EFFICACY AND SAFETY OF DOLUTEGRAVIR VERSUS EFAVIRENZ BASED FIRST LINE ANTI-RETROVIRAL REGIMEN AMONG HIV POSITIVE PATIENTS AT JIMMA MEDICAL CENTER, JIMMA, SOUTHWEST ETHIOPIA, 2020

BY: Dr. Melat Dadigeba (Internal Medicine Resident)

A THESIS SUBMITTED TO THE DEPARTMENT OF INTERNAL MEDICINE, FACULTY OF MEDICAL SCIENCES, INSTITUTE OF HEALTH, JIMMA UNIVERSITY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR CERTIFICATE OF SPECIALIZATION IN INTERNAL MEDICINE

MAY 2021

JIMMA, ETHIOPIA

EFFICACY AND SAFETY OF DOLUTEGRAVIR VERSUS EFAVIRENZ BASED FIRST LINE ANTI-RETROVIRAL REGIMEN AMONG HIV INFECTED PATIENTS AT JIMMA MEDICAL CENTER, JIMMA, SOUTHWEST ETHIOPIA, 2020

BY: Dr. Melat Dadigeba (MD, Internal Medicine Resident)

ADVISORS: Dr. Daniel Yilma (MD, Internist, Associate Professor)

Mr. Fassikaw Kebede (BSc, MPH in Epidemiology)

MAY 2021

JIMMA, ETHIOPIA

Abstract

Background*: Dolutegravir (DTG) is a once-daily unboosted second-generation novel HIV-1 entry and integrase strand transfer inhibitors with that along with two nucleoside reverse transcriptase inhibitors (NRTI) preferred first line that is in use in Ethiopia in 2018.*

Objective: *To assess the efficacy and safety of Dolutegravir based first line Antiretroviral Therapy regimens compared with Efavirenz based regimen among HIV-positive Patients in Jimma Medical Center, 2020.*

Methods: *This study was facility-based retrospective cross-sectional study among newly diagnosed HIV patients starting ARV drugs with TDF+3TC+DTG and TDF +3TC+EFV at Jimma medical center, who were started ART from August 2018 to April 2020. Data was collected from patients' chart. Data was edited, coded, entered into Epi data and then exported to SPSS version 20 for cleaning and analysis respectively. The data were summarized and described using tables, graphs and percentages. Descriptive statistics were used to put results of the study in the form of findings and percentages. Bivariate association was assessed by using chi-square test for categorical variables and t-test for continuous variables.*

Result: *240 patient charts were reviewed, which comprised of equal number of Patients on TLD and TLE. The mean age of the study subjects was 34.78±11.99 and 36.7±9.92 years among the TLD and TLE groups respectively. The distribution of age, sex, residency, marital status, educational level and occupation of the study groups was similar. The TLD treatment group showed better CD4 recovery than the TLE group. An independent sample t test reported a significant difference in mean CD4 change among HIV patients receiving TLD and TLE regimens, t (238) = 3,747, p <.001, 95% C.I. [24.49–78.78]. There is a statistically significant relationship between the regimen and viral suppression (p=0.029). 72.5%, n=87 of the patients' viral load that were recruited for TLD were suppressed as compared to that of TLE (59.17%, n=71).*

Conclusion: *The efficacy and safety of TLD were superior over TLE regimen for the treatment of newly diagnosed HIV patients with lower side effects.*

Recommendation: *TLD, including DTG containing regimens should be monitored regularly, and the current TLD containing treatment regimens in Ethiopia should be strengthened to get benefitted.*

Key words: *HIV/AIDS, ART, first line regimens, dolutegravir (DTG), efavirenz (EFV)*

Acknowledgements

First, I would like to express my deeply felt gratitude to my advisors Dr. Daniel Yilma and Mr Fssikaw Kebede for their comments and constructive suggestions from the inception of the study to the realization of this research thesis.

Next, I would like to give special acknowledgment to Jimma University for providing this opportunity and planning to fund this study.

I would also like to give special acknowledgment to my husband Addisu G/yesuse for his encouragement, support and appreciations in all part of my study.

Last but not least, I would like to thank my friends, who took part in reading, editing, and correcting project paper to improve it.

Table of contents

List of Tables

List of Acronyms

3TC - Lamivudine

AE - Adverse Effect

AIDS - Acquired Immunodeficiency Disease Syndrome

ART-Antiretroviral Therapy

cART- Combination Antiretroviral Therapy.

DTG - Dolutegravir

EFV - Efavirenz

HAART - Highly Active Antiretroviral Therapy

HIV - Human Immunodeficiency Virus

INSTIs - entry inhibitors, and integrase strand transfer inhibitors

NNRTIs - non-nucleoside reverse-transcriptase inhibitors,

NRTIs - nucleoside and nucleotide reverse-transcriptase inhibitors,

PIs – protease inhibitors

RAL - raltegravir

STR - single-tablet regimen

TLD - Tenofovir/Lamivudine/Dolutegravir

TLE - Tenofovir/ Lamivudine/ Efavirenz

UNAIDS— United Nations Program in HIV/AIDS

WHO— World Health Organization

1. Introduction

1.1. Background

Human Immuno-Deficiency Virus (HIV), the cause of Acquired Immuno-Deficiency Syndrome (AIDS) is one of the major public health problems worldwide. According to Global Health Statistics report, there were approximately 38 million people across the globe with HIV/AIDS in 2019. Among these, 36.2 million were adults (>14 years old). Most people with HIV are in low- and middle-income countries (1). In 2018, there were 20.6 million people with HIV (57%) in eastern and southern Africa, 5.0 million (13%) in western and central Africa, 5.9 million (16%) in Asia and the Pacific, and 2.2 million (6%) in Western and Central Europe and North America (1, 2).

Global AIDS-related deaths have been reduced by more than 55% since the peak in 2004. In 2018, around 770,000 people died of AIDS-related illnesses, compared to 1.2 million in 2010 and 1.7 million in 2004. Further, the HIV epidemic not only affects the health of individuals, it also impacts households, communities, and the development and economic growth of nations. Most of the countries affected by the endemic are also suffering from other infectious diseases, food insecurity, and other serious problems (3).

Ethiopia is among the countries where the burden of HIV disease is significant. According to the United Nations Program in HIV/AIDS (UNAIDS) report, about 690,000 people were living with HIV in Ethiopia in 2018 with estimated national prevalence of 1%. About 11,000 people died from an AIDS-related illness in the same year (4, 5).

With the advent of effective highly active antiretroviral therapy (HAART) a major reduction of AIDS-related morbidity and mortality has been observed globally (6-9). Because of this, incidence of HIV infection and the risk of transmission of the virus was lowered in those receiving HAART than the new patients (10). On top of this, to achieve long-term suppression of the virus and the recovery of the immune system, evidence-based selection of the medicines from available alternatives is critical (11). There is also an increasing need for HIV/AIDS medications with fewer interactions higher genetic barrier to resistance, low pill burden, reduced side effects and toxicity and with cheaper prices (3).

The type of ART regimen used to treat HIV/AIDS is changing from time to time as the scientific discovery and knowledge increases. Effectiveness and safety of a regimen are the principal factors that dictate preference of one regimen from another regimen. However, there are also other important factors that can influence selection of a given ART regimen; such as availability and accessibility, drug formulation, presence of comorbidity, age of patient, adherence issues, and pregnancy status among others (3).

Starting from the approval of zidovudine in 1987, there has been an increasing number of anti-retroviral agents developed targeting the human immunodeficiency virus (HIV). The currently available classes antiretroviral drugs include the nucleoside and nucleotide reverse-transcriptase inhibitors (NRTIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), entry inhibitors, and integrase strand transfer inhibitors (INSTIs) (12, 13).

The antiretroviral drug class INSTs, block integrase (an HIV enzyme) prevents HIV from replicating Raltegravir and Elvitegravir were the first to be approved for use from this group (14-16).

Dolutegravir (DTG) which was discovered by Shionogi and GlaxoSmithKline research collaboration is a second-generation novel HIV-1 INSTIs (17). It was recently approved for the treatment of HIV-1 infection having several advantages over existing HIV integrase inhibitors and has been shown to be highly active against wild-type and drug-resistant viruses, including integrase-resistant strains (18). It is generally recommended in combination with other antiretroviral agents. It can be taken once daily and has been co-formulated into a single-tablet regimen (STR) (19, 20).

Dolutegravir has better suppressing the resistant strains capability in addition to viral load suppressive capability. It is also available as fixed dose combination with cheaper price. The use of DTG in all age groups was not well developed. For instance, the safety and efficacy of DTG in pregnant women and HIV/TB patient was not strong. There is concern for risk of neural tube defect in pregnant women using DTG. Accordingly, WHO guideline recommended against use of DTG in the first trimester (2-4, 21).

1.2. Statement of the Problem

In low- and middle-income countries where availability, accessibility, and cost are major limiting factors, use of a regimen with established efficacy and safety in different HIV sub-population is highly desirable. The combination of two nucleoside reverse transcriptase (NRTI) with a non-nucleoside reverse transcriptase inhibitors (NNRTI), particularly Efavirenz has been in use as a first line initial ART regimen for a long time (22). However, the current recommendations from national and international guidelines have changed to DTG with two NRTI as a preferred first line regimen (3, 21, 23).

In contrast to the benefits of DTG, there are some common adverse effects reported. These include nausea, headache, and diarrhea, occurring at frequencies like that with other INSTIs. 2-3% patients developed the grades 1-2 adverse events that led to discontinuation of the agent. Less than 1% of patients experienced a serious drug-related adverse event (16, 20).

Ethiopia is one of the most heavily affected countries with HIV pandemics, with 690,000 peoples are living with HIV (2018). About 11,000 people died from an AIDS-related illness in the same year. And all of them need ART in 2007, 436,000 peoples are currently taking ART (4, 5). Despite the challenges associated with lack of universal access to ART drugs and poor adherence, Ethiopia is among the countries where HIV/TB confection burden is high (24). In 2017, the percentage of people living with HIV and tuberculosis who were being treated for both diseases was 54.2%, up from 43.1% in 2015 (5). DTG was institutionalized for use in Ethiopia starting from 2018 (4).

In countries like Ethiopia, where contraceptive use is not uniform and where there is high HIV/TB co-infection burden, the safety and efficacy of DTG based regimen needs further studies. As far as our knowledge is concerned, there is no study done in Ethiopia to compare the safety and efficacy of EFV based regimen with that of DTG based regimen. Therefore, the primary aim of this study is to assess the safety and efficacy of DTG based regimen in our patients and to compare it with that of EFV based regimen.

1.3. Significance of the Study

By assessing the treatment response and adverse drug effects of Dolutegravir based regime and comparing with efavirenz based regimen will give additional information to clinicians in the care of HIV patients and to act proactively if anything new happens.

The rationale for conducting this research was the fact that there is no adequate study done on treatment response and common side effect in Africa, and as far as we know no study has been done in Ethiopia.

Result of this study can be used by policy-makers as evidence for different recommendations, for future researcher as a reference tool and will allow health systems to maximize the potential benefits of this exciting new regimen.it will also give additional information to the government and non-governmental organizations to salvage regimen and reduce the cost of patient care.

2. Literature Review

Systematic reviews and meta-analysis study result by WHO indicated on the combination of HAART DRUG containing DTG in new and pretreated HIV patients, shows effective and rapid viral suppression. HIV patients including pregnant and TB patients, has antiviral effect to HIV2 virus, low incidence of adverse effect (<5%). The common adverse effects were gastrointestinal symptoms (nausea, vomiting), hypersensitivity skin reactions and central nervous system effects (insomnia, dizziness) which are mild and relived by itself with low drug discontinuation rate (3).

According to Brazil national online records patient recorded data from April 2017 to December 2017 GC, the combination of antiretroviral therapy among newly started HIV patients showed undetectable of viral load (<50 copies/mL) within 3 months and 10-11 months after treatment with DTG 81% and 88% respectively; which was higher when compared to EFV contain HAART (83%) and it also assessed the adverse effect, reported 2% Adverse effect (AE) and 89% were mild, 149 patients were changed to another drug due to AE. The result released from Brazil was comparable with clinical trial report released earlier (3, 25).

Botswana released one report in 2017 on DTG which shows the virological suppression, greater than 90% by 6 months, with fewer than 1% AEs, gastrointestinal disturbance was the commonest AE. Treatment failure was detected in 53 patients, 3 of them had integrase mutations (<0.75%). Reports from Kenya in 2017 and 2018 on DTG contain combination antiretroviral therapy on viral suppression were 88.7% and 90% respectively (3).

Retrospective cohort study done in a real world of, elvitegravir (EVG), DTG (DTG), and raltegravir (RAL) in 104 newly treatment started HIV patients and 219 patients switched INSTI contain regimen from another cART regimen, between May 2007 and December 2014. Assessed the adverse effect and viral load at 12 months after initiation of treatment, report shows, 92% of patients in the first-line group (EVG: 96%, n=22/23; DTG: 92%, n=34/37; RAL: 90%, n=28/31) and 88% of patients in the switch group (EVG: 94%, n=32/34; DTG: 90%, n=69/77; RAL: 85%, n=67/79) had undetectable viral load (<50 copies/mL). Adverse effect was 12% (n=12/104) of patients in the first-line group, and 10% (n=21/219) of patients in the switch group. In the switch group neuropsychiatric side effects (depression, vertigo, and sleep disturbances) commonly reported with DTG (11%, n=10), EVF: (2%, n=1); and RAL (1%, n=1), discontinuation of

treatment due to side effect was rare (first-line-group: 2%, n=2/104; switch groups: 1%, n=3/219). In conclusion, INSTI-based ART-regimens were highly efficacious with no significant differences between any of the 3 INSTIs. Overall, adverse effect were mild and rarely reported in all subgroups (26).

Cohort study, in a large Italian HIV drug resistance network, 89 HIV-1-positive patients started DTG for duration of 18.8 [0.4-76.2] months. All patients had undetectable HIV-1 RNA and significantly decreased in patients with CD4 count >200/μ (27).

Prospective study done on virological suppression in 659 randomly selected HIV patients taking HAART for at least 6 months, between May 2009 and April 2012 in 10 health-care facilities in Addis Ababa, Ethiopia. The result shows, 94.5% of the patients had the viral decrement of below 400 copies/ml after a median of 26 (17-35) months on HAART. Predictor factors for detectable viremia were younger age, low educational status <95% medication adherence, low base line CD4 count (28).

Longitudinal cohort study done to compare the viral load and adherence of patients to HAART at two approved treatment hospitals in Yaoundé, Cameron from May 2016 to June 2017 on patients taking either Tenofovir (TDF), Lamivudine (3TC) and EFV (EFV) or TDF / Zidovudine (AZT), 3TC and Nevirapine (NVP) drugs. From the total 256 study subjects about 180(70%) completed the study. The undetectable viral load was 1.8 times higher with the EFV regimen at 24 weeks and was 1.2 times higher in the NVP regimen at 48 weeks. The treatment failure rate at 48 weeks in patients on EFV and NVP contain HAART was 12.0 and 40.0% respectively. The adherence rate with EFV and NVP based ART at 24 and 48 weeks was 84.0 to 74.0% and 65.5 to 62.5% respectively (29).

In conclusion, the rate of viral load decrease was higher in the NVP based regimen than with the EFV regimen. The adherence rate to ART was higher in the EFV regimen, compared to the NVP regimen. This evidence contributes to EFV regimen is the preferred ART combination for non-nucleoside reverse transcriptase inhibitors (NNRTIs) (29).

A retrospective study done in Thohoyandou Community Health Centre, South Africa from medical records of HIV patients using 1247 patients on combination antiretroviral therapy (cART) evaluated the viral suppuration and immunologic improvement of HIV patients between January

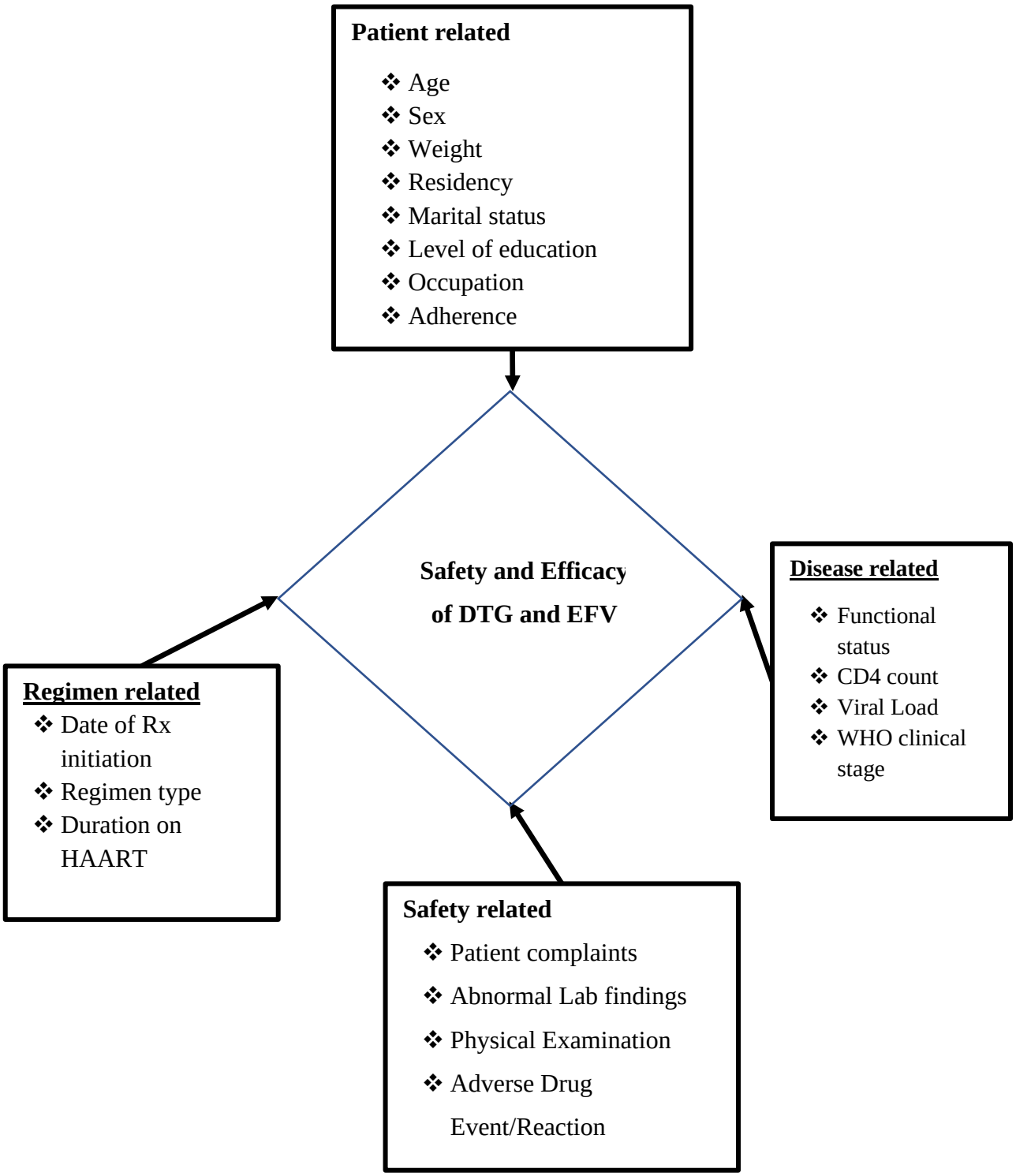
2004 and July 2016. With 76% of the cohort being female and 98% first-line cART. The result reported undetectable viral load at 6 months and 60 months was 64% and 72 % respectively. The improvement of mean CD4 count was 227 cells/μL at baseline increased to 538 cells/μL at 60 months (30).

A prospective observational cohort study in a developing Caribbean country, between January 2002 and March 2003, a total of 158 new HIV patients started combination antiretroviral therapy and follow up. Assessed CD4 cell counts improvement and viral load suppression at 6 months. The result was, 82% of patients (123 of 150) achieved viral loads of <50 copies/mL, 79.5% of patients had achieved immunological success and 17.9% had an increase in CD4 cell count of > or =200 cells/microL from the baseline value, irrespective of gender. The 156 patients had a median increase in CD4 cell count 122 cells/microL at 6 months (31).

In a phase 3b, randomized, open-label, multi-center, international, 96-week study aimed at comparing the safety and efficacy of the two single-tablet regimens (STRs), rilpivirine/emtricitabine/tenofovir (RPV/FTC/TDF) and efavirenz/emtricitabine/tenofovir (EFV/FTC/TDF), in HIV-1-infected, treatment-naive adults, 50.5%, 37.5% and 21.2% of the study participants developed Nervous system, psychiatric and rash events respectively. The nervous system events were dizziness (22.2%), insomnia (14%), somnolence (6.9%) and headaches (13.5%). And the reported psychiatric events were depression (8.4%) and anxiety among 8.4% of the study subjects. This led to discontinuation of EFV/FTC/TDF regimen. In addition to these, Grade 3 or 4 laboratory abnormalities occurred in 16.2% of participants which include increase in ALT (3.4%), AST (3.3%), GGT (2.6%), amylase (1.8%), creatine kinase (5.1%), and TC (1.1%), as well as glycosuria (1.0%) and hematuria (1.3%) (32).

With respect to DTG, the most commonly reported adverse events in different studied globally includes nausea, diarrhea, headache, fatigue, asthenia, nasopharyngitis, insomnia, dizziness, abnormal dreams, pyrexia, Grade 2 dyspepsia, grade 4 Burkitt's lymphoma and depression. And the common laboratory abnormalities observed were elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholesterol, creatine phosphokinase, activated partial thromboplastin time, prothrombin time and lipase; decreased concentrations of phosphorus, neutrophil count and hyperglycemia (20, 33, 34).

2.1. Conceptual framework



3. Objective

3.1. General Objective

To assess the efficacy and safety of dolutegravir based ART regimen compared to efavirenz based ART regimen among newly diagnosed HIV patients at Jimma Medical Center, 2020

3.2. Specific Objectives

To assess the efficacy of dolutegravir based ART regimen among HIV patients at Jimma Medical Center, 2020

To assess the efficacy of efavirenz based ART regimen among HIV patients at Jimma Medical Center, 2020

To assess the safety of dolutegravir based ART regimen among HIV patients at Jimma Medical Center, 2020

To assess the safety of efaverinez based ART regimen among HIV patients at Jimma Medical Center, 2020

4. Methods and Materials

4.1. Study Area and Period

The study was conducted at Jimma Medical Centre, which is located in Jimma city, Oromia Region, Southwest Ethiopia and is about 346 km away from the country's capital Addis Ababa (35). Jimma Medical Centre is one of the oldest public hospitals found in the Southwestern part of the country that runs under Jimma University. It is currently the only teaching and referral hospital in this part of the country serving a total population of about 15 million. The centre has ART clinic and provided HAART service from 2002 for 7486 ART clients. The ART clinic services involve HIV care and treatment, TB treatment, post exposure prophylaxis service and prevention of mother to child transmission services (36). This study was conducted from August 25-September 24, 2020.

4.2. Study Design

Hospitals based retrospective comparative cross-sectional study design was employed to compare the efficacy and safety of DTG versus to EFV based first line regimens, which was retrospective data from patient charts.

4.3. Population

4.3.1. Source Population

All HIV infected adult patients who were on ART with regular follow-up in Jimma Medical Center registered from August 2018 to April 2020

4.3.2. Study Population

All antiretroviral naïve adult HIV patients started treatment with Tenofovir/Lamivudine/ Efavirenz (TLE) based or Tenofovir/Lamivudine/Dolutegravir (TLD) based regimen between August 2018 up to April 2020 who fulfilled the eligibility criteria.

4.4. Inclusion and Exclusion Criteria

4.4.1. Inclusion Criteria

- All naive patients initiated with TDF+3TC+EFV and TDF+3TC+EFV between August 2018 and April 2020
- Patients who had registered baseline CD4 and/or Viral load count
- Patients who have at least six months of follow-up (since the patient needs 6 months treatment to assess the efficacy)
- Those with good adherence (since poor adherence to treatment affects the efficacy of the medications)

4.4.2. Exclusion Criteria

- HIV Patients on second line ART
- HIV patients on regimens other than TLD or TLE regimen
- HIV patients for whom data is incomplete registration on patient charts.
- Patients who had undetectable (<50 copies/ml) viral load at baseline (since the viral suppression is to on the required undetectable level no need to compare the outcome)

4.5. Sample Size Determination and Sampling Procedures

The sample size required for the study was calculated using the formula

$$n = \frac{z^2 p(1-p)}{d^2}$$

Whereas n= desired sample size

Z=level of significance at 95% confidence interval

p=maximum expected proportion (0.5)

d= margin of error (5%)

$$n = \frac{(1.96)^2(0.5)(0.5)}{(0.05)^2} = 384$$

Since the number of populations is less than 10,000, the sample size will be adjusted. Therefore, the corrected sample size will be;

$$n_f = \frac{n}{1 + \frac{n}{N}}$$

Where, n_f =desired sample size

n = sample from an infinite population (384)

N =population size 7486 (total number of patients attending)

$$n_f = \frac{384}{1 + \frac{384}{7486}} = 331$$

And considering 10% contingency, the final sample size will be:

$$331 + (331 \times 0.1) = 364$$

Accordingly, equal number of patient cards (182 on DTG and 182 on EFV) was considered for the study. But as the number of naïve HIV infected patients on TLD was 194, it was decided to include all naïve ART patients who fulfilled the inclusion criteria.

4.6. Data Collection Procedure

Data was collected from the patient's record review, all relevant information such as socio-demographic characteristics, clinical information and treatment regimens recorded by trained ART clinic working nurses.

Procedure of data collection

All adults receiving DTG and EFV were evaluated at baseline and at least at 6 months. At each visit, weight and CD4 lymphocyte count was collected. At each visit clinical staging and drug side

effect was assessed. HIV RNA viral load was determined at 6 months after initiation of therapy. To ensure the quality of data, pre-structured data collection sheet was used, data collectors were trained, and the principal investigator supervised closely throughout the process of data collection.

Measures to Prevent COVID 19 During Data Collection

First clearly data collection teams and surrounding staffs were communicated and educated about what COVID -19 is, how it spread, how they could catch the virus and infect others, about symptoms and how symptoms take a while to appear. The teams were encouraged to apply preventive practices, use a face mask, hand wash with high quality soap for >20 seconds or use hand sanitizer gel with 60% alcohol content every time before and after data collection, use hand sanitizer between each patient chart review.

4.7. Variables

4.7.1. Dependent Variables

- Viral Load
- CD4 count

4.7.2. Independent Variables

- The independent variables used in this study comprised of age, gender, duration of ART, Weight, clinical stage, type of ART regimen, drug adherence, residency, Marital status, level of education, occupation, WHO clinical stage, Functional status, months put on therapy, laboratory Test, patient complaints, Physical Examination and ADR/ADE.

4.8. Measurements

1. Efficacy

The efficacy was measured as the proportion of patients with viral suppression at Week 24 and/or 48. Accordingly two end points were considered as a measure

a) Proportion of patients with HIV-1 RNA fewer than 50 copies/mL at week 24 and/or 48 for both groups as the primary endpoint.

b) Median increase in $CD4^+$ count or change in $CD4^+$ at 24 and/or 48 weeks for both groups as a secondary endpoint

4.9. Data analysis, processing and interpretation

Data was edited, coded, entered Epi data and then exported to SPSS version 20 for cleaning and analysis respectively. The data was summarized and described using tables, graphs and percentages. Descriptive statistics were used to put results of the study in the form of findings and percentages. Bivariate associations were assessed by using chi-square test for categorical variables and t-test for continuous variables.

4.10. Ethical Consideration

Ethical clearance was secured from the Institutional review board of Jimma University, Institute of Health. Then officials at and responsible bodies in JUMC was communicated through a letter.

4.11. Limitations of the Study

The retrospective study design in poor recording practice setting is somewhat difficult. In this study, due to poor record keeping practice, 74 patient charts from TLD groups were excluded. In addition to these, some of the records were not complete; for instance, the type of ADR or side effect of TLD or/and TLE were not clearly written for those patients who were reported for drug-related adverse effects. This was not analyzed.

4.12. Plan for Dissemination of Finding

The findings of the study will be disseminated to JMC, Jimma zone health desk, Jimma town health bureau, Oromia regional health bureau, FMoH, and Jimma University through submission of hard copy and publication on reputable journals.

4.13. Operational Definition

Adherence: the extent to which a patient continues the agreed upon medication as prescribed. It was taken from the follow-up record, which estimated adherence from patient self-report as (4)

a) **Good adherence**: estimated adherence level of >95% as recorded by ART physicians/Nurses (for missing fewer than three doses per month).

b) **Fair Adherence**: estimated adherence level of 85%-95% as recorded by ART physicians/Nurses (for missing three up to eight doses per month and poor) and

c) **Poor Adherence**: estimated adherence level of <85% as recorded by ART physicians/Nurses (for missing nine and above doses per month)

Adult: Age above 14 years

Antiretroviral-naive patients: A patient with no previous history of taking a highly active antiretroviral therapy (HAART) regimen.

Functional status: defined as:

a) Working: the patient that able to perform usual work in or out of the house.
b) Ambulatory: the patient that able to perform activities of daily living but not able to work.
c) Bedridden: the patient that does not able to perform activities of daily living (3).

Lost to follow up: A patient who has missed any drug pick-up appointment.

Regimen change: A switch from first-line regimen containing Efavirenz or Dolutegravir to another regimen not containing Efavirenz or Dolutegravir respectively.

5. Results

5.1. Sociodemographic characteristics

The total number of patient charts included in the study was 240, in which equal number, i.e., 120 of each TLD and TLE groups were included. As shown in table 1, the mean age of the respondents was 34.78±11.99 and 36.7±9.92 years among the TLD and TLE groups respectively, showing similar age distribution. The sex, residency, marital status, educational level and occupation among the two groups were similar ($p>0.05$); indicating no significant difference among both groups in socio-demographic characteristics.

Table 1: Socio-demographic characteristics of study participants, JMC, 200

SN	Characteristics	TLD based regimen N=120	TLE based regimen N=120	P-Value
1	**Age**	34.78±11.99	36.7±9.92	**0.083**
2	**Sex**			**0.605**
	Male	54(45)	59(49.2)	
	Female	66(55)	61(50.8)	
3	**Residency**			**0.611**
	Rural	29(19.2)	19(80.8)	
	Urban	97(15.8)	101(84.2)	
4	**Marital status**			**0.141**
	Married	66(55.0)	78(65.0)	
	Unmarried	29(24.2)	18(15.0)	
	Widowed	4(3.3)	1(0.8)	
	Divorced	21(17.5)	23(19.2)	
5	**Educational level**			**0.160**
	Unable to read and write	17(14.2)	11(9.2)	
	Primary	42(35.0)	58(48.3)	
	Secondary	42(35.0)	38(31.7)	
	Tertiary	19(15.8)	13(10.8)	
6	**Occupation**			**0.140**
	Housewife	17(14.2)	19(15.8)	
	Farmer	5(4.2)	6(5.0)	
	Merchant	17(14.2)	33(27.5)	
	Government employee	47(39.2)	36(30.0)	
	Student	12(10.0)	7(5.8)	
	no job	22(18.3)	19(15.8)	

The baseline mean height, mean weight, mean CD4, mean Body Mass Index, WHO clinical stage and functional status among patients on the TLD and TLE regimens were similarly distributed among the two groups ($p>0.05$). The baseline CD4 among TLD and TLE groups were 306.89 and 316.01 respectively. Regarding months of therapy, the TLE groups were more experienced with the therapy (18.56±4.53 months) than the TLD groups (9.91±1.65 months). This shows there was a significant difference in months of therapy among the treatment groups ($p<0.05$).

Table 2: Baseline Patient and clinical characteristics before treatment, JMC, 2020

SN	Characteristics	TLD based regimen	TLE based regimen	P-value
1	Baseline height of the patients (cm), (mean ±S D)	162.39±9.04	164.28±8.62	0.234
2	baseline weight of the patients (kg), (mean ± SD)	53.75(10.3)	56.81(12.35)	0.061
3	Mean Months on Therapy at baseline	9.91±1.65	18.56±4.53	0.000
4	Baseline CD4 T cell count (cells/ul), (mean + SD)	306.89±170.17	316.01±181.02	0.457
5	Body Mass Index (mean + SD)	20.3230±3.31	21.03±4.12	0.174
6	WHO clinical stage at the baseline, n (%)			0.078
	Stage I	101(84.2)	106(88.3)	
	Stage II	19(15.8)	13(10.8)	
	Stage III	0(0)	1(0.8)	
	Stage IV	0(0)	0(0)	
7	Functional Status at baseline, n (%)			0.325
	Working	71(59.2)	78(65)	
	Ambulatory	45(37.5)	32(26.7)	
	Bed ridden	4(3.3)	10(8.3)	

5.2. Comparison of CD4 count at the 6 months of therapy

As shown in table 3, a multiple regression was run to predict change in CD4 count from regimen, age, sex, baseline CD4 and adherence. These variables statistically significantly predicted change in CD4, $F(5, 95) = 9.946$, $p < .0005$, $R2 = 0.175$. Regimen, baseline CD4 and adherence variables added statistically significantly to the prediction, $p < 0.05$.

Table 3: Change in CD4 count among HIV Positive patients at 6 months of therapy, JMC, 2020.

Variables	B (95%CI)	P	B (95%CI)	P
Regimen	51.633[24.488 - 78.779]	0.000	40.851[14.892 - 66.811]	0.002
Age	-0.96[-1.366 - 1.173]	0.881	0.518[-0.677 - 1.713]	0.394
Sex	23.143[-4.683 - 50.969]	0.103	22.696[-3.581 - 48.972]	0.090
Baseline CD4	-0.065[-1.45 - 0.014]	0.106	-0.123[-0.199 - (-0.046)]	0.002
Adherence	89.168[53.516 - 125.096]	0.000	97.113[60.841-133.385]	0.000

5.3. Viral Suppression

There is a statistically significant difference in viral suppression among the TLD and TLE groups (P-value=0.030). As indicated in table 4, the binary logistic regression was done to study the effect of the regimen on the viral suppression. Controlling age, sex, baseline CD4 and adherence in the model the odds of viral suppression among the TLD group increase by 1.683[0.907-3.123].

Table 4: Bivariate analysis of Viral Suppression at 24 weeks of treatment among HIV-positive patients, JMC, 2020

Variables	COR (95%CI)	P	AOR (95%CI)	P
Regimen, TLD	1.819462[1.059-3.126]	0.030	1.683[0.907-3.123]	0.099
Regimen, TLE			1	
Age	0.987[0.963-1.011]	0.282	1.002[0.972-1.033]	0.898
Sex, Male	1.872[1.091-3.212]	0.023	1.838[0.974-3.470]	0.060
Sex, Female			1	
Baseline CD4	1.005[1.003-1.007]	0.000	1.004[1.002-1.006]	0.001
Adherence, Good	15.022[5.511-40.946]	0.000	9.468[3.331-26.829]	0.000
Adherence, poor or fair			1	

5.4. Level of Adherence

Regarding the level of adherence to the treatment regimen, 88.33% (n=106) of the TLD treatment group had a good adherence the regimen and 82.5% (n=99) had good adherence to the treatment regimen (table 5). This showed that there is no significant difference on the adherence level among both study groups (p>0.05).

Table 5: Adherence to treatment among HIV-positive patients at JMC, 2020

Regimen	**Adherence**			**P Value**
	good	Fair	Poor	
TLD	106 (88.33%)	14 (11.67%)	0 (0%)	0.100
TLE	99 (82.5%)	19 (18.83%)	2 (1.67%)	

5.5. Safety

As far as safety of the study regimens was considered, 6.67%, n=8 and 17.5%, n=21 of TLD and TLE study participants experienced side effects/ADR (p=0.035) (table 6).

Table 6: Side effects of TLD/TLE experienced and reported by HIV-positive patients at JMC, 2020.

Regimen	ADR		Remarks
	Yes	No	
TLD	8 (6.67%)	112 (93.33%)	X^2=4.364, P=0.035
TLE	21 (17.5%)	99 (82.5%)	

6. Discussion

6.1. Demographics, clinical baseline and patient characteristics

There was also a similar distribution among other socio-demographic characteristics such as age, sex, residency, marital status, educational level and occupation. Regarding patient and clinical characteristics, the baseline height, mean weight, mean CD4, mean Body Mass Index, WHO clinical stage and functional among both study groups were also similarly distributed.

6.2. Efficacy of study regimens

The current study showed that the TLD group exhibited a better CD4 recovery that the TLE groups and the change in CD4 among TLD was also statistically significant. It is comparable with a result of systematic reviews and network meta-analysis in which better CD4 change was recorded among Dolutegravir group than Efavirenz group done by Kanters et al. (37) and Snedecor et al. (38).

This study demonstrated a better viral suppression among the TLD group. Compared to a study conducted in Cameroon, the percentage difference of viral suppression of current study showed better suppressive power of TLD (39). Similar viral suppression difference was reported in China (11.3%) (40). Another study conducted in South Africa showed 6% difference in viral suppression (41); and results from SPRING-1 showed 10% difference (34). The difference between current study and other studies might be associated with difference in study settings. In the current study, better CD4 recovery was observed. The odds of viral suppression of DTG were 1·683 times more than that of TLE at 48 weeks of therapy. It is comparable to the result of a systematic review and network meta-analysis on comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection, which was 1·87 [1·34–2·64] (37). The similarity in result might be due to similarity of efficacy of DTG.

Concerning the level of adherence to the treatment regimen, 88.33% (n=106) of the TLD treatment group had a good adherence the regimen and 82.5% (n=99) had good adherence to the treatment regimen. This showed that there is no significant difference on the adherence level among both study groups.

6.3. Safety of study regimens

To the extent that safety of the study regimens was considered, 6.67%, n=8 and 17.5%, n=21 of TLD and TLE study participants experienced side effects/ADR. Compared to SINGLE, there was a lower rate of SEs DTG (2%) and EFV (10%) (42). The reason for variation might be the methodology employed by both study settings.

7. Conclusion and Recommendations

7.1. Conclusion

TLD was found not inferior to TLE. And better treatment outcome was observed in achieving undetectable viral load and better CD4 recovery at 48 weeks in treatment of newly diagnosed HIV patients. Similarly, the safety profile of TLD was comparable to TLE, ever lesser side effects were reported by the patients.

7.2. Recommendations

TLD, including DTG containing regimens should be monitored regularly, and the current TLD containing treatment regimens in Ethiopia should be strengthened to get benefitted. Academic institutions should conduct further studies on the safety profile of DTG in Ethiopian population.

References

1. UNAIDS. Global HIV & AIDS statistics — 2020 fact sheet: UNAIDS; 2020 [cited 2012 July 9]. Available from: https://www.unaids.org/en/resources/fact-sheet.
2. World Health Organization. Policy brief: update of recommendations on first- and second-line antiretroviral regimens. Geneva: World Health Organization; 2019 2019. Contract No.: WHO/CDS/HIV/19.15.
3. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2nd ed. France: World Health Organization; 2016.
4. Federal Ministry of Health. National Consolidated Guidelines for Comprehensive HIV Prevention, Care and Treatment. Addis Ababa2018.
5. UNAIDS. Ethiopia 2020 [cited 2020 July 7]. Available from: https://www.unaids.org/en/regionscountries/countries/ethiopia.
6. Rodger AJ, Lodwick R, Schechter M, Deeks S, Amin J, Gilson R, et al. Mortality in well controlled HIV in the continuous antiretroviral therapy arms of the SMART and ESPRIT trials compared with the general population. AIDS (London, England). 2013;27(6):973-9.
7. Samji H, Cescon A, Hogg RS, Modur SP, Althoff KN, Buchacz K, et al. Closing the Gap: Increases in Life Expectancy among Treated HIV-Positive Individuals in the United States and Canada. PLOS ONE. 2013;8(12):e81355.
8. Vo TTN, Ledergerber B, Keiser O, Hirschel B, Furrer H, Battegay M, et al. Durability and Outcome of Initial Antiretroviral Treatments Received during 2000–2005 by Patients in the Swiss HIV Cohort Study. The Journal of Infectious Diseases. 2008;197(12):1685-94.
9. Zaragoza-Macias E, Cosco D, Nguyen ML, Del Rio C, Lennox J. Predictors of success with highly active antiretroviral therapy in an antiretroviral-naive urban population. AIDS Res Hum Retroviruses. 2010;26(2):133-8.

10. Bernardini C, Maggiolo F. Triple-combination rilpivirine, emtricitabine, and tenofovir (Complera™/Eviplera™) in the treatment of HIV infection. Patient Prefer Adherence. 2013;7:531-42.

11. Mayer KH, Venkatesh KK. Antiretroviral therapy as HIV prevention: status and prospects. Am J Public Health. 2010;100(10):1867-76.

12. Günthard HF, Aberg JA, Eron JJ, Hoy JF, Telenti A, Benson CA, et al. Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society-USA Panel. Jama. 2014;312(4):410-25.

13. Warnke D, Barreto J, Temesgen Z. Antiretroviral drugs. Journal of clinical pharmacology. 2007;47(12):1570-9.

14. DeJesus E, Rockstroh JK, Henry K, Molina JM, Gathe J, Ramanathan S, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet (London, England). 2012;379(9835):2429-38.

15. Sax PE, DeJesus E, Mills A, Zolopa A, Cohen C, Wohl D, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. Lancet (London, England). 2012;379(9835):2439-48.

16. Raffi F, Rachlis A, Stellbrink HJ, Hardy WD, Torti C, Orkin C, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet (London, England). 2013;381(9868):735-43.

17. Underwood M, Johns B, Sato A, Fujiwara T, Spreen W, editors. S/GSK1349572: a next generation integrase inhibitor with activity against integrase inhibitor-resistant clinical isolates from patients experiencing virological failure while on raltegravir therapy. 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention: Cape Town, South Africa; 2009.

18. Rathbun RC, Lockhart SM, Miller MM, Liedtke MD. Dolutegravir, a Second-Generation Integrase Inhibitor for the Treatment of HIV-1 Infection. Annals of Pharmacotherapy. 2014;48(3):395-403.

19. Gohil K. Pharmaceutical approval update. P T. 2014;39(11):746-72.

20. Cahn P, Pozniak AL, Mingrone H, Shuldyakov A, Brites C, Andrade-Villanueva JF, et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. The Lancet. 2013;382(9893):700-8.

21. World Health Organization. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2018 2018. Contract No.: WHO/CDS/HIV/18.51.

22. Rakhmanina NY, van den Anker JN. Efavirenz in the therapy of HIV infection. Expert Opin Drug Metab Toxicol. 2010;6(1):95-103.

23. Zamora FJ, Dowers E, Yasin F, Ogbuagu O. Dolutegravir And Lamivudine Combination For The Treatment Of HIV-1 Infection. HIV AIDS (Auckl). 2019;11:255-63.

24. Teweldemedhin M, Asres N, Gebreyesus H, Asgedom SW. Tuberculosis-Human Immunodeficiency Virus (HIV) co-infection in Ethiopia: a systematic review and meta-analysis. BMC Infectious Diseases. 2018;18(1):676.

25. World Health Organization. Dolutegravir (DTG) and the fixed dose combination (FDC) of tenofovir/lamivudine/dolutegravir (TLD) Briefing note. 2018 May 2018.

26. Brehm TT, Franz M, Hüfner A, Hertling S, Schmiedel S, Degen O, et al. Safety and efficacy of elvitegravir, dolutegravir, and raltegravir in a real-world cohort of treatment-naïve and—experienced patients. Medicine. 2019;98(32):e16721.

27. Rusconi S, Adorni F, Tau P, Borghi V, Pecorari M, Maserati R, et al. Dolutegravir (DTG)-containing regimens after receiving raltegravir (RAL) or elvitegravir (EVG): Durability and virological response in a large Italian HIV drug resistance network (ARCA). Journal of

clinical virology : the official publication of the Pan American Society for Clinical Virology. 2018;105:112-7.

28. Mekuria LA, Nieuwkerk PT, Yalew AW, Sprangers MA, Prins JM. High level of virological suppression among HIV-infected adults receiving combination antiretroviral therapy in Addis Ababa, Ethiopia. Antiviral therapy. 2016;21(5):385-96.

29. Chendi BH, Okomo Assoumou MC, Jacobs GB, Yekwa EL, Lyonga E, Mesembe M, et al. Rate of viral load change and adherence of HIV adult patients treated with Efavirenz or Nevirapine antiretroviral regimens at 24 and 48 weeks in Yaoundé, Cameroon: a longitudinal cohort study. BMC Infectious Diseases. 2019;19(1):194.

30. Edet A, Akinsola H, Bessong PO. Virologic and immunologic responses of patients on highly active antiretroviral therapy in a rural community health center in Limpopo, South Africa: A retrospective study. South Afr J HIV Med. 2019;20(1):818—.

31. Kilaru KR, Kumar A, Sippy N, Carter AO, Roach TC. Immunological and virological responses to highly active antiretroviral therapy in a non-clinical trial setting in a developing Caribbean country. HIV medicine. 2006;7(2):99-104.

32. Cohen C, Wohl D, Arribas JR, Henry K, Van Lunzen J, Bloch M, et al. Week 48 results from a randomized clinical trial of rilpivirine/emtricitabine/tenofovir disoproxil fumarate vs. efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV-1-infected adults. AIDS (London, England). 2014;28(7):989-97.

33. Fantauzzi A, Turriziani O, Mezzaroma I. Potential benefit of dolutegravir once daily: efficacy and safety. Hiv/aids (Auckland, NZ). 2013;5:29.

34. van Lunzen J, Maggiolo F, Arribas JR, Rakhmanova A, Yeni P, Young B, et al. Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial. The Lancet infectious diseases. 2012;12(2):111-8.

35. Ademe BW, Tebeje B, Molla A. Availability and utilization of medical devices in Jimma zone hospitals, Southwest Ethiopia: a case study. BMC Health Services Research. 2016;16(1):287.

36. Tesfaye T, Darega J, Belachew T, Abera A. HIV positive sero-status disclosure and its determinants among people living with HIV /AIDS following ART clinic in Jimma University Specialized Hospital, Southwest Ethiopia: a facility—based cross-sectional study. Archives of Public Health. 2018;76(1):1.

37. Kanters S, Vitoria M, Meg Doherty, Socias ME, Ford N, Forrest JI, et al. Comparative efficacy and safety of fi rst-line antiretroviral therapy for the treatment of HIV infection: a systematic review and network meta-analysis. Lancet HIV. 2016.

38. Snedecor SJ, Radford M, Kratochvil D, Grove R, Punekar YS. Comparative efficacy and safety of dolutegravir relative to common core agents in treatment-naïve patients infected with HIV-1: a systematic review and network meta-analysis. BMC Infectious Diseases 2019;19(484).

39. Group NAS. Dolutegravir-based or low-dose Efavirenz—based regimen for the treatment of HIV-1. New England Journal of Medicine. 2019;381(9):816-26.

40. Punekar YS, Guo N, Tremblay G, Piercy J, Holbrook T, Young B. Improving access to antiretrovirals in China: economic analyses of dolutegravir in HIV-1 patients. Cost Effectiveness and Resource Allocation. 2019;17(1):1-9.

41. Venter WD, Moorhouse M, Sokhela S, Fairlie L, Mashabane N, Masenya M, et al. Dolutegravir plus two different prodrugs of tenofovir to treat HIV. New England Journal of Medicine. 2019;381(9):803-15.

42. Walmsley S, Baumgarten A, Berenguer J, Felizarta F, Florence E, Khuong-Josses M-A, et al. Brief report: dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naive patients: week 96 and week 144 results from the SINGLE randomized clinical trial. Journal of acquired immune deficiency syndromes (1999). 2015;70(5):515.

Annexes

Annex A: Data collection Tool

Jimma University

Institute of Health

Faculty of Medical sciences

School of Medicine

Dear,

This data collecting format is prepared to collect data on "Efficacy and Safety of DTG based vs EFV based first line ART regimens among HIV patients at Jimma University Specialized Hospital, ART clinic".

This study is conducted as part of my Clinical speciality in collaboration with Jimma University School of graduate studies. The aim of the study is to assess the safety and efficacy of DTG vs EFV based regimens among PLWHA at JUSH. The finding of this study will help in identifying the safest regimen in terms of better treatment outcomes in this specific population group. The information extracted from patients' medical record was kept confidential and not exposed to other parties.

<16>Name of investigator: Dr.Melat Dadigeba

Phone number—0911806862

Email-dadigebamelat@gmail.com

Data collector's	**Supervisor's**
Name _____	Name _____
Sign_____	Sign_____
Phone number _____	Phone number _____

Instruction

Select your answer for the questions by marking "✓" in the box provided and if your answer is out of the choice provided; write it in the space provided

Code _____

Part I: Socio-demographic data

Part 1 socio-demographic status of the patients

Unique ART no._____

10<47>1. Age in years……...

102. Sex A. Male ☐ B. Female ☐

103. Residency A. rural ☐ B. urban ☐

10<61>4. Marital status A. Married ☐ B. Unmarried ☐ C. Widowed ☐ D. Divorced ☐

105. Levels of education A. unable to read and write ☐ B. Primary ☐ C. Secondary ☐ D. Tertiary ☐

106. Occupation A. house wife ☐ B. farmer ☐ C. merchant ☐ D. Governmental Employee ☐ E. Others (specify) ----------

Part 2. General aspect of patient ART regimen

201. ART initiation date __/__/____ (dd/mm/yyyy)

202. ART initiation A. Age ____ B. Height _____

203. HAART regimen initiated TLD ☐ TLE ☐

204. For How many months put on therapy_____ months

Part 3. Check list for efficacy of doltiglavir and efavirnaze based combination HAART regimen

301. $CD4^+$ A. at baseline _____ B. 3 months_____ C. 6 months _____ D. 12 months_____

302. VL A. at baseline _____ B. 6 months_____ C. 12 months_____

303. Functional Status (W, A, B) A. at baseline _____ B. 3 months_____ C. 6 months _____ D. 12 month_____

304. WHO clinical stage (I /II/ III /IV) A. at baseline _____ B. 3 months_____ C. 6 months _____ D. 12 month_____

305. Weight A. at baseline _____ B. 3 months_____ C. 6 months _____ D. 12 month_____

Part 4: check list of Safety of the Drugs

4.1 Laboratory Test Abnormalities

401. Hemoglobin A. 8.0-9.4 g/dL ☐ B. 7.0-7.9 g/dL ☐ C. 6.5-6.9 g/dL ☐ D. <6.5 g/dL ☐

402. Absolute Neutrophil Count A. 1,000-1,500 mm 3 ☐ B. 750-990 mm 3 ☐ C. 500-749 mm 3 <500 mm 3 ☐

403. Platelets A. 75.0000—99,000 mm3 ☐ B. 50,000-74,999 mm 3 ☐ C. 20.0000-49,999 mm 3 ☐ D. <20,000 mm 3 ☐

404. ALT A. 1.25-2.5 X upper normal limit ☐ B. 2.5-5 X upper normal limit ☐ C. 5.0-10 X upper normal limit ☐ D. 10 X upper normal limit ☐

405. Bilirubin A. 1-1.5XULN ☐ B. 1.5-2.5 X ULN ☐ C. 2.5-5 x upper limits of normal ☐ D. >5 x upper limits of normal ☐

406. Amylase/lipase A. 1-1.5XULN ☐ B. 1.5-2 X ULN ☐ C. 2-5 x upper limits of normal ☐ D. >5x upper limits of normal ☐

407. Triglycerides A. 200-399mg/dL ☐ B. 400-750 mg/dL ☐ C. 751-1200mg/dL ☐ D. >1200 mg/dL ☐

408. Cholesterol

A. 1.0–1.3 X Upper normal limit ☐ B. 1.3-1.6 X Upper normal limit ☐

C. 1.6-2.0 X Upper normal limit ☐ D. 2.0 X Upper normal limit ☐

409. Patient complaints

A. Nausea, vomiting, diarrhea_____

B. Abdominal pain, yellowish discoloration of the eye_____

C. Joint and muscle pain_____

D. Neuropsychiatric symptoms, insomnia_____

E. Pruritus_____

F. Skin rash_____

Others specify_____

410. Physical examination findings—

A. icteric sclera_____

B. Abdominal tenderness_____

C. Skin rash_____

D. Mental status change_____

E. Muscle bulk and power_____

F. Other specify_____

412. Adverse Events

i.	at baseline	A. Yes ☐	B. No ☐	C. If Yes, Specify _____
ii.	At 3 months.	A. Yes ☐	B. No ☐	C. If Yes, Specify _____
iii.	At 6 months.	A. Yes ☐	B. No ☐	C. If Yes, Specify _____
iv.	At 12 months.	A. Yes ☐	B. No ☐	C. If Yes, specify _____