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A COMPARATIVE EVALUATION OF THE EFFECTIVENESS OF FIRST-LINE ANTI-RETROVIRAL THERAPY REGIMENS: TENOFOVIR VERSUS ZIDOVUDINE IN MANAGING HUMAN IMMUNODEFICIENCY VIRUS AMONG PEOPLE LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS

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ABSTRACT:

Human immunodeficiency virus (HIV) infection remains a global health challenge, with approximately 39 million people worldwide living with HIV in 2022. Transmission routes include illicit injections, blood transfusions, multiple sexual partners, and vertical transmission from mother to child. Without treatment, HIV can progress to acquired immunodeficiency syndrome (AIDS), leading to severe immunosuppression and increased susceptibility to opportunistic infections. The World Health Organization (WHO) recommends tenofovir (TDF) as a first-line antiretroviral treatment (ART) due to its efficacy and safety profile. This review article critically evaluates the safety and efficacy of TDF-based ART regimens compared to zidovudine (ZDV)-

based regimens, focusing on cross-sectional research methodologies. Our analysis reveals that TDF-based regimens demonstrate superior efficacy, characterized by lower mortality rates, increased CD4 cell counts, and enhanced virologic suppression, particularly in treatment-naïve HIV patients. Moreover, TDF exhibits fewer harmful side effects compared to ZDV-based regimens, emphasizing its importance in HIV management. This review consolidates current evidence supporting TDF as a cornerstone of first-line ART regimens, offering insights into its role in improving patient outcomes and reducing the global burden of HIV/AIDS.

KEYWORDS: Human immunodeficiency virus (HIV), Acquired immune deficiency syndrome (AIDS), antiretroviral therapy (ART), Tenofovir (TDF), Zidovudine (ZDV), CD4 cells, side effects.

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INTRODUCTION

HIV (human immunodeficiency virus) damages the body's immune system. HIV and AIDS symptoms vary depending on the person and the phase of infection [1]. Primary infection, also known as acute HIV, can cause flu-like symptoms like fever, headache, muscle aches, joint pain, rash, sore throat, mouth sores, swollen lymph glands, diarrhoea, weight loss, cough, and night sweats [2]. Clinical latent infection, also known as chronic HIV, occurs when HIV is still present in the body and white blood cells, but many people don't show symptoms or infections [2]. Symptomatic HIV infection can result in mild infections or long-term symptoms like fever, fatigue, swollen lymph glands, diarrhoea, weight loss, oral yeast infection, shingles, and pneumonia [2]. The World Health Organization (WHO) estimates that by 2023, 39 million individuals worldwide were HIV positive and 40.4 million people had died from HIV/AIDS. Of them, 29.8 million individuals (about 75%) are taking antiretroviral therapy [3]. In 2022, there were around 630,000 HIV/AIDS-related fatalities [3]. HIV is treated and prevented by antiretroviral therapy (ART)[4]. When the initial therapy for HIV infection is given to people who have never taken anti-retroviral treatment, tenofovir and zidovudine-based ART regimens are used [5]. The preferred first-line antiretroviral therapy (ART) regimen for adults and adolescents is tenofovir disoproxil fumarate (TDF) +

lamivudine (3TC) (or emtricitabine, FTC) + efavirenz (EFV) 600 mg, according to the WHO's consolidated guidelines on the use of antiretroviral (ARV) drugs for treating and preventing HIV infection. Since then, programming experience and scientific data supporting the use of dolutegravir (DTG) in first- and second-line ART have been gathered [5].

FDA-approved prescription drug tenofovir DF (brand name: Viread) is used to treat HIV infection in adults and children two years of age and older who weigh at least 22 lb (10 kg) [6]. Tenofovir is a member of the nucleotide analog reverse transcriptase inhibitor (NtRTI) class of antiretroviral medications [6]. NtRTIs inhibit reverse transcriptase, an enzyme vital to the replication of viruses in individuals with HIV [7]. As a result, the HIV viral load may be controlled by decreasing the viral replication Label. The fumarate salt of the prodrug tenofovir disoproxil is called tenofovir disoproxil fumarate [7]. After being absorbed, tenofovir disoproxil is changed into tenofovir, an analog of a nucleoside monophosphate (nucleotide), in its active form [7]. The cell's constitutively expressed enzymes then convert tenofovir into its active metabolite, tenofovir diphosphate, a chain terminator [8]. By directly competing for binding with the natural deoxyribonucleotide substrate (deoxyadenosine 5'-triphosphate), tenofovir diphosphate inhibits HIV-1 reverse transcriptase [8]. This results in viral DNA chain termination after the drug is integrated into DNA [8]. This medication inhibits enzymes required for HIV-1 viral replication in the host cell, preventing viral DNA chain elongation [9]. HIV medications are always taken combined with tenofovir DF. Tenofovir is a nucleotide analogue that is prescribed to treat HIV infections [9]. When treating HIV infection, nucleotide reverse transcriptase inhibitors (NtRTIs) like tenofovir are frequently used in conjunction with other ARVs [9]. In individuals who have never had antiretroviral medication, tenofovir has been demonstrated to be extremely efficacious and to have less toxicity than other antivirals [9]. The standard dosage is one oral dose of 300 mg, either with or without meals [9].

The FDA approved zidovudine as the first drug for treating HIV-1 (human immunodeficiency virus) [10] Zidovudine is categorized as a nucleoside reverse transcriptase inhibitor (NRTI) and is a synthetic analog of the nucleoside thymidine [10]. By replacing thymidine in freshly synthesized viral DNA and functioning as a viral DNA chain terminator, zidovudine serves as an anti-viral drug [10]. This disrupts the HIV-1 life cycle by preventing HIV-1 reverse transcriptase from creating viral DNA from the RNA template [10]. Following the nucleotide analog's inclusion, it suppresses HIV-1 reverse transcriptase (RT) activity by causing DNA chain termination [11]. It binds with viral DNA and competes with the natural substrate dGTP [11]. Additionally, it is a mild inhibitor of cellular DNA polymerase α and γ. It is used to treat human immunodeficiency virus (HIV) infections combined with other antiretroviral medications [11]. In antiretroviral therapy (ART) regimens, zidovudine is used as an alternative to tenofovir; however, it is also linked to side effects such as persistent anaemia, which may have an impact on patients' quality of life [11]. Oral 600 mg/day in split doses is the typical dosage. Overdosage symptoms include headache, nausea, vomiting, and fatigue [11].

DISCUSSION:

We conducted a literature on comparative evaluation of the effectiveness of first-line anti-retroviral therapy

regimens: tenofovir versus zidovudine in managing human immunodeficiency virus among people living with human immunodeficiency virus. We conducted an electronic data base search from the time of 2011-2020 in PubMed, science direct, Wiley, research square Which included ten articles, four abstracts in our analysis.

According to ***Abel Terafe*** [20] ***et al., 2020*** conducted a study comparing tenofovir and zidovudine-based regimens in Ethiopia found that tenofovir-based treatment is the preferred first-line treatment. The study involved 223 patients, with 164 (73.5%) using tenofovir and 59 (26.6%) using zidovudine. The results showed that tenofovir-based treatment had a higher risk of toxicity-driven regimen substitution and better survival for toxicity-driven regimen changes compared to zidovudine-based treatment. The study supports the recommendation of tenofovir-based treatment as the preferred first-line ART in Ethiopia. The study found that the TDF-based regimen showed less toxicity-driven substitution and extended time to toxicity-driven substitution compared to the AZT-based regimen. The TDF group had better effects on eGFR at 6 and 12 months of follow-up, indicating superior safety profiles and comparative effectiveness, reinforcing the latest WHO recommendation in resource-limited Ethiopian settings.

According to ***Jilian O. Etenyi*** [13] ***et al.,2018*** conducted a study to compare the health-related quality of life (HRQoL) and prevalence of symptoms on either zidovudine or tenofovir-based regimens of HIV-naïve patients. It was noticed that out of 501 adult patients, using a comparative cross-sectional study. There are 301 patients on tenofovir and 200 patients on a zidovudine-based regimen. Zidovudine and tenofovir form the backbone of antiretroviral therapy (ART). In this study, patients receiving zidovudine had greater levels of both the Physical Health Summary Score (PHSS) and Mental Health Summary Score (MHSS) in contrast to those receiving tenofovir. PHSS was adversely correlated with patients who reported being unable to cope and having any disease symptoms; on the other hand, PHSS was positively correlated with those who had a consistent source of income. Individuals using second-line regimens experienced fewer symptoms, whereas those on tenofovir regimens displayed higher signs and symptoms of disease. Zidovudine-based regimens appear to perform better in all areas of the HRQoL score compared to tenofovir-based regimens, aided by fewer adverse events and side effects. The prevalence of adverse symptoms and side effects was low.

According to ***Adane Teshome Kefale*** [19] ***et al., 2018*** conducted a review aimed to identify and appraise the best available evidence on the efficacy and safety of TDF based regimens compared to ZDV based regimens. A three-step search strategy was used to locate published and unpublished studies. Results showed that ZDV based regimens had better outcomes in preventing mortality and lower virologic failure, while TDF based regimens were more tolerable. The difference in incidence of opportunistic infection was not significant. There is lower mortality and lower virologic failure in the ZDV group, but better safety profile among TDF based regimens. Comparing TDF-based and ZDV-based regimens for PLWHA adherence and quality of life was conducted. Four observational studies enrolled 28,149 participants, with TDF-based regimens showing a 1.31 times higher mortality rate than ZDV-based regimens. The study also found that TDF-based regimens were better tolerated than ZDV-based regimens, with patients 85% more likely to be protected. However, ZDV-based regimens had

more significant adverse events and were more tolerable than TDF-based regimens. The study also found that ZDV-based regimens had better outcomes for virologic failure, with TDF-based regimens having a better outcome (OR = 1.44) despite heterogeneous studies. The study found that participants in the TDF group maintained a lower plasma HIV RNA of <400 copies/ml compared to the ZDV-based group, possibly due to different viral RNA cut-off points and confounding effects of NNRTIs. However, there was no significant difference in virologic response <400 copies/ml between the two regimens. The TDF group reported 16% of opportunistic infections, while the ZDV group had 19%. These findings suggest that TDF-based regimens are better tolerated than ZDV-based regimens.

According to ***Phihaniar Insaniputri*** [12] ***et al., 2017*** conducted a study to compare the zidovudine combination and the tenofovir combination and their side effects among a total group of 128 HIV patients. The effectiveness and frequency of hemoglobin (Hb)-related side effects in HIV/AIDS patients receiving zidovudine and tenofovir-based regimens were compared in this study. All HIV/AIDS patients treated until 2015 had their medical records examined as part of a cross-sectional comparative research design. There are 53 patients on a tenofovir-based regimen and 75 patients on zidovudine in the sample. The outcomes demonstrated that in patients with initial CD4+ cell counts ≤ 200 cells/mm3, both therapy combinations were beneficial in raising CD4+ cell counts. Individuals on a zidovudine combination regimen were 4.59 times more likely to experience hemoglobin depletion than those on a tenofovir combination regimen. The effectiveness of treatment and hemoglobin reduction can be influenced by factors like sex, weight fluctuations, WHO clinical stage, CD4 cell count, medication adherence, and treatment duration. Nonetheless, tenofovir-based regimens had a lower propensity to induce anemia than zidovudine-based regimens.

Tegene Legese Dadi [14] ***et al., 2017*** conducted a review to compare the efficacy and tolerability of tenofovir (TDF)/emtricitabine (FTC)/ efavirenz (EFV) and zidovudine (ZDV)/ lamivudine (3TC)/ efavirenz (EFV) as first-line regimens for adult patients new to HIV-1 infection. The study included randomized clinical trials on adults and involved an examination of data from four articles with a total of 2381 participants. The findings showed higher suppression of the viral load and showed that the TDF arm outperformed the ZDV arm in achieving a viral load of fewer than 50 HIV RNA copies/mL. TDF-based regimens had a higher likelihood of being tolerated than ZDV-based regimens, even though there was no appreciable difference in the mortality forest plot. When TDF/FTC/EFV was compared to ZDV/3TC/EFV, the first-line therapy showed superior suppression of viral load and tolerability.

According to ***Cedric P. Cheung*** [16] ***et al., 2017*** conducted a study on zidovudine versus tenofovir-based antiretroviral therapy for the initial treatment of HIV infection. Tenofovir (TDF)-based highly active antiretroviral treatment (HAART), as advised by World Health Organization guidelines for patients who are HIV-naive, has not been widely used. This research compared the efficacy of TDF-based HAART with zidovudine (ZDV). The main goal was to achieve an HIV viral load of <50 copies/mL. Changes in CD4 level, adverse events, death, and prolonged virologic suppression were examples of secondary end goals. Out of 361 patients, those receiving TDF-

based HAART had a higher chance of maintaining virologic suppression and achieving a viral load <50 copies/mL. Tenofovir and female sex were identified as independent predictors of achieving a viral load <50 copies/mL. The study concludes that a TDF-based regimen is suggested for the initial treatment of HIV infection.

According to ***Teshale Ayele [17] et al., 2017***, in a retrospective cohort study, 280 patients on regimens based on tenofovir (TDF) had their immunological outcomes examined at Jimma University Specialized Hospital in Ethiopia. After accounting for baseline characteristics, data were gathered for the study between September 2012 and July 2014. With STATA 13.1, the data were examined, and the difference in CD4+ change between groups and the change in the expected CD4 count attributable to each regimen were evaluated using mixed effect linear regression. Since 2013, there has been little data on the immunologic outcomes of TDF in Ethiopia, according to the study. The study found that TDF-based regimens showed more efficacy than AZT-based regimens, with a mean follow-up duration of 714.2 days and 708.8 days for TDF and AZT groups, respectively. Most groups completed their follow-up, with a statistically significant difference in immunologic recovery over time. The predicted CD4+ count for TDF/3TC/EFV was higher than that of AZT/3TC/EFV. The study recommends further research with quality design to assess the prevalence of sub-optimal CD4+ response among TDF users in low-income countries like Ethiopia.

According to ***Kimberly K. Scarsi [18] et al., 2015*** conducted a retrospective cohort study analyzed patients initiating nevirapine-based antiretroviral therapy (ART) with either tenofovir-emtricitabine or lamivudine or zidovudine-lamivudine. Clinical, virologic, and immunologic evaluations were performed at baseline and every 6 months. Virologic failure was defined as 2 consecutive HIV-RNA values >1000 copies/mL. Factors influencing time to failure were modeled using Cox proportional hazards regression and inverse probability weighted pooled logistic regression. A study of 5547 patients found that tenofovir regimen and higher baseline HIV-RNA were associated with virologic failure. However, higher baseline CD4+ cell count and increasing age decreased the risk of virologic failure. The use of tenofovir-lamivudine or emtricitabine in combination with nevirapine was a strong predictor of virologic failure, which was not explained by other risk factors or regimen selection criteria. Zidovudine is preferred over tenofovir when combined with nevirapine, indicating the need for systematic evaluations before inclusion in ART guidelines.

According to ***Chi Benjamin H [15] et al., 2011*** conducted a study to compare the outcomes of tenofovir-based and zidovudine-based regimens among HIV patients. Tenofovir (TDF) is a common component of antiretroviral therapy (ART), but recent evidence suggests inferior outcomes when combined with nevirapine (NVP). A study comparing outcomes among patients initiating TDF + emtricitabine or lamivudine (3TC) + NVP, TDF + 3TC + efavirenz (EFV), zidovudine (ZDV) + lamivudine (3TC) + NVP, and ZDV + 3TC + EFV was conducted between July 2007 and November 2010. The study found that patients on TDF + 3TC + NVP had a higher post-90-day mortality rate when exposure was categorized by initial prescription. ZDV + 3TC + NVP was associated with better outcomes when compared with the 2 EFV-based regimens (ZDV + 3TC + EFV, TDF + 3TC + EFV), an unexpected result given the demonstrated equivalence of EFV and NVP in clinical studies. The study concludes

that TDF + 3TC + NVP was associated with higher mortality when compared with ZDV + 3TC + NVP but not consistently across sensitivity analyses.

According to ***Spaulding A [21] et al., 2011*** conducted a study to evaluate the effectiveness, safety, and tolerability of TDF in comparison to AZT when used in first-line antiretroviral therapy (ART) for HIV-positive individuals in settings with limited resources in conjunction with one non-nucleoside reverse transcriptase inhibitor (NNRTI) and one NRTI. The introduction of antiretroviral therapy (ART) has significantly improved HIV mortality and morbidity worldwide. However, deciding which treatment regimen to begin for first-line treatment in ART-naïve patients remains a challenge. Two commonly used medications, tenofovir (TDF) and zidovudine (AZT), were reviewed. Included were randomized controlled trials involving HIV-positive patients who were five years of age or older. Mortality, major adverse events, virologic response to antiretroviral therapy (ART), and adherence/tolerance/retention were the main outcomes of interest. The development of ART drug resistance, the immune response to ART, and the prevention of HIV transmission through sexual intercourse were among the secondary outcomes. Two controlled trials involving 586 participants found no significant difference between TDF and AZT in serious adverse events or virologic response. However, TDF-containing regimens had higher adherence and immunologic response rates. Drug resistance was more common in TDF than AZT, but the quality of the literature is low. Two randomized controlled trials found no significant difference in serious adverse events or virologic response, but TDF was superior in immunologic response, adherence, and resistance emergence. Future studies should focus on specific toxicities and tolerability when comparing these two medications. Initial ART regimens with TDF are equivalent to AZT in virologic response and adverse events, but TDF is superior in immunologic response, adherence, and resistance emergence.

CONCLUSION:

Based on above studies, the ART regimens based on tenofovir are more superior and effective than those based on zidovudine. An antiretroviral regimen based on tenofovir is the first line of treatment. While zidovudine- and tenofovir-based regimens were equally efficient in raising CD4 cell counts in certain trials, tenofovir-based regimens were less likely to result in anemia than zidovudine-based regimens. When compared to zidovudine (ZDV), tenofovir (TDF) is a more effective viral load suppressor and more tolerable first line regimen for naïve HIV-1 infected adults.

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CONFLICT OF INTEREST:

The content of this article is free of conflicts of interest, according to the authors.

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