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A Review on Antiretroviral Drugs and Therapy

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ABSTRACT:

The use of antiviral medications to treat patients, which can suppress HIV-1 replication to undetectable levels, has been the most significant advancement in the medical management of HIV-1 infection. Antiviral medications of the antiretroviral variety are very beneficial and effective against HIV. Zidovudine, the first antiretroviral medication to receive a licence, went on sale in 1987. The antiretroviral medications that were accessible and authorised for clinical use up until December 1995 Since then, various other antiretroviral medications and antiretroviral medication classes have been developed. Depending on the molecular mechanisms and resistance profiles of these medications, they are divided into six different classes. Since zidovudine's first approval, antiretroviral therapy has made great strides. Only nearly half of the 31 antiretrovirals that the FDA has approved are regularly used. Plasma viremia can be effectively and long-lastingly suppressed by administering chronic combination antiretroviral therapy that targets various phases of the human immunodeficiency virus replication cycle. The patient survival rate has dramatically increased as a result of this suppression. This article reviews the history of antiretroviral drug development and discusses the Antiretroviral therapy, efficacy, toxicities and discuss in detail about antiretroviral drugs most commonly used in clinical practice to date.

KEYWORDS: - Antiretroviral Drugs, HIV, Zidovudine, Antiretroviral, Therapy, FDA

INTRODUCTION:

Acquired Immunodeficiency Syndrome, also known as AIDS, was a severe and newly emerging disease that caused devastating effects in the 1980s. The key turning point in the management of this illness was the discovery of the retrovirus, now known as the Human immunodeficiency virus (HIV), as the causal pathogen in the middle of the 1980s. The identification of possible therapeutic targets to stop or reduce the replicative cycle of HIV in human CD4+ T-cells resulted from the discovery of the multi-step HIV replication process. This led to unheard-of scientific advancement in the process of finding new drugs and developing existing ones.

The first antiretroviral drug to be approved for usage was zidovudine, a nucleoside reverse transcriptase inhibitor (NRTI), in 1987 after it shown a striking survival benefit. when advanced AIDS patients were matched to a placebo[1]. The HIV epidemic's trajectory was drastically altered by the mid-1990s introduction of three HIV protease inhibitors (PI). Rapid reduction of HIV RNA, enhanced immunological function[2], remission of challenging opportunistic infections such Kaposi's sarcoma[3] and progressive multifocal leukoencephalopathy, and decreased mortality[4] were all outcomes of combination therapy using a PI and 2-NRTI. Combination antiretroviral therapy has since taken over as the mainstay of treatment.

Six separate mechanistic classes of antiretroviral medications have received US approval for usage. Many of the older medications are no longer used in clinical practise because newer ones that are more potent, less poisonous, have fewer pills to swallow, and require less frequent administration, have taken their place. The professionals have a wide range of alternatives to customise treatment because to this extensive arsenal of medications. Despite the effectiveness of the most recent antiretroviral treatments, HIV is still present in several sanctuary reservoirs. Since almost all patients have viral rebound after even brief treatment interruptions, medication must be continued forever in order to sustain viral suppression using the current approach[5]. For many asymptomatic HIV patients, strong adherence to long-term antiretroviral medication presents a problem. Intermittent compliance may select for drug resistance mutations, limiting alternatives in the future. With a primary focus on the pharmacology of frequently used antiretroviral medicines, this article will provide an overview of the objectives and guiding principles of antiretroviral treatment, considerations to take into account when choosing a regimen for a specific patient, and more. Finding therapeutic targets that would interfere with the virus without also hurting the cells of the host organism is challenging because viruses utilise the host's cells to proliferate. Additionally, viral diversity is a major contributor to the difficulties in generating vaccinations and anti-viral medications[6]. Antiretroviral (ARV) drug expectations are at an all-time high. With an estimated 2.5 million fatalities avoided since 1995[7], the rapid expansion of ART access over the past ten years has shown that providing ART as a public health intervention is feasible. More recent research has shown that broad ART usage has the ability to lower HIV transmission among the general population, findings that present tremendous prospects to stop the epidemic. Similar to this, there are now 27 US FDA-approved ARVs that together target five separate stages of the HIV life cycle, offering more alternatives for ART than ever before [8]. The need to diagnose more patients earlier in the course of their disease, to enable quick linkage to care, to enhance retention in care and adherence to ART are all ongoing problems. Access to the finest ART regimens will probably need to be made easier in order to see improvements in uptake and long-term adherence to therapy [9]. Prioritizing treatment alternatives is crucial, especially for environments with limited resources, since it will help influence clinical research, future guidelines, and advocacy initiatives. In order to provide recommendations on ARV regimens and strategies to support further scaling-up of treatment in resource-limited settings, an expert consultation was

organised in September 2011 by Medicines Sans Frontières, SOLTHIS (Solidarity Therapeutique & Initiatives contre le SIDA), and Esther (Ensemble pour une solidarité thérapeutique hospitalière en Réseau)[10].

ANTIRETROVIRAL THERAPY (ARV):

GOALS AND PRINCIPLES OF ANTIRETROVIRAL THERAPY:-

The key goals of antiretroviral therapy are to:

- Achieve and maintain suppression of plasma viremia to below the current assays' level of detection;
- Improve overall immune function as demonstrated by increases in cd4+ t cell count;
- Prolong survival;
- Reduce hiv associated morbidity;
- Improve overall quality of life; and
- Reduce risk of transmission of hiv to others

In order to achieve these goals, the clinicians and patients must recognize several key principles:

- Current antiretroviral regimens do not eradicate HIV, viral rebound occurs rapidly after treatment discontinuation, followed by CD4 decline, with potential for disease progression
- Strict adherence to the prescribed regimen is essential in order to avoid viral rebound and the potential for selection of drug resistance mutations
- A combination regimen should consist of preferably 3 (but at least 2) active agents based on genotype resistance test results

Target characteristics of future treatment regimens:-

The main goal of clinical drug development is to establish therapeutic efficacy. Efficacy is a crucial need for any successful regimen and is crucial in developing nations where access to genotyping and viral load monitoring is still restricted. However, more than only effective medications are needed to deliver ART in environments with low resources. People with HIV can anticipate a nearly normal lifetime with proper treatment [11,12]. As a result, effective treatment over a lengthy period of time requires long-term treatment techniques, such as a series of regimens.

Six key principles guide ART choice:- simplicity, tolerability and safety, durability, universal applicability, affordability and heat stability.

Simplicity:-

Many nations have streamlined HIV care such that treatment can be given at primary healthcare facilities by nurses or community health workers in order to increase access. Simple regimens, focusing on fixed-dose combos (FDCs), once-daily formulations, medications that can be administered weekly or monthly, and regimens with minimal laboratory testing, food or fluid requirements, are necessary in such decentralised settings.

Tolerability and safety:-

Poor adherence, drug substitution, and treatment cessation are all key contributors to side effects, which jeopardise treatment and preventative efforts. In instance, using ART as a form of preventive entails doing so to patients who may not yet have had a clinical condition and may be less willing to take medications that have negative effects.

Durability:-

With good treatment, patients with HIV are likely to continue taking ART for several years following their HIV diagnosis, significantly longer than the typical half-life of the majority of older-generation ARVs. Drugs must have a strong genetic barrier against resistance mutations in order to optimise durability. Long-term support, follow-up, and an adequate amount of adherence instruction and counselling must continue to be offered with ART.

Universal applicability:-

According to age, pregnancy, the presence of comorbidities, and interactions with other medications, current regimens necessitate regular substitutes. The ideal regimen would be one that can be used throughout pregnancy, is suitable for newborns, children, and adults, and can be used with medications for co-infections, particularly tuberculosis and viral hepatitis.

Affordability:-

Strategies that lower treatment costs should be prioritized. These include dose reduction, improved drug bioavailability, cost reduction of active pharmaceutical ingredient through improved chemistry process and novel drug delivery systems.

Heat stability:-

Finally, drug formulations need to be stable without the need for refrigeration[13]

Short-term recommendations (One-three years):

First line antiretroviral therapy -

Dolutegravir or bictegravir are the two integrase inhibitors included in the majority of first-line HIV therapies that are advised. It is typically given in a three-drug combination together with a nucleotide backbone. Dolutegravir, tenofovir disoproxil, and emtricitabine are the five alternatives. In light of the aforementioned six fundamental principles, the WHO-recommended combination of tenofovir (TDF), lamivudine (3TC), and efavirenz (EFV), which is available as a once-daily FDC, is the ideal first-line regimen for adults and adolescents [14]. To increase its use, however, three problems must be resolved: efavirenz safety during pregnancy, tenofovir toxicity, and cost reduction.

A practical strategy has recently been proposed by WHO, taking into account the significant benefits of EFV when used as part of a once-daily regimen and the repercussions of switching to possibly less effective and safe alternatives, like nevirapine [15]. Although TDF is linked to long-term renal and bone toxicity as well as an elevated risk of fracture, the clinical significance of these toxicities is still unknown [16], and the overall risk-benefit equation favours giving this medication priority while also requiring ongoing monitoring and reporting of adverse events [17]. An ideal formulation for first-line treatment of children over three years would be a scored, adult-strength, dispersible FDC tablet of TDF/3TC/EFV. Treatment programmes could then use the same pill for almost all patients.

A number of active investigations may result in cheaper EFV and TDF expenses. These consist of the clinical assessment of the tenofovir prodrugs CMX157 and GS 7340, their reformulation, and an EFV dose reduction experiment [18]. These trials might also show a decrease in adverse medication reactions.

Second-line antiretroviral therapy -

When patients have first-line drug regiment failure, second-line antiretroviral therapy (ART) regimens are employed. Maximizing the amount of time patients spend on second-line therapy is necessary because it is expensive, unaffordable, and not frequently offered for patients in resource-constrained settings. The TB medications used to treat drug-resistant TB are referred to as second line medications. It is urgently necessary to lower the cost of new medications used in third-line regimens, particularly darunavir (DRV), etravirine (ETV), and raltegravir (RAL), in order to advance and expand second-line therapy. A hopeful option for the future is dolutegravir (DTG), a once-daily integrase inhibitor in development whose very inexpensive active pharmaceutical ingredient may allow for low-cost production [19]. Last but not least, expanding access to straightforward, affordable viral load monitoring is a top aim in order to enhance first-line therapy adherence and identify treatment failure early.

The TB medications used to treat drug-resistant TB are referred to as second line medications. Levofloxacin, moxifloxacin, bedaquiline, delamanid, and linezolid are among the second-line medications. Pretomanid is a brand-new second-line medication that was suggested in 2019 for the treatment of drug-resistant TB.

Mid- to long-term recommendations (three-ten years):

For patients initiating antiretroviral treatment –

For use in resource-constrained settings, the TDF or rilpivirine-based regimen, also available as once-daily FDC, will need to be carefully evaluated. Although cost might still be a concern, DTG co-formulated with abacavir and 3TC is likely to become another single daily co-formulated pill. Once-daily ATV/r or DRV/r could be choices as first-line anchor medicines, but these medications need to be developed as affordable FDCs in order to be used as a first-line regimen. A first-line regimen with a high genetic barrier to resistance is preferred. The cost of an FDC including darunavir, cobicistat, tenofovir, and emtricitabine is still being worked out [20].

Subsequent treatment options –

A variety of recently developed technologies have the potential to revolutionise ART in the long run. With the promise of weekly or even monthly therapy, long-acting formulations could increase patient adherence and the effectiveness of health services like prescriptions, drug supply, and pharmacy management. Rilpivirine, S/GSK 744, and CMX 157 are only a few of the medications that are now being tested in humans for their long-acting potential [19]. However, it is yet unknown if it is possible to combine many medications into a single long-acting combination therapy. New delivery methods, including as injections, patches, and implants, are also being developed and may increase adherence. Last but not least, by boosting medication activity,

decreasing toxicity profiles, and lowering cost, nanotechnology holds potential for better treatments (by reducing the amount of active ingredient). A nanosuspension of rilpivirine is currently in development. The clinical challenges related to the implementation of these delivery systems will require careful assessment.

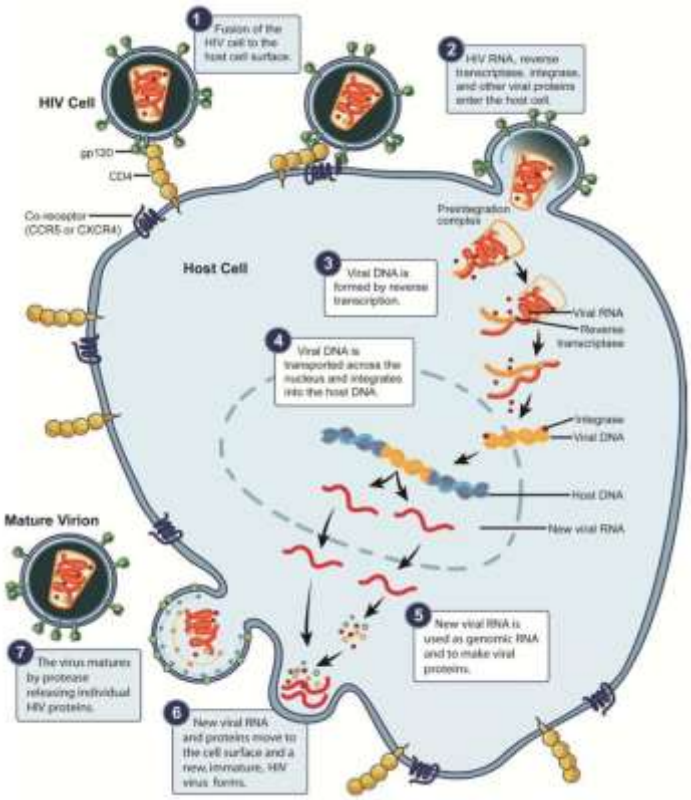

Fig 1. Hiv Replicative Life Cycle

HIV Replicative 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.

HIV LIFE CYCLE AND TARGETS OF ANTIRETROVIRAL DRUG THERAPY :

Figure 1 illustrates the different steps of the HIV life cycle and drug targets [21]. HIV virions enter the CD4+ T-cells and utilize the CD4 cells as the machinery for reproduction of new virions. The currently approved antiretroviral drugs aim at halting viral replication at 6 different stages of the HIV life cycle. Table 1 lists the drugs approved by the FDA within each drug class.

Table 2

US FDA Approved Antiretroviral Agents (listed in chronological order by year of drug approval) and Their Targets in the HIV Life Cycle -

Drug Class	**CCR5 Antagonist**	**Fusion Inhibitor**	**NRTI**	**NNRTI**	**INSTI**	**PI**
FDA Approved Drugs	Maraviroc	Enfuvirtide	Zidovudine Didanosine Zalcitabine Stavudine Lamivudine Abacavir Tenofovir Emtricitabine	Nevirapine Delavirdine Efavirenz Etravirine rlipivirine	Raltegravir Elvitegarvir1 Dolutegravir	Saquinavir Indinavir Ritonavir Nelfinavir Amprenavir Lopinavir2 Fosamprenavir Atazanavir Tipranavir Darunavir

1. Only approved as a fixed dose combination product with cobicistat (a pharmacokinetic enhancer), tenofovir, and emtricitabine
2. Only approved as a fixed dose combination product with low dose ritonavir as a pharmacokinetic enhancer

Abbreviations – NRTI = nucleos(t)ide reverse transcriptase inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, INSTI = integrase strand transfer inhibitor, PI = protease inhibitor.

The introduction of antiretroviral drugs has made significant advancements, and HIV infection has gone from being a fatal disease to a chronic, manageable condition. The physicians will be better able to choose a regimen that is most appropriate for a given patient if they are aware of the potency of the medications and drug regimens, the toxicity profile, the possibility for drug interactions, and the potential for drug resistance.

Some Important Antiretroviral Drugs:

1] ZIDOVUDINE :

available drug for the treatment of HIV infection. Zidovudine is no longer recommended as first-line therapy because of its adverse effect profile, most notably metabolic complications such as lipoatrophy and lactic acidosis[22,23] but also anemia. Metabolic adverse effects are closely linked to thymidine analogues, especially stavudine.[24,25] Zidovudine was the first medication to be FDA approved for the treatment of human immunodeficiency virus type 1 (HIV-1).[26] Currently, the indications of zidovudine include:

❖ ***FDA Approved Indications -***

- Treatment of HIV-1 infection[26]
- Prevention of perinatal HIV-1 transmission (mother to fetus transmission)[27]

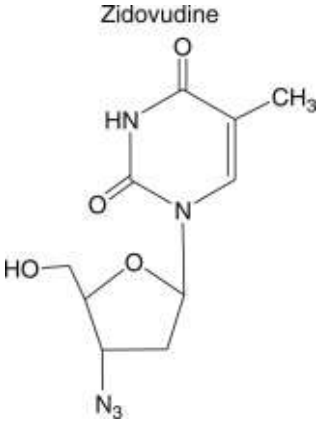

Fig 2. Strucure of Zidovudine

❖ ***Mechanism of Action:***

Host cell kinases are required for the intracellular conversion of zidovudine into the active triphosphate form. Zidovudine has a half-life in the plasma of about an hour, however it is held inside cells due to intracellular conversion to the triphosphate form. Zidovudine permits a more logical dosing frequency due to the intracellular trapping as well as the intracellular half-life of roughly 7 hours. [28]

Zidovudine's antiretroviral actions against HIV-1 are also thought to work against adult T cell leukemia-lymphoma, which is brought on by the retrovirus human T cell leukemia/lymphotropic leukaemia virus type 1 (HTLV-1).

The bioavailability of zidovudine is around 64%, with food only slowing the absorption and not reducing the amount absorbed. About 14% of zidovudine is renally excreted unchanged, and 74% is renally excreted as zidovudine 5'-glucuronide after being glucuronidated. A small portion is also metabolized by other microsomal pathways.[29]

Fig 3. Zidovudine Tablet

❖ ***Administration:***

Zidovudine is administered orally and intravenously; however, the injectable formulation is not readily available.

Treatment of HIV-1 Infection (not to be used as monotherapy)

- Adult oral dosing[30] :
    - 300 mg twice daily
- Pediatric oral dosing[31] :
    - 4 to < 9 kg: 12 mg/kg twice daily
    - ≥9 to <30 kg: 9 mg/kg twice daily
    - ≥30 kg: 300 mg twice daily

Prevention of Perinatal HIV-1 Transmission given Intrapartum -

Monotherapy with zidovudine is now considered suboptimal.

- IV: Loading dose of 2 mg/kg for 1 hour, followed by a continuous infusion of 1 mg/kg/hour

HIV-1 Nonoccupational Postexposure Prophylaxis [32] **-**

- Orally: 300 mg twice daily in combination with other antiretroviral agents for 28 days

ATL in Combination with IFN -

- Orally: 750 mg/m^2 twice daily tapered down to 300 mg twice daily as tolerated.[33]

❖ ***Adverse Effects :***

Zidovudine has a high frequency of several side effects that limits its use.[34]

Side effects include:[35]

- Nausea/vomiting (18.8 to 89%)
- Diarrhea (7 to 78%)
- Headaches (15 to 38%)
- Myalgias
- Insomnia
- Bone marrow suppression (has been reported as high as 45%)
- Peripheral myopathy
- Elevated liver enzymes
- Lactic acidosis
- **Hepatotoxicity:**

A slight increase in liver enzymes can result with long-term zidovudine therapy. Due of the increased liver enzymes' generally asymptomatic and temporary nature, dosage changes are not necessary. Rare examples of noncirrhotic portal hypertension, severe acute fatty liver, and acute cholestatic hepatitis with lactic acidosis. Zidovudine has been linked to some of the hepatotoxicity by inhibiting mitochondrial gamma polymerase, which results in mitochondrial depletion and malfunction.

Neutropenia, leukopenia, and anaemia are all symptoms of zidovudine-induced bone marrow suppression. Zidovudine use was associated with anaemia that required blood transfusions at a rate as high as 19.7%. Usually, stopping zidovudine will cure anaemia and neutropenia. [36]

❖ ***Enhancing Healthcare Team Outcomes :***

Although it is not currently advised as a first-line agent or used as monotherapy, zidovudine is a NRTI that is FDA-approved for the treatment of HIV-1 infection and the prevention of perinatal HIV-1 transmission. [37,38] [Level 1] Additionally, it has been researched for usage in ATL coupled with IFN and non-occupational postexposure prophylaxis for HIV-1. Zidovudine monotherapy is thought to be utilised in about 81% of cases of HIV-1 non-occupational post-exposure prophylaxis, despite no longer being the first-line treatment. [38] [Level 3] Zidovudine was formerly administered intravenously, but more recently, it has only been taken orally. Due to the high frequency of its negative effects, zidovudine use has been restricted.

Nurses should keep an eye out for typical side effects such headaches, myalgias, nausea, vomiting, and diarrhoea, and report any they observe to the provider. The effectiveness of antiviral medication will be enhanced by this multidisciplinary approach to patient care. [Level 5] Clinicians must inform patients about the value of continuing to take zidovudine as prescribed. Patients are better able to maintain a healthy immune system and are less likely to develop neoplasms or opportunistic infections. The quality of life and survival rates of people with HIV-1 will consequently improve thanks to this treatment. Infected women who get pregnant should receive appropriate counselling on treatments to assist prevent vertical transmission from the mother to the foetus. . HIV-1 needs to be on all clinicians' differentials when dealing with certain opportunistic infections, neoplasm, and patient populations. Those who are infected should receive prompt, highly active antiretroviral therapy. Treatment with zidovudine has proven to be effective in several clinical scenarios.[39,40]

Specialty trained HIV care nurses review the importance of compliance with patients, check for side effects, follow up on laboratories, and inform prescribing providers of patient issues. Board-certified infectious disease pharmacists can consult with the prescriber on appropriate dosing and regimen, evaluate interactions, and educate patients. These interprofessional interventions are examples of how coordinated healthcare team dynamics can improve patient outcomes when using zidovudine therapy.

2] Atazanavir:

In conjunction with other antiretroviral medications, atazanavir is FDA-approved for treating HIV-1 infection in patients 3 months of age or older who weigh 5 kilos or more. It belongs to the group of HIV-1 drugs called protease inhibitors. Atazanavir's indications, mechanism of action, administration, side effects, contraindications, and monitoring will be highlighted in this exercise as they relate to healthcare team members managing patients with HIV/AIDS.

Combining atazanavir therapy with additional anti-HIV medications helps. HIV polymerase's high mistake rate causes extensive mutations and encourages the emergence of strains resistant to antiretroviral medications. Multiple drugs are administered in order to treat this issue in at least two

separate ways. The HIV viral load can be lowered to undetectable levels in the blood when two nucleoside analogs are combined with protease inhibitors, such as atazanavir. [41]

The choice of drug regimen should be influenced by knowledge of the baseline mutations in the virus, as revealed by genotyping testing, due to cross-resistance among antiretroviral drugs, particularly in individuals who have previously had therapy with protease inhibitors.

Children under three months of age should not take atazanavir, and the ideal dosage is still unknown. As a competitive inhibitor of an enzyme that catalyzes bilirubin glucuronidation, atazanavir has the potential to cause kernicterus in this population. Additionally, it is not advised to take atazanavir while nursing.[42]

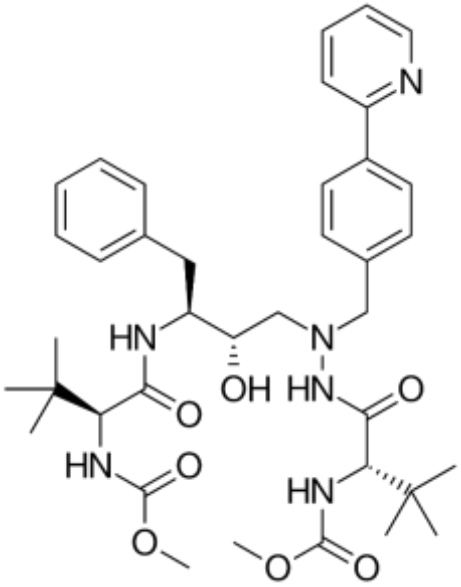

Fig 4. Strucure of Atazanavir

- ***Mechanism of Action:***

HIV protease has been the target of anti-HIV medications because of its critical function in the development of the mature virus. Amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, saquinavir, and tipranavir are the 10 protease inhibitors that the FDA has approved. These medications are peptide mimics that compete with the natural HIV protease substrates Gag and Gag-Pol proteins. [43] Incomplete packaging of the virus occurs when the protease cleaves these precursor proteins. The UGT1A1 enzyme, which is in charge of bilirubin glucuronidation, is inhibited by protease inhibitors, such as atazanavir, causing a buildup of bilirubin in the serum. However, compared to other protease inhibitors, using atazanavir is linked to fewer negative effects on the heart and lipid profile.[44] to counteract the quick rate of mutation that causes HIV's development of treatment resistance. HIV patients receiving highly active antiretroviral combination therapy (HAART) need to take HIV protease inhibitors because HIV protease mutations cause drug resistance. The first protease inhibitor to be approved for once-daily dosage was atazanavir. In comparison to other antiretroviral therapeutics used alone, protease inhibitors have demonstrated improved efficacy in lowering HIV viral load. However, they are also a major source of the most serious antiretroviral side effects, which have a negative impact on patient adherence to pharmacotherapy.

Fig 5. Atazanavir Tablet

❖ ***Administration:***

Oral administration of atazanavir is the preferred method. It has been shown that administering with food improves bioavailability and lowers pharmacokinetic variability. Atazanavir must dissolve with the help of stomach acid. Therefore, careful planning for different dose times is necessary when co-administering antacids, buffered medicines, proton pump inhibitors, and histamine H2-receptor antagonists.[45]

The first once-daily protease inhibitor, atazanavir, is administered along with low dose ritonavir or cobicistat. Inhibitors of cytochrome P450 (CYP3A4) include cobicistat and ritonavir. Atazanavir is metabolized by the same enzyme, so taking it alongside cobicistat or ritonavir will boost its bioavailability. Patients with underlying hyperlipidemia may receive atazanavir without these pharmacokinetic boosts because ritonavir-boosted medication may increase the risk of hyperlipidemia.[44]

❖ ***Toxicity:***

Atazanavir toxicity has no particular antidote. Healthcare professionals should offer supportive and symptomatic care. It is crucial to monitor the patient for respiratory distress symptoms and other vital signs. It is advised that the patient undergo electrocardiogram monitoring since atazanavir may exacerbate AV block due to PR interval prolongation. Clinicians should keep an eye out for lactic acidosis symptoms in patients if a concurrent overdose with nucleoside reverse transcriptase inhibitors is suspected. [46]

❖ ***Enhancing Healthcare Team Outcomes :***

According to estimates, there are more than a million HIV-positive individuals in the US. Antiretroviral therapy should be started right away after a patient is diagnosed with HIV infection in order to prevent the disease from progressing to acquired immunodeficiency syndrome (AIDS). This strategy necessitates a multidisciplinary team effort.

Adherence to the treatment plan is equally crucial to prevent HIV transmission to others by reducing viral load.[47] Additionally, studies have shown that the stigma associated with HIV infection negatively impacted treatment adherence. This factor poses a non-trivial challenge to the entire healthcare team to not only monitor the patient for adverse drug events to improve adherence to drug therapy and test for the occurrence of drug resistance but also to provide effective counseling on the importance of therapy adherence and behavioral modifications to reduce patient risk for opportunistic infections and minimize public risk for the spread of HIV infections. Treatment adherence improves by the healthcare team when it is attentive to patient concerns about adverse events, providing strategies to reduce dosing forgetfulness, and increasing disease and health literacy. Recently, research has shown that a single-tablet regimen improved pharmaceutical adherence over multi-tablet regimens.[48]

In summary, interprofessional healthcare teams can enhance HIV treatment outcomes in various ways, especially by improving drug adherence through education, careful monitoring, and consideration of the patient's needs and lifestyle. [Level 5]

3] Abacavir:

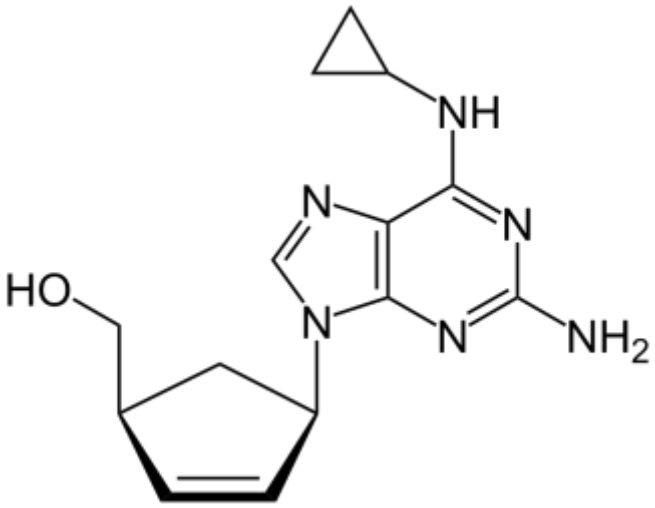

Fig 6. Structure of Abacavir

The active metabolite of abacavir, carbovir triphosphate, which is a carbocyclic nucleoside analog, suppresses the activity of HIV reverse transcriptase (ZIAGEN 2013). Orally, it is quickly and thoroughly absorbed. Alcohol dehydrogenase and glucuronyl transferase break it down. Patients with renal impairment do not require a dose adjustment. Abacavir, which is available as a fixed dose combination with zidovudine and lamivudine or with lamivudine and zidovudine, is frequently used as a 2-NRTI backbone in conjunction with lamivudine. Abacavir and lamivudine can be administered once daily without regard to food, even though a 3-NRTI combination of abacavir, zidovudine, and lamivudine has been approved as an initial regimen for patients

who are antiretroviral-naive. However, this regimen is generally not advised due to its inferior potency. The use of abacavir has been linked to a systemic hypersensitivity reaction that is immunologically mediated and characterized by symptoms like flu-like illness, high fever, generalized skin rash, gastrointestinal problems, and compromised respiratory function. These symptoms typically appear within the first few weeks of starting treatment, and abacavir should be stopped as away if they do. Re-challenging a patient who has had this hypersensitivity reaction is not advised because it can quickly cause the onset of more serious symptoms like profound hypotension and vascular collapse. The HLA-B*5701 allele has been found to be strongly associated with this reaction. Prior to starting abacavir, HLA-B*5701 should be tested, and people who test positive shouldn't receive this medication. Abacavir use, whether current or recent, has been linked to cardiovascular events including acute myocardial infarction in some but not all prospective and retrospective investigations, particularly in patients with a significant history of cardiac disorders.[49]

Fig 7. Abacavir Table

4] Emtricitabine and lamivudine:

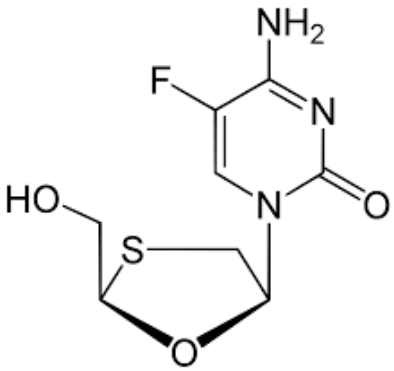

Fig 8. Structure of Emtricitabine

Lamivudine and emtricitabine have comparable structures and actions. They both have HIV-1 resistance profiles that are comparable, with M184V being the most frequently chosen resistance mutation. They should be included in a regimen for patients who have hepatitis B co-infection since they are both effective against the hepatitis B virus (HBV). After starting (as a method of immunological reconstitution) or stopping these medications, hepatitis can worsen. These two medications can be taken orally and are quickly absorbed, however emtricitabine has a somewhat longer intracellular half-life. Both are eliminated through the kidneys, thus dosage adjustments are required for those who have impaired kidney function. The most frequently reported side effect of these medications is skin darkening, which is normally extremely well tolerated.[50]

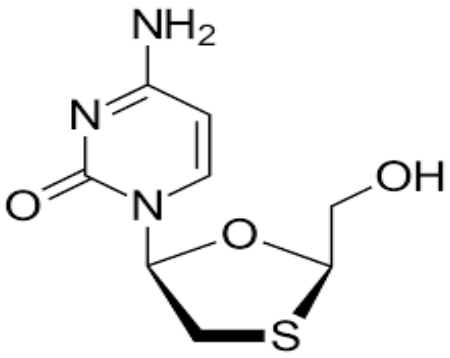

Fig 9. Structure of Lamivudine

Conclusion:

Antiretroviral medications work well to treat HIV. Antiretroviral therapy (ART) should be started as soon as possible for everyone who tests positive for the virus, according to organizations around the world. ART can lessen the chance of difficulties brought on by HIV, halt the virus' growth, and limit further transmission. Additionally, it can lengthen a person's life and improve their quality of life.

With ART, some people occasionally have side effects. After a few days or weeks of treatment, some of symptoms tough to go. If not, a medical expert may be required to prescribe other drugs. 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.

More details on ART and advice on certain treatment choices can be found from healthcare specialists.

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