



A Concise Review of Existing Therapies and Recent Advances in the Management of HIV Infection

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ABSTRACT

Human immunodeficiency virus (HIV) is an RNA retrovirus capable of replicating its genome by the DNA dependent RNA polymerase (DdRp). The virus infects the lymphocytes with the help of viral glycoproteins like Gp 120 and Gp 41. The entry of virus leads to the release of viral RNA inside the host cell, which is further replicated, and assembly of virion particles leads to the release of viral particles that further infect the other host cells. Established therapies include those that inhibit the entry of virus in the host cell, those inhibiting the integrase activity, those acting as protease inhibitors and also we have Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and Non-Nucleoside reverse transcriptase inhibitors (NNRTIs) with NRTIS being the competitive inhibitors of DdRp also show mitochondrial toxicity. Protease inhibitors are known for their adverse effect profile and several drug interactions due to their enzyme inhibitory property. The most effective approach in the management is the highly active antiretroviral therapy containing the combined use of drugs having varied mechanisms of action. Still, long term use of these agents can end up in resistance against these agents. Well documented adverse effect profile along with various drug interactions associated with anti-HIV drugs mandates the need for the development of newer drugs against HIV. Newer molecules provide a better safety profile and better alternatives for drug-resistant cases. Therefore, this review focuses on existing therapies along with various newer pipeline drugs with their mechanisms and advantages over the existing therapies.

Keywords: HIV; Antiretroviral; Recent advances; AIDS; Drugs.

INTRODUCTION

HIV (Human Immunodeficiency Virus) infection has been a major cause of concern in the health care scenario for a long time. Recent data from United Nations AIDS (UNAIDS) reported that in 2019, approximately 38 million people were living with HIV in the world out of which 36.2 million were adults, 1.8 million were below 15 years and about 7.1 million HIV positive were unaware of their positive status for HIV infection.¹ With time, HIV gradually leads to the development of Acquired immunodeficiency syndrome (AIDS) with decreased CD4 count with increased susceptibility to opportunistic infection which have been found to be a major contributor to mortality in AIDS patients.² A great deal of improvement have been made in antiretroviral therapy (ART) for the treatment of HIV infection since starting potent combination therapy. These aggressive and combined interventions have dramatically reduced the morbidity and mortality of these patients along with an improved lifestyle of HIV positive individuals by transforming HIV infection into a manageable chronic condition.³ The prophylactic use of ART has been found to be highly effective in preventing HIV infection in exposed individuals.⁴ The development of resistance to ART is a major hurdle faced in the treatment of HIV patients.

With the rise in the number of cases, a simple, rapid, economical, accurate diagnostic method for the detection of new cases and follow up of infected one is a need of the hour. Various modalities are currently available to screen

and diagnose HIV infection which includes serological assay (ELISA, Rapid agglutination test, Dot blot assay), molecular assay (PCR, P24 antigen assay) and confirmatory assay (western blot assay, indirect immunofluorescence assay).⁵ Laboratory tests should be performed along with confirmation of HIV infection during the initial patient visit to act as a baseline to guide the selection of ARV drug regimens and follow up on the patient. These tests include CD4 T lymphocyte cell count, Plasma HIV RNA count, serologies for hepatitis virus, Complete blood count, transaminase levels, blood urea nitrogen, creatinine, urinalysis, fasting blood glucose and serum lipids. Genotypic resistance testing along with a test for the sexually transmitted disease should also be performed.^{6,7}

Structure of HIV

HIV is a single-stranded RNA retrovirus. The virus particle contains two identical RNA strands along with enzymes such as integrase, reverse transcriptase, and protease in the capsid core.⁸ The nucleocapsid protein stabilizes the RNA of the virus and the mature virion particle is conical in shape.⁹ It is surrounded by lipid envelope embedded with transmembrane proteins. Various proteins in HIV are utilized as targets by the drugs to control the infection in an individual. The various protein components of HIV and their function and applications are summarized in table 1.



Table 1: Overview of various protein in HIV and their function

Genes	Proteins	Function and application
gag	Capsid protein (p24) Matrix protein Nucleocapsid	Capsid formation, used in diagnosis Coats the inner surface of virus, early stages of virus replication as well as envelope incorporation into virions and assembly. ¹⁰ Nucleic acid binding, condensing and chaperoning ¹¹
pol	Protease Reverse transcriptase Integrase	Cleavage of translated proteins into mature structural proteins and enzymes Conversion of RNA into proviral DNA Integrate the transcribed DNA into host genome
env	Surface glycoprotein (gp120) Transmembrane protein (gp41)	Attaching of virus to host cell Fusion of virus into host cell

PHARMACOTHERAPIES IN THE MANAGEMENT OF HIV

From the inception of therapy against the HIV, there have been many additions in the management of HIV infection. We do have a wide array of drugs acting against HIV and are used accordingly in patients in a case to case basis. The various drugs used in HIV management are summarized as follows:

A) Existing therapy in the management of HIV

1) Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTI)-

These drugs inhibit the enzyme reverse transcriptase to prevent the transcription of viral RNA to proviral DNA by getting incorporated into the replicating DNAs and terminate the elongation prematurely.¹² These drugs need to be triphosphorylated by the host cell to have activity against the virus except for tenofovir which requires 2 phosphorylation only.^{12,13} The nucleoside reverse transcriptase inhibitors include Zidovudine, Stavudine, lamivudine, Efavirenz, Abcavir, etc. The only nucleotide reverse transcriptase inhibitor is tenofovir.¹²

2) Nonnucleoside reverse transcriptase inhibitor (NNRTI)-

The NNRTIs bind to p66 subunit of the reverse transcriptase to induce a conformational change structure of the enzyme thus acting as noncompetitive inhibitors of NNRTIs are virus-strain specific which is active only against HIV-1.^{12,14} The approved NNRTIs are nevirapine, efavirenz, etravirine, rilpivirine, and delavirdine.¹²

3) HIV protease inhibitors-

The protease inhibitors (PIs) competitively inhibit the enzyme aspartyl protease in a virus with cleavage at the N-terminal side of proline residues. These inhibit the cleavage of large polyprotein into structural proteins and enzymes.^{12,15} These are saquinavir, ritonavir, fosamprenavir, lopinavir, atazanavir, darunavir, indinavir, nelfinavir, tipranavir. Low dose ritonavir is mostly used as pharmacokinetic enhancer.^{12,16}

4) Integrase inhibitors-

These inhibit the integration of Viral DNA into the host DNA by inhibiting the catalytic activity of integrase to form a covalent bond between them. These agents are active in the virus which has become resistant to other antiretrovirals.^{12,17} The drugs available are Raltegravir, Elvitegravir, Dolutegravir. Dolutegravir is active against a virus which is resistant to even raltegravir, elvitegravir and can act without a booster.¹⁸

5) Entry inhibitor-

The drugs that are approved and available in this category have a varied mechanism of action. Enfuvirtide binds to gp41 subunit to prevent the fusion of viral and host cell membranes.¹² It is the only antiretroviral agent given parentally. Maraviroc blocks the binding of gp120 to CCR5 chemokine receptors which is an important step in the entry of the virus into the host cell. It is mainly active against CCR5 tropic virus with no effect on CCR4 tropic or dual tropic virus.^{12,19,20}

The National technical guidelines on anti-retroviral treatment recommend Tenofovir + Lamivudine + efavirenz as the first-line therapy for HIV patients.²¹ For HIV-2 infection efavirenz is recommended to be replaced by Lopinavir/ ritonavir.²¹

B) Recent advances in the therapy of HIV

The newer molecules developed for the therapy of HIV can be divided into two parts. Firstly, the new drugs developed on existing or known viral targets and secondly, newer drugs on novel targets. The various newer drugs developed are summarized as follows:

I. Newer drugs on existing targets:

The newer drugs on existing targets should be better than their previous counterparts hence the main focus of development of such molecules was directed towards either development of long-acting congeners, better safety profile, or overcoming the current resistance faced by already available drugs.

1) Newer NRTI

Islatravir- It is an NRTI with high potency. The islatravir-triphosphate intracellular half-life has been found to be about 78.5–128.0 hour thus making weekly dosing of this drug possible.²² The drug-eluting implants of this molecule are hypothesized to provide HIV prophylaxis for about 1 year and phase 1 trials have shown that the implants were

well tolerated.²³ Other molecules of this class are MK-8504 and MK-8583 which are long-acting prodrug of tenofovir have been tried in phase 1 and the data from the trials have raised questions about the feasibility of these molecules in extended-interval dosing regimens.²⁴

2) Newer NNRTI

Rilpivirine- A injectable long-acting nanosuspension has been formulated with dosing every 4-8 weeks either singly for preexposure prophylaxis or can be given as two-drug injectable maintenance therapy with cabotegravir for maintenance regime.²⁵ Studies have shown that it has got a better safety profile as compared to efavirenz in terms of neuropsychiatric and neurological side effects.²⁶

Doravirine- It is a novel once-daily NNRTI with good efficacy and safety profile. It has demonstrated a good in vitro activity against resistant HIV-1 mutants associated with the use of other NNRTIs, including newer agents such as etravirine, rilpivirine.^{27,28,29,30}

Elsulfavirine- It is a prodrug of VM-1500A which reversibly binds to carbonic anhydrase in red blood cells (RBCs) with a half-life of 9 days in RBC. The RBCs serve as a natural slow-release depot for this molecule which can provide a prolonged plasma exposure and slow elimination of this drug which can help the drug to be tried for once a month dosing.³¹

3) Integrase inhibitors-

Cabotegravir LA- It is a dolutegravir analog and integrase strand transfer inhibitor.³² It has long elimination half-life of 40 days and is currently under phase 3 trials as a single agent for both HIV treatment and HIV prevention.^{33,34}

4) Entry inhibitor-

Combinectin- It is a multi-specific entry inhibitor of HIV and contain anti CD4 adnectin and an adnectin targeting gp41 with an inhibitory domain for fusion inhibition.³⁵ Adnectin are 10th fibronectin type III domain-based small therapeutic proteins with high affinity and specificity.³⁶

II. Drugs on Novel Targets

Novel mechanism of action can help in the development of newer drugs with less or no cross-resistance with existing available therapy and with lesser side effects. The main focus of newer targets is mainly directed towards trying to cure the disease instead of just managing the disease or associated morbidity.

Broadly neutralizing monoclonal antibodies (bNAbs)-

Ibalizumab- It is a humanized monoclonal antibody which acts by impeding the conformational change in CD4 – gp120 complex causing post attachment inhibition by a steric hindrance to stop interaction of CCRX4 and CCRX 5 with gp120 and causes rearrangement of gp41 to inhibit fusion of viral particle.³⁷

Leronlimab- It is an anti CCR5 monoclonal antibody active against HIV -1 virus.³⁸ It is seen that Leronlimab act

synergistically with other small molecule CCR5 inhibitors with the first causing competitive inhibition and other causing allosteric inhibition which can lay a path for novel combination for resistant HIV treatment.³⁹

CD4 binding antibodies-

UB-421 is a humanized anti Cd4 antibody that binds to the site of gp 120 attachment without affecting the function of the immune cell.⁴⁰ These are active against all subtypes regardless of resistant status or tropism with 50-100 times more affinity for CD4 cells as compared to HIV.⁴¹ Other CD4 binding monoclonal antibodies are under trials are VRC01, 3BNC117, VRC01-LS and VRC07-523LS.^{42,43,44}

Elipovimab- It is an effector enhanced monoclonal antibodies against HIV infected cell which targets gp120/41 on the surface of infected cell and FCγRs of the immune cells such as phagocytes, macrophage simultaneously.⁴⁵

Capsid Inhibitors-

GS-6207 and GS-CA1 are capsid inhibitors under investigation. These act through interference with assembly and disassembly of capsid along with inhibition of nuclear transport and formation of new virion particles for release.^{46,47} Effective drug concentration has been detected after 12 weeks of a single dose for GS6207 in healthy individuals giving it a potential for long-acting action with easy dosing regimen.⁴⁸

Maturation inhibitor-

Bevirimat - It causes the production of immatures capsid proteins by interfering with the processing of polyprotein Gag leading to the release of the noninfectious immature virion particle.⁴⁹ It is active against all HIV resistant to all of the currently available drugs.⁵⁰

Attachment inhibitor-

Fostemsavir- A recently approved prodrug that acts on the first step of the viral life cycle by attaching itself to viral gp120 and inhibiting its entry into CD4 cells.⁵¹ No cross-resistance to other drugs have been demonstrated invitro, including entry inhibitors.^{52,52,54}

ABX464- It is an investigational drug having both anti-inflammatory and antiviral activity by interfering with pre mRNA splicing and have been investigated for a wide range of diseases such as HIV, Ulcerative colitis, COVID 19 and Rheumatoid arthritis etc.^{55,56,57,58}

A wide array of molecules have been developed for the therapy of HIV infections. Yet, we are still away from developing a complete cure from this long ailing morbid and mortal condition. The diseases needs a combination of drugs to combat the illness and with increase in number of medications the chances of development of adverse effects increases. The adverse effects whether new ones or known, should be reported to the respected pharmacovigilance centers so as to minimize the further risk of development of such incidences.^{59,60} Rational use of



medication would prevent the frequent development or emergence of side effects with these medications.⁶¹ However, the development of newer drugs on novel targets can definitely help in the management of the condition in a better way.

CONCLUSION

Early screening, diagnosis, and treatment of the infection have led to a decrease in morbidity and mortality due to associated complications with this disease. Despite the recent development in antiretroviral therapy, there is still need of new alternatives that are equally efficacious and cheaper as compared to the contemporary treatment available. Even after plenty of development, we still have a long way to go to find a permanent cure for this condition.

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