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HIV Virus: Combination Therapy Approved by FDA

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Abstract

Currently 33 anti-HIV compounds have been formally approved for clinical use in the treatment of HIV/AIDS. These compounds divided into eight different categories: Nucleoside reverse transcriptase inhibitors or Nucleotide Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs), Fusion Inhibitors (FIs), post attachment inhibitors, co-receptor (CCR5/CXCR4) inhibitor, Integrase Inhibitors (INIs) and pharmacokinetic enhancer. They are targeting critical steps involve in HIV replication including viral entry, fusion, reverse transcription and integration process. These compounds are also used in drug combination regimens to achieve the highest possible benefit, tolerability and compliance and to diminish the risk of resistance development. In this review we will summarized the basic fact about HIV/AIDS, life cycle of HIV virus in various stages, target with drug class and also include recently approved drugs and their combination therapy by FDA.

Keywords: HIV/AIDS; Antiretroviral therapy; Chemokin Receptor-5 (CCR5); Monoclonal antibody (mAb) activity

Introduction

HIV (Human Immunodeficiency Virus) is the virus that causes AIDS (Acquired Immunodeficiency Syndrome). HIV can be transmitted during sexual intercourse; by sharing syringes and less likely from mother to child during pregnancy, childbirth, or breastfeeding. HIV is a virus that attacks the immune system of human body, which is our body's natural defense against illness. The virus destroys a type of White Blood Cells (WBC) in the immune system called a T-helper cell, and makes copies of that virus inside these cells. T-helper cells are also called as CD4 cells. The virus is actually not one, but several different in the class of retroviridae and the genus lentivirus. The species differs and there is a largest list of subtypes. There are two major types: HIV 1 and HIV 2. HIV 1 is thought to originate from chimpanzees and gorillas in western Africa as well as found worldwide. However HIV 2 originates from sooty mangabeys found in Senegal and Ghana.

Methodology

The first cases of AIDS were reported in 1981. The first antiretroviral drug, AZT (zidovudine) belonging to class nucleoside reverse transcriptase inhibitor was approved in 1987. After that many classes of drug used to treat HIV infection. Like Non–Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Nucleoside/Nucleotide Reverse Transcriptase Inhibitor (NRTI), Protease Inhibitors (PIs), Fusion Inhibitors (FIs), Integrase Inhibitor (INIs), Antiretroviral Therapy (ART). The objective of this study was to recognize different classes of drug which are derived to reach reduction in morbidity and mortality, increase potency, less toxicity and more convenient to the patient. For better treatment of HIV infection is require a combination of different medications, also called Antiretroviral Drugs (ARV) (Figure 1) [1].

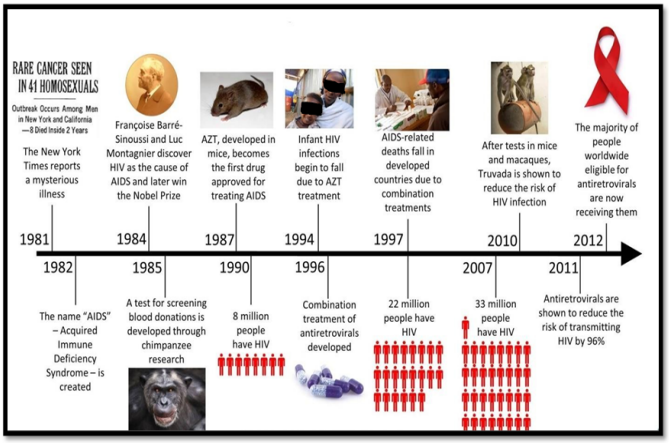

Figure 1: History of HIV/AIDS.

HIV/AIDS: How it spreads?

As HIV destroys more CD4 cells and makes more copies of itself, it gradually breaks down a person's immune system. The virus infects the body's macrophages, dendrite cells, and T-cells. HIV infected person would develop AIDS in 10 years to 15 years which is last clinical stage. HIV mainly found in blood, semen, vaginal and rectal fluids and breast milk. However, it cannot be spread through skin-to-skin contact, hugging, shaking hands, air or water, tears, sweat, saliva, urine (unless mixed with blood from an infected person) and also not spread from mosquitoes or other insects. Currently, there is no cure for HIV but with early diagnosis and effective Antiretroviral (ARV) treatment, people with HIV can live a long and normal, healthy life. Therefore, it is important to take correct treatment regularly.

The drugs currently available for HIV block the replication by interfering at various stages of the life cycle. These drugs have their own toxicities and many have reported development of resistance. We have left with very few or little options against HIV (Figures 2 and 3) [2].

The three stages of HIV involved are:

- Acute HIV infection
- Clinical latency
- AIDS (Acquired Immunodeficiency Syndrome).

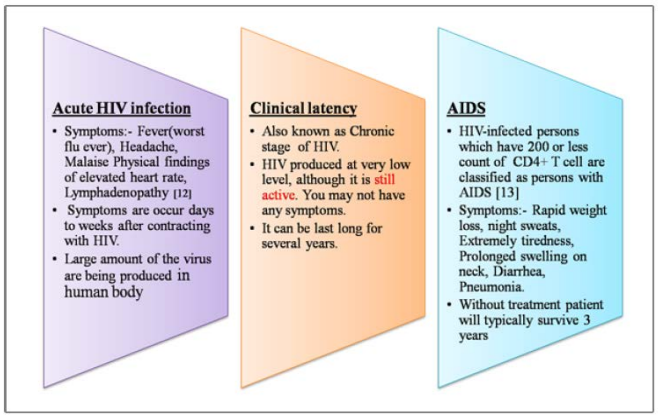

Figure 2: Different stages of HIV infection.

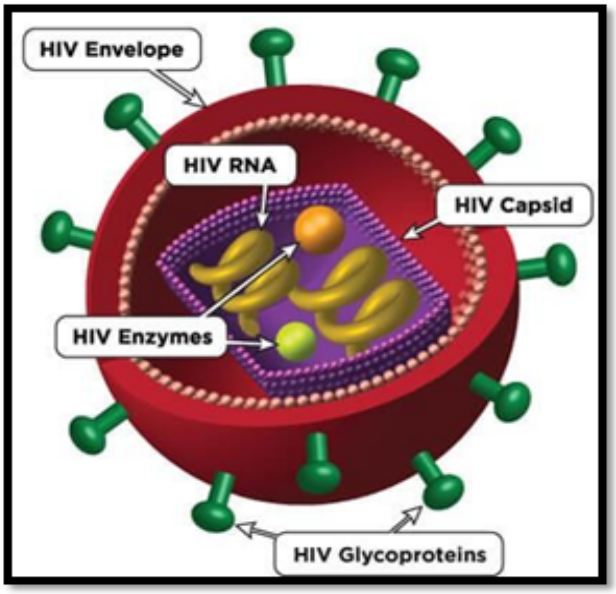

Figure 3: HIV Virus with their different parts.

- The envelope glycoprotein of HIV consists of a complex of gp120 and gp41.
- The capsid of HIV virus has a cone-shaped shell; it is made of the capsid protein including two copies of viral RNA and the enzymes reverse transcriptase and intergrade.
- Genetic material of HIV virus used in reverse transcription process.
- The HIV envelope glycoprotein's play an essential role in the virus replication cycle. They act by moderating the fusion between viral and cellular membranes during the entry process.
- Proteins those are used to carried out virus life cycle. Ex: RT, integrase, protease, etc.

Life cycle of HIV

HIV only infects certain types of cells in human body. They are called as T-helper cell or CD4 cell present on lymphatic system used as defense mechanism. When HIV comes into contact with surface of T-Lymphocytes (CD4 cells). They start their life cycle with host cell (CD4 OR T4 cell). The life cycle of HIV is randomly divided into two different phases: First one is the early phase refers to the steps of infection start from cell binding (attachment) to the host cell and remain up to the integration of the viral DNA into the cell genome (genomic RNA), whereas the second phase is late phase begins with the expression of viral genes and continues through to the release and maturation of another virus getting ready to infect other cells. The overall effect of infection with HIV virus cause severe damage to the immune system called as human body's natural defense mechanism has very vast effect on immunity power and make human more weaker than a normal [3].

The seven stages of the HIV life cycle are:

- Binding
- Fusion
- Reverse transcription
- Integration
- Replication
- Assembly
- Budding

The entry of HIV is common mechanism as we know it is carried out through CD4 receptor. But, this mechanism is not enough for HIV virus for entering into cell. So, they need second mechanism in which HIV virus fused with the surface of host cell with the help of Chemokine receptor 5 (CCR5 co receptor). Researcher now focuses on this step so that they inhibit entry of HIV RNA, reverse transcriptase enzyme, integrase enzyme and other viral proteins into the host cell. So, the development of CCR5 antagonist helps to prevent entry of viruses (Figures 4 and 5).

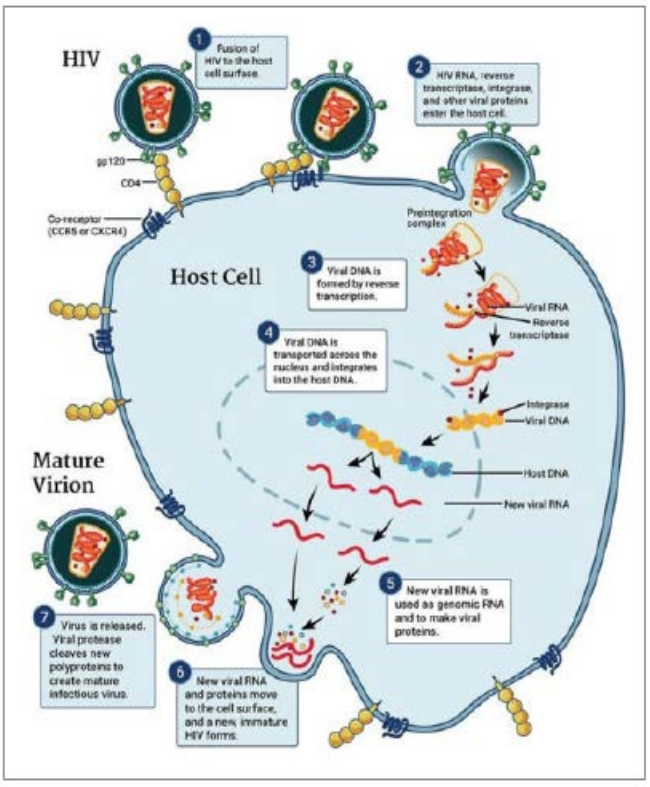

Figure 4: Life cycle of HIV virus.

After that another step of life cycle includes viral RNA conversion in viral DNA through reverse transcription process. This process is experienced by the virus-coded Reverse Transcriptase (RT) protein, which is a primary target in the current treatments for HIV infection can be inhibit or stop by RT-Inhibitors (NRTIs and NNRTIs). Reverse transcriptase inhibitors and protease inhibitors have already made significant advances in antiretroviral therapy but cannot achieve complete suppression and avoid risk from HIV/AIDS that's why many trials done to develop integrase inhibitors. Nowadays, viral integration process is required for viral replication; because reverse transcription of the viral genome and the production of viral proteins require that the viral DNA is fully integrated into a chromosome. HIV integrase is a rational target for treating HIV infection and preventing AIDS. It took approximately 12 years to develop clinically usable inhibitors of integrase process (Tables 1 and 2) [4].

ARV drugs approved by FDA	Nucleoside Reverse Transcriptase Inhibitor (NRTI)	Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)	Protease Inhibitors (PI)	Fusion inhibitors	Post attachment inhibitor	Integrase inhibitors	CCR5	Pharmaco kinetic enhancer
Before 2012	Zidovudine Lamivudine Stavudine Emtricitabine Abacavir Tenofovir Zalcitabine Didanosine	Delavirdine Efavirenz Etravirine Rilpivirine Nevirapine	Saquinavir AtazanavirIndinavir Amprenavir Ritonavir Lopinavir Tipranavir Nelfinavir Darunavir Fosamprenavir	Enfuvirtide		Raltegravir	Maraviroc	
After 2012	Tenofovir-Alafenamide					Dolutegravir Elvitegravir Cabotegravir		Cobicistat
Recent drugs (2018-19)		Doravirine			Ibalizumab-uiyk			

Table 1: FDA approved ARV drug class.

ARV drugs approved by FDA	Combination HIV Medicines
Before 2012	Abacavir and lamivudine (Epzicom)
	Abacavir, lamivudine, and zidovudine
	Lopinavir and ritonavir
	Lamivudine and zidovudine
	Emtricitabine and tenofovir disoproxil fumarate
	Emtricitabine, rilpivirine, and tenofovir disoproxil fumarate
After 2012	Abacavir, dolutegravir, and lamivudine(Triumeq)
	Emtricitabine and tenofovir alafenamide
	Emtricitabine, rilpivirine, and tenofovir alafenamide
	Dolutegravir and rilpivirine
	Darunavir and cobicistat

Recent drugs (2018-19)	Lamivudine and tenofovir disoproxil fumarate
	Efavirenz, lamivudine, and tenofovir disoproxil fumarate
	Doravirine, lamivudine, and tenofovir disoproxil fumarate
	Darunavir, cobicistat, emtricitabine, and tenofovir alafenamide
	Dolutegravir and lamivudine

Table 2: FDA approved ARV combination therapy.

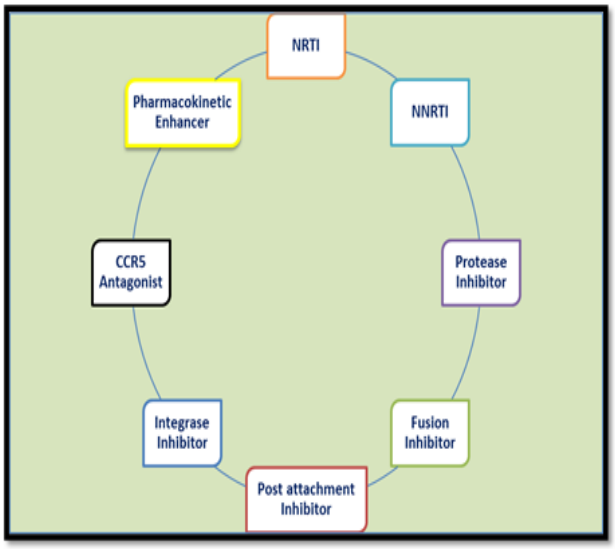

Figure 5: Classification of HIV drug.

Results and Discussion

Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

Nucleoside or nucleotide RT inhibitors are integral components of almost all anti-HIV treatments. NRTIs were the first class of antiretroviral drugs to obtain regulatory approval: In 1987 zidovudine (AZT) was the first drug to be licensed for the treatment of HIV infection. It was originally developed in 1964 as a possible cancer treatment but was found to be ineffective against tumor cells. However, collaboration between the National Cancer Institute and the Burroughs Welcome Company led to the discovery of AZT's ability to treat HIV replication. NRTIs act by incorporation into the DNA of the virus thereby stopping the building process of transcription from RNA to DNA. The resulting DNA is incomplete and cannot create a new virus. Before 2012, there are eight FDA-approved NRTIs: Abacavir (ABC, Ziagen), Didanosine (ddI, Videx), Emtricitabine (FTC, Emtriva), Lamivudine (3TC, Epivir), Stavudine (d4T, Zerit), Zalcitabine (ddC, Hivid), Zidovudine (AZT, Retrovir), and Tenofovir disoproxil fumarate (TDF, Viread), a nucleotide RT inhibitor. There is structural diversity in the eight NRTIs that have been approved by regulatory agencies for HIV treatment shown in following. NRTIs are the most important for current combination ARV therapy.

The standard of care for HIV patients, referred to as Highly Active Antiretroviral Therapy (HAART), consists of three or more HIV drugs, most commonly two NRTIs in combination with a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI), protease inhibitor or, mostrecently, integrase inhibitor shown in Figure 6 [5].

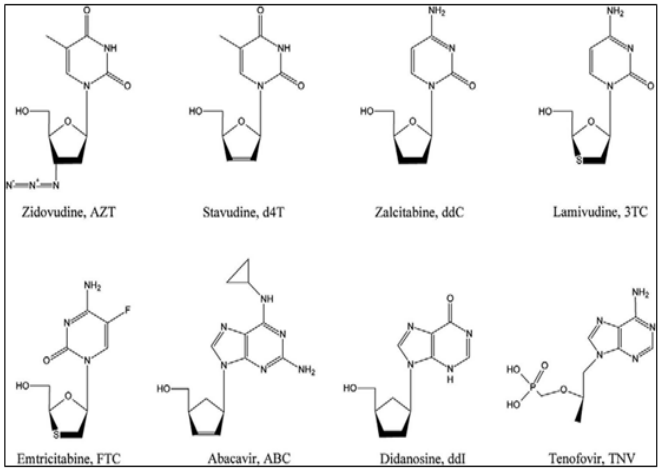

Figure 6: Example of NRTIs.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIS)

NNRTIs act by stopping HIV production by binding directly onto reverse transcriptase (non-competitively) and preventing the conversion of RNA to DNA. NNRTIs in combination with other antiretroviral drugs have been used for the treatment of HIV-1 infection for over a decade. Before 2012 five drugs of this class have been approved by regulatory authorities, although several others have entered clinical development, but were discontinued for efficacy, pharmacokinetic and safety reasons. The first generation NNRTIs were approved by the FDA in 1996. The five drugs nevirapine, delavirdine, efavirenz, etravirine and rilpivirine approved by FDA. Two of them, nevirapine and efavirenz, are heart of first line HAART (Highly Active Antiretroviral Therapy), whereas delavirdine is rarely used nowadays. Rilpivirine used in treatment for ingenuous patients. Rilpivirine shows very good bioavailability, and is easier to formulate with a daily dose of 25 mg, it is an excellent candidate for co-formulation with other antiretroviral drugs. In 2019 there is a new drug Doravirine become approved NNRTI by FDA. There are two products available after approval first one is doravirine (Pifeltro) and

another one is combination of doravirine/lamivudine/tenofovir disoproxil fumurate (Delstrigo). Doravirine used as 100 mg oral daily dose, for the treatment of HIV-1 infection in naive adults. This approval was based on clinical trials as part of a single dose with 100 mg as Pifeltro per day and single tablet daily regimen in combination with Tenofovir Disoproxil Fumarate (TDF) 300 mg and lamivudine (3TC) 300 mg as Delstrigo. It has potency to minimize toxicity effect compared to other drug class (Figure 7) [6].

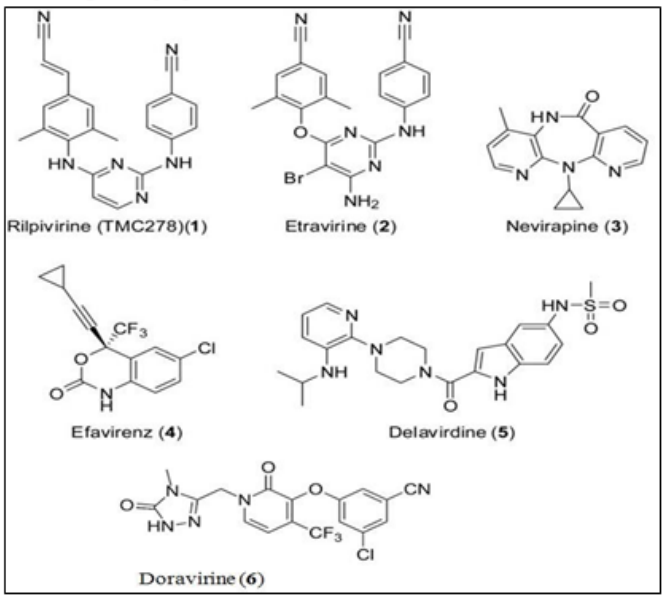

Figure 7: Example of NNRTIs.

Protease Inhibitors (PIS)

The aspartic protease of Human Immunodeficiency Virus (HIV-PR) is responsible for viral maturation process which leads to the final morphological rearrangements, and it is essential for production of infectious viral particles. PIs (Protease inhibitors) act by binding to the viral protease, thereby preventing the correct cleavage of viral proteins. Thus, they prevent HIV from being successfully assembled and released from the infected cells. Currently, there are 10 PIs available which are approved by FDA for clinical use: Saquinavir, Atazanavir, Indinavir, Amprenavir, Ritonavir, Lopinavir, Tipranavir, Nelfinavir, Darunavir, Fosamprenavir. Most of them are prescribed with concomitant low dose of Ritonavir as boosting agent.

The first protease inhibitor to be approved in 1995 by the FDA for use in antiretroviral combination therapy was Saquinavir. Soon after approval of saquinavir two other protease inhibitors were licensed in the US for clinical use as monotherapy or as part of combination therapy: Ritonavir and Indinavir. PIs made possible the dual class triple combination therapy that became known as HAART (Highly Active Antiretroviral Therapy) (Figure 8) [7-10].

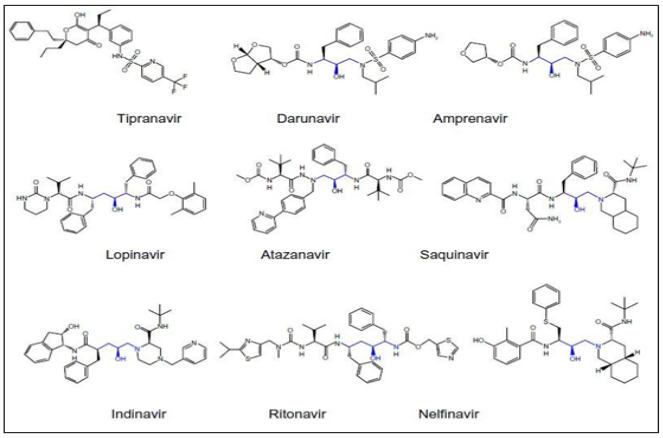

Figure 8: Example of PIs.

Fusion Inhibitors (FIS)

The HIV entry process includes virus and cell membrane fusion, resulting in the subsequent delivery of the viral genome into the host cell. The attachment of virus to the cell is carried out by the binding of the viral envelope glycoprotein (gp120) to its primary CD4 receptor present on the surface of host cell (generally T cells). So, that kind of entry process serves as drug targets. The inhibitors act by binding to the receptor present on cell surface and give antagonistic effect in which they prevent membrane fusion. Fusion inhibitors prevent HIV from attaching to the human CD4 T cell and block HIV replication in the first stage of the HIV life cycle. The first US FDA approved HIV fusion inhibitor drug Enfuvirtide which is act by inhibiting entry of HIV virus to the cell. Enfuvirtide is in peptide form therefore, oral administration is not possible as it would be rapidly broken down by gastrointestinal peptidases. So; it is administered by subcutaneous injection. Targeting viral fusion or entry will optimistically provide relief for patients who have limited treatment options following the emergence of multi-drug resistance or antiretroviral therapy (Figure 9) [11-14].

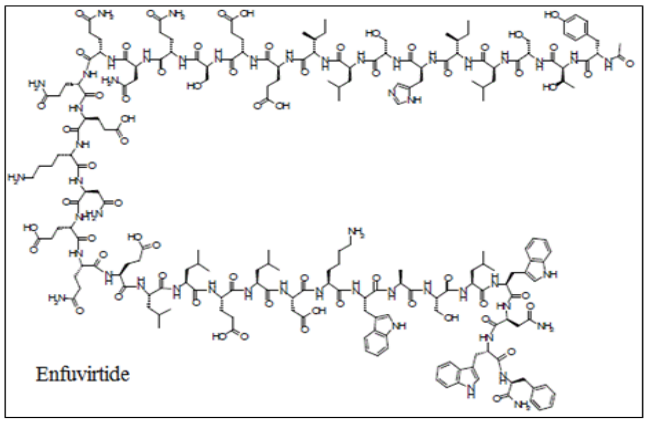

Figure 9: Example of FIs.

Post attachment inhibitors

Post-attachment inhibitors block CD4 receptors on the surface of certain immune cells which is responsible to enter HIV virus in to the cells. The CD4-directed post attachment inhibitor, ibalizumab, is the first medication approved in March 2018. It is a recombinant humanized monoclonal antibody, represents the first novel agent for HIV-1 management in over a decade. It is indicated HIV-1 infection in heavily treated adults with multidrug-resistant infection failing their current antiretroviral therapy. The monoclonal antibody (mAb) ibalizumab is improved IgG4 mAb that binds to the second stage of CD4. Ibalizumab does not prevent binding of gp120 to CD4, but is suspicions to decrease the flexibility of CD4, thereby hindering access of CD4-bound gp120 to CCR5 and CXCR4. Ibalizumab is a parenterally administered. Antiviral activity of it has been demonstrated both safety and efficacy in the treatment of HIV-1 infection. Ibalizumab now sold under the trade name TROGARZO approved by FDA. It is available in form of IV injection. It is available in a single-dose, 2 mL vial containing 150 mg/mL of ibalizumab-uiyk. Each vial delivers approximately 1.33 mL containing 200 mg of ibalizumab-uiyk [15-17].

Integrase Inhibitor (INIS)

Integration of the viral genome into host cell chromatin is an essential and unique step in the replication cycle of retroviruses, including HIV. Inhibiting HIV replication by specifically blocking the viral integrase enzyme is helpful to prevent HIV infection. After combined efforts, the first viable integrase inhibitors were developed and approved by the US FDA in 2007, raltegravir. Raltegravir also known as Merck's MK-0518. Dolutegravir and Elvitegravir approved by FDA after 2012. Dolutegravir, Raltegravir, and Elvitegravir have all been recommended as components for first-line therapy for inhibition of integration in HIV. GSK1265744 is known as Cabotegravir. It is in form of second generation drug category for integrase inhibitors. It has a two-metal binding scaffold and is in the same structure formula as Dolutegravir. It has a two-metal binding scaffold and is in the same structure formula as Dolutegravir (Figure 10) [18-21].

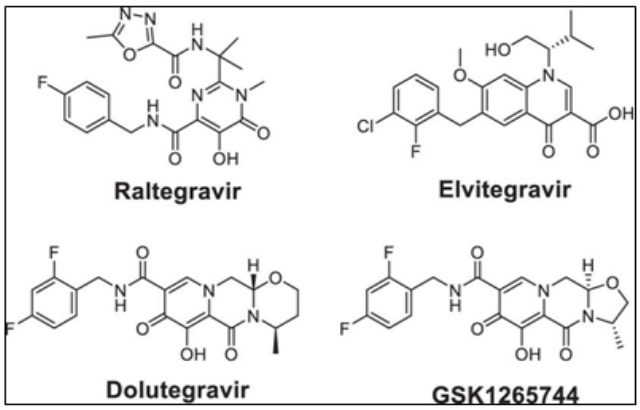

Figure 10: Example of INIs.

CCR5 Antagonist

Small-molecule CCR5 antagonists are a new class of drugs that block HIV entry into host cells, first drug of this class is Maraviroc (MVC). These drug bind to a hydrophobic pocket formed by the transmembrane helices of CCR5, inducing conformational changes in the Extracellular Loops (ECLs) of the receptor. They are work by blocking co-receptors (CCR5/CXCR4) needed for the HIV virus to enter the host cell. CCR5 antagonists have great therapeutic potential in the treatment and prevention of HIV. Even though, some CCR5 antagonists have been evaluated in clinical trials, only maraviroc has been approved by FDA for clinical use in the treatment of HIV-infected patients. The point of viral entry is a especially attractive target because drug activity is not dependent on intracellular access. Small-molecule CCR5 antagonists have some potential advantages and have been identified as a encouraging new class of CCR5 antagonist with proven efficacy (Figure 11) [22,23].

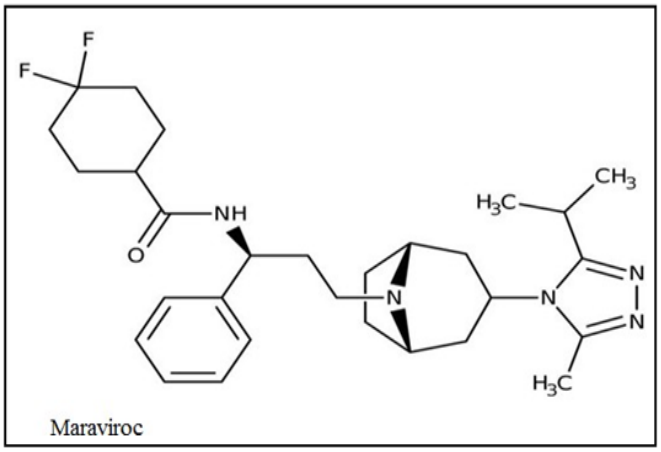

Figure 11: Mechanism of Maraviroc.

Pharmacokinetic enhancer

Pharmacokinetic enhancers, which are also named boosters or boosting agents, are compounds used in combination with a primary therapeutic agent. Both Ritonavir and Cobicistat act as pharmacokinetic enhancer. Pharmacokinetic enhancement, coadministration of a boosting agent to increase drug concentrations. Cobicistat is act as pharmacokinetic enhancer (booster) of the HIV-1 Protease Inhibitors (PIs) atazanavir and darunavir in adults.

Cobicistat is an emerging alternative to ritonavir for the pharmacokinetic enhancement of PIs in adults with HIV-1 infection. In addition to ritonavir, which has been in use since 1996, cobicistat, a new pharmacokinetic enhancer, has been approved in 2012 by FDA and is widely used now. It is coformulated into fixed-dose combinations in order to reduce pill burden and improve adherence with once-daily HIV regimens but it is also available as a single agent (Figure 12)[24,25].

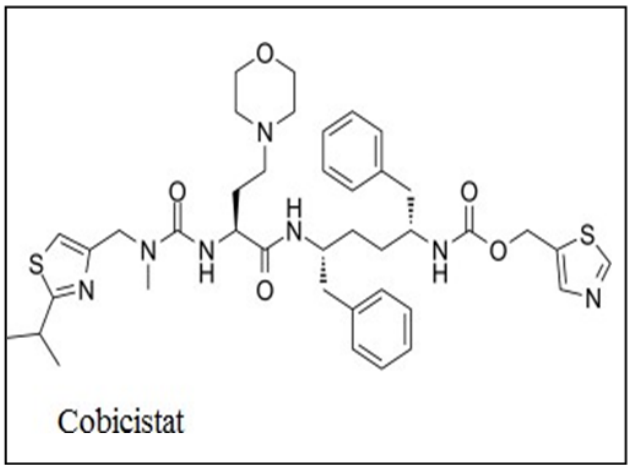

Figure 12: Example of pharmacokinetic enhancer.

Finally, the novel agents for treatment of HIV improve the efficiency and quality of drug to overcome morbidity and mortality rate. Novel drug targets are essential to improve the outcomes from HIV related disease. Around 50 million people worldwide are infected with HIV, and a significant number of these infections have become resistant to current antiretroviral therapies. The viral enzymes used during HIV replication make many mistakes while copying the parental viral genome into progeny virus, and these mistakes translate into numerous mutations. Some of these mutations contribute to make the virus resistant to antiretroviral drugs, and this resistance results in treatment failure. Ultimately, these technologies may lead to fundamental changes in the HIV healthcare. So, aim of the work is to provide recent research for awareness to the people who suffering from infections regarding to HIV virus [26,27].

Conclusion

The main purpose of this research is to recognize novel drug targets and gathering information regarding to approval of drugs by Food and Drug Administration (FDA). After all reviewing it is concluded that new approaches for any kind of class to treat HIV being helpful to survive people infected from it. Different classes of drug used in HIV/AIDS have novel drug approval from FDA in recent 2018-19 are mentioned. Currently there are widely used ART and HAART therapy to prevent infection in patients. They both are combination of drug class which are already used as single or multidrug regimen to treat HIV infection. ART (antiretroviral therapy) include drug combination of different classes used in treatment in HIV/AIDS. Whereas, HAART (highly active antiretroviral therapy) as name shows that they are highly active in comparison to ART. They have combination of two or more HIV drugs including NNRTIs, NRTIs, INIs or PIs in recent. The novel advancement in research to reach reduction in morbidity and mortality rate from HIV infection, increase potency of drug, less toxicity and more convenient to the patient.

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