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A Look Back at Anti-Retroviral Medication and its Current Scenario

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Abstract

AIDS is not a virus, but rather a set of symptoms caused by the HIV virus. AIDS is diagnosed when a person's immune system is too weak to withstand infection and they develop certain differentiating symptoms and disorders. Because AIDS weakens the immune system, patients are more vulnerable to infections and diseases. The development of efficient medicine delivery methods for the treatment of AIDS and HIV infections is a global issue. HIV is a chronic disease with no known cure, although many researchers are working hard to find one. With medical treatment, including antiretroviral therapy, it is possible to manage HIV and live with the virus for many years. HIV treatment began with monotherapy, and patients were later given a variety of drugs in regimens that required them to take 11–16 tablets every day. The therapy is currently based on a single set dosage of Tenofovir, Lamivudine, and Efavirenz per day or Zidovudine, Lamivudine, and Nevirapine twice per day. Toxicity, resistance, and adherence are still major concerns. Long-acting depot formulations that are effective for prevention and treatment while having fewer side effects are required. AIDS and HIV infection have reached pandemic proportions in many parts of the world. More efficient medication delivery systems are necessary due to the complexities of the viral infection cycle and the goals of antiretroviral medicine administration.

***Keywords:** AIDS, Anti-Retroviral, UNAIDS, HIV, Virus*

INTRODUCTION

The UNAIDS Global Report 2010 estimates that 33 million people globally are infected with HIV [1–2]. Sub-Saharan Africa has the world's highest HIV load, with 22.5 million HIV-positive people. Our area of the globe has the second highest number of HIV infections, with an estimated 4.1 million people infected. Even with enough resources, combating HIV in high-burden Asian and African nations is becoming increasingly difficult due to poverty, illiteracy, and widespread ignorance.

The human immunodeficiency virus causes acquired immunodeficiency syndrome (AIDS) [3–4], a chronic, sometimes deadly condition caused by the virus (HIV). HIV reduces your body's ability to fight disease-causing bacteria by wreaking havoc on your immune system. Without treatment, HIV can destroy your immune system for years, eventually leading to AIDS.

There is no cure for HIV/AIDS; however, there are medications that can dramatically postpone the disease's progression. These drugs have reduced AIDS deaths in several developed nations. This means that an HIV-positive person who is not receiving treatment may find it increasingly difficult to combat infections and diseases. If HIV is not treated, it can take ten to fifteen years for the immune system to become so weak that it can no longer fight the virus. However, the pace at which HIV spreads is determined by age, health, and family history. The HIV virus causes AIDS.

HIV is a retrovirus that attacks the immune system, which is responsible for keeping the human body healthy. This virus multiplies and eventually destroys T-helper cells (CD4). The most frequent types are HIV-1 and HIV-2. Type 1 HIV is the most common type. However, HIV-2 is mostly found in Western Africa, with occasional cases in India and Europe.

HIV treatment began with monotherapy, and eventually patients were given numerous medications in regimens that required them to take 11–16 pills per day. The therapy is now based on a single fixed-dose combination of Tenofovir, Lamivudine, and Efavirenz per day or Zidovudine, Lamivudine, and Nevirapine twice per day. Toxicity, resistance, and adherence continue to be critical issues. We require long-acting depot formulations that are effective for prevention and therapy while having fewer negative effects. In many regions of the world,

AIDS and HIV infections have reached epidemic proportions. Because of the intricacies of the virus infection cycle and the objectives for antiretroviral medicine administration, more effective drug delivery methods are required.

A global problem is the development of effective medication delivery systems for the treatment of AIDS and HIV infection. The introduction of combination, highly active antiretroviral therapy (HAART) has extended the life expectancy of HIV patients. HIV is a chronic disease with no known treatment, but many scientists are trying hard to develop one. It is feasible to control HIV and live with the infection for many years with medical care, including antiretroviral medication. A person infected with HIV is at risk of developing AIDS if they do not receive treatment. The immune system is too weak at that stage to fend off additional illnesses and infections. AIDS has a three-year life expectancy if left untreated. HIV can be well controlled with antiretroviral medication, and life expectancy can be comparable to that of someone who has not contracted HIV.

To develop effective screening methods and identify potential targets, a greater understanding of the biological processes involved in individual viral infections, including interaction with specific host components, is essential. A lot of data obtained from large-scale sequencing techniques used on people and pathogens will very certainly be useful in this process. In the development of future antiviral medications, drug effectiveness, toxicity, and cost must all be addressed.

The global HIV/AIDS objective is 90-90-90. This is a lofty therapeutic goal that might contribute to the abolition of the AIDS epidemic. By 2020, 90% of persons living with HIV will know their HIV status, 90% of people with confirmed HIV infection will get long-term ARV medication, and 90% of people on ARV therapy will have viral suppression.

To reach this aim, we need additional bullets in the form of new medications that are less hazardous and more effective. New medication research initiatives are continually attempting to provide more efficacious and less harmful compounds. However, no medication is perfect. There are constraints, such as the lack of platforms for larger clinical studies with a large number of patients to search for adverse medication effects.

In addition, genetic differences in PK/PD due to ethnicity are not known in all

situations. The costs of these newer treatments, once authorised by the FDA, are also uncertain because a lot of research and regulatory work has gone into them. Once accessible in the market, continual unbroken supply of these pharmaceuticals at a reasonable cost to the patient or free of charge under a national programme are important factors to consider. Another major concern is patient acceptance of the medicine and adherence to the specified doses and time schedules.

Basic Facts about HIV

1. The earlier HIV is diagnosed; the sooner treatment can start – leading to better long term health. So regular testing for HIV is important.
2. HIV cannot be transmitted through sweat, saliva or urine.
3. Using male condoms or female condoms during sex is the best way to prevent HIV.
4. HIV is a sexually transmitted infection (STI).
5. If you inject drugs, always use a clean needle and syringe, and never share equipment.
6. If you are pregnant and living with HIV, the virus in your blood could pass into your baby's body, or after giving birth through breastfeeding.
7. Taking HIV treatment virtually eliminates this risk.

Baseline Laboratory Tests

The necessary baseline laboratory investigations are listed below, the choice depends on the requirements of patient and clinical judgment of the ART clinician.

1. CD4 cell count.
2. Complete Blood Count, Haemoglobin percent.
3. ALT/SGPT – If needed other LFT (Liver function test).
4. Serum Creatinine – If needed other Kidney function test (Urea, Electrolytes).
5. Chest X ray, Sputum for AFB.
6. Hepatitis B and Hepatitis C screening test (for current or past PWID).
7. Urine for pregnancy test (if indicated in female).
8. Urine for Routine & Microscopic examination; Urinalysis to assess proteinuria.
9. Blood Sugar level.
10. For women, cervical Pap smear or other method of cervical cancer screening.

Guideline for Initiation of Anti Retroviral Drugs

Different guidelines exist for the treatment of HIV/AIDS which mainly include

Centre for Disease Control (CDC), World Health Organization (WHO), British HIV association (BHIVA), and HIV clinical guidelines programme, New York and World Health Organization (NACO), India. Though ART is recommended for all HIV-infected individuals in most of the guidelines, regardless of CD4 count, NACO India is yet to implement this policy. ART is also recommended for HIV-infected individuals to prevent HIV transmission. Patient education and counselling is very important before initiating ART to overcome the challenges with the improper use of ART and to maximize the benefits.

Current Situation

Currently, 16 antiretroviral drugs are approved for treatment of HIV infection. However, even the best currently available regimens pose challenges with regard to adherence, toxicity, antiviral activity, and resistance. New drug development thus confronts the need for improved convenience and tolerability, reduced toxicity, and improved activity against both wild-type and drug-resistant viruses.

Other goals of drug development include improved drug penetration into viral reservoirs (eg: genital tract and central nervous system) and exploitation of additional viral targets with the aims of achieving additive or synergistic effects with drugs from existing classes, reducing or preventing viral resistance, and improving treatment options in cases of drug resistance.

Major Goals of Antiretroviral Drugs

1. Maximal and durable suppression of viral load.
2. Restoration and/or preservation of immunologic function.
3. Reduction of HIV-related morbidity and mortality.
4. Improvement of quality of life of HIV infected persons.
5. Prevention of Mother to Child Transmission (PMTCT).
6. Providing Post Exposure Prophylaxis (PEP).
7. Minimise adverse effects of the treatment.
8. Prevent onward transmission of HIV.

These goals are achieved by suppressing viral replication completely for as long as possible, by using well tolerated and sustainable treatment taken with good adherence. With prolonged viral suppression, the CD4+ lymphocyte count usually increases, which is accompanied by a restoration of pathogen-specific immune function. For most patients, this

results in a dramatic reduction in the risk of HIV-associated morbidity and mortality. It is still unclear whether immune function ever returns to full normality. Long- term cohorts show that patients who adhere well to ART have a near-normal life expectancy.

CLASSIFICATION

ANTIRETROVIRAL DRUG [5-14]

This classification does not represent all the ARV drugs described above, these are the drugs currently recommended by guideline development team for the use. Depending on the mechanism of action, ARVs are categorized into following classes:

1. Nucleoside and nucleotide analogs (NRTI).
    a. Nucleoside reverse transcriptase inhibitors.
    b. Nucleotide reverse transcriptase inhibitors.
2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs).
3. Protease inhibitors (PIs).
4. Integrase inhibitors.
5. Fusion inhibitors.
6. Pharmacokinetic enhancers.

The role of the antiretroviral treatment for prevention of HIV transmission has also been demonstrated. This underlines the need of ensuring access to quality treatment for all people living with HIV. The development of current ART guidelines is based on two fundamental principles of HIV care- to provide standardized treatment regimens and to promote more than ninety-five percent adherences to the regimens. This will ensure effective antiretroviral therapy with minimal possibilities of resistance development to ARV, and reduce chances of further HIV transmission.

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors

The first effective class of antiretroviral drugs was the Nucleoside analogues. These are structural analogues of nucleosides and mimic the DNA building blocks there by stopping the viral replication process. The resulting DNA is incomplete and cannot create new virus. Nucleotide analogues work in the same way as nucleosides.

All nucleoside analogs have been associated with lactic acidosis as their common side effects. For the details of individual ARV of this class, refer the Table 1.

Table 1: List of Nucleoside/Nucleotide Reverse Transcriptase Inhibitors

S. No	GenericName	Dose	Adverse effects
1	Zidovudine (Mar1997)	300mg twice daily.	Anaemia, Neutropenia, Bone Marrow Suppression, GastroIntestinal Intolerance, Headache, Insomnia, Myopathy, Skin and Nail Hyper Pigmentation.
2	Lamivudine (Nov 1995)	150 mg twice daily or 300mg once daily.	Headache, Diarrhoea, Nausea, Vomiting, Minimal Toxicity.
3	Tenofovir (Oct2001)	300mg once daily.	Asthenia, Headache, Diarrhoea, Nausea, Vomiting, Flatulence Renal Insufficiency.
4	Abacavir (Dec1998)	300 mg twice daily or 600mg once daily.	Hypersensitivity Reaction, Fever, Rash, Fatigue, Nausea, Vomiting, Anorexia, Respiratory and Cardiac Problems.
5	Emtricitabine (July2003)	200mg once daily.	Diarrhoea, Headache, Nausea, Rash, Skin Discoloration, Hepato Toxicity or lactic acidosis.

Non-Nucleoside Reverse Transcriptase Inhibitors

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) stop HIV production by binding onto reverse transcriptase and preventing the conversion of RNA into DNA. These are called "non-nucleoside" inhibitors because they are not nucleoside analogues and act by physically blocking the reverse transcriptase. For the details refer the Table 2.

Table 2: List of Non-Nucleoside Reverse Transcriptase Inhibitors

S.No	GenericName	Dose	Adverseeffects
1	Nevirapine(Mar2011)	200mg once daily for 14 days followed by200mg twice daily.	Hepatitis, Hepatic Toxicity; Skin Rash, Stevens Johnson Syndrome.
2	Efavirenz (Sep1998)	600mg once daily.	CNS Symptoms, Insomnia, Confusion, Hallucinations, & Personality Change.
3	Rilpivirine(May2011)	25mg once daily.	Blistering Skin, Redness or Swelling of Eyes, Insomnia, Confusion.

Protease Inhibitors

Protease inhibitors work at the last stage of the viral reproduction cycle. These drugs prevent HIV from being successfully assembled and released from the infected C

Table 3: List of Protease Inhibitors

S.No	GenericName	Dose	Adverse effects
1	Lopinavir (Sep2000)	200mg Twice daily.	Diarrhoea, Nausea, Vomiting, Abnormal Lipid Profiles, Glucose Intolerance.
2	Saquinavir (Dec1995)	1000mg Once daily.	Diarrhoea, Nausea, Vomiting, Headache, Photosensitivity.
3	Atazanavir (June2003)	300mg Once daily.	Hyperbilirubinemia, Lipid Problem, Hyperglycaemia.
4	Darunavir (June2006)	600mg or 800mg Twice daily.	Diarrhoea, Nausea, Vomiting, Headache, Abnormal Lipid Profiles, Skin Rash.
5	Ritonavir (Mar1996)	50mg Twice or 100mg Once daily.	Diarrhoea, Nausea, Vomiting, Abnormal Lipid Profiles, Glucose Intolerance.
6	Tipranavir(June2005)	250mg Twice or 500mg Once daily.	Joint pain or Stiffness, Diarrhoea, Headache. Throat Tightness, Redness or Swelling of Eyes, Insomnia, Confusion.

Integrase Inhibitors

An enzyme found in HIV (and other retroviruses). HIV uses integrase to insert (integrate) its viral DNA into the DNA of the host CD4 cell. Integration is a crucial step in the HIV life cycle and is targeted by a class of antiretroviral (ARV) HIV drugs called integrase strand transfer inhibitors (INSTIs). By blocking integrase, integrase inhibitors prevent HIV from multiplying and can reduce the amount of HIV in the body, refer Table 4.

Table 4: List of Integrase Inhibitors.

S.No	GenericName	Dose	Adverseeffects
1	Raltegravir (Oct2007)	400mg Twice daily	Diarrhoea, Nausea, Vomiting, Headache, Insomnia.
2	Dolutegravir (Aug2013)	50mg Onceor Twice daily	Diarrhoea, Nausea, Vomiting, Headache, Abnormal Lipid Profiles, Skin Rash.

Fusion Inhibitors

Entry inhibitors, also known as fusion inhibitors, are a class of antiretroviral drugs, used in combination therapy for the treatment of HIV infection. This class of drugs interferes with the binding, fusion and entry of the HIV virions to a human cell. By blocking this step in HIV's replication cycle, such agents slow the progression from HIV infection to AIDS, refer the Table 5.

Pharmacokinetic Enhancers

A pharmacokinetic enhancer is used to boost the effectiveness of another drug. When the two drugs are given together, the pharmacokinetic enhancer interferes with the breakdown of the other drug, which allows the drug to remain in the body longer at a higher concentration. Pharmacokinetic enhancers are used in HIV treatment to increase the amount of other HIV medicines in the blood, refer the Table 6.

MECHANISMS OF ACTION

To understand the mechanism of action of ARV, one needs to understand the basic steps of the viral replication, in other words life cycle of HIV virus. Virus enters into the CD4 (host) cell involving glycoprotein of the virus and receptors of host cells. The process is called fusion. ARVs interfering with the fusion are called fusion inhibitors. This is the new class of ARV and it includes the drugs like T 20 (Enfuvirtide), CCR5 entry inhibitors (Maraviroc) and CXCR4 antagonist.

Table 5: List of Fusion Inhibitors

S.No	Generic Name	Dose	Adverse effects
1	Maraviroc (Aug2007)	150mg Twice or 300 mg Once daily.	Nausea, Upper Stomach Pain, Loss of Appetite, Dark Urine, Jaundice.
2	Enfuvirtide (Mar2003)	90mg Twice daily.	Constipation, Diarrhoea, Rapid Heart Rate, Nausea, Abnormal Lipid Profiles, Skin Rash.

Table 6: List of Pharmacokinetic Enhancer.

S.No	GenericName	Dose	Adverseeffects
1	Cobisistat (Sep2014)	150mg Once daily.	Nausea, Constipation, Diarrhoea, Loss of Appetite, Skin Rash.

After the fusion with the host cell membrane, viral particles including the viral RNA and the enzymes (reverse transcriptase, integrase and protease) enter into the cytoplasm of the host cell. The first process inside the host cell is the reverse transcription in which viral DNA is synthesized from viral RNA. The process involves the reverse transcriptase enzyme. The ARVs interfering with this process are called nucleoside and nucleotide reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI).

The viral DNA synthesized in cytoplasm travels to the nucleus of the host cell, where it integrates with the DNA of the host cell with the help of integrase. Integrase inhibitors are the ARVs that block the process of integration. After integration, the DNA of the infected cell converts into the viral DNA and starts to produce copies of viral RNA.For the production of viral particles, the RNA copies thus produced need to be cut into particles of exact size with the help of protease. Protease inhibitors (PI) interrupt this process. The boosted PIs (combination of two types of PI) increase the effectiveness, stability of ARV and minimize the side effects. The viral RNA after the action of protease converts into the viral particles. These particles assemble with the enzymes into a capsule, which eventually leaves the infected cell by the process called budding.

The viruses after budding develop into the mature viruses. There are some ARV inhibiting the process of maturation and are called maturation inhibitors. The following graphic represents the process viral replication and the action of the ARV in different stages of the replication as shown in Fig.1, Fig.2 and refer the Table 7.

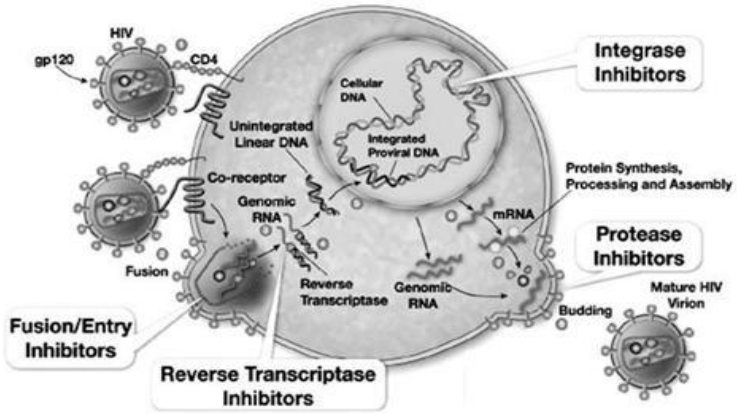

Figure. 1: Targets of Antiretroviral Drugs in the HIV Life Cycle.

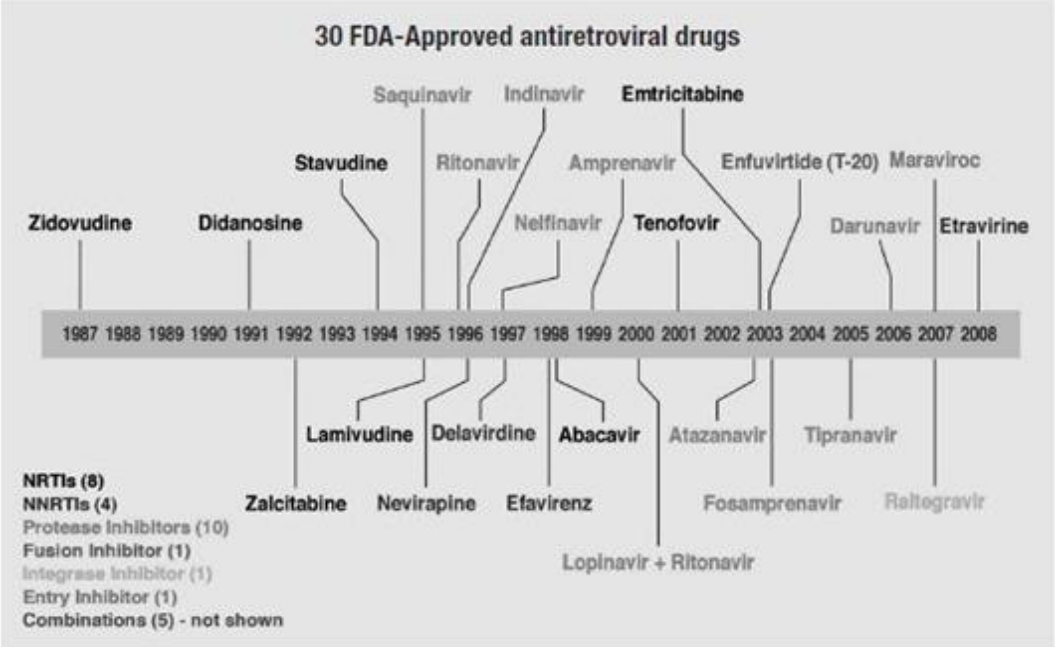

Figure. 2: Antiretroviral drugs approved for HIV infection

Table 7: List of Fixed-dose combinations for antiretroviral drugs

Brand	**DrugNames**	**FDAApproval**	**Company**
Combivir	Lamivudine+Zidovudine	26-9-1997	Glaxo Smith Kline
Kaletra	Lopinavir+Ritonavir	15-9-2000	Abbott Laboratories
Trizivir	Abacavir+Lamivudine+Zidovudine	15-11-2000	Glaxo Smith Kline
Epzicom, Kivexa	Abacavir+Lamivudine	2-8-2004	Glaxo Smith Kline
Truvada	TenofovirDisoproxilFumarate+Emtricitabine	2-8-2004	Gilead Sciences
Atripla	Emtricitabine+Efavirenz + TenofovirDisoproxilFumarate	12-7-2006	Gilead Sciences, Bristol-Myers Squibb
Complera, Eviplera	Emtricitabine+Rilpivirine+ TenofovirDisoproxilFumarate	10-8-2011	Gilead Sciences, Janssen Therapeutics
Stribild	Elvitegravir+Cobisistat+Emtricitabine+Tenofovir DisoproxilFumarate	27-8-2012	Gilead Sciences
Triumeq	Abacavir+Dolutegravir+Lamivudine	22-8-2014	ViiV Healthcare

Evotaz	Atazanavir+Cobisistat	29-1-2015	Bristol-Myers Squibb
Prezcobix	Darunavir+Cobisistat	29-1-2015	Janssen Therapeutics
Dutrebis	Lamivudine+Raltegravir	6-2-2015	Merck& Co.
Genvoya	Elvitegravir + Cobisistat + Emtricitabine + TenofovirAlafenamideFumarate	5-11-2015	Gilead Sciences
Descovy	TenofovirAlafenamideFumarate+Emtricitabine	4-4-2016	Gilead Sciences
Odefsey	Emtricitabine+Rilpivirine+ TenofovirAlafenamide	1-3-2016	Gilead Sciences
Juluca	Dolutegravir+Rilpivirine	21-11-2017	ViiV Healthcare
Biktarvy	Bictegravir+ Emtricitabine +TenofovirAlafenamideFumarate	21-2-2018	Gilead Sciences

CONCLUSION

New antiretroviral medications are required to improve antiretroviral therapy's convenience, tolerability, safety, and antiviral efficacy. Promising agents are being developed in both existing and new classes (HIV entry inhibitors and HIV integrase inhibitors). Additional viral life cycle phases, such as viral uncoating and viral assembly, as well as additional enzymes, can and should be targeted in future therapeutic development. Additional immunotherapies, such as interleukin-2 and therapeutic HIV vaccines, may be used to supplement the use of present and future antiretroviral medications. As we learned from the HIV experience, monotherapy should be regarded as inadequate therapy, and combination medicines are predicted to predominate in the treatment of viral infections in the future. Good combination treatments make use of numerous targets and/or mechanisms of action. More scientific and clinical research is required to find and develop potential antiretroviral medicines.

Abbreviations

AIDS – Acquired Immunodeficiency Syndrome ARD– Anti-Retroviral Drugs
HIV – Human Immunodeficiency Virus
CDC – Centre for Disease Control
WHO – World Health Organization

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