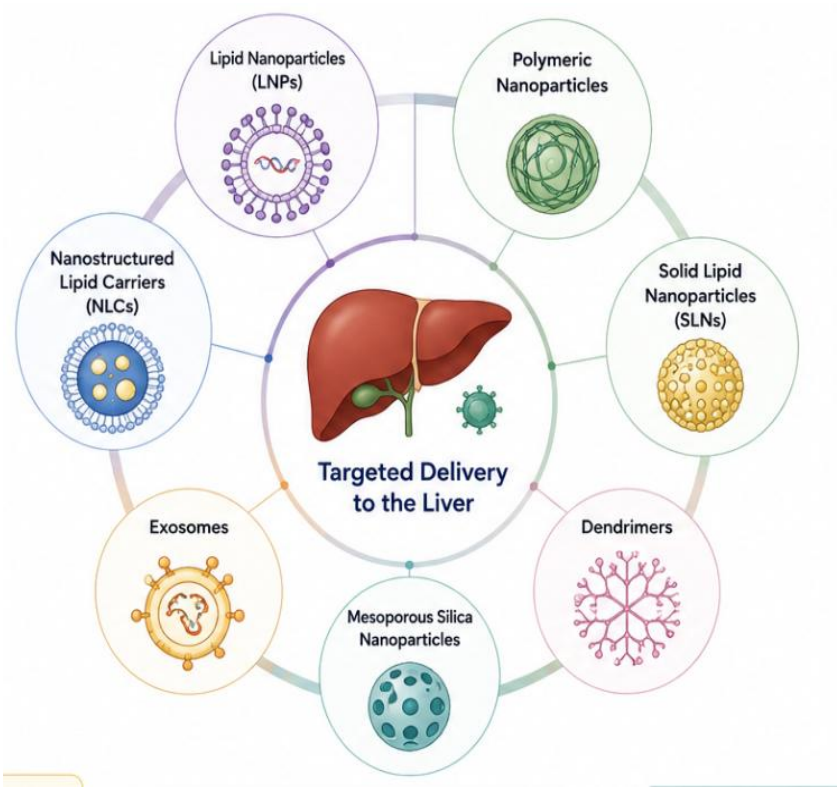

Figure 8: Nanotechnology-Based Drug Delivery Systems for Hepatitis

Table 8.1: Nanotechnology-Based Drug Delivery Systems for Hepatitis

Nanocarrier	Major Advantages	Applications	References
Lipid nanoparticles (LNPs)	Protect nucleic acids, efficient intracellular delivery	mRNA vaccines, siRNA therapy	56-60
Polymeric nanoparticles	Controlled release, biodegradability	Antiviral drug and gene delivery	
Liposomes/Nanoemulsions	Improve drug solubility and bioavailability	Drug and vaccine delivery	
Solid lipid nanoparticles (SLNs)	Sustained release, low toxicity	Hepatic antiviral drug delivery	
Targeted hepatic nanocarriers	Liver-specific targeting, reduced toxicity	Targeted HBV/HCV therapy	
Gene and vaccine nanocarriers	Efficient delivery of DNA, RNA, CRISPR,	Gene therapy and therapeutic vaccines	

	vaccines		

9. Artificial Intelligence and Computational Drug Discovery

Artificial intelligence (AI) and computational drug discovery have revolutionized the pharmaceutical industry by improving various aspects of drug development, such as target identification, lead optimization, toxicity prediction, and clinical decision-making. Conventional drug discovery is costly and time-consuming, but AI algorithms, machine learning (ML), and computational modeling can minimize both of these factors, and enhance the likelihood of selecting the right candidate. They are being used more and more in the development of antiviral drugs and vaccines to combat viral diseases such as hepatitis and for personalized and precision medicine [61, 62].

9.1 Artificial Intelligence in Drug Discovery

AI is using state-of-the-art computational algorithms to process vast amounts of information from biological, chemical and clinical studies to discover new drug candidates. AI can predict molecular interactions, optimize lead compounds and repurpose existing drugs to reduce drug development time. Antiviral drug discovery has been extensively used with the help of AI platforms, such as for the treatment of hepatitis viruses [61, 64].

9.2 Machine Learning for Drug Target Identification

Machine learning uses statistical and deep learning models to integrate genomic, transcriptomic and proteomic data to identify genes, proteins and signaling pathways associated with diseases. Chronic viral infections like Hepatitis B and C can be treated with personalized treatments, with improved prediction of novel therapeutic targets and biomarkers by ML algorithms [63, 65].

9.3 Structure-Based Drug Design

Structure-based drug design (SBDD) is a method based on the 3D structure of a target protein to create molecules that will bind to it with good binding affinity and specificity. Rational design of antiviral drugs against viral enzymes including polymerase and proteases from hepatitis virus, is possible by using computational methods like molecular dynamics simulations and protein modeling [66].

9.4 Molecular Docking and Virtual Screening

Molecular docking: It can be used to predict the drug interactions with the target protein, and virtual screening can be used to evaluate thousands of compounds and select the promising candidates to be evaluated in the laboratory. The computational methods decrease experimental work load, and have been widely applied to identify inhibitors for hepatitis viral proteins and other targets of infectious diseases [67, 68].

9.5 Predictive Toxicology

The term predictive toxicology refers to the use of AI and computational models to predict the safety of a drug candidate prior to laboratory or clinical testing. The machine learning algorithms can predict

hepatotoxicity, cardiotoxicity, mutagenicity, and other toxicities based on the chemical structure and biological information, which helps to minimize drug attrition and enhance patient safety [69].

9.6 AI in Clinical Decision Support

Disease diagnosis, treatment selection, prognosis, patient monitoring – these are all areas where AI-powered clinical decision support systems (CDSS) can help healthcare professionals. For instance, in the field of hepatitis management, AI algorithms can be used to analyse patients' health records and lab results as well as imaging information, forecast disease progression, and tailor treatment to each individual's needs [62, 70].

10. Precision Medicine and Personalized Therapy

In Precision medicine, the goal is to provide personalized treatment depending on the genetic makeup and characteristics of a patient's illness, with the help of biomarkers and clinical data. Personalized therapeutics in viral hepatitis increases the efficacy of the treatment, minimize adverse drug reactions and maximize the long term clinical outcome. In recent years, new technologies in the field of genomics, molecular diagnostics and biomarker discovery have enabled personalized antiviral treatment for hepatitis B and C infections [71, 72].

10.1 Pharmacogenomics in Hepatitis Treatment

Pharmacogenomics is the science that examines the variations in genes and their effect on a person's reaction to a drug. In the context of hepatitis therapy, genetic polymorphisms (such as IL28B/IFNL3) can have a significant influence on the efficacy of interferon therapy in chronic hepatitis C, consequently playing a role in selecting the most suitable antiviral therapy, optimizing the doses of the drugs administered, and reducing toxicity of the treatment, thereby improving therapeutic outcomes [71, 73].

10.2 Biomarker-Guided Therapy

Biomarker-guided therapy is the use of molecular and virological markers for the selection of therapy and for monitoring the response to therapies. An important aspect of monitoring disease activity and treatment efficacy is the use of biomarkers, including hepatitis B virus (HBV) DNA, hepatitis C virus (HCV) RNA, hepatitis B surface antigen (HBsAg), and markers of liver fibrosis. New markers are also expected to help improve the management of hepatitis infections, with circulating microRNAs and host immune markers among the emerging ones which could help achieve this goal [72, 74].

10.3 Personalized Antiviral Regimens

Personalized antiviral therapy includes the choice of the treatment, depending on the viral genotype, mutations associated with resistance, stage of liver disease and patient-specific factors. The advent of direct acting antiviral (DAA) drugs has brought a new era of personalized treatment for hepatitis C, with SVR rates exceeding 95% in the majority of patient populations. There is also an increased role

of tailored antiviral strategies in the long-term management of chronic hepatitis B, by decreasing resistance and treatment failure [72, 75].

10.4 Companion Diagnostics

Companion diagnostics are laboratory determinations of patients most likely to respond to a certain therapeutic approach. In the clinical practice of managing hepatitis, the molecular diagnostic assays measure viral load, identify viral genotypes and the resistance mutations to the antiviral agents to choose the most appropriate treatment option. The adoption of companion diagnostics with precision medicine enables more effective treatment outcomes and individualised care [71, 75].

11. Clinical Trials and Emerging Therapeutics

Clinical trials are an important part of the process of assessing the safety, effectiveness and long-term effects of new vaccines and treatments for viral hepatitis. Advances in the recent past have encompassed next-generation vaccines, new antiviral drugs, therapeutic vaccines and gene therapy, and nanomedicines as drug delivery systems. The novel strategies seek to enhance clearance and slow disease progression, as well as to achieve a functional cure, especially in chronic hepatitis B and hepatitis C virus (HCV) infection [1, 39].

11.1 Recent Vaccine Clinical Trials

There are a number of clinical trials assessing next generation hepatitis vaccines, such as mRNA vaccines, viral vector vaccines and recombinant protein vaccines. These vaccines are engineered to generate greater humoral and cell-mediated immune responses than conventional vaccines and could provide better immunity to chronic hepatitis virus infection [1, 76].

11.2 Investigational Antiviral Agents

There are many investigational antiviral agents that are being tested clinically against various stages of the viral life cycle. These include modulation of capsid assembly, RNA interference (RNAi) therapeutics, antisense oligonucleotides and entry inhibitors of hepatitis B virus. The use of combination therapy is being explored to provide sustained viral suppression and functional cure [33, 39].

11.3 Therapeutic Vaccine Trials

Therapies vaccines are designed to produce immune responses against a virus in people who already have chronic hepatitis not to prevent infection. DNA vaccines, peptide vaccines, viral vector vaccines and mRNA therapeutic vaccines (either standalone or in combination with antiviral drugs) are currently being tested in clinical trials for their ability to improve immune-mediated viral clearance [33, 76].

11.4 Gene Therapy Clinical Studies

Gene therapy is a new approach that seeks to effectively inhibit or even eradicate the hepatitis virus replication for good. To target viral genome and infected hepatocytes, clinical studies are underway on genome editing technologies like CRISPR/Cas9, RNA interference and gene-silencing method.

While useful, these therapies are also in need of further investigation for the purposes of long-term safety and efficacy. [33, 77].

11.5 Nanomedicine-Based Clinical Applications

Nanomedicine formulations enhance the targeted delivery of antiviral drugs, nucleic acids, and vaccines to liver tissues with a reduced systemic toxicity. In the field of antiviral therapy for viral hepatitis, lipid nanoparticles, polymeric nanoparticles and liposomal systems have demonstrated promising results in preclinical and early clinical trials due to their ability to improve the stability, bioavailability and therapeutic efficiency of the drug [1, 77].

12. Challenges and Future Perspectives

As impressive as the progress in vaccines and antiviral treatment has been, there remain a number of scientific, clinical and socioeconomic challenges to the goal of global viral hepatitis elimination. Solving the issue of antiviral resistance, viral mutations, treatment availability, and regulatory hurdles will be critical to meeting the World Health Organization's hepatitis elimination target by 2030 [1, 72].

12.1 Antiviral Drug Resistance

Antiviral therapy over the long term, especially chronic hepatitis B, can result in the emergence of antiviral drug-resistant variants because mutations can occur in the viral polymerase genes. Newer nucleos(t)ide analogues (tenofovir, entecavir) have high genetic barriers to resistance, but continued surveillance and development of new antiviral drugs are important to ensure treatment efficacy [33, 72].

12.2 Viral Mutation and Immune Escape

Hepatitis viruses are known to undergo very frequent mutations that help them evade the immune system and lower vaccine and treatment-induced immune responses. Mutations in the virus can change its antigens, allowing virus persistence and making antiviral treatments and vaccination less effective. It is therefore critical to monitor the evolution of viruses continuously in order to improve vaccines and develop new therapeutic strategies [1, 33].

12.3 Achieving Functional Cure for Chronic Hepatitis B

Sustained loss of hepatitis B surface antigen (HBsAg) with or without seroconversion is still a challenge. The available antiviral drugs are useful in suppressing the viral replication, but they are not very useful in clearing the major reservoir of persistent infection, covalently closed circular DNA (cccDNA). Several new treatments are under investigation to achieve long-term viral control, such as immune modulators, RNA interference, gene editing, and therapeutic vaccines [33, 53].

12.4 Global Vaccine Accessibility and Equity

While very effective vaccines are available to protect against HAV and HBV, poor access to vaccines is still a problem, low quality of the health system, and insufficient financial resources are still

limiting vaccine coverage in many low- and middle-income countries. The global burden of hepatitis could be reduced by strengthening immunization programmes, making vaccines more affordable and increasing public health programmes.

12.5 Cost and Regulatory Challenges

Novel antivirals, biologics, gene therapies and advanced vaccine technologies are very expensive, creating a major hurdle for widespread adoption. Beyond this, the regulatory approval process can be lengthy, along with manufacturing challenges and quality assurance measures can slow down the delivery of innovative therapies. Effective treatment access would be easier with international collaboration and harmonised regulatory frameworks [53, 72].

12.6 Future Research Directions

Development of curative drugs for chronic hepatitis B, broad-spectrum antiviral drugs, second-generation vaccines, personalized medicine, and AI-driven drug discovery and nanotechnology-based delivery systems should be investigated in future studies. The ability to combine multidisciplinary research and global public health strategies will be crucial in order to pave the way for sustainable hepatitis elimination and better patient outcomes globally [33, 53].

Conclusion

Despite significant advances in vaccines, antiviral medicine and disease management, viral hepatitis is still a significant public health problem. Hepatitis A and B vaccines have been highly effective in lowering incidence of Hepatitis A, Hepatitis B, and associated liver disease; and direct-acting antivirals for Hepatitis C and powerful nucleos(t)ide analogues for Hepatitis B have revolutionised clinical results, enhancing viral suppression and decreasing liver related complications. However, resistance to antiviral drugs, viral mutations, inequalities of access to health care and the fact that most of the world remains without a vaccine for HCV and that vaccines against hepatitis E are limited have prevented the global elimination of hepatitis.

Promising therapeutic vaccines, gene editing technologies, RNA interference, monoclonal antibodies and immune modulators and nanotechnology-based drug delivery systems have been developed in recent years with the potential of achieving sustained control and functional cure of the virus. In addition, the use of AI, computational drug discovery, pharmacogenomics, biomarker-driven drug targeting, and precision medicine is speeding up the discovery of novel drug targets and the development of personalized therapeutic approaches. Current clinical studies and translational research efforts continue to expand the therapeutic options and create new possibilities to enhance patient care. Future research and development should include the development of therapeutic tools against chronic hepatitis B, increasing the world-wide vaccination rate, making innovative treatment tools more affordable and accessible, and facilitating international cooperation in research and public health. Sustained funding of multi-disciplinary efforts for development of vaccines, discovery of new antiviral drugs, innovative biotechnology, and digital health technologies will continue to be critical to meeting the World Health Organization's target of eliminating viral hepatitis as a public health threat.

Together, these advances provide a promising roadmap for the future of viral hepatitis prevention, treatment, and control, globally.

References

1. World Health Organization. Global hepatitis report 2024: action for access in low- and middle-income countries**.** Geneva: WHO; 2024.
2. World Health Organization. Global Health Sector Strategies on HIV, Viral Hepatitis and Sexually Transmitted Infections 2022–2030. Geneva: WHO; 2022.
3. World Health Organization. WHO sounds alarm on viral hepatitis infections claiming 3500 lives each day. Geneva: WHO; 2024.
4. World Health Organization. Global hepatitis report 2026. Geneva: WHO; 2026.
5. Blach S, Terrault NA, Tacke F, et al. Global change in hepatitis C virus prevalence and cascade of care between 2015 and 2022: a modelling study. *J Hepatol*. 2024;81(2):251–263.
6. Centers for Disease Control and Prevention. Viral Hepatitis Surveillance—United States, 2023. Atlanta (GA): CDC; 2024.
7. Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2022: a modelling study. *Lancet Gastroenterol Hepatol*. 2024;9(6):507–520.
8. Lemon SM, Ott JJ, Van Damme P, Shouval D. Type A and E viral hepatitis. *Lancet*. 2018;392(10161):2526–2537.
9. European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines on hepatitis B, C, D and E. *J Hepatol*. 2024;81(2):300–389.
10. Cooke GS, Andrieux-Meyer I, Applegate TL, et al. Accelerating the elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission. *Lancet Gastroenterol Hepatol*. 2019;4(2):135–184.
11. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B. *Hepatology*. 2018;67(4):1560–1599.
12. Blach S, Terrault NA, Tacke F, et al. Global change in hepatitis C virus prevalence and cascade of care between 2015 and 2022: a modelling study. *J Hepatol*. 2024;81(2):251–263.
13. Fields BN, Knipe DM, Howley PM. *Fields Virology*. 7th ed. Philadelphia: Wolters Kluwer; 2021.
14. Knipe DM, Howley PM. *Fields Virology: Emerging Viruses*. 7th ed. Philadelphia: Wolters Kluwer; 2021.
15. Rehermann B, Thimme R. Insights from antiviral therapy into immune responses to hepatitis B and C virus infection. *Gastroenterology*. 2019;156(2):369–383.
16. Bertoletti A, Kennedy PTF. The immune tolerant phase of chronic HBV infection: new **perspectives** on an old concept. *Cell Mol Immunol*. 2022;19(5):509–520.

17. McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of hepatocellular carcinoma. *Hepatology*. 2021;73(S1):4–13.
18. Plotkin SA, Orenstein WA, Offit PA, Edwards KM. *Plotkin's Vaccines*. 8th ed. Philadelphia: Elsevier; 2024.
19. Centers for Disease Control and Prevention. Prevention of hepatitis A through active or passive immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2020;69(RR-5):1–38.
20. Zhang J, Shih JW, Xia N. Long-term efficacy and safety of the hepatitis E vaccine (HECOLIN®). *Hum Vaccin Immunother*. 2020;16(3):530–536.
21. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines a new era in vaccinology. Nat Rev Drug Discov**.** 2018;17(4):261–79.
22. Dolgin E. The race for next-generation vaccines. Nature. 2021;597(7875):318–24.
23. Liu MA. A comparison of plasmid DNA and mRNA as vaccine technologies. Vaccines (Basel). 2019;7(2):37.
24. Hobernik D, Bros M. DNA vaccines how far from clinical use? Int J Mol Sci. 2018;19(11):3605.
25. Draper SJ, Heeney JL. Viruses as vaccine vectors for infectious diseases and cancer. Nat Rev Microbiol. 2010;8(1):62–73.
26. Appaiahgari MB, Vrati S. Adenoviruses as gene/vaccine delivery vectors. Expert Opin Biol Ther. 2015;15(3):337–51.
27. Cunningham AL, Garçon N, Leo O, Friedland LR, Strugnell R, Laupèze B, et al. Vaccine development: from concept to early clinical testing. Vaccine. 2016;34(52):6655–64.
28. Kushnir N, Streatfield SJ, Yusibov V. Virus-like particles as a highly efficient vaccine platform. Hum Vaccin Immunother. 2012;8(3):264–76.
29. Mohsen MO, Zha L, Cabral-Miranda G, Bachmann MF. Major findings and recent advances in virus-like particle vaccines. Semin Immunol. 2017;34:123–32.
30. Purcell AW, McCluskey J, Rossjohn J. More than one reason to rethink the use of peptides in vaccine design. Nat Rev Drug Discov**.** 2007;6(5):404–14.
31. De Groot AS, Rappuoli R. Genome-derived vaccines. Expert Rev Vaccines**.** 2004;3(1):59–76.
32. Bertoletti A, Kennedy PTF. Therapeutic vaccination for chronic hepatitis B. J Hepatol. 2015;62(1 Suppl):S134–43.
33. Revill PA, Chisari FV, Block JM, Dandri M, Gehring AJ, Guo H, et al. A global scientific strategy to cure hepatitis B. Lancet Gastroenterol Hepatol**.** 2019;4(7):545–58.
34. Burton DR. Advancing vaccine design using broadly neutralizing antibodies and structure-based approaches. Nat Rev Immunol**.** 2022;22(8):481–95.
35. World Health Organization. Hepatitis A**.** Geneva: WHO; 2024.

36. Nelson NP, Weng MK, Hofmeister MG, et al. Prevention of hepatitis A virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep. 2020;69(5):1–38.
37. Ghany MG, Morgan TR. Hepatitis C guidance 2023 update. Hepatology. 2023;77(4):1468–95.
38. World Health Organization. Updated recommendations on hepatitis C virus treatment. Geneva: WHO; 2022.
39. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on hepatitis D virus infection. J Hepatol**.** 2023;79(2):433–60.
40. Wedemeyer H, Aleman S, Brunetto M, et al. Bulevirtide for chronic hepatitis D. N Engl J Med. 2023;388:135–46.
41. Kamar N, Izopet J, Dalton HR. Chronic hepatitis E virus infection. Nat Rev Gastroenterol Hepatol. 2019;16(12):713–23.
42. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on hepatitis E virus infection. J Hepatol. 2018;68(6):1256–71.
43. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Liver transplantation. J Hepatol. 2016;64(2):433–85.
44. Martin P, DiMartini A, Feng S, Brown R Jr, Fallon M. Evaluation for liver transplantation in adults. Hepatology**.** 2014;59(3):1144–65.
45. Pawlotsky JM. New hepatitis B and hepatitis C therapies: progress and challenges. Gastroenterology. 2023;164(5):1014–28.
46. Blank A, Markert C, Hohmann N, et al. First-in-human application of the entry inhibitor bulevirtide. Clin Pharmacol Ther**.** 2018;103(2):341–48.
47. Pawlotsky JM. Hepatitis C virus resistance to direct-acting antiviral drugs. Gastroenterology. 2016;151(1):70–86.
48. Yuen MF, Agarwal K, Gane EJ, et al. Safety, pharmacokinetics, and antiviral activity of ABI-H0731 in chronic hepatitis B. Lancet Gastroenterol Hepatol**.** 2020;5(2):152–66.
49. Gane EJ, Schwabe C, Wedemeyer H, et al. Capsid assembly modulators for chronic hepatitis B**.** J Hepatol. 2021;75(5):1187–99.
50. Locarnini S, Zoulim F. cccDNA elimination and silencing: future directions for hepatitis B cure. Nat Rev Gastroenterol Hepatol**.** 2023;20(2):85–102.
51. Hu J, Seeger C. HBV genome replication and cccDNA as therapeutic targets. Nat Rev Gastroenterol Hepatol. 2015;12(11):653–65.
52. Durantel D, Zoulim F. New antiviral approaches targeting host factors in hepatitis B virus infection. Antiviral Res. 2016;133:148–58.
53. Yuen MF, Chen DS, Dusheiko GM, Janssen HLA, Lau DTY, Locarnini SA, et al. Hepatitis B virus infection. Nat Rev Dis Primers**.** 2018;4:18035.

54. Yuen MF, Schinazi RF, Yuen Chan HL, et al. Emerging RNA interference and antisense oligonucleotide therapies for chronic hepatitis B. Lancet Gastroenterol Hepatol. 2024;9(2):150–63.
55. Shi M, Liu ZW, Wang FS. Immunomodulatory properties and therapeutic application of mesenchymal stem cells in liver diseases. J Hepatol**.** 2011;54(6):1294–306.
56. Hou X, Zaks T, Langer R, Dong Y. Lipid nanoparticles for mRNA delivery. Nat Rev Mater. 2021;6(12):1078–94.
57. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy and gene delivery. Nat Nanotechnol. 2007;2(12):751–60.
58. Sercombe L, Veerati T, Moheimani F, Wu SY, Sood AK, Hua S. Advances and challenges of liposome-assisted drug delivery. Front Pharmacol. 2015;6:286.
59. Mehnert W, Mäder K. Solid lipid nanoparticles: production, characterization and applications. Adv Drug Deliv Rev**.** 2012;64(Suppl):83–101.
60. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. Nat Biotechnol**.** 2015;33(9):941–51.
61. Vamathevan J, Clark D, Czodrowski P, Dunham I, Ferran E, Lee G, et al. Applications of machine learning in drug discovery and development. Nat Rev Drug Discov. 2019;18(6):463–77.
62. Paul D, Sanap G, Shenoy S, Kalyane D, Kalia K, Tekade RK. Artificial intelligence in drug discovery and development. Drug Discov Today**.** 2021;26(1):80–93.
63. Zhavoronkov A, Vanhaelen Q, Oprea TI. Will artificial intelligence for drug discovery impact clinical pharmacology? Clin Pharmacol Ther. 2020;107(4):780–5.
64. Zhavoronkov A, Vanhaelen Q, Oprea TI. Will artificial intelligence for drug discovery impact clinical pharmacology? Clin Pharmacol Ther**.** 2020;107(4):780–5.
65. Chen H, Engkvist O, Wang Y, Olivecrona M, Blaschke T. The rise of deep learning in drug discovery. Drug Discov Today**.** 2018;23(6):1241–50.
66. Lionta E, Spyrou G, Vassilatis DK, Cournia Z. Structure-based virtual screening for drug discovery: principles, applications and recent advances. Curr Top Med Chem. 2014;14(16):1923–38.
67. Meng XY, Zhang HX, Mezei M, Cui M. Molecular docking: a powerful approach for structure-based drug discovery. Curr Comput Aided Drug Des**.** 2011;7(2):146–57.
68. Shoichet BK. Virtual screening of chemical libraries. Nature. 2004;432(7019):862–5.
69. Raies AB, Bajic VB. In silico toxicology: computational methods for the prediction of chemical toxicity. WIREs Comput Mol Sci**.** 2016;6(2):147–72.
70. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med**.** 2019;25(1):44–56

71. Pirmohamed M. Personalized pharmacogenomics: predicting efficacy and adverse drug reactions. Annu Rev Genomics Hum Genet**.** 2014;15:349–70.
72. European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol**.** 2023;79(6):1819–98.
73. Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature**.** 2009;461(7262):399–401.
74. European Association for the Study of the Liver (EASL). EASL recommendations on treatment of hepatitis **C.** J Hepatol**.** 2020;73(5):1170–218.
75. World Health Organization. Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. Geneva: World Health Organization; 2024
76. Michel ML, Deng Q. Therapeutic vaccination strategies for chronic hepatitis B virus infection. Vaccine. 2023;41(18):2878–86.
77. Kulkarni JA, Cullis PR, van der Meel R. Lipid nanoparticles enabling gene therapies: from concepts to clinical applications. Nat Rev Drug Discov. 2021;20(4):246–61.