
syndrome (AIDS)
Human Immunodeficiency Virus (HIV)
acquired immune deficiency

What HIV \ AIDS:

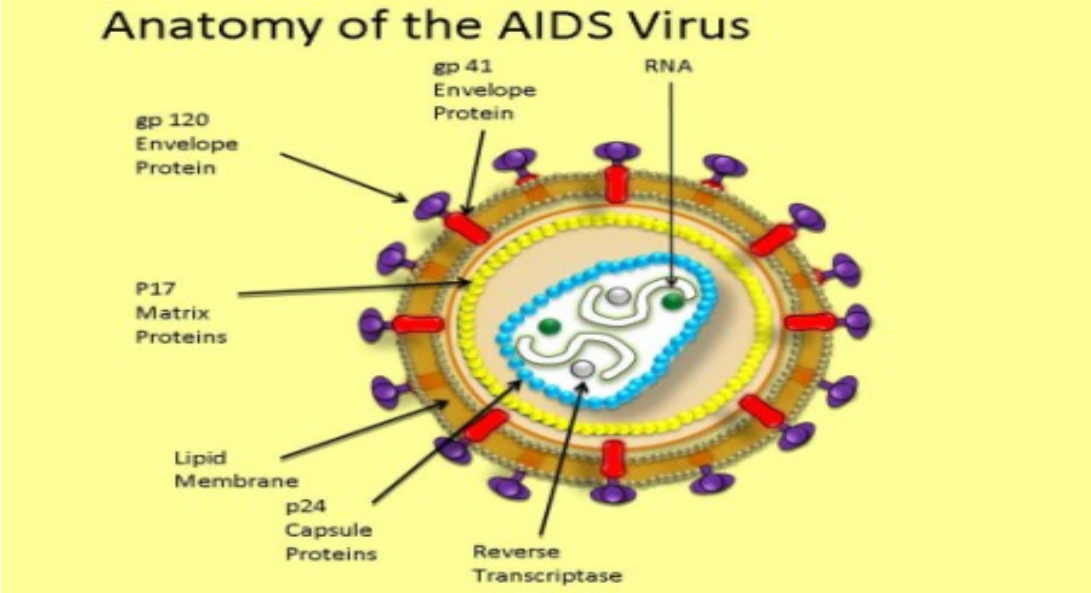
Acquired Immunodeficiency Syndrome (AIDS) occurs when infection with the Human Immunodeficiency Virus (HIV) destroys the body's natural protection from illness. The immune system weakens to the point where it can be invaded by "opportunistic" infections and certain cancers. (1) People should now about it because it no symptom in early infected some have flu-like symptoms and now about how to transmission to prevent from HIV\AIDS. we do not know how many people developed AIDS in the 1970s, or indeed in the years before.

"The dominant feature of this first period was silence, for the human immunodeficiency virus (HIV) was unknown and transmission was not accompanied by signs or symptoms salient enough to be noticed. While rare, sporadic case reports of AIDS and sero-archaeological studies have documented human infections with HIV prior to 1970, available data suggest that the current pandemic started in the mid- to late 1970s. By 1980, HIV had spread to at least five continents (North America, South America, Europe, Africa and Australia). During this period of silence, spread was unchecked by awareness or any preventive action and approximately 100,000-300,000 persons may have been infected.(2)

Classification	
Order	Virales
Family	Retroviridae
Subfamily	Orthoretrovirinae
Genus	Lentivirus.
Species	Human Immunodeficiancy Virus-Causes harm to the immune system and causes AIDS

Table 1: explain the Classification of HIV (3)

The basic structure of HIV virus is:



The viral envelope, the outer coat of the virus, consists of two layers of lipids; outer consisting glycoprotein (gp) 120 and the transmembrane gp41. The lipid membrane is borrowed from the host cell during the budding process (formation of new particles). gp120 is needed to attach to the host cell, and gp41 is critical for the cell fusion process.The HIV matrix proteins (consisting of the p17 protein), lie between the envelope and core, the viral core, contains the viral capsule proteinp24 which surrounds two single strands of HIV RNA and the enzymes needed for HIV replication.(4)

Transmission and Penetration:

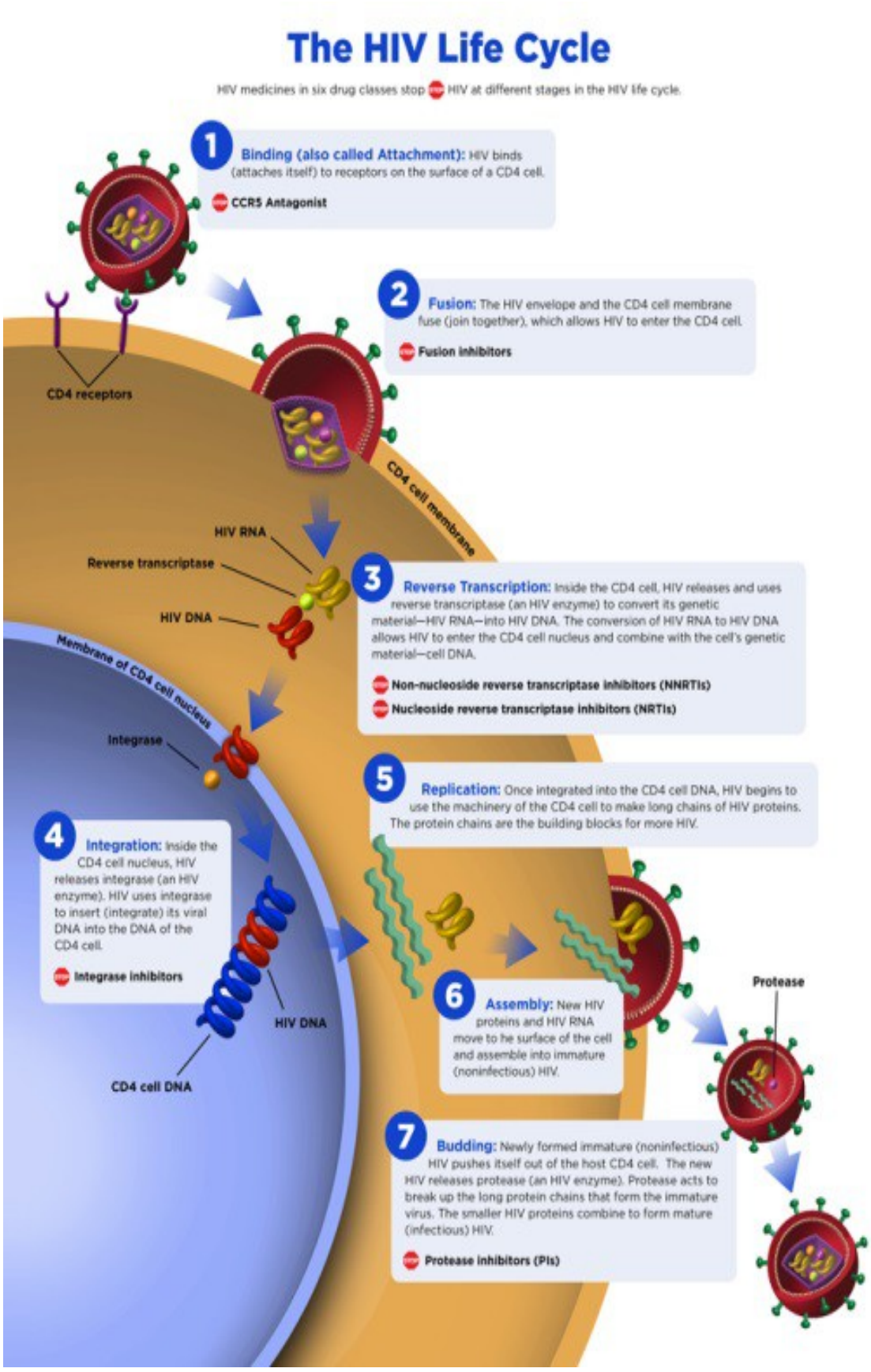
Understanding how the human immunodeficiency virus (HIV) works inside the human cell gives scientists important clues about how to attack it at its most vulnerable points. Knowing the secrets of how the virus functions and reproduces itself -- a process called its life cycle -- can help scientists design new drugs that are more effective at suppressing HIV and have fewer side effects. For people with HIV, knowing how HIV works can make it easier to understand the way the drugs work in the body.

Viruses cannot reproduce without the aid of a living cell. Although HIV can infect a number of cells in the body, the main target is an immune cell called a lymphocyte, more specifically a CD4 helper cell, a type of T-cell. T-cells are an important part of the immune system because they help facilitate the body's response to many common but potentially fatal infections. Without enough T-cells, the body's immune system is unable to defend itself against many infections. By ways that are not yet completely understood, HIV's life cycle directly or indirectly causes a reduction in the number of T-cells in the body, eventually resulting in an increased risk of infections.

After HIV enters the body -- through unsafe sex, contaminated needles, blood transfusions or from mother to child (vertical or perinatal transmission) -- it comes in contact with its favorite host cell - the T-cell. When this happens, HIV will hijack the host cell's cellular machinery to reproduce thousands of copies of itself. HIV has to complete many steps in order for this to happen. At each step of HIV's life cycle, it is theoretically possible to design a drug that will stop the virus. Designing drugs to interfere with specific steps in the viral life cycle is called rational drug design.(5)

Figure(1):How to HIV transmission

The following sections outline some of the better understood steps in the viral life cycle, along with the classes of drugs that inhibit these steps. Scientists are just now uncovering the ways HIV manipulates the immune system to spread its infection throughout the body. This review will focus on events that take place when virus and cell are in close proximity. (5)



Figure(2)

1-Viral Attachment

Once HIV comes into contact with a T-cell, it must attach itself to the cell so that it can fuse with the cell and inject its genetic material (a blueprint for making more HIV) into it. Attachment is a specific binding between proteins on the surface of the virus and proteins that serve as receptors on the surface of the T-cell. Normally, these receptors help the cell communicate with other cells. Two receptors in particular, CD4 and a beta-chemokine receptor (either CCR5 or CXCR4), are used by HIV to latch onto the cell. On the surface of the viral envelope, two sets of proteins (also known as antireceptors) called gp120 and gp41 attach to CD4 and CCR5/CXCR4.

2-Viral Penetration/Fusion

After attachment is completed, viral penetration occurs. Penetration allows the nucleocapsid -- the genetic core -- of the virus to be injected directly into the cell's cytoplasm. gp120 actually contains three sugar-coated proteins (glycoproteins) and, once gp120 attaches itself to CD4, these three proteins spread apart. This allows the gp41 protein, which is normally hidden by the gp120 proteins, to become exposed and bind to the chemokine receptor. Once this has occurred, the viral envelope and the cell membrane are brought into direct contact and essentially melt into each other.

3-Uncoating and Reverse Transcription

Once HIV has penetrated the cell membrane, it is ready to release its genetic information (RNA) into the cell. The viral RNA is protected in the nucleocapsid. The nucleocapsid needs to be partially dissolved so that the virus's RNA can be converted into DNA, a necessary step if HIV's genetic material is to be incorporated into the T-cell's genetic core.

The process by which HIV's RNA is converted to DNA is called reverse transcription. This transcription process happens in almost every human cell, but in the opposite direction -- from DNA to RNA. DNA from the cell nucleus is transcribed into messenger RNA, which then directs the cell's various metabolic functions needed to do its job in the body. HIV uses an enzyme called *reverse transcriptase* to accomplish this transcription. The single-stranded viral RNA is transcribed into a double strand of DNA, which contains the instructions HIV needs to hijack a T-cell's genetic machinery in order to reproduce itself. Reverse transcriptase uses nucleotides -- building blocks of DNA -- from the cell cytoplasm to make this process possible.

4-Integration

If HIV succeeds in translating its instructions from RNA to DNA, HIV must then insert its DNA (also called the preintegration complex) into the

cell's DNA. This process is called integration. In most human cells, there is a structure called the cell nucleus, where the cell's DNA is stored. In order for integration to occur, the newly translated DNA must be transported across the nuclear membrane into the nucleus.

Although the exact mechanism that HIV uses to transport its genetic cargo into the cell nucleus is still unclear, viral protein R (VPR), which is carried by HIV, may facilitate the movement of the preintegration complex to the nucleus. Once the viral RNA has successfully bridged the nuclear membrane and been escorted to the nucleus, HIV uses an enzyme called *integrase* to insert HIV's double-stranded DNA into the cell's existing DNA.

5- Replication

After successful integration of the viral DNA, the host cell is now latently infected with HIV. This viral DNA is referred to as provirus. The HIV provirus now awaits activation. When the immune cell becomes activated, this latent provirus awakens and instructs the cellular machinery to produce the necessary components of HIV, like plastic pieces of a model airplane. From the viral DNA, two strands of RNA are constructed and transported out of the nucleus. One strand is translated into subunits of HIV such as protease, reverse transcriptase, integrase, and structural proteins. The other strand becomes the genetic material for the new viruses. Compounds that inhibit or alter viral RNA have been identified as potential antiviral agents.

6- Assembly

Once the various viral subunits have been produced and processed, they must be separated for the final assembly into new virus. This separation, or cleavage, is accomplished by the viral protease enzyme.

If cleavage is successfully completed, the HIV subunits combine to make up the content of the new virons. In the next step of the viral life cycle, the structural subunits of HIV mesh with the cell's membrane and begin to deform a section of the membrane. This allows the nucleocapsid to take shape and viral RNA is wound tightly to fit inside the nucleocapsid. Researchers are looking at drugs called zinc finger inhibitors, which interfere with the packaging of the viral RNA into the nucleocapsid.

7- Budding

The final step of the viral life cycle is called budding. In this process, the genetic material enclosed in the nucleocapsid merges with the deformed cell membrane to form the new viral envelope. With its genetic material tucked away in its nucleocapsid and a new outer coat made from the host

cell's membrane, the newly formed HIV pinches off and enters into circulation, ready to start the whole process again.

During HIV's life cycle, the T-cell, known as the host cell, is altered and perhaps damaged, causing the death of the cell. Scientists are not sure exactly how the cell dies but have come up with a number of scenarios. First, after the cell becomes infected with a virus or other pathogen, internal signals may tell it to commit suicide. This is known as apoptosis or programmed cell death -- a self-destruct program intended to kill the cell with the hopes of killing the virus as well. A second possible mechanism for the death of the cell is that, as thousands of HIV particles bud or escape from the cell, they severely damage the cell's membrane, resulting in the loss of the cell. Another possible cause for the cell's death is that other cells of the immune system, known as killer cells, recognize that the cell is infected and inject it with chemicals that destroy it.

Whatever the mechanism of the cell's death, there is one less T-cell in the body, and with this happening on a monumental scale, T-cells begin to decline. Over time, there are not enough T-cells to defend the body. At this stage, a person is said to have acquired immunodeficiency syndrome, or AIDS, and becomes susceptible to infections that a healthy immune system could deal with. If this process of immune destruction is halted, a weakened immune system may be able to repair some of the damage over time. (5)

HIV virus replication:

Acquired immunodeficiency syndrome (AIDS) is a disease that affected of immune system in vivo by Human Immunodeficiency Virus (HIV) by inter the nerve cells via specific stages[1]. The capsid of HIV (p24) plays a major role in pathogenesis of HIV [2]. Lymphoid tissue is a main reservoir established by HIV during HIV infection [3]. The T cells zone of lymph nodes is a network of Fibroblastic reticular cells(FRC) which can form a scaffold for T cell migration and provide the live factors unlike $CD4^{+}$ T cells that used for fixing and build the FRC network [4]. Using cultured central memory $CD4^{(+)}$ T cells and replication-competent HIV-1 that generates infected cells that can be activated by latency reversing agents in the presence of antiretroviral drugs [5]. HIV

replication shows that only small fraction of CD4 $^{(+)}$ T cells are infected with (HIV-1) in vivo but some studies suggested that plasma viremia in asymptomatic HIV-infected being active viral replication is more common [6]. However in mature HIV virion the viral genome made from the viral capsid(CA)protein[Table2] , The CA protein and the structure that approximately make it easy to complete every step of infection through a series of interactions with multiple host cell factors [7]. As we knew that HIV virus considers in Retrovirus group, so it has protein envelope to let it's to inter the host cell (T cell) by two ways, one of them is fusion [8, 9]. In fusion HIV virus can attach via HIV envelope protein(A) binds to the receptor CD4(B), the co-receptor on the target cell CCR5(C) change the shape of CD4 to be able to attach with HIV virus, this step is the first step of replication which called Attachment state (figure3) [8, 9].

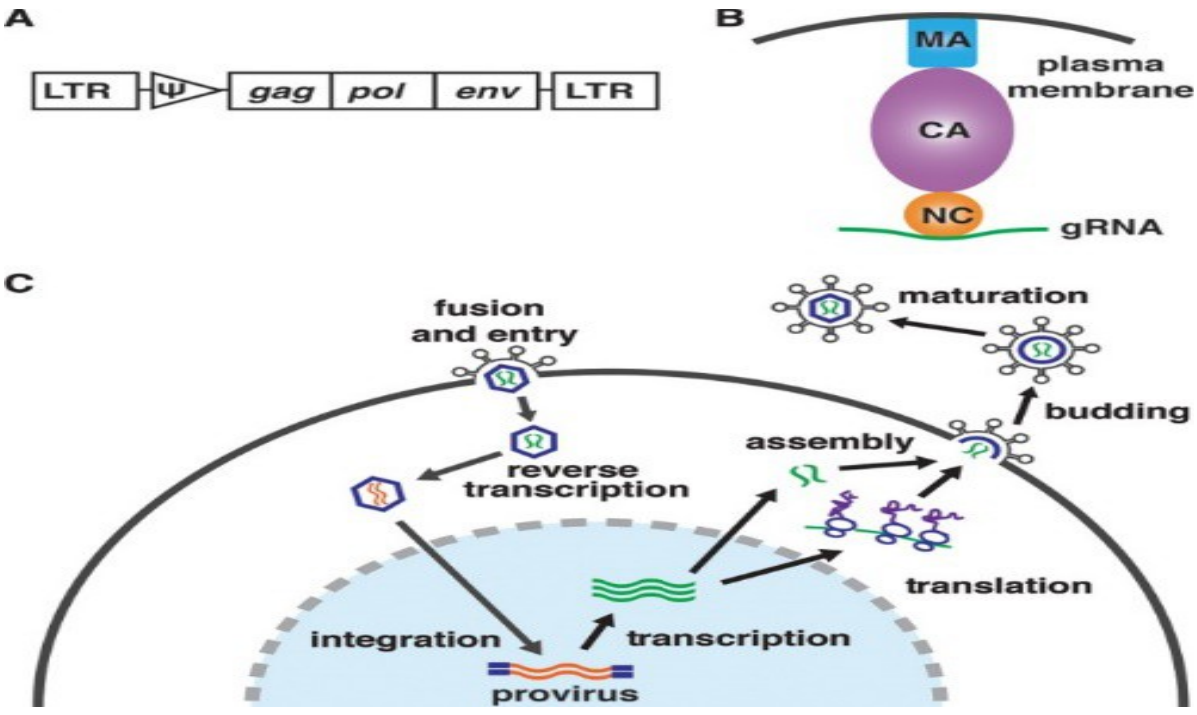


Figure (3): the replication of Retrovirus(HIV) among the envelope protein of HIV virus(A), the receptor CD4 on the surface of target cell(B) and the co-receptor CCR5 which change the conformation of receptor(C). [8].

The next stage of HIV replication is penetration by fuse the practical contents into T cell after releasing the viral and cellular membrane from infected cell to the uninfected cell through virological synapses [10]. The HIV-1 capsid plays a major role in replication cycle the infection or un-infection are depend on the un-coating of virus which means releasing capsid in the cytoplasm to active the infection [11, 12]. Currently the HIV-1 is going to be prepared to synthesis its genome by reverse transcription (RT) [13, 14]. HIV-1 has RNA as genetic materials, this RNA has to duplicate to give two identical RNA each of them has viral information [15]. Packaging the genome let the genetic information protect from damaging through viral replication especially when DNA synthesized after dimerizing of RNA into virons [15]. The RNA react with viral protein (Gag) in the cytoplasm then the RNA-Gag complex transported to the plasma membrane [15]. The Gag proteins are going towards the plasma membrane with most of RNA to aggregate and package into viral complex, to assembly of these complexes [15, 16]. However, the RNA and Gag become near to the plasma membrane by the time and the envelope protein re-coating the virus, thus assembly stage is an important significant to study the viral replication [15, 16]. Finally, the endosomal sorting complexes required for transport (ESCRT) proteins alter the conformation of the plasma membrane of host cell by budding then the host cell can release the HIV-1 virus [17].

Some of HIV proteins with its functions:

HIV proteins	Functions

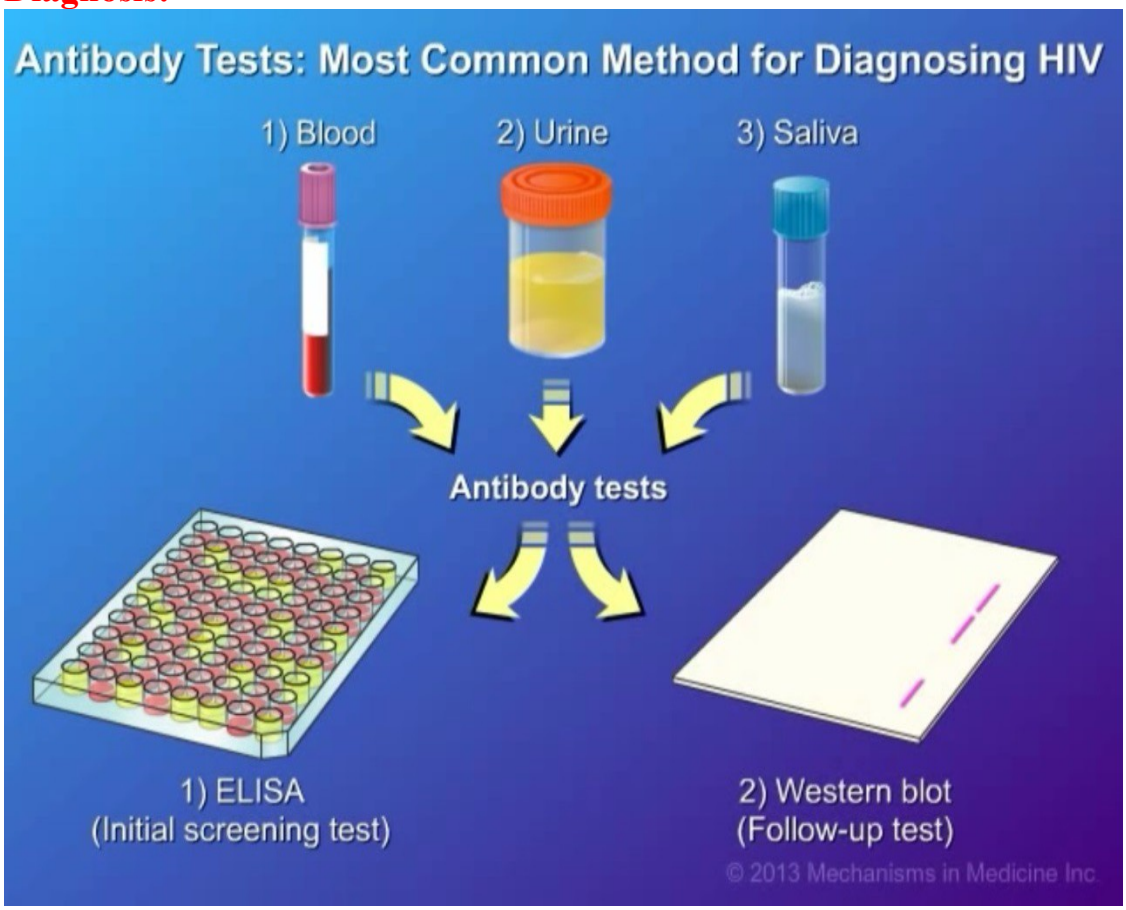
The endosomal sorting complexes required for transport (ESCRT)	Make buds of membranes and severs membrane necks from their inner face.
NADH-coenzyme Q oxidoreductase (complex I)	Exist in the the inner mitochondrial membrane and catalyzes the first step of electron transfer by the oxidation of NADH.
The HIV-1 protease (PR)	It is catalyzing the cleavage of the Gag and Gag-Pro-Pol structural polyproteins.
Reverse transcriptase (RT)	Enzyme that transcript the reverse genetic material.
The HIV-1 Gag protein	Leads to particle assembly at the plasma membrane.
Immunoglobulin A (IgA)	Protein that has many functions: **1-** Serving as a first-line barrier that protects the mucosal epithelium from pathogens. **2-** Maintenance. **3-** Positioning.
HIV-1 integrase (IN)	Plays a major role virus replication, each sub unite assemble into a tetramer and form a stable synaptic complex (SSC), which mediates integration of the reverse transcribed HIV-1 genome into chromatin.

Table **2**: explain the main functions of main HIV proteins [17-24].

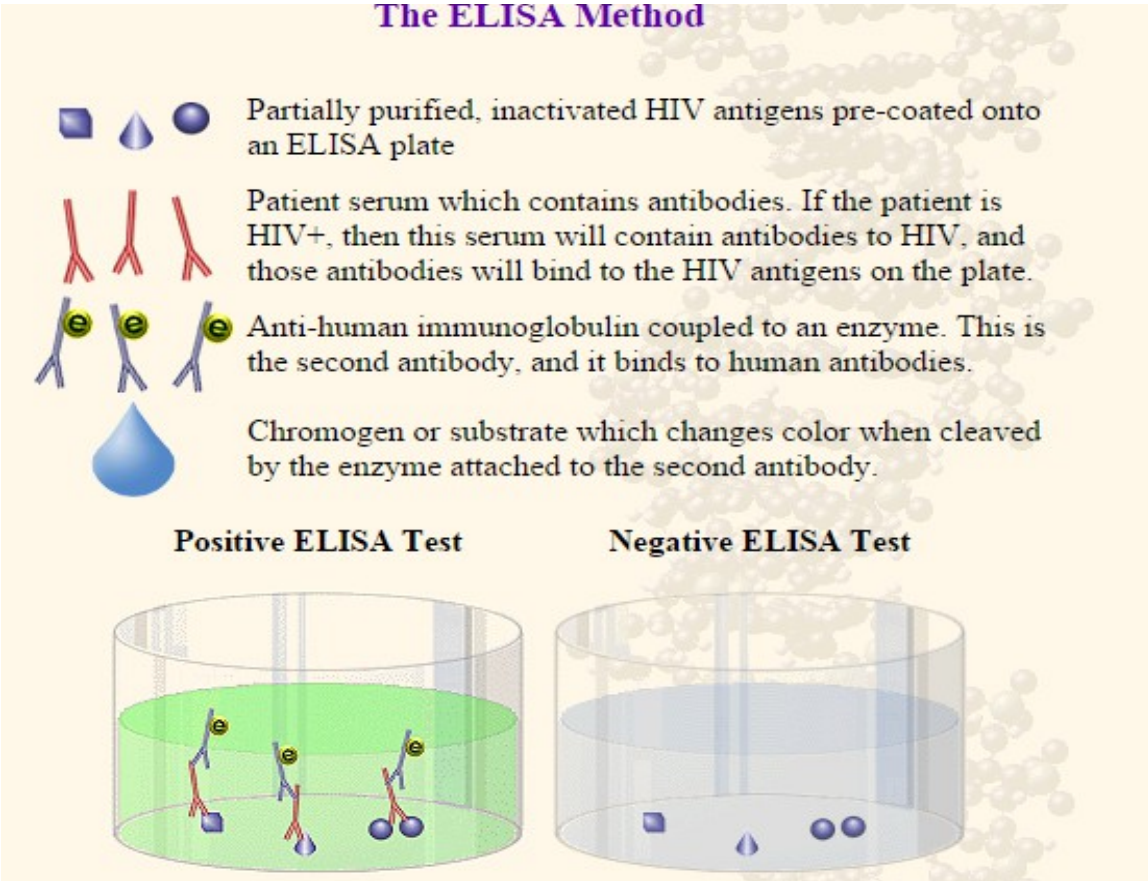
Symptoms and Signs of HIV Infection:

Recognising primary/acute HIV infection can be a clinical challenge; symptoms can be nonspecific and may not be recognised at initial presentation. Symptoms and signs typically appear two to six weeks after exposure to HIV and this may include fever, myalgia, sore throat, headache, rash, nausea, diarrhea, and vomiting. This presentation is similar to those of many other illnesses, including other viral syndromes, influenza and mononucleosis; however, general lymphadenopathy, rash, thrush, and mucosal ulceration are sufficiently uncommon in most adult febrile illnesses that they should, when present, trigger suspicion of acute HIV infection. (7)

Diagnosis:



Figure(4)



Figure(5)

Treatment :

HIV is treated using a combination of medicines to fight HIV infection. This is called antiretroviral therapy (ART). ART isn't a cure, but it can control the virus so that you can live a longer, healthier life and reduce the risk of transmitting HIV to others.

ART involves taking a combination of HIV medicines (called an HIV regimen) every day, exactly as prescribed.

These HIV medicines prevent HIV from multiplying (making copies of itself), which reduces the amount of HIV in your body. Having less HIV in your body gives your immune system a chance to recover and fight off infections and cancers. Even though there is still some HIV in the body, the immune system is strong enough to fight off infections and cancers.

By reducing the amount of HIV in your body, HIV medicines also reduce the risk of transmitting the virus to others.(8)

1. **Fusion Inhibitor drugs :**

Drugs that inhibit CD4 receptor on the surface of cell host to bind with HIV envelope protein thus, the virus can not effect on another cells (Liu, Lu et al. 2005).(9)

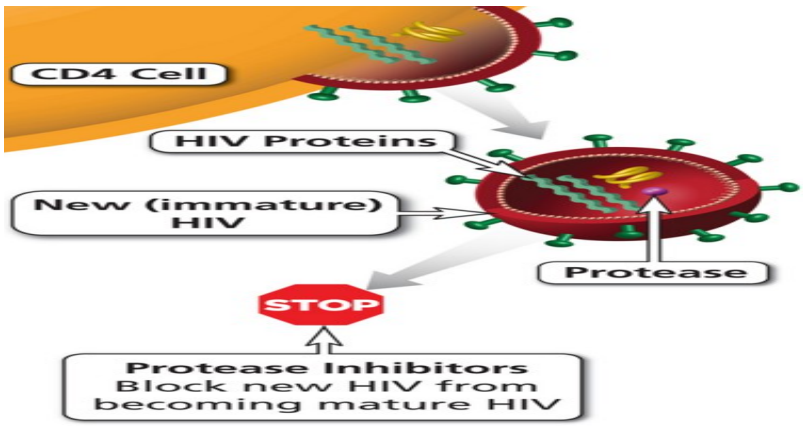
There are many drugs that have this technique such as: Antiretroviral (ARV).(10)

2. **CCR5 Antagonist drugs :**

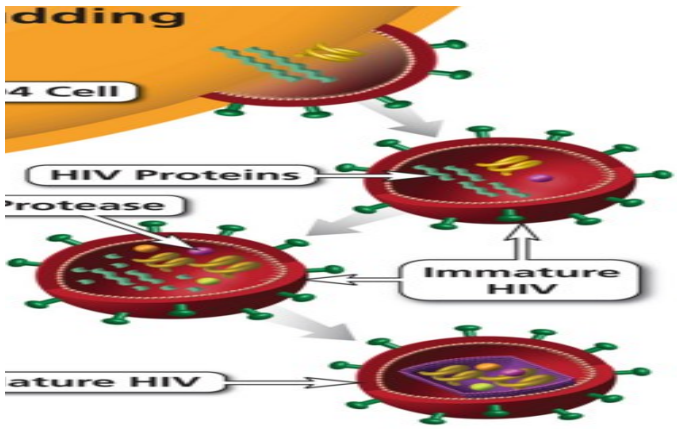
These drugs prevent the host cell from inter the HIV-1 into the cell by block the co-receptor CCR5 on the surface of immune cells from accepting the virus (Esmaeilzadeh, Farshbaf et al. 2015).(11)

3. **Protease Inhibitor (PI) drugs :**

These drugs target the viral protease (12)



Figure(6)



Figure(6)

How can prevent transmitting HIV?

To prevent infecting another person with HIV:

• Use a condom every time you have sex.

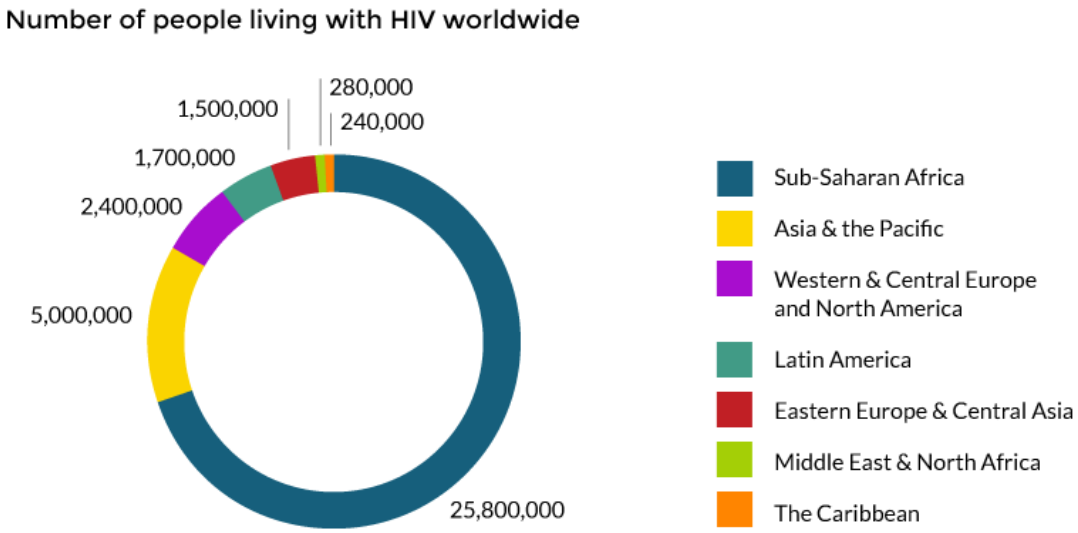
• If you inject drugs, don't share your needles or syringes.

• Don’t share your razor, toothbrush, or other items that may have your blood on them.

• Take your anti-HIV medications according to your health care provider’s directions.

• If you are a mother infected with HIV, don't breastfeed your baby. (13)

:Recent discoveries for HIV



Figure(7)

Sub-Saharan Africa

More than two-thirds (70%) of all people living with HIV, 25.8 million, live in sub-Saharan Africa—including 88% of the world's HIV-positive children. In 2014, an estimated 1.4 million people in the region became newly infected. An estimated 790,000 adults and children died of AIDS, accounting for 66% of the world's AIDS deaths in 2014.

Asia and the Pacific

In Asia and the Pacific, nearly 340,000 people became newly infected in 2014, bringing the total number of people living with HIV there to 5 million. AIDS claimed an estimated 240,000 lives in the region in 2014.

Caribbean

Approximately 13,000 people became newly infected in the Caribbean in 2014, bringing the total number of people living with HIV there to 280,000. AIDS claimed an estimated 8,800 lives in 2014.

Latin America

There were an estimated 87,000 new HIV infections and 41,000 AIDS-related deaths in Latin America in 2014. This region currently has 1.7 million people living with HIV.

North Africa and the Middle East

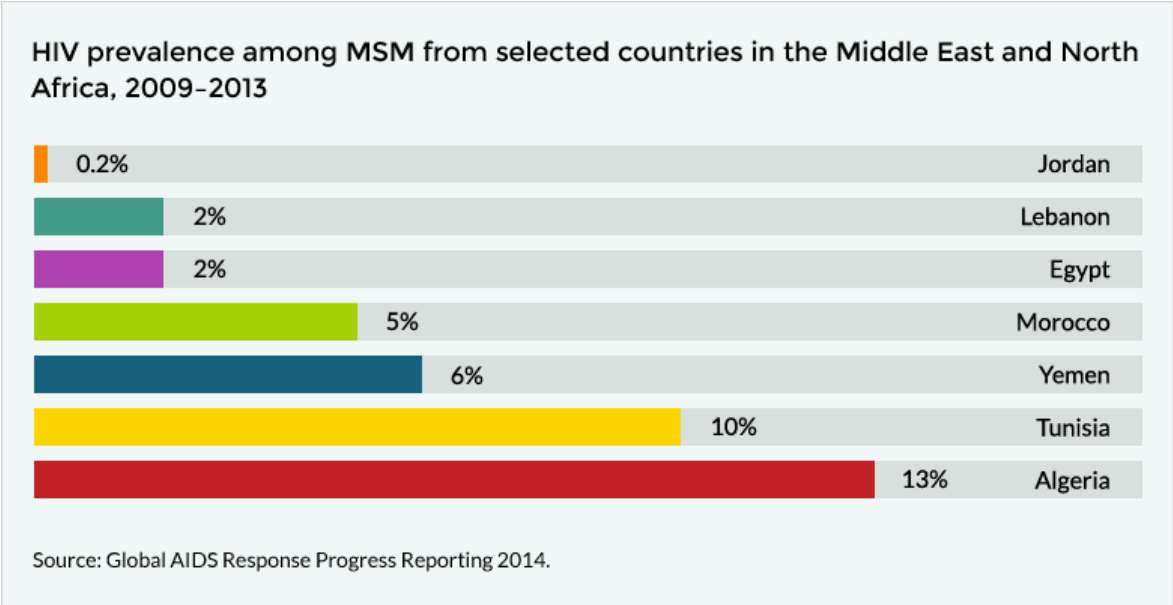
Approximately 240,000 people are living with HIV in this region and an estimated 22,000 people became newly infected in 2014. An estimated 12,000 adults and children died of AIDS in 2014.

Eastern Europe and Central Asia

Some 140,000 people were newly infected with HIV in 2014, bringing the number of people living with HIV to 1.5 million. AIDS claimed 62,000 lives in 2014.

Western and Central Europe and North America

In 2014, there were 85,000 new cases of HIV, bringing the number of people living with HIV in Western and Central Europe and North American to 2.4 million. An estimated 26,000 people in these regions died of AIDS in 2014.(14)



Figure(8)

The mid-1980s saw the first reported cases of HIV and AIDS in the Middle East and North Africa. By 1990, every country in the region had detected HIV in their populations. This was linked primarily to exposure abroad as well as contaminated blood transfusions and organ transplants. However, by the early 1990s, a new pattern of transmission had emerged among certain groups.

People who inject drugs (PWID) in MENA

People who inject drugs (PWID) are one of the groups of people vulnerable to HIV transmission in many parts of the Middle East and North Africa . One study that has collated data on the HIV epidemic among PWID in MENA estimated that there are about 626,000 PWID. HIV among this group was present in one third of MENA countries and had an HIV prevalence between 10 and 15%.4 More alarming statistics have come from places like Tripoli in Libya, where studies have detected an HIV prevalence of up to 87.2% among PWID.

Injecting drug use is the major route of HIV transmission in Afghanistan, Pakistan and Iran and accounts for an estimated 90% of HIV cases in Libya. This practice is also common in Oman and Bahrain, and a growing issue in Morocco and Egypt.

Spread of HIV in MENA

The first cases of AIDS in the MENA region were reported in mid-1980s. By 1990, every country had detected people living with HIV, the vast majority of these linked to HIV exposure abroad and through HIV-contaminated blood products or organ transplants. In the early 1990s, however, a new pattern of transmission emerged among "key populations" at greatest risk of infection. With the exception of South Sudan, parts of Somalia, and Djibouti where most HIV transmission is now taking place in the general population, HIV in MENA is concentrated in certain groups with behaviors that put them at a higher risk of infection—namely, men who have sex with men, female sex workers, and people who inject drugs.

Today, the number of new infections is increasing in every MENA country, although the principal routes of transmission vary from one country to another (see table). In Iran and Libya, for example, the majority of infections occur among people who inject drugs and their networks of sexual and injecting partners. On the other hand, in Djibouti, South Sudan, and parts of Somalia, HIV has spread through commercial sex networks.(15)

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Figure:

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