Chapter

Substituted Azoles as Non-Nucleoside Reverse Transcriptase Inhibitors Activity

Rohit Singh and Avneet Kaur

Abstract

This Review article gives an overview of substituted azole based synthetic medicine and their significance application in treating various ailments. The chemical reactions of azoles with other heterocyclic compounds/chemical reagents produce a lot of new substituted molecules, which have plentiful biological actions and potential pharmaceutical applications. Azoles is considered a major class of heterocyclics and worldwide researchers have put great efforts in studying this nucleus in order to design and synthesize various new derived of imidazole and hybrid molecules with the identification of their significant role in many classes of drugs such as antiviral including anti-HIV. Azoles has inspiring molecular geometric structure that offers a suitable skeleton to build newer chemical entities which has encouraged medicinal chemists to design and synthesis of novel and effective molecule as potential therapeutic agents. However, there is an urgent need to study the mechanism of action at molecular level of several pharmacological actions resulting from azoles scaffold through modern methods to furnish safer and effective new molecules for the treatment of various diseases.

Keywords: azoles, heterocyclic compounds, hybrid compounds, synthetic reactions and biological application

1. Introduction

AIDS (Acquired immune deficiency syndrome) is the major cause of death which leads to pandemic worldwide. In today's scenario combination of Nucleoside reverse transcriptase inhibitors (NRTI), Non nucleoside reverse transcriptase inhibitors (NNRTI) and Protease inhibitors (PI). Highly active antiretroviral therapy (HAART) also called as anti retroviral therapy which is a combination of two or more combination of antiviral drugs become unsuccessful because of mutational change and virus getting resistant against anti viral drugs. Non nucleoside reverse transcriptase Inhibitors (NNRTI) binds to specific active site of reverse transcriptase of HIV are the important cascade of anti HIV-1 drugs mechanism. Molecular modeling studies of HIV enzyme complexes and chemical generation of second and third generation of

NNRTI's led to higher specificity of NNRTI's against HIV-1 and leads to major discovery in the generation of anti-viral drugs [1].

Non nucleoside reverse transcriptase inhibitor binding pocket were found to play an important role in binding site with drugs and found less prone against mutation. Here we also describe the chronological history of non nucleoside reverse transcriptase inhibitors development and basically focused on small molecules belonging to NNRTI class against AIDS management therapy [2].

In this review the chronological advancement of non nucleoside reverse transcriptase inhibitors and their belongings to NNRTI class in the management of drugs used in treatment of AIDS have been focused. The generation of resistance against NNRTI drugs and pharmacokinetic problems are the serious concern in management therapy.

2. Reverse transcriptase

RT is the replicative enzyme of HIV and other retroviruses. RT copies the single-stranded viral genomic RNA into double-stranded DNA (**Figure 1**), which is subsequently integrated into host cell DNA.

Reverse transcriptase (RT) is a key enzyme which plays an essential and multifunctional role in the replication of the human immunodeficiency virus type- 1 (HIV-1) and thus constitutes an attractive target for the development of new drugs useful in AIDS therapy [3].

Reverse Transcriptase is a major target for anti HIV drug development along with two classes of inhibitors, the nucleoside or nucleotide reverse transcriptase inhibitors and non nucleoside reverse transcriptase inhibitors (NNRTIs) have been approved by US Food and Drug Administration (FDA) for the treatment of HIV-1 infection. Reverse Transcription (RT) is formation of double stranded DNA from single stranded RNA genome which is an essential step in life cycle of HIV-1 replication. This is one is very important and complex step required for both DNA polymerase and ribonuclease active sites of HIV-1 reverse transcriptase [4, 5].

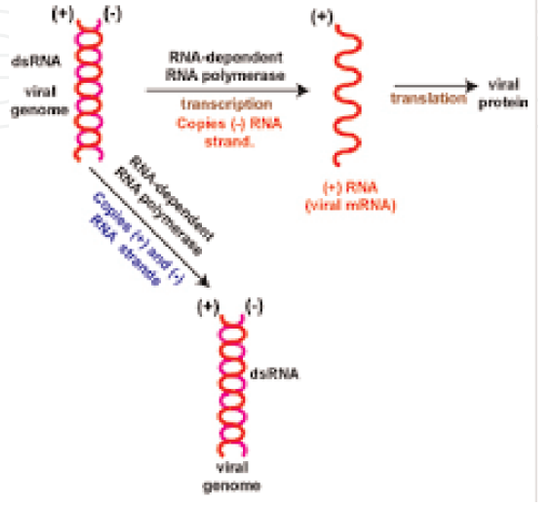
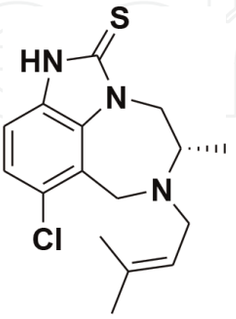


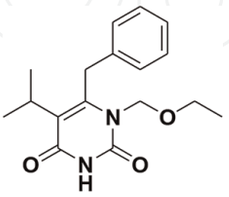
Figure 1.
Reverse transcriptase copies the single-stranded viral genomic RNA into double-stranded DNA (reverse transcription).

3. Non nucleoside reverse transcriptase inhibitors (NNRTIs)

The era of NNRTIs began before two decades, with the discovery of TIBO [4, 6] and HEPT [7] as specific inhibitors of reverse transcriptase. NNRTIs are highly specific and potent inhibitors of HIV-1 RT, and do not interfere with cellular or mitochondrial DNA synthesis [8]. However, the rapid emergence of resistant virus variants and the problem of resistance have limited their clinical use [9].

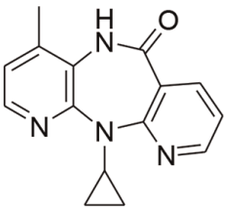


(1)



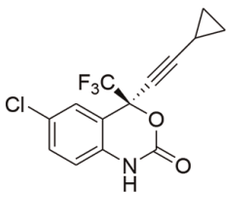
(2)

Nevirapine, Delavirdine and Efavirenz are the three Non nucleoside reverse transcriptase inhibitors which were approved as anti-HIV drugs in the year 1996, 1997 and 1998. Out of which Nevirapine is one the agent used to inhibit mother to child transmission of HIV [10–12].



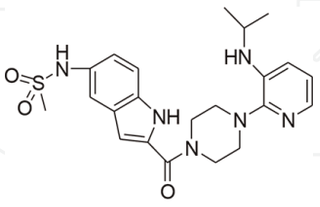
NEVIRAPINE

(3)



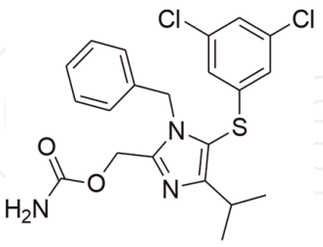
EFAVIRENZ

(4)



DELAVIRDINE

(5)



CAPRAVIRINE

(6)

Non Nucleoside Reverse Transcriptase Inhibitors (e.g. Nevirapine, Delavirdine, Efavirenz and Etravirine) are used as antiviral compounds which prevent the possibility transmission from mother to child. The interaction between NNRTI and NNRTI binding pocket mechanism from DNA polymerase active site has shown in **Figure 2.**

Basically in cytoplasm with the process of reverse transcription begins with entry of viral particle to the target cell of viral genome as a part of nucleoprotein conjugation whose structure is not well defined. This DNA is formed on the template of RNA but its terminal contains duplications which is known as long terminal repeats (LTRs)

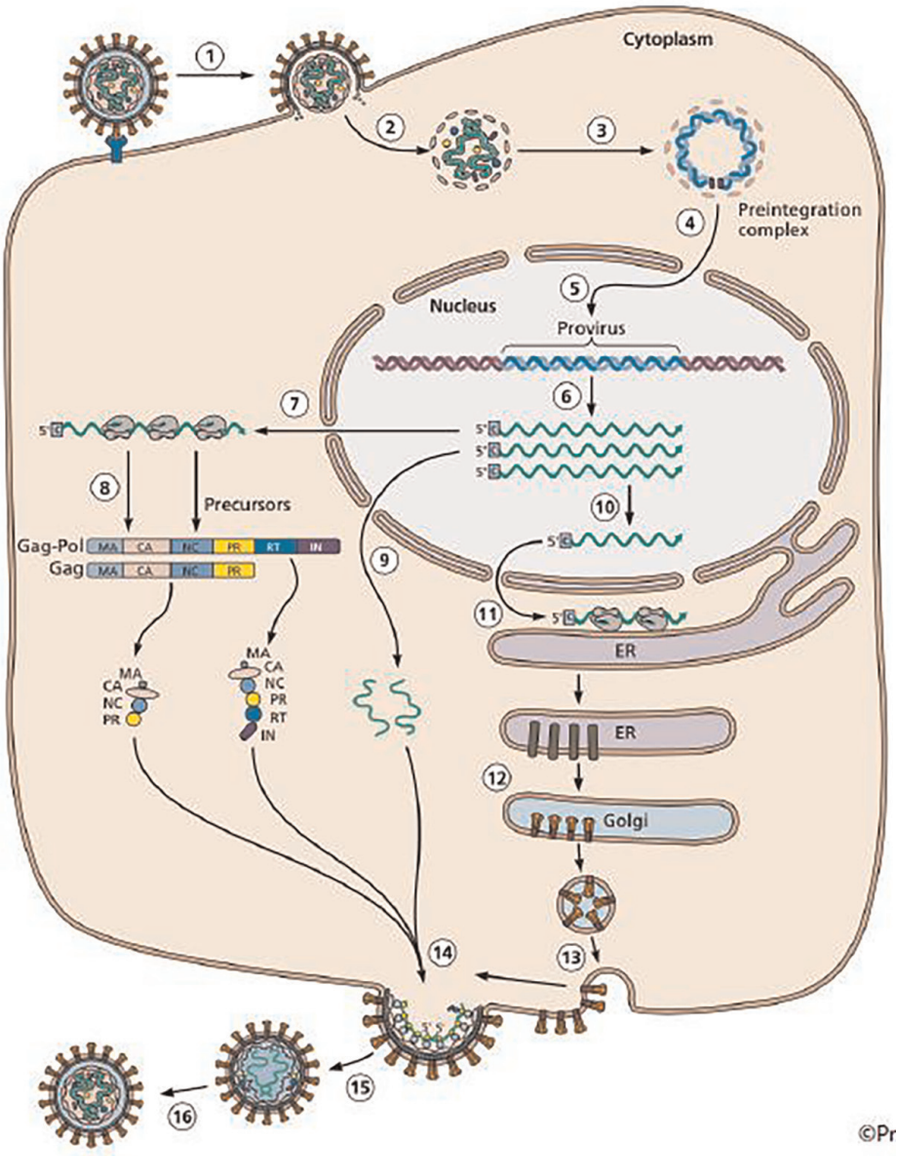


Figure 2.
Mechanism of NNRTI inhibition.

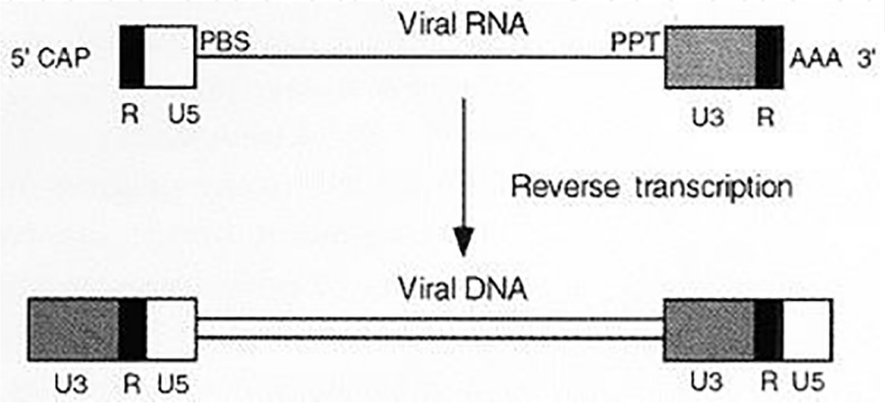


Figure 3.
Strand transfer reaction or jumps required to generate long terminal repeats (LTR's).

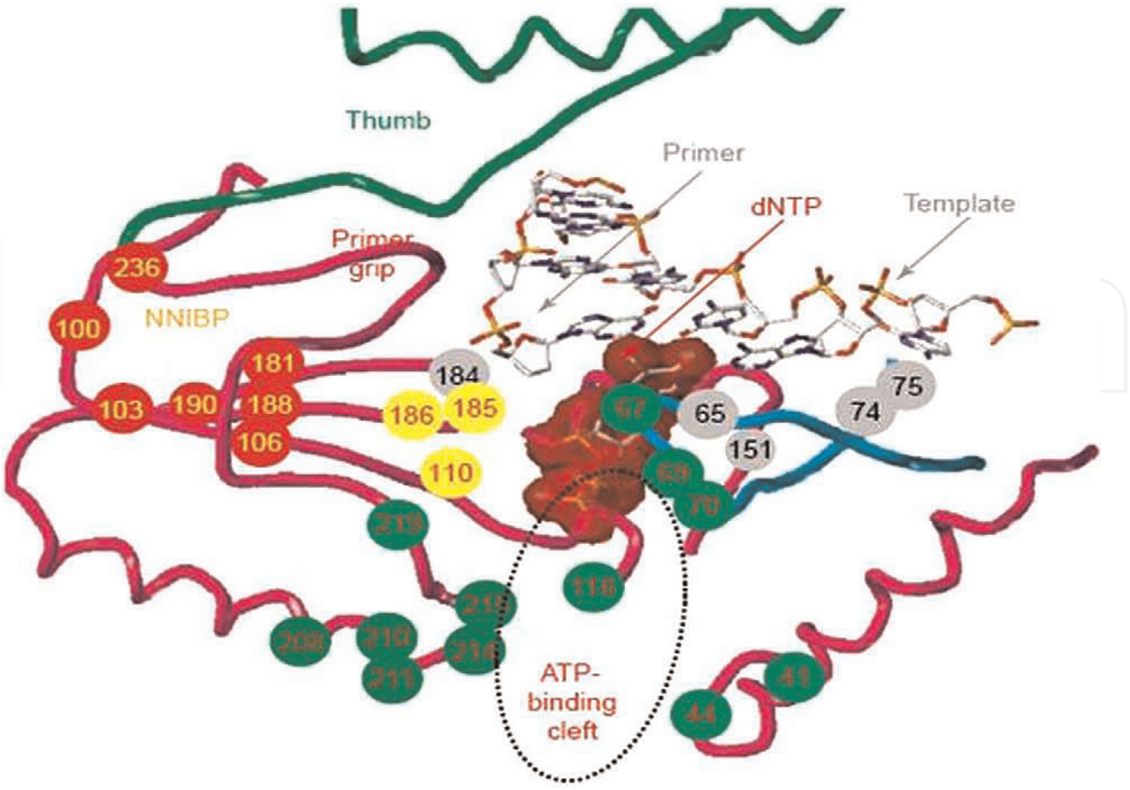


Figure 4.
The structure of HIV-1 RT in the region near the polymerase active site.

which is not present in viral RNA. (**Figure 3**) Strand transfer reactions or jumps are required to generate long terminal repeats (LTRs) which is perfect model for reverse transcription propose two specialized template switches [13, 14].

Reverse transcriptase enzyme is a type of replicative enzyme of HIV-1 and other type of retroviruses where retro viruses generates double stranded DNA by copying from single stranded genomic viral RNA and subsequently integrated with host cell DNA. Reverse transcriptase (RT) has two enzymatic activities: First one is polymerase which copy either DNA or RNA and second one is RNAase that degrade RNA strand of RNA-DNA intermediates formed during viral DNA synthesis. Human immunodeficiency syndrome virus (HIV-1) has two subunits p66 and p51. Polymerase chain of domain site p66 and p51 contain four subdomain namely fingers, palm, thumb and connection. Folding and connections of both subdomain p66 and p51 are similar in nature but their spatial arrangements are different. Domain p66 contains active site for both polymerase as well as RNAse while domain p51 plays primarily structural role for DNA and RNA.

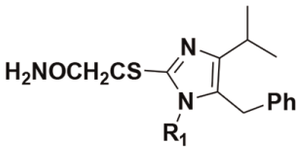
Fingers and palm size of domain p66 are highly conserved region and together with two helices of thumb subdomain acts as a clamp that holds the position template primer (**Figure 4**). One of these region which is part of palm subdomain act as a primer group of DNA. The primer group is the candidate solely responsible for the exact placement of primer terminus at the active site of polymerase enzyme and involved in translocation of DNA template primer followed by 4–7 nucleotide incorporation. Exact positioning or binding of template primer is also very much important for cleavage of DNA/RNA template by the RNase activity of reverse transcription

enzyme. Now a days HIV-1 reverse transcriptase inhibitors currently available as anti HIV drugs in the management of AIDS by targeting enzymatic activity of DNA polymerase activity [15–17].

3.1 Capravirine

Capravirine (formerly known as S-1153 or AG1549) is a 1,2,4,5-substituted imidazole derivative (**Figure 2**) that inhibits HIV-1 replication in a standard $CD4^+$.

Capravirine exhibited significant expansion as antiviral spectrum as anti HIV agent and covered many typical resistant mutant strain of NNRTI including single K103N mutation and double K103N-L100I and K103N-P225H mutations [18–20]. Y181C was also other common mutation which arises under nevirapine pressure and also inhibited by capravirine [21].



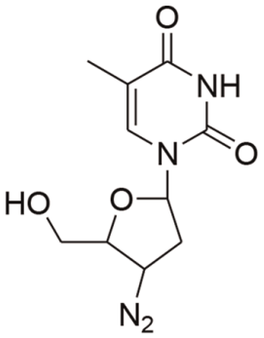
R1 = Me, Et, Cyclohexyl

(7)

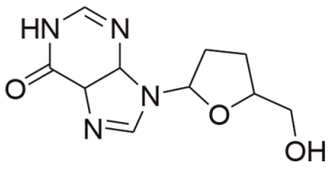
Barreca et al. were carried out their research in the fields of Non nucleoside reverse transcriptase inhibitors (NNRTIs).

4. Nucleoside reverse transcriptase inhibitors (NRTI's)

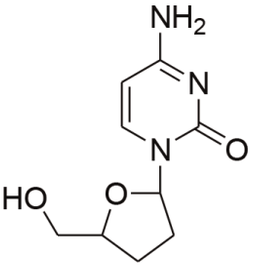
Out of the 13 compounds that have been formally approved for the treatment of human immune deficiency virus (HIV) infections, nine are targeted at the viral reverse transcriptase (RT), the other four (saquinavir, ritonavir, indinavir and nelfinavir) being targeted as the viral protease. Of the nine RT inhibitors that have been licensed, six can be considered as nucleoside reverse transcriptase inhibitors (NRTI's) namely zidovudine (AZT) **(1);** Didanosine (ddI) **(2)**; Zalcitabine (ddC) **(3)**; Stavudine (d4T) [4]; Lamivudine (3TC) **(5)** and Abacavir (ABC) **(6).**



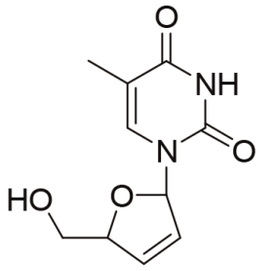
8. Zidovudine



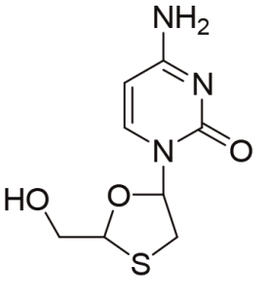
9. Didanosine



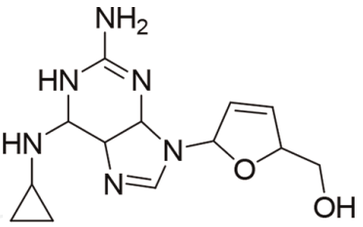
10. Zalcitabine



11. Stavudine

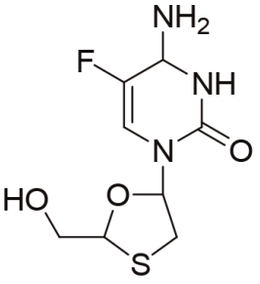


12. Lamivudine

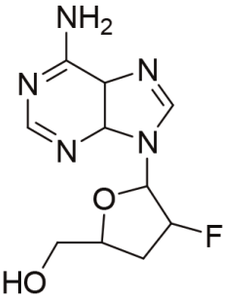


13. Abacavir

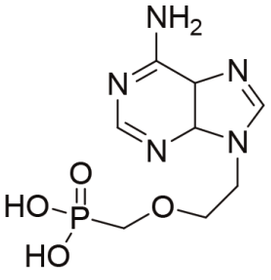
Some of these compounds are still in pre clinical stage of development but others have already proceeded to phase I, II or III clinical trial. Most advanced among new RT inhibitors are (−) FTC (emitricitabine), F-ddA (lodenosine), PMEA (adefovir) and its oral prodrug form bis (POM)-PMEA [adefovir dipivoxil], PMPA (tenofovir) and its oral prodrug form bis (POC)-PMPA (tenofovir disoproxyl fumarate), which can be considered as NRTI's.



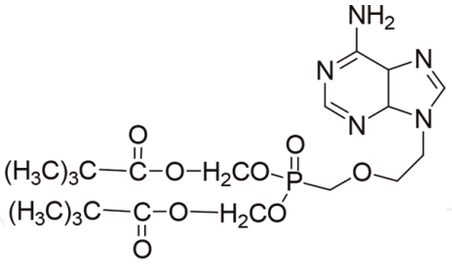
14 . (-) FTC Emitricitabine



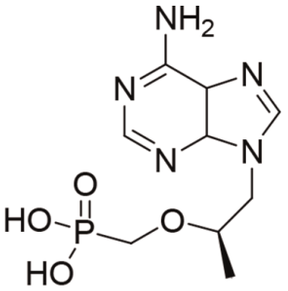
15. F-ddA (Lodenosine)



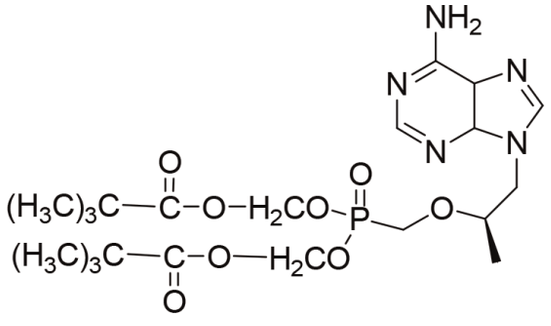
16. Adefovir



17. Adefovir dipivoxil



18. Tenofovir



19. Tenofovir disoproxyl fumarate.

Agents	Major side effects
Nucleoside reverse transcriptase inhibitors (NRTI'S)	
1. Zidovudine (AZT, Retrovir)	Osteoporosis, bone marrow anemia, GI disturbances, insomnia, neutropenia
2. Didanosine (ddI, Videx)	Pancreatitis, Peripheral neuropathy, GI disturbances.
3. Zalcitabine (ddC, Hivid)	Peripheral Neuropathy, stomatitis.
4. Stavudine (d4T, Zerit)	Peripheral Neuropathy, pancreatitis.
5. Lamivudine (3TC, Epivir)	Nasal symptoms, lactic acidosis, liver problems etc.
6. Abacavir (ABC, Ziagen)	Hypersensitivity, Skin Rash (Stevens-johnson syndrome), abdominal and stomach pain.
Non nucleoside reverse transcriptase inhibitors (NNRTI'S)	
7. Nevirapine (NVP, Viramune)	Rash (Stevens-johnson syndrome), tingling, burning & prickly sensations.
8. Delavirdine (DLV, Rescriptor)	Rash (Stevens-johnson syndrome), excessive tiredness.
9. Efavirenz (EFV, Sustiva)	Convulsions, false-positive test for urine, dizziness, drowsiness.
Protease inhibitors	
10 Saquinavir (SQV, Invirase)	GI symptoms, hepatitis, increased TGC, dry lips or skin.
11. Ritonavir (RTV, Norvir)	Muscles or joint pains, itching, numbness of mouth area, headache, dizziness, pancreatitis, heart problem.
12. Indinavir (IDV, Crixivan)	Itchy skin, blurred vision, headache, dizziness, GI symptoms rashes.
Integrase inhibitors	
13. Raltegravir (RAL, Isentress)	Blue in urine, joint pain, stiffness, headache.
Fusion and entry inhibitors	
14. Enfuvirtide (T-20, Fuzeon)	Nervousness, muscle pain, nausea, depression.
15. Maraviroc (MVC, Selzentry)	Selzentry, diarrhea, constipation, dizziness.

Table 1.
Side effects of anti-HIV compounds [23, 24].

The description of the RT inhibitors as anti-HIV agents should be viewed in the broad scope of anti-HIV therapy (1) and therapeutic approaches for intervention with HIV infections (2), and strategies to overcome or prevent the problem of HIV resistance development to anti-HIV agents in general (3) and NNRTI's particular (4).

Nucleoside reverse transcriptase inhibitors (NRTIs) were the first class of drugs as antiretroviral drugs to gain regulatory approval in 1987. Zidovudine (AZT) was the first drug to be licensed for the treatment of HIV infection [22], a mere four years after the identification of HIV as the etiology agent for AIDS (**Table 1**) [23, 24].

5. Non nucleoside reverse transcriptase inhibitors (NNRTIs)

Non nucleoside reverse transcriptase inhibitors (NNRTI's) causing an allosteric inhibition of reverse transcriptase enzyme by binding directly to enzyme at different site of nucleoside binding component. Nevirapine, delavirdine and efavirenz are the

three members of this group which are used clinically. These agents are given in combination with other antiviral compounds for the treatment of AIDS. All class of NNRTI's are rapidly absorbed from gastrointestinal tract and with highly bound plasma proteins. These NNRTI's are extensively metabolized by cytochrome P450 enzyme along with variable amount of administered drug which are being recovered from urine as a metabolite. Skin rashes is the most common adverse effect associated with NNRTI class of drugs [25].

6. Protease inhibitors

Protease inhibitors (PI's) interfere with replication of viruses, maturation and infection of new viral cells by inhibiting the cleavage of enzyme necessary for viral protein precursors. Like NNRTI's, protein inhibitors are also metabolized by cytochrome P450 enzymes which leads to drug-drug interaction. PI's can also cause gastrointestinal side (GI's) effects and elevation in liver transaminase enzyme. Some protease inhibitors like saquinavir have first pass metabolic effect which results poor bioavailabilty which may be improved by administrating with food.

Physiological factors like achlorhydria, malabsorption and poor hepatic dysfunction may impair the bioavailability of protease inhibitors in HIV infections which may influence their antiHIV activity *in vitro*. PI's like ritonavir and indinavir may displace other protease inhibitors like saquinavir, from plasma protein and inhibit their metabolism. In addition PI's can worsen diabetes, insulin resistance, hypercholesterolemia, hypertension and hyperlipidemia [26].

7. Integrase inhibitors

Integrase is the viral enzyme which catalyzes the integration of DNA derived from virus into the DNA of host cell present in the nucleus and form proactive virus that can be activated to produce viral proteins.

Integrase inhibitors are the type of antiretroviral therapy agents and they rely on the fact that HIV needs integrase enzyme to replicate and the integrase inhibitor drugs blocks the enzymatic action of integrase enzyme and without the help of this enzyme HIV cannot take over T cells to copy itself. The US food and drug administration (FDA) approved the use of integrase inhibitors in year 2007. Raltegravir, dolutegravir, elvitegravir, bictegravir etc. are some marketed drugs of integrase inhibitors are in use. Raltegravir is the first approved integrase inhibitors, is a valuable addition to the drug therapy against multidrug resistance. Dolutegravir and elvitegravir are also present in combination medication such as genvoya (elvitegravir + emtricitabine + tenofovir alafenamide fumarate + cobicistat), stribild (elvitegravir + emtricitabine + tenofovir disoproxil fumarate + cobicistat), triumeq (Dolutegravir + abacavir + lamivudine), juluca (Dolutegravir + rilpivirine) and biktarvy (biktegravir + emtricitabine + tenofovir alafenamide fumarate) [27, 28].

8. Fusion and entry inhibitors

Fusion inhibitors are also known as entry inhibitors is a class of antiviral drugs which prevent the entry of virus to host cell by blocking the receptors. They are used in combination therapy for the treatment of HIV infections by blocking the steps

involved in HIV replication cycle. Once virus enters into the host cell the viral surface protein gp120 form complex with CD4 receptor with co-receptors like CCR5 and CXCR4 which is necessary step for viral entry into the host cell.

Enfuvirtide, the first approved drug of this class which interfere with viral attachment with host cell membrane by inhibiting the necessary conformational change in particular viral envelop protein (gp41) which trigger the formation of transmembrane pore through which virus would enter the host cell. Maraviroc is also a new chemokine co-receptor antagonist (CCR5 antagonist) drugs that blocks the binding of HIV to CCR5 co-receptor in HIV infection [29, 30].

9. Conclusion

Drugs like Nucleoside reverse transcriptase inhibitors, Non nucleoside reverse transcriptase inhibitors, Protease inhibitors, Integrase inhibitors and Fusion or Entry inhibitors are the potent candidates as anti HIV and efforts are still continuing to develop potent molecules which will be effective in the management of AIDS, and search is still going on as viruses exhibited rapid mutation which makes the drug ineffective against the treatment of AIDS and develop resistance against multiple drug therapy and drug become active only for short span of life.

As most of anti HIV agents have diverse chemical structures showed in this book chapter which exhibited potent action against many viruses and considered as best candidate as anti HIV.

The current Covid-19 problem is an excellent example of mutant variation of viruses which exhibited variant strain rapidly and for the reason of developing resistance against many anti-viral drugs. Combination of NRTI and NNRTI along with PI are used administered to combat with drug resistance and be a part of multi drug resistance therapy.

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