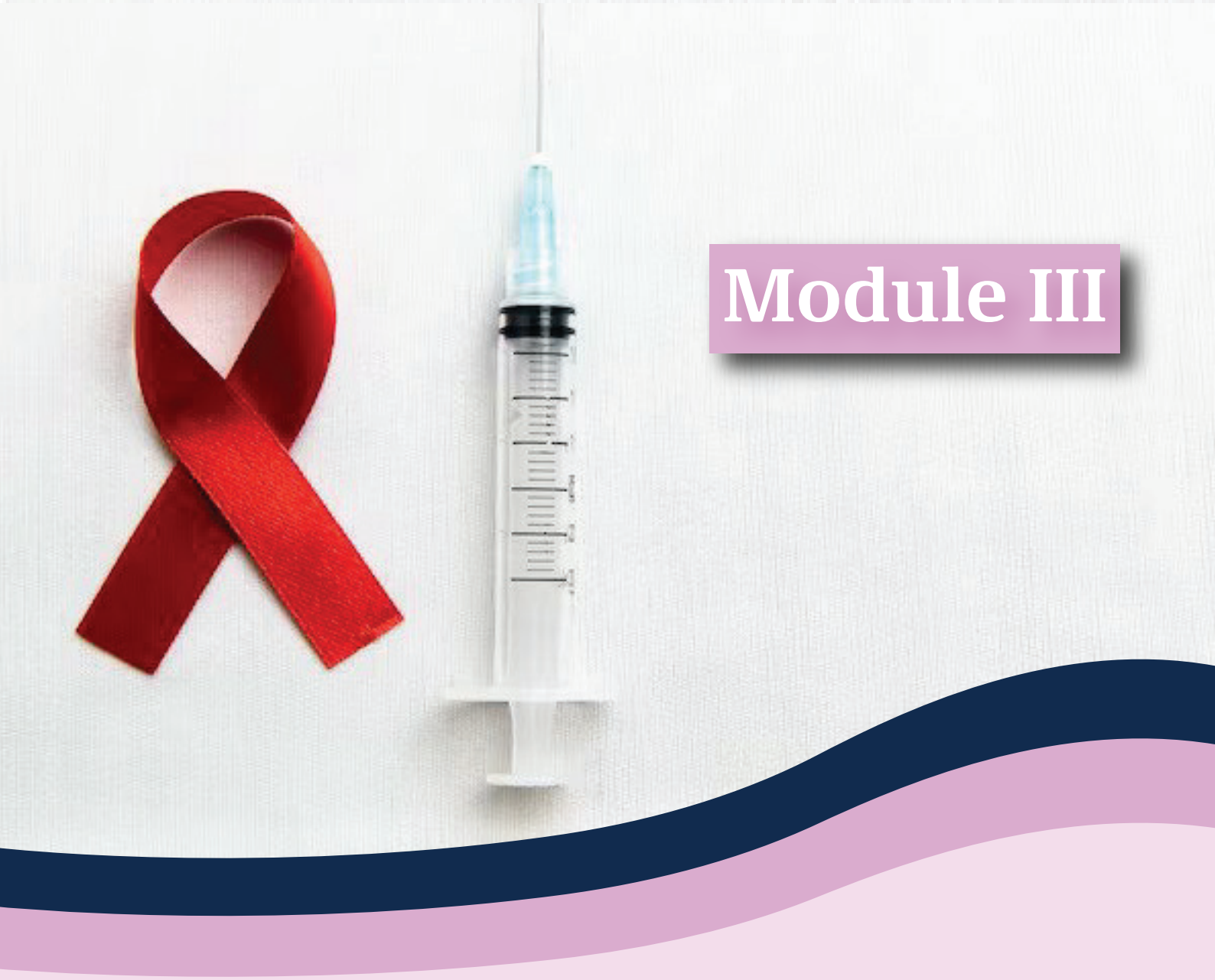
Module on Advances in HIV management



Module III

Special Challenges with Antiretroviral Therapy

CONTENT

Introduction

A significant advancement in the understanding of an HIV replication and its pathogenesis has helped in the identification of different pharmacological targets. This has resulted into availability of a large number of antiretroviral (ARV) drugs. The antiretroviral therapy (ART) has evolved from monotherapy with azidothymidine (AZT) to combination of 2 ARVs from nucleoside reverse transcriptase inhibitors (NRTIs) to highly active antiretroviral therapy (HAART). The triple therapy has resulted into significant improvement in an immune status, quality of life, and reduced morbidity and mortality associated with HIV infection. With the advent of the different drug regimens, the disease scenario has changed from a 'virtual death sentence' to a 'chronic manageable disease'. The continued search for different drug combinations, preferential change in first line drugs and identification of novel drugs has been a boon for an effective viral suppression. However, the success of the drug treatment is achieved at the cost of life threatening adverse drug effects, drug-drug interactions and an inconvenience of lifelong therapy. Since the disease has stepped into its 3rd decade, there are several treatment-experienced patients living either with drug toxicity or facing the threat of treatment failure due to a multi-drug resistance. Moreover, there is likelihood of newly infected untreated patients harboring HIV mutants that are already resistant to commonly used ARV drugs. Thus, there are many critical issues associated with the use of ARV drugs that need to be addressed. In addition, a great deal of attention has also been focused on prevention of an HIV infection through sexual contact.

Challenges with the Use of ARV Drugs

The critical issues associated with ART are related to the characteristic features of the virus (HIV), ARV drugs and HIV positive patients. These factors are a major challenge for an effective long term treatment.HIV related factors

HIV, a retrovirus, multiplies at a rate of approximately 1010 copies per day. At such a high rate of replication, the virus often commits mistakes and results into mutants. High mutation rate leads to development of multiple strains and threatens the development of drug resistance.

Once infected, the virus becomes an integral part of host cell and survives the full life span of infected host cell, especially in T-lymphocytes and urogenital secretions. Surprisingly, despite a complete plasma viral load suppression for 6-12 months, the virus remains detectable in seminal fluid and more often than not, these are drug resistant variants. The existence of virus in potential 'reservoirs' and the subsequent replication may cause relapse following cessation of ART, necessitating lifelong treatment. Different treatment strategies have been tried for the persistent forms, but to date, no clinical or virological benefit has been reported

Increasing reports of multi-drug resistant (MDR) virus in treatment-experienced patients are also being encountered.

ARV related factors

Attempts to eradicate the virus from the 'reservoir' have failed despite intensifying the ARV treatment, implying that drugs cannot reach in adequate concentration in the latent reservoir cells.

Each class of ARV drugs has the potential to cause toxicities, many of which are shared by drugs likely to be used concomitantly in HIV positive patients. This complicates the treatment, causes difficulty in causality assessment and may require treatment withdrawal in serious life threatening reactions. Long term use of HAART has been reported to produce morphologic and metabolic abnormality syndrome, especially hypertriglyceridemia (HTG). This in turn has increased the risk of cardiovascular (CVS) and cerebrovascular diseases in patients receiving ART.

Clinically significant drug-drug interactions, frequently seen in patients on ART, can adversely affect the patient care and complicate ART. Interactions have been observed in 14% to 26% of HIV infected patients in USA and Netherlands. The therapeutic risk of interactions is due to potent induction or inhibition of cytochrome P450 (CYP450) isoenzyme, which also metabolizes a number of other medications. On the other hand, the evaluation of the potential interactions during clinical trials is mostly incomplete and becomes evident only during drug therapy.

Further, the drugs belonging to same class also differ in their potential to cause the interactions. For example, first licensed integrase inhibitor, raltegravir is predominantly metabolized by UGT1A1- medicated glucoronidation with little potential to interact with CYP450 enzymes, whereas elvitegravir is largely metabolized by CYP3A4. Moreover, ritonavir boosting effect is due to inhibition of CP450 3A4 enzyme, but it also inhibits other CYP isoenzymes and is an inducer of several liver enzymes, resulting into complicated pharmacokinetic interactions with other drugs. The drug treatment of co-existing medical disease (s) and opportunistic infections can also complicate the ART. The use of over the counter drugs and herbal drugs may potentially compromise the management.

Reduction of the plasma viremia to undetectable levels strongly correlates with strict adherence to ARV regimen that includes taking multiple drugs twice or thrice a day for rest of life. The recommended practice to combine 3 or more drugs from different classes of ART results in high pill count that, along with toxicities, may cause inconvenience to the patient and poor adherence.

All classes of ARVs demonstrate the in vivo resistance. However, the rate of development of drug resistance differs amongst them. Non-thymidine-containing NRTI/NtRTI combination regimens and NNRTIs have a low genetic barrier to resistance; thereby, they require fewer critical mutations to render the treatment ineffective. Drug resistance is not only associated with rapid virologic failure but also present the daunting task in designing an effective treatment regimen.
The limited availability of ARV drugs and safe alternatives in resource poor countries further add to the problem. The lack of monitoring for adverse events and poor access to therapeutic drug monitoring facilities also interfere with effective ART management.
Host related factors

Patients with pre-existing risk factors like obesity, fatty liver, psychiatric disorders, and abnormal liver and renal functions are more likely to develop ADRs and require a close monitoring. Presence of co-existing diseases like tuberculosis, anemia, diabetes mellitus and hyperlipidemia further complicate therapy, affect compliance, increase chances of drug interactions and overlapping toxicity. Clinical manifestations of intercurrent illness like hepatitis A and malaria may often present as ARV drug toxicity and challenge the treatment. Hence, it becomes difficult to differentiate between complications of HIV disease and ARV toxicity as these may present with similar signs and symptoms.

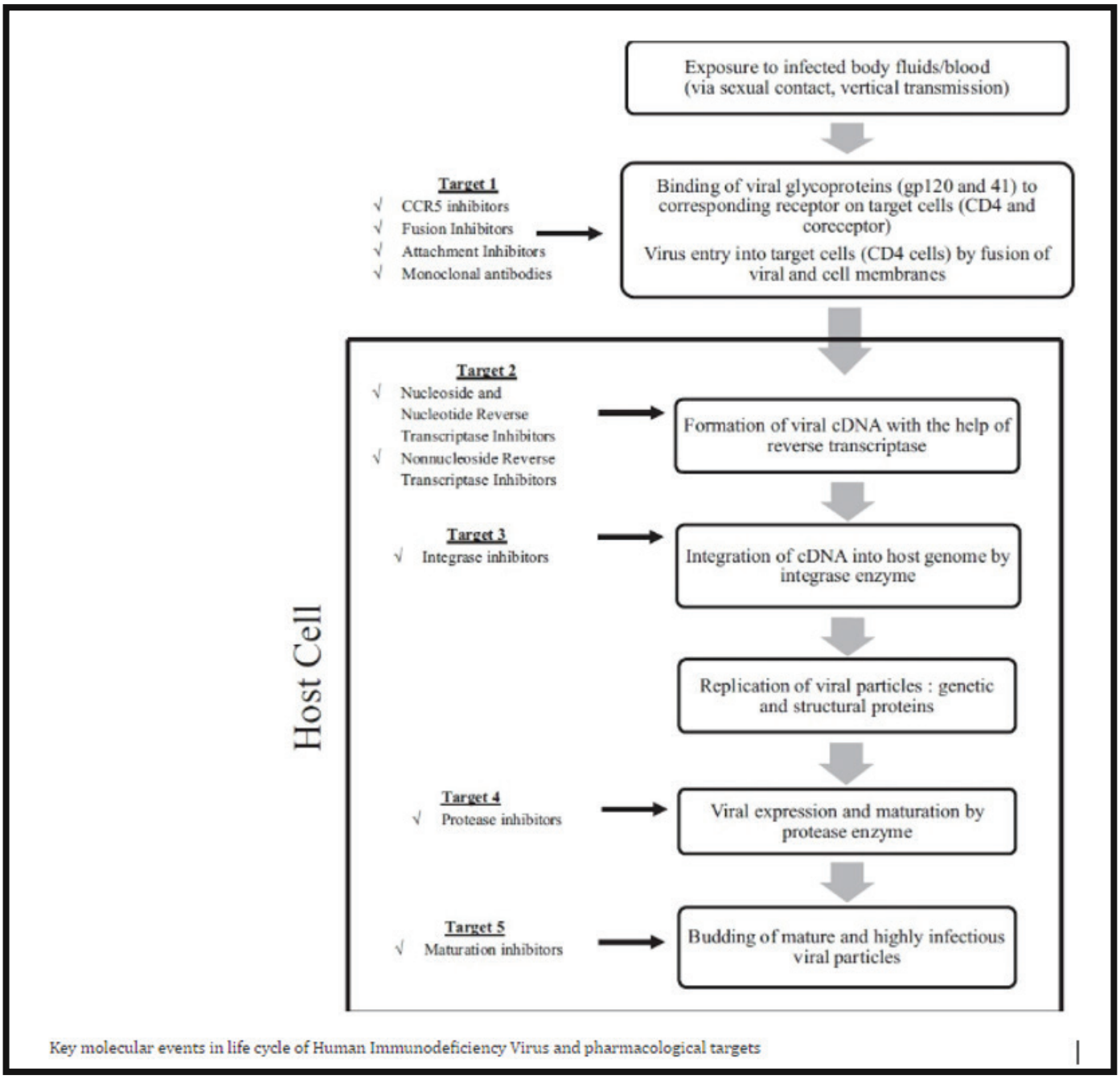
The success of HAART has increased the life expectancy of HIV patients. This has resulted into increased number of patients over 50 years, living with HIV. It is likely that these elderly patients are exposed to broad range of concomitant medications along with ARV regimens. However, the choice of these medications may not be always straightforward. The metabolic side effects of these ART increase the risk of CVS disease. The selection of antihypertensive and antihyperlipidemic agents need extra care, and the most appropriate drug may not always be a first line agent.

Many ARVs are contraindicated or may require dose modification or adjustment in special group of patients like pregnant women and children. Treatment of HIV-1 infected young pediatric patients is a daunting task due to limited approval of appropriate pediatric drugs, dosage formulations and fixed dose combinations. The safety and correct dosing of key ARVs have not been established in young children, and appropriate child adapted formulations do not exist.

A pre-treatment counseling of patient and family members regarding the disease, strict adherence to drug treatment, regular follow-up, changing the life style and dietary measures are essential elements for successful treatment. All these require deep understanding and co-operation from HIV patients that may be challenging in developing countries.

Challenges with the Use of ARV Drugs

A thorough understanding of life cycle of an HIV has identified potential pharmacological targets to interfere with viral replication. The key molecular events include virus entry, nuclear import, reverse transcription, genomic integration and viral maturation [Figure 1]. Prior to entry of HIV into the host cell, the virus envelope glycoprotein gp120 attaches to CD4 receptor on the host cell membrane, undergoes conformational changes and interacts with chemokine receptors, such as CCR5 or CXCR4. This in turn allows insertion of gp41 subunit in the host cell membrane, resulting in fusion of viral and host cell membrane. These interactions take place before an HIV enters into the host cell. The viral entry has been recognized as an attractive point of interest and led to a novel drug class known as entry inhibitors. Following an entry into the cell cytoplasm, the viral protein is transported to the host cell nucleus. Reverse transcription of single stranded viral RNA into DNA takes place within the pre-integrated complex in the nucleus of the host cell with the help of reverse transcriptase (RT) enzyme. Reverse transcriptase inhibitors interfere with RT activity either by competing with the natural substrates and incorporating into viral DNA to act as chain terminators in the synthesis of proviral DNA or by allosteric inhibition of RT. HIV integrase enzyme processes the viral DNA into the host genome to form the provirus. This step is an essential target for prospective new and novel class of ARV drugs, the integrase inhibitors. The integrase inhibitors prevent the integration of viral DNA into host cell chromosomes, inhibiting viral protein production. The HIV protease enzyme covers the virus particles by protein layers, resulting into a fully mature and infective virus. Targeting protease enzyme by Protease Inhibitors (PIs) has been an important target to disrupt the viral replication as it result into immature and defective virus. A final and important stage for virus maturation involves protein precursor, Gag, that induces major structural and morphological changes in the HIV particle. A class of drug that inhibits processing of Gag protein disrupts the maturation process, known as maturation inhibitors.



Key molecular events in life cycle of Human Immunodeficiency Virus and pharmacological targets

Existing Antiretroviral Drug Classes

Currently, there are 6 classes of ARV agents with 25 drugs approved for single drug treatment and 12 as fixed dose combination by US-FDA [Tables [Tables1 and and2]. These drugs target 4 distinct proteins i.e. host cell receptor, reverse transcriptase, integrase and protease to retard HIV replication. The conventional classes of ARVs are nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitor (PIs). The recently approved newer groups include fusion inhibitors, chemokine co receptor (CCR) antagonists and integrase inhibitors. The agents with unique mechanisms under development are CD4 attachment inhibitors, maturation inhibitors, lens epithelium derived growth factor inhibitors and capsid assembly inhibitors [Table 2].

Table 1

Antiretroviral drugs approved by the US FDA

Categories	NRTIs	NNRTIs	PIs	Entry Inhibitors (CCR5 and Fusion inhibitors)	Integrase Inhibitors
Treatment naïve patients	Zidovudine (AZT) Stavudine (d4T) Lamivudine (3TC) Didanosine (ddI) Zalcitabine (ddC) Abacavir (ABC)	Nevirapine (NVP) Delviradine (DLV) Efavirenz (EFV) Rilpivirine ()	Ritonavir (RTV) Indinavir (IDV) Saquinavir (SQV) Nelfinavir (NFV) Amprenavir (APV) Fosamprenavir (FPV) Atazanavir (ATV)	-	-
Treatment experienced patients	Tenofovir (TDF)* Emtricitabine (FTC)*	Etravirine (ETV)	Tipranavir (TPV) Darunavir* (DRV)	Maraviroc* Enfuvirtide	Raltegravir*
Prevention of vertical transmission (WHO guidelines)	Zidovudine Lamivudine Tenofovir Emtrictabine	Nevirapine Efavirenz	-	-	-
Children	Zidovudine Stavudine Lamivudine Didanosine Emtricitabine Abacavir	Nevirapine	Ritonavir Nelfinavir Darunavir	Enfuvirtide	-
For post exposure prophylaxis	Zidovudine (AZT) Stavudine (d4T) Lamivudine (3TC) Didanosine (ddI) Emtricitabine (FTC) Tenofovir (TDF)	Efavirenz	Indinavir Nelfinavir Ritonavir Saquinavir Fosamprenavir Atazanavir Ritonavir/Lopinavir	Enfuvirtide	-
For pre exposure prophylaxis	Tenofovir and Emtricitabine in MSM				

*Approved for both treatment naïve and treatment experienced patients MSM – Men who have sex with men
NRTI = Nucleoside Reverse Transcriptase Inhibitors; NNRTI = Non Nucleoside Reverse Transcriptase Inhibitors; PI = Protease Inhibitors

Table 2

Fixed dose combinations of Antiretroviral drugs approved by US FDA

Approved for adult use	Approved for pediatric use
Zidovudine + Lamivudine	Zidovudine + Lamivudine
Zidovudine + Lamivudine + Nevirapine	Stavudine + Lamivudine
Stavudine + Lamivudine	Ritonavir + Lopinavir
Stavudine + Lamivudine + Nevirapine	
Abacavir + Lamivudine	
Zidovudine + Abacavir + Lamivudine	
Lamivudine + Tenofovir	
Lamivudine + Tenofovir + Efavirenz	
Tenofovir + Emtricitabine	
Tenofovir + Emtricitabine + Efavirenz	
Ritonavir + Lopinavir	
Amprenavir + Ritonavir	

I. Nucleoside reverse transcriptase inhibitors (NRTIs)

NRTIs were the first to be approved and form the backbone of an HIV treatment. They are preferred as first line drugs because of favorable pharmacokinetic profile, especially long intracellular half life, high oral bioavailability and administration without regard to food, availability as fixed dose combinations (FDC) with convenient once or twice daily dosage schedule and low risk for drug-drug interactions.

However, NRTIs have low genetic barrier for drug resistance, and continued treatment is reported to accumulate mutations that causes resistance and cross-resistance to agents within the class. Moreover, the current drugs in this class are associated with bone marrow suppression and high mitochondrial toxicity. The potential to cause serious and irreversible toxicity increases with long term use of stavudine. Hence, the recent WHO guidelines recommend a gradual phase out of stavudine. However, in developing countries, it is still widely used as first-line treatment because of its low cost and an easy availability. Recently, the guidelines for the industrialized nations have been revised by the US Department of Health and Human Services (DHHS) where tenofovir (TDF) and emtricitabine (FTC) combination is the preferred NRTI component in an initial regimen. This combination has shown superior virologic and immunologic response as compared to AZT + 3TC and is also effective against hepatitis B virus with lower rate of lipotrophy as compared to stavudine and AZT. Although nephrotoxicity has been a concern with TDF, it is rare in treatment-naive patients but requires a periodic monitoring of renal function. Even abacavir (ABC) has been stepped down to alternative option on an initial therapy due to reports of high virologic failure, hypersensitivity and cardiovascular risk, especially myocardial infarction. The new agents apricitabine and elvucitabine are currently being evaluated against HIV-1 isolates resistant to conventional NRTIs.

a) Apricitabine (AVX754, formerly SPD754)

Apricitabine is a cytidine analogue, active against HIV-1, isolates resistant to lamivudine, zidovudine and other NRTIs. Interestingly, the preclinical studies have failed to demonstrate mitochondrial toxicity or any effect on mitochondrial DNA in high doses. It has been observed that apricitabine was effective in 50 treatment-experienced patients, failing to respond to lamivudine or emtricitabine containing regimen. A phase II trial of 600 mg-800 mg apricitabine at 24 weeks demonstrated higher antiviral activity as compared to lamivudine containing regimen. The drug seems to be promising against NRTIs-resistant HIV strains for treatment-experienced patients.

b) Elvucitabine

Elvucitabine is also a new cytidine analogue, active against HIV 1, and is compared to lamivudine. A phase II trial at 48 weeks showed similar efficacy and safety profile in treatment-naive patients as compared to 3TC.

c) Amdoxovir

Amdoxovir is an investigational compound, having activity against HIV-1 isolates. It is particularly designed and developed for use against the first line NRTI resistant HIV mutants with an improved safety and efficacy. It is well-tolerated and shown to act synergistically in combination with low and standard doses of AZT by significant reduction in viral load as compared to amdoxovir alone.

II. Non-nucleoside reverse transcriptase enzyme inhibitors (NNRTIs)

NNRTIs are an integral part of initial treatment regimen along with 1 or 2 NRTIs and a PI. In developing countries, nevirapine or efavirenz is commonly included in an initial regimen due to their efficacy, low cost and convenient dosage schedule. Nevirapine is also safe in pregnancy and has been extensively used to prevent vertical transmission. However, nevirapine-based regimen has been reported to cause fatal cutaneous hypersensitivity and hepatotoxicity. In resource-rich countries, efavirenz is now preferred over nevirapine in initial regimen as it is available as once a day formulation or as FDC along with tenofovir and emtricitabine (TDF + FTC). Efavirenz has short term CNS side effects and is also teratogenic. Moreover, both the drugs are a substrate for cytochrome enzyme (CYP 3A4) that results into frequent interactions with drugs metabolized through same pathway. Like NRTIs, NNRTIs also have low genetic barrier to drug resistance. Even a single mutation may result into cross-resistance. Interestingly, virus isolates resistant to AZT or ddI can get selected and have shown resistance to nevirapine or delaviridine. It is also estimated that 5% to 7% of newly infected patients already have NNRTI-resistant mutants. Hence, patients who fail to respond to one NNRTI are not prescribed other NNRTI in future regimen. The limitations associated with first generation NNRTIs have resulted into search for new agents that can take care of the critical issues.

a) Etravirine (TMC 125)

Etravirine (ETV), a second generation NNRTI, has been approved by US-FDA. An evaluation of its efficacy, safety and tolerability in treatment-experienced patients has been promising. It has significant activity against first generation NNRTI-resistant HIV-1 virus with some activity against HIV-2. The drug is specially developed with a high genetic barrier to resistance with unique genotypic resistance profile. It is specially recommended for patients with documented NNRTI resistance. The long half life, high barrier to resistance and good antiviral efficacy of etravirine make it a major force in this class of drugs. However, it is also a substrate and inhibitor of several CYP 3A4 enzymes, and therefore, contraindicated for use with anticonvulsants, antimycobacterials and other NNRTIs. It also requires dosage adjustment if used with drugs, metabolized by CYP enzyme system.

b) Rilpivirine (TMC 278)

Rilpivirine, an addition in the list of NNRTI, has also shown in vitro activity against HIV resistant strains. It has been evaluated as an alternative to efavirenz in a phase III clinical trial in the dose of 25 mg per day with TDF/FTC regimen. The convenient dosage schedule, high genetic barrier to drug resistance, effectiveness against HIV strains resistant to conventional NNRTIs, lack of antagonism with other ARV drugs and fewer adverse reactions are some important characteristics of rilpivirine.

c) RDEA806

This is a new NNRTI that has shown activity against HIV-1 resistant mutant in phase II trials. Unlike other NNRTIs, it does not inhibit or induce cytochrome enzyme system.
III. Protease inhibitors (PIs) PIs have high genetic barrier for drug resistance, and the use of low dose ritonavir as boosting agent is now considered as first line option for patients who do not respond to or tolerate an initial treatment regimen. However, the mutations that arise from selection pressure from any PI can grant cross-resistance to other drugs in the same class. Most of the PIs except nelfinavir are available with ritonavir boosting and have been approved and preferred options for an initial ART by the US Department of Health and Human Services and International AIDS society USA guidelines. Low dose ritonavir as boosting agent has not only increased the utility of PIs-based regimen but also opened a new area of research for novel class of drugs. The limitations of PIs include insulin resistance, dyslipidemia, hypertriglyceridemia, high risk of coronary artery disease and clinically significant interactions with antifungals, antimycobacterials, hormonal contraceptives, HMG-coenzyme reductase inhibitors, antihistaminics, anticonvulsants, psychotropics, ergot alkaloids and sedatives.

a) Atazanavir (ATV)

Atazanavir is a second generation PI and is claimed to have a 20 times more potent antiviral activity than other PIs. Boosted ATV has been preferred over LPV/r in treatment-naive and experienced patients due to once a day administration, convenient dosage schedule and minimal effect on lipid profile.

The drug has similar pharmacological actions as other PIs, including metabolism by cytochrome P450. It has also been reported to elevate serum transaminase levels and cause hyperbilirubinemia, prolong PR interval and asymptomatic heart block. Rare but serious ADRs like S.J. syndrome and hepatotoxicity have also been reported. H2 receptor blockers and proton pump inhibitors should be avoided as ATV requires acidic pH for complete absorption.

b) Tipranavir (TPV)

Tipranavir is a second generation PI, approved for use in patients with PI resistant strains. Its combination with NNRTIs and NRTIs is additive while with fusion inhibitor, enfuviritide, it is observed to have the synergistic action. A phase III clinical trial of ritonavir-boosted 500 mg TPV showed superior virologic and immunologic response as compared to ritonavir-boosted peptidomimetic PIs. It requires 15-20 mutations in HIV protease gene to develop resistance to TPV as compared to few mutations to peptidomimetic PIs. It can be administered with high fat meal and is metabolized by CYP 450 that may result into interactions.

c) Darunavir (DRV)

Darunavir, a new non-peptidic PI, has been developed and studied for treatment-experienced patients with PI-resistant mutations. The results of phase III clinical trials of riotnavir-boosted darunavir (100 mg+600 mg twice daily) showed an improved virologic response and hence the drug was approved for patients with multi-drug resistant HIV infection. Several other studies have also observed greater virologic and immunologic benefit with DRV as compared to standard PIs for treatment-experienced patients with PI resistant mutations. Darunavir has also been tested in treatment-naive patients. A phase III clinical study, comparing darunavir (800 mg) plus ritonavoir (100 mg) once a day or LPV/r once or twice a day along with TDF plus FTC, showed similar viral suppression with minimal gastrointestinal and lipid side effects at 48 weeks. Hence, darunavir is now the preferred ritonavir-boosted PI for treatment–naive patients in developed countries. However, the incidence of lipid abnormalities with DRV use is similar to other PIs. Tipranavir and darunavir have been approved as they have superior virologic and immunologic response as compared to riotnavir-boosted PI. Both the drugs are specially recommended for use in treatment-experienced patients, especially in presence of multi-drug resistant virus and documented treatment failure.

d) Brecanavir (GW 640385)

Brecanavir, a new PI, has shown high activity against the PI resistant strains of HIV-1 virus. Co-administration with ritonavir markedly increases an oral bioavailability. However, its development has been stopped due to failure of drug formulation to achieve the effective blood levels.

New Antiretroviral Drug Classes

The intricate details of viral entry and maturation process have identified new classes of ARV drugs, especially entry inhibitors (chemokine receptor and fusion inhibitors) and integrase inhibitors. A few of them are approved for clinical use, and many more are in pipeline. These drugs achieve high level of viral suppression in patients with multi-drug resistant HIV-1, especially in a failing regimen. Currently, their status is limited as add on therapy in highly treatment-experienced patients. Search is also on to find new drugs acting on host cell receptors, which may provide a greater variety and opportunity to disrupt viral replication. New classes with unique mechanism of action, which are currently under development, are CD4 receptor attachment inhibitors, maturation inhibitors, pharmacokinetic enhancers, capsid assembly inhibitors and lens epithelium derived growth factor inhibitors [Table 3].

Table 3

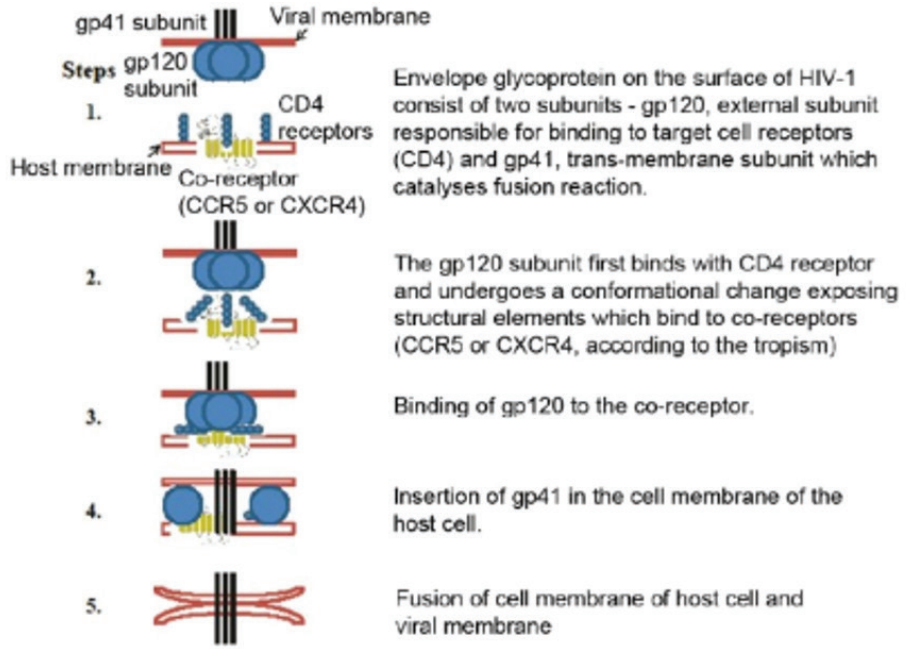
List of novel antiretroviral drugs and HIV targets

Drug Group	Name of the drug	Target	Current status
Fusion Inhibitors	Enfuvirtide	gp41 subunit of envelop protein	Approved in 2003
CCR5 inhibitors	Maraviroc	Small molecule CCR5 receptor antagonist	Approved in 2007
	Aplaviroc		Trials discontinued due to hepatotoxicity
	Vicriviroc		Trials discontinued due to poor antiviral activity
	PRO140	Monoclonal antibody against CCR5 receptors	Completed phase II clinical trials
Integrase inhibitors	Raltegravir	Integrase enzyme	Approved in 2007
	Elvitegravir		Undergoing phase III clinical trials
Attachment inhibitors	Ibalizumab	Monoclonal antibody against CD4 receptors of host cells	Completed phase II clinical trials
Maturation inhibitors	Bevirimat	gag structural protein	Completed phase II trials
Lens epithelium derived growth factor inhibitors	CX00287	Block the interaction of LEDGF/p75 with integrase enzyme of HIV-1, prevents integration of proviral DNA	Under development
Capsid Inhibitors	PF-3450071	Inhibitor of HIV-1gag polypeptide assembly	Under development
	PF-3450074	and also dismantles assembled HIV-1 caspid assembly tubes	

I. Entry inhibitors

HIV-1 entry into the host cell is a multistep process, involving attachment of virus to CD4 and chemokine receptors (CCR5 or CXCR4). A complex interaction between host cell receptors and viral glycoprotein brings both viral and host cell membranes in close proximity, resulting into fusion [Figure 2]. This knowledge has helped in identifying novel drug classes like fusion inhibitors and chemokine receptor antagonists. Pharmacologically, sequential inhibition of the successive steps of viral entry pathway by combination of fusion inhibitor and chemokine receptor blocker would result into synergism.

Figure 2



Multistep process of viral entry pathway

i) Chemokine receptor inhibitors

The chemokine receptors, CCR5 and CXCR4 belong to G protein coupled receptor family and help in activation and migration of T cells. HIV-1 isolates bind to a specific co-receptor known as HIV tropism in order to gain an entry into host cell. Commonly, R5 strains bind with CCR5 and X4 binds with CXCR4. However, initially HIV-1 isolates use a single co-receptor (most commonly CCR5), but as the disease progresses, other co-receptors (such as CXCR4, CCR3 and CCR2b) are also detected. An interaction between HIV-1 and CCR5 can be prevented by small molecule antagonists, monoclonal antibodies and modified natural CCR5 ligands

a) CCR5 receptor inhibitors

Aplaviroc was the first CCR5 inhibitor and has been followed by maraviroc and vicriviroc. Further evaluation of aplaviroc and vicriviroc has been discontinued due to adverse reactions and poor antiviral activity, respectively. Initially, maraviroc was approved for use in treatment-experienced patients, based on the results of phase III trials (MOTIVATE 1 and 2) with better suppression of viral load at 48 and 96 weeks (150 mg to 300 mg once or twice a day) as compared to placebo. Investigations in treatment-naïve patients have demonstrated it to be similar to efavirenz, and therefore, the approval was expanded to include ART naïve patients with CCR5 tropic virus. The drug is well-tolerated with minimal side effects like abdominal pain, asthenia and postural hypotension. Maraviroc is a substrate for the CYP 3A4, and therefore, dose adjustment is necessary when co-administered with other drugs that use the same pathway. A tropism testing is also necessary prior to use of maraviroc as patients with CXCR4 or mixed HIV-1 do not respond well. In addition, resistance patterns have already been observed with CCR5 inhibitors, either through selection of minority variants of CXCR4 or a dual/mixed tropic virus or by development of mutations. This is potentially dangerous as CXCR4 tropic virus is associated with greater and faster decline in CD4 counts.

b) CXCR4 chemokine receptor inhibitors

AMD-070 is an investigational compound with potent in vitro antiviral activity against wild type X4 virus but with no action against R5 tropic virus. The development of CXCR4 compound has been slow as unlike CCR5, which is present in more than 50% of HIV infected patients, X4 is found in mixtures with R5. Hence, simple inhibition of CXCR4 may not be sufficient to decrease the plasma viral load substantially. On the other hand, combination of CXCR4 and CCR5 would be more effective. Preliminary studies with AMD3100 showed inhibition of the X4 component of the virus population, but further development of this parenterally administered drug as an antiretroviral agent was discontinued due to QTc prolongation.

ii) CCR5 antibodies

PRO140 is a humanized monoclonal antibody against chemokine receptor CCR5, which inhibits R5 tropic HIV-1 at low concentration that does not affect natural action of CCR5. It received fast track status by the FDA in 2006. PRO140 acts by binding to an extracellular site on the CCR5 co-receptor and prevents fusion of HIV-1 membrane with host cell and the subsequent infection of healthy host cells. In vitro studies have shown synergism between CCR5 inhibitors and antibodies.

A proof of concept study with a single intravenous infusion of PRO140 showed potent, rapid and dose-dependent reduction of viral load of more than 10 fold, lasting for 2-3 weeks. Significant antiviral activity was also observed in a randomized, double blind trial as compared to placebo. Subcutaneous PRO140 has also been investigated with similar results. A Cochrane review on PRO140 concluded that although preliminary studies look promising, an evidence is insufficient, and larger trials would be required to provide conclusive proof of efficacy in HIV infected patients.

iii) Fusion inhibitors

a) Enfuvirtide (T-20)

Enfuvirtide is the only fusion inhibitor approved by US FDA for treatment-experienced patients who failed other antiretroviral therapy. It is a synthetic peptide and is structurally similar to a section of gp41. It blocks the conformational changes in gp41 and hence blocks an entry of virus in the host cell. An advantage of enfuvirtide over CCR5 inhibitors is that it targets both R5 and X4 tropic virus. Enfuvirtide along with optimal background treatment (OBT) has demonstrated significant antiviral activity in treatment-experienced patients at 24 weeks as compared to patients receiving OBT alone. It was also assessed as a part of multi-drug antiretroviral regimen and has shown a greater decline in viral RNA load when combined with darunavir/ritonavir (POWER 1 and 2), tipranavir, tenofovir and zidovudine. Hence, it is important as add on therapy. An evaluation of enfuviritide in treatment-experienced children, adolescents and for prevention of mother to child HIV transmission has been encouraging. The common ADRs are local reaction due to subcutaneous administration and bacterial pneumonia. Parenteral administration of the drug, local site reactions, cost and inconvenience associated with its use place the drug in a reserve category for patients when all treatment fails. Resistance to enfuviritide develops within a few weeks due to mutation of HR1 region of gp41 as well as HR2 indicate low genetic barrier.

b) Sifuviritide

Sifuviritide, an investigational fusion inhibitor, is more potent against HIV-1 than enfuviritide. However, in vitro studies have reported an HIV variant resistant to sifuviritide due to specific mutations at gp120. The mutant viruses also demonstrated variable degrees of cross-resistance to enfuvirtide, some of which are preferentially more resistant to sifuviritide.

c) T1249

T1249, a second generation fusion inhibitor, is shown to be effective even against enfuvirtide resistant HIV-1 strains as well as HIV-2 and simian immunodeficiency virus (SIV).

II. Integrase inhibitors

Integrase inhibitors inhibit strand transfer of viral DNA to host cell DNA. The first agent 'raltegravir' has been approved by US-FDA for both treatment-experienced and naïve patients. The rational for prescribing this drug in treatment-naïve patients is to preserve NNRTI and PI for future regimens. The second drug 'elvitegravir' is undergoing phase III trials.

a) Raltegravir

Raltegravir demonstrated significant antiviral activity against HIV isolates resistant to a variety of antiretroviral drugs such as protease inhibitors, NRTIs and NNRTIs. It is as effective as efavirenz in reducing viral RNA count at 48 and 96 weeks. Even in treatment-experienced patients with documented virologic failure, a combination of raltegravir, etravirine and darunavir/ritonavir demonstrated a decrease in HIV RNA count to <50 cells/ml in 90% and 86% patients at 24 and 48 weeks, respectively. Raltegravir is also shown to be non-inferior to enfuvirtide in patients with multi-drug resistant HIV-1 infection who are averse to subcutaneous injections of enfuvirtide. Unlike PIs, it improves lipid profile, and the chances of interactions are few as compared to other antiretrovirals. Co-administration with atazanavir and tenofovir can increase drug levels of raltegravir as both inhibit UGT1A1, which metabolizes raltegravir. This interaction could be beneficial as the dose of raltegravir required can be decreased. Raltegravir has potential for use at all stages of HIV treatment in treatment-experienced and naïve patients due to significant antiviral activity, short term safety and tolerability and fewer chances for interactions

b) Elvitegravir (formerly GS-9137 and JTK-303)

Elvitegravir is a quinolone derivative with potent antiviral activity. A difference between raltegravir and elvitegravir is that the former is metabolized by glucuronidation and the latter is first metabolized by CYP 3A4/5. The clinical importance of this fact is that co-administration of elvitegravir with ritonavir or any pharmacoenhancer results in almost 20 fold increase in plasma concentration, requiring only once-daily dose. A 10 day monotherapy in both treatment-naïve and experienced patients (elvitegravir with ritonavir) has shown significant reduction in HIV RNA levels. A randomized, phase II trial in treatment-experienced patients showed that elvitegravir is as effective as boosted PI regimen at 48 weeks.

However, integrase inhibitors have a low genetic barrier to resistance i.e. even a single mutation can cause a decrease in susceptibility. Failure of therapy due to resistance to raltegravir has been demonstrated even in phase III trials. Out of 105 patients who experienced virologic failure in the BENCHMARK studies, 64 patients had genotypic experience of an integrase resistance.

c) GSK-1349572

GSK-1349572 (S/GSK-1349572), an investigational second generation integrase inhibitor for oral treatment of HIV infection, displayed in vitro activity against integrase-resistant HIV-1 isolates from patients experiencing virological failure while receiving raltegravir. The pharmacokinetic profile of GSK-1349572 supports once-daily dosing without boosting with ritonavir. In phase I and II clinical trials, side effects reported are similar to placebo and not related to the dose or duration of treatment. Phase IIb trials of GSK-1349572 are being conducted in antiretroviral-naïve and in experienced patients. With the high demand for second-generation integrase inhibitors for antiretroviral experienced patients and once-daily dosing without ritonavir-boosting for treatment-naïve patients, GSK-1349572 has the potential to become a highly valued product.

III. Pharmacokinetic enhancers

The current strategy is to exploit the pharmacokinetic profile of one ARV drug to enhance the therapeutic effect of the concomitant ARV drug. This has opened the possibility of pharmacokinetic enhancers without having anti-HIV activity. Ritonavir is already being used extensively to boost other PIs. Surprisingly, it has been observed that ritonavir can also boost drugs in other classes such as, elvitegravir (an integrase inhibitor) and vicriviroc (a CCR5 inhibitor). However, ritonavir is associated with gastrointestinal intolerance, dyslipidemia and diabetes. Pharmacokinetic enhancers are a major step towards identifying ritonavir alternatives.

Cobicistat (GS-9350), SPI-452

Cobicistat and SPI-452 are 2 compounds under investigation. Cobicistat has no anti-HIV activity but is a potent inhibitor of CYP3A. It increases the blood level of certain ARV drugs, allowing once-daily dosing. It is found to be safe and well-tolerated in escalating single and multiple dose-ranging studies in healthy volunteers. It is under trial as a standalone boosting agent for PIs, especially atazanavir and integrase inhibitor elvitegravir as FDC and found to be comparable with ritonavir. It also has a low potential to cause lipid and glucose abnormalities than ritonavir. SPI-452 is another investigational pharmacokinetic enhancer without anti-HIV activity. It is being investigated to increase the exposure of darunavir and atazanavir. Both the drugs have been shown to enhance the plasma levels of PIs.

IV. CD4 receptor attachment inhibitors

The attachment of outer membrane gp120 to CD4 receptor is inhibited by investigational compounds that constitute the new class of CD4 receptor attachment inhibitors.

a) Ibalizumab (TNX-355)

Ibalizumab, a humanized monoclonal IgG4 antibody against CD4 receptors, was granted fast track status by US-FDA in 2003. It inhibits viral entry by attaching with extracellular domain of CD4 receptors. The binding site is distinct from gp120 and is designed in a way so as not to interfere with immunological function of CD4 receptors. Its novel mechanism of action leads to potent antiviral activity in spite of HIV tropism and an unlikely cross-resistance with other antiretrovirals. A single dose, proof of concept study showed efficacy and tolerability of a range of doses (0.3 mg/kg to 2 5 mg/kg). The greatest effect in reducing viral load and increase in CD4 count is seen at 25 mg/kg. Adverse effects have been observed to be headache, rashes, nasal congestion and urticaria. Similar efficacy was also seen in phase Ib study with once and twice a week regimens. A phase Ib study was found to decrease the HIV-RNA copy initially for 2 weeks, however, the levels increased back towards baseline, indicating reduced susceptibility. It has also shown synergistic effect with fusion inhibitors. Parenteral administration of the agent may be a problem for regular use. The drug is under further evaluation.

V. HIV maturation inhibitors

This is an emerging class of drugs that targets internal structural protein precursor Gag, which is vital in final stage of virus development for a mature and infectious virion.

a) Bevirimat (formerly PA-457)

Bevirimat is a novel agent that acts on the last and important stage of HIV maturation before it buds from host cell. The primary target of the drug is gag polyprotein precursor, the main structural protein of the assembly and budding of the viral particles. It prevents the cleavage of the precursor protein to a mature viral capsid protein. This disrupts gag processing and results in defective, immature, non-infectious viral particle. The pharmacokinetic profile is favorable with long half life and once a day dosing. A preliminary phase IIb trial in patients with resistance to 3 antiretroviral drug classes has shown decline in plasma HIV-RNA level. The initial results are encouraging, and it seems that maturation inhibitors may find a place in HIV therapeutics in coming years. Bevirimat has been granted the fast track status by the FDA in 2005.

VI. Lens epithelium derived growth factor inhibitor

HIV-1 can integrate their DNA at different sites in host DNA. During the pre-integration complex, the HIV integrase interacts and binds with host cell factors. Researchers have identified lens epithelium derived growth factor (LEDGF) that directs HIV-1 DNA integration to different sites in host genome. This interaction has been an interesting target for antiviral therapy. Researchers used rational design to identify small molecules to fit the interaction by a series of 2 - (quinoline-3-yl) acetic acid derivatives. These compounds have been investigated as lens epithelium derived growth factor inhibitor. It has been observed that CX00287 moderately inhibits LEDGF and HIV replication in vitro. Further research is going on.

VII. Capsid assembly inhibitors

Capsid assembly inhibitors are a new class of drugs for treating HIV infection. Virus capsid is made up of identical, symmetrically arranged protein blocks that maintain the structure of the virus particle. It plays an important role in early and late stages of viral replication and is essential for the survival and infectivity of the virus. Hence, virus capsid has been recognized as a potential target for new class of ARV drugs. The molecule that inhibits the interactions between structural proteins would affect the integrity and survival of the virus.

a) PF-3450071 and PF-3450074

PF-3450071 and PF-3450074 act early in the HIV-1 replication cycle at a step following HIV-1 envelope-mediated entry. Both the compounds were evaluated in single cycle infection assays and in the viral production-infectivity assay, using NFV (PI) and EFV (NNRTI) as late stage and early stage inhibitor controls. Both of them inhibited the production of infectious virus.

Preventive Measures for HIV Infection

Until recently, the prevention of HIV-1 infection has centered on the pregnant women to prevent mother to child transmission of virus. The use of AZT and NVP to prevent neonatal HIV-1 infection achieved considerable success in resource-rich countries. The idea of HIV-1 treatment as preventive measure generated tremendous interest as it is believed to prevent or reduce the rate of sexual transmission of virus to uninfected partner. A number of population-based prevention studies are currently under pilot or at planning stage. In addition to drug treatment, the current HIV prevention measures also include behavioral messages such as, "ABC" approach (Abstinence, Be faithful, Condom use). However, they have limited impact on the incidence rate of HIV in women. A search for prevention techniques that can be easily used by women, effective in presence of seminal fluid, compatible with latex and acceptable to all partners is underway.

a) Microbicides

Microbicides are used for an application in vagina and rectum to prevent transmission of sexual transmitted diseases including HIV. They are also called topical pre-exposure prophylaxis (PrEP). Agents that can disrupt viral membrane, surfactants, especially 9-non-oxynol, anionic polymers etc., have been tested, but results have generally been disappointing. Tenofovir disoproxil has been tested in a gel formulation as a vaginal microbicide. In vitro and in vivo studies have demonstrated its efficacy both as pre-exposure and post-exposure prophylaxis. The CAPRISA004 trial has shown tenofovir to decrease an HIV infection in uninfected women by 39% when applied vaginally in 2 doses over a period of 24 hours. Efficacy of an oral tenofovir with emtricitabine has also been tested with positive results i.e. 44% reduction in HIV transmission. CDC has already recommended the use of this combination for prophylaxis. Similarly, trials studying the efficacy and safety of combined oral and topical tenofovir are also going on. An NNRTI being developed as a vaginal gel is dapivirine, which has demonstrated efficacy in in vitro studies. However, the advent of PrEP has raised issues like the use of drugs in uninfected individuals, increased chances of risky sexual behavior (complacency), an adherence of the patient, resistance to antiretrovirals, acceptability of drugs with substantial ADRs and cost of the regimen that need to be addressed. Hence, PrEP can only be an adjunct along with behavioral change therapy.

b) HIV Vaccine

The development of vaccine against an HIV is considered to be worthwhile as majority of the patients live in developing countries and cannot afford treatment, lifelong therapy, side effects and problems of multi-drug resistance. While a lot of research is being done, it is not without pitfalls. None of the vaccines tested so far has been successful, the main problems being diversity of the virus, an ability of the virus to elude the immune system and lack of animal models. The STEP study tested the efficacy of recombinant Ad5 HIV-1 vaccine (viral vector carrying HIV-1 gag, pol and env antigens), but lack of efficacy and an increased HIV-1 acquisition in some subjects lead to premature termination of the trial.

Conclusion

Current antiretroviral drugs are highly effective, but drug resistance, drug-drug interactions, long term adverse events and compliance continue to be a challenge. New agents in conventional classes have revived the hopes for treatment-naïve and experienced patients. Promising new agents offer new choices as second line treatment options for treatment-experienced patients. However, an impact of their long term use on drug safety and drug-drug interactions is yet to be assessed. Several agents in entirely novel classes are under an investigation. However, none of the new agents have shown to eradicate the virus and is free from adverse events. Hence, there is a need for continuing search for novel drugs and to optimally utilize the available drugs to combat multi-drug resistant strains and eliminate virus replication. Parallel to HIV treatment, ARVs have also been shown to reduce the rate of sexual transmission of HIV-1. Thus, ARVs are recommended for pre-exposure prophylaxis to prevent HIV transmission through sexual contact. Making available an effective microbicide or vaccine that prevents HIV-1 acquisition still remains a major area of further research.

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Office No:- 99, 9th Floor, Kalpataru Avenue, Opp. ESIC Hospital,
Kandivali (East), Mumbai - 400101. M: 9322615653 | W: www.wmefi.co.in