Drugs for AIDS

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Abstract: AIDS, the fatal disease, caused in human by the fast spreading human immunodeficiency virus (HIV), was detected in 1981. To check its rapid growth, affecting various parts of the world population, there are various FDA approved drugs, released in the market for treating AIDS. These belong to 5 different categories which differ in their mechanism of action. These are i) reverse transcriptase inhibitors, ii) protease inhibitors, iii) fusion inhibitors, iv) entry inhibitors and v) HIV integrase strand transfer inhibitors. These drugs are mostly used in a combination therapy, named as Highly Active Anti Retroviral Therapy (HAART), using 2 to 3 compounds in combination, for a more effective and beneficial treatment. However, none of the drugs can be considered ideal for curing the disease. A study of structural requirement for different types of anti-HIV activities may help in designing a suitable drug for AIDS.

Key Words: Anti HIV, AIDS, protease inhibitor, reverse transcriptase inhibitor, integrase inhibitor, fusion inhibitor.

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is a condition in human created by a retrovirus, Human Immunodeficiency Virus (HIV), first detected in December, 1981.

Under the above condition the immune system of the human body begins to fail, leading to life-threatening opportunistic infections [1]. It is estimated that world wide 31.3 million adults and 2.1 million children were living with HIV at the end of 2008 [2].

To check the rapidly spreading HIV infection, a large number of compounds belonging to various categories were developed to fight the disease and some of them were approved by FDA for treatment. However, none can be considered as totally effective in curing the infection.

When exposed to HIV, vital cells in the human immune system helper T cells (specifically $CD4^+$ T cells), macrophages and dendritic cells are infected. The infection leads to low levels of $CD4^+$ T cells through three main mechanisms: i). direct viral killing of infected cells ii). increased rates of apoptosis in infected cells and iii) killing of infected $CD4^+$ T cells by CD8 cytotoxic lymphocytes that recognize infected cells.

Macrophages play a key role in the process of HIV infection and perhaps the source of HIV production. When CD4+ T cell counts decline below a critical level, cell mediated immunity is lost and the body becomes progressively more prone to opportunistic infections, developing Acquired Immuno Deficiency Syndrome. Macrophages and microglial cells are the cells infected by HIV in the central nervous system. Antiretroviral treatment reduces both the mortality and the morbidity of HIV infection [3].

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There are two species of human immunodeficiency virus, HIV-1 and HIV-2. The first one is the virus that was initially discovered and termed Lymphadenopathy-Associated Virus (LAV). It is more virulent, relatively easily transmitted, and is the cause of the majority of HIV infections globally. HIV-1 binds to any appropriate DNA, whereas HIV-2 prefers to bind to DNA which is used to create the gag protein itself and is therefore, relatively less transmittable.

Transmission of HIV infection occurs through blood, semen, vaginal fluid, pre-ejaculate, or breast milk. The major routes are unprotected sexual intercourse, use of contaminated needles, infected blood transfusion and transmission of infection from infected mother to her baby at birth. Once the virus has infected the cell, it either becomes latent, and the infected cell continues to function or becomes active and replicates, creating a large number of virus particles which then infects normal body constituents.

To check the growing population of HIV infected people, particularly in highly infected areas, a proper HIV test is very important. HIV-1 test is performed by Enzyme-Linked Immunosorbent Assay (ELISA) using anti-bodies to HIV-1. Specimens with a non-reactive result are considered HIV-negative. Those with a reactive ELISA result are retested in duplicate and a confirmatory testing is done through more specific supplemental test e.g. Western blot [4, 5]. Also, nucleic acid testing by viral RNA or proviral DNA amplification method is helpful in the diagnosis in certain situation [5].

Currently there is no vaccine or cure for HIV or AIDS. However, some antiretroviral drugs have been developed which are effective in reducing the risk of infection as well as the viral load. However, none can be considered totally effective and ideal. For a more effective and beneficial treatment, highly active antiretroviral therapy (HAART) is adopted as a combination therapy, consisting of typically, two nucleoside analogue reverse transcriptase inhibitors (NARTIs or NRTIs) plus either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor (NHRTI) [6-10].

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Table 1. NRTI and NNRTI Drugs

Brand Name	Generic Name(s)	Manufacturer Name	Approval Date	Time to Approval
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)				
Retrovir	Zidovudine, axidothymidine, AZT, ZDV	GlaxoSmitKline	19-Mar-87	3.5 months
Videx	Didanosine, dideoxyinosine, ddl	Bristol Myers-Squibb	9-Oct-91	6 months
Hivid	Zalcitabine, dideoxycytidine, ddC	Hoffmann-La Roche	10-June-92	7.6 months
Zerit	Stavudine, d4T	Bristol Myers-Squibb	24-Jun-94	5.9 months
Epivir	Lamivuddine, 3TC	GlaxoSmitKline	17-Nov-95	4.4 months
Ziagen	Abacaivr sulfate, ABC	GlaxoSmityKline	17-Dec-98	5.8 months
Truvada	Tenofovir disoproxil fumarate and emtricitabine	Gilead Sciences, Inc.	02-Aug-04	5 months
Emtriva	Emtricitabine, FTC	Gilead Sciences	02-Jul-03	10 months
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)				
Viramune	Nevirapine, NVP	Boehringer Ingelheim	21-Jun-96	3.9 months
Rescriptor	Delavirdine, DLV	Pfizer	4-Apr-97	8.7 months
Sustiva	Efavirenz, EFV	Bristol Myers-Squibb	17-Sep-98	3.2 months
Intelence	Etravirine	Tibotec Therapeutics	18-Jan-08	6 months

This combination generally causes improvement of $CD4^+$ cell counts and viral load measures, thereby reducing the risk of developing life threatening infections (opportunistic infections).

Based on their mechanism of action, anti-AIDS compounds are classified under the following heads.

1. Reverse Transcriptase Inhibitors- i) Nucleoside Reverse Transcriptase Inhibitors (NRTIs), ii) Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
2. Protease inhibitors (PIs).
3. Fusion inhibitors.

Table 2. Protease Inhibitors (PIs), Fusion Inhibitors, Entry Inhibitors – CCR5 co-Receptor Antagonist and HIV Integrase Strand Transfer Inhibitors

Brand Name	Generic Name(s)	Manufacturer Name	Approval Date	Time to Approval
Protease Inhibitors (PIs)				
Fortovase	Saquinavir (no longer marketed)	Hoffmann-La Roche	7-Nov-97	5.9 months
Norvir	Ritonavir, RTV	Abbott Laboratories	1-Mar-96	2,3 months
Crixivan	Indinavir, IDV	Merck	13-Mar-96	1.4 months
Viracept	Nelfinavir mesylate, NFV	Agouron Pharmaceuticals	14-Mar-97	2.6 months
Agenerase	Amprenavir, APV	GlaxoSmithKline	15-Apr-99	6 months
Kaletra	Iopinavir and ritonavir,/ LPV/RTV	Abbott Laboratories	15-Sep-00	3.5 months
Lexiva and Telzier	Fosamprenavir Calcium, FOS-APV	GlaxoSmitKline	20-0ct-03	10 months
Reyataz	Atazanavir sulfate, ATV	Bristol-Myers Squibb	20-Jun-03	6 months
Aptivus	Tipranavir, TPV	Boehringer Ingelheim	22-Jun-05	6 months
Prezista	Darunavir	Tibotec, Inc,	23-Jun-06	6 months
Fusion Inhibitors				
Fuzeon	Enfuvirtide, T-20	Hoffmann-La Roche & Trimeris	13-Mar-03	6 months
Entry Inhibitors – CCR5 co-receptor antagonist				
Selzentry	Maraviroc	Pfizer	06-August-07	8 months
HIV integrase strand transfer inhibitors				
Isentress	Raltegravir	Merck & Co., Inc.	12-Oct-07	6 months

4. Entry inhibitors – CCR5 co-receptor antagonist.
5. HIV integrase strand transfer inhibitors.

Within a very short period, after HIV was detected in early 80s, a good number of compounds belonging to the above categories were developed and approved by FDA, which are given in Tables **1** and **2**.

A detailed description of the above categories is mentioned below:

1. REVERSE TRANSCRIPTASE INHIBITORS (RTIS)

The enzyme reverse transcriptase present in the cells, copies the viral single- stranded RNA genome of HIV infections into a double- stranded viral DNA. The viral DNA thus produced, is then integrated into the host chromosomal DNA which then allows host cellular process, such as transcription and translation, to reproduce the virus. The process causes growth of HIV in the body. The role of Reverse Transcriptase Inhibitor (RTI) is to block the activity of the enzyme reverse transcriptase, interfering with the formation of the double stranded viral DNA, to prevent HIV from multiplication.

Reverse Transcriptase Inhibitors (RTI) may be classified into following two categories- i) Nucleoside & Nucleotide Reverse Transcriptase Inhibitors (NRTIs) and ii) Non-Nucleotide Reverse Transcriptase Inhibitors (NNRTIs).

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

NRTIs are analogs of naturally occurring deoxyribonucleosides which lack a 3'-hydroxy group on the ribose sugar. NRTIs are metabolically converted by host cell enzymes to the corresponding 5' – triphosphates [11,12]. This triphosphate competes with analogous dNTP substrate and enters into the nascent viral DNA chain. This results in termination of further elongation of the DNA chain due to lack of 3'-hydroxyl in the ribose sugar thus introduced in the viral DNA chain [13].

NRTI Drugs

(i). Zidovudine [14] (Retrovir, AZT)

[3'-azido-3'-deoxythimidine] (Fig. **1**) is the first approved drug for the treatment of HIV.

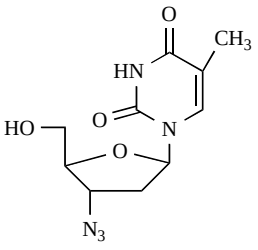


Fig. (1).

Its efficacy in treating AIDS was discovered by Fischl *et al.* [15]. It has been found that pregnant women treated with zidovudine were only one-third as likely to pass HIV on to their babies as compared to women without this drug [16].

The azido group of zidovudine increases its lipophilic nature, allowing it to cross cell membranes more easily and also to cross blood-brain barrier. Its conversion to its 5'-triphosphate through action of cellular enzymes interferes with the DNA chain formation. It also inhibits cellular DNA polymerase which is used by normal cells for cell division [17]. Long term use of zidovudine causes myopathy (loss of muscle). Some other side effects are anemia, white blood cell depression, lip, mouth and tongue sores, bone marrow damage, headache, skin rash, itching, weakness, nervousness, dizziness, nausea, stomach pain, sore throat or abnormal bruising or bleeding etc.

(ii). Didanosine (Videx, dideoxyinosine, ddI)

[9-[5-(hydroxymethyl)oxolan-2-yl]-3H-purin-6-one](Fig. **2**) is a synthetic purine nucleoside analogue active against HIV. This RTI is used in combination with other retroviral drug therapy as part of HAART.

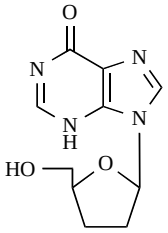


Fig. (2).

Didanosine was discovered and patented by Morris J. Robins [18]. It is susceptible to acid and is unstable in stomach. It is therefore taken as a chewable tablet that contains antacid. Later it was developed as capsule containing coated microspheres under the name Videx EC.

Didanosine is a nucleoside analogue of adenosine. It differs from other nucleoside analogues, because it does not have the regular bases, instead it has hypoxanthine base. Within the cell ddI is converted to its triphosphate ddATP by cellular enzymes and its incorporation by competing with dATP results in chain termination and inhibits viral reverse transcriptase [18,19].

Common side effects observed with didanosine are diarrhea, nausea, vomiting, abdominal pain, fever, headache and rash.

(iii). Zalcitabine [20]

[4-amino-1-(2R,5S)-5-(hydroxymethyl) tetrahydrofuran-2-yl) pyrimidin- 2(1H) –one] (Fig. **3**) was developed in National Cancer Institute (NCI) by Samuel Broder *et al.* [21] and was licensed to Hoffmann-La Roche.

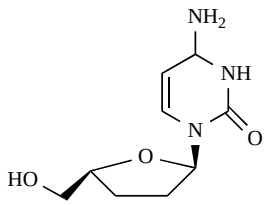


Fig. (3).

Zalcitabine interferes with the progress of viral DNA double strand through its metabolism to its active triphosphate form, ddCTP. The absence of the 3'-hydroxyl group in the ddCTP, prevents elongation of the DNA chain.Resistance to zalcitabine develops infrequently compared to other NRTIs, and generally occurs at a low level [22].

Zalcitabine appears to be less potent than some other nucleoside RTIs and is associated by serious adverse side effects. These include severe allergic reactions, convulsions, fast, shallow breathing, constipation, diarrhea, fatigue, headache, itching, loss of appetite, nausea, severe nerve problems, and swelling of the pancreas.

The sale and distributiojn of zalcitabine has been discontinued since December 2006.

(iv). Stavudine (Zerit,)

[1-[(2R, 5S)-5-(hydroxymethyl)-2, 5-dihydrofuran-2-yl]-5-methyl pyrimidine-2,4-dione)] (Fig. **4**) was first synthesised by Horwitz *et al.* [23] starting from 3',5'-dimesylthymidine and later modified by Liu *et al.* [24].

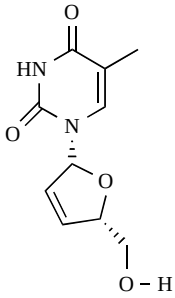


Fig. (4).

Stavudine is a NRTI with activity against HIV-1[25 a, b]. Like other NRTIs, its active triphosphate competes for incorporation into viral DNA. It inhibits the HIV reverse transcriptase enzyme competitively and acts as a chain terminator of DNA synthesis, preventing viral growth.

Side effects of stavudine include peripheral neuropathy, lipodystrophy, burning, numbness, or pain in the feet, total lactic acidosis, severe liver enlargement and failure.

(v). Lamivudine [26a, b] (Epivir, 3TC)

[(2R, cis)-4-amino-1-(2-hydroxy methyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one] (Fig. **5**) was discovered by Bernard Bellean and Nghe Nguyen-Ga at IAF Biochem International Inc Laboratories in 1989 and later developed by Glaxo Smith Kline. A simple, economical, cost effective method for its preparation was developed by Encure Pharmaceuticals Ltd. (India) [27].

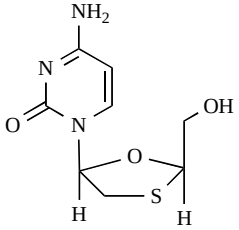


Fig. (5).

Lamivudine is the (-) enantiomer of a dideoxy analogue of cytidine. It has also been referred to as (-) 2', 3'-dideoxy-3'-thiacytidine. The intracellularly produced metabolite of lamivudine, its triphosphate (L-TP), inhibits viral RT by DNA chain termination. Lamivudine shows synergistic antiretroviral activity with zidovudine and is generally used in combination with at least one other NRTIs, NNRTIs or PI.

Lamivudine has few side-effects, mainly nausea, vomiting, headaches, and hair loss. It may also cause damage to nerves in the hands and feet, pancreatitis in children. Patients with severe liver disease should avoid treatment with lamivudine [28].

(vi). Abacavir [29, 30]

[(1R)-4-[2-amino-6-(cyclopropyl amino) purin-9-yl]-1-cyclopent-2-enyl] methanol] (Fig. **6**) is used in the form of abacavir sulfate "Ziagen". It is a carbocyclic nucleoside analogue that is converted by cellular enzymes to carbovir triphosphate to compete with the natural substrate dGTP, thus preventing further synthesis of the viral DNA.

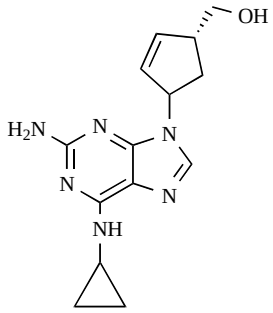


Fig. (6).

In vitro, abacavir shows synergetic activity in combination with other RTIs amprenavir, nevirapine, & zidovudine and additive activity with didanosine, lamivudine and zalcitabine. It is also used in combination with other RTIs or protease inhibitors. Its side effects include fatal hypersensitivity, fatigue, nausea vomiting, diahorrea, abdominal pain, skin rashes and fever.

(vii). Tenofovir Disoproxil Fumarate (TDF) [31] (Truvada, Viread)

[9-[(R)-2[[bis[[(isopropoxy carbonyl)oxy]-methoxy]phosphinyl] methoxy] propyl] adenine fumarate (1:1)](Fig. **7**) has been launched as a drug for AIDS under the brand name Viread by Gilead and is also sold under the name `Truvada' which is a combination of TDF and emtricitabin.

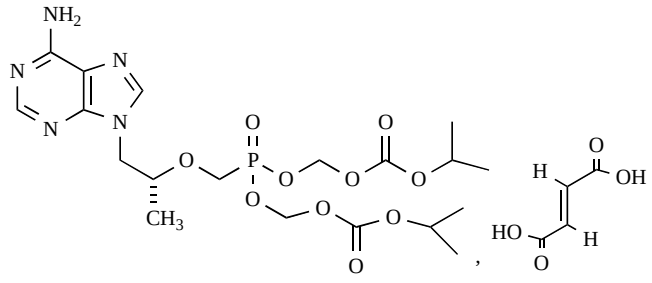


Fig. (7).

TDF is a nucleotide analog that inhibits HIV reverse transcriptase and shows potent *In vitro* and *in vivo* activities against HIV [32 a,b].

Tenofovir DF is indicated in combination with other retrovirals for the treatment of HIV infection. Its long half life allows once a day administration [33] and has a prolonged intracellular half life [34].

TDF undergoes hydrolysis to tenofovir followed by conversion to tenofovir diphosphate that inhibits the activity of HIV-1 RT by competing with the natural substrate doxyadenosine 5'-triphosphate for incorporation into DNA, subsequently leading to DNA chain termination. Tenofovir diphophate is a weak inhibitor of mammalian DNA polymerase α, β, and into chondrial DNA polymerase γ. Potential side effects of tenofovir are nausea, diarrhea, vomiting and flatulence.

(viii). Emtricitabine [35] (Emtriva)

[5-fluoro-1-(2R, 5S) - [2-hydroxymethyl)-1, 3-oxathiolan-5-yl] cytosine] (Fig. **8**) is a (-) enantiomer. It was discovered by Dennis *et al.* in 1996 and later developed by Gilead Sciences.

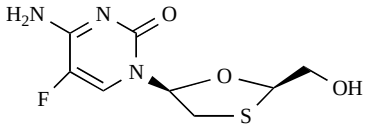


Fig. (8).

Emtricitabine, a synthetic analog of cytidine, is phosphorylated by cellular enzyme to form emtricitabine 5 -triphosphate that competes with the natural substrate deoxycytidine 5'-triphosphate for incorporation into nascent viral DNA and results in DNA chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerase α, β, ξ and mitochondrial DNA polymerase γ.

In vitro studies showed emtricitabine is associated with a mutation in the HIV RT gene codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine. Emtricitabine- resistant isolates of HIV have been recovered from some patients treated with emtricitabine.

A combination of emtricitabine and tenofovir, was found to cause reduction of bone mineral density. Emtricitabine does not affect fertility in male rats. Fertility was normal in the offspring of mice exposed daily from before birth through sexual maturity. Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

Emtricitabine develops resistance mutation which makes HIV 8 fold less susceptible [36].

The side effects associated with emtricitabine include abnormal skin sensation, change in color of skin, depression, diarrhea, dizziness, headache, stomach pain, vomiting, weakness, severe allergic reactions, fever, sore throat, rapid breathing.

SAR

Various 3'-deoxy nucleosides (**1-6,8**) and one nucleotide (**7**), with modified sugar and bases, have been introduced for treating HIV patients. All these NRTIs follow the same mechanism of action and differ in terms of contra indications, preclinical indications, common side effects and dosing [37]. There is no significant SAR study in this regard.

Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)

NNRTI is a group of small hydrophobic molecules with diverse structures that specifically inhibit HIV-1 reverse transcriptase directly by binding to the enzyme and interfering with its function. The binding site of the enzyme is P66 sub unit of the P66/5 hetero dimeric enzyme, known as NNRTI-binding pocket (NNRTI-BP). The binding results in both short range and long range distortion of RT structure [38]. NNRTI some times induce liver toxicity [39].

NNRTI Drugs

(i). Nevirapine (NVP) [40] (Viramune)

[11-Cylopropyl-5, 11-dihydro-4-methyl-6H-dipyrido-[3, 2-b: 2', 3'-e] [1,4] diazepin – 6 – one] (Fig. **9**), a dipyridodiazipinone derivative, is a NNRTI, which stops HIV-1 from multiplying by inhibiting RT enzyme action.

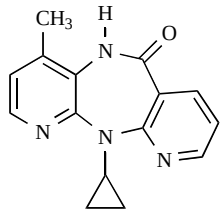


Fig. (9).

Nevirapine is generally not given to HIV infected women with over 250 CD4 cell count or in men with over 400 CD4 cells due to the risk of liver problem. Nevirapine in triple combination therapy, suppresses viral load effectively when used as initial antiretroviral therapy [41]. It is not effective against HIV-2 [42].

Nevirapine does not appear to harm pregnant women or increase the risk of their fetus. Nevirapine prevents transmission of HIV from a pregnant woman to her new child [43]. It is therefore, safest NNRTI for pregnant women in the first 3 months of pregnancies. However, resistance to nevirapine develops in many women who use it when they are pregnant [44]. This resistance can be transmitted through breast-feeding.

Nevirapine given along with other anti-retroviral drugs, can reduce the viral load to a very low level and increase CD4 cell counts.

The most common side effect of nevirapine is skin rash, particularly in women. It may also cause liver damage.

(ii). Delavirdin (DLV) [40] (Rescriptor)

[1-[3-[(1-methyl ethyl) amino]-2]pyridinyl)-4-[[5[(methyl sulfonyl) amino]-1H-indol-2-yl] carbonyl] piperazine, monomethane, sulfonate] (Fig. **10**) is a NNRTI of HIV-1.

It binds directly to RT and blocks its RNA & DNA dependent DNA polymerase activities. HIV-2 RT and human

cellular DNA polymerases α, β or б are not inhibited by delavirdine. In addition, HIV-1 group O, a group of highly divergent strains that are uncommon in North America, may not be inhibited by delavirdine.

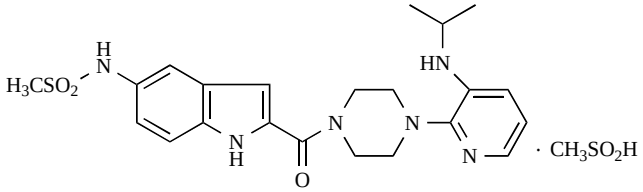


Fig. (10).

A unique feature of delavirdine is its capability of raising the plasma level of all approved protease inhibitors [45]. Common side effects observed with delavirdine use are dizziness, fatigue, headache, nausea, vomiting, diarrhea, and rash.

(iii). Efavirenz, [46] (EFV) (Sustiva)

[(4S)-6-chloro-4-(2-cyclopropylethynyl)-4-(trifluoromethyl)-2,4-dihydro-1H-3,1-benzoxazin-2-one] (Fig. **11**), like other NNRTI, directly inhibits the activity of the enzyme RT. It does not kill existing HIV virus and it is not a cure for HIV [47].

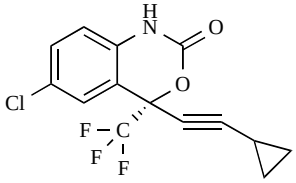


Fig. (11).

Efavirenz must be used in combination with other antiretroviral drugs to treat HIV. It is usually combined with two NRTIs.

Within NNRTIs, efavirenz can be considered a safer drug for liver than nevirapine [39]. Side effects observed with efavirenz are dizziness, insomnia, drowsiness and vivid dreams. These side effects usually get adjusted while taking the medicine. Neuropsychiatric adverse reactions were found associated with efavirenz treatment [48, 49 a, b].

(iv). Etravirine [50] (Intelences, TMC 125)

[2-(4-cyanophenyl)-4-(2,6-dimethyl)-4-cyanophenyl) oxy-5-bromo-6-amino-pyrimidine] (Fig. **12a**), has been marketed as the first NNRTI to show antiviral activity [51, 52] and to show antiviral activity in patients with NNRTI resistant virus [53].

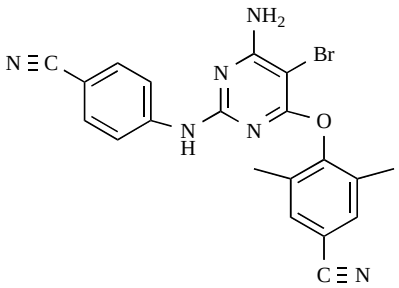


Fig. (12a).

Etraverine blocks the RT, the key enzyme the HIV virus uses to replicate. Etraverine, in combination with other antiretroviral (ARV) agents, is indicated for the treatment of HIV-1 infection in ARV treatment for experienced adult patients who have evidence of viral replication and HIV -1 strain resistant to a NNRT and other ARV agents. The use of other ARV agents with etraverine is associated with an increased likelyhood of treatment response. Etraverine does not cure HIV infection or AIDS and does not prevent passing HIV to others.

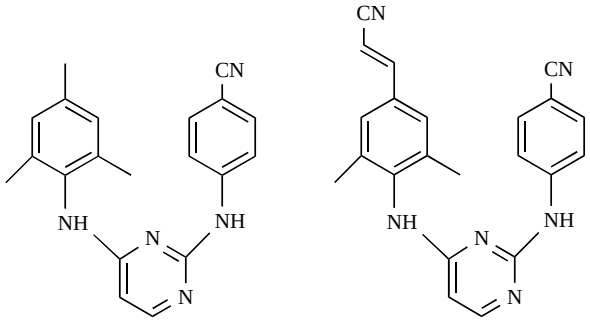
NNRTI drug resistance occurs when HIV undergoes mutation that partially or completely stops the NNRTI from binding to RT enzyme, causing the drug to lose effectiveness.

Molecular flexibility of TMC 125 relative to other NNRTIs, permits the compound to retain its binding affinity to the RT in spite of the binding site changes induced by the presence of common NNRTI resistance mutations.

The most common side effects associated with etravirine are skin rash and nausea. In rare cases, severe skin rash may result. Other possible side effects are diarrhea, vomiting, abdominal pain, tiredness, headache, and high blood pressure, pain in hands & feet, numbness.

SAR

NNRTI drugs in the market today basically differ in the molecular frame work. Majority of these accepted molecules have come up through SAR studies [54] of the concerned group of compounds. Three major active compounds belonging to the class of diaryl pyrimidines were TMC120 [2-(4-cyano phenyl amino)-4-(2,4,6-trimethyl phenyl amino)-pyrimidine] (Fig. **12b**). TMC 278 [(2-(4-cyano phenyl-amino)-4-(4-(2-cyano ethylene)-2,6-dimethyl amino) pyrimidine] (Fig. **12c**) and TMC 125 [2-(4-cyanophenyl)-4-(2,6-dimethyl)-4-cyanophenyl)oxy-5-bromo-6-amino-pyrimidine] (Fig. **12a**). Of these TMC 125 was found to be most potent and has a good stability in human microsomes [55].



b **c**

Fig. (12b, 12c).

In delavirdine its central part piperazine is connected through carbonyl to an indole residue on the left and to substituted pyridine on the right. The carbonyl group can be replaced by CH_2. The indole as well as the pyridine heterocyclic residues has better anti-viral potency and a reduced inhibitory effect to the cellular DNA polymerases, 5-substituted indole analogs showed better metabolic stability and potency leading to the effective drug delavirdine [56a-f].

The basic dipyrido diazepinone structure of nevirapine is important. Replacement of either pyridine rings by benzene, lowers the activity. Substitution on either pyridine drugs is generally beneficial at 4-position. Potency is reduced or abolished on N-5 substitution or removal of the cyclopropyl drug. Diazepinthione modification though acceptable, but may undergo metabolism rapidly and are often less water soluble [57a, b].

Efavirenz has been developed through optimization of the substituted 4-amyl-dihydro-benzopyrimidine-2-thione (thiourea scaffold) which had shown anti-HIV-1 RT activity. Corresponding urea scaffold (2-one), and 4,4-dialkyl substitution showed better metabolic stability and potential safety. Replacement of the dihydro benzo pyrimidine unit by a benzoxazinone scaffold, proper substitutions and specific stereochemistry at C-4, led to the development of efavirenz [58 a, b].

2. PROTEASE INHIBITORS

Multiple growth of HIV on its entry to human body cell goes through many steps. HIV in the form of viral DNA, a single stranded, positive-sense, enveloped DNA virus, on its entry to the target body cell is converted into a double stranded DNA and uses proteins and chemicals inside the cell to form a polypeptide sequence using several individual proteins including reverse transcriptase, protease and integrase. These enzymes become functional only when they are out from the long peptide chain. This is affected by the enzyme, viral protease. On the basis of the understanding regarding chemical mechanism of the viral enzymes, development of efficient inhibitors of HIV-1 protease as PI [59] is one of the effective approaches in designing drugs for AIDS. PI blocks the ability of the viral protease to cleave the viral polypeptide chain into the functional enzymes which helps in the formation of double - stranded viral DNA by RT and its integration into cellular DNA by the enzyme integrase, leading to a HIV infected cell. By blocking the protease, using PI, HIV makes copies of it self and cannot infect new cells. Thus, it reduces amount of virus in the blood and increases CD4 cell counts.

However, it has been observed that the beneficial effect of PI reduces with time. This happens because during the production of each new HIV, virus produced may go through slight modification. The new protease that the virus has made may resist the drug (protease inhibitor) that worked for viruses with the older type of protease. With the development of this drug resistance, use of PI becomes less effective.

To avoid drug resistance likely to develop during use of PI, it is essential to stop or reduce repeated production of HIV in the body. Thus, to keep HIV level low, PIs are given in combination with at least two other anti HIV drugs.

Protease inhibitors combined with nucleoside analogues with antiretroviral activity, cause profound and sustained suppression of viral replication, reduce morbidity and prolong life in patients with HIV infection [60]. Certain adverse side effects are found in PIs which include dyslipidemia, lipodystrophy, insulin resistance, and premature atherosclerosis [61a,b,c].

FDA approved protease inhibitors available in the market are shown in Table **2**. Detailed description of the protease inhibitors is given below.

1st Generation HIV Protease Inhibitors

(i). Saquinavir

[N-[1-benzyl-2-hydroxy-3- [3-(tert-butyl-carbamoyl) 1, 2, 3, 4,4a, 5,6,7,8, 8a-decahydro isoquinolin-2-yl]propyl]-2-quinolin-2-ylcarhonylamino-butane-diamide] (Fig. **13**) is the first PI in clinic developed through structure- based drug design. It was introduced by Hoffmenn- La Roche but suffered from very low bioavailability [62]. It was synthesized by Parkes *et al.* [63] and an improved synthesis was reported by Yang *et al.* [64].

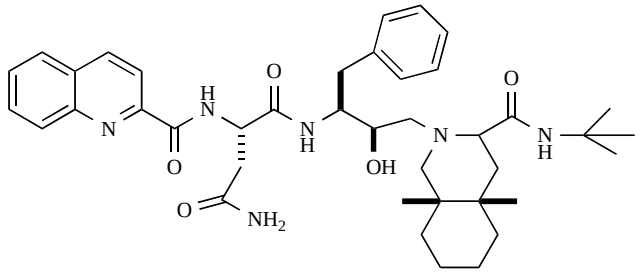


Fig. (13).

Saquinavir has two formulations: i) a hard gel capsule formulation of the mesylate with trade name invirase, which requires combination with ritonavir to increase its bioavailability and ii) a soft-gel capsule formation under the trade name fortovase, which has been withdrawn.

Saquinavir inhibits both HIV-1 and HIV-2 proteases which are responsible for viral replication within the cell and release of mature viral particle from an infected cell.

Saquinavir, in the form of invirase, has a low and variable bioavailability when given alone. The other formulation fortovase shows eight fold more activity. However, both these formulations show significant increase in the biological activity when given in combination with another protease inhibitor ritonavir. It has been found that ritonavir inhibits the cytochrome P450 3A4 isozyme which metabolizes saquinavir to an inactive form [65].

The most common side effects associated with saquinavir are mild gastrointestinal symptoms, including diarrhea, nausea, loose stools and abdominal discomfort. Invirase is better tolerated than fortovase.

(ii). Ritonavir (Norvir)

[1,3-Thiazol-5-ylmethyl-N-[(2S,3S,5S)-3-hydroxy-5-[[(2S)-3-methyl-2-[[(methyl-[(2-propan-2-yl-1)-thiazol-4-yl)methyl]carbamoyl]amino]butanoyl]-1,6-(diphenyl)hexan-2-yl]carbamate](Fig. **14**),is the seventh antiretroviral drug in USA, introduced in March 1996, comes under protease inhibitor class and is used to treat HIV infection and AIDS. It is a potent inhibitor of HIV-1 protease and HIV in MT4 cells, without killing normal cells. Synthesis of ritonavir has been reported by Bellani *et al.* [66].

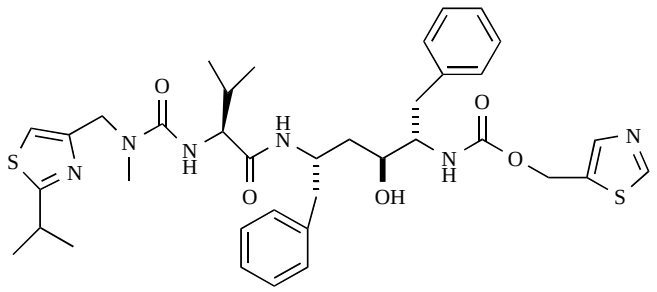


Fig. (14).

Ritonavir is generally prescribed with HAART, not for its anti-viral action but to booster the activity of other protease inhibitors and HAART by blocking the activity of the liver enzyme CYP3A4, to create higher plasma concentration of these latter drugs, thereby allowing to lower their dose and frequency and improving their clinical efficacy and development of resistance [67a,b,68].

The most common side effects associated with ritonavir are asthenia, nausea & vomiting, abdominal pain, dizziness, insomnia, sweating, taste abnormality, hypercholesterolemia, and hypertriglyceridemia, elevated CPK, elevated trans aminases etc.

(iii). Indinavir (Crixivan, L735524)

[1-[2-hydroxy-4-[(2-hydroxy-2,3-dihydro-IH-inden-1-yl) carbomoyl]-5-phenyl-pentyl]-4-(pyridine-3-ylmethyl).N-tert-butyl-piperazine-2-carboxamide] (Fig. **15**) is a potent inhibitor of HIV-1.

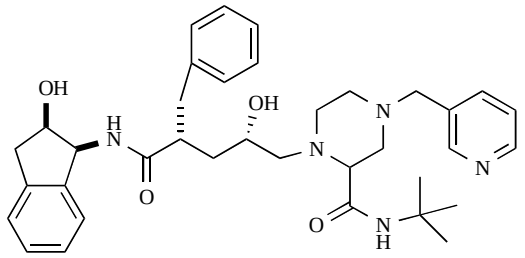


Fig. (15).

This PI is used in combination with HAART to treat HIV infection and AIDS. Besides its anti HIV activity, it shows memory restoration in dementia.

Synthesis of indinavir has been reported by Askin [69]. Solid phase synthesis of indinavir and its analogs has also been developed [70].

Since indinavir wears off quickly after administration, it is given every eight hourly in order to thwart HIV from forming drug resistant mutations. During treatment with indinavir, there is some restriction on food intake.

The common side effects associated with indinavir are kidney stones, metabolic abnormalities including hyperlipidemia, lipodystrophy.

(iv). Nelfinavir (AG 1343, Viracept)

[2-[2-hydroxy-3-(3-hydroxy-2-methyl- benzoyl) amino-4-phenylsulfanyl-butyl]-N-tert-butyl-1,2,3,4,4a,5,6,7,8, 8a-decahydroisoquinoline-3-carboxamide](Fig. **16**) was developed by Agouron Pharmaceuticals. It is effective in HIV-1 and HIV-2 infections. Synthesis of nelfinavir (US Patent 6303786, issued on December 7, 2004) has been described by various groups [71-73].

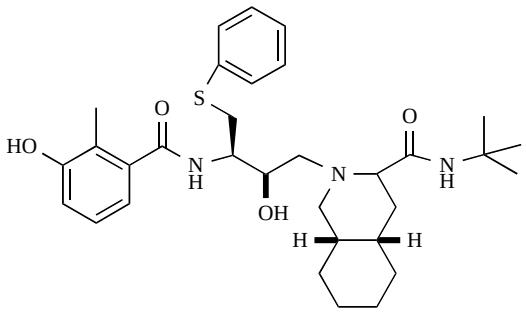


Fig. (16).

Nelfinavir is the best tolerated of the first generation HIV PIs and displays acute viral reductions >90%. Nelfinavir mesylate (Viracept) shows potent oral bioavailability and is widely prescribed in combination with HIV RTIs. Nelfinavir is taken with food which increases its bioavailability 2.5 to 5 times.

It can produce common adverse side effects such as diarrhea, abdominal pain, fatigue, urination, rash, mouth ulcers or hepatitis etc.

(v). Amprenavir (Agenerase, VX478, Vertex/GSK/Kissei)

[Tetrahydrofuran-3-yl-[3-[(4-aminophenyl) sulfonyl-(2-methyl propyl) amino]-1-benzyl-2-hydroxypropyl] amino-methanoate] (Fig. **17**) is a protease inhibitor, was introduced as a potent inhibitor of HIV-1 protease and HIV-1 replication, having a good oral bioavailability.

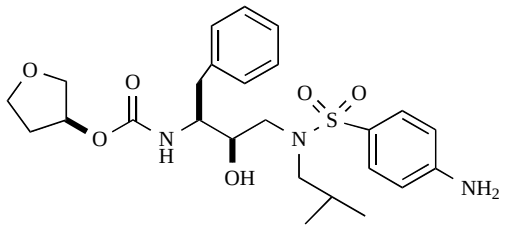


Fig. (17).

However, production of amprenavir was discontinued in December 2004 and replaced by its prodrug fosamprenavir. An efficient and industrially applicable method for synthesis of amprenavir and fosamprenavir has been reported by Honda *et al.* [74]. Its side effects include dibetes, lipodystrophy, hepatitis.

(vi). Lopinavir(ABT-378)

[(2S)-N-[(2S,4S,5S)-5-[[2-(2,6-dimethylphenoxy)acetyl] amino]-4-hydroxy-1,6-di(phenyl)hexan-2-yl]-3-methyl-2-(2-oxo-1,3-diazinan-1-yl)butanamide] (Fig. **18**) is an antiretroviral agent belonging to PI family synthesized by Stoner *et al.* [75].

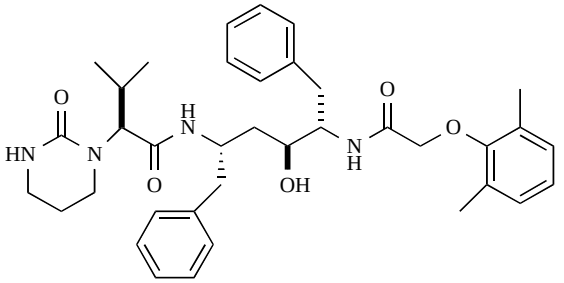


Fig. (18).

It is an analogue of ritonavir with 10 fold higher potency and effective against ritonavir resistant HIV strain [76]. It has been marketed by Abbott as Kaletra (capsules) and Aluvia (non-refrigerated tablets), both in combinations with ritonavir. Lopinavir, an inhibitor of the HIV protease, prevents cleavage of the gag-pol polyprotein, resulting in the production of immature, non-infectious viral particles. It is highly bound to plasma proteins (99%), inhibits protein synthesis and induces eEF2 phosphorylation [77].

The most common adverse effects observed with lopinavir/ritonavir are diarrhea, nausea, abdominal pain, as thenia, headache, vomiting, and rash [78a-c].

(vii). Fosamprenavir (Lexiva and Telzier)

[(2R, 3S)-1-[(4-aminophenyl)sulfonyl-(2- methylpropyl) amino]-3-{[(3S)-oxolan-3-yl]oxy-carbonylamino}-4-phenyl-butan-2-yl]-oxyphosphoric acid] Fig. **19**], the prodrug of amprenavir has been made available as a potent HIV-protease inhibitor [79] in October 2003.

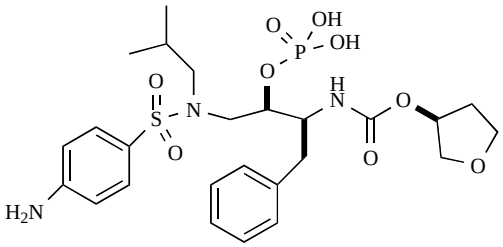


Fig. (19).

Fosamprenavir has higher oral bioavailability than amprenavir, and its greater water solubility enables much lower doses to be administered.

A study of combination drugs, fosamprenavir-ritonavir versus lopinavir-ritonavir along with antiretroviral drugs showed a comparable potency of both the combinations [80].

Fosamprenavir, in combination with ritonavir once daily, was found to be better tolerated than nelfinavir twice a day, each administered with abacavir and lamivudine [81].

Side effects of fosamprenavir reported by FDA include pyrexia, hepatitis, rash maculo-papular, nausea, jaundice, hypersensitivity.

2nd Generation HIV-Protease Inhibitors

Atazanavir (Reyataz, BMS-232632)

[Methyl N-[(1S)-1-[[[(2S, 3S)-2-hydroxy-3-[[(2S)-2-(methoxy carbonyl amino)-3, 3-dimethyl-butanoyl] amino]-4-phenyl-butyl]-[(4-pyridin-2-ylphenyl) methyl] amino] carbamoyl]-2,2-dimethyl-propyl] carbamate] (Fig. **20**) is a second generation tetrapeptide- mimicking protease inhi-bitor, featuring a 2-hydroxy-1, 3-diaminopropane transition state isostere, an aza-dipeptide core, and an extended PI substituent.

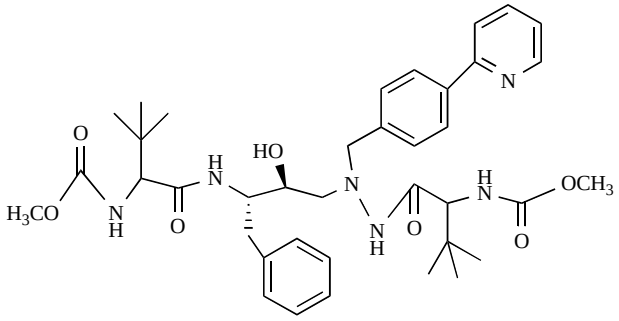


Fig. (20).

It has also been approved as a part of combination therapy. In humans; a 400 mg po dose of atazanavir results in a half life of 6.5 to 7.9 hr and permits a single daily dosing. In Phase III trials with 400 to 600 mg po dose/day, it did not alter LDL, cholesterol, or triglyceride concentration [82].

Atazanavir was also found to be effective against cancer. It inhibits growth of brain tumor cells in culture [83]. Atazanavir causes a rise in the bilirubin level as its side effect.

(ii). Tipranavir (Aptivas)

[N-[3-[(1R)-1-[(6R)-2-hydroxy-4-oxo-6-phenyl ethyl-6-propyl-5H-pyran-3-yl] propyl] phenyl]–5–(trifluoromethyl) pyridine-2-sulfonamide] (Fig. **21**) or tipranavir disodium, is the first non-peptide protease inhibitor [84a,b,c] and has also been approved for pediatric use.

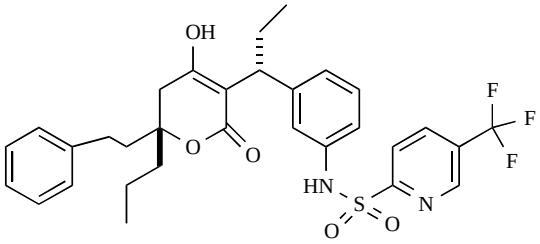


Fig. (21).

Tipranavir is very potent and is effective in salvage therapy for patients with some drug resistance. It may cause severe side effects such as intracranial hemorrhage [85], hepatitis, and diabetes mellitus. It may also increase total cholesterol and triglycerides.

(iii). Darunavir (Prezista)

[(1R,5S, 6R)-2,8-dioxbicyclo[3.3.0]oct-6-yl]-N-[(2S, 3R)-4-[(4-aminophenyl)sulfonyl-(2-methyl propyl)amino]-3-hydroxy-1-phenyl-butan-2-yl]carbamate] (Fig. **22**) is a second generation PI for treating HIV infection. It was discovered by Arun k Ghosh [86] and developed by pharmaceutical company Tibotec.

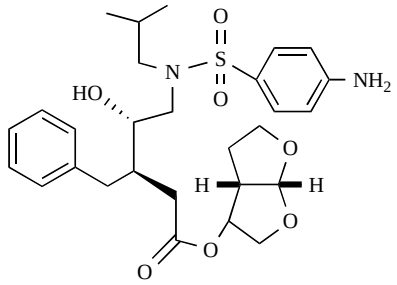


Fig. (22).

This PI was designed to overcome problems associated with other PIs such as indinavir. It creates robust interaction with protease enzyme from many strains of HIV including those generated through drug resistance [86].

Darunavir shows superiority to lopinavir and other PIs in POWER trials designed for treatment –experienced patients [87].

Common side effects associated with darunavir include diarrhea, headache, abdominal pain, constipation, vomiting and rash.

SAR

Modification of PI structures and their hybridization has produced multiple resistant PIs with high anti-retroviral activity [88, 89]. Introduction of heterocycles such as oxazoles, thiazoles, electronegative groups and various sulfonyl substituents in specific areas, showed improvement in PI activity.

Protease inhibitors with peptide nature, show low oral bioavailability and rapid secretion which results in poor pharmacokinetic profile. Structural mimics of peptides with little or no peptide character, were found to be more efficient. Replacement of the amide carbonyl with SO_2 group, resulted in additional hydrogen bonding and subsequent optimization of the sulfonamide moiety leading to a second generation HIV protease inhibitor, tipranavir [90].

3. FUSION INHIBITORS

These are compounds that disrupt the HIV-1 molecular machinery at the final stage of fusion with the target cell, preventing uninfected cells from becoming infected. Acting at the early stage of viral life cycle, fusion inhibitors prevent viral entry, and have a novel highly specific mechanism of action with a low toxicity profile.

(i). Enfuvirtide (T-20, Fuzeon)

The only anti-HIV fusion inhibitor, is a polypeptide (Fig. **23**). Enfuvirtide synthesis is usually carried out utilizing both solid and liquid phase procedures and combine groups of specific peptide fragments to produce enfuvirtide [91].

Ac-Tyr-Thr-Ser-Leu-Ile-His-Ser-Leu-Ile-Glu-Glu-Ser-Glu-Asu-Glu-Glu-Glu-Asu-Glu-Glu-Glu-Leu-Leu-Glu-Leu-As p-Lys-Trp-Ala-Ser-len-Trp-Asu-Trp-Phe-NH_2

Fig. (23).

This biometric peptide was rationally designed to mimic components of the HIV-1 fusion machinery and displace them, preventing normal fusion. HIV binds to the host CD4+ cell receptor *via* the viral protein GP 120. Upon binding, GP 120 deforms, allowing the viral protein GP 41 to embed itself into the host cell's plasma membrane [92, 93].

Entry inhibitors bind to glycoprotein gp 41 preventing the creation of an entry pore for the capsid of the virus by blocking gp 41 structural rearrangements at a transitional pre-fusion conformation [94], keeping it out of the cell [95].

Enfuvirtide is active against HIV-1 only [96, 97]. *In vitro* studies have indicated very low activity against HIV-2 isolates. A detailed study of the mechanism of action, the activity and benefits of fusion inhibitors etc. have been reviewed by Greenberg and Cammack [98].

Enfuvirtide is particularly used in combination therapy with other ARVs in patients where all other treatments have failed. Two elaborate clinical trials have shown that fusion, when combined with other drugs, is effective for patients who have failed in treatment with other anti HIV drugs. Because of its fragile structure, enfuvirtide cannot be taken orally and is given in an injectable form.

Common adverse reactions associated with enfuvirtide therapy include injection site reactions, peripheral neuropathy, insomnia, depression, cough, anorexia, infections, fever, nausea, vomiting and hypotension.

4. ENTRY INHIBITOR

HIV uses a co-receptor Chemokine (C-C motif) receptor 5 to get into target cells, the CD4 T-cells, the main coordinator of the immune system. Entry inhibitors are CCR 5 antagonists that stop the virus from getting into the cells by blocking the main entry point common to most people who have the infection.

(i). Selzentry [99] (Celsentri, Maraviroc, UK 427, 857)

[4,4-difluoro-N-((1S)-3-(exo-3-(3-isopropyl)-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo(3,2,1)oct-8-yl)-1-phenyl-propyl) cyclohexane carboxamide](Fig. **24**) is an entry inhibitor. It is the first attachment inhibitor drug. It blocks HIV from entering human cells [100-104]. Synthesis of selzentry has been reported by Price *et al.* [105].

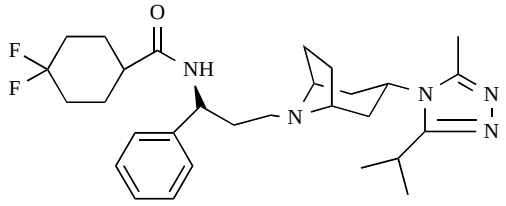


Fig. (24).

Selzentry acts as CCR5 antagonist by binding to it and prevents virus entry into the target cells. However, as the disease progresses, the virus adapts to use an alternative entry point, the CXCR4 receptor.

Selzentry holds promise for HIV-positive patients who no longer respond to other HIV drugs. It is effective in reducing the viral load in people with HIV that uses CCR5 receptor and not the alternate CXCR4.

Specifically, selzentry is approved for use in combination with other antiretroviral drugs for the treatment of adults with CCR5-tropic HIV-1 who have elevated levels of HIV in their blood despite treatment with other HIV medications.

Common side effects associated with selzentry therapy are cough, fever, cold, rash, muscle and joint pain, and dizziness. Some serious side effects which have also been observed in patients under treatment with selzentry are liver toxicity, cardiovascular problems including heart attack.

5. HIV INTEGRASE INHIBITOR

Integrase is a viral enzyme that is essential for HIV -1 replication, catalyzing the insertion of proviral DNA into the host-cell genome [106, 107]. The role of integrase inhibitors is to prevent the viral growth by blocking the enzyme integrase.

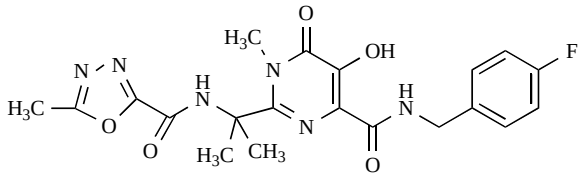


Fig. (25).

(i). Raltegravir (Isentress)

[N-[(4-fluorophenyl) methyl]-1, 6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[(5-methyl-1,3,4-oxa-diazol-2-yl)carbonyl]amino]-ethyl]-6-oxo-4-pyrimidine caboxamide mono-potassium salt] (Fig. **25**) is the first pharmacological agent, designed as HIV integrase strand transfer inhibitor. It is used in combination with other anti-retroviral therapy for the treatment of HIV infection. It reduces HIV load in blood of patients and increases white blood cells, called CD4+ T-cells, that helps fight off other infections.

While similar to established HIV drugs in targeting HIV after it has invaded the host's immune cells, integrase inhibitors differ in that they act on the HIV integrase enzyme that is responsible for insertion of viral DNA into human DNA, an early stage in HIV life cycle.

Use of raltegravir along with optimized background therapy (OBT), in patients infected with HIV-1 that has triple-class drug resistance in whom antiretroviral therapy had failed, has been suggested [108].

The absorption, metabolism, and excretion of raltegravir were studied using ^{14}C-raltegravir [109].

Because HIV-1 integrase represents a distinct therapeutic target, integrase inhibitors would be expected to maintain activity against HIV-1 strains even when resistant to other classes of anti-retroviral drugs [107, 110, 111]. Raltegravir specifically inhibits proviral DNA, strand transfer, with potent *In vitro* activity against HIV-1 that is susceptible or resistant to other classes of anti-retroviral drugs [110-112].

SAR

Integrase inhibitors showing potent anti-HIV activity mainly belong to 3 different classes i) the benzoylpyruvic acid derivatives, ii) the 8-hydroxy quinoline derivatives and iii) the polyphenols. Patented compounds with various substitutions in the basic unit with anti-HIV activity have been reported [113].

CONCLUSION

In a very brief period, significant number of drugs for AIDS was developed and many of them were cleared by Food and Drug Administration for treatment. Though none of the compounds can be considered as an ideal drug but their introduction in the market has helped in reducing the viral load on patients suffering from AIDS. This has helped in controlling the rapid spread of AIDS in the world population and in treating patients for reducing the viral load on them. However, none can be considered effective in curing the disease and therefore there is an urgent need for a drug for curing AIDS.

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