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Full Length Research

A Literature Review on Recent Advancements in the Treatment of Human Immunodeficiency Virus

[1]**COKER**, A. O. (Professor) & [2]**OLUNAIKE,** Jesuloluwa Hannah
Department of Microbiology,
Faculty of Science,
Caleb University,
Imota, Nigeria.
[2]Corresponding Author Email: lolu.olunaike2000@gmail.com

[3]**ADEWOLE,** Esther Abisola
Department of Chemistry,
Faculty of Physical Sciences,
Federal University of Technology,
Akure, Nigeria
[2]Co-Author Email:estheradewole32@gmail.com

[4]**OLAIFA**, Yetunde Damilare
Department of Applied Chemistry,
Osun State Polytechnic,
Iree, Nigeria
Co-Author Email: yettyolaifa82@gmail.com

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Abstract: The aim of this study is to conduct an extensive literature review on recent advancements in the treatment of human immunodeficiency virus (HIV). This is because in extant studies, the care of the HIV infected patient has changed dramatically in the last few years. Potent new antiretroviral drugs combined with updated treatment strategies have now achieved efficient inhibition of HIV replication in most patients. Classes of drugs include both nucleoside and non-nucleoside inhibitors of the viral enzyme reverse transcriptase (RT) and inhibitors of the viral protease and integrase enzymes. The methodology used in this study was reviewed from secondary sources of information including journals, articles, newspaper, and textbooks. In this study, authors found that a major drawback of the highly active antiretroviral therapy (HAART) is the selection of resistant mutants under suboptimal dosage, in advanced stages of disease or after pre-treatment with mono- or double-combination regimens. In addition, monitoring of antiretroviral therapy is achieved by measurement of viral load using nucleic acid amplification techniques. Strict adherence to HIV drug regimens was reported to be essential for reaching and maintaining therapeutic levels of anti-retro-virals and avoiding development of drug-resistant HIV strains. This strict dosage-taking adherence makes HIV therapies among the most challenging treatments with which to adhere. Future researchers are encouraged to adopt a scientific approach in investigating the various constructs that have emerged in this study in other to

provide more generalized findings for the research community and public policy makers.

Keywords: Antiretroviral Drugs: Combination Therapy: Medication: Transmission: Inhibitors: Immune System.

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1.0 Introduction of the Study

Acquired Immune Deficiency Syndrome (AIDS) was the great pandemic of the second half of the twentieth century; it was first described in 1981 (Shehu et al., 2022; Ukonu et al., 2022a). AIDS is the result of an infection by the Human Immunodeficiency Virus (HIV), a positive strand, enveloped RNA virus within the family Retrovirodae. HIV/AIDS is a leading cause of mortality and morbidity worldwide (Willey *et al.,* 2013). HIV infection has now spread to every country in the world. Approximately 40 million people are currently living with HIV infection, and an estimated 25 million have died from this disease. The scourge of HIV has been particularly devastating in sub-Saharan Africa, but infection rates in other countries remain high. In the United States, approximately 1 million people are currently infected. Globally, 85% of HIV transmission is heterosexual (Sharma *et al.,* 2015).

HIV research has come a long way since the disease was discovered. Antiretroviral therapy was a major milestone that has changed the lives of millions, but the goal of scientists worldwide has been to find an HIV cure (Kaplan, 2013; Fernández, 2018). A number of recent developments in HIV/AIDS research which includes gene therapy, immunotherapy, stopping the replication of the disease etc, Fernández (2018) concluded that reports have led to renewed optimism among the HIV/AIDS research community about the prospects of controlling or perhaps even curing the disease.

2.0 Review of Literature

In order to understand HIV and AIDS, it is important to understand the meanings behind these terms.

2.1 HIV/AIDS Overview

Human Immunodeficiency Virus is one of a group of viruses known as retroviruses. After getting into the body, the virus kills or damages cells of the body's immune system (Meg *et al.,* 2019). The body tries to keep up by making new cells or trying to contain the virus, but eventually the HIV wins out and progressively destroys the body's ability to fight infections and certain cancers (UNAIDS, 2015; Sharma *et al.*, 2015).

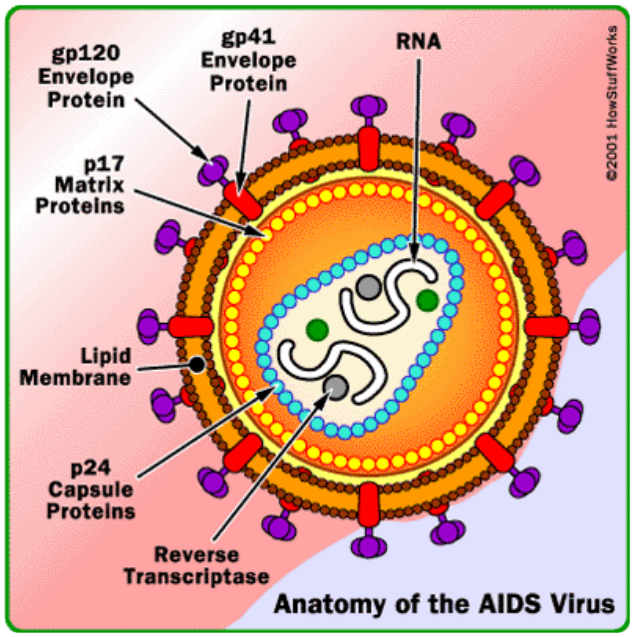

Figure 1: The AIDS Virus Illustrations, scanning electron micrographs (SEM), and transmission electron micrographs (TEM) of the HIV (Sharma *et al.*, 2015).

2.1.1 HIV/AIDS Transmission

Human Immunodeficiency Virus (HIV) is transmitted when the virus enters the body, usually by injecting infected cells or semen. There are several possible ways in which the virus can enter. Most commonly, HIV infection is spread by having sex with an infected partner (Fajardo-Ortiz *et al.*, 2017). The virus can enter the body through the lining of the vagina, vulva, penis, rectum, or mouth during sex (Shete, 2013). HIV frequently spreads among injection-drug users who share needles or syringes that are contaminated with blood from an infected person (Willey *et al.*, 2013). Women can transmit HIV to their babies during pregnancy or birth, when infected maternal cells enter the baby's circulation. HIV can be spread in health-care settings through accidental needle sticks or contact with contaminated fluids (Sharma *et al*., 2015).

Very rarely, HIV spreads through transfusion of contaminated blood or blood components. Blood products are now tested to minimize this risk. If tissues or organs from an infected person are transplanted, the recipient may acquire HIV (Meg *et al.*, 2019; Olunaike, 2019). Donors are now tested for HIV to minimize this risk. The virus does not spread through casual contact such as preparing food, sharing towels and bedding, or via swimming pools, telephones, or toilet seats. The virus is also unlikely to be spread by contact with saliva, unless it is contaminated with blood (Sharma *et al.*, 2015).

2.1.2 HIV/AIDS Symptoms and Signs

Many people with HIV do not know they are infected. Many people do not develop symptoms after they first get infected with HIV. Others have a flu-like illness within several days to weeks after exposure to the virus (UNAIDS, 2015). They complain of tiredness, and enlarged lymph nodes in the neck. These symptoms usually disappear on their own within a few weeks. After that, the person feels normal and has no symptoms. This asymptomatic phase often lasts for years. The progression of disease varies widely among individuals. This state may last from a few months to more than 10 years (Ukonu et al., 2022b; Owolabi et al., 2022; Sharma *et al*., 2015). During this period, the virus continues to multiply actively and infects and kills the cells of the immune system. The virus destroys the cells that are the primary infection fighters, a type of white blood cell

called CD4 cells. Even though the person has no symptoms, he or she is contagious and can pass HIV to others through the routes listed above (Willey *et al.,* 2013; Sharma *et al.,* 2015).

2.1.3 HIV/AIDS Diagnosis

Human Immunodeficiency Virus (HIV) infection is commonly diagnosed by blood tests. There are three main types of tests that are commonly used: (1) Antibody tests (2) RNA tests (3) A combination test that detects both antibodies and a piece of the virus called the p24 protein. In addition, a blood test known as a Western blot is used to confirm the diagnosis (Kaplan, 2013; Olunaike, 2019). No test is perfect. Tests may be falsely positive or falsely negative. Therefore, if the initial antibody test is negative, a repeat test should be performed three months later. Early testing is crucial; because early treatment for HIV helps people avoid or minimize complications. Furthermore, high-risk behaviours can be avoided, thus preventing the spread of the virus to others (Sharma *et al.,* 2015). Testing for HIV is usually a two-step process. First, an inexpensive screening test is done. If that test is positive, a second test (Western blot) is done to confirm the result (Kaplan, 2013). Antibody tests are the most common initial screening test used. There are different types of antibody screening tests available:

Most commonly, blood is drawn for an enzyme immunoassay (EIA). The test is usually run in a local laboratory, so results can take one to three days to come back (UNAIDS, 2015). Other tests can detect antibodies in body fluids other than blood such as saliva, urine, and vaginal secretions. Some of these are designed to be rapid tests that produce results in approximately 20 minutes. These tests have accuracy rates similar to traditional blood tests (Meg *et al.*, 2019; Owhe-Ureghe et al., 2022).

All positive antibody screening tests must be confirmed with a follow-up blood test called the Western blot to make a positive diagnosis (Shete, 2013). If the antibody test and the Western blot are both positive, the likelihood of a person being HIV infected is >99%. Sometimes, the Western blot is "indeterminate," meaning that it is neither positive nor negative. In these cases, the tests are usually repeated at a later date. In addition, an RNA test for the virus might be done (Willey *et al.,* 2013; Sharma *et al.,* 2015).

2.1.4 HIV Prevention

Despite significant efforts, there is no effective vaccine against HIV. Prevention methods for HIV can be broadly classified as behavioural and biological methods. Behavioural prevention methods classically known as ABC of HIV prevention (Abstinence, behavioural changes and condom usage) still continue to be the mainstay of HIV prevention because of limitations of the biological options (Shete,2013) .The only way to prevent infection by the virus is to avoid behaviours that put you at risk, such as sharing needles or having unprotected sex. In this context, unprotected sex means sex without a barrier such as condom. Because condoms break, even they are not perfect protection. Many people infected with HIV don't have any symptoms. There is no way to know with certainty whether a sexual partner is infected. Here are some prevention strategies (Sharma *et al.,* 2015).

Abstain from sex. This obviously has limited appeal, but it absolutely protects against HIV transmission by this route (Willey *et al.,* 2013). Have sex with a single partner who is uninfected. Mutual monogamy between uninfected partners eliminates the risk of sexual transmission of HIV. Use a condom in other situations. Condoms offer some protection if used properly and consistently. Occasionally, they may break or leak. Only condoms made of latex should be used. Only water-based lubricants should be used with latex condoms (Saxena *et al.,* 2015). Do not share needles or inject illicit drugs. If you work in a health-care field, follow recommended guidelines for protecting yourself against needle sticks and exposure to contaminated fluids. If you have engaged in risky behaviours, get tested to see if you have HIV (UNAIDS, 2015). The risk of HIV transmission from a pregnant woman to her baby is significantly reduced if the mother takes medications labor, and delivery and her baby takes medications for the first six weeks of life (Willey *et al.,* 2013). Even shorter

courses of treatment are effective, though not as optimal. The key is to get tested for HIV as early as possible in pregnancy. In consultation with their physician, many women opt to avoid minimizing the risk of transmission after the baby is born (Fajardo-Ortiz *et al.,* 2017).

2.2 Antiretroviral Drugs

An HIV diagnosis is no longer the death sentence it used to be. Thirty years ago, doctors had little more than comforting words to offer people who had been diagnosed with the virus (Ho *et al*., 2006; Olunaike, 2019). But today, while there remains no cure for HIV or AIDS, remarkable advancements in treatments and clinical understanding of how the virus progresses are allowing people with HIV to live longer, fuller lives (Holland & Timothy, 2017). The main treatment for HIV today is antiretroviral drugs. These drugs don't cure HIV. Instead, they suppress the virus and slow its progression in the body. They don't eliminate the virus from the body, but in many cases, they can suppress it to undetectable levels (Holland & Timothy, 2017). This keeps the immune system strong enough to fight off disease (Kaplan, 2013). If an antiretroviral medication is successful, it can add many healthy, productive years to a person's life and reduce the risk of transmission to others (Saxena *et al.,* 2015; Holland & Timothy, 2017). There are more than 40 antiretroviral drugs approved to treat HIV today. Mostly two or more of these drugs each day are taken by HIV patients for the rest of their lives (Meg *et al.,* 2019). These drugs must be taken at the right time and in the right way for them to work properly. Taking these medications the way a healthcare provider has prescribed them is called adherence (Watson & Zara, 2019).

2.2.1 Side Effects of Antiretroviral Medications

Antiretroviral drugs can cause side effects that can be very severe, they include; Appetite loss, lipodystrophy , diarrhea, fatigue, higher than normal levels of cholesterol and triglycerides, mood changes, depression, and anxiety, nausea and vomiting, rash, trouble sleeping, hypersensitivity or allergic reactions, with symptoms such as fever, nausea, and vomiting, bleeding, bone loss, heart disease ,high blood sugar and diabetes, lactic acidosis (high lactic acid levels in the blood),kidney, liver, or pancreas damage ,numbness, burning, or pain in the hands or feet due to nerve problem (Ho *et al*., 2006; Watson & Zara, 2019). Sticking to a treatment is not always easy. But if a person with HIV skips doses of these drugs, the virus can start copying itself in their body again. This could cause HIV to become resistant to the drugs. If that happens, the drug will no longer work, and that person will be left with fewer options to treat their HIV (Shete, 2013; Watson & Zara, 2019).

2.2.2 Types of Antiretroviral Medications

The most commonly prescribed antiretroviral medications can be divided into four classes. They are:

2.2.2.1 Reverse transcriptase (RT) inhibitors: RT inhibitors interrupt the life cycle of an HIV-infected cell as it tries to replicate itself. There are two types of RT inhibitor: NNRTIs and NRTIs (Holland & Timothy, 2017).

a. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs): Non-nucleoside reverse transcriptase inhibitors (NNRTIs) prevent HIV from making copies of itself. Commonly used NNRTIs include: Efavirenz (Sustiva), Rilpivirine (Endurant) and Etravirine (Intelence) (Holland & Timothy, 2017).

b. Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs): Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) keep HIV-infected cells from making copies of themselves by interrupting the reconstruction of the virus's DNA chain. The most commonly used NRTIs include: Tenofovir disoproxil fumarate (Viread), Tenofovir alafenamide, Abacavir (Ziagen), Lamivudine (Zeffix and Epivir), and Imtricitabine (Emtriva) (Holland & Timothy, 2017). The most commonly used combination NRTIs include: Emtricitabine/tenofovir disoproxil fumarate (Truvada), Emtricitabine/tenofovir alafenamide (Descovy), and Abacavir/lamivudine (Epizicom) (Holland & Timothy, 2017).

2.2.2.2 Protease inhibitors (PIs): Protease inhibitors (PIs) disable protease, a protein that HIV needs to make copies of itself. PIs include: Tazanavir (Reyataz), Darunavir (Prezista), Lopinavir (Kaletra, in combination with ritonavir), Ritonavir (Norvir), Saquinavir (Invirase, Fortovase), Indinavir (Crixivan), Nelfinavir (Viracept), Fosamprenavir (Lexiva, Telzir), and Tipranavir (Aptivus) (Holland & Timothy, 2017).

2.2.2.3 Entry or fusion inhibitors: Entry or fusion inhibitors block HIV from entering CD4 T cells. These inhibitors include: Maraviroc (Selzentry), Enfuvirtide (Fuzeon), Ibalizumab (Trogarzo) (Holland & Timothy, 2017).

2.2.2.4 Integrase inhibitors (INSTIs): Integrase inhibitors disable integrase, a protein that HIV uses to infect CD4 T cells. INSTIs include: Bictegravir, Dolutegravir, Elvitegravir raltegravir (Holland & Timothy, 2017).

2.2.3 Multidrug Combination Therapy

Human Immunodeficiency Virus (HIV) can mutate and become resistant to a single medication. Therefore, most doctors today prescribe several HIV medications together. A combination of three or more antiretroviral drugs is called **highly active antiretroviral therapy (HAART**) (Fajardo-Ortiz *et al.,* 2017 and Holland and Timothy, 2017). Highly Active Antiretroviral Therapy **(**HAART) is a powerful therapy. When it was first introduced in the late 1990s, AIDS-related deaths was greatly reduced (Murrill *et al.,* 2014). The most common HAART treatments today consist of two NRTIs and either an INSTI, an NNRTI, or a boosted protease inhibitor (Meg *et al.,* 2019 and Holland & Timothy, 2017).

Advances in medications are also making adherence to HAART much easier. These advances have reduced the number of pills a person must take, and reduced the side effects for many people using HAART (Saxena *et al.,* 2015). Adherence means sticking with a treatment plan. Adherence is critical for HIV treatment. If a person with HIV does not take their medications as prescribed, the drugs could stop working for them and the virus could start spreading in their body again (UNAIDS, 2015).

2.2.4 Combination Pills

A major advancement that is making adherence easier for people on HAART is the development of combination pills. These medications are now the most commonly prescribed drugs for people with HIV who haven't been treated before (Cohen *et al.,* 2011). Combination pills contain multiple drugs within one pill. Currently, there are seven combinations containing three or more antiretroviral drugs (Arora et *al.,* 2010). Atripla, which was approved in 2006, was the first effective combination tablet. However, it's used less often now due to its side effects such as sleep disturbances and mood changes. Integrase inhibitors **(**INSTI) based combination tablets are the regimens recommended now for most people with HIV. This is because they are effective and cause fewer side effects than other regimens (Holland & Timothy, 2017). Current combination medications include:

1. Triumeq: dolutegravir **+** abacavir **+** lamivudine

2. Biktarvy: bictegravir **+** tenofovir alafenamide fumarate **+** emtricitabine

3. Genvoya: elvitegravir **+**cobicistat **+** tenofovir alafenamide fumarate **+** emtricitabine

4. Stribild: Elvitegravir + cobicistat + emtricitabine + tenofovir disoproxil fumarate

5. Atripla: Efavirenz + tenofovir disoproxil fumarate + emtricitabine

6. Complera: Rilpivirine+ tenofovir disoproxil fumarate+ emtricitabine

7. Odefsey: rilpivirine+tenofovir alafenamide fumarate+ emtricitabine

8. Symfi: efavirenz+lamivudine+tenofovir disoproxil fumarate.

9. Symfi Lo: Efavirenz+ lamivudine +tenofovir + disoproxil fumarate (Holland and Timothy, 2017).

2.3 Treatment Adherence

The advent of highly active antiretroviral treatment(HAART) has dramatically improved the prognosis for HIV-positive patients, substantially reducing the rate of disease progression and death (Arora et *al.,* 2010). Regarding ART clinical management, the World Health Organization (World Health Organization, 2016) states, "ART should be started in all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count". Early ART initiation is associated with decreased new infections (Cohen *et al.,* 2011). Adherence to antiretroviral therapy, however, is critically important for the success of the therapy. Strict adherence to HIV drug regimens is essential for reaching and maintaining therapeutic levels of antiretrovirals and avoiding development of drug-resistant HIV strains. Studies suggest that near-perfect adherence, i.e., higher than 95%, is necessary to achieve suppression of HIV replication (Fettig *et al.,* 2014; Dybul *et al.,* 2002).

Many factors have been studied for their association with the behavior of taking antiretroviral medication correctly (Dybul *et al.,* 2002). Sociodemographic characteristics were not associated with adherence in some studies. The following factors have been associated with non adherence in a number of studies: sociodemographic characteristics such as younger age, low income, low levels of schooling and psychological factors such as depression, high levels of stress, psychiatric conditions excessive drinking, and drug use (Herek et al., 2013). Some studies also suggest that non adherence tends to increase with the number of times medications must be taken per day and the number of different medications. Patients who are experiencing adverse effects are less likely to adhere than patients who are tolerating the medication (Herek et al., 2013).

Managing complicated antiretroviral regimens requires complex cognitive skills that can be easily disrupted by factors such as substance abuse, neurocognitive impairment, and poor literacy. Thus, HIV treatment adherence will likely remain a significant problem in the growing population of substance abusing and economically disadvantaged persons living with HIV/AIDS (Dybul *et al.,* 2002; Herek et al., 2013).

3.0 Methodology of the Study

The study adopts an extensive review of literature such as conference papers, journal articles, internet sources, books. The aim of this study was to conduct an extensive literature review on recent advancements in the treatment of human immunodeficiency virus (HIV). This is because in extant studies, the care of the HIV infected patient has changed dramatically in the last few years. Future findings will contribute to existing body of knowledge in the field of human immunodeficiency virus and future authors will be guided to adopt scientific approach to test the constructs that would emerge from this study, so as to provide more valid results.

4.0 Conclusions and Suggestions to Future Authors

The aim of this study was to conduct an extensive literature review on recent advancements in the treatment of human immunodeficiency virus (HIV). This is because in extant studies, the care of the HIV infected patient has changed dramatically in the last few years. Potent new antiretroviral drugs combined with updated treatment strategies have now achieved efficient inhibition of HIV replication in most patients. Authors in this study used secondary sources of information including journals, articles, newspaper, and textbooks. In this study, authors found that a major drawback of the highly active antiretroviral therapy (HAART) is the selection of resistant mutants under suboptimal dosage, in advanced stages of disease or after pre-treatment with mono- or double-combination regimens. In addition, monitoring of antiretroviral therapy is achieved by measurement of viral load using nucleic acid amplification techniques. Strict adherence to HIV drug regimens

was reported to be essential for reaching and maintaining therapeutic levels of anti-retro-virals and avoiding development of drug-resistant HIV strains. This strict dosage-taking adherence makes HIV therapies among the most challenging treatments with which to adhere. Future researchers are encouraged to adopt a scientific approach in investigating the various constructs that have emerged in this study in other to provide more generalized findings for the research community and public policy makers.

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