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Anti-HIV/AIDS Drugs: An Overview

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ABSTRACT

Human Immunodeficiency Virus (HIV) is an enveloped virus, belonging to the viral family Retroviridae. It is a highly evolved virus which has grasped the attention of all researchers with its special features like morphology, genetics and also by its emerging nature[3]. The special feature of all retro viruses is the presence of an enzyme called Reverse transcriptase which plays major role in reverse transcription process[4]. HIV enters the host body, damages immune system and will cause life-threatening opportunistic infections finally leads to AIDS (Acquired Immunodeficiency Syndrome).Many advances have been made in the prevention of HIV transmission and management of HIV/AIDS since the virus was discovered in the early 1980s[7]. One of the most important discoveries has been antiretroviral treatment, which can halt the replication of HIV and ease symptoms, turning AIDS into a chronic condition instead of a rapidly terminal illness. Despite advances, HIV remains a major public health challenge. This article reviews the genus, life cycle, and transmission of HIV, as well as workplace issues surrounding the virus and the challenges of developing an HIV vaccine[12].

Keywords: Acquired Immunodeficiency Syndrome.

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INTRODUCTION OF AIDS

Definition

AIDS is the last stage in a progression of diseases resulting from a viral infection known as the Human Immunodeficiency Virus (HIV or AIDS virus). The diseases include a number of unusual and severe infections, cancers and debilitating illnesses, resulting in severe weight loss or wasting away, and diseases affecting the brain and central nervous system[6]. There is no cure for HIV infection or AIDS nor is there a vaccine to prevent HIV infection. However, new medications not only can slow the progression of the infection, but can also markedly suppress the virus, thereby restoring the body's immune function and permitting many HIV-infected individuals to lead a normal, disease-free life[8].

Description

The immune system is a network of cells, organs and proteins that work together to defend and protect the body from potentially harmful, infectious microorganisms (microscopic life-forms), such as bacteria, viruses, parasites and fungi[14]. The immune system also plays a critical role in preventing the development and spread of many types of cancer. When the immune system is missing one or more of its components, the result is an immunodeficiency disorder. AIDS is an immunodeficiency disorder[17].

Lymphocytes (white blood cells) are one of the main types of immune cells that make up the immune system[20]. There are two types of lymphocytes: B cells and T cells. (T cells are also called CD4 cells, CD4 T cells, or CD4 cell lymphocytes). B cells secrete antibodies (proteins) into the body's fluids to ambush and attack antigens (foreign proteins such as bacteria, viruses or fungi)[25]. T cells directly attack and destroy infected or malignant cells in the body. There are two types of T cells: helper T cells and killer T cells. Helper T cells recognize the antigen and activate the killer T cells. Killer T cells then destroy the antigen[4]. When HIV is introduced into the body, this virus is too strong for the helper T cells and killer T cells. The virus then invades these cells and starts to reproduce itself, thereby not only killing the CD4 T cells, but also spreading to infect otherwise healthy cells[5]. The HIV virus cannot be destroyed and lives in the body undetected for months or years before any sign of illness appears. Gradually, over many years or even decades, as the T cells become progressively destroyed or inactivated, other viruses, parasites or cancer cells (called "opportunistic diseases") which would not have been able to get past a healthy body's defense, can multiply within the body without fear of destruction[4]. Commonly seen opportunistic

diseases in persons with HIV infection include: pneumocystis carinii pneumonia, tuberculosis, candida (yeast) infection of the mouth, throat or vagina, shingles, cytomegalovirus retinitis and kaposi's sarcoma[9].

The first cases of acquired immunodeficiency syndrome (AIDS) were reported in the United States in the spring of 1981[11]. By 1983 the human immunodeficiency virus (HIV), the virus that causes AIDS, had been isolated. Early in the U.S. HIV/AIDS pandemic, the role of substance abuse in the spread of AIDS was clearly established. Injection drug use (IDU) was identified as a direct route of HIV infection and transmission among injection drug users[13]. The largest group of early AIDS cases comprised gay and bisexual men. Early cases of HIV infection that were sexually transmitted often were related to the use of alcohol and other substances, and the majority of these cases occurred in urban, educated[17].

Currently, injection drug users represent the largest HIV-infected substance-abusing population in the United States. HIV/AIDS prevalence rates among injection drug users vary by geographic region, with the highest rates in surveyed substance abuse treatment centers in the Northeast, the South, and Puerto Rico[22]. From July 1998 through June 1999, 23 percent of all AIDS cases reported were among men and women who reported IDU (Centers for Disease Control and Prevention [CDC], 1999).IDU practices are quick and efficient vehicles for HIV transmission. The virus is transmitted primarily through the exchange of blood using needles, syringes, or other IDU equipment (e.g. cookers, rinse water, cotton) that were previously used by an HIV-infected person. Lack of knowledge about safer needle use techniques and the lack of alternatives to needle sharing (e.g., available supplies of clean, new needles) contribute to the rise of HIV/AIDS. Another route of HIV transmission among injection drug users is through sexual contacts within relatively closed sexual networks, which are characterized by multiple sex partners, unprotected sexual intercourse, and exchange of sex for money[21]. The inclusion of alcohol and other no injection substances to this lethal mixture only increases the HIV/AIDS caseload. A major risk factor for HIV/AIDS among injection drug users is crack use; one study found that crack abusers reported more sexual partners in the last 12 months, more sexually transmitted diseases (STDs) in their lifetimes, and greater frequency of paying for sex, exchanging sex for drugs, and having sex with injection drug users.

HIV TRANSMISSION

HIV cannot survive outside of a human cell. HIV must be transmitted directly from one person to another through human body fluids that contain HIV-infected cells, such as blood, semen, vaginal secretions, or breast milk. The most effective means of transmitting HIV is by direct contact between the infected blood of one person and the blood supply of another. (See Figure 1-1 for an illustration of the structure of the virus.) This can occur in childbirth as well as through blood transfusions or organ transplants prior to 1985. (Testing of the blood supply began in 1985, and the chance of this has greatly decreased.) Using injection equipment that an infected person used is another direct way to transmit HIV[11].

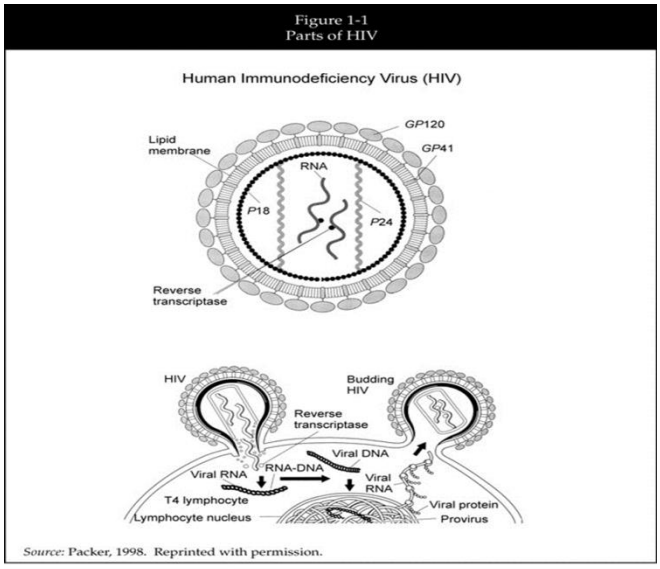


Figure 1-1: Parts of HIV.

Sexual contact is also an effective transmission route for HIV because the tissues of the anus, rectum, and vagina are mucosal surfaces that can contain infected human body fluids and because these surfaces can be easily injured, allowing the virus to enter the body. A person is about five times more likely to contract HIV through anal intercourse than through vaginal intercourse because the tissues of the anal region are more prone to breaks and bleeding during sexual activity.

A woman is eight times more likely to contract HIV through vaginal intercourse if the man is infected than in the reverse situation (Center for AIDS Prevention Studies, 1998)[23]. HIV can be passed from a woman to a man during intercourse, but this is less likely because the skin of the penis is not as easily damaged. Female-to-female transmission of HIV apparently is rare but should be considered a possible means of transmission because of the potential exposure of mucous membranes to vaginal secretions and menstrual blood. Oral intercourse also is a potential risk but is less likely to transmit the disease than anal or vaginal intercourse. Saliva seems to have some effect in helping prevent transmission of HIV, and the oral tissues are less likely to be injured in sexual activity than those of the vagina or anus. However, if a person has infections or injuries in the mouth or gums, then the risk of contracting HIV through oral sex increases[18].

Role of circumcision in male infectivity:

A possible link between male circumcision and HIV infectivity was first observed during studies conducted in Kenya in the late 1980s. Since then, numerous studies have been done on the possible relationship between male circumcision and HIV infectivity. Data have not revealed a direct causal link between circumcision and HIV transmission, and scientific opinion has been divided on this topic. While some studies indicate that circumcision can play a protective role in preventing HIV infection[17]. The bulk of recent scientific research has concluded that the reverse is true and that circumcision can actually increase the rate of HIV transmission. Clearly, further research and analysis of circumcision as a prophylactic against HIV transmission is needed[19]

Risks of Transmission:

Several factors can increase the risk of HIV transmission. One factor is the presence of another STD (e.g., genital ulcer

disease) in either partner, which increases the risk of becoming infected with HIV through sexual contact. This is because the same risk behaviors that resulted in the person contracting an STD increase that person's chance of contracting HIV[15]. STDs also can cause genital lesions that serve as ports of entry for HIV, they can increase the number of HIV target cells (CD4+ T cells), and they can cause the person to shed greater concentrations of HIV (CDC, 1998a). For this reason, all sexually active clients, especially women, should be checked regularly for STDs such as gonorrhea and chlamydia. Many STDs that cause symptoms in men are asymptomatic in women. When genital ulcers are treated and heal, the risk of HIV transmission is reduced.

Another factor that increases risk is a high level of HIV circulating in the bloodstream. This occurs soon after the initial infection and returns late in the disease[16]. New drug therapy can keep this level (called viral load) low or undetectable, but this does not mean that other individuals cannot be infected. The virus still exists--it is simply not detectable by the currently available tests. Because the correlation between plasma and genital fluid viral load varies, transmission may still occur despite an undetectable serum viral load[12]. Once HIV passes to an uninfected person who is not taking anti-HIV drugs, the virus reproduces very rapidly. It is known that drug-resistant viruses can be transmitted from one person to another. The treatment implications for a person infected with a drug-resistant virus are not yet known, but treatment will likely be difficult.[20] There are many misconceptions regarding HIV transmission. For example, HIV is not passed from one person to another in normal daily contact that does not involve either exposure to blood or sexual contact. It is not carried by mosquitoes and cannot be caught from toilet seats or from eating food prepared by someone with AIDS. No one has ever contracted AIDS by kissing someone with AIDS, or even by sharing a toothbrush (although sharing a toothbrush still is not advised)[10]. Other misconceptions people may have included the following: "It can't happen to me."--HIV can infect anyone who has sex with or shares injection equipment with, someone who is infected. "I would know if my sex partner (injection partner) were infected."--Most people infected with HIV do not look or feel sick and do not even know they are infected.

"As long as I get treated for any sexual infections I pick up, I'll be safe."--No current form of treatment can cure or prevent HIV, and although treating other infections reduces risk, there is still a high chance of getting HIV through unprotected sex or sharing injection equipment[9]. "If I'm only with one sexual partner, and don't share injection equipment, I don't need to worry about HIV."--This is true only if the partner is uninfected and has no ongoing risk of infection. If the partner is or becomes infected, then anyone who has sex with him or shares his injection equipment is at high risk for HIV, and the only way to detect infection is to be tested. "If I douche or wash after sex, I won't get HIV."--Douching and washing will not prevent HIV. "If I don't share my own syringe, I won't get HIV."--HIV can also be spread through shared cookers, filters, and the prepared drug[5].

Life Cycle of HIV:

It is possible to prevent transmission even after exposure to HIV. In San Francisco, postexposure prophylaxis is being offered to people who believe they have high risk for HIV transmission because of exposure with a known or suspected HIV-infected individual. Treatment is started within 72 hours of exposure and includes combination therapy, which may include a protease inhibitor, for a period of 1 month and follow up for 12 months[2].

Once an HIV particle enters a person's body, it binds to the surface of a target cell (CD4+ T cell). The virus enters through the cell's outer envelope by shedding its own viral envelope, allowing the HIV particle to release an HIV ribonucleic acid (RNA) chain into the cell, which is then converted into deoxyribonucleic acid (DNA)[14]. The HIV DNA enters the cell's nucleus and is copied onto the cell's chromosomes. This causes the cell to begin reproducing more HIV, and eventually the cell releases more HIV particles. These new particles then attach to other target cells, which become infected. Figure 1-2 illustrates how HIV enters a CD4+ T cell and reproduces.

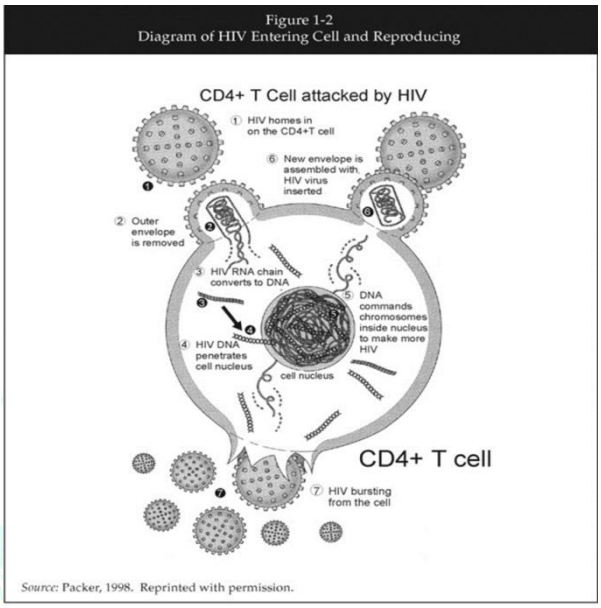


Figure 1-2: Diagram of HIV Entering Cell and Reproducing.

Measuring HIV in the Blood:

Physicians can measure the presence of HIV in a person by means of (1) the CD4+ T cell count and (2) the viral load count. The CD4+ T cell count measures the number of CD4+ T cells (i.e., white blood cells) in a milliliter of blood. These are the cells that HIV is most likely to infect, and the number of these cells reflects the overall health of a person's immune system.CD4+ T cells act as signals to inform the body's immune system that an infection exists and needs to be fought[4]. Because HIV hides inside the very cells responsible for signaling its presence, it can survive and reproduce without the infected person knowing of its existence for many years. Even though the body can produce sufficient CD4+ T cells to replace the billions that are destroyed by untreated HIV each day, eventually HIV kills so many CD4+ T cells that the damaged immune system cannot control other infections that may make the person sick. This is the late stage of HIV, when AIDS is often diagnosed based on the presence of specific illnesses (i.e., opportunistic infections)[18].

The viral load represents the level of HIV RNA (genetic material) circulating in the bloodstream. This level becomes very high soon after a person is initially infected with HIV, then it drops. Viral load tests measure the number of copies of the virus in a milliliter of plasma; currently available tests can measure down to 50 copies per milliliter, and even more sensitive tests can measure down to 5 copies per milliliter. To explain the relationship between CD4+ T cell count and viral load count and how together they are used to gauge a person's stage in disease progression, a "moving train" analogy can be used. The CD4+ T cell count is used to measure the person's distance to the point of high risk of contracting opportunistic infections, or death. The viral load

count is used to measure the rate at which CD4+ T cells are being destroyed[19]. Therefore, the CD4+ T cell count is the train's position on the track, and the viral load is the train's speed toward the outcome (i.e., AIDS and then death). After a person is infected with HIV, the body takes about 6 to 12 weeks and sometimes as long as 6 months to build up proteins to fight the virus. These proteins are called HIV antibodies (disease-fighting proteins) and are detected by an HIV test called the ELISA (enzyme-linked immunosorbent assay)[5] The ELISA is very sensitive--it almost always detects HIV if it is there. Rarely, ELISA tests will give false-positive readings (a positive test in someone uninfected). For this reason, a positive ELISA test must always be confirmed with a second, more specific test called the Western blot. According to the CDC, the accuracy of the ELISA and the Western blot together is greater than 99 percent. Rapid HIV tests and home sample collection tests also are options for clients; see Chapter 2 for a more detailed discussion of these types of tests.[13] The 6 to 12 weeks between the time of infection and the time when an ELISA test for HIV becomes positive are called the "window period." During this period, the individual is extremely infectious to any sexual or needle-sharing partner but does not test positive unless a more expensive viral load test is performed. The level of virus is determined by using a viral load test; three types of viral load tests are HIV-RNA polymerase chain reaction (PCR), HIV branched DNA (bDNA), and HIV-RNA nucleic acid sequence-based amplification (NASBA). Each of these tests measures the amount of replicating or reproducing virus in the bloodstream; thus a lower value signifies less risk of rapid progression[17]. The best viral load test result is "none detected," although this does not mean the virus is gone, only that it is not actively reproducing at a measurable level[12].

Disease Progression:

Once a person is infected with HIV, she should understand the progression of the disease from initial infection, through the latency period, symptomatic infections, and finally AIDS. The course of untreated HIV is not known but may go on for 10 years or longer in many people[11]. Several years into HIV infection, mild symptoms begin to develop, and then later severe infections that define AIDS occur. Treatment appears to greatly extend the life and improve the quality of life of most patients, although estimating survival after an AIDS diagnosis is inexact[24].

Initial infection

Primary HIV infection can cause an acute retroviral syndrome that often is mistaken for influenza (the flu), mononucleosis, or a bad cold. This syndrome is reported by roughly half of those who contract HIV (Russell and Sepkowitz, 1998) and generally occurs between 2 and 6 weeks after infection. Symptoms may include fever, headache, sore throat, fatigue, body aches, weight loss, and swollen lymph nodes. Other symptoms are a rash, mouth or genital ulcers, diarrhea, nausea and vomiting, and thrush. The CD4+ T cell count can drop very low during the early weeks, although it usually returns to a normal level after the initial illness is over[21]. The initial illness can last several days or even weeks. The greatest spread of HIV occurs throughout the body early in the disease. Approximately 6 months after infection, the level of virions produced every day may reach a "set point." A higher set point usually means a more rapid progression of HIV disease. Early treatment may be recommended to reduce the set point, potentially leading to a better chance of controlling the infection. Alcohol and drug counselors should discuss symptoms that suggest initial HIV infection with their clients and encourage clients to be tested for HIV if they experience such symptoms. This not only will encourage clients who are infected to enter treatment early but also will provide an opportunity for the counselor to help uninfected clients remain that way[13].

Latency period:

After initial infection comes the latency period, or incubation period, during which untreated persons with HIV have few, if any, symptoms. This period lasts a median of about 10 years. The most common symptom during this period is lymphadenopathy, or swollen lymph nodes. The lymph nodes found around the neck and under the arms contain cells that fight infections. Swollen lymph nodes in the groin area may be normal and not indicative of HIV. When any infection is present, lymph nodes often swell, sometimes painfully. With HIV, they swell and tend to stay swollen but usually are not painful.

Early Symptomatic Infection:

After the first year of infection, the CD4+ T cell count drops at a rate of about 30 to 90 cells per year. When the CD4+ T cell count falls below 500, mild HIV symptoms may occur.[12] Many people, however, will have no symptoms at all until the CD4+ T cell count has dropped very low (200 or less). Bacteria, viruses, and fungi that normally live on and in the human body begin to cause diseases that are also known as opportunistic infections. Early symptoms of infection may include chronic diarrhea, herpes zoster, recurrent vaginal candidiasis, thrush, oral hairy leukoplakia (a virus that causes white patches in the mouth), abnormal Pap tests, thrombocytopenia, or numbness or tingling in the toes or fingers. Most of these infections occur with a CD4+ T cell count between 200 and 500. Symptoms of these infections usually signal a problem with the immune system but are not severe enough to be classified as AIDS. Please refer to Appendix D for a complete checklist of symptoms[17].

TYPES OF HIV:

HIV Types There are two types of HIV that cause AIDS: HIV type 1 (HIV-1) and HIV-2. We know little about HIV-2. Studies have shown striking similarities but also important differences between HIV-1 and HIV-2. They have the same modes of transmission and are associated with the same opportunistic infections, but HIV-2 appears to progress more slowly. Most HIV-2 cases are found in western Africa and in countries related to western Africa in some way such as Portugal, France, Angola, Mozambique, Brazil, and India. Various subtypes of HIV-1 have been found in specific geographic areas and in specific high-risk groups[1]. A person can be coinfected with different subtypes. The following are HIV-1 subtypes and their geographic distributions: Subtype A: Central Africa, sub-Saharan Africa Subtype B: South America, Brazil, United States, Thailand, Europe, Caribbean, India, Japan Subtype C: Brazil, India, South Africa Subtype D: Central Africa, sub-Saharan Africa Subtype E: Thailand, Central African Republic, Southeast Asia Subtype F: Brazil, Romania, Democratic Republic of Congo (Zaire) Subtype G: Democratic Republic of Congo (Zaire), Gabon, Thailand, Russia, Central Africa Subtype H: Democratic Republic of Congo (Zaire), Gabon, Russia, Central Africa Subtype I: Cyprus Subtype O: Cameroon, Gabon.

TEST of HIV

Various blood tests now are used to detect HIV. The most frequently used test for detecting antibodies to HIV-1 is enzyme immunoassay. If it indicates the presence of antibodies, the blood is more definitively tested with the Western blot method[1]. A test that measures directly the viral

genes in the blood is helpful in assessing the efficacy of treatments. There is no cure for AIDS, but it may be treated with a number of different antiretroviral drugs, often in combination. Early treatment with retrovirals, as soon as a person tests positive for infection with HIV, has been shown in studies to reduce to the transmission of HIV. Drugs such as AZT, ddI, and 3TC, which are reverse transcriptase inhibitors, have proved effective in delaying the onset of symptoms in certain subsets of infected individuals. The addition of a protease inhibitor, such as saquinovir, amprenavir, or atazanavir, to AZT and 3TC has proved very effective, but the drug combination does not eliminate the virus from the body. Efavirenz (Sustiva), another type of reverse transcriptase inhibitor, must be taken with protease inhibitors or older AIDS medicines. Highly active antiretroviral therapy (HAART), a combination typically of three or more anti-AIDS drugs, is now the preferred treatment. Opportunistic infections are treated with various antibiotics and antivirals, and patients with malignancies may undergo chemotherapy[3]. These measures may prolong life or improve the quality of life, but drugs for AIDS treatment may also produce painful or debilitating side effects. Many experimental AIDS vaccines have been developed and tested, but none has yet proved more than modestly effective, including some that underwent full-scale testing. The development of a successful vaccine against AIDS has been slowed because HIV mutates rapidly, causing it to become unrecognizable to the immune system, and because, unlike most viruses, HIV attacks and destroys essential components of the very immune system a vaccine is designed to stimulate[8]

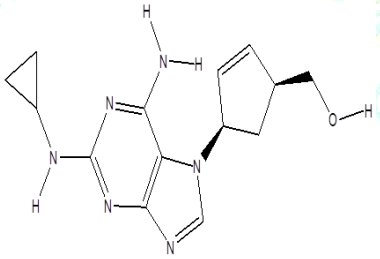
HIV TREATMENT

FDA-Approved HIV Medicines

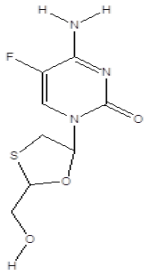
Treatment with HIV medicines is called antiretroviral therapy (ART). ART is recommended for everyone with HIV. People on ART take a combination of HIV medicines (called an HIV regimen) every day. A person's initial HIV regimen generally includes three HIV medicines from at least two different drug classes. ART can't cure HIV, but HIV medicines help people with HIV live longer, healthier lives[2]. HIV medicines also reduce the risk of HIV transmission. The following table lists HIV medicines approved by the U.S. Food and Drug Administration (FDA) for the treatment of HIV infection in the United States. The HIV medicines are listed according to drug class and identified by generic and brand names. Click on a drug name to view information on the drug from the AID Sinfo Drug Database. Or download the AID Sinfo Drug Database app to view the information on your Apple or Android devices[5].

A) Nucleoside Reverse Transcriptase Inhibitors (NRTIs):

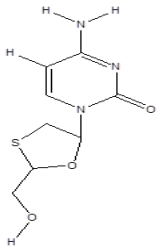
Abacavir



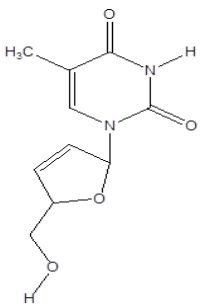
Emitricitabin



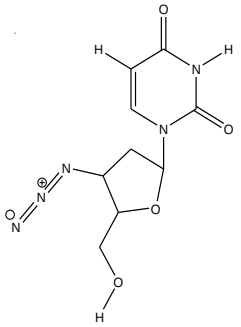
Lumivudine



Stavudine

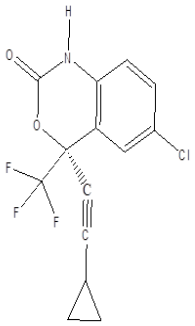


Zidovudine

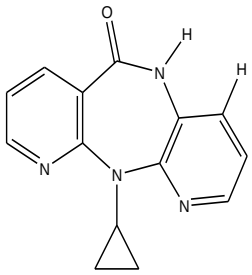


B) Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs):

Enfuviretide

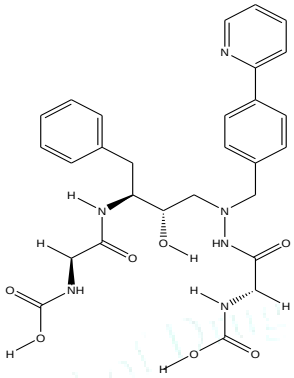


Rilpivirine

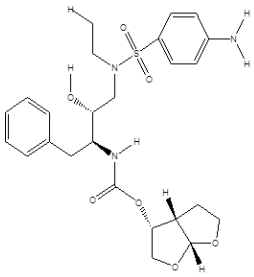


C) Protease Inhibitors (PIs):

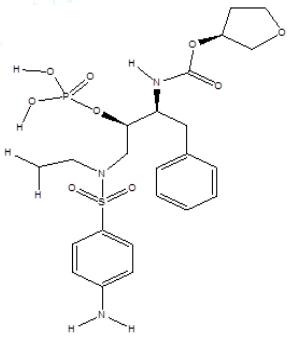
Atazanavir



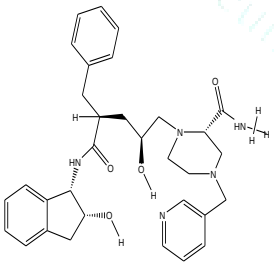
Darunavir



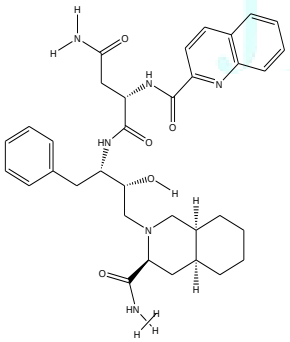
Fosamprenavir



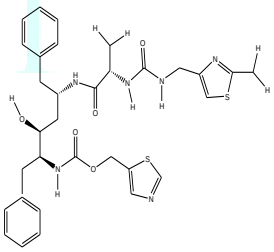
Indinavir



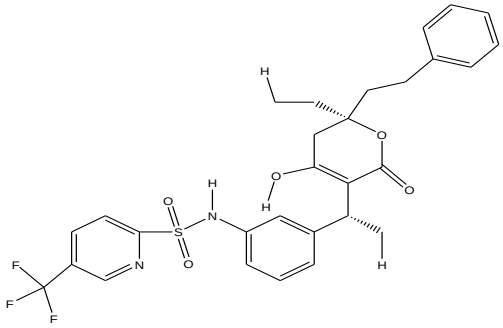
Nelfinavir



Sequinavir

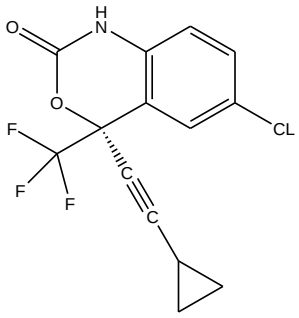


Tipranavir



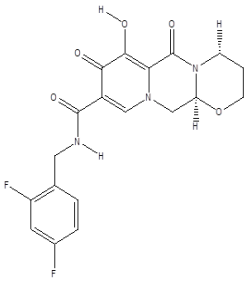
D) Fusion Inhibitors:

Enfuvirtide

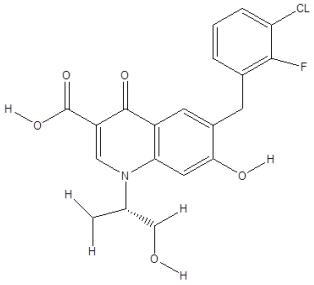


E) Integrase Inhibitors:

Dolutegravir



Elvitegravir



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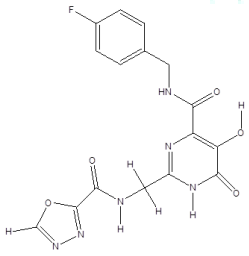
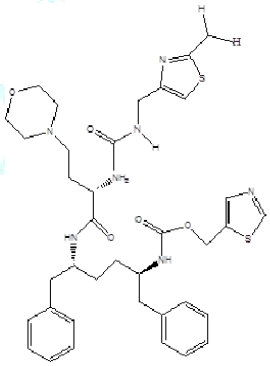


F) Pharmacokinetic Enhancers:

Cobiciatat



MECHANISM OF ACTION OF HIV DRUG:

When HIV infects a cell, reverse transcriptase copies the viral single stranded RNA genome into a double-stranded viral DNA. The viral DNA is then integrated into the host chromosomal DNA, which then allows host cellular processes, such as transcription and translation, to reproduce the virus[9]. RTIs block reverse transcriptase's enzymatic function and prevent completion of synthesis of the double-stranded viral DNA, thus preventing HIV from multiplying. A similar process occurs with other types of viruses. The hepatitis B virus, for example, carries its genetic material in the form of DNA, and employs a RNA-dependent DNA polymerase to replicate. Some of the same compounds used as RTIs can also block HBV replication; when used in this way they are referred to as polymerase inhibitors[10].

RTIs come in three forms:

- Nucleoside analog reverse-transcriptase inhibitors (NARTIs or NRTIs)
- Nucleotide analog reverse-transcriptase inhibitors (NtARTIs or NtRTIs)
- Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)

The antiviral effect of NRTIs and NtRTIs is essentially the same; they are analogues of the naturally occurring deoxynucleotides needed to synthesize the viral DNA and

they compete with the natural deoxynucleotides for incorporation into the growing viral DNA chain. However, unlike the natural deoxynucleotides substrates, NRTIs and NtRTIs lack a 3′-hydroxyl group on the deoxyribose moiety. As a result, following incorporation of an NRTI or an NtRTI, the next incoming deoxynucleotide cannot form the next 5′–3′phosphodiester bond needed to extend the DNA chain[7]. Thus, when an NRTI or NtRTI is incorporated, viral DNA synthesis is halted, a process known as chain termination. All NRTIs and NtRTIs are classified as competitive substrate inhibitors[8].

Unfortunately, NRTIs/NtRTIs compete as substrates for not only viral but also host DNA synthesis, acting as chain terminators for both. The former explains NRTIs'/NtRTIs'antiviral effect, while the latter explains their drug toxicity/side effects.

In contrast, NNRTIs have a completely different mode of action. NNRTIs block reverse transcriptase by binding directly to the enzyme. NNRTIs are not incorporated into the viral DNA like NRTIs, but instead inhibit the movement of protein domains of reverse transcriptase that are needed to carry out the process of DNA synthesis. NNRTIs are therefore classified as non-competitive inhibitors of reverse transcriptase[12].

Nucleoside analog reverse-transcriptase inhibitors (NARTIs or NRTIs):

Nucleoside analog reverse-transcriptase inhibitors (NARTIs or NRTIs) compose the first class of antiretroviral drugs developed. In order to be incorporated into the viral DNA, NRTIs must be activated in the cell by the addition of three phosphate groups to their deoxyribose moiety, to form NRTI triphosphates. This phosphorylation step is carried out by cellular kinase enzymes[14]. Zidovudine, also called AZT, ZDV, and azidothymidine, has the trade name Retrovir. Zidovudine was the first antiretroviral drug approved by the FDA for the treatment of HIV. Didanosine, also called ddI, with the trade names Videx and Videx EC, was the second FDA-approved antiretroviral drug. It is an analog of adenosine. Zalcitabine, also called ddC and dideoxycytidine, has the trade name Hivid. This drug has been discontinued by the manufacturer.Stavudine, also called d4T, has trade names Zerit and Zerit XR. Lamivudine, also called 3TC, has the trade name Zeffix and Epivir. It is approved for the treatment of both HIV and hepatitis B. Abacavir, also called ABC, has the trade name Ziagen, is an analog of guanosine. Emtricitabine, also called FTC, has the trade name Emtriva (formerly Coviracil). Structurally similar to lamivudine, it is approved for the treatment of HIV and undergoing clinical trials for hepatitis B. Entecavir, also called ETV, is a guanosine analog used for hepatitis B under the trade name Baraclude. It is not approved for HIV treatment[17].

Nucleotide analog reverse-transcriptase inhibitors (NtARTIs or NtRTIs):

As described above, host cells phosphorylate nucleoside analogs to nucleotide analogs. The latter serve as poison building blocks (chain terminators) for both viral and host DNA, causing respectively the desired antiviral effect and drug toxicity/side effects[20]. Taking nucleotide analog reverse-transcriptase inhibitors (NtARTIs or NtRTIs) directly obviates the initial phosphorylation step. Tenofovir, also known as TDF is a so-called 'prodrug' with the active compound deactivated by a molecular side chain that dissolves in the human body allowing a low dose of tenofovir to reach the site of desired activity. One example of the prodrug form is tenofovir disoproxil fumarate with the trade name Viread (Gilead Sciences Inc USA)[25]. It is approved in the USA for the treatment of both HIV and hepatitis B. Adefovir, also known as ADV or bis-POM PMPA, has trade names Preveon and Hepsera. It not approved by the FDA for treatment of HIV due to toxicity issues, but a lower dose is approved for the treatment of hepatitis B.While often listed in chronological order, NRTIs/NtRTIs are nucleoside/nucleotide analogues of cytidine, guanosine, thymidine and adenosine:

- Thymidine analogues: zidovudine (AZT) and stavudine (d4T)
- Cytidine analogues: zalcitabine (ddC), lamivudine (3TC), and emtricitabine (FTC)
- Guanosine analogues: abacavir (ABC) and entecavir (ETV)
- Adenosine analogues: didanosine (ddI), tenofovir (TDF), and adefovir (ADV)

Non-nucleoside reverse-transcriptase inhibitors (NNRTIs):

Non-nucleoside reverse-transcriptase inhibitors (NNRTIs) are the third class of antiretroviral drugs that were developed. In all cases, patents remain in force until beyond 2007.[6] This class of drugs was first described at the Rega Institute for Medical Research (Belgium)[23]

1. Efavirenz (Efavirenz has the trade names Sustiva and Stocrin)
2. Nevirapine
3. Delavirdine (Delavirdine, currently rarely used, has the trade name Rescriptor)
4. Etravirine
5. Rilpivirine

Portmanteau inhibitors:

Researchers have designed molecules which dually inhibit both reverse transcriptase (RT) and integrase (IN). These drugs are a type of "portmanteau inhibitors"[18].

Mechanisms of resistance to reverse transcriptase inhibitors:

While NRTIs and NNRTIs alike are effective at terminating DNA synthesis and HIV replication, HIV can and eventually does develop mechanisms that confer the virus resistance to the drugs. HIV-1 RT does not have proof-reading activity[17]. This, combined with selective pressure from the drug, leads to mutations in reverse transcriptase that make the virus less susceptible to NRTIs and NNRTIs. Aspartate residues 110, 185, and 186 in the reverse transcriptase polymerase domain are important in the binding and incorporation of nucleotides[14]. The side chains of residues K65, R72, and Q151 interact with the next incoming nucleotide. Also important is L74, which interacts with the template strand to position it for base pairing with the nucleotide. Mutation of these key amino acids results in reduced incorporation of the analogs.[13]

NRTI resistance:

There are two major mechanisms of NRTI resistance. The first being reduced incorporation of the nucleotide analog into DNA over the normal nucleotide. This results from mutations in the N-terminal polymerase domain of the reverse transcriptase that reduce the enzyme's affinity or ability to bind to the drug[12]. A prime example for this mechanism is the M184V mutation that confers resistance to lamivudine (3TC) and emtricitabine (FTC). Another well

characterized set of mutations is the Q151M complex found in multi-drug resistant HIV which decreases reverse transcriptase's efficiency at incorporating NRTIs, but does not affect natural nucleotide incorporation. The complex includes Q151M mutation along with A62V, V75I, F77L, and F116Y. A virus with Q151M alone is intermediately resistant to zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), and slightly resistant to abacavir (ABC). A virus with Q151M complexed with the other four mutations becomes highly resistant to the above drugs, and is additionally resistant to lamivudine (3TC) and emtricitabine (FTC).[8]

The second mechanism is the excision or the hydrolytic removal of the incorporated drug or pyrophosphorlysis. This is a reverse of the polymerase reaction in which the pyrophosphate/PPI released during nucleotide incorporation reacts with the incorporated drug (monophosphate) resulting in the release of the triphosphate drug.[5] This 'unblocks' the DNA chain, allowing it to be extended, and replication to continue. Excision enhancement mutations, typically M41L, D67N, K70R, L210W, T215Y/F, and K219E/Q, are selected for by thymidine analogs AZT and D4T; and are therefore called thymidine analog mutations (TAMs).Other mutations including insertions and deletions in the background of the above mutations also confer resistance via enhanced excision[4].

NNRTI resistance:

NNRTIs do not bind to the active site of the polymerase but in a less conserved pocket near the active site in the p66 subdomain. Their binding results in a conformational change in the reverse transcriptase that distorts the positioning of the residues that bind DNA, inhibiting polymerization.[11] Mutations in response to NNRTIs decrease the binding of the drug to this pocket. Treatment with a regimen including efavirenz (EFV) and nevirapine (NVP) typically results in mutations L100I, Y181C/I, K103N, V106A/M, V108I, Y188C/H/L and G190A/S[17]. There are three main mechanisms of NNRTI resistance. In the first NRTI mutations disrupt specific contacts between the inhibitor and the NNRTI binding pocket. An example of this is K103N and K101E which sit at the entrance of the pocket, blocking the entrance/binding of the drug. A second mechanism is the disruption of important interactions on the inside of the pocket. For example Y181C and Y188L result in the loss of important aromatic rings involved in NNRTI binding[12]. The third type of mutations result in changes in the overall conformation or the size of the NNRTI binding pocket. An example is G190E, which creates a steric bulk in the pocket, leaving little or no room for an NNRTI to tightly bind[13].

SYMPTOMS OF HIV

The initial stage of HIV is known as primary HIV infection or seroconversion. Many people develop symptoms, although they might not recognise them at the time. Their symptoms usually occur two to six weeks after they are infected with HIV[18].

Symptoms of primary HIV infection include:

- Fever
- Sore throat
- Tiredness
- Joint pain
- Muscle pain
- Swollen glands (nodes)
- A blotchy rash

These early symptoms are often very mild, so it is easy to mistake them for another condition, such as a cold or glandular fever. However, it is unusual to get these symptoms in association with a rash, so anyone concerned about the risk of HIV infection should request a test[2,5]. After the initial symptoms have gone, HIV will often not cause any further symptoms for many years. This is known as asymptomatic HIV infection. During this time, the virus is still reproducing and damaging your immune system.

- Possible symptoms of a serious infection caused by a damaged immune system include:
- Persistent tiredness
- Night sweats
- Unexplained weight loss
- Persistent diarrhoea
- Blurred vision
- White spots on your tongue or mouth
- Dry cough
- Shortness of breath
- A fever of above 37C (100F) that lasts a number of weeks
- Swollen glands that last for more than three months

AIDS-related illnesses, such as TB, pneumonia and some cancers, may appear. Many of these, though serious, can be treated to some extent and some are likely to improve if you start treatment and your CD4 count increases[1,5,7].

CAUSES OF HIV

HIV almost certainly arose from a very closely related virus, known as SIVcpz (simian immunodeficiency virus), which is found in chimpanzees living in parts of Africa[7]. The virus spread from infected chimps to humans when human blood came into contact with contaminated chimpanzee blood during the hunting of chimpanzees. It is thought that for many years, the human form of HIV was limited to a remote part of Africa. However, when new transport links opened up that part of Africa, the virus spread to other parts of Africa, before slowly spreading across the world[16].

TREATING AND LIVING WITH HIV

Although there is no cure for HIV, treatments are now very effective, enabling people with HIV to live long and healthy lives. Medication, known as antiretroviral, work by stopping the virus replicating in the body, allowing the immune system to repair itself and preventing further damage. These medicines come in the form of tablets, which need to be taken every day[19]. HIV is able to develop resistance to a single HIV drug very easily, but taking a combination of different drugs makes this much less likely. Most people with HIV take a combination of three antiretroviral and it is vital that the medications are taken every day as recommended by your doctor. For people living with HIV, taking effective antiretroviral therapy (where the HIV virus is "undetectable" in blood tests) will significantly reduce the risk of passing on HIV to sexual partners. It is rare for a pregnant woman living with HIV to transmit it to their babies, provided they receive timely and effective antiretroviral therapy and medical care. You will also be encouraged to take regular exercise, eat a healthy diet, stop smoking and have yearly flu jabs to minimize the risk of getting serious illnesses. Without

treatment, the immune system will become severely damaged and life-threatening illnesses such as cancer and severe infections can occur. This is known as late-stage HIV infection or AIDS[18].

PREVENTING HIV

Anyone who has sex without a condom or shares needles is at risk of HIV infection. The best way to prevent HIV is to use a condom for sex and to never share needles or other injecting equipment (including syringes, spoons and swabs).[15] Knowing your HIV status and that of your partner is also important. For people with HIV, effective antiretroviral therapy significantly reduces the risk of passing HIV to sexual partners[11].

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