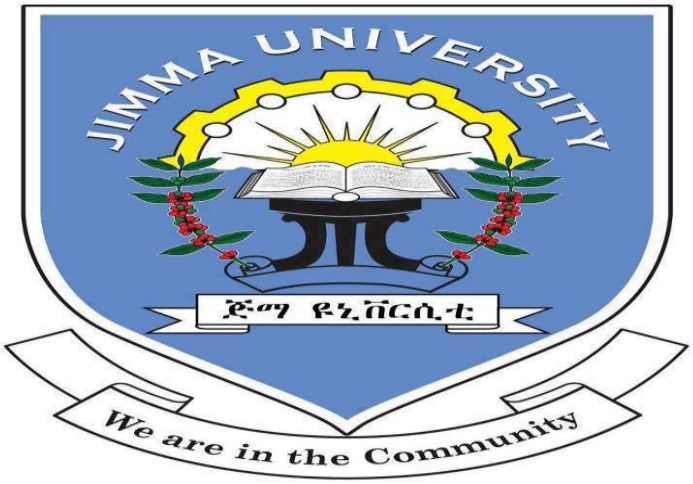
Dolutegravir versus efavirenz-based regimen treatment outcome and its predictors at Jimma medical center, ART clinic, southwest Ethiopia. Comparative, retrospective observational study.



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A research thesis submitted to the School of Pharmacy, Institute of Health, and Jimma University for the partial fulfillment of the requirements for the Master of science in clinical Pharmacy (MSc).

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Jimma, Ethiopia

JIMMA UNIVERSITY

INSTITUTE OF HEALTH SCIENCE

SCHOOL OF PHARMACY

DOLUTEGRAVIR VERSUS EFAVIRENZ-BASED REGIMEN TREATMENT OUTCOME AND ITS PREDICTORS AT JIMMA MEDICAL CENTER, ART CLINIC, SOUTHWEST ETHIOPIA. COMPARATIVE, RETROSPECTIVE OBSERVATIONAL STUDY.

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ABSTRACT

Introduction: Comparison studies show that the efavirenz-based first line was associated with less rate of virologic suppression and more drug-related adverse events which leads to frequent discontinuation when compared to the dolutegravir-based regime. Due to these, dolutegravir, the second-generation integrase strand transfer inhibitor, was recommended by the world health organization to be part of antiretroviral treatment in 2018. However, most of the evidence comes from a clinical trial with restricted patients exposure.

Objective: To compare treatment outcomes and its predictors among patients who were on efavirenz-based first-line and shifted to dolutegravir-based first-line.

Methods: A retrospective observational study was conducted from September 1, 2017, to August 31, 2021, among three hundred fifty-six participants at Jimma medical center ART clinic. The primary outcome was virologic suppression and immunological response. SPSS version 26 software was used for data analysis. Binary logistic regression between independent variables and treatment outcome was done. The variables with p-value <0.25 were entered into a multivariate logistic regression model to determine the independent predictors of treatment outcome and variables with p-value <0.05 were considered statistically significant.

Results: The mean age of the participants was 40.61 ± 9.2 years and 212 (59.6%) were female. Virologic suppression was achieved in 89.6% of participants on dolutegravir and 78.9% on an efavirenz-based regimen. Independent predictors of virologic suppression were good adherence (AOR=9.22, 95% CI: 3.70- 22.92, p<0.001), secondary/tertiary educational level (AOR=6.20,95% CI: 2.15-17.61, p-0.001) and having no opportunistic infections (AOR=4.23,95% CI: 1.83-9.78, p-0.001). In another case 172 (72.3%) participants have a CD4 cell count greater than 350 cells/mm3 on TLE while 202 (84.9%) participants have a CD4 count greater than 350 cells/mm3 on DTG. Female (AOR= 2.83,95%CI: 1.30- 6.20, p-0.009) and isoniazid preventive therapy use (AOR= 2.82, 95%CI:1.06-7.50, p-0.038) were independent predictors of immunologic response.

Conclusion and recommendation: This study identified that DTG based regimen maintains virologic suppression and increases immunologic response. Adherence, educational level, and having no opportunistic infection were significantly associated with viral suppression. Female and isoniazid preventive therapy use were independent predictors of immunologic response. Continuous monitoring of long-term virological and immunological outcomes of DTG-based regimens among HIV/AIDs patients is also essential to observe the consistency of DTG-based favorable outcomes.

Keywords: Treatment outcome, dolutegravir, efavirenz, HIV, virologic suppression, predictors, Ethiopia.

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ABBREVIATIONS AND ACRONYMS

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
CPT	cotrimoxazole preventive therapy
DTG	dolutegravir
HAART	highly active antiretroviral therapy
HIV	Human Immunodeficiency Virus
INSTIs	integrase strand transfer inhibitors
IPT	isoniazid preventive therapy
JMC	Jimma medical center
NNRTI	non-nucleoside reverse transcriptase inhibitors
NRTI	nucleoside reverse transcriptase inhibitors
OI	opportunistic infections
PI	protease inhibitors
PLWHIV	people living with HIV
TB	tuberculosis
TLD	tenofovir/lamivudine/dolutegravir
TLE	tenofovir/lamivudine/efaverenz
UNAIDS	united nation program for HIV/AIDS
WHO	world health organization

1. INTRODUCTION

1.1. Background

Human immunodeficiency virus (HIV) is a retroviral infection that harms the human immune system and leads the body's defense mechanism to become weakened in fighting external pathogens which thereby minimizes or no longer protects from opportunistic infection. Finally, it leads the infected person to an acquired immune deficiency syndrome (AIDS) defining stage(1).

According to Joint United Nations Programs on HIV/AIDS (UNAIDS)report of 2021, an estimated 37.7 million people globally were living with HIV in 2020 with 1.5 million newly infected in the same year. Out of these, more than half (73%) of the patients are accessing antiretroviral therapy. Sub-Saharan Africa is home to two-thirds (67%) of people living with HIV(2).Since 2010, the number of new HIV infections has decreased by up to 23%, majorly a significant drop of 38% in eastern and southern Africa. In contrast, the number of new HIV infections has increased by 72% in eastern Europe and central Asia, by 22% in the middle east and north Africa, and by 21% in Latin America(3).Ethiopian Public Health Institute (EPHI) estimates that the national HIV prevalence for 2018 would be 0.96%, with regional prevalence varying from 4.8% in Gambella to less than 0.1% in Somalia(4).

Highly active antiretroviral treatment (HAART)is combination of three agents, primarily from different classes which is used to lower the viral load in people with HIV. HAART can prolong survival with improved or maintained quality of life by reducing viral load, delaying or avoiding the emergence of opportunistic infection that causes the patient to proceed to the AIDS-defining stage, and delaying the disease's progression to the end stage. More than 20 years have passed since its introduction, which shifted the paradigm of HIV/AIDS from a once-fatal virus to a chronic treatable disease(1).

The preferred initial antiretroviral therapy (ART) recommended by World Health Organization (WHO) consolidated guidelines until 2018 was the combination of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse-transcriptase inhibitor (NNRTI) mainly Efavirenz (5). However, clinical trial showed that dolutegravir (DTG) based regimen has more consistent virologic suppression and immunologic response which was a challenge to efavirenz- based regimen(6).

The lack of data among the special populations like pregnant women and breastfeeding, HIV-Tuberculosis (TB) co-infection, and children on DTG did not allow for recommending it as first-line in 2016 WHO published updated consolidated guidelines. However, starting from 2018, WHO updated recommendations for the first line and second line of antiretroviral regimens incorporate DTG as the first line of HAART treatment for adults and adolescents including pregnant women. Since then, the DTG-based fixed-dose combination is widely used as the first line in many countries including in Africa(7). DTG is a class of second-generation integrase strand transfer inhibitors (INSTIs) that work by halting the function of the HIV integrase-DNA complex to which it was chemically synthesized to bind(8). DTG has been used as loose tablet preparation since 2017 in low- and middle-income countries. But as of 2018, it is marketed as a fixed-dose combination and has got the approval from both the European Medicines Agency(EMA) and the Food and Drug Administration (FDA) (9).

DTG is well-positioned to serve as a standardized anti-retroviral medication alternative for a variety of population groups (adults, adolescents, TB, pregnancy, PWID (those who inject drugs), and HIV-2 infection). Preliminary findings from current trials and pharmacokinetic modeling support the use of tenofovir/lamivudine/dolutegravir (TLD) for every one greater than six years and weighing above15kg(10). DTG has a lengthy half-life of 14 hours, allowing for once-daily treatment with little inter-individual variability. Unlike other medications in the class, it does not require a formulation of pharmacologic booster, avoiding the side effects associated with boosters as well as drug-drug interactions(11).

One of the best things is that DTG has less interaction with liver enzymes and this has the advantage of less interaction with other drugs leading to no or little treatment change when administered with agents like contraceptives, statins, anti-TB, and other drugs that are metabolized through the hepatic pathway. However, its blood concentration may be decreased when administered with some antacids and multivitamins concomitantly(12).

Relative to other drugs in the same class, such as raltegravir and elvitegravir, dolutegravir has a high genetic barrier to resistance. It is effective against mutations chosen by other antiretroviral drugs(13–15).A systematic review conducted by WHO indicates that DTG containing first-line treatment is cause fewer drug-related side effects and leads to less discontinuation rate as compared to 600 efavirenz (EFV).

1.2. Statement of the problem

United nation program for HIV/AIDS estimates showed that since the AIDS pandemic began, 36.3 million individuals have died from AIDS-related diseases. A total of 680 000 individuals died from AIDS-related diseases in 2020, and there were 37.7 million people living with HIV by the end of this year. UNAIDS also predicts that in order to end AIDS as a worldwide public health problem by 2025, 29 billion US$ would be needed for the AIDS response in low- and middle-income countries (2).

The most commonly used regimens for the treatment of HIV/AIDS until 2018 consisted of combinations of two NRTIs as the cornerstone and NNRTIs or boosted protease inhibitors. However, all these recommended combination therapies have been hindered by resistance, adverse drug events, and medication interactions(16).

Comparison studies show that efavirenz-based first line was associated with less rate of virologic suppression and more drug-related adverse events which leads to frequent discontinuation when compared to the dolutegravir-based regimen(17–19). It also stated that the efavirenz-based regimen is inferior to the dolutegravir-based regimen in increasing CD4 count(18).

Due to this, regimens based on second-generation INSTIs, such as dolutegravir, are increasingly being used as the first-line therapy, as compared to regimens based on NNRTIs, like EFV. Dolutegravir was more successful than efaverenz-based regimens, with better and faster viral suppression, CD4 cell count recovery rates, decreased risk of treatment discontinuation and better genetic barrier to medication resistant(10).

Dolutegravir effectiveness has been proven in randomized control studies involving both new and experienced antiretroviral treatment patients (SINGLE, SPRING, FLAMINGO) and STRIIVING)(9). Due to safety issues, most of the evidence regarding the efficacy of antiretroviral drugs at the beginning comes from clinical studies done with few patients and strict control settings with few study subjects without including many diversities. However, once the drug is marketed, it reaches everyone who requires it without any restriction according to national guidelines recommendation(20).

Even though several clinical trials demonstrated that DTG has undeniable efficacy, safety, and tolerance, WHO suggests that data from real-world is still lacking on its short and long-term effects specially from resource limited countries(14,21–23).

Hence, it may have a different outcome in those who are previously not exposed. Due to this, real-life studies which involve actual patients from all over the world are still needed to contribute knowledge regarding the effectiveness of antiretroviral drugs in uncontrolled exposure to forward valuable evidence for individual patients as well as for those who need to make programmatic decisions(24).

In Ethiopia, as far as our knowledge is concerned, a study is scarce regarding the effectiveness of the newly recommended first line. So, it should be assessed whether dolutegravir is working according to the finding reported from clinical trials. For this reason, this study aimed to describe the effectiveness (measured as viral load suppression and CD4 increment) and its predictors of dolutegravir as compared to efavirenz based regimen.

1.3. Significant of the study

When WHO initially recommend dolutegravir as first line, most of the evidences are from clinical trials. It was suggested by WHO as still the ongoing observed evidence is needed from actual patients' communities on its efficacy and other important concerns(25). Despite this gap, to the best of our knowledge, studies are scarce in our setup about treatment outcome of dolutegravir and its predictors as compared to efaverenz.

Hence, this study is very important in producing data about the treatment outcome of dolutegravir and its predictors as compared to efaverenz in order to validate the recommendation of newly introduced drug.

It is also used as additional data for future research that needs to involve a similar area of the study. Apart from this, it will help the stakeholder who is directly involved in the care of the patients.

2. LITERATURE REVIEW

2.1. virologic suppression

A comparative retrospective cohort study was conducted in Brazil among107647 patients to compare the effectiveness of first-line antiretroviral therapy. Among these patients,71.5% initiated with tenofovir/lamivudine/efaverenz and 10.5% with tenofovir/lamivudine/dolutegravir. In this study, virologic suppression (<50copies/ml) by 12 months was 84% with TLE and 90.5% with TLD, and below 80% for protease-inhibitor-based regimens. The study concludes that in a real-world cohort of HIV-positive people, dolutegravir outperforms efavirenz and protease inhibitor-based regimens in reducing viral replication(20).

A prospective study was conducted in 2021 in China with HIV-naive patients treated with DTG+3TC (27 patients) versus efavirenz plus tenofovir disoproxil fumarate and 3TC (28 patients) to assess the proportion of participants with virologic success. In this study, after six months of treatment, the proportion of patients with viral loads<50 copies/mL in the dolutegravir based was 100% compared with 83.3% in the efaverenz based regimen(26).

A retrospective cohort study was conducted in 2020 in Tanzania. The purpose of this study was to look at the immunological and virological outcomes among HIV-infected people who had received therapy by reviewing 397 patients' medical records using secondary data sources. In this study, after the use of a new fixed-dose combination of dolutegravir based regimen for at least 24 weeks, the overall rate of virological suppression (<50 copies/ml) was 89.9% which was 52.7% on efaverenz based regimen (27).

An open-label, multicenter, randomized, phase 3 noninferiority trial was conducted in 2017 in Cameroon to determine the efficacy between dolutegravir-based or low-dose efavirenz-based regimen for the treatment of HIV-1 infection. The proportion of individuals with a viral load of less than 50 copies/ml at 12 months was the main objective of the study. After one year of follow-up, viral load of less than 50 copies/ml was observed in 231 of 310 participants (74.5%) in the dolutegravir group and 209 of 303 participants (69.0%) in the efaverenz group(28).

Meta-analysis of literatures was conducted in 2019 to evaluate the effectiveness of dolutegravir- and efavirenz-based treatment regimens in HIV-positive individuals. It was explained that a dolutegravir-based regimen offers a quicker-acting and longer-lasting pharmacological impact than a regimen based on EFV (29).

A comprehensive literature review and network meta-analysis based on 156 publications including 68 trials were carried out in 2020 to assess the effectiveness, tolerability, and safety of dolutegravir and efavirenz among antiretroviral treatments for first-line HIV therapy. The main result of this study was virologic suppression at week 24 of less than 50 copies/ml. Dolutegravir was shown to have higher probabilities of viral suppression than efavirenz at all time periods(30).

A systematic review on two trials was conducted to compare dolutegravir plus two NRTIs versus efavirenz plus two NRTIs as first line treatment. The primary endpoint of these two studies was viral suppression to <50 copies/mL at 48, 96, and 144 weeks. In this review, dolutegravir-containing regimens were superior in virologic suppression to efaverenz-containing regimens at 48 weeks and 96 weeks (31).

An observational retrospective study was conducted in 2020 in Debre Markos hospital in Ethiopia on 349 patients to assess the virological suppression of a dolutegravir-based regimen. In this study, it was reported that overall dolutegravir-based virological suppression was about (321) 92% as compared to the pre-dolutegravir-based regimen which was around 284 (81.4%)(32).

2.2. Immunologic response

A retrospective study was conducted in 2022 in the United States among 258 participants with the aim of immunological outcomes among patients initiated efavirenz and dolutegravir-based regimen. This study showed that at week 96, dolutegravir had a greater increment in CD4 count than the efavirenz-based regimen (33).

A prospective study was conducted in 2021 in China with HIV-naive patients as already explained above found that dolutegravir based regimen was better in change in CD4 count as compared to efaverenz based regimen. At six months, the dolutegravir arm's mean change in CD4 was 209.68 cells/L, whereas the efaverenz arm's mean change was 73.28 cells/L (26).

A prospective, interventional study was conducted in 2021 in South Africa involving 57 patients to evaluate the virologic effectiveness of tenofovir, lamivudine, and dolutegravir as second-line antiretroviral therapy in adults who had failed a first-line regimen based on tenofovir-emtricitabine-efavirenz. In this study, the CD4 count was measured twice: once at the baseline level of 248 cells/l and once 24 weeks after switching to a DTG-based regimen. The median CD4 cell count at week 24 was 373 cells/mm3 (34).

A single-centered retrospective cohort research was carried out in 2021 in Tanzania. This study used secondary data sources to evaluate the medical records of 397 individuals in order to look into the immunological and virological outcomes among HIV-infected patients who had received therapy. The average CD4+ cell count at the beginning of the study was 457.1 cells/mm3, and 8.3% of the patients had a CD4+ cell count below 200 cells/mm3 before starting dolutegravir. With the change from an efaverenz to a dolutegravir-based regimen, CD4 count less than 200 reduces from 8.3% to 6.3%, resulting in very minor but substantial alterations in CD4+ cell count (27).

A thorough analysis of the existing literature was performed to identify phase 3/4 randomized controlled clinical trials. In a treatment-naive HIV-1-infected patient, dolutegravir's 48-week effectiveness and safety were compared to those of frequently used third drugs. The analysis includes 31 trials with a total of 17,000 patients. Dolutegravir was anticipated to have considerably larger mean CD4+ cell increases than ATV/r, DRV/r, EFV, LPV/r, and RPV. Dolutegravir had the highest relative rise in CD4+ count when compared to efaverenz (37.9 cells/mL)(35).

A randomized controlled clinical trial was conducted to determine the impact of dolutegravir and efavirenz on immune recovery markers by enrolling a total of 833 participants with at least one dose of DTG-ABC-3TC (n =414) or EFV-TDF-FTC (n = 419). In this study, three immunologic markers were used: (a) the achievement of CD4/CD8 ratio normalization at cutoffs of 0.5 and 1, (b) the achievement of CD4% normalization at a cutoff of 29%, and (c) the achievement of Multiple T-cell marker recovery (MTMR). Change from baseline in CD4 cell counts was consistently greater in the DTG-ABC-3TC arm than in the EFV-TDF-FTC arm (week 48: 267 cells/mm3 vs. 208 cells/ mm3; $p < 0.001$; week 96: 325 cells/mm3 vs. 281 cells/mm3; p 0.004; week 144: 378 cells/mm3 vs. 332 cells/mm3 15.6 to 78.2 cells/mm3; p 0.003)(36).

2.3. Predictors of treatment outcome

2.3.1. predictors of virologic suppression

A cross-sectional study was conducted in 2007 in India to assess adherence to antiretroviral therapy and virologic suppression among HIV-infected patients receiving care. In this study, 279 patients were participated. In this study it was found that patients who have good adherence (having taken >95% of the prescribed doses) were significantly associated with virologic suppression (37).

A hospital-based retrospective study was conducted in 2022 in Ghana to assess factors associated with viral suppression and rebound among adult HIV patients on treatment. In this study,720 HIV patients' medical records were reviewed. This study report that having good adherence to ART was independently associated with increased odds of viral suppression(38).

A retrospective study was undertaken in 2020 in Kenya with 600 HIV patients to assess the prevalence and risk factors for viral rebound or suppression in HIV patients receiving combination antiretroviral treatment. According to this study, individuals who have good adherence to their ART regimen are more likely to experience virological suppression(39).

A quantitative cross-sectional survey was conducted in 2021 in South Africa to assess determinants of viral suppression among adolescents on antiretroviral therapy. It include 192 HIV adolescents study participants. This study reveals that good adherence was strongly associated with viral suppression(40).

An observational retrospective study was conducted in Debre Markos hospital in Ethiopia as already explained above showed that adherence was found to be significantly associated with virological suppression. The odds of having virological suppression were six times higher among patients having good adherence (32).

A cross-sectional study was conducted in 2015 in the United States to measure rates of ART use and virologic suppression among perinatally infected and behaviorally infected youth. In this study,649 perinatally infected and1,547 behaviorally infected youth was included in this study. It was reported that Virologic suppression was significantly associated with greater educational attainment(41).

A retrospective cohort research was conducted in 2017 in Europe to evaluate differences by educational level in responses to combination antiretroviral therapy and survival in HIV-positive men and women. The study includes 24,069 HIV-positive individuals who began antiretroviral therapy between 1996 and 2013. In this study, virological response was attained in 67% of patients without basic education, 85% with a primary school, 82% with a secondary school, and 87% with a tertiary education(42).

A multi-center observational clinic-based cohort research was carried out in 2013 in Nigeria to evaluate the immuno-virologic outcomes and immune-virologic discordance in people who were alive and receiving anti-retroviral medication at the end of the 12-month study. There are 628 patients in this cohort as a whole. In this study, it was found that decreased odd of virologic failure was associated with post-secondary and tertiary educational level (43).

A retrospective study was done in 2016 in Ethiopia to assess a high level of virologic suppression among HIV-infected adults receiving combination antiretroviral therapy. This study includes a total of 656 patients. In this study, detectable viremia (>40HIV-1RNA copies/ml) was strongly associated with no education (44).

A retrospective study was conducted in 2017 in Haiti to assess the virologic suppression rate in 2,313 patients who had been on ART for more than six months. This study reports that Virologic suppression was negatively associated with TB co- infections (45).

A retrospective study was done in 2013 in Uganda among 1094 HIV-infected patients to know the effect of opportunistic infections on HIV RNA viral load andCD4- T cell count among HIV-positive adults. This study showed that participants who had an opportunistic infections had four times the odds of having a detectable(>50 copies/m) HIV RNA viral load as compared to who had not opportunistic infections(46).

A cross-sectional study was conducted in 2017 in South Africa with 244,370 patients to evaluate factors associated with unsuppressed viral load (VL > 400 copies/ml) in patients on first-line ART. This study showed that being on TB treatment was associated with unsuppressed viral load (47).

A retrospective study was conducted in Ethiopia among 348 patients in 2022 to evaluate the prevalence and determinants of viral load reduction among HIV-positive people receiving enhanced adherence counseling. In this study, the hazards of virologic suppression were 1.85 greater among participants who had no recurrent OI than those who had(48).

2.3.2. predictors of immunologic response

An observational prospective study was done in 2016 in Brazil among 332 patients to assess long-term immune and virological responses in HIV-infected patients receiving antiretroviral therapy. This study found that female had around 3 times more likely to have immune success as compared to males (49).

A retrospective study was conducted in 2017 in Spain among 10469 study participants. The purpose of this study was to determine how sex and age together affected HIV-infected individuals responded to antiretroviral medication. It was found that women have a better immunological response as compared to males (50).

Researchers conducted retrospective study in 2011 in China among 3457 study participants to evaluate the variations between genders in the patient's immune response to ART and 2-year mortality. This study found that as compared to men, women had higher CD4 count after initiation of treatment (51).

Collaborative analysis of prospective studies was done to describe the immunologic response of patients on ART from Sub-Saharan Africa, Latin America, and Asia among 19967 patients. This study found that females had higher CD4 counts than males (52).

A cross-sectional study was conducted in 2020 in Ethiopia among 423 patients to examine the immunological response to HAART and the factors influencing the present CD4+ T-cell count. This study showed that decreased CD4 count was observed among males as compared to females (53).

A multicenter cohort was conducted in 2017 in Germany with 10,671 HIV-infected patients. In this study, the immunological improvement in HIV patients with TB was evaluated. According to this study, patients who did not develop TB had an average change in CD4+ cell count recovery that was 33 cells/l higher than those who developed. After the first three months of

ART, 65.6% of patients who did not develop TB had a CD4+ count greater than 400 cells/l, but only 11.3% of patients who did developed TB had similar immunological state(54).

An open-label randomized, controlled, exploratory study was conducted in 2015 in Uganda with 291 household contacts to see the effect of isoniazid preventive therapy on immune responses to mycobacterium tuberculosis. In this study, it was explained that using isoniazid preventive therapy(IPT) has a protective effect on immune response and against tuberculosis (55).

A retrospective study was conducted in 2017 in South Africa with 43 971 patients to see the safety and effectiveness of isoniazid preventive therapy in pregnant women on antiretroviral therapy was protective against incident TB to the 12-monthpost-pregnancy outcome. Although the CD4 count was ≥350 cells/μL in the majority of the cohort, protective effect was greatest in the presence of immunocompromise (CD4 <350 cells/μL)(56).

A retrospective study in 2019 from Ethiopia with 220 patients was done to evaluate the effectiveness of isoniazid preventative treatment in HIV patients. The mean CD4 count of participants was evaluated and compared between the two groups (IPT use and not use) in this study at baseline, six months, and twelve months. Following a six-month follow-up, the mean CD4 improvement was generally higher in exposed individuals (538.37 cell/mm3) than in unexposed individuals (502.10 cell/mm3), but this difference was not statistically significant. After treatment, the CD4 count was higher overall in the exposed group than in the unexposed group (57).

Another retrospective cohort study was conducted in 2013 in Ethiopia with 492 patients. The objective of this study was to compare the immunological response of HIV/AIDS patients receiving nevirapine versus efavirenz-based treatment. Taking IPT therapy is significantly associated with immunological response. The odds of developing the outcome among patients who received the prophylaxis were 1.36 times higher compared to those who didn't take prophylaxis(58).

A hospital-based retrospective study was done in 2017 in Ethiopia to assess isoniazid preventive therapy in the reduction of tuberculosis among ART patients with 271 patients. IPT prophylaxis significantly reduces acquiring of TB. However, there is no difference concerning CD4 improvement between IPT users and non-users. At the baseline, both groups' mean CD4+T-cellcount value was not significantly different. Both the IPT group and non-IPT group had significant CD4+T-cell count improvement(59).

2.4. conceptual framework

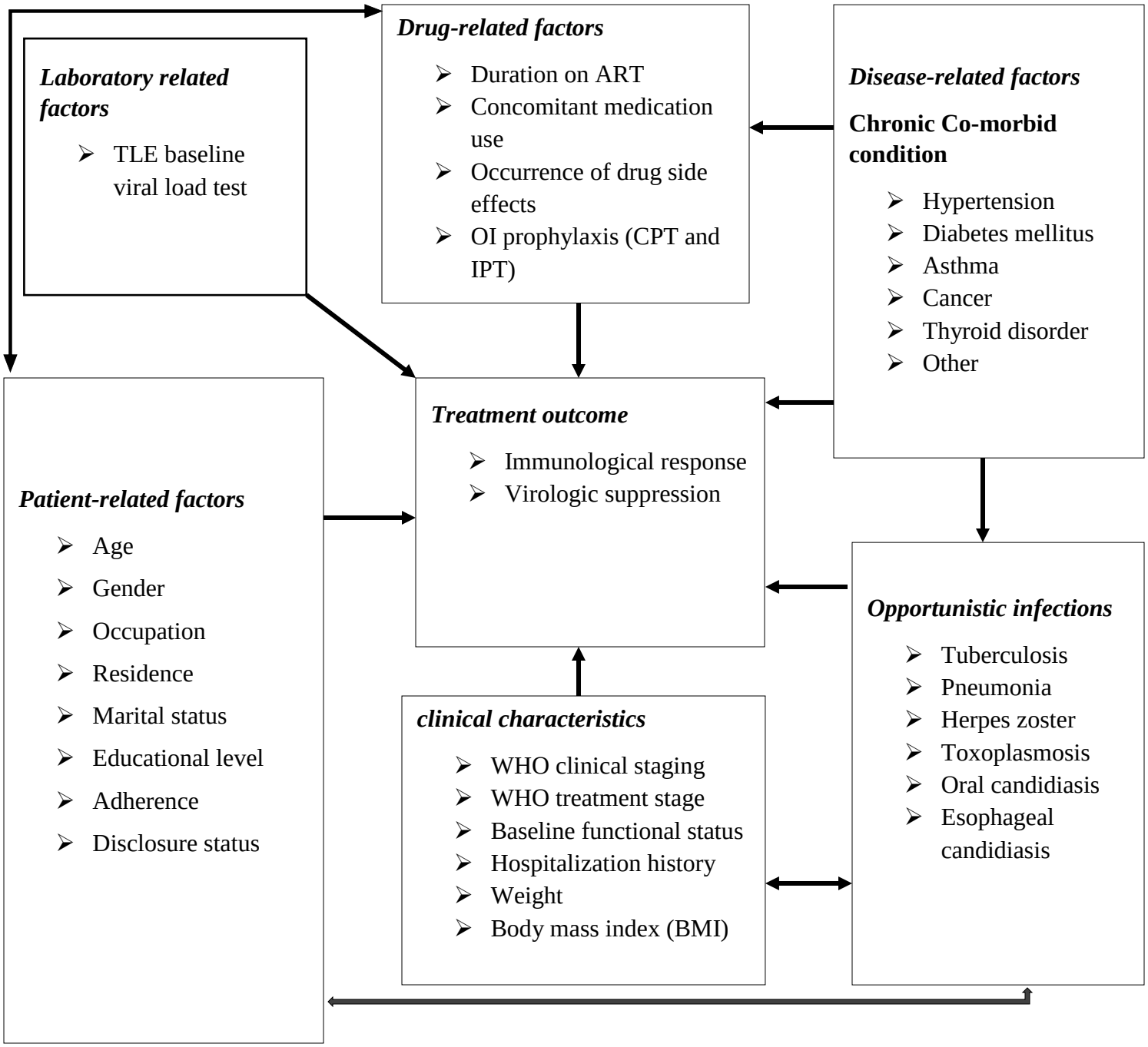

Diagram 1. A conceptual framework for comparative treatment outcome and its predictors of dolutegravir-based regimen and efavirenz-based first-line regimens among patients on follow-up at Jimma medical center, southwest Ethiopia, 2022.

3. OBJECTIVES OF THE STUDY

3.1. General objective

- To assess treatment outcomes and predictors among patients who were on efavirenz first-line versus dolutegravir-based first-line after transitioning in PLWHIV who had follow-up at Jimma medical center (JMC), ART clinic, from September 1, 2017, to August 31, 2021.

3.2. Specific objectives

- To assess the magnitude of viral suppression of dolutegravir-based regimen compared to efavirenz-based first-line regimens among adult PLWHIV at JMC.
- To assess the magnitude of immunologic response of dolutegravir-based regimen compared to efavirenz-based first-line regimens among adult PLWHIV at JMC.
- To assess predictors of viral suppression among adult PLWHIV who were on efavirenz first-line and shift to a dolutegravir-based regimen at JMC.
- To assess predictors of immunologic response among adult PLWHIV who were on efavirenz first-line and shift to a dolutegravir-based regimen at JMC.

4. METHODS

4.1. Study setting and periods

The study was conducted at JMC, ART clinic. JMC is located in Jimma town; 352 km Southwest of Addis Ababa, Ethiopia. It is the only teaching and referral hospital in the southwestern part of the country with a bed capacity of 800. It provides services for approximately 16000 inpatients and 220,000 outpatient clients per year with a catchment population of about 20 million people. It can serve 12,000 emergency cases and 4500 deliveries per year. It has 1600 staff members and 32 care units. ART clinic is one of the units in JMC. It gives service to about 3108 adult patients and comprises ART pharmacy, TB clinic, adult and pediatric follow-up, voluntary counseling and testing (VCT), cervical cancer screening, laboratory testing, post-exposure prophylaxis service and prevention of mother to child transmission services(60). The study was conducted from September 1, 2017, to August 31, 2021.

4.2. Study design

A retrospective observational study was used.

4.3. Population

4.3.1. Source population

All adult patients with HIV/AIDS on HAART who had follow-ups at the ART clinic of JMC.

4.3.2. Study population

All adult patients with HIV/AIDS on HAART who had follow-ups at the ART clinic of JMC from September 1, 2017, to August 31, 2021, fulfilling inclusion criteria.

4.4. Inclusion and exclusion criteria

4.4.1. Inclusion criteria

- Adult patients > 18 years old who were on follow-up at JMC ART clinic.
- Being on the efavirenz-based first line before the transition to TLD with two viral load test and one CD4 cell count.
- Having at least one viral load test and CD4 cell count after transitioning to DTG.

4.4.2. Exclusion criteria

- Newly diagnosed patients commenced directly on TLD.
- Incomplete patient medical record information.

- Lost-to follow-up

4.5. Sample size and sampling technique

A simple random sampling technique was used. The sample size was calculated by using single population proportion formula based on the following assumptions:

1) Study from Debre Markos hospital on virologic suppression pre and post-dolutegravir shows about 92% (0.92) overall virologic suppression after the transition to dolutegravir.

2) With an expected margin of error (d) was 0.05

3) Confidence interval (Z) is 95%.

Sample size, calculated by

n- Required number

$$N = \frac{(Z1-\alpha/2)^2 * P (1-P)}{d2}$$

1-p=q =0.08

d= Expected margin of error =0.05

Z α/2= 95%confidence interval (C.I) =1.96

Thereby n = $((1.96)^2$ x 0.92x 0.08)/ (0.05)2=113

The source population was the total number of adult patients under follow-up at the JMC ART clinic which was 3108. This information is obtained from the ART registered data. Since the source population is less than 10,000, the sample size should be corrected using the following correction formula.

$$\text{Corrected sample size } nf = n/(1+\frac{n}{N}) = \frac{113}{1+\frac{113}{3108}} = \mathbf{109}$$

The calculated sample size; by using the above correction formula was 109. When 10% (~11) of exclusion is added, the final adjusted sample size was =**120.** This is the minimum sample size requirement. However, by using the above formula with p- value of 0.5, in this study, three hundred and fifty-six participants were included to increase generalizability.

4.6. Study variables

4.6.1. Dependent variables

Primary outcomes

- Virologic suppression
- Immunological response

4.6.2. Independent variables

Sociodemographic characteristics

- Age,
- Gender
- Occupations
- Residence
- Marital status
- Educational level
- Adherence
- Disclosure of serostatus

Clinical related factors

- WHO clinical stage
- WHO T- staging
- Baseline functional status
- Hospitalization history
- Weight
- BMI

Laboratory related factors

- TLE Baseline viral load test

Disease-related factors

Co-morbidity

- Hypertension
- Heart failure
- Diabetes mellitus
- Asthma
- Cancer
- Thyroid disorder
- Others

Opportunistic infections

- Tuberculosis
- Pneumonia
- Herpes zoster
- Toxoplasmosis
- Oral candidiasis
- Esophageal candidiasis

Drug-related Variables

- Concurrent medication use
- Duration on ART
- Occurrence of drug side effects
- OI prophylaxis (IPT and CPT)

4.7. Data collection procedures (instrument, personnel, technique)

4.7.1. patient recruitment

Patients greater than 18 years old and who were on an efavirenz first-line regimen at the time of the specified period and transferred to a dolutegravir-based regimen were identified. Patients who were on efavirenz based regimen were switched to dolutegravir based regimen starting from early September 2019. Hence, the duration on dolutegravir was 24 months and data were obtained in this interval. We also included the data of 24 months on efavirenz back from September 2019 before transition. The selected participants were then listed according to their card number order. Sampling was made from these lists by using random number generator software (https://www.random.org/)by simple random sampling.

Clinical information like, viral load, CD4 count, WHO clinical staging or treatment stage, prophylaxis given, opportunistic infections occurred, side effects encountered, concomitant medication, functional status, co-morbid condition and other important data was extracted from the patient's medical record. We obtained viral load and CD4 measurements for individuals in each regimen group at baseline or closest to baseline after the start of the study period and nearest to24 months after ART introduction because, as expected in a real-life dataset, not all participants had laboratory measurements consistently performed.

4.7.2. Data collection Process, instrument, and personnel

The data retrieval checklist was prepared by reviewing previously published literatures on comparative treatment outcomes and its predictors of the efavirenz-based regimen and dolutegravir-based regimen (32,61–65).

Data was collected through medical record reviews using a data retrieval checklist. The checklist has three parts: the first one assesses the Sociodemographic characteristics. The second part is about medication adherence which was measured by pill count during the patients visit schedule and recorded on their cards. Pre and post-dolutegravir-based regimen adherence levels were extracted from the medical charts. Then, based on WHO guidelines, reported intake of ≥ 95% of the prescribed medication was categorized as "good adherence"; and 85–95% intake as "fair adherence" and "poor adherence" was <85% intake(66). The third part is about clinical and treatment-related questions. The data was collected by one nurse and one pharmacist working in an ART clinic after one day of training.

4.8. Data quality assurance

The data retrieval checklist and medical records of the patients were checked thoroughly for completeness before the commencement of the actual data collection. The training was given to the data collectors for one day focusing on how to handle data and overall understanding of the checklist. The data collectors were supervised by the principal investigator. A pre-test was done on 5% at the same area but not included in the study. The data collectors were making frequent checks on the data collection process to ensure data quality.

The collected data was checked for its completeness, accuracy, clarity, and consistency after conducting data collection. It's also compiled, coded, and categorized before exporting to SPSS for analysis. Any erroneous, ambiguous, and incomplete data were excluded.

4.9. Data processing and statistical analysis

Data were entered by using epidata version 4.6.0.2and then exported to SPSS version 26.0 software. All statistical tests were performed using SPSS version 26.0 for analysis. Descriptive statistics were applied for the analysis of patient characteristics, including frequency, means, standard deviations (SD), and percentiles. The characteristics of the study participants were presented by frequency distribution when the variables were categorical and by means and standard deviation for quantitative or continuous variables.

Binary logistic regression analysis was performed to examine the association between independent variables and treatment outcome. In binary logistic regression analysis, variables with p- values < 0.25 was selected for further multiple logistic regression analysis. Multiple logistic regression analyses were then used to determine the independent predictors of treatment outcome. During the multivariate analysis, variables were excluded from the model starting with those that had the highest P-value by using a backward elimination approach in which all potentially associated factors were initially included in the model.

To investigate the association between the treatment group and virologic suppression, Wilcoxon signed-rank test was performed to see the difference in median virologic suppression. The odds ratio with a 95% CI was calculated to measure the strength of association between predictor and outcome variables. Probability values less than 0.05 was accepted as statistically significant. The omnibus test result was significant with p-value =0.000, and the Hosmer and Lemeshow test showed a good model fit with p-value=0.72, which signifies the goodness fit of the model. The absence of multicollinearity was established when it was revealed that all variance inflation factor (VIF) values were less than 10 and tolerance was greater than 0.37. The outputs of processed data were presented using tables and figures accordingly.

4.10. Outcome measures

4.10.1. The primary endpoints

The primary endpoint of the study is to assess the effectiveness of the regimens defined as the proportion of patients with virological suppression and immunologic response after the commencement of the dolutegravir-based regimen as compared to pre-transition.

According to the Food and Drug Administration (FDA) snapshot algorithm of 2015, viral load suppression is defined as blood HIV-1-RNA copies of less than 50 copies/mL(67).

Immunological response, that is, an increase in CD4 cell count from baseline is also another outcome that was assessed at the end of the follow-up. The immunologic response can be categorized into two based on the definition. good immune response (GIR)participants with CD4≥350cells/ µl at the time of virologic suppression and immune non-respondents (INR), those patients, who have absolute CD4 measure of <350 cells/µl at the time of sustained virologic suppression(68–70).

Treatment outcome was defined as "virologically suppressed" if

The patient's viral load is decreased to less than 50copies/ml after 6 months of treatment initiation or switching to another regimen.

4.11. Ethical consideration

Ethical clearance & approval was obtained from the Institutional review board (IRB) of Jimma University. The hospital director and head of the ART clinic were informed about the purpose of the study to get cooperation. All other concerned bodies were informed about the aim of the study. Consent from patients was not obtained because of the retrospective, nature of the study. During data collection, confidentiality was ensured and for this reason, the name and address of the patient were not recorded in the data collection checklist. The patient's data is used only for research purposes.

4.12. Plan for data dissemination

The result of this finding will be disseminated to the Jimma University, advisors and examiners. It will also be disseminated to the school of pharmacy, institute of health, Jimma university medical center, and ART clinic. Attempts will be made to publish the results of the finding on reputable journals for international use.

4.13. Definition of terms and operational definition

Viral load: The quantity of HIV RNA (ribonucleic acid) in the blood(1).

HAART: regimens that typically include three or more antiretroviral medications and are anticipated to lower plasma HIV-l RNA levels below the limits of quantitation (71).

Adherence: the degree to which a person complies with medical professional suggestions for taking medicine, adhering to a diet, and/or making lifestyle modifications. (66).

Good adherence: Drug adherence of 95% or ≤ 2 missed drug doses of 30 doses or ≤ 3 missed drug doses of 60doses.

Fair Adherence: Drug adherence of 85–94% or 3–5missed drug doses of 30 doses or 3–9 missed drug doses of 60 doses.

Poor Adherence: Drug adherence of < 85% or ≥ 6 doses of missed ART drug doses of 30 doses or > 9 doses missed ART drug doses of 60 doses.

Incomplete medical record: Medical records that do not have full information like WHO clinical stage, CD4, viral load (VL), Body Mass Index, and weight to be used in the study.

Viral suppression: when an individual's viral load (HIV RNA) falls below the detection threshold (20 copies/ml)(72).

TLE baseline viral load: viral load test while the patient was on efavirenz based first line regimen closest to the start of the study period.

5. RESULT

5.1. Participant enrolment

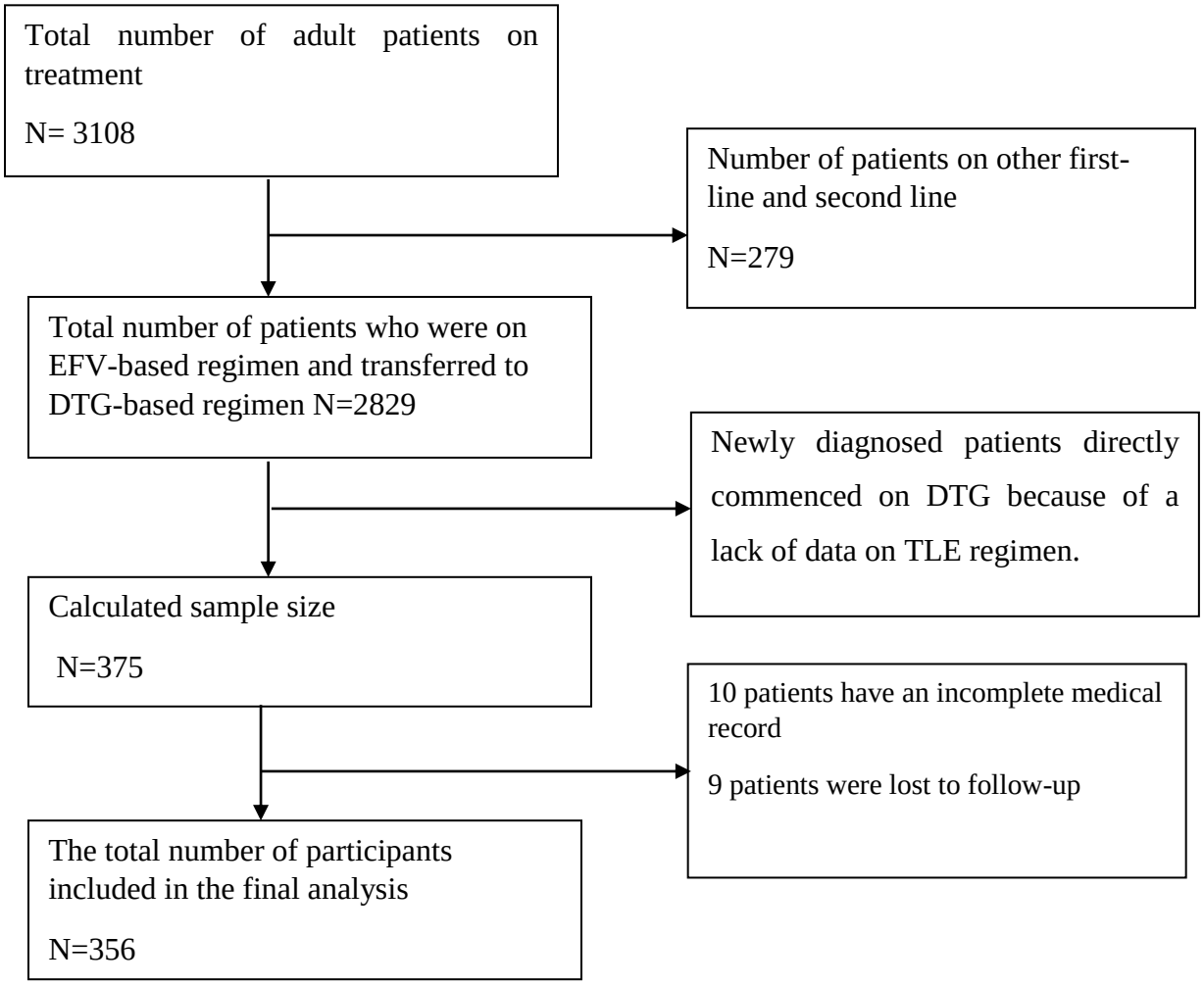

Diagram 2: A patient's enrollment for treatment outcome and its predictors of dolutegravir-based regimen and efavirenz-based first-line regimens among patients on follow-up at Jimma medical center, southwest Ethiopia.

5.2. Socio-Demographic Characteristics.

In this study around 356 patient documents were reviewed. The mean age of the participants was 40.61 ± 9.2 years and 212 (59.6%) were female. The majority of participants, 312 (87.6%), were urban dwellers. Out of the study participants, 163(45.8%), had achieved secondary or tertiary educational level **(table 1).**

Table 1: Socio-demographic characteristics of study participants at Jimma medical center, ART clinic from September 1, 2017- August 31, 2021.

variables		N	%
Age	mean (40.61±9.2)		
Age category	20-32	68	19.1
	33-45	189	53.1
	46-58	84	23.6
	59-71	15	4.2
Sex(gender)	male	144	40.4
	female	212	59.6
Marital status	single	22	6.2
	married	201	56.5
	divorced	82	23
	widowed	51	14.3
Residency	urban	312	87.6
	rural	44	12.4
Educational level	no formal education	57	16
	primary school (1-8)	136	38.2
	Secondary/tertiary*	163	45.8
Occupation	government employee	53	14.9
	Private jobs	239	67.1
	unemployed	64	18
Disclosure of serostatus	yes	356	100
	No	--	---

*Secondary/tertiary includes grade 9-12, diploma, bachelor degree, MSc and PHD

5.3. disease-related characteristics

Almost307 (86.2%) of the study participants had no co-morbidity. Asthma was commonly observed as comorbidity,14 (3.9%). Regarding opportunistic infections, 109 (30.6%), had an opportunistic infection. Out of this, pulmonary tuberculosis takes a major part, 90 (25.3%). The mean overall duration of ART was 9.9 ±3.4 years **(table 2).**

Table2: Disease-related characteristics of study participants at Jimma medical center, ART clinic from September 1, 2017- August 31, 2021.

variables		N	%
Comorbid condition	Yes	49	13.7
	No	307	86.2
Types of comorbidity	Asthma	14	3.9
	Hypertension	8	2.2
	toxic multinodular goiter	5	1.4
	Heart failure	6	1.7
	Diabetes mellitus	7	2
	Breast cancer	3	0.8
	Cervical cancer	4	1.1
	Others*	2	0.6
Opportunistic infections	Yes	109	30.6
	No	247	69.4
Types of opportunistic infections	TB	90	25.3
	pneumonia	7	1.9
	Herpes zoster	3	0.8
	Esophageal candidiasis	4	1.1
	oral candidiasis	2	0.6
	CNS toxoplasmosis	2	0.6
	meningitis	1	0.3
Baseline TB screening	Positive	85	23.9
	Negative	271	76.1
Hospitalization	Yes	44	12.4
	No	312	87.6
Reason for hospitalization	HIV-related illness	6	1.7
	Non-HIV related illness	38	10.7
WHO baseline clinical stage	I/II	190	53.4
	III/IV	166	46.6
WHO T-stage	I/II	335	94.1
	III/IV	21	5.8
Baseline Functional status	working	351	98.6
	ambulatory	3	0.8
	Bedridden	2	0.6

*epilepsy, migraine headache

5.4. Drug-related characteristics

Cotrimoxazole preventive therapy was given to 301 (84.6%) and 313 (87.9) was used isoniazid preventive therapy. 38 (10.7%) study participants encountered side effects **(table 3).**

Table 3: Drug-related characteristics of study participants at Jimma medical center, ART clinic from September 1, 2017- August 31, 2021.

Variables		**N**	**%**
Cotrimoxazole preventive therapy	Yes	301	84.6
	No	55	15.4
Isoniazid preventive therapy	Yes	313	87.9
	No	43	12.1
Side effects encountered	yes	38	10.7
	no	317	89.3
Types of side effects	abdominal pain	9	2.5
	anemia	1	0.3
	diarrhea	3	0.8
	fatigue	2	0.6
	headache	7	2
	hepatitis	1	0.3
	Numbness	1	0.3
	nausea	3	0.8
	nightmare	2	0.6
	rash	9	2.5
Concomitant medications	yes	87	24.4
	No	269	75.6
Types of medications	RUTF	42	11.8
	Salbutamol puff	12	3.4
	Enalapril	12	3.4
	Metformin	5	1.4
	PTU	4	1.1
	Amlodipine	3	0.8
	Beclomethasone	2	0.6
	Others*	7	2.1
Duration of ART treatment (years)	4-9	153	43
	10-15	180	50.6
	16-20	23	6.5
Total duration on TLE (years)	2-5	135	37.9
	6-9	218	61.2
	10-12	3	0.8

* albendazole, amitriptyline, ciprofloxacin, diclofenac, omeprazole, doxorubicin+cyclophosphamide, insulin. PTU-propylthiouracil, RUTF-ready to use therapeutic food.

5.5. Weight and body mass index

In this study, prior to the initiation of the dolutegravir-based regimen, the mean weight of the participants was 57.77 ± 11kg which was increased to 60.35 ± 12 kg after the dolutegravir-based regimen was initiated.

The highest weight gain was recorded among male participants with 64.9 ± 11.7 kg gain whereas, the highest mean weight gain was seen in the age group 59–71 which was found to be 64.5± 15.7kg. The Wilcoxon signed rank test was run and shows that post-DTG weight is significantly different from pre-DTG weight (Z scores 9.449; p< 0.001) **(table 4).**

Table 4: Mean weight distribution by gender and age, and body mass index of study participants at Jimma medical center, ART clinic from September 1, 2017- August 31, 2021.

	On efavirenz based-regimen		**On dolutegravir based-regimen**	
	baseline (mean±SD)	Before transition (mean±SD)	baseline (mean±SD)	current (mean±SD)
gender				
male	58.6 ± 10.6	62.5 ± 11.3	63.1 ± 11.5	64.9 ± 11.7
female	51.3 ± 8.8	54.5 ± 9.6	54.8 ± 9.8	57.3 ± 11.3
age				
20-32	52.2 ± 9.4	54.7 ± 8.9	54.8 ± 8.6	56.3 ± 10.6
33-45	53.8 ± 9.5	57.6± 10.6	58.1 ± 10.9	60.7 ± 11.9
46-58	55.8 ± 11.2	59.7 ± 12.5	59.8 ± 12.5	62.0 ± 12.2
59-71	60.7 ± 13.1	63.6 ± 13.3	64.3 ± 15.6	64.5± 15.7
Body mass index on efavirenz: N (%)			**Body mass index on dolutegravir: N (%)**	
Underweight	64 (18)		44 (12.4)	
Normal weight	240 (67.4)		230 (64.6)	
Overweight	41 (11.5)		62 (17.4)	
Obesity class-I	11 (3.1)		20 (5.6)	

5.6. Adherence

Overall, most of the participants have good medication adherence (>95) according to WHO patients' medication adherence classification. Among 356 participants, 294 (82.6%) have good adherence while 46 (12.9%) participants have poor medication adherence to TLD **(fig. 1).**

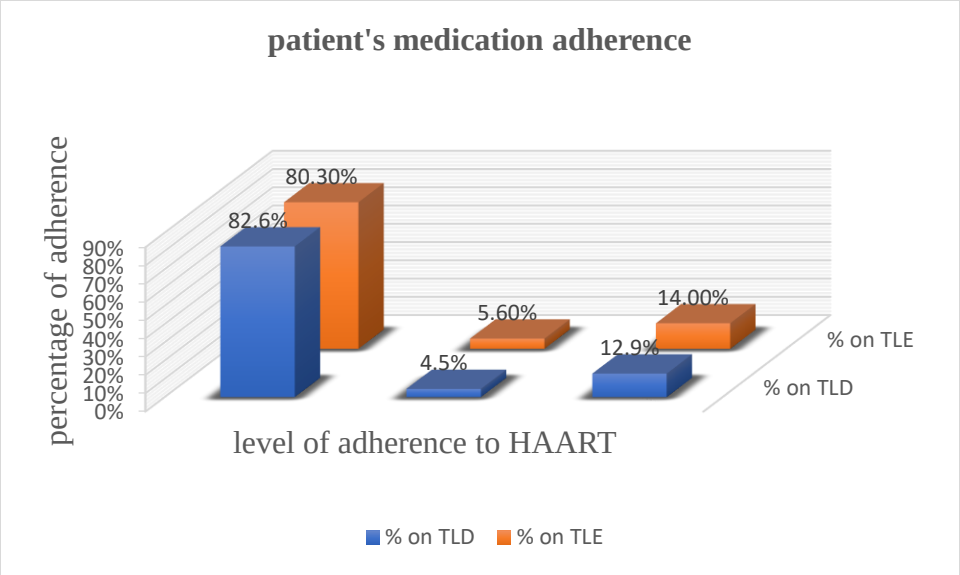

Figure 1: Level of adherence of study participants at Jimma medical center, ART clinic from September 1, 2017- August 31, 2021.

5.7. Virologic and immunologic outcome

The present study showed that, out of 356 participants, the proportion of virologic suppression on the TLE regimen was 281 (78.9%). However, after switching to DTG based regimen, 319 (89.6%) (95%CI 86% - 93%) participants were virologically suppressed in 24 months follow-up (**fig.2).** The data were skewed and the Wilcoxon signed rank test was performed which showed that the pre-dolutegravir based regimen median viral load score and post-dolutegravir based regimen median viral load score were significantly different (Z scores -4.647; p< 0.001).

Patients with viral load greater than 1000copies/ml were present in 17 (4.8%) on TLE based regimen while it was dropped to 4 (1.1%) on DTG based regimen. Out of study participants, 238 were present for assessing their CD4 count. The current mean CD4 count during the TLE regimen was 508.87 ± 240.25 cells/mm3. After the DTG regimen was initiated, this count was increased to 609.92 ± 256.8 cells/mm3. In another case 172 (72.3%) participants have a CD4 cell count greater than 350 cells/mm3 on TLE while 202 (84.9%) participants have a CD4 count greater than 350 cells/mm3 on DTG **(fig. 2).**

Table 5: Immunologic response distributed by virologic outcome of study participants at Jimma medical center, ART clinic from September 1, 2017- August 31, 2021.

	immunologic response	
TLD virologic outcome	good respondents N (%)	non-respondents N (%)
suppressed	**181(76.1)**	33(13.9)
not suppressed	21(8.8)	3(1.3)
TLE virologic outcome		
suppressed	**142(59.7)**	47(19.7)
not suppressed	30(12.6)	19(8)

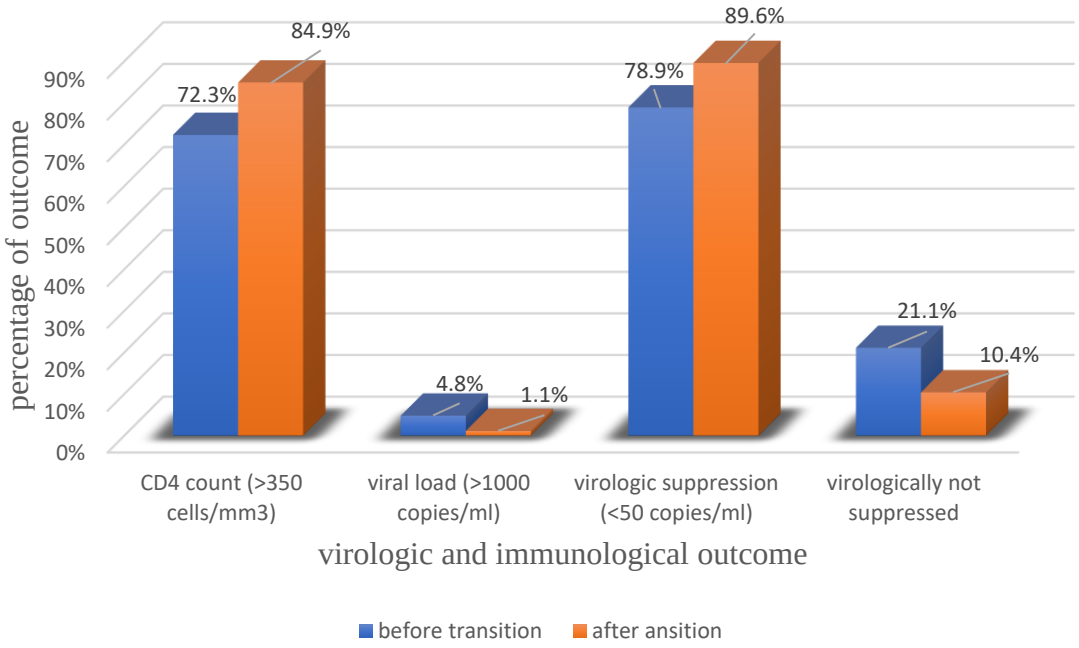

Figure 2: Immunological and virological outcomes before and after the switch to dolutegravir at Jimma medical center, ART clinic from September 1, 2017- August 31, 2021.

5.8. Factors Associated with Virological Suppression

In the bivariate logistic regression analysis, it was illustrated that virologic suppression was more likely associated with patient good medication adherence p<0.001, COR= 11.53, CI= 5.06-26.25, secondary/tertiary educational level p<0.001, COR=5.46, CI= 2.30- 13.04, TLE baseline viral load p=0.027, COR= 3.10, CI=1.14-8.47, patient occupation P=0.218,COR = 2.38, CI = 0.59-9.47, IPT use history p=0.066,COR=2.24, CI=0.95-5.30,

side effects p=0.108, COR=2.10, CI=0.85-5.15, baseline WHO clinical staging P<0.001, COR=4.10, CI=1.86-8.93, baseline TB screening p<0.001, COR=3.56, CI=1.77-7.16 having no opportunistic infections p<0.001, COR= 6.72, CI=3.20-14.20 were significantly associated with virological suppression. A cutoff point of p-value ≤ 0.25 was used to select variables for the multivariable binary logistic regression.

From the above bivariate output, patient good medication adherence, secondary/tertiary educational level, and occurrence of opportunistic infections are found to be independent predictors of virologic suppression in multivariate logistic regression analysis. Consequently, the odds of having virologic suppression are about 9 times (AOR= 9.22 95% CI: 3.70- 22.92, P= <0.001) higher among participants who have good adherence as compared to poor adherence. Furthermore, the odds of achieving virologic suppression are 6 times (AOR=6.20, 95% CI: 2.15-17.61, P= 0.001) higher for those participants who achieved secondary and above education level as compared to those who have no formal education. Lastly, having no opportunistic infection was 4 times (AOR=4.23, 95% CI: 1.83- 9.78, P= 0.001) more likely to be virologically suppressed as compared to those who develop opportunistic infections **(table 6).**

Table 6: Factors associated with virological suppression of study participants at Jimma medical center, ART clinic from September 1, 2017- August 31, 2021.

Variables	Outcomes					
Patient medication adherence	suppressed N (%)	**not suppressed N(%)**	**COR (95% CI)**	**P- value**	**AOR (95% CI)**	**P- value**
good	281(78.9)	13(3.7)	11.53(5.06-26.25)	< 0.001	9.22 (3.70- 22.92)	**< 0.001**
fair	8(2.2)	8(2.2)	0.53 (0.16-1.69)	0.285	0.74 (0.182-2.995)	0.672
poor	30(4.5)	16(8.4)	1		1	
Educational level						
illiterate	42(11.8)	15(4.2)	1		1	
primary	124(34.8)	12(3.4)	3.69(1.60-8.51)	0.002	4.40(1.56-12.24)	0.005
secondary/tertiary	153(43)	10(2.8)	5.46(2.30-13.04)	<0.001	6.20(2.15-17.61)	**0.001**
TLE baseline viral load						
<50copies/ml	261(73.3)	28(7.9)	3.10 (1.14-8.47)	0.027	2.33 (0.65-8.40)	0.196
50-1000copies/ml	40(11.2)	3(0.8)	4.44(0.99-19.78	0.050	4.40(0.73-26.65)	0.107
>1000copies/ml	18(5.1)	6(1.7)	1		1	
Patients' occupation						
government employee	50(14)	3(0.8)	2.38(0.59-9.47)	0.218	1.96(0.37-10.30)	0.425
private	213(59.8)	26(7.3)	1.17(0.50-2.72)	0.715	1.12(0.40-3.20)	0.828
unemployed	56(15.7)	8(2.2)	1		1	
IPT use history						
yes	284(79.8)	29(8.1)	2.24(0.95-5.30)	0.066	0.70(0.24-2.60)	0.695
no	35(2.2)	8(9.8)	1		1	
Side effects						
yes	32(9)	7(2)	1		1	
no	287(80)	30(8.4)	2.1(0.85-5.15)	0.108	1.75(0.55-5.40)	0.388
Baseline WHO clinical staging						

less advanced (I/II)	181(50.8)	9(2.5)	4.10(1.86-8.93)	< 0.001	1.41(0.50-4.10)	0.64
more advanced (III/IV)	28(7.9)	138(38.8)	1		1	
Opportunistic infections						
yes	83(23.3)	26(7.3)	1		1	
no	236(66.3)	11(3.1)	6.72(3.20-14.20)	< 0.001	4.23(1.83-9.78)	**0.001**
TB baseline screening						
Positive	67(18.8)	18 (5.1)	1		1	
Negative	252(70.8)	19 (5.3)	3.56 (1.77-7.16)	< 0.001	0.86(0.24-3.20)	0.827

5.9. Factors associated with immunologic response

Binary logistic regression was also run to see the immunologic response of the study participants. The output revealed the following variables to be more likely associated with the immunologic response of the study participants. Female gender (p=0.003,COR=3.06 CI= 1.46-6.40), urban residence (p=0.065,COR= 2.34, CI= 0.95- 5.76), patients medication adherence (p=0.079,COR= 2.24, CI= 0.91- 5.52), baseline WHO clinical stage (p=0.022,COR= 2.40, CI= 1.13-5.04), concomitant medications (p=0.151,COR= 1.78, CI= 0.81- 3.92), side effects (p=0.082,COR= 2.32, CI= 0.89- 6.01), opportunistic infections (p=0.083,COR= 0.52, CI= 0.25-1.10), IPT use (p=0.004, COR= 3.87, CI= 1.56- 9.64), hospitalization (p=0.051, COR= 2.36, CI= 0.99- 5.60).

From the above variables, being female have more likely to achieve good immune response as compared to males (p=0.009, AOR= 2.83CI= 1.30- 6.20), and IPT use, using IPT is more likely associated with good immunologic response (p=0.038, AOR= 2.82, CI= 1.06- 7.50) are independent predictors of good immunologic response on multiple logistic regression (**table 7)**.

Table 7: Factors associated with the immunologic response of study participants at Jimma medical center, ART clinic from September 1, 2017- August 31, 2021.

Variables	Outcomes					
Gender	Good immunologic respondents N (%)	Immunologic non-respondents N (%)	**COR (95% CI)**	**P- value**	**AOR (95% CI)**	**P- value**
Male	74 (31.1)	23 (9.7)	1		1	
female	128 (53.8)	13 (5.5)	3.06 (1.46-6.40)	0.003	2.83 (1.30- 6.20)	**0.009**
Residence						
Urban	180 (75.6)	28 (11.8)	2.34 (0.95-5.76)	0.065	2.03 (0.78-5.30)	0.144
Rural	22 (9.2)	8 (3.4)	1		1	
Patients medication adherence						
Good	174 (73.1)	27 (11.3)	2.24 (0.91-5.52)	0.079	1.85 (0.67-5.10)	0.232
fair	5 (2.1)	1 (0.4)	1.74 (0.17-17.22)	0.636	1.23 (0.11-14.50)	0.866
poor	23 (9.7)	8 (3.4)	1		1	
Baseline WHO clinical stage						
Less advanced (I/II)	110 (46.2)	12 (5)	2.40 (1.13-5.04)	0.022	1.72 (0.78-3.78)	0.180
More advanced (III/IV)	92 (38.7)	24 (10.1)	1		1	
concomitant medications						
Yes	40 (16.8)	12 (5)	1		1	
No	162 (68.1)	24 (10.1)	1.78 (0.81-3.92)	0.151	1.73 (0.73-4.10)	0.210
Medication side effects						
yes	19 (8)	7 (2.9)	1		1	
no	183 (76.9)	29 (12.2)	2.32 (0.89-6.01)	0.082	2.71(0.97-7.56)	0.057
Opportunistic infections						
yes	55 (23.1)	15 (6.3)	0.52 (0.25-1.10)	0.083	0.74 (0.20-2.74)	0.66
no	147 (61.8)	21 (8.8)	1		1	
Isoniazid preventive therapy (IPT)						

yes	186 (78.2)	27 (11.3)	3.87 (1.56-9.64)	0.004	2.82 (1.06-7.50)	**0.038**
no	16 (6.7)	9 (3.8)	1		1	
Hospitalization history						
yes	25 (10.5)	9 (3.8)	1		1	
no	177 (74.4)	27 (11.3)	2.36 (0.99-5.60)	0.051	1.15 (0.40-3.40)	0.804

6. DISCUSSION

6.1. Magnitude of virologic suppression

Effective HIV therapy raises CD4+ cell counts, which enhance immunological recovery and lower HIV viral loads (27,73).This study aimed to explain virological suppression and immunologic response among HIV patients treated at Jimma medical center. Ideally, HIV patients should achieve undetectable levels of virologic suppression within six months of medication if they begin treatment or switch from one regimen to another for any reason(74).

It was found that 319 (89.6%) (95%CI 86% - 93%) of the participants achieved viral suppression after switching to the dolutegravir-based regimen. Prior to switching, the virologic suppression on TLE was 281 (78.9%).This proportion of viral suppression was comparable with a Tanzanian(27)study by dolutegravir viral suppression that showed substantial levels of virologic suppression were 52.7% on TLE, with 89.9% of patients continuing to achieve virologic suppression after switching to TLD. Another study conducted in Brazil(20) also found that viral suppression by 12 months was84.0% with TLE and 90.5% with TLD which is in line with our finding. Comparable result was also reported from Ethiopia(32) with virologic suppression of 92% after the patients were shifted to the dolutegravir-based regimen which was 81.4% before transition.

A study conducted in china(26) on a comparison of dolutegravir and efavirenz-based regimens also found that virologic suppression < 50cpies/ml was achieved in 100% of dolutegravir arm while 83.3% with efavirenz arm after 24 weeks of follow up duration. This finding is higher than our finding. This is probably due to the study design used. They used a prospective study design while ours is retrospective. In the prospective study the patients were followed strictly but in the retrospective study important information might have been missed. Another justification is that their patients were treatment naïve while ours is treatment experienced.

Dolutegravir efficacy is also reported in a study done in Cameroon(28) which reports 74.5% of participants to have a viral load of less than 50 copies/ml on dolutegravir-while it was 69% on an efavirenz-based regimen. This finding is lower than ours probably due to the shorter duration (12-months) of follow-up.

A systematic review conducted to compare the two drug-based regimens also favors the greater efficacy of dolutegravir-based regimens as compared to efavirenz-based regimens(29–31).When compared to an EFV-based regimen, the DTG-based regimen's efficacy has also been shown in other research(75,76).

Overall, the results reported in the present study are also consistent with randomized controlled trials results of the SINGLE (2013), FLAMINGO (2014) ADVANCE (2018),and NAMSA (2019) studies, which demonstrated high virologic suppression on DTG based regimen(17,23,75,77).

6.2. factors associated with virologic suppression

In our study, three independent variables show significant association with virologic suppression in both bivariate and multivariate logistic regression. These include the patient's medication adherence, educational level, and occurrence of opportunistic infections.

In this study, participants with good adherence experienced virological suppression around nine times greater as compared to participants with poor adherence(P=0.000). This result is consistent with research from Kenya(39) which correlates patients who have good ART adherence have viral suppression below the detectable limit (<40copies/ml), and Ghana(38) where having good adherence is associated with viral suppression less than 50copies/ml, India(37) which reports good adherence as an independent predictor of virologic suppression, and Ethiopia(78,79) on other ART regimens, where good adherence was found to be a major predictor of viral load reduction.

One study in Ethiopia, which was similar in aim and study participants, is also in line with our finding which favors good adherence for virologic suppression (P=0.002) (32).This association was also reported by other similar studies(80,81).This can also additionally aid the concept that both good adherence or poor adherence is associated with virological suppression or non-suppression, respectively. This might be as a result of HIV replication not being suppressed when the medication concentration in bodily fluids drops, which then results in a rise in viral load(78,82).

Another independent predictor of virologic suppression in our study was educational level. It was found that achieving a higher education level (secondary/tertiary- 0.001) is strongly associated with treatment success.

This finding can also interpret as being illiterate or having no formal education is associated with less likely to achieve virologic suppression. This finding is in line with other studies from Spain(42), the United States(41), Brazil(83), the United Kingdom(84), Nigeria (43), and Ethiopia (44) which support higher education levels as a protective or lower educational level against the achievement of virologic suppression.

This is owing to the fact that educational level, which likely reflects patients' access to knowledge, has previously been demonstrated to be a predictive factor for viral load reduction and treatment adherence in other Brazilian research(85,86).Additionally, lifestyle and educational attainment are known to be related, and both of these factors affect adherence. Higher educational attainment is positively correlated with employment preference, higher wages, and thus more financial stability. The capacity to follow medical instructions and patient education guidelines, as well as leading better lives(no smoking, good nutrition, and exercise), are all related to educational success (87,88).

In contrast to our finding, one study from Papua New Guinea report that participants who had higher levels of education were more likely to experience virological failure. However, they acknowledge that the number of participants who had secondary school and tertiary education was small(n = 13) and this may be the possible reason for this discrepancy (89).

Furthermore, the opportunistic infections are another independent variable that determines virologic suppression in our study finding. Accordingly, the odds of virologic suppression are increased for the patients who didn’t develop opportunistic infections(p-0.001). This result is in harmony with previous research finding from Uganda(46,82), Ethiopia(48,90,91) South Africa(47) Brazil(92), and Haiti(45) which found that opportunistic infections lead to ART virological non-suppression.

Possible reasons for this is the inverse relationship between viral load suppression and occurrence of opportunistic infections which decrease the immunity of patients and there by

leads to advanced disease by making the patients non adherent to their medication(93).Studies regularly note significantly related aspects such the existence of opportunistic infections, low CD4 cell count, progressed WHO clinical stage, and baseline non-working functional status. This is due to the fact that CD4 cell count is the foundation of immunity development that supports in disease protection and can halt viral replication in the body.

The rate of viral replication rises as patients' immune systems deteriorate, increasing the likelihood that they may get opportunistic infections and bringing on the disease's severe stage. As a result, the patient discontinue medications, stops follow-up, and places more attention on the urgent issue than the chronic HIV, which results in poor adherence and HIV treatment failure(94–97).

6.3. Magnitude of immunologic response

The CD4 cell T-count is a valuable alternative for immunological response and a crucial marker for measuring the advancement of HIV infection. According to studies, immunodeficiency is linked to both AIDS and non- AIDS defining illness(98).When highly active antiretroviral medication is started, the CD4 cell count rises quickly in the first few weeks, then recovers more slowly with the help of newly created T cells. In many different types of study, the criteria used to establish the CD4 count as the definitive point are quite variable. Thus, it is challenging to evaluate and integrate consistent and reliable data from many research groups in the absence of agreed-upon standards (70).

This study showed that the mean CD4 count during the TLE regimen was 508.87 ± 240.25 cells/mm3. After the DTG based- regimen was initiated, this count was increased to 609.92 ± 256.8 cells/mm3. In another case 172 (48.3%) participants have a CD4 cell count greater than 350 cells/mm3 on TLE while 202 (56.7%) participants have a CD4 count greater than 350 cells/mm3 on DTG.

This finding is in line with a study conducted in Tanzania(27) which supports the effectiveness of dolutegravir in increasing immunologic response. A systematic literature review (30,35) found that change from baseline CD4 was consistently higher in the dolutegravir-based regimen as compared to efavirenz. A study conducted in the United States(15,33) shows that the DTG group had a greater increment of CD4+ T-cell count than the EFV group.

6.4. factors associated with immunologic response

The objective of HAART treatment is the restoration of the immune system by viral suppression and elevated CD4+ T-cell counts. However, a number of variables play a role in achieving the desired immunological response(53). In the current study, being female and IPT use was independent predictor of CD4+ T-cell count.

Compared with male, female participants have more likely to achieve a good immunologic response. This result is in line with study findings in Spain(50) Ethiopia(53,99), Brazil(49),China(51), and in a multicenter study(52).In contrast, a study of immunological recovery in patients indicated that gender was not associated with the immunological response(100).

This gender difference might be account due to the fact that females may have easier access to regular HIV testing during prenatal care, and as a result, they may be initiate ART earlier before the advancement of the disease, which might account for the higher CD4+ T-cell counts among females. Compared to men, females have a higher likelihood of receiving an HIV diagnosis sooner.(101,102).In turn, this could enhance the immune response. The poor health-seeking behavior of men, on the other hand, may lead to lower rates of HIV testing, a lower acceptance of screening results, and a lower access to ART facilities following an HIV-positive diagnosis.(103,104). A delay in the diagnosis of HIV and failure to initiate HAART early favor a poor response to HAART.

The use of IPT was shown to have a beneficial effect on immunologic response in this particular study. The use of IPT is shown to reduce the incidence(105) of TB development and this in turn has a protective effect on immunologic recovery(55). This finding is in line with other studies which report supporting evidence of IPT use to help the patient CD4 increment from Ethiopia(57,58,105) and other countries such as Uganda(55), South Africa(56) and Germany(54).This might be explained by that IPT use decrease the incidence of TB opportunistic infections. ART aids in the minimization of viral load and recovery of the immune status of the patients which in turn reduces the development of opportunistic disease. The other reason might be due to the good adherence of the participants in this study.

On the contrary, a study conducted in Arba Minch, Ethiopia found that there is no difference between IPT-exposed and non-exposed(59). This discrepancy may be secondary to the types of ART use and the definition of immune response to assess CD4 count.

7. CONCLUSION

This study identified that DTG based regimen maintains virologic suppression and increases immunologic response. Good ART adherence, educational level (achieving higher education), and having no opportunistic infections are associated with virologic suppression while being female and IPT use are independent predictors of immunologic response.

8. RECOMMENDATION

For ART pharmacists and other health workers

- ✓ Adherence was found to be an important indicator of treatment success in this research and a well-known factor in another finding.
- ✓ Hence, ART pharmacists and other health workers should provide consistent professional advice to maintain good adherence for those who are taking their medication well and identify factors hindering those who have poor adherence.

For physicians

- ✓ Early screening of opportunistic infections and initiating treatment is a very important measure and pre-condition for virologic and immunologic success.
- ✓ So, physicians shall continue to screen their patients every visit and initiate treatment if it occurs, or considering prophylaxis for candidate patients should be a usual practice as this condition is found to be a predictor of treatment outcome.

For Jimma medical center ART clinic

- ✓ HIV infected treatment experienced patients on other combinations should be shifted to dolutegravir based regimen if they are eligible
- ✓ Continuous monitoring of long-term virological and immunological outcomes of DTG-based regimens among HIV/AIDs patients is essential to observe the consistency of favorable outcomes.

For future researchers

- ✓ This study finding is based on secondary data and has some limitations. Therefore, we recommend that it would be better if a prospective cohort study with a sufficient sample size could be conducted in the future.
- ✓ It is not possible to generalize the findings to treatment-naïve participants. Therefore, future research shall be conducted on treatment-naïve HIV patients on a dolutegravir-based regimen.
- ✓ Even though the association was not tested in this study, weight of participants on DTG shows increment. Weight gain after its use needs further research to check long term effects of this gain.

9. STRENGHT AND LIMITATION

This study includes relatively large sample size. It also includes immunologic outcome relative to study conducted previously. The study was limited by its retrospective design that involved the use of secondary data and important variables like patients' behavior have been missed. It would be better if a prospective cohort study could be conducted in the future. Treatment naïve were not included in the study. This also may affect the true result because these are important study subjects.

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11. ANNEXES

Data collection tool English form

<table>
<tr><td colspan="3">Part I. socio-demographic characteristics</td></tr>
<tr><td>1.CardNo _____</td><td>2.Age (year)_____</td><td>3.Gender: Male ☐ Female ☐</td></tr>
<tr><td>4.Marital status
Single ☐
Married ☐
Divorced ☐
Widowed ☐
7.Residence:
Rural ☐
Urban ☐</td><td>5.Educational status
unable to read ☐
Primary school (1-8) ☐
Secondary school (9-10) ☐
Tertiary school
(TVET/College/University) ☐</td><td>6.Occupation:
Gov’t employee ☐ NGO ☐
Farmer ☐ Daily laborer ☐ Retired ☐
Merchant ☐ Housewife ☐ unemployed ☐
If other (specify)_____
8.Have you disclosed your serostatus to your family/ friends?
Yes ☐ No ☐
9.If yes, who know your HIV status?
Suppose/wife/husbund ☐ own child/ren ☐
parents ☐ brother/sister ☐ relatives ☐
friends ☐ others _____</td></tr>
<tr><td colspan="2">Part II. adherenceon TLE
Good > 95% ☐
Fair 85-95% ☐
Poor < 85% ☐</td><td>adherenceon DTG
Good > 95% ☐
Fair 85-95% ☐
Poor < 85% ☐</td></tr>
<tr><td colspan="3">Part III</td></tr>
<tr><td colspan="3">Clinical characteristics</td></tr>
<tr><td colspan="2">1. Total duration of HIV of treatment (in years) __</td><td>2. Total duration on TLE___ on DTG_____</td></tr>
<tr><td colspan="2">3.Weight (Kg) on TLE
Baseline ___ just before transition ___</td><td>Weight (Kg) on DTG
Baseline_____ current _____</td></tr>
<tr><td colspan="2">4. Height (Cm) on TLE___
BMI on TLE___</td><td>BMI on DTG_____</td></tr>
<tr><td colspan="2">5. WHO Clinical Stage: baseline ☐</td><td></td></tr>
</table>

6.WHO T- stage ☐	
7. baseline Functional status (W, A, B) _____	
8.CD4 Count (cells/mm3): on TLE Baseline ___ just before transition ___	CD4 Count (cells/mm3): On DTG Baseline_____ current _____
9. Viral load at initiation_____ Viral Load (copies/ml): on TLE Baseline ___ just before transition ___	Viral Load (copies/ml): on DTG Baseline_____ current _____
Drug related characteristics	
10. Cotrimoxazole Preventive Therapy (CPT)? Yes ☐ No ☐	
11. Isoniazid Preventive Therapy (IPT) Yes ☐ No ☐	
12. is any concomitant medications use? Yes ☐ No ☐	
13.if yes for question number 12, what was the type of medication used? _____	
14. Were there any side effects encountered? Yes ☐ No ☐	
15. If yes for question number 14, what types of adverse drug reaction occurred? _____	
Disease related characteristics	
16.Was there any Comorbidity? Yes ☐ No ☐	
17. If yes for question number 16, what was the type of comorbidity? _____	
18. Was there any Opportunistic Infections? Yes ☐ No ☐	
19. If yes for question number 18, what was the type of opportunistic infection? _____	
20. Is there any hospitalization? Yes ☐ No ☐	
21. If yes, what was the reason for hospitalization? HIV related illness ☐ Non-HIV related illness ☐	
22. Baseline TB screen Positive ☐ Negative ☐	

ASSURANCE OF PRINCIPAL INVESTIGATOR

The undersigned clinical pharmacy, MSc student acknowledge that this thesis is my original work. All information obtained from other sources are properly acknowledged and cited. I agree to accept responsibility for the scientific ethical and technical conduct of the research project and for provision of required progress reports as per terms and conditions of institute of Health, school of pharmacy Jimma University in effect at the time of grant is forwarded as the result of this application.

Name of the student: _____

Date. _____ Signature _____

APPROVAL OF THE FIRST ADVISOR

Name of the first advisor: _____

Date. _____ Signature _____

APPROVAL OF THE EXAMINER

Name of the examiner: _____

Date. _____ Signature _____

APPROVAL OF SCHOOL OF HEAD

Name of school head: _____

Date. _____ Signature _____