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HIV Treatment Methods: A Complete Guide

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ABSTRACT

HIV (Human Immunodeficiency Virus) is a virus that attacks immune system of human body. If it is not treated, it can lead to AIDS (Acquired Immuno-Deficiency Syndrome) characterized by very weak immune system which cannot fight against ordinary infections and diseases that leads to death. Currently, there is no cure for HIV but many medications and treatments are used to treat HIV patients to delay HIV proliferation and improve complications. FDA (Food and Drug Administration) has approved some of the drugs that show their efficiency at delaying viral multiplication and complexities. These are divided into several different classes according to their mode of action. It is suggested that, any three drugs to be used from at least two classes for initial treatment. Currently, drugs like Tenofovir, emtricitabine, Doravirine, Extravirin, Nevirapine, Rilpivirine, cocktail of drugs (mixture of multiple types of drugs), antiretroviral therapy and some other type of drugs are being used as treatment. Some of the drugs have major side effects. The mode of action, efficacy and side effect of the very recent drugs are discussed here along with their classes. Researchers are working hard and soul to find a treatment method which can surely remove HIV and save millions of lives.

Keywords: AIDS; Treatment; Anti-retroviral therapy; T-lymphocyte; Mode of action

INTRODUCTION

AIDS was first identified in young gay men during the summer of 1981. The disease was initially thought to be a "gay plaque". In 1982, the disease was diagnosed and named as AIDS by CDC and SIDA. In 1983, the disease was also reported in heterosexual people [1]. The disease continued steady propagation until now, and considered as global epidemic according to WHO. Most common symptoms at early stage of the disease are fever, sore throat, fatigue, weight loss, and myalgia [2]. In Late stage of the disease the patient suffers from different types of cancers and infections due to decreased number of CD4 T cells [3]. The virus attaches to the CD4 antigen of T helper cell. Then, the viral membrane gets fused with the cell membrane and RNA enters to the cell. RNA is converted into DNA by reverse transcriptase. Then the DNA is integrated into the DNA of host cell which is transcribed and translated to produce viral protein. These viral proteins get matured by protease. These mature proteins and replicated RNA makes some new complete viruses. Then the virus comes out from the cell [4]. The genetic changes and activities made by the virus causes destruction of the cell. Rapid destruction of T helper leads to lower level of Th cells, which subsequently causes immune dysregulation most commonly for dendritic cells and B cells that leads to immunodeficiency [5]. Drugs have been made to halt different stages of life cycle of the virus which may suppress their activity. But none of the drugs can fully recover patients from the disease but they can help to boost up immunity and delay complications.

MATERIALS AND METHODS

As there is no treatment method invented which can cure the disease completely, so it is a field of enormous interest and alacrity for the researchers and scientists. Google Scholar, BASE, CORE, Microsoft Academic, Science.gov were studied to know about the latest discoveries about the treatment method of HIV virus. Articles related to the disease up to 15th November, 2020 were searched and the information that was found in the articles was included here in the paper with references.

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RESULTS AND DISCUSSION

Treatment methods of HIV virus can be divided into the following classes according to the target points.

CLASS 1: Nucleoside reverse transcriptase inhibitor

Tenofovir: Tenofovir Disoproxil Fumarate is an oral prodrug of Tenofovir, that is, the drug converts to tenofovir after absorption which is an acyclic nucleotide analogue of deoxyadenosine monophosphate (dAMP). Tenofovir can enter into cells and gets metabolized into anabolite tenofovir diphosphate which is a nucleotide analogue of deoxyadenosine triphosphate (d ATP) that can act as precursor of DNA. The reverse transcriptase of the HIV cannot distinct well between natural substrate and Tenofovir Diphosphate. So, Tenofovir Diphosphate gets incorporated into DNA during viral DNA synthesis. This faulty building block inhibits further elongation of DNA chain and causes premature termination (Figure 1) [6-8].

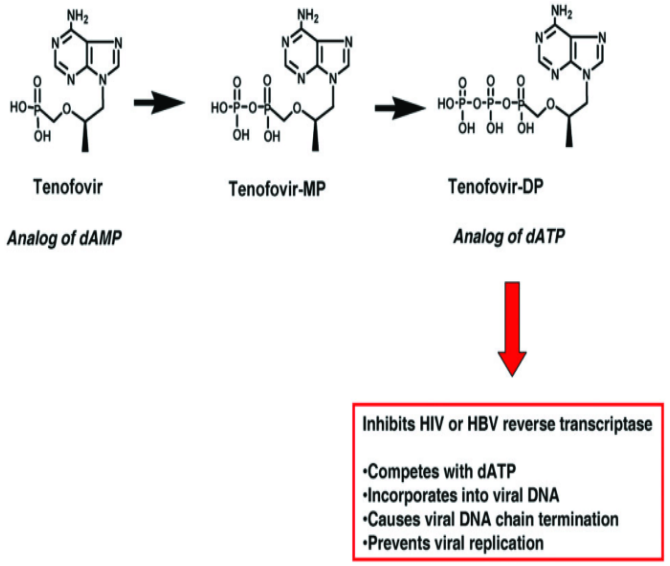


Figure 1: Tenofovir DF converts to Tenofovir after absorption.It converts to Tenofovir-DP after getting into cells. Then it prevents viral replication by competing with d ATP and acting as false precursor of DNA.

An important disadvantage of Tenofovir disoproxil fumarate is that most of the Tenofovir remains in the blood plasma. This high tenofovir level in blood may cause kidney (renal impairment, kidney failure) and bone (osteopenia and osteoporosis) problem [9,10]. To solve these problems Tenofovir alafenamide is introduced which acts as same mechanism of Tenofovir disoproxil fumarate. This derivative of tenofovir accumulates at a very less amount in blood plasma compared to TDF. It is found that 25 gm of TAF can act as antiviral equivalent to 300 mg of TDF [10]. Thus, it clears about 90% of tenofovir in blood plasma. Moreover, TAF derived tenofovir gets out of the body easily through renal elimination (Figure 2) [9-11].

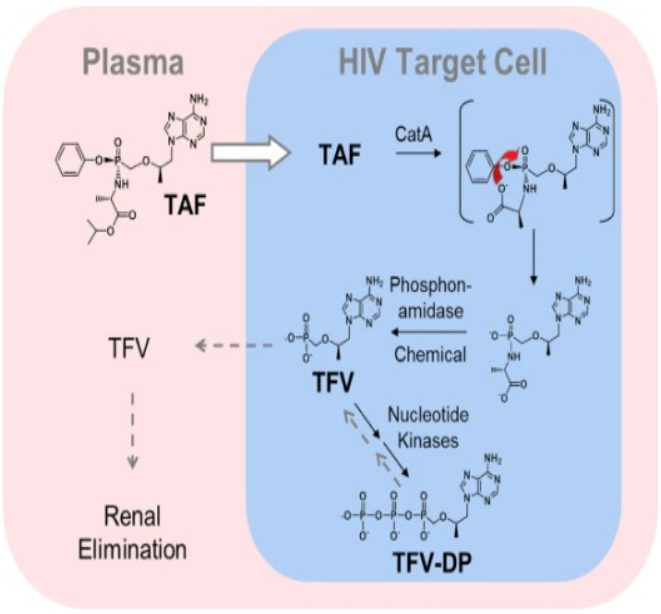


Figure 2: TAF is a L- alanine derivative of tenofovir. It can enter to the affected cell easily and forms tenofovir by releasing the phenol and alanine via enzymatic or chemical degradation. The Free tenofovir then undergoes phosphorylation to form tenofovir diphosphate (TFV-DP). TFV-DP has a similar structure with nucleoside precursor and thus binds to the DNA. This faulty DNA cannot elongate further and undergoes premature termination. Unused tenofovir may get out of the body through renal elimination causing no harm to the body.

A trial was done to determine efficacy and safety of the two drugs. 959 patients were included for TAF therapy and 477 patients were included for TDF. The treatment continued for 96 weeks. After 96 weeks, 93% of TAF and 89% of TDF received patients were found to have number of viral RNA lower than 50 copies per ml. Side effects like osteopenia, renal complications were less in TAF received patients [12].

Abacavir: Abacavir is a prodrug that converts to Carbovir triphosphate by intracellular hosphorylation. After oral digestion the drug gets absorbed quickly through passive absorption by the infected cells. There it undergoes through phosphorylation to convert into abacavir monophosphate by adenosine phosphotransferase. The Abacavir monophosphate converts to carbovir triphosphate by losing the amino group with the help of cytosolic deaminase. Then intramolecular kinases bind two more phosphate group to the monophosphate side to produce carbovir triphosphate. Carbovir triphosphate is an active state of the drug which is a nucleoside analogue of deoxy guanosine triphosphate (dGTP). Viral reverse transcriptase cannot distinguish between endogenous dGTP and carbovir triphosphate. So, the carbovir triphosphate gets incorporated into new viral DNA. But carbovir triphosphate has no 3-hydroxyl group necessary to attach another nucleoside, thus causes premature termination of DNA synthesis (Figure 3) [13-15].

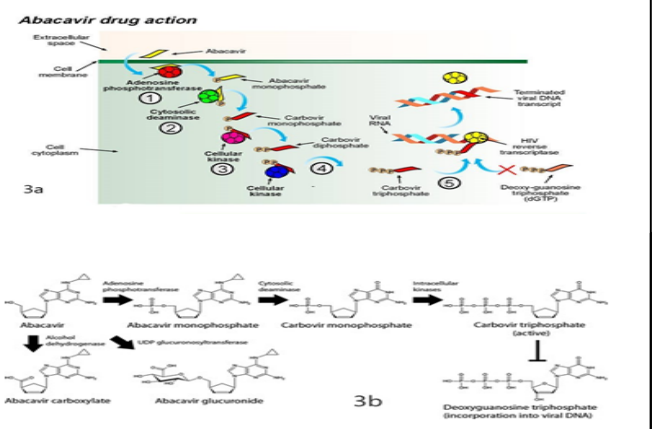


Figure 3: (a) Abacavir enters to cells and converts into Carbovir triphosphate which competes with deoxy guanosine triphosphate, a nucleotide precursor of DNA and gets incorporated in to the synthesizing DNA. But, Carbovir triphosphate has no free 3-OH group to incorporate further nucleotide. Consequently, the DNA undergoes premature termination. (b) Molecular changes of Abacavir.

However, the drug shows hypersensitivity by modifying the self-peptide. Abacavir may change the protein composition is self-peptide by influencing a loader HLA-B*5701. This causes the CD8 T cells to identify self-antigen as foreign and get activate against them. This phenomenon leads to T-cell autoimmune responses and multi organ systemic toxicity [16,17]. Sometimes Neuropsychiatric reaction are reported but they are very rare [18,19].

Lamivudine: Lamivudine is a synthetic nucleoside analogue of deoxycytidine. It is taken orally and after absorption in a cell, it is phosphorylated into lamivudine triphosphate with the help of intracellular kinases. Lamivudine triphosphate is the active form of the drug which is an analogue of deoxycytidine triphosphate (d CTP) [20,21]. So, like other drugs the lamivudine triphosphate is incorporated into synthesizing DNA strand and causes premature termination. Side by side, lamivudine triphosphate also inhibits viral RNA dependent DNA polymerase and DNA dependent DNA polymerase. So, it can affect 4 steps of viral replication. First one is reverse transcriptase enzyme activity. It prevents minus strand DNA formation from RNA. The next one is DNA dependent DNA polymerase activity. This causes inhibition in plus strand DNA formation from minus strand DNA. The third site is covalently closed circular DNA (cccDNA) formation. And the fourth one is initiation and amplification step (Figure 4) [22,23].

Lamivudine is considered as a safe drug. However, in some rare cases some gastrointestinal complications, Hyperamylasemia and pancreatitis are reported as side effects of the drug [24].

Emtricitabine: Emtricitabine is a pyridine analog having antiviral activity against retro viruses. It is a prodrug and it converts to its active form Emtricitabine 5-Triphophate (ETP). ETP is an analogue of deoxycytidine triphosphate (d CTP). So, ETP competes with dCTP and gets incorporated into synthesizing DNA. This causes premature termination due to lack of free 3-OH group on (Figure 5) [25].

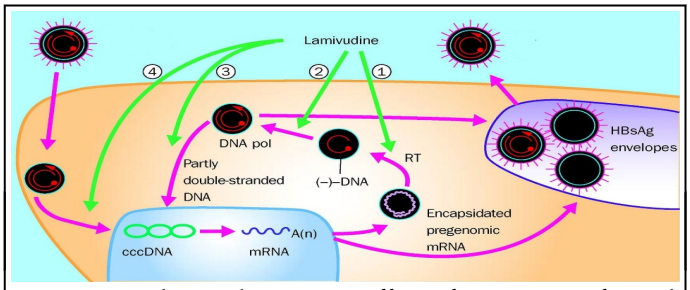


Figure 4: lamivudine can affect four area of viral replication. The sites are minus strand DNA formation from RNA, formation of plus strand DNA from minus strand DNA, cccDNA formation and initiation and amplification stage.

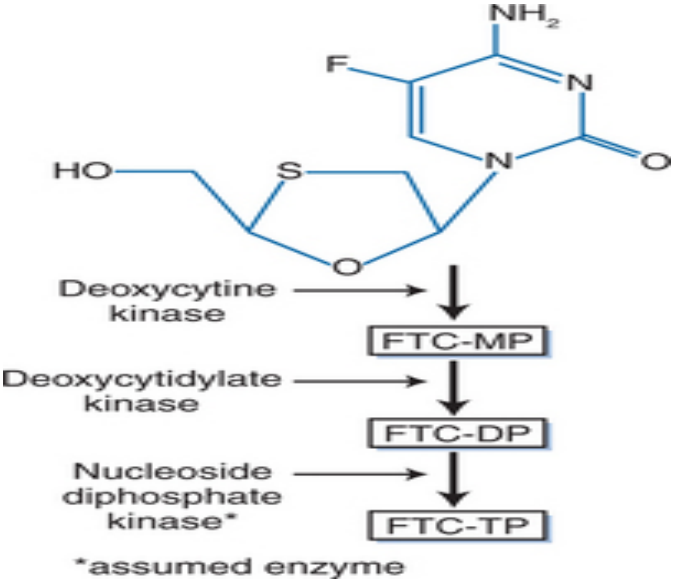


Figure 5: molecular structure and it changes during phosphorylation.

These drugs have shown better result applying in combination. Usually Emtricitabine-Tenofovir or lamivudine-abacavir combination is used as Nucleotide Reverse Transcriptase Inhibitor. In a randomized, blind equivalence study, Emtricitabine-Tenofovir or lamivudine-abacavir is given to patients with efavirenz or ritonavir-boosted atazanavir. All the patients had HIV RNA levels more or equal to 100,000 copies per milliliter. It was found that the virological failure of lamivudine- abacavir were 14% and incase of Emtricitabine-Tenofovir it was 7%. Virological failure means HIV RNA count more than 1000 after 16 weeks or HIV RNA count is more or equal to 200 after 24 weeks [26]. In another trial done in 2015 to 2016, 631 patients were enrolled. Among them, 316 patients were given bictegravir, emtricitabine, and tenofovir alafenamide, on the other hand, 315 patients were given dolutegravir, abacavir, and lamivudine. At 96 weeks, 88% patients of the bictegavir group and 90% of the dolutegravir group were found to have HIV RNA counts less than 50 per level [27]. These stats show that both of the regimen was able to reduce the number of

HIV RNA. Many other trials havebeen done with the combination of these NRTI with other class and have shown evidences of their efficacy [28].

CLASS 2: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI

NNRTI are the drugs which can inhibit Reverse Transcriptase (RT) enzyme directly. These drugs bind to the allosteric hydrophobic site of reverse transcriptase, which is adjacent to the active site. This binding causes conformational changes in the enzyme results in loss of functionality. Consequently, the enzyme cannot bind to the RNA or DNA and cannot perform its polymerase activity. Eventually, viral replication stops (Figure 6) [29,30].

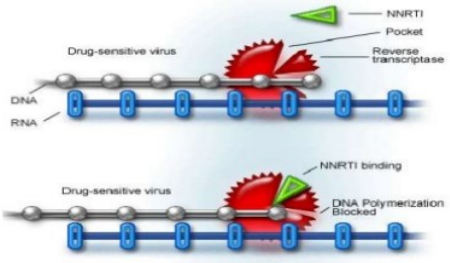


Figure 6: NNRTI binds to the active site of reverse transcriptase enzyme and causes conformational changes. As a result, the enzyme losses its effectivity and viral replication halts.

Different sort of NNRTI drugs are used nowadays that use the above-mentioned mechanism. These drugs can be divided into two classes. First generation and second generation. First generation drugs are highly selective, that is, any changes or single mutation in the NNRTI may make the drug ineffective. For this reason, viruses are found to get resistant against them [31]. Examples of first-generation drugs are Doravirine, nevirapine, efavirenz. Recently second-generation drugs are being invented which have a flexible binding surface and they can maintain their affinity for the reverse transcriptase after several mutations. Some strain of HIV has undergone mutations and gained resistant to different drugs. HIV is now can be classified as two types. HIV-1 and HIV-2, though both of them weaken immune system, their RT structure is different. Besides, there are three strain of HIV-1: M, N and O. these strains also have their genetical differences. So, it is difficult to find effective drugs that can suppress all the strains of the virus.

First generation drugs

Doravirine: Doravirine is a pyridone non-NNRTI drug. It has a trifluoromethyl-pyridone core with a methyl-triazolone and a chlorophenol with a cyano group. Its chemical name is 3-chloro-5-[[1-[(4,5-dihydro-4-methyl-5-oxo-1H-1,2,4-triazol-3-yl) methyl]-1,2-dihydro-2-oxo-4-(trifluoromethyl)-3-pyridinyl] oxy] benzonitrile (Figure 7) [32,33].

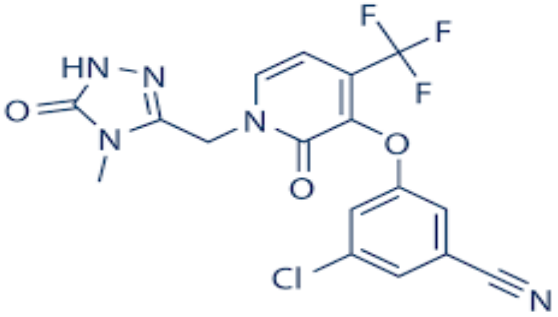


Figure 7: 3-chloro-5-[[1-[(4,5-dihydro-4-methyl-5-oxo-1H-1,2,4-triazol-3-yl) methyl]-1,2-dihydro-2-oxo-4-(trifluoromethyl)-3-pyridinyl] oxy] benzonitrile.

By studying the crystal structure of the doravirine, it is found that chlorophenol moiety contacts with Y188 and cyano moiety contacts with p66 subunit (RT has two subunits, p51 and p66) inside hydrophobic tunnel which is only about 10 Angstrom away from the active site of reverse transcriptase. This attachment of Doravirine causes changes in the relative position of the units. That is, the drug induces conformational changes making the enzyme non-functional [32,33].

A drive forwarded trial with 766 participants having viral RNA more or equal to 1000. Half of them were given ritonavir-boosted darunavir and rest half of them were given doravirine. On the 48th week, 84% people receiving doravirine and 80% of people receiving ritonavir-boosted darunavir were found to have HIV RNA level less than 50 per ml in blood plasma. And the number of people having side effects were very rare. In another drive ahead study, 728 people were enrolled in which half of them were given fixed dose of doravirine, lamivudine, tenofovir and other half were given fixed dose of efavirenz, emtricitabine, tenofovir. On the 48th week, 84.3% of the participant of doravirine group and 80.8 of the participants from efavirenz group were found to have HIV RNA number less than 10 copies per ml in blood plasma. The side effects were also less in doravirine group compared to efavirenz group. These stats show that the drug doravirine is safe and effective [33].

Nevirapine: Nevirapine is a compound of dipyridodiazepinone chemical class. Its chemical formula is 11-cyclopropyl-4-methyl-5,11-dihydro-6Hdipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one. This drug is highly specific. That is why any change or mutation on its binding site may make it non-functional (Figure 8) [34,35].

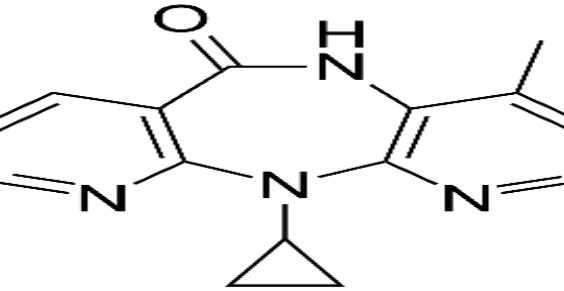


Figure 8: molecular structure of nevirapine.

Like all other NNRTIs, nevirapine binds to the hydrophobic pocket of reverse transcriptase which is located 10 Angstrom away from the active site of the enzyme. The binding of nevirapine affects in three ways. First one is by loosening primer grip. Nevirapine binding causes to shift the primer grip by 4 Angstrom, that moves away the DNA primer away from the P site of the enzyme. This leads to fall off interaction between the terminus of the primer and the active site of the enzyme [36,37]. Secondly, nevirapine causes changes in the shape of the β3-β4 motif, which has a crucial role in dNTP incorporation and base pairing. The third one is by making inward movement of the thumb domain of the reverse transcriptase enzyme that subsides the interaction between DNA and polymerase domain [35,36].

To test the efficacy of nevirapine, a randomized, Double-Blind, Placebo-Controlled Trial was conducted with 68 patients who had a CD4 cell count less than 200 per ml and higher HIV RNA about 5.8log 10. Among them, 32 patients received tiple combination regimen of nevirapine, zidovudine, and didanosine and other 36 patients received zidovudine and didanosine. After 24 hours, median RNA reduction and median CD4 response increment of the patients receiving triple therapy were 2.69 log10 and 81 cell per ml respectively which were much more convincing than the double therapy recipients who had median RNA reduction and median CD4 response increment of 1.05 log10 and 64 cells per ml respectively. After 48 weeks, the scenario remains the same. Patients receiving triple therapy had a median RNA reduction and median CD4 response increment of 1.97log10 and 101cells per ml respectively. Patients receiving double therapy had a median RNA reduction and median CD4 response increment of 1.2log10 and 27per ml respectively [38]. In another study with 398 adults who have CD4 cell count less than 350 the patients receiving triple combination regimen were found to have an increment of about 18% mean absolute CD4 cell count, decrease inmean infectious HIV-1 titer by 0.32 log10 and in mean plasma HIV-1 RNA level by 0.25 log10 than the double combination regimen [39].

The major side effects that are rarely reported are hepatotoxicity, cutaneous of baseline CD4 cell count and some skin rash [40, 41]. But due to its high specificity and low genetic barrier, single mutation in the virus may create resistance to it. This phenomenon is more common in the child bearing mother having HIV and if Nevirapine used as only medication [42].

Delavirdine: Delavirdine is an amide that is originated from condensation reaction of 5-[methylsulfonylamino]-1H-indole-2-carboxylic acid and 4-amino group of 1-[3-isopropylaminopyridin-2-yl] piperazine. Its IUPAC name is N-[2-[4-[3-(propan-2-ylamino)pyridin-2-yl]piperazine-1-carbonyl]-1H-indol-5-yl]methanesulfonamide (Figure 9).

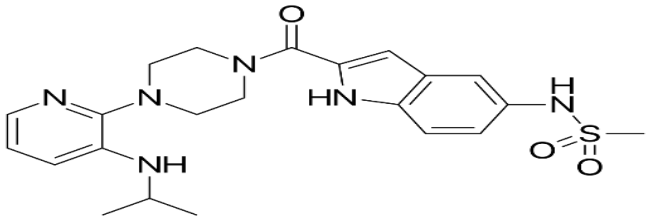


Figure 9: Molecular structure of Delavirdine.

Delavirdine does not inhibit the reverse transcriptase directly, rather it inhibits its action allosterically. That is, it does not bind to the nucleic acid binding site. Rather binding to the other side inhibits the reverse transcriptase polymerase function by obstructing binding of dNTP and primer with the enzyme making changes in the amino acid of the active site. It is confirmed from the kinetic study of Delavirdine,which shows that Delavirdine inhibits both RNA and DNA dependent polymerase but does not inhibit RNase H function. This obstruction of Delavirdine results in disruption in reverse transcriptase enzyme activity and prohibits viral replication [43]. Besides, the drug inhibits CYP3A4-mediated metabolism of HIV protease inhibitors and enhances the antiviral activity of viral protease inhibitors [44].

To test the potency of the delavirdine a trial with 85 people were included who had HIV-1 infection and CD4 T cell count 100 to 300 per ml. There were 4 groups in the trial. First group was given zidovudine (ZDV) plus Didanosine, second group was given zidovudine plus Didanosine plus Delavirdine (DLV), third group was givenonly DLV, and the fourth one ZDV plus DLV per day. Among the four group, second group patients shown a promising improvement overall. This depicts that DLV gives better result when combined with a nucleoside inhibitor [45]. The efficacy of this combination was tested in another large randomized, double-blind, placebo-controlled study was done with 48 to 54 weeks' duration. Triple combination therapy (delavirdine, zidovudine and lamivudine) was given to half of the people and dual combination therapy to the other half. After 50 weeks, 40% of the patients receiving triple combination therapy had HIV RNA level less or equal 50 per ml. On the other hand, only 6% patients receiving dual therapy had achieved HIV RNA level less or equal to 50 per ml. These stats depict the efficacy of the DLV and DLV with nucleoside inhibitors [46]. Though 50% of the people had rash on their skins, the intensity was mild most of the case. No other adverse effects were found [46]. However, DLV may interact with methadone which may cause moderate nausea, urination difficulty and drowsiness [47].

Efavirenz: EFV is a 1,4-Dihydro-2H-3,1-benzoxazin-2-one that is substituted by cyclo-propyl-ethynyl and trifluoromethyl groups at the position 4 and by chlorine at the 6 position. It's IUPAC name is (4S)-6-chloro-4-(2-cyclopropylethynyl)-4-(trifluoromethyl)-1H-3,1-benzoxazin-2-one (Figure 10) [48,49].

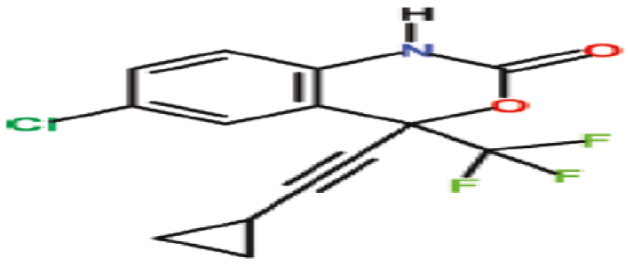


Figure 10: molecular structure of Efavirenz.

Efavirenz binds to hydrophobic pocket of the p66 subunit in case of p66/p51 heterodimer reverse transcriptase (RT). RT maybe present as p66/p66 and p51/p51 monomer as well. Both of the monomers are found to bind with efavirenz with micromolar affinity. The mass spectra changes in presence of efavirenz suggest that p51 becomes more compact and p66 becomes more facile and undergoes cleavage [50]. This binding and conformational changes causes inhibition in DNA polymerase activity, enhancing polymerase-dependent RNase H activity (3'-DNA directed) and partially inhibiting polymerase-independent RNase H activity (5'-RNA directed). It also inhibits plus strand DNA initiation. At last stage of HIV-1 replication, efavirenz increases processing and homodimerization of a 90 kDa Pol polyprotein, Gag and Gag-Pol precursor polyproteins in HIV infected cells. This increasing amount of polyprotein results in decrease in number of constructs required to incorporate into a budding particle and form fully formed virus.Consequently, the virus production is decreased [51].

A combination of emtricitabine, didanosine, and efavirenz was found effective and safe in a trial with 37 patients. After 96 weeks, 32 patients out of 37 achieved HIV RNA level less than 400 copies per mL, and 26 patients of 37 were found to have HIV RNA level less 50 copies per mL. CD4 count also increased from 310 per µL to 329 per µL [52]. In another randomized open-label, noninferiority study involving 517 patients with HIV infection. Some of them were given a regimen of tenofovir disoproxil fumarate (TDF), emtricitabine, and efavirenz(group-1) and the other patients were provided with zidovudine, lamivudine plus efavirenz(group-2). After week 48, it was found that 84% of patients from the group-1 and 73% patients from group 2 had HIV RNA count less than 400 per mL. 80%patients of group 1 and 70% on group 2 were found to achieve HIV RNA level less than 50 per mL. CD4 cell count increment in group 1 was 190 per cubic millimeter and it was 158 per cubic millimeter in case of group 2 [53]. So, these two regimens have good effect on reducing the HIV, but tenofovir disoproxil fumarate (TDF), emtricitabine, and efavirenz has shown better clinical improvement.

Efavirenz alters mitochondrial respiration, increases reactive oxygen productionand inhibits mitochondrial electron transport chain complexes. These energetic fluctuation affects glial cells and neuron cells. This leads to central nervous system (CNS) related complications like dizziness, impaired concentration, nervousness, sleep disturbances, psychosis, suicidal ideation, and neurocognitive impairment [54]. Sometimes the drug is also associated with hepatotoxicity which may cause serious liver damage [55].

Second generation NNTIs

Etravirine: Etravirine is a diarylpyrimidine derivative with a polycyclic molecule having three aromatic rings with single bonds between the rings. Its IUPAC name is 4-[6-amino-5-bromo-2-(4-cyanoanilino)pyrimidin-4-yl]oxy-3,5-dimethylbenzonitrile. It is the first second generation NNRTI that is approved by FDA (Figure 11) [56,57].

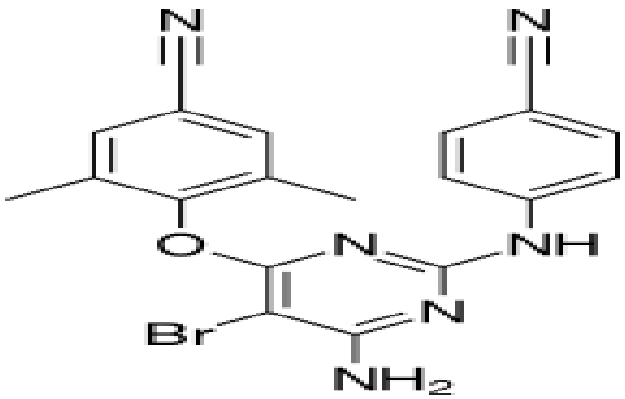


Figure 11: Chemical structure of Etravirine.

Like other NNTIs, it binds non- competitively to the hydrophobic pocket of the p66 subunit of reverse transcriptase enzyme. After binding, it causes conformational changes that results in distortion in structure and DNA-dependent and RNA-dependent polymerase activity allosterically. The three rings on the compound, provides it with great flexibility and torsion which makes different from other first generation NNRTIs. This characteristic of the drug allows it to adapt to the changes of the binding site. So, this drug can continue its functions after single or several mutations in the binding site. This makes the drug suitable for use against several subtypes of HIV-1 from both M group and O group [56]. Although etravirine is reported to have more activity against HIV-2 than previous NNRTIs, due to presence of L181 and other structural differences in the HIV-2 NNRTI-pocket, they are resistant to etravirine [58].

To test the efficacy of etravirine, a complete phase 3, randomized trial was done with 1203 HIV-1 patients who have HIV RNA level more than 5000 copies per ml and have NNRTI and protease inhibitor resistance. Among them, 599 patients were provided with etravirine and 603 patients were given placebo. After 96 weeks, it was found that, 57% of patients in the etravirine group and 36% in the placebo group had HIV RNA level less than 50 per ml. Mean CD4 count increased by 128 cells per ml among the patients receiving etravirine,on the contrary to 86 cell per ml in case of patients receiving placebo [59]. No complication was found among the patients receiving etravirine in the trial.In another trial, 79 patients were given etravirine and 78 patients were given efavirenz. All the patients had HIV RNA level more than 5000 copies per ml. After 48 weeks, the percentage of patients having RNA copies less than 50 copies per ml were 76% and 74% among the patients receiving etravirine and efavirenz respectively. The most

distinguishing feature is that only 6.3% patients receiving etravirine had ongoing neuropsychiatric adverse events on the contrary to 21.5%patients having the adverse effect who received efavirenz [60]. These results depict that etravirine is effective and safe to treat HIV-1 patients with resistance to first generation NNRTIs.

Rilpivirine: Rilpivirine is an aminopyrimidine in which the amino groups at positions 2 and 4 are substituted by 4-cyanophenyl and 4-[(E)-2-cyanovinyl]-2, 6-dimethylphenyl groups respectively. Its IUPAC name is 4-[[4-[[4-[(E)-2-cyanoethenyl]-2, 6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile monohydrochloride (Figure 12) [61].

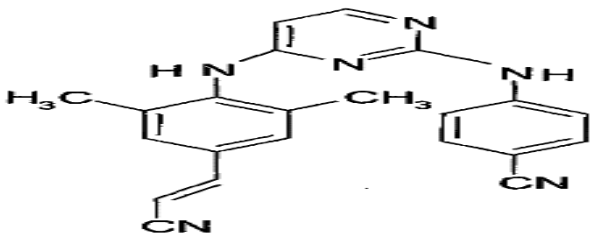


Figure 12: Molecular structure of rilpivirine.

Rilpivirine can bind to both wild-type and first-generation NNRTI-resistant HIV-1 efficiently. This is because; the flexible dihedral angle between the aniline ring and the cyanovinyl moiety confers torsional flexibility. This flexibility allows rilpivirine to bind to pockets of first-generation NNRTI-resistant HIV-1 [62,63]. Moreover, the cyano group of the rilpivirine contacts with trp229 of the hydrophobic pocket, that increases its potency [64]. Binding allosterically to the RT, rilpivirine induces conformational changes for which the enzyme losses its functionality and cannot continue its RNA and DNA dependant polymerase activity. Consequently, viral replication gets stopped [65,66].

To test the efficacy of rilpivirine, a double blinded, randomized trial was done with 688 patients who have HIV RNA count more than 5000 copies per ml. 340 of them were given rilpivirine and 338 of them were given efavirenz alongside NTRIs regimen. After, 96 weeks, it is found that 86% of patients who received rilpivirine achieved HIV RNA count less than 50, compared with 82% of patients receiving efavirenz. Treatment related complication was found in 16% patients receiving rilvipirine and 31% patients receiving efavirenz. Most common side effects reported were rash and dizziness [67]. In another randomized, open label phase 3 trials, 513 participants were randomly given dolutegravir plus rilpivirine. Though 511 patients' standard ART regimen 477 patients switched to dolutegravir plus rilpivirine after 52 weeks. At weeks 100, 95% patients in the early switch group and 93% patients in late switch group had HIV RNA level less than 50 copies per ml. 20% in the early switch and 12% patients in the late switch group had adverse effects [68]. So, these results depicts that rilpivirine is safe and effective against HIV-1.

Resistance may occur if rilpivirine is used only. In ECHO/THRIVE trial virological failure occurred more to the parients receiving rilpivirine than the patients receiving Efavirenz. The most common reason of this viral failure was resistance associated mutation (RAM) at E138K [69]. This resistance is also active against etravirine. To prevent this resistance formation, triple drug combination should be used. That is, rilpivirine should be used alongside with two other NRTIs. Trials done with rilpivirine with tenofovir plus emtricitabine or zidovudine plus lamivudine were reported to have better result and no resistance has been reported against them [70].

CLASS 3: Protease inhibitor

When HIV viral RNA enters into cells, it is accompanied by Integrase, reverse transcriptase and protease enzyme. After the viral RNA is translated into polyprotein named Gag-Pol polyprotein, it is cleaved into different functional protein by the protease enzyme. This functional protein combines to form a potent virus. So, HIV protease plays as indispensable role in viral replication. It is a homodimeric aspartyl protease which has two monomers consisting 99 amino acid. Each of the monomers has aspartic acid residue at position 25 which is essential for catalytic activity. This protease enzyme cleaves gag and gag-pol polypeptide precursor at nine sites to make active protein which makes a new virus. The catalytic site covered by two flexible β-hairpin flaps which opens when substrates are allowed to enter into catalytic site [71]. The protease inhibitors mimic the actual substrate of the protease, but the NHCO group in peptide linkage is replaced by CH2CH(OH) that makes the peptide unfavorable to cleavage by the protease active catalytic site (Figure 13) [72].

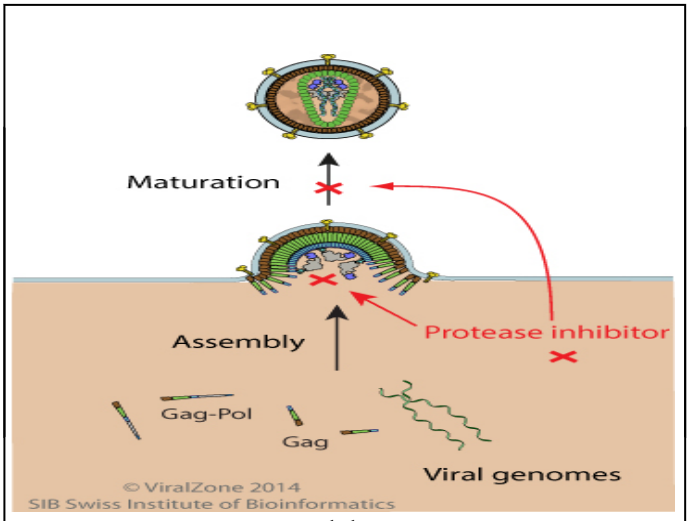


Figure 13: Protease enzyme inhibiting protein maturation.

This inhibition of protease enzyme suppresses viral replication. By applying the above-mentioned mechanism, many drugs are invented. Some of them are discussed below.

Saquinavir: Saquinavir is a five mimicry of peptides with a Hydroxy-ethylamine isostere in place of the cleavable peptide bond.it is the first protease inhibitor It's IUPAC name is (2S)-N-[(2S,3R)-4-[(3S,4aS,8aS)-3-(tert-butylcarbamoyl) -3,4,4a,5,6,7,8,8a-octahydro-1H-isoquinolin-2-yl]-3-hydroxy-1-phenylbutan-2-yl]-2-(quinoline-2-carbonylamino) butanediamide (Figure 14) [73,74].

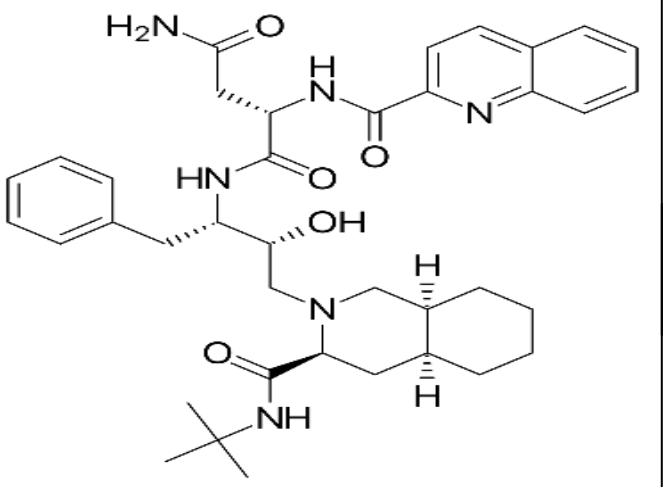


Figure 14: Saquinavir chemical structure.

Saquinavir is a mimicry of pentapeptide sequence Leu-Asn-Phe-Pro-Ile that were identified in gel pol polypeptide which is cleaved by the protease in the middle of phenylalanine and proline. Hydroxy-ethylamine isostere(-CH2-CH(OH)-) is inserted on the place of the peptide bond between phenylalanine and proline. HIV protease enzyme is unable to hydrolyze Hydroxy-ethylamine isostere and remains filled up with the substrate [75]. So, the enzyme does not come in contact with the gel pol polypeptide. Consequently, viral replication is inhibited. But this structure has low inhibitory activity. That is why,decahydroquinoline is added on the place of phenylalanine and proline to limit conformational changes of the drug. This addition improves aqueous solubility and potency of the drug [76]. As mammalian proteases do not hydrolyze the Phe-pro peptide bond, the drug is not supposed to inhibit human proteases.

To test the efficacy and safety of the drug, a double blinded trial was done with 302 patients who had CD4+ counts of 50 to 300 cells per ml. A group of patients were given saquinavir plus zidovudine plus zalcitabine and other group were given saquinavir plus zidovudine. After 24 weeks, it was found that the patients receiving three drugs regimen were found to have increased CD4 cells and reduced level of HIV RNA [77].In another trial, saquinavir was compared with lopinavir. 167 patients received saquinavir and 170 patients received lopinavir. After 48 weeks it was found that 64.7% patients in the saquinavir group achieved HIV RNA counts less than 50 copies per ml on the contrary to 63.5% patients receiving lopinavir [78]. These stats depict about safety and efficacy of the drug.

Ritonavir: Ritonavir is a peptidomimetic agent containing a hydroxyethyl transition state mimic, terminal thiazole rings and hydrophobic Phenylalanine and Valine residues [79]. Its IUPAC name is 1,3-thiazol-5-ylmethyl N-[(2S,3S,5S)-3-hydroxy-5-[[(2S)-3-methyl-2-[[methyl-[(2-propan-2-yl-1,3-thiazol-4-yl)methyl]carbamoyl]amino]butanoyl]amino]-1,6-diphenylhexan-2-yl]carbamate (Figure 15) [80].

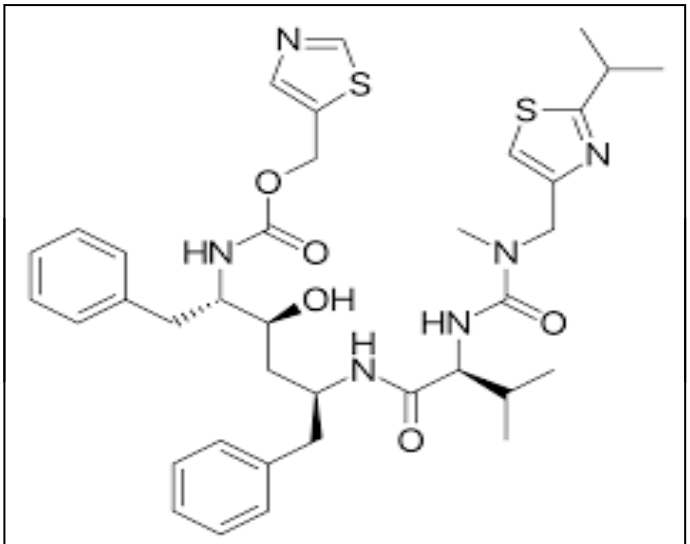


Figure 15: chemical structure of ritonavir.

Ritonavir uses symmetric nature of protease enzyme. For this reason, the drug gets three advantages. First one is that the drug has higher affinity towards viral protease enzyme and shows higher selectivity and specificity for the viral enzyme because mammalian protease enzymes are not symmetrical. Secondly, symmetrical molecules are less recognized by peptidase, that means they will be degraded slowly and bioavailability will increase. And thirdly, benzyl residue can be attached on the two sides improves solubility and potency [75]. So, it binds to the viral protease and inhibits its function. Though, it was originally produced as protease inhibitor, later it was found that the drug also inhibits CYP3A. CYP3A is responsible for clearance of 60% drugs. So, ritonavir increases half-life of other drugs by inhibiting CYP3A and increases their bioavailability [79].

The drug showed less efficacy in inhibiting the virus alone. Rather it is found to inhibit viral replication in together with other drugs. In a randomized, controlled, open-label trial, 199 HIV patients were included. Among them 99 patients were provided with ritonavir or lopinavir and other 100 patients were given standard care. No differences of the condition of patients were found after 14 days [81]. However, it has shown efficacy when another drug is used along with it. A randomized, multinational, phase IIB trial was done with 230 patients for 48 weeks. 110 patients were given darunavir-ritonavir and other 120 received other protease inhibitors. After 48 weeks, it was found that 67 patients from darunavir-ritonavir receiving group and 18 patients from the other protease inhibitor receiving group were found to have viral load reductions of 1 log10 copies per ml. And rates of adverse effects were almost similar in both the groups [82].

Lopinavir: Lopinavir is a drug designed by making some changes in ritonavir [75]. Its IUPAC name is (2S)-N-[(2S,4S,5S)-5-[[2-(2,6-dimethylphenoxy) acetyl]amino]-4-hydroxy-1, 6-diphenylhexan-2-yl]-3-methyl-2-(2-oxo-1,3-diazinan-1-yl) butanamide (Figure 16) [83,84].

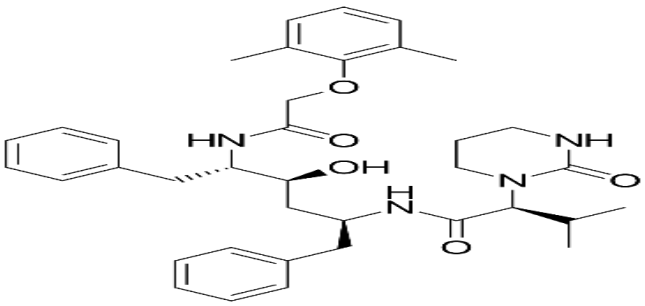


Figure 16: chemical structure of lopinavir.

Single use of ritonavir has shown a great risk of resistivity. Because there is an important hydrophobic interaction among the P3 thiazolyl group of ritonavir and theisopropyl side chain of Va1ine at the position 82. So, any mutation in the valine amino acid can easily make them resistant to the drug. So, P3 thiazolyl group is removed and urea isincorporated to enhance hydrogen bonding with S2subsite. This interaction balances out the loss of thiazolyl interaction [75]. This drug can now bind to the protease of ritonavir resistant HIV virus and inhibit viral replication.

Though lopinavir and ritonavir are marketed together as a single capsule, they are found less effective in inhibiting viral replication. Rather they are found to be effective to improve the function of other inhibitory drugs [75,81,82].

Indinavir: Indinavir is analogue of phenylalanine-proline cleavage site of the HIV Gag-polyprotein prepared by a hybridization strategy. Its IUPAC name is (2S)-1-[(2S,4R)-4-benzyl-2-hydroxy-5-[[(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl] amino]-5-oxopentyl]-N-tert-butyl-4-(pyridin-3-ylmethyl) piperazine -2-carboxamide (Figure 17) [85,86].

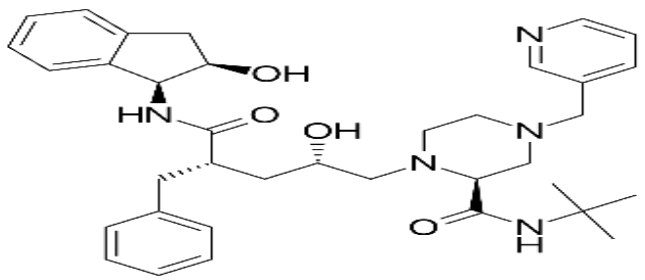


Figure 17: Chemical structure of Indinavir.

Indinavir is a hybrid compound of saquinavir and hydroxy-ethylene transition state isostere or L 685434. Half of saquinavir and half of L 685434 is combined to form the indinavir design. Half of saquinavir provides more solubility and half of L 685434 is for its lack of peptide character. Piperazine and some other modification is done to improve solubility and bioavailability. Acting as an analogue of phenylalanine and proline, indinavir compound binds to the protease efficiently and inhibits viral replication [75].

The safety and efficacy of the drug is tested by a randomized trial with 1156 HIV patients having CD4 count less than 200 cells per ml. A group of them were given indinavir plus zidovudine plus lamivudine and the other group were given only zidovudine and lamivudine. It was found that patients in the indinavir receiving group had lower rate of mortality and AIDS formation which is 6% and 1.4% respectively compared with 11% and 3.1% in case of patients receiving only zidovudine plus lamivudine [87].

Indinavir has a disadvantage that its concentration decreases rapidly. Thus, it has a short acting time and requires a dosage of 800 mg every 8 hours [88]. Moreover, this drug may have different insulin sensitivity and lipodystrophy [89,90].

Amprenavir: Amprenavir is a simple analogue of peptide having low molecular weight and less peptide character, which increases oral bioavailability. It is a tetrahydrofuryl ester, a sulfonamide and a carbamate ester. Its IUPAC name is [(3S)-oxolan-3-yl] N-[(2S, 3R)-4-[(4-aminophenyl)sulfonyl-(2-methylpropyl)amino]-3-hydroxy-1-phenylbutan-2-yl]carbamate (Figure 18) [91,92].

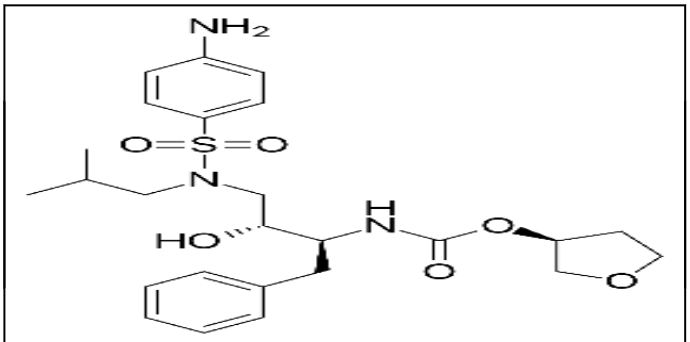


Figure 18: chemical structure of amprenavir.

Amprenavir has a similar core like saquinavir with different functional group at the end. A tetrahydrofuran carbamate group was added at one to for better binding to S2 subsite and to decrease the peptide character. An amino group has been added on Isobutylphenyl sulfonamide on the other end to increase solubility and oral bioavailability. These changes results in few chiral carbons. That is why, the drug is easy to synthesize, has more solubility and oral bioavailability [75].

To test the efficacy the drug is tested alone or with zidovudine plus lamivudine among 92 patients. But 7 patients did not complete the trial. among 85 patients 42 patients were given amprenavir alone and 43 patients were provided with amprenavir plus lamivudine plus zidovudine regimen. After 88 days, 15 of 42 patients receiving monotherapy had an HIV RNA increase above baseline or 1 log10 compared to 1 of 43 patients receiving triple-therapy regimen. After 24 weeks, patients receiving triple therapy regimen had HIV RNA level decreased up to 2.04 log10 copies per ml, and 63% patients had HIV RNA Copies less than 500 copies per ml [93].

Fosamprenavir: Fosamprenavir is a phosphate ester prodrug of amprenavir [71]. Its IUPAC name is [(3S)-oxolan-3-yl] N-[(2S,3R)-4-[(4-aminophenyl)sulfonyl-(2-methylpropyl)amino]-1-phenyl-3-phosphonooxybutan-2-yl]carbamate (Figure 19).

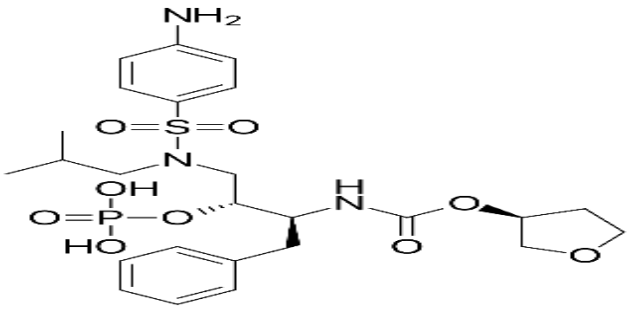


Figure 19: chemical structure of fosamprenavir.

Foramprenavir is a prodrug of amprenavir. That means, the drug converts to amprenavir after administration, metabolized by the body. But the metabolization of the drug does not happen at once, rather it is occurred slowly. Thus, amprenavir is released slowly inside the body. This process increases duration of availability of the drug, solubility and bioavailability [71]. For many of these advantages, fosamprenavir is in most of the cases instead of amprenavir.

In an open-label, non-inferiority study which included 878 HIV patients, 434 patients were provided with fosamprenavir-ritonavir and rest 444 patients were provided with lopinavir-ritonavir. After 48 weeks, it was found that, 73% patients of fosamprenavir-ritonavir group and 71% of patients of lopinavir-ritonavir group achieved HIV RNA level less than 400 copies per ml. But the discontinuation of treatment due to adverse effect were more in fosamprenavir-ritonavir group(12%) than lopinavir-ritonavir group(10%) [94]. Most common adverse effect was diarrhea and nausea. This result depicts that fosamprenavir is effective against HIV virus.

Atazanavir: Atazanavir is an isoamyl compound which makes it potent against HIV-1 but decreases its bioavailability. Isopropyl group is substituted by cyclohexyl that improves its bioavailability [95, 96]. It also has a large phenyl-pyridyl P1 group and a benzyl P1′group which are asymmetric to each other [71]. A great advantage of this drug is that it has good gastrointestinal tolerability. Once daily dosing enough for its activity that lowers pill burden. Moreover, it has lesser side effects than other protease inhibitors. It has no insulin sensitivity and serum lipid concentration issue [95]. However, the drug is reported to cause proximal tubulopathy (Figure 20) [97].

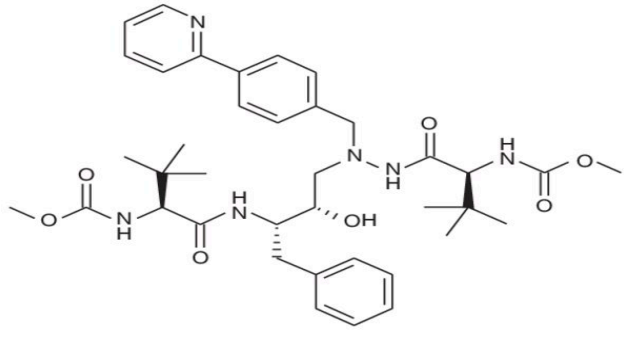


Figure 20: Chemical structure of Atazanavir.

In a trial, 708 HIV patients were included who had HIV RNA level more than 5000 copies per ml. 353 were given cobicistat (COBI), emtricitabine (FTC), tenofovir disoproxil fumarate (TDF) and elvitegravir (EVG) regimen. And other 355 patients were provided with Atazanavir (ATV), ritonavir (RTV) plus emtricitabine (FTC), tenofovir disoproxil fumarate (TDF). 89.5% of the patients from the EVG/COBI receiving group had HIV RNA level less than 50 copies per ml compared to 86.8% in case of patients from ATV/RTV receiving group. So, both of the atazanavir and elvitegravir is found to effective from the trial [98].

Darunavir: Darunavir is a nonpeptidic analogue of amprenavir which is the latest protease inhibitor till date. It is a second-generation drug that means it has a higher genetic barrier and can able to retain its activity instead of several mutation in the protease enzyme. Its IUPAC name is [(3aS,4R,6aR)-2,3,3a,4,5,6a-hexahydrofuro[2,3-b]furan-4-yl]N-[(2S,3R)-4-[(4-aminophenyl)sulfonyl-(2-methylpropyl)amino]-3-hydroxy-1-phenylbutan-2-yl]carbamate (Figure 21) [99].

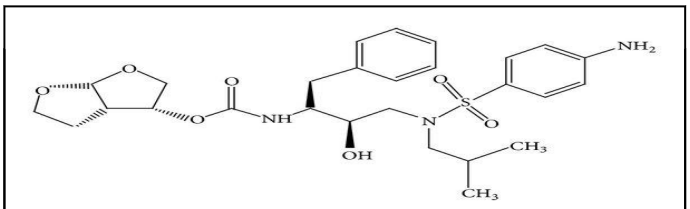


Figure 21: Chemical structure of Darunavir.

The structure of Darunavir is very much similar to amprenavir. The only difference is that a single tetrahydrofuran (THF) group in the amprenavir is replaced by two fused tetrahydrofuran group that is bis-THF moiety. This structural changes confers orientational changes that allows darunavir to have more hydrogen bonds with the Asp 29 residues of HIV protease and provides the ability to bind to mutated protease enzyme [71, 100].

To test the efficacy of the drug Darunavir, a randomized, controlled, phase III trial (TITAN) were carried out for 48 weeks with 595 HIV patients. Among them, 286 patients were provided with darunavir plus ritonavir and 293 patients were provided with lopinavir plus ritonavir regimen. After 48 weeks, it was found that, 77% patients of the Darunavir receiving group had HIV RNA level less than 400 copies per ml and 68% patients fromlopinavir-ritonavirreceiving group found to achieve that. 21% and 36% virological failures on the two groups respectively depicts that the mutation formation is also less in darunavir receiving patients [101]. Another trial was done with 256 patients having HIV RNA less than 50 copies per ml. 127 patients were given monotherapy of darunavir and 129 patients were provided darunavir with two Nucleoside reverse transcriptase inhibitors. After 48 weeks, 86.2% patients receiving monotherapy and 87.8%of the patients receiving triple therapy retained HIV RNA level less than 50 copies per ml. This trial says that darunavir is more effective when applied with two nucleoside RT inhibitors [102].

CLASS 4: CCR5 antagonists

CCR5 is a chemokine receptor of immune cells. This protein remains on the surface of the cell, attaches to chemokine and the cell moves towards the signal came from the chemokine. Different immune cells like T cells, macrophages, dendritic cells, eosinophils. This process drives the immune cell towards the infection site. So, this receptor plays an important role in our immune system [103]. The receptor is exploited by the HIV virus. HIV envelope has a glycoprotein structure which can bind to the CD4 cell. Binding of the envelope protein is not enough to get entry into cell. It needs binding t the co receptor. Envelope protein consists of 2 subunits, Gp120 and Gp41. Gp120 acts a chemokine mimic and produces false signal to the cell. The CD4 and CCR5 binding induces release of a fusion peptide that fuses viral membrane with the cellular membrane. And the viral RNA enters into the cell. CCR5 antagonists changes the structure of CCR5 such that the GP120 cannot bind to it [104].Till date, FDA has approved only one drug that is Maraviroc.

Maraviroc: Maraviroc is the first CCR5 antagonist that is active against HIV virus. It IUPAC name is 4,4-difluoro-N-[(1S)-3-[(1S,5R)-3-(3-methyl-5-propan-2-yl-1,2,4-triazol-4-yl)-8-azabicyclo [3.2.1]octan-8-yl]-1-phenylpropyl]cyclohexane-1-carboxamide [105].

During HIV infection, after env protein of HIV binds to CD4, the gp120 binds with CCR5 of the cell by a multi-point interaction. This interaction is formed by the binding of second extracellular loop of CCR5 to one of V3 loop of gp120 which is highly variable and thus determinant of co-receptor specificity. Side by side, the tyrosine-sulfated N-terminus (Tyr-Nt) of CCR5 binds to the bridging sheet which is an antiparallel, 4-stranded β sheet that connects the inner and outer domains of gp120 [104, 106]. These two steps of multi point interaction is necessary to induce fusion peptide release. To stop this interaction is the aim of maraviroc drug. It is a small compound that binds to a hydrophobic cavity formed by the first, second, third and seventh transmembrane domain helices of CCR5. In the cavity, maraviroc interacts with different amino acids and changes the conformation of the second extracellular loop which is used to interact with V3 loop of the HIV virus. The changed extracellular loop does not bind to the V3 loop and HIV cannot transduce signal and internalize [104,106]. Thus, the viruses are prevented from entry into the cells (Figure 22).

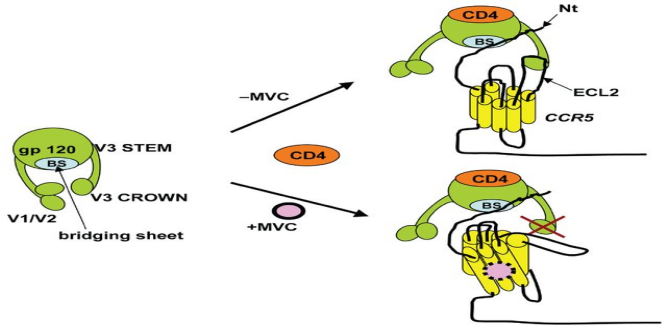


Figure 22: Maraviroc prevents ECL-2 from interacting with V3 loops and prevents multi point interaction formation which results in fusion peptide release.

It is to be mentioned that the HIV may have another receptor CXCR4. But not all of the viruses have CXCR4 receptor. Rather most of the viruses use CCR5 receptor. So, this drug is effective only against the virus using CCR5 receptor. To test the efficacy of the drug, 10 day orally administrated monotherapy were provided to 63 HIV-1 patients who do not have CXCR4 using virus. After 10 days mean reduction of HIV RNA level 1.6 log10 copies per ml was observed all doses of 200mg twice a day [107]. Then two trials named MOTIVATE were done which included 1049 HIV patients who did not have any

CXCR4 using virus. They were randomly provided with Optimized Background Therapy (OBT) and maraviroc. After 48 weeks, it was found that 47% of patients receiving OBT plus two dose of daily maraviroc group and 42% in the OBT plus once dose of daily maraviroc group had HIV RNA level less than 50 copies per ml but only 16% of patients who received only OBT could have achieved that HIV RNA level [106]. These two trials depict that the drug is effective against HIV-1 virus using CCR5 receptor. But in case of CXCR4 using virus this drug produces no good impact. This impact was tested on a Double-Blind, Placebo-Controlled Trial which included 167 patients who had CXCR4 using HIV-1. They were given placebo or maraviroc randomly. After 24 weeks, no significant differences were found that says that the drug is not effective against CXCR4 using viruses [108]. Some common side effects of the drug are diarrhea, nausea and headache [109].

CLASS 5: Integrase inhibitor

HIV integrase is an important enzyme for their replication which incorporates viral DNA into host chromosome. HIV integrase has 3 independent domains. They are N-terminal Domain (NTD), catalytic Core Domain (CCD) and C-terminal Domain (CTD) [110]. NTD consists of two histidine and two cysteine residue which form a HHCC zinc-finger motif. The zinc-finger motif chelates one zinc atom per IN monomer. Its main function is to form multimer [111]. CCD comprises of two aspartate residues and a glutamate amino acid. These negatively charged amino acids form the DDE motif that coordinate divalent metal ions mostly Magnesium and manganese ion [112]. And the other one is CTD that binds to DNA nonspecifically. Integrase enzyme works through two steps. First step is 3 ´endonucleolytic processing of viral DNA ends,also referred as 3 ´processing which removes a GT nucleotide. And the other one is the joining of 3´-processed viral DNA into hosts chromosomal DNA, also called strand transfer [113]. Integrase plays an inevitable role in viral replication because the genome cannot be replicated if it does not get integrated along with host DNA. For this reason, different integrase inhibitors are under study. Different inhibitors act on different strategy. Among them, raltegravir and Dolutegravir are approved by FDA.

Raltegravir: Raltegravir is the first integrase inhibitor to get approved by FDA. Its IUPAC name is N-(2-(4-(4-fluorobenzylcarbamoyl)-5- hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)propan-2-yl) -5-methyl-1,3,4-oxadiazole-2-carboxamide (Figure 23) [114,115].

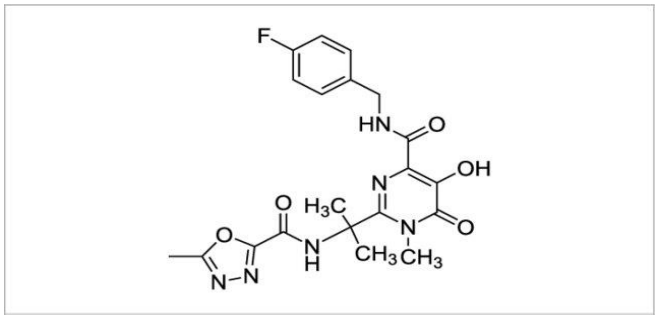


Figure 23: Chemical structure of raltegravir.

Raltegravir changes the conformation of the integrase and inhibits its activity. It is a INSTI class drug that is it inhibits strand transfer activity of the integrase. Raltegravir has a benzyl moiety that docks into a highly hydrophobic pocket near the catalytic site or the DDE motif of IN which is available only after processing of the 3´ viral DNA ends. Raltegravir has aβ-hydroxy-ketone structural motif that chelates mg2+ ionsinside the DDE motif [116]. These ions are necessary for the integrase strand transfer activity. Moreover,the drug changes the conformation allosterically that inhibits integrase-viral DNA complexActivity (Figure 24) [117,118].

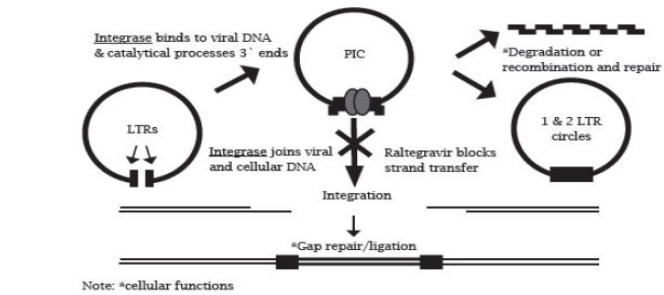


Figure 24: LTR is the long terminal repeat sequence found at the end of viral DNA. The integrase binds at the end and form pre integration complex which completes 3-processing activity. Raltegravir binds to the docking site created after the processing of 3-end.

To test the efficacy of the drug, a randomized trial was done with 179 HIV patients who had HIV RNA more than 5000 copies per ml and resistance to at least 1 NTI,1 NNTI and protease inhibitor. 44 patients were randomly provided with 200 mg raltegravir, 45 patients received 400 mg raltegravir, and 45 patients received 600 mg raltegravir; 45 patients received placebo only. After 24 weeks, it was found that mean viral reduction were 1.80 log10 copies per mL in the 200 mg raltegravir group, 1.87 log10 copies per mL in the 400 mg raltegravir group, 1.84 log10 copies per mL in the 600 mg raltegravir group, and 0.35 log10 copies per mL for the placebo group. So, the result says that raltegravir is effective in all doses the doses studied [119]. In STARMARK trial, HIV patients having HIV RNA level more than 5000 were provided with raltegravir or efavirenz randomly each combined with tenofovir or emtricitabine. After 96 weeks, 81% patients receiving raltegravir and 79% patients receiving efavirenz achieved HIV RNA level less than 50 copies per ml. 47% of the patients receiving raltegravir had modest side effect compare to 78% patients receiving efavirenz. This implies that raltegravir is much more effective and safer when combined with tenofovir or emtricitabine [120].

Dolutegravir: Dolutegravir is the first second generation student approved by FDA having highgenetic barrier and low cross resistance [121]. Its IUPAC name is 4-{[(2S, 4R)-1-(4-Biphenylyl)-5-ethoxy-4-methyl-5-oxo-2-pentanyl] amino}-4-oxobutanoic acid [122]. Dolutegravir consists of three main structural parts; tricyclic metal-chelating core, di-fluorophenyl ring and long and flexible linker that act as a bridge between them [123].Tricyclic metal-chelating core binds to the intasome (tetrameric assembly of IN around the viral DNA ends) by interacting with mg2+ with three coplanar oxygen atoms [124]. The di-fluorobenzyl group occupies the hydrophobic pocket and the extended linker region of allows it to enter deeper into the pocket, to make more compatible bonding with the viral DNA [125]. This allows dolutegravir to bind more efficiently even after mutation in one or two amino acids (Figure 25).

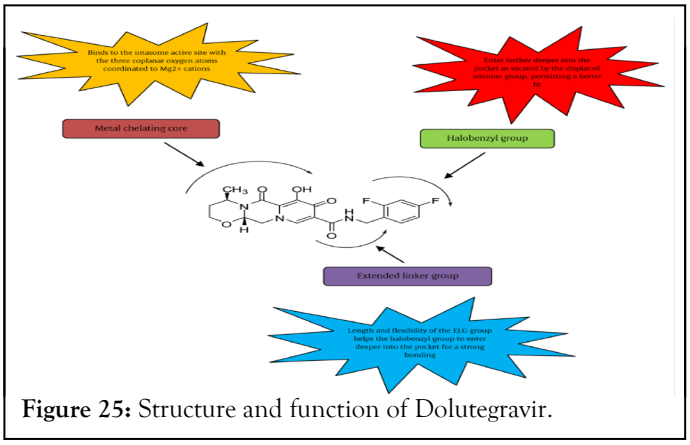


Figure 25: Structure and function of Dolutegravir.

To test the efficacy, a phase 3b, open-label, parallel-group, non-inferiority, active-controlled trial was performed with 627 HIV patients who had HIV RNA level more than 400. 312 patients were given dolutegravir with two NRTIs and 315 patients were given ritonavir-boosted lopinavir. 84%patients in the dolutegravir group achieved HIV RNA level less than 50 copies per ml compared to 70% patients in the ritonavir-boosted lopinavir group. So, dolutegravir with two NRTIs were fund to be superior than ritonavir boosted lopinavir [126].

CLASS 6: Attachment inhibitor

To enter into a cell the virus has to attach to cell surface first. It is done by interaction of envelope protein of the virus with CD4 of the T helper cells. Envelope protein is a gp120 and gp41 heterodimer both of which are formed after the cleavage of gp160. Gp120 is a chemokine mimic and binds to the N terminus of CD4 receptor to induce signal to enter into the cells. The gp120 protein is highly dynamic. That is, it is undergoing multiple conformational changes that make it difficult for neutralizing antibodies.CD4 binds at a highly conserved site which is composed of some regions from the outer and bridging sheet domains. The interaction of gp120 with CD4 stabilizes changes on the part on which the CD4

binds. These highly conserved sites are preoccupied by the attachment inhibitors and induce conformational changes of gp120 and gp41 in such a way that it cannot bind to the CD4 receptors. Thus, viral entry is prevented.

Fostemsavir (BMS-663068): Fostemsavir is a prodrug that is hydrolyzed to the active drug temsavir (BMS-626529), which binds to HIV envelope glycoprotein 120. Its IUPAC name is [3-[2-(4-benzoylpiperazin-1-yl)-2-oxoacetyl]-4-methoxy-7-(3-methyl-1,2,4-triazol-1-yl)pyrrolo[2,3-c]pyridin-1-yl]methyl dihydrogen phosphate .

Though Temsavir is a potent attachment inhibitor, it has a low solubility and poor intrinsic dissolution properties which needs to improve. When fostemsavir drug is swallowed and reaches the intestine, enzymes there convert it into temsavir. This process increases solubility and bioavailability of temsavir [127]. Temsavir binds to gp120 before contacting with CD4. This binding stabilizes conformation changes of the gp120 and blocks binding site of the CD4. Moreover, the compound also induces changes in the conformation which inhibit CCR5 binding [128, 129]. This way viral entry is inhibited (Figure 26).

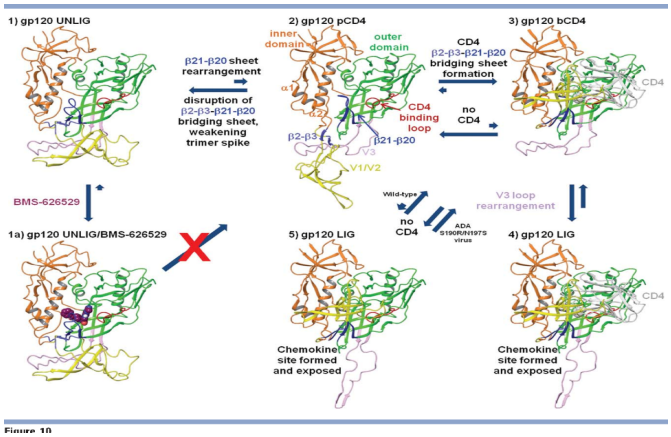


Figure 26: conformation changes of gp120 in different stages. Binding of CD4 stabilizes the gp120 and induces changes that expose CCR5 receptor. But binding of BMS-626529 or temsavir changes the conformation of gp120 in such a way that it cannot bind to CD4.

The efficacy of the drug is tested by BRIGHTE, a two-cohort phase 3 trial which included 371 HIV patients who went through heavy antiretroviral therapy but failed. Among them, 272 participants were in the randomized cohort that is patients with one or two fully active antiretrovirals remaining were given fostemsavir plus background therapy with any other antiretroviral therapy and 99 patients were in non-randomized cohort group that is provided with fostemsavir plus background therapy. 53% and 60% patients in the randomized cohort group at 24 weeks and 48 weeks respectively achieved HIV RNA level less than 40 copies per ml. whereas 37% patients in the non-randomized group achieved that level. Mean increase in CD were 205 cells per ml in the randomized cohort and 119cells per ml in the non-randomized cohort at week 96. Only 7% discontinued due to adverse effect [130]. This result says that it is safe and effective for HIV patients.

CLASS 7: Post attachment inhibitors

The dynamic gp120 undergoes conformational changes after binding with CD4 cell receptor. The V1 and V2 domain of the gp120 moves away from the V3 and bridging sheet reorders which exposes the CCR5 or CXCR4 binding site. Extracellular domain-2 of CCR5 binds to V3 and tyrosine sulfated N-terminus binds to bridging sheet that transduce signal to form fusion peptide. The post attachment inhibitors bind to the CD4 cells, it prevents these conformational changes within the complex of the CD4 T cell and the HIV envelope gp120. FDA has approved. Ibalizumab is the drug approved by FDA as a post attachment inhibitor on 2018.

Ibalizumab: Ibalizumab is a recombinant humanized immunoglobulin (Ig) G4 Monoclonal Antibody (Mab) derived from mouse Mab that is used as a post attachment inhibitor. Using Mab as treatment may provide advantages like ability to restore CD4 T cell counts, minimal mechanisms for acquired resistance, and low potential for toxicities. Ibalizumab binds to L96, P121, P122, and Q163 amino acid sites of extracellular domain 2 and E77 and S79 amino acid sites on extracellular domain 1 of human CD4 T cell receptors. The binding of ibalizumab induces steric inhibition, which prevents these conformational changes within the CD4 T cell receptor and gp120 complex [131,132]. This inhibition results in failure in binding of gp120 with CCR5 or co- receptor of the cell and gp41 cannot perform necessary changes to produce fusion peptide. Consequently, viral entry is prevented (Figure 27).

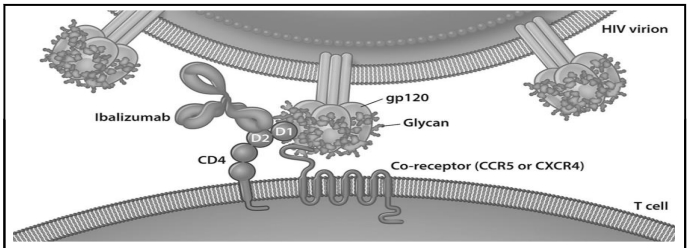


Figure 27: ibalizumab binding to Domain 1 and 2. This binding induces hinders in the conformation of CD4-gp120 complex which prevents downstream processes for membrane fusion.

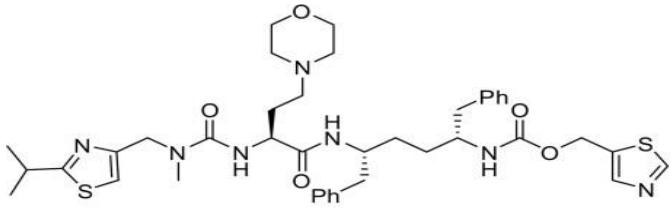
To test the efficacy a Phase 2, multicenter, randomized, double-blind, placebo-controlled trial was done with 82 HIV patients who were resistant to multiple drugs. These patients were provided with ibalizumab or placebo randomly. After 48 weeks, it was found that patients receiving ibalizumab had a mean decrease in HIV RNA were between 0.71 and 0.96 log10 copies per ml. and mean absolute CD4 T cell count increased by 48–51 cells per mm3. On the contrary, mean decrease of HIV RNA in placebo receiving patients were 0.14log10 copies per ml and mean increase in CD4 cell count were 1 cell/mm3 in the placebo arm [131]. In another phase 3 trial, 40 patients were provided with ibalizumab plus optimized background regimen. After 24 weeks, patients had a mean decrease of 1.6 log10 copies per ml. Moreover, 43% of the patients had HIV RNA level less than 50 copies per milliliter, and 50% had a HIV RNA level less than 200 copies per milliliter [133].

As ibalizumab is recombinant humanized immunoglobulin (Ig) G4 Monoclonal Antibody it produces low immune responses as there is very less affinity for ACCC in igG4 type's antibody. Moreover, it binds to a distant site from the MHC molecule, thus there is a less chance of hyper-immunity responses [131, 132]. So, the drug is considered safe. Only some mild adverse effect like diarrhea is reported.

CLASS 8: Pharmacokinetic enhancers

Pharmacokinetic enhancers are compounds which are used with any other drug and improve its effectivity. These compounds are not used as primary agent. Rather, they are used as secondary agent that can improve the primary drugs efficiency. Usually, For HIV treatment, the enzymes responsible for degradation of the drugs are inhibited for long lasting efficacy of the primary drugs. Pharmacokinetic boosters can work by inhibiting hepatic drug metabolizing enzymes like CYP3A4 which is responsible for most of the drug degradation. Another process is by inhibiting drug specific metabolizing enzymes [134]. Till now, FDA has approved Cobicistat and ritonavir as pharmacokinetic enhancer. ritonavir has both pharmacokinetic boost and protease inhibitory activity and it is mentioned earlier.

Cobicistat: Cobicistat is a compound structurally closely related to ritonavir, but it is only used as a pharmacokinetic booster. Its IUPAC name is Thiazol-5-ylmethyl N-[1-benzyl-4-[[2-[[(2-isopropylthiazol-4-yl)methyl-methylcarbamoyl] amino]-4-morpholinobutanoyl]amino]-5-phenylpentyl]carbamate (Figure 28) [134, 135].



cobicistat

Figure 28: chemical structure of cobicistat.

Cobicistat has no inhibitory activity of its own. Rather it is used to boost up the efficiencies of other drugs. It is done by inhibiting CYP3A4 and blocking P-glycoprotein efflux transporters [134]. CYP3A4 is responsible for degradation of drugs. P-glycoprotein effluxes a wide range of therapeutic drugs out of the cells [136]. Although ritonavir and cobicistat can be used as same purpose, cobicistat has some advantages. Such as it has higher aqueous solubility and better physicochemical properties which makes it more efficient inhibitor of CYP3A. It has lower off-target drug interactions than ritonavir. Ritonavir inhibits additional CYP enzymes (2C19, 2C8, 2C9, 2D6, and 2E1) inhibitory activities which may cause adverse effects [134, 137]. But cobicistat hardly inhibits other CYP enzyme than CYP34A. Moreover, it is believed that cobicistat has less incidence of occurrence of lipid metabolism, gastrointestinal disturbances, and pronounced drug-drug interactions [134].

To assess efficacy and safety of cobicistat, a phase 2, randomized, partially placebo-controlled, double-blinded trial was performed in which HIV patients having HIV RNA level more than 5000 were randomly provided with atazanavir plus cobicistat or atazanavir plus ritonavir. After 48 weeks, it was found that 82 %of the patient receiving atazanavir plus cobicistat and 86% of the patients receiving atazanavir plus ritonavir achieved HIV RNA level less than 50. Mean CD4 count increase was 208 and 177cells per micro liter for the patients receiving cobicistat and ritonavir respectively [138]. In a phase 3 trial, 626 HIV patients were given Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) regimen and 109 received Darunavir/cobicistat plus emtricitabine/tenofovir alafenamide (control group). At 96 weeks, 85.1% of the patents in the (D/C/F/TAF) receiving groupand 83.7%of patients in control group had achieved HIV RNA level less than 50. No mutation of tenofovir or darunavir were found in the trial [139]. These results clearly depict the efficacy of the drug.

CLASS 9: Fusion inhibitor

Gp41 consists of three domains. They are extracellular, transmembrane, and cytoplasmic domains. It's extracellular domain or ectodomain has four functional regions: a hydrophobic, glycine-rich fusion peptide. N-terminal Heptad Repeat (NHR), C-terminal Heptad Repeat (CHR) and a tryptophan-rich region [140]. After binding with CD4, the gp120 binds with co-receptor CCR5 or CXCR4. This binding with co-receptor results in changes in conformation of the envelope complex that activates gp41. In brief, Gp120 moves away from the gp41 during these changes that allow the N-terminal fusion peptide of gp41 to be exposed. The exposed gp41 is then inserted into the cell membrane of the T cell [141]. This fusion peptide forms a pre-hairpin configuration that connects the virus and the targeted cell. Three C-terminal Heptad Repeats (CHR) fold in an anti-parallel wayinto thethree coiled N-terminal Heptad Repeats (NHR) that forms thermostable sixhelix bundlestructure [140-142]. This structure formation brings the two membranes together and promotes the formation of the fusion pore. the viral RNA is inserted through this pore and it gets active for replication [142]. Fusion peptide inhibits the fusion by binding to the gp41. FDA has approved enfuvirtide on March 13, 2003.

Enfuvirtide: Enfuvirtide is the first and only viral fusion inhibitor that is still in the market and is used in combination therapy of HIV-1 infection. It is a linear 36 L-amino acid synthetic peptide with an acetylated N-terminus and a carboxamide at C-terminus end. It is peptide derived from C-terminal heptad repeats or CHR [141,143].

It is found that, peptides derived from the CHR or NHR regions can be used as an antiviral agent due to their competitive binding to their counterpart. This binding to counterpart prevents the formation of viral six-helix bundle structure [141]. Enfuvirtide being a peptide derived from the CHR, can compete with the CHR of the gp41 to bind to NHR. And its binding to NHR causes inhibition in formation of six-helix bundle structure. Consequently, the two membrane cannot fuse together and viral replication gets prevented (Figure 29) [143, 144]

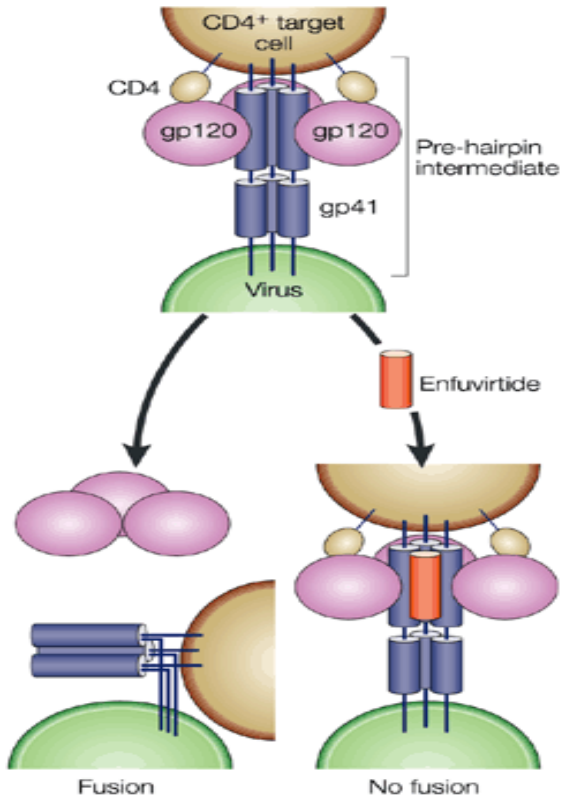


Figure 29: Enfuvirtide mechanism of action. It binds to the NHR and prevents six helix bundle structure formation.

The efficacy of the enfuvirtide is depicted from (TORO) 1 and TORO 2 which are open-label, controlled, parallel-group, phase 3 trials that included 661 patients to receive enfuvirtide plus an Optimized Background (OB) with retroviral drug and 334 HIV patients to receive only OB. 37.4% patients had a viral reduction more than 1log10, 30.4% had HIV RNA level less than 400 copies per ml , and 18.3% patients had HIV RNA level less than 50 copies per ml in the enfuvirtide receiving group . On the contrary, 17.1%of the patient had a viral reduction of 1log10, 12.0%of the patients had achieved HIV RNA level less than 400 copies er ml, and 7.8% patients had HIV RNA level less than 50 copies per ml [145-150].

CONCLUSION

Till now, no treatment is invented which can eliminate HIV from the body completely. Because the virus becomes resistant frequently and can hide inside the cells. Though combinations of three or more drugs are supposed to be most effective treatment for HIV patients, but it is not enough to eradicate all of the viruses. Hope that scientists will be able to invent a drug which can cure HIV patients completely.

DECLARATION

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

Author's contribution

The concept of writing this article was designed by both of the authors. Data collection and analysis has been done by Halima Habib. Data interpretation, drafting of the article, critical relations of the article were done by Ayman Bin Abdul Mannan. After a series of revision, the article was finalized by both of the authors.

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Author's contribution

The concept of writing this article was designed by both of the authors. Data collection and analysis has been done by Halima Habib. Data interpretation, drafting of the article, critical relations of the article were done by Ayman Bin Abdul Mannan. After a series of revision, the article was finalized by both of the authors.

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