Pharmacophore 2014, Vol. 5 (1), 01-23 USA CODEN: PHARM7 ISSN 2229-5402

Pharmacophore

(An International Research Journal)

Available online at http://www.pharmacophorejournal.com/

Review Article

RECENT ADVANCES AND MANAGEMENT APPRAISAL FOR THE CHEMOTHERAPY OF AIDS

Aaditi Mukadam[1]*, Gaurav M. Doshi[2] and Pratip K. Chaskar[2]

[1]Department of Pharmacology, Vivekanand Education Society's College of Pharmacy, Mumbai, India

[2]Department of Pharmacology and Pharmaceutical Chemistry, Vivekanand Education Society's College of Pharmacy, Mumbai, India

ABSTRACT

As we all know that Acquired Immuno Deficiency Syndrome is a deadly disease and observed on every 1st December. Our review enlightens the vision to focus on newer targets and details of their status in perspective with clinical trials data. The article encompasses newer targets related to disease such as attachment inhibitors, fusion inhibitors, chemokine co-receptors as well as lighting modern approaches like ethosomes, vaccines and various targeted delivery systems which have been found effective in comparison to the existing conventional targets such as Nucleoside Reverse Transcriptase Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors for existing AIDS therapy. The review paper definitely attracts the readers mind towards the newer targets which are set to accelerate in near future for a better treatment regimen.

Keywords: Human Immunodeficiency Syndrome (HIV), CD4 Lymphocytes, Glycoprotein (gp), Highly Active Antiretroviral Therapy (HAART), Targeted drug delivery systems.

INTRODUCTION

AIDS is a disease of the human immune system caused by infection with human immunodeficiency virus (HIV). During the initial infection, a person may experience a brief period of influenza-like illness. This is typically followed by a prolonged period without symptoms. As the illness progresses, it interferes more and more with the immune system, making the person much more likely to get infections, including opportunistic infections.[1] HIV is transmitted primarily *via* unprotected sexual intercourse (including anal and even oral sex), contaminated blood transfusions, hypodermic needles and from mother to child during pregnancy, delivery or breastfeeding. Some bodily fluids, such as saliva and tears, do not transmit HIV. Prevention of HIV infection, primarily through safe sex and needle-exchange programs, is a key strategy to control the spread of the disease. There is no cure or vaccine; however, antiretroviral treatment can slow the course of the disease and may lead to a near-normal life expectancy. While antiretroviral treatment reduces the risk of death and complications from the disease, these medications are expensive and may be associated with side effects.[2]

Virus Structure

Human immunodeficiency virus is a RNA virus of retrovirus family retroviride. HIV is a

lentivirus. Retrovirus are 0.08 µm-0.1 mm in diameter and seen as a biological nanostructure (around 100-150 nm), composed by a host derived membrane and a nucleocapsid. These make a complementary DNA copy of their RNA which is necessary for their replication. The complementary DNA formed gets incorporated into host cell genes as part of infection cycle.[2,3,4] HIV may enter and exit the host cells through special area of cell membrane (human) known as lipid raft. These lipid rafts are rich in cholesterol and glycolipids. These proteins consists of a cap made up of three molecules called gp 120 and stem consisting of gp 41 molecules that anchors the structure in the viral envelope. The capsid surrounds two single strands of HIV RNA. Each RNA contains nine genes of HIV.[2] HIV has a small RNA genome of 9300 base pairs.[1] The genetic material is in the form of RNA containing three structural genes. Two copies of the genome are contained in a nucleocapsid core surrounded by a lipid bilayer or envelope that is derived from the host cell plasma membrane. The viral genome includes three major open reading frames;

- *gag* encodes a polyprotein that is processed to release the major structural proteins
- *pol* overlaps gag and encodes three important enzymatic activities-an RNA-dependent DNA polymerase or reverse transcriptase, HIV protease, and the viral integrase
- *env* encodes the large transmembrane envelop protein responsible for cell binding and entry.

Several small genes encode regulatory proteins that enhance virus production or combat host defenses, including tat, rev, nef, and vpr.[1] The two glycoproteins present in the outer viral membrane, gp 120 and gp 41, are responsible for recognizing the CD4 receptor and the CCR5 or CXCR4 co-receptors of the host cell membrane, and for virus/cell fusion, respectively. As a consequence of constant transcription errors, these viral structures present high polymorphism which leads to mutation, thus constituting a major source of antiretroviral-resistance development.[2,3]

Pathogenesis

Retroviruses are evolved to establish chronic persistent infection with gradual onset of clinical symptoms. Replication is constant following infection; while some infected cells may harbor non-replicating, but infectious virus for years. Humans and chimpanzees are the only hosts for these viruses.[5] There are two major families of HIV. Most of the epidemic involves HIV-1 and 2.[5] HIV-2 is associated with slower progression to immunodeficiency and is less efficiently transmitted. HIV-2 is also much less prevalent than HIV-1, being HIV-2 mostly found in individuals from West Africa, India, and scarcely in Portugal and African colonies.[4,6] HIV-1 is genetically diverse, with at least five distinct subfamilies or clades. HIV-1 and HIV-2 have similar sensitivities to most antiretroviral drugs, although the non nucleoside reverse transcriptase inhibitors have no activity against HIV-2.[5]

Viral replication consists of several steps. Antiviral agents can potentially target any of these steps.[1] These are;

- Attachment of virus to host cell
- Entry of virus through the host cell membrane
- Uncoating of viral nucleic acid
- Synthesis of early regulatory proteins *e.g.* Nucleic acid polymerases
- Synthesis of RNA or DNA
- Synthesis of late structural proteins
- Assembly (mutation) of viral particles
- Release from the cell

Viral Life Cycle

HIV tropism is controlled by the envelope (*env*) protein gp 160. The major target for *env* binding is the CD4 receptor present on lymphocytes and macrophages; cell entry also requires binding to a coreceptor, generally the chemokine receptor CCR5 (present on macrophage lineage cells) or CXCR4 (present on T-cells). It is believed that, this virus is responsible for sexual transmission of HIV and the first cells infected in sexual transmission express is CCR5. A shift from

CCR5 to CXCR4 is associated with advancing disease and the heralds accelerated loss of CD4 helper T cells and increases the risk of immunosuppression. The doligatory role of coreceptors in HIV entry provides a novel target for pharmacotherapy. The gp 41 domain of *env* controls the fusion of the virus lipid bilayer with that of the host cell. Thereafter, full-length viral RNA enters the cytoplasm and is replicated by reverse transcriptase to a short-lived RNA-DNA duplex; the original RNA is degraded by RNase H to allow creation of a full-length double-stranded DNA copy of the virus. As the HIV reverse transcriptase is error-prone and lacks a proof reading function, mutation is quite frequent (~3 bases/9300base-pair replication). Viral DNA is transported into the nucleus, where it is integrated into a host chromosome by the viral integrase in a random or quasi-random location. Following integration, the virus may remain quiescent, not producing RNA or protein but replicating as the cell divides. When a cell that harbors the virus is activated, viral RNA and proteins are produced. Structural proteins assemble around full-length genomic RNA to form a nucleocapsid. The transmembrane envelope and other structural proteins assemble at the cell surface and are concentrated in lipid rafts. The nucleocapsid cores are directed to these sites and bud through the cell membrane, creating a new enveloped HIV particle containing two complete single stranded RNA genomes. Reverse transcriptase is incorporated into this particle; thus, replication can begin immediately after the virus enters a new cell.[1]

How the Virus Causes Disease

Sexual acquisition of HIV infection is thought to be mediated by infectious virus particles. Soon after infection, there is a rapid burst of replication peaking at 2-4 weeks, with number of cells becoming infected. This peak is associated with a transient dip in the number of peripheral CD4 (helper) T lymphocytes. As a result of new host immune responses and target cell depletion, the number of infectious virions declines to quasi steady state. This set point of viral activity reflects the interplay between host immunity and the pathogenicity of the infecting virus. In the average infected individual, several billion infectious virus particles are produced every few days. Eventually, the CD4 lymphocyte count begins a steady decline, accompanied by a rise in the plasma HIV RNA concentration. Once the peripheral CD4 count falls to < 200 cell per mm^3, there is an increasing risk of opportunistic infection. Occasional patients can harbor HIV for more than two decades without significant decline in CD4 count or clinical immunosuppression; this may reflect a combination of favorable host immunogenetics and immune responses.[1]

Principles of HIV Chemotherapy

Current treatment assumes that, all the aspects of the disease are derived from direct toxic effects of HIV on host cells, mainly CD4 T lymphocytes. The goal of the therapy therefore, is to suppress viral replication as much as possible for as long as possible. Deciding when to initiate the therapy has been the subject of some debate. The advent of more effective drugs capable of increasing CD4 cell counts to normal or near normal levels, led to advocate a strategy of early use of combination drug therapy, regardless of disease stage or symptoms. It now appears that, true eradication of HIV is not possible, at least with current drugs, as there is a reservoir of long-lived, quiescent T-cells harboring infectious HIV RNA incorporated into the host chromosome. Natural history studies also point to a low risk of short-term disease progression when the CD4 cell count is > 350 cells per mm^3 or plasma HIV RNA concentrations were < 50,000 copies per mL. The toxic risks of long-term combination chemotherapy, the need for nearly perfect adherence to prescribed regimens, the inconvenience of some regimens, and the high cost of life long treatment point to a risk-benefit ratio that favors for treating the patients with low CD4 counts and/or very high viral load. Drug resistance is also an extensive and serious problem. Because of the high mutation rate of HIV and the tremendous number of infectious virions, combination of active agents is needed to

prevent the drug resistance. Intentional drug holidays allow the virus to replicate and increase the risk of drug resistance and disease progression; they therefore are not recommended. The standard of care is to use at least three drugs simultaneously for the entire duration of treatment. The expected outcome of initial therapy in a previously untreated patient is an undetectable viral load (plasma HIV RNA <50 copies/mL) within 24 weeks of starting treatment. Four or more drugs are often used simultaneously in pretreated patients harboring drug-resistant virus, but the number of agents a patient can take is limited by toxicity and inconvenience. Most clinicians prefer to use drugs that attack at least two different molecular sites. In treatment of naïve patients, a three-drug regimen containing a single drug class is less effective than the one that includes drugs from two classes. Regimens containing three or four different classes are reserved for treatment-experienced patients who have failed multiple previous regimens. This acknowledges the benefit of reserving at least one drug class for future treatment in case of failure.

Failure of an antiretroviral regimen involves;

- A persistent increase in plasma HIV RNA in a patient who previously responded.
- Failure to reduce plasma HIV RNA significantly in a patient who has taken the prescribed regimen for more than 12 weeks.

This indicates resistance to one or more of the drugs and necessitates a change in treatment. The selection of new drugs is based on the patient's treatment history and viral resistance testing. Treatment failure generally requires a completely new drug combination. The risk of failing a regimen depends on the percent of prescribed doses taken in any given treatment period.[1]

Approaches

As disease progression is associated with higher HIV RNA levels in blood (viral load), an important objective of antiretroviral therapy is to reduce viral loads below the limit of detection of approved assays.[6] The various approaches for AIDS treatment is based on the structure and replication cycle of HIV. The different target sites for treatment of HIV are lipid raft, *env* protein, *gif* gene, reverse transciptase enzyme, protease enzyme, integrase enzyme and the fusion of HIV T-cell and HIV RNA.[2] In order to prevent the survival of mutant-superior-resistant virus, it has become a standard practice to administer a cocktail of at least three anti-HIV medications, with the rationale that, if a successful mutation has occurred enabling the virus to bypass the inhibitory effect of the drug, it may still be blocked by a drug targeting another enzyme or step in its process of replication. This is referred to as combination antiretroviral therapy (cART). Adding a fourth antiretroviral drug (ARD) to this cocktail does not have a superior effect on viral suppression, but may adversely affect the side-effect profile of the combination.[7,8] When virological failure develops, usually first seen sign is the loss of viral suppression. Resistance may have developed to one or more classes of cART. Highly active antiretroviral therapy (HAART) as a initiating cART regimen, described by some as 'hit early hit hard', has now become an attainable goal in salvage therapy-'also hit hard later'.[4]

Aim of Treatment

During the early stages of HIV infection, a pool of latent CD4 cells is established[9] which cannot be eradicated, even with prolonged treatment. Therefore, the goal of therapy should be the achievement of HIV RNA below 50 copies/mL for both, treatment-naïve and experienced patients. Achieving such goal allows to stop any ongoing HIV infection of additional CD4 cells, thereby increasing the number of uninfected CD4 cells. For a majority of patients, a recovery of immune function occurs, decreasing the likelihood of opportunistic infections.[4]

Treatment Regimen

Indications for treatment

Initiation of antiretroviral treatment (ART), according to the United States Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents Dec 1, 2009[10], is advised for;

- All the persons who have had an AIDS-defining-illness
- All the persons whose CD4 count is below 350 cells/microl
- All the persons who have been diagnosed with HIV-associated nephropathy
- All the persons who have Hepatitis B co-infection needing treatment
- All the persons who are pregnant

Current regimens

In the DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (Dec 1, 2009),[10] four regimens of currently registered compounds are listed as preferred for initiating non-pregnant naïve patients;

a) Efavirenz + Tenofovir/Emtricitabine
b) Atazanavir + b- Ritonavir + Tenofovir/Emtricitabine (b refers to boosting-dose)
c) Darunavir + b- Ritonavir + Tenofovir/Emtricitabine (b refers to boosting-dose)
d) Raltegravir + Tenofovir/Emtricitabine;

The recommendation for initiating pregnant patients remains lopinavir/ritonavir plus zidovudine/lamivudine. The choice of regimen requires consideration of clinical and cost factors, whereas the local treatment programmes may restrict availability of certain initiating regimens.

Indications for treatment in resource limited settings

Four key messages:

- Start cART earlier, when CD4 threshold is less than 350cells/mm^3
- Use less toxic and more patient-friendly options to reduce the risk of adverse events and improve adherence by using less toxic drugs as fixed dose combinations
- To improve management of TB/HIV and HBV/HIV co infections, start cART in all HIV-infected patients who have active TB and chronic active hepatitis B disease irrespective of CD4 cell count
- Promote strategic use of laboratory monitoring by using laboratory monitoring such as CD4 counts and viral load to improve efficiency and quality of HIV treatment and care.

WHO recommends starting cART in the following situations;

- In all patients with HIV who have CD4 count < 350cells/mm^3 irrespective of clinical symptoms.
- CD4 testing is required to identify whether the patients with HIV and WHO clinical stage 1 or 2.
- In all patients with HIV and WHO clinical stage 3 or 4 irrespective of CD4 count.

The panel also considered that starting ART earlier is feasible if introduced in a phased manner, with the speed and completeness determined by health system capacity, HIV burden, ART coverage, equity of access and funding.

Classes of Antiretroviral Targets

Conventional targets

The viral target sites at which current treatment strategies aimed are entry inhibitors, reverse transcriptase inhibitors represented by the nucleoside analog reverse transcriptase inhibitors (NRTI) and non-nucleoside analog reverse transcriptase inhibitors (NNRTIs), integrase inhibitors and protease inhibitors (PIs).

Reverse Transcriptase Inhibitors

This large group of drugs inhibits the function of RT (reverse transcriptase) and a DNA polymerase in two possible manners;

- They may directly block the binding site in a competitive manner by mimicking the deoxynucleotide building blocks of DNA, the substrate of RT, and are therefore called nucleoside analog reverse transcriptase inhibitors (NRTI).
- If they work by binding elsewhere to the enzyme, resulting in conformational change and diminished binding affinity to the substrate nucleotides, they are called non-nucleoside analog RT Inhibitors (NNRTI).[4]

Nucleoside Analog Reverse Transcriptase Inhibitors (NRTIs)

Nucleoside analog reverse transcriptase inhibitors (Table 1) are the oldest ARDs around. They are competitive substrate inhibitors. Before incorporation into viral DNA, they have to be activated by cellular kinase enzymes. Nucleotide analogs differ from nucleoside analogs in that one less step is required for conversion to active state. The conversion of viral RNA to proviral DNA is prevented by inhibiting reverse transcriptase enzyme action. They prevent acute infection of susceptible cells but have little effect on the cells already infected with HIV. They competitively block the active site on enzyme. These drugs are first phosphorylated by host enzyme in the cytoplasm and then they become active. These drugs lack 3'-OH group, when incorporated into DNA and terminates chain elongation.[2]

Non-Nucleoside Analog Reverse Transcriptase Inhibitors

Non-nucleoside analog reverse transcriptase inhibitors (Table 2) are the most prescribed anti-HIV drugs. These compounds are not known to interfere with cellular or mitochondrial synthesis.[4] These drugs bind to the site adjacent to active site non-competitively, inducing conformational changes in the active site of the enzyme. NNRTI do not undergo phosphorylation for its action.[2] These compounds are supplied as a combination therapy.[11] Stavudine is considered as an alternative ARV because it is associated with a high incidence of adverse events including peripheral neuropathy, pancreatitis, hyperlactetemia, lipodystrophy and dyslipidaemia that may not be reversible on treatment discontinuation (Table 3).

Integrase Inhibitors

After genetic code is changed from single strand by reverse transcriptase enzyme, integrase inhibitors (Table 4) gets inserted into the genetic code of the infected cell. Then the HIV genetic code is read producing new viruses. Scientists hope that integration can be another point in HIV life cycle that can be targeted by drug.[2] Integrase inhibitors inhibit the insertion of HIV RNA into the host cell genome. Efficacy is maintained against virus resistant NNRTI and PIs, R5- and X4-tropic virus and different viral subtypes. It also has anti-HIV-2 activity.[4]

Protease Inhibitors

HIV protease is a non competitive inhibitor which is a dimer of 99 amino acid monomer. Each monomer has one aspartic acid in the active site for drug binding, which act as a catalytic site. Human protease like rennin and cathepsin are monomers. These structural differences between HIV proteases and human proteases cause 1000 times more affinity of protease inhibitors for HIV proteases than human proteases. All the protease inhibitors (Table 5) bind reversibly to active site of HIV protease. This prevents protease from cleaving the viral polyprotein into active enzyme, which leads to immature and noninfectious viruses.[2]

Other Targets

Maturation inhibitors

Maturation inhibitors (Table 6,7)[11-15] inhibit the last step in *gag* processing in which the viral capsid polyprotein is cleaved and, therefore, prevents the production of mature capsid protein p24. Defective and non-infectious virus particles are released from the host cell.

Haart

Treatment of HIV-1 infected individuals by HAART usually allows reducing the plasma viral load to undetectable levels improves $CD4^+$ T-cell counts, delays disease progression and promotes survival. Although the development of HAART was certainly the greatest success of AIDS research and allows the reduction of morbidity and mortality wherever it is available, it also has major limitations.[16] Furthermore, HAART is expensive and requires an infrastructure with a functional healthcare system allowing the medical monitoring of the success of antiretroviral therapy to prevent or at least delay the emergence of drug-resistant HIV-1 strains.[17] HAART requires life-long daily treatment because it does not allow eliminating resting long-lived cells containing integrated proviruses and thus, fails to eradicate the virus entirely. A

major barrier for curing HIV infection remains the ability of HIV to integrate in the host genome and remain latent. The thus-generated viral reservoirs cause viral rebound upon HAART interruption and impose lifelong antiretroviral therapy with its many associated side effects and possible development of resistance.[17] Even if HAART regimens present considerable anti-HIV activity, several factors frequently compromise its success. To begin with, current therapy is not able to provide a cure mainly because of HIV's ability to persist in latency state in cellular and anatomical reservoir sites. Beside this fact, problems of current antiretroviral therapy also include prolonged treatment periods with drugs possessing important adverse effects, poor drug-regimen compliance, drug resistance, drug–drug interactions, poor drug pharmacokinetics, viral levels rebound after therapy cessation and costs. Drug resistance is the most common cause of antiretroviral treatment failure and has been described for virtually every antiretroviral drug currently used in therapy. An important contributing factor for the emergence of HIV/AIDS therapy resistance, is the inability to attain effective and/or sustained drug levels with currently used formulations and drug-schedules, thus contributing to ineffective viral suppression.[18] The use of multi-drug regimens, each of them often possessing considerable toxicity, is also one of the most problematic issues that may delay therapy initiation or determine its interruption.[19] The type, severity and frequency of clinical adverse events are variable and dependent on individual drugs, drug regimens and patients.[20,21] The problem of drug toxicity is even more dramatic while considering them for effective viral suppression. It is essential to follow the perfect compliance of drug regimen for long periods, often chronically, with interruption of drug treatment frequently resulting in increased morbidity and mortality. Also, interactions between antiretroviral drugs or with other drugs are frequent and highly complex. Since no curative therapy is available, prevention is a cornerstone in the battle against HIV/AIDS, particularly for stopping sexual heterosexual HIV transmission.[3]

Novel Targets

Entry inhibitors

The process by which the HIV enters the host cell may be targeted by blocking;

- Attachment of HIV to the host cell
- Chemokine co-receptors CCR5 or CXCR4
- Fusion of HIV membrane with the host cell membrane.[4]

Attachment inhibitors

Virions first attach themselves to the host cells in a nonspecific manner. This occurs as an electrostatic attraction between the positively charged regions of *env* of host cells and negatively charged glycans on the viral cell surface *e.g.* cyanovirin-N[4].

CD4-gp 120 Binding inhibitors

After non-specific adhesion of the virus to the host cell membrane, specific binding of viral gp 120 to the CD4 receptor occurs. Inhibitors of the binding are called the 'CD4 blockers'. Many molecules can inhibit this CD4-gp 120 binding by different modes of action: targeting gp 120, targeting CD4, or by the prevention of conformational rearrangement.[4] The first step in the HIV entry process is initiated by the binding of HIV gp 120 to CD4 on the target cell surface.[22,23] The viral protein gp 120 is composed of an inner and an outer domain connected by a bridging sheet, a four-stranded antiparallel β-sheet. In these domains are localized, five conserved (C1–C5) and five variable (V1–V5) regions. The most critical regions involved in the viral entry process are V1/V2, V3 and C4. The three-dimensional functional structure of gp 120 has been characterized and shown to contain intramolecular disulphide bonds[24,25], which are critical for the interaction with the CD4 receptor and any potential drug inhibitor. The CD4 receptor binds between the outer and inner domains of HIV gp 120. Its binding creates a cavity that is well-protected and conserved among different HIV strains. Moreover, this cavity does not contain glycosylation sites.[26,27]

Electrostatic forces mainly drive the CD4–gp 120 binding, with the positive charge at the primary end of CD4 attracted to the primary negative charge cavity of HIV gp 120. Furthermore, van der Waals forces and hydrogen bonds help to stabilize the CD4–gp 120 interaction (Table 8). The CD4 phenylalanine is the only residue that binds to this cavity. This residue is quite significant in CD4–gp 120 binding because it is estimated that it alone accounts for 23% of the total energy of CD4–gp 120 binding.[26,27] Following the CD4–gp 120 binding, the gp 120 conserved core undergoes conformational changes, moving from the rigid to a flexible state, allowing a subsequent interaction with the chemokine co-receptors.[28] The Phe-43 cavity in HIV gp 120 was initially pursued as a potential target for small molecules that could bind it and block the HIV entry.[27,29,30]

CCR5 and CXCR4 Inhibitors

An alternative approach is the specific knock-down of CCR5/CXCR4 using RNA interference. Individual homozygous having a defect in CCR5 expression have been identified as being highly resistant to HIV infection, while this defect does not cause significant health problems. Infected individual heterozygous for the defective gene appears to exhibit delayed disease progression.[17] Most CCR5/CXCR4 antagonists are small molecules which block the gp 120–CCR5 interaction after binding to the co-receptor. CCR5/CXCR4 is a seven transmembrane G-protein coupled receptor. The α-helical structure is composed of 4 transmembrane domains, 3 extracellular loop and 1 N terminal domain. CD4-gp 120 binds through V3 loop to any chemokine co-receptor. The targeted drug molecule mimics chemokine co-receptor which are natural molecules and make V3 loop inaccessible for binding. The CCR5 co-receptor binding site in HIV gp 120 is concealed by V1/V2 and V3. Once the HIV gp 120 binds to CD4, different conformational changes occur and the CCR5 co-receptor binding site is exposed. In the absence of CCR5 antagonists (Table 9), the CCR5 N-terminus interacts with residues located in the bridging sheet and the V3 stem of HIV gp 120, whereas ECL2 interacts with the V3 crown. In the presence of an inhibitor, the conformation of ECL2 is modified and it can no longer interact with the V3 crown, thereby inhibiting viral entry.[31]

CXCR4 Inhibitors

The binding site for CXCR4 antagonists (Table 10) is located in the ECL2 of the CXCR4 co-receptor.[32-34] Due to the highly negative charge that CXCR4 exhibits on the surface, it is thought that the interactions with the HIV gp 120 V3 loop are mainly achieved by means of electrostatic forces.[35] The best approach would be to combine CCR5 and CXCR4 inhibitors to give dual effect.

Fusion inhibitors

This is a new class of anti-HIV drug intended to protect cells from infection by HIV by preventing the virus from attaching to a new cell and breaking through the cell membrane (Table 11). Researchers hope that these drugs can prevent infection of cell by either free virus (in the blood) or by contact with an infected cell.[2] Following the interaction between the gp 120–CD4 complex and the chemokine receptor CCR5 or CXCR4, additional conformational changes take place in the viral envelope that cause a shift from a non-fusogenic to a fusogenic state of the HIV gp 41, which ultimately drive the fusion process. The N-terminal domain of gp 41 is exposed and inserted through the fusion peptide (FP) into the cellular membrane. Later, gp 41 experiences a structural reorganization that provokes the interaction between the heptad repeat regions HR1 and HR2, forming a thermostable, six-helix bundle structure, which is critical for the viral and cellular membrane fusion. The change in free energy associated with the formation of the six-helix bundle provides the force necessary for the fusion pore formation, and the viral capsid enters the target cell through this process.[36,37]

Ribozyme

RNA, in addition to its role in information storage, could also function as an enzyme.[38,39] Ribozymes (Rz) are RNA molecules capable of catalytically cleaving specific phosphodiester bonds in complementary RNA molecules.[40,41]

When delivered intracellularly, they can interfere with both pre-integration and post-integration events of the HIV replication cycle, by cleaving incoming viral RNA and transcribed mRNAs.[42] Delivery of Rz to cells has been attempted by;

- Endogenous expression of the Rz-encoding gene or
- Exogenous delivery of chemically-synthesized (pre-formed) Rz targeted to highly conserved regions of the virus.[43]

Engineered ribozymes have the capacity to specifically base pair with, cleave and functionally destroy a given RNA. Targeted ribozymes possess site-specific cleavage mediated cleavage, cleavage of multiple substrates and the ability to be engineered for improved cleavage specificity and enhanced catalytic turnover.[44,45] HIV-1 is a retrovirus with an RNA genome. In all phases of its life cycle, HIV is a target for ribozyme mediated cleavage and multiple targeting strategies offer most effective method. Steps and sites for ribosome mediated intervention of HIV-1 life cycle are;

- Cleavage of cellular co-receptor mRNA
- Cleavage of viral genomic RNA upon entry
- Cleavage of viral mRNA
- Cleavage of proviral genomic RNAs prior to and during packaging

Many of the genetic elements of the retroviral genome have been targeted including functional proteins, leader sequences and regulatory protein sequences.[46,47] Both hammerhead and hairpin ribozymes have demonstrated a marked protection against HIV-1. First approach involves autologous T-cell transduction of a retroviral vector expressing dual hairpin ribozymes ribozymes targeting Pol and 5'-LTR regions.[48] Another approach is to transduce hematopoietic precursors or stem cells with ribozyme expressing constructs. These cells should generate populations of differentiated hematopoietic cells (T-cells, monocytes, dendritic cells) which express anti-HIV-1 ribozymes and thus, are protected from infection and spread of the virus. Another newer approach involves making a chimera between the HIV primer transfer RNA and a ribozyme targeted to a sequence immediately after 5' position of the HIV primer-binding site.[49,50] A different approach involved fusing an anti-HIV hairpin ribozyme with the *Rev* binding element.[51] A number of problems need to be addressed before pre-formed Rz can be used successfully for therapy;

- Stabilization of the Rz against serum and cellular nucleases without compromising its catalytic activity;
- Efficient delivery to the target cells;
- Intracellular localization of an active Rz;
- Co-localization of the Rz with its mRNA target inside cells.

In contrast to endogenous expression, exogenous delivery permits the use of chemically modified Rz which are more resistant to degradation by nucleases, while maintaining cleavage capability.[52]

Nanotechnology based systems

General properties of nanosystems that favor their use in antiretroviral drug delivery include versatility (virtually all drugs may be encapsulated), good toxicity profile (depending on used excipients), targeted delivery, possibility of drug-release modulation, high drug payloads, relative low cost, easiness to produce and possible scale-up to mass production scale[53,54], ability to escape bioelimination process, adequate shelf life and long term stability. Their ability to incorporate, protect and/or promote the absorption of non-orally administrable anti-HIV drugs, namely mono- or oligonucleotides.[55,56] Once bioavailable, protection of incorporated drugs from metabolism is a favorable feature of nanosystems, allowing prolonged drug residence in the human body, thus reducing needed doses and prolonging time between administrations. There is a possibility of incorporating different antiretroviral drugs in the same delivery system and modulate their release individually.[57] This simplifies drug administration schedules, as well as the reduction of antiretroviral drug administration errors.

Liposomes

Liposomes are spherical vesicles composed of one or more phospholipid bilayers (in most cases phosphatidylcholine). Lipophilic drugs can be incorporated into the lipid bilayers while hydrophilic drugs are solubilized in the inner aqueous core.[58,59] Membrane permeability can be adapted by the selection of the phospholipids and the incorporation of additives (*e.g.* cholesterol). It is possible to prevent a rapid reticuloendothelial uptake of the liposomes by the incorporation of natural compounds or by the use of chemical modified polyethylene glycols.[60,61]

Solid lipid nanoparticles (SLN)

The main aim is to achieve controlled drug release because drug mobility in a solid lipid is considerably lower as compared with liquid oil. Nanopellets, nanospheres are produced by dispersing melted lipids with high speed mixers or ultrasound and contains relatively high amount of microparticles.[62,63]

Ethosomes

Ethosomes are vesicular carrier containing phospholipids, alcohol (ethanol/isopropyl alcohol) in relatively high concentration and water. Ethosomes were shown to permeate through the stratum corneum barrier and possess significantly higher transdermal flux in comparison to liposomes. The synergistic effects of combination of phospholipids and high concentration of ethanol in vesicular formulations are responsible for deeper distribution and penetration in the skin lipid bi-layers. Ethosomal carriers have been shown to be effective permeation enhancers.[7]

Nanoemulsion

Advantages include toxicological safety and a high content of the lipid phase as well as the possibility of large scale production by high pressure homogenization. Controlled drug release from nanoemulsions is limited due to the small size and the liquid state of the carrier.[64,65]

Nanosuspensions

Nanosuspensions are colloidal particles which are composed of the drug and the emulsifier prepared by ball milling[66] or high pressure homogenization.[64,65]

Lipid nanocapsules (LNC)

Lipid nanocapsules (Table 12) are the core-shell structures composed of a liquid oily core and an amorphous surfactant shell and derived from nanoemulsions; by Phase Inversion Temperature (PIT) method. Biocompatible excipients like medium-chain triglycerides (caprilic triglycerides) as the oil phase, a polyoxyethylene-660-12-hydroxy stearate as the PEO nonionic surfactant and MilliQpsy® water plus NaCl as the aqueous phase are generally chosen for the development of NLC.[7]

Vaccines

Rationally designed nanoparticles will have the capacity to present antigens to both D-cells (encapsulated) and B-cells (surface absorbed). Targeting antigen delivery to D-cells with surface-functionalized nanoparticles presents a major opportunity for delivery of antigens and initiation of immune responses. Another major benefit of nanoparticle vaccines is that, they can be optimized for various routes of administration and expanded opportunity for oral and nasal vaccinations.[58]

HIV gene code vaccination targets are;

- *Env*: gp 120 and gp 41
- *Gag*: internal structural and capsid proteins
- *Pol*: three replication enzymes
- *Nef*: interferes with host for survival of infected T-cells
- *Tat*: transcription activator protein

DNA vaccines

Instead of using the whole organism or its parts, these vaccines use the microbe's genetic material. The DNA is vaccinated and then the cells take up this material. The cells secrete the antigens (a molecule that stimulates an immune response) and display them on their surfaces. In other words, the body's own cells become vaccine-making factories. The DNA vaccine couldn't cause the disease because it wouldn't contain bacterium *X*, just copies of a few of its genes. In addition, DNA vaccines are relatively easy and inexpensive to design and produce in Phase I and Phase II trials while some have a boost.

Viral vector vaccines

HIV genes are put in a non-disease causing viruses. Viral vectors 'transfect' the cell. The cell generates and presents proteins. The body responds to this as it does any other foreign substance. The aim is to get the immune system to recognize the HIV proteins and prepare long-lived memory cells that will remember the HIV proteins and act against the whole virus if a person later becomes exposed naturally through high-risk behavior. However, the body's immune response to the viral vector, mutations of the virus in the body and toxicity issues could limit effectiveness. They use viruses that are not harmful to human body *i.e.* body recognize the vector and have a reaction to it but does not cause disease once injected. The virus vector has the same infectivity as wild-type virus, but lacks the ability to reinfect and spread (replicate over and over). Another advantage of choosing a specific viral vector is that the virus does not cause disease in humans because its natural host is a rodent (as the case for our Sendai vector). For instance, several viral vectors belong to the poxvirus family and are safe because they cannot replicate in humans. The Ad5 vector is modified (by specific gene deletions on the vector or modifications to it) so that it cannot grow. Sometimes a viral vector vaccine may be used in a two-step 'prime boost' strategy. Usually, a small portion of HIV genetic material (in the form of a DNA vaccine) is given first to 'prime' the immune system, followed by a viral vector vaccine 'boost'. The hope is that the 'prime' inoculation will focus the immune response better against the HIV immunogen rather than the proteins that make up the viral vector. In naked DNA vaccines, use of the HIV material is carried out.

Therapeutic HIV vaccines

The goal of a therapeutic vaccine is to bolster the immune responses against HIV in hopes of boosting the body's ability to control HIV replication.

Dendritic cell vaccines

Dendritic cells orchestrate the body's immune response. They grab foreign bodies in the blood and present them to other immune cells to trigger powerful immune system responses to destroy the foreign invaders. HIV infection normally hijacks these important immune system responses and uses the dendritic cells to cross the mucosa and get to the CD4 cells. The major challenges in the development of a preventive HIV/AIDS vaccine have been the extensive viral strain and sequence diversity, viral evasion of humoral and cellular immune responses, coupled with the lack of methods to elicit broadly reactive neutralizing antibodies and cytotoxic T-cells.[67]

CHALLENGES FOR PURSUING NEW HIV TARGETS

Very limited information is often available on naive targets, and no established small-molecule inhibitors exist that can be used as templates for denovo drug design. Although high content screening, high throughput X-ray crystallography, structural analysis and computational modeling techniques are available, more effective synthetic methods and other technologies have been introduced into the drug discovery process over the past few years, all of which should increase the chances of finding effective inhibitors of novel targets, the outcome of which, still remains unpredictable. Information about target structure and how it relates to its function is a very important aspect in the target selection process, as it can shed light on the 'drugability' of the target of interest. The interference with target functions *via* a small molecule binding can be particularly challenging for protein–protein interactions that represent the basis of the vast majority of novel anti-retroviral targets. Another major challenge is the development of relevant screening assays that reliably model the physiological functions of the target of interest. Although, it is not always fully appreciated *e.g.* HIV-1 protease. Many early biochemical screening assays with HIV-1 protease were established and used at pH <5.0 because of the highest enzymatic activity; yet it is unlikely that this would represent the native condition for virion maturation. It can be argued that the protease inhibitor design was highly successful, as it led to multiple approved drugs,

but it should be realized that most protease inhibitors have not been identified through a naive high throughput screening under physiologically relevant conditions, but rather by a rational substrate derivatization using peptidomimetics, which is not a suitable strategy for most of the novel HIV targets. Hence, close attention should be paid to the functional validation of newly developed screening assays. In the absence of some established small molecule inhibitors, functional assay validation can only be performed by using characterized mutant variants that either reduce or eliminate the target function in the context of viral infection. These mutants should behave the same way in the target screening assay. Alternatively, if available, biologically active peptides known to interact specifically with the target of interest can be used to validate screening assays.[6]

Economical feasibility

This issue can be decisive in translating experimental results into clinical development and practice, particularly considering the current inability to provide effective antiretroviral therapy to most of the infected population, namely in low-income and developing countries. No relevant study about the subject has been conducted and one may only infer about it.[68] Nanotechnology-based systems may help in resolving some of troublesome issues, being able to revive several of these drugs. Also, the recent rising of companies and the introduction of nano-system-based drug products will further allow cost reduction of their currently relatively expensive formulation scale-up and production; innovative nanosystems are also expected to allow the enhancement of effective patent protection in a rapidly increasing pharmaceutical market segment.[69,70] Economical aspects of preventive strategies seem even more complex, particularly in the field of microbicides. Additionally, potential market dimensions, public agencies and non-governmental organizations providing financial supports are strong arguments for the development of nanotechnology-based products.[71] Finally and more importantly, indirect savings of hindering the HIV/AIDS pandemic are expected to assure economic return.[72-74]

CONCLUSION

Having reviewed the path of development for an almost overwhelming list of anti-HIV compounds, one again realizes that finding suitable molecules to treat HIV infection has not been easy. Efficacy, safety and adherence considerations demand equal attention during the formulation process. Recently licensed drugs and candidates under development have given hope that the growing arsenal has not yet reached the end of the line. The patients and their caregivers can look forward to some interesting prospects reaching the market. The biggest obstacles for HIV treatment in under-resourced countries remain co-morbidity due to late presentation for initiation of cART and limited access to salvage treatment combinations. The introduction of nanotechnology in the field of drug delivery opened exciting perspectives towards the development of new therapeutic options for the treatment of several devastating and complex diseases.In this manuscript we confirmed the ability of nanotechnology-based systems to provide a rationale approach for anti-HIV therapy and prevention. Adding to previous work in the field, new developments in nanocarrier systems for antiretroviral drugs are consolidating this strategy as a particularly interesting approach towards the improvement of HIV/AIDS treatment. One of the most interesting feasibility in nanocarrier based delivery of anti HIV/AIDS drugs is the multifunctionalization of the nanocarrier system. With multi-functionalisation, one could incorporate several therapeutic agents (e.g., HAART) in one formulation for maximum clinical effect.

Even if treatments are not providing a way to cure HIV/AIDS, nanotechnology based systems may improve drug therapy in infected patients as demonstrated by *in vitro* and animal *in vivo* studies. Various nanosystems have shown the ability to improve antiretroviral activity of several drugs, while reducing their toxicity and potentially simplifying drug regimens. Within the domain of non-polymeric nanocarriers,

ethosomes seem to be more promising and shows greater scope for polymer based functionalized nanocarriers. Also, other nanostructures that have not yet been studied for this purpose, such as cyclodextrin-drug complexes, nanogels and SLNs, are starting to be considered in the formulation of novel targets. Even so, some particular aspects of these nanosystems still need to be fully assessed in order to open road towards human clinical trials and market launch of the anti-HIV nanotechnology-based medicines.

Table 1: Nucleoside Analog Reverse Transcriptase Inhibitors (NRTIs)

Sr.	Name of drug	Application	Current status of progress
1	Zidovudine or AZT (Retrovir®, GSK Inc)	Thymidine analogue	Still in widespread use
2	Didanosine or ddI (Videx®, Bristol Myers Squibb Inc)	Purine nucleoside analogue	Widespread use
3	Zalcitibine or ddC (Hivid®, Roche Inc)	Major adverse effects	Discontinued
4	Stavudine or d4T (Zerit®, Bristol Myers Squibb Inc)	Thymidine analogue	Still used
5	Lamivudine or 3TC (Epivir®, GSK Inc)	Low genetic barrier to resistance Had only a temporary suppressive effect.	First "happy" dual combination therapy, added on to Zidovudine monotherapy
6	Emtricitabine or FTC (Emtriva®, Gilead Inc)	Related to lamivudine and longer plasma half-life	Largely replaced lamivudine in the form of convenient once-daily combination tablet with tenofovir and is also available in one pill-a-day combination with tenofovir and efavirenz, called Atripla® (Bristol-Myers Squibb, Gilead, Merck & Co. Inc)
7	Tenofovir (Viread®, Gilead Inc)	Adenosine analog	Dosed as a single daily tablet
8	Abacavir (Ziagen®, GSK Inc)	Analog of guanosine	Fifteenth approved antiretroviral drug in the United States

Table 2: Non-Nucleoside Analog Reverse Transcriptase Inhibitors (NNRTI)

Sr.	Name of drug	Application	Current status of progress
1	Efavirenz (Sustiva® or Stocrin®, Merck & Co Inc)	Nucleoside unrelated compound	One tablet daily May cause central nervous system (CNS) symptoms Known for its hepatotoxicity, which may be treatment limiting in patients with higher baseline CD4 counts
2	Nevirapine (Viramune®, Boehringer-Ingelheim Inc)	Nucleoside unrelated compound	One tablet twice daily

3	Delavirdine (Rescriptor®, Pfizer Inc)	Directly inhibits enzyme without intracellular phosphorylation	Two tablets three times a day, represent the first generation NNRTIs. Significant disadvantages are cross resistance conferred by single point mutations and the side-effect profile
4	Delavirdine, capravirine (originally by Agouron Inc, but acquired by Pfizer Inc) GSK Inc	Directly inhibits enzyme	Stopped
5	Etravirine or TMC125 (Intelence®, TibotecInc)	Second-generation NNRTIs	Approved for use in January 2008)
6	Rilpivirine or TMC278 (Tibotec Inc)	Second generation NNRTIs	Have a higher genetic barrier to resistance than their first generation counterparts. There is cross-resistance between travirine and rilpivirine. Completed 96 weeks phase IIb safety and efficacy testing in antiretroviral-naïve HIV-1 patients. Phase-III study double-blind randomized controlled trial with 2NRTIs plus either efavirenz or rilpivirine is underway. There is potential for the co-formulation: tenofovir/emtricitabine/ rilpivarine- one pill daily.
7	Family of 3-phosphoindoles INX899 (Idenix Pharmaceuticals Inc)	Second generation	Entered phase IIb clinical trials
8	Pyrazole Lersivirine or UK-453061 (Pfizer Inc)	Second generation	Entered phase IIb clinical trials
9	Sulfanyltriazoles and –tetrazoles RDEA 806 (Ardea Biosciences Inc)	Second generation	Promising anti-HIV-1 potency Has entered phase IIb clinical trials

Table 3: Recommended NNRTI based regimens for INDIA (1 NNRTI + 2 NRTIs)[11]

Sr.	NRTI	NNRTI
1 2	**Preferred** a) Zidovudine + Lamivudine or b) Tenofovir + Lamivudine or **Alternative** a) Stavudine* + Lamivudine or b) Abacavir + Lamivudine or c) Didanosine + Lamivudine	Nevirapine or Efavirenz

Table 4: Integrase inhibitors

Sr	Name of target	Application	Current status of progress
1	S1360 by Shionogi and GSK	Inhibit HIV integrase	Currently in phase II clinical trial.
2	L000870810	Inhibit HIV integrase	Investigational drug that is not yet approved by FDA
3	Raltegravir (Isentress® Merck & Co Inc),	First integrase inhibitor Inhibits the HIV enzyme integrase four times longer	Registered for use in triple-class resistant patients Registered for use in naive patients and has been included in the DHHS Guidelines for the use of antiretroviral agents in HIV-1 Infected Adults and Adolescents (Dec 1, 2009), as one of the four preferred regimens for naïve patients. Resistance may occur due to mutations in the integrase gene and cross-resistance between members of this class
4	Elvitegravir (Gilead Inc)	Integrase inhibitor	Dosed daily Phase III development Resistance may occur due to mutations in the integrase gene and cross-resistance between members of this class
5	MK-2048 (Merck Inc)	Second generation integrase inhibitor	Clinical trial

Table 5: Protease Inhibitors (PIs)

Sr	Name of target	Application	Current status of target
1	Saquinavir (Invirase®, Fortovase®, Roche Inc)	First protease inhibitor for treatment of HIV1 and HIV 2)	Released in 1995
2.	Ritonavir (Norvir® Abbott Laboratories)	Strong cytochrome P450 inhibitor	Still only available as a capsule which is heat unstable. Not available in a fixed dose combination with other compounds. Used as a pharmacokinetic booster with protease inhibitors lopinavir (in a fixed dose tablet Aluvia®)
3.	Nelfinavir (Viracept®, Agouron Inc, Roche Pharmaceuticals, then Pfizer Inc)	Bioavailibility is erratic	First non-peptidomimetic. Protease inhibitor and taken only twice daily, but still carries a high pill burden- ten tablets daily. Released in 1997 and discontinued in 2007
4.	Amprenavir	Protease inhibitor	Released its related compound in 1999

	(Agenerase®, GSK Inc)		
5.	Fosamprenavir (Lexiva®, Telzir®, GSK)	Rapidly metabolized to amprenavir	Replaced in 2004 When boosted with Ritonavir, has brought the daily PI pill count down from twenty amprenavir capsules to two fosamprenavir, which has led to the withdrawal of amprenavirb recanavir (GSK Inc), was withdrawn from development due to problems with achieving adequate therapeutic drug levels
6.	Lopinavir/ritonavir co-formulation (Kaletra®, Abbott Laboratories)	Improve bioavailability in combination with RTV	Released in 2000. Showed superior efficacy compared to nelfinavir. The tablet formulation (Aluvia®, Abbott Laboratories), was released in 2005. Lopinavir/ritonavir was licensed for once-daily use in 2008
7.	Atazanavir or BMS-232632 (Reyataz®, Bristol Myers Squibb)	Protease inhibitor	Registered for use in 2003.
8.	Tipranavir (Aptivus®, Boehringer-Ingelheim Inc) and Darunavir or TMC-114 (Prezista®, TibotecInc)	Both show improved binding with the protease enzyme and antiviral activity against resistant HIV	Released in 2005 and 2006
9.	CTP-518 (Concert Pharmaceuticals Inc in strategic alliance with GSK Inc)	Investigational protease inhibitor Based on the atazanavir compound	In phase Ib clinical study since November 2009.

Table 6: Maturation inhibitors

Name of target	Application	Current status of target
Bevirimat or DSB or PA-457 (Panacos Pharmaceuticals Inc),	BA analog (fusion inhibitors), is the first maturation inhibitor Prevents late-stage *gag* polyprotein processing. Shows activity against ARD-resistant and wild-type HIV, and synergy with ARDs from all classes	In Phase IIb clinical development

Table 7: Antiretrovirals approved for use

Sr.	NRTI	NNRTI	RI	Entry inhibitor
1. 2. 3. 4.	Zidovudine (ZDV) Stavudine (d4T) Lamivudine (3TC) Didanosine (ddI)	Nevirapine (NVP) Efavirenz (EFP) Delaiviridine (DLV)	Saquinavir (SQV) Indinavir (IDV) Ritonavir (RTV) Nelfinavir (NFV)	Enfuvirtide* (T-20)

5. 6. 7. 8. 9.	Zalcitabine* (ddC) Abacavir (ABC) Emtricitabine* (FTC) Tenofovir (TDF) (Nucleotide RTI)		Lopinavir (LPV/r) Atazanavir* (ATV) Amprenavir* (APV) Fosamprenavir*-(FPV) Tipranavir* (TPV)	
* Drugs not available in India				

Table 8: CD4-gp 120 binding inhibitors

Sr.	Name of target	Application	Current study progress
1.	DCM 205 (University of California)	Entry inhibitor that can interfere with viral host CD4 binding by interfering with the v3 loop on the gp 120 of the virus. Binding to the virus occurs without the presence of host target cell	Entered phase II clinical trials
2.	Pro-542 (Progenics Pharmaceuticals Inc)	Recombinant IgG2 antibody fusion protein which blocks the CD4 binding site on gp 120. Reduced the viral load after a single dose, well tolerated.	In phase II clinical trials
3.	BMS-488043 and BMS-377806	CD4 attachment inhibitors Small azaindole derivatives with selective binding to the gp 120 at both its X4 and R5 binding sites leads to conformational change in gp 120.	In phase I/II clinical development
4.	NBD-556 and NBD-557	Bind to unliganded HIV-1 gp 120 but not to the cellular CD4 Potent inhibitors of R5 and X4 viruses without affecting other viral targets such as RT, IN or protease The binding of NBD-556 to gp 120 is CD4 competitive	Later stage of clinical trials

Table 9: CCR5 inhibitors

Sr.	Name of target	Application	Current study progress
1.	RANTES First CCR5 inhibiting natural ligand	Member of the interleukin-8 family of cytokines Modified to remove the agonistic effects on the CCR5 pathway.	Phase 2 'CALM' clinical trials
2.	PRO-140 (Progenics Pharmaceuticals Inc)	Murine monoclonal antibody Blocking gp 120-CCR5 interaction, without preventing chemokine signaling Synergistic with maraviroc and vicriviroc Active against maraviroc and vicriviroc resistant strains *in vitro*.	In phase II development
3.	TAK-799 (Takeda	First non-peptide small molecule CCR5	Published phase II clinical trials

	Chemical Industries, Ltd)	antagonist Modified to TAK-652 to improve oral availability	result
4.	TAK-652	CCR5 antagonist	Entered clinical phase of development
5.	Maraviroc or UK-427 857 (Selzentry®, Pfizer, Inc.)	CCR5 antagonist Trials known as Motivate 1 and 2 (Maraviroc *versus* Optimized Therapy in Viremic Antiretroviral Treatment-Experienced Patients) Treatment failure of maraviroc was associated with the emergence of X4 tropic virus. Discontinuation of maraviroc resulted in reversion to R5 tropism in most cases	Approved for use in antiretroviral therapy (ART)-experienced patients with R5 tropic virus.
6.	Vicriviroc, initially known as SCH-D or SCH-417 690 (Schering-Plough Inc, or since recently Merck & Co Inc) AD101 orSCH-350 581 (Schering-Plough, Inc)	Other members of the vicriviroc family Blocks the gp 120/CD4 complex plus has CCR5 interaction	In late Phase III clinical study with treatment experienced patients (VICTOR-E 3&4) In preclinical development
7.	Aplaviroc or GW873140 (GSK Inc) GSK 163929	Another candidate	Failed in Phase II clinical trials due to hepatotoxicity Completed pre-clinical studies
8.	SCH 532706 (Schering-Plough Inc)	Small molecule CCR5 co-receptor antagonist Safe, well-tolerated and active against HIV-1 in combination with ritonavir	In early human testing.
9.	PF-232798 (Pfizer Inc)	Second generation CCR5 antagonist Has *in vitro* activity against MVC-resistant strains	In early human trials
10.	INCB 9471 (Incyte Corporation Inc)	CCR5 antagonist	In Phase II clinical development Further development of INCB 9471 is uncertain, as the company has been looking at out-licensing the compound

Table 10: CXCR4 inhibitors

Sr	Name of target	Application	Current study progress
1.	T-134, T-140 (Trimeris, Inc) and FC131 (Kureha Pharmaceuticals)	Mimicing SDF-1, analogs	Under clinical trials

2.	ALX40-4C (Allelix Biopharmaceuticals Inc)	First candidate to be tested in humans	Development was discontinued
3.	CGP 64222 (Novartis Ltd)	Has an X4 blocker which also inhibits Tat/TAR RNA interaction	Advanced phase III clinical trial
4.	KRH-2731(Kureha Chemical Industries)	X4 antagonist	Phase II clinical trial
	AMD3100 (Genzyme Corporation Inc) AMD11070 (Genzyme Corporation Inc)	Third generation related compound Highly specific X4 inhibitor	Discontinued in clinical development due to cardiac effects Entered Phase II clinical study.

Table 11: Fusion inhibitors

Name of target	Application	Current study progress
Enfuvirtide or T-20 (Fuzeon®, Trimeris Inc)	Mechanism of action is the prevention of fusion of viral and host cell membranes with resulting failure of opening of pores through which the viral capsid may enter the target cell. It mimics the HR-2 region of gp 41. By binding to the HR-1 region of the same molecule, it prevents the formation and release of the energy needed for the fusion	First non-RT or -PI targeting anti-HIV drug to be approved foruse by FDA on March 13, 2003

Table 12: Nanotechnology based system

Type of targeted system	Nanotechnology platform	Developmental stage
Protein and peptide vaccine	Liposomes, nanoemulsion, PLA nanoparticles, nanopartpoly (γ-glutamic acid) nanoparticles	Preclinical
DNA vaccine	Liposomes, nanoemulsion, PLA nanoparticles	Preclinical
Inactivated viral particle	Polystyrene nanosphere	Preclinical
Microbicide	L-lysine dendrimer, PLGA nanoparticle, PLGA Nanoparticles, lipid, cholesterol conjugation	Preclinical I/II Preclinical

Abbreviations
AIDS, Accuired Immunodeficiency Syndrome
HIV, Human Immunodeficiency Virus
RT, Reverse Transcriptase
cDNA, complementary DNA
mRNA, messenger RNA;
RNase H, ribonuclease H;
gp 120 + gp 41, extracellular and intracellular domains

REFERENCES

1. Katzung, BG (2006), "***Antiviral Agents; Basic and Clinical Pharmacology***", 10, McGraw-Hill, New York, 798.
2. Gupta, SD; Ramteke, S; Gupta, A and Moorthy NSHN (2007), "AIDS, a review of targets and approaches for treatments", ***Ind J Pharm Sci***, Vol. 69, 173-179.
3. Coogan, MM; Greenspan, J and Challacombe, SJ (2005), "Oral Leisions in infection with human immunodeficiency virus", ***Bull World Health Organ***, Vol. 83, 700-706.
4. Levy, JA (2007), "***HIV and the pathogenesis of AIDS***", 3, American Society of Microbiology Press; Washington DC.
5. Brunton, L and Parker, K; Blumenthal, D and Buxton, L (2011), "***Antiretroviral agents; Goodman and Gilman's Manual of***

Pharmacology and Therapeutics", 12, McGraw-Hill, New York, 1273.

6. Barre-Sinoussi, F; Chermann, JC and Rey, F (1983), "Isolation of a T-lymphotrophic retrovirus from a patient at risk for Acquired Immune Deficiency Syndrome (AIDS) ", ***Science***, Vol. 220, 868-871.
7. Portilla, J; Boix, V; Garcia-Henarejos, JA; *et al (*2005), "Quadruple-2 protease inhibitors (PI)-therapy does not accelerate viral decay and suppression in PI-naive HIV-1 infected patients with severe immunosuppression and high viral load as compared with standard triple therapy", ***Int J STD AIDS,*** Vol. 16, 807-810.
8. Maggiolo, F; Ripamonti, D; Callegaro, A; *et. al. (*2005), "Quadruple-drug induction HAART in advanced HIV infection", ***HIV Clin Trials***, Vol. 6, 1-4.
9. Wong, JK; Hezareh, M; Gunthard, HF; *et al (*1997), "Recovery of replication-competent HIV despite prolonged suppression of plasma viremia", ***Science***, Vol. 278, 1291-1295.
10. DHHS (2009), ***"Guidelines for the Use of Antiretroviral Agents in HIV-1 infected adults and adolescents***", In December 1; 2009.
11. Gupta, SB; Pujari, SN; Joshi, SR and Patel, AK (2006), "API Consensus Guidelines for use of Antiretroviral Therapy in Adults (API-ART Guidelines)", ***J Asso Physician India***, Vol. 54, 57-74.
12. Martin, DE; Blum, R; Doto, J; Galbraith, H and Ballow, C (2007), "Multiple-dose pharmacokinetics and safety of bevirimat; a novel inhibitor of HIV maturation; in healthy volunteers", ***Clin Pharmacokinet***, Vol. 46, 589-598.
13. Martin, DE; Blum, R; Wilton, J; *et. al. (*2007), "Safety and pharmacokinetics of Bevirimat (PA-457); a novel inhibitor of human immunodeficiency virus maturation; in healthy volunteers", ***Antimicrob Agents Chemother***, Vol. 51, 3063-3066.
14. Martin, DE; Salzwedel, K and Allaway, GP (2008), "Bevirimat, a novel maturation inhibitor for the treatment of HIV-1 infection", ***Antivir Chem Chemother***, Vol. 19, 107-113.
15. Temesgen, Z and Feinberg, JE (2006), "Drug evaluation, bevirimat-HIV Gag protein and viral maturation inhibitor", ***Curr Opin Investig Drugs***, Vol. 7, 759-765.
16. Gill, CJ; Griffith, JL; Jacobson, D; *et. al.* (2002), "Relationship of HIV viral loads; CD4 counts; and HAART use to health-related quality of life", ***J Acquir Immune Defic Syndr***, Vol. 30, 485-492.
17. Macpherson, JL; Ely, JA and Sun, LQ; Symonds, GP (1999), "Ribozyme in gene therapy of HIV-1", ***Front Biosci***, Vol. 4, D497-D505.
18. Johnson, VA; Brun-Vezinet, F; Clotet, B; *et al (*2008), "Update of the drug resistance mutations in HIV-1", ***Top HIV Med,*** Vol. 16, 138–145.
19. Tymchuk, CN and Currier, JS (2008), "The safety of antiretroviral drugs", ***Exp Opin Drug Safety***, Vol. 7, 1-4.
20. Carr, A (2003), "Toxicity of antiretroviral therapy and implications for drug development", ***Nat Rev Drug Discov,*** Vol. 2, 624–634.
21. Drugs for HIV infection (2009)", "***Treat Guidel Med Lett***, 11–22.
22. Dalgleish, A; Beverley, P; Clapham, P; *et. al.* (1984), "The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus", ***Nature,*** Vol. 312, 763–767.
23. Sattentau, Q and Weiss, R (1988), "The CD4 antigen, physiological ligand and HIV receptor", ***Cell,*** Vol. 52, 631–633.
24. Hoxie, J (1991), "Hypothetical assignment of intrachain disulfide bonds for HIV-2 and SIV envelope glycoproteins", ***AIDS Res Hum Retrovir***, Vol. 7, 495–499.
25. Leonard, C; Spellman, M; Riddle, L; *et al* (1990), "Assignment of intrachain disulfide bonds and characterization of potential glycosylation sites of the type 1 recombinant HIV envelope glycoprotein (gp 120) expressed in Chinese hamster ovary cells", ***J Biol Chem***, Vol. 265, 10373–10382.

26. Madani, N; Perdigoto, A; Srinivasan, K; *et al.* (2004), "Localized changes in the gp120 envelope glycoprotein confer resistance to HIV entry inhibitors BMS-806 and #155", ***J Virol***, Vol. 78, 3742–3752.
27. Kwong, P; Wyatt, R; Robinson, J; *et al.* (1998), "Structure of an HIV gp 120 envelope glycoprotein in complex with the CD4 receptor and a neutralizing human antibody", ***Nature***, Vol. 393, 648–659.
28. Myszka, D; Sweet, R; Hensley, P; *et al.* (2000), "Energetics of the HIV gp120-CD4 binding reaction", ***Proc Natl Acad Sci USA***, Vol. 97, 9026–9031.
29. Kwong, P; Wyatt, R; Majeed, S; *et al.* (2000), "Structures of HIV-1 gp120 envelope glycoproteins from laboratory-adapted and primary isolates", ***Structure***, Vol. 8, 1329–1339.
30. Wyatt, R; Kwong, P; Desjardins, E; *et al.* (1998), "The antigenic structure of the HIV gp120 envelope glycoprotein", ***Nature***, Vol. 393, 705–11.
31. Tsamis, F; Gavrilov, S; Kajumo, F; *et al.* (2003), "Analysis of the mechanism by which the small-molecule CCR5 antagonists SCH-31125 and SCH-350581 inhibit HIV type 1 entry", ***J Virol***, Vol. 77, 5201–5208.
32. Donzella, G; Schols, D; Lin, S; *et al.* (1998), "AMD3100; a small molecule inhibitor of HIV-1 entry *via* the CXCR4 co-receptor", ***Nat Med***, Vol. 4, 72–77.
33. Murakami, T; Nakajima, T; Koyanagi, Y; *et al.* (1997), "A small molecule CXCR4 inhibitor that blocks T cell line-tropic HIV-1 infection", ***J Exp Med***, Vol. 186, 1389–1393.
34. Labrosse, B; Brelot, N; Heveker, N; *et al.* (1998), "Determinants for sensitivity of HIV coreceptor CXCR4 to the bicyclam AMD3100", ***J Virol***, Vol. 72, 6381–6388.
35. Brelot, A; Heveker, N; Pleskoff, O; *et al.* (1997), "Role of the first and third extracellular domains of CXCR4 in HIV coreceptor activity", ***J Virol,*** Vol. 71, 4744–4751.
36. Poveda, E; Briz, V and Soriano, V (2005), "Enfuvirtide; the first fusion inhibitor to treat HIV infection", ***AIDS Rev,*** Vol. 7, 139–147.
37. Weiss, C (2003), "HIV-1 gp41, Mediator of fusion and target for inhibition", ***AIDS Rev,*** Vol. 5, 214–421.
38. Kruger, K; Grabowski, PJ; Zaug, AJ; *et al* (1982), "Self-splicing RNA, autoexcision and autocyclization of the ribosomal RNA intervening sequence of Tetrahymena", ***Cell,*** Vol. 31, 147–157.
39. Guerrier-Takada, C; Gardiner, K; Marsh, T; Pace, N and Altman, S (1983), "The RNA moiety of ribonuclease P is the catalytic subunit of the enzyme", ***Cell,*** Vol. 35, 849–857.
40. Sarver, N; Cantin, EM; Chang, PS; *et al* (1990), "Ribozymes as potential anti-HIV-1 therapeutic agents", ***Science,*** Vol. 247, 1222–1225.
41. Zaia, J; Chatterjee, S; Wong, KK; Elkins, D; Taylor, NR and Rossi, JJ (1992), "Status of Ribozyme and Antisense-Based Developmental Approaches for Anti-HIV-1 Therapy", ***Ann New York Acad Sci,*** Vol. 660, 95–106.
42. Yu, M; Poeschla, E and Wong-Staal F; (1994), "Progress towards gene therapy for HIV infection", ***Gene Ther,*** Vol. 1, 13–26.
43. James, HA and Gibson, I (1998), "The Therapeutic Potential of Ribozymes", ***Blood,*** Vol. 91, 371–382.
44. Rossi, JJ (1994), "Practical ribozymes. Making ribozymes work in cells", ***Curr Biol,*** Vol. 4, 469–471.
45. Rossi, JJ and Sarver, N (1992), "Catalytic antisense RNA (ribozymes), Their potential and use as anti-HIV-1 therapeutic agents", ***Adv Exp Med Biol,*** Vol. 312, 95–109.
46. Rossi, JJ; Elkins, D; Zaia, JA and Sullivan, S (1992), "Ribozymes as anti-HIV-1 therapeutic agents, principles; applications; and problems", ***AIDS Res Hum Retrovir,*** Vol. 8, 183–189.
47. Kijima, H; Ishida, H; Ohkawa, T; Kashani-Sabet, M and Scanlon, KJ (1995),

"Therapeutic applications of ribozymes", ***Pharmacol Ther,*** Vol. 68, 247–267.

48. Wong-Staal, F; Poeschla, EM and Looney, DJ (1998), "A controlled; Phase 1 clinical trial to evaluate the safety and effects in HIV-1 infected humans of autologous lymphocytes transduced with a ribozyme that cleaves HIV-1 RNA", ***Hum Gen Ther,*** Vol. 9, 2407–2425.
49. Westaway, SK; Cagnon, L; Chang, Z; *et al (*1998), "Virion encapsidation of Trna (3Lys)-ribozyme chimeric RNAs inhibits HIV infection", ***Antisense Nucleic Acid Drug Dev,*** Vol. 8, 185–197.
50. Westaway, SK; Cagnon, L; Chang, Z; *et al (*1995), "A chimeric tRNA (Lys3)-ribozyme inhibits HIV replication following virion assembly", ***Nucleic Acids Symp Ser,*** Vol. 33, 194–199.
51. Yamada, O; Kraus, G; Luznik, L; Yu, M and Wong-Staal, F (1996), "A chimeric human immunodeficiency virus type 1 (HIV-1) minimal Rev response element-ribozyme molecule exhibits dual antiviral function and inhibits cell–cell transmission of HIV-1", ***J Virol,*** Vol. 77, 1596–1601.
52. Christoffersen, RE and Marr, JJ (1995), "Ribozymes as human therapeutic agents", ***Med Chem,*** Vol. 38, 2023–2037.
53. Vyas, TK; Shah, L and Amiji, MM (2006), "Nanoparticulate drug carriers for delivery of HIV/AIDS therapy to viral reservoir sites", ***Expert Opin Drug Deliv,*** Vol. 3, 613–628.
54. Shahiwala, A and Amiji, MM (2007), "Nanotechnology-based delivery systems in HIV/AIDS therapy", ***Future HIV Ther,*** Vol. 1, 49–59.
55. Hillaireau, H; LeDoan, T; Besnard, M; *et al (*2006), "Encapsulation of antiviral nucleotide analogues azidothymidine-triphosphate and cidofovir in poly(iso-butylcyanoacrylate) nanocapsules", ***Int J Pharm,*** Vol. 324, 37–42.
56. Hillaireau, H; LeDoan, T; Chacun, H; Janin, J and Couvreur, P (2007), "Encapsulation of mono-and oligo-nucleotides into aqueous-core nanocapsules in presence of various water-soluble polymers", ***Int J Pharm,*** Vol. 331, 148–152.
57. Choi, SU; Bui, T and Ho, RJ (2008), "pH-dependent interactions of indinavir and lipids innanoparticles and their ability to entrap a solute", ***J Pharm Sci,*** Vol. 97, 931–943.
58. Csaba, N; Garcia-Fuentes, M and Alonso, MJ (2009), "Nanoparticles for nasal vaccination", ***Adv Drug Deliv Rev,*** Vol. 61, 140–157.
59. VanHoute, AJ and Snippe, H (1984), ***"Liposomes as carriers of immunogenic determinants in Liposome Technology"***, 2, CRC Press Inc, Boca Raton, 125.
60. Gregoriadis, G; Florence, AT and Patel, HM. (1993), ***"Liposomes in Drug Delivery"***, Harwood Academic Publishers; Amsterdam.
61. Woodle, MC and Lasic, DD (1992), "Sterically stabilized liposomes", ***Biochim Biophys Acta,*** Vol. 1113, 171–199.
62. Speiser, P. Lipid Nanopelletsals Trager system fur Arzneimittel zurperoralen Anwendung. Eur Patent EP 0167825; 1990.
63. Domb, AJ. Lipospheres for controlled delivery of substances; US Patent 188837; 1993.
64. Muller, RH and Peters, K (1998), "Nanosuspensions for the formulation of poorly soluble drugs. I. Preparation by a size-reduction technique", ***Int J Pharm,*** Vol. 160, 229–237.
65. Ford, J; Woolfe, J and Florence, AT (1999), "Nanospheres of cyclosporin A, poor oral absorption in dogs", ***Int J Pharm,*** Vol. 183, 3–6.
66. Merisko-Liversidge, E; Sarpotdar, P; Bruno, J; *et al (*1996), "Formulation and antitumor activity evaluation of nanocrystalline suspensions of poorly soluble anticancer drugs", ***Pharm Res,*** Vol. 13, 272–278.
67. Fahmy, TM; Demento, SL; Caplan, MJ; Mellman, I and Saltzman, WM (2008), "Design opportunities for actively targeted nanoparticle vaccines", ***Nanomed,*** Vol. 3, 343–355.
68. Sahoo, SK and Labhasetwar, V (2003), "Nanotech approaches to drug delivery and imaging", ***Drug Discov Today,*** Vol. 8, 1112–1120.

69. Lux Research (2004), ***"Sizing Nanotechnology's Value Chain"***, New York.
70. Bawarski, WE; Chidlowsky, E; Bharali, DJ and Mousa, SA (2008), "Emerging nanopharmaceuticals", ***Nanomedicine,*** Vol. 4, 273–282.
71. Pharmaco-Economics Working Group (2002), ***"The Economics of Microbicide Development, a Case for Investment; Rockefeller Foundation Microbicide Initiative"***, New York.
72. Wilson, DP and Coplan, PM (2008), "Mathematical models and health economic aspects of microbicides", ***Curr Opin HIV AIDS,*** Vol. 3, 587–592.
73. Berry, CC (2008), "Intracellular delivery of nanoparticles *via* HIV-1 tatpeptide", ***Nanomedicine,*** Vol. 3, 357–365.
74. Wan, L; Zhang, X; Gunaseelan, S; *et al* (2006), "Novel multi-component nanopharmaceuticals derived from poly(ethylene) glycol; retroinverso-Tat nonapeptide and saquinavir demonstrate combined anti-HIV effects", ***AIDS Res Ther,*** Vol. 3, 12-14.

Correspondence Author:
Aaditi Mukadam
Department of Pharmacology, Vivekanand Education Society's College of Pharmacy, Mumbai, India
Email : aaditimukadam@yahoo.in

Cite This Article: Aaditi, Mukadam; Gaurav M, Doshi and Pratip K, Chaskar (2014), "Recent advances and management appraisal for the chemotherapy of AIDS ", ***Pharmacophore***, Vol. 5 (1),01 -23.