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Role of Marine Natural Products in the Genesis of Antiviral Agents

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Graphical Abstract

1. INTRODUCTION

Mammals have complex biological systems and are constantly prone to infections by a wide array of bacteria, fungi, viruses, and parasites, a significant challenge to the constant development of disease-strains resistance to current drugs.¹ As a result, there is always a need to identify new anti-infective agents against these organisms. An anti-infective agent is defined by Webster as “an agent capable of acting against an infection, by inhibiting the spread of an infectious agent or by killing the infectious agent outright”.² Some of the emerging and drug-resistant infectious diseases having research priority are human immunodeficiency virus (HIV) or AIDS, hepatitis B and C viruses, respiratory infections such as influenza and respiratory syncytial virus (RSV), and dengue fever.¹ Figures 1 and 2 provide us with the data in regards to the mortality and incidence rates, respectively, of people with viral diseases.^{3–5}

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Notes

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Supporting Information

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Parameters necessary to analyze the pharmacokinetic and toxic properties of the reported marine drugs and the FDA-approved drugs (PDF)

Search engines utilized to identify the literature reviewed here include Google scholar, Scifinder, Pubmed, government documents from the CDC, NIH, and the World Health Organization (WHO), academic journals, and books.

2. HUMAN IMMUNODEFICIENCY VIRUS DEMOGRAPHICS

HIV-1 and HIV-2 can infect humans and cause severe immunosuppression through depletion of CD4⁺ cells. HIV-2 was first isolated in West Africa in 1986, and its mode of transmission is similar to HIV-1 except that it is generally less infectious and the disease develops more slowly and is milder. As the disease progresses, there are more infections with shorter durations compared to that of HIV-1. HIV-2 is seen predominately in Africa, but increasing incidences have been documented in the United States since 1987.⁶

HIV and the resulting AIDS-associated infections have become an international epidemic,⁷ resulting in over 30 million AIDS-related deaths worldwide.⁸ In 2011, around 2.5 million people were diagnosed with HIV, and an estimated 1.7 million men, women, and children died from the complications of AIDS. Around 34 million people were living with HIV by the end of 2011, with 69% of those infected in Sub-Saharan Africa. Following Sub-Saharan Africa, the regions most affected with HIV are the Caribbean, Eastern Europe, and Central Asia, where 1% of infected adults were living in 2011.⁷

In Asia, it is estimated that at least 4.8 million people are currently living with HIV, with China accounting for 780 000 of those infected individuals followed by Thailand and Indonesia. Eastern Europe and Latin America each has around 1.4 million infected people.⁹

In the United States, more than half a million people have died from AIDS-related complications,¹⁰ and it has been estimated that over 1.3 million people are infected with HIV,⁷ some of whom may not even be aware of their infection status.¹¹ Those at greatest risk for infection include individuals engaged in high-risk behaviors, such as intravenous (IV) drug use.¹² During 2007, in the United States, HIV was the fourth leading cause of death for Latinos and Hispanics between the ages of 35–44 and the sixth leading cause of death between the ages of 25–34.¹³ According to the National HIV/AIDS strategy,¹⁴ HIV and AIDS are most commonly seen among African Americans. AIDS was first documented by the United States CDC in 1982, in two females, one Latina and the other African American. The epidemic of AIDS began to spread among the African American population from this point forward.¹⁵

2.1. Nomenclature of HIV/AIDS

The first instances of AIDS can be traced back to 1981,⁶ when a strange illness began occurring in the homosexual communities; however, the pandemic is reported to have started in the late 1970s¹⁶ originating in Africa. In 1982, AIDS had different names that included gay cancer, gay-related immune deficiency (GRID),¹⁷ gay compromise syndrome,¹⁸ and community-acquired immune dysfunction. The term AIDS derived its acronym in July 1982, at a meeting in Washington, DC.¹⁹ Initially it was thought to be the disease of the “four H club” that included heroin addicts, hemophiliacs, homosexuals, and Haitians.¹⁶

The virus that was known to cause AIDS was initially named as lymphadenopathy-associated virus, or LAV, in May 1983.¹⁶ On April 23, it was announced that the virus known to cause AIDS was isolated and was named Human T-cell Leukemia Virus-III (HTLV-III). It was thought that the LAV and HTLV-III could be the same virus.²⁰ In March 1985, the United States Food and Drug Administration (FDA) licensed the first blood test for AIDS²¹ created by Abbott Laboratories to identify possible antibodies (for HIV).²² The name HIV or Human Immunodeficiency Virus was given by the International Commission on Virological Nomenclature in May 1986.¹⁶

2.2. Emergence of Drugs From Marine Sources

Nature plays an important role in the generation of unique drug prototypes of which about 60% of anticancer agents are derived from natural sources and around 95% of the earth's biosphere are represented by the marine ecosystem.²³ Hence, marine sources can be an invaluable source for the discovery of new compounds for the treatment of diseases like AIDS or cancer. As an example, three compounds, spongosine, spongothymidine,²⁴ and spongouridine,²⁵ were isolated from *Cryptotethia crypta*, a Caribbean marine sponge. These compounds were some of the first reported bioactive nucleosides isolated from a marine species. The first anticancer lead from marine organisms was cytosine arabinoside or ara-C (1), a synthetic derivative developed from a sponge natural product prototype.²⁵ The syntheses of ara-C were first reported by Walwick in 1959, and Lee first reported the syntheses for ara-A (vidarabine) (2) in 1960.²⁶ Ara-A was used as an antiviral agent for the treatment of herpes simplex virus type 1 and type 2 infections for many years, although acyclovir (83) is more widely prescribed. Ara-C is used for the treatment of acute myelocytic leukaemia and Hodgkin's lymphoma.²⁶ The above mentioned drugs are the first FDA-approved marine-derived products used for the treatment of disease. They were also the basis for the synthesis and development of zidovudine (3'-azido-3'-deoxythymidine, AZT or ZDV) (3), which was initially tested for cancer as an antibacterial but was later approved for HIV. Since then, extensive investigations have taken place for the treatment of various diseases from marine sources as well as for the further development of nucleosides (Schemes 1 and 2).

2.3. History of AIDS/HIV

Jerome Horwitz synthesized AZT (3) in 1964 as an anticancer drug.¹⁶ Samuel Broder and Hiroaki Mitsuya, who were investigators at the National Cancer Institute (NCI), determined its potent anti-HIV activity in February 1985, which led to its clinical development. In 1974, it was shown to inhibit the Friend leukemia virus (murine leukemia virus) replication,²⁷ and in 1986, the clinical trials were conducted on HIV-infected persons.¹⁶ The drug was first approved by the FDA in March 1987²¹ under the commercial name Retrovir.¹⁶ AZT (3) in its triphosphate form inhibits HIV reverse transcriptase, thereby blocking the expression of p24 gag protein of the virus.²⁸ AZT (3) was the first drug to be used in the treatment of AIDS,²¹ and the first AIDS campaign coordinated by the nation was launched in 1988.²⁹

In October 1991, FDA approved didanosine or 2',3'-dideoxyinosine (4).³⁰ In June 1992, zalcitabine, also known as 2',3'-dideoxycytidine (ddC) (5), a nucleoside reverse transcriptase inhibitor (NRTI), was approved by the FDA;⁸ it was mainly used in patients who were

resistant to AZT.³¹ During the same year, a combination therapy was developed that became successful in utilizing both AZT (**3**) and ddC (**5**).³² In 1993, many cases occurred where people were resistant to AZT (**3**),³³ and in June 1994 the FDA approved another NRTI, stavudine (**6**).^{8,34} It was also shown that the transmission of HIV from mother to child could be reduced by up to 66% with the use of AZT (**3**) during pregnancy.³⁵ A recent example corresponding to this includes the antiretroviral therapy (ART) given 30 h after birth to an infant born with HIV-1 infection. ART was continued with detection of HIV-1 DNA and RNA; after the discontinuation of the therapy when the child reached 18 months of age, the child was found with undetectable HIV-1 antibodies, suggesting that early ART may help alter the long-term persistence of HIV-1 infection.³⁶ However, the child was later found viral positive after two years off ART, suggesting continued challenges in controlling HIV infection.³⁷

In 1995 the protease inhibitor saquinavir (inivirase) (**7**) was approved by the FDA,³⁸ and during the same year in November, the FDA approved the NRTI lamivudine or 3TC (**8**).³⁹ In 1996 a new non-nucleoside reverse transcriptase inhibitor (NNRTI) viramune, also known as nevirapine (**9**), was approved by the FDA,⁴⁰ and in the same year, the viral load test called Amplicor HIV-1 Monitor Test was introduced. This test gave clinicians the ability to document the progression of the disease.⁴¹ In September 1997, the FDA approved an NRTI combivir, which is a combination of lamivudine (**8**) and zidovudine (**3**).³⁹ In 1998, two clinical trials proved that the combination of AZT (**3**) with ddC (**5**) was much more effective in prolonging life and delaying the disease compared to AZT (**3**) used alone.⁴² Abacavir (**10**),⁴³ another NRTI, was approved by the FDA in December of the same year.⁸ In 1999, the original source of HIV was found to be from *Pan troglodytes*, a type of chimpanzee common in West Central Africa. It is hypothesized that the virus entered the human population when hunters were exposed to the infected blood of the chimpanzee.⁴⁴

Nonoxynol-9, a spermicide, was proven to be an ineffective microbicide in the reduction of transmission of HIV during sex.⁴⁵ The first HIV vaccine trial took place in Oxford, U.K., in September of 2000.⁴⁶ In 2001 an Indian company, Cipla, offered AIDS drugs for as low as \$1 per day,⁴⁷ and in 2002 WHO provided guidelines for antiretroviral drugs and also released a list of 12 drugs that could be used for AIDS.⁴⁸ T-20 (Fuzeon) (**15**), a fusion inhibitor, also came into existence as an injectable drug,⁴⁹ bringing forth a new campaign for the control of the spread of HIV that was called ABC, short for “Abstinence, Being faithful, and Condom use”.⁵⁰

A great mission of rescue was initiated by the former United States president George W. Bush in 2003 to combat AIDS in the Caribbean and in Africa.⁵¹ In the same year, Vaxgen made an announcement regarding the failure of the AIDS vaccine to reduce the HIV infection rate,⁵² and in November the vaccine was found to be a failure in a clinical trial in Thailand.⁵³ On March 15, 2003, the FDA approved a new type of anti-HIV drug for the prevention of HIV entry into human cells. Fuzeon, also known as enfuvirtide or T-20 (**15**), was the first drug to be classified as a “fusion inhibitor”. Fuzeon was available in the form of an injection, and it could be used as combination therapy in patients resistant to other antiretroviral drugs.⁵⁴ The unnatural L-nucleosides, lamivudine (**8**) and emtricitabine (**11**), became commercially available, and they revolutionized the treatment of HIV (and hepatitis

B virus (HBV)), since these drugs are now part of many highly effective fixed-dose combinations.⁵⁵ In July 2003, the FDA approved emtricitabine (**11**),^{8,56} and on December 1, 2003, World AIDS Day, the WHO declared a “three by five” campaign of providing antiretroviral treatment to three million people in resource-poor countries by 2005.⁵⁷ Another similar policy called the “Four Free and One Care” was declared by the Chinese government that included many services such as providing free antiretroviral agents to the poor and rural communities, free testing and counseling, free drugs for the prevention of the transmission from mother to child, free schools for orphans of AIDS-related deaths, and proper care and economic help for people afflicted with HIV or AIDS.⁵⁸

In 2004, for the first time in their history, the Global Fund stopped the funding scheme to fight AIDS.⁵⁹ In March, the first oral fluid rapid test for HIV was approved by the United States FDA,⁶⁰ and President George W. Bush’s PEPFAR, also known as the “President’s Emergency Plan For AIDS Relief” was fully implemented in June 2004. This was designed to focus on 15 countries in Africa as well as Haiti, Guyana, and Vietnam.⁶¹

In January 2005, the FDA approved an antiretroviral agent co-packaged drug regimen (lamivudine (**8**)/zidovudine (**3**) and nevirapine (**9**)) made by Aspen Pharmacare, a South African company. This marked the first HIV drug regimen to be approved by a non-United States based pharmaceutical company, a milestone that represented a huge turning point in Africa for providing cheaper pharmaceutical treatments for HIV-1.⁶² In September 2005, the patent period for AZT came to an end, allowing many pharmaceutical companies to produce the drug and sell it at greatly reduced prices.⁶² In 2006, for the first time, a pill that could be taken only once a day for the treatment of HIV-1 infection was approved in United States. Now widely used in first-line treatment, Atripla included a combination of three drugs: Emtriva (emtricitabine (**11**)), Sustiva (efavirenz (**19**)), and Viread (tenofovir disoproxil fumarate or TDF-(**16**)).^{63–65}

In 2007, the FDA approved two new drugs, raltegravir (Isentress) (**12**)⁶⁶ and maraviroc (Selzentry) (**13**),⁶⁷ that could be used in patients resistant to all other classes of anti-HIV drugs. In October the initial results of a vaccine being developed by Merck pharmaceutical company were found to be ineffective, resulting in terminating the trial being conducted on hundreds of participants.⁶⁸ In 2008, the American funding program PEPFAR was renewed for the treatment of HIV/AIDS, malaria, and tuberculosis for the years 2009–2013.⁶⁹

In 2009 President Obama promised to lift the travel ban that had been implemented for 22 years that prevented people infected with HIV/AIDS from entering the United States,⁷⁰ and finally on January 2010 the ban was lifted.⁷¹ The results from a microbicide trial CAPRISA 004 highlighted the biannual International AIDS Conference in July 2010. According to Phase IIb trial results, it was found to be safe and effective to use an antiretroviral-based gel on HIV-negative women that reduced the risk of acquiring the infection by 40%.⁷² In October 2011, a new drug application for a single-drug regimen also known as the “QUAD” pill was submitted by Gilead Sciences, Inc., and this included elvitegravir (**53**), cobicistat (**14**), emtricitabine (**11**), and TDF (**16**).⁷³ Truvada, a fixed-dose combination of emtricitabine (**11**) and tenofovir disoproxil fumarate (**16**), was approved by the FDA in July 2012 for the pre-exposure prophylaxis (PrEP) of HIV and was manufactured by Gilead.⁷⁴ Dolutegravir

(54) or Tivicay was approved by the FDA in August 2013 and was marketed by ViiV Healthcare and manufactured by GSK for use in treatment-naïve and treatment-experienced patients.⁷⁵ The history of HIV/AIDS is outlined from its conception until 2014, and all of the HIV/AIDS drugs that are currently available in the market can only be used to prevent further replication of the virus in the body and to extend the lifetime of people who are HIV-positive by a few more years. A cure to eradicate or eliminate HIV completely has yet to be identified (Figure 3).

2.4. Description of the Virus

The virus particles are spherical with a diameter of one ten-thousandth of a millimeter. The viral envelope, which is the outer coat, includes two layers of lipids that are taken from the human membrane by the virus when a new virus is formed from the cell. Throughout the viral envelope, proteins including 72 copies of complex HIV-1 protein called env are embedded. The surface of the virus is spiked with these env copies and is called a “virion”. env includes glycoprotein 120 (gp120), which is a cap containing three molecules, and glycoprotein 41 (gp41), which is a stem with three molecules. These two proteins adhere to the structure of the viral envelope, and research concerning an HIV vaccine is mainly focused on these proteins.⁷⁶

A bullet-shaped capsid or core is present inside the viral envelope that is made of ~2000 copies of p24, the viral protein. Surrounding the capsid are two single-stranded HIV-1 RNA, each including a complete copy of the viral genes. Gag, pol, and env are the three structural genes that carry information necessary for the formation of structural proteins for new viral particles. Similarly tat, nef, vif, vpr, vpu, and rev are the six regulatory genes responsible for the control of the virus in regards to infecting the host and producing the disease. An RNA sequence called the long terminal repeat (LTR) is present at the end of each strand of the viral RNA. These regions control the production of the new viruses. The nucleocapsid protein p7 is present in the core, and the matrix protein p17 is present between the core and the envelope. The virus also requires three enzymes for the completion of its replication cycle: reverse transcriptase, protease, and integrase (Figure 4).⁷⁶

2.5. Virus Replication Cycle

HIV can only reproduce in humans, and its replication cycle occurs in six stages, beginning with its binding to a CD4 receptor along with one of the co-receptors (among the two) on the CD4⁺ T-lymphocyte surface. This leads to the fusion of the virus (HIV-1) to the host cell, thereby leading to the release of viral RNA into the cell. This is called the Binding and Fusion stage. In stage II, called the Reverse Transcription stage, the reverse transcriptase enzyme present in the virus (HIV-1) converts single-stranded viral RNA to double-stranded viral DNA. Stage III is the Integration stage, where the viral DNA formed in stage II enters into the host cell nucleus and incorporates the viral DNA within the host cell's own DNA by the viral enzyme integrase. This integrated viral DNA is called a provirus and could reproduce few or no copies or remain inactive for many years.

The fourth stage, Transcription, is where the provirus produces copies of the viral genome as well as messenger RNA or mRNA (shorter strands of RNA) with the help of the host's RNA

polymerase enzymes. This occurs whenever a signal is sent to the host cell to become active. The mRNA produced above is used to further produce long chains of viral proteins. Assembly is the fifth stage, where the long chains are cut into shorter individual proteins by the viral enzyme protease. These proteins along with the copies of viral RNA form a new virus particle. The sixth and the final stage is Budding. The above assembled virus buds out of the host cell. During this stage, the virus takes some of the cell's outer membrane that contains sugar or protein combinations called HIV glycoproteins. These are required by the virus in order to bind with the CD4 and the co-receptors. After this is complete, these copies are now ready to infect new cells (Figures 5 and 6).⁷⁷

2.6. HIV–HCV Coinfection

HIV coinfection with hepatitis C virus (HCV) is common due to the shared routes of transmission,⁷⁸ and it is known to affect about one-third of all the people infected with HIV worldwide. The prevalence can vary depending on the factors of transmission.⁷⁹ In the United States, approximately 25% of people infected with HIV are also infected with HCV. The statistics greatly increase for those that have additional risk factors such as intravenous drug use.⁸⁰

HIV–HCV coinfection leads to higher concentrations of HCV RNA, thereby increasing the risk of cirrhosis by accelerating the progress of HCV-related liver disease. In HIV-infected persons, the natural progression of HCV is drastically increased as a result of the HCV infection simulating opportunistic diseases.⁸¹ Transmission by sexual or vertical factors is more important in cases of HIV than HCV, but coinfection of HIV–HCV increases the risk of both vertical and sexual transmission of HCV.⁸² As the infection of HIV progresses, it leads to a decrease in cell-mediated immunity that further enhances HCV replication, leading to an increase in infection rate and hepatocyte injury. The immune cells cannot respond to HCV in coinfecting persons because they are impaired.⁸³ High CD4 cell counts can result in significant fibrotic progression in coinfecting patients.⁸⁴ HIV–HCV coinfection also leads to hepatocellular carcinoma (HCC), which is known to have a higher incidence compared to those infected with HCV alone.⁸⁵

Along with liver problems, HIV–HCV coinfecting people exhibit symptoms of kidney disease and have a bleaker renal prognosis.^{86,87} There is an increased risk of significant kidney function deterioration in HIV–HCV coinfecting women.⁸⁸ Other coinfecting persons developed membranous nephropathy, immunotactoid glomerulopathy, mesangial proliferative glomerulonephritis, and immune-deposited collapsing glomerulopathy.⁸⁹ In summary, these coinfections lead to complicated diagnoses, clinical progression of the disease, monitoring, treatment, and the basic immunology.⁷⁸

The treatment for the coinfection of HIV–HCV usually includes dual combination therapy of interferon (IFN)–ribavirin (RBV) and highly active antiretroviral therapy (HAART). However, the coinfection increases the complexity of the treatment. Problems arise with the safety and efficacy of the drugs in these individuals.⁹⁰ There are viral genome replication inhibitors that are used for the treatment of HIV–HCV coinfection.

The clinical symptoms and pathogenesis of HIV and HCV are similar. The polymerases of HIV include RNA-dependent DNA polymerase, also known as reverse transcriptase, and that of HCV includes RNA-dependent RNA polymerase, referred to as RNA replicase. Whereas HIV protease is an aspartyl protease, HCV's protease is a serine protease. Some of the drugs belonging to different categories used in the treatment of HIV and HCV are mentioned below.

As of 2015, the only nucleotide reverse transcriptase inhibitor (NtRTI) approved for the treatment of HIV is TDF or Viread (**16**), although all the currently approved nucleoside analogues require phosphorylation for inhibition of HIV polymerase.⁹¹ The non-nucleoside reverse transcriptase inhibitors (NNRTIs) used in the treatment of HIV include nevirapine (**9**), rilpivirine or edurant (**17**), etravirine (**18**),⁸ efavirenz (**19**), and delavirdine (**20**) (Figure 7).⁹²

The known nucleoside RNA replicase inhibitors (NRRIs) possessing anti-HCV activity in vitro known to date include valopicitabine (**21**),⁹³ 2'-*C*-methyladenosine (**22**),^{94,95} 7-deaza-7-fluoro-2'-*C*-methyladenosine (**23**),^{94,96} 2'-*O*-methylcytidine (**24**),⁹⁴ 7-deaza-2'-*C*-methyladenosine (**25**),⁹⁷ 2'-*C*-methylguanosine (**26**),^{98,99} 4'-azidocytidine (**27**),¹⁰⁰ 2'-deoxy-2'-fluoro-2'-*C*-methylcytidine (**28**),¹⁰¹ oral prodrugs like R1626 (**29**),^{102,103} and novel analogues of 4'-azido-2'-deoxynucleoside (Figure 8).¹⁰⁴

To possess anti-HCV activity, the presence of a methyl group or a fluorine group at the 2'-*C* position or an azido group at the 4'-*C* position is essential. Any new nucleoside derivatives containing both substitutions in a single molecule would be an area of exploration for anti-HCV activity (Figure 9).⁹²

Sofosbuvir or GS-7977 (**30**), previously named as PSI-7977,¹⁰⁵ is a uridine nucleotide analogue currently in Phase 2 trial for the treatment of HCV infection.¹⁰⁶ It is a selective inhibitor of HCV NS5B polymerase. Combination with pegylated interferon and ribavirin is also being tried for the efficacy of sofosbuvir (**30**) in treating HCV,¹⁰⁷ although interferon-free treatments are now more popular (e.g., the use of sofosbuvir (**30**) with the NS5A inhibitor ledipasvir (**31**), a combination called Harvoni that has been approved by the FDA in October 2014).¹⁰⁸ Simeprevir (**32**), a second-generation macrocyclic compound, is a NS3/4A HCV protease inhibitor that binds non-covalently to the HCV protease and was approved by the FDA in November 2013.¹⁰⁹ Daclatasvir (**33**), a NS5A replication complex inhibitor manufactured by Bristol-Myers Squibb, was in Phase III clinical trials in combination with sofosbuvir (**30**) for the treatment of HCV,¹¹⁰ and its use in combination with other antiviral drugs for the treatment of HCV was declined by the FDA in November 2014.¹¹¹ The FDA approved Viekira Pak in December 2014, which is a combination of ombitasvir (**34**), paritaprevir (ABT-450) (**35**), and ritonavir (**46**) tablets that are co-packed with dasabuvir (**36**) tablets for the treatment of chronic HCV infection (Figure 10).¹¹²

The proteases of HIV and HCV are attractive drug targets. The viral protease inhibitors used for the treatment of HIV include amprenavir (**37**), indinavir (**38**), lopinavir (**39**), fosamprenavir (**40**), nelfinavir (**41**),⁸ darunavir (**42**), tipranavir (**43**), and atazanavir (**44**).⁹²

Another protease inhibitor, brexnavir (**45**), could be used in combination with ritonavir (**46**) for the treatment of HIV-1-infected persons (Figure 11).^{113,114}

The HCV serine protease inhibitors include boceprevir (**47**),¹¹⁵ telaprevir (**48**),¹¹⁶ ciluprevir (**49**),¹¹⁷ and SCH446211 (**50**) (Figure 12A).¹¹⁸

Other anti-HIV-1 drugs that are still in clinical trials include entry inhibitors such as PRO 140,¹¹⁹ TNX-355 or ibalizumab,¹²⁰ BMS-663068 (**51**)¹²¹ and cenicriviroc (**52**),¹²² integrase inhibitors such as elvitegravir (**53**)¹²³ and dolutegravir (**54**),¹²⁴ maturation inhibitor vivecon,¹²⁵ NNRTIs like lersivirine (**55**)¹²⁶ and dapivirine (**56**),¹²⁷ and NRTIs like KP 1461 (**57**),¹²⁸ apricitabine (**58**),¹²⁹ elvucitabine (**59**),¹³⁰ racivir (**60**),¹³¹ festinavir (**61**),¹³² alovudine (**62**),¹³³ and amdoxovir (**63**) (Figure 12B, C, and D and Schemes 1 and 2).¹³⁴

Bevirimat (**64**), a maturation inhibitor,¹³⁵ and dextelvucitabine or reverset (**65**), a NRTI,¹³⁶ are examples of discontinued anti-HIV-1 drugs that have undergone clinical trials (Figure 12E and Scheme 1). A schematic representation of all the anti-HIV-1 drugs that act at various stages of the viral replication cycle is shown (Figure 13).

3. PNEUMONIA

Pneumonia is the second leading cause of death globally, with around 3.3 million cases annually in the United States. The proper medications to completely treat the disease state do not exist.¹³⁷ Pneumonia can occur in continuum to the acute influenza syndrome when it is caused by the virus alone, termed as “primary infection”, or it could be caused as a mixed infection of viruses and bacteria that is termed as “secondary infection”,¹³⁸ which often is difficult to identify the etiological pathogen with many different bacterial strains such as *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Haemophilus influenzae*, and *Legionella pneumophila*. The common cause of death due to pneumonia is mainly from the secondary bacterial infections due to one or several of the above mentioned strains leading to a combined bacterial/viral or post-influenza pneumonia.¹³⁷

Influenza viruses belong to the family of *Orthomyxoviridae* and are enveloped with lipids, negative sense, single-stranded, segmented RNA viruses that exist in three forms: influenza A, B, and C. Influenza A virus is known to infect mammals, including horses and pigs, and birds, whereas influenza B and C are known to infect only humans.¹³⁹

3.1. Past Pandemics

There are three known pandemics during the 20th century, which include the 1918 H1N1, Spanish flu; the 1957 H2N2, Asian flu; and the 1968 H3N2, Hong Kong flu. The Spanish flu pandemic resulted in higher morbidity and mortality compared to the 1957 or 1968 pandemics that are thought to have their origins in Asia. The 2009 A(H1N1) influenza virus was the first influenza pandemic in the 21st century.¹³⁹

3.2. Transmission and Pathogenesis

The cause of transmission could be through the spread of droplets via small-sized aerosols produced from talking, coughing, or sneezing. Patients exposed to mechanical ventilation or

intubations are infected through airborne transmission. The incubation period is about 24–48 h, and the viral shedding begins in 24 h in the absence of antiviral environment.¹³⁸

Following inhalation, the virus deposits on the epithelium of the respiratory tract and becomes attached to the ciliated epithelial cells through the surface hemagglutinin. Some of the viral particles will be eliminated by the secretion of the IgA antibodies or mucociliary clearance. The viral particles then invade the respiratory epithelial cells and continue the viral replication. The newly formed viruses then infect the epithelial cells in large numbers and eliminate the synthesis of the critical proteins and lead to the death of the host cells.¹³⁹

3.3. Treatment

Various antiviral drugs used for the treatment of influenza include the neuraminidase inhibitors that include oseltamivir (66) and zanamivir (67)¹⁴⁰ and adamantane drugs that include amantadine (68) and rimantadine (69).¹⁴¹ These antiviral drugs do not reduce the risk of complications, and vaccination is the only means of controlling or preventing influenza (Figure 14).¹⁴²

4. HEPATITIS B

Hepatitis B is the third leading cause of death globally and also the first major viral disease with which most people are chronically infected. Currently, more than 240 million³ people are carriers of hepatitis B and are at increased risk of developing hepatic decompensation, hepatocellular carcinoma, and cirrhosis. Hepatitis B is a chronic necro-inflammatory liver disease caused by hepatitis B virus (HBV) that could be further divided into HBeAg positive and negative chronic hepatitis B.¹⁴³

4.1. Description of the Virus

HBV is the smallest known DNA virus (hepadnavirus) possessing only 3200 bases in its genome. The genome consists of circular DNA that is partly double-stranded where one strand is termed “minus”, which is almost completely circular and includes overlapping genes encoding the replicative proteins like polymerase, X, and structural proteins like surface, core, and pre-S, while the other is termed “plus”, which is short and varied in length (Figure 15).¹⁴⁴

ENH I and ENH II are two enhancer elements where ENH I functions competently in the hepatocytes only and is tissue-specific while ENH II acts on the surface gene promoters stimulating the transcriptional activity.¹⁴⁴ HBV has a nucleocapsid that is a 27 nm sphere bearing a core antigen along with HBV e antigen, the viral DNA, and the DNA polymerase. The nucleocapsid is enveloped with a HBV surface antigen, HBsAg, which has the determinant *a*. In addition to the determinant *a*, the nucleocapsid also carries one of the two pairs of the subtypes *w* and *r* or *d* and *y*. This results in four subtypes of HBsAg that include *ayr*, *ayw*, *adr*, and *adw*, which represent the phenotypic expression of the HBV genotypes.¹⁴⁵

The viral particle has four mRNA transcripts whose functions are known. The longest transcript is 3.5 kb that templates both for expression of polymerase and pre-core/core

proteins and also for genome replication, while the second longest transcript that is 2.4 kb codes for HBsAg, pre-S1, and pre-S2. The third transcript is 2.1 kb that codes for HBsAg and pre-S2, while the smallest transcript is 0.7 kb encoding the X protein.¹⁴⁴

The core gene possessing the pre-core region codes both the core antigen, HBcAg, and the cleavage product, HBeAg, which is an e antigen. Transcription of pre-core leads in cleavage by targeting the HBcAg to the endoplasmic reticulum (ER) and further secretion of HBeAg. HBcAg is the integral part of the core-particle and is essential for viral package. The pre-S gene on the surface codes the viral envelope and is essential for HBV attachment to hepatocytes.¹⁴⁴

4.2. HBV Viral Replication

HBV viral replication is known to proceed in three stages where in the first phase the DNA strands are synthesized with the completion of the minus strand prior to the synthesis of the other strand. During the second phase, the virus polymerase acts as a reverse transcriptase, and in the final phase, the minus strand is primed at the 5' end with a terminal protein while the plus strand is primed by oligoribonucleotide resulting from the genomic viral RNA.¹⁴⁴

HBV binds to the surface of the cell followed by penetration into the cell. The viral core then transports into the nucleus where the circular viral DNA is further converted to covalently closed circular DNA, cccDNA, that acts as a template for the synthesis of viral RNA. HBV does not undergo integration during normal replication as seen with retroviruses. The minus strand DNA synthesis is initiated at the 3' DR1 (short direct repeats) with polymerase as primer while the plus strand DNA synthesis is initiated at the 3' DR2 and continues until the passage of the 5' end of the minus strand. This leads to the production of an open circular DNA similar to the matured HBV. The matured core particles will then be packed into HBsAg/pre-S in the ER and exported out of the cell. The nucleus maintains a stable pool of cccDNA for the transport of freshly synthesized DNA back to the nucleus (Figure 16).¹⁴⁴

4.3. Treatment

Lamivudine (**8**) is used in the treatment of HBV by inhibiting the viral DNA synthesis from becoming incorporated into the growing DNA and resulting in premature termination of the chain. Adefovir dipivoxil (**70**),¹⁴⁶ a nucleotide analogue of AMP (adenosine monophosphate), is the prodrug of adefovir used in the treatment of HBV by inhibiting both the DNA polymerase and also reverse transcriptase activities by incorporating into the viral DNA and resulting in chain termination. Entecavir (**71**)¹⁴⁷ acts by inhibiting the HBV replication at three different stages: DNA polymerase priming, negative-strand DNA reverse transcription, and positive-strand DNA synthesis.¹⁴³ Entecavir (**71**) is also being used in persons suffering from chronic hepatitis B with decompensated liver disease.¹⁴⁸ Telbivudine (**72**),¹⁴⁹ a L-nucleoside analogue reverse transcriptase inhibitor,¹⁵⁰ is another drug with selective potent antiviral activity against hepatitis B virus (Figure 17).¹⁴³

Emtricitabine (**11**), a potent HIV inhibitor, is also used in the treatment of HBV by inhibiting the viral replication. Tenofovir DF (**16**), a nucleotide analogue also used in the

treatment of HIV, is used in persons with hepatitis B,¹⁴³ especially those who are resistant to the treatment of lamivudine (8).¹⁵¹ Clevudine (73),¹⁵² a pyrimidine nucleoside, is also effective in inhibiting the viral replication, but it is only approved in South Korea. Thymosin (74),¹⁵³ a thymic-derived peptide, has the potency to stimulate the function of T-cells and is still under clinical trials (Figure 17 and Schemes 1 and 2).¹⁴³

5. HUMAN PAPILLOMA VIRUS

Papillomaviruses were first discovered as viral particles in 1949 with around 73 more genotypes identified later. Papillomaviruses are found in mammals, birds, and reptiles like turtles. The mode of transmission is not clear, but the basal layer infections seem to play the major role. Anogenital human papilloma virus (HPV) infection is known to be transmitted through sexual contact.¹⁵⁴

HPVs are non-enveloped, double-stranded DNA viruses belonging to the family *Papillomaviridae*. They are known to infect the skin mucosal surfaces and epithelial cells. The virus has a circular genome that is 8.0 kb and is encircled in a protein shell made of major, L1 and minor, L2 capsid proteins. There are seven ORFs (open reading frames) that encode the viral proteins with six “early” proteins, E1–E6. The early proteins are encoded by the transcripts present in the suprabasal and basal epithelial cells that allow viral transcription and replication. The E6 and E7 proteins play a major role in the cell transformation and immortalization. The L1 ORF encrypts the viral protein shell and its surface, while the L2 ORF encrypts the capsid mass, playing a major role in the viral genome encapsulation. The L1 protein also helps in assembling the structures to virus-like particles, VLPs.¹⁵⁵

HPV results in various cancers and genital warts, especially cervical cancer, with more than 100 types of HPV;¹⁵⁶ the first FDA-approved test for its identification was the cobas HPV test in 2011, which is a follow-up to the Pap test.¹⁵⁷ The treatment of HPV does not include specific antiviral therapy except for the presence of lesions, and two vaccines have been licensed in the United States against HPV 16 and 18 types causing cervical cancer.¹⁵⁶

6. RESPIRATORY SYNCYTIAL VIRUS

Respiratory syncytial virus (RSV) is considered the major pediatric respiratory pathogen,¹⁵⁸ which was first isolated from a chimpanzee,¹⁵⁹ causing life threatening illness during the first few months. RSV has been placed in the genus *Pneumovirus* belonging to the family *Paramyxoviridae*.¹⁵⁸

RSV is a medium-sized, linear, enveloped RNA virus with 10 viral polypeptides of which 8 are structural proteins with 7 largest that include SH, L, F, P, M, N, and G and two NS proteins, NS1 and NS2. The polymerase (L), nucleoprotein (N), and phosphoprotein (P) are the viral capsid proteins linked with the mRNA genome. The non-glycosylated membrane proteins M and M2 are the two matrix proteins. The attachment protein (G), the small non-glycosylated hydrophobic protein (SH), and glycosylated fusion protein (F) are all part of the transmembrane surface proteins. The G and F proteins play a major role in immunity (Figure 18).¹⁵⁸

6.1. Treatment

RSV is extremely contagious; at least half of the infants acquire RSV during their first year, and 40% of these result in lower respiratory tract diseases leading to pneumonia and/or bronchiolitis. Ribavirin (**75**), a synthetic nucleoside, has been approved for RSV infection, which is known to interfere with mRNA expression.¹⁵⁸ Palivizumab (Synagis), a humanized monoclonal antibody, IgG1 κ ,¹⁶⁰ is another drug that was approved by the FDA in June 1998.¹⁶¹ Synagis is known to possess fusion and neutralizing inhibitory activity against RSV.¹⁶⁰ The first vaccine for the treatment of RSV was developed in the 1960s, which was the alum-precipitated, formalin-inactivated vaccine (Figure 19).¹⁵⁸

7. HEPATITIS E

Hepatitis E virus (HEV) is the causative organism of hepatitis E and was initially termed as non-A, non-B hepatitis.¹⁶² HEV was recognized in the year 2004 as the major cause of acute hepatitis worldwide with four genotypes.¹⁶³ HEV spread to other developing countries apart from Asia and is a major concern in pregnant women, leading to liver disease.¹⁶⁴

HEV has been categorized in the genus *Hepevirus* belonging to the family *Hepeviridae*. Hepatitis E viral genome is 7.2 kb in size with three ORFs and 3' and 5' cis elements that play a major role in HEV transcription and replication. ORF1 encodes for replicase, methyl transferase, protease, and helicase; ORF2 encodes for the protein capsid, and ORF3 encodes for a protein of non-defined function.¹⁶⁴ The natural host for HEV is humans, with animals acting as a possible reservoir in the amplification of the virus.¹⁶⁴

The mode of transmission for HEV could be through transfusion. There is no specific treatment for HEV infection, but ribavirin therapy has been effective in some persons, although it is contraindicated with pregnant women. Combination of ribavirin (**75**) and interferon- α has also been used in chronically infected patients.¹⁶³ Sofosbuvir (**30**) was reported at the EASL (European Association for the Study of the Liver) 2015 meeting to be a modest inhibitor of HEV in culture (Figure 19 and Scheme 1).¹⁶⁵

8. DENGUE

Dengue and dengue hemorrhagic fever, DHF, are arthropod-borne viral infections¹⁶⁶ known to be caused by the four virus serotypes, DEN 1–4, belonging to the genus *Flavivirus*. People in dengue endemic areas could have all four types of infections in their lifetime as cross-protective immunity is not provided when infected with one of the serotypes. Dengue is considered an urban disease, and the virus completes its cycle in humans via the day-biting mosquito, *Aedes aegypti*.¹⁶⁷

8.1. Pandemics of Dengue

The first pandemic of dengue occurred in 1779–1780 in North America, Asia, and Africa, where simultaneous outbreaks were seen followed by a global pandemic after World War II in Southeast Asia. The geographical distribution of the multiple viral serotypes expanded to the Americas, and the Pacific region and Southeast Asia had their epidemic in the 1950s, leading to multiple hospitalizations and deaths by 1975 in many countries. The Maldives,

India, and Sri Lanka had their first epidemics in the 1980s, whereas Pakistan had an epidemic in 1994. Although dengue was eradicated for a few years in the American region, it slowly migrated into the United States by 1995.¹⁶⁷ Dengue started to emerge worldwide, and currently an estimated 100 million people are at risk annually with this viral disease.¹⁶⁸

8.2. Dengue Virus

Dengue virus (DENV) belongs to the genus *Flavivirus* comprising over 70 viruses, most of which are arthropod-borne infections. The virus has a lipid envelope with an inner nucleocapsid comprising single-stranded RNA and capsid protein. The viral RNA is transformed into a polyprotein during infection, which is further cleaved into structural and non-structural (NS) proteins. The components of the matured viral particles include the envelope (E), the structural capsid (C), and the membrane (M), which are all thought to be involved in the viral replication (Figure 20).

The NS proteins include NS1, NS2A–2B, NS3, NS4A–4B, and NS5, which are only expressed in the host cell and thought to play a role in viral replication. The function of NS1 is not completely understood. NS2B, NS3, and its cofactor are known to be involved in the process of the viral polyprotein, while NS3 also shows nucleotide triphosphatase and RNA helicase activities. NS2A and NS4A–4B are hydrophobic proteins, and their functions are not completely understood but are thought to be involved in anchoring viral replicase proteins to the cell membranes and contributing to the assembly of the virions; NS5 plays a role in the capping of the viral RNA progenies. NS4A also has a role in membrane alterations and helps in the complex formation of viral replicase.¹⁶⁹

8.3. Transmission, Characteristics, and Treatment

The primary vector of dengue is the *Aedes aegypti* mosquito, and transmission to humans occurs from the bites of the infected female mosquitoes. The incubation period is 4–10 days, and the infected mosquito has the ability to transmit the virus for the rest of the insect's life. The infected humans serve as the source of the virus for the uninfected mosquitoes and could transmit the infection in 4–5 days during which the appearance of the first symptoms occur. A secondary vector for the spread of dengue is *Aedes albopictus*.¹⁶⁸

Dengue fever (DENV) is a severe, flu-like infection affecting adults, infants, and young children, leading to occasional deaths. The fever is usually accompanied by vomiting, rash, severe headache, joint and muscle pains, pain behind the eyes, and swollen glands. The symptoms last for about 2–7 days following the incubation period. Dengue becomes deadly when one or more of the following symptoms occur: organ impairment, plasma leaking, respiratory stress, fluid accumulation, or severe bleeding.¹⁶⁸ Currently, there is no proper treatment or vaccination for DENV. In cases of severe dengue, the medical practitioners and nurses give the necessary medical care and maintain the volumes of the patient's body fluids.¹⁶⁸

9. SEVERE ACUTE RESPIRATORY SYNDROME

Severe acute respiratory syndrome (SARS) is caused by a coronavirus¹⁷⁰ and could be termed as atypical pneumonia, first identified in China in Guangdong Province, that later

resulted in the spread to many countries.¹⁷¹ Coronaviruses belong to the family that includes enveloped viruses where the replication occurs in the host-cell cytoplasm. They include a plus sense, single-strand RNA with a 3' polyadenylation tract and a 5' cap structure. Following the infection, the 5' ORF of the virus is transformed to a polyprotein that is further cleaved by the proteases, releasing many nonstructural proteins that include the ATPase helicase, Hel, and the RNA-dependent RNA polymerase, which are responsible for the viral replication and protein synthesis (Figure 21).¹⁷¹

The viral membrane includes the major proteins spike, S, and membrane, M, which insert into the ER of the Golgi compartment while the RNA plus strands accumulate in the nucleocapsid protein. The protein–RNA complex is then associated with the membrane protein of the ER, and the formed viral particles bud into the ER lumen. The viral particles then migrate into the Golgi complex, exiting the cell by means of exocytosis.¹⁷¹

There are no FDA-approved drugs for the treatment of SARS, although a few drugs like ribavirin have been considered but proven to be ineffective in preventing SARS viral growth inhibition.¹⁷² The literature also shows the combination therapy with lopinavir (39)–ritonavir (46) for the treatment of SARS, which is thought to reduce the viral load.¹⁷³

10. NOROVIRUS

Noroviruses belonging to the family *Caliciviridae* (derived from calyx, meaning “cup” in Greek)¹⁷⁴ and the genus *Norovirus* were discovered in the year 1972 and were previously called Norwalk-like viruses. Like other viruses, this virus also has a single-strand, plus sense RNA of 7.5 kb including three ORFs. ORF1 is known to encode the non-structural polyprotein that could be cleaved by the viral protease into 6 proteins, while ORF2 and 3 encode the major and minor capsid proteins, VP1 and VP2, respectively. The VP1 protein is involved in the formation of two domains: shell, S, and protruding, P (P1 and P2). The P2 subdomain is further involved in immune recognition and cellular interactions.¹⁷⁵ The virus-encoded 3C-like cysteine protease [3CLpro] processes the mature polyprotein for the generation of the six non-structural proteins: p48 [NS1 and NS2], NTPase/RNA helicase [NS3], p22 [NS4], VPg [NS5], protease [NS6], and a RNA-dependent RNA polymerase [RdRp] [NS7].¹⁷⁶

Five genotypes of noroviruses are known from the molecular characterization where GI, GII, and GIV are found in humans while GIII and GV strains are seen in cattle and mice, respectively.¹⁷⁵ Noroviruses are the major causative organisms of acute gastroenteritis.¹⁷⁷ The common genotype responsible for many of the outbreaks worldwide is GII.¹⁷⁴

10.1. Transmission and Treatment

The primary mode of transmission includes either the oral or fecal routes, and the other common routes include water- or foodborne and person-to-person contacts. Humans are thought to be the only hosts for human noroviruses. The virus can sustain a wide range of temperatures and exists in various food items including fruits, vegetables, and raw oysters along with drinking water. Noroviruses also result in repeated infections and undergo mutations, resulting in the evolution of novel strains infecting the hosts. The disease results

in fever, watery diarrhea, and vomiting along with other symptoms such as myalgias, headaches, and chills.¹⁷⁴

There are no known FDA-approved antiviral agents for the treatment of norovirus gastroenteritis except for oral rehydration with electrolytes and fluids. Antisecretory and antimotility drugs are used in adults suffering from diarrhea.¹⁷⁴ Ribavirin (**75**) and interferons are known to inhibit the Norwalk viral replication whose therapeutic efficacy needs further evaluation.¹⁷⁸ Rupintrivir (**76**), formerly known as AG7088, an irreversible inhibitor of 3CLpro that possessed in vitro antiviral activity against picornaviruses,¹⁷⁹ is known to display anti-norovirus activity.¹⁸⁰ Favipiravir (**77**), also known as T-705, currently in advanced clinical developments for influenza virus, is considered to be an RdRp inhibitor of norovirus, inhibiting the viral replication.¹⁸¹ Suramin (**78**), a naphthalene sulfonate derivative, is another RdRp inhibitor that is known to inhibit the genome replication and prevent the synthesis of viral sub-genomic RNA.¹⁸² 2'-C-Methylcytidine (**79**), a nucleoside analogue, is considered to be a potent inhibitor of norovirus-induced diarrhea and mortality in vitro in a mouse model.^{183,184} Certain deubiquitinase and eIF4F inhibitors (**80–81**) are considered promising candidates in the development of norovirus therapeutics (Figures 19 and 22).^{185,186}

11. MIDDLE EAST RESPIRATORY SYNDROME CORONAVIRUS

Middle East Respiratory Syndrome Coronavirus (MERS-CoV), a coronavirus that could lead to severe pulmonary disease in humans,¹⁸⁷ was first identified in Jeddah, Saudi Arabia, in September 2012,¹⁸⁸ from a patient suffering from renal failure and pneumonia. The infection is known to be linked geographically to the Middle Eastern countries like Saudi Arabia, the United Arab Emirates, Jordan, and Qatar.¹⁸⁹

MERS-CoV belongs to the subfamily *Coronavirinae* that represents a new species in the genus *Betacoronavirus* that currently includes *Pipistrellus bat coronavirus HKU5* and *Tylonycteris bat coronavirus HKU4*. This novel virus seem to relate to the viruses belonging to the families *Nycteridae* and *Vespertilionidae* that include insectivorous African and European bats, respectively. The infection is thought to be zoonotic primarily with limited transmission from human to human.¹⁸⁹

To date, there are no effective antivirals against MERS-CoV and emphasis is placed on organ support for renal and respiratory failures. IFN- α has shown inhibition of in vitro MERS-CoV replication while its action in vivo is unknown.¹⁹⁰

12. WEST NILE

West Nile fever is a mosquito-borne viral disease that led to sporadic outbreaks of equine and human diseases in Europe. The largest outbreak occurred in 1996–1997 in Romania, near Bucharest, which was considered the major arboviral illness in Europe.¹⁹¹

West Nile virus (WNV), a member of the Japanese encephalitis, belongs to the genus *Flavivirus* of the family *Flaviviridae*. This virus was initially isolated from the blood of a febrile female in Uganda in the year 1937 from the West Nile district. The primary vectors

of the virus include mosquitoes, predominantly belonging to the genus *Culex*, and the primary hosts are wild birds.¹⁹¹

Currently, there are no FDA-approved drugs or licensed vaccines available for the treatment of WNV.¹⁹² An adjuvant therapy used in the treatment of WNV encephalitis is intravenous immunoglobulin (IVIG).¹⁹³

13. HEPATITIS D AND A

Hepatitis D is caused by the hepatitis D virus (HDV) and leads to severe liver disease. Hepatitis D is uncommon in the United States, and it generally occurs as a coinfection with hepatitis B virus.¹⁹⁴ HDV is a hepatotropic defective virus that is dependent on the HBV for its envelope provision. HDV includes a hepatitis B surface antigen, HBsAg, and the RNA genome, which is a rodlike, circular structure possessing self-ligation and autocatalytic cleavage properties. RNA polymerase II effects the RNA replication, and the only protein that is encoded by the HDV-RNA is the hepatitis D antigen, HDAG, whose short and long forms play a role in the morphogenesis and replication of the virus.¹⁹⁵

The only treatment available for chronic hepatitis D is alpha interferon, although inhibiting HBV results in a decrease in hepatitis D virus replication.¹⁹⁵ Hepatitis D complications are preventable with hepatitis B vaccine.¹⁹⁶

Hepatitis A is caused by the hepatitis A virus (HAV), an enterovirus, belonging to the family *Picornaviridae*.¹⁹⁷ The large epidemics of hepatitis A occurred in the years 1954, 1961, and 1971.¹⁹⁸ HAV has a single-molecule RNA surrounded by a small protein capsid of 27 nm diameter and has an incubation period of 10–50 days.¹⁹⁷

Chronic infection is not seen with hepatitis A, and the common mode of transmission is through person-to-person contact with oral ingestion as the major route. The clinical illness could be protected by giving immune globulin during the incubation period or before the exposure to the HAV, and certain hepatitis A vaccines are also effective against the disease.¹⁹⁸

14. ROTAVIRUS

Rotavirus is the leading cause of diarrhea among children worldwide.¹⁹⁹ The viral genome includes an 11-segmented double-stranded RNA that is enclosed in a three-layered viral capsid with four major capsid proteins—VP2, VP4, VP6, and VP7—and two minor proteins—VP1 and VP3. The co-expression of the major capsid proteins as different combinations resulted in the production of stable virus-like particles (VLPs) that are responsible for the maintenance of the functional and structural characteristics of the matured viral particles. The outer layer is composed of the glycoprotein, VP7, and dimeric spikes of VP4 responsible for inducing neutralizing antibodies, with VP4 as the viral hemagglutinin. The inner capsid has VP6 as the major protein, which constitutes more than 80% that is known to possess RNA polymerase activity. The core part includes VP1–VP3, and the 11 double-stranded RNA segments with VP2 covering >90% of the core-protein mass (Figure 23).²⁰⁰

Rotavirus is known to infect the intestine, leading to diarrhea that could last for about 8 days. There is no treatment for rotavirus infection, and this disease could be prevented through vaccination. The severity of the disease lies in dehydration that can be treated through fluids.²⁰¹

15. SHINGLES

Varicella-zoster virus (VZV) is a herpesvirus leading to both chicken pox (varicella) and shingles (herpes zoster). The virus includes a nucleocapsid encapsulating the core with a linear double-stranded DNA whose arrangement is done in short and long unique segments with 69 ORFs with about 125 000 bp and a tegument made of protein that separates the capsid from the lipid envelope. The lipid envelope incorporates the main viral glycoproteins. VZV is the smallest known human herpesvirus (Figure 24).²⁰²

People infected with chicken pox are prone to shingles that can occur in all ages with the risk increasing with growing age. Chicken pox develops into blisters or rash, meaning that the virus is dormant in the nerve cells and can reactivate by producing shingles²⁰³ and travel through the nerves to the skin. Inflammation is seen in the nerves leading to after-pain, termed as post-herpetic neuralgia (PHN) that could be chronic and severe.²⁰⁴

VZV transmission occurs through respiratory route, and zostavax is the vaccine used against VZV that has been approved by the FDA and is the only U.S.-licensed vaccine known to date.²⁰⁴ The antiviral drugs that have been approved for the treatment of VZV infections include valacyclovir (**82**),²⁰⁵ acyclovir (**83**),²⁰⁶ and famciclovir (**84**),²⁰⁷ which replaced the nucleoside analogues IFN- α and vidarabine or Ara-A (**2**). Acyclovir (**83**) and valacyclovir (**82**) (a valine ester derivative of acyclovir) act as competitive inhibitors and result in the chain termination of the viral DNA polymerase.²⁰² Varizig (varicella zoster immune globulin) was approved by the U.S. FDA in December 2012 as an orphan drug that could be given after exposure to VZV (Figure 25 and Scheme 2).²⁰⁸

16. HERPES SIMPLEX VIRUS

Genital herpes, a sexually transmitted disease (STD), is caused by two types of viruses, herpes simplex virus type 1 and type 2. It is highly common in the United States, and its transmission occurs through anal, oral, or vaginal sex with any person infected with the disease.²⁰⁹

Herpes simplex virus (HSV) is the largest herpes virus belonging to the family *Herpesviridae*. The viruses belonging to this family are enveloped viruses including a tegument, a capsid, and a genome. The viral envelope is fragile, and the space between the capsid and the viral envelope is called a tegument, which usually contains the glycoproteins and the enzymes necessary for the viral replication. The nucleocapsid is icosahedral with about 150 hexameric and 12 pentameric capsomeres that are doughnut-shaped. The viral genome is a linear, double-stranded DNA wrapped in a core (Figure 26).²¹⁰

HSV-1 and -2 have similar genome structures with 83% homology in the protein-coding and 40% homology in the sequencing regions. HSV-1 is associated with oral disease whereas

HSV-2 is associated with genital disease in certain parts of the world such as Sub-Saharan Africa, where HSV-1 is known to occur in childhood and HSV-2 is sexually transmitted. In contrast, based on the anatomical site, HSV-2 is responsible for genital herpes in developed countries.²¹¹

Current medications for the treatment of HSV infection include antiviral agents like acyclovir (**83**), vidarabine (**2**), idoxuridine (**85**),²¹² ribavirin (**75**), and phosphonoformate (**86**),²¹³ of which acyclovir (**83**) or its valyl prodrug form known as valacyclovir are widely used. Acyclovir (**83**), a purine analogue, acts as a substrate for the viral thymidine kinase, thereby inhibiting the viral DNA polymerase selectively. Because of the viral resistance to acyclovir (**83**), new antivirals have evolved for the treatment of HSV. Phosphonoformate (**86**), which is a derivative of phosphonoacetic acid, is a potent inhibitor of the HSV DNA polymerase (Scheme 2 and Figures 19, 25, and 27).²¹⁴

17. EBOLA VIRUS

Ebola hemorrhagic fever (Ebola HF) is a viral disease caused by the Ebola virus (EBOV) that gains importance in this review due to the current, ongoing outbreak in West Africa along with Guinea, Liberia, and Uganda since March 2014.²¹⁵ Reports showed around 21 deaths and 37 cases that have been reported from Guinea, 13 cases from Sierra Leone, and 1 suspected case in Liberia between May 29 and June 1 of 2014.²¹⁶ The number of ebola deaths has been raised since then to 7 857 between December 24 and 27 of 2014, with 3 413 deaths in Liberia, 2 732 deaths in Sierra Leone, 1 697 deaths in Guinea, 8 deaths in Nigeria, 6 deaths in Mali, and 1 death in the United States.²¹⁷ The first human outbreak of Ebola virus that has been recorded was in 1976 followed by major outbreaks in 2001 and 2003 in Gabon and the Republic of Congo.²¹⁸

17.1. Description of EBOV

The EBOV is a non-segmented, enveloped, negative strand RNA virus belonging to the family *Filoviridae*. Four species of EBOV (Sudan, Côte d'Ivoire, Reston, and Zaire) are known to cause disease in humans, with Zaire being associated with the highest human lethality. The genome consists of seven genes responsible for the synthesis of eight proteins.²¹⁹

Ebola virus is enclosed with a membrane of the infected cell enveloped with ebola glycoproteins. The inner membrane is supported with a layer of matrix proteins and possesses a central cylindrical nucleocapsid that is necessary for the storage and delivery of the RNA genome. The ebola glycoprotein binds to the cell-surface receptors to get the genome inside. The EBOV shares many features similar to the HIV envelope glycoprotein and influenza hemagglutinin covered with carbohydrate chains that would help the virus hide from the immune system. The virus could transform into a different shape when bound to the cell surface, dragging the cell and the virus close enough to cause membrane fusion.²²⁰

The matrix protein, also called VP40, helps in the shape and budding of the virus. The proteins present on the membrane help make the connection between the nucleocapsid and

the membrane. The nucleocapsid, present at the center of the virus, helps protect the viral genome; however, the nucleoprotein subunits are not rigid as in other viruses, showing a wavy structure.²²⁰

Transcription of the fourth gene leads to the expression of glycoprotein that is transmembrane-linked (GP) and a secreted glycoprotein (sGP). GP remains the key target for the design of entry inhibitors and vaccines. GP is cleaved by furin post-translationally yielding GP1 and GP2 subunits, which are disulfide-linked. GP1 is known to effect the attachment to the host cells while GP2 facilitates the fusion of the host and viral membranes (Figure 28).²¹⁹

There is no standard treatment for EBOV HF, but it is limited to the supportive therapy that includes balancing the electrolytes and fluids of the patients, maintaining blood pressure and oxygen supply, and treating for further complicated infections. The early symptoms of EBOV HF include fever and headache, which are difficult to diagnose for EBOV. No known treatments are yet available for humans for the treatment of Ebola virus,²²¹ but recently favipiravir (**77**), a pyrazinecarboxamide derivative, showed successful suppression of the replication of Zaire EBOV both in vitro and in vivo at an IC₉₀ of 110 μ M.²²²

18. MARINE DRUGS FOR THE TREATMENT OF HIV/AIDS

Although there are many drugs available commercially from synthetic sources, limitations including drug resistance, side effects, cell toxicity, and long-term drug treatment are all possible explanations for the failure of the previously mentioned anti-HIV drugs. In addition, the evolution and development of nucleoside antivirals reveal the tremendous potential marine products have for the identification of novel prototypes and also reveals the necessity of developing drugs from natural resources such as the marine environment.²²³ Marine species cover over two-thirds of the planet, making them a significant source for the production of novel compounds with possibly fewer adverse effects and higher inhibition activity.²²⁴ The compounds obtained from marine sources that are discussed in the following sections were found to possess anti-HIV-1 activity (Figure 29).

18.1. Phlorotannins

Phlorotannins are tannin derivatives that were isolated from brown algae and are biosynthesized by the polymerization of the phloroglucinol monomer units acquired from the pathway of acetatemaleonate. These are highly water-soluble compounds.^{225,226} They can be classified into four different categories: phlorotannins containing an ether linkage (fuhals and phlorethols), phenyl linkage (fucols), phenyl and ether linkage (fucophloroethols), and dibenzodioxin linkage (eckols).²²⁷ 8,4'''-Dieckol (**88**) and 8,8'-bieckol (**87**) are isolated from *Ecklonia cava*, a brown algae, and show inhibitory activity on HIV-1 reverse transcriptase and protease at inhibitory concentration (IC₅₀) values of 5.3 and 0.5 μ M, respectively.²²⁸ This is due to the inhibition of the gp41 six-helix bundle formation.^{229,230} 6,6'-Bieckol (**89**), a natural derivate in *Ecklonia cava*, possesses lytic effects, causes p24 antigen production, and has inhibitory activity against HIV-1-induced syncytia formation. It showed selective inhibition against the HIV-1 entry and the activity of HIV-1 reverse transcriptase enzyme at an IC₅₀ of 1.07 μ M.²³¹ Diphlorethohydroxycarmalol

(**90**), derived from *Ishige okamurae*, also possessed inhibitory activity against HIV-1. It inhibits HIV-1 reverse transcriptase and integrase at IC₅₀ values of 9.1 and 25.2 μ M, respectively (Figure 30).²³²

ADMET predictor shows that 8,8'-bieckol (**87**), 8,4'''-dieckol (**88**), 6,6'-bieckol (**89**), and diphlorethohydroxycarmalol (**90**) violate three criteria of the Lipinski guidelines. These compounds also show low permeability and tend to be poor at permeating the cell membranes based on the polar surface area.

6,6'-Bieckol (**89**), a phloroglucinol derivative, did not exhibit any cytotoxicity at concentrations that inhibited HIV-1 replication almost entirely.²³¹ The phloroglucinol derivatives exhibited HIV-1 inhibition similar to that of flavonoids where they block the interaction between reverse transcriptase (RT) and the RNA template.²³³ 6,6'-Bieckol (**89**) is a viral entry inhibitor, and so the above-mentioned factors like permeability may not be a problem; this could be considered as an important lead as this compound could inhibit the viral entry.

Most of the currently synthesized and FDA-approved drugs could only inhibit the virus at various replication stages. Hence, the above-mentioned limitations for various compounds could be overcome by changing the route of administration (using intravenous or subcutaneous (SC) instead of oral) (Table S1).

18.2. Chitin, Chitosan, and Chitooligosaccharide Derivatives

Chitin is widely found in crustaceans, fungi, invertebrates, and insects.²³⁴ It is a long-chain polymer of *N*-acetylglucosamine that is most abundantly seen in the shells of shrimp and crabs.²³⁵ Chitosan is formed by deacetylating chitin. The sulfated derivatives of chitin (**91**) and chitosan (**92**) possess activities including anti-HIV-1, antimicrobial, antioxidant, and others.²²³ *N*-carboxymethylchitosan *N,O*-sulfate (NCMCS), a derivative of *N*-carboxymethyl chitosan, is known to inhibit the transmission of HIV-1 in human CD4⁺ cells. This inhibition is due to the blockade of the interactions between the glycoprotein receptors present on the viral coat and the target proteins present on the lymphocytes, thereby inhibiting the HIV-1 reverse transcriptase.²³⁶ The sulfation at the 2 and 3 positions led to the complete inhibition of HIV-1 infection to T-lymphocytes at 0.02 μ M concentrations without any cytotoxicity. These results show that the biological activity of the sulfated chitins can be controlled by changing the sulfate group position.²³⁷ Chitosan is converted to chitooligosaccharides to improve its water solubility and, therefore, its biological activity.²²³

Low molecular weight sulfated chitooligosaccharides (SCOSs) (**93**) are known to possess anti-HIV activity.²³⁸ They show lytic effects and inhibit HIV-1-induced syncytia formation at median effective concentration (EC₅₀) values of 1.43 and 2.19 μ g/mL, respectively. The p24 antigen production could be suppressed at EC₅₀ values of 7.76 and 4.33 μ g/mL for HIV-1_{Ba-L} and HIV-1_{RF}, respectively.²³⁸ They also inhibited viral entry and cell fusion by preventing the bond between gp120 of the HIV and CD4 surface receptor (Figure 31).²²³

ADMET predictor shows that sulfated chitins violate three criteria of the Lipinski guidelines whereas the chitosans violate all four criteria. In addition, they also show low permeability,

low flexibility, and a tendency to not permeate the cell membranes. However, as per the mechanism of action, these are known to inhibit the viral entry and fusion and so permeability could not be considered as a limiting factor.

SCOSs inhibit HIV-1 replication by binding to the V3 loop of gp120 and thereby interfering with the gp120–CD4 binding.²³⁸ They possess a high rate of intestinal absorption, which is a crucial property for a drug candidate.²³⁹ The main drawback with chitosan and its sulfated oligosaccharide derivatives is its high anti-coagulant activity that limits SCOS to be clinically tested and approved on infected HIV subjects.²⁴⁰ The above limitation could be overcome by SAR (structure–activity relationship) studies and by trying various medicinal chemistry alterations to alleviate the anticoagulant activity (Table S1).

18.3. Sulfated Polysaccharides

Sulfated polysaccharides (**94**) are macromolecules that are chemically anionic and present in marine algae along with mammals and invertebrates, although marine algae are the major source.^{241,242} They also possess anti-HIV-1, along with anticancer and anticoagulant activities (Figure 32).²²³

The SPs (sulfate polysaccharides) prevent the virus from attaching to the target molecules on the cell surface. The SPs possess a binding site on the CD4 that is relatively similar to the HIV–gp120 binding region.²⁴³ Hence, by binding to this lymphocyte, the SPs inhibit the binding of the monoclonal antibodies to the initial two domains of the CD4,²⁴⁴ thereby disrupting the CD4–gp120 interaction. The anti-HIV activity of the SPs is by shielding off the positively charged sites on the V3 loop of the gp120 protein, thereby preventing the virus attachment to the cell surface.²⁴⁵

The SPs from red algae are also known to possess anti-HIV-1 activity.²⁴⁶ *Schizymenia dubyi*, a red algae, produces a sulfated glucuronogalactan that is known to possess anti-HIV-1 activity. This polysaccharide suppressed the syncytial formation completely at a concentration of 5 $\mu\text{g/mL}$ and also inhibited the HIV-1 reverse transcriptase at the same low concentration without any cytotoxicity to the MT4 cells.²⁴⁷ Its mechanism of action involves inhibiting the attachment of virus to the host cell. Nakashima et al. prepared an extract of citrate buffer, sea algal extract (SAE) from the marine red alga *Schizymenia pacifica*, that showed inhibition against HIV replication and HIV reverse transcriptase. SAE is a sulfated polysaccharide with a molecular weight of $\sim 2\,000\,000$ belonging to the family of λ -carrageenan that includes 3,6-anhydrogalactose (0.65%), sulfonate (20%), and galactose (73%), with the sulfate residues being responsible for the inhibition of the HIV reverse transcriptase at an inhibitory dose of 9.5×10^3 IU/mL.^{248,249}

Brown algae are also known to produce SPs with anti-HIV-1 activity via a different mechanism of action.²²³ Fucans are present mainly in brown algae, and they have high molecular weights and possess a repeated chain of sulfated fucose. Fucans derived from the seaweed species of *Lobophora variegata*, *Spatoglossum schroederi*, *Fucus vesiculosus*,²⁵⁰ and *Dictyota mertensii* inhibit the reverse transcriptase of HIV-1. The galactofucan fractions of *L. variegata* showed reverse transcriptase inhibition at 1.0 $\mu\text{g/mL}$ concentration with 94% synthetic polynucleotides inhibition. Fucan A from *D. mertensii* and *S. schroederi* displayed

inhibition activity against the reverse transcriptase enzyme at 1.0 mg/mL with 99.3% and 99.03% inhibition, respectively. Fucan B from *S. schroederi* showed inhibition activity of 53.9% at the same concentration. The fucan fraction from *F. vesiculosus* showed high inhibition activity of 98.1% on the reverse transcriptase enzyme of HIV-1 at 0.5 $\mu\text{g/mL}$ concentration.²⁵¹ Similarly, fractions of galactofucan from *Adenocystis utricularis* also presented anti-HIV-1 activity by blocking the prior events of virus replication. EA1-20 and EC2-20 displayed strong inhibition activity on HIV-1 replication at low IC_{50} values of 0.6 and 0.9 $\mu\text{g/mL}$, respectively.²⁵² SPs are also produced by the microalgae. Naviculan is one such example that is isolated from *Navicula directa* that possesses anti-HIV-1 activity. It demonstrated inhibitory effect against the formation of cell–cell fusion between CD4-expressing HeLa cells and HIV gp160 at an IC_{50} value of 0.24 μM .²⁵³ A new type of D-galactan sulfate was isolated from *Meretrix petechialis* (clam) that possessed anti-HIV-1 activity by inhibiting syncytia formation at 200 $\mu\text{g/mL}$ concentration with 56% inhibition.²⁵⁴ Laminaran (95), also termed laminarin, is a water-soluble polysaccharide including 20–25 glucose units possessing (1,3)- β -D-glucan with β (1,6) branching isolated from the brown algae. Laminaran (95) along with the laminaran polysaccharides prepared from kelp are known to inhibit the HIV reverse transcriptase and adsorption at a concentration of 50 $\mu\text{g/mL}$, suggesting good inhibition against HIV replication (Figure 33).²⁵⁵

Galactan sulfate (GS), a polysaccharide isolated from *Agardhiella tenera*, a red seaweed, showed activity against HIV-1 and HIV-2 at IC_{50} values of 0.5 and 0.05 $\mu\text{g/L}$, respectively. GS prevents the binding of HIV-1 to cells along with the binding of anti-gp120 mAb to HIV-1 gp120. It is also known to be active against enveloped viruses including togaviruses, arenaviruses, herpesviruses, and others.²⁵⁶ Carrageenans are extracted mainly from certain genera of red seaweeds that include *Hypnea*, *Eucheuma*, *Gigartina*, and *Chondrus*. Yamada and co-workers reported anti-HIV activity for O-acylated carrageenan polysaccharides with various molecular weights by means of sulfation and depolymerization.^{257,258}

Calcium spirulan (Ca-SP), a sulfated polysaccharide isolated from the marine blue–green alga *Arthrospira platensis*, showed potent anti-HIV-1 activity at an IC_{50} value of 2900 $\mu\text{g/mL}$ and reduced viral replication at ED_{50} values of 11.4 and 2.3 $\mu\text{g/mL}$. Ca-SP is also known to inhibit the viral replication of other viruses that include HCMV, measles, polio, and coxsackie virus by preventing the penetration of the virus into the host cells.²⁵⁹ Xin et al. reported 911, a marine polysaccharide derived from alginate that inhibited the HIV replication both in vivo and in vitro, attributing to the inhibition of the viral reverse transcriptase, interfering with the viral adsorption, and enhancing immune function.^{260,261} Woo et al. reported the inhibitory effects of the marine shellfish polysaccharides from seven different shellfish, including *Meretrix lusoria*, *Meretrix petechialis*, *Ruditapes philippinarum*, *Sinonovacula constricta* Lamark, *Scapharca subcrenata*, *Scapharca broughtonii*, and *Mytilus coruscus*, against HIV-1 in vitro by inhibiting the viral fusion gp120/gp41 with the CD4 protein on the T-lymphocyte surface.²⁶²

SPs effectively inhibit the cell–cell adhesion.²⁴⁵ Studies proved that SPs could be used as antiviral vaginal formulations because they do not disturb the functions of the epithelial cells in the vagina or the normal bacterial flora.^{223,245}

18.4. Lectins

Lectins are proteins that bind to carbohydrates present in prokaryotes, algae, fungi, plants, corals, vertebrates, and invertebrates.²²³ They have specificity for different glycan structures. Hence, they bind to the glycans present on the gp120 molecule of the HIV envelope, resulting in inhibition of viral cell fusion,²⁶³ HIV infectivity,^{264,265} and syncytium formation.²⁶⁶ Several different lectins like griffithsin (GRFT), obtained from the red algae *Griffithsia* sp., have been reported to possess anti-HIV-1 activity. This lectin possesses about 120 common amino acids along with an unusual one at position 31. The cytopathic effects produced by the laboratory strains and the HIV-1 clinical primary isolates on the T-lymphoblastic cells are inhibited at concentrations as low as 0.000043 μM . GRFT blocks the cell-to-cell fusion of the uninfected and infected cells. It also prevents the binding of gp120, which is a CD4-dependent glycoprotein, with 2G12 and 48d monoclonal antibody.²⁶⁷

In recent years, marine invertebrates have become new sources for unusual lectins. One such example is CVL, a β -galactose specific lectin isolated from *Chaetopterus variopedatus*, a marine worm. It inhibited the cytopathic effects caused by HIV-1 and the viral p24 antigen production at EC₅₀ values of 0.0043 and 0.057 μM , respectively. At an EC₅₀ value of 0.073 μM , CVL caused blockade of HIV-1 infected and uninfected cell-to-cell fusion process. At concentrations of 0.07 and 0.33 μM , CVL exhibited 21% and 86% inhibition, respectively, of HIV-1 entry into the host cells.²⁶⁸ Another lectin, CGL, isolated from the *C. grayanus* mussel, presented a high affinity to the mucin type glycoproteins. Two other lectins, DTL and DTL-A, were isolated from ascidium *D. ternatanum*.²⁶⁹ Similarly, SVL-1 and SVL-2, isolated from the marine worm *Serpula vermicularis*, are calcium (Ca^{2+})-independent lectins shown to possess anti-HIV-1 activity.²²³ CGL, DTL, DTL-A, and SVL-2 displayed inhibition of HIV-1 III_B induced syncytium formation at EC₅₀ values of 27.9, 0.002, 0.36, and 0.15 $\mu\text{g/mL}$, respectively. Among them, the CGL, DTL, and DTL-A showed activity against the cell fusion between the HIV-1/H9 cells that are infected chronically and the uninfected C8166 cells at EC₅₀ values of 35.12, 1.37, and 6.97 $\mu\text{g/mL}$, respectively.²⁶⁹

18.5. Bioactive Peptides

Bioactive peptides are widely isolated from marine organisms by means of enzymatic hydrolysis. It is reported that many marine bioactive peptides have anti-HIV-1 activity.²²³ Some oysters possess antiviral and anti-bacterial substances that prevent infectious diseases. Hence, a large isolation effort has been made to discover HIV-1 protease inhibiting substances from the oyster *Crassostrea gigas*, yielding two peptides Leu-Leu-Glu-Tyr-Ser-Ile (**96**) and Leu-Leu-Glu-Tyr-Ser-Leu (**97**). They exhibited strong inhibition of the HIV-1 protease at IC₅₀ values of 0.02 and 0.015 μM , respectively. The inhibitory activity was found to be related to the length of the amino acid sequence and the presence of C-,N-terminal hydrophobic amino acid (Figure 34).²⁷⁰

Cyanovirin-N (CV-N) isolated from the cyanobacterium *Nostoc ellipsosporum* is a 101-amino-acid antiviral peptide with a molecular weight of 11 kDa with inhibitory effects against HIV-1 and HIV-2 at low nanomolar concentrations. CV-N prevents the transmission of HIV from infected to uninfected cells by preventing cell-to-cell fusion.²⁷¹ The peptides polyphemusins I (**98**) and II (**99**) and tachyplesins I-II (**100–101**) isolated from the hemocyte

debris of the horseshoe crabs *Limulus polyphemus* and *Tachypleus tridentatus* were found to inhibit HIV cell fusion.^{272,273} Many synthetic peptide analogues have been prepared of which the synthetic peptide T22 analogue of polyphemusin II (**99**) showed the strongest anti-HIV activity with low in vitro cytotoxicity at EC₅₀ value of 2.6 μ M, which is comparatively less than that of azidothymidine (**3**) (5.2 μ M) (Figure 35).²⁷³

18.6. Miscellaneous Antivirals Possessing Anti-HIV Activity

Macrolactin-A (**102**), an antiviral compound isolated from the marine bacteria, included 24-membered ring lactones, open-chain acids, and related glucose β -pyranosides that inhibited HIV replication at a concentration of 10 μ g/mL.²⁷⁴ The diterpenes Da-1 (**103**) and AcDa-1 (**104**) isolated from *Dictyota menstrualis*, the marine alga, inhibited the replication of HIV-1 virus at EC₅₀ values of 40 and 70 μ M, respectively. The above diterpenes did not affect the viral internalization or viral attachment but instead inhibited the HIV reverse transcriptase at IC₅₀ values of 10 and 35 μ M, respectively (Figure 36).²⁷⁵

The antivirals equisetin (**105**) and phomasetin (**106**) isolated from the marine fungi *Fusarium heterosporum* and a *Phoma* sp. showed inhibition against HIV-1 integrase at IC₅₀ ranging between 7 and 20 μ M (Figure 37).²⁷⁶

Thalassiolins A–C (**107–109**) isolated from the Caribbean sea grass *Thalassia testudinum* are sulfated flavone glycosides that inhibited HIV replication at IC₅₀ 30 μ M, targeting the integrase-catalyzed strand transfer at IC₅₀ 0.4 μ M. Thalassiolins A–C (**107–109**) showed potency against HIV integrase due to the presence of sulfated glucose functionality (Figure 38).²⁷⁷

Didemnaketals A (**110**) and B (**111**), isolated from the ascidian *Didemnum* sp., were shown to inhibit the HIV-protease at IC₅₀ values of 2 and 10 μ M, respectively.²⁷⁸ Cyclo-didemniserinol trisulfate (**112**), isolated from the extracts of Palauan ascidian *Didemnum guttatum*, showed inhibition of the HIV-integrase at IC₅₀ 60 μ g/mL (Figure 39).²⁷⁹

Lamellarins were first isolated from the prosobranch mollusks belonging to the genus *Lamellaria*,²⁸⁰ and lamellarin α 20-sulfate (**113**), isolated from the Arabian Sea ascidian, was shown to inhibit the HIV-integrase. Lamellarin α 20-sulfate (**113**) inhibited the strand-transfer activity at an IC₅₀ of 22 μ M and the integrase terminal cleavage activity at IC₅₀ of 16 μ M (Figure 40).²⁸¹

19. ANTIVIRALS FROM PORIFERA

Sponges have historically produced promising drug leads. Most of the drugs obtained from sponges are being used for the treatment of HIV and also HSV.²⁸² Some examples of the compounds isolated from sponges that are now being used for the treatment of HIV-1 are discussed in detail in the following sections.

19.1. Sesquiterpene Hydroquinones

Avarol (**114**) was first isolated from the marine sponge *Disidea avara*, and avarone (**115**) is synthesized by the silver oxide oxidation of avarol.²⁸³ These structures have a rearranged

drimane skeleton.²⁸⁴ They showed an inhibitory effect on the replication of AIDS and HTLV IIIB-infected H9 human cells at 0.3 μM .²⁸³ Its mechanism involves the blockade of p17 and p24 gag proteins after viral infection and, thereby, prevents replication of the virus. After further exploration of the mechanism of action, avarol was shown to block the tRNA, required for glutamine synthesis, which plays a vital role in the synthesis of viral proteases necessary for its replication (Figure 41).²⁸²

ADMET predictor shows that avarol (**114**) violates only one criterion of the Lipinski guidelines and avarone (**115**) does not violate any. The carbonyl group of the quinone ring includes a hydroxyl group at the ortho position, which is known to be responsible for the blockade of the reverse transcriptase activity.²⁸⁵ Hence, both of them may likely be good candidates to be considered for further in vivo studies because the limitations are minor (Table S1).

Curcuphenol (**116**), a sesquiterpene phenol, was isolated from the sponges *Didiscus oxeata*, *Didiscus flavus*, *Myrmekioderma styx*, and *Epipolasis* sp. Semi-synthetic analogues a (**117**), c (**118**), j (**119**), and r (**120**) had anti-HIV-1 activity at EC₅₀ values of 31.2, 29.2, 18.4, and 18.2 μM , respectively.²⁸⁶ Isoquinoline derivatives have been previously patented for the treatment of anti-HIV-1 activity by inhibiting the reverse transcriptase enzyme²⁸⁷ or protease enzyme²⁸⁸ or by viral entry inhibition,²⁸⁹ whereas indole alkaloids act as reverse transcriptase inhibitors.²⁹⁰ The anti-HIV-1 activity is known to increase with indole substitution.²⁹¹ Hence, the analogues showed activity due to the presence of one of the above-mentioned moieties. The activity was shown to improve with the alkylation of the indole nitrogen as seen in analogue j (**119**) (Figure 42).²⁸⁶

ADMET predictor shows that curcuphenol (**116**) and its analogues violate only one criterion of the Lipinski guidelines. Hence, they may be considered as potential candidates for the syntheses because as compared to some FDA-approved drugs like saquinavir (**7**) or fosamprenavir (**40**), which violate more than one criterion, the limitations are less in this case (Table S1).

19.2. Cyclic Depsipeptides

Papuamides, isolated from the marine sponges *Theonella swinhoei* and *Theonella mirabilis*, are known to possess anti-HIV-1 and cytotoxic effects.²⁹² Papuamides A (**121**) and B (**122**) were isolated from the sponge *T. mirabilis* and exhibited anti-HIV-1 activity at a concentration of 0.003 μM .²⁹³ Papuamides A (**121**), B (**122**), C (**123**), and D (**124**) were isolated from *T. swinhoei* (Figure 43).²⁸²

Papuamide A (**121**) has a membrane-targeting mechanism, and this mechanism of action has been shown to be responsible for its virucidal activity.²⁹⁴ Its mechanism of action involves inhibition of HIV pseudo-type viruses that express glycoprotein envelope from the amphotropic murine leukemia virus or vesicular stomatitis virus, suggesting that the entry inhibition is not HIV-1 envelope glycoprotein specific. It inhibits the virus only at the initial stage of the viral replication cycle, and it targets the virus and not the cell. Hence, it exhibits a direct virucidal mechanism of HIV-1. Papuamide B (**122**) targets the phospholipid,

phosphatidylserine (PS), present on the virus. Papuamides C (**123**) and D (**124**) also inhibit the viral entry (Figure 43).²⁹⁴

ADMET predictor shows that papuamides A (**121**), B (**122**), C (**123**), and D (**124**) violate three criteria of the Lipinski guidelines. They also show low flexibility and do not possess the tendency to permeate the cell membranes. In addition, most peptide-derived drugs must be administered IV. This could overcome the permeability limitation, and they also represent potentially challenging molecules (Table S1).

Callipeltin A (**125**), isolated from a sponge belonging to the genus *Callipelta*, also possesses anti-HIV-1 activity. The HIV-1-induced cytopathic effects were inhibited at a median effective dose (ED₅₀) value of 0.007 μ M.²⁹⁵ Similarly, neamphamide A (**126**), isolated from *Neamphius huxleyi*, possesses cytoprotective activity against HIV-1 infection at an EC₅₀ value of 0.028 μ M.²⁹⁶ Certain mirabamides that inhibit HIV-1 fusion were isolated from the sponge *Siliquariaspongia mirabilis*. Among them, mirabamide A (**127**) was shown to be active against HIV-1 fusion assays and neutralization at IC₅₀ values between 0.04 and 0.14 μ M, respectively. The mirabamides were shown to be more selective for HIV-1 by inhibiting them at the membrane fusion level.²⁹⁷ Celebeside A (**128**) and theopapuamide B (**129**) were also isolated from the same sponge, *S. mirabilis*. Celebeside A (**128**) showed HIV-1 entry inhibition at an IC₅₀ value of 2.13 μ M, whereas theopapuamide B (**129**) showed inhibition at an IC₅₀ value of 0.99 μ M. Additionally, celebeside A (**128**) possesses anti-HIV-1 activity due to the presence of a phosphoserine residue that is absent in theopapuamide B (**129**) (Figure 44).²⁹⁸

ADMET predictor shows that callipeltin A (**125**), mirabamide A (**127**), and celebeside A (**128**) violate three criteria of Lipinski guidelines whereas neamphamide A (**126**) and theopapuamide B (**129**) violate all four criteria. In addition, they also show low permeability, low flexibility, and no tendency to permeate the cell membranes. All of the above-mentioned compounds belong to the class of depsipeptides, and their mechanism of action is similar to that of papuamides. The limitations could be overcome similar to that of any other peptide. The route of administration should be intravenous to limit the permeation factor (Table S1).

Microspinosamide (**130**) was isolated from the Indonesian sponge *Sidonops microspinosa*. The peptide contains 13 amino acid residues. Both organic and aqueous extracts showed anti-HIV-1 activity. It showed anti-HIV-1 activity at a concentration of 0.12 μ M.²⁹⁹ Homophymine A, a new anti-HIV-1 compound, was isolated from the *Homophymia* sp. It possessed cytoprotective activity against the infection of HIV-1 at an IC₅₀ value of 0.075 μ M (Figure 45).³⁰⁰

ADMET predictor shows that microspinosamide (**130**) violates three criteria of the Lipinski guidelines. In addition, it also shows low permeability, low flexibility, and a low tendency to permeate the cell membranes. However, the interesting fact about microspinosamide (**130**) is that its structure could incorporate 13 amino acid residues along with numerous uncommon amino acids, and this is the first natural peptide that includes a β -hydroxy-p-bromophenylalanine residue.²⁹⁹ Hence, it is always a challenge to develop such molecules.

Different techniques can be adopted to synthesize such compounds and to reduce their limitations (Table S1).

19.3. Alkaloids

Dragmacidin F (**131**), a new bromoindole alkaloid isolated from the sponge belonging to the genus *Halicortex* from the southern coast of Ustica Island in Italy, showed in vitro activity against HIV-1 and HSV-1 at EC₅₀ values of 0.9 and 96 μ M, respectively.³⁰¹ This compound is known to inhibit the syncytia formation later to infecting the HIV-MT4, without causing any direct toxicity to the cell (Figure 46).^{301–303}

ADMET predictor shows that dragmacidin F (**131**) violates two criteria of the Lipinski guidelines. In addition, it also possesses a low tendency to permeate the cell membranes. Because there is no direct toxicity involved to the cells using this compound, the side effects could be reduced to some extent. Fosamprenavir (**40**), an FDA-approved drug (Table S4), also violates more than one criterion of the Lipinski guideline. Hence, this should not be a limiting factor for Dragmacidin F (**131**) to avoid considering it for further development and bringing it to clinical trials (Table S1).

Manzamine A (**132**) was isolated from the *Haliclona* sp.³⁰⁴ It has a unique complex polycyclic ring system that is coupled with a β -carboline moiety and is known to possess anti-HIV-1, antiparasitic, antimicrobial, and other biological activities.²⁸² Manzamine A (**132**), 6-deoxymanzamine X (**133**),³⁰⁵ neokauluamine, and 8-hydroxymanzamine (**134**) also showed anti-HIV-1 activity at EC₅₀ values of 4.2, 1.6, 2.3, and 0.6 μ M, respectively (Figure 47).³⁰⁶

ADMET predictor indicates that manzamine A (**132**) violates two criteria of the Lipinski guidelines. This compound showed low metabolic clearance, good oral bioavailability (20.6%), and long half-life from the oral and IV pharmacokinetic studies conducted in rats. Manzamine A (**132**) has a good acid solubility, which suggests that it readily dissolves in the stomach.³⁰⁶ Hence, this could be considered as a potentially good candidate for clinical assessments and further development (Table S1).

Manadomanzamines A (**135**) and B (**136**) were isolated from the Indonesian sponge *Acanthostrongylophora* sp. Manadomanzamines A (**135**) and B (**136**) and xestomanzamine A (**137**) showed activity against HIV-1 at EC₅₀ values of 11.5, 27.0, and 40.5 μ M, respectively. These also exhibited activities against AIDS opportunistic fungal infections and HIV-1 (Figure 48).³⁰⁷

ADMET predictor shows that manadomanzamines A (**135**) and B (**136**) violate two criteria of the Lipinski guidelines whereas the xestomanzamine A (**137**) does not violate any of the criteria. The structures of manadomanzamines A (**135**) and B (**136**) are the unprecedented rearrangement of the skeleton of manzamine.³⁰⁷ Hence, these compounds could be considered similar to manzamine and could be dealt with accordingly (Table S1).

Batzelladines A–E, which are also known to possess anti-HIV-1³⁰⁸ activity, were isolated from the sponges belonging to the *Batzella* and *Monanchora* genera. These are known to be

the first small-molecular-weight (between 400 and 800) HIV-1 entry inhibitors. They were shown to inhibit gp120–CD4 interaction.³⁰⁸ Crambescidins 800 (**138**) and 826, isolated from starfishes and the sponges of the genus groups *Batzella* and *Monanchora* showed similar anti-HIV-1 activity by inhibiting HIV-1 envelope-mediated fusion along with fromiamycalin, isolated from starfishes and some synthetic batzelladine analogues. Crambescidine 800 (**138**) had activity against HIV-1 with an EC₅₀ value of 0.04 μ M. Similarly, ptilomycalin A (**139**), isolated from the sponge *Monanchora unguifera* and starfishes, is also known to exhibit anti-HIV-1 activity at an EC₅₀ value of 0.011 μ M; meanwhile, batzelladine C (**140**) showed inhibition at an EC₅₀ of 7.7 μ M. Comparatively, batzelladine and ptilomycalin show potent activity against AIDS opportunistic infections and HIV-1 (Figure 49).³⁰⁹

ADMET predictor shows that ptilomycalin A (**139**) and crambescidin 800 (**138**) violate three criteria of the Lipinski guidelines whereas batzelladine C (**140**) does not violate any. In addition, ptilomycalin A (**139**) shows low flexibility and a low tendency to permeate into cell membranes whereas crambescidin 800 (**138**) exhibits low permeability, low flexibility, and less tendency to permeate the cell membranes. Batzelladine C (**140**) shows low permeability and less flexibility. Because these compounds are HIV-1 entry inhibitors, limitation of permeability should not be considered as a serious issue, and one should rather concentrate on improving the limitations for further development (Table S1).

Isoaaptamine (**141**) and aaptamine (**142**) were isolated from various sponges belonging to the *Suberites*, *Hymenlacidon*, and *Aaptos* genera. They are known to possess anti-HIV-1 activity at concentrations of 0.6 and 1.30 μ M, respectively. The potency of this activity has been further explored through a SAR of fluorine substitution on an indole heterocyclic system (Figure 50).³¹⁰

ADMET predictor predicts that isoaaptamine (**141**) and aaptamine (**142**) do not violate any of the Lipinski guidelines. This could be a good indicator that they might not be involved in any potential side effects or problems, and perhaps they could be considered as potential candidates for further development (Table S1).

Petrosin (**143**) and petrosin A (**144**) are bisquinolizidine alkaloids isolated from the Indian marine sponge *Petrosia similis*, which showed inhibition against HIV-1 replication at IC₅₀ values of 41.3 and 53 μ M, the recombinant reverse transcriptase at IC₅₀ values of 10.6 and 14.8 μ M, and the formation of giant cells at IC₅₀ 21.2 and 36.1 μ M, respectively (Figure 51).³¹¹

19.4. Diterpenes

In 1992, four cyanthiwigins were isolated from *Epipolasis reisiwigi*, a Jamaican sponge. These included cyanthiwigins A, B (**145**), C, and D. Among these, only cyanthiwigin (**145**) B is known to possess moderate anti-HIV-1 activity at an EC₅₀ value of 42.1 μ M. This may be due to the C-8 ketone group, which is only present in cyanthiwigin B and is absent in the other three compounds (Figure 52).³¹²

ADMET predictor shows that cyanthiwigin B (**145**) does not violate any of the Lipinski guidelines. The structure looks simple to prepare, and because it does not have any limitations, this could be another likely candidate to be considered for preclinical trials and further development (Table S1).

19.5. Sulfated Sterols

Two sulfated sterols isolated from the species *Xestospongia* and the other from an unidentified haplosclerid sponge are known to possess the unusual steroidal sulfamate esters—haplosamates A (**146**) and B (**147**), which showed inhibition towards HIV-1 integrase at IC₅₀ values of 50 and 15 $\mu\text{g/mL}$, respectively. The sulfamate group present in the haplosamates is responsible for the inhibition of HIV-1 integrase (Figure 53).³¹³

Clathsterol (**148**) is an active and novel sulfated sterol isolated from the Red Sea sponge *Clathria* sp. that showed inhibition against HIV-1 reverse transcriptase at 10 μM (Figure 54).³¹⁴

19.6. Miscellaneous Antivirals Possessing Anti-HIV Activity

Polyacetylenetriol (PAT) (**149**), isolated from the marine sponge *Petrosia* sp., showed selective inhibition against DNA- and RNA-dependent DNA polymerase activities of the retroviral reverse transcriptase at an IC₅₀ value of 0.95 μM . PAT is considered to be a reversible, noncompetitive inhibitor and is known to interfere with the catalytic steps of the viral DNA polymerization (Figure 55).³¹⁵

A new C22 furanoterpene isolated from the Madagascan sponge, *Lendenfeldia*, is designated as dehydrofurodendin (**150**), which showed inhibition against HIV-1 reverse transcriptase associated DNA- and RNA-directed DNA polymerase at IC₅₀ values ranging between 3.2 and 5.6 μM (Figure 56).³¹⁶

Cimino et al. reported a new anti-HIV polysaccharide named rosacelose (**151**) that comprises glucose and fucose sulfate isolated from the aqueous extract of the marine sponge *Mixylla rosacea*, which possessed a linear polysaccharide structure comprising 4,6-disulfated 3-*O*-glycosylated α -D-glucopyranosyl and 2,4-disulfated 3-*O*-glycosylated α -L-fucopyranosyl residues in a molar ratio of 3:1 (Figure 57).³¹⁷

Table 1 shows the summary of all the marine antivirals possessing anti-HIV-1 activity.

20. MARINE DRUGS FOR THE TREATMENT OF OTHER VIRAL DISEASES

20.1. Hepatitis B

The marine polysaccharide 911 that is isolated from alginate is known to prevent the replication of hepatitis B virus (HBV) by inhibiting the activity of HBV DNA-polymerase, improving the host-cell immune function.³¹⁸ Wu et al. reported that the DNA replication of the duck HBV could be inhibited by the oyster polysaccharides by reducing the duck HBV-DNA content from the serum, thus showing anti-HBV in vivo effects.³¹⁹ Guan identified that the polymeric mannuronic acid sulfate could effectively reduce the antigen levels and the DNA levels of the HBV in duck blood, thus improving the cellular and humoral immune

function.³²⁰ The replication of HBV is also known to be indirectly inhibited by the sulfated polymannuroguronate (SPMG) (**152**) isolated from the brown algae by improving the cellular and humoral immune functions (Figure 58).^{261,318}

20.2. HCV

Discorhabdins A (**153**) and C (**154**) and dihydrodiscorhabdin C (**155**) isolated from the *Latrunculia* genus of the Alaskan sponge species exhibited anti-HCV activity at EC₉₀ concentrations of <10 μ M (Figure 59).^{321,322}

20.3. HPV

Buck et al. established that carrageenans could inhibit the HPV infection process, and the antiviral effect is known to be better in the ι -carrageenan (**156**) isolated from *Eucheuma denticulatum* compared to λ - (**157**) and κ -carrageenans (**158**).³²³ Carrageenans bind to the HPV capsid, inhibiting the viral adsorption process along with the viral-entry and viral-uncoating processes. The mechanism involved in the inhibition of HPV is known to be independent of heparin sulfate after the viral adsorption (Figure 60).³²⁴

20.4. Influenza Virus

Extracellular sulfated polysaccharides isolated from the marine microalgae *Cochlodinium polykrikoides*, A1 and A2, are known to inhibit the cytopathic effects of the influenza virus (IAV) types A and B.³²⁵ The active sulfated calyceramides A–C (**159–161**) isolated from the marine sponge *Discodermia calyx* are known to inhibit the IAV neuraminidase inhibitors. Calyceramides A–C (**159–161**) are known to inhibit the neuraminidase from *Clostridium perf ringens* at IC₅₀ values of 0.4, 0.2, and 0.8 μ g/mL, respectively (Figure 61).³²⁶

Weinbersterols A (**162**) and B (**163**),³²⁶ isolated from the sponge *Petrosia weinbergi*, are known to inhibit the mouse influenza virus.³²⁷ A novel terpenoid stachyflin (**164**), isolated from the fungus *Stachybotrys* sp. RF-7260, is known to inhibit influenza A virus (H1N1) at an inhibitory concentration of 0.003 μ M, which is known to be better than the other anti-H1N1 drugs such as zanamivir (**67**) and amantadine (**68**). Stachyflin (**164**)³²⁸ possesses a novel cis-fused decalin along with a pentacyclic moiety and is known to exhibit antiviral activity by inhibiting the viral host-cell membrane and envelope (Figure 62).^{329,330}

Tang et al. showed that the low-molecular-weight (MW) carrageenans along with their derivatives exhibited significant inhibition activity against influenza virus in mice (FM1-induced pulmonary edema).³³¹ Wang and co-workers reported the inhibition of IAV replication both in vitro and in vivo by the low MW carrageenan oligosaccharide KCO (κ -carrageenan oligosaccharide) (**165**) along with their sulfated derivatives. The sulfate content, specific sugar linkage, and certain sugar length of KCO (**165**) are known to be essential for the anti-IAV activity of the κ -carrageenan (**165**) oligosaccharide. KCO (**165**) inhibits the replication phase of the IAV life cycle following viral internalization and prior to the release of the virus. κ -Carrageenan (**165**) saccharide, being the most active, has a molecular weight of 1–3 kDa with sulfate content 0.8–1.0 mol/mol of disaccharide (Figures 60 and 63).^{332,333}

Lüscher-Mattli and Glück reported the anti-IAV activity of dextran sulfate (**166**) through the inhibition of the IAV fusion with cell membranes and suppression of the viral replication in vivo.³³⁴ Ivanova et al. reported the inhibitory effect on IAV by ulvan polysaccharides (**167**) isolated from the green algae whose effect is known to be strain-specific and dose-dependent.³³⁵ Akamatsu et al. reported a new type of fucose polysaccharide, MC26, isolated from the brown seaweed that is known to possess excellent anti-IAV effects in vitro and in vivo.³³⁶ Zhang et al. reported the inhibition activity of marine polysaccharides isolated from *Perna viridis* against the replication of IAV in MDCK cells and its additive effect on the ribavirin anti-IAV actions, suggesting further investigation on these marine polysaccharides as anti-IAV agents (Figure 64).³³⁷

A low-molecular-weight (<5 kDa) oligomeric mannuronic acid (OM) (**168**), which is an oligosaccharide derivative of polymannuronic acid polysaccharide, showed good activity against H1N1 influenza A virus both in vitro and in vivo.³³⁸ Guan reported another polymannuronic acid derivative, polymannuronic acid propyl sulfate (PMS) (**169**), prepared by the propyl modification and sulfation of polymannuronic acid polysaccharide,³³⁹ which showed an inhibitory effect on neuraminidase activity of IAV along with alleviating pneumonia symptoms effectively caused by influenza A viral infection, reducing the mortality rate in mice (Figure 65).³⁴⁰

Kim et al. reported p-KG03, a sulfated polysaccharide isolated from the marine microalga *Gyrodinium impudium*, which showed maximum inhibition activity against IAV infection targeting the viral internalization and adsorption, preventing the viral replication.³⁴¹ Wang et al. reported a low-molecular-weight κ -carrageenan (**165**) oligosaccharide that is known to effectively inhibit the IAV replication both in vitro and in vivo.^{332,333} It was also noted that the carrageenan oligosaccharide CO-1 (**170**) could enter into the host cells, inhibiting the protein translation and mRNA transcription after the internalization, thereby preventing the viral replication (Figures 60 and 66).³³²

20.5. Respiratory Syncytial Virus

The isolation of two extracellular sulfated polysaccharides, A1 and A2 from *Cochlodinium polykrikoides*, was reported by Hasui et al. and showed inhibition on the cytopathic effects against RSV types A and B growing on Hep-2 cells.³²⁵

20.6. Dengue

A fucan polysaccharide, fucoidan (**171**)³⁴² isolated from *Cladosiphon okamuranus* comprising the sulfated fucose units and glucuronic acid, showed inhibition of BHK-21 cells in DENV-2 with little effect on the other three types, DENV-1, -3, and -4.³⁴³ Talarico and co-workers reported ι - (**156**) and λ -carrageenans (**157**) that interfere with the internalization and adsorption of the DENV-2 host cells.³⁴⁴ The mechanism that is involved in inhibition is thought to be due to the interference of carrageenans on the subsequent uncoating and release of DENV from the endosomes. ι -Carrageenan (**156**) exhibited inhibition through direct interaction with the viral membrane glycoprotein E (gE).^{344–346} Talarico et al. found that the ι -carrageenan (**156**) exhibited inhibition of DENV replication in both mammalian

and mosquito cells,³⁴⁴ affecting the potential targets within the DENV host cells (Figures 60 and 67).³⁴⁷

20.7. Herpes Simplex Virus

Two novel exopolysaccharides EPS-1 and EPS-2, isolated from the marine bacteria *Geobacillus thermodenitrificans* and *Bacillus licheniformis*, respectively, are known to inhibit HSV-2 replication at 200 and 300 $\mu\text{g/mL}$.^{348,349} A1, an extracellular sulfated polysaccharide isolated from a marine microalgae, *Cochlodinium polykrikoides*, showed activity against HSV-1.³²⁵ Fucoidan (**171**), a sulfated polysaccharide isolated from *Fucus vesiculosus*, a brown seaweed, is known to inhibit the replication of HSV-1 and HSV-2 viruses.^{350,351} Calcium-spirulan (Ca-SP), a sulfated polysaccharide isolated from *Arthrospira platensis*, a marine blue-green alga, is also known to inhibit the replication of HSV-1 and influenza-A.²⁵⁹

Naviculan, isolated from *Navicula directa*, is a sulfated polysaccharide that inhibited the early viral replication stages at IC_{50} values ranging between 7 and 14 $\mu\text{g/mL}$.²⁵³ Halovirs A (**172**), B (**173**), C (**174**), D(**175**), and E (**176**) isolated from the marine fungus *Scytidium* species showed potent antiviral activity against HSV-1 and HSV-2 at ED_{50} values 1.1, 3.5, 2.2, 2.0, and 3.1 μM , respectively. Halovir A (**172**) also inhibited the replication of HSV-1 and HSV-2 at an ED_{50} of 280 nm. The mechanism of action is not yet known but is thought to be due to membrane destabilization (Figures 67 and 68).³⁵²

Eudistomins (**177**)³⁵³ and their related β -carboline alkaloids isolated from the tunicate *Eudistoma olivaceum* showed inhibition against HSV-1 and HSV-2.³⁵⁴ Didemnins (**178**)³⁵⁵ isolated from *Trididemnum* sp. of tunicates are cyclic depsipeptides that showed in vivo and in vitro antiviral activities against HSV-1 (Figure 69).³⁵⁶

Studies indicated the use of heparin polysaccharides and low-molecular-weight heparin (**179**) as natural inhibitors of HSV-1 that require a unique sulfation moiety.^{357,358} The marine heparinoid polysaccharides are considered to be structurally similar to heparin (**179**), possessing glycosaminoglycan (GAG)-like biological properties, and include ulvans (**167**), alginates, and their sulfated derivatives along with chitosan sulfate and dextran sulfate (**166**). Recent studies indicated the cell-surface heparinoid sulfate proteoglycans as the initial receptors of HSV-1 and HSV-2.^{359–361} Heparinoid polysaccharides are known to prevent the viral binding to the cell surface by interacting with the positively charged regions of the cell-surface glycoproteins (Figures 64 and 70).³⁵⁹

Yu et al. studied the inhibitory actions of the scallop skirt GAG (SS-GAG) on HSV-1 at various concentrations with significant in vitro effects, and the antiviral effect of SS-GAG is known to increase gradually with prolonged duration of action.³⁶² Carlucci et al. identified the firm binding of λ -carrageenan (**157**) to HSV, leading to the virion inactivation, thereby inhibiting the HSV replication.³⁶³ The studies also suggested the structural changes of HSV-glycoproteins gB and gC by carrageenan.^{363,364} Further it was also noted that cyclized μ (**180**)-/t-carrageenan (**156**) isolated from *Gigartina skottsbergii* also showed potent antiviral effects against HSV-1 and HSV-2 during the viral-adsorption stage (Figures 60 and 71).³⁶⁵

Harden et al. also reported the direct inactivation of HSV-2 by carrageenan polysaccharides isolated from red algae at low concentrations. The virucidal activities of the carrageenan polysaccharides are known to increase with increasing molecular weight until 100 kDa.³⁶⁶ The direct virucidal activity of carrageenans is known to be due to the formation of stable carrageenan–virion complex, making the binding irreversible and filling the viral envelope sites necessary for viral attachment to the host cells with sulfated polysaccharide preventing the completion of the viral infection process.³⁶⁷ Kanekiyo et al. reported that nostoflan, an acidic polysaccharide isolated from *Nostoc flagelliforme*, an edible blue–green alga, showed good inhibitory activity against HSV-1, preventing the binding of virus to the host cells.³⁶⁸

Perry et al. reported the isolation of mycalamide A (**181**) and B (**182**) from the New Zealand sponge *Mycale* in the year 1988 that inhibited herpes simplex virus type I at a concentration of 5 ng/disc. Of the two, mycalamide B (**182**) was found to be more potent at a concentration of 1–2 ng/disc. 4-Methylaaptamine (**183**) isolated from the marine sponge *Aaptos* sp. showed anti-HSV-1 activity at an EC₅₀ of 2.4 μ M and was found to be more potent than acyclovir (**83**) [EC₅₀ 8.6 μ M]. Dragmacidin F (**131**), a bromoindole alkaloid isolated from the marine sponge *Halicortex*, showed antiviral activity against HSV-1 at an EC₅₀ of 96 μ M. Hamigeran B (**184**) isolated from the marine sponge *Hamigera tarangaensis* also showed inhibition against herpes virus (Figures 25, 46, and 72).²⁸²

21. IN THE PIPELINE: HIV AND HCV DRUGS UNDER DEVELOPMENT

21.1. HIV

GS-7340 (**185**) also known as tenofovir alafenamide fumarate (TAF)³⁶⁹ is an anti-HIV-1 prodrug that has been patented by Gilead (no. WO2002008241). GS-7340 belongs to the NRTIs and is currently under Phase III clinical trials.³⁷⁰ It is known to inhibit the reverse transcriptase enzyme, thereby preventing viral replication, and is also known as a prodrug of tenofovir.³⁷¹

SPI-452 is another anti-HIV-1 drug currently in Phase II clinical trials that has been patented by Sequoia Pharmaceuticals (no. WO2008022345).³⁷⁰ The drug is a boosting agent that has no antiviral properties but enhances the levels of the second drug taken.³⁷²

There are investigational NNRTIs for the treatment of HIV-1, namely, DPC 083 (**186**).³⁷³ DPC 083 (**186**)³⁷⁴ is a quinazolinone derivative of efavirenz (**19**), but Bristol-Myers Squibb never developed this potent molecule.^{375,376} Some of the entry inhibitors that are in investigation include PRO 542, Schering C (**187**), and T-1249 (**189**).³⁷³ PRO 542 could be classified under CD4-attachment inhibitors that show activity against viral isolates by binding to viral gp120.³⁷⁷ Schering C or SCH-C (**187**) belongs to the class of chemokine receptor (CCR5) inhibitors and has oral bioavailability.³⁷⁸ T-1249 (**189**) is a synthetic 39-amino-acid peptide belonging to the class of HIV fusion inhibitors.^{379,380} S-1360 (**188**), a 1,3-diketone derivative, is an investigational HIV integrase inhibitor and shows anti-retroviral activity when the amino acids are substituted at the active site of the integrase.³⁸¹ T-1249 (**189**) has oral bioavailability and is currently undergoing Phase I/II clinical studies.³⁷³ MK-1439 (**190**),³⁸² an investigational oral HIV NNRTI, is currently undergoing Phase II clinical trials by Merck & Co., Inc.³⁸³ S/GSK1265744 (**191**),³⁸⁴ also known as

cabotegravir, a HIV integrase inhibitor, is in ongoing Phase II clinical trials under GlaxoSmithKline (Figure 73).³⁸⁵

21.2. HCV

Mericitabine (**192**), also known as MCB or RG7128 once bioconverted to its 5'-NTP (nucleotide triphosphate), is a HCV nucleoside inhibitor of NS5B RNA-dependent RNA polymerase.³⁸⁶ It was studied up to Phase II clinical trials, but it was not found to be as potent as sofosbuvir (**30**) and is not being developed by Roche in the U.S. or Europe.³⁸⁷ Danoprevir³⁸⁸ (**193**) is a macrocyclic peptidomimetic compound that inhibits HCV NS3/4A protease and is currently in Phase II clinical trials managed by Roche.³⁸⁷ Setrobuvir³⁸⁹ (**194**) is another HCV non-nucleoside inhibitor that inhibits NS5b RNA polymerase.³⁸⁷

BI 201335³⁹⁰ (**195**) is an oral HCV NS3/4A protease inhibitor that was stopped at Phase III clinical trials managed by Boehringer-Ingelheim. Similarly BI 207127 or deleobuvir (**196**),^{390,391} an oral HCV NS5B RNA-dependent polymerase inhibitor, was undergoing Phase II clinical trials.³⁹²

Merck Co. has two HCV drugs: MK-5172 (**198**),³⁹³ an oral NS3/4A protease inhibitor, and MK-8742 (**197**),³⁹⁴ an oral NS5A protease inhibitor undergoing Phase II clinical trials. MK-7009³⁹⁵ or vaniprevir³⁹⁶ (**199**) is an investigational oral NS3/4A protease inhibitor that is currently undergoing Phase III clinical trials.³⁸³ GSK2336805 (**200**)³⁹⁷ is a HCV inhibitor that is undergoing Phase II clinical trials under GlaxoSmithKline (Figure 74).³⁸⁵

21.3. Pneumonia

Merck Co. developed a pneumoconjugate vaccine V114 that is currently under Phase II clinical trials. V114 is an investigational vaccine that showed protection against pneumococcal disease that is caused by serotypes present in the vaccine.³⁹⁸

21.4. HBV

Gilead Sciences developed three drugs for the treatment of chronic HBV infection—tenofovir alafenamide (TAF), also GS-7340 (**185**), a nucleotide reverse transcriptase inhibitor³⁹⁹ that is currently under Phase III clinical trials;⁴⁰⁰ GS-4774, a therapeutic vaccine that is a tarmogen T cell immunity stimulator;⁴⁰¹ and GS-9620 (**201**), a toll-like receptor 7 (TLR-7) agonist⁴⁰²—which are under Phase II clinical trials (Figures 73 and 75).⁴⁰⁰

21.5. HPV

Merck developed HPV vaccine V503 against HPV-related cancers; it is an investigational human papillomavirus (HPV) vaccine that targets nine subtypes—6, 11, 16, 18, 31, 33, 45, 52, and 58. V503 is being evaluated for the prevention of HPV, which is currently under review.³⁹⁸

21.6. Norovirus

Romark Laboratories developed nitazoxanide (**202**), a thiazolide agent for the treatment of viral gastroenteritis, and conducted a double-blind placebo-controlled clinical trial for the

evaluation of its activity against norovirus, adenovirus, and rotavirus. Nitazoxanide (**202**) is known to interfere with the enzyme-dependent transfer reactions of pyruvate ferredoxin oxidoreductase [PFOR] necessary for the anaerobic energy metabolism, preventing the synthesis of the viral proteins (Figure 76).⁴⁰³

21.7. Influenza

Roche developed RG7745, a human monoclonal antibody that is designed to neutralize the influenza A virus against a wide range of strains. RG7745 binds to the epitope on the influenza A hemagglutinin stalk region that is highly conserved and is currently under Phase II clinical trials.³⁸⁷ GlaxoSmithKline developed relenza (zanamivir) (**67**), a neuraminidase inhibitor for the treatment of influenza that is currently under Phase III clinical trials.³⁸⁵ Nitazoxanide (**202**), a broad-spectrum antiviral, is in Phase III clinical trials for the treatment of influenza.⁴⁰⁴

21.8. RSV

Gilead developed GS-5806, a fusion inhibitor for the treatment of respiratory syncytial virus (RSV) that is currently under Phase II clinical trials. GS-5806 blocks RSV replication by inhibiting the RSV F-mediated fusion of the viral RNA.⁴⁰⁰ GlaxoSmithKline developed a pediatric recombinant viral vector vaccine for the treatment of RSV that is currently in Phase I clinical trials.³⁸⁵

21.9. Shingles

Merck Co. developed a herpes zoster inactivated VZV vaccine, V212, that is being evaluated for the prevention of herpes zoster (HZ) and HZ-related complications in immunocompromised subjects, currently under Phase III clinical trials.³⁹⁸

22. CONCLUSION

Natural products continue to provide an excellent source of new leads for the development of anti-HIV agents. A summary of the marine organisms possessing anti-HIV-1 activity and other antiviral activities are shown in Tables 1 and 2. As per the Lipinski guidelines, the “Lipinski rule of five” states that the compound should have a molecular weight <500, a log *P* value not more than 5, hydrogen bond donors of <5, and hydrogen bond acceptors of <10 for it to have oral bioavailability and better absorption.⁴⁰⁵ However, most oral drug formulations available in the market fail in at least one Lipinski guideline that, for example, includes didanosine (**4**), which exceeds the log *P* value and yet is available as chewable tablets.⁴⁰⁶ Zalcitabine (**5**) (which is now rarely used for the treatment of HIV) also fails in one Lipinski guideline by exceeding the log *P* value and is available in tablet form.⁴⁰⁷ There are many such examples (see Table S4).

All the absorption criteria mentioned in the Supporting Information are not followed by many of the FDA-approved drugs. Most drugs fail in at least two to three criteria and yet are considered as drugs favored to treat HIV-1. Similarly there are compounds isolated from the marine sources that are not different to these kinds of drugs. These compounds could be synthesized as oral formulations and are inexpensive to formulate based on their structures.

Some include avarol (**114**), curcuphenol (**116**) and its analogues a (**117**), c (**118**), j (**119**), and r (**120**), manzamine A (**132**), manadomanzamines A (**135**) and B (**136**), xestomanzamine A (**137**), crambescidin 800 (**138**), ptilomycalin A (**139**), batzelladine C (**140**), isoaaptamine (**141**), aaptamine (**142**), and cyanthiwigin B (**145**) that could be considered for syntheses in the treatment of HIV-1. The same could be said in the case of distribution, metabolism, and toxicity criteria (see Supporting Information).

All the information discussed above is only a prediction (from ADMET predictor), and hence, the drugs isolated from the marine sources need to undergo in vivo assays, advanced toxicological evaluation, and clinical trials to further strengthen the results and validate safety and efficacy profiles. Although some of the drugs fail in many criteria, they could still be adjusted or altered to better treat the disease. Any further progress could be made only when the compounds from the marine sources can undergo further tests and assays.

The major challenges involved in natural product drug development are drug resistance, long drug-development processes, and sometimes toxic side effects. Many of the sponge-derived compounds have shown toxic effects. This could potentially be solved by applying biochemical technologies such as combinatorial biosynthesis, synthetic biology, metabolic engineering, medicinal chemistry, and post-genomic techniques.^{223,408}

When the virus becomes resistant to one drug, then it is not possible to treat that virus with any other naturally occurring derivative with similar activities against the virus.⁴⁰⁹ So for the discovery of new drugs, different derivatives belonging to a common class synthesized by multiple organisms could be a solution.

Identifying, cloning, and modifying gene expression using synthetic biology are some of the techniques used to combat the large-scale production problems.²²³ Therefore, understanding the biology and the natural living conditions that affect the growth and metabolite production of sponges is necessary.²⁸²

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Biographies

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Dr. Mark T. Hamann is a Professor of Pharmacognosy, Pharmacology and Chemistry & Biochemistry as well as a Research Professor with the National Center for Natural Products Research at the University of Mississippi and is an Associate Member of the UMMC Cancer Center.

Dr. Hamann has several years experience in GMP pharmaceutical manufacturing at Solvay Pharmaceuticals in Baudette, Minnesota, and completed a Ph.D. degree in Organic/Natural Product Chemistry in 1992 at the University of Hawaii, Chemistry Department, under the guidance of the late Professor Paul Scheuer, a pioneer in the discovery and development of marine products. Dr. Hamann then completed Postdoctoral Studies with Prof. Bill Baker doing field studies in Antarctica. During his research career, Dr. Hamann has published over 190 scientific papers, reviews, and book chapters and currently serves as an Associate Editor for *Biochimica et Biophysica Acta*, General Subjects. His group is actively involved in the isolation, structure determination, and synthetic optimization of marine/terrestrial natural products and toxins with a focus on plant and invertebrate microbiomes. His group is currently working on the preclinical development of a small pipeline of natural products with activity against infectious diseases, cancer, and neuropsychiatric disorders.

Figure 1.
Mortality versus viral diseases.³⁻⁵

Figure 2.
Incidence rates versus viral diseases.³⁻⁵

Figure 3.

Anti-HIV-1 drugs referenced in the history. Compounds include saquinavir (7),⁴¹⁰ nevirapine (9),⁴¹⁰ raltegravir (12), maraviroc (13), cobicistat (14),⁴¹¹ and fuzeon (15).⁴¹²

Figure 4.
Structure of HIV.

Figure 5.
Schematic representation of the virus replication cycle.

Figure 6. Crystal structures of HIV reverse transcriptase,⁴¹³ integrase,⁴¹⁴ RNA polymerase,⁴¹⁵ and protease⁴¹⁶ and scanning electron micrograph of HIV.⁴¹⁷ Courtesy: National Institute of Allergy and Infectious Diseases, <http://www.nih.gov/science/hiv/>.

Figure 7.

NNRTIs used for the treatment of HIV that include rilpivirine (17),⁴¹⁰ etravirine (18),⁴¹⁰ efavirenz (19),⁴¹⁰ and delavirdine (20).⁴¹⁰

Figure 8.

Various NRRIs possessing anti-HCV activity. NRRIs include valopicitabine (21), 2'-C-methyladenosine (22), 7-deaza-7-fluoro-2'-C-methyladenosine (23), 2'-O-methylcytidine (24), 7-deaza-2'-C-methyladenosine (25), 2'-C-methylguanosine (26), 4'-azidocytidine (27), 2'-deoxy-2'-fluoro-2'-C-methylcytidine (28), and R1626 (29).

Figure 9.
Structure–activity relationship (SAR) of anti-HCV NRRIs.

Figure 10.

Structures of ledipasvir (31),⁴¹⁸ simeprevir (32),⁴¹⁹ daclatasvir (33),⁴¹⁸ ombitasvir (34),⁴²⁰ paritaprevir (35),⁴²¹ and dasabuvir (36).⁴²²

Figure 11.

HIV protease inhibitors including amprenavir (37),⁴¹⁰ indinavir (38),⁴¹⁰ lopinavir (39),⁴¹⁰ fosamprenavir (40),⁴¹⁰ nelfinavir (41),⁴¹⁰ darunavir (42),⁴²³ tipranavir (43),⁴¹⁰ atazanavir (44),⁴¹⁰ brexanavir (45),⁴²⁴ and ritonavir (46).⁴¹⁰

A: HCV protease inhibitors that include boceprevir (**47**), telaprevir (**48**), ciluprevir (**49**) and SCH446211 (**50**).

B: HIV-1 entry inhibitors BMS-663068 (**51**)⁴²⁷ and cenicriviroc (**52**).

C: HIV-1 integrase inhibitors elvitegravir (**53**)⁴²⁸ and dolutegravir (**54**)⁴²⁸

D: HIV-1 NNRTIs lersivirine (**55**)¹²⁶ and dapivirine (**56**)⁴¹²

E: HIV-1 maturation inhibitor, Bevirimat (**64**).

Figure 12.

(A) HCV protease inhibitors that include boceprevir (**47**), telaprevir (**48**), ciluprevir (**49**), and SCH446211 (**50**). (B) HIV-1 entry inhibitors BMS-663068 (**51**)⁴²⁵ and cenicriviroc (**52**). (C) HIV-1 integrase inhibitors elvitegravir (**53**)⁴²⁶ and dolutegravir (**54**). (D) HIV-1 NNRTIs lersivirine (**55**)¹²⁶ and dapivirine (**56**)⁴¹⁰ (E) HIV-1 maturation inhibitor, Bevirimat (**64**).

Figure 13.

Schematic representation of all the anti-HIV-1 drugs that act at various stages of viral replication cycle including the crystal structures of CD4⁴²⁷ and CCR5.⁴²⁸

Figure 14.

Neuraminidase inhibitors: oseltamivir (**66**) and zanamivir (**67**); adamantane drugs: amantadine (**68**) and rimantadine (**69**).

Figure 15. Structure of hepatitis B virus with crystal structure of HBV e antigen⁴²⁹ and cryo-electron microscopy (CryoEM) structure of HBV core antigen.⁴³⁰

Figure 16.
Viral replication of Hepatitis B virus.

Figure 17.

HBV drugs: adefovir dipivoxil (**70**), entecavir (**71**), telbivudine (**72**), clevudine (**73**), and thymosin (**74**).

Figure 18. Structure of RSV along with crystal structures of nucleoprotein,⁴³¹ matrix protein,⁴³² and fusion protein.⁴³³

Figure 19.
Chemical structure of ribavirin (75).

Figure 20.
Structure of dengue virus along with the crystal structure of the envelope protein (E)⁴³⁴

Figure 21. Structure of the SARS virus along with the crystal structures of spike glycoprotein,⁴³⁵ nucleocapsid phosphoprotein,⁴³⁶ and RNA.⁴³⁷

Figure 22.

Norovirus inhibitors: rupintrivir (**76**),⁴³⁸ favipiravir (**77**), suramin (**78**),⁴³⁹ 2'-C-methylcytidine (**79**), deubiquitinase [WP1130] (**80**), and eIF4F inhibitors (**81**).

Figure 23. Structure of rotavirus along with the crystal structures of VP7,⁴⁴⁰ VP1,⁴⁴¹ and VP6.⁴⁴²

Figure 24.
Structure of varicella-zoster virus (VZV).

Figure 25.
Chemical structures of valacyclovir (**82**), acyclovir (**83**), and famciclovir (**84**).

Figure 26.
Structure of HSV.

Figure 27.
Chemical structures of idoxuridine (**85**) and phosphonoformate (**86**).

Figure 28.

Structure of Ebola virus.²²⁰ Reprinted with permission from ref 210. Copyright 1989 American Chemical Society. Image from the RCSB PDB October 2014 Molecule of the Month featured by David Goodsell (DOI: 10.2210/rcsb_pdb/mom_2014_10)], crystal structures of glycoprotein,²¹⁹ matrix proteins,^{443,444} and electron scanning microscopic image⁴⁴⁵ (Courtesy: National Institute of Allergy and Infectious Diseases, <http://www.niaid.nih.gov/news/newsreleases/2014/Pages/EbolaDisparities.aspx>).

Figure 29.

Schematic representation of the marine metabolites that are active at various stages of the viral replication cycle including the crystal structure⁴⁴⁶ of lectin.

Figure 30.

Phlorotannins 8,8'-bieckol (**87**), 8,4'''-dieckol (**88**), and 6,6'-bieckol (**89**) isolated from a brown algae, *Ecklonia cava*, and diphlorethohydroxycarmalol (**90**) isolated from *Ishige okamurae*.

Figure 31.
Sulfated chitin (91), chitosan (92), and chitooligosaccharide (93) derivatives.

Sulfated Polysaccharides (**94**)

Figure 32.
Sulfated polysaccharides (**94**) isolated from red seaweeds.⁴⁴⁷

Figure 33.
Structure of laminaran (95).

Figure 34.
Structures of Leu-Leu-Glu-Tyr-Ser-Ile (**96**) and Leu-Leu-Glu-Tyr-Ser-Leu (**97**).

Polyphemusin I (**98**) Polyphemusin II (**99**) Tachyplesin I (**100**) Tachyplesin II (**101**)

Figure 35.
Structures of polyphemusin I (**98**)–II (**99**) and tachyplesins I (**100**)–II (**101**).

Figure 36.
Structures of macrolactin-A (102), Da-1 (103), and AcDa-1 (104).

Figure 37.
Structures of equisetin (**105**) and phomasetin (**106**).

Thalassiolin A (**107**) R = OH
Thalassiolin B (**108**) R = OMe
Thalassiolin C (**109**) R = H

Figure 38.
Structures of thalassiolins A (**107**), B (**108**), and C (**109**).

Figure 39.

Structures of didemnaketals A (**110**) and B (**111**) and cyclodidemniserinol trisulfate (**112**).

Lamellarin α 20-Sulfate (113)

Figure 40.
Structure of lamellarin α 20-sulfate (113).

Figure 41.
Avarol (114) and avarone (115) possessing anti-HIV-1 activity.

Figure 42.

Curcuphenol (**116**) and its analogues a (**117**), c (**118**), j (**119**), and r (**120**) isolated and modified from the sponges *Didiscus oxeata*, *Didiscus flavus*, *Myrmekioderma styx*, and *Epipolasis* sp.

Figure 43.

Papuamides A (121), B (122), C (123), and D (124) isolated from the marine sponges *Theonella swinhoei* and *T. mirabilis*.

Figure 44.

Callipeltin A (**125**) isolated from *Callipelta*, neamphamide A (**126**) isolated from *Neamphius huxleyi*, mirabamide A (**127**), celebeside A (**128**),⁴⁴⁸ and theopapuamide B (**129**)⁴⁴⁸ isolated from *Siliquariaspongia mirabilis*.

Figure 45.
Microspinosamide (**130**) isolated from the Indonesian sponge *Sidonops microspinosa*.

Dragmacidin F (131)

Figure 46.

Dragmacidin F (**131**) isolated from the marine sponge belonging to the *Halicortex* genus from the southern coast of Ustica Island in Italy.

Manzamine A (**132**) 6-deoxymanzamine X (**133**) 8-hydroxymanzamine (**134**)

Figure 47.

Manzamine A (**132**), 6-deoxymanzamine X (**133**), and 8-hydroxymanzamine (**134**) isolated from *Haliclona* sp.

Manadomanzamine A (**135**) R = β H
Manadomanzamine B (**136**) R = α H

Xestomanzamine A (**137**)

Figure 48.

Manadomanzamines A (**135**) and B (**136**) and xestomanzamine A (**137**) isolated from the Indonesian sponge *Acanthostrongylophora* sp.

Figure 49.

Ptilomycalin A (**139**), isolated from the sponge *Monanchora unguifera*, and crambescidine 800 (**138**) and batzelladine C (**140**) isolated from the *Batzella* and *Monanchora* genera.

Isoaaptamine (**141**) $R_1 = \text{H}$ $R_2 = \text{CH}_3$
Aaptamine (**142**) $R_1 = \text{CH}_3$ $R_2 = \text{H}$

Figure 50.

Isoaaptamine (**141**) and aaptamine (**142**) isolated from the sponge *Aaptos aaptos*.

Figure 51.
Structures of petrosin (**143**) and petrosin A (**144**).

Cyanthiwigin B (145)

Figure 52.

Cyanthiwigin B (145) isolated from the Jamaican sponge *Epipolasis reisiwigi*.

Haplosamate A (**146**) $\text{R} = \text{H}$

Haplosamate B (**147**) $\text{R} = \text{SO}_3\text{Na}$

Figure 53.
Structures of haplosamates A (**146**) and B (**147**).

Figure 54.
Structure of clathsterol (**148**).

Figure 55.
Structure of polyacetylenetriol (**149**).

Dehydrofurodendin (**150**)

Figure 56.
Structure of dehydrofurodendin (**150**).

Figure 57.
Structure of the repeating unit of rosacelose (**151**).

Sulfated Polymannuroguronate (SPMG) (**152**)

Figure 58.

Structure of sulfated polymannuroguronate (SPMG) (**152**).

Figure 59.
Structures of discorhabdins A (**153**) and C (**154**) and dihydrodiscorhabdin C (**155**).

Figure 60.

Structures of ι - (**156**), λ - (**157**), and κ -carrageenans (**158**).

Calyceramide A (159)	$R_1 = \text{H}$	$R_2 = \text{CH}_2(\text{CH}_3)_2$	$R_3 = (\text{CH}_3)_2$
Calyceramide B (160)	$R_1 = \text{CH}_3$	$R_2 = \text{CH}_3$	$R_3 = \text{CH}_2(\text{CH}_3)_2$
Calyceramide C (161)	$R_1 = \text{H}$	$R_2 = \text{CH}_2\text{CH}_2(\text{CH}_3)_2$	$R_3 = \text{CH}_3$

Figure 61.

Structures of calyceramides A (**159**), B (**160**), and C (**161**).

Weinbersterol A (**162**) $R_1 = \text{H}; R_2 = \text{OH}$

Weinbersterol B (**163**) $R_1 = \text{OH}; R_2 = \text{H}$

Stachyflin (**164**)

Figure 62.

Structures of weinbersterols A (**162**) and B (**163**) and stachyflin (**164**).

Figure 63.
Structure of KCO (**165**).

Figure 64.
Structures of dextran sulfate (**166**) and ulvan (**167**).

Figure 65. Structures of oligomeric mannuronic acid (OM) (**168**) and polymannuronic acid propyl sulfate (PMS) (**169**).

Figure 66.
Structure of the carrageenan oligosaccharide CO-1 (**170**).

Figure 67.
Structure of fucoidan (**171**).

Halovir A (172)	R ₁ = CH ₃	R ₂ = OH	n = 12
Halovir B (173)	R ₁ = H	R ₂ = OH	n = 12
Halovir C (174)	R ₁ = CH ₃	R ₂ = H	n = 12
Halovir D (175)	R ₁ = CH ₃	R ₂ = OH	n = 10
Halovir E (176)	R ₁ = CH ₃	R ₂ = H	n = 10

Figure 68.
Structures of haloviruses A (172), B (173), C (174), D (175), and E (176).

Figure 69.
Structures of eudistomins (177) and didemnins (178).

Figure 70.
Structure of heparin (179).

Figure 71.
Structure of μ -carrageenan (180).

Figure 72.

Structures of mycalamide A (**181**), mycalamide B (**182**), 4-methylaaptamine (**183**), and hamigeran B (**184**).

Figure 73.

HIV drugs in late stage development: GS 7340 (185),⁴⁴⁹ DPC 083 (186), SCH-C (187), S-1360 (188), T-1249 (189), MK-1439 (190),⁴⁵⁰ and S/GSK1265744 (191).⁴⁵¹

Figure 74.

Novel HCV drugs: mericitabine (**192**),⁴⁵² danoprevir (**193**),⁴⁵³ setrobuvir (**194**),⁴⁵⁴ BI 201335 (**195**),⁴⁵⁵ BI 207127 (**196**), MK-8742 (**197**),⁴⁵⁶ MK-5172 (**198**), MK-7009 or vaniprevir (**199**), and GSK 2336805 (**200**).⁴⁵⁷

GS-9620 (201)

Figure 75.
Structure of GS-9620 (201).⁴⁵⁸

Nitazoxanide (**202**)

Figure 76.
Structure of nitazoxanide (**202**).⁴⁵⁹

Scheme 1.

Systematic Representation of the Chronological Order of HIV-1 and HCV Drugs Having Similar Structures to Ara-C, the First Anticancer Lead from a Sponge; All the Drugs and Compounds Mentioned in This Scheme Are NRTIs except for Dexelvucitabine (65), Which Is an HIV-1 Maturation Inhibitor, and Mericitabine (192), Which Is an HCV Nucleoside Inhibitor

Scheme 2.

Systematic Representation of the Chronological Order of HIV-1 and HCV Drugs Having Similar Nuclei to Ara-A, an Antiviral Agent; All the Drugs and Compounds Mentioned in This Scheme Are NRTIs

Table 1

Summary of the Marine Organisms Showing Anti-HIV-1 Activity

compound	type	source	cellular target	activity	ref
8,4''-dieckol	phlorotannin	<i>Ecklonia cava</i>	reverse transcriptase	HIV-1 IC ₅₀ 5.3 μ M	227 and 228
8,8'-bieckol	phlorotannin	<i>Ecklonia cava</i>	reverse transcriptase	HIV-1 IC ₅₀ 0.5 μ M	227 and 228
6,6'-bieckol	phlorotannin	<i>Ecklonia cava</i>	entry and reverse transcriptase	HIV-1 IC ₅₀ 1.07 μ M	231
diphlorethohydroxycarmalol	phlorotannin	<i>Isigoe okamurae</i>	reverse transcriptase	IC ₅₀ 9.1 and 25.2 μ M	232
N-carboxymethyl chitosan	chitin polysaccharide	shells of shrimps & crabs	reverse transcriptase	HIV-1 IC ₅₀ 0.02 μ M	236 and 237
sulfated glucuronogalactan	sulfated polysaccharide	<i>Schizymenia dubyi</i>	syncytial formation and reverse transcriptase	HIV-1 5 μ g/mL	247
sea algal extract (SAE)	citrate buffer extract	<i>Schizymenia pacifica</i>	reverse transcriptase	9.5×10^3 IU/mL	248 and 249
fucan A	fucan	<i>Dictyota mertensii</i> and <i>Lobophora variegata</i>	reverse transcriptase	HIV-1 1.0 mg/mL	251
fucan B	fucan	<i>Fucus vesiculosus</i>	reverse transcriptase	HIV-1 0.5 μ g/mL	251
naviculan	sulfated polysaccharide	<i>Navicula directa</i>	cell-cell fusion	IC ₅₀ 0.24 μ M	253
laminaran	polysaccharide	<i>Kelp</i>	reverse transcriptase	HIV-1 50 μ g/mL	255
galactan sulfate	polysaccharide	<i>Agardhiella tenera</i>	cell binding	HIV-1 and HIV-2 IC ₅₀ 0.5 and 0.05 μ g/L	256
calcium spirulan (Ca-SP)	sulfated polysaccharide	<i>Arthrospira platensis</i>	viral replication	HIV-1 ED ₅₀ 11.4 and 2.3 μ g/mL	259
griffithsin (GRFT)	lectin	<i>Griffithsia</i> sps.	cell-cell fusion	HIV-1 EC ₅₀ 0.000043 μ M	267
CVL	β -galactose specific lectin	<i>Chaetopterus variopedatus</i>	cytopathic effects cell-cell fusion	EC ₅₀ 0.0043–0.057 μ M EC ₅₀ 0.073 μ M	268
CGL	lectin	<i>Crenomytilus grayanus</i>	syncytium formation	EC ₅₀ 27.9 μ g/mL	269
DTL and DTL-A	lectins	<i>Didemnum ternatanum</i>	syncytium formation	EC ₅₀ 0.002 and 0.36 μ g/mL	269
SVL-2	GlcNAc-specific lectin	<i>Serpula vermicularis</i>	syncytium formation	EC ₅₀ 0.15 μ g/mL	223 and 269
Leu-Leu-Glu-Tyr-Ser-Ile	peptide	<i>Crassostrea gigas</i>	protease	IC ₅₀ 0.02 μ M	270
Leu-Leu-Glu-Tyr-Ser-Leu	peptide	<i>Crassostrea gigas</i>	protease	IC ₅₀ 0.015 μ M	270
polypheumisin II	peptide	<i>Limulus polyphemus</i> and <i>Tachypleus tridentatus</i>	viral adsorption preceding reverse transcription	HIV-1 EC ₅₀ 2.6 μ M	272 and 273
macrolactin-A	lactone	marine bacteria	replication	10 μ g/mL	274

compound	type	source	cellular target	activity	ref
Da-1	diterpene	<i>Dictyota menstrualis</i>	replication reverse transcriptase	HIV-1 EC ₅₀ 40 µM HIV-1 IC ₅₀ 10 µM	275
AcDa-1	diterpene	<i>Dictyota menstrualis</i>	replication reverse transcriptase	HIV-1 EC ₅₀ 70 µM HIV-1 IC ₅₀ 35 µM	275
equisetin	acyl tetrameric acid	<i>Fusarium heterosporum</i>	integrase	IC ₅₀ 7–20 µM	276
phomasetin	acyl tetrameric acid	<i>Fusarium heterosporum</i>	integrase	IC ₅₀ 7–20 µM	276
thalassiolins A–C	sulfated flavone glycosides	<i>Thalassia testudinum</i>	integrase	IC ₅₀ 30 µM	277
didemnaketals A and B	spiroketals	<i>Didemnum</i> sp.	protease	IC ₅₀ 2 and 10 µM	278
cyclodidemmisertol trisulfate	sulfated serinolipid	<i>Didemnum guttatum</i>	integrase	IC ₅₀ 60 µg/mL	279
lamellarin α 20-sulfate avarol	alkaloid	Arabian Sea ascidian	integrase	IC ₅₀ 16 µM	281
sesquiterpene hydroquinone	sesquiterpene	<i>Disidea avara</i>	replication	HIV-1 IC ₅₀ 0.3 µM	283
curcuphenols a, c, j, and r	sesquiterpene phenols	<i>Didiscus oxeata</i> , <i>D. flavus</i> , <i>Myrnekioderma spyx</i> and <i>Epipolasis</i> sps.	reverse transcriptase, protease, and viral entry	EC ₅₀ 31.2, 29.2, 18.4, and 18.2 µM	286
papuanamides A and B	cyclic depsipeptides	<i>Theonella swinhoei</i> and <i>T. mirabilis</i>	viral entry and phospholipids	HIV-1 EC ₅₀ 0.003 µM	293
callipeltin A	cyclic depsipeptide	<i>Callipelta</i> genus	cytotoxicity	ED ₅₀ 0.007 µM	295
neamphamide A	cyclic depsipeptide	<i>Neamphius huxleyi</i>	cytoprotective	EC ₅₀ 0.028 µM	296
mirabamide A	cyclic depsipeptide	<i>Siliquariaspongia mirabilis</i>	fusion	IC ₅₀ 0.04 and 0.14 µM	297
celebeside A	cyclic depsipeptide	<i>S. mirabilis</i>	entry	IC ₅₀ 2.13 µM	298
theopapuamide B	cyclic depsipeptide	<i>S. mirabilis</i>	entry	IC ₅₀ 0.99 µM	298
microspinosamide	cyclic depsipeptide	<i>Stidonops microspinososa</i>	cytopathic effect	HIV-1 EC ₅₀ 0.12 µM	299
homophymine A	cyclic depsipeptide	<i>Homophymia</i> sps.	cytoprotective effect	IC ₅₀ 0.075 µM	300
dragmacidin F	alkaloid	<i>Halicortex</i> genus	syncytia formation	EC ₅₀ 0.9 µM	301
manzamine A	alkaloid	<i>Haliclona</i> sps.	unknown	EC ₅₀ 4.2 µM	304 and 306
manadomanzamines A and B	alkaloids	<i>Acanthostrongylophora</i> sps.	unknown	EC ₅₀ 11.5 and 27.0 µM	307
xestomanzamine A	alkaloid	<i>Acanthostrongylophora</i> sps.	unknown	EC ₅₀ 40.5 µM	307
batzelladine C	alkaloid	<i>Batzella</i> and <i>Monanchora</i> genera	gp120-CD4 interaction	EC ₅₀ 7.7 µM	309
crambescidin 800	alkaloid	<i>Batzella</i> and <i>Monanchora</i> genera	fusion	EC ₅₀ 7.7 µM	309
ptilomycalin A	alkaloid	<i>Monanchora unguifera</i>	unknown	EC ₅₀ 0.011 µM	309
isoaptamine	alkaloid	<i>Aptos aptos</i>	unknown	EC ₅₀ 0.6 µM	310
aaptamine	alkaloid	<i>Aptos aptos</i>	unknown	EC ₅₀ 1.3 µM	310

compound	type	source	cellular target	activity	ref
petrosin	bisquinolizidine alkaloid	<i>Petrosia similis</i>	replication and reverse transcriptase	IC ₅₀ 41.3 and 10.6 μ M	311
petrosin A	bisquinolizidine alkaloid	<i>Petrosia similis</i>	replication and reverse transcriptase	IC ₅₀ 53 and 14.8 μ M	311
cyanthiwiggin B	diterpene	<i>Epipolasis reisiwigi</i>	unknown	EC ₅₀ 42.1 μ M	312
haplosamates A and B	sulfated sterols	<i>Xestospongia</i> sp.	integrase	HIV-1 IC ₅₀ 50 and 15 μ g/mL	313
clathsterol	sulfated sterol	<i>Clathria</i> sp.	reverse transcriptase	10 μ M	314
polyacetylenetriol	polymer	<i>Petrosia</i> sp.	reverse transcriptase	IC ₅₀ 0.95 μ M	315
dehydrofurodendrin	C22 furanoterpene	<i>Lendenfeldia</i>	reverse transcriptase	IC ₅₀ 3.2–5.6 μ M	316

Table 2

Summary of the Marine Organisms Possessing Antiviral Activity

compound	type	source	target	activity	ref
disorhabdins A and C	alkaloids	<i>Larunculia</i>	HCV	EC ₅₀ < 10 μ M	321 and 322
dihydrodisorhabin C	alkaloid	<i>Larunculia</i>	HCV	EC ₅₀ < 10 μ M	321 and 322
<i>L</i> -carrageenan	linear sulfated galactan	<i>Eucheuma deniculatum</i>	HPV capsid	unknown	323 and 324
A1 and A2	sulfated polysaccharides	<i>Cochlodinium polykrikoides</i>	influenza virus and RSV	unknown	325
calyceramide A–C	sulfated ceramides	<i>Discodermia calyx</i>	influenza neuraminidase	IC ₅₀ 0.4, 0.2, and 0.8 μ g/mL	326
weibersterols A and B	sulfated tetrahydroxy steroids	<i>Petrosia weinbergi</i>	influenza virus	unknown	326 and 327
stachyflin	terpenoid	<i>Stachybotrys</i>	influenza A virus	0.003 μ M	328, 329 and 330
ulvan polysaccharides	polysaccharides	green algae	influenza virus	unknown	335
MC26	fucose polysaccharide	brown seaweed	influenza virus	unknown	336
p-KG03	sulfated polysaccharide	<i>Gyrodinium impudicum</i>	influenza virus	unknown	341
fucoidan	sulfated (fucan) polysaccharide	<i>Cladosiphon okamuranus</i>	DENV	unknown	342 and 343
EPS-1 and EPS-2	exopolysaccharides	<i>Geobacillus thermodenitrificans</i> and <i>Bacillus licheniformis</i>	HSV	200 and 300 μ g/mL	348 and 349
A1	sulfated polysaccharide	<i>Cochlodinium polykrikoides</i>	HSV-1	unknown	325
fucoidan	sulfated (fucan) polysaccharide	<i>Fucus vesiculosus</i>	HSV-1 and HSV-2 replication	unknown	350 and 351
calcium spirulan	sulfated polysaccharide	<i>Arthrospira platensis</i>	HSV-1 and influenza	unknown	259
naviculan	sulfated polysaccharide	<i>Navicula directa</i>	HSV replication stages	IC ₅₀ 7–14 μ g/mL	253
halovirs A–E	peptides	<i>Scytidium</i>	HSV-1 and HSV-2	ED ₅₀ 1.1, 3.5, 2.2, 2.0, and 3.1 μ M	352
eudistomins	β -carboline alkaloids	<i>Eudistoma olivaceum</i>	HSV-1 and HSV-2	unknown	354
didemmins	cyclic depsipeptides	<i>Trididemnum</i>	HSV-1	unknown	355 and 356
μ - and <i>L</i> -carrageenan	linear sulfated galactans	<i>Gigartina skottsbergii</i>	HSV-1 and HSV-2	unknown	365
nostoflan	acidic polysaccharide	<i>Nostoc flagelliforme</i>	HSV-1	unknown	368
mycalamide A and B	tetrahydropyran trioxadecalins	<i>Mycale</i>	HSV-1	5 ng/disc	282
4-methylaaptamine	alkaloid	<i>Aaptos</i>	HSV-1	EC ₅₀ 2.4 μ M	282
dragmacidin F	bromoindole alkaloid	<i>Halicortex</i>	HSV-1	EC ₅₀ 96 μ M	282
hamigeran B	tricyclic benzo-fused hydrindane	<i>Hamigeran tarangaensis</i>	HSV	unknown	282