Antiviral Drugs

Virus and viral enfection

Viruses are small particles of genetic material (either DNA or RNA) that are surrounded by a protein coat. Some viruses also have a fatty "envelope" covering. They are incapable of reproducing on their own. Viruses depend on the organisms they infect (hosts) for their very survival. Viruses get a bad rap, but they also perform many important functions for humans, plants, animals, and the environment. For example, some viruses protect the host against other infections. Viruses also participate in the process of evolution by transferring genes among different species. In biomedical research, scientists use viruses to insert new genes into cells.

Viruses and bacteria are two types of potentially disease-causing (pathogenic) particles. Viruses are much smaller than bacteria and can't reproduce without the assistance of a host. Bacteria are capable of reproducing on their own. The symptoms of viral and bacterial illnesses are sometimes similar. A doctor can determine the underlying cause of an illness based on the patient's symptoms and other factors. Lab tests may help clarify whether an illness is due to a virus, bacteria, or other infectious agent or disease process.

A viral infection is a proliferation of a harmful virus inside the body. Viruses cannot reproduce without the assistance of a host. Viruses infect a host by introducing their genetic material into the cells and hijacking the cell's internal machinery to make more virus particles. With an active viral infection, a virus makes copies of itself and bursts the host cell (killing it) to set the newly-formed virus particles free. In other cases, virus particles “bud” off the host cell over a period of time before killing the host cell. Either way, new virus particles are then free to infect other cells. Symptoms of the viral illness occur as a result of cell damage, tissue destruction, and the associated immune response.

Certain viruses -- like the ones that cause chickenpox and cold sores -- may be **inactive** or “latent” after the initial infection. For example, you may have a cold sore that erupts and then heals. The cold sore virus remains in your cells in a dormant state. At a later date, a trigger, such as stress, sunlight, or something else, may reactivate the virus and lead to new

symptoms. The virus makes more copies of itself, releases new virus particles, and kills more host cells.

Contagiousness refers to the ability of a virus to be transmitted from one person (or host) to another. Viral infections are contagious for varying periods of time depending on the virus. An incubation period refers to the time between exposure to a virus (or other pathogen) and the emergence of symptoms. The contagious period of a virus is not necessarily the same as the incubation period.

Viruses can be transmitted in a variety of ways. Some viruses can spread through touch, saliva, or even the air. Other viruses can be transmitted through sexual contact or by sharing contaminated needles. Insects including ticks and mosquitoes can act as "vectors," transmitting a virus from one host to another. Contaminated food and water are other potential sources of viral infection.

Viruses and Cancer

Viruses insert themselves into host cell DNA in order to make more virus particles. Cancer is a disease that occurs as the result of mutations or alterations to DNA. Because viruses affect the DNA of host cells, viruses are known to contribute to several different types of cancer. Viruses known to increase the risk of cancer include:

- Epstein-Barr virus (EBV) for nasopharyngeal cancer, Burkitt lymphoma, Hodgkin's lymphoma, and stomach cancer
- Hepatitis B and hepatitis C for liver cancer
- Human immunodeficiency virus (HIV) for Kaposi sarcoma, invasive cervical cancer, lymphomas, and other cancers
- Human T-lymphotrophic virus-1 (HTLV-1) for T-cell leukemia/lymphoma (ATL)
- Human papilloma virus (HPV) for cervical cancer
- Merkel cell polyomavirus (MCV) for a rare skin cancer called Merkel cell carcinoma

Prevention

Vaccines can reduce the risk of acquiring some viral illnesses. Vaccines are available to help protect against the flu, hepatitis A, hepatitis B, chickenpox, herpes zoster (shingles), cancer-causing strains of human papillomavirus (HPV), measles/mumps/rubella (MMR), polio, rabies, rotavirus, and other viruses.

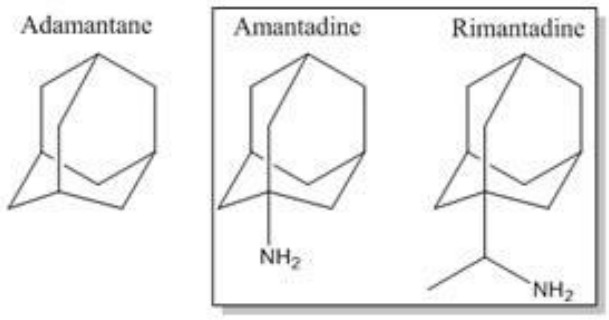
Vaccines vary in effectiveness and in the number of doses required to confer protection. Some vaccines require booster shots to maintain immunity.

Types of Antiviral agents

1. **Adamantane antivirals**
2. **Chemokine receptor antagonist**
3. **Miscellaneous antivirals**
4. **Neuraminidase inhibitors**
5. **NNRTIs**
6. **NS5A inhibitors**
7. **Nucleoside reverse transcriptase inhibitors (NRTIs)**
8. **Protease inhibitors**
9. **Purine nucleosides**
10. **Antiviral interferons**
11. **Antiviral combinations**

1. Adamantane antivirals

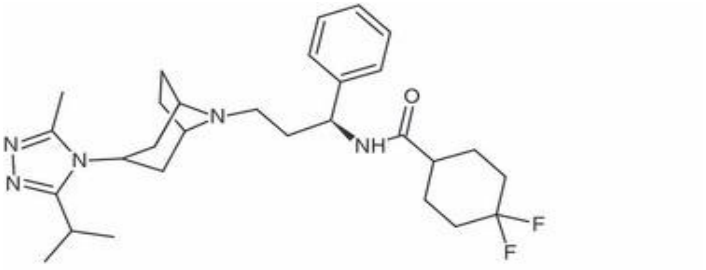
Adamantane antivirals are only active against **influenza A** virus, an RNA virus, but has no action against **influenza** B virus. A viral membrane protein, M2, functions as an ion channel at two stages of the viral replication within the host cell. These stages are the fusion of viral membrane and endosome membrane, and the assembly and release of new virions. Adamantane antivirals block this ion channel.



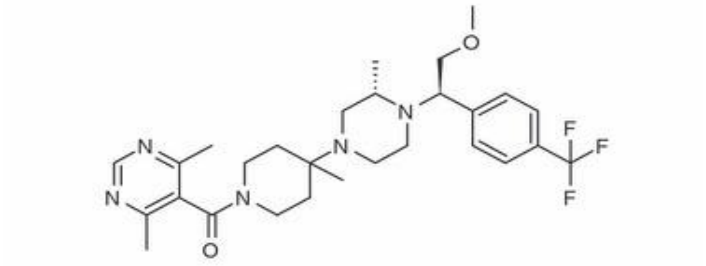
2. Chemokine receptor antagonist

Chemokine receptor antagonists inhibit the entry of human immunodeficiency virus (HIV) into the host cell. Two chemokine receptors, CXCR4 and CCR5, are necessary for the virus to enter the cell, so by inhibiting these chemokine receptors the disease can be slowed.

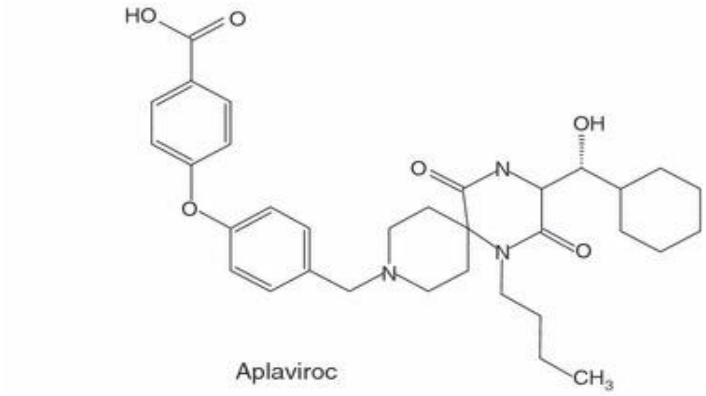
CCR5 (chemokine receptor 5) inhibitors are a new class of antiretroviral drug used in the treatment of HIV. They are designed to prevent HIV infection of CD4 T-cells by blocking the CCR5. When the CCR5 receptor is unavailable, 'R5-tropic' HIV (the variant of the virus that is common in earlier HIV infection) cannot engage with a CD4 T-cell to infect the cell.



Maraviroc



Vicriviroc



Aplaviroc

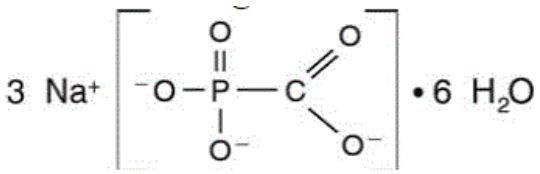
3. Miscellaneous antivirals

Antiviral agents are used to inhibit production of viruses that cause disease. Most antiviral agents are only effective while the virus is replicating.

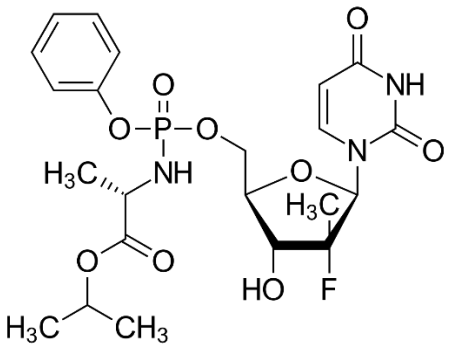
It is difficult to find medicines that are selective for the virus as viruses share most of the metabolic processes of the host cell. However, some enzymes are only present in viruses and these are potential targets for antiviral drugs.

Agents that inhibit the transcription of the viral genome are DNA polymerase inhibitors and reverse transcriptase inhibitors. Protease inhibitors inhibit the post-translational events. Other antiviral agents inhibit the virus from attaching to or penetrating the host cell.

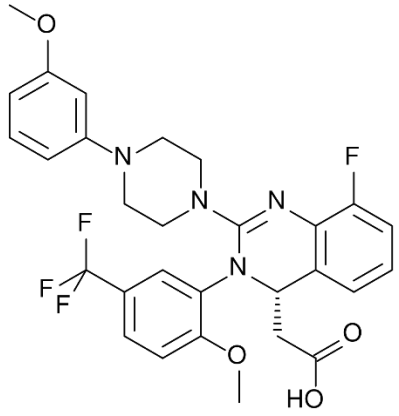
Immunomodulators induce production of host cell enzymes, which stop viral reproduction. Integrase strand transfer inhibitors prevent integration of the viral DNA into the host DNA by inhibiting the viral enzyme integrase. Neuraminidase inhibitors block viral enzymes and inhibit reproduction of the viruses.



Foscavir



Sobosfovir



Letermovir

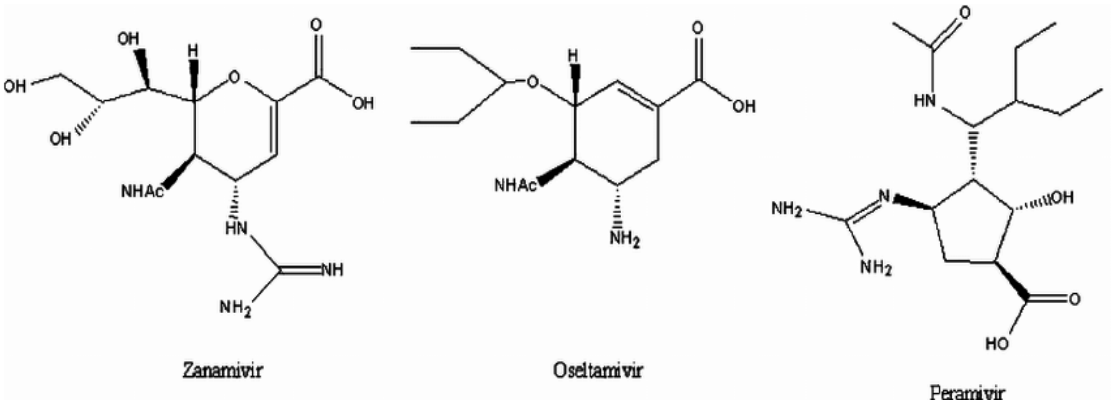
4. Neuraminidase inhibitors

Neuraminidase inhibitors are drugs that block the function of the viral neuraminidase protein. By blocking this protein enzyme it stops the release of viruses from the infected host

cell and prevents new host cells from being infected. These antiviral agents inhibit all subtypes of neuraminidase enzymes, therefore are effective against **influenza** viruses A and B.

Neuraminidase, also called **sialidase**, any of a group of enzymes that cleave sialic acid, a carbohydrate occurring on the surfaces of cells in humans and other animals and in plants and microorganisms. these enzymes are known to occur as antigens (foreign proteins that stimulate the production of antibodies) on the surfaces of certain viruses, namely those of the families Orthomyxoviridae and Paramyxoviridae, as well as on the surfaces of some infectious bacteria and other microorganisms.

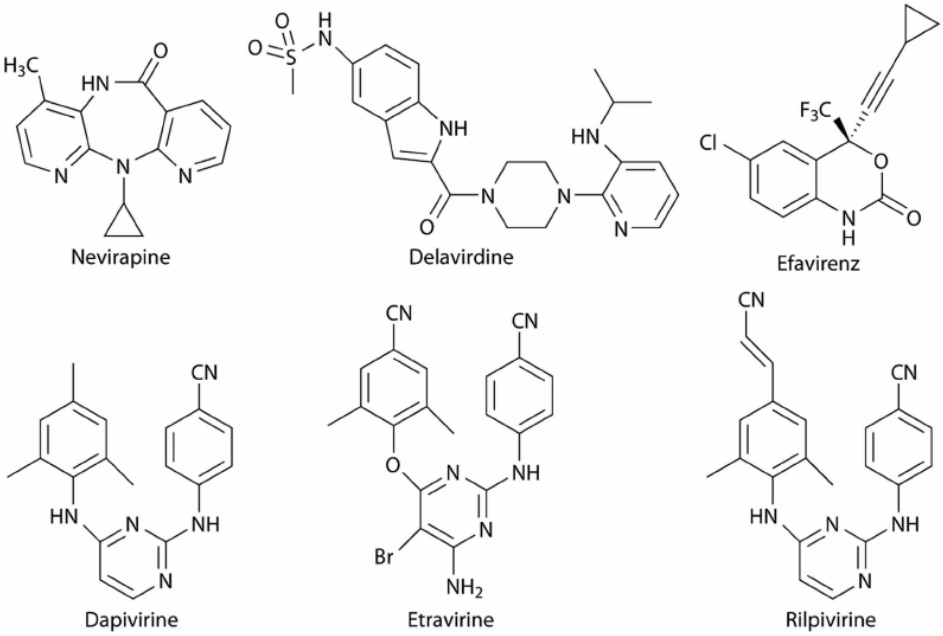
Antigenic neuraminidases occurring on influenza viruses have been well characterized. Following host-cell infection, these viruses manipulate the cell machinery to replicate themselves. When the replicated viruses bud from the host cells, they remain attached to the host-cell surface by binding between hemagglutinin (another antigenic protein on the surface of the virus) and sialic acid. Neuraminidase cleaves the sialic acid molecule, thereby freeing the virus to infect other cells in the host organism. Antibodies against neuraminidase that are generated by the host's immune system following infection bind to a portion of the neuraminidase antigen known as an epitope. This binding targets the virus particles for immune destruction. The genes encoding the neuraminidases of influenza viruses are highly susceptible to genetic mutations that modify the epitopes of the antigen. The emergence of a new neuraminidase epitope enables an influenza virus to escape immune recognition, at least until new, matching antibodies have been generated against it. Genetic alterations affecting neuraminidase may arise through antigenic drift or antigenic shift—processes that can give rise to influenza viruses capable of causing epidemics or pandemics. There are 9 different forms of neuraminidase, designated N1 through N9, that are associated with influenza type A viruses. Together with various forms of hemagglutinin, neuraminidase is used to distinguish between subtypes of influenza A viruses (e.g., H1N1, H5N1).



5. NNRTIs Non-Nucleoside Reverse Transcriptase Inhibitors

Antiretroviral (ARV) HIV drug class. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) bind to and block HIV reverse transcriptase (an HIV enzyme). HIV uses reverse transcriptase to convert its RNA into DNA (reverse transcription). Blocking reverse transcriptase and reverse transcription prevents HIV from replicating.

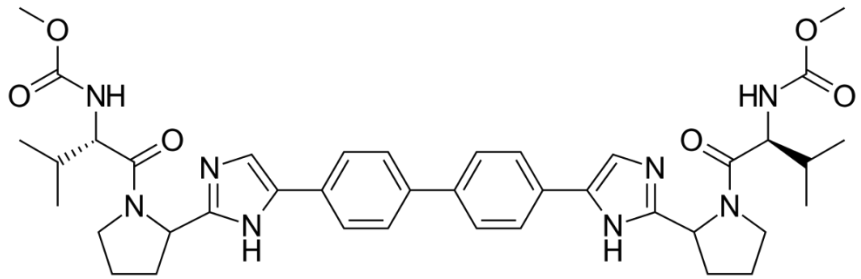
On the whole, NNRTIs are very effective for reducing HIV replication when used in combination with NRTIs; however, they are not without their side effects. The main NNRTIs recommended by the WHO in guidelines for treating HIV are efavirenz and nevirapine, as well as the newer drugs etravirine and rilpivirine. These drugs are all generally used in combination with NRTIs.



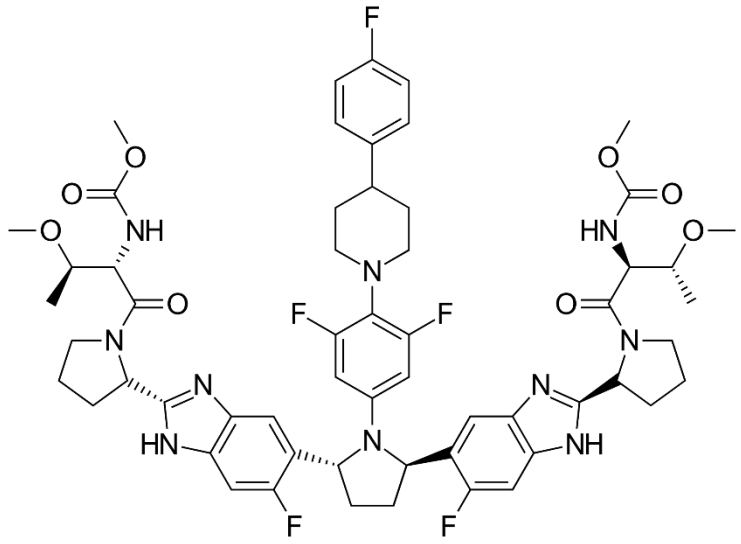
6. NS5A inhibitors

Nonstructural protein 5A (**NS5A**) is a zinc-binding and proline-rich hydrophilic phosphoprotein that plays a key role in Hepatitis C virus RNA replication. It appears to be a dimeric form without trans-membrane helices. The NS5A protein has a substantial role in viral replication, packaging, assembly and complex interactions with cellular functions. Therefore NS5A inhibitors treat viral infections by reducing the ability of the virus to replicate. NS5A inhibitors may be used to treat specific HCV genotypes and are often used in conjunction with other antiviral agents.

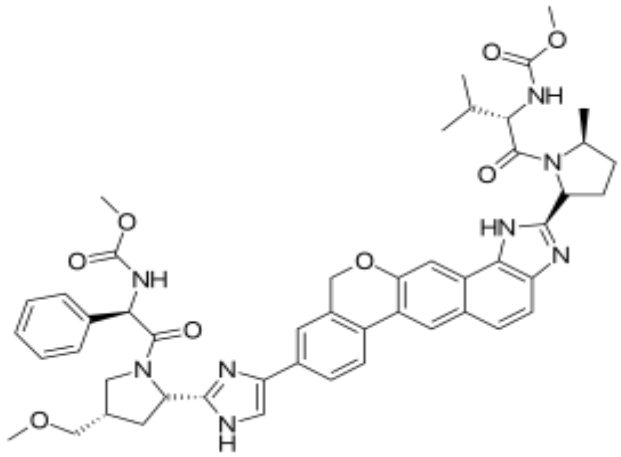
Nonstructural protein 5A (**NS5A**) **inhibitors** belong to a class of antiviral drugs called protease inhibitors. They are direct acting antiviral agents (DAAs) that target viral proteins, and their development was a culmination of increased understanding of the viral life cycle.



Daclatasvir



Pibrentasvir



Velpatasvir

7. Nucleoside reverse transcriptase inhibitors (NRTIs)

The first group of antiretroviral drugs is the nucleoside reverse transcriptase (pronounced "trans-krip-tase") inhibitors (NRTIs).

NRTIs were the first type of drug available to treat HIV. They remain effective, powerful, and important medications for treating HIV when combined with other drugs. They are better known as nucleoside analogues or "nukes."

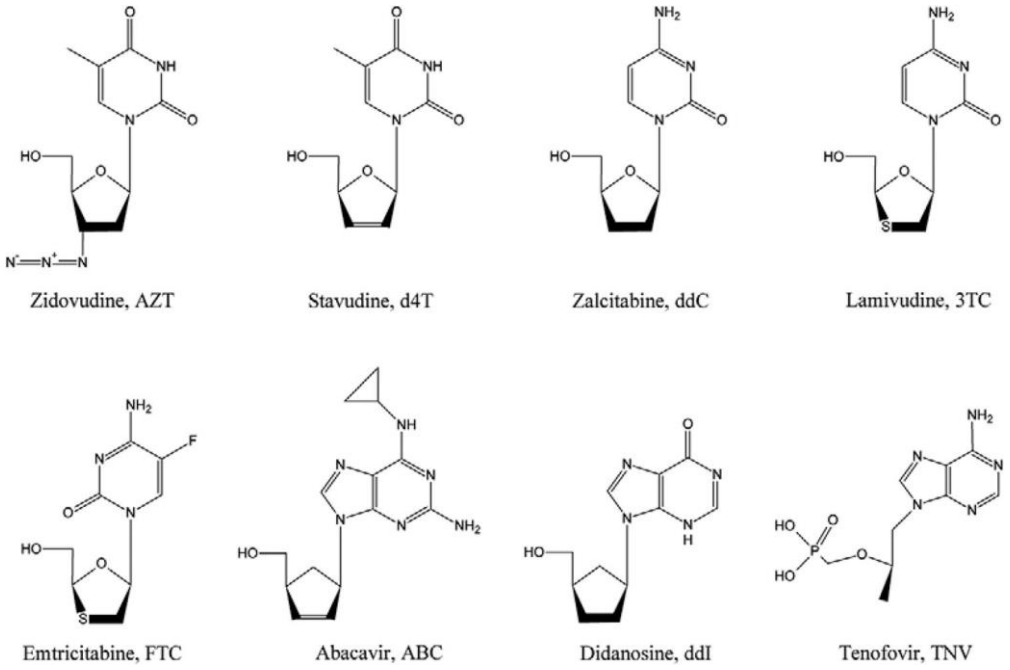
When the HIV virus enters a healthy cell, it attempts to make copies of itself. It does this by using an enzyme called reverse transcriptase. The NRTIs work because they block that enzyme. Without reverse transcriptase, HIV can't make new virus copies of itself.

When HIV infects a CD4 cell in a person's body, it copies its own genetic code into the cell's DNA. In this way, the cell is then "programmed" to create new copies of HIV. HIV's genetic material is in the form of RNA. In order for it to infect CD4 cells, it must first convert its RNA into DNA. HIV's reverse transcriptase enzyme is needed to perform this process.

NRTIs, sometimes called "nucleoside analogues" or "nukes," contain faulty versions of the building blocks (nucleotides) used by reverse transcriptase to convert RNA to DNA. When reverse transcriptase uses these faulty building blocks, the new DNA cannot be built correctly. In turn, HIV's genetic material cannot be incorporated into the healthy genetic material of the cell and prevents the cell from producing new virus.

While nucleotide analogues (Viread is the only nucleotide analogue approved at this time) are technically different than nucleoside analogues, they act very much the same way. In

order for nucleoside analogues to work, they must undergo chemical changes (phosphorylation) to become active in the body. Nucleotide analogues bypass this step, given that they are already chemically activated.



8. **Protease inhibitors**

Protease inhibitors are synthetic drugs that inhibit the action of **HIV**-1 protease, an enzyme that cleaves two precursor proteins into smaller fragments. These fragments are needed for viral growth, infectivity and replication. Protease inhibitors bind to the active site of the protease enzyme and prevent the maturation of the newly produced virions so that they remain non-infectious.

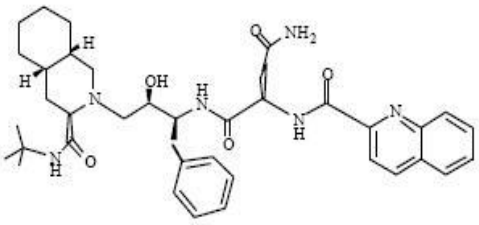
Protease inhibitors are used in the treatment of human immunodeficiency virus (**HIV infection**) and **acquired immune deficiency syndrome** (AIDS).

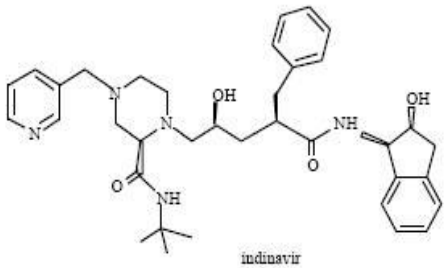
Protease inhibitor, class of antiretroviral drugs used to treat HIV retrovirus infection in AIDSpatients. Protease inhibitors are characterized by their ability to block activation of an HIV enzyme called protease. The protease enzyme is involved in the synthesis of new viral particles, which can lead to the spread of HIV to uninfected cells. However, in the

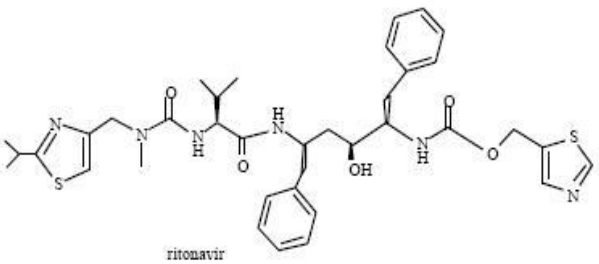
presence of a protease inhibitor HIV produces only noninfectious viral particles. Examples of protease inhibitors include ritonavir, saquinavir, and indinavir.

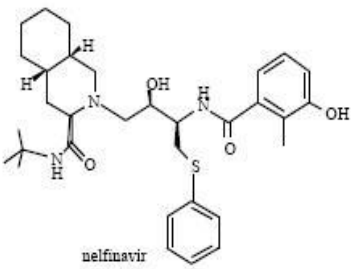
Single-agent therapy with a protease inhibitor can result in the selection of drug-resistant HIV. Therefore, protease inhibitors are generally used in combination with other antiretroviral agents, especially agents that act at different points in the life cycle of HIV. For example, the use of a protease inhibitor in combination with a reverse transcriptase inhibitor, which blocks the conversion of retroviral RNA into DNA, suppresses HIV replication better than either drug alone. The most effective combination therapy used to suppress the emergence of resistant virus is highly active antiretroviral therapy (HAART), which combines three or more reverse transcriptase and protease inhibitors.

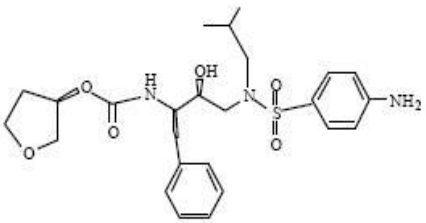
The principal adverse effects of protease inhibitors are nausea and diarrhea. Long-term use can bring on a syndrome known as lipodystrophy (wasting of peripheral fat, accumulation of central fat, increased levels of fat in the blood, and insulin resistance).

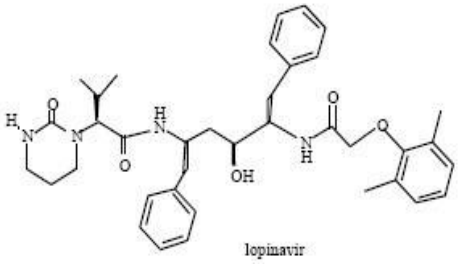

saquinavir


indinavir


ritonavir


nelfinavir


amprenavir

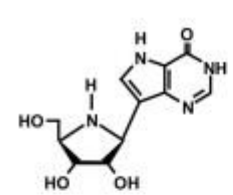

lopinavir

9. **Purine nucleosides**

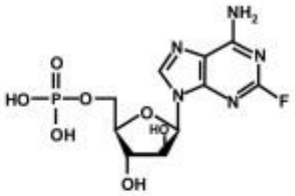
Purine nucleosides are antiviral agents that have selective activity against herpes simplex virus types 1 (**cold sores**) and 2 (genital herpes) and varicella zoster virus (chicken pox).

The purine nucleoside molecule is converted to a monophosphate by viral thymidine kinases. The monophosphate is then converted to diphosphate and then into a triphosphate form by cellular enzymes. The triphosphate form blocks the replication of viral DNA by inhibiting viral DNA polymerase and terminating the growing viral DNA chain.

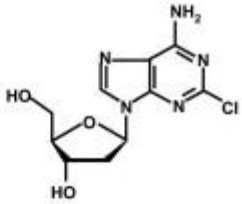
Purine nucleosides are more potent against the viral enzymes than the host enzymes.



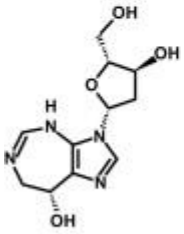
Forodesine



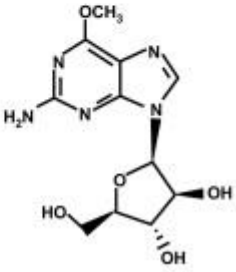
Fludarabine



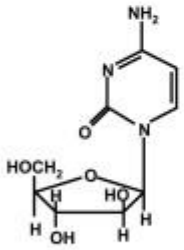
Cladribine



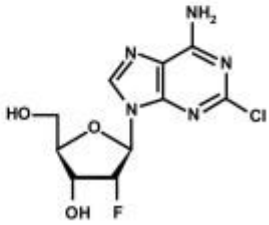
Pentostatin



Nelarabine



Cytarabine



Clofarabine

10. **Antiviral interferons**

Interferon is the name given to a group of proteins known primarily for their role in inhibiting viral infections and in stimulating the entire **immune system** to fight disease. Research has also shown that these proteins play numerous roles in regulating many kinds of cell functions. Interferons can promote or hinder the ability of some cells to differentiate, that is, to become specialized in their function. They can inhibit cell division, which is one reason why they hold promise for stopping cancer growth. Recent studies have also found that one

interferon may play an important role in the early biological processes of pregnancy. Although once thought to be a potential cure-all for a number of viral diseases and cancers, subsequent research has shown that interferons are much more limited in their potential. Still, several interferon proteins have been approved as therapies for diseases like chronic **hepatitis** , genital warts, multiple sclerosis, and several cancers.

Natural interferons are produced by lymphocytes as part of an immunological response to viral antigens. Synthetic interferons, made by recombinant DNA technology, are used as antiviral agents to treat infections such as hepatitis and **herpes zoster** virus.

Interferons induce the production of enzymes in the ribosomes of the host cells and inhibit the translation of viral mRNA into viral proteins, therefore stop viral reproduction.

11. **Antiviral combinations**

Antiviral combinations have more than one antiviral agent in the one pill or dose. Using a combination of antiviral agents reduces the risk of resistant virus strains from emerging.

Antiviral agents are used to inhibit production of viruses that cause disease. Most antiviral agents are only effective while the virus is replicating.

It is difficult to find medicines that are selective for the virus as viruses share most of the metabolic processes of the host cell. However, some enzymes are only present in viruses and these are potential targets for drugs.

Agents that inhibit the transcription of the viral genome are DNA polymerase inhibitors and reverse transcriptase inhibitors. Protease inhibitors inhibit the post-translational events. Other antiviral agents inhibit the virus from attaching to or penetrating the host cell. Immunomodulators induce production of host cell enzymes, which stop viral reproduction. Integrase strand transfer inhibitors prevent integration of the viral DNA into the host DNA by inhibiting the viral enzyme integrase. Neuraminidase inhibitors block viral enzymes and inhibit reproduction of the viruses.