

## Review Article

# Receptor based treatment: A solution to clinical problems in HIV/AIDS

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### ABSTRACT

One of the most fatal and epidemic disease, Acquired Immunodeficiency Syndrome (AIDS) since the past century has shown its adverse effects on the society all over the globe. The current population of people suffering from AIDS/HIV is about 36.6 million. During years of research on human immunodeficiency virus (HIV), we have gathered a lot of information on its receptor cells which were studied as CCR5 along with CD4 and CXCR4. These studies have enlightened our knowledge about Acquired immunodeficiency syndrome (AIDS) and its pathogenesis. The study of the receptors and its interaction with the glycoproteinaceous envelope of HIV led to anti-retroviral drugs therapy based on blocking the fusion or docking of virus to the host cell. CCR5 receptor polymorphism helps us to determine its resistance to the HIV infection.

## 1. INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) has been fatal and dangerous since last century. It was first described about 35 years ago and since then the virus has taken the lives of about 40 million, infecting over 75 million people [1], causing pain and family suffering. During the first 10 years of HIV, poor disease understanding, ill effects of religion, economy and power have led to the widespread of the epidemic. The prevention efforts and the international response towards the disease changed the thinking about the epidemic. Today the vision of HIV eradication is only a few steps closer. This became clear after the first detailed description of AIDS given in 1981[2] that specific decrease in the amount of CD4 T-helper lymphocyte cells is the characteristic attribute underlying the disease. The conformation of the discovery of AIDS was done with the help of samples collected from AIDS patients in Africa and America, after 1 year of discovery of HIV-1 in 1983[3,4,5].

Firstly, the HIV-1 virus was analysed by the scientists who thereafter came out with the diagnostic tests for the identification

of the infection, leading to safe blood donations again. Secondly, HIV was recognised as a retrovirus leading to anti-retroviral drug based therapy development which gradually decreased the rate of mortality and morbidity due to AIDS in the areas where the treatment was available. Thirdly, the virus load measurement (the HIV genomes number in the plasma) became an important prognostic marker, alongside CD4 T-cell counts, for monitoring the health of patients [6]. Fourthly, the ineffectiveness of the immune response towards the HIV virus and the enormous antigenic diversity of the virus [7] has made it difficult for the development of an efficacious vaccine.

### 1.1 Current Status of HIV

The current worldwide gauge for individuals living with the HIV is 36.9 million [8] and the sexual mode predominates all others. Epidemiologically the epidemic has been broadly classified. The first are “generalised epidemics” which is generally seen in pregnant women undergoing antenatal clinics where its

prevalence is about 1% and heterosexual sex is the major reason. Whereas second are “concentrated epidemics” wherein the spread of HIV is seen in specific populations such as homosexuals and commercial sex workers (CSW) having pervasiveness rates more than 5%, however with rates under 1% in the general community [9]. However, caution is to be taken interpreting these definitions. The label “generalized epidemic” for the most part disregards the occurrence of “concentrated epidemics” inside a similar populace, with a resulting underestimation of the requirement for focused intercessions in the higher prospect groups [10]. Amid 2014, there were about 1.2 million passing’s along with an increase in about 2 million new cases of HIV [8]. These figures speak a lot much about the unbearable and inadmissible load of the infection. According to the estimations 19 million lives were saved in between 1990 and 2013, reason being the HIV prevention and treatment program [11]. The implementation of different development techniques has helped us manage the epidemic in the crucial manner which has otherwise a devastating effect worldwide. The number of people undergoing the Anti-retroviral therapy increased to more than 15 million in 2015 from about 200,000 people in the year 2000, showing one of the greatest achievements in public health care sector of the century. Control over the vertical transmission is one of the most successful stories. The placental HIV transmittal bar program has downsized the amount of recent infections in kids by fifty-eight in the last 15 years [8]. In 2015, Cuba became the pioneer country on the earth to pocket validation from the World Health Organization (WHO) for elimination of placental transmittal of HIV and syphilis, and many other countries are on their way to success [12]. The evolution is supported and encourages the eradication of placental transmission till 2030. However, the progress which is observed is still uneven around the world. For example, in Central Asia and Eastern Europe, where the rates of HIV have been persistently increasing since the start of the 21<sup>st</sup> century [13].

## 2. PATHOPHYSIOLOGY OF HIV

The typical feature of the HIV virus infection is that it leads to dynamic suppression of the immunity which in turn causes number of signs and symptoms such as tumours, capable infections, severe deterioration of the central nervous system (CNS) and weight loss along with diarrhoea or chronic weakness. Gradual loss of the CD4 T cells is the main cause of this immune system suppression. Several mechanisms govern this loss of the CD4 T cells which include pyroptosis, blockade of the medullary region of the brain, destruction of the infectious cells and non-infectious cells other than apoptosis [14,15]. Along with the CD4 T cells destruction, mechanisms such as stimulation of the immune system and alterations induced due to different metabolic processes caused by the virus cumulatively

supports the pathological features and condition of HIV infection [16,17,18]. There is an inverse proportion between the rate of loss of CD4 cells to the increase of the viral load and both are the determining factors for the clinical progression as well as the death.

Occasionally (~1%), some patients even in the truancy of drug therapy spontaneously control the load of the HIV virus [19], Elite Controller’s (ECs) is the name given to such patients. These patients without undergoing any type of treatment for the epidemic can maintain the CD4 levels for several years. Better suppression activity of the innate CD8 T cells is a characteristic feature exhibited by these ECs [20,21]. The reason for the same lies in the genetics of their body makeup, more frequency of heterozygous status for mutation on the chemokine co-receptors on their HIV target cells (CCR5-Δ32 allele), more frequent protective HLA alleles (HLA-B27 and -B57) or proven infection with an attenuated virus [22]. No viral replication has been observed in these patients when analysed by standard methodologies, however the higher levels of immune activation and inflammation than the HIV- negative individuals and some studies predicts a worse clinical outcome [23,24].

### 2.1 HIV Virus envelope and viral cycle

The figure 1 shows the RNA genome of the viral moiety along with its outer envelope and the glycoprotein spikes. (Adapted from London eye lit up to celebrate royal birth: ITV news; Clive Gee/PA Wire) [25]. HIV belongs to the family Retroviridae and is a Lentivirus. The appropriate model of the cross-section of the HIV virus can be properly explained with the help of a Ferris wheel called the London eye having a diameter about 135 m which is 10<sup>9</sup> times magnified than the virus (Figure 1). The ‘spikes’ those recognise the cell receptors to which the binding of the HIV virus takes place in the first step of the viral entry are glycoproteins in nature and are studded in the viral envelope. Each spike is composed of three surface glycoprotein (gp120) weighing about 1,20,000 Daltons coupled with three transmembrane glycoprotein (gp41) weighing about 41,000 Daltons (Figure 2). About fifty percent of this Gp120 is made up of carbohydrates and the rest is glycosylated especially with mannose residues which are linked to the nitrogen atom [26]. They form receptor-binding pockets which are chemically peptidoglycans [27]. The virus also contains enzymes named proteases, integrases and reverse transcriptase. The genome is made up of two linear RNA strands which replicate by the process of retro transcription. The HIV genome consists of three structural genes common to all the retrovirus (gag, pol and env) and six other regulatory genes (Tat, Rev., Nef, Vif, Vpr, Vpx, and Vpu) [28]. The R5 strain of HIV has an affinity for the CCR5 receptor and is the predominant type of HIV at early phase of infection as opposed to the X4 strain that is generally seen later in the course of HIV disease [29,30].



Fig. 1. London Eye as a 'model' of HIV.<sup>1</sup>



Fig. 2. The London Eye as a 'model' of HIV showing globular gp120 and transmembrane gp41 with the help of the close up of the trimetric spike [51].

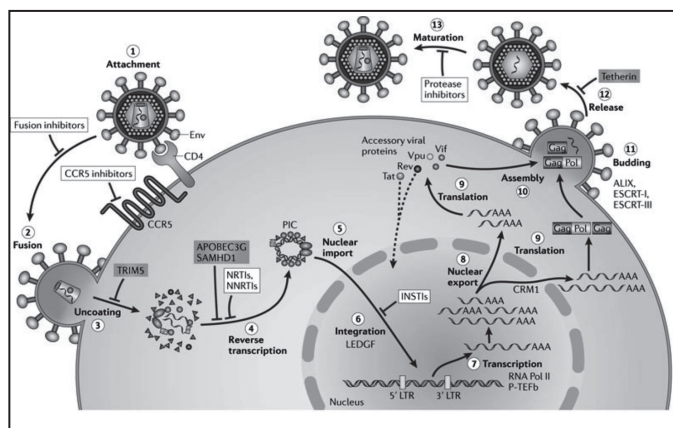


Fig. 3. Viral cycle of HIV [52]

Series of steps are involved for the establishment of infection (Figure 3). At first, the virus need to pass through the primary barrier that is the mucosal barrier at the exposure site so as to establish contact with cell that could sustain replication. The

infection can be facilitated by altering the quality of the mucosal barrier which is generally caused due to ulcers, infections, erosion of the layer and hormonal changes. The virus starts to infect the CD4 lymphocytic cells along with pancreatic cells (Langerhans cells), dendritic cells of the submucosa which is the primary basis for the judgement of the homogeneous spread of viral population of the HIV [31]. Virus now reaches the lymph nodes where they target the lymphocytes cells. The time taken by the virus to reach the lymph nodes is about 48-72 hours and the result of this attack leads to rapid replication of the HIV virus in all the tissues. The cellular level interactions between the CD4 receptor and gp120 leads to the entry virus into the cell. These interactions induces conformational changes favouring the fusion of the HIV viral domain to the host cell. The anchorage of the HIV virus takes place due to the interaction between the surface glycoprotein (gp120) and the natural chemokine receptors CXCR4 along with CCR5[32]. After the viral entry into the host cell the virus can lead into two directions either it can transfix into the host cell nucleus in an activated form or persevere to be inactive within the cytoplasm [33]. After the entry of the virus into the nucleus, the HIV-RNA strand is now transcribed into proviral DNA (two DNA strands) by the enzymatic action of reverse transcriptase. Further, the proviral DNA is concatenated with the host DNA by the action of integrase enzyme. Proofreading of the DNA molecules is an important step as it looks over the mismatched nucleotide pair of the DNA strand but in the case of the reverse transcriptase this is not possible. The production of new variants and mutants takes place at the time of every replication cycle. The integrated DNA acts as a model for the synthesis of the messenger RNAs which forms new viral particles when transported outside the nucleus. The protein is cut into pieces with the help of the enzyme protease and which further converts into the new viral moieties which start to replicate and infect other cells.

## 2.2 The shape of the viral recognition site and the CD4 receptor

The killing of the CD4+ T-helper lymphocytic cells is the main cause for the immunodeficiency, which is eventually termed as AIDS. The knowledge of the fact about the replication of the HIV virus and its influence on only the CD4-plus cell population was given to us by the *in-vitro* studies conducted by David Klatzmann and colleagues [34]. They differentiated the CD3-plus T-lymphocytic cells into CD8-plus and CD4-plus T-lymphocytic cells and enriched its fractions to observe the effect of the HIV virus and the effects were seen on the CD4-plus cells only [34]. Further *in vitro* studies proved that the HIV infection was competitively blocked by the monoclonal antibodies specific to CD4 [35, 36]. Later the monoclonal antibodies, site specific mutagenesis and structural studies on the amino terminal domain were used to map the binding epitope on the CD4 receptor, which concluded that for binding to gp120 pocket phenylalanine residue at position 43 is necessary [37].

CD4 belongs to the immunoglobulin superfamily and is a class I membrane glycoprotein. Adhesion molecule ICAM-I from the rhinovirus group and serogroups of poliovirus were

<sup>1</sup> London eye lit up to celebrate royal birth: ITV news; Clive Gee/PA Wire

lately identified after the recognition of CD4 as the HIV receptor [38,39]. The protein that binds the receptors contains deep pockets or crevice which acts as the binding site for the receptors as in the case of influenza virus where sialic acid on the hemagglutinin acts as the binding site. On the basis of these studies Michael Rossman postulated a hypothesis known as the canyon hypothesis [38]. The hypothesis stated that the penetration into the canyon on the virus is not possible in the case of bulky antibodies as they contain light and heavy chains at the antigen-binding sites because of which such small surface receptors were adopted by these viruses.

### 2.3 Chemokine co-receptors and intrusion to HIV

CD4 T-lymphocytic cells are not the only cells which are infected by the HIV, cells like macrophages and brain cells (microglia) which have same linkage are highly infected by the virus irrespective of low presence of CD4 in them. These observations soon gave an idea that CD4 was imminent but not ample for the HIV infection, as susceptibility to viral entry is not only due to the interaction of CD4 on murine cells [40]. After ten years of study the discovery of the seven-transmembrane chemokine receptors took place and it was termed as co-receptor [41], and was found that the co-receptor for cell-lined adapted strains of HIV-1 was CXCR4. Three months prior to this discovery it was reported that the infection could be blocked by three chemokine molecules namely CCL3L1, CCL4 and CCL5 [42]. CCR5 was found to be the only receptor which could bind to all these chemokine molecules. CCR5 was demonstrated as the co-receptor for HIV strains that infect T-cells and macrophages after the discovery of CXCR4.

The major genetic resistance factor for the infection was identified rapidly after the discovery of CCR5. The infection of HIV has been a puzzle for several years as partners exposed to high intimacy have managed to escape the infection. Genetic variations have not only caused problems but also they have increased the chances of survival in some cases. The *in vitro* study on a patient showed that his cells were not infected by the HIV virus because the patient was a natural CCR5 resistant, which means the patient showed same set of allele deletion on the first axon of the CCR5 gene ( $\Delta 32$ ). The population containing one set of two different alleles (heterozygous) are not completely intrusive towards the HIV but the chances of these people getting affected is relatively less, and even if they are affected the rate of progression of the disease is slow as compared to the normal population. These types of genetic modifications are generally seen in the Caucasian populations. The effective strength of the viral entry depends on the chemokines concentration and the bulkiness of the CCR5 on plasma and the lymphocytic cells respectively. Many other chemokine receptors can act as functional moieties but the studies till date have not provided any facts about their part played *in vitro* [43]. The migration of the virus and its susceptibility towards the co-receptors is increased fur to the binding of HIV to DC-SIGN on the dendritic cell, which is an adhesion molecule [44].

### 2.4 The dynamism of fusion and viral entry

As the HIV virus enters the cell it initiates the conformational changes within the envelope which is composed of the glycoproteins. These changes takes place because of the interaction between the receptors and the virus [43,45]. A site is induced because of the conformational changes that occurs in gp120 due the anchoring of the CD4 receptor into it and the exposed site is called as CD4 induced site (CD4i). One of the three hypervariable loops of gp120, named variable loop 3 or V3 loop gets swelled due to the conformational change (Figure 4).

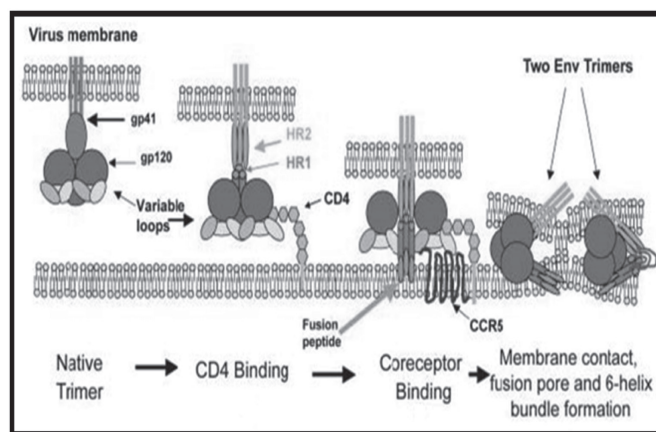


Fig. 4. Model of HIV entry [53]

The chemokine receptors now interact with the V3 loop along with CD4i, where the V3 loop acts a determinant for tropism of R5 and C5. A site is induced because of the conformational changes that takes place in the gp120 due the anchoring of the CD4 receptor and protrusion amongst one of the loops is observed. The CCR5 and the HIV envelope trimer comes closer to one another because of the bending of the hinge region present between the globular domains 2 & 3 of the CD4 receptor. Further, due to the untightening of the gp120 induction of six-helix bundle formation takes place as gp41 undergoes radial rearrangement leading to the initiation of cell membrane and viral envelope fusion.

The close contact between the cells and the virus forms a ‘virological synapse’ with the target immune cell due to which the infection prevails from one cell to another [46]. The HIV particles along with the CD4 and CCR5 move across from cell to cell with the help of this synapse, held together by the adhesion molecules.

### 3. AVAILABLE TREATMENTS

Antiretroviral drug treatment has been a back bone for the treatment of AIDS. A perfect treatment which can cure AIDS has not been found till date but the treatment aims at suppression of the spread of AIDS in the infected subject. The following categories of drugs are currently in use and FDA has approved the following for the current antiretroviral therapy (Table 1).

**Table 1.** FDA-approved antiretroviral drugs currently in use [47].

Drug Class	Generic Name (Other names and acronyms)	Brand Name	FDA Approval Date
<b>Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</b>			
NRTIs block reverse transcriptase, an enzyme HIV needs to make copies of itself.	abacavir (abacavir sulfate, ABC)	Ziagen	December 17, 1998
	didanosine (delayed-release didanosine, dideoxyinosine, enteric-coated didanosine, ddI, ddI EC)	Videx	October 9, 1991
		Videx EC (enteric-coated)	October 31, 2000
	emtricitabine (FTC)	Emtriva	July 2, 2003
	lamivudine (3TC)	Epivir	November 17, 1995
	stavudine (d4T)	Zerit	June 24, 1994
	tenofovir disoproxil fumarate (tenofovir DF, TDF)	Viread	October 26, 2001
zidovudine (azidothymidine, AZT, ZDV)	Retrovir	March 19, 1987	
<b>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</b>			
NNRTIs bind to and later alter reverse transcriptase, an enzyme HIV needs to make copies of itself.	efavirenz (EFV)	Sustiva	September 17, 1998
	etravirine (ETR)	Intelence	January 18, 2008
	nevirapine (extended-release nevirapine, NVP)	Viramune	June 21, 1996
		Viramune XR (extended release)	March 25, 2011
rilpivirine (rilpivirine hydrochloride, RPV)	Edurant	May 20, 2011	
<b>Protease Inhibitors (PIs)</b>			
PIs block HIV protease, an enzyme HIV needs to make copies of itself	atazanavir (atazanavir sulfate, ATV)	Reyataz	June 20, 2003
	darunavir (darunavir ethanolate, DRV)	Prezista	June 23, 2006
	fosamprenavir (fosamprenavir calcium, FOS-APV, FPV)	Lexiva	October 20, 2003
	indinavir (indinavir sulfate, IDV)	Crixivan	March 13, 1996
	nelfinavir (nelfinavir mesylate, NFV)	Viracept	March 14, 1997
	ritonavir (RTV)	Norvir	March 1, 1996
	*Although ritonavir is a PI, it is generally used as a pharmacokinetic enhancer as recommended in the <i>Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents</i> and the <i>Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection</i> .		
	saquinavir (saquinavir mesylate, SQV)	Invirase	December 6, 1995
tipranavir (TPV)	Aptivus	June 22, 2005	

<b>Fusion Inhibitors</b>			
Fusion inhibitors block HIV from entering the CD4 cells of the immune system.	<u>enfuvirtide</u> (T-20)	Fuzeon	March 13, 2003
<b>Entry Inhibitors</b>			
Entry inhibitors block proteins on the CD4 cells that HIV needs to enter the cells.	<u>maraviroc</u> (MVC)	Selzentry	August 6, 2007
<b>Integrase Inhibitors</b>			
Integrase inhibitors block HIV integrase, an enzyme HIV needs to make copies of itself.	<u>dolutegravir</u> (DTG, dolutegravir sodium)	Tivicay	August 13, 2013
	<u>elvitegravir</u> (EVG)	Vitekta	September 24, 2014
	<u>raltegravir</u> (raltegravir potassium, RAL)	Isentress Isentress HD	October 12, 2007 May 26, 2017
<b>Pharmacokinetic Enhancers</b>			
Pharmacokinetic enhancers are used in HIV treatment to increase the effectiveness of an HIV medicine included in an HIV regimen.	<u>cobicistat</u> (COBI)	Tybost	September 24, 2014
<b>Combination HIV Medicines</b>			
Combination HIV medicines contain two or more HIV medicines from one or more drug classes.	<u>abacavir and lamivudine</u> (abacavir sulfate / lamivudine, ABC / 3TC)	Epzicom	August 2, 2004
	<u>abacavir, dolutegravir, and lamivudine</u> (abacavir sulfate / dolutegravir sodium / lamivudine, ABC / DTG / 3TC)	Triumeq	August 22, 2014
	<u>abacavir, lamivudine, and zidovudine</u> (abacavir sulfate / lamivudine / zidovudine, ABC / 3TC / ZDV)	Trizivir	November 14, 2000

### 3.1 Treatment of AIDS by targeting the viral entry and its prevention

The earliest step for the treatment of HIV aims at preventing the entry of the drugs with the help of drugs rather than penetrating into the cytoplasm or nucleus for the action [48]. The first potential drug which potently neutralised X4 was itself a form of soluble CD4, but it was impotently active against the R5 strains. Potent anti-HIV activity was observed when head of IgG heavy chain was replaced by the CD4 receptor's two amino terminal domains.

The six-helix bundle formation is blocked by Enfuvirtide which is a twenty amino acid peptide. It also mimics the mechanism of formation of gp41 sequence but the administration is to be done with the help of injection. Maraviroc as an entry inhibitor prevents the CCR5 to act as a HIV coreceptor because it binds to the transmembrane domains of the co receptor. It is one of the most effective inhibitors used to avoid the entry and is approved for the clinical use.

Drugs such as Maraviroc which target on the cell receptors should not cause any genetic resistance in the viral genome. However, the HIV virus has the art to modify itself under strong selective

pressure causing resistance for the drug [48]. The interaction between amino terminal domain of CCR5 and Maraviroc resistant virus takes place due to the mutation in the V3 loop domain of gp120. This also leads to less dependency for the secondary loop, nearer to the binding site of the drug within the transmembrane region [49].

The vaccine development can be correlated with the HIV receptor and its interaction between the glycoprotein envelopes [27]. Receptors should be blocked with the help of antibodies secreted from the immunogens and should be protective. The CD4-binding site on gp120 is recognised by some immunized animals and monoclonal antibodies derived from naturally infected humans. Some of the antibodies have the ability and they act as potent drug for the treatment.

### 4. CONCLUSION

The treatment based on the development of anti-retroviral drugs and the approaches to the vaccine discovery has been incurred due to the help of the knowledge of the receptors and the entry of the viral genome into the cell. Furthermore, the opportunity for the treatment of HIV also kicks in when the restriction factors

are introduced after the process of entry and development of the viral genome [50]. With the interaction of the HIV virus with the cell our knowledge about the cell and molecular biology is illuminated which indeed leads to information related to the working of the cell.

In addition to vaccine, the process of HIV entry can also lead to prevention of the epidemic infection. For example, the mucosal infection can be blocked in women with the use of vaginal microbicide which can be developed using the mini-CD4 cells along with neutralising mini-antibodies that can block the receptor interaction [27]. The use of regular and repeated drugs for the treatment of the HIV can lead to resistance which can be reduced by these neutralising antibodies.

In spite of all the research till date there is still a gap between the invention of means to block the viral entry and application of these as a part of the public health measures. A well maintained CD4 cell count along with the low viral load gives a chance of better survival and provide a reasonable quality of living to the infected person. As a reviewer, I feel that the research and development in the field of HIV protection has reached a way long distance from nowhere to the place where we stand today and surely the cure will be found soon.

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