1-Prevention and treatment of viral diseases

2-Antiviral Drugs

There are two aspects to the prevention and treatment of viral diseases:

1- Prevention: Vaccination

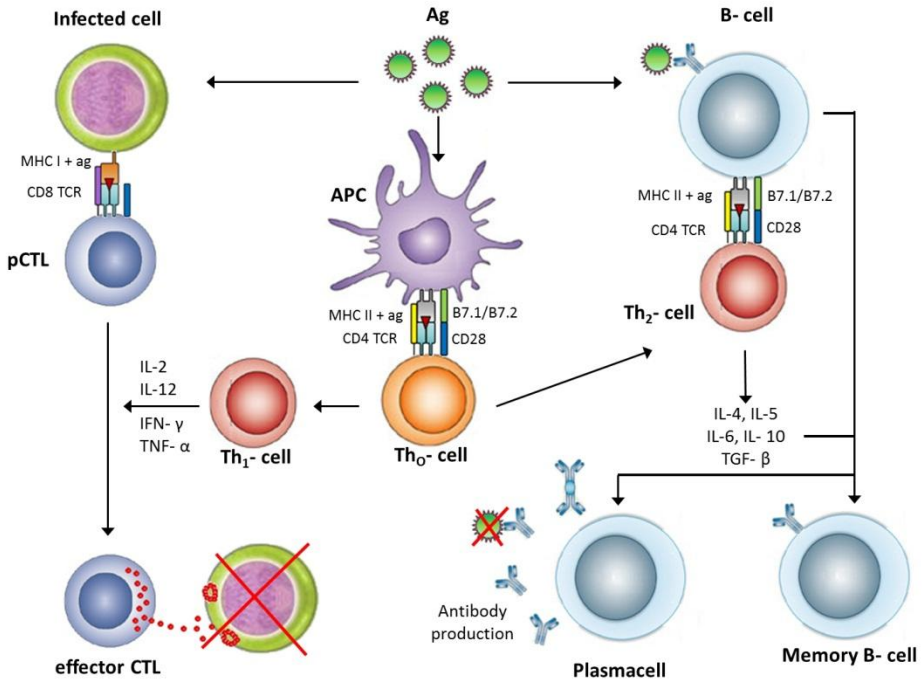
2- Treatment; Antiviral drug

Vaccination

Vaccines were used to prevent viral infections long before the discovery of the actual viruses. Their use has resulted in a dramatic decline in morbidity and mortality associated with viral infections such as NDV, Bovine herpes virus 1, sheep pox and rabies. Vaccines **are available to prevent viral infections of animals and human.**

The main idea

Vaccines contain a weak form of virus/microbe that is not pathogenic (not causing disease) **but elicit a secondary immune response that will eliminate the pathogen and stimulate the macrophages, which present the antigens to T and B cell.**



History

The term vaccine derives from Edward Jenner's 1796 use of cowpox (from vacca, cow) to immunize humans, providing them protection against smallpox.

Vaccine comes from the latin word "vacca" which refer to cow.

First vaccine (1796) **Edward Jenner inoculated milkmaids with cowpox confer protective immunity against smallpox.**

In 1796 Jenner took pus from the hand of milkmaid with cowpox, **inoculated an 8-year-old boy with it, and six weeks later variolated the boys arm with smallpox, afterwards observing that the boy did not catch smallpox.**

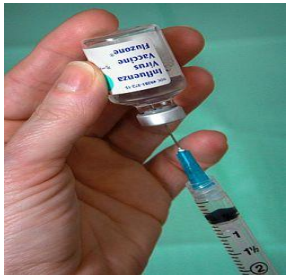
Louis pasture generalized Jenner idea by developing what he called **a rabies vaccine.**

First attenuated vaccine (1885): Louis pasture developed a vaccine to protect against rabies; **vaccine is made from viable virus with reduced virulence** (lower degree of pathogenicity).

Vaccines:

A vaccine is a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism, and is often made from weakened or killed forms of the microbe or its toxins. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters.

The vaccines are very effective on stable viruses, but they are also difficult to successfully deploy against rapidly **mutating viruses**, such as influenza (the vaccine for which is updated every year) and HIV antiviral drugs are particularly useful in these cases.



Types of vaccine:

1-Live(attenuated) vaccines
2- Inactivated vaccines
3- Combination vaccines
4- Subunit vaccines
5- DNA vaccines:

1-Live (attenuated) vaccines

Live, attenuated vaccines contain a version of the living virus that has been **artificially weakened in the lab(Consist of a live form of the virus that has been artificially weakened** (**in tissue culture like sheep pox vaccine** or **in chicken embryos like Newcastle virus** vaccine), so it **can't** cause disease. Because a live, attenuated vaccine is the closest thing to a **natural infection**, these vaccines are good "teachers" of the immune system.

The advantages:

Elicit good immune response, **inexpensive**, **and required few doses one or two.**

The disadvantage:

Reversion to virulent form is a high occurrence and **must be stored refrigerated to maintain viability**.

It is the nature of living things to change, or mutate, and the organisms used in live, attenuated vaccines are no different.

2- Inactivated vaccines

Method to production –exposure to denaturing agent (by using heat, radiation or chemicals) a virus is killed and is no longer infectious.

Results in **loss of infectivity without loss of antigenicity.**

The advantages

Stable and safe, no need refrigeration.

The disadvantages are the immunogenicity is **lowered** and multiple doses will be required.

Adjuvants, administrated simultaneously to enhance immune response.

Adjuvant: Certain substance when administered simultaneously with specific antigen will enhance the immune response to that antigen, such as aluminium salts, liposomes, complete and in complete freunds adjuvant.

3- Combination vaccines

The advantage is several vaccines are combined into one dose, like MMR(measles, mumps, rebella) Vaccines.

4- Subunit vaccines

Instead of the entire virus, subunit vaccines include only the **antigens that best stimulate the immune system.** In some cases, these vaccines use epitopes—the very specific parts of the antigen that antibodies or T cells recognize and bind to. Because subunit vaccines contain only the **essential antigens** and not all the other molecules that make up the virus, the chances of adverse reactions to the vaccine are lower.

The advantages:

The newest type; completely safe, except for rare adverse reactions. Unfortunately, they also tend to be the least effective.

The disadvantages:

(Relatively) poor antigenicity(specially short periods), vaccine delivery (carriers/ adjuvants needed).subunit included:

a-Synthetic vaccines

b- Recombinant vaccine

c- Virus vectors

a-Synthetic vaccines
b- Recombinant vaccine
c- Virus vectors

A- is a vaccine consisting mainly of **synthetic peptides**, **carbohydrates,** or antigens. They are usually considered to be safer than vaccines from bacterial cultures. Creating vaccines synthetically has the ability to increase the speed of production. This is especially important in the event **of a pandemic**.

B- Recombinant vaccines are created by utilizing bacteria or yeast to produce large quantities of a **single** viral or bacterial protein. This protein is then purified and injected into the patient, and the patient's immune system makes antibodies to the disease agent's protein, protecting the patient from natural disease.

C- Virus vectors: Are a tool commonly used by molecular biologists to deliver genetic material into cells. This process can be performed inside a living organism (*in vivo*) or in cell culture (*in vitro*). Viruses have evolved specialized molecular mechanisms to efficiently transport their genomes inside the cells they infect.

5- DNA vaccines:

DNA vaccines are present experimental, but hold promise for future therapy since they will evoke both humoral and cell-mediated immunity, without the dangers associated with live virus vaccines.

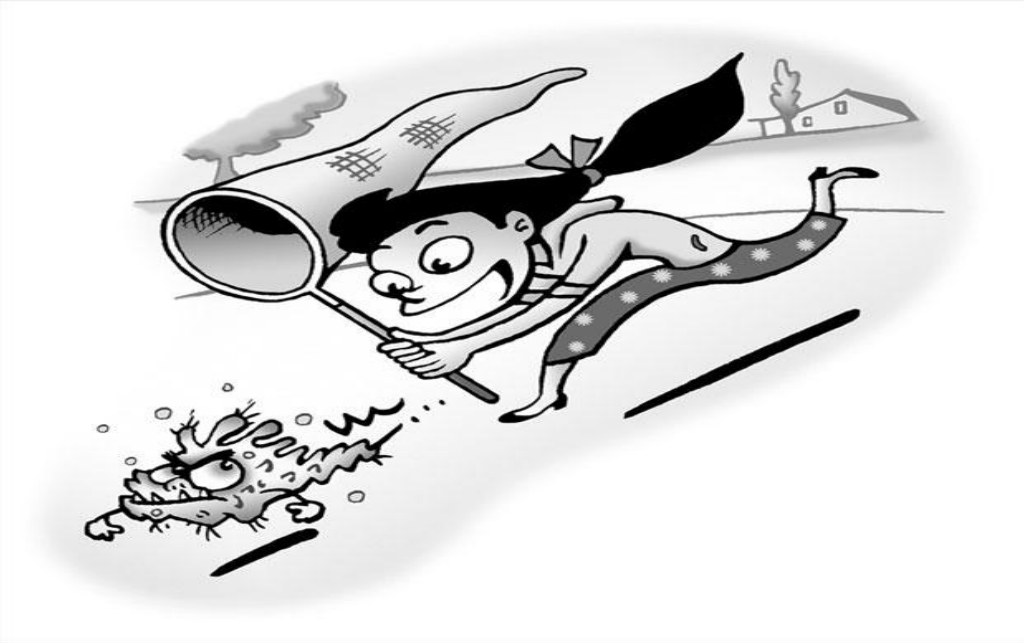
DNA vaccines take immunization to a new technological level.

Those genes would be introduced into the body, taken up some of the cells those host cells **would then produce the antigens molecules**, allowing them to be displayed and stimulating the immune system.

(Researchers have found that when the genes for a microbe's antigens are introduced into the body, some cells will take up that DNA. The DNA then instructs those cells to make the antigen molecules. The cells secrete the antigens and display them on their surfaces. In other words, the body's own cells **become vaccine-making factories**, creating the antigens necessary to stimulate the immune system).

Antiviral Drugs

Are classes of medication use specifically for treating viral infections. Like antibiotics for bacteria, specific antiviral are used for specific viruses. **Unlike most antibiotics antiviral drugs do not destroy their target pathogen; instead that they inhibit their development.**



Antiviral drugs are one class of antimicrobials, a larger group which also includes antibiotic (also termed antibacterial), antifungal and antiparasitic drugs, **or antiviral drugs** based on monoclonal antibodies.

Most antivirals are considered relatively **harmless to the host**, and therefore can be used to treat infections.

They should be **distinguished** from viricides, which are not medication but **deactivate or destroy virus particles**, either inside or outside the body.

Antivirals also can be **found in essential oils of some herbs**, such as eucalyptus oil and its constituents.

Medical uses

Selective toxicity is a problem- the antiviral drug must **be toxic to the virus without harming the host**. This is a problem since viruses be dependent on their host cells for most of the components used in the expression and replication of their genomes.

Designing safe and effective antiviral drugs is difficult, because viruses use the **host cells to replicate**. This makes it difficult to find targets for the drug that would interfere with the virus without also harming the host organism's cells. Moreover, the major difficulty in developing vaccines and anti viral drugs is due to viral variation.

Most of the antiviral drug now available is designed to help deal with **HIV, Herpes viruses, the hepatitis B and C viruses**, which can cause liver cancer, and influenza A and B viruses.

Researchers are working to extend the range of antivirals to other families of pathogens.

Virus life cycle

Viruses consist of a genome and sometimes a few enzymes stored in a capsule made of protein (called a capsid), and sometimes covered with a lipid layer (sometimes called an 'envelope'). Viruses cannot reproduce on their own, and instead propagate by subjugating a host cell to produce copies of themselves, thus producing the next generation. Researchers working for developing antiviral have tried to **attack viruses at every stage of their life cycles.**

Viral life cycles vary in their precise details depending on the species of virus, but they all share a general pattern;

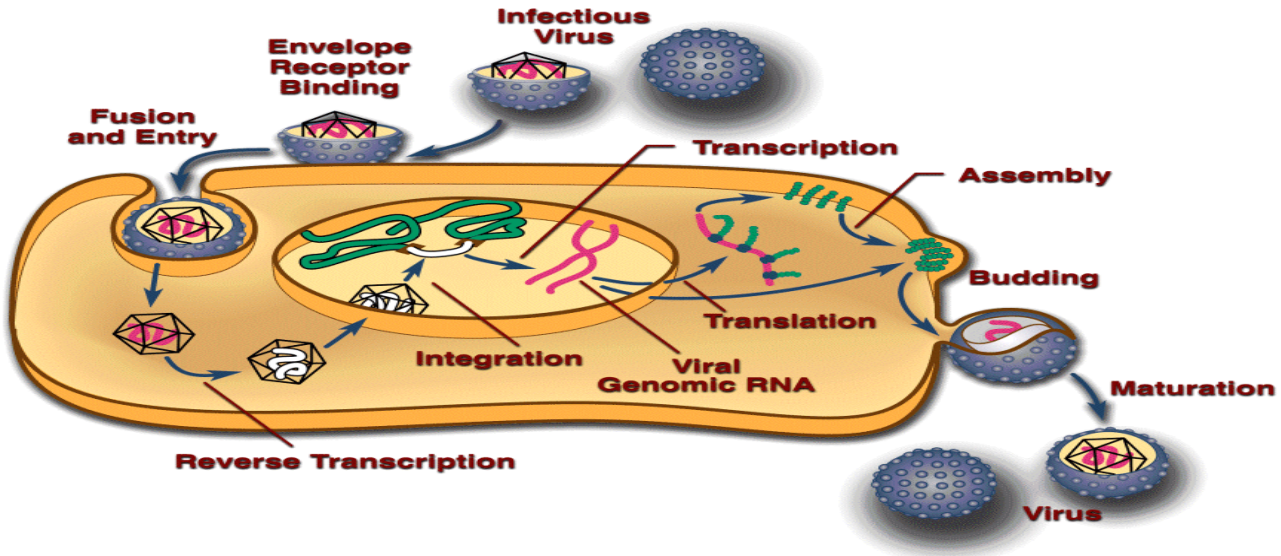
1-Attachment to a host cell

2-Pentration of viral genes and possibly into host cell.

3-Replication of viral components using-cell machinery.

4-Assembly of viral components into complete viral particles.

5-Release of viral particles to infect new host cells.



Before cell entry

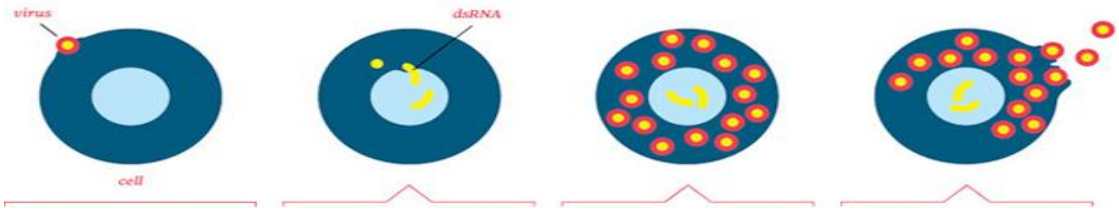
One anti-viral strategy is to interfere with the ability of the virus to infiltrate a target cell. The virus must go through a sequence of steps to do this, beginning with **binding to a specific receptor molecule on the surface of the host cell** and ending with the virus uncoating inside the cell and releasing its contents.

Viruses that have a lipid envelope must also fuse their envelope with the target cell, or with a vesicle that transports them into the cell, before they can uncoated.

This stage of viral replication can be inhabited in two ways:

1- Using agents which mimic the **virus-associated protein** (VAP) and bind to the cell receptors.

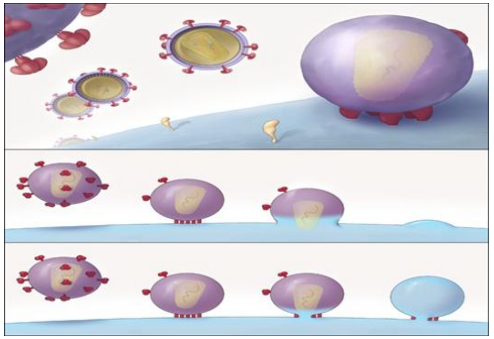
2- Using agents which mimic the cellular receptor and bind to the VAP.This strategy of designing drugs can be **very expensive**.



Virus Entry inhibitor

A very early stage of viral infection is **viral entry**, when the virus attaches to and enters the host cell. A number of "entry-inhibiting" or "entry-blocking" drugs are being developed to **fight HIV**.

HIV most heavily targets the immune system's **white blood cells** known as "helper T cells", and identifies these target cells through T-cell surface receptors designated "CD4" and "CCR5". Attempts to interfere with the binding of HIV with the CD4 receptor have failed to stop HIV from infecting helper T cells, but research continues on trying to interfere with the binding of **HIV to the CCR5** receptor in hopes that it will be more effective.



HIV infects a cell through fusion with the cell membrane, which requires **two different cellular molecular participants, CD4 and a chemokine receptor**.

Approaches to blocking this virus/cell fusion have shown some promise in preventing entry of the virus into a cell. At least one of theses entry **inhibitors—a biomimetic peptide marketed under the brand name Fuzeon**—has received FDA approval and has been in use for some time. Potentially, one of the benefits from the use of an effective entry-blocking or entry-inhibiting agent is that it potentially may **not only prevent the spread of the virus within an infected individua**l but also the **spread from an infected to an uninfected individual.**

One possible advantage of the therapeutic approach of blocking viral entry (as opposed to the currently dominant approach of viral enzyme inhibition) is that it may prove more difficult for the **virus to develop resistance to this therapy** than for the virus to mutate or evolve its enzymatic protocols.

HIV entry

Proteins

There are several key proteins involved in the HIV entry process.

-**CD4**, a **protein receptor found on the surface of helper T cells** in the human immune system, also called CD4+ T cells.

-CCR5, a **second receptor found on the surface of CD4+** cells and **macrophages,** called a **chemokine co-receptor.**

CXCR4, **another chemokine co-receptor found on CD4+ cells**

-**gp120**, a **protein on HIV surface that binds to the CD4** receptor

gp41, a HIV protein, closely associated with gp120, that penetrates the cell membrane.

Binding, fusion, entry sequence:

HIV entry into a human cell requires the following steps in sequence:

1-The **binding** of HIV surface protein gp120 to the CD4 receptor.

2-A conformational change in gp120, which both increases its affinity for a co-receptor and exposes gp41.

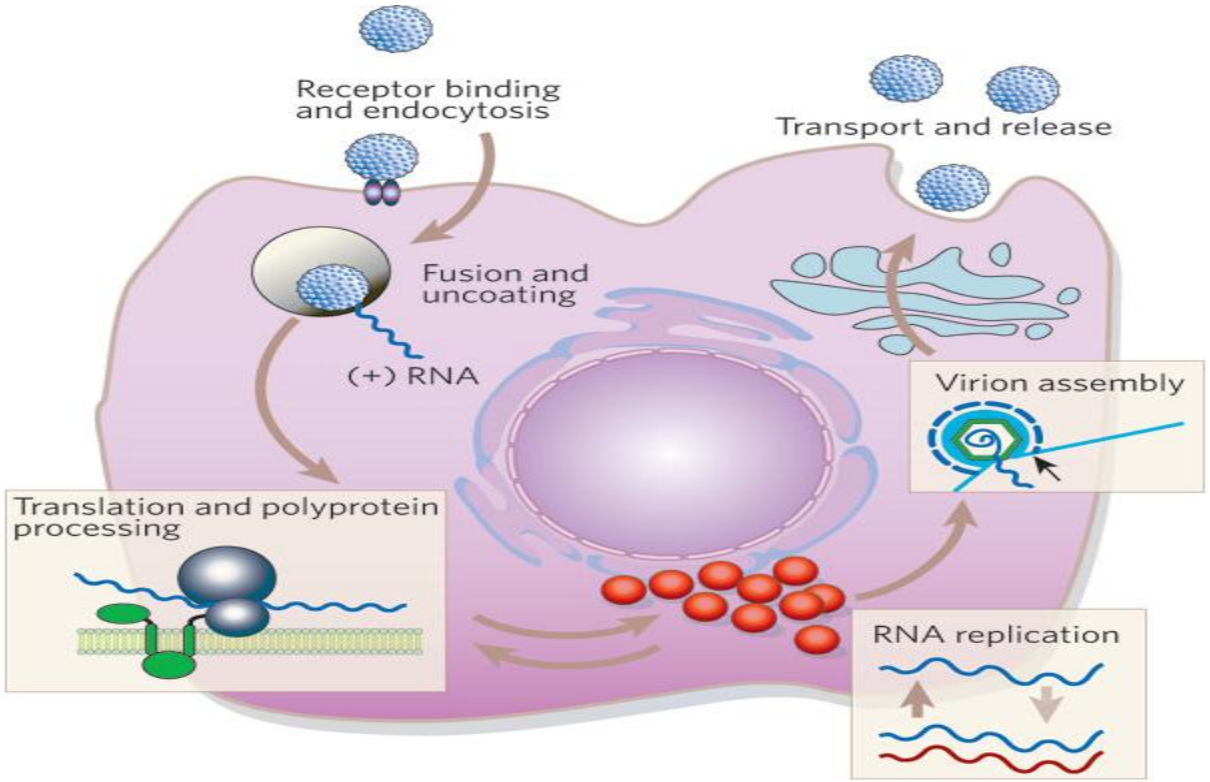
3-The binding of gp120 to a co-receptor either CCR5 or CXCR4

4-The penetration of the cell membrane by gp41, which approximates the membrane of HIV and the T cell and promotes their **fusion.**

5-The **entry** of the viral core into the cell.

Uncoating inhibitors

Inhibitors of uncoating have also been investigated **Amantadine and Rimantadine**, have been introduced to combat influenza. These agents act on penetration/uncoating



Pleconaril works against rhinoviruses, which cause the common cold, by **blocking a pocket on the surface of the virus** that controls the uncoating process. This pocket is similar in most strains of rhinoviruses and enteroviruses, which can cause **diarrhea, meningitis, conjunctivitis, and encephalitis.**

The search for a vaccine against rhinoviruses may have seemed quixotic, because there are more than **100 varieties circulating** around the world. But the immune system can handle the challenge. Rhinoviruses are the most common cause of the common cold; other viruses such as **respiratory syncytial virus**, **parainfluenza virus and adenoviruses** can cause them too. Rhinoviruses also exacerbate asthma attacks. Although rhinoviruses come in many varieties, they do not **drift** to the same degree that influenza viruses do. A mixture of 50 inactivated rhinovirus types should be able to stimulate neutralizing antibodies against all of them to some degree.

During Viral Synthesis: A second approach is to target the processes that synthesize virus components after a virus invades a cell.

Reverse transcription

Deactivate the enzymes that synthesize the RNA. This approach is more commonly associated with inhibition of reverse transcriptase (RNA to DNA) than with normal transcriptase (DNA to RNA). The first successful antiviral (**acyclovir**) is a nucleoside analogue, and is **effective against herpes virus infections**. The first antiviral drug to approve for treating HIV, **Zidovudine** (AZT).

(also called ZDV)is also a nucleoside analogue.

An improved knowledge of the action of reverse transcriptase has led to better nucleoside analogues to treat HIV infections. One of these drugs, **Iamivudine**, has been approved to **treat hepatitis B**, which **use reverse transcriptase as part of its replication process.** Researchers have gone further and developed inhibitors that do not look like nucleosides, but can still block reverse transcriptase.

Protease inhibitors

Block specific proteolytic cleavage of viral proteins. The inhibitors mimic the structure of the amino acids near the cleavage site and so they compete, with the normal substrate, for virus components after virus invades a cell.

For example:

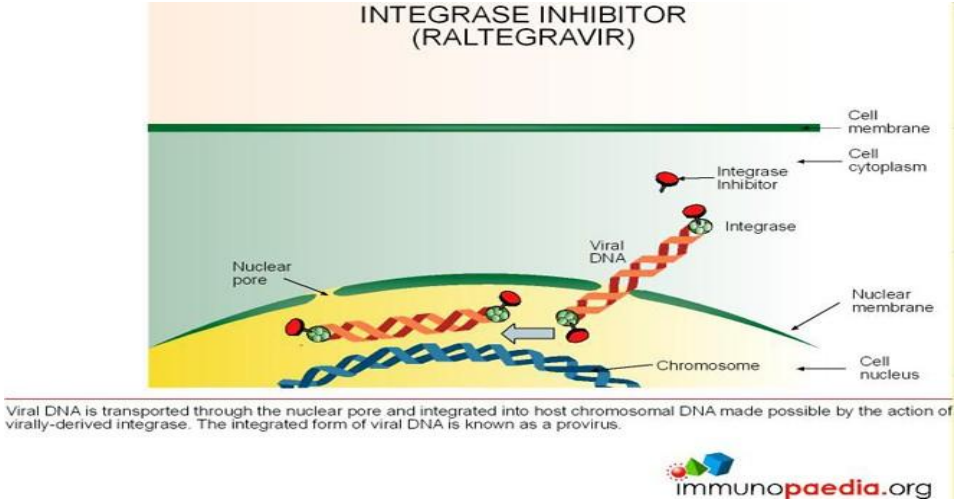
When HIV infects a CD4 cell in a person's body, it copies its own genetic code into the cell's DNA. The CD4 cell is then "programmed" to make new HIV genetic material and HIV proteins. The proteins must be cut up by the HIV protease—a protein-cutting enzyme—to make functional new HIV particles. **(PIs)** block the protease enzyme and prevent the cell from producing new viruses. It is recommended that they be used in combination with at least two other HIV drugs to treat HIV infection.

Integrase

Another target is integrase, which splices the synthesized DNA into the host cell genome.

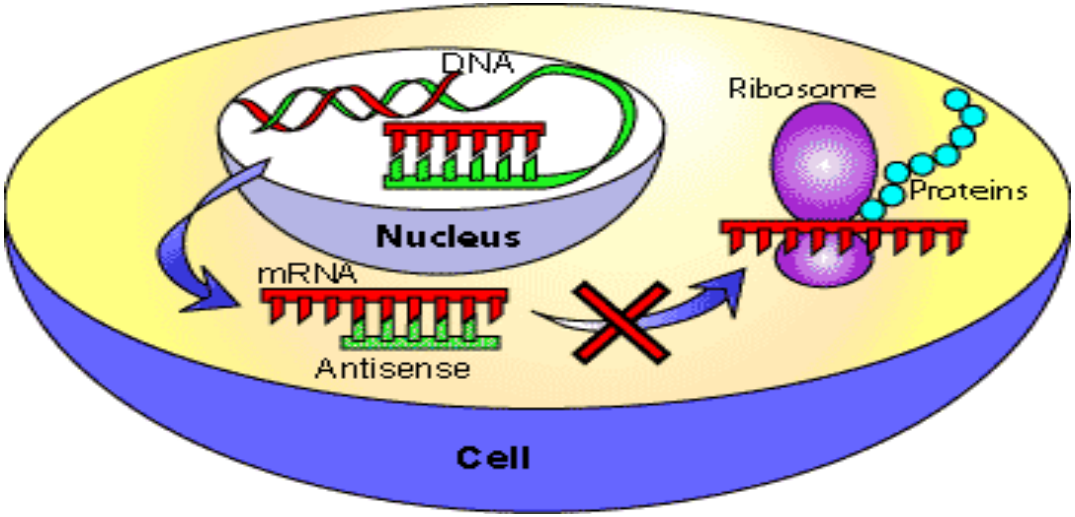
Transcription

Once virus genome become operational in a host cell, it then generates messenger RNA (mRNA) molecules that direct the synthesis of viral proteins. Production of mRNA is initiated by **proteins known as transcription factors**. **Several antivirals** are now being designed to block attachment of transcription factors to viral DNA.



Translation/antisense

Antisense molecules are segments of DNA or RNA that are designed as complementary molecule to critical sections of viral genomes, and binding of these **antisense segments** to these target section blocks the operation of those genomes. **A phosphrothioate antisense drug named (Fomivirsen)** has been introduced, used to treat opportunistic eye infection caused by **retroviruses.**



Protease inhibitors

Some viruses include an enzyme known as a protease that acts **viral protein chains** apart so they can be assembled into their final configuration. Protease inhibitions became available in the 1990s and have proven effective, improved protease inhibitors are now in development.

Protease inhibitors have also be seen in nature. A protease inhibitor was isolated from the mushroom.

Assembly

Rifampicin acts at the assembly phase.

Release phase

The final stage in the life cycle of a virus is the release of completed viruses from the host cell, and this step has also been targeted by antiviral drug developers.

Two drugs named **zanamivir** (Relenza) and **oseltamivir** (Tamiflu) that have been recently introduced to treat influenza prevent the release of viral particles **by blocking a molecule named neuraminidase that is found on the surface** of flu viruses, and also seems to be constant across a wide range of flu strains.

Immune system stimulation

A second category of tactics for fighting viruses involves encouraging the body's immune system to attack them, rather than attacking then directly. Some antiviral of this sort **do not focus on a specific pathogen**, instead stimulating the immune system to attack a range of pathogens.

One of the best –known of this class of drugs are **Interferon** which **inhibit viral synthesis in infected cells.**

One form of human interferon named **"interferon alpha"** is well-**established as part of the standard treatment for hepatitis B and C,** and other interferons are also being investigated as treatments for various diseases.

Acquired resistance

Antiviral resistance can be defined by a decreased susceptibility to a drug through either a minimally effective, or completely ineffective, treatment response to prevent associated illnesses from a particular virus.

Almost all anti-microbials including anti-viral, are subject to drug resistance as the pathogens mutate over time, becoming less susceptible to the treatment, for instance, oseltamivir (Tamiflu)which used for treatment of H1N1 Swine flu.

Origin of antiviral resistance

The genetic makeup of viruses is continuously changing and therefore may alter the virus resistant to the treatments currently available. Viruses can become resistant through spontaneous or intermittent mechanisms throughout the course of an antiviral treatment. Immunocompromised patients, more often than immunocompetent patients, hospitalized with pneumonia are at the highest risk of developing oseltamivir resistance during treatment. Subsequent to exposure to someone else with the flu, those who received oseltamivir for "post-exposure prophylaxis" are also at higher risk of resistance.

Immunocompetence :

is the ability of the body to produce a normal immune response following exposure to an antigen. Immunocompetence is the opposite of immunodeficiency or immuno-incompetent or immuno-compromised. Examples include: a newborn who does not yet have a fully functioning immune system but may have maternally transmitted antibodies – immunodeficient.