Review Article

MODERN ASPECTS FOR ANTIRETROVIRAL TREATMENT

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Accepted on: 18-03-2011; **Finalized on:** 01-07-2011.

ABSTRACT

The widespread of acquired immunodeficiency syndrome (AIDS) causes one of the major causes of death all over the world. The availability of highly active antiretroviral therapy (HAART) has some beneficial effect to improve the lifespan of patient beyond certain limitations. The use of these drugs for several years found to be development of resistance in viruses so effectiveness of the drug is lowered and it is difficult to control the multiplication of Human immunodeficiency virus (HIV) in AIDS patient. For improving and prolonging the life of AIDS patient there is constant need of developing advanced anti-HIV drugs for better result. The use of target oriented highly developed nanosystem is highly effective to avoid drug-drug interaction and adverse effect. The newly developed nanoemulsion, nanoviricide, goldnanopartical and lipid nanocapsule to improve the bioavailability, decreased drug resistance and improvement in patient compliance so increases in lifespan of patient.

Keywords: AIDS, HIV, HAART, Nanoparticle system.

1) INTRODUCTION

The first AIDS sample of HIV is detected in 1959 in blood specimen at Leopoldville in Belgian Congo.[1,2] This was the first known death cause by HIV/AIDS death. The majority cases of HIV positive patient in developing countries and 50% cases in Africa alone. Among one in every hundred sexually active adult infected with AIDS globally. There is alarming rise in incidences of AIDS cases in south Asia consisting of Indian sub-continent and also in Thailand and Indonesia. The total amount of African people among which about 67% people infected by HIV.[4] The homosexuality is also the major cause of death in the developing countries. Although the HAART suppress virological infection and improved immune function but this therapy has also certain limitation and this antiretroviral therapy produces certain adverse effect and high cost for therapy. The drug-drug interaction and cross resistance among different classes of drug has lowered effectiveness of drugs. So there is constant need to develop the newer drug and increases efficacy and safety of drug to obtain a better result.

1.1) The structure of HIV virus

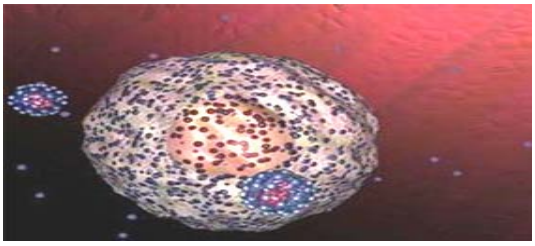

Figure 1: Computerized image of HIV virus

In this computer generated image, the large object is a human CD4+ white blood cell, and the spots on its surface and the spiky blue objects in the foreground represent HIV particles. Outside of a human cell, HIV exists as roughly spherical particles sometimes called virions. The surface of each particle is studded with lots of little spikes. An HIV particle is around 100-150 billionths of a meter in diameter. That's about the same as 0.1 microns, 4 millionths of an inch, one twentieth of the length of an E.coli bacterium, one seventieth of the diameter of a human CD4+ white blood cell. Unlike most bacteria, HIV particles are much too small to be seen through an ordinary microscope. However they can be seen clearly with an electron microscope. HIV particles surround themselves with a coat of fatty material known as the viral envelope (or membrane). Projecting from this are around 72 little spikes, which are formed from the proteins gp120 and gp41. Just below the viral envelope is a layer called the matrix, which is made from the protein p17.[3]

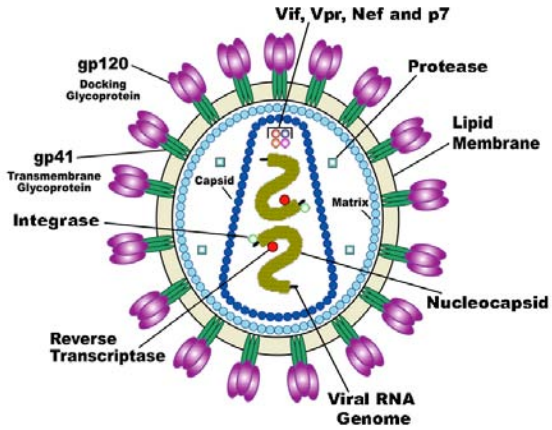

Figure 2: Structure of HIV Virus

The proteins gp120 and gp41 together make up the spikes that project from HIV particles, while p17 forms the matrix and p24 forms the core. The viral core is usually bullet-shaped and is made from the protein p24. Inside

the core are three enzymes required for HIV replication called reverse transcriptase, integrase and protease.

1.2) Various steps in life cycle of HIV infection.[8,9]

1.2.1) Selective tropism for CD4 molecule receptor

HIV can only replicate (make new copies of itself) inside human cells. The process typically begins when a virus particle bumps into a cell that carries on its surface a special protein called CD4. The spikes on the surface of the virus particle stick to the CD4 and allow the viral envelope to fuse with the cell membrane. The contents of the HIV particle are then released into the cell, leaving the envelope behind.

1.2.2) Fusion of virion with host cell

CD4 receptor on which the gp120 of the virion combines with a chemokine receptor is necessary for the fusion of virion with the host cell. While the combination of CD4 receptor and chemokine receptor with the HIVgp41 glycoprotein inernalised in the CD4+ T cell membrane.

1.2.3) Reverse transcription and integration[10]

Once inside the cell, the HIV enzyme reverse transcriptase converts the viral RNA into DNA, which is compatible with human genetic material. This DNA is transported to the cell's nucleus, where it is spliced into the human DNA by the HIV enzyme integrase. Once integrated, the HIV DNA is known as provirus.

1.2.4) Transcription and translation

HIV provirus may lie dormant within a cell for a long time. But when the cell becomes activated, it treats HIV genes in much the same way as human genes. First it converts them into messenger RNA (using human enzymes). Then the messenger RNA is transported outside the nucleus, and is used as a blueprint for producing new HIV proteins and enzymes.

1.2.5) Spreading infection by viral replication

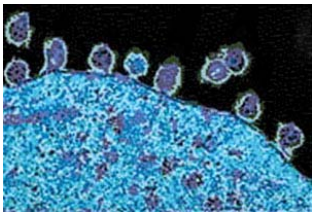

Figure 3: Replication of HIV virus

This electron microscope photo shows newly formed HIV particles budding from a human cell. Among the strands of messenger RNA produced by the cell are complete copies of HIV genetic material. These gather together with newly made HIV proteins and enzymes to form new viral particles, which are then released from the cell. The enzyme protease plays a vital role at this stage of the HIV life cycle by chopping up long strands of protein into smaller pieces, which are used to construct mature viral cores. The newly matured HIV particles are ready to infect another cell and begin the replication process all over again. In this way the virus quickly spreads through the human body. And once a person is infected, they can pass HIV on to others in their bodily fluids.

1.2.6) Destruction of CD4+ cell

The destruction of CD4+ cell takes place by buds from the cell wall of the host cell. As these particles detach from the infected host cell, they damage part of cell membrane of the host cell and cause death of host CD4+ cell by apoptosis.

1.3) Pathological lesion and clinical manifestations of HIV/AIDS

1.3.1) Neurological diseases

1) Peripheral neuropathy 2) Lymphoma of brain 3) Aseptic meningitis 4) Meningoencephalitis 5) Demyelinating lesion of spinal cord 6) AIDS dementia complex

1.3.2) Secondary opportunistic infection

1) fungal- e.g. candidiasis, cryptococcosisnocardia, histoplasmosis. 2) viral-e.g. cytomegalovirus, herpssimplx 1 and 2, herpes zoster 3) bacterial**-** e.g. mycobacteriosis, M.Tuberculosis, salmonellosis

1.3.3) Infection due to secondary tumors

1) Kaposis sarcoma (multicentric) 2) Primary CNS lymphoma 3) Bacillary angiomatosis

1.3.4) Major clinical manifestations

Renal manifestation 2) cardiovascular manifestations 3) Gynecological manifestation 4) endocrine manifestation 5) CNS manifestation 6) ophthalmic manifestation

2) DRUG TREATMENTS AVAILABLE FOR AIDS

2.1) Nucleoside reverse transcriptase inhibitors [NRTIs]

2.1.1) Mode of action

NRTIs are alternative substrate inhibitors of HIV RT. Incorporation of these analogs into nascent DNA results in chain termination of virus by preventing 3¢--5¢ phospodiester bond formation and blocking further extension of DNA. The low fidelity of HIV RT, high level of HIV 1 replication and the high rate of RT medicated recombination contribute to the emergence of resistance against NRTIs.[4,5]

2.1.2) Development of resistance

Two distinct mechanisms are involved in HIV resistance to these drugs namely impairment of the incorporation of the analog into DNA and removal of the analog from the prematurely terminated DNA chain. Mutations in M41L, D67N, K70R and L210W results in high-level resistance towards zidovudine (AZT). A high level of resistance following lamivudine (3TC) monotherapy occurs due to mutation in M184I. The mutation in M184V confers resistance to more recent NRTI such as FTC or even abacavir.[5] Patients receiving didanosine (ddI) monotherapy and also abacavir ABC monotherapyoften have mutation at position L74V. As HIV virus is gradually

becoming resistant to almost all the existing first generation of NRTIs there is growing need for second generation NRTIs. Most of the new NRTIs do not act as immediate chain terminators. Therefore, they are immune to phosphorylatic reaction and cross-resistance.

2.1.3) Zidovudine

Zidovudine itself gets incorporated into viral DNA and terminates chain elongation. After phosphorylation in host cell it inhibits viral reverse transcriptase by converting in active form zidovudine triphosphate. Zidovudine prevents infection of new cell by HIV, but has no effect on virus directed DNA that has already integrated into host chromosome.

2.1.4) Didanosine

It inhibits HIV reverse transcriptase after intracellular conversion to didanosine triphosphate compates with ATP for conversion with viral DNA.

2.1.5) Amdoxovir[11]

This drug is the second generation nucleoside reverse transcriptase inhibitors Amdoxovir is a bioavailable prodrug of anti HIV agent (-)-b-D-dioxolone-guanine (DXG), which has been developed as one of the second-generation NRTISS. Its therapeutic promise is limited due to reports of amdoxovir being associated with lenticular opacities in monkeys and obstructive nephropathy in rat following long term administration. Its clinical development has presently been stopped following reports of resistance and side effects.

2.2) Antiretroviral Protease Inhibitor (PIs)

Saquinavir was the first HIV-Pr inhibitor to enter clinical trials in early 1991 and the first protease inhibitor on the market in December 1995. The drug is now available as a 200-mg hard gel capsule (Invirase) and as a 200-mg soft gel capsule (Fortovase). The oral bioavailability of saquinavir increases markedly by administration with food, so the drug must be taken with meals. FDA-approved doses are 600 mg three times/day for Invirase and 1200 mg three times/dtay for Fortovase. The ability of the HIV-Prto cleave substrates containing proline at P1P was used as a basis for the rational design of selective inhibitors for this viral enzyme. Enzyme inhibitors were prepared by adapting the hydroxyethylamine transition-state mimetic to the P1P proline-containing substrate sequences replacement of the imino acid proline at the P1P site by the (S,S,S)-decahydro-isoquinoline-3-carbonyl group resulted in the design of Ro 31-8959 saquinavir. This compound showed very high binding affinity to HIV-1 Pr, with a Ki value of 0.12 nM, and to the HIV-2 enzyme, with Ki values below 1 nM. It was also highly selective for these two enzymes, showing less than 50% inhibition of human aspartic proteases (renin, pepsin, gastricsin, cathepsinD and cathepsin E) at a concentration of 10 WM and no inhibition of representative proteases from the serine, cysteine and metalloclasses. It also showed potent antiviral activity. Newer protease inhibitors Tipranavir (TPV) and darunavir (DRV) are the latest approved PIs for the treatment of HIV infection. Darunavir and tipranavir these two drugs were approved for therapy in treatment-experienced HIV patients who have developed resistance to other available PIs.[16] Tipranavir is administered orally twice daily and should be given in combination with low-dose ritonavir, which is used to boost its bioavailability. Complete cross-resistance has not yet developed between tipranavir and darunavir.

2.3) Use of newer non-nucleoside reverse transcriptase inhibitors

Etravirine and rilpivirine are two important second-generation NNRTIs that have shown therapeutic promise.

2.3.1) Etravirine

Etravirine to be highly active against both wild-type and NNRTI resistant HIV strains. It has a higher genetic barrier to the development of resistance than currently available NNRTIs. It can overcome common NNRTI-associated mutation such as K103Nby adapting its binding orientation.[8,11] In an earlier Phase IIa study, the Polyethylene glycolated (PEG)formulation of etravirine was effective in reducing the viral loads.

2.4) Integrase inhibitors

Integrase was recognized as a rational therapeutic target for the treatment of HIV infection Remarkable progress in drug development has been made. An integrase inhibitor acts in the integration phase, which falls between reverse transcription and maturation, resulting in decreased HIV integration into host chromosomes.[14] The screening and discovery of integrase inhibitors relies primarily on simple assays that use recombinant integrase.

2.4.1) Raltegravir

It competitively inhibits the strand transfer reaction of proviral DNA integration by metallic ion binding in the active site. Raltegravir exhibits activity against both HIV-1 and HIV-2.It is indicated for treatment experienced HIV-1-infected adults with evidence of ongoing viral replication and multiple drug resistance.

2.5) Entry inhibitors

The infectious cycle of HIV begins with fusion of viral particles to the CD4+ receptor at the cell surface. This interaction is mediated by the HIV envelope protein gp120. The main co-receptors used by HIV-1 for entry into the cell are the chemokine receptors CCR5 and CXCR4. Variants of HIV-1 can be classified as those that exclusively use CCR5 (R5), CXCR4(X4), or both co-receptors (R5X4 or dual-tropic viruses) t o enter cells. HIV-1 isolates of the R5 type have been implicated in most cases of sexually transmitted HIV infection, whereasX4 viruses, which replicate best in T-cell lines often predominate in the later stages of HIV disease and may be associated with rapid progression to AIDS and death.

2.6) Fusion inhibitor

The drug prevents the fusion of viral and cellular membrane. Inhibitor has many advantages compared with the drugs acting inside the cells or targeting cellular proteins. As it acts outside cells and targets the protein of virus, instead of host cell, it is expected to have low drug related toxicity.

2.7) CD4-receptor inhibitor

TNX 355 is a humanized monoclonal antibody that is directed against the extracellular domain 2 of human CD4. It prevents post-viral binding conformational changes required for successful entry of HIV into the cell. Although anti-CD4 antibodies may have immunosuppressive effects, anti-CD4 antibody demonstrated no serious adverse events in the short term and no CD4-celldepletion. Monoclonal anti-CD4 antibodies block the interaction between gp120 and CD4 and inhibit the viral entry process.[15] Ibalizumab, a monoclonal antibody that bindsCD4 is being investigated as an HIV entry inhibitor with the ability to block both CCR5 and CXCR4-tropic viruses, and is currently undergoing a Phase II clinical trial.

3) NEWER ADVANCED DRUG DELIVERY FOR AIDS TREATMENT

3.1) Use of nano viricide in anti-HIV therapy

Specifically they are polymeric nano-micelles a single polymeric chemical chain with covalently attached ligands that specify the virus target. The antiviral spectrum of the drug is determined by the specificity of the set of ligands attached to the chain, in addition to other functionally important aspects inherent in the physicochemical properties. Active pharmaceutical ingredients are optional and can be hidden in the core of the NanoViricide™ 'missile and purportedly reduce toxicity. NanoViricide™ is designed to seek a specific virus type.[28] In contrast to other approaches, a NanoViricide™ micelle is considered to recognize and bind to more than one type of binding site on the virus. Currently NanoViricide system enables design of a drug that binds to as many as three different sites, which is purported to enhance the mechanism of attack. a) Attachment to the virus particle. b) Engulfment or coating of the virus particle, thereby neutralizing the virus's infectivity. c) Destabilization and possibly dismantlement the virus particle. NanoViricides™ act as molecular chisels and may also be made capable of attacking the viral genome thereby destroying the virus completely.

3.2) Gold nanoparticles act by acting on HIV fusion inhibition

There might be some inhibition of HIV exhibited by gold compounds, such as sodium aurothiomalate and aurothioglucose. Due to the biomedical group having a variety of gold-based drugs within their consortium, a range of these compounds has been submittedforHIV screening.[26] The anti-HIV potential of noble-metal nanoparticles has been described as the gold nanoparticles employed as a platform (2.0 nm diameter, mercaptobenzoic acid modified gold particles) transformed a weakly binding and biologically inactive small molecule into a multivalent conjugate that effectively inhibited HIV-1 fusion to human T-cells of significance is the similarity of this class of gold particles to proteins and dendrimers in terms of their atomical precision and mono-disperse nano-size. The mercaptobenzoicacid-coated gold nanoparticles were conjugated to SDC-1721, derivative of TAK-779, which is a known CCR5 antagonist. Structure–activity relationship data generated for TAK-779 has shown that the quaternary ammonium salt was essential for high-affinity binding and effective inhibition of HIV fusion. Since the quaternary ammonium salt imbues TAK-779 with poor pharmacological properties (e.g. significant irritation at the injection site) searches were conducted for alternate small-molecule CCR5 antagonists culminating in the synthesis of SDC-1721 (a fragment of TAK-779 that lacks the quaternary ammonium salt moiety) by Bowman and coworkers. Free SDC-1721 had no inhibitory effect on HIV infection; however, the (SDC-1721)-gold nanoparticle conjugate displayed activity comparable to that of TAK-779.[27] This molecule was thus instituted to demonstrate the feasibility of conjugating a low affinity, biologically inactive small molecule to a gold nanoparticle for the design of biologically active multivalent gold nanoparticle therapeutics. The mechanism of inhibition of viral replication was specific for viral entry.

3.3) Targeted drug delivery by use of nanoparticle

Nanoparticleare solid, biocompatible polymeric particles ranging in size from 10–1000 nm, encapsulated with a drug within the polymeric matrix or adsorbed or conjugated onto thesurface.[28] They are able to target specific sites in the body such as the reticuloendothelial system (RES) due to its nanosize and have also shown potential for controlled drug delivery Furthermore, by appropriate surface modification, for example, coating with poly (ethylene glycol), targeting to other areas may be achieved(In addition to targeted and controlled drug delivery) nanoparticles have also been explored for improving the efficacy of drug with physicochemical problems such as poor solubility that may lead to formulation difficulties . Because of the challenges associated with its physicochemical properties and limitations in biodistribution and cellular uptake, the development of nanoparticles as a novel drug Delivery.[29] The use of nanoparticles for targeted delivery of ARVs to HIV-infected cells and to achieve sustained drug release kinetics may allow for their improved efficacy, decreased drug resistance, a reduction in dosage, a decrease in systemic toxicity landside effects and an improvement in patient compliance.

3.4) Bioavailability enhancement of HIV drugs by use of nanoemulsions and nanosuspensions

Currently nanoemulsions are of considerable interest in anti-HIV/AIDS drug targeting. Recently oil in water

nanoemulsion platform was used to improve the oral bioavailability and brain localization of saquinavir. Nanoemulsions were loaded with tritiated [3H]-saquinavir and administered to fasted mice and compared to aqueous suspensions orally as well as parenterally. The orally administered drug-loaded nanoemulsions resulted in the highest plasma and brain concentrations. Pharmacokinetic analysis suggested that this was attributed to higher rate and extent of absorption with orally administered squinavir encapsulated in nanoemulsions.[17,18] This formulation is claimed to be very promising or targeting delivery of anti-HIV/AIDS therapeutics to viral reservoir sites such as the brain. Nanoemulsions or mini-emulsions are transparent or translucent oil-in-water (o/w) or water-in-oil (w/o) droplets with a mean droplet diameter between 100 and 500 nm. Nanoemulsions are also known as submicron emulsions and unlike the thermodynamically stable microemulsions, nanoemulsions are kinetically stable with great stability in suspension due to their small droplet size. Advantages of nanoemulsions over macroemulsions or coarse emulsions include higher surface area and free energy without the inherent creaming, flocculation, coalescence and sedimentation associated with macroemulsions.[21]

3.5) Anti HIV therapy by using lipid nanocapsules (LNC)

These non-polymeric nanocarriers have recently been reported in the anti- HIV/AIDS drug delivery. Pereira de Oliveira et al. evaluate dindinavir-loaded nanocapsules (INV-LNC) including Solutol HS15, an excipient reported to possess in vitro P-gp inhibiting properties, as means to improve indinavir distribution into brain and testes of mice. The LNC formulation was found to increase indinavir uptake in brain and testes by mechanisms other than, or additional to, Pgp inhibition. Lipid nanocapsules are the core-shell structures composed of a liquid oily core and an amorphous surfactant shell. These are basically derived from nanoemulsions. LNC were introduced by Heurtault et al these are generally prepared by Phase Inversion Temperature (PIT) method. Biocompatible excipients like medium-chain triglycerides (caprilictriglycerides) as the oil phase, a polyoxyethylene-660-12-hydroxystearate as the PEO nonionic surfactant and MilliQpsy® water plus NaCl as the aqueous phase are generally chosen for the development of NLC.

3.6) Liposomes for intravaginal drug delivery[32,34]

Nano-sized systems designed for an intravaginal mode of delivery with diverse therapeutic modalities may also possess relevance for microbicide delivery. Pavelic and co-workers designed liposomal intravaginal drug delivery systems, having the propensity to deliver entrapped drugs during an extended period of time at the site of action. The phosphatidylcholine-based liposomes were prepared by two different approaches specifically the polyol dilution approach and the pro-liposome approach, and incorporated three commonly applied drugs for the treatment of vaginal infections namely clotrimazole, metronidazole and chloramphenicol that were tested for in vitro stability. The extended residence period of the drug delivery system in the vaginal tract may perceive them to be suitable for the delivery of microbicides.

4) APPROACHES TO HIV VACCINES UNDER DEVELOPMENT

Developing a vaccine for HIV is particularly challenging because HIV is one of the most Mutable viruses known thus the prevalence of a wide variety of strains. No HIV vaccine exists at the moment. But thanks to new innovations in biotechnology, vaccine development approaches to HIV vaccines are under development or in clinical trials

4.1) Recombinant subunit vaccines

Introduce a genetically engineered, harmless part of HIV into the body. This is the approach used in Gp 120 protein, the only vaccine in phase 3 clinical trials at the moment. Most candidate HIV vaccines this approach.

4.2) DNA vaccine

Naked DNA vaccine, introduces into the body actual genes of HIV (rather than the antigens) that have been genetically engineered to become virulent. When the HIV genes are introduced into skin or muscle, the cells of the body take up the genetic material and produce viral antigens (HIV proteins) through normal cellular mechanisms. While some HIV vaccines produce a humoral response (antibodies), DNA vaccine has been shown to also trigger cell-mediated immune responses.[29] This vaccine is in phase 1 clinical trials.

4.3) Advanced development in live viral or bacterial recombinant vector vaccines

Bacterial types could have two advantages: they could be given orally and produced cheaply. These are created by inserting HIV genes into alive virus or bacterium that is infectious but does not cause disease to the human body. The engineered virus or bacteria are used to transport the desired HIV antigens to the body. When they enter the cell, they cause the HIV protein to be generated inside the cell, producing both humor land cellular immune responses.[30] Viral types of the vaccine include canary pox, in phase 2 of clinical trials, and vaccine, in phase 1 Bacterial types include salmonella, in phase 1 of trials.

4.4) Newer developed live attenuated virus vaccines

HIV vaccine development is moving from conventional methods to new approaches. The Classical approach used for most viral vaccines today is based on the use of whole but inactivated or live-attenuated viruses. But for ethical and safety reasons, this approach has not been aggressively pursued in HIV vaccine research. The nature of HIV adds another complication to the development of a vaccine the vaccine must be capable of stimulating the immune system to destroy a virus whose prime characteristic is to destroy that same immune system. Several forms of vaccines have been identified as potential candidates. This are made of live but weakened

HIV that is unable to cause disease.[31] When the body responds to the weakened virus, it has the experience of an infection and is thus prepared to react to the full-strength virus. Today this is the most commonly used system for other vaccines, such as those for polio and measles. But the risk that HIV may not be adequately attenuated and could have long-term consequences leading to litigation has held back investigations of this approach in HIV vaccine research and development. At the moment no vaccine of this type is being tried in humans.

CONCLUSION

The modern aspects of anti HIV therapy improves the bioavailability of drugs and reduces the adverse effect. The highly advanced polymeric system and nonpolymeric system are highly beneficial. So this advanced system give reduction in dose and chances of resistance is also reduced. Challenge of successful implementation of long-term control of HIV in patients resistant to ARVs has contributed to accelerated research in the field antiretroviral drug discovery. New classes of drug: namely, entry inhibitors, which include fusion inhibitors, chemokine co-receptor (CCR) inhibitors and monoclonal antibodies, integrase inhibitors and maturation inhibitors. These newer drugs have either been approved or are at a very late stage of clinical development. The recent approvals of the CCR5inhibitor maraviroc, the integrase inhibitor raltegravir, and the latest NNRTI etravirine mark a significant milestone in the treatment of HIV-infected patients, particularly for those with limited treatment options. There is tremendous research work doing on AIDS vaccine so this is beneficial for improving lifespan of AIDS patient and helpful for reducing the burden of AIDS worldwide.

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