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Novel targets for HIV drug delivery

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ABSTRACT:

Untreated HIV infection is characterized by a gradual deterioration of immune function. Most notably, crucial immune cells known as CD4 positive T-lymphocytes are disabled and killed during the typical course of infection. These T-lymphocyte cells play a central in the immune response. The study of HIV structure, genome, and its life cycle has revealed many exciting target sites for acquired immunodeficiency syndrome treatment. Many conventional treatments for acquired immunodeficiency syndrome are merely capable of prolonging the patient's life but are unable to completely eradicate the virus as the virus mutates rapidly and developed resistance. So there are many recent novel approaches under consideration like integrase inhibitors, fusion inhibitors, and ribozymes for the treatment of acquired immunodeficiency syndrome.

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INTRODUCTION:

Human immunodeficiency virus (HIV) is a retrovirus that can lead to acquired immunodeficiency syndrome (AIDS), a condition in humans in which the immune system begins to fail, leading to life-threatening opportunistic infections. Previous names for the virus include human T-lymphotropic virus-III (HTLV-III), lymphadenopathy-associated virus (LAV), or AIDS-associated retrovirus (ARV). HIV infection in humans is now pandemic. As of January 2006, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) estimate that AIDS has killed more than 25 million people since it was first recognized on December 1, 1981, making it one of the most destructive pandemics in recorded history. In 2005 alone, AIDS claimed an estimated 2.4 to 3.3 million lives, of which more than 570,000 were children. It is estimated that about 0.6 % of the World's

living population is infected with HIV. A third of these deaths are occurring in sub-Saharan Africa, retarding economic growth and increasing poverty. According to current estimates, HIV is set to infect 90 million people in Africa, resulting in a minimum estimate of 18 million orphans. Antiretroviral treatment reduces both the mortality and the morbidity of HIV infection, but routine access to antiretroviral medication is not available in all countries [1].

HIV primarily infects vital cells in the human immune system such as helper T cells (specifically $CD4^+$ T cells), macrophages, and dendritic cells. HIV infection leads to low levels of $CD4^+$ T cells through three main mechanisms: firstly, the direct viral killing of infected cells; secondly, increased rates of apoptosis in infected cells; and thirdly, the killing of infected $CD4^+$ T cells by CD8 cytotoxic lymphocytes that recognize infected cells. When $CD4^+$ T cell numbers decline below a critical level, cell-mediated immunity is lost, and the body becomes progressively more susceptible to opportunistic infections. If untreated, eventually most HIV-infected individuals develop AIDS and die; however, about one in ten remains healthy for many years, with no noticeable symptoms. Treatment with antiretrovirals, where available, increases the life expectancy of people infected with HIV. It is hoped that current and future treatments may allow HIV-infected individuals to achieve a life expectancy approaching that of the general public [2].

STRUCTURE OF HIV VIRUS:

The structure of the HIV virus is presented in Fig 1. This virus consists of envelope protein and gag protein. Its nucleic acid is single-stranded RNA.

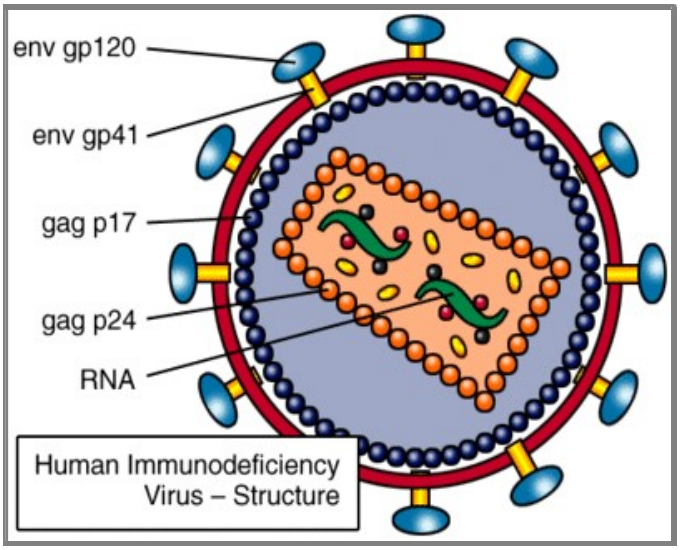

Fig 1. Structure of HIV virus.

DEADLY HIV VIRUS [2,3]:

Human Immunodeficiency Virus (HIV) presents a complex knot for scientists to unravel. After initial contact and attachment to a cell of the immune system (e.g., lymphocytes, monocytes), there is a cascade of intracellular events. The end product of these events is the production of massive numbers of new viral particles, the death of the infected cells, and the ultimate devastation of the immune system. However, the knot is becoming unravelled. Human Immunodeficiency Virus (HIV) is a retrovirus that causes irreversible destruction of the immune system, leading to the occurrence of opportunistic infections and malignancies. During the last decade, even though attempts were being made to eradicate HIV, it was found that eradication of HIV is highly unlikely, and effective antiretroviral therapy is required on a long-term basis to maintain viral suppression and reduce disease progression.

Human Immunodeficiency Virus (HIV) is a retrovirus that can be subdivided into HIV-1 and HIV-2. Both types of HIV infection deplete the helper T-lymphocytes, resulting in the continued destruction of the immune system, leading to the occurrence of opportunistic infections and malignancies. Understanding how the human immunodeficiency virus (HIV) works inside the human cell gives scientists important clues about how to attack it at its most vulnerable point.

LIFE CYCLE OF HIV VIRUS [4-6]:

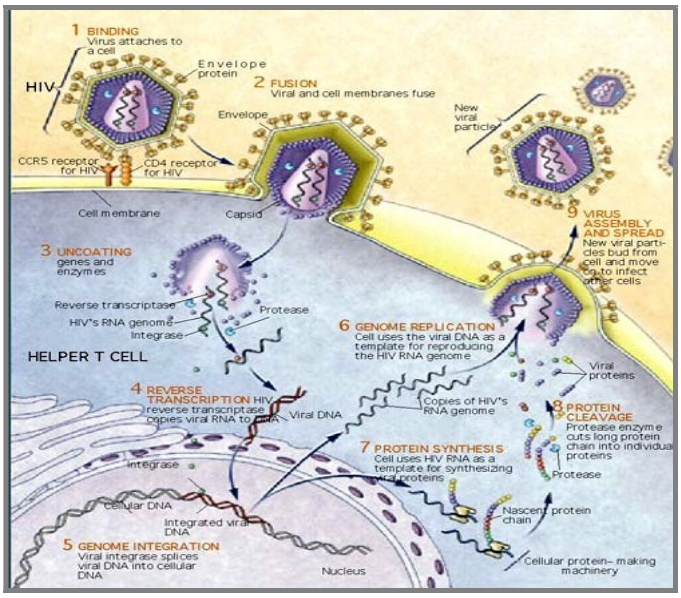

Fig 2. Life Cycle of HIV virus.

Anti-HIV agents. Some facts about HIV: HIV – the Human Immunodeficiency Virus is the retrovirus that causes AIDS Discovered independently by Luc Montagnier.

Stage 1a - Binding:

HIV infection begins with the interaction of the HIV glycoprotein (gp) 120 with the CD4 molecule on the surface of the target cell. Following CD4 binding, a centre material change in the HIV gp 120/41 complexes is induced by the interaction of gp 120 with the chemokine receptors CCR5 or CXCR4. This change in conformation exposes gp 41 allowing it to initiate fusion of the membranes. The significant role of CCR5 in this process has been revealed upon the observation that individuals homozygous for mutations within CCR5 are resistant to infection by HIV-1.

Stage 2 – Penetration:

After the attachment is completed, viral penetration occurs. Penetration allows the nucleocapsid, the genetic code of the virus to be injected directly into the cell's cytoplasm. gp120 actually contains three sugar-coated proteins and, once gp 120 attaches itself to CD4, these three proteins spread apart. This allows the gp 41 protein, which is normally hidden by the gp 120 proteins, to become exposed and bind to the chemokine receptor. Once this has occurred, the viral envelope and the cell membrane are brought into direct contact and essentially melt into each other.

Drugs called fusion inhibitors prevent the binding of gp41 and the chemokine receptor. T-20 (enfuvirtide, Fuzeon), an experimental fusion inhibitor that is nearing FDA approval, binds to a portion of gp41, preventing it from binding to the chemokine receptor.

Stage 3 - Uncoating:

Partial uncoating of the viral core occurs to expose the viral RNA. Once in the cell cytoplasm, the conversion of the viral RNA into double-stranded DNA commences as the viral reverse transcriptase becomes active

Stage 4 - Reverse transcriptase:

Reverse transcriptase synthesizes a double-stranded DNA copy of the single-stranded viral RNA generating a provirus.

Stage 5 - Integration:

The viral DNA migrates to and enters the host cell nucleus (a process facilitated by the HIV proteins vpr and MA) and becomes integrated into the cell DNA with the help of the enzyme integrase. The provirus can then remain latent or be active, generating products for the generation of new virions.

Stage 6 - Transcription:

Inside the nucleus, RNA polymerase II transcribes viral DNA into mRNA.

The 9kb (gnomic) mRNA is used for:

- Synthesis of the gag and gag-pol polyproteins.
- As the genetic material for the new virions formed.
- The 9kb mRNA can be spliced to yield 4kb and 2kb mRNAs. The 4kb viral mRNA is used to synthesize:
- gp 120.
- gp 41.
- Three regulating proteins - vif, vpr, and vpu.
- The 2kb viral mRNA is used to synthesize 3 regulatory proteins: tat, rev, and nef.

Stage 7a - Translation:

The viral mRNA leaves the nucleus. The translation of the viral mRNA results in the synthesis of three polyproteins:

- ENV gp 160 - containing gp 120 and gp 41
- GAG p55 - containing MA (matrix), CA (capsid), and NC (nucleocapsid protein)
- GAG-POL p 160 - containing MA (matrix), CA (capsid), PR (proteinase), (RT) reverse transcriptase, and INT (integrase)
- p55 and p160 are generated from the same mRNA strand by the process of ribosome frameshifting.

Stage 7b - Envelope Processing:

The env (gp160) proteins pass through the entry regulator and Golgi apparatus to be processed into gp120 and gp41 HIV envelope proteins. During movement through the Golgi apparatus, glycosylation of gp120 occurs

Stage 8 - Assembly:

The gag and gag-pol polyproteins associate with the inner surface of the plasma membrane and interact with gp41 present in the plasma membrane. Some of the 9 kb viral RNA interacts with the nucleocapsid portion of p55.

As p55 and p160 accumulate on the inner surface of the plasma membrane, they aggregate and commence assembly to form the virion. As assembly continues, the structure extrudes from the cell.

Stage 9 - Extrusion:

As the virus buds from the cell, it acquires a lipid coat, carrying the gp 120 and gp 41 proteins.

The virus is extruded into extra-cellular space in this immature state.

Stage 10 – Maturation:
During (or soon after) the budding of the new HIV particle from the host cell membrane, the viral proteinase in p160 becomes active, resulting in the cleavage of p160 and p56 into the various subunits and generating the mature form of HIV. This processing of p160 and p56 by the viral proteinase is essential for the generation of infectious viruses.

HIV INFECTION CYCLE [7,8]:

- The first step in the attack on helper T-cells is attaching to the cell. Helper-T cells contain proteins called CD4 proteins in their cell membrane that extend outside of the cell. Normally, these proteins help the cells to bind to antigens in order to stimulate the activation of helper T cells, and they are also required for normal T cell development. Unfortunately, however, CD4 proteins also function as receptors for iv, allowing the virus to attach itself to the cell and thereby gain access to the cell's biochemical machinery.
- Once the virus has attached to a helper T cell, it injects its genetic information (as RNA) into the cell, along with the enzyme reverse transcriptase.
- Reverse transcriptase catalyzes the production of DNA from the viral RNA, making a DNA copy of the virus's genetic material. This DNA copy is capable of incorporating itself into the cell's genetic material because it is now in the same form as the cell's chromosomes. Hence, the step catalyzed by reverse transcriptase is one of the most important steps in the infection cycle.
- The viral DNA copy then enters the nucleus of the infected helper T cells, where it is incorporated into the cell's genetic material (i.e., chromosomes).
- Using the cell's own DNA-replication mechanisms, the viral DNA replicates.
- Using the cell's mechanism for producing proteins from genetic information contained in DNA, many copies of the proteins needed by the virus are made from the replicated HIV DNA. As a part of this step, RNA copies of the viral DNA as made.
- When they are first synthesized, the proteins are too long to be assembled into new viruses. They must be cut to their proper size. The HIV enzyme protease, which is produced by the cell's biochemical machinery from the viral DNA incorporated into the cell's chromosomes, catalyzes the cutting of these proteins to their proper size.
- New HIV particles are assembled inside the cell from the cut viral proteins and the viral RNA copies.
- Once assembled, the new viruses then burst out of the host cell (killing it) and invade new cells, continuing the infection.

TARGETS IN HIV DRUG DEVELOPMENT [9,10]:

In recent years, remarkable progress has been achieved in the treatment of patients infected with HIV. This progress involves not only the improvement of previously known drugs but also the introduction of new classes of anti-HIV agents.

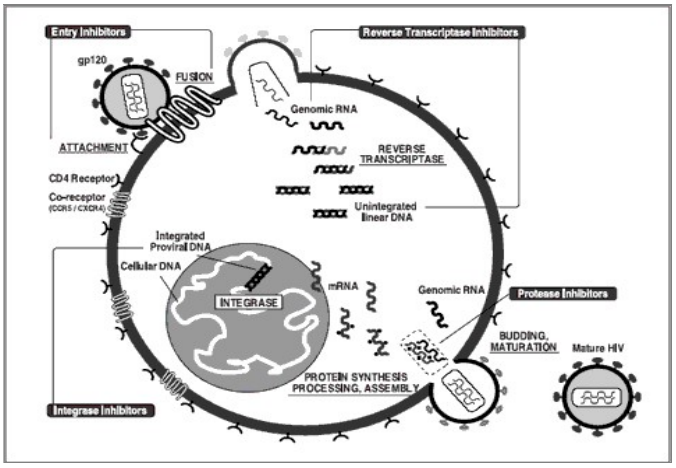

Fig 3. Inhibitors at various sites in the HIV life cycle.

Hiv-1 entry inhibitor [11]:

A great deal of progress has been made in understanding the mechanism of human immunodeficiency virus entry into target cells. Landmark discoveries such as the identification of viral coreceptors and the structure of a portion of the viral envelope protein (Env) bound to its receptor provided important insight into how Env mediates the fusion of the viral and cellular membranes. This knowledge has been successfully applied to the development of inhibitors that target discrete steps of the entry process. Some of these compounds efficiently block HIV-1 replication in vitro and are currently being evaluated in clinical trials. The drugs used for entry inhibition are HNG-105 and MARAVIROC. The drugs currently in use are Efuvirtide and Fuzeon.

CD4 receptor- (Cluster antigen detergent4 factor):
The Human Immunodeficiency Virus is a type of retrovirus, which are single a stranded RNA viruses that can infect a number of different cells, including CD4-bearing macrophages and T-helper lymphocytes within

the host. HIV has proteins on its envelope that are strongly attracted to the CD4+ surface receptor on the outside of the T4-cell.

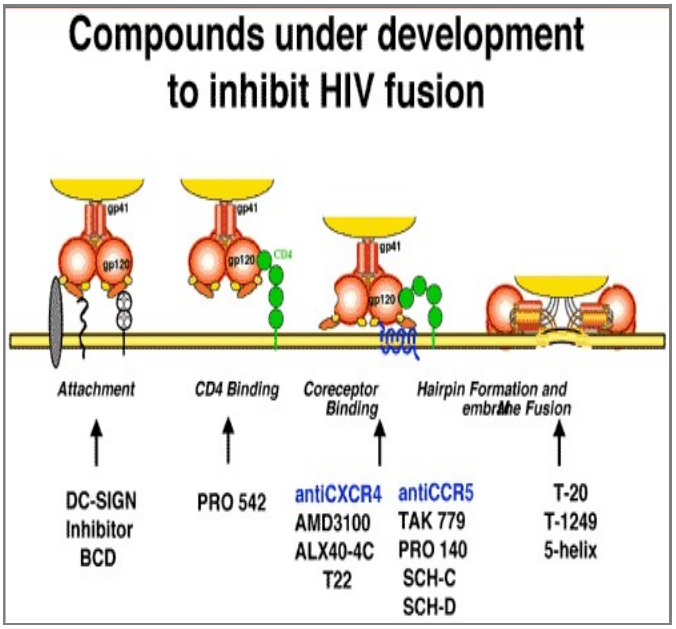

Fig 4. Compounds that inhibit HIV fusion.

When HIV binds to a CD4+ surface receptor, it activates other proteins on the cell's surface, allowing the HIV envelope to fuse to the outside of the cell [12].

Chemokine receptor:

Historically, therapeutic benefit in the treatment of human immunodeficiency virus infection (HIV-1) infection has been best achieved by targeting viral proteins like HIV protease involved in viral replication rather than host cell proteins, like CD4, which facilitate the process of viral infection. Two discoveries in 1996 presented a novel opportunity to redress this issue: 1) The understanding that heptahelical G-protein coupled chemokine receptors on the surface of T cells and macrophages functioned together with CD4 to mediate viral entry, and 2) The observation that CD4 positive T-cells from individuals homozygous for the CCR5 delta 32 null alleles were resistant to infection by macrophage-tropic strains of the virus *in vitro* and *in vivo*. Since that time, data demonstrating that selective blockade of two chemokine receptors, CCR5 and CXCR4, by small molecule chemokine receptor antagonists or receptor-directed biologics could robustly inhibit the infection of human peripheral blood mononuclear cells (PBMCs) by macrophage-tropic and T-cell line tropic strains respectively in vitro has validated this potential approach to therapy [13].

The HIV-1 Tat transactivator protein:

Central to HIV infection is the transactivator protein Tat, which plays a critical role in the nucleus during the HIV infectious cycle, by binding the transactivation-responsive region (TAR) and thereby enhancing transcriptional elongation. Tat appears to gain nuclear entry through a novel mechanism, independent of the normal cellular importin/Ran-dependent pathways and regulated by a cytoplasmic retention mechanism. Since blocking Tat nuclear import is likely to prevent HIV infection, a detailed delineation of Tat's nuclear import pathway is critical to assessing its viability as a therapeutic target. Other feasible anti-HIV therapies include approaches to inhibit Tat-TAR interaction [14].

HIV-1 capsid protein:

During the assembly stage of the human immunodeficiency virus (HIV) replication cycle, several thousand copies of the viral Gag polyprotein associate at the cell membrane and bud to form an immature, non-infectious virion. The gag is subsequently cleaved by the protease, which liberates the capsid proteins for assembly into the polyprotein shell of the central core particle (or capsid) of the mature virus. Viral infectivity is critically dependent on capsid formation and stability, making the capsid protein a potentially attractive antiviral target. Tang C, Loeliger *et al*. reported compounds that bind to an apical site on the N-terminal domain of the HIV-1 capsid protein and inhibit capsid assembly *in vitro*. One compound, N-(3-chloro-4-methylphenyl)-N'-[2-[([5-[(dimethylamino)-methyl]-2-furyl]-methyl)-sulfanyl]ethyl]urea) (CAP-1), is well tolerated in cell cultures, enabling in vivo antiviral and mechanistic studies.

CAP-1 inhibits HIV-1 infectivity in a dose-dependent manner but does not interfere with viral entry, reverse transcription, integration, proteolytic processing, or virus production, indicating a novel antiviral mechanism. Significantly, virus particles generated in the presence of CAP-1 exhibit heterogeneous sizes and abnormal core morphologies, consistent with inhibited CA-CA interactions during virus assembly and maturation. These findings lay the groundwork for the development of assembly inhibitors as a new class of therapeutic agents for the treatment of AIDS [15].

Control of HIV-1 replication by RNA interference:

Recent works have shown that the use of RNAi could inhibit HIV-1 replication by targeting viral or cellular

genes. RNAi can be considered a gene-specific therapeutic option for controlling HIV-1 replication. However, the control of HIV-1 replication has become complex because of the limited effectiveness of existing anti-HIV-1 agents and the high-speed mutation rate of the HIV-1 genome. Careful assessments are required for the potential of RNAi as a gene therapy approach for controlling HIV-1 replication [16].

HIV-1 integrase:

The integration of the HIV genome into the cellular chromosome, a process catalyzed by the viral enzyme integrase, has been shown to be essential for viral replication. Since HIV integrase has no direct cellular counterpart, it presents itself as an attractive Integration that occurs following the production of the double-stranded viral DNA by the viral DNA polymerase, reverse transcriptase.

Integrase acts to insert the proviral DNA into the host chromosomal DNA, a step that is essential for HIV replication.

Integrase catalyzes two reactions;

- The 3'-end processing, in which two deoxynucleotides are removed from the 3' ends of the viral DNA.
- The strand transfer reaction, in which the processed 3' ends of the viral DNA are covalently ligated to the host chromosomal DNA.
- Integration of the proviral DNA is essential for the subsequent transcription of the viral genome which leads to the production of new viral genomic RNA and viral proteins needed for the production of the next round of infectious viruses. Essentially, integrase is a key step in allowing viral DNA to become a permanent member of the host genome. This integrated proviral DNA is then translated using host cell machinery into viral proteins [17].

HIV integrase:

HIV integrase is a protein produced from the C-terminal portion of the pol gene product. Integrase, therefore, is an attractive potential target for new anti-HIV therapeutics. In November 2005, data from a phase 2 study of an investigational HIV integrase inhibitor, MK-0518, demonstrated that the compound had potent antiviral activity, and the manufacturer, Merck, is undertaking further clinical studies. On October 12th, 2007, the Food and Drug Administration approved the integrase inhibitor RALTEGRAVIR (MK-0518, brand name IsentressTM) [18].

The First Two Integrase Inhibitors:

The stage in which HIV genetic material is integrated into human DNA is not fully understood. For that reason, developing an integrase inhibitor that fits the bill and was effective has not been easy. Many have failed very early in clinical trials. However, there are two in the HIV medication pipeline currently that are showing great promise because they act in a different way than their failed predecessors. To explain, viral integration takes place in three stages: the first integrase binds to the cellular DNA; the next works on a specific area of the viral DNA, preparing it for integration; finally, the process viral strand is transferred into the host cell. Many of the first integrase inhibitors that failed worked on the first two stages of integration. The two new integrase inhibitors target the third stage when the viral strand is transferred to the host cell [19].

MK-0518 and GS-9137 - The Two New Integrase Inhibitors:

So, after several trials and many failures, two new integrase inhibitors have emerged and are showing promise. If they prove successful in trials, they represent the first in a brand-new class of HIV medication, which represents new hope for those who have exhausted all conventional combinations [20].

MK-0518:

Merck, the maker of the protease inhibitor, CRIXIVAN, currently has the first integrase inhibitor to enter Phase II trials, MK-0518. There have been two studies of note: In the first study people taking only the experimental drug for 10 days saw a 98 % reduction in their viral load after those 10 days. The participants tolerated the drug very well with minor complaints of headache and dizziness with some fatigue [21].

In a larger study that tested several different doses of the drug in patients with HIV resistance, it was found that over 80 % of patients saw a significant decline in their viral loads with the lowest dose. Ironically the study also suggested that lower doses of the drug actually were more effective in controlling the viral load when compared to higher doses. As in the previous study, the drug was well-tolerated among the participants of the study.

Recent study results released by Roche AG showed that 95 % of patients taking MK-0518 along with Roche's drug FUZEON achieved an undetectable HIV viral load compared to only 60-70% of patients taking MK-0518 without Fuzeon. This study makes it clear that not only

is MK-0518 safe to take along with other HIV medications, but it is also effective as well.

Additional trials have shown that, unlike many HIV medications, MK-0518 does not appear to elevate cholesterol and triglycerides. So, it is obvious that these two early trials show that unlike a number of its predecessors, this integrase inhibitor is well tolerated and is effective in the treatment of HIV.

GS-9137:

The second integrase inhibitor is manufactured by Gilead, makers of the HIV medication VIREAD. GS-9137 has been proven safe, effective, and well-tolerated in two Phase I/II studies.

In one study, 99% of those taking the drug as monotherapy showed a significant decrease in viral load. What's more encouraging is that the drug has proven to be effective in once-daily dosing, a fact that will make adhering to the therapy much easier than other multi-dose per day therapies.

Another study showed the drug to be very effective when boosted with the protease inhibitor NORVIR. In fact, Norvir produced a 20-fold increase in the amount of GS-9137 in the blood compared to taking the drug without Norvir. Additionally, the drug has been found to be significantly more effective when taken with food [22].

The Adenine Nucleotide Translocase:

In addition to its normal function, the adenine nucleotide translocase (ANT) forms the inner membrane channel of the mitochondrial permeability transition pore (MPTP). The binding of cyclophilin-D (CyPD) to its matrix surface (probably on Pro61 on loop 1) facilitates a calcium-triggered conformational change converting it from a specific transporter to a non-specific pore. The voltage-dependent anion channel (VDAC) binds to the outer face of the ANT, at contact sites between the inner and outer membranes, and together VDAC, ANT, and CyP-D probably represent the minimum MPTP configuration. The evidence for this is critically reviewed as is the structure and molecular mechanism of the carrier in its normal physiological mode. This provides helpful insights into MPTP regulation by adenine nucleotides, membrane potential, and ANT ligands such as carboxyatractyloside and bongkrekic acid. Oxidative stress activates the MPTP by glutathione-mediated cross-linking of Cys_{159} and Cys_{256} on matrix-facing loops of the ANT that inhibits ADP binding and enhances CyP-D binding. Molecular modeling of the loop containing the ADP binding site suggests an arrangement of aspartate and glutamate residues that may provide a calcium-binding site. There are other proteins that may bind to the ANT, modulating MPTP opening and hence cell death. These included members of the Bax/Bcl-2 family (both oncoproteins and tumor suppressors) and viral proteins. Vpr from HIV-1 can bind to ANT and convert it into a pro-apoptotic pore, whereas vMIA from cytomegalovirus interacts to inhibit opening. Thus, the ANT may provide a molecular link between physiopathological mechanisms of infection and the regulation of MPTP function and so represents a potential therapeutic target [22].

ATR Kinase:

Anna Marie Skalka and colleagues of Fox Chase Cancer Center have discovered that ATR kinase or one or more of its protein substrates is a target for the discovery of anti-retroviral drugs. Inhibition of ATR kinase in human cells interrupts the integration of retroviral DNA into host cells, resulting in cell death. This effect is specific to ATR kinase; inhibition of a related kinase, ATM, does not have an anti-retroviral effect.

ATR (ATM and rad3 related) kinase and ATM (ataxia telangiectasia mutated) kinase are human checkpoint kinases. These kinases are known to be involved in radiation sensitivity and are under investigation as targets for cancer therapy. Only ATR, however, is necessary for the integration of retroviral DNA into human cells and for the survival of the transduced cells [22].

Nuclear Factor Kappa B:

The Nuclear Factor Kappa B (NF-κB) is a lymphoid-specific transcription factor, which is sequestered in the cytoplasm by the protein IκB. NF-κB plays a major role in the regulation of HIV-1 gene expression. Upon activation, NF-κB is released from IκB, moves to the nucleus, and binds to its sites on the HIV long terminal repeat to start transcription of the integrated HIV genome [22].

Targeting NF-κB for the suppression of the virus does not present the problem of resistance, as NF-κB is a normal part of the human T-4 cell, and is not subject to mutations, as is the virus. An overview of the NF-κB system and its role in HIV-1 is presented, followed by a critical review of its current and potential synthetic inhibitors.

The drugs studied against NF-κB fall mainly into three categories:

- Antioxidants, against oxidative stress conditions, which aid in NF-κB activation, (The antioxidants include N-Acetyl-L-cysteine (NAC), α-Lipoic acid, glutathione monoester, pyrrolidine dithiocarbamate, and tepoxalin, of which NAC is the best studied.)
- IκB phosphorylation and degradation inhibitors (the phosphorylation and degradation of IκB are necessary to make NF-κB free and move to the nucleus), the IκB phosphorylation and degradation inhibitors, which have been studied in the context of HIV-1 include the salicylates (sodium salicylate, and acetylsalicylic acid (aspirin).
- NF-κB–DNA binding inhibitors.

Finally, the NF-κB–DNA binding inhibitors, which have received attention only recently, are reviewed. These include the most potential, aurine tricarboxylic acid (ATA), a chelating agent, which has been found to inhibit NF-κB–DNA binding at a low concentration of 30 μM.

Table 1. Targets for HIV drug development.

Sl. No.	Enzymatic
1	Integrase
2	Adenosine Nucleotide Translocase
3	ATR kinase
4	Reverse Transcriptase
5	Protease
Non-enzymatic	
7	Viral Uncoating Inhibitors
8	Anti-HIV Inhibitors based on Nucleic Acids
9	Nucleocapsid P7 zinc fingers
10	Nuclear Factor Kappa B
11	Control Oh HIV-1 Replication by RNA Interference
12	HIV-1 Capsid Proteins
13	Viral Envelope Glycoprotein gp120
14	Glycoprotein GP41
15	TAT-Transactivator Proteins
16	CD4 Receptors
17	Heparan Sulfate PROTEOGLYCANS (HSGPS)
18	HIV-1 Entry Inhibitor
19	Chemokine Receptors

Nucleocapsid p7 zinc finger inhibitors:

As a first step, we have developed novel antiviral compounds based on a 2-mercaptobenzamide thioester chemotype, including the pyridinioalkanoyl thioesters, which specifically target the zinc fingers of the human immunodeficiency virus nucleocapsid protein (NCp7). Using these compounds in a murine transgenic model, in which infectious human immunodeficiency virus is induced from an integrated provirus, we show inhibition of transgenic spleen cell p24 expression with potencies comparable to acute infection assays using human peripheral blood lymphocytes. Eg., transgenic mice treated in vivo with two 2-mercaptobenzamide thioesters expressed significantly lower plasma p24, and splenocytes from these animals produced fewer infectious virions. Thus, these thioesters may provide an effective means for inhibiting the expression of the human immunodeficiency virus from integrated viral reservoirs [22].

Nucleoside reverse transcriptase inhibitors (NRTI):

These are the first class of antiretrovirals. All compounds in this class are prodrugs that need to be converted intracellularly in the cytoplasm to their active form before exerting their antiviral activity. The active forms of these drugs are substrates for reverse transcriptase enzyme, and they result in the termination of DNA chain elongation of the retrovirus [22].

Drugs currently in use:

The drugs of choice to be used against the HIVs are Zidovudine (AZT), Didanosine (ddI), Zalcitabine (ddC), Stavudine (d4T), Lamivudine (3TC), Nevirapine, Delavirdine, Efavirenz, Abacavir, Tenofovir DF, and Emtricitabine [23,24].

Drugs under investigation:

Under the clinical trial, the drugs that are under investigation are Alovudine, Amdoxovir (DAPD), DPC817, Elvucitabine, Lodanosine, Lobucavir, and Racivir [25].

Molecules under investigation:

In the drug discovery process, the molecules which are under synthetic and clinical investigation to be used against HIV are DPC 083, DMC 961, DMC 963, and TMC 125 [26].

CONCLUSION:

The extensive review study revealed that HIV has a prominent infectious life cycle. Many drugs are available in the market to fight against AIDS very significantly. Nowadays the disease AIDS can be controlled and or cured very effectively. More research is required to

explore such types of the drug so that they can control the AIDS with least side effects at a minimum affordable cost.

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