

Review Article



# Recent Advances in Dengue, Viral Hepatitis, and HIV Infections and Related Management Strategies

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## Abstract

Viral diseases are prevalent among humans, and antiviral medications treat these infections. Each year, billions of people suffer from a variety of viral diseases, and the COVID-19 pandemic alone caused the death of more than a million people worldwide in 2020. New viruses and viral strains continue to be discovered every year, and to keep up with the constantly changing nature of these infections, more and more antiviral drugs are being invented. This review examined recent advances in the area of dengue, hepatitis, and human immunodeficiency virus (HIV), focusing on their epidemiological features, pathological characteristics, and treatment strategies. Furthermore, it explores antiviral drugs used to treat and manage these diseases, highlighting their mechanisms of action and approaches to destroy or inhibit different pathogens. Biological therapies, which represent the future of antiviral treatments, are also discussed. This review summarized current information on how these viral infections continue to claim thousands of lives and aimed to assist researchers in finding new ways to invent newer and more effective antivirals. It also aimed to guide healthcare professionals in determining the probable ways to manage these viral infections, resulting in fewer deaths and minimized suffering.

**Keywords:** Dengue, Viral hepatitis, HIV, Viral disease, Antiviral drugs

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## Background

A virus is a common pathogen responsible for many diseases in humans, plants, and animals (1). Infections are caused by different pathogens, including bacteria, viruses, and fungi. Every living organism has the potential to be infected by pathogens. Infections caused by viruses are typically treated with antiviral medications (2). Additionally, phytomedicines sometimes act as agents to stop the growth of such viruses and combat diseases caused by other microorganisms (3-7). Drugs used to treat viral infections are known as antiviral drugs. Viruses are among the most common biological entities on this planet. To understand how a virus infects an individual, it is essential to have a general understanding of the virus's structure. Viruses have a simple structure that consists of a protein coat, nucleic acid, some enzymes, and in some cases, an envelope around their structures (8). These microscopic organisms usually contain either DNA or RNA as genetic materials, and these genetic materials are the primary cause of their virulence. The structure of

two common viruses is shown in [Figures 1 and 2](#). To fight against these viruses, humans have developed different antiviral drugs. Antiviral drugs employ various strategies to combat the pathogens that infect our bodies (9). Specific antiviral drugs are used for particular infections caused by different viruses. The mechanisms of antiviral drugs differ from those of antibiotics. Antibiotics generally tend to destroy the pathogen, but antiviral drugs tend to inhibit the virus from replicating. The virus replicates in the host cells by entering them, making it difficult to design a drug that serves its purpose without harming the host (10).

Viruses are mainly classified into two types based on their genetic material: DNA viruses and RNA viruses. Many important pathogens consist of DNA such as herpesviruses, smallpox viruses, adenoviruses, and papillomaviruses. These viruses enter the host cell, and replication leads to the production of new viruses. DNA viruses are categorized into three major groups (11):

- Double-stranded DNA viruses (e.g., Poxvirus)
- Single-stranded DNA viruses (e.g., Parvovirus)



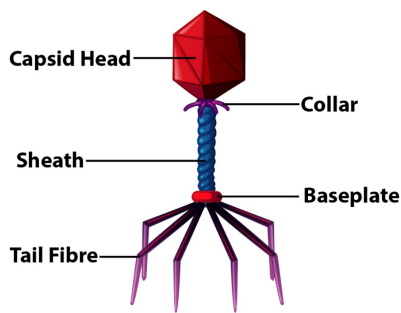


Figure 1. Structure of the T<sub>2</sub> Bacteriophage Virus

- Paratrovirus (e.g., Hepadnavirus)

RNA viruses have RNA strands instead of DNA. Some common RNA viruses include influenza, measles, mumps, colds, meningitis, polio, and retrovirus. Unlike DNA viruses, RNA viruses do not need to enter the host cell (1).

The knowledge regarding viruses and viral diseases is constantly updated through ongoing experiments and research. Moreover, newer viruses and strains are being discovered each year such as the SARS-CoV-2, which is responsible for the COVID-19 pandemic (12-18). Recent advances in the field of viral diseases will be discussed below.

## Dengue Virus

### Epidemiology of Dengue Virus

The dengue virus is an arthropod-borne flavivirus with four stereotypes, responsible for dengue fever, also known as 'breakbone fever.' Dengue fever is endemic to Southeast Asia, Indonesia, South and Central America, and sub-Saharan Africa (19). The dengue virus was originally transmitted to *Homo sapiens* from monkeys and is now transmitted through the blood-feeding activities of female mosquito species, *Aedes aegypti* and *Aedes albopictus*, which serve as reservoirs of the virus (20). According to the World Health Organization (WHO), dengue is considered the most prevalent and dangerous arbovirus and is also the fastest-spreading arbovirus among all the other emerging arboviruses worldwide (21). About 6 162 394 dengue cases and a total of 3,930 deaths were recorded only in the year 2019-2020 (until May 15, 2020) (22-30). Type 1 dengue virus strain (DENV1) causes recurring dengue fever due to the lack of antibodies, whereas type 2 (DENV2) is considered the most virulent strain. Warm humid weather and rainy seasons provide the ideal conditions for annual dengue endemics.

## Mechanism and Pathogenesis of Dengue Virus

### Biochemical Mechanism

#### Viral Entry

The DENV virus enters human cells by attaching its envelope (E) protein to cellular receptors such as DC-SIGN, mannose receptors, and glycosaminoglycans on the surface of the host cells, especially dendritic cells and macrophages. Following binding, the virus forms an endosome inside the host cell as a result of internalization

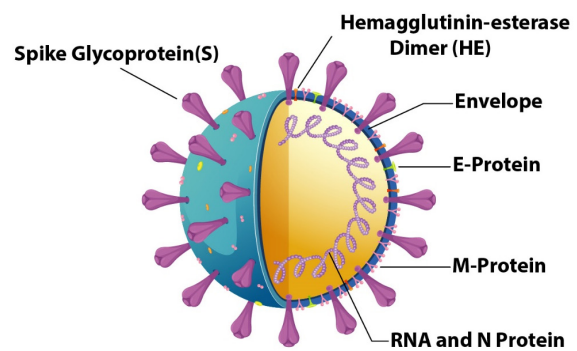


Figure 2. Structure of the SARS-CoV-2 Coronavirus

via receptor-mediated endocytosis. The viral envelope fuses with the endosomal membrane as the endosome becomes acidified, causing a conformational shift in the E protein, which allows the viral RNA to enter the cytoplasm.

### Replication

The positive-sense single-stranded RNA genome of DENV is translated into one polyprotein. Viral and host proteases break this polyprotein into non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) and structural proteins (C, prM, and E). The non-structural proteins assemble into a replication complex on the endoplasmic reticulum (ER), where viral RNA is reproduced. A complementary negative-strand RNA is created by the RNA-dependent RNA polymerase (NS5) and serves as a template for creating new positive-strand viral RNAs.

### Viral Assembly

In the ER, prM and E proteins are also integrated into immature viral particles that contain newly generated viral RNAs. The host protease furin cleaves the prM protein in the immature viral particles as they pass through the Golgi apparatus, resulting in the formation of mature infectious virions.

### Immune Response and Evasion

The host's innate immune response, including the synthesis of interferons (IFNs), is triggered by DENV infection. To prevent this reaction, the viral proteins NS2B/NS3 and NS5 degrade STAT2 and block the JAK-STAT signaling pathway, which is essential for the IFN response. In secondary infections with a different DENV stereotype, previous non-neutralizing antibodies can promote viral entry into host cells, resulting in more severe disease through a process known as antibody-dependent enhancement (31).

### Pathogenesis

Hemorrhage, thrombocytopenia, and increased vascular

permeability are seen during dengue hemorrhagic fever, which in turn might cause plasma leaking into serious spaces. Reports claim that thrombocytopenia results from the decreased synthesis of platelets due to bone marrow suppression caused by the dengue virus (32). Thrombocytopenia, along with increased fibrinolysis, contributes to coagulation abnormalities in most dengue patients, whereas classic disseminated intravascular coagulation does not seem to be a key factor (33). In the acute phase of patients with secondary dengue infections, an inverse correlation was observed between platelet count and the levels of platelet-associated immunoglobulin G (PAIgG) (34). Due to the direct binding between the dengue virus and platelets, immune complexes containing anti-dengue virus IgG antibodies appear on the platelets (35). Other findings suggest that the formation of PAIgG due to anti-dengue virus IgG induces thrombocytopenia during secondary infections (Figure 3). The mechanisms underlying the formation of DHF are not yet fully understood, but based on epidemiological data, two primary hypotheses were proposed to explain the pathogenic changes associated with DHF: (i) the enhancement of dengue virus infection through the secondary heterotypic antibodies, a hypothesis that is widely accepted (36-38), and (ii) the overall combination of viral load, strain virulence, and the host's immune response (39,40).

### Clinical Manifestations, Biochemical Changes in Blood, Diagnosis, Treatment, and Prevention of Dengue Virus

#### Clinical Manifestations

Approximately 50% of dengue patients remain asymptomatic. The incubation period of the dengue virus is typically 4 to 7 days. After this latent period, patients manifest symptoms such as fever, malaise, and headache, and in some cases, more severe symptoms, including high fever, bone and joint pain, arthralgias, myalgias, retro-orbital pain, nausea, vomiting, petechiae and an

erythematous maculopapular rash (19). The most severe manifestations of dengue include dengue shock syndrome and hemorrhagic fever, which may lead to hepatomegaly and hemorrhage. Dengue fever is also called “breakbone fever” due to its association with intense myalgias, arthralgias, and bone pain.

#### Changes in Biochemical Factors in Blood

A significant drop in platelet count (thrombocytopenia) is one of the primary signs and symptoms of dengue. This reduction in platelets increases the risk of bleeding since platelets are essential for blood coagulation. Increased platelet lysis, consumption during coagulation processes, and bone marrow suppression cause thrombocytopenia. Dengue infections can also result in hemorrhage, which can range from mild epistaxis and bleeding gums to potentially lethal gastrointestinal bleeding. Moreover, hemorrhage and thrombocytopenia are commonly associated, which is consistent with other research findings. Thrombocytopenia and bleeding in dengue may result from cytokine-induced immunological dysfunction and platelet death after dengue-specific antibodies bind to virus-infected platelets. Lower platelet counts are more common in instances of severe dengue and are associated with an increased risk of bleeding. During dengue fever, platelet counts decrease until the sickness improves, after which they swiftly rise.

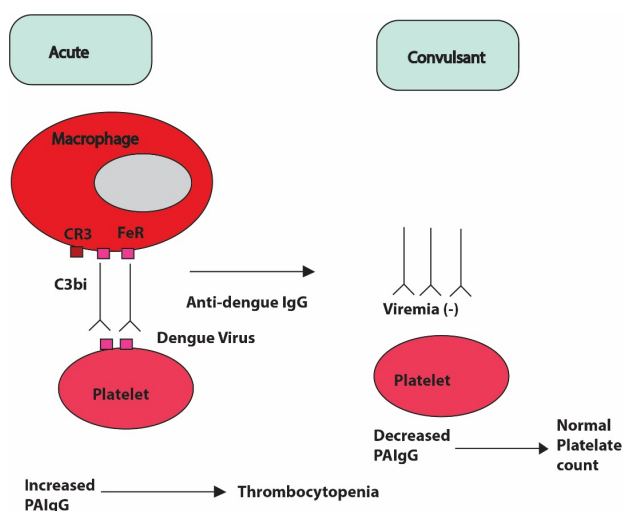
Furthermore, dyspnea was found to be a crucial sign of severe dengue. Published research found a strong association between shock and dyspnea, which may be caused by lung congestion from fluid overload due to capillary leaks (41,42).

Dengue typically results in a reduction in white blood cells (WBCs), particularly during the feverish phase. This leukopenia is typically most noticeable in the later stages of the illness and can make the body more susceptible to further infections.

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are two liver enzymes commonly elevated in dengue patients. These elevations indicate hepatic damage, which can vary in intensity depending on the course of the disease. When assessing the degree of liver damage, AST levels frequently rise more than ALT levels, and in some cases, they may increase excessively. In a study, 972 (28.1%) of the 1,090 dengue patients had low platelet levels, followed by 315 (28.1%) with low hemoglobin, 404 (37.1%) with low WBC, 183 (16.8%) with high ALT, and 148 (13.6%) with elevated AST (42).

#### Diagnosis

The diagnosis and confirmation of dengue virus infection can be made through several methods, including the isolation of dengue virus using cell culture, reverse transcriptase polymerase chain reaction (RT-PCR) to detect viral RNA from serum, plasma, or cerebrospinal fluid, and the detection of dengue virus-specific immunoglobulin M (IgM) and/or IgG in serum during



**Figure 3.** A Hypothetical Mechanism of Thrombocytopenia in Secondary Infected Dengue Patients Due to the Production of PAIgG. Note. PAIgG: Platelet-associated immunoglobulin G

the acute and convalescent stages of infection (19).

#### *NS1 Antigen Test*

In the early stages of infection, the blood can contain the dengue virus's NS1 antigen, a protein secreted by the virus. This test can help diagnose dengue within the first few days after the onset of symptoms.

#### *Dengue Immunoglobulin M and Immunoglobulin G Antibodies*

IgM antibodies signify a recent infection and typically appear 4-5 days post-infection. IgG antibodies develop later during the illness and signify prior exposure or a subsequent infection.

#### *Reverse Transcriptase Polymerase Chain Reaction*

RT-PCR is the gold standard for diagnosing acute dengue infection since it can detect dengue virus RNA. It is most effective in the first week after the onset of symptoms (43).

#### *Treatment*

Currently, no effective antiviral treatment is available for dengue infection, so supportive care, along with fluid resuscitation, is provided. Acetaminophen is used to treat pain and fever in case of hemorrhages instead of NSAIDs. Mosquito abatement and personal insect repellents such as N, N-diethyl-meta-toluamide (DEET) are used to prevent dengue infections.

### **Viral Hepatitis**

#### *Epidemiology of Viral Hepatitis*

Five types of hepadnaviruses (HPV) are responsible for viral hepatitis, which mainly include hepatitis A, B, C, D, and E. Among these, hepatitis A, B, and C are the most common in the United States. According to the Centers for Disease Control and Prevention (CDC), around 24 900 new cases of hepatitis A occur each year. In 2018, there were 22 600 new infections of hepatitis B, with an estimated 862 000 cases recorded to be living with chronic hepatitis B. Hepatitis C remains the most prevalent, with 50 300 new infections reported in 2018 and a total of 2.4 million people living with the virus (44). An effective vaccine is available for hepatitis A and B, whereas about half of patients with hepatitis C are unaware of their infection and are at risk for liver transplantation or hepatic cancer. Hepatitis A infection is transmitted through the ingestion of fecal matter from an infected person, hepatitis B primarily spreads through contamination by blood, semen, or other bodily fluids of an infected person, and hepatitis C spreads through contact with the blood of an infected person or, in some cases, from an infected mother to her child during birth (44).

#### *Mechanism and Pathogenesis of Viral Hepatitis*

Hepatitis A virus (HAV) enters through the ingestion or infection of the intestine and spreads through the bloodstream, ultimately reaching the target organ, the liver.

Viral particles can be diagnosed from feces during this incubation period, as early as 10-14 days from exposure, reaching a peak elevation in serum aminotransferases. Pathological changes due to HAV occur mainly in the liver and include focal activation of the cells lining the sinusoid, parenchymal aggregation of lymphocytes, and an increase in histiocytes, which replace hepatocytes primarily in the periportal areas as liver cells are destroyed due to necrosis (45). Hepatitis B virus (HBV) and hepatitis C virus (HCV) replicate non-cytopathically inside liver cells. Since they are non-cytopathic, the innate immune system of the body cannot respond significantly to the liver's pathogenesis nor play a role in viral clearance (Figure 4). The adaptive immune response plays a crucial role in liver disease pathogenesis and viral clearance in both HBV and HCV, specifically through the response of virus-specific cytotoxic T lymphocytes (CTL), which are further enhanced by the antigen-nonspecific inflammatory cells. Platelets also assist this process by accumulating CTLs in the liver. If the infection persists, failure of the immune response to induction or maintain CTL effector functions is confirmed. Such persistence can result in further complications such as fibrosis, cirrhosis, or hepatocellular carcinoma (HCC) from chronic inflammations, and some extrahepatic disorders of immunological origin (46).

### **Biochemical Mechanism of Viral Hepatitis**

#### *Hepatitis A Virus*

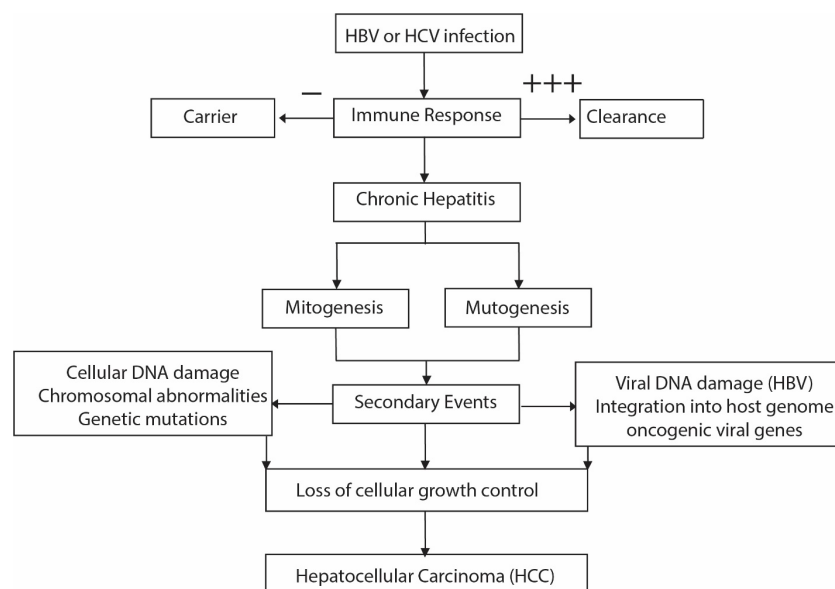
HAV is an RNA virus that spreads through the oral-fecal pathway. After ingestion, the virus enters the bloodstream and travels to the liver, where it infects hepatocytes or liver cells. Viral and host proteases convert the viral RNA into a polyprotein, which is subsequently broken down into functional viral proteins. These proteins facilitate the cytoplasmic replication of viral RNA. Infected hepatocytes become the target of the host immune system, leading to liver inflammation. However, HAV does not result in persistent infection, and the majority of patients recover fully (47)

#### *Hepatitis B Virus*

HBV is a DNA virus that infects hepatocytes and enters the bloodstream through infected body fluids or blood. Hepatocytes contain sodium taurocholate cotransporting polypeptide (NTC6666P) receptors to which the virus binds to enter the cell. Inside the nucleus, the partly double-stranded DNA (cccDNA) is converted into covalently closed circular DNA (cccDNA), which acts as a template for the transcription of viral RNA. Reverse transcriptase, a key step in HBV replication, is one of the proteins produced from the translation of viral RNA. HBV can integrate into the host genome, increasing the risk of liver cirrhosis and HCC and causing chronic infection in some individuals (48).

#### *Hepatitis C Virus*

HCV is an RNA virus spread through blood contact.



**Figure 4.** Mechanism and Pathogenesis of Hepatocarcinogenesis due to Viral Hepatitis. A vigorous (+++) immune response against HPV and HCV might result in viral clearance, whereas a lack of immune response (-) leads to a healthy carrier state. An intermediate immune response (+), on the other hand, results in chronic hepatitis. Note. HPV: Hepatitis P virus; HCV: Hepatitis C virus

Hepatocytes are infected by the virus via receptors such as CD81 and claudin-1. Inside the cell, the viral RNA is translated into a single polyprotein, which is then broken down into functional viral proteins. As HCV replicates in the cytoplasm, it forms a replication complex with the ER, resulting in the production of new viral RNA genomes and the assembly of viral particles. Due to a high number of HCV mutations, the virus can evade immune system responses and cause chronic infection in 70%–85% of cases, resulting in liver fibrosis, cirrhosis, and HCC (49).

#### Hepatitis D Virus

HBV E protein is necessary for the defective RNA virus, hepatitis D virus (HDV), to enter hepatocytes. HDV replicates using host RNA polymerase II, generating RNA that is subsequently encapsulated by HBV surface antigens. HDV can cause serious liver damage, especially when co-infected with HBV. The host immune response to both HBV and HDV triggers significant liver inflammation and damage, often resulting in more severe clinical outcomes (50).

### Clinical Manifestations, Changes in Biochemical Factors in Blood, Diagnosis, Treatment, and Prevention of Viral Hepatitis

#### Clinical Manifestations

Many people with hepatitis exhibit no symptoms and may remain unaware of their infection. Symptoms of acute infection can arise within 2 weeks to 6 months of contact, whereas manifestations of chronic viral hepatitis can develop over decades. Common manifestations of viral hepatitis include fever, fatigue, vomiting, nausea, loss of appetite, dark-colored urine, abdominal pain, pale-colored stools, jaundice, and joint pains (44).

Serologic and molecular assays are used as diagnostic

tools for detecting viral hepatitis. Environmental Impact Assessment (EIA) serologies detect acute HAV infections and assess immune status. Similar immunoassays are used to diagnose HBV by detecting the presence of antigenemia and evaluating the level of infectivity (51).

#### Changes in Biochemical Factors in Blood

A study evaluated 11 blood indicators, including  $\alpha$ 2-macroglobulin, albumin, total bilirubin, AST, ALT,  $\gamma$ -glutamyl transpeptidase (GGT),  $\alpha$ 1-globulin,  $\alpha$ 2-globulin,  $\beta$ -globulin,  $\gamma$ -globulin, and apolipoprotein A1. It found that a combination of five or six blood biochemical markers had high positive and negative predictive values for diagnosing clinically severe fibrosis. The most informative markers were  $\alpha$ 2-macroglobulin, haptoglobin,  $\gamma$ -globulin, total bilirubin, apolipoprotein A1, and GGT (52). The breakdown of hemoglobin results in the production of bilirubin, which the liver processes and excretes as bile. The accumulation of both direct (conjugated) and indirect (unconjugated) bilirubin in the blood is caused by the liver's impaired ability to process bilirubin in hepatitis. This leads to jaundice, which is characterized by yellowing of the eyes and skin (52).

The liver synthesizes albumin and other proteins. Reduced blood levels of albumin and total protein occur due to the liver's diminished synthesis function in chronic hepatitis. This reduction may result in problems such as edema and ascites, resulting from a drop in plasma oncotic pressure. The liver plays a central role in glucose metabolism. In hepatitis, particularly in advanced stages, glucose intolerance or hypoglycemia may develop due to impaired gluconeogenesis and glycogenolysis (53).

#### Treatment of Viral Hepatitis

The treatment of viral hepatitis mainly involves supportive

care to manage symptoms. No medication is currently available for HBV, so regular monitoring of the progression of liver disease is essential. However, some cases of HBV and chronic HCV infections are treated with antivirals. A typical 8-12 weeks course of oral therapy of medication can cure more than 90% of HCV-infected cases, with very few side effects (44). Viral hepatitis can be prevented by avoiding contact with infected individuals, maintaining good hygiene, and avoiding the misuse of syringes and transfusion of infected blood or other body fluids.

### **Human Immunodeficiency Virus**

#### ***Epidemiology of Human Immunodeficiency Virus***

The human immunodeficiency virus (HIV) causes an infection that may progress to acquired immunodeficiency syndrome (AIDS) over time. HIV belongs to the lentivirus genus, a subgroup of the Retroviridae family. The virus spreads through certain body fluids, and upon entering a healthy body, it destroys and impairs CD4 T cells, which are crucial to the immune system. This destroys the body's ability to fight infections and certain types of cancers (54). Interestingly, the most devastating viral infection of the 20<sup>th</sup> century was not caused by HIV, but by Spanish influenza, which killed more than 20 million people worldwide.

#### ***Biochemical Mechanism and Pathogenesis of Human Immunodeficiency Virus***

Initially, HIV attaches to the CD4 receptors on the surface of CD4 + T cells and penetrates the cell with the help of co-receptors such as CCR5 and CXCR4 (55). The viral core then enters the host cell cytoplasm through the fusion of the viral envelope with the host cell membrane, which is mediated by the gp41 protein. After entering the cell, the reverse transcriptase enzyme releases the viral RNA genome, converting it from single-stranded RNA to double-stranded DNA. Due to the error-prone nature of this mechanism, mutations may arise, leading to increased drug resistance.

The double-stranded viral DNA is transported into the nucleus, where it integrates into the host cell's genome, forming a provirus. The provirus has two possible fates: transcription into viral RNA or entering a latent state. The host's RNA polymerase transcribes the incorporated viral DNA into viral RNA. Enzymes such as reverse transcriptase, integrase, and protease, along with structural proteins (Gag, Pol, and Env), are produced when the viral RNA is translated.

At the host cell membrane, viral RNA and proteins assemble to form immature viral particles. The Gag and Gag-Pol polyproteins are necessary for this assembly procedure. The immature viral particles develop an envelope derived from the host cell membrane as they branch off from the host cell. To produce infectious virions, the viral protease enzyme must break the Gag and Gag-Pol polyproteins into mature functional proteins. If untreated, the mature HIV virions can infect new CD4 + T cells,

extending the infection cycle and progressively weakening the host's immune system, eventually culminating in AIDS (55). Beginning with acute infection, the pathogenesis of HIV progresses to chronic infection or clinical latency, eventually leading to HIV (56,57).

### **Clinical Manifestations, Changes in the Biochemical Factors in Blood, Diagnosis, Treatment, and Prevention of HIV**

#### ***Clinical Manifestation***

Fever, headache, rash, and sore throat can be observed in the acute phase of HIV infection, while symptoms such as fatigue, weight loss, and night sweats can be seen in the chronic phase. Blood tests can easily detect antibodies generated against HIV.

#### ***Changes in the Biochemical Factors in Blood***

WBCs known as CD4 + T cells are essential to the immune system and are the primary target of HIV. Over time, HIV causes the depletion of these cells. HIV progression is characterized by a decrease in CD4 + T-cell count, which is also used to stage the illness and assess the risk of opportunistic infections. A normal CD4 + count ranges from 500 to 1500 cells/ $\mu$ L, while a count below 200 cells/ $\mu$ L indicates the presence of AIDS (58). Even in patients receiving antiretroviral therapy (ART), HIV infection is typified by ongoing immune activation and inflammation. Increased morbidity and mortality from cardiovascular disease and other non-AIDS-related illnesses are linked to elevated levels of CRP, IL-6, and other inflammatory cytokines (59). HIV infection and ART, particularly protease inhibitors, are linked to hyperglycemia and insulin resistance, likely increasing the development of type 2 diabetes, which raises their risk of cardiovascular disease (60). Elevated levels of liver enzymes such as ALT, AST, and alkaline phosphatase (ALP) are indicative of liver dysfunction caused by HIV infection or its treatment. These changes can result from direct viral impacts, coinfections (e.g., hepatitis B or C), or the hepatotoxicity of antiretroviral medications (61).

### **Diagnosis or Biochemical Detection of Human Immunodeficiency Virus**

#### ***Human Immunodeficiency Virus Antibody/Antigen Tests (4th Generation)***

The 4th generation HIV test detects both HIV antibodies and the p24 antigen, which appears earlier than antibodies. This combination allows for earlier detection of HIV infection compared to antibody-only tests (62)

#### ***Western Blot or Immunoblot***

The Western Blot is traditionally used to verify HIV infection after a positive screening result. However, in many cases today, more sophisticated methods are replacing it (63).

### ***Treatment of Human Immunodeficiency Virus***

Although there is no cure for HIV, ART is effective in suppressing the virus. Preventive actions for HIV include practicing safe sex, not sharing needles, and getting tested regularly (64).

### ***Steps of Viral Infection***

A viral infection initiates when a virus enters its DNA into the host cell and replicates that DNA inside the host. Then, the replicated DNA releases new viruses. The entire process of viral replication occurs through several additional steps (65).

### ***Types of Different Antiviral Medications***

Antiviral medications are classified according to their mechanism of action. Different drugs work on different stages of the viral life cycle. Drugs according to their modes of action and side effects are listed in [Table 1](#) (66-106). The structures of several antiviral drugs are presented in [Figure 5](#).

### ***Acyclovir***

Acyclovir is most commonly used to treat herpes simplex virus (HSV) infections, as well as cold sores, shingles, and chickenpox (107). It is the first line of treatment for HSV encephalitis, and no other medications are currently available for this condition (108). Acyclovir is also sometimes used in HIV-infected patients if they show eczema herpeticum and for treating infections of the skin, eyes, nose, and mouth. Oral hairy leukoplakia is also treated with acyclovir (109,110).

Acyclovir can be administered orally or intravenously, depending on the situation (111). It works by incorporating itself into viral DNA, preventing further DNA synthesis. When the DNA synthesis is inhibited, and after incorporating into the DNA strand, acyclovir is converted into acyclovir triphosphate by viral and cellular enzymes (112). Although this is a common treatment, there are several adverse effects associated with acyclovir use, including inflammation, nausea, vomiting, transaminitis, and rash (i.e., Steven-Johnson syndrome), particularly when taken intravenously.

### ***Valacyclovir***

The L-valyl ester form of acyclovir is known as Valacyclovir. This drug is converted back to acyclovir by valacyclovir hydrolase in the gastrointestinal tract and Liver. Valacyclovir has three times more bioavailability than acyclovir (113) and is effective in treating HSV and varicella-zoster virus.

### ***Ganciclovir***

Ganciclovir, unlike acyclovir, has an extending hydroxymethyl group. Upon entering the host cell, ganciclovir is replaced by ganciclovir monophosphate by phosphotransferase. This phototransferase gives ganciclovir a superiority over acyclovir, resulting in higher

concentrations of ganciclovir triphosphate in the blood compared to acyclovir (114).

### ***Penciclovir***

Penciclovir is structurally similar to ganciclovir, but it differs in the connection between the methylene group and oxygen in the non-cyclic ribose portion of the particle. Its digestive mechanism and activity are also similar to ganciclovir. Herpes simplex types 1 and 2 and varicella-zoster infection are inhibited by in vitro penciclovir (115).

### ***Ribavirin***

Ribavirin is a simple guanosine with an inadequate purine cycle. The drug enters the cell and undergoes intracellular phosphorylation, resulting in ribavirin triphosphate, which interferes with the initial stages of virus translation (116). This suppression of ribonucleoprotein synthesis stops the virus.

### ***Lamivudine***

Lamivudine was discovered to treat HIV infection. It is a cytidine that is converted intracellularly into lamivudine triphosphate. As an NRTI, lamivudine is combined with other drugs to treat HIV-1. This drug is also used as monotherapy for HBV (117). The high bioavailability of lamivudine allows better therapeutic outcomes in patients upon administration.

### ***Remdesivir***

Remdesivir was first introduced to treat the Ebola virus, but over time, it has been used to treat patients suffering from COVID-19. It is a prodrug, with its active form being GS-441524. The mechanism of remdesivir involves reducing viral RNA production.

### ***Amantadine and Rimantadine***

These drugs are used in combination to treat influenza infection. Amantadine hydrochloride contains a special 10-carbon atom structure, and Rimantadine hydrochloride also has a 10-carbon cycle with an ethyl-carbon linkage. Both drugs work by blocking the M2 protein channel of the virus, thereby reducing the release of viral proteins. Amantadine is extremely effective in elderly patients, with higher bioavailability in this group of patients compared to young adults. Both of these drugs actively inhibit and treat influenza infections (118).

### ***Interferon Alpha***

IFNs inhibit the incorporation of viral proteins into host cells. They are produced in microbes through recombinant DNA strategy. They cannot be administered orally and must be given only via intramuscular or intravenous injection. Although the precise mechanism of action for IFN is not fully understood, it is generally believed that they inhibit viral replication. IFN therapy is used to treat human herpesvirus, papillomavirus, hepatitis B, and C.

**Table 1.** Frequently Used Antiviral Drugs and Their Indications

Type of Antiviral Drug	Therapeutic Use	Side Effects	Reference	
<b>Entry inhibitors</b>				
Enfuvirtide	HIV infection	Decreased appetite, dark urine, swollen glands, arthralgia,	(66)	
Maraviroc	HIV infection	Dizziness, hematuria, dilated neck veins, discharge or excessive tearing	(67)	
Palivizumab	RSV infection	Rash, urticaria, difficulty breathing	(68)	
<b>Uncoating inhibitors</b>				
Amantadine	Influenza A infection	Psychomotor agitation, depression, anorexia, sleep disorder	(69)	
Rimantadine		Abdominal pain, dizziness	(69)	
<b>DNA polymerase inhibitors</b>				
Acyclovir	Herpes virus infection	Skin rash, angioedema, diarrhea, neurotoxic effects	(70)	
Famciclovir		Cramps, diarrhea, headache, heavy bleeding, nausea · stomach pain	(71)	
Valaciclovir		Black, tarry stools, chest pain, chills, cough, decreased frequency or output of urine	(72)	
Ganciclovir		Stomach pain, skin rash	(73)	
Valganciclovir		CMV infection	Blood in the urine or stools, headache, chills	(74)
Brivudine		HSV-1 and VZV infection	No significant side effects recorded	(75,76)
Foscarnet		Herpes virus infection	Seizures, chills, headache	(77)
Cidofovir	CMV infection	Hair loss, chills, proteinuria	(78)	
<b>NRTIs</b>				
Abacavir	HIV infection	Stomach pain, muscle pain, redness and soreness of the eyes, numbness or tingling of the hands, feet, or face	(79)	
Didanosine		Constipation, rash, blurred vision, night sweats	(80)	
Emtricitabine		Dark urine, anorexia, skin rash, muscle pain	(81)	
Stavudine		Diarrhea, decreased appetite, blurred vision, chills	(82)	
Zalcitabine		Peripheral neuropathy	(83)	
Zidovudine		Myalgias, lactic acidosis, headaches, elevated liver enzymes, hepatotoxicity, peripheral myopathy	(84)	
Lamivudine		HIV and HBV infection	Shallow breathing, dizziness, stomach pain, heart arrhythmia,	(82)
Entecavir	HBV infection	Dizziness, anorexia	(85)	
Telbivudine	HBV infection	Cough, diarrhea, arthralgia, back pain	(86)	
<b>NRTIs</b>				
Adefovir	HBV infection	Dark urine, stomach pain, tiredness, bone pain	(87)	
Tenofovir	HIV and HBV infection	Pain, shallow breathing, heart arrhythmia, polydipsia	(88)	
<b>NNRTIs</b>				
Efavirenz	HIV infection	Depression, trouble concentrating diarrhea, anorexia, irritability, drowsiness	(89)	
Etravirine		Rash, muscle pain, mouth sore, diarrhea,	(90)	
Delavirdine		Headache, abdominal pain, confusion	(91)	
Rilpivirine		Sleep disorder, headache, tiredness, dark urine	(92)	
<b>RNA Inhibitor</b>				
Ribavirin	HCV infection, RSV infection, Lassa fever	Fever or chills, chest pain, blurred vision, rash	(93)	
<b>Integrase Inhibitor</b>				
Raltegravir	HIV infection	Dark urine, fever, depression, muscle pain	(94)	
<b>PIs</b>				
Amprenavir	HIV infection	Diarrhea, blistering or peeling of the skin, difficulty breathing, headache	(95)	
Atazanavir		Bloating, blood in the urine, blurred vision, chest pain	(96)	
Fosamprenavir		Rash, high blood sugar, abdominal pain, headache, fatigue	(97)	
Indinavir		Heartburn, polyuria, shortness of breath, headache	(98)	
Lopinavir		Heart arrhythmia, anorexia, heartburn,	(99)	
Nelfinavir		Rash, stomach pain, loss of appetite	(82)	
Ritonavir		Blistering or peeling of the skin, swelling of the eyes, face, tongue, lips, or throat, hives	(99)	
Saquinavir		Cough, skin rash, chest pain, back pain	(100)	
Darunavir		Myalgia, headache, dark urine, skin rash, fever	(101)	
Tipranavir		Rash, hyperglycemia, hyperlipidemia, hepatitis, headache	(102)	
Boceprevir	HCV infection	Fatigue, dry skin, rash, insomnia	(103)	
Telaprevir	HCV infection	Anal or rectal pain, diarrhea, shortness of breath	(104)	
<b>Release inhibitor</b>				
Oseltamivir	Influenza A/B infection	Itching, headache, dizziness	(105)	
Peramivir		Gastro-intestinal disorder, low neutrophil count, diarrhea, chills, swelling in face and throat, confusion, rash	(106)	

Note. HIV: Human immunodeficiency virus; RSV: Respiratory syncytial virus; CMV: Cytomegalovirus; HSV: *Herpes simplex virus*; VZV: *Varicella zoster virus*; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NRTIs: Nucleotide reverse transcriptase inhibitors; NNRTIs: Non-nucleoside reverse transcriptase inhibitors; PIs: Protease inhibitors.



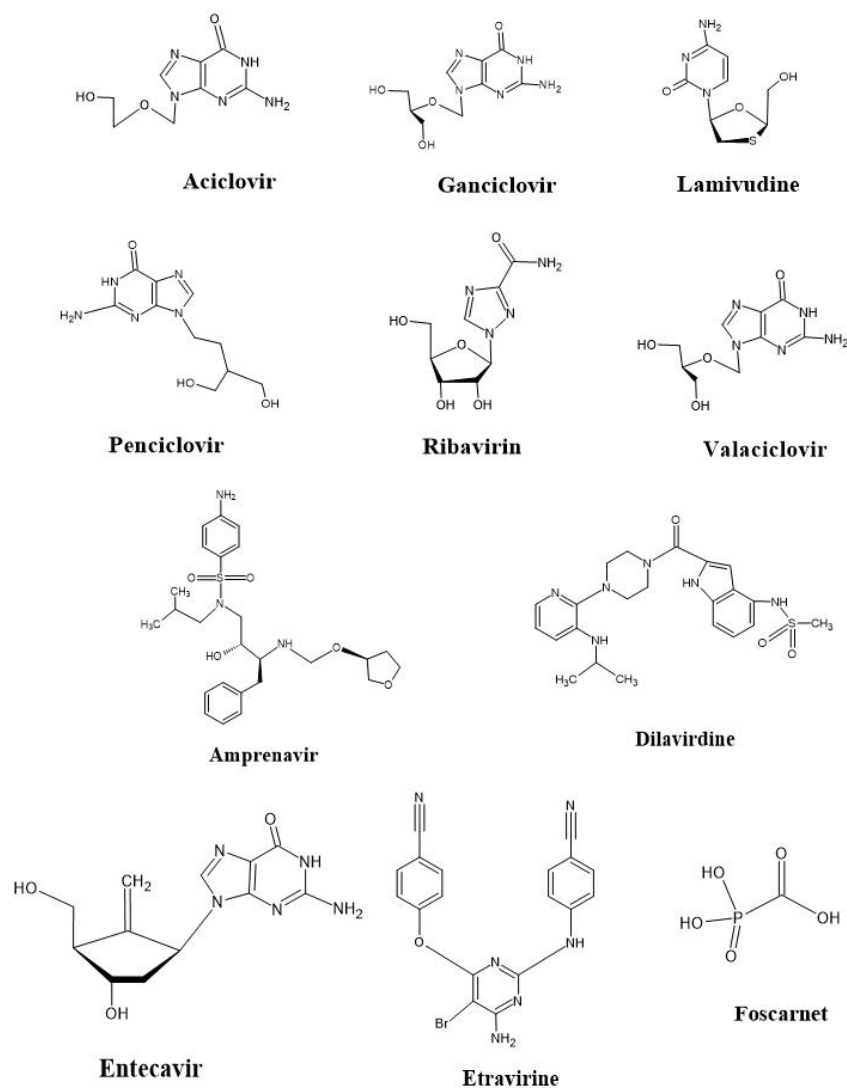


Figure 5. Structures of Commonly Used Antiviral Drugs

### ***Virus-Inactivating Agents***

Some antiviral drugs directly stop infections. One drug is calcium elenolate, extracted from olive trees, which has exhibited in vitro activity against various DNA and RNA viruses. The mechanism of action for this agent involves communication with the protein layer of the virus molecule (119). Certain dihydroisoquinolines also show viral-inactivating effects on influenza A, B, and para influenza infection. Although these agents have exhibited some in vitro usefulness, they have been neglected for human use (120).

### ***Interference in Viral Attachment, Entrance, and Uncoating***

When a virus first attacks the cell film of a eukaryotic cell, it enters the cell layer and its cytoplasm. The virion then pours all its elements into the cell, which causes cellular damage.

This is the least convenient point to attack for antiviral agents. The sulfated polysaccharide has shown some potential to bind with the cell in vitro. This substance has been found effective in infections, including dengue fever,

flu, rabies, and encephalomyocarditis (121).

### ***Inhibition of Enzymes Associated With Virions DNA Replication***

Viral and bacterial infections are often associated with uncontrollable DNA replication. The DNA polymerase enzyme can be targeted to stop this virion from replicating further. DNA polymerase is an enzyme that helps elongate the DNA or RNA strand. Viruses need this enzyme to continue their life cycle. By targeting this essential process, we can achieve therapeutic benefits for the diseases.

Currently, there are several ways to stop DNA replication by targeting DNA polymerase. The most common method is to use agents such as temozolomide and cisplatin. These agents modify DNA structure and inhibit DNA synthesis, preventing cellular proliferation (122). They are effective but have uncontrolled side effects. The nonselective killing of cancerous cells affects infectious agents as well as healthy cells, which may sometimes accelerate disease progression (123).

Another strategy for halting viral infection is by stopping individual enzymes involved in the DNA replication

process. A targeted enzyme is topoisomerase, which is involved in making the knots that form in DNA during replication. Inhibiting this enzyme causes apoptosis by creating single- and double-stranded DNA breaks that interfere with DNA synthesis (124).

Another strategy involves reducing the availability of dNTPs, the building blocks required for DNA synthesis. By inhibiting the enzymes involved in nucleotide metabolism, agents such as methotrexate and hydroxyurea can inhibit DNA synthesis (125). The most effective and direct strategy is the use of nucleoside analogs such as AZT or fludarabine, which targets the enzymatic activity of DNA polymerase (126,127). The common mechanisms are shown in Figure 6.

### ***Inhibition of Translation Process of Viral mRNA***

The virus-host interaction is crucial in controlling viral translation. Viruses rely on the protein synthesis machinery of the host cells to propagate, and the host ribosomes use different mechanisms to produce viral mRNAs. Antiviral medications specifically control the protein synthesis mechanisms responsible for slowing down the infection (128).

Normal mammalian cells contain mRNA that consists of a 7-methylguanosine cap (m7G) at the 5' termini, a 5' untranslated region (5'UTR), and a coding sequence that has a start codon and ends with a stop codon (129). The virus follows the same mechanism, with some special characteristics. It contains three steps in translation: initiation, elongation, and termination (130). By restricting the m7G, we can regulate viral translation in the host cell (131).

### ***Early Viral Polypeptide Chains***

Parafluorophenylalanine exhibits broad-spectrum antiviral activity against RNA and DNA viruses. It replaces phenylalanine, which stimulates antiviral peptide walls. In the absence of phenylalanine, these peptide walls cannot be stimulated, leading to the destruction of the virus (132).

### ***Fusion of Antiviral Agents to Viral DNA***

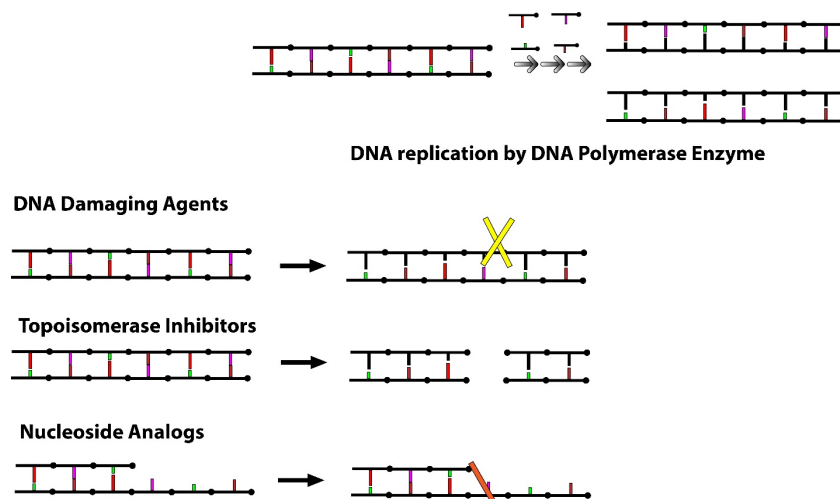
5-IdU is fused with viral DNA in place of thymine, and the result is invested. The fusion of other agents instead of thymine creates a non-functional DNA analog, which damages the genetic material. Other DNA-related deoxy thymine analogs have also been used, yielding positive results.

### ***Gene Editing and Gene Therapy***

Among the CRISPR-Cas systems, the CRISPR-Cas13 method is widely used in diagnostics and antiviral therapeutics because it cuts targeted RNA sequences in a sequence-specific manner (133). Similarly, the CRISPR-Cas 12 system can be used in therapies to cleave single-strand viral DNA. In 2019, Li et al demonstrated that the dengue virus NS3 gene can be effectively cleaved by CRPSIR-Cas13a, suppressing viral replication (134). Yin et al adapted the CRISPR-Cas13 method to target the tat, gag, rev, and LTR regions in HIV-1 virus, limiting HIV-1 replication by 50% (135). Additionally, it was discovered that the CRISPR-Cas13a system effectively targets the internal ribosome entry site of the HCV for antiviral use (136).

### ***Injectable Pre-Exposure Prophylaxis***

Pre-exposure prophylaxis (PrEP) is a form of prevention that significantly lowers the risk of contracting HIV in HIV-negative people who have a greater risk of becoming exposed to the virus through sexual contact with an HIV-positive partner or sharing needles or having multiple sex partners (137). PrEPs currently in use include dapivirine vaginal rings, lenacapavir, rilpivirine, and long-acting cabotegravir injectables of the first generation (138). In 2021, the US Food and Drug Administration (FDA) approved cabotegravir, an integrase strand transfer inhibitor for PrEP of AIDS, which is now available as an intramuscular injection and tablet (139). Afterward, lenacapavir was also approved as PrEP as an HIV-1 capsid inhibitor. Another drug, dapivirine, is a reverse transcriptase inhibitor that is used by women living in



**Figure 6.** DNA Polymerase-Catalyzed DNA Replication and Chemotherapeutic Agents Inhibiting DNA Replication

some parts of Africa (139).

Recently, long-acting ARTs have gained popularity as PrEP due to their ability to provide sustained drug release into the systemic circulation for a long time. Cabotegravir and rilpivirine have demonstrated potential as a combination long-acting therapy for people with HIV-1 infection. Investigations into the possible application of a subcutaneous formulation of lenacapavir for PrEP are still underway (140). In addition, integrase inhibitors and tenofovir, taken as HIV-1 PrEP, can prevent HIV-2 infection. In this context, long-acting cabotegravir formulations may protect individuals living in endemic areas or in relationships with HIV-2 partners from contracting the virus through sexual contact.

### Vaccine Research

A novel tetravalent dengue vaccine called TAK-003 by Takeda Pharmaceutical Company provides potential defense against all four dengue virus serotypes. In 2022, the European Medicines Agency (EMA) approved this vaccine for use according to national recommendations for patients over the age of four. In clinical trials, the vaccine demonstrated great efficacy against virologically proven dengue and severe dengue in individuals aged 4-16 residing in dengue-endemic areas. However, sufficient clinical information for people older than 60 years does not exist (141). Another vaccine, Dengvaxia (CYD-TDV), is extremely effective in treating children aged 9 or older who have previously acquired dengue fever. CYD-TDV is a tetravalent, live, recombinant attenuated dengue vaccine formulated by Sanofi Pasteur. It was approved for clinical use in 2015 and was most recently approved by the FDA for the prophylaxis of dengue caused by DENV1-4 (142). Developed by Glaxo Smith Kline (GSK), Engerix-B, also known as HepB-Eng, was the first recombinant vaccine for Hepatitis B available in Europe. For nearly forty years, the two recombinant vaccines, Engerix-B (GSK) and Recombivax-HB (Merck), have been used with significant effectiveness. HEPISAV-B, a new recombinant vaccine against HBV, was authorized in the United States in 2017 for use and requires only two doses over one month. PreHevbrion is a highly immunogenic HBV that was approved to be used in adults aged 18 and older in the United States (2021), European Union (2022), United Kingdom (2022), and Canada (2022) (143). It is designed to prevent infections caused by all known subtypes of the HBV and the delta virus. One of the most significant is Moderna's mRNA-based HIV vaccine, which uses technology similar to their COVID-19 vaccine. This vaccine tends to elicit a significant immune response by signaling cells to manufacture HIV-related proteins, allowing the body to detect and attack the virus (144). Early trials have yielded positive outcomes, including significant antibody responses.

## Nutritional and Lifestyle Consideration in Dengue, Viral Hepatitis, and Human Immunodeficiency Virus

### Dengue

Nutritional and lifestyle aspects must be taken into consideration when managing dengue fever to promote recovery and avert complications. Since dengue fever, vomiting, and sweating can result in severe fluid loss, it is important to stay properly hydrated. Electrolyte balance is preserved by clear liquids such as broth, coconut water, and oral rehydration treatments. A well-balanced diet full of fruits and vegetables, especially 2 citrus fruits and papaya, helps strengthen the immune system and supply vital vitamins and minerals, including antioxidants and vitamin C, which aid in healing. Zinc is important for immune system performance and helps reduce the intensity of viral infections. By regulating the immune system, vitamin D may lower the likelihood of serious consequences. Iron is also necessary to sustain hemoglobin levels, particularly in dengue-induced anemia, and sufficient folate and vitamin B12 levels are necessary for the synthesis of red blood cells and general energy levels (145). Moreover, consuming enough protein is essential for tissue healing as well. Foods high in protein include lean meats, eggs, and lentils. To minimize the physical strain on the body and reduce the risk of hemorrhagic complications during the acute phase of the illness, adequate rest is crucial (146).

### Hepatitis

Maintaining liver health while managing hepatitis necessitates a balanced diet and significant lifestyle adjustments. In terms of nutrition, the focus should be on lean proteins, fruits, vegetables, high-fiber whole grains, and healthy fats, particularly omega-3 fatty acids. Zinc, selenium, B-complex, vitamins A, C, and E, and other essential vitamins and minerals are crucial for liver regeneration and immune system maintenance. Abstaining from alcohol is also crucial to prevent additional liver damage (147).

Changes in lifestyle include avoiding hepatotoxins, staying hydrated to support liver function, and engaging in regular physical activity to maintain a healthy weight and reduce liver fat. Regular medical monitoring is also crucial for effectively treating the disease and preventing complications. Additionally, stress management techniques such as yoga or meditation can be effective (148).

### Human Immunodeficiency Virus

People with HIV experience nutritional difficulties such as malabsorption, which can result in deficiencies in vital nutrients like zinc, vitamin B12, vitamin D, and selenium, all of which can impair immune function. Moreover, they are at a higher risk of weight loss and wasting syndrome, particularly in the advanced phases of the disease. HIV also affects metabolism, increasing the risk of cardiovascular disease due to insulin resistance and dyslipidemia. Deficits in certain nutrients can affect mental and cognitive

performance, further lowering the quality of life, while chronic inflammation exacerbates nutritional depletion. The Mediterranean diet, which is rich in fruits, vegetables, whole grains, nuts, and olive oil, has anti-inflammatory benefits that can enhance immune function. This eating pattern is particularly beneficial for people living with HIV. The DASH diet, which contains fruits, vegetables, whole grains, and lean proteins, promotes cardiovascular health and reduces inflammation. Diets high in protein and fiber also support gut health, which is necessary for balanced immune responses and the formation of immune cells. Foods high in nutrients guarantee an adequate intake of vitamins and minerals, while foods high in probiotics help repair damaged gut lining and reduce inflammation. It is important to customize these eating habits to the specific needs and tastes of HIV-positive individuals (55).

### Conclusion

Viral infections pose a significant global health risk. Significant efforts have been made in the development of antiviral medications over the past 50 years, leading to substantial success for particular viruses. However, viruses have distinct biochemical pathways and undergo various processes of mutation. As a result, the discovery and development of antiviral medications are challenging. Moreover, developing antiviral resistance is a common phenomenon among people. Future epidemics may have enough time to evolve before a vaccine becomes widely available. Hence, further progress in antiviral drug development is needed. This remains a significant challenge for drug developers. Additionally, further development in the biological field is necessary. However, prevention will always remain the most effective strategy.

### Authors' Contribution

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Not applicable.

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