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AIDS THERAPY: INFLUENCE ON NEW DRUGS

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ABSTRACT

HIV/AIDS has always been one of the most thoroughly global of diseases. The human immunodeficiency virus (HIV) is a lent 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, Transmission, Epidemiology, Pathogenesis, Treatment, Prevention.

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.[1] However, there is substantial evidence that HIV first crossed the simian-human species barrier much earlier, possibly in Cameroon in West

Africa. There is also evidence that HIV found its way to the Caribbean before the 1980s.[2] 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.[3] 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.[4] 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. A person who is infected will be able to develop. 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 use to slow down the diseases so you stay healthier for long time. There is no medicine to get rid of diseases.[5]

Epidemiology

The HIV epidemic arose after zoonotic infections with simian immunodeficiency viruses from African primates; bushmeat hunters were probably the first group to be infected with HIV. HIV-1 was transmitted from apes and HIV-2 from sooty mangabey monkeys.[6] Four groups of HIV-1 exist and represent three separate transmission events from chimpanzees (M, N, and O), and one from gorillas (P). Groups N, O, and P are restricted to west Africa. Group M, which is the cause of the global HIV pandemic, started about 100 years ago and consists of nine subtypes: A–D, F–H, J, and K. Subtype C predominates in Africa and India, and accounted for 48% of cases of HIV-1 in 2007 worldwide. Subtype B predominates in western Europe, the Americas, and Australia. Circulating recombinant subtypes are becoming more common.[7] The marked genetic diversity of HIV-1 is a consequence of the errorprone function of reverse transcriptase, which results in a high mutation rate. HIV-2 is largely confined to west Africa and causes a similar illness to HIV-1, but immunodeficiency progresses more slowly and HIV-2 is less transmissible.[7]

Structure of virus

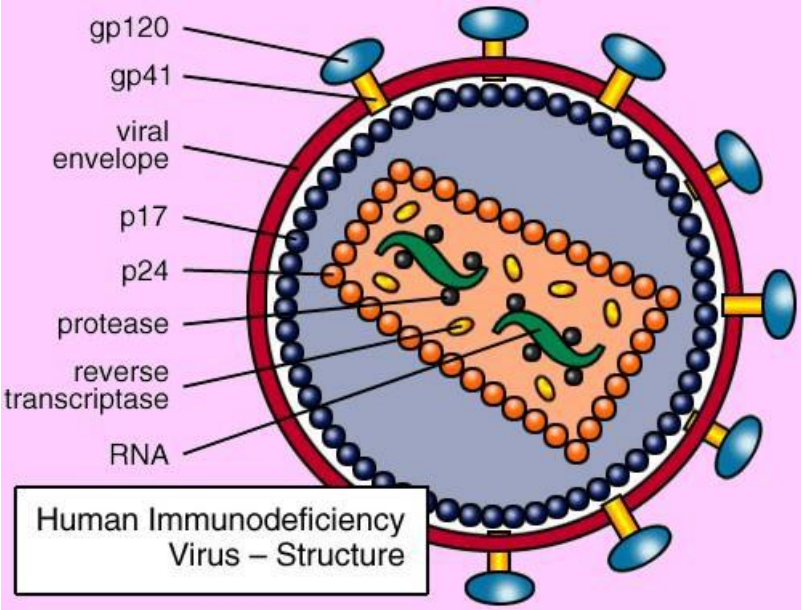

Fig. 1: Structure of HIV virus.

Gp120: The 120 in its name comes from its molecular weight. It is essential for virus entry into the cells as it plays vital role in attachment to specific cell surface receptors.

GP41: It is a subunit of the envelope protein complex of retroviruses including human immunodeficiencies virus. It is family of enveloped viruses that replicate in host cell through process of reverse transcriptase. It targets a host cell. Viral envelope It is envelope through which virus binds.

P17: Viral core is made from protein. It is bullet shaped. Three enzymes required for HIV replication are reverse transcription, integrase and protease.

P24: P24 is component of HIV capsid.

Protease: It is a retroviral aspartyl protease that is essential for life cycle of HIV, the retrovirus that caused AIDS. This enzyme cleaves newly synthesized polyproteins at appropriate place to create nature protein components of infectious HIV virion.

Integrase: Enzyme produce by retrovirus that enables its genetic material to be integrated into the DNA of infected cell.

RNA: All organisms including most viruses store their genetic material on long strands of DNA. Retrovirus is exception because their genes are composed of RNA.[8]

Pathogenesis

HIV life cycle and host immune responses

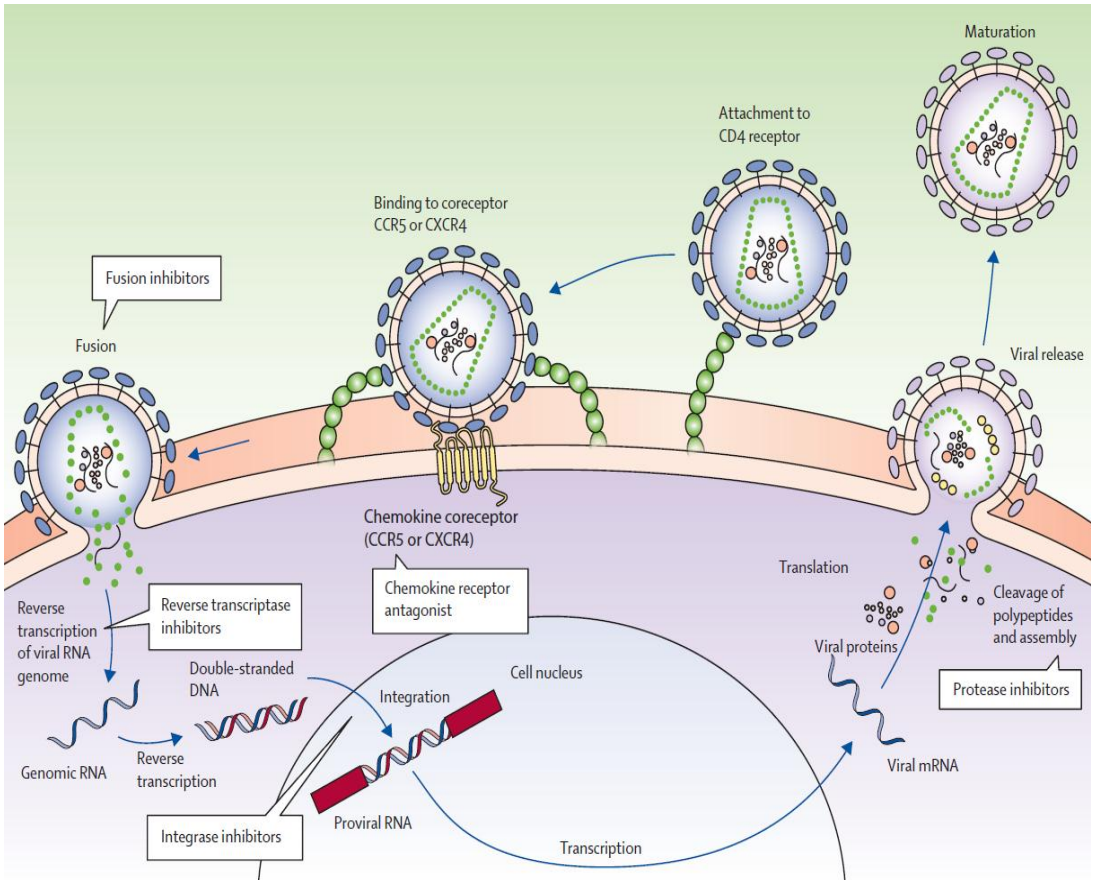

Fig. 2: HIV life cycle showing the sites of action of different classes of antiretroviral drug.

Fig:2 Show the virus life cycle. 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 chemokinereceptors are also infected, including resting CD4 T cells, monocytes and macrophages, and dendritic cells. CD4independent HIV infection of cells can happen, notably in astrocytes and renal epithelial cells,[8] 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.[9]

Transmission of HIV across mucosal membranes is usually established by one founder virus, which has unique phenotypic properties including usage of CCR5 rather than CXR4 for entry, enhanced interaction with dendritic cells, and resistance to interferon-.[10] 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.[11]

Neutralising antibodies arise roughly 3 months after transmission and select for viral escape mutants.[12] Broadly neutralising antibodies, which can neutralise many HIV-1 subtypes, are produced by about 20% of patients. These antibodies are characterised by a high frequency of somatic mutations that often take years to develop.[13] Broadly neutralising antibodies do not usually provide benefit to the patient because of the development of viral escape mutants. The production of broadly neutralising antibodies by use of new immunogen design strategies is a major focus of vaccine research.[14] The innate immune response to HIV is largely mediated by natural killer cells, and is also crucial for virus control. Viral escape mutants also emerge, and restrict the antiviral effects of natural killer cells.[15]

Transmission of HIV

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. 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. HIV is spread primarily by unprotected sexual intercourse, irrespective of gender or sexual orientation, and sharing of unsterilized injection equipment for either medical or illicit purposes. It can be transmitted from an infected mother to an infant in utero during pregnancy, perinatally, or through breast-feeding.

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 (Table 1).

Table 1: Risk of HIV Transmission Associated With Various Sexual Activities.

Risk Level	Sexual Activity
No risk	Dry kissing. Body-to-body rubbing Massage. Nipplestimulation. Using unshared inserted sexual devices. Being masturbated by partner without semen or vaginal fluids. Erotic bathing and showering. Contact with feces or urine on intact skin.
Theoretical risk	Wet kissing. Cunnilingus with barrier. Anilingus. Digital-anal and digital-vaginal intercourse, with or without glove. Using shared but disinfected inserted sexual devices.
Low risk	Sharing nondisinfected personal hygiene items (razors, toothbrushes). Cunnilingus without barrier during or outside menstruation. Fellatio and ejaculation, with or without ingestion of semen. Fellatio, with or without condom. Penile-vaginal intercourse with condom. Penile-anal intercourse with condom.
High risk	Penile-vaginal intercourse without condom. Penile-anal intercourse without condom. Coitus interruptus (intercourse with withdrawal before ejaculation).

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 (24% in 1997). It has been estimated that there are more than 1.5 million injection drug users in the United States.[16]

1. 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.

2. 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.

3. 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 socalled 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.

- 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 diarrhea or vomiting that do not go away,
- vision loss,
- Unexplained weight loss

Stages of HIV infection

There are three stages of HIV infection-

Acute HIV Infection

Acute HIV infection is the earliest stage of HIV infection, and it generally develops within 2 to 4 weeks after infection with HIV. During this time, some people have flu-like symptoms, such as fever, headache, and rash. In the acute stage of infection, HIV multiplies rapidly and spreads throughout the body. The virus attacks and destroys the infection-fighting CD4 cells of the immune system. During the acute HIV infection stage, the level of HIV in the blood is very high, which greatly increases the risk of HIV transmission. A person may experience significant health benefits if they start ART during this stage.

Chronic HIV Infection

The second stage of HIV infection is chronic HIV infection (also called asymptomatic HIV infection or clinical latency). During this stage, HIV continues to multiply in the body but at very low levels. People with chronic HIV infection may not have any HIV-related symptoms. Without ART, chronic HIV infection usually advances to AIDS in 10 years or longer, though in some people it may advance faster. People who are taking ART may be in this stage for several decades. While it is still possible to transmit HIV to others during this stage, people who take ART exactly as prescribed and maintain an undetectable viral load have effectively no risk of transmitting HIV to an HIV-negative partner through sex.

AIDS

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. Without treatment, people with AIDS typically survive about 3 years.[4]

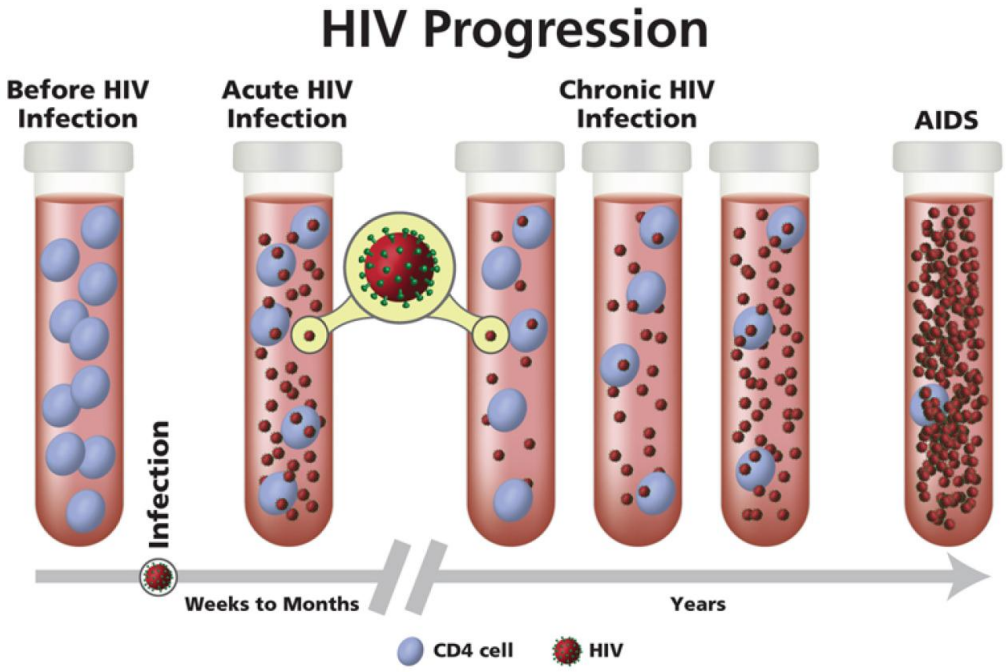

Fig. 3: Stages of HIV infection.

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.

An initial HIV test will either be an antibody test or combination test. It may involve obtaining blood or oral fluid for a rapid test or sending blood or oral fluid to a laboratory. If the initial HIV test is a rapid test and it is positive, the individual will be directed to get follow-up testing. If the initial HIV test is a laboratory test and is positive, the laboratory will usually conduct follow-up testing on the same blood specimen as the initial test. Although HIV tests are generally very accurate, **follow-up testing** allows the health care provider to be sure the diagnosis is right.[17]

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.

Table 2: Summarization of the representative anti-HIV (antiretroviral) therapeutics.

Group	Drug	Type of the molecule	Mechanism of action
NRTIs	Abacavir	A synthetic carbocyclicpurine nucleoside analog	Inhibition of reverse transcriptase.
NNRTIs	Delavirdine	A methanesulfonic acid derivative.	Inhibition of reverse transcriptase.
Protease inhibitor	Atazanavir	Carbamate	Inhibition of viral polyprotein processing.
Fusion inhibitors	Enfurvirte	A synthetic peptide.	Fusion/entry inhibition targeting the hydrophobic.
Chemokine receptor antagonists	Maraviroc	Azabicyclocarbamide.	Interaction with chemokine receptor CCR5.

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 are prodrugs and 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.[20] The viral DNA is stopped because the structural changes ofintegrated nucleotide analogs. Missing functionality, i.e. missing 3'-OH group, prevents the 5’ to 3’ phosphodiester connection necessary for DNA sequence elongation.

HIV resistance occurs through nucleotide associated mutations that remove NRTIs from the 3’ end. The FDA approved NRTIs are: Abacavir, Didanosine, Emtricitabine, Lamivudine, Stavudine, Zalcitabine, Zidovudine, and Tenofovir disoprovil fumarate.[21]

Abacavir

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. Abacavir 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 decreases 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.[22]

Non-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.[25] Unlike NRTIs, these noncompetitive inhibitors do not inhibit the reverse transcriptase of other lentiviruses, such as simian immunodeficiency virus (SIV). Additionally, unlike NRTIs, these molecules do not require metabolic activation through phosphorylation of the 5' nucleoside hydroxyl group to form a biologically active nucleotide. The currently approved NNRTIs are Etravirine, Delavirdine, Efavirenz, and Nevirapine.[18]

Delavirdine

Delavirdine (Fig. 1B) 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. It structure is interesting as it includes a methanesulfonic acid functional group.[26] 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 doses Delavirdine. 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.[19]

2. 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. This may be a base of a viral strategy to counter host defense mechanisms. Protease inhibitors hinder the action of HIV protease through selective binding and blocking proteolytic cleavage of protein precursors essential from the production of

infectious HIV particles. Consequently, the amount of viruses in the viral loads decreases because of the inhibition of protease.[21] 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. (The role of HIV protease is to cleave newly synthesized polyproteins helping to create mature protein components of fully functional HIV virion. Atazanavir is normally taken with Ritonavir. However, recent data indicate that changing the patients with achieved virological suppression from retroviral-boosted-by-Ritonavirtherapy to Atazanavir improves safety (decrease of abnormalities in blood parameters) without a sacrifice of virological efficacy.[22]

3. 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. Monotherapy with fusion inhibitors causes viral loads rebound after two weeks of therapy because of these mutations. Rational design of this type of inhibitors ultimately produced 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 (Fig. 1C) with the N-terminus acetylated and the C-terminus is a carbetamide.[23] Enfuvirtide targets the hydrophobic pocket in the HIV-1 gp41 (the transmembrane subunit of envelope glycoprotein) N-terminal. FDA approved by for being the first HIV fusion/entry inhibitor for treatment of HIV/AIDS patients failing to respond to other currently used antiretroviral drugs. However, Enfuvirtide exhibits low anti-HIV-1 activity because of drug resistance and cross-reactivity with preexisting antibodies in HIV patients and short half-life.

4. 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 human 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 clinicalstudies. Potential resistance mechanisms for chemokine receptor antagonists include binding to CXCR4 instead of CCR5.[25]

Maraviroc

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 hematopoiesis and inflammation. Consequently, they are essential for the immune integrity of the host. Maraviroc is the first clinically used CCR5 antagonist. However, the drug should be specifically used only in the patients infected with HIV strain containing CCR5 receptor.[35] It was demonstrated that the Maraviroccontaining antiretroviral therapeutic regimes are possessing high effectivity. Additionally, these therapeutic regimes are safe for R5-tropic HIV patients.[27]

1. 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. These inhibitors interact with the two essential magnesium metal ions in the integrase active site and also the DNA. As a result the integrase inhibitors contain two essential components which are a metal-binding pharmacophore for the active site magnesium, and a hydrophobic group for the viral DNA. This leads to preventing HIV from augmenting which can reduce the amount of HIV in the body. Mutations on the integrase active site have damaging effects on enzymatic function and viral replicative capacity. Raltegravir is an Integrase inhibitors that was tentatively FDA approved in 2007.

Raltegravir

Raltegravir, the first generation integrase inhibitor, is an aromatic substance containing two heterocycles in its structure. It interferes with the function of integrase - the HIV enzyme integrating the viral genetic material into host chromosomes. This is a very critical step of HIV pathogenesis.[28]

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[38]. Raltegravir is suitable for therapy of new HIV patients but also of patients that underwent previous antiretroviral treatment. Raltegravir cross-resistance properties stimulated the introduction of Dolutegravir, a second generation integrase inhibitor, possessing efficacy, excellent tolerability and infrequent drug-drug interactions.

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 tuberculostatics) 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)toobtainsynergism 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 for mallylicensedforclinicaluse, 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. Whilst 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.[29]

Prevention

Mother-to-child transmission

Prevention of mother-to-child transmission has seen advances in both industrialised and resource-constrained settings. Intrapartum transmission has been reduced by increasing access to interventions such as one dose of nevirapine to mother and new born baby. Concerns about drug-resistant viral strains have led to several trials with combination treatments to reduce transmission during the intrapartum period. In some settings, elective delivery by caesarean section can further reduce HIV-1 transmission during the intrapartum period, but the benefits of the intervention could be countered by post-partum sepsis and increasing maternal mortality.

Because HIV-1 can be transmitted by breastfeeding, replacement feeding is recommended in many settings. Poor access to clean running water precludes, however, the use of formula feeding under these circumstances, and exclusive breastfeeding with abrupt weaning is one option for reducing transmission. A potential novel intervention still being tested is the daily use of antiretrovirals during breastfeeding. More attention is starting to focus on the pregnant mother, especially initiation of antiretroviral therapy in mothers with low CD4+ counts during pregnancy and thereafter. Only limited data are available regarding the health of uninfected children born to HIV-1-positive mothers. 161 In a European cohort of exposed-uninfected children, no serious clinical manifestations were apparent, at least in the short term to medium term (median follow-up 2 years).

Sexual transmission

Reduction of heterosexual transmission is crucial for control of the epidemic in many parts of the world. 1, Prevention is achieved through reduction in the number of discordant sexual acts or reduction of the probability of HIV-1 transmission in discordant sexual acts. The first can be achieved through abstinence and sex between concordantly seronegative individuals. Abstinence and lifelong monogamous relationships might not be adequate solutions for many people and therefore several interventions aimed at lowering the risk of transmission per discordant sexual act are in the process of clinical testing. Male and female condoms provide a proven and affordable prevention option. In combination, these options are also more commonly referred to as the ABC (abstinence, be faithful, condom use) approach.

HSV-2 might increase both the risk of transmitting and acquiring HIV-1. Antivirals (eg, aciclovir, valaciclovir) are effective in reducing viral shedding and HSV-2 transmission in

discordant heterosexual couples. The future of HSV-2 prevention might reside in the vaccine that is currently under development. Whether prophylactic use of aciclovir in populations with high HSV-2 prevalence and incidence rates results in reduced HIV-1 incidence rates remains unresolved but several trials addressing this issue are underway, including HPTN039.

Gender disparities lie at the centre of women's vulnerability. Prevention options need to be provided that can be used by women independently of their male sexual partner's knowledge or consent. Notwithstanding that redressing these disparities is a long-term challenge, several preventive interventions can be implemented in the interim on the basis of our incomplete understanding at a biological level of HIV-1 risk for women. For example, there seems to be a correlation between levels of sexual hormones (eg, progesterone) and transmission risk. Observational studies also highlight the relation between abnormal vaginal flora and increased risk of HIV-1 infection. The high prevalence of vaginal infections such as bacterial vaginosis (30–50%), vulvovaginal candidosis (10–13%), and trichomonas vaginalis (7–23%) in African women is associated with a substantial risk of HIV-1 acquisition.189 In addition to increasing access to female condoms and treatment of other sexually transmitted infections, trials are underway to assess the use of other barrier methods such as cervical caps, invisible condoms, diaphragms, and diaphragms combined with micro bicides. The control of vaginal infections is a potentially important method for decreasing HIV-1 acquisition that has yet to be tested. Periodic presumptive treatment for vaginal infections is being explored as an HIV-1 prevention strategy.

Vaccines

A safe, protective, and inexpensive vaccine would be the most efficient and possibly the only way to curb the HIV pandemic. Despite intensive research, development of such a candidate vaccine remains elusive. Safety concerns prohibit the use of live-attenuated virus as immunogen. Many different approaches with recombinant technologies have been pursued over the past two decades. Initially, efforts were focused on generating neutralising antibodies with recombinant monomeric envelope gp120 (AIDSVAX) as immunogen. This vaccine did not induce neutralising antibodies and, not unexpectedly, the phase III trials failed to show protection. Antibody mediated HIV-1 neutralisation is complicated by the high genetic diversity of the variable Env regions, epitopes masked by a carbohydrate shield (glycosylation), and conformational or energetic constraints. Since CD8 T-cell responses

control to some extent viral replication in vivo, recent vaccine development has focused on eliciting cellular immune responses.

Targeting Latent HIV Reservoirs

Targeting latent HIV reservoirs is aimed to cure HIV by removing cells infected with latent, nonreplicating HIV. The HIV infection has the ability to establish a subset of latent infected CD4+ T cells that are undetectable to the immune system and play a role of latent HIV reservoirs. This is a major roadblock to achieve complete viral eradication. However, histone deacetylase inhibitors (HDACIs) have the ability to induce the reactivation of latent HIV.

Gene Therapy

Gene therapy is a promising, so far experimental, approach for potential HIV cure. It is currently in early stages of clinical testing. In summary, gene therapy is performed by harvesting cells from the patient's body, modifying their genetic information and then injecting them back to the patient. Strategies in gene therapy that are being investigated involve preventing immune cells from being infected, turning off HIV genes and enhancing the immune system's response to HIV.

Other rationale of introducing gene therapy as a part of anti-HIV therapy is based on the fact that about 1% of European descent population is lacking CCR5 co-receptors, which makes it resistant to HIV infection. It was found in 2014 that among six HIV-positive patients who received gene therapy without anti HIV drugs, four patients had elevated CD4+ count. Furthermore, the HIV disappeared completely in one patient who had some T cells that were already resistant to HIV.[50]

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 specialist. Many new chemicals 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. These are nucleoside and non-nucleoside reverse transcriptase inhibitors, fusion inhibitors, integrase inhibitors, protease inhibitors, and chemokine receptor antagonists. 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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