



AIDS THERAPY INFLUENCING ON NEW DRUGS

K. Malleswari*, D. Rama Brahma Reddy, P. Sumalatha, Sk. Reshma, Sk Md. Haneef

Nalanda Institute of Pharmaceutical Sciences, Kantepudi(v), Sattenapalli(m), Guntur(dist),522438,
Mail.id: malleswarirao24@gmail.com.

ABSTRACT

HIV/AIDS has always been one of the most thoroughly global disease. The human immunodeficiency virus (HIV) is a lenti virus that causes HIV infection and AIDS. AIDS is a condition in humans in which progressive failure of the immune system allows life-threatening infections and cancers to thrive. Infection with HIV occurs by the transfer of blood, semen, vaginal fluid, breast milk. Within these bodily fluids, HIV is present as both free virus particles and virus within infected immune cells. HIV infects vital cells in the human immune system such as helper CD4 T cells, macrophages. HIV infection leads to low levels of T cells through a number of mechanisms, including pyroptosis of infected T cells. The symptoms of AIDS are primarily the result of conditions that do not normally develop in individuals with healthy immune systems. Most of these conditions are opportunistic infections caused by bacteria, viruses, fungi and parasites that are normally controlled by the elements of the immune system that HIV damages. This Article provides an update on epidemiology, pathogenesis, treatment, and prevention interventions pertinent to HIV.

KEYWORDS: AIDS, Epidemiology, Pathogenesis, Transmission, Symptoms, Diagnosis, Treatment.

INTRODUCTION

Acquired immune deficiency syndrome (AIDS) is caused by a chronic infection with the HIV. The official start of the epidemic occurred in the summer of 1981 when the US Centres for Disease Control and Prevention (CDC) reported on a cluster of Pneumocystis carinii pneumonia (PCP) in five homosexual men. However, there is substantial evidence that HIV first crossed the simian-human species barrier much earlier, possibly in Cameroon in Africa. There is also evidence that HIV found its way to the Caribbean before the 1980s. ^[1] From 1981, approximately 1.7 million people have been infected with HIV in the United States, 550,000 have subsequently died, and 1.2 million are currently living with HIV/AIDS. Despite improved HIV medications and lower morbidity and death rates in the past decade, there is still great variability in HIV disease progression. ^[2] HIV stands for human immunodeficiency virus, which is the virus that causes HIV infection. The abbreviation —HIV can refer to the virus or to HIV infection. AIDS stands for acquired immunodeficiency syndrome. AIDS is the most advanced stage of HIV infection. HIV attacks and destroys the infection-fighting CD4 cells of the immune system. The loss of CD4 cells makes it difficult for the body to fight off infections and certain cancers. Without treatment, HIV can gradually destroy the immune system and advance to AIDS. HIV is a virus that causes AIDS.

Normally, our body has immune system that attack viruses and bacteria. Immune system has white blood cells which protect us from infections. White blood cells contain CD4+ cells which is also known as helper cells or T cells. These infections take advantage of body's immune system. These infections cause several health problems and even lead to death of a person. HIV has inability to protect against diseases and count of CD4 cells also decreases in HIV. There is no cure of AIDS but there are certain medicines which are used to slow down the diseases so you stay healthier for long time. There is no medicine to get rid of diseases.^[3]

Epidemiology

Some authors consider HIV/AIDS a global pandemic. As of 2016 approximately 36.7 million people worldwide have HIV, the number of new infections that year being about 1.8 million. This is down from 3.1 million new infections in 2001. Slightly over half the infected population are women and 2.1 million are children. It resulted in about 1 million deaths in 2016, down from a peak of 1.9 million in 2005. Sub-Saharan Africa is the region most affected. In 2010, an estimated 68% (22.9 million) of all HIV cases and 66% of all deaths (1.2 million) occurred in this region. This means that about 5% of the adult population is infected and it is believed to be the cause of 10% of all deaths in children. Here, in contrast to other regions, women comprise nearly 60% of cases. South Africa has the largest population of people with HIV of any country in the world at 5.9 million. Life expectancy has fallen in the worst-affected countries due to HIV/AIDS; for example, in 2006 it was estimated that it had dropped from 65 to 35 years in Botswana. Mother-to-child transmission in Botswana and South Africa, as of 2013, has decreased to less than 5%, with improvement in many other African nations due to improved access to antiretroviral therapy.

South & South East Asia is the second most affected; in 2010 this region contained an estimated 4 million cases or 12% of all people living with HIV resulting in approximately 250,000 deaths. Approximately 2.4 million of these cases are in India. During 2008 in the United States approximately 1.2 million people were living with HIV, resulting in about 17,500 deaths. The US Centers for Disease Control and Prevention estimated that in that year, 20% of infected Americans were unaware of their infection. As of 2016 about 675,000 people have died of HIV/AIDS in the US since the beginning of the HIV epidemic. In the United Kingdom as of 2015, there were approximately 101,200 cases which resulted in 594 deaths.

In Canada as of 2008, there were about 65,000 cases causing 53 deaths. Between the first recognition of AIDS (in 1981) and 2009, it has led to nearly 30 million deaths. Rates of HIV are lowest in North Africa and the Middle East (0.1% or less), East Asia (0.1%), and Western and Central Europe (0.2%). The worst-affected European countries, in 2009 and 2012 estimates, are Russia, Ukraine, Latvia, Moldova, Portugal and Belarus, in decreasing order of prevalence.

Pathogenesis

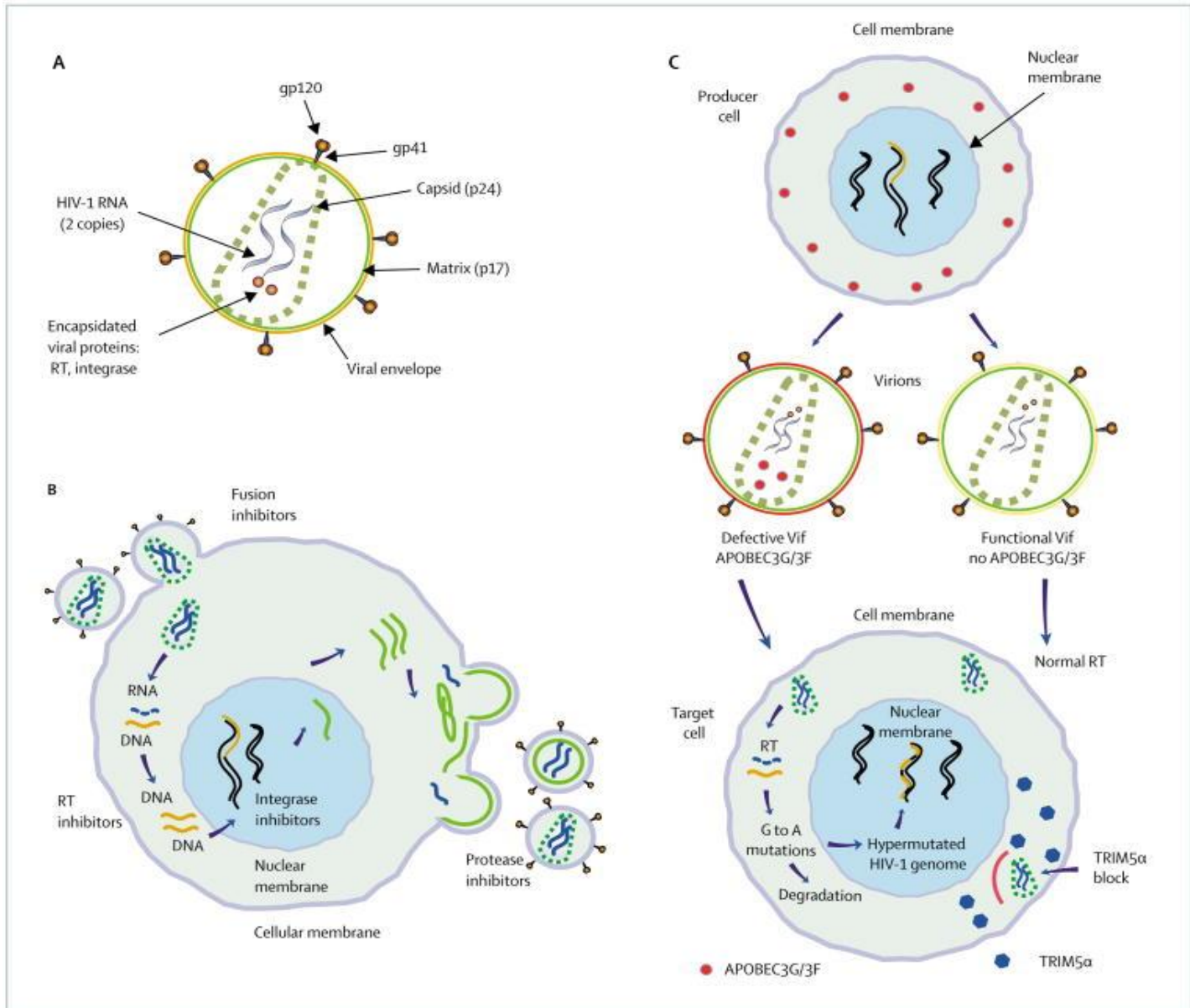


Fig No:1 Pathogenesis of Aids

The main target of HIV is activated CD4 T lymphocytes; entry is via interactions with CD4 and the chemokine coreceptors, CCR5 or CXCR4. Other cells bearing CD4 and chemokine receptors are also infected, including resting CD4 T cells, monocytes and macrophages, and dendritic cells. CD4 independent HIV infection of cells can happen, notably in astrocytes and renal epithelial cells,^[6] and subsequent HIV gene expression has an important role in the pathogenesis of HIV-associated neurocognitive disorder (related to astrocytes) and nephropathy (related to epithelial cells). A range of host proteins interact with HIV proteins or HIV DNA to either restrict or promote virus replication in specific cell types.^[7]

Transmission of HIV across mucosal membranes is usually established by one founder virus, which has unique phenotypic properties including usage of CCR5 rather than CXCR4 for entry, enhanced interaction with dendritic cells, and resistance to interferon.^[8] Transmission of the founder virus is followed by a rapid increase in HIV replication and then a striking induction of inflammatory cytokines and chemokines, which is in stark contrast to the minimum initial response to other chronic viral infections such as hepatitis B or hepatitis C.^[9] Neutralising antibodies arise roughly 3 months after transmission and select for viral escape mutants.^[10]

Transmission

HIV is transmitted through body fluids. It has been isolated from a variety of body fluids, including blood, semen, vaginal secretions, breast milk, urine, saliva, and tears. The risk of transmission through contact with a given fluid is related both to the amount of virus present in the fluid and to the type of exposure to it. HIV is found in such small concentrations in tears, saliva, and urine that transmission through casual contact with these fluids is theoretically possible but highly unlikely.

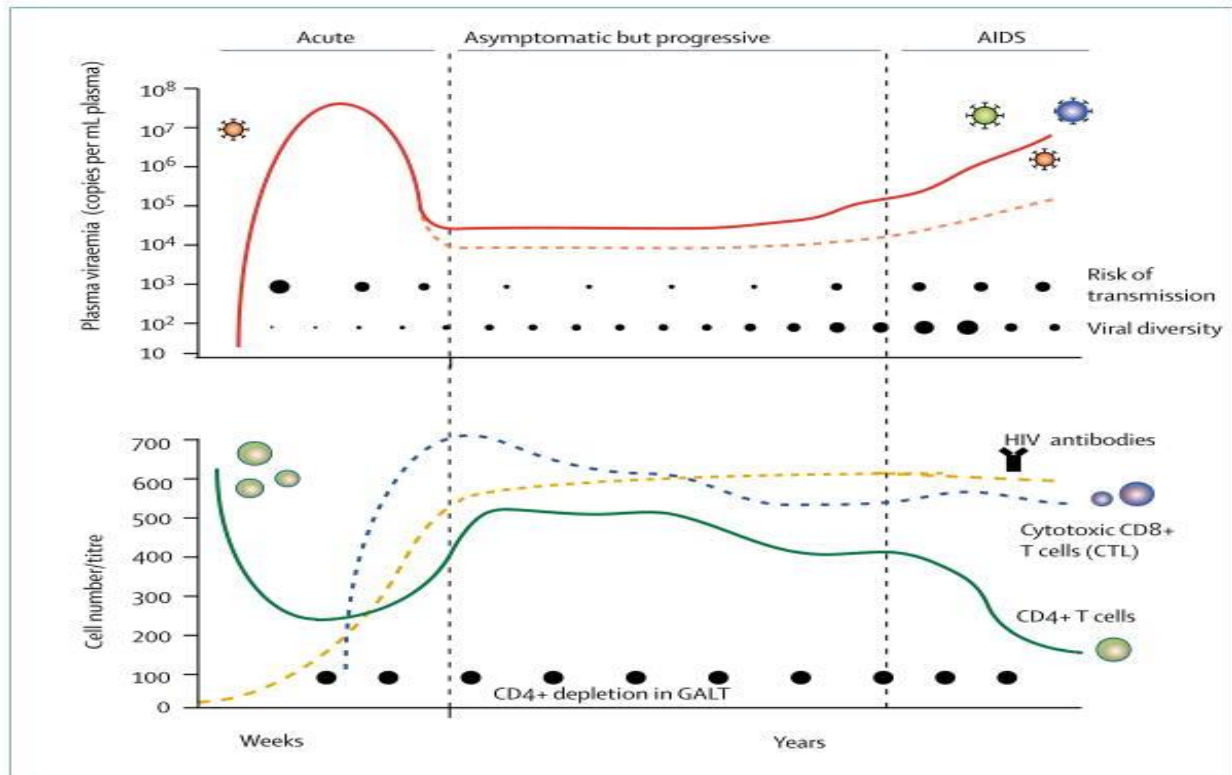


Fig No:2 Transmission period of Aids

On the other hand, behaviors that lead to certain types of exposure to blood, semen, vaginal secretions, and breast milk—all fluids with higher HIV concentrations—may lead to HIV transmission. It can be transmitted from an infected mother to an infant during pregnancy, perinatally, or through breast-feeding^[14].

a) Sexual

Sexual behaviors with exchange of body fluids can transmit HIV. While the rate of HIV transmission is somewhat higher for the recipient of semen than for the donating sexual partner, transmission has been documented in both directions. Penile-anal and penile-vaginal intercourse are considered the highest risk behaviors, with transmission more likely in the presence of other sexually transmitted diseases or genital lesions or during sexual activities that cause a rupture of tissue or bleeding.

b) Injection drug use

Sharing the equipment used to prepare and inject drugs with an HIV-infected person is a very efficient means of transmitting HIV and essentially amounts to a direct inoculation of viral particles from one person to another. The risk of transmission is directly related to the concentration of virus present in the blood and the volume of blood exchanged. Injection drug use is the second most common risk factor for HIV infection, and injection drug users account for an increasing proportion of AIDS cases. It has been estimated that there are more than 1.5 million injection drug users in the United States.^[14]

C) Blood transfusion

Blood transfusion with infected blood products remains a significant risk for acquiring HIV in some parts of the world. In the United States, donated blood has been screened for antibodies to HIV-1 since 1985 and for antibodies to HIV-2 since 1992. Therefore, the risk of transmission from a blood transfusion has become extraordinarily low—less than 0.001%. To further ensure that donated blood is not infected with HIV, since 1996 the American Red Cross

has used the HIV antigen test. This test helps address the problem of false-negative HIV antibody tests in donors who may not have produced detectable antibodies after their initial infection. Before the use of lyophilized factor VIII, recurrent inoculation with pooled donated factor VIII was a major source of HIV transmission in hemophilia patients.

1. Perinatal

Infection from mother to infant can occur during gestation, delivery, or breast-feeding. Because breast milk contains significant numbers of lymphocytes that can lead to HIV transmission from mothers to newborns, it is recommended in the United States and other developed countries that HIV-infected mothers bottle-feed and not nurse their infants.

2. Cofactors for transmission

Cofactors can enhance, but do not cause the transmission of HIV. Physical cofactors include the presence of sexually transmitted diseases (such as gonorrhea, syphilis, and chlamydia, which may cause genital lesions) or genital/mucous membrane bleeding during sexual activity. The use of mood or mind-altering substances may serve as a behavioral cofactor because they can lower sexual inhibitions, impair judgment, or increase impulsivity. Data are inconclusive regarding the effect of mind-altering substances on immunocompetence and HIV susceptibility or progression.

Symptoms

Many people who are living with HIV have no obvious signs and symptoms at all. Recent evidence shows that between 70% to 90% of people who become infected with HIV experience flu-like symptoms within a few weeks after infection. The most common symptoms are a fever, a rash and a severe sore throat all occurring at the same time. These symptoms in an otherwise healthy person may indicate recent HIV infection. HIV infected patients may get yeast infections (oral or vaginal) that do not go away or that occur often. Frequent and severe herpes infections that cause mouth, genital, or anal sores are also common. Herpes zoster (shingles) is more likely to occur in infected patients. Other pulmonary infections (pneumonia) or so called atypical mycobacterial infections can be serious for your loved one. Women may get pelvic inflammatory disease that does not respond to treatment. The virus may attack the nervous system (nerves, spinal cord or brain) and produce a variety of symptoms ranging from tingling in the feet and trouble walking to memory disturbances.

Main symptoms of AIDS

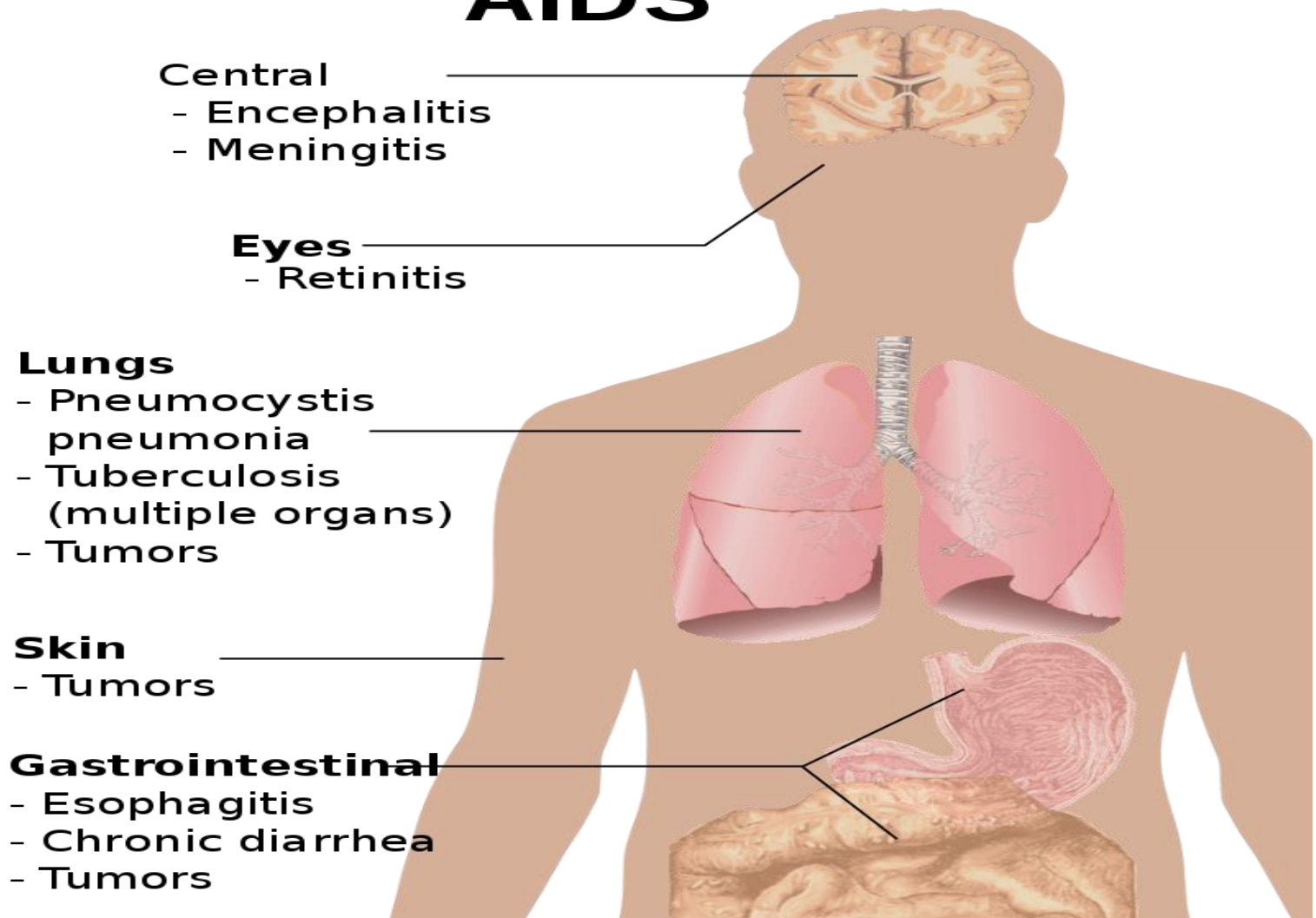


Fig No:3 Symptoms of Aids

Large lymph nodes or "swollen glands" that may be enlarged, for more than three months, frequent fevers and sweats, skin rashes or flaky skin that does not go away, short-term memory loss, slow growth or frequent illness in children, cough and shortness of breath, seizures and lack of coordination, difficult or painful swallowing, confusion and forgetfulness, nausea, cramps, diarrhoea or vomiting that do not go away, vision loss, Unexplained weight loss.

AIDS is the final, most severe stage of HIV infection. Because HIV has severely damaged the immune system, the body can't fight off opportunistic infections. (Opportunistic infections are infections and infection-related cancers that occur more frequently or are more severe in people with weakened immune systems than in people with healthy immune systems.) People with HIV are diagnosed with AIDS if they have a CD4 count of less than 200 cells/mm³ or if they have certain opportunistic infections. Once a person is diagnosed with AIDS, they can have a high viral load and are able to transmit HIV to others very easily.

Diagnosis

HIV Tests for Screening and Diagnosis, HIV tests are very accurate, but no test can detect the virus immediately after infection. How soon a test can detect infection depends upon different factors, including the type of test being used. There are three types of HIV diagnostic tests: antibody tests, combination or fourth-generation tests, and nucleic acid tests (NATs).

- 1. Antibody tests:** Detect the presence of antibodies, proteins that a person's body makes against HIV, not HIV itself. Most HIV tests, including most rapid tests and home tests, are antibody tests. It can take 3 to 12 weeks for a person's body to make enough antibodies for an antibody test to detect HIV infection. In general, antibody tests that use blood can detect HIV slightly sooner after infection than tests done with oral fluid.
- 2. Combination or fourth-generation tests:** Look for both HIV antibodies and antigens. Antigens are a part of the virus itself and are present during acute HIV infection. It can take 2 to 6 weeks for a person's body to make enough antigens and antibodies for a combination test to detect HIV. Combination tests are now recommended for testing done in labs and are becoming more common in the United States. There is also a rapid combination test available.
- 3. NATs:** Detect HIV the fastest by looking for HIV in the blood. It can take 7 to 28 days for NATs to detect HIV. This test is very expensive and is not routinely used for HIV screening unless the person recently had a high-risk exposure or a possible exposure with early symptoms of HIV infection.

Table:1 Days after exposure needed for the test to be accurate

Blood test	Days
Antibody test (rapid test, ELISA 3rd gen)	23–90
Antibody and p24 antigen test (ELISA 4th gen)	18–45
PCR	10–33

Treatment

Antiretroviral drugs are used to treat HIV. These are the drugs active against human immunodeficiency virus (HIV) which is a retrovirus. They are useful in prolonging and improving a quality of life. Antiretroviral drugs are classified as following:

- 1. Nucleoside Reverse Transcriptase Inhibitors (NRTIs).*
- 2. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs).*
- 3. Protease Inhibitors (PIs).*
- 4. Fusion Inhibitors.*
- 5. CCR5 Antagonists.*
- 6. Integrase inhibitors.*

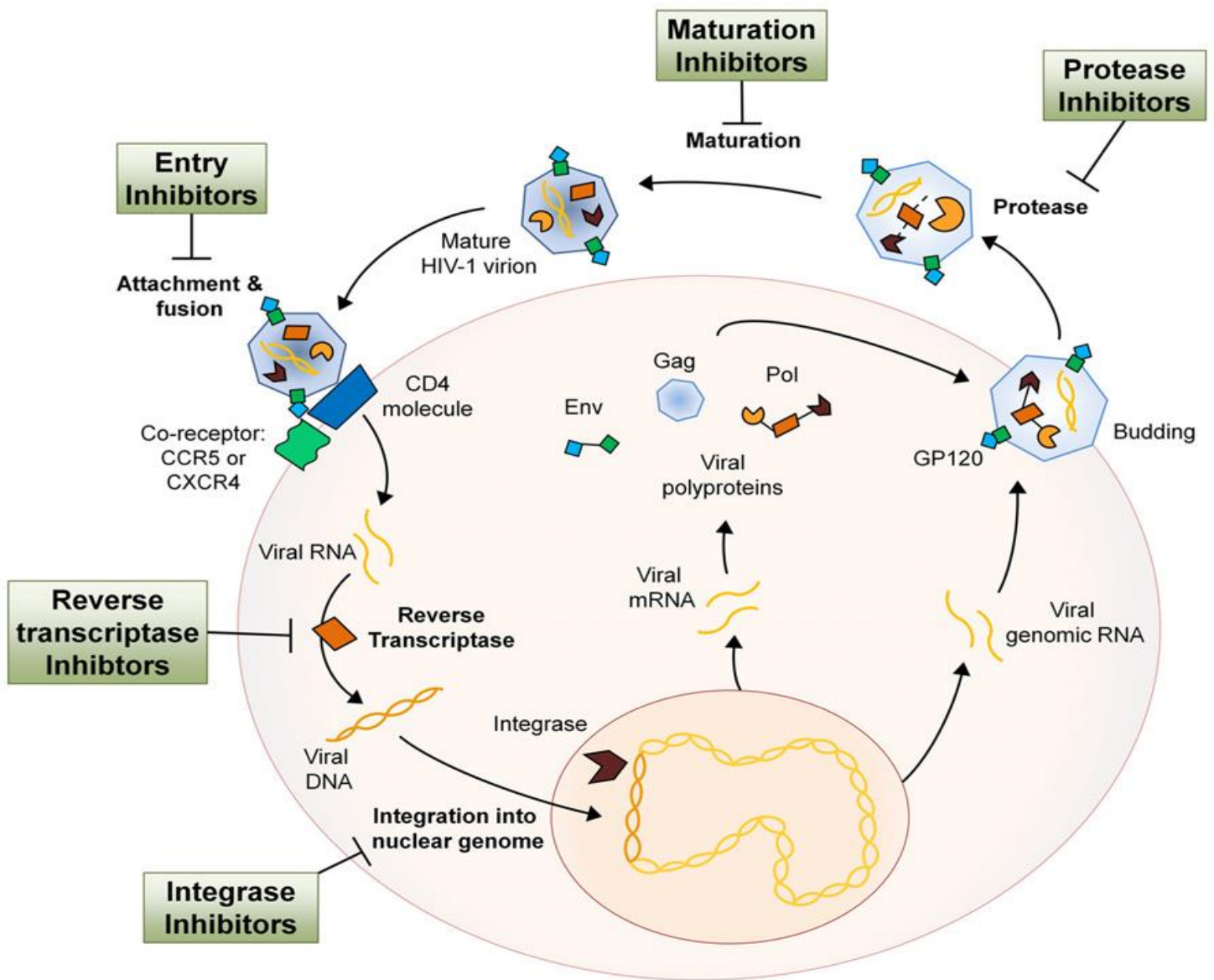


Fig No:4 Mechanism of Action

1. Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

NRTIs represent the first class of drugs that been approved by the Food and Drug Administration (FDA) as anti-HIV therapeutics. NRTIs as such as prodrugs require phosphorylation by cellular kinases to become active. Members of this group competitively prevent HIV reverse transcriptase enzyme and act as DNA synthesis sequence terminators. The viral DNA is stopped because the structural changes of integrated nucleotide analogy. Missing functionality. missing 3'-OH group, prevents the 5' to 3' phosphodiester connection necessary for DNA sequence approved NRTIs are: Abacavir, Diagnosing, Emtricitabine, Lamivudine, Stavudine, Zalcitabine, Zidovudine, and Tenofovir disproval fumarate.

Abacavir is a synthetic purine (guanosine) nucleoside analog with cyclopropyl substituent at the nucleoside base. The sugar moiety of natural nucleosides is replaced by 2,3-cyclopentene thus creating an artificial carbocyclic nucleoside requires phosphorylation of its hydroxyl group to be incorporate into viral DNA.

The phosphorylated Abacavir competitively inhibits the HIV reverse transcriptase enzyme and serves as a DNA chain terminator. It is a strong reverse transcriptase inhibitor.

Therapy with Abacavir leads to a decrease of HIV loads and delays or prevents the damage to the immune system. This reduces the chances of developing AIDS. Abacavir was approved as an anti-HIV drug by the FDA in 1998. Is used as a component of antiretroviral therapies. When used as monotherapy, the loss of response to the therapy occurs.

2. Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

NNRTIs inhibit HIV-1 by directly binding to the enzyme - reverse transcriptase. NNRTIs blocks polymerization through allosteric regulation by changing the position of critical components within the catalytic location of the reverse transcriptase enzyme. This leads to inhibiting an essential step in viral replication. Unlike NRTIs, these non-competitive inhibitors do not inhibit the reverse transcriptase of other lentiviruses, such as simian immunodeficiency virus (SIV).

Delavirdine

Delavirdine was approved in the USA by the Food and Drug Administration (FDA) in 1997 for the use to be used as a medication for treating HIV infection in patients above sixteen years. Its structure is interesting as it includes a methane sulfonic acid functional group. Drug resistance develops fast if Delavirdine is administered as a monotherapy and thus it should always be administered as part of a combination treatment. In humans, toxicity of this drug was reported as skin rash. However, animal studies among rats, mice, rabbits, dogs, and monkeys to observe the effects following the administration of high dose. The most significant toxicity found was necrotizing vasculitis. It happened when the serum concentrations of Delavirdine were at least 7-fold higher than the recommended dose. Other major organs that can be affected in these animals include the liver, bone marrow, kidneys, gastrointestinal tract, lymphoid tissue, lung, endocrine organs, and reproductive organs.^[16]

3. Protease Inhibitors (PIs)

HIV-1 protease is essential for viral infectivity. Its mechanism of action is based on cleaving specific polyprotein precursors during viral maturation. It was shown that cellular proteins can also be cleaved by protease. Consequently, the number of viruses in the viral loads decreases because of the inhibition of protease.^[18] The drugs approved by FDA are Amprenavir, Atazanavir, Darunavir, Fosamprenavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Saquinavir, Simeprevir and Tipranavir.

Atazanavir

The FDA approved the Atazanavir in 2003 to be used in therapy with other HIV medicines in both adults and children. Atazanavir is an HIV-1 protease inhibitor preventing the formation of mature virions through the strong and selective inhibition of viral polyprotein processing in HIV-1 infected cells. Atazanavir is normally taken with Ritonavir. However, recent data indicate that changing the patients with achieved virological suppression from retroviral-boosted-by-Ritonavir therapy to Atazanavir improves safety (decrease of abnormalities in blood parameters) without a sacrifice of virological efficacy.

4. Fusion Inhibitors

The fusion inhibitors stop the interaction of the two domains in the viral glycoprotein gp41 with each other. These drugs are designed to mimic one of the domains thus disturbing the intra-molecular interactions of the virus protein. They are peptides with significant antiviral activity against HIV-1. HIV mutations may occur in gp41 leading to the failure of therapy. Rational design of this type of inhibitors ultimately produce a molecule, Enfuvirtide, with potent antiviral activity in vivo.

Enfuvirtide

Enfuvirtide is an HIV-1 fusion inhibitor approved by FDA in 2003. It is indicated for combination therapy with other anti-HIV agents in patients who are on the anti-retroviral therapy for prolonged time. It is a linear 36-amino acid synthetic peptide with the N-terminus acetylated and the C-terminus is a carbetamide. However, Enfuvirtide exhibits low anti-HIV-1 activity because of drug resistance and cross-reactivity with pre-existing antibodies in HIV patients and short half-life.

5. CCR5 Antagonists

Antagonists of chemokine receptor CCR5 bind to the hydrophobic pockets within the transmembrane helices of CCR5. This binding promotes a receptor conformation that is not recognized and blocks the binding to HIV-1 envelope. Maraviroc and Aplaviroc have been shown to inhibit virus replication in HIV-infected patients. The compound Maraviroc was approved for therapeutic use by the FDA in 2007. CXCR4 is another chemokine receptor for HIV-1 but the development of CXCR4 antagonists fail in clinical studies. Potential resistance mechanisms for chemokine receptor antagonists include binding to CXCR4 instead of CCR5.

Maraviroc is a prescription drug approved by the FDA in 2007 for treatments of HIV infection in adults. Maraviroc as an anti-HIV drug is selective small molecule antagonist of the interaction between HIV-1 and chemokine receptor 5, CCR5. Chemokines and their receptors regulate the trafficking of leukocytes in haematopoiesis and inflammation. Consequently, they are essential for the immune integrity of the host.

6. Integrase inhibitors

These drugs block the integrase HIV enzyme by attaching themselves to the integrase-viral DNA complex making this class the only one in anti-HIV drugs that bind with two essential elements of the virus: the integrase enzyme as well as the viral DNA. Mutations on the integrase active site have damaging effects on enzymatic function and viral replicative capacity. Raltegravir is an Integrase inhibitor that was tentatively FDA approved in 2007.

Raltegravir

Raltegravir, the first-generation integrase inhibitor, is an aromatic substance containing two heterocycles in its structure. This is a very critical step of HIV pathogenesis. A randomized study investigating the effects of high concentrations of Raltegravir in plasma found no severe effect. No evidence of mutagenicity or effect on fertility was observed in animal toxicology studies. Raltegravir was recommended by FDA for combined HIV therapy in 2007. It seems to be important that this drug is active against both HIV-1 and HIV-2. Raltegravir is suitable for therapy of new HIV patients but also of patients that underwent previous antiretroviral treatment.

Anti-HIV drug combinations: highly active antiretroviral therapy (HAART)

Since 1996, the importance of anti-HIV drug combination regimens has become widely accepted. What has been common practice for the treatment of tuberculosis (i.e., a combination of three tuberculostatic) has also been introduced for the treatment of AIDS: it was even given its own acronym, HAART, for highly active antiretroviral therapy. Combination of three (or more) anti-HIV compounds is aimed at the same goals as for the treatment of tuberculosis: (i) to obtain synergism between different compounds acting at different molecular targets; (ii) to lower the individual drug dosages to reduce their toxic side effects; and (iii) to diminish the likelihood of development of drug resistance of the 25 compounds that have been formally licensed for clinical use, some are not yet widely available and others (e.g. delavirdine and zalcitabine) are no longer available or prescribed, but the number of those available is still sufficiently high to allow for an astronomically high number of possible drug combinations.

While in theory, the number of possible anti-HIV drug combinations has been rapidly growing. The number of pills that have to be taken daily for all drugs combined has been drastically reduced from more than 20 pills daily in 1996 to one single daily pill in 2006.

CONCLUSION

In conclusion, HIV infection mechanism and life cycle of the virus in the host cell is a complicated process. Mutations could occur during the HIV RNA translation. This makes HIV virus harder to treat and increases chances of drug resistance. HIV infection and its various complications are constantly drawing attention of many scientists, clinicians and public health specialists. Many new chemical compounds are developed and tested for their activity on HIV virus function and on their potential to be used for the benefit of patients. Currently, six main chemical groups of antiretrovirals acting on HIV infection are clinically relevant. Their use depends on many clinical factors (age, HIV RNA load, CD4+ count, pregnancy, drug resistance etc.) and also on social situation of the patients (marriage, in-partnership, pregnancy etc.). As all of these are very important, the significant development in the research and clinical application of its results is expected for the benefit of both individual patients and society.

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