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TRENDS IN DRUGS MANAGEMENT OF HIV/AIDS AND PREVENTION OF MOTHER TO CHILD TRANSMISSION OF HIV: A REVIEW

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ABSTRACTS
HIV infection continues to pose a major threat worldwide. It is characterized by the depletion of $CD4^+$ T cells, persistent immune inactivation, and increased susceptibility to secondary infections. There had been Pharmacological approach to HIV/AIDS since 1980's when it was discovered. It is the use of antiretroviral drugs, often its combination to treat HIV/AIDS. The aims of the use of ARTs are to: control the growth of the virus, improve the immune system, slow or stop symptoms, prevent transmission of HIV to others most especially, mother to child. The ART basically attack the virus at its different life cycle; binding, fusion, reverse transcription, integration, replication, assembly and budding thereby preventing the virus multiplication or replication. In 1987 the first antiviral drug, Zidovudine, an NRTI was developed and in late 1990's, Saquinavir, a PI was developed. Treatment of HIV was first started as a single treatment but, issues of resistant, toxicity, compliance and others led to combination therapy that attacks the virus at different life cycle stages. Advances in the development of antiretroviral and its combination have resulted in a remarkable reduction in HIV-associated morbidity and mortality. ART leads to effective suppression of HIV replication with partial recovery of host immune system and has successfully transformed HIV infection from a fatal disease to a chronic condition. Additionally, antiretroviral drugs have shown promise for prevention in HIV pre-exposure prophylaxis. However, ART is unable to cure HIV. Other limitations include drug–drug interactions, drug resistance, cytotoxic side effects, cost, and adherence. Alternative treatments options are being investigated to overcome these challenges including discovery of new molecules with increased anti-viral activity and development of easily administer able drug formulations. World Health organization (WHO) and other organizations have proposed the first, second and third lines for better treatment outcome of People living with HIV (PLWHIV). In light of the difficulties associated with current HIV treatment measures, and in the continuing absence of a cure, the prevention of new infections has also arisen as a prominent goal among efforts to curtail the worldwide HIV pandemic. In this review, the new molecules under clinical development like the use of long acting ART in combination with an ideal antibody, Gene –mapping and a host of others were x-rayed. APOBEC3 and HIV vaccines are promising targets.

KEYWORDS: HIV, Antiretroviral therapies, Reverse transcription, Switching, APOBEC3, Gene-mapping, Long-Acting ART and Ideal antibody.

INTRODUCTION

Human Immunodeficiency Virus (HIV) still causes too many avoidable deaths, but by providing the right health services in a timely manner, we can avoid the worst consequences of the virus while following the provided guidelines. The recommendations in these guidelines aim to reduce the number of people dying from HIV and, when fully implemented, will help us to reach our goals

of reducing global annual deaths to less than 200,000 by 2030. As a result of advances and access to antiretroviral therapy (ART), HIV-positive people now live longer and healthier lives. In addition, it has been confirmed that ART prevents onward transmission of HIV due to reduced viral load.[1] Progress has also been made in preventing and eliminating mother-to-child transmission and keeping mothers alive. In 2022, 82% of pregnant women (**1.2 million**) living with HIV received antiretroviral (ARV) drugs.

HIV infects cells of the immune system**,** Infection results in the progressive deterioration of the immune system, breaking down the body's ability to fend off some infections and other diseases. AIDS (acquired immunodeficiency syndrome) ensues with many opportunistic infections**.** In the year 2021, an estimated 6.7% of the 10.6 million people who developed TB worldwide were living with HIV. In the same year approximately 187,000 deaths from tuberculosis occurred among people living with HIV. The WHO African Region accounted for 73% of the estimated number of HIV-related TB deaths. Acquired immunodeficiency syndrome can also be defined by the development of certain cancers or other severe long-term clinical manifestations.

Globally 37.7 million people were living with HIV in 2020 and 36 million were adults. Africa accounts for 70% (26 million) of all AIDS-related deaths in the world. East and Southern Africa remain the most seriously affected. In 2020, HIV prevalence in Ethiopia was 0.9%. Ethiopia is one of the countries hardest hit by HIV/AIDS, with a prevalence of 1.1% among people of all ages and 59% of those infected receiving highly active antiretroviral therapy (HAART)[2]

The management of the opportunistic infections or rather the prevention of opportunistic infection will go a long way to improve the life expectancy and quality of life of patients living with HIV. HIV has though remained without a cure but can be effectively managed with reference to the viral load reduction and keeping measure in place to keep higher levels of the CD4 cells. HIV is still a devastating and lethal disease that has caused widespread suffering worldwide for almost half a century and those infected can expect to continue treatment throughout their lifetime, in recent times, there have been advancements in therapeutics.[3]

The HIV virus cannot operate all by itself, so it not only sets up a home with the host cell but also takes advantage by exploiting its resources. To achieve this feat, the virus must hijack the host's cellular machinery to evade detection by the immune system. HIV integrates its genome within the host chromosomal DNA. The provirus can then remain dormant within the host cell, where it persists for the entire life span of the infected cell. This latent virus can operate silently within the cell; its replication method renders it completely undetectable to the human immune system.[4]

HIV DNA is detectable in $CD4^+$ T cells in the blood and lymphoid tissue in nearly all cases of HIV infection. People with natural resistance to HIV who maintain a viral load of <50 copies/ml without any therapeutic intervention are known as ‘elite’ controllers. Those who exhibit remarkable resistance are called ‘exceptional’ controllers. These individuals have naturally been the focus of intense investigation for many years now for the clues they offer for finding a cure. And hope for such a cure was presented by a case study that involved an infected patient —widely known as the ‘Berlin patient’ – –who underwent bone marrow transplantation courtesy of a donor who was naturally resistant to the virus.[5]

The introduction of daily combination antiretroviral therapy (cART) led to a significant drop in AIDS-related morbidities and mortality. Even so, a mechanism of HIV persistence today is the proliferation of cells that were infected prior to the introduction of ART. In addition, cART therapy comes with a whole host of problems, including premature aging, drug fatigue, toxicity, and inflammatory effects. These side effects exacerbate the incidence of other diseases, such as cardiovascular disease and chronic obstructive pulmonary disease (COPD).

To block HIV-1 before it finds an opportunity to integrate itself with the host chromosomal DNA, scientists have targeted key proteins involved in the replication cycle: reverse transcriptase (RT), integrase (IN), and protease. These enzymes are crucial in the development of modern-day antiretroviral drugs.[7,8]

HIV Replication Life Cycle

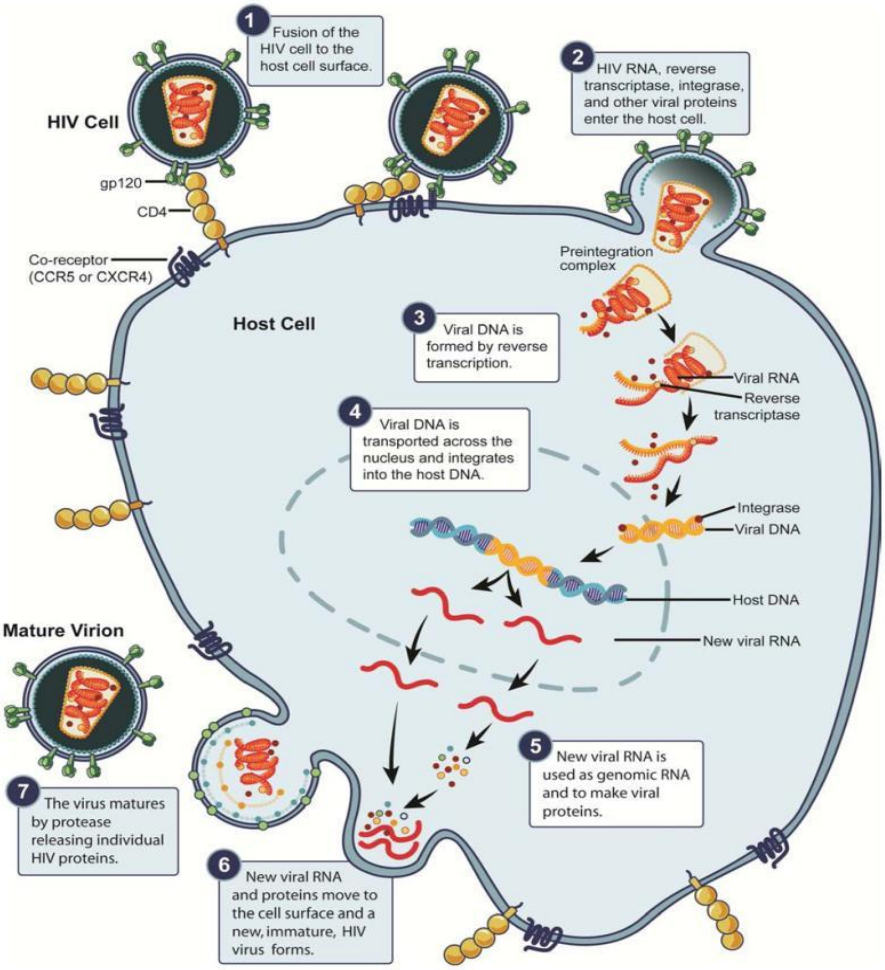
Cell Entry –The first step of cell entry is the attachment of the HIV envelope glycoprotein gp120 onto human chemokine receptors (CCR5 or CXCR4) on the CD4 cell surface. After the initial attachment, the next step requires fusion of the viral and cell membranes, allowing the viral proteins to enter into the cytoplasm.

Reverse Transcription – After cell entry as HIV is a retrovirus, the virus’s RNA template transcribes into a double-stranded viral DNA in the presence of the enzyme reverse transcriptase.

Integration – The viral double-stranded DNA produced after reverse transcription is then transported into the cellular nucleus. In the presence of the integrase enzyme, a multi-step process allows the integration of viral DNA into host genome, and ultimately formation of proviruses.

Formation of Infectious Virons by HIV Proteases – After successful integration of viral DNA into the host genome and formation of proviral proteins, the next step of the HIV-1 life cycle is the cleavage of these

polyproteins and formation of infectious virions. The viral enzyme protease is the key element for this process.[9]



Fgure 1: HIV life cycle and possible sites targets of drugs. Adapted from Ghosn *et al*., 2018.[9]

The benefits of combination antiretroviral therapy (cART) for HIV replication and transmission control have led to its universal recommendation. Many people living with HIV are, however, still undiagnosed or diagnosed late, especially in sub-Saharan Africa, where the HIV disease burden is highest. Further expansion in HIV treatment options, incorporating women-centred approaches, is essential to make individualised care a reality. With a longer life expectancy than before, people living with HIV are at an increased risk of developing non-AIDS comorbidities, such as cardiovascular diseases and cancers. Antiretroviral strategies are evolving towards a decrease in drug burden, and some two-drug combinations have proven efficacy for maintenance therapy. Investigational immune checkpoint inhibitors and broadly neutralising antibodies with effector functions have energised the HIV cure research field as the search for an effective vaccine continues. In this Seminar, we review advances and challenges relating to the goal of an AIDS-free world.[9]

PHARMACOLOGICAL TREATMENT WITH ANTIRETROVIRAL THERAPY (ART)

ART should be initiated for all people living with HIV regardless of WHO clinical stage and at any CD4 cell count.[10]

Since the first cases of AIDS appeared in 1981, human immunodeficiency virus type 1 (HIV-1) infection has reached pandemic proportions. Forty years later, research has led to the approval of more than 30 antiretroviral drugs, while combination therapies have turned HIV-1 infection into a chronic, but manageable disease. Still, drug toxicity and acquired and transmitted drug resistance remain as major threats to therapy success. In this review, we provide an overview on currently available anti-HIV drugs and the latest developments in antiretroviral therapy, focused on new antiretroviral agents acting on known and unexploited antiviral targets, prevention therapies aimed to improve available drug combinations, and research on new long-acting therapies, particularly those involving novel drug candidates such as lenacapavir or islatravir.[11]

One of the major challenges in ART is the dosing route, as most ARVs have poor solubility and bioavailability. Orally applied solid dosage forms are the most common way to administer ARTs although they suffer from significant hepatic first-pass effects, and variable absorption and degradation due to enzymes and extreme pH conditions in the gastrointestinal tract, leading to low bioavailability. Frequent dosing (at least once daily) is required as a result of the short half-life of some ARVs, which may cause reduced patient compliance12.

Furthermore, ARVs may not reliably reach high levels in tissues through the lymphatic system or in the brain across the blood–brain barrier (BBB). Thus, conventional ART fails to target the HIV anatomical (i.e., lymphatic system, central nervous system [CNS], reproductive tract, liver, and lungs), cellular (i.e., $CD4^+$ T lymphocytes and monocytes, etc.) and reservoirs, which increases the risk of relapse.[12]

Better drug delivery systems and development of new drug molecules with high anti-viral potency and longer half-life would enhance the success of HIV treatment. ART can help lower your viral load, fight infections, and improve your quality of life. They can lower your chances of transmitting HIV.[12]

The goals for these medicines are to

- Control the growth of the virus
- Improve how well your immune system works
- Slow or stop symptoms
- Prevent transmission of HIV to others

People with advanced HIV disease should be given priority for initiating ART since they are at high risk of death, particularly if resources are scarce. These people should be evaluated for the risk or presence of opportunistic infections such as TB and cryptococcal meningitis, but ART should be delayed only when meningitis or another central nervous system infection is suspected.

Providing ART to all pregnant and breastfeeding women living with HIV improves the woman's health outcomes, prevents the mother-to-child transmission of HIV and prevents the transmission of HIV from the woman to a sexual partner. Considering ART has individual health benefits for all adults, the recommendation applies to both breastfeeding and non-breast feeding women. Women who initiate lifelong ART, especially those with young children, may face considerable challenges in seeking regular HIV care and maintaining adherence to treatment. Efforts to scale up treatment require a holistic approach to women's lives and parallel investments in community-based support to improve women's treatment literacy, preparedness and agency to remain in follow-up and adhere to treatment.[13,24,15]

Children Infants and young children living with HIV have a high risk of poor outcomes, with up to 52% of children born with HIV dying before the age of two years in the absence of any intervention.[16]

As of 2022, the Food and Drug Administration has approved twenty-six(26) individual drug agents and twenty-two (22) fixed-dosed combination (FDC) drugs comprised of two or more antiretroviral. This includes the first antiretroviral drug regimen, Cabenuva (Cabotegravir/Rilpivirine), which requires a once-a-month or once-every-two-month injection rather than an oral dose daily.[17]

Antiretroviral therapy is quickly changing, with newer drug agents offering fewer side effects, greater durability, and a decreased risk of drug resistance. In the past, antiretroviral therapy was described as a three-drug "cocktail." Today, with improved pharmacokinetics and a longer drug half-life, antiretroviral therapy may involve as few as two co-formulated drug agents. While several new antiretroviral drugs have been added to the treatment arsenal since 2010, older ones like Crixivan (indinavir), Invirase (saquinavir), Rescriptor (delavirdine), Videx (didanosine), Viracept (nelfinavir), and Zerit (stavudine) have been discontinued and are no longer in use. Below are the dosages, how the ARTs are used in management of HIV.[17,18,19]

Entry/Attachment Inhibitors Entry/attachment inhibitors work by blocking the virus's ability to attach to or enter healthy host cells. They do so by binding to different receptors on the surface of the host cell that HIV uses to lock onto and/or enter the cell. Without the means to enter a cell, HIV cannot replicate.

DRUG CLASS: Entry/Attachment Inhibitors			
Brand Name	**Generic Name**	**Typical Adult Dosage**	**Dietary Notes**
Fuzeon	Enfuvirtide	90mg injected 2x/day	Not applicable
Rukubio	Fostemsavir	One 600mg tablet 2x/day	Taken with or without food
Selzentry	Maraviroc	-One 150mg tablet 2x/day -One 300mg tablet 2x/day -Two 300mg tablets 2x/day	Taken with or without food
Trogarzo	Ibalizumab	-2,000mg intravenous infusion as an induction dose -800mg intravenous infusion every two week	Not applicable

Integrase Inhibitors
Integrase inhibitors work by blocking the incorporation of HIV's DNA into the host cell's DNA, a process known as integration. They do so by inhibiting a viral enzyme known as integrase.[5]

DRUG CLASS: Integrase Inhibitors			
Brand Name	**Generic Name**	**Typical Adult Dosage**	**Dietary Notes**
Isentress	Raltegravir	One 400mg tablet 2x/day	Taken with or without food
Isentress HD	Raltegravir	One 600mg tablet 2x/day	Taken with or without food
Tivicay	Dolutegravir	-Untreated patients: One 50mg tablet 1x/day—Patients with resistance to Isentress: One 50mg tablet 2x/day	Taken with or without food
Vocabria	Cabotegravir	One 30mg tablet 1x/day (specifically taken with oral Edurant for one month or two months as the induction dose for Cabenuva extended-release injection—see "FDC Drugs" below)	Taken with food
Vocabria	cabotegravir	One 30mg tablet 1x/day (specifically taken with oral Edurant for one month or two months as the induction dose for Cabenuva extended-release injection—see "FDC Drugs" below)	Taken with food

Nucleoside Reverse Transcriptase Inhibitors
In order for HIV to replicate, it uses an enzyme called reverse transcriptase to translate its viral RNA into double-stranded DNA, which is then integrated into the nucleus of the host cell to "hijack" its genetic machinery. By doing so, HIV can begin to churn out multiple copies of itself.

NRTIs block the action of reverse transcriptase and so prevent the replication of the virus.[6]

DRUG CLASS: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)			
Brand Name	**Generic Name**	**Typical Adult Dosage**	**Dietary Notes**
Emtriva	Emtricitabine	-One 100mg tablet 1x/day -One 150mg tablet 2x/day	Taken with or without food
Epivir	Lamivudine	-One 300mg tablet 1x/day -One 150mg tablet 2x/day	Taken with or without food
Retrovir	AZT, zidovudine	One 300mg tablet 2x/day	Food may ease stomach discomfort
Viread	Tenofovir	One 300mg tablet 1x/day	Taken with or without food
Ziagen	Abacavir	-Two 300mg tablets 1x/day -One 300mg tablet 2x/day	Taken with or without food

Non-Nucleoside Reverse Transcriptase Inhibitors
Non-nucleoside reverse transcriptase inhibitors (NNRTIs) also block reverse transcriptase, NNRTIs bind directly to the enzyme, blocking its action.[7]

DRUG CLASS: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Brand Name	**Generic Name**	**Typical Adult Dosage**	**Dietary Notes**
Edurant	rilpivirine	One 25mg tablet 1x/daily	Taken with a meal
Intelence	etravirine	One 200mg tablet 2x/day	Taken with a meal
Pifeltro	doravirine	One 100mg tablet 1x/day	Taken with or without food
Sustiva	efavirenz	One 600mg tablet 1x/day	Taken on an empty stomach, preferably at bedtime
Viramune IR (immediate-release)	nevirapine	-First 14 days: 200mg tablet 2x/day -Maintenance dose: 200mg tablet 2x/day	Taken with or without food
Viramune XR (extended- release)	nevirapine	-First 14 days: One 200mg IR tablet 1x/day -Maintenance dose: One 400mg XR tablet 1x/day	Taken with or without food

Protease Inhibitors Protease inhibitors work by blocking an enzyme known as protease. Once HIV takes over the genetic machinery of the host cell, it produces long-chain proteins that must be cut into smaller pieces

(by protease) in order to be assembled into a new viral particle. By binding to protease, the long-chain proteins cannot be cut and new viral particles cannot be produced.

DRUG CLASS: Protease Inhibitors(PI)			
Brand Name	**Generic Name**	**Typical Adult Dosage**	**Dietary Notes**
Aptivus	Tipranavir	-Two 250mg capsules + 200mg Norvir 2x/day	Best taken with a meal
Lexiva	fosamprenavir	-Two 700mg tablets 2x/day -Two 700mg tablets + 100mg Norvir 1x/day -**Patients with previous PI failure**: One 700mg tablet + 100mg Norvir 2x/day	Taken with or without food
Lexiva	fosamprenavir	-Two 700mg tablets 2x/day -Two 700mg tablets + 100mg Norvir 1x/day -**Patients with previous PI failure**: One 700mg tablet + 100mg Norvir 2x/day	Taken with or without food
Prezista	Darunavir	-800mg + 100mg Norvir 1x/day -**Patients with known levels of Prezista-associated resistance**: One 600mg tablet + 100mg Norvir 2x/day	Taken with food
Reyataz	Atazanavir	-Two 200mg capsules 1x/day -300mg + 100mg Norvir 1x/day	Taken with light meal

Pharmacokinetic Enhancers

Also called HIV boosters, "boost" the concentration of protease inhibitors in the bloodstream. Without them, the concentration of the accompanying PI would quickly fall beneath the therapeutic level, providing the virus an opportunity to replicate.

DRUG CLASS: Pharmacokinetic Enhancers			
Brand Name	**Generic Name**	**Typical Adult Dosing**	**Dietary Notes**
Norvir	Ritonavir	Dosage varies depending on which PI it is taken with	Taken with or without food
Tybost	Cobicistat	150mg 1x/day	Taken with food

Capsid Inhibitors

Capsid inhibitors disrupt the HIV capsid, a protective protein shell for HIV's genetic material and replication enzymes. These inhibitors can interfere with the HIV capsid at various stages of the viral life cycle.

DRUG CLASS: Capsid Inhibitors			
Brand Name	**Generic Name**	**Typical Adult Dosing**	**Dietary Notes**
Sunlenca	lenacapavir	Day 1: One 600mg tablet + one 927mg injection once. Day 2: 600mg tablet once - Maintenance dose: 927mg injection every 6 months	Taken with or without food

Fixed-Dose Combination Drugs (FDC)

FDC drugs reduce the daily pill burden a PLWHIV may otherwise be faced with when undergoing antiretroviral therapy. Some FDC drugs are used with other antiretroviral agents. Others are entirely used on their own.

Of the 22 FDC drugs approved for use in the United States, 14 are all-in-one treatments taken once daily.

Fixed-Dose Combination (FDC) Drugs			
Brand Name	**Contents**	**Typical Adult Dosage**	**Dietary Notes**
Atripla	600mg Sustiva + 200mg Emtriva + 300mg Viread	One tablet 1x/daily	Taken on an empty stomach, preferably at bedtime
Biktarvy	50mg bictegravir + 200mg Emtriva + 25mg tenofoviralafenamide	One tablet 1x/daily	Taken with or without food
Cabenuva	400-600mg cabotegravir + 600-900mg Edurant (in separate prefilled syringes)	-Initiation injections: One 600mg cabotegravir injection and one 900mg injection of Edurant for Month One (only after an induction dose of Vocabria—see "Intergrase Inhibitors" above)—Maintentance injections: One 400mg cabotegravir injection and one 600mg Edurant injection 1x/month	Not applicable

		or 2x/month thereafter	
Cimduo	300mg Emtriva + 300mg Viread	One tablet 1x/day	Taken with or without food
Combivir	300mg Retrovir + 150mg Epivir	One tablet 2x/day	Food may ease stomach discomfort
Complera	25mg Edurant + 200mg Emtriva + 300mg Viread	-One tablet 1x/day -For people on rifabutin: One tablet plus an additional 25mg Edurant 1x/day	Taken with food
Descovy	200mg Emtriva + 25mg tenofoviralafenamide	One tablet daily	Taken with or without food
Delstrigo	100mg Pifeltro + 300mg Epivir + 300mg Viread	-One tablet 1x/day -For people on rifabutin: One tablet 1x/day followed by 100mg of Pifeltro 12 hours later	Taken with or without food
Dovato	50mg Tivicay + 300mg Epivir	-One tablet 1x/day -For people on rifabutin or carbemazepine: One tablet 1x/day followed by 50mg of Tivicay 12 hours later	Taken with or without food
Epzicom	600mg Ziagen + 300mg Epivir	One tablet 1x/day	Taken with or without food
Evotaz	300mg Reyataz + 150mg Tybost	One tablet 1x/day	Taken with food
Genvoya	150mg elvitegravir +150mg Tybost + 200mg Emtriva + 10mg tenofoviralafenamide	One tablet 1x/day	Taken with food
Juluca	50mg Tivicay + 25mg Edurant	-One tablet 1x/day -For people on rifabutin: One tablet plus an additional 25mg Edurant 1x/day	Taken with food
Kaletra	200mg lopinavir + 50mg Norvir	-Two tablets 2x/day -People with less than 3 mutations associated with lopinavir resistance: Four tablets 1x/day	Taken with or without food
Odefsey	25mg Edurant + 200mg Emtriva + 25mg tenofoviralafenamide	One tablet 1x/day	Taken with food

In line with several combinations to achieve a better treatment outcome using all the ARTs listed in table 1 above. WHO has suggested some combinations as first line, second line and third line respectively. These different combinations are based on the aims of the use of ARTs. The switching from one line to the other could be as a result of treatment failure, toxicity, adverse drug reaction, resistance, cost, availability and others.[20,21,22] The different lines are.

- First line: for adult / adolescents consists of two (2) NRTI and NNRTI or integrase inhibitor. Note that fixed dose combination and a once daily regimens are preferred.
- Second line: consist of two (2) NRTI) and a ritonavir-boosted PI. ATV/r and LPV/r are preferred b/ PI for 2nd line. The rationale for the selection of NRTI in second line therapy is to choose the most logical combination depending on what was used in the first line that failed.
- Third line: consists of new drugs that have anti-HIV activity. An Integrase inhibitor and second generation NNRTI and PIs. Patients on failing second line regimenwith no new ARV options should continue with a tolerated regimen.[10]

New Trends

A recent advance in treatment that has proven promising has been the advent of integrase inhibitors. The process by which the virus integrates its genome within the host chromosomal DNA is controlled by an enzyme called integrase. This protein is highly conserved across the *Retroviridae*family. This means that the targeting of integrase entails the prevention of replication. Currently, a newly identified compound works to boost an experimental approach, dubbed ‘’shock and kill’’ during which the latent virus in the areas where the antiretroviral drugs cannot penetrate to is activated so it can be targeted by the body immune system or ARTs. This is because the virus ordinarily hides inside the immune system, making itself undetectable to the body immune system and resistance to ARTs.[23]

Inhibitor of Polymerase Associated Factor 1 complex (IPAF1C) which has been found to play a role in repressing viral gene expression. In the study the investigators utilized computer modelling to identify a compound which inhibits the Polymerase Associated Factor 1 complex (PAF1C), which had been found to play a role in repressing viral gene expression.[24]

There are remaining knowledge gaps in the campaign against HIV. Challenges to long-acting antiviral therapy involve resistance and understudied populations. The development of drug-resistant mutations has been a barrier to achieving a cure for HIV. Meanwhile, problems with adherence to cART regimens involve adverse drug reactions and limited access to therapy.

For cART patients, medicines that limit the side effects of the therapy, as well as the frequency of dosing, may improve the rate of adherence. Emerging approaches to long-acting antiviral therapies are anticipated to provide novel and simpler options for the prevention and treatment of HIV, thereby providing hope to many sufferers in the future.[23,24,25]

A complete cure for HIV would entail both remission and eradication. The problems of resistant mutations present an ongoing challenge for scientists in the fight against HIV and complicate treatment regimens which must be continually updated. The targeting of integrase has been touted as one of the most promising approaches to combating HIV infection. This protein is highly unique. The inhibitors formulated to inhibit integrase are long-acting and have shown exceptional promise in their capacity to block HIV integration and replication. Meanwhile, another technique that holds promise is the *in-vivo* delivery of gene-editing tools to either target the virus or enhance the immune system or protect cells from becoming infected.[24]

There are opportunities for a collaborative effort and cross-fertilization of concepts from cancer research, for example, by utilizing studies done on immune resistance in the field. The same goes for research into coronavirus disease 2019 (COVID-19), whereby increased knowledge of the mechanisms involved in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral infection could aid further understanding of HIV.[3]

HIV Vaccines Prospect

Researchers are developing a therapeutic HIV vaccine. Therapeutic vaccines treat a condition rather than prevent it. People who already have HIV would get this therapeutic vaccine to help strengthen their immune system's response to the virus. The hope is that the vaccine alone would prevent HIV from progressing to AIDS without the need for ART.[25]

So far, it's been hard to develop an HIV vaccine for prevention. Most traditional vaccines use a dead or weakened form of a virus to prompt the body to make antibodies against it. But that method hasn't worked with weakened HIV, and a live form of the virus is too dangerous to use.

But researchers may be making headway on a different type of vaccine. The HTI vaccine teaches immune cells called T cells to attack a specific part of the virus that allows it to make copies of itself. In one small study of 45 patients, 40 percent of those who got the vaccine were able to stay off of ART for 22 weeks.

Researchers are now studying the vaccine in combination with the experimental drug vesatolimod. This drug may enhance the body's immune response to the vaccine, which could make it effective for more people or make its effects last longer.

Gene Editing, could be another approach to HIV treatment. Gene editing technology changes an organism's DNA. Studies of gene editing are underway in a range of genetic diseases such as cystic fibrosis, hemophilia, and sickle cell disease. Now, researchers are trying to harness it against HIV. Early experiments on animals suggest that a type of gene editing called CRISPR may disable a virus similar to HIV called simian immunodeficiency virus (SIV), found in animals such as monkeys. Very early human clinical trials began at the end of 2021. In the trials, researchers use CRISPR technology to cut out the HIV that wraps around the DNA in cells and makes it so difficult to treat. The hope is that unlike ART, which you have to take for life, a one-time CRISPR treatment may cure the disease.[12]

A final consideration is that at present most of the research into a cure for the virus has been carried out by high-income countries. Here the incidence of infection rates is much lower and tends to be mainly problematic within the remit of the male homosexual population. Bearing this in mind, we need to remain cognizant of the fact, HIV strains are genetically and biologically diverse and vary according to sex, ethnicity, and geographical locale.[3]

Gene mapping and Gene therapy

Gene therapy is a technique used to deliver medicinal gene to a patient's cells. AGT103-T developed by addimmune. Currently on phase 1 clinical trial and it is believed to combat spread of HIV. AGT103-T is a single-dose lentiviral-based autologous cell therapy delivering gene-therapy modified, HIV-specific CD4 T cells to PLHIV. It is designed to induce the exceptional control of viral replication and intact immune responses without ART as shown by two categories of PLHIV= elite controllers and long term non-progressor individuals. It acts by targeting CCR5, reverse transcriptase and TAR.[25,26] There are people whose immune system is resistant to HIV infection, exposing key weakness to HIV and providing researchers with actionable examples on how to defeat the virus.AGT103-T is a gene and cell therapy made up of helper T cells which have been given specialized anti-HIV gene. Helper T cells are central to the adaptive immune system and the primary target of HIV infection, so protection of these cells allows them to coordinate an anti –HIV response without simply becoming infected. Since T cells can divide, persist and can circulate throughout the body, the AGT103-T cells are able to form a self-sizing army of HIV-resistant T cells which can recognize and respond to HIV wherever it is in the body.[26,27]

APOBEC

A family of evolutionary conserved cytidine deaminases. Apolipoprotein B editing complex (APOBEC3) family members are cytidine deaminases that play important roles in intrinsic responses to infection by retroviruses and have also been implicated in the control of other viruses such as parvovirus, herpesviruses and others. The

apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like (APOBEC) mutational signature has only recently been detected in a multitude of cancers through next-generation sequencing. In contrast, APOBEC has been a focus of virology research for over a decade. Many lessons learnt regarding APOBEC within virology are likely to be applicable to cancer.[28] Combination of APOBEC3 with vaccines may end HIV spread.

Long-acting antiretroviral therapy holds the promise of new options for human immunodeficiency virus (HIV) treatment beyond the current paradigm of daily oral pills. Of particular interest is their potential role in addressing challenges with adherence to oral therapy and treatment fatigue. Similar to other conditions where long-acting formulations have proven effective such as contraception and mental health, long-acting antiretroviral therapy could provide additional treatment choices to people with HIV.[29,30]

REFERENCES

1. WHO, 2019. Geneva Policy brief: update of recommendations on first-and second-line antiretroviral regimens. (https://apps.who.int/iris /handle/10665/325892, accessed 1st June 2021).
2. WHO, 2010. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. Geneva. (https:// apps.who.int/iris/handle /10665/44379), accessed, 1 June 2021.
3. WHO, 2013. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: (https://apps.who.int/iris/handle /10665/85321), accessed, 1st June 2021.
4. WHO, 2018. Paediatric Antiretroviral Drug Optimization (PADO) Meeting 4. Geneva. (https://cdn.who.int/media/docs/default-source/hq-hiv-hepatitis-andstis-library/pado4.pdf?sfvrsn=26d4169c_5). accessed 1 June 2021.
5. WHO, 2019. Geneva Policy brief: update of recommendations on first-and second-line antiretroviral regimens. (https://apps.who.int /iris/handle/10665/325892), accessed 1st June 2021.
6. WHO, 2021. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Accessed july 2021.
7. Aboud M, Brites C, Lu H, Supparatpinyo K, Hercilla L, Sievers J., 2016. DTG versus LPV/r in Second Line (DAWNING): outcomes by WHO-recommended NRTI backbone. 23rd Conference on Retroviruses and Opportunistic Infections, Boston, MA, USA, 22–25 (https://www.croiconference.org /abstract/dtg-versus-lpvr-second-linedawning-outcomes-who-recommended-nrti-backbone), accessed 1st June 2021).
8. Back D, Khoo S, Marzolini C, Gibbons S, McAllister K, Chiong J. (2018). HIV drug interactions [website]. Liverpool: University of Liverpool, 2018. (https://www.hiv-druginteractions.org), accessed 1st June, 2021.
9. BurcinYavuz, Patricia LiWang and David L. Kaplan. (2020). Pharmaceutical Approaches to HIV Treatment and Prevention. AdvTher (Weinh), 2018 Oct; 1(6): 1800054.
10. CDC. FDA-Approved HIV medicine. (hivinfo.nih.gov/understanding-hiv/fact-sheets/fda-approved-hiv-medicines). Accessed, January 15th, 2023.
11. Dunn D, Woodburn P, Duong T, Peto J, Phillips A, Gibb D. (2008). Current CD4 cell count and the short-term risk of AIDS and death before the availability of effective antiretroviral therapy in HIV-infected children and adults. Journal of Infectious Disease, 2008; 197: 398–404.
12. Globaldata, 2024. AGT103-T by Addimmune for Human Immunodefficiency Virus (HIV)
13. Infections (AIDS): Likelihood of Approval (Pharmacological Technology). (genengnews.com). February 29, 2024.
14. Hill A, Mitchell N, Hughes S, Liew Z, Pozniak A. (2018) Meta-analysis of dolutegravir for 7340 patients in 13 randomised trials: effects of current HIV RNA suppression on efficacy and safety. (https://www.natap.org/2018/HIV/050118_01.htm), accessed 1st June, 2021.
15. James Myhre & Dennis Sifris, MD. (2023). List of Approved HIV Antiretroviral Drug. Dotdash Media, Inc. HIV/AIDSTreatment. Medically reviewed by Lindsay Cook, PharmD, Updated; August 23, 2023.
16. Jonathan E. Kaplan, MD. (2023). Antiretrovirals: HIV and AIDS Drugs. Written by WebMD Editorial Contributors, Reviewed by on January 20, 2023.
17. Menza M. (2022). The Incidence of Adverse Drug Reaction Among Adult Patients on Antiretroviral Therapy in Ethiopia: Frailty Model.Journals » HIV/AIDS - Research and Palliative Care» DOIhttps://doi.org/10.2147/HIV.S358351, 2022; 14: 155—165.
18. National Institutes for Allergy and Infectious Diseases (NIAID) (2020). Launches First Clinical Trial to Test Antibody–Drug Combination for Long-Acting HIV Treatment. (https://www.hiv.gov/blog /niaid-launches-first-clinical-trial-test-antibody-drug-combination-long-acting-hiv-treatment). Accessed on 3/11/2023.
19. NicolaWilliams, Ph.D. (2023). Recent Advancements in Treating HIV. Reviewed by Aimee Molineux. Accessed January 19, 2023.
20. Olivia Dimmer. (2023). New Directions for HIV Treatment. Clinical breakthroughs. (nberg.northwestern.edu). Accessed March 21, 2023.
21. Paton N, Musazzi J, Kityo CM, Walimbwa SI, Hoppe A and Balyegisawa A. (2021). Nucleosides and darunavir/dolutegravir in Africa (NADIA) Trial:

48 weeks primary outcome. (https://www.croiconference.org/abstract/nucleosides-and-darunavir-dolutegravirin-africa-nadia-trial-48wks-primary-outcome), accessed 1st June 2021.
22. Paton N, Musazzi J, Kityo CM, Walimbwa SI, Hoppe A, Balyegisawa A (2021). Nucleosides and darunavir/dolutegravir in Africa (NADIA) (https://www.croiconference.org/abstract/nucleosides-and-darunavir-dolutegravirin-africa-nadia-trial-48wks-primary-outcome), accessed 1st June, 2021.
23. Rabie H, Denti P, Lee J, Masango M, Coovadia A, Pillay S. (2019). Lopinavir–ritonavir super-boosting in young HIV-infected children on rifampicin-based tuberculosis therapy compared with lopinavir-ritonavir without rifampicin: a pharmacokinetic modelling and clinical study. Lancet HIV, 2019; 6: e32–42. Accessed.
24. Schiller DS and Youssef-Bessler M. Etravirine: a second-generation nonnucleoside reverse transcriptase inhibitor (NNRTI) active against NNRTI-resistant strains of HIV. ClinTher., 2009; 31: 692–704.
25. Tashima K, Smeaton L and Andrade A. (2013). Omitting NRTI from ARV regimens is not inferior to adding NRTI in treatment-experienced HIV+ subjects failing a protease inhibitor regimen: the ACTG OPTIONS Study. 20th Conference on Retroviruses and Opportunistic Infections, Atlanta, GA, USA, 3–6 March 2013.
26. UNAIDS. (2016). *Global AIDS Response Progress Reporting(GARPR)*, https://aidsreportingtool.unaids.org/static/docs/GARPR.(Guidelines_2016_EN.pdf), accessed: April 17, 2018.
27. Vitoria M, Hill A. M, Ford N. P, Doherty M, Khoo SH, Pozniak AL. (2016). Choice of antiretroviral drugs for continued treatment scale-up in a public health approach: what more do we need to know? J Int AIDS Soc., 2016; 19: 20504.
28. Julg B, Bogner JR, *Ther. Clin. Risk Manag*. [PMC free article] [PubMed] [Google Scholar], 2008; 4: 573.
29. National Institutes for Allergy and Infectious Diseases (NIAID) (2020). Launches First Clinical Trial to Test Antibody–Drug Combination for Long-Acting HIV Treatment. (https://www.hiv.gov/blog/niaid-launches-first-clinical-trial-test-antibody-drug-combination-long-acting-hiv-treatment). Accessed on 3/11/2023.
30. Nigerian National Guidelines for HIV Prevention, Treatment and Care. 2020.
31. Menza M. (2022). The Incidence of Adverse Drug Reaction Among Adult Patients on Antiretroviral Therapy in Ethiopia: Frailty Model. Journals » HIV/AIDS - Research and Palliative Care» DOIhttps://doi.org/10.2147/HIV.S358351, 2022; 14: 155—165.